Priapism Secondary to Low-Molecular-Weight Heparins: A Case Report

Priapismo Secundário a Heparinas de Baixo-Peso-Molecular: Um Caso Clínico

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ABSTRACT

Priapism may be a side effect of low-molecular-weight heparins, and its mechanism remains unknown. The authors present a clinical case of a 51-year-old male patient with oligodendroglioma. The patient presented ischemic priapism on the third month after starting tinzaparin, without other recent changes to his medication and he denied the use of other new medicines. The patient went through surgery and the erection was resolved but presented fibrosis of the cavernous body which left him with erectile dysfunction. Since this event, the patient is no longer receiving Heparin and has had no other episodes of priapism. The prompt recognition of this side effect may decrease its morbidity and consequent impact on the quality of life. More studies are needed to better understand its pathophysiology.

Keywords: Heparin, Low-Molecular-Weight/adverse effects; Priapism/chemically induced

RESUMO

O priapismo pode ser um efeito adverso das heparinas de baixo peso molecular, cuja fisiopatologia não é totalmente compreendida. Os autores apresentam o caso de um doente, do sexo masculino, 51 anos, com diagnóstico de oligodendroglioma. O doente apresentou um episódio de priapismo, no terceiro mês sob tinzaparina, sem nenhuma outra alteração recente da sua medicação habitual e com consumo de outros medicamentos negado. Foi submetido a cirurgia, com resolução do priapismo, mas apresentou fibrose sequelar dos corpos cavernosos, com consequente disfunção eréctil. Desde então o doente não retomou heparina e não apresentou novos episódios de priapismo. Um célere reconhecimento do quadro pode contribuir para menores sequelas, com consequente diminuição da morbilidade e impacto na qualidade de vida. Mais investigação é necessária para aumentar o conhecimento sobre a fisiopatologia desta situação.

Palavras-chave: Heparina de Baixo Peso Molecular/efeitos adversos; Priapismo/induzido quimicamente

INTRODUCTION

The word priapism comes from Priapus, a Greek god of fertility renowned for his large phallus.[1] Priapism is a prolonged penile erection in the absence of sexual desire.[2]

Priapism associated with the use of low-molecular-weight heparins (LMWH) treatment has been described.[3,4] The pathophysiology is not fully understood and there are few published cases of LMWH-induced priapism.[5,6] As a case of ischemic priapism, its consequences may be permanent and severe, which explains why erection resolution is an urologic emergency. Ischemic priapism may lead to necrosis of erectile tissue and penile fibrosis,[7] which could then cause significant psychological and social sequelae.[1]

In the future, more cancer patients will receive anticoagulants due to an increased incidence of DVT. This increase could be the result of better overall survival of the cancer population, the prothrombotic effect of anticancer treatments and better accuracy of imaging tests (increasing mainly incidental DVT).[8] The number of cancer patients receiving anticoagulants is expected to be higher too due to an increase in thromboprophylaxis, as a result of recent guidelines updates recommending primary thromboprophylaxis for ambulatory cancer patients at higher risk for DVT (defined as a Khorana score higher than two) in the absence of contraindications. Because of this, LMWH-induced priapism may increase in this population.[9] By being familiar with the potential risks associated with medication, physicians can inform the patients of the right attitude if it occurs and make a more rapid diagnosis.[6]

We present a case report of ischemic priapism associated with tinzaparin in a cancer patient.

CASE REPORT

This article reports the case of a 51-year-old male with a medical history of left frontal anaplastic oligodendroglioma, isocitrate dehydrogenase (IDH) 1 mutated, World Health Organization (WHO) grade III, diagnosed in 2005 and a Deep Vein Thromboembolism (DVT) identified in January 2018. The patient was receiving treatment with prednisolone 10 mg daily, phenytoin 100 mg daily, levetiracetam 10 mg twice a day, and temozolomide 225 mg/day for five days, in cycles of

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28/28 days, and started tinzaparin 10 000 U daily in January 2018. There were no relevant prior medical conditions, he presented preserved sexual function and had no history of drug allergies or other conditions.

On the 24th May 2018, the patient presented to the Emergency Department with a persistent, painful penile erection lasting 35 hours. He was not receiving treatment with phosphodiesterase type five inhibitors (PDE5I) or other medicines apart from his usual medication. The physical examination showed a penile erection, soft glans, and no ischemic signs. The penile blood gas analysis revealed a pH of 6.7 (reference range: 7.35 – 7.45), pO2 of 30 mmHg (reference range: 80 – 100 mmHg) and pCO2 of 66 mmHg (reference range: 35 – 45 mmHg), and all other laboratory tests were within the normal range. He went through emergent surgical treatment with lavage with saline solution and phenylephrine, without success, and then an Al Ghorab type shunt was performed (semi-lunar incision on the dorsal side of the gland, dissection, incision of cavernous bodies with blood drainage and abundant lavage -without apparent blood clot washout -, partial penile detumescence and cutaneous closure of the penile gland). After surgery, the rigid erection was resolved without signs of compartment syndrome and pain. He recovered with fibrosis of the cavernous body. Since this event, the patient is no longer under LMWH, and he had no further episodes of ischemic priapism.

The patient currently presents erectile dysfunction, which is non-responsive to PDE5I, and is aware of his irreversible clinical condition and of the possibility of penile prosthesis implantation. He is under the fourth line of antineoplastic palliative systemic treatment with temozolomide (200 mg/m^2/day for five days, in cycles of 28/28 days) associated with bevacizumab (10 mg/kg every 14/14 days) after having presented multiple progressions of oligodendroglioma.

DISCUSSION

A penile erection involves a complex coordination of signals including parasympathetic and sympathetic inputs and smooth muscle to control vasorelaxation and vasoconstriction[10] which allows for increased arterial blood flow and trabecular cavernous tissue distension.[11] Diverse causes of priapism have been described, including neurological, pharmacological, trauma and idiopathic causes.[12]

The mechanism by which LMWH may induce ischemic priapism is not completely known and its low frequency makes it harder to study.[13] Some hypotheses are that heparin causes vasodilatation,[14] while another is that it stimulates rebound thrombosis[15] or increases platelet aggregation by Heparin-induced antiplatelet-antibodies (seen in vivo and in vitro).[16] Nowadays, there is an increase in cancer-associated thromboembolism treatment and prophylaxis, so this adverse effect might be more commonly observed.[8]

Priapism is divided into non-ischemic and ischemic, the latter comprising around 95% of the cases and it is the one associated with LMWH.[17] It is also known as veno-occlusive or low-flow priapism because it is associated with decreased or absent cavernous blood flow, corpus rigidity, and pain.[7] It represents a form of compartment syndrome characterized by increased pressure within the enclosed cavernous space and compressed circulation.[17] Histopathologic studies show time-dependent erectile tissue damage with irreversible corporal damage occurring in episodes lasting six hours (major priapism).[11] Beyond 24 hours, tissue necrosis and fibroblast proliferation could lead to erectile dysfunction (ED), with estimated rates of 90%. Therefore, it is a medical emergency.[1]

For the diagnosis of priapism, it is essential to take a comprehensive medical history, that covers the patient's previous medical conditions (namely hemoglobinopathies), usual medicines and other drugs as well, the occurrence of previous similar episodes, the recent history of trauma (mainly pelvic), the duration of an episode of priapism and whether there is pain.[7,11] Performing a penile arterial blood gas test is essential. The presence of acidosis, hypoxia, and hypercapnia indicates ischemia. The penile blood gas levels in ischemic priapism are pH < 7.25 (reference range: 7.35 – 7.45), pO2 < 30 mmHg (reference range: 80 – 100 mmHg) and pCO2 > 60 mmHg (reference range: 35 – 45 mmHg).[9] In non-ischaemic priapism, cavernous blood gases are similar to arterial blood.[7] Urine and blood toxicology can aid in determining pharmacotherapeutic or recreational drug use.[1] Regarding treatment, the objective is to re-establish venous blood return and relieve pain.[11] Priapism urges the use of stepwise, from least to more invasive, techniques.[18] The initial treatment is conservative (early corpus aspiration and phenylephrine injection) followed by surgery which would shunt cavernous blood return to the corpus spongiosum or local veins, or early placement of a penile prosthesis.[1] The approach of these patients represents a challenge and should involve a multidisciplinary approach.[18]

The existence of several possible risk factors for priapism is a limitation of this case report. The patient presented a central nervous tumour and was under tinzaparin, levetiracetam and phenytoin. Because of the temporal relation and the absence of new episodes with heparin withdrawal, priapism was considered as being most likely caused by LMWH. Nonetheless, priapism may have not occurred again due to cavernous fibrosis and consequent penile erectile dysfunction.

This article describes a case of priapism as a side effect of LMWH. The pathophysiology is not yet fully understood, so more studies aimed at unveiling the mechanism behind it are needed, which would enable improvements in treatment and prevention. As the number of cancer patients under LMWH increases, clinicians should be aware of the existence of this entity that requires prompt and multidisciplinary management.

AUTHORS CONTRIBUTION

JLP, ND: Design and conception of the work.

MB, MS: Design, critical review and approval of the work.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association published in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

All authors report no competing interests.

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