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Case Report
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Ceftriaxone Induced Agranulocytosis

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Abstract

Agranulocytosis from antimicrobial therapy with ceftriaxone is rare. We report a case of agranulocytosis in a patient resulting from ceftriaxone noted 2 weeks into therapy which improved after stoppage of the drug.

Key Learning Points

1. Ceftriaxone is one of the commonly used antibiotics for a broad range of infections because of it's safety and good tolerability.

2. Agranulocytosis due to ceftriaxone is rare, but prolonged duration and higher doses (2g to 4g daily) appear to be risk factors.

3. Management includes withdrawal of the drug, coverage by broad spectrum antibiotics and an infectious disease workup if the patient is febrile. Granulocyte colony-stimulating factors can be administered with daily monitoring of absolute neutrophil count.

4. Rechallenge with the offending drug should be avoided.

Introduction

Drug induced neutropenia is characterized by a sharp decrease in the absolute neutrophil count (ANC) to <500/mm^3; agranulocytosis is said to be present once the ANC reaches < 100/mm^3. Drug induced neutropenia is extremely rare with an incidence of 2.4-15.4 cases per million [1]. Because of it's relative safety, ceftriaxone is commonly used for treating a wide variety of infections [2]. Ceftriaxone induced leukopenia occurs in 0.09% of the courses administered [3]. A literature search has revealed only 16 other reported cases of ceftriaxone-induced agranulocytosis [4].

Case Presentation

A 20 years old male patient with no known comorbidities was admitted with 10 days history of fever which was high grade, continuous, associated with chills. General physical and systemic examination was unremarkable for any finding. On evaluation his baseline investigations were normal except for mild transaminitis. Blood culture grew Salmonella typhi (sensitive to Ceftriaxone) and patient was subsequently started on Inj. Ceftriaxone 2 gm BD. He became afebrile on day 6 of ceftriaxone therapy. On day 10 of ceftriaxone therapy, a routine complete blood count documented an ANC of 696/mm^3, down from 2806/mm^3 10 days previously. His haemoglobin and platelet counts remained unchanged from his baseline complete blood count. Serial blood counts showed progressive decline in ANC with worst ANC of 19/mm^3 which was documented on day 14 of ceftriaxone therapy. On the same day, he developed an acute fever to 102 F. There were no new clinical symptoms or signs, including rash, suggesting an alternative cause. Because of concern for neutropenic fever, ceftriaxone was discontinued, and treatment was broadened to cefepime 2 gm every 8 hours and amikacin 500 mg every 24 hours. There was no new source of infection anywhere; septic screen and additional laboratory workup was unremarkable. Given the prior literature reports on beta lactamase induced agranulocytosis, ceftriaxone was believed to be the most likely cause. Over the next few days, his TLC began to rise, and his fever resolved. On day 22 of admission, 8 days after discontinuation of ceftriaxone, the patient's ANC had returned to normal levels (>1500/mm^3) and was discharged in a stable condition.

Discussion

Nonchemotherapy drug induced agranulocytosis is a rare and severe adverse reaction characterized by a neutrophil count less than 500/mm^3 [5]. Historically, it carries a mortality rate of 10 to 16% [1]. Though the mortality has improved to 5%, the condition is still considered life-threatening and is most dangerous in elderly patients, those with bacteremia, renal failure and

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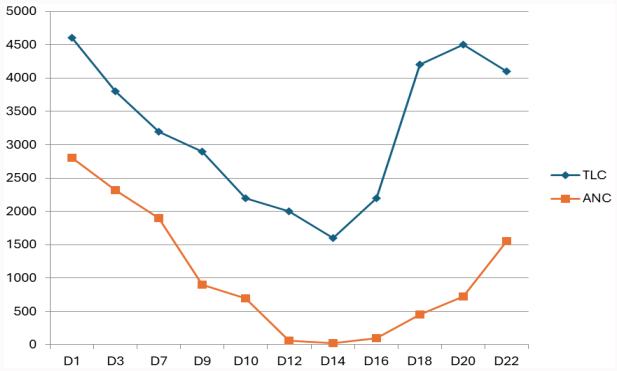


Figure 1: Leukocyte and neutrophil count evolution.

shock at the time of diagnosis [1]. The most common causes of an acquired neutropenia are infections, drugs, nutritional deficiencies and hematological malignancies [6]. Our patient developed agranulocytosis during prolonged treatment with 4 g of ceftriaxone daily, yet he recovered while on cefepime. Although ceftriaxone is used for a broad range of infections, there have been few case reports of ceftriaxone-induced neutropenia. A literature search has revealed only 16 other reported cases of ceftriaxone-induced agranulocytosis [4]. Fever is often the first sign of drug induced acute neutropenia [1]. The pathogenesis of ceftriaxone-induced agranulocytosis remains uncertain [1,7,8], and it is suggested to occur either by an immune mechanism or as a result of toxicity. Direct damage to the bone marrow microenvironment or myeloid precursors is frequent and as a part of immune-mediated mechanisms a drug can act as a hapten and induce antibody formation against neutrophils in a dose-dependent inhibition of granulopoiesis [9]. However, thorough analysis of the clinical findings and bone marrow histology in the earlier reported cases in literature favour an immunologic mechanism over drug toxicity. Andersohn, et al. carried out a systematic review of non-chemotherapy drug-induced agranulocytosis. Of the 492 reported cases, only six were related to ceftriaxone [5]. Neftal, et al. reviewed 50 beta-lactam-induced neutropenia cases from 17 hospitals, six of which were related to ceftriaxone [10].

The treatment of drug-induced neutropenia includes prompt recognition and drug withdrawal, coverage of broad-spectrum antibiotics if appropriate, and administration of recombinant human granulocyte colony-stimulating factor (rhG-CSF) [9].

Conclusion

Studies of ceftriaxone associated neutropenia are limited to case reports and case series. A literature search has revealed 16 other reported cases of ceftriaxone induced agranulocytosis. Our findings suggest that an immunologic mechanism is responsible in most cases. In any patient whose ANC falls during an extended course of ceftriaxone therapy, ceftriaxone induced agranulocytosis should be considered, and this drug should be discontinued followed by close monitoring of blood counts.

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