Agranulocitose Induzida pela Ceftriaxona durante a Terapia para Endocardite por *Streptococcus bovis*

Ceftriaxone-Induced Agranulocytosis during Therapy for *Streptococcus bovis* Endocarditis

Tiago Castro Pinto[1], João Pedro Pereira[2], Inês Chora[1]

Resumo:

A ceftriaxona, um dos antibióticos mais frequentemente utilizados na prática clínica, tem como efeito adverso, raro e potencialmente grave, a agranulocitose. Reportamos um caso de uma mulher de 85 anos em esquema terapêutico prolongado com ceftriaxona para endocardite por *Streptococcus bovis*, que desenvolve agranulocitose ao 25º dia de antibioterapia, com nadir de contagem absoluta de neutrófilos de 0/uL. Outras causas potenciais foram excluídas. A terapêutica antibiótica foi alterada para amoxicilina/ácido clavulânico e realizou ciclo de fator estimulador de colónias de granulócitos, com resolução da neutropenia após 3 dias. Queremos destacar este efeito adverso raro com o uso prolongado da ceftriaxona, salientando a necessidade de monitorização regular das contagens de leucócitos. O tratamento desta condição passa pela suspensão do agente causal e o uso transitório de factor estimulador de colónias de granulócitos até resolução da neutropenia.

Palavras-chave: Agranulocitose/induzida quimicamente; Ceftriaxona/efeitos adversos; Endocardite Bacteriana; Fator Estimulador de Colónias de Granulócitos; Infecções Estreptocócicas; Streptococcus bovis.

Abstract:

Ceftriaxone, one of the most frequently used antibiotics, has agranulocytosis as one rare, but potentially serious side effect. We report a case of ceftriaxone-induced agranulocytosis in an 85-year-old woman on the 25th day of antibiotic therapy for *Streptococcus bovis (S. bovis)* endocarditis that presented with a nadir of absolute neutrophil count (ANC) of 0/uL. Other potential causes were excluded. Ceftriaxone was switched to amoxicillin/clavulanate and granulocyte colony stimulating factor (G-CSF) was prescribed, with resolution of neutropenia in 3 days. Prolonged therapy with ceftriaxone may increase the chance of agranulocytosis, hence the importance of leukocyte monitoring in these treatment schemes. Treatment involves replacing the offending agent and the use of G-CSF until normalization of ANC.

Keywords: Agranulocytosis/chemically induced; Ceftriaxone/adverse effects; Endocarditis, Bacterial; Granulocyte Colony-Stimulating Factor; Streptococcal Infections; Streptococcus bovis.

Introduction

Ceftriaxone induced agranulocytosis has been scarcely reported in the literature. Being one of the most frequently used antimicrobials with a potentially serious side effect, there is a need to establish its incidence, so that more clinicians can detect it promptly.

Case Report

An 85-year-old woman with a bioprosthetic aortic valve was admitted to the general internal medicine ward with fever, anorexia, fatigue and weight loss over a two month period. She had atrial fibrillation, type 2 diabetes mellitus with diabetic nephropathy (stage IIIb) and retinopathy, hypertension, dyslipidemia, chronic gastritis and a mild cognitive impairment as past medical history. She was under three anti-diabetics, two antihypertensives, apixaban, donepezil and quetiapine. She had no recent infections, no recent antibiotic courses, no recent hospital admissions, or surgical procedures.

There was no recent travel or SARS-CoV-2 exposure. On auscultation there was a systolic aortic murmur that had been described in electronic medical records 6 months earlier but dismissed because of its unspecifity. The further physical examination and review of systems were unremarkable.

Upon presentation, laboratory results showed an elevated C-reactive protein (116.8 mg/L normal range <5 mg/L), absence of leukocytosis (10100/uL, normal range 4000-11000/uL) with a relative neutrophilia (81% - ANC of 8200/uL, normal range 1300-8800/uL) and a normal procalcitonin. Transthoracic echocardiography revealed an oscillating intracardiac filiform mass on prosthetic aortic valve and four blood cultures came positive for *Streptococcus bovis (S. bovis)* sensitive for

[1]Serviço de Medicina Interna, Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos, Matosinhos, Portugal
[2]Serviço de Gastroenterologia, Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos, Matosinhos, Portugal

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ceftriaxone, penicillin, and cefotaxime, establishing the diagnosis of infective endocarditis. A 6-week course of intravenous 2 g daily ceftriaxone was initiated. During hospitalization, a colonoscopy identified a vegetative and stenosing colon lesion in the hepatic angle, confirmed as adenocarcinoma in the histological report, emphasising the association between *S. bovis* infective endocarditis and colon cancer. On day 25 of ceftriaxone therapy, a routine complete blood count documented a leukopenia of 1230/uL and ANC of 0/uL, falling from 2830/uL (leukocytes) and 1400/uL (ANC) 3 days prior and 3430/uL (leukocytes) and 2000/uL (ANC) 5 days prior.

No recent drugs had been introduced to her baseline medication, besides ceftriaxone. A peripheral blood smear showed absence of neutrophils or blast cells but also no alterations affecting red cell lineage or thrombopoiesis. Differential causes were ruled out: normal range vitamin B12, folate and TSH levels as well as negative serology for HCV HSV1, HSV2 and Parvovirus and immunity against HBV, HAV, EBV, CMV. A medullar biopsy was not done.

Agranulocytosis was suspected to be drug induced from ceftriaxone, with a Naranjo score (adverse drug reaction probability score) classification as “probable”.

Ceftriaxone was switched to an intravenous regimen of amoxicillin/clavulanate 6.6 g + amoxicillin 1.5 g/day, each one divided in three daily doses targeting endocarditis. In addition, treatment with granulocyte colony-stimulating factor (G-CSF) was started, with 300 µg filgrastim subcutaneously daily. G-CSF was administered for 3 days before the neutrophil count normalized to 3700/µL on day 4 and it stabilized around 3000/µL until patient discharge.

She was submitted to hemicolectomy 1 month after, being currently followed in outpatient consults.

Discussion

Agranulocytosis is defined as severe neutropenia and is associated with an increased risk of infection.[1,2] The ANC cutoffs for the definition of agranulocytosis vary between 0-500/uL according to different studies.[1-4] A drug induced etiology is present in up to 70% of the cases[5] and its incidence increases with age, with 50% of events occurring in people aged over 50 years. The female to male ratio is 2:1, as there are more women taking medications, which may precipitate neutropenia.[6]

The underlying pathophysiology is divided mainly in immunologic-mediated and toxicity-mediated mechanisms.[2,7] The former include haptenization, immune complexes or anti-neutrophil antibodies formation, while the latter includes bone marrow, neutrophil or stromal toxicity.[2,7] Current evidence suggests that ceftriaxone-induced agranulocytosis is likely to be immunologically mediated, similarly to other drugs.[8,9] Observations corroborating this claim, include the fact that a second agranulocytosis event under a same drug occurs in a shorter time window than the first one and usually under moderate doses.[10]

Consistent with previous literature reports,[10,11] agranulocytosis also occurred on the 25th day of ceftriaxone therapy in our case and also in moderate doses (2 g/day). This also contributes to the argument that the duration of exposure is a likely risk factor for the event, due to the generation of an immunologic-mediated response. Naranjo scale, a method for determining the probability of drug induced adverse reaction,[12] strengthens our hypothesis, because of existing previous reports, adverse event resolution after discontinuing ceftriaxone and no other likely explanation for the reported event. Moreover, neutropenia occurred in an inpatient setting with a newly introduced drug, making a pharmacologically mediated cause more likely than a viral one.

In our case, the nadir of the ANC was 0/uL, a value reported in the minority of the available literature.[1,3,4,10,11] More important, is the cutoff <100/uL, reported in the majority of available cases, that is associated with poor prognosis, namely infectious complications, sepsis and mortality.[1,3,4,10]

Ceftriaxone-induced agranulocytosis treatment is similar to other forms of drug-induced agranulocytosis. The central aspects of treatment are the withdrawal of the offending agent and administering G-CSF.

In instances where the ANC <100/uL, G-CSF administration is associated with reduction of the total number of days of neutropenia, shorter hospital stay and lower proportion of infectious or fatal complications.[1,4] There is no standardized plan for G-CSF administration, and it is used empirically until ANC normalisation.[11]

Additionally, if the agranulocytosis is antimicrobial-induced, a switch to an equally effective antibiotic must be made.[13]

In our case, ANC returned to baseline on day 3 of G-CSF, while ceftriaxone was immediately switched to amoxicillin/clavulanate. No signs or symptoms were reported at the time of nadir of the neutropenia.

A case of ceftriaxone-induced agranulocytosis is reported where the switch to other cephalosporin did not recreate the event, making the immunological mechanism not to be class-directed.[10]

Although broad spectrum antimicrobial therapy may be initiated in drug-induced agranulocytosis, there does not seem to exist evidence to recommend broadening spectrum in antibiotic induced agranulocytosis.

In conclusion, we present a case of ceftriaxone induced agranulocytosis, in a patient who was admitted for *S. bovis* endocarditis. Therapeutic schemes in which ceftriaxone is used during several weeks, may increase agranulocitosis risk. Differential leukocyte count should be monitored regularly. Albeit a potentially serious event, treatment is simple, quick and effective when initiated promptly. ■

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IC – Revisão do artigo
Todos os autores aprovaram a versão final a ser publicada.

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Correspondence / Correspondência:

Tiago Castro Pinto - tiagocpinto28@gmail.com
Rua de Dr. Eduardo Torres, 4464-513 - Sra. da Hora

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