Case Report

Ceftriaxone-Induced Pancytopenia: A Case Report and Literature Review on Hematologic Complications of Antibiotic Therapy

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Ceftriaxone-Induced Pancytopenia: A Case Report and Literature Review on Hematologic Complications of Antibiotic Therapy

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Abstract: Cephalosporins are considered safe antibiotics. However, serious hematological abnormalities may occur, although rarely, after their therapeutic use. We present a case of pancytopenia in a patient treated with ceftriaxone, where, after ruling out other potential causes through extensive diagnostic evaluation, an idiosyncratic drug reaction was established. The patient's clinical condition significantly improved following the discontinuation of ceftriaxone and the administration of filgrastim. This case highlights the importance of recognizing the potential for rare but serious hematologic adverse effects associated with commonly used antibiotics such as ceftriaxone. Early identification and prompt management of these adverse effects are critical to ensure optimal patient outcomes and prevent serious complications.

Keywords: pancytopenia; ceftriaxone; idiosyncrasy; filgrastim; antibiotics

Introduction

Pancytopenia is characterized by a simultaneous reduction of red blood cells, white blood cells, and platelets in the peripheral blood, and can be caused by infections, hematologic malignancies, autoimmune disorders, and drugs [1,2]. Among medications, hematologic reactions are more commonly associated with chemotherapy agents but can also occur with antibiotics such as beta-lactams, including cephalosporins [3,4].

Ceftriaxone, a third-generation cephalosporin, is widely used due to its broad antimicrobial spectrum and favorable pharmacokinetics. However, rare hematologic complications such as neutropenia, agranulocytosis, and pancytopenia have been reported [4,5].

Case Presentation

A 72-year-old female was hospitalized for fever and general weakness. She was receiving treatment for a urinary tract infection with ceftriaxone (2 g/day intravenously). After five days of therapy, laboratory findings revealed a significant decline across all blood cell lines (Table 1).

There was no evidence of hemolysis, bleeding, ongoing infection, or infiltrative bone marrow disease. Immunological investigations, viral serologies, and bone marrow aspiration excluded alternative causes.

Ceftriaxone was discontinued, and filgrastim was administered (30 MU/day [approximately 300 mcg/day] subcutaneously). Gradual normalization of blood counts and clinical recovery followed.

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Table 1. Laboratory Parameters During Hospitalization and After Ceftriaxone Withdrawal and Filgrastim Administration.

Parameter	Day 1	Day 5	Day 7	After Ceftriaxone Withdrawal and Filgrastim Administration
Hematology				
White blood cells (WBC) $\times 10^9$/L	3.5	2.2	1.8	4.6
Red blood cells (RBC) $\times 10^{12}$/L	3.8	3.5	3.2	4.0
Hemoglobin (g/L)	112	102	98	120
Hematocrit (%)	33.6	31.2	30.0	36.1
Platelets ($\times 10^9$/L)	130	92	88	101
Neutrophils (%)	75.2	61.2	53.0	68.0
Lymphocytes (%)	22.1	26.8	30.0	24.0
Biochemistry & Inflammatory Markers				
C-reactive protein (CRP) mg/L	22.4	34.2	47.4	18.3
Procalcitonin (PCT) ng/mL	0.23	0.34	0.29	0.10
AST (U/L)	31	38	42	29
ALT (U/L)	26	33	36	25
LDH (U/L)	241	270	296	212
Total bilirubin (μmol/L)	8.7	10.3	11.5	6.2
Creatinine (μmol/L)	83	91	87	79
Urea (mmol/L)	4.6	5.1	4.3	4.0
Microbiological Work-up				
Hemoculture	-	-	-	Negative x3
Urine culture	-	-	-	Negative
Tumor Markers				
CEA (ng/mL)	-	2.0	-	-
AFP (ng/mL)	-	3.5	-	-
CA 19-9 (U/mL)	-	22.5	-	-
CA 15-3 (U/mL)	-	17.8	-	-
CA 125 (U/mL)	-	34.5	-	-
Cyfra 21-1 (ng/mL)	-	1.7	-	-
Immunological & Viral Serology				
ANA	-	-	-	Negative
ENA	-	-	-	Negative
ANCA	-	-	-	Negative
dsDNA	-	-	-	Negative
HBsAg	-	-	-	Negative
Anti-HCV	-	-	-	Negative
Anti-HIV	-	-	-	Negative
CMV IgM	-	-	-	Negative
EBV IgM	-	-	-	Negative
Toxoplasma gondii	-	-	-	Negative
Other Tests				
ASTO (U/mL)	-	-	-	125
Throat and nasal swab	-	-	-	Negative
Bone marrow aspiration	-	-	-	Hypocellular marrow, no malignant infiltration

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AST: aspartate transaminase; ALT: alanine transaminase; LDH: lactate dehydrogenase; CEA: carcinoembryonic antigen; AFP: alpha-fetoprotein; CA 19-9: cancer antigen for pancreatic cancer; CA 15-3: cancer antigen for breast cancer; CA 125: cancer antigen for ovarian cancer; Cyfra 21-1: tumor marker for squamous cell lung cancer; ANA: antinuclear antibody; ENA: extractable nuclear antigens antibodies; ANCA: anti-neutrophil cytoplasmic antibodies; dsDNA: double stranded DNA antibodies; HBsA: hepatitis B surface antigen; Anti-HCV: anti-hepatitis C virus antibody; Anti-HIV: anti-human immunodeficiency virus antibody; CMV IgM: cytomegalovirus immunoglobulin M; EBV IgM: Epstein-Barr virus immunoglobulin M; ASTO: anti streptolysin O test.

Discussion

Drug-induced hematologic reactions can arise from direct toxic effects on hematopoiesis or immune-mediated idiosyncratic mechanisms [2,5,6]. Idiosyncratic drug reactions are unpredictable, dose-independent, and often immune-mediated [7–9]. These reactions can be triggered by a variety of medications, including antibiotics, and their onset is often difficult to predict. The underlying mechanisms behind such reactions are complex and not fully understood, but they are believed to involve immune-mediated processes that lead to hematologic dysfunction.

In this case, the clinical timeline, reversibility after drug withdrawal, and favorable response to granulocyte colony-stimulating factor (G-CSF) strongly suggest an idiosyncratic mechanism [10–12]. The patient exhibited a clear temporal relationship between ceftriaxone administration and the development of pancytopenia, which improved rapidly upon discontinuation of the drug and the introduction of G-CSF. This supports the idea that the hematologic reaction was likely drug-induced and immune-mediated, rather than resulting from a direct toxic effect on the bone marrow.

Although cephalosporins are generally considered safe, serious hematologic adverse effects such as neutropenia and pancytopenia have been reported, particularly in susceptible individuals [4,13]. These reactions are rare, but they can be severe and life-threatening, highlighting the importance of monitoring patients closely during antibiotic therapy, especially when other risk factors are present. The exact mechanism by which cephalosporins induce hematologic toxicity is still unclear, but it may involve immune-mediated destruction of blood cells.

One of the key mechanisms through which ceftriaxone may induce pancytopenia is through immune-mediated processes. Cephalosporins, including ceftriaxone, can trigger the formation of antigens on the surface of blood cells, leading to the production of antibodies that target and destroy these cells. This phenomenon is known as the hapten reaction, where the drug, acting as a hapten, modifies surface proteins on red blood cells, platelets, or leukocytes, leading to their rapid immune-mediated clearance. This process can result in various hematologic disorders, such as hemolytic anemia, neutropenia, and thrombocytopenia, ultimately culminating in pancytopenia. This mechanism is specific to ceftriaxone but can also be seen with other beta-lactam antibiotics [4,6,13].

Recent findings have also shown that medications beyond antibiotics, including antiepileptics and analgesics, have been implicated in drug-induced agranulocytosis and pancytopenia [5,6,14]. This suggests that drug-induced hematologic reactions are not limited to antibiotics and can occur with various medications. Such reactions may often go underreported or overlooked, as their presentation can resemble other hematologic disorders. Therefore, a thorough evaluation and comprehensive drug history are essential for diagnosing patients with unexplained hematologic abnormalities.

Several drugs beyond antibiotics have been associated with pancytopenia through a variety of mechanisms, including direct myelotoxicity, idiosyncratic reactions, and immune-mediated suppression. Table 2 summarizes the main pharmacological classes and representative agents implicated in drug-induced pancytopenia, along with their proposed mechanisms and relevant clinical considerations.

Table 2. Drugs Associated with Pancytopenia.

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Drug Class	Example(s)	Mechanism of Pancytopenia	Notes
Beta-lactam antibiotics	Ceftriaxone, Penicillin, Piperacillin	Immune-mediated or direct bone marrow toxicity	Usually reversible after drug withdrawal
Antithyroid drugs	Methimazole, Propylthiouracil	Idiosyncratic immune-mediated bone marrow suppression	Associated with agranulocytosis and pancytopenia
Antiepileptics	Carbamazepine, Phenytoin, Valproate	Direct toxicity or idiosyncratic reaction	Monitor blood counts regularly
NSAIDs	Phenylbutazone, Indomethacin	Immune-mediated or dose-dependent suppression	Rare but severe cases reported
Antipsychotics	Clozapine	Agranulocytosis with potential for pancytopenia	Requires regular CBC monitoring
Chemotherapy agents	Methotrexate, Cyclophosphamide	Dose-dependent bone marrow suppression	Expected adverse effect; supportive care needed
Antimalarials	Chloroquine, Quinine	Immune-mediated hemolysis and marrow suppression	Rare; often reversible
Antiretroviral drugs	Zidovudine (AZT)	Mitochondrial toxicity affecting marrow cells	Pancytopenia often dose-related
Immunosuppressants	Azathioprine, Mycophenolate mofetil	Inhibition of marrow cell proliferation	Monitor CBC frequently
Biologics & Monoclonal Abs	Rituximab, Infliximab	Immune-mediated cytopenias	Pancytopenia is rare but documented
Sulfonamides	Sulfamethoxazole-trimethoprim	Idiosyncratic or immune-mediated	More common in elderly and HIV patients
Linezolid	Linezolid	Mitochondrial toxicity	Monitor blood counts with prolonged use

The role of genetic and pharmacogenetic factors, particularly human leukocyte antigen (HLA) variants, has been highlighted in recent research on drug-induced hematologic reactions. Studies suggest that specific HLA variants may predispose individuals to these reactions, including those triggered by ceftriaxone [9,15,16]. The genetic makeup of the individual can significantly influence the immune response to the drug. In certain cases, the immune system may recognize modified blood cells as foreign and initiate an immune response that leads to their destruction. This highlights the importance of considering genetic factors in patients who may be at higher risk for such reactions.

While most of the data on HLA associations come from studies on clozapine-induced agranulocytosis, similar immune-mediated mechanisms are likely at play in antibiotic-induced hematologic reactions [8,9,16]. Identifying patients with genetic predispositions could help guide clinical decisions and potentially prevent severe reactions.

In some instances, idiosyncratic reactions, which are specific to individual patients, pose a challenge in identifying the underlying cause of pancytopenia. These reactions are rare and cannot always be predicted, even in patients who have previously tolerated the drug without issues.

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Although these reactions are infrequent, they can be severe and require immediate medical attention. The unpredictable nature of these responses makes early diagnosis and treatment crucial for patient safety.

Management of drug-induced hematologic reactions primarily involves early identification and discontinuation of the offending agent, as well as supportive care. In more severe cases, the administration of G-CSF has been shown to promote hematologic recovery [11,12,17]. G-CSF can accelerate recovery in some cases, although its effectiveness may vary based on the severity of the reaction. It is critical to tailor treatment to each individual patient's needs and their response to therapy.

The effectiveness of G-CSF in facilitating recovery has been demonstrated in several reports, including this case, where G-CSF played a crucial role in the patient's rapid recovery, further supporting the diagnosis of drug-induced myelosuppression [10,11,17]. However, it is important to note that not all patients will respond to G-CSF, and its use should be considered on a case-by-case basis.

This case underscores the importance of vigilance when prescribing even commonly used antibiotics. While ceftriaxone and other cephalosporins are generally considered safe, it is vital for clinicians to remain alert to the potential for rare but serious adverse reactions. Early recognition and timely management of drug-induced hematologic reactions can lead to full recovery and significantly reduce the risk of complications [18,19]. By raising awareness of such reactions, clinicians can improve patient outcomes and prevent the potentially life-threatening consequences of drug-induced hematologic disorders.

Conclusion

This case highlights a rare but serious complication of ceftriaxone therapy—idiosyncratic pancytopenia. The prompt recognition of pancytopenia, exclusion of alternative etiologies, and immediate cessation of the offending drug are critical steps in effective management. The positive response to granulocyte colony-stimulating factor further supports the immune-mediated nature of the reaction. Although cephalosporins are widely regarded as safe, clinicians should be aware of their potential to cause severe hematologic side effects. Future studies focusing on genetic predispositions could lead to better screening and prevention strategies, especially in vulnerable populations.

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