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Case Reports 2017

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PREÂMBULO

Na edição do segundo volume "Livro de Casos Clínicos do CHLN – ano de 2017", apontamentos relevantes dos jovens médicos da sua clínica diária, secundo com igual sentimento pessoal de grande satisfação e orgulho o elevado mérito dos que organizaram com proficiência esta obra, de consideração pelos Mestres da Medicina que credibilizam a frescura e a energia profissionais dos seus jovens autores e, também, na qualidade de Presidente do Conselho de Administração do CHLN o meu reconhecimento por tudo aquilo que espelhe o fecundo prestígio e sonante superioridade da nossa instituição.

Palavras que se aplicam com idêntica expressão ao crescente bom nome e clara evolução que as Jornadas, denominadas – *Junior Doctors International Meeting* –, têm vindo a alcançar entre a comunidade médica, ano após ano, cimentando-se no novo mundo médico, e que permitem tanto apreço, quer pelo amadurecimento e experiência da Comissão Organizadora quer pelo elevado saber do Corpo Editorial.

Jornadas e obra médica juntas, a pensar e a puxar em comum, as gerações dos médicos mais novos, num caminho de afirmação de desafios e sucessos, elevando-os a patamares de elevada referência e competência, desde logo a marca indelével de ambos os Hospitais Universitários de Santa Maria e Pulido Valente, responsáveis pela sua excelente formação e preparação para a vida profissional, em que esta espera daqueles jovens médicos enorme absorção e exigência.

O mais que vos posso desejar é que a linha de horizonte das jornadas seja tão ampla que permita uma extensa internacionalização das mesmas, pelos ensinamentos e conhecimentos que produz e distribui, gerando uma procura crescente de participação. E que o "Livro de Casos Clínicos de CHLN - 2017", na senda do anterior, produza pela sua leitura o designado "efeito da obra sobre o leitor", característica atribuída em exclusivo aos grandes livros e aos grandes trabalhos escritos. Parabéns!

Para vós, jovens Médicos, votos de felicidade pessoal e de realização profissional.

Prof.º Dr. Carlos das Neves Martins

Presidente do Conselho de Administração do CHLN

PREFÁCIO

A formação dos Internos constitui uma oportunidade de procura de conhecimento, uma sucessão de ocasiões na aquisição de competências conduzindo a uma progressiva responsabilidade, que é o elemento diferenciador da maturação médica.

A disponibilização de uma publicação científica como é a edição do segundo Livro de Casos Clínicos (CHLN Case Reports 2017) é prova do dinamismo e qualidade dos Internos do Centro Hospitalar Lisboa Norte que sob o patrocínio da Direcção Clínica e da Direcção do Internato Médico, bem como da Faculdade de Medicina da Universidade de Lisboa e do Instituto de Medicina Molecular, inserindo-se no âmbito do Centro Académico de Medicina de Lisboa, se tem vindo a impor como uma marca de qualidade.

Dra. Margarida Lucas

Diretora clínica do CHLN

EDITORES

A investigação científica nas áreas clínicas é muito importante para o progresso da Medicina. No entanto verifica-se ser especialmente difícil, com muitos obstáculos que derivam sobretudo da imprevisibilidades dos fenómenos nos indivíduos, ao contrário do que acontece na experimentação animal ou com materiais biológicos. É ainda sujeita a condicionantes éticas que têm que ser respeitadas.

A descrição e análise crítica de casos clínicos, caracterizados pela raridade ou particularidade na sua marcha diagnóstica ou terapêutica, é uma excelente forma de introdução à Investigação Clínica, e é por si mesma uma forma de Investigação Clínica. Sendo o Internato de Formação Específica um tempo em que os internos estão especialmente disponíveis para a aprendizagem, esta iniciativa torna-se particularmente útil e interessante.

Esta é já a segunda edição do Livro de Casos Clínicos, sendo que a primeira foi muito bem sucedida, com um conjunto de casos clínicos muitíssimo interessantes. Também nesta edição foi possível reunir casos de áreas muito diferentes e com muito interesse. Mais uma vez, este livro de Casos Clínicos foi uma iniciativa dos internos do Centro Hospitalar Lisboa Norte, com a colaboração de outros elementos e dos coordenadores dos respetivos Serviços.

Sendo esta uma iniciativa de interesse para a formação, a Direção do Internato Médico (DIM), deu o seu apoio através da criação de um corpo de revisores, e nos procedimentos relacionados com a seleção e revisão dos casos clínicos. O Corpo Editorial foi selecionado pela sua qualidade científica, e a DIM agradece a todos os revisores o tempo e o esforço despendido nesta revisão. A DIM dá os parabéns aos internos pelo seguimento desta iniciativa.

Finalmente, uma palavra de agradecimento especial ao trabalho realizado pelo secretariado do DIM, em particular a Isabel Rodrigues.

Prof. Doutora Helena Cortez-Pinto

Diretora do Internato Médico do CHLN

Como referi na Edição do primeiro "Livro de Casos Clínicos" por ocasião das 3as Jornadas do Internato Médico, a análise e reflexão exigentes sobre casos clínicos constitui um dos pilares da promoção da qualidade assistencial e é fundamental para uma correcta incorporação do conhecimento científico novo, bem como da inovação tecnológica na prática clínica diária, nomeadamente no diagnóstico e terapêutica.

Felicito assim a Comissão Organizadora das Jornadas do Internato Médico do CHLN e os Médicos Internos do Centro Hospitalar pela capacidade de concretizar esta Edição do 2º livro de Casos Clínicos.

A publicação de "casos clínicos" constitui um importante "tipo" de investigação clínica, por vezes subvalorizada, mas que pode contribuir muito significativamente para o conhecimento médico, não só pela identificação de casos de doenças raras mas também formas de apresentação clínica menos conhecidas. Por outro lado, este tipo de investigação permite sugerir novas associações entre doenças, reacções adversas medicamentosas raras, bem como evoluções ou respostas terapêuticas atípicas subsequentemente confirmadas por estudos epidemiológicos. Finalmente, o estudo detalhado de alguns casos pode facilitar a colocação de hipóteses sobre novos mecanismos de doença.

Os casos apresentados neste livro ilustram bem estas varias formas de contribuir para o conhecimento médico e constituem um excelente estimulo e treino dos Internos para a "publicação científica ". O empenho dos Internos do CHLN na procura dos mais altos níveis de qualidade assistencial integrando e promovendo o conhecimento científico, são aqui bem evidenciados e traduzem a elevada diferenciação técnica e cientifica da nossa Instituição Hospitalar.

Prof. Doutor Rui M. M. Victorino

Diretor do serviço de Medicina II do CHLN

ANESTHESIC MANAGEMENT OF A PATIENT WITH BRUGADA SYNDROME FOR AN EMEGENCY PROCEDURE

ABORDAGEM ANESTÉSICA DE UM DOENTE COM SÍNDROME DE BRUGADA NUMA CIRURGIA URGENTE

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ABSTRACT

Brugada syndrome is a cardiac abnormality of transmembrane conduction, accounting for up to 20% of sudden deaths in patients without structural cardiac defects. This syndrome has an autosomal dominance inheritance, with variable penetrance, and the most common mutation is in SCN5A gene, rendering cardiac sodium channels inactive. This leads to a distinctive electrocardiographic pattern with right bundle branch block and ST segment elevation in precordial leads V1-V3 without structural cardiac disease. We describe the case of a 35-year old man, diagnosed with Brugada syndrome, proposed to arm laceration suture following a car accident. Our anesthetic approach begun with an interscalene brachial plexus block, but it wasn't successful and conversion to general anesthesia was necessary. In this case report, we intend to emphasize the cardiovascular risks involved with anesthesia administration in these patients and also highlight the importance of having a back-up plan for every situation.

Keywords: Brugada syndrome, anesthesia, arrhythmias.

RESUMO

A síndrome de Brugada é um distúrbio da condução transmembranar cardíaca, responsável por até 20% das mortes súbitas em doentes sem patologia estrutural. Apresenta uma hereditariedade autossómica dominante, com penetrância variável, sendo que a mutação mais prevalente é a do gene SCN5A, que leva a inativação dos canais de sódio cardíacos. O padrão electrocardiográfico característico é um bloqueio do ramo direito e elevação do ST nas derivações precordiais V1-V3, sem doença cardíaca estrutural. Descrevemos o caso clínico de um homem de 35 anos, diagnosticado com síndrome de Brugada, proposto para correção cirúrgica de laceração profunda do braço, após acidente de viação. O nosso plano anestésico iniciou-se com um bloqueio do plexo braquial via interescalénica, que não foi suficiente para o procedimento, com conversão para anestesia geral. Queremos não só enfatizar os riscos cardiovasculares envolvidos na abordagem destes doentes, mas também salientar a importância da elaboração de planos alternativos.

Palavras-chave: síndrome de Brugada, anestesia, arritmias.

INTRODUCTION

Brugada syndrome is a cardiac abnormality of transmembrane conduction, which puts patients at risk for ventricular arrhythmias and accounts for up to 20% of sudden deaths in patients without structural cardiac defects. [1] This syndrome has an autosomal dominance inheritance with variable penetrance and the physiology behind it remains unclear. [2] Mutations in about 10 genes have been linked to Brugada syndrome, although the most common is a mutation in SCN5A gene (prevalence: 18-30%), coding for the cardiac sodium channels insensitive to tetrodotoxin, rendering enhanced inactivation of these channels. [3] Other abnormalities include a decrease in L-type calcium current and decreased transient outward potassium current.[4] This leads to a distinctive electrocardiograph pattern with right bundle branch block and ST segment elevation in precordial leads V1-V3, without structural cardiac disease. [5]

Since patients with diagnosed and undiagnosed Brugada syndrome can present for surgery at any time, it is important for anesthesiologists to be familiar with this syndrome in order to be able to safely manage these patients in the perioperative period. At present time, there is no definite recommendation for general or regional anesthesia. However, some anesthetic agents are noted to have an association with ST segment elevations and can result in an increased risk of arrhythmias, so it is important to avoid their use, whenever possible, in these patients.

Safe	Avoid[B]	Contra-indicated
Muscle relaxants (rocuronium, vecuronium, mivacurium)	Antiarrythmic drugs (quinidine, disopiramide, amiodarone)	Antiarrythmic drugs (procainamide, flecainide, propaphenone)[C]
Autonomic nervous system related drugs (ephedrine, phenylephrine, dopamine, propranolol, atropine, isoproterenol)	Autonomic nervous system related drugs (edophronium)	Autonomic nervous system related drugs (noradrenaline, acetylcholine, neostigmine)[C]
Local anesthetics (lidocaine)	Local anesthetics (cocaine)	Local anesthetics (bupivacaine)[C]
Antiemetics (droperidol, ondansetron, dexamethasone)	Antiemetics (metoclopramide)	Central nervous system drugs (amitriptyline, clomipramine, desipramine, lythium)[C]
Induction agents (propofol, barbiturates, nitrous oxide, volatile anesthetics)	Induction agents (ketamine, propofol infusion)	
Analgesics (narcotics, ketorolac, paracetamol)	Analgesics (tramadol)	
Benzodiazepines		
Hypotensive agents (diltiazem, nifedipine, nitroglycerine)[A]		

Table 1 – Anesthetic Drug Recommendations [7,8] | ([A] class III evidence, [B] class IIa and IIb evidence, [C] class I evidence)

General anesthesia can be performed safely, both as inhalation and as balanced with opiates, although caution and avoidance is advised on the use of medications such as: propofol or ketamine, as they may affect cardiac calcium channel function, promoting ST segment elevation in Brugada patients. The use of inhaled anesthetics, opioids, barbiturates, neuromuscular blockers and sugammadex is considered safe. [6] Regional anesthesia and neuroaxial blockade may be performed with caution. Since local anesthetics affect myocardial sodium channels, they may precipitate ECG alterations and arrhythmias, especially when used in large dosages and high vascularized tissues. [6]

The most important aspect in the anesthetic approach is careful consideration upon the administration of every drug. Besides this, back up plans should be made in advance, as for every patient undergoing any anesthetic procedure.

This case report targets the challenges faced by the anesthesiologist in administering safe anesthesia to a patient with Brugada syndrome and consideration of alternative anesthetic agents for these patients in order to minimize their risks under anesthesia.

CASE PRESENTATION

A 35-year old man, ASA II, diagnosed with Brugada syndrome on routine investigation (accidental discovery on an ECG - figure 1 -, with no previous history of chest pain, syncope or palpitations; family history was negative for Brugada syndrome), was proposed to surgical repair of an arm laceration following a car accident. From this accident, facial trauma with multiple abrasions, fronto-temporal wound and deep laceration in the left arm ensued (figure 2). Only the latter was the subject of the intervention proposed. The patient had no previous history of medical problems, besides the Brugada syndrome diagnosis, no history of previous surgical procedures and displayed a good general status with an effort tolerance greater than 10 metabolic equivalents.

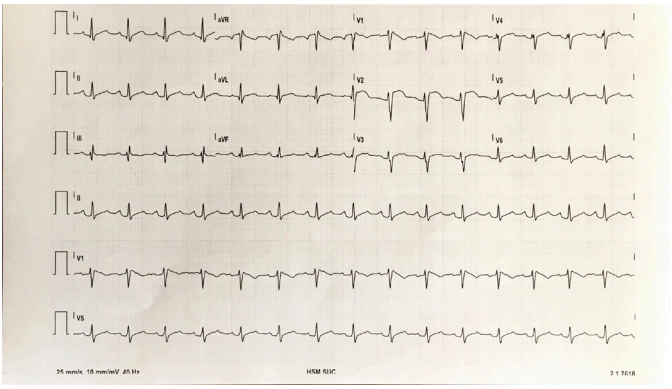

Figure 1 – Patient's ECG trace

Figure 2 – Patient's left arm wound

Upon arrival, the patient was hemodynamically stable (noninvasive blood pressure: 145/94 mmHg), conscious and oriented (Glasgow coma scale: 15), eupneic and breathing comfortably (SatO2 99% at FiO2 0.21). Our preoperative evaluation revealed the patient had 75 kg, 180 cm and normal airway examination. Laboratory analysis showed no electrolyte abnormalities, with no corrections needed preoperatively. The patient displayed an implantable cardioverter defibrillator (ICD) at the left thoracic wall, implanted on June 2006.

After explaining the anesthetic and surgical procedure and associated risks, a written informed consent was obtained. Since the patient presented with a medical history of Brugada syndrome, avoidance of sodium channel blocker medications was the priority. An interscalene brachial plexus block was planned to avoid general anesthesia and associated risks, and two wide bore IV cannula (18G and 16G) were placed. Prior to blockade, the patient was premedicated with midazolam 3 mg IV and remifentanil infusion (0.1 mcg/kg/min).

Due to short surgical procedure with reduced probability of hemodynamic instability, only routine anesthetic monitoring was used (5-lead ECG, noninvasive blood pressure, SpO2, EtCO2), although some authors recommend the use of invasive blood pressure monitoring in all cases, in order to accurately monitor hemodynamic changes. [9] Defibrillator was ready for use in the operating room with pads connected to the patient. Bearing in mind that increased vagal tone has been implicated in the development of ST segment alterations in Brugada syndrome patients [9], atropine, as per routine, was prepared to abolish any vagal effect.

The interscalene brachial plexus block, ultrasound-guided, was performed with 225 mg lidocaine plus adrenaline (Figure 3). However, after 15 min of block completion, the level of surgical anesthesia obtained was incomplete for surgery. Therefore, conversion to general anesthesia ensued: 25 mg of etomidate were administered and a laryngeal mask (number 4) placed. Anesthesia was maintained with sevoflurane and analgesia continued with remifentanil infusion. At the end of the procedure, 1 g intravenous paracetamol was given. Total surgery and anesthesia times were 60 and 95 min, respectively, and no complications (dysrhythmia or bradycardia) were registered.

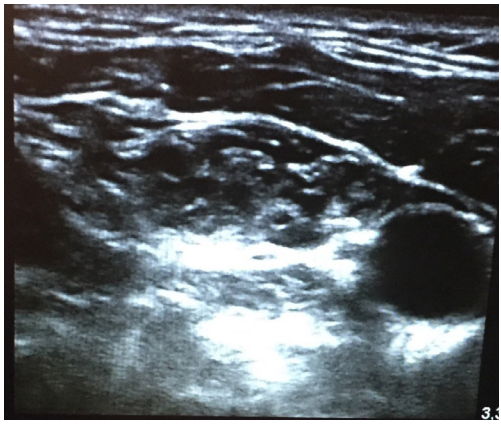

Figure 3 – Ultrasonography of the interscalene brachial plexus block

DISCUSSION AND CONCLUSION

As mentioned, Brugada syndrome imposes an increasing risk of ventricular tachyarrhythmias and sudden death. The molecular basis remains uncertain, although it is recognized that the sodium channel displays loss-of-function features, such as enhanced inactivation. [10] The diagnosis can be difficult,

as the electrocardiographic findings may be concealed in up to 30% of patients and only revealed after administration of sodium channel blockers (flecainide, propafenone and procainamide). [11] Recent evidence indicates the risk of arrhythmias is low in the absence of a resting ECG abnormality, providing that an electrical stimulation does not induce ventricular tachycardia/fibrillation. [12] However, if the electrophysiological study is positive, the risk of sudden death is 5-10%/year and ICD implantation is recommended as the only effective treatment [7], as our patient had.

In anesthesia, drugs that interact with cardiac ion channels (especially sodium channels) are routinely administered. Given this, it is easy to understand that, when undiagnosed, this condition imposes potential risks (induction of malignant arrhythmias) under anesthesia, when the providers are unaware of these condition. Interestingly, lack of adverse events under general anesthesia in the past does not exclude the possibility of intercurrences in the future. [13]

Evidence regarding administration of general anesthesia in Brugada syndrome is still limited at the present, and although general anesthesia was not our primary anesthetic plan, it became necessary, highlighting the importance of defining back-up plans whenever an anesthetic technique is required. As mentioned above, the primary concern regards the safe administration of drugs, as various reports involve anesthetic agents triggering malignant arrhythmias. For instance, class I anti-arrhythmic drugs must be avoided, given their blockade of the cardiac sodium channel, as well as the systemic administration of local anesthetics, once a rapid increase in serum concentrations can potentially inhibit the generation and conduction of action potentials, related to its sodium channel blocking effects. [14] The most commonly used hypnotic agent, propofol, although successfully used to induce general anesthesia, should be avoided as an infusion, due to a potential development of propofol infusion syndrome and ion channel dysfunction. [7,8] Regarding the reversal of neuromuscular blockade, neostigmine is best avoided as it may augment ST segment elevation and sugammadex should be considered instead. [15] Therefore, regarding general anesthesia, safe drugs for induction include midazolam, opioids and etomidate; for maintenance, volatile anesthetics, opioids and muscle relaxants are preferred. Surprisingly, despite the recommendation for isoflurane to be avoided in patients with prolonged QTc syndrome [8], it has been used in patients with Brugada syndrome without adverse events noted. Regional anesthesia can be considered if the total dose of local anesthetic and systemic absorption is limited, with lidocaine being the drug of choice. [16]

In this patient, we intended to avoid unrecommended drugs and general anesthesia altogether with an attempt to perform an interscalene brachial plexus block, using limited doses of lidocaine plus adrenaline to limit systemic absorption. In total, 225 mg were administered, which lag far behind the upper limit of 525 mg of lidocaine with adrenaline (7 mg/kg) in this patient with 75 kg, limiting the possibility of high systemic concentrations and arrhythmias.

As the level of anesthesia was incomplete to perform the surgical procedure, an alternative approach was designed: general anesthesia with induction with etomidate and analgesia with remifentanil perfusion. A laryngeal mask was placed and maintenance was achieved with sevoflurane and remifentanil perfusion continued throughout the procedure. Although no invasive monitoring was considered given the patient's good health status and relatively minor surgical procedure, monitoring

included five-lead electrocardiogram and ST trend analysis, which continued postoperatively. Also, defibrillator pads were attached to the patient since the beginning of the anesthetic technique. Despite the evidence that in any patient with an ICD the device must be disabled immediately before surgery [7], this was not the case with our patient. No ST segments changes ensued throughout the procedure and immediate post-operative period. The immediate recovery period took place in an anesthesia care unit, with discharge to the ward after a few hours. The recommendation for recovery in a high-dependency unit applies only to patients in whom no ICD has been fitted. [14]

In this case report, we intend to emphasize the cardiovascular risks involved with anesthesia administration in Brugada syndrome patients and the importance of vigilance and close cooperation between surgeons, cardiologists and anesthesiologists in formulating pre and post-operative plans. As this concerns an increasingly prevailing disorder, in which perioperative management remains a challenge, it is imperative that further efforts can be implemented to achieve an ideal anesthetic plan, as well as acknowledging in-depth understanding of the physiology of this syndrome. Besides avoiding potentially dangerous drugs, this case also reminds us of the importance of having a back-up plane for every situation.

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ACROMEGALY: A CASE REPORT

ACROMEGALIA: A PROPÓSITO DE UM CASO CLÍNICO

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ABSTRACT

Acromegaly is a rare endocrine disease resulting from excessive production of growth hormone (GH), in most cases resulting from a pituitary adenoma. Signs and symptoms reflect progressive somatic enlargement and most common co-morbidities include diabetes mellitus, hypertension and arthropathy. Biochemical confirmation is established by high levels of IGF-1 and lack of suppression of GH levels after glucose load (OGTT). We present a 57 year-old male who was investigated because of clinical features suggestive of acromegaly (prognathism, nose enlargement, thickened lips and enlarged hands and feet). Following the biochemical diagnosis, magnetic resonance imaging disclosed a pituitary macroadenoma. Treatment included surgery and adjuvant medical therapy with somatostatin analogues. This case illustrates the insidious and slowly progressive nature of acromegaly, which may contribute to a late diagnosis and limit therapeutic outcome. We intend to sensitize clinicians to a rare disease that is curable when diagnosed early.

Keywords: acromegaly, pituitary macroadenoma, clinical manifestations, treatment.

RESUMO

A acromegalia é uma doença endócrina rara resultante da hipersecreção de hormona de crescimento (GH), na maioria dos casos resultante de um adenoma hipofisário. Os sinais e sintomas refletem as alterações somáticas com alargamento progressivo de tecidos moles e ósseo. As comorbilidades mais comuns são a diabetes mellitus, a hipertensão arterial e as artropatias. A confirmação bioquímica inclui níveis elevados de IGF-1 e não supressão dos níveis de GH após sobrecarga com glucose (PTGO). Apresentamos um caso de um doente com 57 anos que foi investigado tendo em conta as características físicas sugestivas de acromegalia (prognatismo, alargamento do nariz, lábios grossos e aumento das mãos e pés) e em que a ressonância magnética mostrou um macroadenoma hipofisário. O tratamento incluiu cirurgia e terapêutica adjuvante com análogos da somatostatina. Com a sua apresentação, pretende-se sensibilizar os clínicos para uma doença rara que é curável quando diagnosticada precocemente.

Palavras-chave: acromegalia, macroadenoma hipofisário, manifestações clínicas, tratamento.

INTRODUÇÃO

A acromegalia é uma doença rara, progressiva e crónica, causada pelo excesso de produção de hormona do crescimento (GH), geralmente devido a um adenoma hipofisário. As alterações físicas estabelecem-se lentamente e a diabetes mellitus e as manifestações cardiovasculares só tardiamente são reconhecidas como secundárias ao excesso de GH e do seu mediador periférico *Insulin-like Growth Factor 1* (IGF-1). Estima-se que o diagnóstico pode ocorrer 10 a 15 anos após o início da doença [1]. A incidência aproximada é de 3-4 casos/milhão/ano e a prevalência de 40 casos por milhão de pessoas [2]. Em Portugal, a incidência da doença rondará os 30-40 novos casos/ano.

Os adenomas da hipófise correspondem a 15% de todos os tumores intracranianos, enquanto 90% dos doentes com acromegalia têm um adenoma hipofisário secretor de GH [3]. Pode haver co-secreção de outras hormonas, sendo a mais frequente a prolactina. Mais raramente, surge em contexto da síndrome de neoplasias endócrinas múltiplas tipo 1 (MEN1) ou associada à produção ectópica de GH e/ou GHRH.

Acomete igualmente ambos os sexos, com maior incidência entre a 3a e 4a décadas de vida [4]. As manifestações clínicas dependem dos níveis de GH e de IGF-1, da idade do doente, das dimensões do tumor e do tempo decorrido entre o início da doença e o seu diagnóstico. Os sinais e sintomas podem distinguir-se entre os que decorrem do tumor e os resultantes da hipersecreção hormonal. Exemplo da primeira situação são as alterações visuais por compressão das vias óticas quando há extensão supraselar, ou os défices hipofisários por compromisso de outras linhas celulares hipofisárias. Resultantes da hipersecreção de GH são as alterações somáticas com alargamento das partes moles e óssea, doença cardiovascular, alterações metabólicas, manifestações respiratórias, articulares e gastrointestinais bem como outras manifestações endócrinas (bócio, diminuição da líbido, irregularidades menstruais, etc.) [5].

A valorização das alterações fenotípicas pode não ser fácil. Queixas como a alteração do tamanho do vestuário e calçado e/ou alargamento dos anéis podem sugerir o diagnóstico. Particularmente importante é a análise comparativa de fotografias que permitem objetivar as mudanças.

A acromegalia está associada a um aumento da mortalidade, de cerca de 2 a 3 vezes em relação à população geral, sendo esta, sobretudo, secundária a doença cardiovascular (60%), respiratória (25%) ou neoplásica (15%) [6].

Apresentamos um caso de acromegalia que ilustra bem como os doentes são o melhor bioensaio das alterações hormonais, desde que o médico esteja sensibilizado para as valorizar.

APRESENTAÇÃO DO CASO

Homem de 57 anos que vai a uma Consulta de Endocrinologia na condição de acompanhante da esposa. Os seus traços faciais levam a que a médica endocrinologista admita a hipótese de acromegalia. Posteriormente, foi possível documentar através de fotografias (Fig. 1) a progressão das alterações fenotípicas.

Figura 1 – Evolução das características faciais do doente ao longo do tempo (1987-2008)

Um interrogatório dirigido permitiu concluir que tinha havido necessidade de alargar a aliança 2 anos antes e que havia queixas de gonalgia crónica bilateral, pelo que tinha sido medicado com Glucosamina. Negava a toma de outros medicamentos ou existência de outras patologias/sintomas concomitantes como hipertensão arterial, diabetes mellitus, síndrome do canal cárpico, roncopatia, fadiga, sintomas gastrintestinais, cefaleias ou alteração da libido ou da potência sexual. Não havia história familiar conhecida de tumores hipofisários ou outra patologia endócrina. Foi-lhe proposta avaliação e orientação em Consulta de Endocrinologia que aceitou.

Ao exame físico apresentava fácies acromegalóide (prognatismo, alargamento da base do nariz, diastema interincisivos superiores centrais e macroglossia), aumento das partes moles das mãos (Fig. 2) e pés; índice de massa corporal de 28Kg/m2 (excesso de peso), e tensão arterial, medida no braço esquerdo e sentado, de 154/88 mmHg; glândula tiroideia palpável não aumentada de volume e de consistência normal.

Figura 2 – Mãos do doente

Da avaliação laboratorial endócrina e metabólica, destacam-se os valores aumentados de IGF-1 e GH (Tabela 1). A restante função hipofisária era normal, incluindo o doseamento de prolactina. Na prova de tolerância à glicose oral (PTGO) com 75g de glicose não se verificou supressão dos níveis séricos de GH (persistentemente acima de 1,0 ng/mL), confirmando assim o diagnóstico de acromegalia.

Parâmetro	Valor	Intervalo de referência
GH (ng/mL)	8,09	<3,0
IGF-1 (ng/mL)	1105,0	81 – 225
Glicémia (mg/dL)	91	70 - 110
HbA1c (%)	5,4	4,0 – 6,0
Colesterol total (mg/dL)	213	<190
Colesterol LDL (mg/dL)	131	<110
Colesterol HDL (mg/dL)	70	>40
Triglicéridos (mg/dL)	61	<150

Tabela 1 – Perfil hipofisário e metabólico inicial

Para estudo complementar, realizou ainda ecocardiograma transtorácico que revelou hipertrofia do ventrículo esquerdo com boa função sistólica, dilatação ligeira biauricular e da raiz da aorta e colonoscopia que não mostrou alterações.

Foi realizada ressonância magnética (RMN) dirigida à região esfeno-selar que revelou uma lesão intra-hipofisária, hipointensa em T1 e T2, com cerca de 16mm, sem compressão opto-quiasmática mas com extensão cavernosa aparente, compatível com macroadenoma hipofisário (Fig. 3). Realizou Perimetria Estática Computorizada (PEC) na consulta de neuro-oftalmologia para avaliação dos campos visuais, que não mostrou alterações em ambos os olhos.

O doente foi avaliado em consulta de neurocirurgia e, após discussão multidisciplinar do caso, foi submetido a ressecção endoscópica do macroadenoma por via transfenoidal transnasal, sem intercorrências pós-operatórias imediatas. O exame anátomo-patológico da peça mostrou arquitetura de adenoma hipofisário com um índice proliferativo (Ki67) de cerca de 3% e imunorreactividade para GH. O doente foi reavaliado cerca de 12 semanas após a cirurgia, e apesar da diminuição significativa dos valores, quer de GH (8,09 -> 4,75 ng/mL), quer de IGF-1 (1105,0 -> 352,0 ng/mL), ambos se encontravam ainda acima do limite superior do intervalo de referência, pelo que foi iniciada terapêutica médica adjuvante com análogo, de ação prolongada, da somatostatina (Octreótido i.m. 20 mg/mês), que o doente tolerou bem, sem sinais ou sintomas de falência hepática ou patologia biliar. Todas as outras hormonas hipofisárias mantiveram-se normais após a cirurgia.

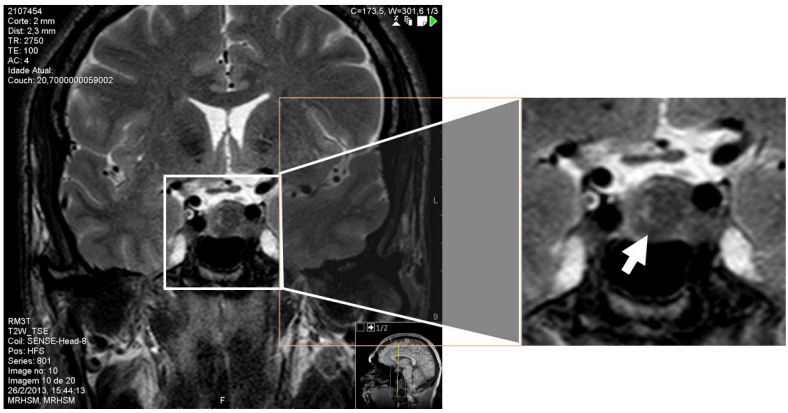

Figura 3 – RMN da região esfeno-selar com imagem sugestiva de macroadenoma

Nas avaliações seriadas laboratoriais subsequentes (Fig. 4) verificou-se uma boa resposta bioquímica, com normalização dos valores de GH e IGF-1 a par da melhoria subjetiva das características fenotípicas, e imagiológico por uma RMN que não mostrava tumor intra-selar, parecendo haver envolvimento do seio cavernoso à esquerda. Um ano após o início da terapêutica com Octreótido, decidiu-se suspender a mesma e avaliar a possibilidade de cura, através da realização de nova PTGO. Não se verificou supressão de GH sendo todos os valores superiores a 1,0 ng/mL, portanto sem critérios de cura. Foi reiniciada a terapêutica com Octreótido, que o doente mantém até hoje, com evolução clínica e laboratorial favorável.

Na última avaliação imagiológica por RMN verificou-se persistência de lesão residual latero-selar esquerda de pequenas dimensões, pouco definida, provavelmente não cirúrgica mas capaz de explicar a persistência bioquímica de doença. Dependendo da evolução futura, não se excluem novas intervenções terapêuticas nomeadamente radiocirurgia estereotáxica.

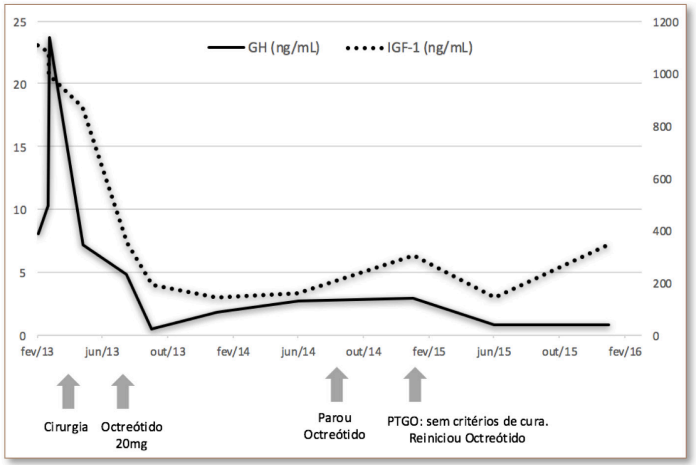

Figura 4 – Evolução dos valores de GH e IGF-1 do doente ao longo do tempo.

DISCUSSÃO

A acromegalia tem uma prevalência estimada em 40 casos/milhão de habitantes e uma incidência anual de 3-4 casos/milhão [2], sendo por isso uma patologia raramente encontrada na prática clínica. O aparecimento insidioso dos sintomas, assim como a subvalorização de alguns achados clínicos chave, quer por parte do doente e da família, quer por parte do clínico, contribui para o atraso no seu reconhecimento.

No caso clínico apresentado, a suspeita de acromegalia surgiu devido a traços fenotípicos sugestivos. O doseamento basal de IGF-1 e a ausência de supressão da secreção de GH após PTGO confirmaram o diagnóstico de acromegalia. Na investigação imagiológica confirmou-se a presença de macroadenoma hipofisário, que foi ressecado, com o exame anátomo-patológico mostrando positividade imuno-histoquímica para GH.

No que concerne o diagnóstico desta patologia, as orientações da *Endocrine Society* recomendam que seja feita a medição dos níveis séricos de IGF-1 em doentes com manifestações clínicas de acromegalia, em particular nos doentes com características fenotípicas sugestivas [7]. A medição da GH basal não deve ser usada para o diagnóstico tendo em conta a pulsatilidade da sua secreção e tratar-se de uma hormona de resposta ao stress [7]. Nos doentes com valores de IGF-1 elevados, o diagnóstico deve ser confirmado demonstrando a ausência de supressão dos valores de GH (persistência de valores acima de 1,0 ng/ml) após a PTGO [8]. Ao diagnóstico bioquímico de acromegalia segue-se o estudo imagiológico, preferencialmente com RMN dirigida à hipófise ou em alternativa TAC, quando a RMN está contraindicada ou não está disponível.

No momento do diagnóstico, e tendo em conta as múltiplas comorbilidades associadas à acromegalia, todos os doentes devem ser avaliados do ponto de vista cardiovascular e metabólico, para exclusão de cardiopatia estrutural, hipertensão arterial, diabetes *mellitus* e dislipidémia [9]. Deve ser feito igualmente o rastreio da síndrome de apneia/hipopneia obstrutiva do sono (SAHOS) se houver clínica sugestiva, uma vez que cerca de 69% dos doentes com acromegalia sofrem desta síndrome [10]. A realização de colonoscopia está preconizada em todos os doentes com acromegalia, visto que foi demonstrado um risco aumentado de neoplasia colo-rectal, mesmo em indivíduos abaixo dos 40 anos [11].

Os objetivos do tratamento visam, por um lado minimizar os efeitos do excesso de GH, e por outro obviar a eventual compressão do tumor sobre as estruturas vizinhas [12]. A cura define-se por níveis de IGF-1 dentro do intervalo de normalidade para a idade e sexo e concentrações de GH < 1.0 ng/ml após PTGO. As alternativas terapêuticas disponíveis incluem a remoção cirúrgica do tumor, a terapêutica médica e a radioterapia dirigida ao adenoma.

Cirurgia: é o tratamento de primeira linha na maioria dos doentes, através de cirurgia transfenoidal por via endoscópica ou microscópica. O sucesso da cirurgia é significativamente maior para os microadenomas (80-90%) em comparação com os macroadenomas (menos de 50%), que infelizmente representam mais de 70% do total de adenomas produtores de GH [13].

Tratamento médico: existem 3 classes de fármacos usados para tratar a acromegalia - análogos da somatostatina, antagonistas do recetor da GH e agonistas dopaminérgicos.

Os fármacos mais largamente utilizados no tratamento da acromegalia são os análogos de longa ação da somatostatina, o Octreótido e o Lanreótido, que inibem a secreção de GH pela hipófise. São habitualmente utilizados nos doentes que não atingiram o controlo bioquímico após cirurgia, como primeira linha nos doentes em que a cirurgia é contraindicada, ou ainda como terapêutica neo-adjuvante nos grandes macroadenomas em que a remoção completa cirúrgica do tumor é improvável [14]. O primeiro é administrado por via intramuscular e o segundo por via subcutânea profunda a intervalos de 28 ou 40 dias, com taxas de normalização da IGF-1 que atingem 67% dos doentes com terapêutica adjuvante [15]. O Pasireótido, um análogo da somatostatina de 2ª geração recentemente aprovado pela Agência Europeia do Medicamento para o tratamento da acromegalia, tem uma afinidade para o subtipo 5 dos recetores da somatostatina cerca de 40 vezes superior à dos análogos atualmente usados o que lhe confere maior eficácia embora possa também ter um maior número de efeitos secundários [16].

O Pegvisomant é um antagonista dos recetores de GH, bloqueia a ação periférica da GH e, portanto, a síntese hepática de IGF-1; é administrado diariamente por via subcutânea em doses de 10, 15 ou 20 mg/dia, e a taxa de doentes com normalização dos níveis de IGF-1 ronda os 63% [17]. Atualmente é recomendado o seu uso nos casos de resistência ou intolerância aos análogos da somatostatina. Não se associa às alterações do metabolismo glucídico registadas com os análogos da somatostatina, mas pode condicionar progressão dimensional do adenoma, pelo que a monitorização imagiológica está indicada ao longo da terapêutica.

Os agonistas dopaminérgicos, que têm particular indicação face a tumores secretores não só de GH mas também de prolactina, vêm sendo cada vez menos usados à medida que foram surgindo alternativas no mercado [18].

Radioterapia: é habitualmente utilizada como terapêutica adjuvante complementar nos casos de insucesso da terapêutica cirúrgica e/ou da terapêutica médica. Pode ser usada radioterapia (RT) externa fracionada ou radiocirurgia. Comparativamente à RT convencional, as novas técnicas, utilizando métodos de localização estereotáxica - quer na denominada radiocirurgia (radioterapia de dose única), com utilização de Gamma-Knife ou acelerador linear (LINAC) quer em RT fracionada (RT Estereotáxica Fracionada - RTEF, RT conformacional, RT de intensidade modulada - IMRT, por exemplo) - associam-se a menor risco de hipopituitarismo e de sequelas por lesão do tecido cerebral circundante a médio/longo prazo [19].

CONCLUSÃO

Em conclusão, apresentámos um caso clínico raro de acromegalia, inicialmente suspeitado pelas características fenotípicas do doente, e mais tarde confirmado pelos exames laboratoriais, imagiológicos e histológicos. Apesar dos avanços no diagnóstico e tratamento desta patologia, estudos recentes revelam que a acromegalia continua a ser subvalorizada e subdiagnosticada [20]. Aceitando que o sucesso terapêutico está diretamente relacionado com o tamanho do tumor e gravidade da doença no momento do diagnóstico, o reconhecimento e tratamento precoces são fundamentais.

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ANGIOLEIOMYOMA OF THE SCROTUM

ANGIOLEIOMIOMA DO ESCROTO

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ABSTRACT

Cutaneous leiomyomas (CLs) are an unusual subset of Leiomyomas arising from superficial smooth muscle and account for less than 5% of all leiomyomas. They can be sporadic or associated with various disorders. CLs compromise three distinct types according to their smooth muscle origin and clinicopathologic features: piloleiomyoma, angioleiomyoma and genital leiomyoma. Typically CLs are benign, despite rare reports of malignant transformation and association with aggressive renal cell carcinoma (RCC) being well-described in the literature.

We report a case 66-year-old caucasian male who presented for urology consultation with right symptomatic hydrocele and pedunculated ulcerated nodule at the right side of the scrotum, non-painful, highly vascularized and clearly separated from homolateral testicle. Patient was submitted to surgical excision of the nodule and hydrocelectomy. Pathology report revealed an angioleiomyoma. At 6 month follow up the patient was well. No suspicious renal masses were found.

Keywords: Leiomyoma, Cutaneous Leiomyoma, Angioleiomyoma, Scrotum, Tumor, Renal Cell Carcinoma.

RESUMO

Leiomiomas cutâneos (LCs) são um tipo raro de leiomiomas que surgem do tecido muscular liso superficial e representam menos de 5% destes. Podem ser esporádicos ou associados a outras patologias. Os LCs dividem-se em 3 grupos consoante a origem muscular e características clinicopatológicas: piloleiomioma, angioleiomioma ou leiomioma genital. Tipicamente os LCs são benignos, apesar de alguns casos descritos de transformação maligna. No entanto, a associação com carcinoma de células renais agressivo encontra-se bem descrita na literatura.

Reportamos o caso de um homem de 66 anos, caucasiano, que vem à consulta de urologia por hidrocelo direito sintomático e uma lesão nodular, pediculada, ulcerada, localizada no hemiescroto direito, não dolorosa, com vascularização exuberante, sendo claramente separada do testículo homolateral.

O doente foi submetido a excisão cirúrgica do nódulo e hidrocelectomia direita. Avaliação anatomo-patológica relatou um angioleiomioma. No follow-up aos 6 meses o doente encontra-se bem clinicamente. Não foram detectadas lesões renais suspeitas.

Palavras-chave: Leiomioma, Leiomioma Cutâneo, Angioleiomioma, Escroto, Tumor, Carcinoma de Células Renais.

INTRODUCTION

Leiomyomas may arise wherever smooth muscle is present in the human body. They are benign soft tissues neoplasms of the smooth muscle. Leiomyomas of the uterus accounts for 95% of cases. Cutaneous leiomyomas (CLs) account for 75% of extra-uterine leiomyomas and are more common in adults than children, affecting both genders equally [1, 2]. Initially named by Rudolf Virchow in 1854 as "tuberculum dolorosum", CLs are unusual and often misdiagnosed and under-recognized. They may be sporadic or inherited tumors of smooth muscle origin associated with various disorders [2]. Three subtypes of CLs are described, including piloleiomyomas, angioleiomyomas and genital leiomyomas. This classification reflects the origin of the smooth muscle tumor and corresponds to the histological site where the leiomyomas are found [3,4]. Piloleiomyomas are the most common CLs and they originate from the arrector pili muscles of the pilosebaceous unit, and may be solitary or multiple usually following Blaschko's lines. 90% of them are painful despite the exact cause of pain is not known, despite several reports proposing impingement of local nerve fibers as the explanatory mechanism [5-7]. Genital leiomyomas derive from dartos muscle, erectile muscle of the nipple and vulvar smooth muscle. They are exceedingly rare with less than fifty cases reported worldwide [8]. Contrary to most piloleiomyomas, genital leiomyomas are typically painless and solitary papulonodules or pedunculated. Angioleiomyomas derive from the tunica media of small to medium-sized arteries and veins. These are well circumscribed, vascularized and differentiated nodules, half of them painful and present themselves in subcutaneous or dermal regions of the extremities. The proposed mechanism is that the elicited pain is due to smooth muscle contraction or ischemia [1, 2].

Usually solitary nodules are of sporadic origin, while multiple papulonodules are inherited in autosomal dominant fashion with variable penetrance [9]. None the less, the scope of presentations is wide and differential diagnoses are numerous, with definitive confirmation relying on surgical biopsy [2]. It has been reported that 70 to 90% of women with CLs also had uterine fibroids [10]. First described in 1973, the simultaneous presence of uterine and CLs, was termed as Reed's Syndrome, an inherited condition. In 2001, Reed's Syndrome was associated with renal cell carcinoma (RCC) resulting in a condition called Hereditary Leiomyomatosis and RCC (HLRCC) [2].

We report a case of a 66 year-old man who initially presented to urology consultation with a painless pedunculated nodule of the scrotum.

CASE PRESENTATION

A 66-year-old man is referred for urologic consultation because of swelling and discomfort of the right hemiscrotum in the last few months. Patient also reported a right nodule in the right hemiscrotum that had been slowly enlarging over more than 18 years. He denied any history of perineal trauma, hematuria, hematospermia or any lower urinary tract symptoms. He had personal history of pacemaker due to arrhythmia, spine surgery due to spinal disk herniation L3/L4 and type 2 Diabetes mellitus. His usual medication was furosemide, nifedipine, simvastatin, metformin, bisoprolol and apixaban. He quit smoking cigarettes 9 years before with an accumulated exposure to tobacco of 35 Smoking Pack Years.

Physical exam showed a non-tender enlarged right hemiscrotum, and a focused beam of light transilluminated the hemiscrotum which were features compatible with a hydrocele. The pedunculated nodule at the right side of the scrotum had around 4 cm, was non-painful, ulcerated, highly vascularized and clearly separated from homolateral testicle and epididymis. At that time, the lesion appeared to be consistent with a sebaceous cyst. No inguinal lymph nodes were noted. Digital rectal exam was unsuspicious.

Figure 1 - Pedunculated nodule

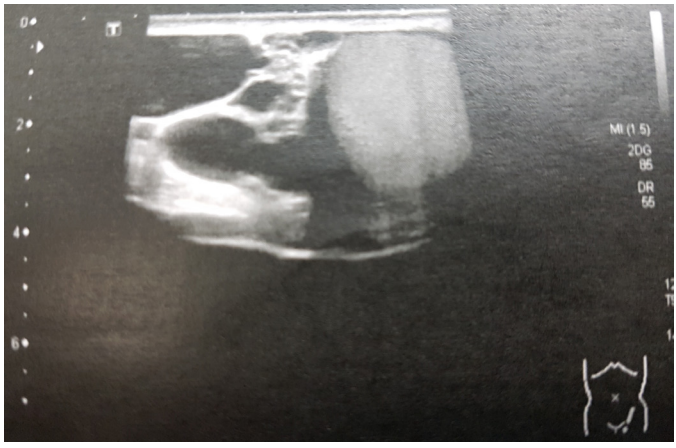

Figure 2 - Scrotal ultrasound demonstrating a septated right hydrocele

Scrotal ultrasound confirmed diagnosis of a septated right hydrocele and pedunculated nodular mass with 44,6 mm that followed superficial skin layers with small internal vessels. Uroflowmetry was unremarkable.

Patient was then proposed for Jaboulay's Hydrocelectomy on the right and surgical excision of the pedunculated nodule, under general anesthesia. Surgery and post-operative period did not have complications.

Histologic assessment revealed interlacing fascicles of bland spindle cells with eosinophilic cytoplasm and blunt-ended, elongated, cigar-shaped nuclei on hematoxylin & eosin. Immunohistochemical

staining demonstrated immunoreactivity of spindle cells to desmin and strong CD34 reaction for smooth muscle and endothelium. The final pathology report was angioleiomyoma of the scrotum.

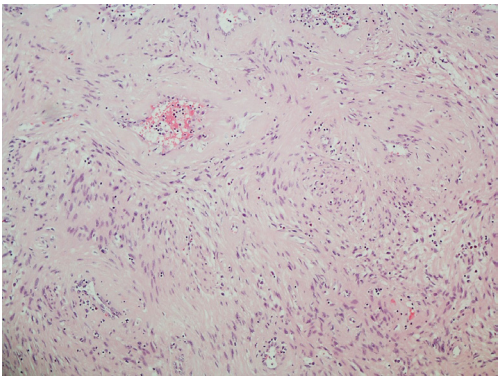

Figure 3 - Histologic features of angioleimyoma (H&E, x100)

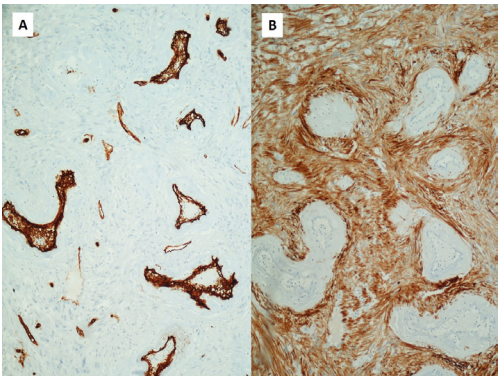

Figure 4 - Histologic features of angioleimyoma (A - desmin, x100) (B - CD34, x100)

At 1 month follow up consultation the patient was well and surgical scar had normal evolution. No dermatologic issue was reported by the patient and physical exam showed no visible nodules. After pathologic diagnosis the patient had a renal ultrasound which showed bilateral simple cysts although no suspicious renal lesions were identified at 6 month follow up. He remains on scheduled consultations.

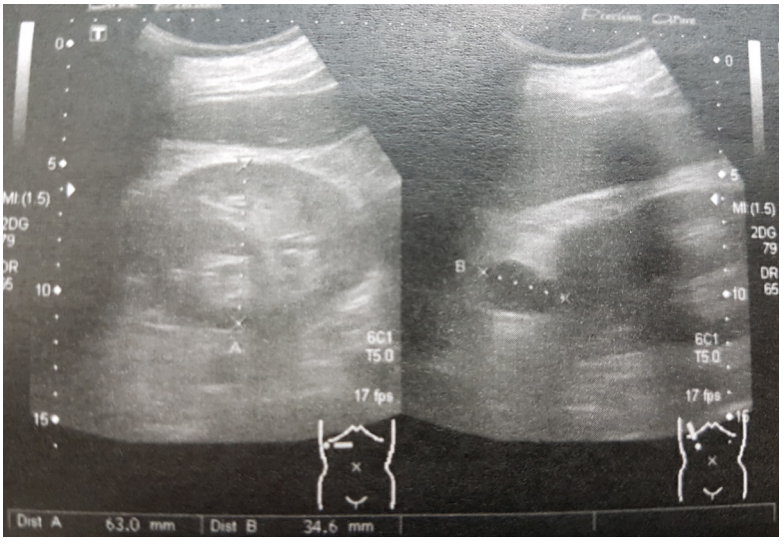

Figure 5 - Renal ultrasound showing bilateral simple renal cysts.

DISCUSSION

Despite the rareness of the scrotum angioleiomyoma it should be considered in the differential diagnosis of paratesticular malign tumors [8]. It is known that 20% of all paratesticular tumors are of malign origin [11]. The differential diagnosis of CLs is comprehensive, and so, complete dermatological and pathologic evaluation are of paramount importance. Adnexal tumors, angiolipoma, dermal nevi, dermatofibroma, hamartoma, keloids, lipoma, metastatic leiomyosarcoma and many other diseases must be taken into account when approaching a putative CL [2]. Malignant transformation of CLs is exceedingly rare and pathological features include hemorrhage as well as diffuse cytologic/nuclear atypia, two or more mitotic figures per 10 highpower fields and necrosis [12]. Notwithstanding, the most striking finding of malignancy seems to be mitotic activity [13].

The majority of CLs have unknown and sporadic pathogenesis. It has been noticed that recurrent loss in 22q11.2, involving one or two chromosomes, is present in solitary angioleiomyomas, despite the exact mechanism of formation is not complete understood [14]. However, some CLs occur in the setting of an underlying hereditary autosomal dominant tumor predisposition syndrome of HLRCC. HLRCC patients may present a wide range of clinical manifestations from solitary to multiple leiomyomas, with or without renal tumors and/or uterine fibroids [12]. A uniformly accepted diagnostic criteria of patients with HLRCC is still lacking [15]. The NIH definition requires that the diagnosis of HLRCC be established with identification of a heterozygous pathogenic variant in the fumarate hydratase (FH) in combination with multiple cutaneous leiomyomas, with at least one histologically confirmed leiomyoma, a single leiomyoma in the presence of a positive family history of HLRCC and/or 1 or more tubulopapillary, collecting duct, or papillary type 2 renal tumors with or without a family history of HLRCC. FH is an enzyme that converts fumarate to malate in the Krebs cycle. A mutated FH is a key event that underlies leiomyomatosis and malignant kidney tumor formation since FH is considered a tumor suppressor. FH regulates hypoxia-inducible factor 1-alpha and 2-alpha which in increased levels are linked to malignancy [2].

In fact the spectrum disorders associated with mutated FH is extensive. Know disorders include breast cancer, human immunodeficiency virus (HIV), Cushing's syndrome, multiple endocrine neoplasia type 1 (MEN1), prostate cancer, polycythemia, rheumatoid arthritis, bladder cancer and others [2].

The most sensitive and specific markers for HLRCC despite its range of manifestations is CLs. However they are not diagnostic since the high prevalence in the general population of uterine fibroids. Forty per cent of HLRCC patients will have mild cutaneous manifestations, with less than five lesions ranging from unnoticeable to extensive [16]. HLRCC predisposes for unusual familial RCC, papillary, often solitary and unilateral, and they are more aggressive than other forms of familial RCC. Metastasis have been reported in the adrenal glands, liver, soft tissue, peritoneum, sternum and lungs [2].

Surgical excision is the gold standard therapy for CLs has if they are left untreated they continue to grow and new lesions may appear [13]. Other destructive methods have been employed such as electrodessication, cryotherapy and carbon-dioxide laser with little advantage over excision and

unwanted scarring [17]. Despite method of treatment, there is a high rate of recurrences ranging from 6 weeks to 15 years. In order to minimize recurrence, all margins must be free of tumor [2]. Leiomyomas associated with pain have been treated with drugs acting on muscle contraction such as nitroglycerine, nifedipine, phenoxybenzamine, doxazosin and more recently botulinum toxin type A injections [18].

Management of HLRCC is more difficult since no established guidelines exist. It has been proposed that at-risk or heterozygous individuals from HLRCC-affected families receive full body skin exams at least every two years, and consult gynecology every year, as well as urology once renal involvement is suggested. Imaging studies remains controversial since some studies favor computerized tomography scans while others contraindicate them due to harmful radiation exposure. Magnetic resonance imaging investigations are generally indicated bi-yearly [2]. Wide surgical excision is the treatment of preference in any size RCC related to HLRCC. In this setting chemotherapy for general papillary RCC has been used for HLRCC-associated renal cancer. This includes combination of drugs such as temsirolimus, interferon, bevacizumab, erlotinib, sunitinib and others, despite lack of randomized controlled trials in this setting.

CONCLUSION

CLs are rare benign neoplasms of superficial smooth muscle origin and can be divided into piloleiomyomas, angioleiomyomas and genital leiomyomas. To achieve definitive diagnosis, biopsy with histological analysis is needed, allowing also the differentiation between CLs and leiomyosarcomas. Pathogenetically CLs can be sporadic or inherited in an autosomal dominant fashion with variable penetrance. Although uncommon, HLRCC has high mortality rates and CLs may be the first clue suggesting diagnosis.

CLs may be managed by surgical excision or by other destructive methods. On the other hand, painful leiomyomas may be treated with local or systemic drugs.

The rates of recurrence of CLs is high and malignant transformation is possible thus vigilant follow up and avoidance of radiation exposure are mandatory.

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SUCCESSFUL TREATMENT OF JUVENILE PSORIATIC ARTHRITIS WITH USTEKINUMAB

ARTRITE PSORIÁTICA JUVENIL EFICAZMENTE TRATADA COM USTEKINUMAB

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ABSTRACT

We present a case of a 15-old male of Roma ethnicity who was diagnosed with psoriasis. He had a severe and difficult to control disease over the years, with several exacerbations and generalized pustular psoriasis. At age eleven he started with joint complaints compatible with Juvenile Psoriatic Arthritis (JPsA). At age 15, he had a very severe flare of JPsA. He was proposed for treatment with Ustekinumab (UST), attending to the high risk of infections and specifically of tuberculosis in his ethnic community. UST is a human monoclonal antibody that targets interleukin-12 (IL-12) and IL-23. UST is approved for the treatment of adult patients with moderate to severe plaque psoriasis and for adults with active psoriatic arthritis. It is not approved in the pediatric population, but there have been reports of its use in severe cases of psoriasis. To the best of our knowledge this was the first report of its successful use in JPsA.

Keywords: Juvenile psoriatic arthritis, psoriasis, ustekinumab.

RESUMO

Os autores apresentam o caso de um jovem de etnia cigana, com o diagnóstico de psoríase aos 15 anos de idade. Ao longo do tempo, apresentou-se com uma doença cutânea grave, de difícil controlo, com várias exacerbações e evolução para psoríase pustulosa. Aos 11 anos, teve inicio um quadro articular compatível com artrite psoriática juvenil, sendo que aos 15 anos um agravamento cutâneo e articular muito grave obrigou a internamento. Foi proposto para terapêutica com Ustekinumab (UST), atendendo ao alto risco de infeções, especificamente tuberculose, na sua comunidade étnica. UST é um anticorpo monoclonal humano contra a interleucina-12 (IL-12) e IL-23. Está aprovado para o tratamento de adultos com psoríase em placas moderada a grave e adultos com artrite psoriática ativa.

Não está aprovado na população pediátrica, mas existem relatos da sua utilização em casos graves de psoríase. No nosso conhecimento, este é o primeiro caso descrito da utilização deste fármaco na artrite psoriática juvenil.

Palavras-chave: artrite psoriática juvenil, psoríase, ustekinumab.

INTRODUCTION

Psoriasis is characterized by the erythematous, scaling plaques on the skin and a spectrum of clinical presentations. Juvenile psoriatic arthritis (JPsA) is diagnosed, according to the International League Against Rheumatism (ILAR), in cases of persistent arthritis for more than 6 weeks with onset of the arthritis prior to the age of 16 and either the presence of a psoriasis or at least 2 of the following: first degree relative with psoriasis, nail pitting or onycholysis, and dactylitis [1].

JPsA management includes non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroid joint injections and methotrexate. For refractory patients, tumor necrosis factor (TNF) blockers are the preferred treatment [1,3]. TNF inhibitor therapy has an increased risk of infections, including tuberculosis reactivation, primary or secondary failure [3,5]. To meet these challenges, new agents targeting different pathways have been developed. Ustekinumab (UST) is a human monoclonal antibody targeting interleukins 12 and 23. While IL-12 participates in T-helper 1 (Th1) cell differentiation, increasing IFN and TNF levels, IL-23 stimulates IL-17 production by Th17 cells, promoting the inflammatory cascade [6-8]. UST is approved for the treatment of adult patients with moderate to severe plaque psoriasis and adults with active psoriatic arthritis, alone or in combination with methotrexate. Although it is not approved to pediatric population, there have been reports of its use in severe cases of psoriasis and a clinical trial CADMUS (A Study of the Safety and Efficacy of UST in Adolescent patients with psoriasis) was recently published [16].

CASE PRESENTATION

We present a case of a Roma ethnicity male who was diagnosed with plaque psoriasis at 8 years-old. He had multiple relatives with psoriasis. He was admitted to hospital presenting an onset psoriasis area severity index (PASI) of 36.6. He was treated with cyclosporine 2mg/kg/day, prednisone 20mg/day, acitretin 10mg/day, topical therapy and phototherapy UVB narrow band 3 times/week. He was also submitted to multiple regimes including oral methotrexate 15mg/week. Due to social factors it was difficult to monitor adherence to therapy.

He had a difficult to control disease, with several exacerbations and generalized pustular psoriasis (Zumbusch variant15), being admitted with disease exacerbations induced by infections.

At age 11, he started joint symptoms with arthritis of the right tibiotarsal joint and second and third proximal interphalangeal joints of the right foot. A diagnosis of JPsA was assumed and he was treated with NSAIDs.

At age 15, he had a very severe flare of the skin and joint disease and he was bedridden with generalized erythroderma, erythematous plaques, some desquamative, others exudative, associated with generalized pustules and areas with melicerous crosts in both legs (figures 1 and 2), ankle arthritis, bilateral Achilles enthesitis and dactylitis of the second and third toe of the right foot. He had fever and hyperesthesia and leukocytosis of 15.15 x106/L; C-reactive protein was 10.8 mg/dl. Blood cultures were negative, ASO titer was 44. HLA-B27, antinuclear antibodies, rheumatoid factor and anticyclic citrullinated peptide antibodies were negative. Skin biopsy showed intraepidermal spongiform pustule, parakeratosis and intracorneal microabscesses, with superficial dermal perivascular lymphocytic infiltrate, consistent with pustular psoriasis. We decided to start biologic treatment. Considering the high risk of infections, particularly of tuberculosis infection in his community [16] and bad compliance to treatment, requiring assisted drug administration, UST was started after ethical commission approval and a signed informed consent. The dosage used was extrapolated from the CADMUS trial [24] (45mg), subcutaneously, at weeks 0, 4 and every 12 weeks.

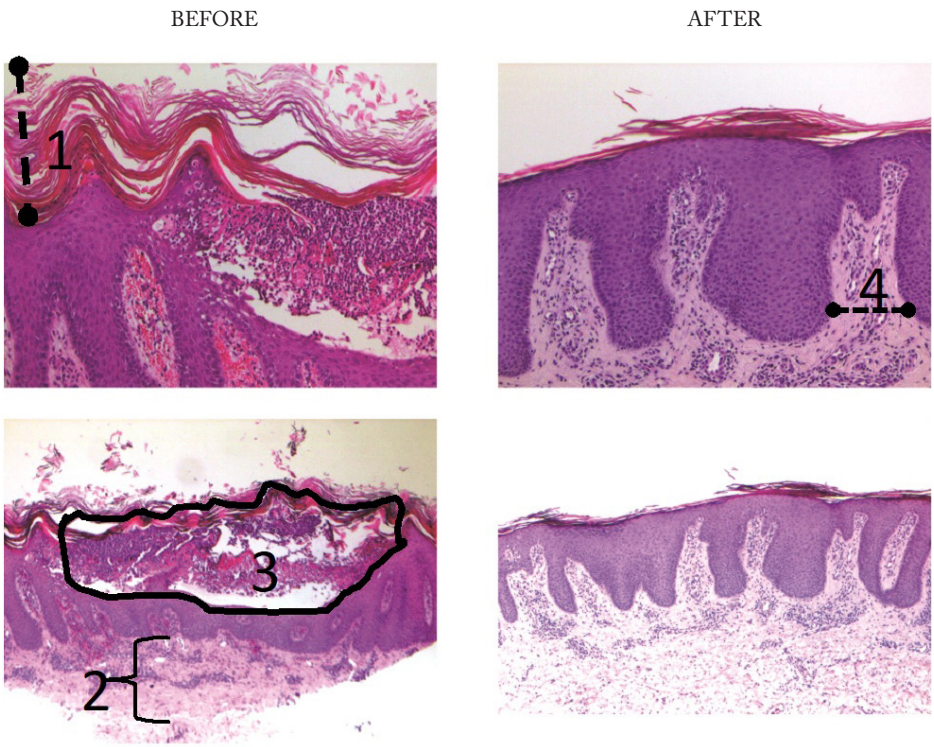


Figure 1 – Histologic findings before UST administration and after the fourth administration at week 24 (1 – increased epidermic descamation; 2 – linfoplasmocitic infiltration; 3 – pustular lesion; 4 – normal dermal papilla)

BEFORE AFTER

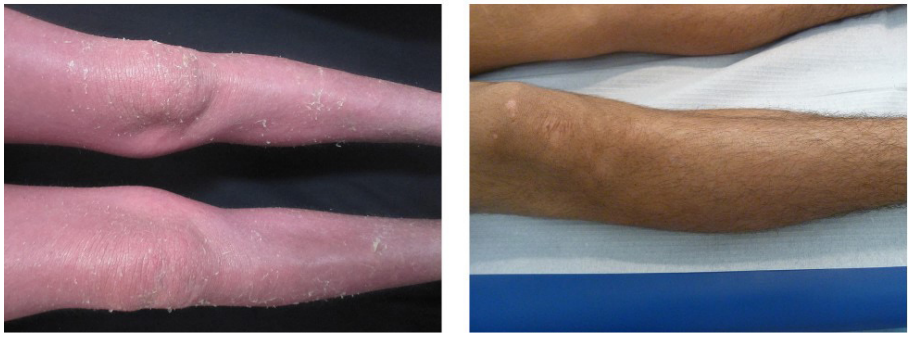


Figure 2 – Lower limb before and after UST administration (week 24). The first photo shows extended epidermis desquamation. After week 24 of UST administration, no psoriatic lesion can be seen.

He was submitted to the baseline screening for biological therapies according to the recommendations of the Portuguese Rheumatology Society [5]. Tuberculin skin test was impossible to be performed due to the extent of the skin disease. The interferon gamma releasing assay (IGRA) test was negative. Though, considering the high prevalence of tuberculosis infection in his community [16], he was treated with isoniazid for 9 months, starting UST after 1 month, according to the national guidelines [5].

When he started UST his Juvenile Arthritis Disease Activity Score (JADAS-27) was 3.8, childhood health assessment questionnaire (CHAQ) was 3 and PASI was 54. Four weeks after the first administration he was already in joint remission, JADAS-27 was 0 and the PASI was 10. Three months later he had no active joints, CHAQ was 0 and PASI was 4.8. He is now over one year of treatment, keeping persistent joint remission and very low skin activity, PASI 2.8. Over this period of treatment he had one infectious lymphadenitis, two months after he started the therapy, with clinical resolution under first-line antibiotic treatment. No other side effects were noted.

DISCUSSION AND CONCLUSION

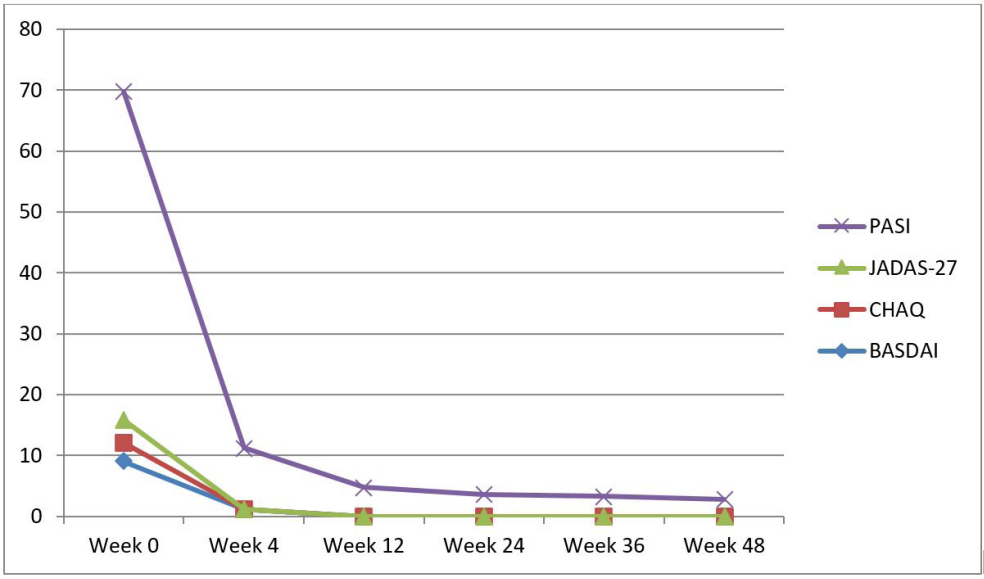
To the best of our knowledge, this is the first report of JPsA successfully treated with ustekinumab. The efficacy was high and sustained, with a good safety profile.

The justification for using UST as the first line biologic in this high infectious risk patient was based in evidence suggesting that UST might have a good safety profile, with a low rate of infections, including low risk of tuberculosis reactivation. In fact, the 5 years follow-up of the Phoenix 2 trial, covering efficacy and safety observations of 1212 psoriasis patients, corresponding to 5037 patient-years of follow-up has confirmed a low incidence of serious infections (<1%) and no case of tuberculosis [17]. The follow-up time for its use in psoriatic arthritis is lower, but suggests a similar safety profile [18]. A recent meta-analysis of all the clinical trials (100) and long term extension studies (63) involving biologics and tofacitinib in the treatment of immune mediated chronic inflammatory diseases was

made with the goal of assessing the risk for tuberculosis. In this review no tuberculosis case was associated with UST [19]. Additional data can be provided by drug survival studies, which reflect effectiveness, safety and tolerability. A recent study from the British Association of Dermatologists Biologic Interventions Register (BADBIR) has shown that UST had the greatest survival in the treatment of psoriasis, as compared to patients treated with etanercept, adalimumab and infliximab. Moreover, the presence of psoriatic arthritis was a predictor of drug survival [20].

Some indirect data suggests that UST might have a better safety profile than TNF inhibitors (particularly when compared to anti TNF monoclonal antibodies), including lower risk of tuberculosis reactivation. Reasons related to the mechanism of action might be behind this differential behavior. TNF is known to be critical for the control of tuberculosis infection9. In vitro and animal studies suggested IL-23/17 axis is also probably involved in the response to tuberculosis [21]. However, clinical observational studies in UST treated psoriasis patients showed that it improves clinical manifestation without affecting cytokine production in memory T cells, T cell maturation, or T cell receptor repertoire diversity, suggesting that T cell immune response remains unaffected in UST treated patients [22].

This report suggest that UST is a valuable treatment option for the treatment of JPsA. The publication of the CADMUS trial [23] has shed light on the use of UST in psoriatic adolescents [14] particularly regarding efficacy, safety and dosing regime. An additional trial on JPsA seems to be justifiable, regarding the good results reported in adult patients and the efficacy and safety observed in our adolescent patient.



Graph 1: The Psoriasis Area Severity Index (PASI), 27-joint Juvenile Arthritis Disease Activity Score. (JADAS-27), Childhood Health Assessment Questionnaire (CHAQ), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI): evolution during the first year of UST treatment

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CONSENT

Both patient and his parents consented in divulgation, by means of publication and oral communication of clinical data and images concerning the case.

BLADDER DIVERTICULUM PRESENTING AS A MESENTERIC CYST

DIVERTÍCULO DA BEXIGA DIAGNOSTICADO COMO QUISTO DO MESENTÉRIO

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ABSTRACT

Bladder *diverticula* results from mucosa and submucosa herniation through the muscularis propria of the bladder wall. They can be classified as congenital or acquired. The latter can be secondary to bladder outlet obstruction, as benign prostatic enlargement (BPE). The etiology may also be neurogenic voiding dysfunction or iatrogenic. Most of diverticula are asymptomatic and detected on the investigation of lower urinary tract symptoms (LUTS) or other conditions. Therefore, their prevalence is probably underestimated.

The diagnosis of diverticula is relevant considering its potential malignant transformation with rapid perivesical involvement as well as complications. The diagnosis relies on radiographic exams and endoscopic evaluation. Differential diagnosis of large diverticula is challenging. Videourodynamic exam may be helpful in these cases. Treatment of the bladder outlet obstruction is crucial before diverticulectomy, when indicated.

We report a case of a patient with large bladder diverticulum initially diagnosed as a mesenteric cyst.

Keywords: Diverticula, urinary bladder, lower urinary tract symptoms.

RESUMO

Os divertículos da bexiga resultam de herniação de mucosa e submucosa através da muscular própria da parede vesical. Podem ser classificados como congénitos ou adquiridos. Estes podem estar associados a obstrução infra-vesical, como hiperplasia benigna da próstata. Também podem ser secundários a disfunção miccional neurogénica ou iatrogenia. A maioria dos divertículos são assintomáticos e diagnosticados no decurso de investigação de sintomas do aparelho urinário inferior ou outras patologias, sendo a sua prevalência provavelmente subestimada.

O diagnóstico, que compreende avaliação imagiológica e endoscópica, é relevante atendendo ao risco de transformação maligna intradiverticular e rápido envolvimento da gordura perivesical, assim como outras complicações. O diagnóstico diferencial de divertículos de grandes dimensões é desafiante, podendo o exame videourodinâmico ser útil nestes casos. O tratamento da obstrução infra-vesical é fundamental previamente à diverticulectomia, quando indicada.

Apresenta-se o caso de um doente com um divertículo vesical de grandes dimensões, inicialmente diagnosticado como quisto do mesentério.

Palavras-chave: divertículo, bexiga, sintomas do trato urinário inferior.

INTRODUCTION

Bladder *diverticula* are a result of mucosa and submucosa herniation through the *muscularis propria* of the bladder wall, via a narrow neck [1]. This is not an uncommon condition and is more frequent among male individuals [2]. Bladder *diverticula* can be classified as congenital or acquired [3]. Acquired bladder *diverticula* are commonly multiple and most likely to occur in adult men in the setting of bladder outlet obstruction [1]. Generally, benign prostatic enlargement (BPE) associated with aging is the main identifiable cause [2]. The prevalence of moderate to large bladder *diverticula* in association BPE is approximately 6% [1,2], while nearly 70% of bladder diverticula occur in this condition [2]. There is no significant association between the prevalence of bladder *diverticula* and the prostate volume [4].

Diverticula may also be secondary to neurogenic voiding dysfunction or iatrogenic following technically inadequate bladder closure after cystostomy [1,2].

Diverticula are usually asymptomatic and most often found in the investigation of lower urinary tract symptoms (LUTS), hematuria or urinary tract infections. Since this condition is not associated with any pathognomonic clinical feature, lack of diagnosis may be frequent [5]. Although infrequent, the potential malignant transformation of the bladder *diverticula* may carry a poor prognosis, considering that the lack of muscular layer leads to early involvement of perivesical fat which is associated with poor response to treatment. In the setting of a possible intra-diverticular tumor, a high suspicion level should be kept in order to achieve early diagnosis and appropriate management [2]. Other complications of bladder diverticula include vesicoureteral reflux, ureteral obstruction (in 5% to 15%) or spontaneous rupture [5].

The diagnosis depends on radiographic exams - such as voiding cystourethrography and endoscopic evaluation [2]. Some cases may be detected incidentally on imagiologic investigation for other conditions [5].

Management of bladder diverticula can include conservative management, surgical excision or endoscopic management. The indications for excision include the presence of complications such as

urinary infection, stones, malignancy [1] or upper urinary tract deterioration as a result of obstruction or reflux [2].

To emphasize the need of a high suspicion level to detect this condition and the difficulties in its differential diagnosis, we report a case of a patient with mild LUTS and a large bladder diverticulum which was initially interpreted as a giant mesenteric cyst.

CASE PRESENTATION

A 75-year-old man was referred to the Urology department due to bilateral ureterohydronephrosis (UHN) in the context of a giant mesenteric cyst incidentally detected on an abdominal CT scan. This had been requested by his general practitioner for investigation of persistent abdominal pain.

The patient had no relevant prior medical history, he had been submitted to total hip replacement for ten years and was not medicated. He reported only mild LUTS, mainly constant sensation of bladder fullness for a couple of years (International Prostate Symptom Score of 5). The physical exam revealed a palpable mass in the periumbilical area and an enlarged prostate on digital rectal examination, without suspicious nodules. The abdominal and pelvic contrast-enhanced CT scan showed a bilateral pyelocaliceal dilatation (26 mm on the left and 16 mm on the right side), with enlargement of both ureters. The intramural segment as well as the vesicoureteral junction was not clearly identified in the CT scan, suggesting obstruction above this level. A structure filled with liquid, with 146 mm of longitudinal diameter and no contrast-enchancement was seen, suggestive of a giant mesenteric cyst (figure 1).

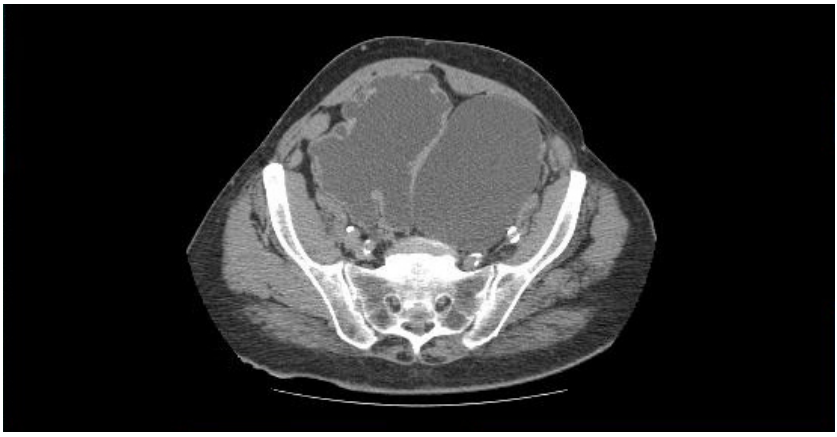

Figure 1

At this point, the UHN was considered to be caused by extrinsic compression by a mesenteric cyst. The enlarged prostate, expected considering the patient's age, as the patient was only mildly symptomatic did not seem to play a critical role. Since there was no evidence of urinary tract infection and the renal function was normal, the decision was not to place ureteral catheters and referral to General Surgery for cyst excision.

After 4 months, the patient developed an episode of acute urinary retention without precipitating factors. An urethral catheter was placed, with drainage of 900 mL of urine.

Considering the clinical suspicion of bladder outlet obstruction, the patient was reevaluated. The prostate specific-antigen (PSA) was 4,7 ng/mL and a transrectal ultrasound demonstrated a prostate of 90 cc. Another abdominal and pelvic CT scan was performed and revealed that the fluid-filled structure was in fact a large bladder diverticulum located on the left posterior aspect of the bladder.

To clarify the diagnosis, the patient underwent a videourodynamic study which confirmed the bladder diverticulum (figure 2) and left vesicoureteral reflux in the filling cystometry phase. In the flow/pressure study, the diverticulum showed incomplete emptying and a bladder outlet obstruction was detected (Qmax= 5 mL/s, Pdet-Qmax= 110 cmH2O, BOOI= 100) associated with a filiform prostatic urethra on x-ray. Cystoscopy evaluation showed obstructive prostatic lobes, the diverticular ostium at the left wall and excluded bladder cancer.

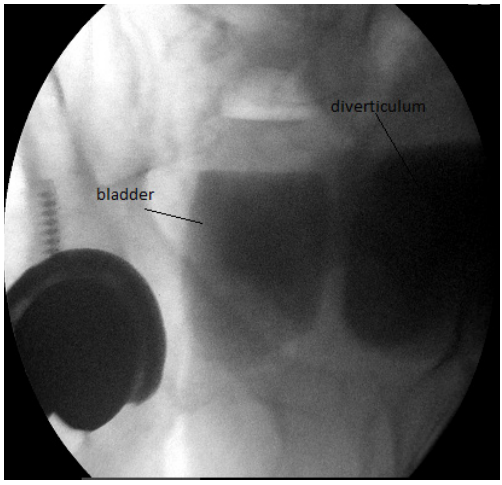

Figure 2

The patient was offered open prostatectomy (Millin's technique) to treat the bladder outlet obstruction and a combined intra and extravesical approach for diverticular excision at the same operating time.

After 3-month follow-up, the patient was asymptomatic, had a PSA of 1,6 ng/mL and an improvement on the urofluxometry parameters with a Qmax of 20,9 mL/s (total volume of 340 mL and a postvoid residual volume of 40 mL). The postoperative ultrasound showed a residual mild UHN with no relapse of the bladder diverticulum.

DISCUSSION AND CONCLUSION

Bladder diverticula are a common condition [2]. However, they may be clinically silent, in the absence of any specific symptoms [5]. Retrospectively, the patient reported only a bladder fullness sensation, possibly related with the large size of the diverticulum. Large diverticula may promote incomplete voiding, due to the absence of muscular layer which leads to urinary stasis, causing a mass effect on the lower abdomen and sensation of incomplete bladder emptying or lower abdominal fullness [2]. Many elderly patients face bladder outlet obstruction associated with the aging process, devaluing the report of urinary symptoms to their physician. This fact highlights the relevance of a thorough clinical history, focusing on this kind of symptoms.

Differential diagnosis of bladder diverticula is a challenging process in the male patient, including conditions related to a fluid-filled structures adjacent to the bladder, such as urachal cysts, ectopic ureter, ureterocele or postoperative lymphocele [5]. In the female patient, adnexal pathology should also be considered. Mesenteric cyst is an uncommon differential diagnosis.

This case report also stands out the usefulness of video-urodynamics, providing information about the functionality of the whole bladder emptying process and real time and accurate anatomic detail on the lower urinary tract. Besides, it provides information concerning the diverticula's site, size, the possible associated vesicoureteral reflux [5] and emptying of the bladder diverticulum by voiding [2], findings that can be useful on planning the surgical strategy.

Video-urodynamics changed the course of this diagnostic investigation. What was initially thought to be a bilateral UHN secondary to extrinsic compression by a mesenteric cyst, turned out to be a bladder outlet obstruction process related to benign prostate enlargement causing the formation of a large bladder diverticulum and dilatation of both ureters and the pyelocaliceal system.

As the bladder diverticulum is believed to be secondary to bladder outlet obstruction, definitive treatment of benign prostate enlargement is indicated prior to formal diverticulectomy [2], in this case by open prostatectomy. Regarding the diverticulum size and the amount of urinary stasis, the surgeon had chosen to perform a combined intra- and extra-vesical approach, with an excellent outcome.

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HOW TO APPROACH POSITIVE BLOOD CULTURES FOR STAPHYLOCOCCUS AUREUS? – AN ILLUSTRATIVE CLINICAL CASE

COMO ABORDAR HEMOCULTURAS POSITIVAS PARA STAPHYLOCOCCUS AUREUS? – UM CASO CLÍNICO ILUSTRATIVO

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ABSTRACT

Staphylococcus aureus bacteraemia is characterized by its invasiveness and morbidity. The risk of treatment failure is high particularly in cases of extensive infection.

The authors present a case of a 63 years old male, admitted with an invasive staphylococcal disease with bilateral involvement of large joints, spondylodiscitis, multiple muscle purulent collections, endocarditis and pneumonia with hematogenous spread, difficult to control despite specific antibiotic therapy and requiring prolonged hospitalization.

Clinical workup of *S. aureus* bacteremia begins with a careful medical history, and clinical evaluation with additional tests, including echocardiography to exclude infective endocarditis, and additional imaging as needed.

Treatment includes source control and administration of appropriate antibiotics with adequate penetration and dosage, for a variable time according to the severity of the infection and extension.

The clinical case described is illustrative of the topics to be addressed in this type of infection, and its potential complications.

RESUMO

A bacteriemia por *Staphylococcus aureus* caracteriza-se pela sua invasividade e morbilidade. O risco de falência terapêutica é elevado sobretudo em casos de infeção extensa.

Os autores apresentam um caso de um doente de 63 anos de idade, admitido com quadro de doença estafilocócica invasiva com envolvimento de grandes articulações bilateralmente, espondilodiscite, múltiplas coleções purulentas musculares, endocardite e pneumonia por disseminação hematogénea, de difícil controlo apesar de antibioterapia dirigida e requerendo internamento prolongado.

A abordagem clínica da bacteriemia a *S. aureus* começa com uma história clínica cuidadosa, e avaliação com exames complementares, incluindo sempre ecocardiografia para exclusão de endocardite infecciosa, e imagiologia adicional, conforme necessário.

O tratamento inclui controlo de foco e antibioterapia com penetração e posologia adequadas, com duração variável de acordo com a gravidade e a extensão da infeção.

O caso clínico descrito é ilustrativo dos tópicos que devem ser abordados neste tipo de infeção, e suas potenciais complicações.

INTRODUÇÃO

O Staphylococcus aureus é um dos principais causadores de bacteriemia adquirida na comunidade e no hospital. Os doentes podem desenvolver uma ampla variedade de complicações potencialmente difíceis de reconhecer inicialmente, o que pode aumentar a morbilidade. Taxas de mortalidade de 20-40% foram descritas [1,2].

Hemoculturas positivas para *S. aureus* devem ser respeitadas como clinicamente significativas, e devem levar a avaliação clínica e início de terapêutica empírica.

Todos os doentes com bacteriemia a *S. aureus* devem ser submetidos a ecocardiografia para avaliar a presença de endocardite [3,4]. O diagnóstico imagiológico adicional deve ser adaptado às conclusões tiradas na anamnese e no exame objetivo.

A falência terapêutica (definida como morte até 30 dias após o tratamento, bacteriemia persistente após 10 dias de terapêutica apropriada, ou recrudescência da bacteriemia até 60 dias após descontinuação terapêutica) é relativamente comum em doentes com bacteriemia por *S. aureus* [5] mesmo sob terapêutica apropriada [6]. A maioria dos estudos incide sobretudo na resistência antibiótica, mas a nossa experiência sugere que a posologia e tempo de tratamento pesam igualmente na falência terapêutica.

Para evitar bacteriemias a *S. aureus* subtratadas, com consequente recidiva infecciosa, apresenta-se um caso de uma doença estafilocócica extensamente invasiva, com múltiplas complicações, destacando os principais aspetos deste tipo de infeção disseminada e a importância de um tratamento adequado.

APRESENTAÇÃO DO CASO

Doente do sexo masculino, 63 anos, leucodérmico, independente nas atividades de vida diária. Antecedentes pessoais de hipertensão arterial essencial, status pós-trombose venosa profunda, hipertrofia benigna da próstata, doença osteoarticular degenerativa da coluna lombar e obesidade mórbida. Medicado com ácido acetilsalicílico, clopidogrel, alopurinol, tansulosina, omeprazol e paracetamol.

Apresentou quadro de artralgias com cerca de cinco semanas de evolução, inicialmente caracterizado por omalgia e dor no cotovelo esquerdos e posteriormente coxalgia e rubor ao nível da face externa do membro inferior direitos, não controlados sob terapêutica anti-inflamatória, e com febre associada. Recorreu ao serviço de urgência de um hospital distrital, onde foi internado com o diagnóstico de celulite do membro inferior direito e medicado empiricamente com vancomicina, piperacilina + tazobactam e doxiciclina (desconhecemos fundamentação terapêutica), sendo isolado posteriormente em hemocultura Staphylococcus aureus meticilino-sensível. Realizou tomografia computorizada (TC) da coluna dorso-lombar, compatível com alterações degenerativas, sem evidência de alterações agudas/infecciosas. Ao 5º dia de internamento o doente foi transferido para o Serviço de Doenças Infecciosas – unidade de internamento (piso 5) do Centro Hospitalar Lisboa Norte – Hospital de Santa Maria. Aquando da admissão, ao exame objetivo destacava-se apirexia, quadro confusional e ausência de sinais meníngeos, alguns fervores bibasais à auscultação pulmonar, queixas de lombociatalgia e sinais de celulite da perna direita. Analiticamente com leucocitose neutrofílica 17.680x106 (88.8%), proteína C reativa 26.8mg/dL e velocidade de sedimentação (VS) 120mm/h. Alterada antibioterapia para flucloxacilina 12g por dia (2g de 4/4h), dose de endocardite, que deve ser iniciada até exclusão da mesma.

No internamento, o doente apresentou inicialmente evolução desfavorável da sua situação clínica, com recrudescência do quadro febril, bacteriemia persistente e exacerbação do quadro confusional, sem alterações relevantes na TC cranioencefálica, na ressonância magnética nuclear (RMN) cranioencefálica, ou na punção lombar. Do ponto de vista respiratório, destacava-se dependência de oxigenoterapia a 2L/min por óculos nasais, sendo visível na telerradiografia de tórax um infiltrado bilateral, admitindo-se infeção respiratória por disseminação hematogénea. Realizou ainda ecocardiograma transesofágico (ETE) que não demonstrou alterações da cinética cardíaca ou vegetações. Do ponto de vista osteoarticular, o doente apresentou agravamento da lombociatalgia e instalação de paresia no membro inferior direito, grau 2/5, pelo que realizou RMN da coluna lombar que revelou alterações compatíveis com espondilodiscite de L2-L3, coleção epidural anterior em L3-L4 com compressão da cauda equina e atingimento da articulação intra-apofisária e foramen neural direitos com compromisso radicular L3 ipsilateral, sendo submetido no dia seguinte a artrodese percutânea de L2-L3-L4. Como intercorrência, o doente apresentou falência respiratória e impossibilidade de extubação no contexto do quadro séptico com envolvimento respiratório, sendo transferido para a Unidade de Isolamento Respiratório (UIR) durante 12 dias. Aí apresentou uma evolução clínica favorável, com tendência à apirexia e descida paulatina dos parâmetros inflamatórios, assim como desmame do suporte ventilatório. Após melhoria, transferido novamente para a unidade de internamento.

Por elevada suspeita de endocardite, repetiu ETE que revelou massa no folheto anterior da válvula mitral compatível com vegetação. Realizou TC-toracoabdominopélvica que revelou coleções intramusculares anteriormente à vertente superior da omoplata direita (4cm de maior eixo axial), posteriormente ao 5º arco costal posterior esquerdo (7cm de maior eixo axial) e no terço distal do músculo psoas-ilíaco direito (12cm de maior eixo axial), e ainda envolvimento articular coxofemoral predominantemente à direita.

Efetuou-se punção aspirativa do abcesso da face anterior da omoplata direita, com saída de líquido seroso ligeiramente turvo, sendo que o exame bacteriológico (sob 32 dias de antibioterapia) foi negativo. As restantes coleções não foram passíveis de drenagem.

Para estudo de outros focos de disseminação da infeção primária, o doente realizou ainda uma cintigrafia marcada com Gálio e estudo tomográfico por emissão de fotão único (SPECT), que revelaram múltiplos focos de hiperfixação do radionúclido no ombro direito, segmento inferior da omoplata esquerda, parede toracoabdominal anterior, coluna dorsal, fémur esquerdo e marcada atividade em toda a coluna lombo-sagrada, alterações sugestivas de corresponder a extensão de múltiplos focos sépticos.

Em controlo ecocardiográfico, após 70 dias de terapêutica antiestafilocócica intravenosa, visualizou-se apenas espessamento da válvula mitral no folheto anterior onde antes havia sido descrita lesão suspeita de vegetação.

Como intercorrências durante o internamento, apresentou várias bacteriemias, tratadas de acordo com os testes de sensibilidade aos antibióticos: bacteriemia com ponto de partida urinário a Klebsiella pneumoniae produtora de beta-lactamases de espetro alargado tratada com meropenem; infeção associada ao catéter venoso central por Klebsiella pneumoniae produtora de carbapenemases tratada com remoção do catéter, colistina e ciprofloxacina; e bacteriemia por Enterococcus faecium, por possível translocação bacteriana intestinal, tratada com vancomicina. Após a resolução das várias infeções nosocomiais, o doente apresentou ainda quadro de intolerância alimentar e dejeções diarreicas, com pesquisa de Clostridium difficile, coproculturas e exame parasitológico de fezes negativos, assumida como síndrome de hiperproliferação bacteriana do intestino delgado e tratado com metronidazol durante cinco dias.

Teve alta ao 88º dia de internamento, com o diagnóstico final de estafilococemia aguda sem ponto de partida evidente, com múltiplos focos metastáticos (endocardite infecciosa estafilocócica, espondilodiscite, envolvimento multiarticular, muscular e pulmonar). Clinicamente apirético, com moderada limitação funcional dada a extensão do envolvimento osteoarticular e permanência no leito prolongada, foi encaminhado para um centro de reabilitação. Do ponto de vista analítico, sem leucocitose e com VS 90mm/h.

Manteve terapêutica antibiótica com flucloxacilina 8g por dia (por já ter completado as seis semanas de tratamento de endocardite, e por necessitar apenas de dose de osteomielite: 2g de 6/6h) por mais oito meses em ambulatório, perfazendo um total de onze meses de terapêutica dirigida, até normalização da VS e recuperação da total mobilidade articular.

DISCUSSÃO

Uma história clínica cuidadosa e um exame objetivo completo são essenciais na abordagem clínica de bacteriemia a *Staphylococcus aureus*. Em circunstâncias em que o foco é incerto, como o caso do doente apresentado, deve-se questionar cuidadosamente acerca de potenciais portas de entrada recentes, incluindo a pele ou infeção dos tecidos moles e presença de dispositivos protésicos (incluindo catéteres, material ortopédico e dispositivos cardíacos).

Os doentes devem ser também questionados sobre sintomas sugestivos de infeção metastática, que pode ocorrer em até 30% dos casos [7]. No caso descrito, o doente referia inicialmente dores osteoarticulares (sugestivas de osteomielite da coluna, discite, abcesso epidural e/ou artrite séptica) desenvolvendo posteriormente défice motor, e febre prolongada (sugestivo de endocardite). Os doentes podem ainda referir sudorese, dor abdominal (podendo refletir enfarte esplénico), ou cefaleia (que podendo significar êmbolos sépticos).

De destacar também a importância de um exame objetivo com uma auscultação cardíaca cuidadosa, procura de sinais de insuficiência cardíaca, e busca vigorosa de estigmas clínicos de endocardite, incluindo sinais de embolização periférica a nível da conjuntiva, pele e dedos. No caso apresentado não constavam quaisquer destes sinais apesar da presença de endocardite, mas estes achados não são raros e, por vezes, negligenciados.

Como também descrito acima, um compromisso neurológico focal de novo é passível de ocorrer como complicação de abcesso epidural com compressão medular, pelo que uma avaliação neurológica deverá constar no exame inicial e nas avaliações diárias subsequentes.

A não identificação atempada de metastização séptica pode levar a complicações catastróficas (por exemplo paralisia ou morte) [8] ou a bacteriemia recidivante por tempo de tratamento inadequado [9], pelo que se sublinha a importância de um exame objetivo meticuloso regular.

Todos os doentes com bacteriemia a *S. aureus* devem ser submetidos a ecocardiografia transtorácica (ETT) para avaliar a presença de endocardite [3,4]. A identificação de uma vegetação na ETT é diagnóstica, mas um estudo negativo não exclui endocardite infecciosa [10,11]. Os resultados da ecocardiografia são úteis mesmo na ausência de alterações, dado que o afastamento da hipótese de endocardite pode afetar a decisão sobre a duração da antibioterapia.

As indicações para a ETE em doentes com bacteriemia a *S. aureus* e nenhuma evidência de vegetação na ETT são controversos, uma vez que a ETE é substancialmente mais sensível na identificação de vegetação valvular [11-13], especialmente quando realizada entre cinco a sete dias após a identificação da bacteremia [14,15]. Quando há elevada suspeita clínica de endocardite e ecocardiograma negativo, a repetição ecocardiográfica deve ser garantida, permitindo melhor precisão diagnóstica. No caso clínico descrito, o primeiro ecocardiograma realizado não revelou alterações, no entanto havia um risco elevado de endocardite (infeção com tempo de evolução incerto e com envolvimento ósseo), pelo que foi pedido novo estudo que confirmou a presença de vegetação na válvula mitral.

Os exames de imagem devem ser adaptados às conclusões retiradas na anamnese e no exame objetivo. No doente apresentado, pelas queixas de lombalgia, foram realizadas TC e RMN da coluna lombar, que confirmaram presença de espondilodiscite.

Uma TC abdominal deverá ser realizada não só em doentes com dor abdominal para avaliar a presença de enfarte esplénico, renal, abcesso do psoas, ou outros locais intra-abdominais de infeção, como também em doentes com endocardite documentada, mesmo na ausência de sintomas focais, para avaliar a presença de infeção metastática subclínica. Doentes com cefaleia e/ou endocardite conhecida ou suspeita devem ser submetidos a RMN-CE.

O tratamento de bacteriemia a *S. aureus* inclui controlo de foco (como remoção de catéteres vasculares envolvidos e/ou drenagem cirúrgica de abscesso, se houver) e antibioterapia.

Virtualmente todos os *S. aureus* meticilino-sensíveis (MSSA) isolados são resistentes à penicilina [16], pelo que o tratamento do MSSA geralmente consiste num beta-lactâmico, tal como flucloxacilina (pelo menos 2g IV a cada seis horas, podendo ser a cada quatro horas se suspeita ou confirmação de endocardite concomitante) [17]. Uma cefalosporina de primeira geração, como cefazolina (2g IV a cada oito horas) é uma alternativa aceitável em doentes com hipersensibilidade à flucloxacilina.

A vancomicina é menos eficaz do que os beta-lactâmicos no tratamento da bacteriémia a *S. aureus* e não deve ser administrada como tratamento primário em estirpes sensíveis à meticilina, a menos que a utilização de um agente beta-lactâmico esteja contraindicada [18]. Por exemplo, um estudo de coorte prospetivo com 298 doentes com bacteriemia a MSSA reportou uma falência microbiológica inferior (0/18 [0%] vs. 13/70 [19%], OR 6.5, 95% CI 1.0-53) nos doentes tratados com nafcilina (grupo das penicilinas) em comparação com os tratados com vancomicina [19]. Este facto poderá ter sido um dos fatores que contribuíram para a evolução desfavorável inicial do caso clínico descrito.

No tratamento de bacteriemia a *S. aureus* resistente à meticilina (MRSA), os antibióticos de eleição são a vancomicina e a daptomicina [4].

Uma vez estabelecido o diagnóstico de bacteriemia a *S. aureus* e tratamento iniciado, hemoculturas devem ser repetidas para documentar clearance de bacteriemia.

A duração do tratamento depende da etiologia da infeção [20]. A determinação do tempo de tratamento requer a diferenciação dos doentes com bacteriemia não complicada (que pode ser tratada com 14 dias de antibioterapia intravenosa a partir da primeira hemocultura negativa), dos doentes com bacteremia complicada (que necessitam de uma maior duração de tratamento intravenoso) [3]. Em geral, pode presumir-se que um doente tem bacteriemia não complicada se houver exclusão de endocardite infecciosa por ecocardiografia e nenhuma outra evidência de infeção estafilocócica metastática, ausência de material protésico, hemoculturas negativas dois a quatro dias após o início da antibioterapia antiestafilocócica intravenosa, e defervescência em 48 a 72 horas após o início da terapêutica e remoção do foco presumido de infeção [4]. Nos doentes com bacteriemia a *S. aureus* que não preenchem todos os critérios acima, como o doente apresentado, deve presumir-se foco profundo de infeção, garantindo tratamento intravenoso por mais de duas semanas. A duração do tratamento para estes doentes depende da natureza da infeção subjacente. Por exemplo, doentes com espondilodiscite, como o descrito, deverão manter terapêutica antiestafilocócica intravenosa durante pelo menos seis semanas, devendo prolongá-la em forma per os até normalização da VS [21].

Foram relatadas taxas de mortalidade de 20 a 40% na maioria das séries de casos de doentes com bacteriemia por *S. aureus*; estas taxas não mudaram ao longo das últimas décadas [1, 22], e refletem a grande percentagem de infeções a MRSA, que, por exemplo, em Portugal, em 2014 representaram 47.4% de um total de 3193 isolamentos microbiológicos [23]. Fatores de risco como presença de endocardite infecciosa, choque séptico e catéter venoso central, assim como infeção por MRSA, estão associados a maior mortalidade [24]. Vários estudos apontam para uma melhoria na sobrevivência assim como

uma redução das recidivas e reinternamentos quando um especialista de Infecciologia é envolvido no tratamento do doente [25].

Em conclusão, o *S. aureus* é dos principais causadores de bacteriemia, quer na comunidade quer em ambiente hospitalar. A sua abordagem deve centrar-se numa história detalhada e no despiste de metastização séptica, com especial destaque na obrigatoriedade de obter um ecocardiograma para exclusão de endocardite. O tratamento antibiótico deve ter uma duração mínima de 14 dias em casos de bacteriemia não complicada, que se pode prolongar várias semanas em casos de infeção extensa.

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CIRCUMSCRIBED CHOROIDAL HEMANGIOMA: A CASE REPORT

HEMANGIOMA COROIDEU CIRCUNSCRITO: UM CASO CLÍNICO

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ABSTRACT

Circumscribed choroidal hemangiomas (CCH) are rare vascular tumors that may cause visual loss due to subfoveal location, associated exudative retinal detachment (RD), cystoid macular edema or subretinal fibrosis. We describe a case of a 59-year-old female patient presented with decreased vision on the left eye (LE) that showed fundoscopy findings consistent with a CCH, further confirmed by complementary exams. Spectral Domain - Optical Coherence Tomography (SD-OCT) showed intraretinal fluid over a dome-shaped choroidal elevation and an adjacent exudative retinal detachment. The patient was successfully treated with photodynamic therapy (PDT) and intravitreal injection of ranibizumab 0.05 ml/0.50 mg. At 1-year follow up, there was no recurrence of the mass but the OCT showed a new inferior epiretinal membrane. Although PDT is an effective and recommended therapeutic option for exudative RD associated with CCH, some complications can emerge, such as epiretinal membranes as we can see in our case report.

Keywords: Circumscribed choroidal hemangioma, photodynamic therapy, Spectral Domain - Optical Coherence Tomography (SD-OCT).

RESUMO

Os hemangiomas coroideus circunscritos (HCC) são tumores vasculares raros que podem causar perda de visão se localizados na região foveal, associando-se a descolamentos da retina (DR) exsudativos, edema macular cistóide ou fibrose subretiniana. O caso clínico descreve uma doente de 59 anos que apresentou uma diminuição da acuidade visual do olho esquerdo, mostrando à fundoscopia alterações compatíveis com o diagnóstico de HCC, posteriormente confirmado através de exames complementares de diagnóstico. O Spectral Domain - Optical Coherence Tomography (SD-OCT) revelou edema intra-retiniano superiormente a uma elevação coroideia em forma de cúpula e um DR adjacente. Realizou terapêutica fotodinâmica (PDT) e uma injeção intra-vítrea de ranibizumab 0.05 ml/0.50 mg, com resolução do quadro. Após 1 ano de follow-up, manteve-se sem recorrência da lesão, mas o SD-OCT mostrou o aparecimento de uma membrana epirretiniana (MER) inferior. Apesar da PDT ser uma terapêutica recomendada, algumas complicações podem surgir, como a MER descrita neste caso clínico.

Palavras-chave: hemangioma coroideu circunscrito, terapêutica fotodinâmica, Spectral Domain - Optical Coherence Tomography (SD-OCT).

INTRODUCTION

Choroidal hemangioma is a vascular hamartoma that may occur sporadically, in a circumscribed isolated form, or in association with Sturge-Weber syndrome, as a diffuse choroidal angiomatosis. Circumscribed choroidal hemangioma (CCH) is almost always unilateral and typically presents in the macular and peripapillary area. Although it is a benign tumor, it can cause visual loss due to subfoveal location, associated exudative retinal detachment, cystoid macular edema or subretinal fibrosis. Various therapeutic modalities are available for the treatment of symptomatic CCH, including laser coagulation, external beam radiation, transpupillary thermotherapy, intravitreal anti-VEGF and photodynamic therapy (PDT). PDT with verteporfin seems to be the ideal method for the treatment of CCH as it can offer site specific tumor destruction while sparing overlying retina and retinal vasculature.

The authors report a case of CCH with macular exudation that was treated successfully with PDT, with complete regression of the tumor and no signs of recurrences after two-year follow-up.

CASE PRESENTATION

A 59-year-old female patient, complained of decreased vision on the left eye (LE). Systemically there was no history of diabetes mellitus, hypertension or malignancy. Best corrected visual acuity (BCVA) was 1/10 in the left eye and 10/10 in the right eye (RE). Pupils were equal, round, and reactive to light, and there was no afferent pupillary defect. Slit lamp examination was unremarkable and intraocular pressures were within normal limits. Ophthalmoscopy showed a subretinal orange mass at the posterior pole, macular inferior, involving the fovea, associated with macular edema (figure 1). Spectral domain optical coherence tomography (SD-OCT) showed a dome-shaped choroidal mass, intra and subretinal fluid over the lesion and adjacent exudative retinal detachment (figure 2 – A, B). Fluorescein angiography (FA) (figure 3 – A, B) revealed early spotty hyperfluorescence, lacy network of intrinsic vessels and late leakage; Indocyanine green (ICG) angiography (figure 3 – C) showed very early hyperfluorescence of tumour vessels with late washout. A and B-Scan ocular ultrasound (figure 4 – A) demonstrated a dome shaped acoustically solid lesion with regular high internal reflectivity and a thickness of 2,7 mm.

Figure 1 – Left eye fundoscopy

The patient was first treated with one intravitreal injection of ranibizumab 0.05 ml/0.50 mg and thirteen days later photodynamic therapy was performed.

One month later, the BCVA had improved to 10/10 with no signs of edema on SD-OCT and no retinal detachment (figure 2 – C, D); US confirmed resolution of the choroidal mass (figure 4 – B).

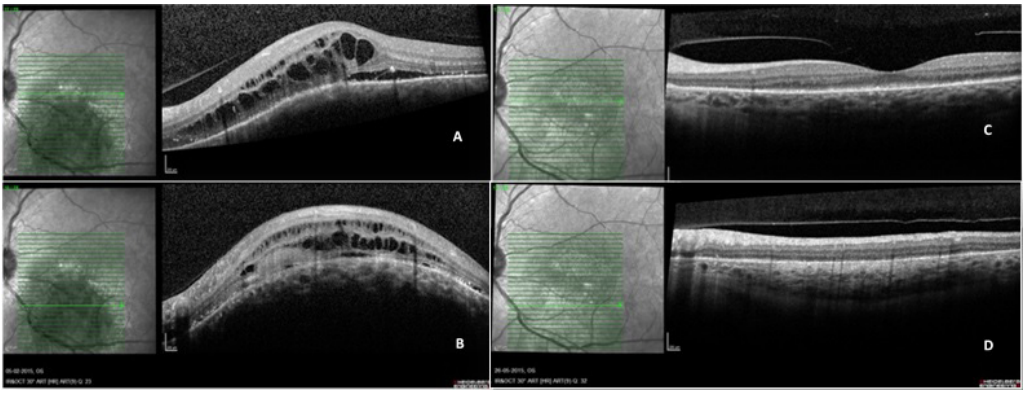

Figure 2 – SD-OCT. A and B: pretreatment; C and D: post treatment

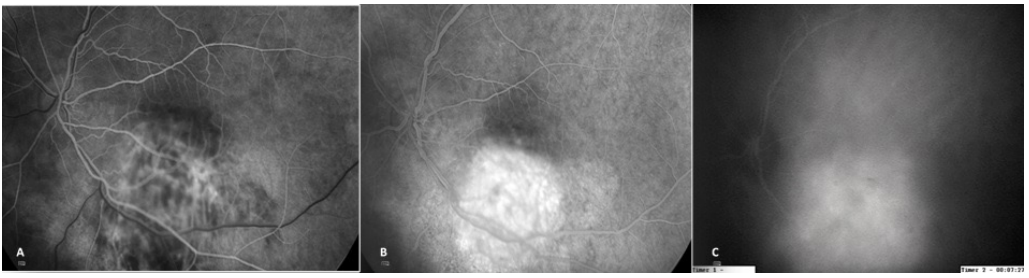

Figure 3 – A and B: fluorescein angiography; C: indocyanine green angiography

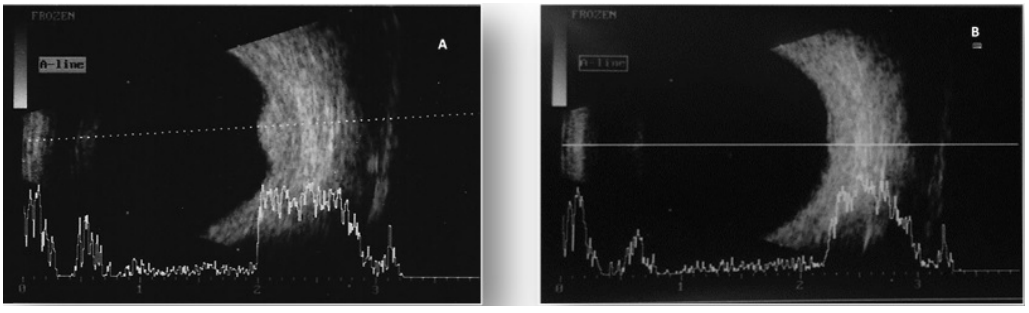

Figure 4 – B-Scan Ocular ultrasound, LE transverse macular scan – A: pretreatment; B: post treatment

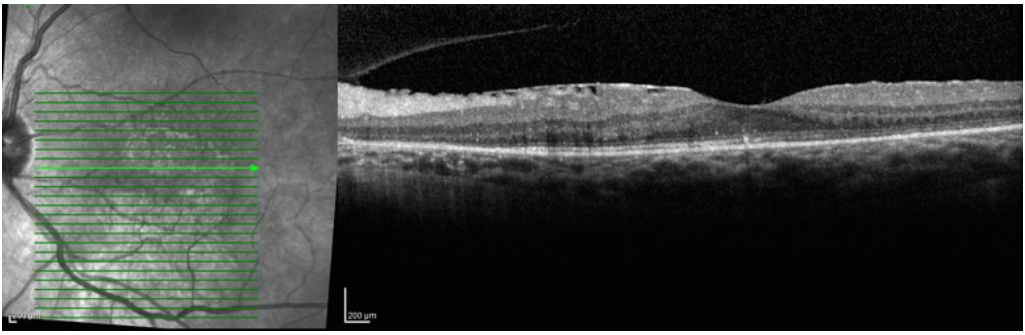

Figure 5 – SD-OCT at 1 year of follow-up

At 1-year follow up, OCT showed scarce intra-retinal fluid related to the presence of an inferior epiretinal membrane (figure 5), but no recurrence of the tumor.

The BCVA remained 10/10, after 2 years of follow-up, without recurrence of the tumor.

DISCUSSION

Choroidal hemangiomas are probably congenital, however the incidence of the disease is difficult to estimate since most circumscribed choroidal hemangiomas are only diagnosed if the patient becomes symptomatic or if they are incidentally discovered during routine examination. CCH is considered rare. Jarrett et al diagnosed one circumscribed choroidal hemangioma for every 15 cases of choroidal melanoma [1]. Average patient age for development of symptoms appears to be in the late twenties to fifties, with a range of 6 to 75 years, depending on the series reported [2,3].

Clinically, CCH appears as a subtle red-orange elevated mass posterior to the equator. Lesions are usually solitary and unilateral, although bilateral choroidal hemangiomas have been reported [4]. In the largest published series of 200 patients by Shields et al the most common reported symptom was blurred vision in up to 81% of patients, while some patients noted visual field defects, metamorphopsia and floaters. They found that the most common cause for decreased vision was chronic subretinal fluid and chronic macular edema [2].

Besides clinical observation and fundus photography, a multimodal imaging approach can help in the diagnosis and follow-up of CCH. Typically A and B scan ultrasonography shows a solid mass with medium to high reflectivity and acoustic solidity.

The most common FA pattern of CCH is mild early hyperfluorescence of the tumor in the pre-arterial and arterial phases, followed by increasing hyperfluorescence and progressive staining of the extravascular tissue of the tumor, with variable leakage in the late phase.

ICG angiography is probably the best technique for studying CCH since it provides better visualization of the choroidal vasculature. CCH have a characteristic pattern of early well-defined hyperfluorescence around 30 seconds and late hypofluorescence due to rapid loss of dye, which is known as “wash out” phenomenon.

SD-OCT provides a detailed image of the retina and choroid, enables visualization of the lesion structure and surrounding tissues, helping in defining treatment and in prognosticating the visual potential [5].

The differential diagnosis should be done with other amelanotic lesions of the ocular fundus such as amelanotic choroidal melanoma, choroidal metastases and some inflammatory diseases.

In our case, patient had no present or past oncologic history. The physical examination as well as ocular anterior segment observation were unremarkable. Besides, the fundus observation disclosed a macular orange subretinal mass clinically consistent with CCH, confirmed by typical findings in imaging studies. A and B-scan ultrasound is the gold standard exam for diagnosing intraocular tumors, allowing the differentiation between melanoma, metastases and hemangioma. In this case ultrasound identified a dome shaped mass with homogeneous hyperreflectivity and no orbital acoustic shadowing. These characteristics are in favour of CCH diagnosis.

The decision to treat CCH is based on the location, size and related ocular symptoms. Asymptomatic hemangiomas with no related subretinal fluid are managed by observation. Hemangiomas with advanced visual deficit and minimal anticipated visual potential can also be observed [6].

There are different treatments for symptomatic serous RD associated with CCH. PDT currently appears to achieve the best results in treating symptomatic CCH with exudative RD [7] and may have the lowest risk of treatment related morbidity [8].

PDT acts by inducing selective destruction of choroidal vascular network of the tumor through photo-chemical reactions without damaging the normal underlying retina [5].

PDT involves administration of photosensitizer drug that reaches the target tissue that is irradiated with light of wavelength coinciding with the absorption maximum of the photosensitizer.

The initial treatment, depending on the size of the lesion, consists of either a single spot covering the entire lesion, one or more overlapping spots, or a single spot only large enough to cover the "most prominent part" of the tumor. The number of treatment sessions in the reported series ranged from one to five. In addition to eliminating the serous RD in almost all patients, PDT reduces the tumor height markedly or completely [9].

In various studies the visual acuity improvement or stabilization after PDT for choroidal hemangioma ranges from 73% to 100% [10].

Various studies had reported the efficacy of PDT in reduction of tumor mass and in the resolution of the exudation, but the complete disappearance of the tumor vascular network documented with ICG, without choroidal atrophy, was not usually reported [5].

Anti-vascular endothelial growth factor (anti-VEGF) agents are known to reduce vascular permeability and are effective for resolution of subretinal and intraretinal fluid in multiple ophthalmic pathologies. The role of anti-VEGF agents in treatment of choroidal hemangioma is still uncertain and more studies are required. Some authors hypothesized that the use of bevacizumab prior to PDT reduces tumor thickness through resorption of subretinal fluid, and this may maximize the effect of PDT [11].

In our patient we obtained visual improvement, fluid resolution and a remarkable tumor reduction with only one injection of anti-VEGF, followed by one session of PDT.

Alt. Epiretinal membrane is a common disease of the vitreoretinal interface, presented by a sheet of avascular fibrocellular translucent tissue growing on the internal limiting membrane. Secondary epiretinal membranes are described after retinal surgery and photocoagulation, but treatment is rarely indicated if visual function is not compromised. Indeed, at 1-year follow up, an epiretinal membrane localized inferiorly to the macula has been identified on fundus examination and SD-OCT of our patient. However, as the BCVA still remained 10/10 no other treatment has been needed and 2 years after PDT our patient remains asymptomatic, with no signs of choroidal tumor or related retinal disease.

CONCLUSIONS

Choroidal hemangiomas are benign vascular hamartomas with no malignant potential. Although recognized clinically, these tumors can be mistaken for amelanotic choroidal melanoma or choroidal metastasis. Diagnosis can be confirmed by means of ancillary studies. Once the diagnosis of choroidal hemangioma has been made, and vision is decreased, treatment should be administered as early as possible in order to achieve a better visual outcome. Treatment depends on tumor size and location. PDT is a minimally invasive but, as demonstrated in our case, effective method of treatment for CCH and may be considered as a treatment of choice. It induces anatomic tumor regression, subretinal fluid resolution and visual acuity improvement.

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ADDISONIAN CRISIS ASSOCIATED WITH ADRENOLEUKODYSTROPHY

CRISE ADDISONIANA ASSOCIADA A ADRENOLEUCODISTROFIA

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ABSTRACT

Adrenoleukodystrophy is a rare inherited X-linked pathology that mainly affects the central nervous system, adrenal cortex, and testicular Leydig cells.

We present the case of a 74-year-old man, partially dependent on daily life activities, diagnosed with adrenoleukodystrophy and undergoing glucocorticoid replacement therapy, who was taken to the emergency department after being burned with hot water in his left foot, with reference to progressively worsening prostration in the last week. Dehydration, hemodynamic stability, bradycardia, 2nd degree burn in the left foot, slight cognitive deficit, spastic paraparesis with hyperreflexia and hypoesthesia of the lower limbs were noted.

We admitted acute adrenal insufficiency secondary to insufficient therapy and 2nd degree burn resulting from adynamia and prostration caused by adrenal insufficiency and hypoesthesia of the lower limbs related to the myeloneuropathic component of adrenoleukodystrophy. After hydrocortisone therapy, rapid clinical improvement was observed.

Keywords: Addison's disease, adrenal insufficiency, adrenoleukodystrophy, adrenomyeloneuropathy.

RESUMO

A adrenoleucodistrofia é uma patologia rara hereditária ligada ao X que afeta sobretudo o sistema nervoso central, o córtex suprarrenal e as células de Leydig testiculares.

Apresentamos o caso de um homem de 74 anos, parcialmente dependente nas atividades de vida diária, com o diagnóstico de adrenoleucodistrofia e sob terapêutica de substituição glucocorticoide, que foi levado ao serviço de urgência por queimadura com água quente no pé esquerdo, havendo ainda referência a prostração com agravamento progressivo na última semana. À observação destacava-se desidratação, estabilidade hemodinâmica, bradicardia, queimadura de 2º grau no dorso do pé esquerdo, défice cognitivo ligeiro, paraparésia espástica com hiper-reflexia e hipostesia dos membros inferiores.

Admitiu-se insuficiência suprarrenal aguda por insuficiência terapêutica e queimadura de 2º grau resultando da adinamia e prostração causadas pela insuficiência suprarrenal e da hipostesia dos membros

inferiores resultante do componente mieloneuropático da adrenoleucodistrofia. Após terapêutica com hidrocortisona, verificou-se melhoria clínica rápida.

Palavras-chave: doença de Addison, insuficiência suprarrenal, adrenoleucodistrofia, adrenomieloneuropatia.

INTRODUÇÃO

O complexo adrenoleucodistrofia/adrenomieloneuropatia (ALD/AMN) engloba um conjunto de fenótipos de uma patologia peroxissomal hereditária ligada ao X que resulta na acumulação de ácidos gordos de cadeia muito longa (AGCML) em todos os tecidos, mas afetando sobretudo o sistema nervoso central (SNC), o córtex suprarrenal e as células de Leydig testiculares [1,2].

O fenótipo adrenomieloneuropatia é o mais comum, apresentando-se tipicamente entre os 20 e os 40 anos [1,3] com paraparésia espástica, perda do controlo de esfíncteres e disfunção sexual, na maioria dos casos com insuficiência suprarrenal. A longo prazo, a maioria (até 63%) desenvolve sintomas de envolvimento cerebral (declínio cognitivo, alterações do comportamento, perda visual, hipoacúsia ou convulsões) e até 41% desenvolvem desmielinização [4].

Deve-se suspeitar de ALD em caso de clínica compatível, incluindo insuficiência suprarrenal isolada, ou em caso de história familiar. O diagnóstico diferencial inclui esclerose múltipla, esclerose lateral amiotrófica, défice de vitamina B12 e paraparésia espástica progressiva [1].

A pesquisa de AGCML no plasma é um teste sensível, sobretudo em homens [5], devendo ser confirmado com análise da mutação do gene ABCD1 (localizado no Xq28) [6]. Após o diagnóstico deve sempre avaliar-se envolvimento cerebral (através de neuroimagem) e a função suprarrenal (concentração sérica de hormona adrenocorticotrópica [ACTH] e aumento do cortisol plasmático após estimulação com ACTH) [1].

Não existe ainda tratamento específico, pelo que o objetivo principal é tratar a insuficiência suprarrenal, se presente [1].

APRESENTAÇÃO DO CASO

Homem de 74 anos, parcialmente dependente nas atividades de vida diária (Zubrod score 3), com o diagnóstico de ALD com o fenótipo de AMN estabelecido desde os 64 anos. Apresentava paraparésia espástica, desequilíbrio na marcha e hipostesia com predomínio nos membros inferiores desde os 40 anos, défice cognitivo desde os 65 anos, perda do controlo do esfíncter vesical desde os 67 anos com infeções urinárias de repetição e insuficiência suprarrenal crónica desde os 68 anos. Apresentava ainda história de hipertensão arterial e dislipidemia desde os 50 anos. Na história familiar destacavam-se dois irmãos também com ALD/AMN. Estava medicado com prednisolona, dexametasona, tizanidina, clonazepam, enalapril, bisoprolol, lercanidipina, atorvastatina, ácido acetilsalicílico e paroxetina.

Foi levado ao serviço de urgência por queimadura com água quente no dorso do pé esquerdo, havendo ainda referência a quadro com uma semana de evolução e agravamento progressivo caracterizado por prostração.

À observação apresentava-se sonolento, mas despertável, orientado e colaborante, com pele e mucosas ligeiramente descoradas e desidratadas, sem hiperpigmentação incluindo nas pregas, escleróticas anictéricas, apirético, eupneico e com boas saturações em ar ambiente, hemodinamicamente estável (PA 137/75mmHg, FC 45ppm), sem alterações na auscultação cardíaca ou pulmonar nem na palpação abdominal e com queimadura de 2º grau no dorso do pé esquerdo, com edema, rubor, dor e exsudação. Ao exame neurológico destacava-se défice cognitivo ligeiro (Mini Mental State Examination 25pontos), paraparésia espástica com força muscular grau 4, reflexos osteotendinosos muito aumentados, reflexos cutâneo-plantares em extensão bilateralmente e hipostesia dos membros inferiores.

Da avaliação laboratorial destacava-se discreta elevação de parâmetros inflamatórios (leucócitos 12,22x109/L, PCR 8mg/dL), com função renal, ionograma e função tiroideia sem alterações. Havia registo de avaliação em ambulatório, dois meses antes, de cortisol matinal e ACTH dentro dos limites da normalidade.

Admitiram-se como hipóteses diagnósticas: 1) crise addisoniana causada por insuficiência terapêutica em doente com insuficiência suprarrenal crónica no contexto de adrenoleucodistrofia; 2) queimadura de 2º grau no dorso do pé esquerdo, resultando da adinamia e prostração causadas pela insuficiência suprarrenal e da hipostesia dos membros inferiores causada pelo componente mieloneuropático da adrenoleucodistrofia.

Decidiu-se substituição de prednisolona e dexametasona por hidrocortisona, com ajuste progressivo de dose, tendo ainda realizado pensos com sulfadiazina de prata e gaze gorda na queimadura.

Ao longo do internamento houve melhoria rápida do quadro, com regresso ao estado basal, tendo alta para o domicílio. No entanto, nos 6 meses seguintes ao internamento, verificaram-se múltiplos episódios de infeções urinárias com agentes multirresistentes e progressivo agravamento do estado geral, culminando na sua morte.

DISCUSSÃO E CONCLUSÃO

Apresentamos este caso por se tratar de uma patologia rara (incidência de 1 em 21.000) [7], mas com consequências muito relevantes e que, ainda que não tenha tratamento específico, beneficia significativamente de uma adequada terapêutica de substituição suprarrenal.

O facto de o doente apresentar sintomatologia desde 24 anos antes do diagnóstico ilustra a complexidade associada, sobretudo relacionada com as hipóteses de diagnóstico diferencial. De facto, o diagnóstico correto só foi estabelecido após o diagnóstico do seu irmão mais velho, que carregou o diagnóstico de esclerose múltipla até ao estabelecimento de insuficiência suprarrenal.

A crise addisoniana, que pode ser causada tanto por défice de glucocorticoides como de mineralocorticóides, manifesta-se habitualmente por choque, mas são também frequentes sintomas inespecíficos,

incluindo fraqueza, fadiga, letargia e confusão [8]. De facto, viria a apurar-se posteriormente provável incumprimento terapêutico relacionado com o agravamento do défice cognitivo.

No tratamento da crise addisoniana a prioridade é a reposição rápida por via intravenosa de fluidos e glucocorticoides. Os fluidos a utilizar não devem ser hipotónicos (pelo risco de agravar hiponatrémia) e devem ser adequados às alterações hidroeletrolíticas presentes. Não existindo estudos comparativos entre glucocorticoides, a abordagem terapêutica escolhida, baseada em consenso de peritos [9], passou pela utilização de glucocorticoide de ação curta (hidrocortisona, 100mg bólus seguido de 50mg a cada 8h), com passagem a terapêutica oral após 3 dias.

Na fase aguda não há necessidade de administração de mineralocorticóide, processando-se a reposição de sódio através de soros intravenosos, havendo ainda vantagem adicional na escolha de hidrocortisona por esta ter alguma atividade mineralocorticóide. A longo prazo, a maioria dos pacientes com insuficiência suprarrenal primária acaba por necessitar de reposição de mineralocorticóides, utilizando-se fludrocortisona em dose variável [9, 10].

Este relato serve o propósito de ilustrar a importância do conhecimento fisiopatológico e farmacológico necessário à prevenção, diagnóstico correto e tratamento atempado da insuficiência suprarrenal, cujas consequências podem ser graves e mesmo fatais.

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CARCINOID CRISIS SECONDARY TO A METASTATIC CARCINOID TUMOR OF THE LUNG: A DIAGNOSTIC AND MANAGEMENT CHALLENGE

CRISE CARCINÓIDE SECUNDÁRIA A TUMOR CARCINÓIDE METASTÁTICO DO PULMÃO: UM DIAGNÓSTICO E UMA ABORDAGEM DESAFIANTES

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ABSTRACT

Carcinoid crisis is an unusual and potentially fatal complication of neuroendocrine tumors and assumed as an exacerbation of carcinoid syndrome. Among patients with pulmonary carcinoid tumor, it is encountered rarely. It implies a collection of signs and symptoms resulting from the massive release of vasoactive substances. Our purpose is to report a distinctive case and alert for the diagnosis, timely and adequately approach to this entity.

A 59-year-old patient with atypical carcinoid tumor with multiple liver and bone metastasis was admitted to the emergency room with an atypical and severe carcinoid crisis. To our knowledge this is a distinguishing case that represents a spontaneous, reversible and severe carcinoid crisis, in a patient with metastatic carcinoid tumor of the lung, following an undefined precipitating factor with atypical multiorgan involvement, namely hemodynamic instability with hypertension and acute renal failure, differentiating it from other previously described cases in the literature.

Keywords: carcinoid crisis, carcinoid crisis management, carcinoid lung tumors.

RESUMO

A crise carcinóide é uma complicação incomum e potencialmente fatal dos tumores neuroendócrinos, e assumida como uma exacerbação da síndrome carcinóide. Nos doentes com tumor carcinóide pulmonar, é raramente encontrada e implica um conjunto de sinais e sintomas resultantes da libertação maciça de substâncias vasoativas. O objetivo dos autores é relatar um caso peculiar e alertar para o diagnóstico e adequada abordagem desta entidade em tempo útil. Trata-se de um doente de 59 anos com tumor carcinóide atípico com múltiplas metástases hepáticas e ósseas assumido no serviço de urgência com crise carcinóide atípica e grave. Trata-se de um caso distinto que representa uma crise carcinóide espontânea, reversível e grave num doente com tumor carcinóide metastático do pulmão, sem fator precipitante definido com envolvimento multiorgânico atípico, nomeadamente, instabili-

dade hemodinâmica com hipertensão arterial e insuficiência renal aguda, diferenciando-o de outros casos previamente descritos na literatura.

Palavras-chave: crise carcinóide, abordagem da crise carcinóide, tumores carcinóides do pulmão.

INTRODUCTION

Carcinoid tumors are rare malignant neuroendocrine tumors (NETs) that can arise from the enterochromaffin cells at several locations, with preponderance source in the gastrointestinal and bronchopulmonary systems [1]. Carcinoid tumors have conventionally been categorized according to their origin from the embryonic divisions of the alimentary tract, namely the foregut (including respiratory tract, thymus, stomach, duodenum, and pancreas), midgut (including small intestine, appendix, and right colon) and hindgut (including transverse colon, sigmoid, rectum and genitourinary system) [2]. Lung carcinoid tumors establish a rare group of pulmonary neoplasms, accounting for 1-2% of all lung malignancies in adults and 20-30% of all carcinoid tumors [3,4]. Lung carcinoid tumors are also divided based upon their biological behavior, histologic grade and differentiation in typical carcinoid tumors and atypical carcinoid tumors [5]. Typical carcinoids are indolent and have metastases in a small percentage of cases, while atypical carcinoids are more aggressive and frequently develop metastasis [6].

Carcinoid crisis is an infrequent and potentially life-threatening complication of carcinoid tumors, with an incidence that varies between different settings. It is characterized by a variable constellation of symptoms and signs and assumed as an exacerbation of carcinoid syndrome occurring in fewer than 10% of all patients with a carcinoid tumor, predominantly in those with metastatic disease [7]. Among patients with pulmonary carcinoid tumor with localized disease, carcinoid syndrome and, thus carcinoid crisis, are encountered rarely and specially with large size tumors (>5 cm) [8]. Nevertheless, carcinoid syndrome may be encountered more frequently in patients with liver metastases from bronchial carcinoids.

Carcinoid crisis has become of countless importance, with the expansive use of medication and invasive procedures for the management of carcinoid tumors. Without effective approach carcinoid crisis is associated with exceptionally high mortality [1]. Additionally, owing to its rarity we report such a unique case encountered in our clinical practice discussing some atypical features of a carcinoid crisis secondary to a metastatic atypical carcinoid tumor of the lung and alert for the diagnosis, timely and adequately approach of this entity.

CASE PRESENTATION

A 59-year-old male patient, with a known history of metastatic atypical carcinoid lung tumor, was admitted to our hospital with a sudden onset of flushing and edema of the face, neck and trunk associated with profuse diarrhea, uncontrollable vomiting, serious asthmatiform crisis, clouding of

consciousness and severe hypertension. He had been diagnosed with an atypical carcinoid tumor (stage I), after a computed tomography (CT) scan of the chest revealed a 5-cm lesion of the right lung. The patient underwent a right superior lobectomy with excision of the regional lymph nodes, without evidence of relapse during three years. During follow-up, imagiologic studies confirmed recurrence with atypical carcinoid tumor with multiple liver (confirmed by biopsy), spleen and bone metastases (stage IV) (figure 1).

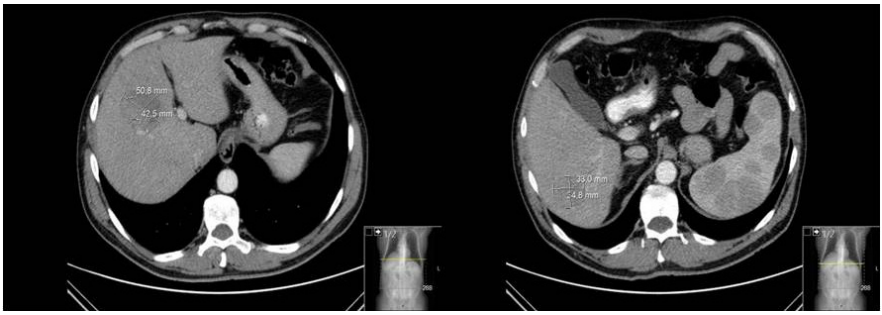

Figure 1 – CT scan of the abdomen revealed two solid and captive nodular formations in the liver parenchyma (the largest located in the right hepatic lobe with about 5.8cm, and the other with 3.5 cm of largest diameter). Spleen with several hypodense nodal lesions, the largest one with about 6cm, suggestive of secondary deposits.

Owing to progressive disease, he received a carboplatinum and etoposide regimen (4 cycles) as first-line therapy with stable disease. After five months of first-line therapy, it is noted dimensional and numeral progression of liver and bone metastases. A scheme of chemotherapy with cyclophosphamide and epirubicin (4 cycles) as second-line therapy was offered to the patient. Owing to continuous progressive disease (figure 2), after second-line therapy, a topotecan-based chemotherapy as third-line therapy was instituted, which he tolerated poorly due to a severe hypersensitive reaction. The treatment was thus discontinued after one cycle.

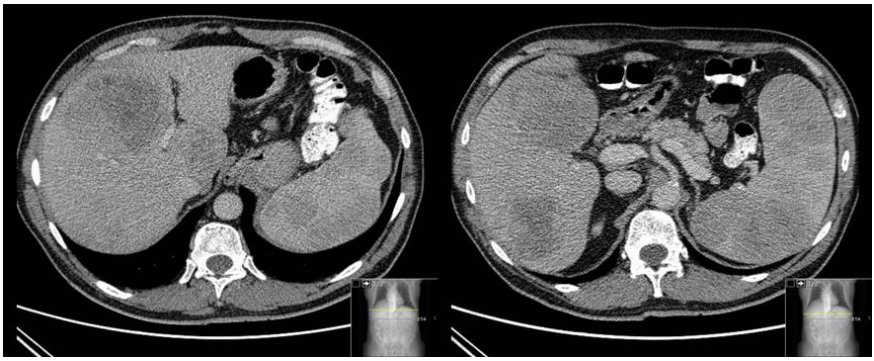

Figure 2 – CT scan of the abdomen revealed enlarged liver with bosselated contours and heterogeneous density with enlargement and new secondary lesions, with areas of probable necrosis. Accentuation of splenomegaly with increased dimensional nodules, Signs of bone metastasis progression, predominantly blastic, with an increase in the number and dimensions of the lesions.

After an octreoscan compatible with extensive bone and liver metastasis due to lesions with somatostatin receptors, the patient was started on therapy with octreotide 0.1mg/ml thrice daily subcutaneously (SC) during two weeks. The described symptomatology came two days after completion of octreotide induction dose. We obtained serum laboratories, which revealed leukocytosis 23.84x10^9/L (normal range: 4.0-11.0x10^9/L) with increase in neutrophil count 21.22x10^9/L (normal range: 1.9-7.5x10^9/L) and raised blood serum creatinine 3.3 mg/dL (normal range: 0.7-1.3mg/dL). The remaining complementary diagnostic study, namely thoracic-radiography showed no significant changes.

The patient's symptoms and signs were thought to be secondary to a carcinoid crisis and therefore, he was immediately treated with intravenous fluids, octreotide (0.2 mg thrice daily intravenously), systemic corticosteroid therapy (methylprednisolone 40mg intravenously twice daily), H1 and H2 histamine receptor blockers (ranitidine 150 mg twice daily and cetirizine 10mg once daily) and antidiarrheal therapeutic. Biochemical studies revealed clearly elevated chromogranin A levels >5000 ng/ml (normal range: 19.4–28.1 ng/ml). Despite medical management, the patient initially remained mildly hypertensive and clouded. The patient's clinical condition progressed, with an improvement in his flushing, a decrease in the edema of the face, neck and trunk, and resolution of the diarrhea and vomiting. Attending to patient's overall clinical condition improved after five days, octreotide was reduced to 0.1mg thrice daily intravenously during five days. During hospitalization, there was a progressive clinical and analytical improvement and he was discharged in stable condition on the 10th day of hospitalization indicated for clinical reassessment in Oncology Pulmonology Day Hospital. Octreotide long-acting release (LAR) 20 mg/month intramuscularly was added to the patient's treatment. Due to symptoms of persistent mild symptomatic diarrhea, Octreotide LAR was augmented to 30 mg/month intramuscularly for 6 cycles. Octreoscan after 4 cycles of octreotide LAR revealed worsening of the disease mainly due to the appearance of new bone lesions. Octreotide LAR was augmented to 40 mg/month intramuscularly but with poor tolerance, maintaining previous dosage. During this period he had two hospitalizations for moderate diarrhoea suggestive of carcinoid syndrome precipitated by concomitant respiratory and urinary infections. Octreotide LAR was again augmented to 40 mg/month intramuscularly after the 25th cycle with good tolerance. The patient fulfilled 27 cycles with imagological stable disease at the 24th cycle (figure 3).

Figure 3 – CT scan of the abdomen showing several hypodense nodal images of the hepatic and splenic parenchyma, the largest are about 13 cm. Countless osteoblastic images in relation to metastasis.

DISCUSSION

The management of locoregional carcinoid lung tumors depends on the patients' general condition, tumor size and burden. Surgery, including lobectomy or other anatomic resection and mediastinal node dissection or sampling is suggested for patients with stage I, II and IIIA broncopulmonary tumors. Systemic therapy may not be suitable for all patients with locoregional unresectable and/or metastatic carcinoid lung tumors. Multidisciplinary discussion is crucial to define the most adequate choice of treatment and there is no data to guide the sequence of the several systemic therapeutic options. Somatostatin receptor-based imaging is recommended to measure the somatostatin receptor status of locoregional unresectable and/or metastatic carcinoid lung tumors if treatment with octreotide or lanreotide is being considered. For symptom control is indicated octreotide 150-250mcg SC TID or octreotide LAR 20-30mg IM every four weeks. Dose and frequency may be further increased for symptom control as needed. Therapeutic levels of octreotide would not be anticipated to be reached for 10-14 days after LAR injection. Short-acting octreotide can be added to LAR formulation for prompt symptoms resolution or for breakthrough symptoms [9,10].

Atypical carcinoid tumours have been associated with a 5-year survival rate of 40-60% and a 10-year survival rate of 31-60%, depending on the series and extension of the disease. Our patient has been alive for seven years since the initial diagnosis. The prognostic heterogeneity and absence of curative therapeutic options at the metastatic stage make quality of life a core issue.

Carcinoid crisis is a rare and the most life-threatening complication of carcinoid syndrome in patients with carcinoid tumors. The mechanism of carcinoid crisis is associated with the systemic and massive release of neuroendocrine substances such as serotonin (5-HT) and other bioactive substances, namely histamine, prostaglandins, kallikrein and bradykinin [11]. When 5-HT and other products are secreted into the portal circulation, they are metabolized by the liver and are not associated with any symptoms or signs. When liver metastases develop and the primary lesions are in the bronchus, the systemic features become evident [2]. Some patients with functioning bronchial carcinoids have clinical and biochemical variations from the classic syndrome. Pulmonary carcinoid tumors lack the aromatic amino acid decarboxylase that converts 5-hydroxytryptophan (5-HTP) to 5-HT and produces 5-HTP instead of 5-HT, originating more rare atypical features. Ectopic serotonin production is rare in pulmonary NETs, occurring in 1-5% of patients [12]. The specific hormone mediator of flushing in patients with bronchial carcinoids is unclear but it could be histamine.

Carcinoid crisis, as an exacerbation of carcinoid syndrome, is characterized by a variable collection of symptoms and signs, specifically hemodynamic instability (hypotension and rarely hypertension), tachycardia, noticeable cutaneous flushing, secretory diarrhea, bronchospasm, and mental abnormalities ranging from light-headedness to coma lasting hours or even days [13]. Cardiopulmonary failure may occur as the result of a massive neuroendocrine substances release. Acute severe pulmonary edema, acute renal failure and coronary artery spasm have also reported to be associated to carcinoid crisis in rare cases [14,15]. It is imperative to identify a carcinoid crisis in patients with lung cancer since it can be precipitated by biopsy, chemotherapy, surgery, anesthesia, use of adrenergic drugs or even spontaneously. Given the clinical case presented, no precipitating factor was identified in our patient,

although carcinoid crisis may be encountered more frequently in patients with liver metastases from bronchial carcinoids. To our knowledge we are not aware of any published case presenting a spontaneous, reversible and severe carcinoid crisis in a patient with metastatic atypical carcinoid tumor of the lung under subcutaneous octreotide, presenting uncommon multiorgan involvement, namely hemodynamic instability with hypertension and acute renal failure, differentiating it from other previously described cases in the literature.

Management of this pathology can be challenging and a multidisciplinary approach to patient care is advised. Management consisted in carcinoid crisis control with somatostatin analogs (intravenous octreotide) that inhibit the release of these substances and are the mainstay of treatment [6]. Symptom relief with additional support therapy contributed to ultimately achieve reversal of the crisis. However, we highlight that treatment dosage and duration is variable in the literature.

In dissimilarity to other carcinoids, mainly in patients with widespread liver metastases, the risk of a carcinoid crisis with pulmonary carcinoids is so small that most clinicians do not recommend prophylactic administration of octreotide previous to tumor manipulation. However, clinicians should be mindful of the impending for carcinoid crisis with manipulation of an actively secreting tumor or even spontaneously and the life-saving benefits of octreotide in this setting. Each tumor secretes a single set of hormones which makes each carcinoid crisis unique leading to discrepancies as regards definition, symptoms and treatment. The effectiveness of the somatostatin analogs prophylaxis remains a subject of marked controversy in the literature.

CONCLUSIONS

Choroidal hemangiomas are benign vascular hamartomas with no malignant potential. Although recognized clinically, these tumors can be mistaken for amelanotic choroidal melanoma or choroidal metastasis. Diagnosis can be confirmed by means of ancillary studies. Once the diagnosis of choroidal hemangioma has been made, and vision is decreased, treatment should be administered as early as possible in order to achieve a better visual outcome. Treatment depends on tumor size and location. PDT is a minimally invasive but, as demonstrated in our case, effective method of treatment for CCH and may be considered as a treatment of choice. It induces anatomic tumor regression, subretinal fluid resolution and visual acuity improvement.

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PSYCHOTIC DEPRESSION AS A PRODROME FOR PANCREATIC CANCER

DEPRESSÃO PSICÓTICA COMO UM PRÓDROMO DE NEOPLASIA DO PÂNCREAS

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ABSTRACT

Over the last decades the correlation between pancreatic cancer and depression has been studied. Because depression tends to appear first, researchers tried to understand the biological mechanisms underlying this type of depression that precede pancreatic cancer. Although there are numerous proposed theories, they have not yet defined the pathophysiological background of the relationship between pancreatic cancer and depression.

Authors report a case of an 86-year-old woman with her inaugural psychiatric admission due to a psychotic depression that preceded a diagnosis of pancreatic cancer by four months. This reminds us that late and sudden psychiatric features, refractory to treatment, suggest an organic cause.

Keywords: cancer, pancreas, depression, psychosis.

RESUMO

Nas últimas décadas a relação entre o cancro pancreático e a depressão tem sido estudada. Face ao frequente aparecimento em primeiro lugar da depressão, os investigadores têm tentado compreender os mecanismos subjacentes deste tipo de depressão que precede o cancro pancreático. Embora existam inúmeras teorias explicativas, não está definida exactamente a correlação fisiopatológica entre estas duas condições clínicas.

Os autores reportam um caso de uma mulher de 86 anos de idade, que apresenta o seu primeiro internamento em psiquiatria com um quadro depressivo com sintomas psicóticos, quatro meses antes de se estabelecer o diagnóstico de neoplasia pancreática. Este caso tenciona reforçar a ideia de que a instalação súbita e tardia de sintomas psiquiátricos, refractários ao tratamento, sugere organicidade.

Palavras-chave: cancro, pâncreas, depressão, psicose.

INTRODUCTION

It is widely known that late and/or sudden onset psychiatric conditions demand an exhaustive investigation of neurological, systemic and other organic underlying causes, such as neoplastic etiologies. This is most significant in elderly patients without relevant psychiatric antecedents.

A clinical correlation of pancreatic cancer with depression has been identified, although this phenomenon remains poorly understood [1]. During the past 80 years [2], three studies have shown a higher prevalence of depression in patients with pancreatic carcinoma compared with those with other types of gastrointestinal carcinomas [1]. The range of reported depression varies widely, from 25% to 75% [3-7].

The authors report a case of a pancreatic cancer preceded by a psychotic depression, four months before the diagnosis of pancreatic cancer.

CASE PRESENTATION

We present the case of an 86-year-old woman, who lived alone in Lisbon, independent in her daily routine, divorced, with a single 43-years-old son, with eleven years of school, retired and previously public employee.

She had a personal medical history of unspecific osteoarticular pathology with mechanical characteristics, without significant impairment as she did escalate as a hobby one year ago. There is no history of mental disorders in her family.

It is a patient with cluster A personality characteristics, mostly of the schizoid spectrum, with previous history of emotional and behavioral disturbances which caused the loss of her child's custody and an anticipated retirement when she was 43 years old. There is reference to some episodes of physical heteroagressivity towards her son, allegedly in context of alcohol abuse. She had no previous psychiatric follow-up; nevertheless she had a psychiatrist friend who episodically gave her health care support. She had no history of admissions to a psychiatric hospital or adhere to any long-term psychopharmacological treatment, including antidepressants, antipsychotics or mood stabilizers.

In May 2016, she was admitted through the emergency department of Hospital de Santa Maria due to intense disorganization of speech and behavior. According to her son, after a fall three weeks before, she started a clinical situation characterized by depressive mood, social isolation, neglect in her personal hygiene, recurrent ideas of suicide, and sudden onset of lower back pain. For the first time, her son needed to intervene more often in his mother's life who was until then independent for her daily routine. Two weeks later, she gradually started to present psychotic symptomatology, asking her son if it was possible to control television shows through the cellphone and having full conviction that she received communications through the television set which ordered her to go to a mall where she was sexually abused in the past.

She accepted to go to the emergency department as she wanted to receive medical and legal counsel. She presented psychomotor agitation, disorganized and incoherent speech, persecutory delusions,

visual, olfactory, cenestesic and auditory hallucinations: "I hear people coming into my house; they enter during the night at someone's command; they belong to a drug dealing gang; they put drugs through my nose when I am sleeping and in the morning I feel strange nasal secretions coming down; I also smell the different perfumes of all those people; one day I felt sperm coming down my legs, I am sure they abused me many times during the night while I was drugged." She had no insight to her psychopathological condition and was admitted to the psychiatric ward.

She presented intense lower back pain on physical exam. Neurologic examination showed no relevant changes, as well as analytical evaluation, including all causes of reversible dementias. Toxicology screen was negative. A magnetic resonance imaging showed only a microvascular leukoencephalopathy pattern, common on the elderly population. Neuropsychological assessment was performed and no significant alterations were reported. A lumbar spine CT scan documented a body vertebral L1 collapse.

Antipsychotic therapy was prescribed (risperidone 2 mg/day) with significant clinical improvement of the psychotic symptoms on the following 2 weeks. On the 3rd week she maintained depressed mood, emotional lability, feelings of guilt and ideas of suicide. After antidepressant treatment introduction (duloxetine 30 mg/day and mirtazapine 7,5 mg/day) she partially improved of her affective symptoms and was discharged in June 2016.

The patient was observed only two times in psychiatric appointments after hospital discharge. She still presented depressive mood, anorexia with weight loss and intense lumbar pain, but with no psychotic symptoms.

In September 2016 she was admitted to a ward of Medicine with an acute confusional state characterized by obnubilation, temporal and spatial disorientation, disorganized speech and behavior, false recognitions, perplexity and sustained left upper abdominal pain. A progressive increase of inflammatory parameters and hepatic enzymology ensued. The abdominal ultrasound documented a large pancreatic mass in the cephalic region and numerous solid masses on the liver, probable secondary lesions. Further investigation was needed to confirm the diagnosis, unfortunately, the patient died 2 days after admission.

DISCUSSION

This clinical case illustrates a rapid evolution of a critical clinical state in 4 months' time, with an inaugural psychiatric context, characterized by depressive and psychotic symptomatology.

In the 16th century, Fernel believed that melancholia and hypochondriasis originated in the pancreas [8]. Classic descriptions of depression with pancreatic carcinoma were noticed in 1931 by Yaskin [2], who studied four patients with no history of mental or neurologic disorders. These patients first presented with depressive symptoms before another diagnosis was known. Although these diagnoses were made before newer imaging exams were available and the study group size was not sufficient to draw a definitive correlation between depression and pancreatic carcinoma, this paper did provide an early glimpse of a potential clinical correlation of these two diseases.

Because depression tends to precede the diagnosis of pancreatic carcinoma in a large number of patients, researchers have attempted to explain this depression in biologic terms [9]. Jacobsson and Ottosson proposed several biological mechanisms [7]. The first was an increase of 5-hydroxyindolaceetic acid (5-HIAA, a metabolite of serotonin produced by neuroendocrine tumors), in urine and a high concentration of 5-hydroxytryptophne (5-HTP) or 5-hydroxytryptamine (5-HT) in some tumors. Joffe et al also proposed an increase in 5-HIAA as a link to depression [10]. The reason for the proposed biologic mechanism is the fact that depression has been reported to be treatment refractory until the tumor is excised. Holland et al proposed a paraneoplastic syndrome that could alter mood [11], pointing to neuropeptides mediated by one of two different methods: (1) antibodies are induced against a protein released by cancer cells that then bind and block receptors for serotonin; (2) antibodies could stimulate the production of anti-idiotypic antibodies that would act as receptors for serotonin and reduce synaptic availability.

Pancreatic cancer has an overall poor outcome. There is metastatic spread beyond the pancreas in 80% to 90% of cases at the time of diagnosis [12]. It is expected for the patient to have a depressive reaction to a perception of having a fatal illness. But, in this case, she developed a psychotic depression episode four months before the neoplasm identification. We should also have to consider the lumbar back pain context that usually causes psychological distress, initially attributed to the fall at home and consequently to L1 collapse, but later seen to be probably secondary to pancreatic neoplasm condition.

No reports of an association between psychosis and pancreatic cancer were present in the literature, except for a single case report of a brief psychotic episode reactive to the information of neoplastic diagnosis and its severity [13]. In this case however, no one (including the patient) knew of her oncological condition, which was diagnosed four months after discharge from the psychiatry ward. The chronological sequence of events corroborates our hypothesis of a biologically-mediated psychotic depression.

It is not possible to establish a physiopathological cause-effect relationship between these two conditions. However, it is significant that an 86-year-old woman, totally independent in her daily life and with a good previous global functioning, has had her first admission to a psychiatric ward just four months before dying due to a pancreatic cancer.

CONCLUSIONS

This comorbidity between depression and pancreatic cancer has been acknowledged for more than 80 years, but we still have a poor understanding of the true prevalence of these two diseases and their mechanisms.

Additional prospective studies must be performed to fully evaluate the correlation and mechanism of pancreatic cancer and depression. Although pain has been examined as a correlate of depression, to improve prevention and treatment, additional studies must also be conducted to better understand this correlation.

The authors emphasize that psychiatric symptoms can be used as a key to make an earlier diagnosis.

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CYSTIC DILATION OF THE *VENTRICULUS TERMINALIS*

DILATAÇÃO QUÍSTICA DO VENTRÍCULO TERMINAL

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ABSTRACT

The *ventriculus terminalis*, or fifth ventricle, is an ependymal-lined cavity in the conus medullaris and is formed during embryogenesis. It may be present in childhood, but it is very rare in adulthood.

Cystic dilation of the *ventriculus terminalis*, whose pathogenesis has not yet been defined, may occur in adults presenting only with pain or even with progressive syndromes of the *conus medularis* or *cauda equina*.

We present the clinical case of a 36-year-old male with progressive weakness of the lower limbs, algic complaints and defective bladder control. The magnetic resonance imaging study revealed a lesion with characteristic features of cystic dilation of the *ventriculus terminalis*. The patient underwent decompressive surgery, with good clinical outcome.

Being a rare pathology with potentially serious consequences, this clinical case is of particular importance because it contributes to its better recognition.

Keywords: *Ventriculus terminalis*, dilation, cyst, neuroradiology.

RESUMO

O ventrículo terminal, ou quinto ventrículo, é uma cavidade no cone medular, revestida por células ependimárias, que se forma durante a embriogénese. Pode estar presente na infância, sendo muito rara na idade adulta.

A dilatação quística do ventrículo terminal, cuja patogénese ainda não se encontra definida, pode manifestar-se em adultos apenas com dor ou até com síndromes progressivas do cone medular ou da cauda equina.

Apresenta-se o caso de um homem de 36 anos com quadro progressivo de diminuição de força dos membros inferiores, queixas álgicas e defeito do controlo miccional.

O estudo imagiológico por ressonância magnética revelou lesão com características típicas de dilatação quística do ventrículo terminal. O doente foi submetido a intervenção cirúrgica descompressiva, com melhoria do quadro.

Sendo uma patologia rara e com consequências potencialmente graves, este caso clínico assume particular importância por contribuir para o melhor reconhecimento da mesma.

Palavras-chave: ventrículo terminal, dilatação, quisto, neurorradiologia.

INTRODUÇÃO

O ventrículo terminal é a designação dada à alteração congénita que consiste no aparecimento de uma pequena cavidade ependimária quística oval no cone medular, preenchida por líquido cefalorraquidiano (LCR) [1]. Esta forma-se durante a embriogénese como resultado da canalização e diferenciação regressiva da medula espinhal [2]. Foi descrito pela primeira vez em 1859 por Stilling como um simples alargamento do canal central. Em 1875, Krause descreveu-o como uma cavidade revestida por epitélio denominando-o "quinto ventrículo".

A sua prevalência é de 2,6% na população pediátrica com menos de cinco anos [3]. No entanto, a sua persistência na idade adulta é muito rara, estando descritos na literatura, até ao momento atual, cerca de 46 casos [4].

Estas lesões são apenas identificáveis histologicamente como cavidades simples, preenchidas por LCR e revestidas por tecido ependimário, sem gliose nem células neoplásicas. Podem ser visualizadas por métodos de imagem neurorradiológicos quando sofrem alterações que desencadeiam a sua dilatação, sendo que, uma vez identificados tendem a regredir ou a manter-se estáveis dimensionalmente. Atualmente, estes mecanismos de dilatação não se encontram bem documentados e são muito raros na idade adulta, havendo referência a alargamentos em contexto pós-traumático, hemorragias meníngeas ou deformidades do canal vertebral [1,5].

São na maioria dos casos, achados acidentais e não requerem tratamento, exceto se sintomáticos. A cirurgia descompressiva é, normalmente, o método terapêutico de escolha e a drenagem simples do quisto é, frequentemente, segura e eficaz [1,6].

Este trabalho tem como objetivo a apresentação de um caso clínico de alargamento quístico do ventrículo terminal, num doente sintomático.

APRESENTAÇÃO DO CASO

Homem de 36 anos, sem antecedentes médicos relevantes, recorreu ao serviço de urgência com quadro de diminuição da força nos membros inferiores com cerca de 6 meses de evolução, mas com agravamento marcado e progressivo nos últimos 3 meses e queixas álgicas dos membros inferiores.

Quando questionado referiu que a diminuição da força era proximal e associada a diminuição do volume muscular da coxa esquerda, queixas de gonalgia bilateral e dificuldades na extensão da perna, que se traduziam por quedas frequentes, disfunção eréctil, hesitação miccional, mas sem alterações do trânsito intestinal nem queixas sensitivas.

Ao exame físico objetivou-se atrofia das massas musculares da face anterior da coxa, diminuição do tónus e da força muscular proximal do membro inferior esquerdo (2/5 na escala Medical Research Council), diminuição dos reflexos ósteo-tendinosos rotuliano e aquiliano ipsilaterais, sem alteração da força muscular no membro inferior direito. Evidenciou-se hipostesia álgica e térmica com distribuição em sela, predominantemente do lado esquerdo, não se detetando alterações da sensibilidade táctil, proprioceptiva e vibratória noutras localizações. Os reflexos cutâneos abdominais permaneciam presentes.

Realizou estudo imagiológico do neuro-eixo por ressonância magnética, que revelou, no estudo da coluna dorso-lombo-sagrada, lesão com características quísticas em topografia intracanalar intramedular localizada ao nível de D_{11}-D_{12} (na região do cone medular). Apresentava evolução de sinal semelhante à do LCR em todas as ponderações: hipossinal nas imagens ponderadas em T1 e hipersinal em T2. Os seus contornos eram regulares e os limites bem definidos, com uma configuração grosseiramente ovalar no plano sagital e condicionado efeito de massa, laminando o parênquima medular à periferia. Nas imagens adquiridas após administração endovenosa de gadolínio não apresentava áreas de realce anómalo. O restante exame era globalmente normal.

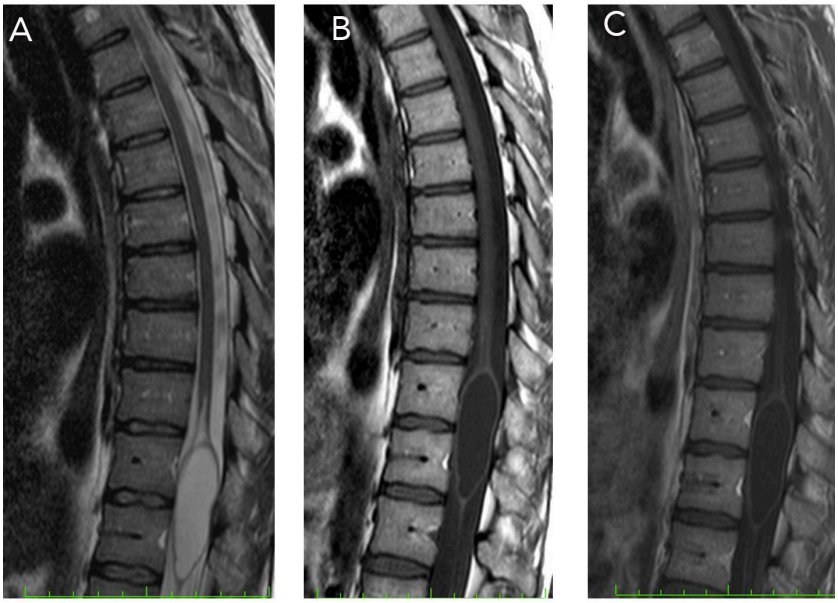

Figura 1 – Estudo por ressonância magnética pré-cirúrgico, no plano sagital. A: imagem ponderada em T2; B: imagem ponderada em T1; C: imagem ponderada em T1 após administração de gadolínio.

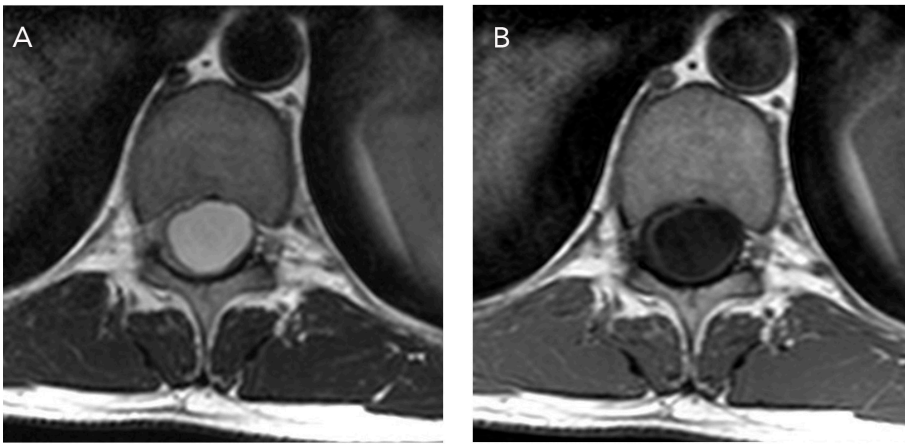

Figura 2 – Estudo por ressonância magnética pré-cirúrgico, no plano axial. A: imagem ponderada em T2; B: imagem ponderada em T1

O doente foi observado por Neurocirurgia que, tendo em conta a sintomatologia e as características típicas encontradas nos estudos imagiológicos, optou por abordagem cirúrgica com esvaziamento da estrutura quística e realização de biópsia da parede. Segundo a equipa cirúrgica, o líquido contido no interior do quisto apresentava características de LCR, não se identificou qualquer tecido anormal sugestivo de tumor e houve colapso imediato da cavidade, dificultando a recolha da amostra tecidual para biópsia.

A análise histopatológica da amostra não revelou evidência de um revestimento por células epiteliais ependimárias ou de outro tipo, pelo que se assumiu inconclusiva.

No pós-operatório imediato o doente apresentou melhorias das queixas álgicas e no estudo por RM realizado nesta altura verificou-se ausência quase completa da lesão quística. À data da alta, o doente apresentava uma evolução neurológica favorável, com melhoria sustentada, não só das queixas álgicas, como também da força muscular, da hiporreflexia e já sem hesitação miccional.

Figura 3 – Estudo por ressonância magnética pós-cirúrgico, no plano sagital. A: imagem ponderada em T2; B: imagem ponderada em T1

DISCUSSÃO E CONCLUSÃO

O ventrículo terminal ou quinto ventrículo pode ser considerado uma etapa normal do desenvolvimento embrionário da medula espinhal que é caracterizado por 3 fases: neurulação, canalização e diferenciação regressiva [3,5,7].

O processo de neurulação começa às 3 semanas de gestação e leva à formação do tubo neural através da fusão dos limites laterais da placa neural, ao nível do terceiro e do quarto sómitos. A partir deste nível, o processo de fusão progride ao mesmo tempo cefálica e caudalmente, encerrando por volta das 23 e 26 semanas, respetivamente. O processo completa-se às 4 semanas e está na origem da maioria da medula espinhal.

As fases seguintes de canalização e diferenciação regressiva dão origem ao cone medular, *filum* terminal e ventrículo terminal através da formação de um segundo tubo neural distal. Esta estrutura tem origem na vacuolização de agregados celulares indiferenciados formados a partir da fusão da notocorda com neuro-epitélio, caudalmente ao neuroporo posterior [5,8].

A coalescência dos vacúolos leva à formação de um tubo revestido por células ependimárias que normalmente se funde com o canal central. A etapa final é caracterizada por um processo de necrose que resulta na dilatação da porção deste canal ependimário, que se encontra no cone medular formando o quinto ventrículo e a estrutura fibrosa denominada *filum* terminal [5].

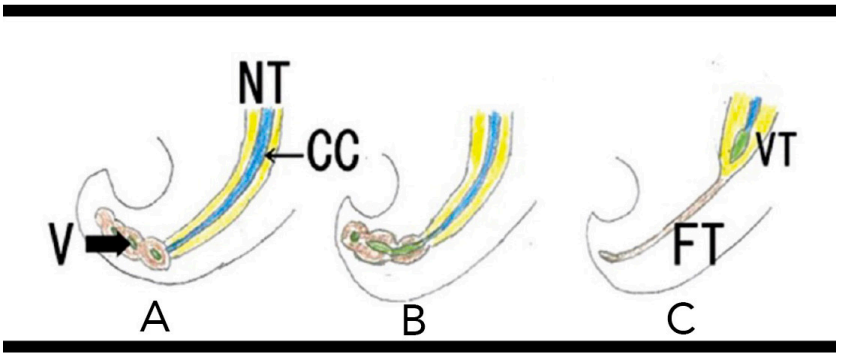

Figura 4 – (adaptada de [8]) Desenvolvimento embrionário da extremidade distal da medula espinhal (CC: canal central, NT: tubo neural); A – vacuolização: pequenos vacúolos (V, a verde) formam-se na massa celular caudal (a castanho); B – canalização: vacúolos fundem-se e formam um tubo revestido por células ependimárias que está em continuidade com o canal central; C – diferenciação regressiva: o canal ependimário dilatado dá origem ao ventrículo terminal (FT = *filum* terminal).

Assim, uma dilatação quística do ventrículo terminal representa uma falha na regressão do ventrículo terminal e as possíveis etiologias podem ser congénitas, traumáticas ou isquémicas.[8, 9] Parece haver uma associação entre esta dilatação quística nas crianças e todo o espectro de disrafismo e medula ancorada, mas a causa exata ainda não foi determinada e, uma vez que se trata de uma condição rara na idade adulta, as associações são difíceis de confirmar [6,8].

O diagnóstico destas lesões passava, antes do advento das técnicas de neuroimagem, em particular da RM, pela cirurgia para exclusão de eventual lesão tumoral como causa de expansão do cone medular [10]. A maior disponibilidade desta técnica de aquisição de imagem tornou a identificação deste tipo de patologia mais fácil, não sendo mandatória a investigação cirúrgica possibilitando a monitorização clínica e *follow-up* imagiológico [9].

Nestes estudos imagiológicos, a dilatação quística do ventrículo terminal surge como uma lesão quística no cone medular, bem circunscrita, sem realce após administração endovenosa de contraste paramagnético – gadolínio. Este quisto apresenta intensidade de sinal semelhante ao do LCR em todas as sequências [3,9]. Não são frequentemente identificadas outras anomalias de sinal da medula espinhal, contudo, está descrito em alguns casos a presença de edema medular [11]. Na ausência de extensão cranial para além da região do cone medular, que indicaria hidrosiringomielia, estes achados são consistentes com a dilatação quística do ventrículo terminal. O diagnóstico diferencial inclui tumores, tais como ependimoma, astrocitoma, oligodendroglioma e hemangioblastoma, mas a grande maioria das lesões neoplásicas apresentaria realce de contraste. Ainda assim, sempre que possível e dada a escassez de informação disponível sobre este tipo de lesões, não se devem excluir as lesões tumorais apenas pela ausência de realce já que há descrição de um caso de lesão quística intramedular do cone sem realce de contraste, cuja histologia provou tratar-se de um astrocitoma [9,11].

Doentes sem sintomas ou com queixas lombares não específicas estáveis devem ser tratados de forma conservadora. Aqueles que apresentam défices neurológicos focais devem ser abordados cirurgicamente. Existem, atualmente, várias abordagens cirúrgicas que podem ir desde a aspiração percutânea do quisto, passando pela fenestração com excisão de uma "janela" com ou sem drenagem subaracnoide [8] ou criação de shunt entre a lesão e o espaço subaracnoide [4], até à drenagem simples do quisto [6].

Em conclusão, apresentamos um caso de dilatação quística do ventrículo terminal, patologia rara na idade adulta, em que os aspetos imagiológicos na ressonância magnética são patognomónicos: lesão quística no cone medular, bem circunscrita, sem realce nas imagens após gadolínio e com intensidade de sinal semelhante ao do LCR em todas as sequências. Tradicionalmente o diagnóstico deste tipo de lesões era feito com recurso à histopatologia mas a presença de uma lesão com estas características imagiológicas, num doente sintomático, deve ser considerada descompressão cirúrgica com drenagem simples do quisto, intervenção segura e eficaz [6].

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NON-CARDIAC THORACIC PAIN: A CASE REPORT

DOR TORÁCICA NÃO CARDÍACA: A PROPÓSITO DE UM CASO CLÍNICO

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ABSTRACT

Non-cardiac thoracic pain, namely of musculoskeletal origin, is highly prevalent particularly in the context of the non-urgent medical evaluation. However, the diagnosis isn't always straightforward requiring the integration of clinical data with information relating to professional activity, hobbies, habits and, in some cases, further imaging studies.

We report the case of a 30-year-old female worker, with a BMI of 19 Kg/m2 and without any relevant clinical priors, who had been suffering for weeks of thoracic pain unresponsive to analgesic therapy. After several admissions to the emergency department, without clarification of origin, she sought the Occupational Health Service for help.

It was only after a chest CT scan that a fracture of the postero-internal margin of the 3rd left rib was discovered which required the eviction or adaptation of some tasks in order to allow the complaints to subside.

Keywords: thoracic pain, rib fracture, fitness for work.

RESUMO

A dor torácica não cardíaca, nomeadamente a de origem músculo-esquelética, tem uma elevada prevalência, principalmente fora do contexto de avaliação médica não urgente. No entanto, o diagnóstico nem sempre é linear, necessitando de integrar informação relativa a dados clínicos, à atividade profissional, a possíveis hobbies e hábitos e, em alguns casos, ao recurso a estudos imagiológicos mais especializados ou dirigidos.

Descreve-se o caso de uma trabalhadora de 30 anos de idade, não fumadora, índice de massa corporal (IMC) de 19 Kg/m2, sem antecedentes pessoais relevantes, que recorre ao Serviço de Saúde Ocupacional por dor torácica com algumas semanas de evolução e com vários atendimentos em urgências, sem se conseguir apurar a origem da dor e sem resposta à analgesia. Só após a realização de tomografia torácica foi possível evidenciar fratura na vertente interna posterior do 3º arco costal esquerdo, tendo sido necessária a evicção de algumas tarefas e o posterior ajuste de outras para favorecer a recuperação das queixas.

Palavras-chave: dor torácica, fratura costal, aptidão para o trabalho.

INTRODUÇÃO

A dor torácica apresenta um amplo leque etiológico, algumas das quais poderão incluir situações ameaçadoras para a vida, enquanto outras têm um comportamento benigno. Doenças do coração, aorta, pulmões, esófago, mediastino, pleura, entre outras, podem causar dor torácica [1,2].

Embora as condições que afetam as estruturas músculo-esqueléticas da parede torácica estejam entre as causas mais comuns de dor torácica, particularmente de desconforto frequentemente descrito como dor torácica atípica ou não cardíaca, a determinação da causa que lhe está associada representa, algumas vezes, um verdadeiro desafio diagnóstico [3]. Essa dor poderá ter um grande impacto na qualidade de vida dos pacientes e associar-se a um aumento muito significativo da utilização dos serviços de saúde.

Reconhecer precocemente a origem músculo-esquelética da dor torácica, constitui um elemento importante na abordagem eficiente e específica da dor em doentes com estas condições [3].

Os autores relatam o caso de uma trabalhadora observada no Serviço de Saúde Ocupacional com dor torácica não cardíaca, no contexto de fratura costal sem história de traumatismo recente.

APRESENTAÇÃO DO CASO

Trabalhadora do sexo feminino, de trinta anos de idade, técnica de diagnóstico e terapêutica, consultou o serviço de Saúde Ocupacional por dor torácica à esquerda de cinco semanas de evolução, de início súbito, que iniciava no ápex e irradiava à grelha costal posterior e omoplata, sem referir história recente de traumatismo ou de sintomas compatíveis com infecção respiratória. A dor agravava com a respiração profunda e com os movimentos dos membros superiores realizados acima do nível dos ombros, o que limitava a sua atividade profissional.

Caracterização da atividade profissional: encarregada do manuseamento e verificação dos equipamentos de radioterapia (alguns com componentes que ficam acima do nível dos ombros), do posicionamento/imobilização dos doentes e a execução dos tratamentos de radioterapia previamente aprovados.

Recorreu por quatro vezes aos serviços de urgência de dois hospitais onde, para além da avaliação clínica, realizou vários eletrocardiogramas, radiografias do tórax e análises clínicas (incluindo enzimas cardíacas), que não revelaram alterações significativas. Posteriormente foi avaliada em consulta de fisiatria e colocada a hipótese de eventual dor neuropática.

A trabalhadora nunca foi fumadora e não havia nada de relevante nos seus antecedentes pessoais ou familiares. À data da consulta no Serviço de Saúde Ocupacional, encontrava-se medicada com anti-inflamatórios, pregabalina e vitamina B12, sem melhoria das queixas. Negava outros sintomas para além da dor e não se recordava ter sofrido qualquer traumatismo torácico à data da instalação da dor.

À observação, a trabalhadora apresentava-se eupneica, apirética, tinha um IMC de 19 Kg/m2, a expansão do tórax era simétrica, sem pontos dolorosos à palpação, sem crepitações ou sinais de enfisema subcutâneo e sem lesões na pele. A auscultação cardíaca e pulmonar era normal. Apresentava aumento

das queixas álgicas com a extensão do membro superior esquerdo e a elevação do mesmo acima do nível do ombro.

Perante o tempo de evolução da dor, a limitação para o desenvolvimento da sua atividade profissional, a falta de achados clínicos concretos, a normalidade dos exames complementares e análises clínicas e a fraca resposta à medicação instituída, foi requisitada tomografia axial computorizada do tórax a qual revelou a existência de solução de continuidade compatível com traço fraturário, já com esboço de formação de calo ósseo, na vertente interna posterior do 3º arco costal esquerdo (figuras 1 e 2). Não se observaram alterações pulmonares relevantes.

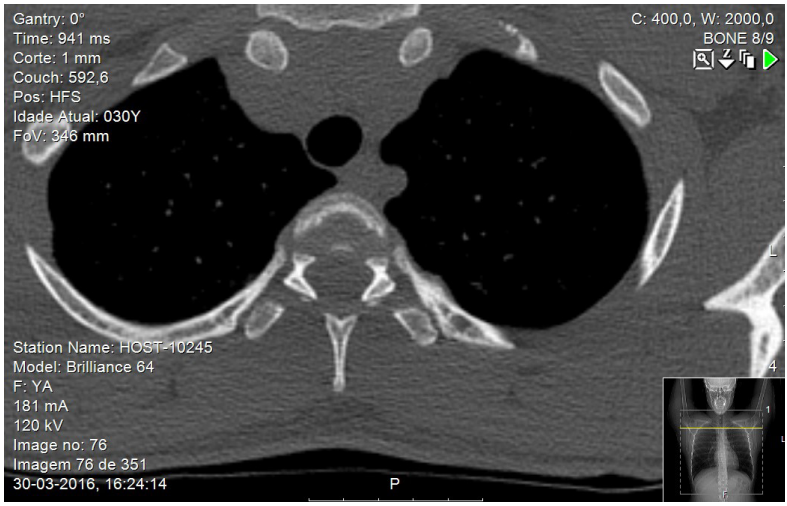

Figura 1 – Corte axial da tomografia computorizada – Calo ósseo.

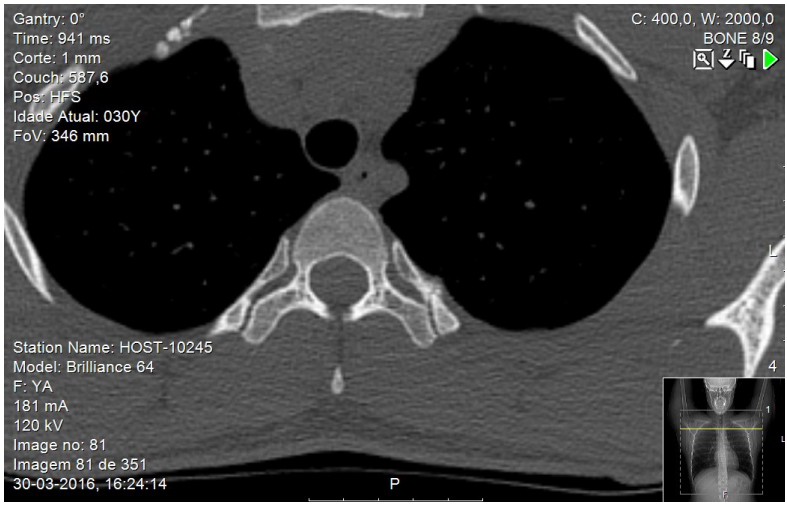

Figura 2 – Corte axial da tomografia computorizada – Traço fraturário.

Inicialmente foi sugerida incapacidade temporária para o trabalho e reforço da analgesia e, posteriormente, aptidão condicionada temporária para o trabalho, onde se limitaram as tarefas com movimentos dos membros superiores acima do nível dos ombros. Durante o seguimento do caso, não houve necessidade adicional de recorrer ao serviço de urgência, mas só passadas doze semanas após o esclarecimento do diagnóstico, a trabalhadora referiu melhoria significativa da dor. Foi excluído o diagnóstico de fratura associada a lesão secundária.

DISCUSSÃO

A dor torácica com duração de dias a semanas é um sintoma frequente e de etiologia muito variada. Apesar da localização e da caracterização da dor, dos sinais e sintomas que lhe podem estar associados, dos fatores desencadeantes e/ou agravantes poderem orientar o diagnóstico, o esclarecimento da sua etiologia não é, muitas vezes, linear. Estudos indicaram que as causas mais frequentes de dor torácica são causas não cardíacas, podendo envolver sistemas como o respiratório, o gastrointestinal, o músculo-esquelético, ou ser uma manifestação psicológica [1-4]. Esta diversidade de possibilidades etiológicas, entretanto, não torna menos importante o seu esclarecimento, dado que a causa subjacente pode necessitar de um tratamento dirigido, estabelecer um prognóstico ou, como no nosso caso, adaptar a atividade profissional à situação de saúde da trabalhadora, limitando as tarefas profissionais (e não só) que possam vir a agravar o quadro clínico ou a atrasar o processo de recuperação [5].

Estudos têm estimado que aproximadamente 30 a 50% dos pacientes com dor torácica observados fora dos serviços de urgência sofrem de dor torácica músculo-esquelética, 10 a 20% têm causas gastrointestinais, 10% apresentam angina estável, 5% têm condições respiratórias e aproximadamente 2 a 4% têm isquémia miocárdica aguda (incluindo enfarte do miocárdio) [1].

A etiologia da dor torácica é multivariada e inclui causas não isquémicas (dissecção da aorta, insuficiência cardíaca, pericardite ou miopericardite, estenose mitral), pulmonares (trombo-embolismo pulmonar, pneumotórax, pneumonia, pleurite, neoplasias), gastrointestinais (esofagite, refluxo gastroesofágico), músculo-esqueléticas (costo-condrite, artrite reumatoide, fibromialgia, fratura dos arcos costais), psiquiátricas (ataques de pânico) e outras (relacionada com consumo de substâncias, dor referida, herpes zóster) [1]. Na origem músculo-esquelética da dor, o diagnóstico baseia-se na capacidade de reproduzir a dor pela palpação das áreas dolorosas, fenómeno que, no nosso caso, não foi possível evidenciar, provavelmente pela localização da lesão. Por outro lado, a ausência de história de traumatismo direto ou indireto dificultou o diagnóstico etiológico precoce da toracalgia.

Perante uma situação de dor torácica, designadamente de etiologia músculo-esquelética, a reabilitação do doente poderá implicar, para além do tratamento médico, a adaptação temporária da atividade profissional. Assim, a caracterização das tarefas e das suas exigências específicas são fundamentais para que essa adaptação possa ser efetuada, permitindo a recuperação clínica e funcional dos trabalhadores.

CONCLUSÃO

A avaliação inicial do doente com dor torácica visa excluir as condições que poderão colocar a vida em perigo. No entanto, a avaliação fora do contexto de urgência, deve ponderar as outras causas mais frequentes. O esclarecimento sobre a sua etiologia permite uma intervenção mais dirigida, não só farmacológica, como também laboral, que é muito importante para a recuperação. Assim, a evicção e/ou o ajuste temporário de determinadas tarefas que podem agravar a dor estão claramente recomendadas.

Embora a origem músculo-esquelética da dor torácica seja muito frequente e de fácil diagnóstico na maioria dos casos, o recurso a diferentes estudos imagiológicos pode ser necessário perante situações que não cedem ao tratamento médico.

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ACUTE HEMORRHAGIC EDEMA OF INFANCY – IS IT AN EASY DIAGNOSIS?

EDEMA HEMORRÁGICO AGUDO NA INFÂNCIA – UM DIAGNÓSTICO SIMPLES?

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ABSTRACT

Acute hemorrhagic edema of infancy (AHEI) is a rare acute benign cutaneous leukocytoclastic vasculitis, characterized by fever, purpuric skin lesions and peripheral edema, affecting children younger than 2 years of age.

In this case report, we present two cases of children with 20 and 9 months old diagnosed in *Centro Hospitalar Lisboa Norte – Hospital de Santa Maria*, in 2016 and 2017, respectively. Both presented with fever and purpuric skin lesions after acute upper respiratory tract infection. In the first case with Adenovirus identification.

Since AHEI is a self-limited disease that resolves spontaneously without sequelae, its recognition is crucial for the early diagnosis avoiding unnecessary investigations and treatments.

Keywords: acute hemorrhagic edema of infancy, leukocytoclastic vasculitis, purpura, infancy.

RESUMO

O edema hemorrágico agudo da infância é uma doença rara que, consequentemente, se torna um desafio diagnóstico. É uma vasculite leucocitoclástica cutânea aguda, benigna, caracterizada pelo aparecimento de febre, lesões purpúricas e edema das extremidades, que atinge crianças com idade inferior a 2 anos.

Apresentamos dois casos de crianças de 20 e de 9 meses de idade, diagnosticados no Centro Hospitalar Lisboa Norte – Hospital de Santa Maria, nos anos de 2016 e 2017, respectivamente, caracterizados por febre associada a lesões de púrpura palpável após infeção respiratória alta, no primeiro caso com identificação de *Adenovírus*.

O reconhecimento desta entidade torna-se importante para o diagnóstico precoce, evitando investigação ou tratamentos desnecessários, dado o curso autolimitado e ausência de sequelas associadas.

Palavras-chave: edema hemorrágico agudo da infância, vasculite leucocitoclástica, púrpura, infância.

INTRODUÇÃO

O edema hemorrágico agudo da infância (EHAI) é uma doença rara que, consequentemente, se torna um desafio diagnóstico. Foi descrita pela primeira vez, em 1913, como uma variante da Púrpura de Henoch-Schonlein, sendo atualmente considerada uma entidade distinta [1]. É uma vasculite leucocitoclástica cutânea aguda, benigna, que atinge crianças com idade inferior a 2 anos, caracterizada pela tríade de febre, edema e lesões cutâneas purpúricas localizadas preferencialmente na face, pavilhões auriculares e extremidades. A sua etiologia permanece desconhecida, no entanto, estão descritos alguns fatores desencadeantes, nomeadamente infeções virais (respiratórias altas, gastroenterite aguda) e bacterianas, a vacinação e fármacos. Ocorre mais frequentemente no inverno, o que suporta a sua ligação com infeções virais, tendo predominância no sexo masculino (rácio sexo masculino-feminino de 4,6:1) [2].

Apresentamos dois casos de crianças de 20 e de 9 meses diagnosticados no Hospital de Santa Maria - Centro Hospitalar Lisboa Norte (HSM-CHLN), nos anos de 2016 e 2017, respectivamente, caracterizados por febre associada a lesões de púrpura palpável após infeção respiratória alta, no primeiro caso com identificação de Adenovírus. Pretende-se com estes dois casos clínicos dar a conhecer o EHAI, especialmente aos pediatras, passando a incluí-lo no diagnóstico diferencial de púrpura cutânea aguda na infância, permitindo eliminar investigações e terapêuticas desnecessárias, dado o curso benigno desta patologia.

APRESENTAÇÃO DOS CASOS

Caso 1

Criança de 20 meses, sexo feminino, previamente saudável, que iniciou quadro caracterizado por tosse seca e rinorreia mucosa com 4 dias de evolução. No quarto dia de doença iniciou febre baixa. Ao sétimo dia de doença, por hiperémia conjuntival e exantema dos membros e pavilhões auriculares, recorreu ao serviço de urgência (SU). À observação apresentava bom estado geral; hiperémia conjuntival, sem exsudado, com discreto edema palpebral esquerdo; pequena adenopatia pré-auricular esquerda; exantema purpúrico atingindo as extremidades e pavilhões auriculares bilateralmente e discreto edema dos pés (figura 1).

As análises revelaram: hemoglobina (Hb) de 11 g/dL; leucócitos de 21.300/mL (70% neutrófilos, 7% eosinófilos, 18% linfócitos); plaquetas 630.000/mL; proteína C-reactiva (PCR) de 3,5 mg/dL; restante bioquímica, coagulação e urina tipo II sem alterações. Foi identificado *Adenovírus* na pesquisa de vírus respiratórios por *polymerase chain reaction* no exsudado nasal.

Ao décimo quarto dia de doença, foi reavaliada em consulta de Infecciologia Pediátrica, apresentando-se assintomática, com resolução espontânea das lesões cutâneas, sem outras alterações ao exame objectivo.

A análise histopatológica da amostra não revelou evidência de um revestimento por células epiteliais ependimárias ou de outro tipo, pelo que se assumiu inconclusiva.

Figura 1 – Lesões cutâneas ao exame físico

No pós-operatório imediato o doente apresentou melhorias das queixas álgicas e no estudo por RM realizado nesta altura verificou-se ausência quase completa da lesão quística. À data da alta, o doente apresentava uma evolução neurológica favorável, com melhoria sustentada, não só das queixas álgicas, como também da força muscular, da hiporreflexia e já sem hesitação miccional.

Caso 2

Lactente de 9 meses, sexo masculino, aparentemente bem até seis dias antes da vinda ao SU, altura em que iniciou quadro de febre baixa, rinorreia mucosa e diarreia. Seis dias após o início do quadro, surgiu um exantema das extremidades e da face, apresentando nesta altura febre mais intervalada. Foi observado no mesmo dia no SU, onde se objetivou bom estado geral, lesões papulares eritematosas urticariformes na face, dorso das mãos e membros inferiores. Analiticamente apresentava: Hb de 11,4 g/dL; Leucócitos 10.050/mL (44% de neutrófilos e 42% de linfócitos); Plaquetas 282.000/mL; PCR de 5,25 mg/dL; restante bioquímica e Urina II sem alterações. Realizou radiografia de tórax que revelou reforço brônquico bilateral, sem outras alterações pleuroparenquimatosas.

Teve alta para o domicílio com indicação para reavaliação no dia seguinte, tendo regressado, no entanto, menos de 12 horas depois, durante a madrugada, por irritabilidade e edema marcado dos pavilhões auriculares, mãos e pés. Ao exame objetivo apresentava alguma irritabilidade, pressão arterial (PA) 103/50 mmHg, frequência cardíaca (FC) de 115 bpm, saturação periférica de oxigénio (SpO_2) de 96% em ar ambiente e temperatura timpânica (Tt) de 36,9ºC; edema dos pavilhões auriculares, mãos, antebraços e pés, com progressão do exantema, poupando apenas tronco e períneo (figura 2). Fez nova avaliação analítica que se revelou sobreponível.

Figura 2 – Dia 1 de exantema e edema

Neste contexto, por suspeita de angioedema com rápida progressão das lesões cutâneas e edema das extremidades, fez adrenalina intramuscular e prednisolona 10 mg *per os*, sem efeito.

Ficou em vigilância no serviço de observação (SO), onde foram observadas as lesões purpúricas nas localizações anteriormente descritas (figura 3).

Figura 3 – Dia 2 de exantema e edema

Após discussão do caso clínico com a Infecciologia Pediátrica, foi feito o diagnóstico de EHAI e tranquilizados os pais.

Ao 17º dia de doença, foi reavaliado em Consulta de Infecciologia Pediátrica, apresentando-se nessa altura assintomático, com resolução quase total das lesões cutâneas e total do edema, persistindo apenas algumas máculas numulares rosadas em involução (Figura 4).

Figura 4 – 17º dia de doença

DISCUSSÃO

Os dois casos clínicos relatados são típicos, tendo sido ambos precedidos por infeção respiratória alta, no primeiro caso com identificação de Adenovírus, não tendo sido feitas outras investigações etiológicas.

O EHAI já foi descrito na literatura com inúmeros nomes e epónimos, nomeadamente Doença de Finkelstein, Doença de Seidlmayer e Púrpura em medalhão com edema, entre outros.

É caracterizado pela tríade clássica de febre, púrpura e edema. Geralmente, a criança apresenta bom estado geral, sem ar doente, apesar da progressão rápida e impressionante da doença.

A febre é frequentemente baixa, havendo casos de EHAI afebril descritos na literatura. O edema é mole, sem godet, e atinge preferencialmente as orelhas, face e extremidades, podendo estar presente noutras localizações como a pálpebras, lábios ou testículos. A púrpura é o achado mais consistente. As lesões cutâneas iniciam-se por máculas/pápulas eritematosas ou placas urticariformes que progridem rapidamente para lesões purpúricas em forma de medalhão, com atingimento preferencial da face e extremidades, tendencialmente simétrico, mas podendo atingir qualquer parte da pele, poupando geralmente as mucosas [1-5].

Nestes dois casos não verificámos manifestações extra-cutâneas, como hematúria, proteinúria, dor abdominal ou artralgias, sendo estas raras e transitórias quando presentes.

A maioria dos testes laboratoriais são inespecíficos e não-diagnósticos, podendo ser úteis apenas na exclusão de outras patologias se houver incerteza quanto ao diagnóstico de EHAI. Pode existir leucocitose, com linfocitose ou eosinofilia, trombocitose e aumento dos parâmetros inflamatórios (proteína C-reativa e/ou velocidade de sedimentação). A análise da urina é, geralmente, normal, embora possa surgir transitoriamente proteinúria ou hematúria, sem lesão renal associada [3,4].

Histologicamente, o EHAI é caracterizado por vasculite leucocitoclástica, limitada aos pequenos vasos da derme. Os estudos de imunofluorescência direta são tipicamente negativos, mas podem ser positivos para fibrinogénio, complemento C3, C1q, imunoglobulina G, M, E ou até A [2]. A ausência de

deposição de imunoglobulina A é pertinente para a diferenciação do EHAI com a Púrpura de Henoch-Schonlein, uma vez que no primeiro a deposição de IgA ocorre apenas numa minoria dos casos, comparativamente com o último em que a deposição de IgA é habitual [2]. No entanto, a biópsia cutânea não está recomendada – pela invasividade e ausência de impacto na atitude terapêutica.

Embora a etiologia do EHAI não seja bem compreendida, vários autores consideram-na uma vasculite mediada por imunocomplexos [5], na grande maioria precedida por um período prodrómico sugestivo de infeção viral ou, menos frequentemente, infeção bacteriana, vacinação ou medicação.

O diagnóstico desta entidade é clínico, baseado na idade de aparecimento, morfologia e distribuição das lesões cutâneas, presença de edema, infeção prévia, bem como ausência de manifestações sistémicas.

O diagnóstico diferencial de lesões cutâneas purpúricas é amplo, abrangendo desde doenças agudas potencialmente fatais a doenças benignas e autolimitadas. Os diagnósticos diferenciais do EHAI incluem Púrpura de Henoch-Schonlein, Urticária Aguda, Eritema Multiforme, Meningococémia, Doença de Kawasaki, Toxidermia, entre outros [4,5].

Não existe terapêutica comprovadamente eficaz, pelo que o uso de corticoides e de anti-histamínicos é controverso, não parecendo alterar a história natural da doença [6].

Com ou sem tratamento, o EHAI geralmente resolve completamente em 1 a 3 semanas, sem sequelas, apresentado portanto um excelente prognóstico [5-7].

No segundo caso, a rapidez de instalação e a exuberância do quadro clínico levaram à instituição de medidas diagnósticas e terapêuticas a posteriori consideradas excessivas. No entanto, em ambos os casos a evolução clínica foi excelente, com recuperação espontânea num curto período de tempo.

CONCLUSÃO

A raridade e o desconhecimento desta entidade pode levar ao seu subdiagnóstico ou ao uso excessivo de exames complementares bem como atitudes terapêuticas desnecessárias.

De facto, as manifestações clínicas do EHAI parecem dramáticas, podendo levar a pensar, erradamente, numa doença grave.

O reconhecimento desta entidade torna-se, assim, importante para o diagnóstico precoce, evitando investigação ou tratamentos desnecessários, dado o curso autolimitado e ausência de sequelas associadas.

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BILATERAL OPTIC NEURITIS IN THE SETTING OF NEUROMYELITIS OPTICA: CLINICAL, IMAGING AND ELECTROPHYSIOLOGICAL FEATURES

NEVRITE ÓTICA BILATERAL NO CONTEXTO DE NEUROMIELITE ÓTICA: CARACTERÍSTICAS CLÍNICAS, IMAGIOLÓGICAS E ELETROFISIOLÓGICAS

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ABSTRACT

Neuromyelitis Optica (NMO), or Devic's disease, is a rare inflammatory autoimmune disease of the central nervous system that preferentially targets the optic nerves and spinal cord, differentiated from Multiple Sclerosis by imaging and laboratorial features, and response to treatment. We report a case of NMO in a 33 year-old female patient that presented with simultaneous bilateral optic neuritis with papilitis, with preserved visual acuity, followed by acute myelitis, with almost full recovery with corticotherapy. There was seropositivity for antibody against myelin oligodendrocyte glycoprotein, which is present in some seronegative patients for antibody against aquaporin 4, the most frequent in this disease. The purpose of this study is to describe the most common aspects of NMO and the specific features of this clinical case, seeking to raise awareness of this disease and its early diagnosis.

RESUMO

A Neuromielite Ótica (NMO), ou Doença de Devic, é uma doença inflamatória autoimune do sistema nervoso central rara, que afeta preferencialmente os nervos óticos e a medula, com aspetos imagiológicos, laboratoriais e de resposta ao tratamento que a distinguem da Esclerose Múltipla. Neste trabalho relata-se um caso de uma doente de 33 anos que apresentou um quadro clínico de nevrite ótica bilateral com papilite, sem diminuição da acuidade visual, seguida de mielite aguda, com recuperação quase total do quadro com corticoterapia. Apresentava seropositividade para o anticorpo anti-glicoproteína da mielina do oligodentrócito, o que pode ocorrer em alguns doentes seronegativos para o anticorpo anti-aquaporina 4, o mais frequente nesta patologia. O objetivo deste trabalho é descrever os aspetos mais frequentes da NMO e as especificidades deste caso clínico, procurando sensibilizar para a existência desta doença e o seu diagnóstico precoce.

INTRODUÇÃO

A Neuromielite Ótica (NMO), ou Doença de Devic, é uma doença inflamatória autoimune grave do sistema nervoso central (SNC), que afeta predominantemente os nervos óticos e a espinal medula, com curso monofásico ou recidivante. É uma doença rara, geralmente esporádica, com prevalência estimada de 0.51-4.4/100000 [1]. Inicialmente classificada como subtipo de Esclerose Múltipla (EM), atualmente é reconhecida como uma doença distinta, embora também tipicamente recidivante (80-90% dos casos), mas com características clínicas, laboratoriais, imagiológicas e de resposta ao tratamento que as diferenciam. O seu aspeto mais distinto é a presença de anticorpo contra o canal aquoso aquaporina 4 (anti-AQP4), presente nos podócitos dos astrócitos [2]. É mais frequente em mulheres (80-90% dos casos) na quinta década de vida, cerca de 10 anos mais tarde que a idade média na EM [3]. Com a recente descoberta dos anti-AQP4, o espetro de autoimunidade atribuída a este anticorpo foi alargado e as patologias associadas designadas, no seu conjunto, como Doenças do Espetro da Neuromielite Ótica (NMOSD). Os critérios para o seu diagnóstico, recentemente revistos, preconizam a presença de positividade para anti-AQP4 associada à presença de pelo menos uma característica clínica principal, como a nevrite ótica (uni ou bilateral), a mielite aguda (tipicamente longitudinalmente extensa, isto é, com envolvimento de pelo menos 3 segmentos vertebrais contíguos na RM) ou a síndrome da área postrema; é possível definir-se NMOSD com anti-AQP4 negativos, contudo é necessária a ocorrência de pelo menos 2 características clínicas principais (em diferentes áreas neuroanatómicas), e a presença de lesões na RM compatíveis com os respetivos fenótipos típicos [4]. Em alguns doentes seronegativos para anti-AQP4 com critérios de NMOSD, o anticorpo anti-glicoproteína da mielina do oligodendrócito (anti-MOG) pode estar presente, normalmente com curso clínico monofásico e, consequentemente, um melhor prognóstico [5,6]. A nível neuroftalmológico, a NMO apresenta-se frequentemente com nevrite ótica bilateral, ao contrário do que acontece na EM, e a acuidade visual é geralmente mais afetada e com menor probabilidade de recuperação [7].

O objetivo deste trabalho é a descrição das características clínicas, imagiológicas e eletrofisiológicas de um caso clínico de NMO.

APRESENTAÇÃO DOS CASOS

Doente do sexo feminino de 33 anos, com antecedentes de miopia (-2.75D em ambos os olhos (ODE)), sem outros antecedentes patológicos relevantes, que se apresentou no Serviço de Urgência (SU) de Oftalmologia com quadro de uma semana de evolução de dor retrobulbar bilateral agravada com os movimentos oculares, associada a vómitos e mal-estar geral com algumas horas de evolução. Apresentava acuidade visual corrigida de 10/10 ODE, reflexos pupilares simétricos e motilidade ocular preservada contudo dolorosa. À biomicroscopia não apresentava alterações, e à fundoscopia apresentava discos óticos com limites mal definidos, sobretudo do olho direito. Pelo quadro inicial de possível edema bilateral do disco ótico e vómitos, suspeitou-se de hipertensão intracraniana. Realizou tomografia computorizada crânio-encefálica e das órbitas, que não apresentava alterações significativas, e foi pedida avaliação de Neurologia, onde se considerou tratar-se de um quadro sistémico as-

sociado a provável coexistência de drusen dos discos óticos, pelo que foi orientada para Consulta de Oftalmologia para realização de exames complementares e foi também pedida avaliação de Medicina Interna mas a doente abandonou o SU.

Três dias após a primeira observação, recorreu novamente ao SU por quadro de alteração da sensibilidade dos membros inferiores e região infra-umbilical, retenção urinária e dificuldade na marcha, evidenciando, ao exame neurológico, paraparésia espástica grau 4, hiperreflexia generalizada, hiperestesia e alodínia nos membros inferiores, que fez levantar a hipótese de doença inflamatória do sistema nervoso central, tendo sido internada no Serviço de Neurologia.

Foi realizada punção lombar, com pressão de abertura de 160 mmH_20 e o exame citoquímico do líquido cefalorraquidiano (LCR) revelou a presença de pleiocitose de 80,0 células/mm^3, com predomínio linfocitário, hiperproteinorráquia de 71,5 mg/dL, glicorráquia normal. A pesquisa de vírus neurotrópicos no LCR foi positiva para citomegalovirus (CMV).

Na RM de medula identificavam-se múltiplas áreas intramedulares de hipersinal na ponderação T2 em C5 e C6, C7-D1 e D6-D7 a D7-D8 (figura 1). A RM crânio-encefálica revelou lesões parenquimatosas infracentimétricas hiperintensas em T2 na substância branca frontal justa cortical direita, parietal direita, frontoparietal esquerda e a envolver posteriormente o corno occipital do ventrículo lateral direito e lesão talâmica posterior direita hiperintensa nas sequências de TR longo e hipersinal em T2 FLAIR (Gad) dos sulcos parafalceais esquerdos, do sulco central esquerdo e dos sulcos corticais cerebelosos bi-hemosféricos e do vérmis. Não apresentava reforços anómalos de sinal das paquimeninges e das leptomeninges intracranianas e intrarraquidianas (figura 2).

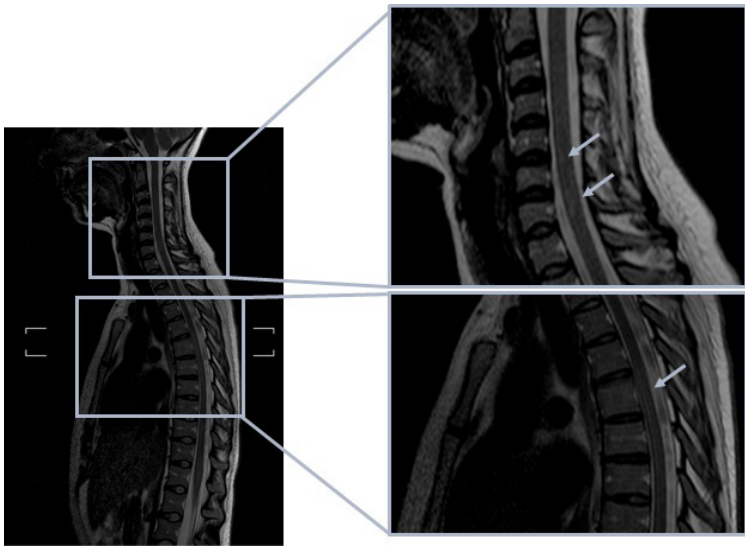


Figura 1 – Ressonância magnética da medula (plano sagital): áreas intramedulares de hipersinal em T2 (setas)

A avaliação analítica revelou seropositividade para o anticorpo anti-MOG e a pesquisa de anticorpos anti-AQP4 foi negativa.

Realizou retinografia (figura 3A) e tomografia de coerência ótica (OCT) da camada de fibras nervosas (CFN) peripapilar (figura 4) que objetivavam elevação bilateral do disco ótico, autofluorescência do fundo ocular e ecografia oftálmica que excluíram a presença de drusen do disco ótico.

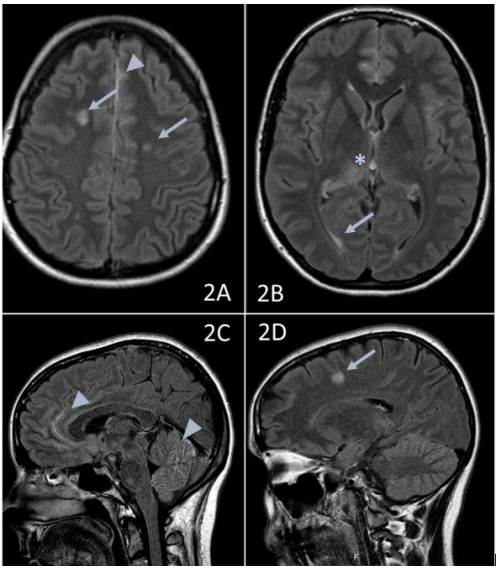


Figura 2 – Ressonância magnética crânio-encefálica: 2A e 2B – planos axiais, ponderação T2 FLAIR; 2C e 2D – planos sagitais, ponderação T2 FLAIR. Lesões parenquimatosas hiperintensas na substância branca subcortical (setas) e talâmica posterior direita (asterisco). Hipersinal dos sulcos parafalceais esquerdos, do sulco central esquerdo e dos sulcos corticais cerebelosos (cabeça de seta).

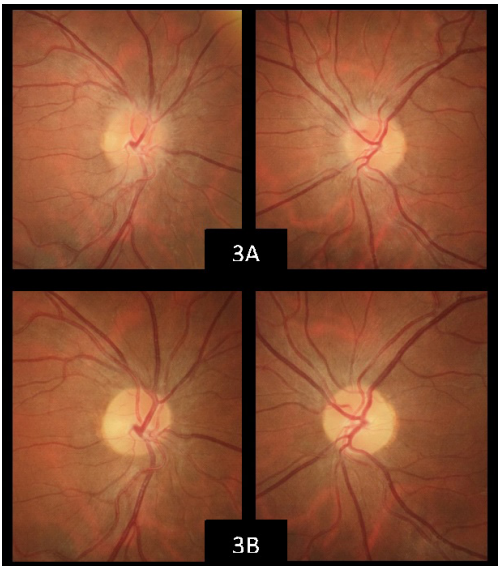


Figura 3 – Retinografia ODE – 3A (4 dias após a apresentação) mostra indefinição do contorno dos discos óticos, sobretudo à direita; 3B (após 6 meses) mostra palidez dos discos óticos, mais evidente à esquerda.

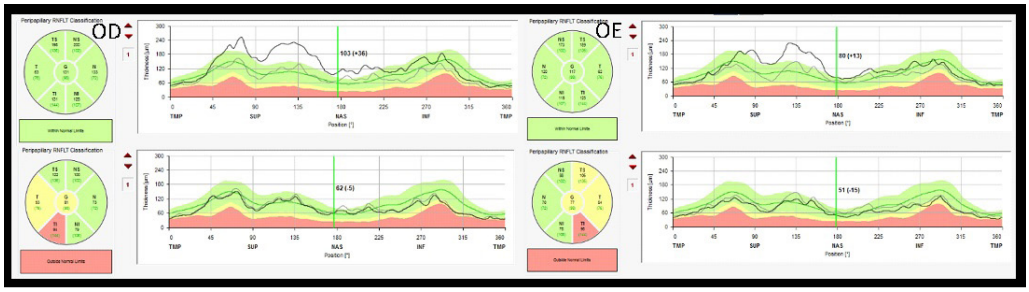
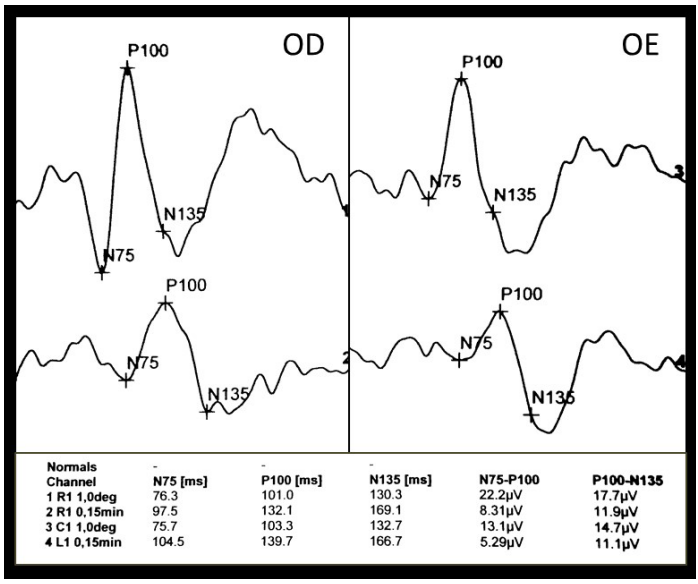


Figura 4 – Tomografia de coerência ótica da camada de fibras nervosas peripapilar ODE: mostra aumento da espessura desta camada ODE 4 dias após a apresentação e diminuição sectorial da espessura após 6 meses

As sucessivas avaliações dos campos visuais, por perimetria estática computorizada (Humphrey 24-2) e da visão cromática (Farnsworth D15) não apresentaram alterações. Apresentava aumento de latência da onda P100 ODE nos potenciais evocados visuais (PEV-*pattern*), traduzindo perturbação bilateral da condução nas vias óticas pré-quiasmáticas (figura 5).



Normals	-	-	-	-	-
Channel	N75 [ms]	P100 [ms]	N135 [ms]	N75-P100	P100-N135
1 R1 1,0deg	76.3	101.0	130.3	22.2µV	17.7µV
2 R1 0,15min	97.5	132.1	169.1	8.31µV	11.9µV
3 C1 1,0deg	75.7	103.3	132.7	13.1µV	14.7µV
4 L1 0,15min	104.5	139.7	166.7	5.29µV	11.1µV

Figura 5 – PEV pattern realizado 2 meses após a apresentação: aumento da latência em OD (132ms) e OE (140ms) e amplitude mais reduzida em OE.

Durante o internamento no Serviço de Neurologia foi medicada com metilprednisolona 1g E.V. durante 5 dias e, posteriormente, prednisolona oral 1 mg/kg/dia, que foi suspensa ao fim de 6 meses após redução progressiva, com recuperação quase total do quadro neurológico, mantendo apenas espasmos tónicos noturnos dos membros inferiores. A nível neuroftalmológico, mantém acuidade visual de 10/10, PEV com perturbação bilateral da condução, sobretudo à esquerda (figura 5), palidez dos discos óticos (figura 3B), perda axonal documentada através de OCT CNF (figura 4) e diminuição da espessura da camada de células ganglionares, detetada por OCT macular (figura 6).

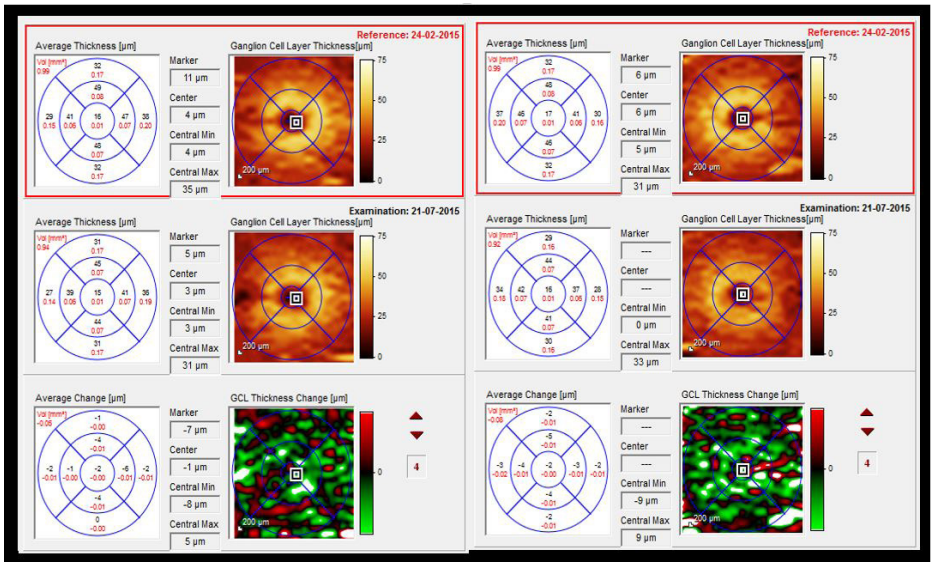


Figura 6 – tomografia de coerência ótica macular com segmentação da camada de células ganglionares ODE: verifica-se diminuição da espessura média desta camada em todos os sectores e redução do seu volume total em ambos os olhos.

DISCUSSÃO E CONCLUSÃO

As nevrites óticas nos adultos são geralmente unilaterais, com diminuição da acuidade visual na maioria dos doentes, movimentos oculares dolorosos, e defeito pupilar aferente relativo do olho afetado. Está frequentemente presente discromatopsia, mais marcada que a diminuição da acuidade visual [7,8]. Neste caso clínico, por se ter apresentado com papilite, e consequente edema do disco ótico bilateral, com vómitos associados, acuidade visual preservada e reflexos pupilares simétricos, foi inicialmente colocada hipótese de hipertensão intracraniana.

O quadro clinico descrito enquadra-se no diagnóstico de NMOSD uma vez que se verificou um quadro clínico de associação de nevrite ótica bilateral, mielite longitudinalmente extensa e lesões cerebrais não compatíveis com o diagnóstico de EM.

A NMO é uma doença inflamatória do SNC semelhante em diversos aspetos clínicos à EM, no entanto, é importante fazer a distinção destas entidades, visto que o prognóstico é diferente e, sobretudo, pelo facto de terapêuticas imunomoduladoras utilizadas no tratamento da EM, como o interferão-beta, poderem mesmo agravar a NMO [7].

A doente apresentava seronegatividade para os anticorpos anti-AQP4, como acontece em cerca de 10-25% do total de doentes com fenótipos de NMO, e seropositividade para o anticorpo anti-MOG. A MOG está presente na superfície externa da bainha de mielina no sistema nervoso central. Atualmente permanece por esclarecer como as imunoglobulinas (Ig) G anti-MOG causam lesões *in vivo*, no entanto, a ligação destas IgG pode resultar em alterações estruturais da mielina. Estes anticorpos

podem estar presentes, não só na NMO, mas também noutras doenças neurológicas, como alguns casos de EM e Encefalomielite Disseminada Aguda (ADEM), e ainda em indivíduos saudáveis [2].

O resultado positivo para CMV na pesquisa de vírus no LCR foi interpretado como falso positivo para infeção aguda a este agente, dado que clinicamente não se justificava esta mesma infeção e porque é relativamente frequente a deteção por PCR de vírus neurotrópicos no LCR (por exemplo o CMV e vírus Epstein-Barr) no contexto de processo inflamatório concomitante ao nível do SNC. Assim sendo, os resultados positivos têm um baixo valor preditivo positivo e requerem uma cuidadosa correlação dos dados clínicos e laboratoriais [10].

Nesta doente, a acuidade visual central, os campos visuais e a visão cromática são normais, o que não é frequente na NMO. No entanto, as sequelas do processo de desmielinização são aparentes pelo aumento da latência da onda P100 nos potenciais evocados visuais bem como pela redução da espessura das CNF peripapilar e camada de células ganglionares da mácula [9].

A nevrite ótica bilateral simultânea, como no caso descrito, é mais frequente na NMO anti-MOG+ do que na NMO anti-AQP4+ ou NMO seronegativa. A presença dos anticorpos anti-MOG está também associada a melhor acuidade visual, a doença monofásica ou com menor número de recidivas e melhor prognóstico [2].

Os doentes com NMO podem apresentar-se em primeiro lugar ao oftalmologista, como no caso descrito, pelo que é importante reconhecer a existência desta patologia uma vez que a recuperação é dependente do intervalo entre o início dos sintomas e a instituição de terapêutica [3]. Deve ser colocada a hipótese de nevrite ótica bilateral no caso de um doente com dor retrobulbar bilateral agravada pelos movimentos oculares e edema do disco ótico, mesmo que a acuidade visual central esteja preservada, e isso deve fazer levantar a suspeita de NMO, sobretudo caso se trate de uma mulher jovem. Apesar de estes doentes serem geralmente tratados no âmbito da Neurologia, o papel da Neuroftalmologia é fundamental, nomeadamente para diagnosticar a nevrite ótica e a sua repercussão tanto funcional, com avaliação da acuidade visual central, campos visuais, visão cromática e potenciais visuais evocados, como estrutural, com estudo da eventual perda axonal por OCT.

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EXIT – ESTABLISHING ADEQUATE NEONATAL VENTILATION WHILE ON UTERO-PLACENTAL BYPASS: EXPERIENCE OF A PORTUGUESE REFERENCE CENTRE

EXIT – PERMEABILIZAÇÃO DA VIA AÉREA DO RECÉM-NASCIDO DURANTE BYPASS UTEROPLACENTÁRIO: EXPERIÊNCIA DE UM CENTRO DE REFERÊNCIA PORTUGUÊS

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ABSTRACT

Prenatal diagnosis of congenital airway obstruction has prompted new procedures to improve neonatal outcome. Ex-utero intrapartum treatment (EXIT) provides time to establish adequate neonatal ventilation, while on utero-placental bypass. The procedure involves techniques to maintain uterine hypotonia, placental perfusion and fetal oxygenation during surgery, while minimizing maternal risks. We present three cases of EXIT that took place at our hospital. The first case refers to a fetus with congenital high airway obstructive syndrome (CHAOS). The last two refer to fetuses with giant neck lymphangiomas.

Keywords: congenital airway obstruction, EXIT, utero-placental bypass, neonatal ventilation, fetal surgery, CHAOS, neck lymphangioma.

RESUMO

O diagnóstico pré-natal de oclusão congénita da via aérea incitou ao desenvolvimento de novas terapias para melhorar o desfecho neonatal. O procedimento EXIT (ex-utero intrapartum treatment) permite estabelecer uma ventilação neonatal adequada, enquanto se mantém o recém-nascido em bypass uteroplacentário. O procedimento envolve técnicas que permitem manter a hipotonia uterina, a perfusão placentária e a oxigenação fetal durante a cirurgia, minimizando os riscos maternos. Apresentam-se os três casos de EXIT realizados no nosso hospital. O primeiro refere-se a um feto com síndrome de oclusão congénita da via aérea superior. Os últimos referem-se a fetos com suspeita de linfangioma cervical gigante.

Palavras-chave: oclusão congénita da via aérea, EXIT, bypass uteroplacentário, ventilação neonatal, cirurgia fetal, linfangioma cervical.

INTRODUCTION

Lesions that compromise fetal airway constitute a threat to the newborn, with risk of hypoxia, ischemic brain injury and/or death [1]. Advances in prenatal ultrasonography have enhanced our ability to diagnose these conditions, prompting new strategies to improve neonatal outcome.

Initially designed for reversal of tracheal occlusion in fetuses with congenital diaphragmatic hernias, the *ex-utero intrapartum* treatment (EXIT) was adapted to prevent the hypoxic period between cord clamp at birth and airway establishment in neonates with prenatal diagnosis of a variety of conditions with airway compromise [1-3]. EXIT affords a period of utero-placental bypass, while establishing neonatal airway during delivery (EXIT-to-airway) [1-3].

Illustrating different indications and outcomes for this technique, we report the three cases of EXIT procedure that took place at our hospital. The first refers to a fetus with congenital high airway obstructive syndrome (CHAOS), a fatal pathology in which intrinsic obstruction of the airway prevents the egress of lung fluid, leading to tracheobronchomalacia, heart failure and hydrops [4]. The obstruction can be caused by laryngeal atresia, web or cyst or by tracheal atresia [1,2]. The last two cases reported refer to fetuses with giant neck lymphangiomas, a cervical lymphovenous malformation causing extrinsic tracheal obstruction.

CASE REPORTS

1) EXIT for CHAOS

A 29-year-old *primigravida* was referred to our department at 22 weeks' gestation, following an obstetric ultrasound-scan revealing bilaterally enlarged fetal lungs, compressed heart, plain diaphragm, ascites and polyhydramnios, consistent with CHAOS. The poor prognosis was carefully explained to the pregnant, who chose to continue the pregnancy.

According to the protocol at that time, the patient was referred to the Fetal Medicine Centre in London. A fetoscopy with tracheoscopy was performed at week 25, revealing a complete laryngeal obstruction below the vocal cords, consistent with laryngeal atresia. Toraco-amnyotic shunts were placed, with incipient effect at pulmonary decompression. A decision was made to perform an EXIT procedure at 36 weeks. The patient returned to our institution, being monitored with weekly ultrasound-scanning.

Preterm premature rupture of membranes (PPROM) occurred at 31 weeks. The patient was admitted and a course of betamethasone was administered to improve fetal lung maturity. Taking into consideration the clinical status of the fetus, a multidisciplinary team decided to attempt an emergent EXIT-to-airway procedure. Under general anesthesia, a Pfannenstiel incision and a low transverse histerotomy were performed. Fetal head and upper arms were extracted. Amnioinfusion with warm Ringer's lactate solution was performed throughout the procedure to prevent uterine contraction and placental abruption. While on utero-placental bypass the fetus underwent a tracheostomy (figure 1), with successful placement of the tracheostomy tube, after failed attempt of

direct laryngoscopy. Surfactant was administered, followed by umbilical cord clamp (histerotomy-to-cord clamp = 42 min).

Figure 1 – Preparing for tracheostomy while on utero-placental bypass. Neonate thorax (x) and maternal abdominal skin (*) are identified.

A male neonate weighting 1488g was delivered and admitted to the neonatal intensive care unit (N-ICU) on mechanical ventilation. Refractory pulmonary hypertension subsequent to iatrogenic pneumothorax after removal of thoracic shunts led to neonatal death eight hours after delivery.

There were no maternal intrapartum or postpartum complications.

2) EXIT for neck lymphangioma

A 25-year-old woman, G2P0, was referred to our institution at 23 weeks' gestation, following an obstetric ultrasound-scan revealing a fetal neck tumor. The right sided fetal neck lesion – measuring 57x31x21mm – was cystic, multiseptated and infiltrated the upper mediastin along the major blood vessels, being consistent with a lymphangioma. There were no other malformations and fetal karyotype was normal (46, XX).

The pregnant chose to continue the gestation, which was monitored with monthly ultrasound scanning. The lesion increased to 81x38x30mm in 11 weeks. A fetal magnetic resonance imaging at 37 weeks confirmed a large, cystic, multiseptated, predominantly right sided cervical mass with displacement of the trachea to the left.

Taking into account fetal trachea deviation and probable neonatal airway compromise, a multidisciplinary team scheduled an EXIT procedure to the 38th week. The initial steps were similar to those described above. While on utero-placental bypass, fetal airway was successfully assessed by

direct laryngoscopy and endotracheal intubation was achieved (figure 2), followed by umbilical cord clamp (histerotomy-to-cord clamp = 2.5 min).

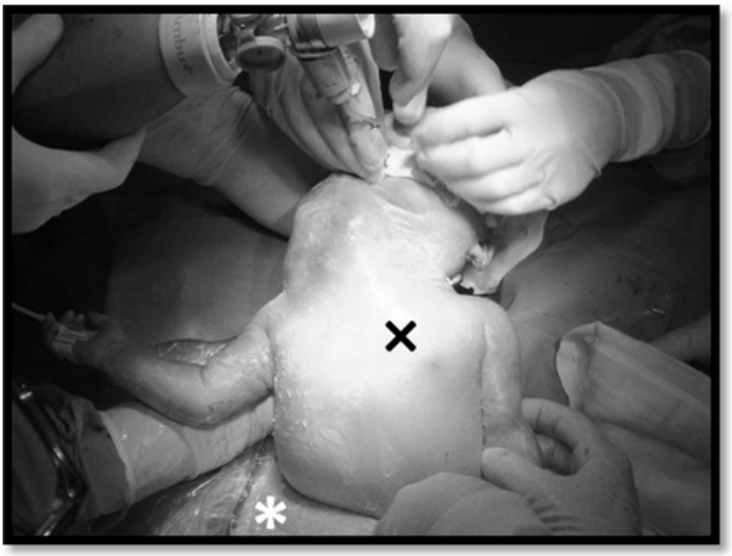

Figure 2 – Endotracheal intubation while on utero-placental bypass. Neonate thorax (x) and maternal abdominal skin (*) are identified.

A female neonate weighting 3470g was delivered and admitted at the N-ICU. After two months and two mass reduction surgeries, the baby was discharged without oxygen therapy support.

There were no maternal intrapartum or postpartum complications.

3) EXIT for neck lymphangioma

A 37-year-old woman, G2P0, was referred to our institution at 30 weeks' gestation for an obstetric ultrasound-scan revealing a fetal neck lesion. A cystic multiseptated and right sided fetal neck lesion – measuring 66x53x38mm – was consistent with a lymphangioma with probable tongue involvement. There were no other malformations. Fetal karyotype was not assessed on maternal request.

Fetal well-being and neck lesion were monitored with monthly ultrasound scanning. Lesion dimensions remained stable throughout pregnancy. A fetal magnetic resonance imaging at 36 weeks confirmed a cystic, multiseptated, right sided cervical mass with displacement of the trachea to the left but without mediastin invasion.

Foreseeing neonatal airway compromise, an EXIT procedure was planed to the 38th week of gestation. The initial steps were similar to the ones previously described. Successful endotracheal intubation was achieved by direct laryngoscopy (figure 3), with histerotomy-to-cord clamp = 4 min.

Figure 3 – Airway assessment by direct laryngoscopy, while on utero-placental bypass. Neonate thorax (x) and maternal abdominal skin (*) are identified.

A male neonate weighting 3220g was delivered and admitted at the N-ICU on ventilatory support. Surgery is to be scheduled.

DISCUSSION

EXIT is commonly supposed to be a special cesarean-section, but they are different surgical techniques [1]. During a cesarean-section the uterus tone is maximized to prevent hemorrhage and the transplacental diffusion of anesthetics is minimized to avoid neonatal depression. Contrarily, the central principle of EXIT is controlled uterine hypotonia to prevent placental abruption, preserving utero-placental circulation and fetal oxygenation [1]. It requires deep maternal anesthesia while maintaining normal maternal blood pressure, and also fetal anesthesia but without fetal cardiac depression [1]. The key to the successful outcome of this highly specialized fetal surgical technique is orchestration of a multidisciplinary team [2], including obstetrics, anesthesiology, pulmonology, otolaryngology, pediatric surgery, neonatology and nurses. Exhaustive technique description has been thoroughly performed [1,2] and outdoes this paper purpose.

On the first case here reported, PPROM and the associated risk of infection prevented transferring the patient to the reference fetal surgery unit. This first attempt to perform an EXIT procedure at our institution was thoroughly reported [5]. EXIT had been successfully performed on cases of CHAOS [3-6] and the attempt to give the newborn the best chance of survival led our department to perform it for the first time. Current guidelines [7] suggest that patients with PPROM before 34 weeks should be managed expectantly if no contraindication exist. Our decision to end the pregnancy at 31 weeks was established on the fetal bad prognosis, the need of mechanical ventilation regardless the gestational

age at delivery and the attempt to avoid an out-of-schedule procedure without a multidisciplinary team being prepared. Preparing and coordinating this team in a short period of time was a meritorious achievement of our institution. The procedure was considered a success due to the effective airway establishment while on utero-placental bypass, without maternal complications. Neonatal death was not related to the procedure.

As with CHAOS, neonates with giant neck masses present high morbidity and mortality mostly due to delay in airway establishment [8]. In the presence of significant tracheal compression and/or deviation, EXIT is suggested [8]. On the second and third cases reported, EXIT was performed at our institution with good outcome. Team experience and airway assessment by direct laryngoscopy allowed shorter bypass time.

Our short experience illustrates that an adequately preparation and synchronization of a multidisciplinary team allows EXIT procedure to be performed at our institution, with good neonatal outcome and without maternal complications.

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NEUROTROPHIC KERATOPATHY: DIAGNOSTIC AND THERAPEUTIC CHALLENGES, HERPETIC RECURRENCE AND NEW REMODELING THERAPIES

QUERATOPATIA NEUROTRÓFICA: DESAFIOS DIAGNÓSTICOS E TERAPÊUTICOS, RECORRÊNCIA HERPÉTICA E NOVAS TERAPIAS REMODELADORAS

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ABSTRACT

Our purpose is to report a challenging case of neurotrophic keratopathy, documented with a series of anterior segment photographies. Neurotrophic keratopathy is one of the most difficult and challenging ocular diseases, which lacks specific treatment. The prognosis depends on the cause and severity of the trigeminal damage, and on the presence of associated ocular surface disease. Our case shows that diagnosis can be masked, and wrong, leading to inappropriate therapy with ocular surface damage. Careful anamnesis and detailed ophthalmologic examination are therefore essential. This case report also illustrates an herpetic recurrence associated with this condition. In our patient, clinical evidence seems to show that topical treatment with RGTA® drops, the new extracellular matrix regeneration therapy, improves the final outcome of the disease. New and different clinical trials will be encouraged to define the best therapeutic standard.

Keywords: neurotrophic keratopathy, herpes simplex.

RESUMO

A queratopatia neurotrófica é uma patologia muito desafiante e difícil de lidar. O objetivo deste trabalho é apresentar um caso clínico desta patologia, que demonstra como o diagnóstico inicial pode ser mascarado, e errado, levando a terapêutica desadequada com prejuízo da superfície ocular. É por isso essencial uma anamnese cuidada e exame oftalmológico detalhado. O caso ilustra também a importância do tratamento com lubrificantes oculares, que condicionam uma melhoria inicial, e uma recorrência herpética que, após terapêutica dirigida, permitiu a resolução do quadro. Por fim queremos destacar o papel das novas terapias de regeneração da matriz extracelular da córnea, com um novo tratamento de RGTA® que permitiu a regeneração completa da superfície ocular neste caso.

Palavras-chave: queratopatia neurotrófica, herpes simplex.

INTRODUCTION

Neurotrophic keratopathy (NK) is a rare degenerative corneal disease caused by impairment of trigeminal innervation, leading to corneal epithelial breakdown, poor healing, and development of corneal ulceration, melting, and perforation. The hallmark of NK is a decrease or absence of corneal sensation [1].

NK was initially described as "neuroparalytic keratitis" and demonstrated by Magendie, who hypothesized the presence of trophic nerve fibers in the trigeminal nerve regulating tissue metabolism. It is now demonstrated that the trigeminal nerve provides corneal sensation and also supplies trophic factors to the cornea, playing a key role in maintaining the anatomical integrity and function of the ocular surface. The ocular surface epithelium, tear gland, and sensory and autonomic nerve fibers exert a mutual influence on their structures and functions by the release of cytokines, neuropeptides, and neuromediators [1,2].

There are a number of causes of disease of the trigeminal nerve, resulting in corneal hypoesthesia or anesthesia. NK can be caused by ocular and systemic conditions, with damage at any level of the fifth cranial nerve, from the trigeminal nucleus to the corneal nerve endings. The most common ocular causes are herpetic keratitis (*herpes simplex, varicella zoster)*, chemical burns, physical injuries, corneal dystrophy, chronic use of topical medications, contact lens overuse and anterior segment surgery. The systemic conditions associated are diabetes, intracranial space-occupying lesions, drugs, multiple sclerosis and congenital syndromes. Neurosurgical procedures that damage the trigeminal branch can also cause NK [3].

An NK classification, based on severity, distinguished 3 stages: the first one is characterized by corneal epithelial changes, the second stage is characterized by a recurrent and/or persistent epithelial defect and the third stage is characterized by corneal ulceration with stromal lysis that may be complicated by stromal melting and possible perforation [4].

Functional signs of NK include decreased visual acuity, moderate conjunctival hyperemia, eye watering and absent or moderate pain. The diagnosis is based on the clinical history. Patients rarely complain of ocular symptoms and a discrepancy between clinical findings and symptoms can be found [5].

Treatment of NK is challenging. The priority is to discontinue any element of toxicity from topical medications on the ocular surface. Medical and surgical treatments aim to improve epithelial healing, to avoid stromal lysis and to prevent potential complications. Up to now, there are no specific treatments [6].

Open studies have reported the efficacy of several pharmacological treatments in promoting corneal ulcer healing in NK. Treatment with eye drops containing RGTA® – polycarboximetilglucose sulfate – belongs to the regenerating agent family. These agents are used for corneal matrix repair therapy, a matrix agent mimicking heparin sulfate, achieved complete healing in eight out of eleven patients, with closing of the NK ulcer after a mean period of 8.7 weeks [7].

Nerve growth factor-1 represents a more promising future therapeutic approach, since it is able to improve tear and nerve function and stimulate regeneration and survival of both the corneal epithelium and sensory nerves [8].

CASE PRESENTATION

This article presents the case of a 74-year-old woman, institutionalized, and totally dependent in activities of daily living, who was brought to the emergency room (ER) due to a left (OS) red-eye discomfort, photophobia and low visual acuity (VA) with one-month evolution.

She had Parkinson's disease and diabetes mellitus (DM) diagnosed for over than 20 years with target organ disease. Her past ocular history included previous OSD cataract surgery (10 years ago) and non specific episodes of red-eye.

Under observation she had a VA OS = fingers count 20cm, a moderate ciliary hyperemia, small mucopurulent discharge, corneal ulcer with 3mm diameter with smooth edges on the visual axis, diffuse stromal edema with Descemet folds and neovascular pannus (figure 1).

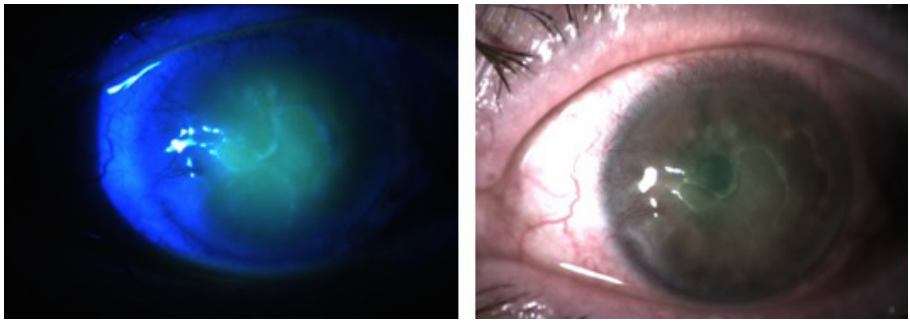

Figure 1 – Day 1

The patient was admitted and began treatment with fortified eye drops (Vancomycin, Ceftazidime) 1/1 hour.

After 3 days of hospitalization and institutional treatment, no improvement frame was detected (figure 2).

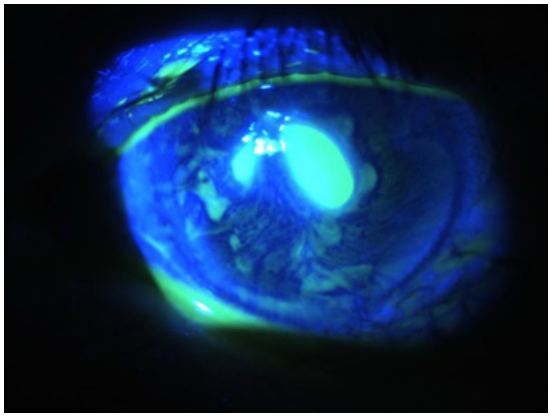

Figure 2 – Day 3

She maintained an epithelial defect with smooth edges, stromal limited to the defect region edema, adjacent thickened and non-adherent epithelium, and sectoral iris atrophy without reaction in the anterior chamber (AC). The corneal sensitivity tested with cotton swab was frankly decreased in OS and the frequency of blinking was recorded at 6 times per minute, with a positive Bell phenomenon. The funduscopic examination of the right eye (OD) revealed non-proliferative diabetic retinopathy.

Then we considered a hypothetic diagnosis of neurotrophic keratopathy with neurotrophic component and increased exposure due to anticholinergic action of drugs.

She suspended fortified eye drops and started Doxycycline 100mg 2id, Moxifloxacin eye drops and ocular lubricants preservative-free 4id 8id.

Eight days after, there was an improvement of the frame, with reduced epithelial defect hyperemia and stromal edema (figure 3).

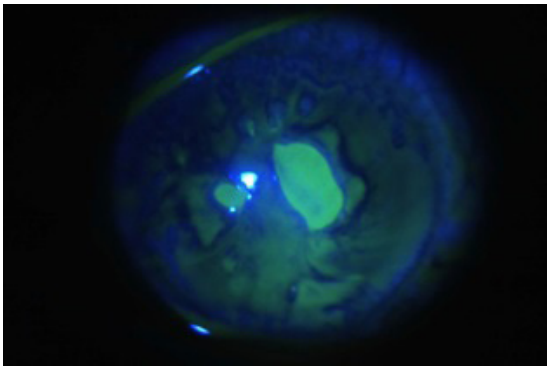

Figure 3 – Day 8

Thirteen days later, patient had worsening of symptoms with increasing of the epithelial defect, stromal edema and fine tyndall in AC inferior keratic precipitates (KPs) (figure 4). The ophtalmotonus was apparently high.

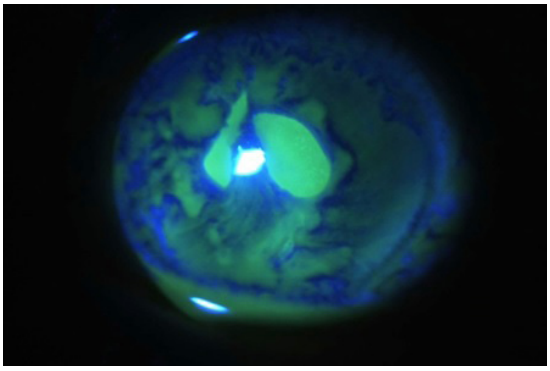

Figure 4 – Day 13

On the hypothesis of a recurrence of stromal keratitis herpetic, acyclovir 400 mg 5id was added to the established therapy. Subconjunctival injections of dexamethasone and cacicol® - RGTA® (polycarboximetilglucose sulfate) instillation were also performed in alternate days. The epithelial defect was gradually decreasing and symptoms were also improving (figure 5).

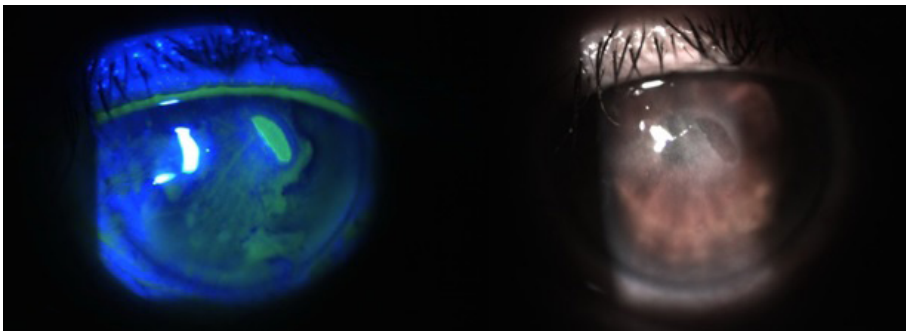

Figure 5 – Day 20

Thirty five days later, complete epithelial regeneration was achieved, with an AV = 0.05 (figure 6). The patient was asymptomatic.

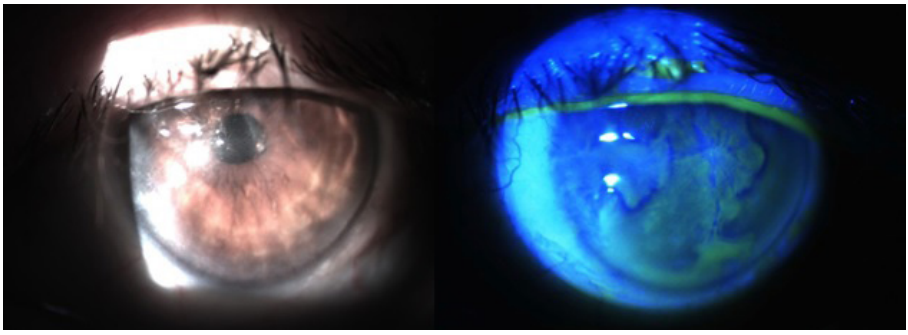

Figure 6 – Day 35

DISCUSSION

This case demonstrates how the initial diagnosis of the NK can be masked and difficult resulting in inadequate therapy of ocular surface damage. A careful history, a detailed eye examination and a high level of suspicion are essential for the diagnosis of this disease.

This report illustrates a case of NK, probably caused by previous ocular herpes infection and associated systemic conditions. The management of the disease is challenging.

Importance of treatment with ocular lubricants that conditioned an initial improvement seems highly likely. A herpetic recurrence, that after directed treatment and with a new RGTA® treatment resulted in complete epithelial regeneration.

The new topical treatment RGTA® (polycarboxymethyl glucose sulphate) is a promising therapy to these patients. It belongs to the polysaccharides family, derived from dextran by chemical substitutions with carboxymethyl, sulphate and hydrophobic groups. This biopolymer is engineered to replace the heparin-sulphates destroyed upon tissue injury and to specifically bind extracellular matrix proteins and growth factors, protecting them from proteolysis.

CONCLUSIONS

NK is one of the most difficult and challenging ocular diseases that lacks a specific treatment. The prognosis depends on the cause and severity of the trigeminal damage and on the presence of associated ocular surface disease.

In this case report, clinical evidence seems to show that topical treatment with RGTA® drops improves final outcome.

Experimental and clinical evidence shows that several novel treatments, such as growth factors, may improve the clinical outcome of NK. New and different clinical trials will be encouraged to define the best therapeutic standard.

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DRUG-INDUCED NEPHROPATHY – A RARE CAUSE FOR A FREQUENT ASSOCIATION?

LESÃO RENAL INDUZIDA POR FÁRMACOS – UMA CAUSA RARA PARA UMA ASSOCIAÇÃO FREQUENTE?

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ABSTRACT

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis is a potential life-threating disease, which rarely can be drug-induced. We present the case of a patient with Graves' disease on long-term propylthiouracil (PTU) treatment with rapidly progressive renal failure in the setting of ANCA positivity. Renal biopsy confirmed the suspicion of a pauci-immune necrotizing glomerulonephritis. Unfortunately, despite PTU withdrawal, immunosuppression initiation and plasma exchange, the patient progressed to end-stage renal disease. Due to its rarity, the association of PTU and ANCA vasculitis is not well known among clinicians. Timely diagnosis and high level of suspicion are important to prevent irreversible damage.

Keywords: antineutrophil cytoplasmic antibody, propylthiouracil, vasculitis.

RESUMO

A vasculite associada a anticorpos anti-citoplasma de neutrófilos (ANCA) é uma entidade potencialmente fatal, que em casos raros pode ser induzida por fármacos. Os autores apresentam o caso de um doente com doença de Graves sob terapêutica de longa duração com propiltiouracilo (PTU), que desenvolve serologia ANCA positiva e insuficiência renal rapidamente progressiva. A biópsia renal realizada confirmou a suspeita de uma glomerulonefrite necrotizante pauci-imune. Infelizmente, apesar da suspensão do PTU, instituição de imunossupressão e plasmaferese, o doente progrediu para doença renal terminal. Dada a sua raridade, a associação entre PTU e vasculite ANCA não está bem difundida entre a comunidade médica. O seu diagnóstico precoce e elevado nível de suspeição são essenciais para prevenir danos irreversíveis.

Palavras-chave: anticorpo anti-citoplasma de neutrófilos, propiltiouracilo, vasculite.

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a pauci-immune necrotizing small vessel vasculitis. ANCA may be specific for myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA). Additionally, cases of ANCA-negative AAV can occur. AAV include microscopic polyangiitis, granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis. AAV can also be limited to a specific organ, specially a subset referred to as renal-limited AAV. AAV affects most commonly caucasian older adults, although it has been reported at all ages, and there is a slight male predominance [1]. Drug-induced vasculitis (DIV) is also an important cause of AAV, usually with less severe presentation than idiopathic AAV [2].

CASE PRESENTATION

We report the case of an 85-year-old caucasian man with Graves' disease on propylthiouracil (PTU) treatment for 33 months. He had a normal renal function with a baseline serum creatinine (sCr) of 1.0 mg/dL (estimated glomerular filtration rate 68 mL/min, CKD-EPI). One month earlier, in another centre, renal dysfunction was detected, which was not valued at this point, with a serum urea (sU) of 81 mg/dL and sCr 2.1 mg/dL. At presentation, on routine laboratory testing, bicytopenia was identified (haemoglobin 6,7 g/dL, leucocytes 1.290x109/L), further abnormal renal function (serum urea 240 mg/dL, sCr 8.2 mg/dL) and haematoproteinuria. The patient was asymptomatic and examination was unremarkable. PTU was immediately suspended. Regarding additional investigation: renal ultrasound revealed normal kidney appearance, with no features of chronicity and no evidence of obstruction. Serological evaluation revealed double ANCA positivity for MPO (331.6 UQ) and PR3 (751.9 UQ). All other serologies were negative, including anti-double strand DNA (anti-dsDNA), anti-nuclear antibodies (ANA), anti-histones, anti-glomerular basement membrane and virology. There was also no evidence of dysproteinaemia, and no previous or current infections. Pulmonary haemorrhage was discarded and, while the renal biopsy was planned, patient initiated low-flux haemodialysis due to uremic symptoms. Renal biopsy was compatible with a pauci-immune necrotizing glomerulonephritis affecting one of six glomeruli. Due to dialysis-dependent renal failure, unresponsive to PTU interruption, immunosuppression with methylprednisolone (500 mg, IV, 3 days), followed by oral prednisolone (1 mg/kg/day) and cyclophosphamide (500 mg, IV) was started. Additionally, the patient also received plasma exchange (replacement fluid: 5% human albumin, 50 mL/Kg, 7 sessions) and co-trimoxazole prophylaxis. The clinical course was further complicated by an extensive spontaneous hematoma and a mixed hepatocellular-cholestatic hepatitis, as consequence, respectively, of plasma exchange and co-trimoxazole. Due to frailty, absence of recovery of renal function after three weeks of therapy and no other systemic symptoms, immunosuppression was withdrawn with progressive steroid tapering. Eighteen months later, currently on methimazole, the patient is clinically stable although dialysis dependent.

DISCUSSION

AAV is a rare disease with a prevalence of 0.006% in Europe [1]. Even less commonly, AAV can be drug-induced. Drugs that can be responsible for ANCA, and the clinical picture of AAV, include tumor necrosis factor (TNF) inhibitors, levamisole-adulterated cocaine, hydralazine, penicillamine and thioamides, namely propylthiouracil (PTU) [2,3]. PTU-induced AAV, although being one of the most common associations, is a rare event, occurring in 0.01% of patients [2]. Asymptomatic serum ANCA positivity is well documented with long-term use of PTU, in up to 27-41% of patients, increasing with duration of therapy, with median onset at 42 months (1 week to 7 years) [4,5,6,7]. The clinical significance of the presence of these antibodies and why some patients develop systemic disease and others do not is not well understood.

DIV is almost universally MPO positive. Double ANCA positivity is also commonly seen and should favour a secondary cause instead of a primary cause for the AAV [2]. Frequently, DIV patients can also have concomitant ANA, anti-histones and anti-dsDNA positivity.

Regarding clinical presentation, it can be very similar to idiopathic AAV, with constitutional symptoms – fever, arthralgias and myalgias – associated with single or multiple organ involvement [2,8]. In DIV, as in idiopathic AAV, the kidney is the most commonly involved organ [2]. Clinical course in DIV is usually less severe than in idiopathic AAV, and the majority of cases resolves with drug interruption. PTU patients are frequently switched to methimazole. Although methimazole can also induce ANCA, clinical AAV is extremely rare and AAV remission is usually maintained with methimazole [9,10]. In most severe DIV presentations, with pulmonary-renal syndrome, an immunosuppression protocol similar to the idiopathic form is recommended with apheresis being an indication for patients with pulmonary haemorrhage or dialysis-dependent renal failure. Although extremely rare, fatalities have also been reported in DIV [2,11].

Our patient presented with rapidly progressive renal failure and active urinary sediment, which is typical of AAV. Agranulocytosis, not typical of AAV, is a common adverse effect of PTU [12]. Despite presenting with severe anaemia, no evidence of alveolar haemorrhage was present and this could also be an adverse effect of PTU, probably enhanced by the degree and prolonged course of renal dysfunction [13].

In this case, despite double ANCA positivity on a long-term PTU patient favouring a secondary cause, we acknowledge that this clinical picture could also have been caused by an idiopathic AAV. Renal-limited vasculitis can occur in both idiopathic and drug-induced AAV and our patient, being a caucasian elderly man, represents the most frequently affected group in idiopathic AAV. Due to frailty, adverse effects and no renal response, we decided to interrupt immunosuppression, which is justified in DIV but would be insufficient in an idiopathic case [14]. Unfortunately, in this case, recognition of this iatrogenic presentation was too late to prevent end-stage renal disease.

CONCLUSIONS

Drug-induced vasculitis is a rare potential fatal disease. A high index of suspicion is required to allow prompt diagnosis and prevent evolution to end-stage renal disease or life-threating conditions.

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PSYCHIATRIC MANIFESTATIONS OF HUNTINGTON'S DISEASE

MANIFESTAÇÕES PSIQUIÁTRICAS DA DOENÇA DE HUNTINGTON

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ABSTRACT

Huntington's disease (HD) is an autosomal-dominant neurodegenerative disorder characterized by a triad of motor, cognitive and psychiatric symptoms. About a clinical case, we intent to highlight the importance of knowledge of psychiatric manifestations of HD and the need for appropriate treatment of them, in order to improve the prognosis. There are no large controlled studies of psychiatric treatments in HD, but case reports and clinical experience indicate that many of psychiatric symptoms respond readily to treatment.

Keywords: Huntington's disease, neuropsychiatry, behaviour and treatment.

RESUMO

A Doença de Huntington (DH) é uma doença neurodegenerativa autossómica dominante caraterizada por uma tríade de sintomas motores, cognitivos e psiquiátricos, sendo a prevalência dos sintomas psiquiátricos mais elevada do que na população em geral. A propósito da apresentação de um caso clínico, pretendemos realçar a importância do conhecimento das manifestações psiquiátricas da DH bem como a necessidade de tratamento adequado das mesmas a fim de melhorar o prognóstico. Apesar de não existirem muitos estudos sobre o tratamento das manifestações psiquiátricas da DH, a experiência clínica indica que a maioria destas manifestações respondem rapidamente ao tratamento.

Palavras-chave: Doença de Huntington, neuropsiquiatria, comportamento e tratamento.

INTRODUÇÃO

A Doença de Huntington (DH), cuja prevalência mundial estimada é de 4 a 10 por 100000 [1], foi descrita por George Huntington em 1872. Em 1993 foi identificada a sua etiologia: expansão anormal da repetição do trinucleótido CAG (>38) no braço curto do cromossoma 4, que codifica uma proteína citoplasmática mutante, a huntingtina [2]. A huntingtina é expressa de forma ubíqua em todo o organismo, porém a morte celular expressa-se particularmente em áreas específicas do cérebro, particularmente no estriado, no córtex e no hipotálamo, resultando na alteração de múltiplos mecanismos intracelulares que conduzem à disfunção das vias nigro- e corticoestriadas [3].

Na maioria dos casos o aparecimento dos primeiros sintomas surge apenas na idade adulta, entre os 35 e os 50 anos de idade [4]. A idade de início está inversamente relacionada com o tamanho da repetição de CAG comprovando-se que a doença é mais precoce em indivíduos que possuem as repetições mais longas [5]. A doença progride e torna-se fatal dentro de 15 a 20 anos após o início dos primeiros sintomas [4]. A prevalência de sintomas psiquiátricos é significativamente mais elevada do que na população em geral, estando os mesmos associados a uma morbilidade significativa [6]. A relação entre o comprimento da repetição de CAG e as manifestações psiquiátricas da DH também tem sido investigada em amostras relativamente pequenas de doentes com resultados contraditórios [7,8].

Tendo presente que a literatura científica é muito pobre no que respeita à evolução clínica destes doentes é apresentado um caso clínico ilustrativo da necessidade de reconhecer precocemente as manifestações psiquiátricas nos doentes com DH tendo em vista as estratégias de tratamento mais adequadas, a fim de melhorar a qualidade de vida e o prognóstico destes doentes. Apresentam-se também os resultados da pesquisa bibliográfica realizada sobre as manifestações psiquiátricas da DH e seu tratamento.

APRESENTAÇÃO DO CASO

Mulher de 43 anos, natural de Elvas, 12º ano de escolaridade, desempregada, separada, dois filhos, residente no Lumiar, sem antecedentes psiquiátricos conhecidos até 2000, altura em que surge, no pós-parto, o primeiro episódio depressivo "major". Este episódio era caraterizado por humor deprimido, anedonia, ideação suicida, lentificação motora, ansiedade psíquica e somática e pessimismo, sem necessidade de interrupção da atividade laboral, tendo iniciado acompanhamento em Consulta de Psiquiatria. Em 2007 iniciou seguimento em consulta de Neurologia tendo-lhe sido diagnosticada DH. Entre 2007 e 2015 registaram-se vários episódios depressivos, tendo sido medicada com diversos antidepressivos que não consegue especificar. A doente, progressivamente, desenvolveu sintomatologia da DH com alterações moderadas na execução dos movimentos, dificuldades na resolução de problemas do dia-a-dia, irritabilidade, sintomas depressivos e alterações motoras associadas à perda de coordenação dos movimentos voluntários.

Em 2016 recorreu ao Serviço de Urgência de Psiquiatria do Hospital de Santa Maria, acompanhada pela mãe, por instalação progressiva de sintomatologia psicótica com evolução de 3 meses e paralela ao

incumprimento terapêutico. A doente referia "os meus colegas de trabalho e a minha família querem matar-me e aos meus filhos também (…) a minha irmã era solicitadora e agora é bruxa, troca-me a medicação e dá-me comida envenenada, tendo ciúmes de mim porque eu sou bonita e ela é feia". Este quadro clínico além de ter levado a doente a despedir-se do seu emprego como auxiliar de ação educativa, gerou conflitos graves no contexto familiar. Neste contexto, a doente foi internada, voluntariamente, no Serviço de Psiquiatria.

Dos antecedentes familiares destacam-se perturbação depressiva recorrente (mãe) e DH (pai, dois irmãos e primo paterno) (figura 1). Relativamente aos antecedentes pessoais, DH confirmada em 2007 com teste genético pré-sintomático, seguida em consulta de Neurologia no Hospital Fernando da Fonseca; duas depressões pós-parto (uma em 2000 e outra em 2007) e duas tentativas de suicídio (duas ingestões medicamentosas voluntárias) em 2007, seguida em consulta de Psiquiatria no Hospital Militar desde 2000. Nega hábitos tóxicos. Medicada habitualmente com quetiapina 50mg/ dia, clonazepam 0.25mg/ dia, escitalopram 40mg/ dia, alprazolam 0.25mg/ dia e mirtazapina 15mg/ dia.

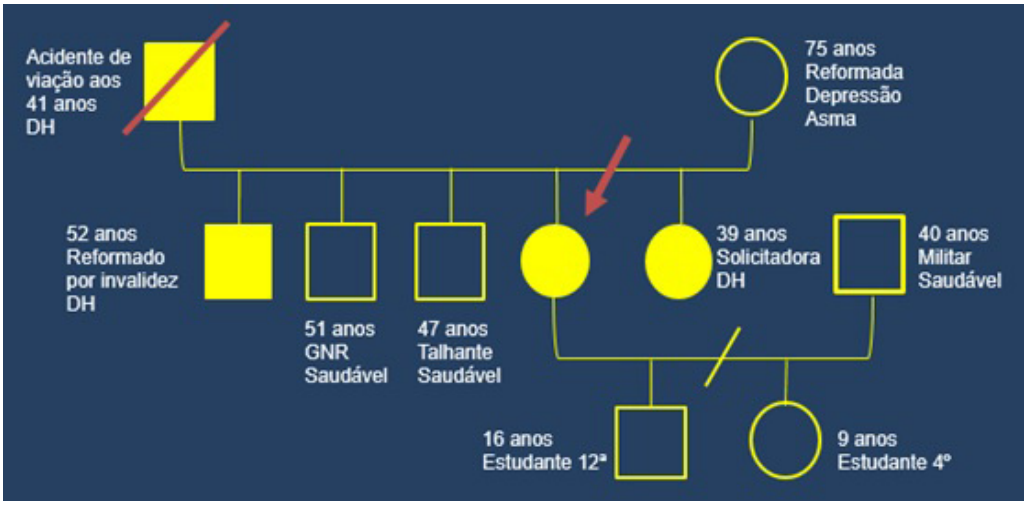

Figura 1 – Genograma familiar

A doente descreve-se como "introvertida e ansiosa", mencionando como qualidades "sou boa mãe, honesta e trabalhadora" e como defeitos "impaciente e teimosa".

No exame físico sumário não foram encontradas alterações. No exame neurológico: movimentos oculares com latência e decomposição das sacadas horizontais, apraxia oculomotora, impersistência motora, coreia generalizada ligeira (mais evidente nos membros inferiores) e marcha de base alargada (coreia). No exame psicopatológico: doente vigil, orientada nas quatro referências, pouco colaborante, com contacto evitante, discurso fluente mas com baixa espontaneidade, lentificação psicomotora, humor ansioso/ irritável, ideias delirantes persecutórias, de auto-referência, de prejuízo e de envenenamento, fenómenos de leitura do pensamento e ausência de crítica para a situação mórbida.

Os exames complementares de diagnóstico (avaliação analítica, urina tipo II, electrocardiograma e raio-x tórax) não revelaram alterações. Na avaliação neuropsicológica apuraram-se alterações acentuadas da atenção na compreensão áudio-verbal e atenção sustentada; alterações moderadas das funções executivas, da fluência e iniciativa verbal, da memória episódica e visual e aprendizagem associativa; alterações ligeiras da memória semântica; moderada a acentuada sintomatologia depressiva e alterações nas atividades instrumentais da vida diária, com necessidade de supervisão de terceira pessoa.

Tratando-se assim de uma psicose orgânica sem outra especificação, iniciou-se olanzapina 10mg/ dia, mantendo-se a terapêutica de ambulatório. Dada a manutenção da sintomatologia psicótica de caráter persecutório, com deficiente resposta à olanzapina, fez-se *switch* para risperidona 6mg/ dia, suspendeu-se a quetiapina e o alprazolam, reduziu-se a dose de escitalopram e clonazepam e aumentou-se a dose de mirtazapina.

A doente teve alta ao quadragésimo quinto dia de internamento, significativamente melhorada apesar de manter ideias delirantes com menor dinamismo e medicada com clonazepam 1mg/ dia, escitalopram 20mg/ dia, mirtazapina 30mg/ dia e risperidona 6mg/ dia.

Em posterior consulta de Psiquiatria identificou-se marcada lentificação psicomotora pelo que a dose de risperidona foi ajustada de 6mg/ dia para 4mg/ dia com uma boa resposta, mantendo contudo alguma apatia. Atualmente, a doente apresenta crítica parcial para a sua situação mórbida, não se apurando sintomatologia psicótica ativa ou sintomas da linha ansiosa ou depressiva.

DISCUSSÃO

As manifestações psiquiátricas e comportamentais da DH são várias, tais como depressão, suicídio, psicose, ansiedade, perseveração, irritabilidade, apatia, desinibição e défices na cognição social. A conclusão geral de vários estudos foi a de que os sintomas psiquiátricos, embora possam ocorrer em qualquer fase da doença são a primeira manifestação da DH em 31% dos casos, podendo preceder os sintomas motores por uma década, sendo a depressão a condição psiquiátrica mais frequente nestes doentes.

A prevalência da depressão major nos doentes com DH varia entre 20 e 56% [9 e 10]. Na população em geral a depressão é mais prevalente nas mulheres do que nos homens, ao passo que na DH não há diferença entre géneros. A sua etiologia inclui fatores psicossociais e biológicos [1]. A depressão na DH pode apresentar-se com agitação, mudanças na personalidade ou isolamento social [6]. Os sintomas depressivos atingem o pico na fase 2 da DH, diminuindo depois nas últimas fases [11]. Ainda não foram realizados ensaios clínicos aleatorizados para a o tratamento da depressão na DH, não existindo um algoritmo para o tratamento da depressão nestes doentes. Os princípios do tratamento são, assim, similares aos da depressão em geral [12]. Existe, contudo, evidência acerca da existência de alterações nas vias serotoninérgicas dos núcleos da rafe no tronco cerebral em indivíduos com DH e depressão, o que suporta o uso de Inibidores Seletivos da Recaptação de Serotonina (ISRSs) nestes doentes [13]. Tal como na população sem DH, a eletroconvulsivoterapia pode ser considerada uma opção terapêutica na depressão grave [6]. Relativamente à psicoterapia, embora com potencial utilidade, existe pouca evidência acerca da sua eficácia nos doentes com DH e depressão [6].

O humor deprimido é um preditor muito importante da ideação suicida que afeta aproximadamente 10% dos doentes com DH [14]. Estudos mais antigos relataram que 25% dos doentes tiveram pelo menos uma tentativa de suicídio ao longo da doença e o suicídio foi a causa final da morte em até 10% dos doentes [15]. A etiologia do suicídio na DH é multifatorial, incluindo além da depressão, o pobre ajustamento ao diagnóstico, a negação da doença, a impulsividade e a irritabilidade [6]. São propostos dois períodos críticos para o aumento do risco de suicídio: imediatamente depois do doente receber o diagnóstico formal e durante a fase 2 [16]. Apesar da proporção de doentes com pensamentos suicida diminuir depois da fase 2, a gravidade dos pensamentos suicida aumenta com a progressão da doença [16].

A psicose é uma das manifestações psiquiátricas menos prevalentes da DH, com uma prevalência estimada de 10,4% nesta população [17] (10 a 11,5% para delírios e 1,9 a 3% para alucinações [1]), comparativamente com 3,48 a 11,6% na população mundial em geral [18]. Tal facto poderá dever-se ao uso de fármacos antidopaminérgicos para controlo dos sintomas motores nestes doentes. A sua etiologia ainda não é completamente conhecida e várias teorias têm sido propostas, incluindo a lesão direta do núcleo caudado, os estados hiperdopaminérgicos por perda neuronal e a hipofrontalidade [6].

A psicose desenvolve-se frequentemente nas fases mais avançadas da doença e/ou em indivíduos com uma doença de longa duração. Um estudo coorte europeu revelou que a psicose foi mais prevalente na fase 3 da DH [11]. Apesar dos ensaios clínicos aleatorizados para os sintomas psicóticos na DH serem escassos, a olanzapina e a risperidona foram os fármacos mais frequentemente prescritos para tratar a psicose num estudo de casos Europeus [19]. Os antipsicóticos atípicos com baixa incidência de efeitos extrapiramidais são os fármacos preferidos para o tratamento da psicose na DH [6].

As perturbações de ansiedade têm sido menos estudadas do que os outros sintomas psiquiátricos da DH. A prevalência estimada das perturbações de ansiedade na DH varia entre 16,7% e 24% [9], comparativamente com a prevalência de 16,6% na população mundial em geral [20]. A perturbação de ansiedade generalizada e a perturbação de pânico são as mais prevalentes [9]. A ansiedade apresenta um pico na altura em que se realiza o teste genético [21], diminui nos cinco anos seguintes e volta a aumentar na fase 2 aquando do surgimento dos sintomas ligeiros a moderados da DH [16]. Apesar de não terem sido realizados ensaios clínicos controlados para a tratamento da ansiedade nos doentes com DH, no geral o tratamento é similar ao dos doentes sem DH. Um estudo de casos Europeus revelou que o clonazepam e o lorazepam foram os fármacos mais prescritos para os sintomas ansiosos nos doentes com DH [19]. Deve ter-se em atenção que as benzodiazepinas têm de ser cuidadosamente monitorizadas dado os riscos inerentes a este grupo farmacológico.

A perseveração define-se como a tendência para continuar a ter determinado comportamento, mesmo depois de o mesmo já ter cumprido a sua finalidade [22]. Difere dos comportamentos compulsivos repetitivos da perturbação obsessivo-compulsiva, uma vez que os doentes com perseveração na DH nem sempre demonstram insight para os pensamentos/ comportamentos repetitivos (provavelmente devido à inflexibilidade cognitiva), não tentando controlá-los [23]. Relativamente ao tratamento, um estudo reportou o efeito benéfico de 10mg de buspirona administrada duas vezes ao dia em dois pacientes com perseveração e agressividade [24]. O Consenso Internacional suporta o uso de inibidores seletivos da recaptação de serotonina (ISRSs) e incluem também a clomipramina como primeira escolha [25].

Outras manifestações comportamentais da DH que exigem igualmente atenção clínica são a irritabilidade, a apatia e a desinibição (incluindo a hipersexualidade).

Por fim a demência, um estado terminal, para o qual culmina a progressão da DH associada ao declínio psiquiátrico e cognitivo.

O caso clínico descrito realça a importância clínica das manifestações psiquiátricas na DH, comprovando o que está descrito na literatura de que as manifestações psiquiátricas precedem os sintomas motores. Neste sentido, são muitas vezes os psiquiatras que primeiro contactam com estes doentes. No caso apresentado o primeiro diagnóstico realizado foi o de Depressão "Major", o que está de acordo com a bibliografia. Relativamente ao tratamento desta condição, os ISRSs são os fármacos de eleição. Só numa fase mais avançada da DH surgiu a psicose, o que também está de acordo com a literatura. Um estudo de casos Europeus revelou que a olanzapina e a risperidona foram os fármacos mais frequentemente prescritos no tratamento dos sintomas psicóticos. No caso clínico em questão, a olanzapina não resultou na remissão dos sintomas psicóticos, tendo sido necessário o *switch* para risperidona, com boa resposta.

CONCLUSÃO

Em conclusão, consideramos muito importante que o diagnóstico de DH não seja adiado até ao aparecimento dos sintomas motores. É, assim, relevante o estudo das manifestações psiquiátricas nos doentes com DH, bem como a aplicação de testes neuropsicológicos a indivíduos portadores da doença, a fim de permitir uma intervenção em fases mais precoces, minimizando assim as consequências negativas destas comorbilidades, nomeadamente o suicídio.

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MARSUPIALIZATION – PROMOTING BONE REGENERATION IN THE TREATMENT OF "GIANT" MAXILLARY ODONTOGENIC CYSTS

MARSUPIALIZAÇÃO – PROMOÇÃO DA REGENERAÇÃO ÓSSEA NO TRATAMENTO DE QUISTOS ODONTOGÉNICOS "GIGANTES" DOS MAXILARES

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ABSTRACT

Odontogenic cysts are frequent maxillary lesions which slowly grow through the augment of hydrostatic pressure. They can reach important dimensions, leading to bone resorption and/or lesion by compressing local vital structures. In this paper we report a case of a 55 year old woman who presented a dentigerous cyst in the mandibular body near impacted 4.7 and 4.8. Given the high risk of fracture of the mandible and lesion of the inferior alveolar nerve, we opted for the decompression of the cyst with a marsupialization and subsequent enucleation of the remnant.

Keywords: odontogenic cyst, dentigerous cyst, marsupialization, decompression.

RESUMO

Quistos odontogénicos são lesões dos maxilares muito frequentes, que crescem lentamente através do aumento da pressão osmótica no seu interior. Podem atingir grandes dimensões, levando a reabsorção óssea e/ou lesão por compressão de estruturas nobres locais. Apresentamos o caso de uma mulher de 55 anos com um quisto dentígero do corpo mandibular direito e dentes 4.7 e 4.8 inclusos. Pelo risco de fratura da mandíbula e de lesão do nervo alveolar inferior, optou-se por descompressão do quisto com marsupialização e posterior enucleação da lesão remanescente.

Palavras-chave: quisto odontogénico, quisto dentígero, marsupialização, descompressão, boné regeneration.

INTRODUÇÃO

Quistos odontogénicos são lesões dos maxilares muito frequentes. Têm origem nos remanescentes do epitélio embrionário dos dentes, aumentando de volume pela pressão hidrostática no seu interior. Este aumento de volume é em regra lento podendo gerar lesões de grandes dimensões e condicionar reabsorção óssea dos maxilares. Podem ser assintomáticos ou manifestar-se por tumefações indolores. Dor e parestesias podem surgir por sobreinfeção bacteriana aguda. Radiograficamente são imagens radiotransparentes com halo radiopaco circundante [1].

O tratamento definitivo dos quistos odontogénicos é a enucleação completa com exérese de todo o epitélio. No caso de quistos de grandes dimensões que condicionem fragilidade óssea e risco de fratura durante a cirurgia, ou que estejam próximos de estruturas nobres, recomenda-se que a exérese do quisto seja precedida de um período de marsupialização [2]. A diminuição da pressão intra-quística promove a redução de volume e regeneração do osso circundante, minimizando o risco de fratura óssea e de lesão de estruturas nobres (nervo alveolar inferior, nervo lingual, dentes ou gérmenes de dentes, seio maxilar, cavidade nasal) durante a enucleação [2-5]. A marsupialização pode ser realizada através da excisão local da mucosa e membrana quística com sutura da parede do quisto à mucosa oral [2] ou através da colocação de um tubo de drenagem fixo por sutura de modo a manter a patência da incisão [2,3]. As desvantagens deste método são a necessidade de cooperação dos doentes na irrigação diária da cavidade, maior número de visitas médicas e radiografias de controlo e um maior tempo total de tratamento [2].

Apresentamos o caso de uma doente tratada no serviço de Estomatologia com um quisto dentígero da mandíbula de grandes dimensões, tratado com marsupialização seguida de enucleação.

APRESENTAÇÃO DO CASO

Doente do sexo feminino, de 55 anos de idade, caucasiana, referenciada pelo médico de família, por indicação do seu dentista assistente, para a consulta de Cirurgia Oral do Serviço de Estomatologia do CHLN, em Outubro de 2015, por achado radiológico de imagem radiotransparente no corpo direito da mandíbula, associada a 4.7 e 4.8 inclusos. A doente apresentava-se assintomática, nomeadamente, sem dor ou parestesias e o seu exame objetivo intra e extra-oral era normal. A ortopantomografia revelou lesão quística ocupando parcialmente o corpo mandibular direito, envolvendo as coroas de 4.7 e 4.8 inclusos horizontais, característico de um quisto odontogénico dentígero ou queratoquisto. As lâminas corticais eram finas mas permaneciam íntegras. A TC maxilo-facial revelou osso restante da lâmina cortical com 2 mm de espessura. O quisto apresentava 35 mm de maior eixo (ântero-posterior), 22 mm de eixo crânio-caudal e 5,7 cc de volume e encontrava-se em íntima relação com o nervo alveolar inferior, que estava deslocado inferiormente em relação à sua posição anatómica normal (figura 1).

Perante as dimensões do quisto, a fina espessura da lâmina cortical e a relação de proximidade com o nervo alveolar inferior, programou-se marsupialização e biópsia do quisto, com vista a posterior enucleação da lesão remanescente. Sob anestesia local, em Fevereiro de 2016, procedeu-se a biópsia da parede do quisto e marsupialização com colocação de tubo de drenagem. Instruiu-se a doente para irrigação diária com soro

Figura 1

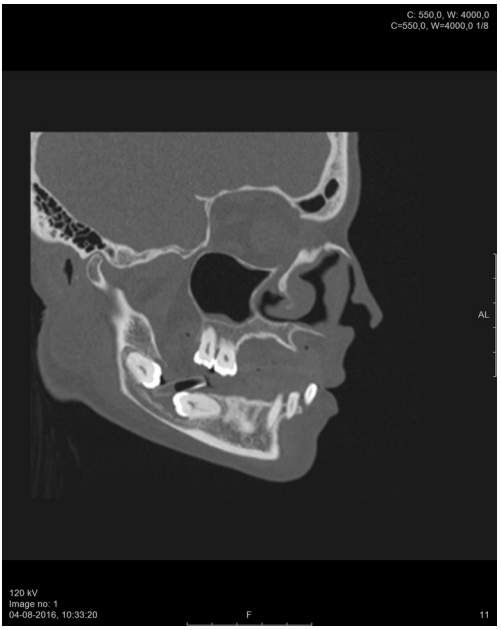

Figura 2

fisiológico através do tubo de marsupialização. O exame anátomo-patológico da parede do quisto confirmou o diagnóstico de quisto dentígero. Em controlo radiológico realizado 3 meses após a marsupialização, verificou-se diminuição do tamanho da lesão e individualização de canal do nervo alveolar inferior. A TC maxilo-facial revelou osteosclerose marginal reparativa, circunscrevendo o nervo alveolar inferior e aumento da espessura da parede mandibular. O quisto remanescente exibia 25 mm de maior eixo e 1,3 cc de volume, que representa uma diminuição de aproximadamente 80% do seu volume inicial (figura 2). Sob anestesia geral, procedeu-se a enucleação do quisto e exodontia de 4.7 e 4.8 inclusos. O pós-operatório decorreu sem intercorrências. O exame anátomo-patológico mostrou quisto dentígero com características inflamatórias.

DISCUSSÃO

A redução da pressão hidrostática intra-quística e no osso envolvente interrompeu o ciclo de reabsorção óssea e permitiu a sua regeneração gradual. A duração da marsupialização não está protocolada, sendo habitualmente entre 6 meses e 1 ano [6-7]. Nesta doente, a decisão de interromper a marsupialização e proceder à enucleação foi tomada quando a regeneração óssea local diminuiu significativamente o risco de complicações como a fratura ou a lesão do nervo alveolar inferior. A realização da biópsia da parede do quisto é essencial durante a marsupialização para exclusão de alterações ameloblásticas ou neoplásicas malignas [1]. Neste caso a discrepância anátomo-patológica entre a biópsia inicial da parede da lesão e a peça cirúrgica é explicada pelas alterações inflamatórias induzidas pela marsupialização, mantendo-se o diagnóstico clínico-radiológico e anátomo-patológico de quisto odontogéni-

co dentígero. O tratamento conservador deve prevalecer sempre que possível, pois a preservação de estruturas da face é um fator de bem-estar e determinante para a estética facial e para o sucesso da reabilitação dentária com próteses removíveis ou implantossuportadas.

CONCLUSÃO

A marsupialização pré-enucleação traz grandes benefícios no tratamento de quistos odontogénicos dos maxilares: redução do tamanho do quisto, promoção da regeneração óssea e redução do risco de complicações cirúrgicas durante a sua enucleação.

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PANCREATIC TUMOR IN A PATIENT WITH PLASMA CELL LEUKEMIA

NÓDULO PANCREÁTICO EM DOENTE COM LEUCEMIA A PLASMÓCITOS

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ABSTRACT

Plasma cell leukemia is a rare and aggressive variant of multiple myeloma, accounting for about 2-3% of all plasmocytic dyscrasias. It usually occurs at younger ages and has a more aggressive clinical course than myeloma, being frequent the pleural effusion and extramedullary tumors. The pancreatic involvement, however, is extremely rare, with only 50 cases described in the international literature so far. In this case, an elderly woman with inaugural diagnosis of plasma cell leukemia is identified with pleural effusion and multiple extramedullary nodules including a pancreatic one.

Keywords: plasma cell leukemia, pancreatic mass.

RESUMO

A leucemia a plasmócitos é uma variante agressiva e rara do mieloma múltiplo, perfazendo 2-3% das discrasias plasmocitárias. Geralmente ocorre em idade mais jovem e tem manifestações clínicas mais agressivas relativamente ao mieloma, sendo comuns o derrame pleural neoplásico bem como massas extramedulares. O envolvimento pancreático, contudo, é raro, com apenas 50 casos descritos na literatura internacional até à data. Apresenta-se o caso de uma idosa com diagnóstico inaugural de leucemia a plasmócitos em que se identificaram derrame pleural e várias massas extra-medulares, nomeadamente pancreática.

Palavras-chave: leucemia a plasmócitos, massa pancreática.

INTRODUCTION

Plasma cell leukemia (PCL) is a rare disease with European estimated incidence of 0.04 cases per 100.000 inhabitants a year, accounting for about 0.9% of all cases of acute leukemia [1].

The diagnosis relies on the presence of more than 20% of plasma cells in peripheral blood or an absolute plasma cell count greater than $2x10^9$/L[1-3]. It is primary when the diagnosis is *"de novo"* or secondary when it comes due to the regular progression of monoclonal gammopathy of unknown significance (MGUS) to multiple myeloma (MM) culminating in a leukemic form. In initial stages of MM, tumor cells are strongly dependent on bone marrow (BM) microenvironment, however, they can latter egress to peripheral blood stream and form extramedullary disease. This progression is described in only 1-4% cases of plasmacytic dyscrasia [1].

Patients with PCL are typically 10 years younger than MM patients (65 and 75 years-old, respectively) and usually have more aggressive clinical course [1]. They frequently have dyspnea, pallor and hemorrhagic diathesis due to cytopenias as a result of BM infiltration by plasma cells and higher levels of beta2-microglobulin and free-light chains in urine [1]. The prevalence of lytic bone lesions, however, is lower than in MM patients [1]. At physical examination, patients may present with hepatosplenomegaly, pleural effusion and extramedullary soft tissue plasmacytomas [1].

The pancreatic involvement in hematological malignancies is sorely rare and mainly due to non-Hodgkin lymphomas, reported to occur in 5-30% of all lymphomas [4]. In the specific case of PCL, the pancreatic involvement is exceptional, with only 50 cases described in international literature so far, comprising less than 0.1% of all pancreatic masses [5]. Clinical manifestations, if present, are obstructive jaundice and abdominal pain [5].

Despite the recent therapeutic approaches, the prognosis of patient with PCL is still poor, with estimated median survival ranging from 7 to 13 months [1].

CASE PRESENTATION

An 83-year-old woman, autonomous and without previous relevant medical conditions, was admitted because of consumption syndrome and mental confusion in the previous month.

At physical examination she had reasonable general condition, temporal disorientation but no neurological signs, no skin or mucosal signs of hemorrhage, neither palpable lymphadenopathies nor abdominal masses. Pulmonary murmur was abolished in the right hemithorax.

Blood tests revealed normocytic normochromic anemia (hemoglobin 9.9 g/dL) and slight thrombocytopenia ($130.000x10^9$/L); leukocyte count was normal. The peripheral blood smear had 15% of plasmocytes ($3.67x10^9$/L) and the serum electrophoresis showed a peak of 3.3 g/dL in gamma fraction (figure 1) with total proteins of 7.5 g/dL and albumin of 2.5 g/dL. Serum immunofixation showed monoclonal gammopathy IgG Lambda and the urinary one had Lambda Bence Jones proteinuria. Creatinine was 1.16 mg/dL and serum calcium corrected to the albumin levels of 9.5 mg/dL. Beta2-microalbumin (14.46 mg/dL), lactic dehydrogenase (8600 UI/L) and uric acid (17.2 mg/dL) were increased. The myelogram had infiltration of 62.8% by dysmorphic plasma cells with immunophenotype CD 138+ / CD38+ / CD19- / CD45- / CD56+ (74,2%) and CD56+ (25,8%).

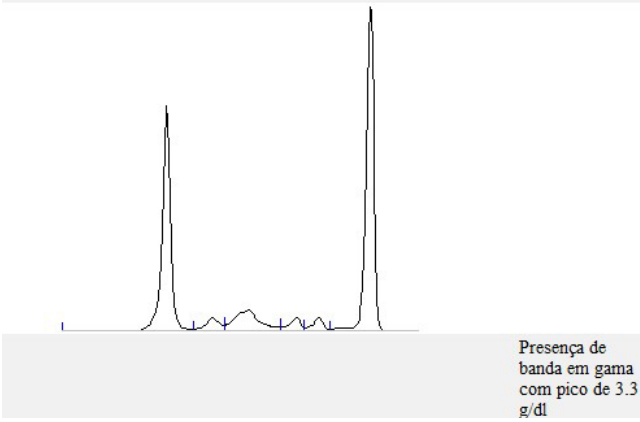

Figure 1 – Serum electrophoresis: peak of 3.3 g/dl in gamma fraction.

Thoracic x-ray showed pleural effusion (figure 2), and the thoracocentesis (800 ml of transudate) and pleural biopsy were positive to plasma cells. Cranial tomography scan had no encephalic changes but revealed a small osteolytic lesion in the skull (figure 3).

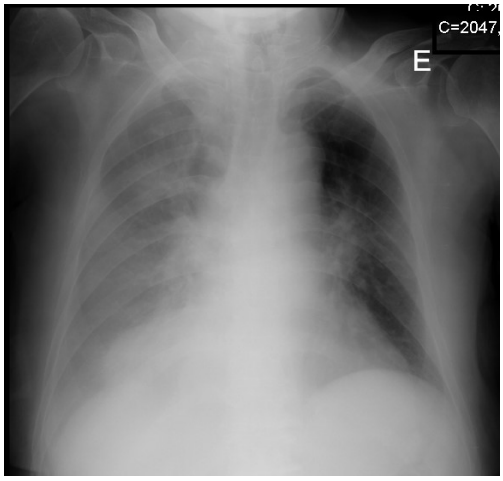

Figure 2 – Thoracic x-ray: pleural effusion in right hemithorax.

Figure 3 – Cranial Computed Tomography Scan: small osteolytic lesion in the skull (left frontal topography).

A slightly elevation in transaminases (aspartate aminotransferase 69 UI/L, alanine aminotransferase 22 UI/L; alkaline phosphatase, gamma-glutamyltransferase and bilirubin were normal) worked-out in an abdominal ultrasound which revealed an hypoechogenic mass in the pancreatic body of 3x2 cm,

further characterized by abdominal tomography (figure 4) that additionally revealed soft-tissue masses in the mediastinum (figure 5), diaphragm (figure 6) and in pre-sacrum topography (figure 7).

Tumor markers carcinoembryonic antigen (CEA) and cancer antigen 19.9 (CA 19.9) were normal (2.1 ng/mL and 10.6 UI/mL, respectively).

Figure 4

Figure 5 – Thoraco-abdominal Tomography Scan: mediastinical mass.

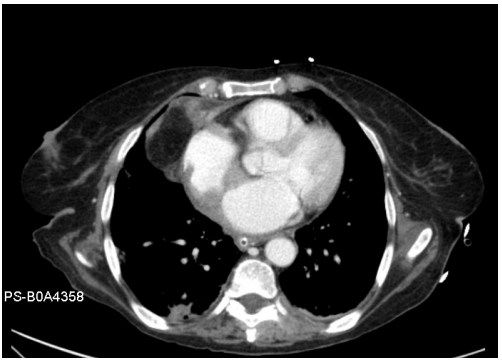

Figure 6 – Thoraco-abdominal Tomography Scan: diaphragmatic mass

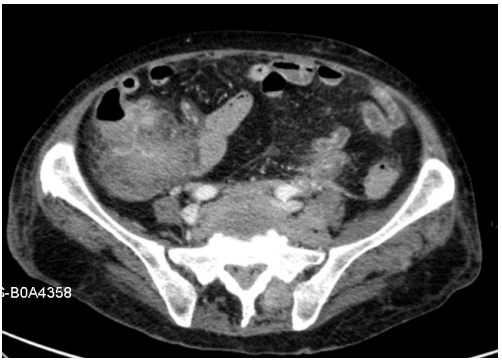

Figure 7 – Thoraco-abdominal Tomography Scan: mass in pre-sacrum topography.

Diagnosis of PCL with pleural effusion and multiple extramedullary masses was made and dexamethasone therapy was immediately initiated. Notwithstanding, the patient died in 2 days due to urosepsis by *Klebsiella pneumoniae*.

DISCUSSION AND CONCLUSION

PCL is a rare condition usually arising in younger patients. The reported patient was 83 year old, which prompted us to infer that it was probably secondary to an asymptomatic evolution from MM to PCL over the years. This is also in agreement with the extensive radiological changes, namely pleural effusion and multiple soft-tissue masses (probably plasmacytomas).

In the course of the disease, it is common the progression with extramedullary tumors, mostly the ones in mediastinum, diaphragm and pre-sacrum topography, making us to believe that they probably were due to the plasma cell dyscrasia. The pancreatic one, however, due to its rarity, is difficult to accept as being attributable to the PCL.

In fact, the BM study and the immunophenotyping were conclusive about the diagnosis of this entity and the additional study of the pleural effusion and pleural biopsy also revealed the presence of plasma cells.

Due to the sudden clinical denouement with death in the first days after admission, it was impossible to conduct more detailed studies, namely with biopsies of the soft-tissue tumors which would be conclusive and would allow us to infer that they were really plasmacytomas. Necropsy study was not accomplished.

Although tumor markers CEA and CA 19.9 were negative, their sensitivity for primary pancreatic neoplasm is very low [6], being impossible to totally exclude this hypothesis once pancreatic biopsy was not conducted. However, in the presence of a hematological disseminated disease, together with the fact that the computed tomography scan showed no evidence of a further primary tumor and the tumor markers possibly implicated in the natural history of pancreatic cancers were negative, we can conclude that this pancreatic mass is most probably secondary to PCL.

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RECURRENT PAROTITIS AS A MANIFESTATION OF HIV INFECTION IN CHILDREN

PAROTIDITES DE REPETIÇÃO COMO APRESENTAÇÃO DE INFEÇÃO POR VIH NA CRIANÇA

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ABSTRACT

Recurrent parotitis in children is a recurrent inflammatory enlargement of the parotid gland (unilateral or bilateral), usually painful and accompanied by fever and malaise. It mainly affects male children from 3 to 6 years of age. Diagnosis is essentially clinical and the parotid ultrasound is the imaging tool of choice. Aetiology is multifactorial and determines both treatment and prognosis.

We present the clinical case of a two year-old boy from Guinea, with recurrent parotitis starting at the age of 6 months, anaemia and developmental delay, confirmed to be caused by human immunodeficiency virus type-1 infection (HIV-1).

The aim of this case is to highlight the HIV infection as a cause of recurrent parotitis in children, especially if coming from countries with high incidence of HIV infection, being a manifestation seen in up to 30% of symptomatic HIV positive children.

Keywords: child, parotid gland, parotitis, recurrent parotitis, HIV infection.

RESUMO

A parotidite recorrente da infância (PRI) consiste na inflamação recorrente da glândula parótida (uni ou bilateralmente), acompanhada de dor e, habitualmente, febre e mal-estar geral. Atinge preferencialmente crianças do sexo masculino dos 3 aos 6 anos, sendo o diagnóstico fundamentalmente clínico e a ecografia parotídea o exame de eleição. A etiologia é multifatorial e condiciona o tratamento e o prognóstico.

Apresentamos o caso clínico de uma criança de 2 anos, natural da Guiné, com parotidite recorrente desde os 6 meses, anemia e atraso do desenvolvimento, cuja etiologia se confirmou ser infeção por vírus da imunodeficiência humana (VIH) tipo 1.

O objetivo desde caso é destacar a infeção por VIH como causa de parotidite recorrente, particularmente em crianças procedentes de países com elevada incidência, sendo uma manifestação presente em até 30% das crianças com infeção por VIH sintomática.

Palavras-chave: Criança, glândula parótida, parotidite, parotidite recorrente, infeção VIH.

INTRODUÇÃO

A Parotidite Recorrente da Infância (PRI) consiste na inflamação recorrente da glândula parótida (uni ou bilateralmente), acompanhada de dor e, habitualmente, febre e mal-estar geral, com episódios de duração variável (de um dia a várias semanas) [1], atingindo preferencialmente crianças do sexo masculino dos 3 aos 6 anos [2]. O diagnóstico é fundamentalmente clínico e confirmado por ecografia parotídea.

Na maioria dos casos esta doença tem um carácter benigno e auto-limitado, mas pode ser manifestação de doenças sistémicas.

A parotidite epidémica causada pelo Paramixovírus é uma causa muito infrequente na atualidade desde a introdução da vacina a nível mundial, não sendo causa de parotidite recorrente [3]. Agentes etiológicos virais causadores de parotidite recorrente são a influenza A, parainfluenza 2 e 3, adenovírus, enterovírus, rinovírus, coronavírus [4], herpes simplex 1 e 2, vírus de Epstein Barr (EBV) e citomegalovírus (CMV). A parotidite bacteriana é causada maioritariamente pelo *S.aureus* e cursa com febre elevada e secreção de saliva purulenta pelo canal de Stenon [2]. Outros agentes infecciosos menos frequentes, que cursam com linfadenopatias generalizadas, febre, perda de peso e dor são o *M. tuberculosis* e micobactérias não tuberculosas, *Bartonella henselae*, *Francisella tularensis* e *Toxoplasma gondii*. Para além das parotidites infecciosas existem as secundárias a imunodeficiências (défice de IgA e VIH), malformações canaliculares e linfomas (muito raros na infância, unilaterais, duros e com sintomas sistémicos) [2]. A partir dos 6 anos, a etiologia auto-imune (síndrome de Sjögren, LES), apesar de infrequente, deve ser considerada e pesquisados sintomas acompanhantes (xerostomia, queratoconjuntivite, xeroftalmia, artralgias) [2]. A história familiar de casos familiares com parotidite de repetição levanta a suspeita de parotidite recorrente autossómica dominante, muito rara na infância [1].

O diagnóstico etiológico da parotidite recorrente é estabelecido após realização de ecografia parotídea e avaliação analítica inicial com serologias para agentes infecciosos. Muito raramente será necessário a realização de sialografia ou tomografia computorizada (TC), e de estudos imunológicos.

O tratamento na maioria das ocasiões é conservador, com analgésicos anti-inflamatórios e medidas locais, e dirigido à patologia de base.

Apresentamos o caso clínico de uma criança de 2 anos, natural da Guiné, com história de parotidites de repetição desde os 6 meses, anemia e atraso do desenvolvimento psico-motor.

APRESENTAÇÃO DO CASO

Lactente de 2 anos de idade, sexo masculino, natural da Guiné, a residir em Portugal com a mãe desde há 1 semana. Gestação vigiada na Guiné, com ecografias normais e serologias maternas negativas (informação verbal materna). Parto de termo por cesariana, sem motivo conhecido, índice de Apgar: 9 (1')/ 10 (5'), com peso ao nascer de 2.550g. Período neonatal sem intercorrências, aleitamento materno exclusivo até os 6 meses, com diversificação alimentar desde então (papas, sumos e sopas). Vacinas atualizadas segundo o programa de vacinação da Guiné. Evolução estaturo-ponderal entre os

percentis 10 e 25. Apresentava atraso psico-motor marcado, com comunicação por sons ininteligíveis, sem palavras e marcha instável de base ampla, de etiologia não esclarecida.

Como antecedentes patológicos destacam-se múltiplos internamentos na Guiné por febre, parotidites (de 4-5 dias de evolução, resolvidas com e sem antibiótico), e otites de repetição, anemia (transfusão de concentrado eritrocitário por hemoglobina de 6 g/dL) e paludismo. Sem outras intercorrências.

Sem antecedentes familiares de relevo (nomeadamente história familiar de parotidites). Mãe de 26 anos, licenciada e com anemia cuja etiologia não sabe especificar; pai de 32 anos, arquiteto e irmão de 7 anos, ambos saudáveis e residentes na Guiné.

Recorreu ao serviço de urgência a 17/03/2016 (2 anos e 2 meses de idade) por febre com 7 dias de evolução (Tª máxima: 39ºC), com intervalos de apirexia de 6/6 horas e cedência parcial aos antipiréticos, associado à tumefação da região parotídea bilateral, presente desde os 6 meses de idade. Ao exame objetivo apresentava bom estado geral, com atraso marcado no desenvolvimento psico-motor, encontrando-se hemodinamicamente estável e apirético, com tumefação bilateral das glândulas parótidas e hepatoesplenomegalia (ambos palpáveis 3 cm abaixo do bordo costal). Não apresentava outras alterações (figura 1).

Figura 1

Realizou avaliação analítica, apresentando anemia normocítica e normocrómica (hemoglobina: 9.7 g/dL), leucócitos: 5.320 (neutrófilos: 28%, linfócitos: 65.1%), trombocitopenia de 123.000/uL, velocidade de sedimentação (VS): 37 mm/1ªh, glicose: 90 mg/dL, ureia: 16 mg/dL, creatinina: 0.3 mg/dL, Na^+: 137 mmol/L, K^+: 3.6 mmol/L, proteína C reativa (PCR): 0.20 mg/dL, AST: 59 U/L, ALT: 43.2 U/L, LDH: 634 U/L e Ca^{2+}: 8.6mg/dL. A ecografia parotídea revelou "aumento do tamanho das glândulas parotídeas bilateralmente". Teve alta com o diagnóstico de parotidite viral e indicação para realizar tratamento anti-inflamatório, com orientação para consulta de Hematologia Pediátrica em 4 dias para estudo de alterações hematológicas e para saber os resultados das serologias virais e pesquisa de *Plasmodium*.

À data da consulta encontrava-se em apirexia mantida, com bom estado geral mas com aumento do volume da região parotídea bilateralmente, otite média aguda à direita e supurada à esquerda. Mantinha anemia (hemoglobina: 9.4 g/dL) e trombocitopenia (170.000/uL), sem leucocitose; tinha PCR negativa e VS: 85 mm/1ªh. As serologias infecciosas (CMV, EBV, rubéola, herpes simplex tipo 1 e 2, toxoplasma e sífilis) e pesquisa de *Plasmodium* foram negativas.

Teve alta com o diagnóstico de parotidite viral e otite bilateral, medicado com amoxicilina + ácido clavulânico. Foi referenciado a consulta de Infecciologia Pediátrica a 08/04 onde se pediu serologia para VIH, que foi positiva para VIH-1 (ELISA e Western Blot). A carga viral era de 2.532.352 cópias /mL, com linfócitos T-CD4+ de 463 células/mm3 (11.8%) e sem mutações de resistência.

A pesquisa do alelo HLA B*5701 foi negativa e foram feitas serologias maternas, que resultaram ser também positivas para VIH-1, pelo que foi referenciada ao serviço de Infecciologia do CHLN para acompanhamento e in de terapêutica anti-retroviral.

O pai, residente na Guiné, apresentava serologias, previamente conhecidas, positivas para VIH-1 tendo recusado inicio de terapêutica anti-retroviral. O irmão da criança, residente na Guiné com o pai, teria serologias negativas (informação verbal materna).

Foi decidido internamento eletivo na Unidade de Infecciologia Pediátrica para inicio de terapêutica anti-retroviral a 07/05/2016. Ao exame objetivo à entrada apresentava várias adenopatias a nível do ângulo da mandíbula (dolorosas e móveis), hepatomegalia (3 cm) e esplenomegalia (3 cm) e um quadro clínico compatível com pneumonite intersticial linfóide, sem dificuldade respiratória.

Iniciou terapêutica anti-retroviral combinada (TARc) ajustada ao peso (12 kg) com abacavir (ABC) 20 mg/dL (5mL 12/12h), lopinavir (LPN) 80 mg/dL + ritonavir (RTV) 20 mg/dL (3mL de 12/12 horas) e lamivudina (3TC) 1% 5mL de 12/12 horas. A pesquisa de infecções oportunistas (*Plasmodium*, hemocultura em aerobiose, anaerobiose e micológica, coproculturas, vírus respiratórios, IGRA, pesquisa de micobactérias no suco gástrico - *M. tuberculosis* com exame directo e cultural, serologia e cultura de *Bartonella* e Ag *Criptococcus*) resultou negativa.

Foi realizada ecografia abdominal com "hepatomegalia ligeira difusamente grosseira e heterogénea, moderada esplenomegalia heterogénea com inúmeras imagens nodulares milimétricas hipoecogénicas, aspetos sugestivos de etiologia infecciosa. Sem outras alterações".

Durante o internamento verificaram-se tensões arteriais elevadas com tensão arterial sistólica (TAS): 97-100 mmHg e tensão arterial diastólica (TAD): 56-62 mmHg (>P99 para a idade) e alterações urinárias (pH: 7.0, densidade: 1.014, leucócitos: 500/campo, nitritos negativos, eritrócitos: 25/campo e cilindros granulosos com creatinúria normal), com urocultura negativa. A função renal (creatinina, ureia e taxa de filtração glomerular) manteve-se sempre sem alterações. Realizou ecografia renal com Doppler nesse contexto, que não apresentou alterações, e ecocardiograma, com "derrame pericárdico pequeno, sem alterações hemodinâmicas significativas e VE normal". Analiticamente à data de alta apresentava ainda anemia (hemoglobina: 8.8 g/dL) com leucócitos de 19.170 (linfócitos: 71.9%), trombocitopenia (plaquetas: 166.000 u/L), PCR negativa (0.59 mg/dL) com VS ainda elevada (109 mm/1ªh) com descida ligeira do nível de AST (57 U/L). A função renal e o ionograma não apresentavam alterações.

Ficou com indicação de manter TARV e profilaxia com co-trimoxazol em ambulatório.

Manteve seguimento em consulta de Infecciologia Pediátrica, com evolução favorável, normalizando o valor de hemoglobina, plaquetas e sedimento urinário um mês depois do início da TARc, e mantendo

valores tensionais normais sem terapêutica. A rápida normalização do sedimento urinário e dos valores da tensão arterial com função renal e ecografia renal normais levaram a que não fosse efetuada biópsia renal que poderia confirmar a existência de nefropatia associada ao VIH.

Na última avaliação, após 11 meses de TARV, a carga viral era indetetável, com recuperação dos linfócitos T-CD4+ para 28%. Clinicamente apresentava resolução do quadro de parotidite, melhoria marcada na progressão da curva estaturo-ponderal (atualmente entre os percentis 25 e 50) e melhoria do quadro de atraso psico-motor (ainda comunicação por sons, com uso de 3-4 palavras, marcha de base estreita, melhoria do comportamento e interesse pelo entorno).

Manteve também seguimento em consulta de Cardiologia (ecocardiograma normal, sem derrame pericárdico e boa função ventricular) e ORL, com indicação para miringotomia e colocação de tubos trans-timpânicos, que ainda não realizou.

DISCUSSÃO E CONCLUSÃO

A parotidite recorrente é uma manifestação frequente da infeção por VIH na criança e está habitualmente associada a outras manifestações de hiperplasia linfóide como linfadenomegalias, hepatomegalia, esplenomegalia e pneumonite intersticial linfóide. O aumento do tamanho parotídeo pode ser a primeira manifestação da infeção VIH adquirida por transmissão vertical na criança e ocorre quando os valores de CD4+ ainda estão dentro dos parâmetros da normalidade [5], [6]. A TARc permite actualmente obter boa resposta clínica, virológica e imunológica.

A nível mundial, 1.8 milhões dos infetados pelo VIH são crianças com menos de 15 anos [7], a maioria na África subsaariana, sendo a via materna o mecanismo mais frequente de infeção, durante a gravidez (23%), parto (65%) ou aleitamento (12%). A taxa de transmissão global sem TAR é de 20-30%, mas atinge os 63% em grávidas com carga viral superior a 100.000 cópias/ml [8]. Com uma intervenção eficaz (uso de TARc na mãe, parto por cesariana, evicção de aleitamento), a taxa de transmissão pode ser inferior a 2%, mas estas medidas continuam a estar indisponíveis em muitos países em vias de desenvolvimento.

Em Portugal quase a totalidade dos novos casos de VIH são crianças procedentes de África e a apresentação clínica é diversa: linfadenopatia generalizada, hepatoesplenomegalia, atraso no desenvolvimento estaturo-ponderal, pneumonite intersticial linfóide ou infeções típicas da infância (parotidites ou otites recorrentes). 25% das crianças infetadas por transmissão vertical tem uma doença definidora de SIDA no primeiro ano de vida e 57% são sintomáticas nesse período [9].

Não obstante, a situação tem mudado nos países desenvolvidos com a terapia anti-retroviral, onde já não é uma condição fatal mas sim uma doença crónica.

A parotidite causada pelo VIH pode estar presente nas crianças (lesão de grupo 1) e nos adultos (grupo 2) [10], podendo estar presente em 10-30% das crianças com infeção VIH sintomática (sendo o tempo médio de apresentação 4.6 anos) e em até 58% os doentes VIH + em alguma altura da vida [11], [12]. A hipertrofia parotídea bilateral e crónica em adultos estabelece o diagnóstico de infecção por VIH [11].

A parotidite causada pelo VIH cursa com hipertrofia parotídea homogénea, bilateral e persistente, sem sinais inflamatórios, com ou sem dor ou febre e com sintomas acompanhantes como má progressão estaturo-ponderal, diarreia crónica ou infeções recorrentes [2]. Está associada à presença de pneumonite intersticial linfóide, mais frequente na raça negra. Os episódios de dificuldade respiratória ou pneumonias nestas crianças são frequentes e muitas vezes tem o diagnóstico de asma. As infeções de repetição (otite, sinusite, pneumonia e diarreia) são muito mais comuns do que nos doentes com parotidite causada por outras etiologias [1].

A causa do atingimento parotídeo é controversa, podendo envolver mecanismos relacionados diretamente com a ação do vírus VIH ou fenómenos imunológicos no contexto de linfadenopatia generalizada. Os doentes com parotidites recorrentes causadas pelo VIH também podem ter outros sintomas de disfunção glandular como xeroftalmia, xerostomia e artralgias, com infiltração linfóide desses tecidos ou síndrome de linfocitose invasiva difusa [10]. Torna-se necessário o diagnóstico diferencial com a síndrome de Sjögren (neste caso predominam os linfócitos T CD8+ e não CD4+) [6].

Na linfocitose invasiva difusa (com ou sem atingimento parotídeo), existe disfunção imunológica, com aumento CD8+ mais significativo que redução CD4+, pelo que pode ser marcador de menor progressão para SIDA e, portanto, de bom prognóstico [6], [10], [11].

É importante excluir a presença de sarcoma de Kaposi e linfomas parotídeos em adolescentes VIH+ em casos de aumento rápido do volume cervical de forma assimétrica e não generalizada, com adenopatias de consistência endurecida e com a presença de sintomas constitucionais exuberantes ou citopenias periféricas não explicadas pela própria infeção VIH [13].

Com a TARc, as alterações induzidas pela linfocitose invasiva difusa (pneumonite intersticial linfóide, infiltração parotídea, hepatoesplenomegalia) e inclusive o atraso no desenvolvimento estaturo-ponderal, são potencialmente reversíveis desde que não existam alterações estruturais (bronquiectasias).

No nosso caso, a associação deste quadro à proveniência da Guiné torna a infeção VIH a primeira hipótese de diagnóstico a investigar – e constitui um alerta diagnóstico importante no nosso país atendendo às inter-relações com países onde a infeção VIH tem ainda uma elevada prevalência.

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BILATERAL MEIBOMITIS RELATED KERATOCONJUNCTIVITIS ASSOCIATED WITH ANTERIOR UVEITIS

QUERATOCONJUNTIVITE ASSOCIADA A MEIBOMITE COMPLICADA COM UVEÍTE ANTERIOR BILATERAL

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ABSTRACT

Meibomitis related keratoconjunctivitis is a recent established clinical entity, in which corneal changes occur consequently to a posterior blepharitis with meibomian gland dysfunction and inflammation. Corneal changes vary from mild subepithelial cellular infiltrates to dense infiltrates with superficial corneal neovascularization. The pathogenic cause is credited to a delayed-type hypersensitivity to *Propionibacterium acnes*. Main goal of treatment is the improvement of meibomian gland function, topical anti-inflammatory agents and antibiotics. We present a rare case of severe bilateral meibomitis related keratoconjunctivitis associated with anterior uveitis and its challenging diagnosis.

Keywords: meibomiam gland dysfunction, keratoconjunctivitis, anterior uveitis, keratouveitis.

RESUMO

A queratoconjuntivite associada a meibomite é uma entidade clínica recentemente descrita, na qual alterações da córnea ocorrem na sequência de uma blefarite posterior com disfunção e inflamação das glândulas de meibomius. As alterações na córnea são variadas podendo ser infiltrados celulares subepiteliais moderados até infiltrados densos com neovascularização da córnea superficial. A patogénese desta entidade clínica é creditada a uma reação de hipersensibilidade tardia ao *Propionibacterium acnes*. O tratamento passa por melhorar a função das glândulas de meibomius, anti-inflamatórios tópicos e antibióticos. É apresentado um caso raro de uma meibomite bilateral com queratoconjuntitivite e uveíte anterior e o seu desafio diagnóstico.

Palavras-chave: disfunção da glândula de meibomius, queratoconjuntivite, uveíte anterior, queratouveíte.

INTRODUCTION

Meibomitis related keratoconjunctivitis (MRKC) is a recent clinical entity that was first described by Suzuki in 2000 [1,2]. This type of keratoconjunctivits usually presents bilaterally with meibomian gland dysfunction and inflammation, meibium stagnation, hyperemia and edema of the lid margin and tarsal conjunctiva [3,4]. The corneal manifestations with subepithelial infiltrates have a similar pattern to that seen in marginal keratitis and phlyctenular keratitis [3,4]. Other signs as superficial corneal vascularization may also be present [3]. We present a rare case of severe bilateral meibomitis related keratoconjunctivitis associated with anterior uveitis and its challenging diagnosis.

CASE PRESENTATION

A 71-year-old woman presented to the eye casualty department with a bilateral red eye and aqueous exudation beginning two weeks before. A diagnosis of bilateral viral conjunctivitis with pseudomembrane formation was done after slit lamp examination and the patient was discharged with ocular lubricants and topical azithromycin to avoid secondary bacterial infection.

Her past medical history included hypertension, asthma, dyslipidemia, obesity and depression. Her ophthalmologic history was notable for high myopia, uncomplicated cataract surgery of the right eye four months before, cataract in the left eye and bilateral mild primary open angle glaucoma. She was taking antihypertensive drugs, oral acetazolamide, and topical latanoprost, timolol and brimonidine. This medication had been introduced 8 years before and although having asthma she did not complain of respiratory symptoms with timolol. Her best-corrected visual acuity (VA) was 20/25 in the right eye (OD) and 20/50 in the left eye (OS) according to a recent ophthalmologic examination record.

After three months of ocular treatment with no improvement the patient returns to the emergency department also complaining of decreased visual acuity in both eyes.

VA examination was of counting fingers at two meters in OD and 20/200 in OS (Snellen chart). The intraocular pressures were symmetrically increased, with 30 mmHg in both eyes. Slit-lamp examination revealed bilateral redness and swelling of the eyelid margin and palpebral conjunctiva, stagnation of meibium, superficial punctate keratopathy, inferior sterile corneal subepithelial infiltrates, superficial inferior corneal neovascularization, non granulomatous keratic precipitates and moderate anterior chamber cells with flare (figure1). Right eye had posterior synechia to the intraocular lens, and left eye had 360 degrees posterior synechia with a non-reactive iris to mydriatics. No iris defects were present in both eyes.

Fundus examination revealed bilateral chorioretinal atrophic lesions associated with high myopia. No signs of posterior inflammation were present.

At this point due to the bilateral anterior non granulomatous uveitis, the patient was referred to the ocular inflammation department which considered etiologic testing.

Complete blood test and renal function were normal. Serology tests were negative to: Interferon gamma release assay, *Herpes simplex* (type I and II), *Borrelia burgdorferi, Coxiella burnetii, Treponema*

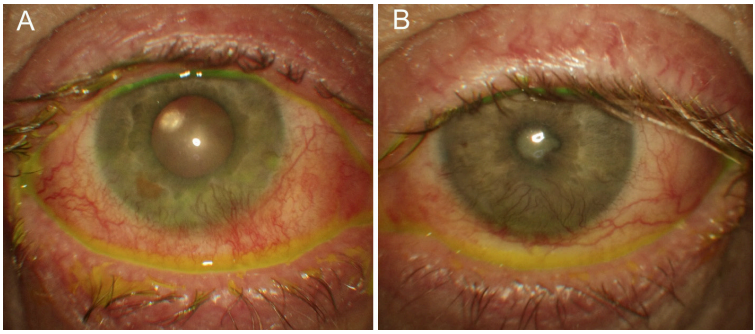

Figure 1 – Severe posterior blepharitis with meibomitis and ocular surface inflammation. Meibomian gland orifices were obstructed, and redness and swelling of the inferior eyelids margin were present. Extensive inferior subepithelial sterile infiltrates with superficial corneal neovascularization and non-granulomatous keratic precipitates were present in both eyes. (A – right eye; B – left eye).

pallidum (VDRL*). Cytomegalovirus* IgG positive and IgM negative. Angiotensin-converting enzyme was normal [22U/L]. Conjunctival exudate and corneal infiltrates scraping were negative for bacteria and fungus. Brain and chest computed tomography scans were unremarkable with no evidence of lesions. Abdomen ultrasound was unremarkable. Anterior chamber tap with aqueous humor analysis was negative for virus, bacteria and fungus.

Differential diagnosis

The clinical findings at presentation were consistent with a bilateral anterior non granulomatous keratouveitis of unidentified cause. A diagnosis of mascarade syndrome was considered by the ocular inflammation department but since a full body imagological study did not find any relevant findings the patient was eventually referred to a corneal consultation two months after presentation on the emergency department.

After careful examination of the posterior lids, the cornea department suggested the diagnosis of severe meibomian gland dysfunction with meibomitis and obstruction as the cause of the keratoconjunctivitis and uveitis. Other active diagnosis as severe dry eye syndrome and anterior blepharitis were also considered in the pathogenesis and chronicity of this episode.

Differential diagnosis included bilateral herpetic keratouveitis and marginal keratitis and as these could not be excluded with certainty, treatment addressed both pathologies.

Treatment

The patient was started on doxycycline 100mg BID, valaciclovir 1g BID and acetazolamide 125mg TID on admission. As eye drops the patient started preservative free lubricants, azithromycin BID, dexamethasone TID, timolol BID and tropicamide TID. Lid hygiene was indicated as vital.

Outcome and follow-up

Remarkably, soon after starting treatment, prompt resolution of the hyperemia and anterior chamber cells occurred associated with a progressive decrease of the superficial corneal neovascularization, superficial punctate keratopathy and corneal subepithelial infiltrates at one month (figure 2). There was also partial resolution of the anterior and posterior blepharitis. However, stromal scarring lead to a mild diffuse opacity in both eyes.

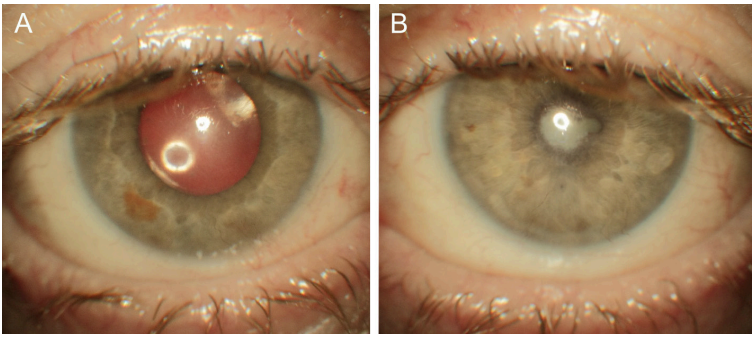

Figure 2 – Bilateral clinical improvement at one month after beginning treatment. Less redness of palpebral and bulbar conjunctiva, decrease of keratic precipitates and anterior chamber cells, as reduction in corneal neovascularization were observed. (A – right eye; B – left eye).

At a follow-up appointment three months later, the patient was under oral doxycycline 100mg ID and acetazolamide 250mg BID, preservative free eye drops with dexamethasone TID, timolol BID and lubricant as needed. Right eye visual acuity improved significantly, from counting fingers on admission to 20/50, the left eye maintained a visual acuity of 20/200 due to cataract. Normal intraocular pressures (OD 16 mmHg and OS 19 mmHg), and an unchanged fundus appearance were observed. However, the patient was not discharged of oral acetazolamide due to poor intraocular pressure control without this medication and awaits drainage device implantation in both eyes.

Despite the remarkable improvement in the visual acuity of the right eye, the prognosis in terms of visual gain are poor due to stromal corneal scarring in both eyes. The left eye is expected to gain some vision after cataract surgery.

DISCUSSION

Meibomitis related keratoconjunctivitis (MRKC) pathogenesis is thought to be a delayed-type hypersensitivity reaction to *Propionibacterium acnes* and the majority of patients tend to be young women.[3] Unlike most cases, our patient was older. We suggest the severity of the initial pseudomembranous viral conjunctivitis might have been the trigger for the general aggravation of the posterior blepharitis and consequent meibomitis and corneal disease. The anterior uveitis might be explained by the severity and chronicity of the associated keratitis, as seen in previous reports.[5]

Appropriate and proper treatment of meibomitis related keratoconjunctivits (MRKC) is critical because the cornea might be severely compromised.[3] The main goal of MRKC treatment is the reduction of *Propionibacterium acnes*, which might cause meibomitis with systemic and topical antibitotics, namely cephalosporins, macrolids and tetracyclines.[3,4,6] Treating the underlying meibomian gland dysfunction and blepharitis is also important. Therefore, lid hygiene, and low-dose corticosteroids can also be effective particularly if ocular surface inflammation is a concern.[3]

In this patient, the differential diagnosis included marginal keratitis, bilateral herpetic keratouveitis and a mascarade syndrome.

The presence of sterile corneal infiltrates might lead to a diagnosis of marginal keratitis related to *Staphylococcus aureus* hypersensitivity reaction. However, in this patient the infiltrates did not follow the typical pattern of a marginal keratitis: bilateral involvement; not self-limited in time; large infiltrates not separated from the limbus, with some extending to the corneal axis; and the associated corneal neovascularization.[7]

The evidence that bilateral herpetic corneal involvement can happen (1-10%), explains why we addressed *Herpes simplex* treatment.[8] In 2015, Martín-Secured et al. reported a case of bilateral herpetic keratouveitis.[9] *Herpes simplex* keratouveitis usually presents with corneal neovascularization and high intraocular pressure. The presence of severe posterior lid inflammation with meibomitis, no iris transillumination defects, a negative anterior chamber tap and serology to *Herpes simplex* lead us not to consider *Herpes simplex* keratouveitis.

The diagnosis of a mascarade syndrome was considered by the ocular inflammation department after major causes of infectious and noninfectious anterior uveitis were excluded. However, since a full body imagiological study did not find any relevant finding, this diagnosis was discharged particularly after taking in consideration the lid and meibomian gland inflammation in the pathogenesis.

This case is remarkable in the sense that it is an important diagnosis to consider whenever a keratitis is present with associated posterior blepharitis and meibomitis. Knowing MRKC not only can avoid unnecessary examinations but also provide a better visual prognosis.

Finally, this case also shows the clinical challenge when managing patients with severe corneal disease and high intraocular pressure. Choosing preservative free drugs or non benzalkonium chloride preserved medications might help on corneal recovery. (10) However, in this patient, the fact that only oral acetazolamide assures a good intraocular pressure control lead us to schedule a glaucoma drainage device implantation.

CONCLUSIONS

Meibomitis and posterior blepharitis might lead to severe corneal disease if not treated promptly. Meibomitis related keratoconjunctivitis is a recent established clinical entity to take in consideration if corneal scarring and neovascularization are present. This case is remarkable in the sense that unlike most cases, our patient showed an associated anterior uveitis and it sustains the need to expand the knowledge of this entity in order to speed up diagnosis to preserve visual function and avoid unnecessary complementary examinations.

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AN ADVERSE REACTION TO PATENT BLUE DYE: A CASE REPORT

REAÇÃO ALÉRGICA AO CORANTE AZUL PATENTE: UM CASO CLÍNICO

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ABSTRACT

Patent blue dye is a synthetic dye used to identify sentinel lymph nodes during breast cancer surgery. Few cases of anaphylactic reactions to this dye are reported worldwide with an estimated incidence of 0.6-2.7%.

We report a case of a grade-1 hypersensitivity reaction on a 64-year-old female patient with breast cancer, submitted to tumorectomy with sentinel lymph node biopsy, following the administration of patent blue dye. The patient was on general anesthesia and exhibited a generalized rash and blue vesicles over trunk and abdomen skin. She was treated with intravenous hydrocortisone, fluids and antihistamines.

In the perioperative period, patient exposure to any substance may produce adverse reactions, including anaphylactic reactions. Patent blue and synthetic dyes are rare causes of anaphylaxis. However, due to the increasing indications for its use, the incidence of anaphylaxis is expected to increase. In a patient submitted to general anesthesia, the early signs may go unnoticed.

Keywords: hypersensitivity reaction; patent blue dye; sentinel lymph node biopsy.

RESUMO

O corante azul patente é um corante sintético usado para identificar gânglios linfáticos sentinela durante a cirurgia do cancro da mama. São relatados poucos casos de reações anafiláticas a este corante em todo o mundo, com uma incidência estimada de 0,6-2,7%.

Descrevemos um caso de reação de hipersensibilidade grau 1 de uma paciente de 64 anos com cancro da mama, submetida a tumorectomia com biópsia de gânglio sentinela sob anestesia geral, após a administração de azul patente. A paciente apresentou rash cutâneo generalizado com vesículas azuis da pele do tronco e abdómen, tendo sido medicada com hidrocortisona endovenosa, fluídos e antihistamínicos.

No período perioperatório, a exposição do doente a qualquer substância pode produzir reações adversas, incluindo reações anafiláticas. Os corantes azul patente e sintéticos são causas raras de anafilaxia.

No entanto, devido às indicações crescentes para o seu uso, a incidência de anafilaxia deverá aumentar. Num paciente sob anestesia geral, os sinais iniciais podem passar despercebidos.Palavras-chave: disfunção da glândula de meibomius, queratoconjuntivite, uveíte anterior, queratouveíte.

Palavras-chave: reação adversa a medicamento; corante azul patente; biópsia gânglio sentinela.

INTRODUCTION

Intraoperative allergic reactions are caused mostly by muscle relaxants (70%), latex (10%) and antibiotics with a mortality rate of 3.5–4.7% [1]. Patent blue dye is one of the synthetic dyes used intraoperatively to help identify sentinel lymph nodes during breast cancer surgery, avoiding total lymphadenectomy. It is also used in textiles and as a food additive (E 131) and may expose the general population to the risk of allergic sensitization [2].

Few cases of anaphylactic reactions to patent blue dye are reported worldwide, even with an estimated incidence rate of 0.6-2.7%, the first ones dating back to the early 1960's [3]. With its increasing use in sentinel lymph node biopsy due to renewed interest in its medical role and since we do not know the real prevalence in our country of patent blue dye adverse reaction, we considered really important to present this case report.

Another effect observed with patent blue dye is the pulse oximetry variation, depending on the interference in the wavelength reading, used to measure oxyhemoglobin [4].

In this case report, we describe a case of a grade 1 hypersensitivity reaction following the administration of patent blue dye in a patient undergoing tumorectomy and lymph node biopsy. The timing of the reaction suggests patent blue to be the causative agent.

CASE PRESENTATION

We describe the case of a 64-year-old woman with ductal breast carcinoma who was scheduled to undergo tumorectomy with sentinel lymph node biopsy under general anesthesia.

The patient presented a history of depression, medicated with lamotrigine and duloxetine. She had no knowledge of allergies, neither to food nor drugs. She was a previous smoker. There was no other significant medical, drug or family history. Her preoperative evaluation, including blood panel, electrocardiography and chest radiography showed no significant alterations.

She was pre-medicated with hydroxyzine 25 mg po. Anesthesia was induced with fentanyl 0.15 mg, propofol 140 mg, rocuronium 50mg and maintained with desflurane. Immediately after induction, she was given dexamethasone 4 mg. Antibiotic prophylaxis was assured with the administration of cefazolin 2 g, according to hospital protocol.

Before surgical incision, a peritumoural injection with 1.5 ml of patent blue dye was made to allow the identification of the sentinel lymph node.

Nearly 90 minutes after blue dye injection, the patient exhibited a generalized rash and blue vesicles over abdomen and limb's skin (figures 1 and 2). There were no significant hemodynamic changes registered (chart 1).

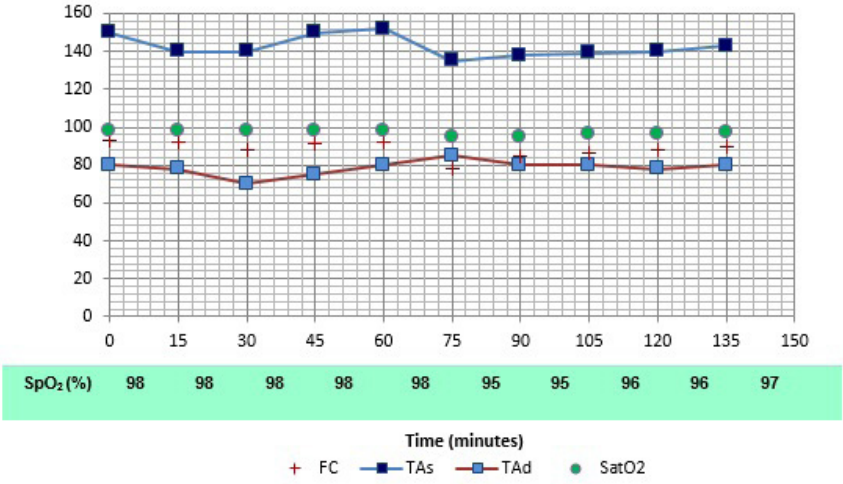
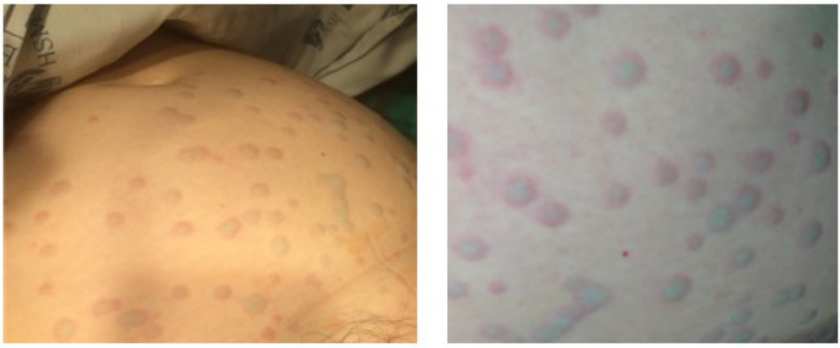


Chart 1 – Evolution of vital signs over time.



Figures 1 and 2 – Presence of maculopapular rash and vesicles of blue color in the trunk and abdomen.

The patient was treated with intravenous 100 mg of hydrocortisone. Given the hemodynamic stability, the surgery was completed. At the end of the procedure sugamadex 200 mg was administered to reverse neuromuscular blockade. No edema of the larynx and airway was observed and the endotracheal tube was removed uneventfully.

Upon emergence the patient complained of pruritus. She didn't report difficulty in breathing or any other symptom. The patient was then transported to the post-anesthesia care unit.

On immediate post-operative period the patient remained hemodynamically stable, eupneic with oxygen support (3L/min). She was given fluids and antihistamines (hydroxyzine) and a dermatology consult was required. Approximately two hours later there were signs of partial reversion of the skin rash. At this time the patient didn't present any symptomatic pruritus and she maintained hemodynamic and ventilatory stability. However, it was observed a blue coloration of the patient's urine. One day after the breast surgery, the skin gradually faded. The patient was discharged 3 days later without any sequelae.

DISCUSSION

In the perioperative period, patient exposure to any substance may produce adverse reactions, including anaphylactic reactions. Although anaphylactic reaction to drugs given during anesthesia is rare (estimated incidence 1:10000-1:20000), the increasing use of compounds with a propensity to elicit anaphylaxis, requires an increased awareness of the possibility of sensitization and increased likelihood of anaphylaxis [1].

Patent blue and synthetic dyes are rare causes of anaphylaxis. First exposure and subsequent sensitization results from the presence of patent blue and other dyes that have similar structure in food (E 131) and objects from every-day life such as clothing, paint, inks, laxatives, suppositories, cosmetics, antifreeze, and carpets [5, 6]. However, due to the increasing indications for its use, namely in breast cancer, the incidence of anaphylaxis is expected to increase. Medical staff involved in blue dye administration should have competent personnel and facilities to deal with such situations [7].

Three degrees of severity related to hypersensitivity reactions to blue patent have been described [6, 8]: grade I (69-87%) – blue hives, urticaria, pruritus and/or generalized rash; grade II (3.2-8%) – transient hypotension (systolic blood pressure <70 mmHg) without requiring vasopressor support and the absence of bronchospasm and laryngospasm; and grade III (1.1%) – severe cardiovascular collapse requiring vasopressor with suspension of the surgical procedure and transfer of the patient to intensive care unit.

The initial signs of allergic reaction to patent blue are hypotension and rash without bronchospasm or airway edema. Although they are an early manifestation, skin changes are not always immediately detected because of the surgical fields' presence [9]. The onset of hypersensitivity occurs 10-45 minutes after the injection of the dye (mean = 17 minutes), unlike the usual hypersensitivity reactions observed during an anesthesia, which are earlier, and they often delay the differential diagnosis of the allergic reaction [9, 10]. Skin reactions usually disappear within 1-20 hours [10].

Our patient presented a hypersensitivity reaction with a generalized rash and blue vesicles over abdomen and limb's skin, detected after taking off the surgical fields (about 90 minutes after patent blue injection). She was immediately treated with corticosteroid and fluids and she didn't show hypotension intra nor postoperatively. It's important to take in mind that allergic reactions to patent

blue may be biphasic and a subsequent episode of hypotension can occur 6 to 8 hours after the initial event. Patients should be monitored in the post-anesthesia care unit or intensive care unit during this time, even if they are hemodynamically stable [9].

Another observed effect with patent blue is interference in the reading of pulse oximetry, which causes an apparent drop in oxygen saturation. This interference is due to the light absorption peak of patent blue (638 mm) is very close to the 660 mm of deoxyhemoglobin [9]. The increase in light absorption in this region can be interpreted by the pulse oximeter as presence of deoxyhemoglobin and false oxygen saturation decreasing. The latency and duration of the drop-in oxygen saturation depend on the location of injection. When administered within the breast parenchyma, a maximum reduction of 11% (mean of 5%) occurs 15 to 30 minutes after injection [9]. Our patient exhibited a maximum 3% decrease in oxygen saturation.

Patent blue dye, which is now being used more often in medicine for varied indications, has a potential to cause adverse reactions. It is very important to the anesthesiologist to recognize and discern this reaction from others. The severity is most often low. The characteristic blue wheals must be looked for.

The mechanisms of immediate-type reactions to patent blue dye are still a matter of discussion. Some studies suggest an IgE-mediated mechanism and that patent blue dye bounds to a protein, sugar or lipid and can serve as a hapten for an IgE complex [11-12].

The surgical team requested clinical evaluation to Dermatology. Our patient has probably exhibited a grade 1 hypersensitivity reaction and she has evolved without sequelae. Unfortunately, she wasn't subjected to allergy tests to confirm patent blue dye allergy. We considered when this situations do happen, the patients should have serial samples sent for mast cell tryptase levels measurement and referred for skin prick/intradermal tests.

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RETROPERITONEAL EXTRASKELETAL EWING SARCOMA

SARCOMA DE EWING EXTRA-ÓSSEO NO RETROPERITONEU

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ABSTRACT

Ewing sarcoma is a rare aggressive tumour that belongs to the Ewing's family of tumours, sharing common genetic translocations involving chromosome 22. A minority of cases of Ewing sarcomas arise from soft tissue other than bone and are defined as extraskeletal or extraosseous Ewing sarcomas. Extraskeletal Ewing sarcomas are uncommon in adults older than 30 years and most frequently affect the paravertebral region, lower extremities, and chest wall, whereas a minority of cases have been reported in the retroperitoneum. Clinical manifestations will depend on the location of the mass and the extent of invasion into adjacent structures. Imaging findings are nonspecific and definite diagnosis relies on biopsy and pathological examination.

In this study, we report a case of a 42-year-old man with a large retroperitoneal Ewing sarcoma who presented to the emergency department with a bulky palpable abdominal mass.

Keywords: Ewing sarcoma, extraskeletal Ewing sarcoma, retroperitoneum, soft-tissue mass, ultrasound, computed tomography, magnetic resonance imaging.

RESUMO

O sarcoma de Ewing é um tumor agressivo raro que pertence à família dos tumores de Ewing e partilha translocações genéticas semelhantes envolvendo o cromossoma 22. Em contraste com a habitual origem óssea, uma minoria dos casos de sarcoma de Ewing surge nos tecidos moles, denominando-se sarcoma de Ewing extra-ósseo. O sarcoma de Ewing extra-ósseo é incomum em adultos com mais de 30 anos e geralmente localiza-se na região paravertebral, membros inferiores e parede torácica, sendo que casos de tumores com origem no retroperitoneu são mais raros. A apresentação clínica depende da localização do tumor e sua extensão/invasão para órgãos adjacentes. Os achados imagiológicos são inespecíficos e o diagnóstico assenta no resultado da biópsia.

Neste estudo os autores descrevem o caso clínico de um homem de 42 anos diagnosticado com um sarcoma de Ewing retroperitoneal que se apresentou como uma volumosa massa abdominal palpável.

Palavras-chave: sarcoma de Ewing, sarcoma de Ewing extra-ósseo, retroperitoneu, massa dos tecidos moles, ecografia, tomografia computorizada, ressonância magnética.

INTRODUCTION

Ewing sarcoma is a rare aggressive tumour that belongs to the Ewing's family of tumors, sharing common genetic translocations involving chromosomes 22. Approximately 80% of cases will occur during the first two decades of life, and 80% of these cases will arise in the skeleton [1]. Ewing sarcomas arising from structures other than bone are quite uncommon and are termed as extraskeletal or extraosseous Ewing sarcomas (EES). In contrast to younger groups, half or more of primary adult Ewing sarcomas are extraskeletal [2].EES most frequently affects the paravertebral region, lower extremities, and chest wall, whereas only 11% of cases have been reported in the retroperitoneum [3]. Clinical manifestations depend on the site and the size of the tumour but it commonly presents as a large, rapidly growing, solitary mass [4]. Since the retroperitoneal space is highly expandable and can easily hide masses, early detection of retroperitoneal EES is difficult.

Imaging features are not specific and usually do not allow differentiating it from other soft-tissue tumors. At radiography, retroperitoneal EES may manifest as a large soft-tissue mass or demonstrate a normal appearance. On ultrasound, lesions are most frequently hypoechoic and may present anechoic areas due to hemorrhage or necrosis. Computed Tomography (CT) can readily identify the retroperitoneal solid mass and confirm the absence of bone involvement [5], however, direct invasion of adjacent bone structures may occur in the terminal stage of the disease. On magnetic resonance imaging (MRI), a heterogeneous mass with signal intensity approximately equal to that of skeletal muscles on T1-weighted and heterogeneously hyperintense on T2-weighted images can be seen [4]. Multiplanar reconstructions are often performed to better define invasion or compression of the aorta, inferior vena cava, and psoas muscle [4]. Prominent contrast enhancement is observed at both CT and MRI. Nuclear medicine studies including bone scintigraphy and FDG-PET typically reveal increased radionuclide uptake.The final diagnosis is based on histological findings of small, round, blue cells with abundant glycogen and absent cytoplasmic filaments [6]. Staining and genomic techniques can confidently identify immunohistochemical and molecular features of Ewing sarcomas [6].Currently, most protocols recommend surgical resection combined with chemotherapy rather than radiation therapy if possible, using postoperative radiation for positive margins or residual disease [4]. When unresectable, radiotherapy is frequently performed to promote improved local control [4].

In this study, the authors present a challenging case of a 42-year-old man diagnosed with an advanced retroperitoneal Ewing sarcoma, presenting as a bulky, palpable abdominal mass.

CASE PRESENTATION

A 42-year-old man presented to the emergency department with a long-standing right-sided abdominal pain. Except for previous appendectomy during childhood and paranoid schizophrenia, his past medical history was unremarkable. Physical examination revealed a bulky tender mass on the right upper and lower abdominal quadrants. Laboratory results included mild leukocytosis and a C-reactive protein of 8.3 mg/dL.

The patient underwent an abdominal x-ray, which depicted a large right-sided intra-abdominal opacity displacing the small bowel loops (figure 1). Subsequently, an abdominal ultrasound was performed,

revealing a large heterogeneous mass with solid components and areas of cystic/ necrotic degeneration occupying the right abdominal quadrants (figure 2).

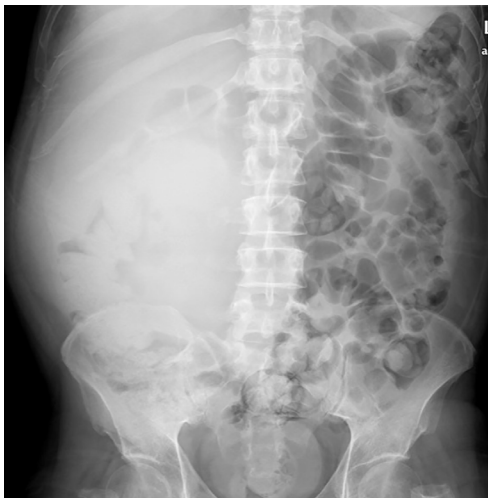

Figure 1 – Abdominal x-ray depicting an extensive opacity occupying the right abdominal quadrants and displacing the small bowel loops to the left side.

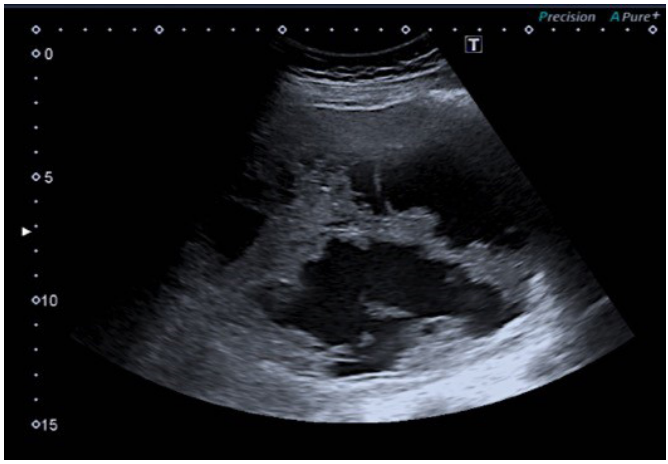

Figure 2 – The abdominal ultrasound reveals a large heterogeneous complex mass occupying the right abdominal quadrants, with solid components and evident areas of cystic/ necrotic degeneration.

Additional evaluation with contrast-enhanced computed tomography (CT) confirmed a complex right-sided retroperitoneal tumour with contiguous involvement of ipsilateral psoas muscle and loss of fatty plane with the posterior thoracic/ abdominal wall musculature (figure 3). Mild and predominant peripheral enhancement was observed (figure 3). A hypodense central area suggested intra-tumoural

necrosis (figure 3). Calcification or new bone formation was not observed within the lesion. No periosteal reaction neither bony destruction of the adjacent ribs and vertebrae were noticed. The right kidney and bowel loops were considerably displaced by the mass but didn't present signs of invasion (figure 3).

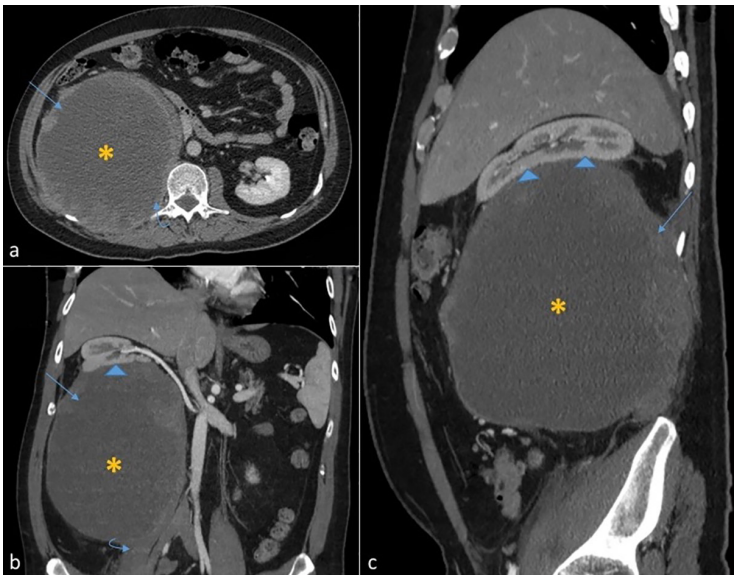

Figure 3 – Post-contrast computed tomography on axial (a), coronal (b) and parasagittal (c) planes show a large retroperitoneal right-sided mass (arrows) displacing the kidney superiorly (arrowheads), with contiguous involvement of ipsilateral psoas muscle (curved arrow). Note the hypodense central area suggesting intratumoral necrosis (asterisk). The right kidney was displaced but didn't present signs of invasion.

An ultrasound-guided core needle biopsy was performed and revealed a small, round blue cell neoplasm, markedly positive for CD99, Vimentin and S-100, suggesting Ewing sarcoma. Additional immunohistochemical and genetic evaluation confirmed the diagnosis.

The patient had no evidence of nodal or distant metastasis but the tumour was considered unresectable due to the involvement of psoas muscle and posterior thoracic/ abdominal wall. Chemotherapy with cyclophosphamide, doxorubicin and vincristine was offered yet, the post-treatment CT showed minimal response.

DISCUSSION

EES, also called primary Ewing's sarcoma of soft tissue, is defined as an Ewing's sarcoma in which no underlying bone involvement is found. Chest wall, lower extremities, and paravertebral region are the most frequent sites of development of EES, while the retroperitoneum is less frequently involved (11%) [3]. Clinical manifestations will depend on the location of the mass and the extent of invasion

into adjacent structures [7]. Since the retroperitoneum is highly expandable, tumours in this location may be only clinically evident or symptomatic at a late stage [7], as our presented case. Possible concomitant signs include intermittent fever, anaemia, leucocytosis, increased sedimentation rate, and other symptoms of inflammatory systemic illness.

Towards an abdominal palpable mass, imaging exams are mandatory. Ultrasound is a highly available method that can be useful in the initial evaluation of intra-abdominal masses and help manage patient work-up. As soon as the diagnosis of a complex retroperitoneal tumour was assumed, a complementary CT scan was performed to better characterize the nature, location and extent of the lesion. On CT, EES usually appears as a large heterogeneous soft-tissue mass that can displace, encase, or invade adjacent organs but usually do not cross the midline [5], similarly to our case report. Necrosis and haemorrhage may also be noticed, presenting as areas of lower density within the mass [4], as did our patient. CT is also useful for staging, particularly to evaluate distant metastasis.

Because the preoperative assessment of resectability was achieved by CT, further evaluation with MRI was considered dispensable.

The clinical presentation and imaging findings of our patient were not specific and included a considerable differential diagnostic list. Given the age, retroperitoneal location and the soft-tissue nature of the mass, hypothesis such as sarcoma (liposarcoma, leiomyosarcoma), lymphoma, and malignant peripheral nerve sheath tumour (MPNST) were considered. Liposarcomas are the most common soft tissue tumours occurring within the retroperitoneum and are classically a fat containing mass [8]. Since the tumour in our patient did not reveal areas of macroscopic fatty tissue, this diagnosis was thought to be less likely. Leiomyosarcomas of the retroperitoneum are the second most common primary malignant sarcoma at this site [8]. Similarly to EES, large retroperitoneal leiomyosarcomas tend to develop massive areas of necrosis, and fat and calcification are not typically present [8].

MPNSTs are defined as malignant mesenchymal tumours arising from cells of the peripheral nerve sheath, and comprise the malignant form of schwannoma, neurogenic sarcoma and neurofibrosarcoma [8]. Approximately half of the cases arise in patients with neurofibromatosis I and imaging findings include a progressively growing, painful, heterogeneous mass that infiltrates adjacent soft-tissues [8].

Lymphoma is the most common retroperitoneal malignancy, accounting for 33% of all of these cases, and approximately 14% of the patients with non-Hodgkin lymphoma present with a retroperitoneal mass [8]. It usually appears as a well-defined homogeneous mass, with mild homogeneous contrast enhancement, that spreads between normal structures without compressing them, therefore, we considered it a less likely diagnosis in this case.

The definite diagnosis of EES still relies on biopsy and pathological examination. The histological analysis of EES appears similar to the classical Ewing sarcomas, [9] showing the characteristic small round cells arranged in sheets with round nuclei, indistinct nucleoli, high nuclear-cytoplasmic ratio and scant vacuolated cytoplasm due to the presence of glycogen which is responsible for the Periodic Acid Schiff (PAS) positivity [7]. On immunohistochemistry, Ewing sarcomas reveal a strong, diffuse, membranous positivity with CD99. Vimentin, NSE and S-100 are also frequently expressed [7]. Our case was also positive for PAS, CD99, Vimentin and S-100. The histologic and immunohistochemical findings were conclusive of an Ewing sarcoma.

Owing to its rarity, the optimal management of EES is uncertain [10]. Aggressive management with surgical resection and neoadjuvant and/or adjuvant chemotherapy is recommended to improve survival rates [6]. Given the advanced stage of the tumour and its unresectability, our patient was proposed to palliative chemotherapy. Even in cases of good initial response, EES has a propensity for aggressive recurrence with both local and metastatic disease in many patients [11].

CONCLUSION

Given the rarity of EES and its non-specific imaging features diagnosis can be challenging. Definite diagnosis still relies on biopsy and pathological examination. In patients who present with large, rapidly growing soft-tissue tumour, ESS should be considered in the differential diagnosis.

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SEPSIS DUE TO SPONDYLODISCITIS AND PROSTATITIS AS A RARE CAUSE OF SECONDARY IMMUNE THROMBOCYTOPENIC PURPURA

SÉPSIS POR ESPONDILODISCITE E PROSTATITE COMO CAUSA RARA DE PÚRPURA TROMBOCITOPÉNICA IMUNE SECUNDÁRIA

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ABSTRACT

There is a clear relationship between the severity of the septic process and the presence of thrombocytopenia. Within the differential diagnosis of severe thrombocytopenia, immune thrombocytopenic purpura (ITP) is one of the entities involved. ITP is rarely a manifestation of severe sepsis. We present the case of an 84-year-old man with a diagnosis of severe sepsis due to spondylodiscitis to MSSA and prostatitis, who developed abdominal wall haematoma and gingival bleeding, with thrombocytopenia of 4000 platelets and Hb of 5.5 g/dL and positive anti-platelet antibodies for GP IIb / IIIa and GP Ia / IIa glycoproteins. Incidentally, the link between ITP and severe sepsis is reviewed, with a special focus on the role of anti-platelet antibodies in the diagnosis of this entity.

Keywords: Immune thrombocytopenic purpura, septicemia, autoantibodies, blood platelets.

RESUMO

Existe uma relação clara entre a gravidade do processo séptico e a presença de trombocitopenia. Dentro do diagnóstico diferencial de trombocitopenia grave, a púrpura trombocitopénica imune (PTI) é uma das entidades em causa, sendo uma manifestação rara de sépsis grave. Apresenta-se o caso de um homem de 84 anos, com diagnóstico de sépsis grave por espondilodiscite a MSSA e prostatite, que desenvolve hematoma da parede abdominal e gengivorragias, com trombocitopenia de 4000 plaquetas e Hb de 5,5 g/dL, com anticorpos antiplaquetários positivos para glicoproteínas GP IIb/IIIa e GP Ia/IIa. A propósito, revê-se a ligação entre PTI e sépsis grave, com especial incidência para o papel dos anticorpos antiplaquetários no diagnóstico desta entidade.

Palavras-chave: púrpura trombocitopénica imune, septicémia, autoanticorpos, plaquetas.

INTRODUÇÃO

É comum a presença de trombocitopénia em doentes com sépsis e é conhecido o seu papel como marcador de morbilidade e mortalidade [1]. Aliás, a sua importância justificou a sua inclusão em escalas preditoras de prognóstico, como o *Sequential Organ Failure Assessment* (SOFA) [1]. Existem cinco mecanismos para a trombocitopénia nestes doentes: diminuição da produção plaquetária, disfunção dos receptores plaquetários, destruição plaquetária imuno-mediada, sequestração plaquetária e coagulação intravascular disseminada. Embora a sépsis seja a causa mais comum de trombocitopénia nas unidades de cuidados intensivos (UCIs) [2], outros diagnósticos devem ser considerados, nomeadamente síndromes mielodisplásicos, anemias aplásticas, iatrogenia ou púrpura trombocitopénica imune [3].

A púrpura trombocitopénica imune (PTI) é uma doença autoimune caracterizada por trombocitopénia motivada pela ligação de autoanticorpos a antigénios plaquetários, causando destruição prematura pelo sistema reticulo-endotelial [4]. A PTI pode ser primária ou secundária, nomeadamente a lúpus eritematoso sistémico, vírus da hepatite C ou doenças linfoproliferativas. A incidência varia entre 1,6 a 3,9/100000 nos adultos [5]. Em 30-40% dos doentes com PTI, não é possível detetar autoanticorpos antiplaquetários [6]. Cerca de 30% dos doentes internados nas UCI com sépsis apresentam anticorpos antiplaquetários inespecíficos, sendo que 30% destes doentes têm autoanticorpos contra as glicoproteínas GP IIb/IIIa [1]. Apesar disso, o diagnóstico de PTI por sépsis grave é incomum.

Assim, apresenta-se um raro caso de PTI secundária a sépsis por espondilodiscite e prostatite, relevando o papel do diagnóstico precoce desta entidade com possibilidade de terapêutica dirigida.

APRESENTAÇÃO DO CASO

Homem de 84 anos, desenvolve lombalgia tipo ciática, disúria e polaquiúria com quatro dias de evolução. Ao exame objetivo, hipotensão de 86/48 mmHg, normocárdico, pele e mucosas descoradas e desidratadas, hematoma da parede abdominal latero-inferior direito e petéquias na região dorsal. Laboratorialmente, anemia normocítica normocrómica com Hb de 9,7 g/dL, 44000 plaquetas, creatinina de 1,5 mg/dL, INR de 1,3, PSA total de 64,7 mg/dL e proteína c-reactiva de 20 mg/dL, bem como hiperlactacidémia de 21 mg/dL e eritroleucocitúria em análise sumária de urina. Esfregaço de sangue periférico sem esquizócitos. Duas hemoculturas com isolamento de *Staphylococcus aureus* sensível à meticilina (MSSA). Ecografia abdominal sem alterações. Ressonância magnética da coluna dorso-lombar revelou coleções peridurais entre D12 e L4, em topografia anterior e posterior. Admitida sépsis grave por espondilodiscite a MSSA e prostatite, iniciou antibioterapia dirigida com flucloxacilina, com estabilização hemodinâmica, apirexia e, laboratorialmente, com normalização de lactacidémia e parâmetros inflamatórios em curva descendente. A evolução laboratorial detalhada encontra-se na tabela 1. Manteve, contudo, extensão do hematoma da parede abdominal e desenvolveu gengivorragias, com agravamento progressivo de trombocitopenia até um mínimo de 4000 plaquetas e com Hb entre 5,5 g/dL e 6,3 g/dL. Apresentou anticorpos antiplaquetários positivos para glicoproteínas GP IIb/IIIa e GP Ia/IIa. Necessitou de transfusão diária de plaquetas e de unidade de concentrado eritrocitário, entre o 2º e o 5º dia de internamento, com ausência de resposta plaquetária (plaquetas entre 4000 e 6000).

Laboratorialmente, manteve valores de coagulação, produtos de degradação da fibrina, fibrinogénio e bilirrubina total normais. A partir do 6º dia, apresentou recuperação progressiva de contagem plaquetária, com resolução das gengivorragias e do hematoma da parede abdominal. Manteve contagem plaquetária normal ao longo do restante internamento. Cumpriu 9 semanas de antibioterapia com resolução do quadro.

	4 meses antes	D1	D3	D6	D8	D30
Hb (g/dL)	10.6	9.7	5,5	5,0	7,6	8,9
Htc	31.9	28.3	16,3	23,0	22,0	26,3
VGM (fL)	89.2	85.8				
HGB (pg)	29.7	29.5				
Leuc	7500	5330	15000	12500	13190	8860
Plaquetas x10^9/L	227	44	4	17	41	379
INR		1,3	1,09			
D-Dímeros			0,77			
Creatinina (mg/dL)		1,5	1,2	0,9		0,9
Ureia (mg/dL)		119	110			44
PCR (mg/dL)		20	14,3	3,6		3,62
PSA total (mg/dL)		2,6	64,7	14,4		1,23

Hb – hemoglobina; Htc – hematócrito; VGM – Volume globular médio; Leuc – contagem leucocitária; INR – razão normalizada internacional; PCR – proteína c-reactiva; PSA – antigénio específico da próstata

DISCUSSÃO E CONCLUSÃO

A trombocitopenia tem uma incidência de 20-40% nas UCI's [7] e associa-se a maior mortalidade e morbilidade [8]. Num estudo por *Gucluet* al. [9], entre 145 doentes sépticos detectou-se trombocitopenia em 33,8%, contra apenas 4% no grupo de controlo. Ainda nesse trabalho, havia uma relação clara entre a gravidade do processo infeccioso e a presença de trombocitopenia (40,9% nos doentes com sépsis grave e 22,8% dos doentes com sépsis não grave). *Venkataet* al. [7], em 304 doentes admitidos numa unidade de cuidados intensivos, demonstraram que os doentes que desenvolviam trombocitopenia tinham maior gravidade de doença (APACHE IV e SOFA mais elevados), mais hiperlactacidémia, maior risco de hemorragia e maior tempo de internamento.

Na relação entre sépsis e trombocitopenia predominam a ativação das plaquetas, os mecanismos imunitários dependentes de anticorpos antiplaquetários, o aumento de consumo das plaquetas (coagulopatia vascular disseminada em 25% dos casos) [7] e a supressão medular da medula óssea.[9] A trombocitopenia inferior a 20x109/L, como no nosso doente, é causada por falência medular aguda, coagulopatia vascular disseminada ou destruição plaquetária mediada pelo sistema imunitário. Em caso de falência medular ou coagulopatia vascular disseminada, existe expectavelmente resposta plaquetária a suporte transfusional, dentro de aproximadamente uma hora [8]. No caso clínico descrito, não houve resposta plaquetária a suporte transfusional, o que sugeriu uma etiologia autoimune [10]. Na ausência de fármaco que classicamente curse com trombocitopenia iatrogénica e na presença dos anticorpos descritos, a atribuição da trombocitopenia a um mecanismo autoimune semelhante ao descrito nas PTI's primárias e secundárias tornou-se clara.

A PTI é uma doença autoimune onde predomina a destruição plaquetária acelerada [4]. Pode considerar-se como primária, na ausência de outras doenças identificáveis, ou secundária a vários insultos, nomeadamente doenças autoimunes, doenças hemato-oncológicas, processos infecciosos ou fármacos [4]. Fisiopatologicamente, há uma relação conhecida com a produção de anticorpos contra as glicoproteínas GPIIb/IIIa, Ia/IIa e Ib/IX. Estes anticorpos parecem ser responsáveis quer pela opsonização plaquetária e consequente destruição pelos macrófagos a nível do baço, quer pela inibição da produção e maturação plaquetária [3]. As suas principais manifestações clínicas são hemorragias mucocutâneas [4]. Os sinais e os sintomas correlacionam-se com a contagem plaquetária, sendo rara a expressão clínica com contagens de plaquetas superiores a 50x109/L [10]. O diagnóstico de PTI baseia-se na exclusão de outras causas de trombocitopenia [11,12].

Uma das questões levantadas pela literatura prende-se com a utilidade da deteção de anticorpos para o diagnóstico de PTI. Entre 61 doentes em estado grave e com trombocitopenia, 18 tinham anticorpos IgG contra as plaquetas, sendo que destes 6 tinham autoanticorpos antiplaquetares (4 contra a glicoproteína IIb/IIIa e 2 contra a glicoproteína Ib/IX) [1]. Sendo a sépsis uma resposta inflamatória intensa, existe um aumento da imunorreatividade contra as proteínas do *self*, o que leva a um rápido aumento dos autoanticorpos na fase aguda em 46% dos doentes [13]. Embora a medição destes anticorpos tenha vindo a ganhar robustez no diagnóstico de PTI, apresentam uma especificidade de 78 a 92% e uma sensibilidade de 49 a 66%, o que leva a um valor preditivo positivo 80-83% [5]. Devido à sua baixa sensibilidade, não são ainda considerados rotineiramente perante suspeita de PTI [12,14], embora se sugira que tenham implicação na estratificação de risco e orientação terapêutica [15]. Em termos de terapêutica, pode-se diminuir a *clearance* causada pelos autoanticorpos antiplaquetares com corticosteroides e imunoglobulinas intravenosas. Como 2ª linha, uma das opções é a esplenectomia, uma vez que o baço é o local onde ocorre a ativação de células B e T contra as plaquetas e onde as plaquetas são destruídas, e outra é o Rituximabe. Este fármaco causa destruição esplénica ou apoptose das células B, o que diminui a quantidade de autoanticorpos antiplaquetários. Nos doentes que não respondem a estes tratamentos, opta-se por agonistas do recetor TPO, como o *Eltrombopag* e o *Romiplostim*, que vão induzir a produção de plaquetas [6].

Assim, apresenta-se um raro caso de PTI secundária a sépsis, que acrescenta aos raros casos descritos.

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SYPHILIS IN ADOLESCENCE

SÍFILIS NA ADOLESCÊNCIA

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ABSTRACT

Adolescence is a growth period associated with the sexual behaviour development. There are several factors in this group that contribute to the increased risk of sexually transmitted infections. A 16-year-old male adolescent, with two partners in the last 6 months and a previous history of gonorrhoea, was referred to the emergency department because of perianal and genital papules, not pruritic, with one month evolution, painful plaques in the tongue with odynophagia and non-pruritic maculopapular rash with palmoplantar involvement, lasting four days. Fever and adenomegaly were also present. One partner had painless ulcer on the penis. The diagnosis of secondary syphilis was made. In the follow up, serology became positive for the human immunodeficiency virus. The aim of this paper study is to address the particularities of approaching these diseases in adolescence and an assessment of tracking and educating the patient for appropriate protective measures.

Keywords: Syphilis, HIV, adolescence.

RESUMO

A adolescência é um período de crescimento associado ao desenvolvimento do comportamento sexual. Existem vários fatores de risco nesta faixa etária que contribuem para o aumento do risco de infeções sexualmente transmissíveis. Relata-se o caso de adolescente de 16 anos, sexo masculino, 2 parceiros nos últimos 6 meses, com antecedentes de gonorreia, que recorre ao serviço de urgência por pápulas perianais e genitais, não pruriginosas, com 1 mês de evolução, placas túmidas na língua, dolorosas, com odinofagia associada e exantema maculopapular não pruriginoso com atingimento palmo-plantar desde há 4 dias. Febre e adenomegalias. Um dos parceiros teve úlcera indolor no pénis. Foi realizado o diagnóstico de sífilis secundária. Em consultas posteriores, verificou-se serologia positiva para o vírus de imunodeficiência humana. Este caso pretende abordar as particularidades da abordagem destas doenças na adolescência e a importância de rastrear e educar o doente relativamente a medidas de proteção adequadas.

Palavras-chave: Sífilis, VIH, adolescência.

INTRODUCTION

Adolescence is a period of heterogeneous growth that marks the passage from childhood to adulthood, being associated with the development of sexual behaviour and increased risk of sexual transmitted infections (STI) [1,2]. There are several biopsychosocial factors that should be known when addressing these diseases in this group.1 Men who have sex with men (MSM) are currently one of the groups at high risk for STI, and it is known that many sexual behaviours are acquired in adolescence, which must be a target of intervention at the educational level [3,4].

CASE PRESENTATION

A 16-year-old male adolescent with two partners in the last 6 months presented at the emergency department with perianal and genital papules, not pruritic, with one month evolution, painful plaques in the tongue with odynophagia, non-pruritic maculopapular rash including palmoplantar involvement with four days evolution and fever (38.5ºC). One partner had painless ulcer on the penis. The patient had gonorrhoea at 15 year of age and had also been followed in psychiatry because of depression and suicide attempted two years before.

In the physical examination, there were whitish, tumid plaques papules and plaques (Figure 1), and identical lesions in the glans (Figure 2), and tongue (Figure 3). A violet maculopapular rash with palmoplantar involvement was evident (Figure 4), as well as moth-eaten alopecia (Figure 5).

Figure 1 – Perianal papules and plaques (condylomata lata).

Figure 2 – Papules in the glans (condylomata lata).

The patient had also cervical and inguinal adenomegalies, that were non adherent and not painful.

The search for *Treponema pallidum* by PCR was positive in the three sites (perianal region, glans and tongue). The titration of VDRL was 1/64 and screening of other STIs (gonorrhoea, Chlamydia trachomatis, Hepatitis B and C and Human Immunodeficiency Virus) was negative. The diagnosis was then secondary syphilis with condylomata lata.

The recommended treatment with 2.4 million units intramuscularly of benzathine penicillin was performed with positive Jarisch-Herxheimer reaction. Despite efforts to convene partners for

Figure 3 – Smooth and moist plaques in the tongue (condylomata lata).

Figure 4 – Violet maculopapular rash.

Figure 5 – Moth-eaten Alopecia on the temporal area.

treatment, they did not attend. The adolescent was referred to the venereology outpatient clinic and monitored through the VRDL titers at 4, 6, 12 and 24 months. Four months later, seropositivity for the Human Immunodeficiency Virus was found and the patient was referred to the infectious disease outpatient clinic and started antiretroviral therapy. He was also referred to the Unit for Adolescence and Psychiatry for psycho-social support.

DISCUSSION

Syphilis is caused by infection with *Treponema pallidum*, a not-yet-cultivable spiral-shaped bacterium that is usually transmitted by sexual contact with an infected partner or by an infected pregnant woman to her fetus. Diagnosis and treatment of infected individuals and their contacts is key to syphilis control programs, that must also include sex education and promotion of condom use [5,6].

Syphilis can progress through four stages: primary, secondary, latent and tertiary [5,6,7,8].

Primary syphilis occurs following an incubation period of 2-6 weeks and it is characterized by the presence of a painless, indurated ulcer at the site of inoculation (typically the genital, anal or oral mucosa) and by moderate regional lymphadenopathy [5,6].

Secondary syphilis results from widespread multiplication of disseminated *T. pallidum*. This stage, which occurs simultaneously with, or up to six months after, the healing of the chancre, is typically

characterized by malaise, headache, low-grade fever, generalized lymphadenopathy, a localized or generalized skin rash with lesions on the palms and soles, mucous patches in the oral cavity or genital tract, wart-like lesions (condylomata lata), and patchy hair loss. Secondary syphilis can last for weeks or months [5,6].

Latent syphilis is the period lasting from the disappearance of the secondary stage until manifestations to the occurrence of the tertiary stage. Latent syphilis is divided into early latent (i.e., within one year of infection) and late latent (i.e., after one year of infection). Clinical symptoms are not apparent, but serological tests for detection of antibodies to *T. pallidum* remain positive, indicating that treponemes are still present in the lymph nodes and spleen. However, about two-thirds of untreated syphilis patients remain in the latent stage for life [5,6,7].

Tertiary syphilis is rare today due to curative antibiotics given for early syphilis or even to unrelated infections, as pulmonary or urinary. Manifestations include cardiovascular syphilis, neurosyphilis, and gummatous syphilis. Symptoms can include difficulty in movement coordination, paralysis, numbness, blindness, and dementia. Because so few treponemes are present, sexual transmission is very unlikely [5,6,7].

The primary and secondary stages are therefore the most infectious [5].

Serological tests for syphilis (STS) are traditionally divided into two types: nontreponemal and treponemal. Nontreponemal STS detect IgM and IgG antibodies to lipoidal antigens that are putatively released from damaged host cells. These tests include the venereal disease research laboratory (VDRL), rapid plasma reagin (RPR), and toluidine red unheated serum test (TRUST). Nontreponemal tests are widely available, rapid, and inexpensive and can be used quantitatively to monitor the effectiveness of antibiotic treatment. They lack sensitivity in primary and tertiary syphilis [6,7,8]. Treponemal STS use native or recombinant *T. pallidum* antigens and detect IgM and IgG antibodies to treponemal components. These tests include the *T. pallidum* particle agglutination assay (TPPA), the fluorescent treponemal antibody absorption assay (FTA-ABS), the most common used. They are more sensitive and specific than nontreponemal tests for all stages of syphilis. However, these tests cannot distinguish active infection from past or treated infection, so they cannot be used to monitor the effectiveness of antibiotic treatment [6,7,8].

Treatment with a single intramuscular (IM) injection of 2.4 million units (MU) of benzathine penicillin g is curative for early, uncomplicated syphilis in adults (i.e., primary, secondary, or early latent stage). An IM injection of 2.4 MU of BPG given once weekly for 3 weeks is recommended for late latent syphilis, syphilis of unknown duration and tertiary syphilis. Those who are allergic to penicillin may be treated with doxycycline (100 mg orally, twice daily for 14 days) or tetracycline (500 mg orally, four times daily for 14 days) or ceftriaxone (1 g daily either IM or intravenously (IV) for 10-14 days). Adults with HIV co-infection should be treated the same as those without HIV infection [7,8].

The follow-up in primary and secondary syphilis, with clinical and serological evaluation should be performed at 3, 6 and 12 months after treatment. Patients with HIV infection should be evaluated clinically and serologically at 3, 6, 9, 12, and 24 months after therapy [8].

New challenges have emerged in the syphilis epidemiology and treatment. Individuals who acquire one STI are more likely to acquire another STI, and they may sometimes coexist, with a close correlation between syphilis and HIV. In 2014, between 29 and 40% of cases of early syphilis patients were co-infected with HIV [8]. Also in this year, more than half of the new cases of syphilis in Europe occurred in men who have sex with men, with these numbers being attributed to increased risk behaviours [7].

In Portugal, there were 990 new cases of HIV infection in 2015, and the majority of cases occurred in men who have sex with men, with 69% of patients under the age of 30 years, as in the case of our patient [9]. This also implies an important economic impact, given the need for antiretroviral therapy over many years.

In adolescence there is an increased risk of sexually transmissible infections (STI) [1,2,8]. Several risk factors for STI acquisition have been described in this age group but there is a paucity of studies on syphilis prevalence in adolescence. Classic factors are multiple partners, new partners, partners with multiple partners, inconsistent use of condoms, alcohol or drug use. There are also biological risk factors that must be considered, for example, it is thought that cervical ectopy may predispose to STI, since it is more susceptible than the squamous epithelium to HPV, Chlamydia and Neisseria infection. Factors such as self-esteem, personal values and motivation also positively influence the attitude towards sexuality [1,3,4].

Lack of economic and educational resources and inaccessibility to medical care are also associated with a higher prevalence of STI [1,4].

CONCLUSION

Adolescence is a life period with an increased risk of acquiring sexually transmitted diseases, given the various associated risk factors. All physicians should insist on the consistent use of condoms and when an STI is diagnosed it is important to search for others, call the partners for treatment and, especially when socioecconomic and psychosocial problems are present in adolescence, to have a multidisciplinary approach that involves dermatovenereology, pediatrics, psychiatry and social assistance.

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CHARGE SYNDROME: A RARE CAUSE OF HYPOGONADOTROPIC HYPOGONADISM

SÍNDROME DE CHARGE: UMA RARA CAUSA DE HIPOGONADISMO HIPOGONADOTRÓFICO

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ABSTRACT

CHARGE Syndrome (CS) is a rare cause of hypogonadotropic hypogonadism (HH), usually diagnosed in paediatric age when pubertal development is compromised. Here in, we report atypical CS case. The fifteen adolescent was referred to the paediatric endocrinology unit due to phenotypic alterations and psychomotor and cognitive impairment. At 8 years of age she was diagnosed with semicircular channels bilateral agenesis with profound bilateral deafness. CS was considered and genetic tests were performed. The karyotype was 46 XX and a missense mutation in the CHD7 gene was identified (c.484C>T/p.Q162X). CS is rare, however it should be considered in the differential diagnosis of HH particularly in presence of an abnormal phenotype. Mutations in the CHD7 gene cause more than half of all cases of CS and most of the times are new mutations as occurred in the current case. Different malformations may be present justifying a long term follow up.

Keywords: hypogonadism, CHARGE, puberty, mutation, CHD7.

RESUMO

A Síndrome de CHARGE (SC) é uma causa rara de hipogonadismo hipogonadotrófico (HH) frequentemente diagnosticado em idade pediátrica, quando há compromisso no desenvolvimento pubertário. Este artigo reporta um caso de SC atípica. A adolescente de 15 anos foi referenciada à consulta de endocrinologia pediátrica por possuir alterações fenotípicas e atraso no desenvolvimento psicomotor e cognitivo. Aos 8 anos foi-lhe diagnosticada agenesia bilateral dos canais semicirculares com surdez bilateral profunda. O diagnóstico de SC foi suspeitado e foram realizados exames genéticos. O cariótipo era 46,XX com identificação de mutação missense no gene CHD7 (c.484C>T/p.Q162X). A SC é rara, contudo deve ser suspeitada no diagnóstico diferencial do HH, particularmente na presença de fenótipo anormal. As mutações no gene CHD7 são responsáveis por mais de metade dos casos de SC e a maioria são mutações de novo, como no caso descrito. Diferentes malformações podem estar presentes justificando um seguimento a longo prazo.

Palavras-chave: hipogonadismo, CHARGE, puberdade, mutação, CHD7.

INTRODUÇÃO

O hipogonadismo hipogonadotrófico (HH) carateriza-se por baixas concentrações de estrogénio ou testosterona, com valores de gonadotrofinas (FSH e LH) inadequadamente baixos, devido à disfunção do eixo hipotálamo-hipófise. Quando o defeito se encontra no hipotálamo, a hormona comprometida é a GnRH, que estimula a produção de FSH e LH pela hipófise anterior. Tal défice é, na maioria dos casos, congénito, associando-se muitas vezes a alterações do olfato, nomeadamente anósmia. Destacam-se a Síndrome de Kallmann (SK), o hipogonadismo hipogonadotrófico idiopático (HHI) e a Síndrome de CHARGE (SC). A primeira e a última podem associar-se a anósmia, enquanto no HHI tal não se verifica [1].

A SK é responsável por 2/3 dos casos de HH, devendo-se a alterações no desenvolvimento do sistema olfativo, com perturbação da migração embrionária dos neurónios produtores de GnRH do epitélio olfativo para a região hipotalâmica [2-4].

No HHI há também hipogonadismo secundário, habitualmente sem alteração do olfato, embora alguns estudos apontem que o HHI e a SK têm bases genéticas distintas [2].

A SC é uma doença muito mais rara do que os dois anteriores, com uma prevalência de 1:100000 recém-nascidos. O acrónimo original é composto pela presença de coloboma (Coloboma), cardiopatia congénita (Heart malformation), atraso do crescimento/desenvolvimento (Retardation), anomalias genitais (Genital anomalies) e anomalias do ouvido (Ear anomalies) [5]. Nos atuais critérios de diagnóstico, a SC assume 3 formas principais, típica, atípica e parcial, tendo em conta a combinação de sinais major e minor. De acordo com esta classificação, o HH constitui um critério minor [6]. A SC deve-se a mutações no gene *CHD7*, encontradas em 70% dos casos, e, tal como na SK, a anósmia/hipósmia pode estar presente. Raramente, podem associar-se à SC défice de hormona do crescimento e hipotiroidismo secundário [7]. A principal manifestação do HH é o atraso pubertário, diagnosticado habitualmente na adolescência (13-14 anos).

Apresentamos um caso de Síndrome de CHARGE, em que o HH constituiu um sinal minor para o diagnóstico.

APRESENTAÇÃO DO CASO

O caso clínico refere-se a uma doente do sexo feminino, enviada à consulta de endocrinologia pediátrica por atraso pubertário aos 15 anos. Trata-se da terceira filha de um casal saudável, não consanguíneo. Os irmãos são saudáveis. À nascença confirmou-se a presença de fenda palatina, contudo, sem outras intercorrências registadas durante a gravidez ou no parto. O desenvolvimento estaturo-ponderal foi normal (P5-10) (figura 1), não se verificando o mesmo em relação ao desenvolvimento psicomotor, que decorreu com importante atraso.

Aos 10 anos frequentava o 2º ano de escolaridade. Aos 8 anos tinha-lhe sido diagnosticada surdez mista bilateral moderada a grave, mostrando a tomografia computorizada agenesia bilateral dos canais semicirculares, motivo pelo qual lhe foram colocadas próteses auditivas. À observação destacava-se

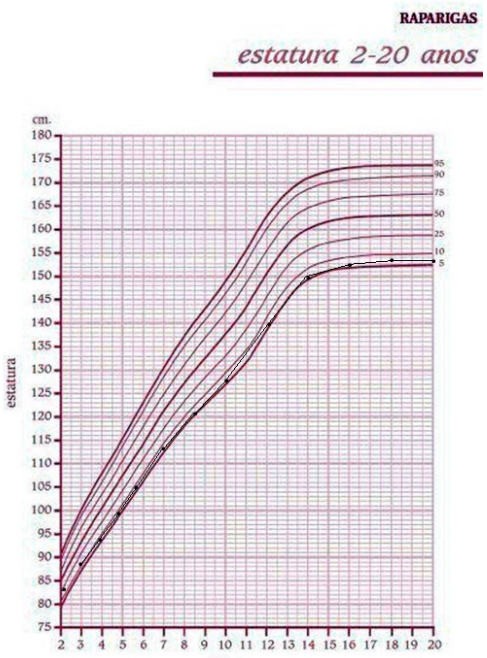

Figura 1 – Evolução da estatura da doente, no P 5-10. Altura final: 153 cm.

evidente dismorfia facial, com baixa implantação dos pavilhões auriculares, assimetria facial resultante de paralisia no nervo facial, achatamento da ponta do nariz e cifoescoliose dorsal. A marcha era atáxica e mantinha um défice cognitivo ligeiro. Negava alteração do olfato. Apresentava um atraso pubertário (estádio 2 de Tanner, P2S2). A avaliação laboratorial mostrou níveis pré-púberes de FSH, LH e estradiol, mantidos após estimulação com hormona libertadora de hormona luteinizante (LHRH) (tabela 1).

A restante avaliação laboratorial foi normal. A idade óssea mostrava um atraso de 2 anos relativamente à idade cronológica. Os genitais externos tinham morfologia normal e a ecografia pélvica mostrou um útero e ovários de pequenas dimensões, sem evidência de atividade folicular. A observação oftalmológica não mostrou alterações. A tomografia computorizada crânio-encefálica foi normal, tal como o ecocardiograma e a ecografia renal e vesical. O cariótipo era normal, 46,XX, e não foi encontrada a deleção 22q11 (de acordo com o fenótipo e para investigação de Síndrome de DiGeorge). Após observação na consulta de genética, foi pedido o estudo do gene *CHD7*, com identificação da mutação c.484C>T p.Q162X, já descrita nesta síndrome.

Tempo (minutos)	LH (mUI/mL)	FSH (mUI/mL)
0’	0,08	0,5
30’	0,3	1,1
60’	0,3	1,7
120’	0,2	1,4

Tabela 1 – Valores de LH e FSH após administração LHRH. LH pré-púbere < 0,2 mUI/mL, FSH pré-púbere < 2,2 mUI/mL

A doente foi medicada com valerato de estradiol 2 mg/norgestrel 0,5 mg em toma cíclica com hemorragia de privação, e, manteve seguimento na consulta de endocrinologia pediátrica e otorrinolaringologia.

Aos 20 anos, foi transferida para a consulta de endocrinologia de adultos, já com o desenvolvimento pubertário completo, mantendo-se medicada com valerato de estradiol 2 mg/norgestrel 0,5 mg.

A osteodensitometria mostrou osteopenia da coluna lombar e do colo do fémur, pelo que foi medicada com carbonato de cálcio e colecalciferol. Uma vez que a síndrome de CHARGE tem transmissão autossómica dominante, com 50% de probabilidade de transmissão à descendência, foi-lhe fornecido aconselhamento genético e informada da necessidade de apoio da Medicina da Reprodução quando pretender engravidar.

DISCUSSÃO E CONCLUSÃO

A SC é uma doença rara, pleomórfica e fenotipicamente heterogénea, que deve fazer parte do diagnóstico diferencial do hipogonadismo secundário, com ou sem anósmia, e do atraso da puberdade [8].

Apesar de primeiramente descrito em 1978, e dada a sua heterogeneidade, a sua classificação e critérios de diagnóstico têm sido progressivamente reformulados, tendo a última atualização decorrido em 2005 por parte de Verloes (tabela 2) [6]. A hipoplasia dos canais semicirculares constitui o sinal mais consistente, invariavelmente presente [9]. De acordo com esta classificação, a doente deste caso clínico é portadora de uma forma atípica da doença (um sinal major, hipoplasia dos canais semicirculares; 4 sinais minor, atraso mental, anomalias ouvido externo, disfunção hipotálamo-hipofisária e disfunção rombencefálica com paralisia do VII par).

Sinais major (3 "C")
· Coloboma
· Atrésia das coanas
· Hipoplasia dos canais semicirculares
Sinais minor
· Disfunção rombencefáliaca (disfunção do tronco cerebral, paralisia VII a XII pares cranianos e surdez neurossensorial)
· Disfunção hipotálamo-hipofisária
· Anomalias do ouvido médio e externo
· Malformações dos órgãos do mediastino (coração, esófago)
· Atraso mental

S. de CHARGE típica
· 3 sinais major, 2/3 sinais major + 2/5 minor
S. de CHARGE parcial
· 2/3 major + 1/5 minor
S. de CHARGE atípica
· 2/3 major + 0/5 minor
· 1/3 major + 2/5 minor

Tabela 2 – Classificações dos sinais e tipos de SC de acordo com Verloes [6]

O gene *CHD7* (chromodomain helicase DNA binding protein 7), localizado no cromossoma 8, é o único gene conhecido associado à SC, encontrando-se mutado em praticamente todos os casos de síndrome de CHARGE típica (95%) e em 60-70% dos casos atípicos ou parciais [6]. Esta proteína, em conjunto com outras, participa na regulação da remodelação da cromatina, sendo essencial para a formação e migração das células da crista neural e para o desenvolvimento embrionário [10, 11].

Além da SC, mutações neste gene parecem associar-se a escoliose idiopática e fenda palatina, ambos presentes nesta doente, e a um aumento de risco de cancro do pulmão [12, 13]. Nos casos de suspeita de SC, mutações no gene CHD7 devem ser pesquisadas.

Do ponto de vista endócrino, além do hipogonadismo, os doentes com SC têm frequentemente défice de hormona do crescimento (GH), manifestado por atraso do crescimento e baixa estatura, e mais raramente, hipotiroidismo secundário, devendo estes ser excluídos [7].

Nos doentes do sexo masculino com SC, deve ser efetuada terapêutica com testosterona nos primeiros meses de vida, de forma a promover o crescimento do pénis. Na puberdade, o tratamento do HH consiste na administração de hormonas sexuais, testosterona no sexo masculino e estrogénios no sexo feminino, de forma a induzir o desenvolvimento pubertário e a prevenir complicações, nomeadamente a osteoporose, que deve ser pesquisada e tratada [8].

A síndrome de Kallmann, o hipogonadismo hipogonadotrófico idiopático e a síndrome de CHARGE são as principais causas congénitas de hipogonadismo secundário, com ou sem anósmia. A SC é rara, mas deve fazer parte do diagnóstico diferencial do HH, sobretudo se estiverem presentes outros sinais desta síndrome. Os doentes com SC são complexos, exigindo um seguimento permanente por parte de uma equipa multidisciplinar.

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HORNER SYNDROME SECONDARY TO BREAST CARCINOMA METASTASES

SÍNDROME DE HORNER SECUNDÁRIO A METASTIZAÇÃO DO CARCINOMA DA MAMA

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ABSTRACT

INTRODUCTION: Horner syndrome (HS) results from damage to the oculosympathetic pathway. About 25% of preganglionic HS are due to malignancies.

MATERIAL AND METHODS: We present two cases of women with HS caused by cervical metastases of breast adenocarcinoma (ADC). Physical examination and additional exams were performed.

RESULTS: Case 1: 49-yo, with breast ADC for 8 years, presented with anisocoria. Clinical examination revealed right eye ptosis and miosis. PET-CT showed enlargement of multiple cervical lymph nodes, leading to compression of the sympathetic chain. Case 2: 52-yo, complained of hoarseness and ptosis. Clinical examination disclosed left eye miosis and ptosis. Neck MRI showed an enlarged supraclavicular lymph node. Biopsy disclosed breast carcinoma infiltration.

CONCLUSION: Recognition of the presence of HS allows appropriate clinical investigation that in some cases could lead to diagnosis of primary tumors or metastases. This can prevent permanent nerve damage, and is essential for choosing the appropriate treatment.

Keywords: Horner Syndrome, lymph node metastases, breast cancer.

RESUMO

INTRODUÇÃO: O Síndrome de Horner (SH) resulta da lesão da via oculossimpática. Aproximadamente 25% dos casos de SH pré-ganglionar devem-se à compressão tumoral.

MATERIAL E MÉTODOS: Apresentam-se dois casos de SH causado por metástases ganglionares cervicais de adenocarcinoma (ADC) da mama.

RESULTADOS: Caso 1: 49 anos, antecedentes de ADC da mama há 8 anos, com queixas de anisocoria. Ao exame oftalmológico apresentava ptose e miose à direita. A PET-TC revelou aumento de

múltiplos gânglios cervicais à direita com compressão da cadeia simpática ipsilateral. Caso 2: 52 anos, com queixas de disfonia e ptose. À observação apresentava ptose e miose à esquerda e paralisia da hemilaringe esquerda. Realizou RM do pescoço, onde apresentava adenopatia supraclavicular. A biópsia revelou infiltração por ADC da mama.

CONCLUSÃO: O diagnóstico do SH permite iniciar uma investigação clínica que pode levar ao diagnóstico de neoplasias primárias ou metástases, sendo essencial para instituir o tratamento dirigido.

Palavras-chave: síndrome de Horner, metástases ganglionares, cancro mama.

INTRODUCTION

Claude-Bernard-Horner syndrome results from the damage to the ipsilateral oculosympathetic pathway. The disruption of sympathetic innervation to the eye gives rise to a constellation of symptoms consisting of miosis (with a normal reactive pupil), ptosis, and anhidrosis. [1,2] This syndrome was initially described in animals by Claude Bernard, [3] however Johann Friedrich Horner is credited to be the first to completely describe this syndrome in 1869 and to correctly attribute it to oculosympathetic paresis. [4] The course of sympathetic fibers destined for the orbit is divided into first-, second- (preganglionic), and third-order (postganglionic) segments, that will innervate the sweat glands of the lower face and forehead, lacrimal gland, iris dilator muscle and Muller's muscle. [1,2]

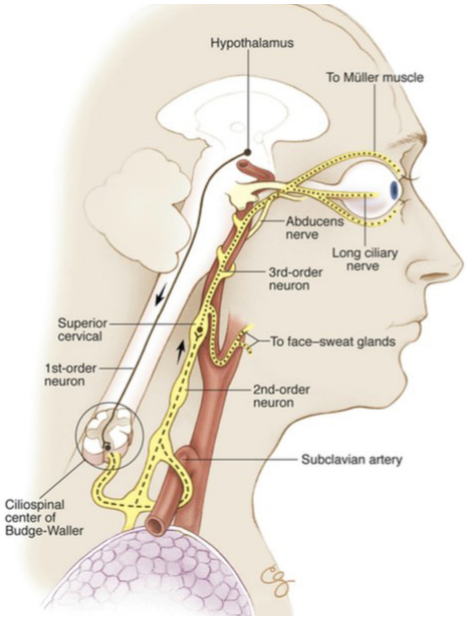

Figure 1 – Oculo-sympathetic pathways, showing first, second and third order neuron. From Bhatti, M. Basic and Clinical Science Course, Section 5: Neuro-Ophthalmology. AAO; 2015.

In a series of 450 patients with Horner syndrome, 65% were found to have an identifiable cause. Of these, 13% had a central lesion, 44% had a preganglionic lesion, and 43% had a postganglionic lesion. [5] In another large series, malignancy was the cause of about 25% of cases of preganglionic Horner syndrome. The most common tumors, were lung and breast cancer. [5] In these series Horner syndrome presented long after the diagnosis of cancer had been established and only rarely was part of the initial presentation. [5,6]

Accordingly to United Kingdom's Office of National Statistics (2015), Breast cancer is the leading cancer in female sex and the second most common cause of tumor-related death in women. [7] Breast cancer has a tendency to spread to the

lungs, bones, liver [8] and remarkably, around 16-19% of breast cancers have metastasized to the lymph nodes at presentation. [9,10]

Breast cancer is usually known to metastasize first via the lymphatics. The occurrence of supraclavicular lymph node metastases is common. [11,12,13] Tumor involvement of the supraclavicular lymph nodes is considered a late stage of regional metastatic involvement, and predicts widespread dissemination, with 80–90% of the patients subsequently developing distant metastases. [11,13,14] In the 7th Edition of the American Joint Committee on Cancer (AJCC) Staging System for Breast Cancer, ipsilateral supraclavicular lymph node metastases are classified as pN3c and so are considered stage IIIc (if no distant metastases). The supraclavicular region comprises the neck level IV and V. In contrast, lymph nodes from levels II and III do not belong to breast lymphatic drainage system. Thus, according to the latest version of the AJCC Staging System all metastases located superiorly to the supraclavicular fossa (levels II–III) must be identified as real distant metastases (M1). [15]

CASE PRESENTATION

We describe two cases of patients with breast adenocarcinoma and supraclavicular lymph node metastasis, presenting with Horner Syndrome.

Case 1:

A 49-year-old Caucasian woman presented with anisocoria (OD < OE) and ptosis of the right eye for two weeks. Patient denied other associated symptoms. Her medical history was notable for the diagnosis of right side breast adenocarcinoma in 2008. She was treated with total mastectomy with axillary lymph node dissection, adjuvant chemotherapy and hormone therapy with for five years. There was family history of cancer (mother: thyroid tumor, father and uncle: lung tumor; grand-mother: colon tumor).

On ophthalmic examination visual acuity was normal (best corrected visual acuity (BCVA) was 10/10 in each eye). Pupils were anisocoric (OD was 2 mm smaller than OE), and anisocoria increased in scotopic conditions, pupils were equal and reactive to light with normal accommodation reflex. Ocular globes were symmetric and presented no displacement, on palpation there were no masses and orbital bones contour was normal. The eyelids fitted smoothly around the eyeball with no palpable masses, although eyelid fissures were asymmetric in primary gaze, with OD measuring 8 mm and OE 11 mm (see Figure 2).

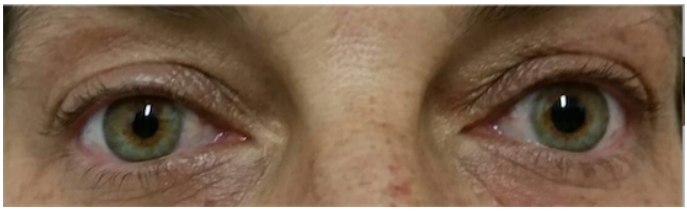

Figure 2 – Right Horner syndrome. Note right-sided upper lid ptosis, right miosis, and "upside-down" ptosis of right lower lid.

There was normal hidrosis face's skin. Extraocular muscle testing was normal, with no concomitant oculomotor nerve palsies. No relevant clinical findings were found in the slit lamp exam, fundus examination or macular and optic nerve optical coherence tomography (OCT).

The patient underwent testing with topical apraclonidine (1%) which revealed dilation of both pupils, confirming the diagnosis of Horner syndrome.

Under the presence of a Horner syndrome an extensive metastatic work-up was then undertaken. PET-CT showed fluorodeoxyglucose (FDG)-avidity in multiple lymph nodes in the supraclavicular and cervical chain (Figure 3A and B) and in the posterior mediastinum. It also showed increased avidity in the apex of the right lung (Figure 3C) and a left frontal hypermetabolic lesion in the brain (Figure 3D). The cervical and supraclavicular lymph node metastases were responsible for the preganglionic Horner syndrome.

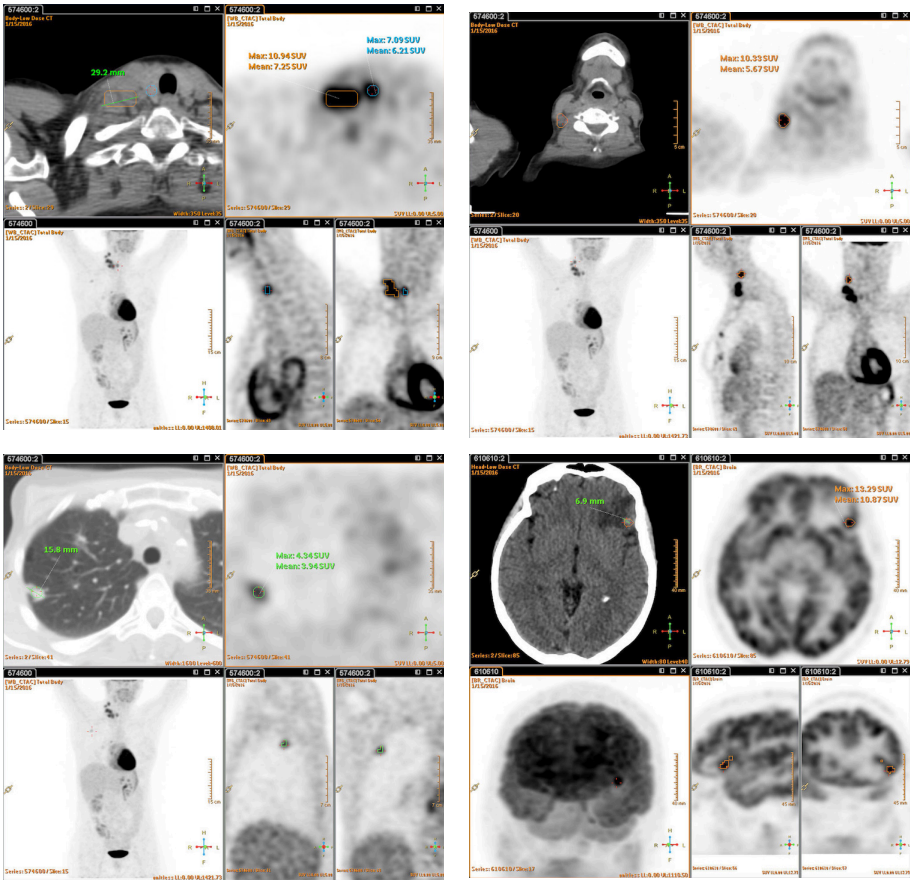

Figure 3 – PET-CT showing FDG-positive metastases evident in the right supraclavicular lymph nodes (A) and in the cervical chain (B). The CT scan affords exact localization. (C) Coronal PET image detects a lung metastasis and CT shows location at the external border of right superior lobe (D) PET showing a hypermetabolic metastasis at the cerebral frontal cortex on the left, and CT disclosing edema surrounding the mass.

Patient started treatment with chemotherapy (capecitabine and carboplatin), holo-cranial radiotherapy and local radiotherapy for lung metastasis. Six months after treatment control PET-CT showed reduction of the lymph nodes, lung and brain metastases. After a year of follow-up patient is still under chemotherapy, and on the ophthalmic re-evaluation there was no clinical improvement with ptosis and miosis still subsiding.

Case 2:

A 52-year-old Caucasian woman, with no relevant past medical history, complained of hoarseness for five months, she also noted a mild ptosis of the left eye that started around the same time. Patient denied any other upper digestive system symptoms. There was no history of trauma or surgery.

Head and neck examination was unremarkable except for the flexible nasopharyngoscopy exam which revealed a left hemilarynx paralysis.

On ophthalmic examination visual acuity was normal (best corrected visual acuity (BCVA) was 10/10 in each eye). Pupils were anisocoric (OE was 2 mm smaller than OD) and anisocoria increased in scotopic conditions, pupils were equal and reactive to light with normal accommodation reflex. Ocular globes were symmetric and presented no displacement. On palpation there were no masses and orbital bones contour was normal. The eyelids fitted smoothly around the eyeball with no palpable masses, although eyelid fissures were asymmetric in primary gaze, with OD measuring 12 mm and OE 7 mm (see Figure 4). There was no anhidrosis. Extraocular muscle testing was normal, with no oculomotor nerve palsies. No relevant clinical findings were found in the slit lamp exam, fundus examination or macular and optic nerve OCT.

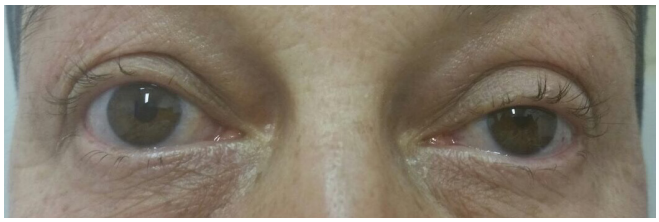

Figure 4 – Left Horner syndrome. (A) Note left-sided upper eyelid ptosis, left miosis, and "upside-down" ptosis of left lower lid. (B) After apraclonidine 1% test, note ptosis and miosis reversal of the left eye.

Under the suspicion of Horner syndrome testing with topical apraclonidine (1%) was performed. As seen in figure 3B, there was left reversal of the left side ptosis and left side miotic pupil responded with dilation, thus confirming the diagnosis of left-side Horner syndrome.

A complete clinical examination was performed, although no other clinical findings were found.

In the presence of a Horner syndrome on the left side with an ipsilateral hemilarynx paralysis the patient underwent imaging investigation with contrast magnetic resonance imaging scan (MRI) of the neck. The MRI revealed a heterogeneous mass with 3.1 x 2.3 cm, in close contact with the left jugular vein and carotid bifurcation (Figure 5).

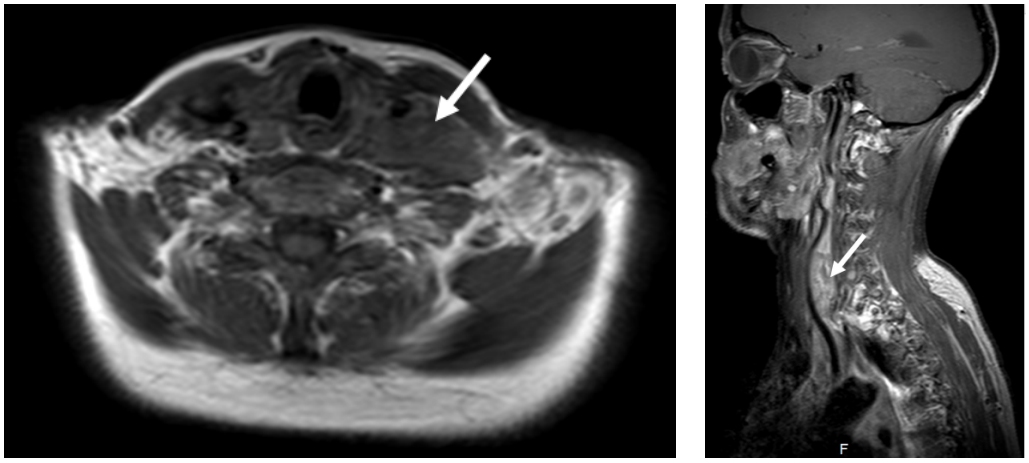

Figure 5 – Neck MRI with gadolinium T1-wieghted images disclosing enlarged supraclavicular lymph node on the left side (arrow). (A) axial scan; (B) sagital scan.

One month after the first consultation the patient underwent neck lymphadenectomy at level V. Pathology examination disclosed breast adenocarcinoma infiltration.

Under the suspicion of an occult breast adenocarcinoma with lymph node metastasis an extensive imaging work-up was performed. Breast MRI disclosed a right breast mass occupying the central quadrant with approximately 5 x 2.5 cm with signs of carcinomatous mastitis and extension to the nipple-areolar complex. PET-CT revealed FDG-avidity in the right breast; lymph nodes (supraclavicular bilaterally, pre-tracheal, right axillary and superior mediastinum); bone (vertebral column, hip, right humerus and femur); left hilum; right anterior thorax wall. Patient was diagnosed with breast adenocarcinoma stage IV.

Patient started chemotherapy with Paclitaxel and Denosumab. After the first chemotherapy cycle, a control PET-CT was performed showed great morphologic response with no FDG-avidity in the previous areas detected. Two months after treatment the ptosis and anisocoria still subsides. Currently, the patient is waiting for breast surgery.

DISCUSSION

We present two cases of lymph node metastases from breast ADC causing pressure on the paravertebral sympathetic plexus leading to pre-ganglionic Horner Syndrome. In case 1, the patient had a past history of breast adenocarcinoma and Horner syndrome was the first clinical manifestation of metastatic disease. In case 2, the patient had no previous relevant medical history and Horner syndrome was the first manifestation of breast adenocarcinoma, at that point already with distant metastases.

The etiologies of acquired Horner Syndrome are summarized in Table 1. According to the literature, the single major cause of Horner's syndrome is neoplasia, with malignant lesions being twice as

frequent as benign tumors. [16] Metastatic breast cancer can lead to Horner syndrome by compressing the sympathetic chain in several points: brain metastases (first order neuron), lung and cervical lymph nodes (second order neuron), and metastases to the orbit or the eye (third order neuron). [11,16,17,18] Patients with breast cancer can be found a wide spectrum of ophthalmic manifestations including: paralysis of II, III, IV or VI cranial nerves, compression of the optic pathway by brain metastasis, Horner syndrome, choroidal masses, strabismus by extraocular muscles tumors and proptosis/blindness by orbital tumors, among others. [17,18]

Central nerve lesions	Preganglionic nerve lesions	Postganglionic nerve lesion
1st order neuron	2nd order neuron	3rd order neuron
Brainstem stroke Multiple Sclerosis Pituitary or skull base tumors Meningitis Neck trauma Arnold-Chiari malformation Spinal cord tumors	Apical lung tumors Lymphadenopathy Trauma or surgical injury Lower brachial plexus or cervical rib trauma Aneurysms: Aorta, subclavian or common carotid arteries Neuroblastoma Mandibular dental abscesses	Cluster headache or migraine Herpes zoster infection Internal carotid artery dissection Para-trigeminal syndrome Carotid-cavernous fistula

Table 1 – Acquired Horner syndrome etiologies.

In breast cancer patients, neurologic complications of the upper part of the thoracic region can occur due to surgery, radiotherapy, or metastatic disease. [19] Brachial plexopathy is a well-known complication of radiation. Involvement of the lower trunk of the plexus is usually caused by the direct extension of the tumor, while involvement of the upper trunk is usually caused by radiation. Taxanes can also produce peripheral neuropathies; metastatic disease can cause neurologic complications in breast cancer patients, although these complications rarely include Horner syndrome. [1,20]

The lymphatic drainage pathways of the breast (axillary, internal mammary, and supraclavicular nodal groups) are the regional areas most likely to be involved with metastatic breast cancer. Supraclavicular metastases are considered a late stage of regional metastatic involvement; however, some patients have a long disease-free survival with aggressive combined modality therapy. [13]

In the two presented cases, Horner Syndrome was a consequence of the disruption of the sympathetic second order neurons, by cervical lymph node metastasis of breast ADC. Patient from case 1 previous history of breast ADC, diagnosed 8 years before. On hospital admission, the patient complained of ptosis and anisocoria for two weeks. Metastatic spread to the lung, cervical lymph nodes and brain was detected by PET-CT. On contrary, patient from case 2, had a Horner syndrome as the first manifestation of breast ADC. The patient complained of hoarseness and mild ptosis for 5 months.

On examination left sided Horner syndrome associated to left hemilarynx paralysis led to imagiologic investigation. MRI disclosed a supraclavicular lymph node mass that was promptly biopsied. The confirmation of breast carcinoma was obtained with pathology examination and breast MRI that detected right side breast tumor.

For the confirmation of the oculosympathetic dysfunction of the pupil the topical apraclonidine test (1%) is essential. Apraclonidine is a weak a1-adrenergic agonist, and only sympathetically denervated eyes will respond to this drug with dilation of the pupil. That is because the iris dilator muscle is supersensitive to adrenergic substances. [1,2] Normal pupils will not present any changes with the application of an apraclonidine drop. Both our patients had positive apraclonidine test, which in the presence of ptosis confirmed the diagnosis of Horner syndrome.

In general, the treatment for Horner's syndrome depends upon the cause. In many cases, no effective treatment is known. Treatment in acquired cases is directed toward eradicating the disease that is producing the syndrome. After treatment, both patients improved, with reduction of the lymph nodes and lung metastases (case 1 and 2), brain metastases (case 1) and bone metastases (case 2), although there was no clinical improvement of Horner syndrome with ptosis and miosis still subsiding.

CONCLUSION

Patients presenting with new onset of a Horner syndrome should always demand the investigation of tumor infiltration or compression. In these patients, a multidisciplinary approach and multimodality imaging is required in order to achieve the correct diagnosis.

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TOO FAST, TOO FURIOUS: A CASE OF ULTRA-RAPID CYCLING BIPOLAR DISORDER

TOO FAST, TOO FURIOUS: UM CASO DE DOENÇA BIPOLAR COM CICLOS ULTRA-RÁPIDOS

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ABSTRACT

Rapid cycling – the presence of at least four mood episodes within a year – is a transient but common phenomenon among patients with bipolar disorder. Its prevalence increases with illness duration and it is often associated with a worse disease prognosis and poor therapeutic response. Some patients experience a type of rapid cycling named ultra-rapid cycling, defined by very briefs cycles lasting for days. Authors report a case of a 47-year-old woman with an ultra-rapid cycling type I bipolar disorder to highlight the clinical relevance of rapid cycling. Prevention is possible through early recognition of risk factors for rapid cycling, early diagnosis of this phenomenon and a proper therapeutic approach. Bipolar disorder constitutes a chronic and debilitating mental disorder, so that this approach is crucial to improve disease outcome.

Keywords: bipolar disorder, rapid-cycling, ultra-rapid cycling, risk factors, prognosis.

RESUMO

Os ciclos rápidos – a presença de pelo menos quatro episódios afetivos no intervalo de um ano – é um fenómeno transitório mas comum entre os doentes com doença bipolar. A prevalência de ciclos rápidos aumenta com a duração da doença e está frequentemente associada a pior prognóstico e a fraca resposta terapêutica. Alguns doentes desenvolvem ciclos ultra-rápidos, um subtipo de ciclo rápido caraterizado por variações do humor que ocorrem em poucos dias. É relatado o caso de uma mulher de 47 anos, com perturbação afetiva bipolar de tipo I com ciclos ultra-rápidos. O reconhecimento precoce dos fatores de risco para ciclos rápidos, o seu diagnóstico precoce e a instituição de uma adequada abordagem terapêutica permitem prevenir estes fenómenos. A doença bipolar é uma doença mental crónica e debilitante, pelo que uma correta abordagem diagnóstica e terapêutica é essencial para melhorar o prognóstico.

Palavras-chave: doença bipolar, ciclos rápidos, ciclos ultra-rápidos, fatores de risco, prognóstico.

INTRODUCTION

Bipolar disorder (BD) is a chronic mental disorder characterized by severe and recurrent mood episodes, either depressive, manic or mixed. Each episode is followed by a period of clinical remission or by another mood episode of different polarity. The duration of the remission periods and the frequency of mood cycles vary significantly between individuals and even in the same patient.

BD has multiple deleterious effects well beyond the acute clinical presentation, thus the global burden of BD should not be underestimated. Contrary to past beliefs, BD does not always have a better overall prognosis than schizophrenia. In fact, a recent study suggests that, when in remission, type I bipolar disorder (BD-I) patients do not differ from patients with schizophrenia with regards to disability level, quality of life, stigma and suicidality [1].

Rapid cycling (RC) is a frequent, although underrecognized, condition in BD [2], currently defined as a course specifier in DSM-5. It applies to patients with four or more mood episodes within a year [3]. RC prevalence ranges from a 12-month prevalence of 9 to 32% to a lifetime prevalence of 26 to 43% [4]. RC is not a stable characteristic, but rather a transient phenomenon in many BD patients, with increasing prevalence with illness duration [5] and often associated with worse disease outcomes and severe disability [6]. Some patients experience a type of RC named ultra-rapid cycling (URC), which can be defined as very briefs cycles lasting for days [6].

The presence of RC is relevant in the clinical management of bipolar disorder. The authors report a case of BD with URC to highlight the importance of early recognition of risk factors for RC and the need of an early diagnosis and proper therapeutic approach to improve disease outcomes.

CASE PRESENTATION

We present the case of a 47-year-old caucasian woman of Portuguese nationality, living in Lisbon with her father, currently single and without descendants. With a higher degree on sociology, she has been unemployed for the last 15 years, having previously worked as a journalist.

She has a personal medical history of hypothyroidism. There is no history of drug or alcohol dependence or abuse. There is a family history of mental illness in her first and second-degree relatives, with her mother and her father's cousin also diagnosed with bipolar disorder.

She had her first mood episode at age 16, with depressive symptoms following adjustment issues regarding poor adequacy to academic performance expectations. The clinical picture was associated with significant impairment, including social isolation and reduced school attendance. Within two months her symptoms remitted spontaneously without clinical evaluation or psychopharmacological treatment.

Her psychiatric follow-up started after she had her first hospital inpatient admission at age 30, caused by a manic episode. Following this episode, frequent and rapid mood cycles ensued, along with a pattern of medication non-adherence. This clinical pattern kept unchanged despite numerous pharmacological and non-pharmacological therapeutic interventions. Interventions in the first admissions due to depressive episodes included the use of antidepressants such as fluoxetine, along with mood stabilizing therapy.

In March 2017, she was admitted to our inpatient psychiatric unit due to a manic episode characterized by increased psychomotor activity, thought acceleration with pressure of speech, dysphoric mood, social disinhibition, grandiose thinking with increased vital energy and goal-directed activities, and a decreased need for sleep. Psychotic symptoms were identified, namely delusional ideas of grandiosity, exhibiting poor judgment and no insight for her condition.

Both physical and neurologic examinations as well as analytical evaluation showed no relevant changes. Toxicology screen was negative. A brain computed tomography scan showed no significant changes. Neuropsychological assessment was performed and reported moderate deficits in sustained attention and episodic memory, mild deficits in executive functions and minor deficits in visuospatial processing and semantic verbal fluency.

Mood stabilizing therapy was prescribed but, after 12 days of admission, she switched to a depressive episode with depressed mood, feelings of hopelessness and helplessness, anhedonia, psychomotor inhibition with claustrophilia and clinophilia. Because of the significant impact of these depressive symptoms, the introduction of an antidepressant was necessary - bupropion 150 mg/day was chosen in accordance with its low potential for inducing hypomanic or manic switches. However, only 3 days after bupropion introduction, mood elevation occurred and a manic episode ensued. Multiple other mood episodes of opposite polarity occurred during the same hospitalization period and under optimized mood stabilizing therapy with anticonvulsants and antipsychotics, with an average cycling rate of 9 to 12 days between switches.

Presently, with 47 years of age, the patient counts a total of 35 inpatient admissions, with a pattern of alternating depressive and manic episodes, most with psychotic symptoms (figure 1). The average time between episodes has been so short that the course of the disease seems to have contributed to an overall functional impairment, with major instability in most domains of her life. She never resumed her career as a journalist after her first hospitalization; emotional instability might have contributed to two divorces and multiple episodes of verbal and physical hostility towards her family; she has a history of self-aggression, including at least 5 suicide attempts.

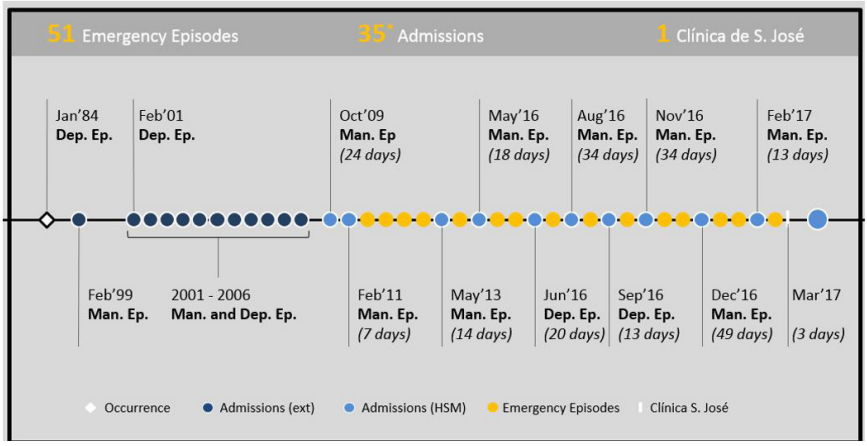

Figure 1 – Psychiatry history

In what concerns her treatment plan, the patient is currently on risperidone long-acting injection (LAI), 50 mg every 2 weeks, valproic acid 800 mg/day, lamotrigine 150 mg/day and quetiapine 200 mg/day. Because of the occurrence of URC, antidepressant therapy was discontinued. Our aim is to keep the treatment plan with progressive lamotrigine titration until the maximum tolerable dose. She will also start a psychosocial rehabilitation program in our day hospital. Hypothetically, if no adequate therapeutic response is achieved with this double intervention, and if the high pattern of admissions persists, electroconvulsive therapy will be considered.

DISCUSSION

As described in this case report, RC development during BD is associated with poorer clinical outcomes. Thus, early recognition of risk factors for RC represents an essential task for the clinical management of BD.

Several socio-demographic and clinical features in this case report suggest the presence of possible risk factors for RC, according to the available evidence (table 1).

Features associated with rapid cycling bipolar disorder
Type II bipolar disorder [7]
Early age of disease onset [2] [4] [6]
Longer duration of the disease [4]
More lifetime mood episodes [4]
Poor therapeutic response [5] [10]
Worse disease prognosis [3] [10]
Female gender [6] [7]
Hypothyroidism [2] [5]
Antidepressants [2] [5] [10]
Atypical depressive symptoms [6]
Higher rate of antidepressant use [4]
Higher number of suicidal attempts [4] [6]
Higher rate of drug and alcohol abuse [2]

Table 1 – Features associated with rapid cycling bipolar disorder

Although RC is more common and sometimes considered a particular feature of type II BD (BD-II), we should acknowledge its presence in type I BD [7].

In spite of some controversy and uncertainty about the relationship between sex and risk for RC, female gender could be considered a significant predictor of RC, cycle acceleration and increased severity of mood episodes over time [7]. For some authors, despite the overall predominance of RC in BD-II, the association between female gender and rapid cycling is stronger in BD-I [7].

An earlier age of disease onset is another characteristic feature of RC patients. Our patient's first depressive episode occurred when she was sixteen. This might be understood as the first mood episode of BD, especially considering her posterior evolution to RC later in life [4].

The premorbid satisfactory academic and professional adjustment, the association between mood variations and self-destructive behavior, the lack of self-destructive behavior during childhood and adolescence and the lack of a pattern of drug abuse seem to be more accordance with BD rather than with an unstable personality disorder. Regarding this case report, the absence of euthymic periods due to RC may be confounded with an unstable personality disorder.

Hypothyroidism is in line with recent evidence that suggests this condition as a correlate of RC. However, the possible causal relations remains a source of debate [5].

Though the etiology of RC remains unclear, antidepressant therapy is probably implicated as a casual or triggering factor [2]. An association between antidepressant use and accelerations in cycle frequency has long been established [8]. According to the literature, the emergence of URC in our patient occurs a few days after the introduction of an antidepressant. A higher rate of antidepressant use is usually associated with RC [6]. Thus, antidepressants should be administered with caution in RC BD patients and only in combination with an antimanic agent, because of their higher potential to induce manic switches [9].

With regard to the characteristics of the depressive episodes, atypical symptoms (mood reactivity, hyperphagia with weight gain, hypersomnia and feeling of leaden paralysis) [3] tend to occur at a higher rate among RC patients when compared with non-RC patients [5]. The depressive episodes reported by our patient developed with typical depressive symptoms.

Additionally, a higher number of suicide attempts is associated with RC, which is also the case of our patient who has a history of at least five attempts [5].

Another clinical feature possibly associated with RC, which is not present in this case report, is a higher rate of drug and alcohol abuse among patients with RC [2]. However, gender differences may play a role, with men having a higher tendency to substance use disorders when compared to women [7].

The absence of a significantly long period of clinical remission, the cognitive deterioration on neuropsychological evaluation, the functional impairment on multiple domains of her life, all together emphasize the burden of RC in patients with BD. The early onset of symptoms, the longer duration of the disease and the high number of lifetime mood episodes explain the worse outcome of RC BD, and why RC should be understood as a deteriorating conditioning in BD patients [5].

In terms of medication non-adherence, it seems difficult to understand its exact relationship with RC. Some authors suggest RC as predictive of nonadherence [10], while others speculate that poor medication adherence may contribute to cycling frequency [11]. In fact, treatment nonadherence among individuals with RC is relatively common, with non-adherence rates of at least 20% [12]. When we look into the clinical features associated with poor adherence in BD, not only RC but also the presence of suicide attempts and the earlier onset of illness are significantly associated with poor adherence, making very difficult to individualize each contribution to a nonadherence pattern in this case report [10].

The literature examining the pharmacological treatment of RC is still sparse and there is, therefore, no clear consensus. RC patients tend to show a less favorable long-term outcome, with initial response unable to predict long-term drug efficacy [13]. Lithium and anticonvulsants show comparable but low clinical response. Current evidence suggest effective response in acute RC with atypical antipsychotics [13], justifying our rationale for the prescription of risperidone LAI and quetiapine in this situation. Although no randomized studies have examined the value of the combination of mood stabilizers and atypical antipsychotics in RC patients [13], based on low clinical response with anticonvulsants alone in RC and in our clinical experience in the management of RC BD patients, we cautiously decided to use combined therapy in this patient.

CONCLUSIONS

URC BD can be considered as a severe presentation of the disease with significant implications in the patient's daily life and worse clinical long-term prognosis. Achieving euthymia and relapse prevention are the primary goals for long-term treatment. Complex and demanding treatment strategies must be accounted for in these cases. Further investigation is necessary to clarify the appropriate treatment of RC.

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BLUE URTICARIA: ANAPHYLAXIS TO PATENT BLUE: "CASE REPORT"

URTICÁRIA AZUL: ANAFILAXIA POR AZUL PATENTE: "CASE REPORT"

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ABSTRACT

Patent blue is the synthetic dye commonly used for sentinel lymph node identification prior to biopsy performance in several types of cancer. It can cause different types of anaphylactic reaction.

We present a case report of blue urticaria with generalized blue hives occurring during the performance of this procedure in a 74 year old patient with breast cancer. There was no hemodynamic or respiratory repercussion, the surgery proceeded without complications, the patient was treated according to protocol with full recovery, while still keeping orotracheal intubation and being transferred to intensive care unit (ICU) for a couple of hours. Posteriorly, the allergy to patent blue was confirmed in the Imuno-allergology unit.

We also undertook a literature review, where several cases are reported. Our goal is to create awereness of the importance of ready diagnosis and treatment in this situation, mainly among anesthesiologists and surgeons.

Keywords: allergy, patent blue, blue urticaria, sentinel lymph-node biopsy, breast cancer.

RESUMO

O azul patente é o corante sintético vulgarmente utilizado para a deteção do gânglio sentinela em vários tipos de neoplasia. Pode produzir reações alérgicas sob diversas formas.

Apresentamos um caso de urticária azul sob a forma de pápulas azuis generalizadas durante a realização deste procedimento numa doente de 74 anos de idade com neoplasia da mama. Não houve alteração dos parâmetros hemodinâmicos ou respiratórios, a cirurgia decorreu sem quaisquer intercorrências, a doente foi tratada segundo o protocolo com recuperação total, embora tenha mantido, por algumas horas, a intubação oro-traqueal e sido transferida para a Unidade de Cuidados Intensivos, para vigilância. Posteriormente foi confirmada, na consulta de Imunoalergologia, a alergia ao corante.

Efetuámos também uma revisão da literatura, onde estão referidos alguns casos, sendo que o nosso objetivo é alertar os anestesiologistas e cirurgiões para a necessidade do pronto reconhecimento e terâpeutica desta intercorrência.

Palavras-chave: alergia, azul patente, urticária azul, biópsia do gânglio sentinela, neoplasia da mama.

INTRODUCTION

Sentinel lymph node (SLN) biopsy is the routine procedure for breast cancer staging and treatment in patients with early breast cancer (T1/T2 N0 M0), thus avoiding classical axillary lymphadenectomy morbidity.

In our department, patients undergo SLN mapping procedures with the combined technique of subdermal radioisotope injection the day before surgery (lymphocintigraphy) and another subdermal injection of 2 ml 2,5% sodic Patent blue V (Guerbet, France) immediately after anesthetic induction. During surgery, using the probe and the lymphatic vessels blue coloring, the SLN is found, excised and sent to the usual histopathologic evaluation.

For decades, the literature has reported cases of anaphylactic reactions to synthetic dyes, namely to patent blue, assuming different aspects and severity degrees, from blue urticaria to anaphylactic shock. With the widespread use of this technique, not only in breast cancer and melanoma but also in other types of cancer, there is a predictable rise in number of such cases, so that it is very important a prompt recognition and treatment of this situation.

We report a case of blue urticaria as anaphylactic reaction to patent blue.

CASE PRESENTATION

A 74 year-old woman presenting with a left breast T1b N0 M0 invasive carcinoma NST was admitted for SLN biopsy and lumpectomy. Her medical history included arterial hypertension and dyslipidemia under medication with atenolol, hydroclorothiazid+captopril and sinvastatin. She was not atopic.

In the OR, after anesthesia induction with midazolam, fentanyl, propofol, rocuronium and prophylactic cefazolin, we started the surgery and 20 minutes after SLN biopsy we detected blue hives on the patient's breast and left arm (figure 1). There was no hemodynamic or ventilatory instability, the patient was medicated with 100 mg hydrocortisone and surgery proceeded with no further incidents.

Figure 1

After removal of the surgical drapes there was a generalized blue urticaria (figure 2) and blue edema of eyelids and auricular pavilions (figure 3). Laringoscopy showed a very mild epiglotic edema without involvement of lips, tongue or glotis but we considered prudent to maintain orotracheal intubation.

Figure 2

Figure 3

The patient was medicated with histamine blockers (clemastin 4 mg iv in the OR and hydroxizin 50 mg 8/8 h posteriorly), and was admitted in the ICU. She was extubated 18 hours later, transferred to the ward without the blue rash and discharged three days later without further symptoms.

She was referred to the Imuno-allergology unit, where patent blue allergy was confirmed after skin prick-test and intra-dermal skin test. All drugs were tested; only intra-dermal skin test (1/10.000 dilution) was positive.

DISCUSSION

Patent blue is a frequently used dye in food and textile industries, cosmetics and agriculture.

In literature, there have been consistent reports of anaphylactic reactions to patent blue (more used in Europe) [1-8] or to isosulfan blue (more used in the USA) [9-14]. Their chemical structure is very similar, because the latter is an isomer of the former and produces the same type of anaphylactic reactions [15].

The use of patent blue can cause some expected "accessory effects", such as blue urine colouring, grayish skin and mucosae colouring which can mimic anemia and results from the intracapilar dye circulation [15], or a false hypoxemia on peripheric oximetry, due to the dye absortion of red light with arterial blood gas test showing no drop of pO_2 [7,15].

These kind of anaphylaxis is due to an IgE mediated, type I hypersensibility reaction [6-8,15]. Probably, these skin and systemic reactions are a consequence of a previous contact with the dye, so that sensibilization can occur [6,7,15].

Three severity degrees are described, related to the patent blue hypersensibility: grade I (blue urticarial, generalized rash and pruritus), grade II (arterial hypotension without need of vasopressors and/or bronchospasm or laryngospasm) and grade III (anaphylactic shock, leading to procedure interruption and admission in the ICU). The first signs are hypotension and blue urticaria but this one can be overlooked because the surgical drapes hide it, just like in our case-report [6-8]. The patients must be monitored because reaction can be delayed with symptoms appearing 6 to 8 hours later [7, 8].

This diagnosis can be confirmed by measuring plasmatic histamine and tryptase levels within the first 3 hours after the reaction and repeating them in 24 hours. Unfortunately they are not available in all institutions [6-8,15].

In a broad literature review, several authors reported patent blue or isosulfan blue hypersensibility during SLN biopsy in breast cancer and melanoma patients. In about 3400 evaluated patients, the incidence of allergic reactions was between 1,1% [3,6] and 1,6% [10], both as blue urticaria and anaphylactic shock. There were no mortality reports.

In our Department with 600 breast and melanoma patients operated with this technique, we report only two cases of grade I Patent Blue allergic reaction (0,3%).

With rising numbers of these episodes, some authors sugest changing these dyes for Methilene Blue. There is no worsening of the technique reliability.but Methilene Blue can cause an intense skin reaction with necrosis and ulceration, allowing only intra parenchimatous injections [7,15]. Others sugest the use of skin test or prophylactic administration of anti-histaminics prior to surgery but, these are not consensual solutions [7,8,15].

CONCLUSIONS

SLN biopsy is the standard procedure for staging and treating breast cancer. The use of dyes like Patent or Isosulfan Blue produce between 0,1% and 2,2% of allergic reactions, from blue urticaria to anaphylactic shock.

With generalization of this technique there will be a rising number of these reactions, so it is very important to promptly recognize and treat these situations, in order to minimize its potencial morbidity.

Using Methilene Blue is also a prudent alternative, particularly in patients with an atopic past or with previous reactions to some of these dyes.

We recommend systematic referring of these patients to Imuno-allergic Units to confirm the allergy in order to avoid future contacts with these products.

The patients must be informed of the procedure risk and this must be included in the informed consent.

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