CASO CLÍNICO / *CLINICAL CASE*

Osteomielite por *Clostridium perfringens* num doente com Artrite Reumatóide

Osteomyelitis caused by Clostridium perfringens *in a patient with Rheumatoid Arthritis*

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/ Resumo

A osteomielite causada por bactérias anaeróbias é muito rara e, na revisão efetuada, não encontrámos relatos anteriores de osteomielite causada por Clostridium perfringens afetando fémur e acetábulo.

Descrevemos o caso de um homem de 48 anos com artrite reumatóide sob tocilizumab intravenoso e artrite bilateral das coxofemorais, que se apresentou com dor intensa na articulação coxofemoral esquerda e fadiga. A investigação efetuada, que incluiu cultura óssea, permitiu o diagnóstico de osteomielite, causada por *Clostridium perfringens*, afetando o fémur e o acetábulo. O paciente iniciou tratamento com penicilina G endovenosa e cotrimoxazol, que foi depois substituído por amoxicilina/ácido clavulânico por via oral. O controlo imagiológico por ressonância magnética nuclear demonstrou redução do edema da medula óssea e do derrame articular e, apesar da limitação funcional, o doente apresenta controle da dor e recusa a cirurgia.

Palavras-chave: *Clostridium perfringens*; osteomielite; imunossupressão

/ Abstract

Osteomyelitis caused by anaerobic bacteria is very rare and the authors are not aware of any previous reports of osteomyelitis caused by this bacterium affecting femur and acetabulum. The authors describe the case of a 48-year-old male with rheumatoid arthritis under intravenous tocilizumab and bilateral hip osteoarthritis, presenting with new onset severe left hip pain and fatigue. After the diagnostic workup, including bone culture, he was diagnosed with osteomyelitis, caused by Clostridium perfringens*, affecting femur and acetabulum. The patient initiated treatment with intravenous G penicillin and cotrimoxazole, which were then shifted to oral amoxicillin and clavulanic acid that was maintained continuously. The follow-up magnetic resonance imaging demonstrated reduction of bone marrow oedema and joint effusion and, despite the functional limitation, the patient has controlled pain and refuses surgery.*

Keywords: Clostridium perfringens*; osteomyelitis; immunosuppression*

/ Introduction

The age of biological therapies revolutionized the treatment of patients with inflammatory rheumatic diseases, particularly rheumatoid arthritis.

Historically, treatment paradigms in such disease have advocated starting with non-biologic disease-modifying agents with or without short-term low-dose prednisone. In patients who do not achieve disease control with DMARDs, an anti- anti-TNF-agent or other biologic agent such as anti-IL6-agents should be started.[1]

Due to their marked efficacy on host immunological pathways, their use may be associated with the occurrence of infections, whose diversity and severity depends on the particular immune target.[1]

Most infections occur within the first year of biological therapy use, and major concerns are severe bacterial infections, mycobacterial and fungal diseases, herpes zoster and hepatitis B virus (HBV) reactivation and finally travel-associated infections.[1]

However, osteomyelitis caused by anaerobic bacteria is very rare in in immunocompetent and immunocompromised individuals.[2] There are some reports of spondylodiscitis caused by *Clostridium perfringens*, but the authors are not aware of any previous reports of osteomyelitis caused by this bacterium affecting femur and acetabulum.[3–5]

/ Case Description

The authors describe the case of a 48-year-old male with rheumatoid arthritis under intravenous (iv) monthly tocilizumab and bilateral hip osteoarthritis presenting at the outpatient Rheumatology clinic with new onset severe left hip pain and fatigue.

He had been examined in the emergency department 2 weeks earlier and was discharged with non-steroidal anti-inflammatory drugs (NSAIDs). There were no gastrointestinal, genitourinary or respiratory symptoms or history of trauma.

Physical examination revealed body temperature of 38ºC, intense left hip pain with minimal mobilization, very painful decreased range of movement and polyarthritis.

Laboratory tests presented white blood cell count of $11.6x10^9$/L (normal range: 4.0-11.0x10^9L) with neutrophilia of 8.4x10^9L (normal range: 2.00 – 7.50x10^9/L), C-reactive protein(CRP) of 12.35 mg/dl (normal range < 0.5mg/dL) and erythrocyte sedimentation rate of 71 mm/h (normal range < 20 mm/h). Procalcitonin was normal. Blood and urine cultures were negative.

A magnetic resonance imaging (MRI) revealed increased acetabulum and femoral head bone marrow intensity that reflects bone oedema and effusion (figure 1a).

Hip synovial fluid collection and osseous biopsies were performed. Direct examination and culture of synovial fluid was negative. Bone culture was positive for Clostridium perfringens. A diagnosis of septic arthritis and osteomyelitis, caused by *Clostridium perfringens*, affecting femur and acetabulum was established.

The treatment approach included a multidisciplinary team (Rheumatology, Orthopaedics and Infectious Diseases Department). Considering the pros and cons of surgery, in an immunocompromised patient with an infection and the patient's refusal to undergo orthopedic procedures, a conservative treatment was adopted.

The patient initiated treatment with iv G penicillin (4 million units six times a day) and iv clindamycin (600 mg four times a day). Clindamycin was switched for cotrimoxazole due to a cutaneous reaction. The treatment was maintained 6 weeks, intravenously, and then shifted to oral amoxicillin and clavulanic acidy, continuously.

Concurrently, polyarthritis was treated with sulphassalazine, hydroxycloroquine, low dose steroids and NSAIDs.

A follow-up MRI, 2 months after iv antibiotic therapy, demonstrated reduction of bone marrow oedema and effusion (figure 1b) and, despite the functional limitation, the patient has controlled pain. After 2 years since clinical presentation, there was no worsening of hip pain intensity or symptoms suggesting infection recurrence; rheumatoid arthritis remains in low disease activity.

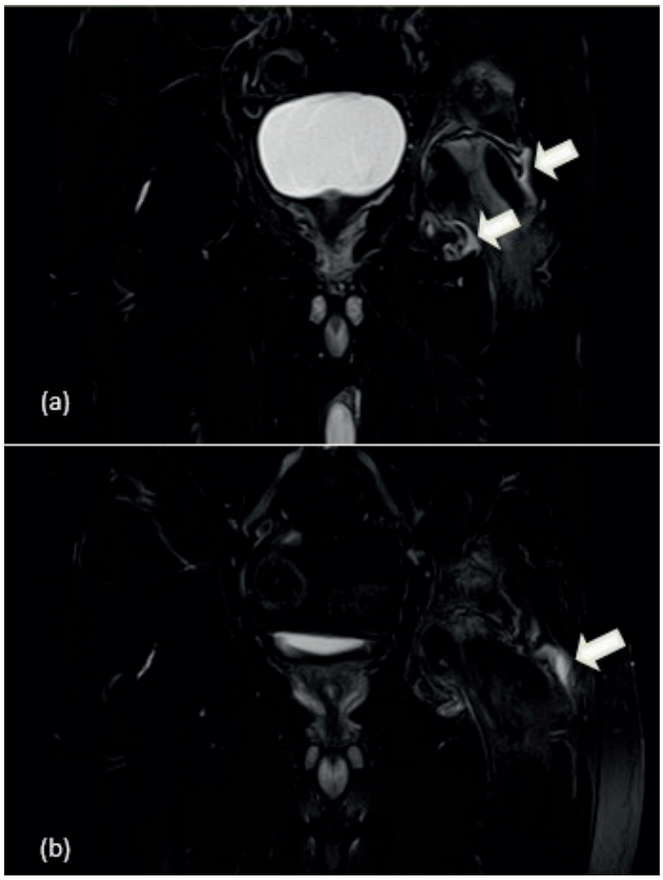

Figure 1 – Coronal T2 -weighted image with fat suppression at baseline (a) revealing increased femoral head bone marrow intensity that reflects bone oedema and effusion (white arrows). Follow- up MRI (b) demonstrate reduction of signal intensity on bone marrow and reduction of effusion (white arrow)

/ Discussion

Tocilizumab is a humanized IgG1 monoclonal antibody that selectively neutralizes both the soluble and membrane-bound forms of IL-6R. In rheumatic diseases, it is approved to treat rheumatoid arthritis, systemic juvenile idiopathic arthritis and giant cell arteritis.[6,7]

Tocilizumab shows a rapid onset of action leading to reductions of inflammatory markers, particularly CRP levels. This prompt suppression of inflammation can increase threatening infections with minimal clinical (fever) or laboratory markers signs.[8] However, the increased risk of opportunistic and serious bacterial infection is similar to other biological therapies, such as anti-TNF-α agents.[8]

The most common infections associated with tocilizumab are pneumonia, urinary tract infections and cellulitis.[9]

In our case, the immunosuppression with tocilizumab was associated with osteomyelitis by an uncommon agent, in the absence of other host risk factors.

Clostridium perfringens is a Gram-positive, anaerobic, spore-forming bacillus, ubiquitous in the soil and water and it is also considered a commensal of the gastrointestinal tract.[3] The virulence of *Clostridium perfringens* is due mainly to toxin production.[3] Septic arthritis and osteomyelitis due to *Clostridium perfringens* are an unusual clinical occurrence that is rarely documented, and most cases were associated with traumatic penetrating injury, which wasn't present.[10] Haematogenous route has been reported; however, in some cases, the aetiology is unknown, as in this patient.[10]

The treatment of chronic osteomyelitis requires a combined surgical and medical approach, involving an aggressive surgical debridement followed by a long course of antibiotic therapy (intravenously at least for 4-6 weeks after surgical debridement, followed by an oral agent for 3 to 6 months). As previously mentioned, in this case, a conservative treatment, without surgery, was assumed.[11,12]

Concerning management of infections in rheumatic patients receiving biological therapies, the Portuguese Society of Rheumatology recommendations[13] state that biological therapy should be discontinued at least during antimicrobial therapy and the reintroduction of the treatment should be decided on a case by case basis, taking into account the activity of the rheumatic disease and the risk of reinfection. The permanent discontinuation of biological therapy should be considered in severe or recurrent infection. In our case, the patient maintained signs of infection, therefore he proceeded without biological therapy.

/ Conclusion

Physicians should be aware of these rare pathogenic agents causing bone infections. This case emphasizes the importance of considering alternative explanations for new onset of hip pain, even in patients with osteoarthritis or inflammatory arthropathies, especially if immunocompromised. A high level of clinical suspicion and a multidisciplinary approach are required to reach a correct diagnosis, to guide early and correct treatment and to achieve a better outcome.

In our clinical practice, the infectious diseases outpatient clinic, dedicated to preventing the risk of immunosuppression, has contributed to providing better care to rheumatologic patients.

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