

Case Report

Agranulocytosis - A Rare Side Effect of Standard Dose Ceftriaxone Therapy

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A B S T R A C T

In the current era of medical science, agranulocytosis is rarely found. Chemotherapeutic agents and various non-chemotherapeutic drugs commonly cause agranulocytosis. Agranulocytosis can occur any time during the therapy in hospital, and patients may remain symptomless. So, we should do regular cell count to reach the diagnosis in such cases. An appropriate antibiotic or drug-change, investigations to rule out sepsis and granulocyte colony-stimulating factor (G-CSF) injection can be given as the management part. The patient should be monitored daily and observed till the normalization of neutrophil counts. Here, we report a case of ceftriaxone-mediated agranulocytosis, which was completely reversible after withdrawing the antibiotic.

Keywords: Agranulocytosis, Ceftriaxone, Chemotherapeutic Agents, G-CSF

Introduction

Agranulocytosis means deficiency of granulocytes in the blood. Agranulocytosis has a high mortality rate of up to 16%. Due to recent advancements of science, the death rate has decreased to 5%, but this is still known to be life-threatening, especially in those with underlying bacteremia, renal failure, shock, or age greater than 65 years at the time of admission.¹

Ceftriaxone is a third-generation cephalosporin, most commonly used in the treatment of Gram-negative infections due to its broad spectrum of antimicrobial activity, long half-life, and low side effect profile.^{2,3} Injection ceftriaxone is a very commonly prescribed antibiotic for some of the common conditions like soft tissue and skin infections.⁴ Occurrence of agranulocytosis is a very rare side effect of chemotherapeutic agents and antibiotics.

The population incidence is about 2.2–15.4/million/year.⁵ Frequency of severe neutropenia or agranulocytosis, linked with ceftriaxone, is not known. Only five cases of ceftriaxone-associated agranulocytosis were observed in a systematic review of 980 case reports from 1966 to 2006, with drug-induced agranulocytosis.⁶ To the best of our knowledge, only a few case reports with agranulocytosis, as a side effect of ceftriaxone, are reported. Here, in this article, we have reported the rare side effect-ceftriaxone-associated agranulocytosis.

Case Presentation

A 78-year old male patient presented in emergency department with chief complaints of 5 to 6 episodes of vomiting per day for the last 3 days. He also had complaint of dyspnea for the same duration. The patient was a known case of ischemic stroke with right-sided hemiparesis since

2002 and fracture of left femur since one year. Due to this morbid condition, he was bedridden and had developed bed sores over sacral area.

At the time of admission, his blood pressure was 100/80 mm Hg, pulse rate was 100/min, respiratory rate was 28 breaths/min, body temperature was 98.4° F and partial pressure of oxygen (Sp_o₂) was 84%, measured by a pulse-oximeter. Physical examination revealed altered mental status with Glasgow coma scale (GCS)-E3V4M5. An infected bed sore of size approximately 6×8 cm dimension was present over sacral area. On chest auscultation, bilateral coarse crepitation⁵(R>L) were present.

In view of lower respiratory tract infection and infected bed sore, the patient was treated with intravenous antibiotic (ceftriaxone 1 gm twice a day), along with other supportive treatments. On day 11 of injection ceftriaxone treatment, his laboratory parameters showed agranulocytosis. The pattern of his total leucocyte count, after institution and stoppage of ceftriaxone, has been shown in Table 1.

degree of neutropenia, which means ANC <100/ μ L. Chemotherapeutic drugs are the commonest culprit.

Drug-mediated agranulocytosis was explained by two mechanisms - immunologic and non-immunologic - but none of them was found proven. More research is needed for explaining the mechanism of agranulocytosis.

Sometimes, patients with neutropenia and agranulocytosis are asymptomatic or may have variable symptoms like fever, generalized weakness, chills, flu-like symptoms, or infections like pneumonia, tonsillitis, sore throat, septic shock, and altered mental status.

As most of the patients with agranulocytosis are asymptomatic or have mild symptoms, so agranulocytosis is diagnosed generally on routine lab testing. Currently, we have no specific laboratory test to make a diagnosis of drug-induced agranulocytosis.

Hypersensitivity reactions due to cephalosporin are the commonest adverse effects. Immediate reactions like

Table I. Hematological profile during hospital stay

Day from admission	0 Baseline	3 Ceftriaxone started from day 1	9	11 Ceftriaxone stopped	12	15
Total leukocyte count (cells/mm ³)	4600	3200	2300	2000	2700	3600
Differential leukocyte count (Neutrophils N and lymphocyte L %)	N82 L15	N70 L10	N50 L9	N00 L8	N7 L12	N20 L35
Hemoglobin (gm/dL)	11.8	9.6	8.6	9.2	8.2	8.9
Platelets (Lac cells/mm ³)	1.6	1.2	1.21	1.73	1.69	1.76

Discussion

Neutrophils provides the main defense mechanism of innate immunity in response to fungal and microbial infections. The most common type of white blood cells (WBCs) are the neutrophils, and these constitute approximately 60% of total white blood cell corpuscles of human blood. Cytokine granulocyte colony-stimulating factor (G-CSF) keeps control on bone-marrow formation of neutrophils. Their life span in blood circulation is about 4-6 hours, after this period they get destroyed within spleen, liver, and marrow.

A count of lesser than 1500/ μ L of absolute neutrophils is called neutropenia. It may be mild (<1500/ μ L), moderate (<1000/ μ L), or severe (<500/ μ L). Decreased formation in bone marrow or increased damage may be a cause for it. Bacterial and viral infections are the commonest etiologies for the development of neutropenia. Benign ethnic neutropenia is an inherited cause of neutropenia, which is more prevalent in African-descent people. There is no increased risk of infection due to neutropenia.

Agranulocytosis is defined by severe deficiency of absolute neutrophil count (ANC). The same term is used for profound

anaphylaxis, urticaria, bronchospasm, maculopapular rashes, etc., are commonly observed. Patients treated with large doses of cephalosporin frequently develop positive Coombs reaction while hemolysis is rarely found. Bone-marrow suppression due to cephalosporin is rarely found.⁷ Non-chemotherapeutic medicines cause idiosyncratic agranulocytosis. Despite all these, long-term use of ceftriaxone may lead to the development of agranulocytosis.⁵

After the occurrence of agranulocytosis, the first point in its management is to withdraw the suspected offending drug and initiate to work up to rule out other possible etiologies of agranulocytosis. Improved survival with the injection of G-CSF was seen in some of the studies.

Conclusion

This case illustrates a very rare but serious complication due to the use of a standard dose and duration of parenteral ceftriaxone therapy. In a patient with falling leucocyte counts during the course of ceftriaxone therapy, ceftriaxone-induced agranulocytosis can be considered, and this drug should be discontinued.

Conflict of Interest: None

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