Case Report

Agranulocytosis after High Cumulative Doses of Ceftriaxone in Infective Endocarditis: A Rare but Serious Adverse Reaction

Amal Baicha*, Khaoula Aboubakr, Salma Driouach, Najat Mouine, Aatif Benyass

Department of Cardiology, Mohamed V Training Military Hospital, Rabat, Morocco.

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Highlights

- Ceftriaxone-induced agranulocytosis is rare but can occur after high cumulative doses (≥60 g) or prolonged therapy.
- Routine CBC monitoring is essential during long-term ceftriaxone treatment, especially in infective endocarditis.
- Prompt drug withdrawal, antibiotic switch, and rhG-CSF (filgrastim) administration lead to rapid neutrophil recovery.
- The Naranjo adverse drug reaction probability scale is a useful tool for causality assessment in antibiotic-induced agranulocytosis.

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ABSTRACT

Background: Agranulocytosis is a serious, life-threatening condition characterized by a severe reduction in the number of peripheral neutrophils (<0.5 × 10^9/L). It is most commonly caused by chemotherapy drugs but can be induced by antibiotics. Ceftriaxone is a widely used and generally safe third generation antibiotic for conditions such as infective endocarditis. Ceftriaxone induced agranulocytosis is an extremely rare adverse reaction. Evidence suggests that this adverse reaction is dose dependent and typically occurs following prolonged courses or high cumulative doses of the antibiotic. Despite improvements in management that reduce the mortality rate to approximately 5%, prompt recognition and treatment remain vital.

Case Presentation: A 56-year-old man diagnosed with native valve infective endocarditis (Streptococcus mitis) was treated with 2 g/day of intravenous ceftriaxone. In the fifth week of treatment, after receiving a cumulative dose of 60 g, the patient developed severe agranulocytosis, reaching a neutrophil nadir of 0.1 × 10^9/L. Ceftriaxone was promptly stopped and replaced with teicoplanin, and the patient received filgrastim (recombinant human granulocyte colony stimulating factor [rhG CSF]). The case was classified as a probable adverse drug reaction (Naranjo score, 6). Neutrophil recovery was complete by the seventh day, and the patient successfully underwent double valve replacement surgery.

Conclusion: Ceftriaxone induced agranulocytosis, albeit rare, is a potentially fatal complication of prolonged therapy. Regular complete blood count monitoring and prompt management—based on drug withdrawal, appropriate antimicrobial coverage, and rhG CSF administration—are essential for favorable outcomes.

*** Corresponding Author:**
Amal Baicha
Department of Cardiology, Mohamed V Training Military Hospital, Rabat, Morocco.
E-mail: amalbaicha4@gmail.com

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Introduction

Agranulocytosis is a serious and potentially life-threatening condition characterized by a decrease in the number of peripheral neutrophils to <0.5 × 10^9/L.[1]

Historically, this condition has had a high mortality rate of approximately 10%–16%. Earlier detection and improved management strategies have reduced this rate to approximately 5%. Despite this improvement, agranulocytosis remains dangerous, especially for patients older than 65 years or those with a history of bacteremia, renal failure, or shock at diagnosis.[2, 3]

Chemotherapy drugs are the most common cause of agranulocytosis, but various nonchemotherapy medications can also trigger this reaction. These include certain antibiotics, analgesics, and psychiatric drugs.[4] Among antibiotics, ceftriaxone—a widely used third-generation antibiotic—is generally considered safe and effective, with broad-spectrum activity.[5] It is often prescribed in combination with aminoglycosides as a first-line treatment for infective endocarditis due to oral streptococci.[6] Although rare, cases of ceftriaxone-induced agranulocytosis have been documented in the medical literature.[4,5]

We report this case to highlight the importance of routine hematologic monitoring during long-term ceftriaxone treatment and to emphasize prompt recognition and management of this complication.

Case Presentation

A 56-year-old man with a history of chronic exertional dyspnea related to previously undiagnosed valvular heart disease was admitted to the cardiology department for fever and worsening shortness of breath. He had no known comorbidities, was not receiving any chronic medication, and had no history of drug allergies.

On admission, the patient was hemodynamically stable, with a body temperature of 38.7 °C. Cardiovascular examination revealed a systolic and diastolic murmur at the mitral area and a diastolic murmur at the aortic area, without clinical signs of congestive heart failure.

Initial laboratory investigations showed elevated inflammatory markers, with a C-reactive protein level of 50 mg/L, anemia of inflammation (hemoglobin, 8.9 g/dL), and leukocytosis (white blood cell count, 15 × 10^9/L). Blood cultures grew penicillin-susceptible Streptococcus mitis. Transthoracic echocardiography demonstrated severe mitral and aortic regurgitation associated with severe mitral stenosis (Figures 1 and 2), consistent with previously undiagnosed rheumatic valvular disease. The left ventricle was dilated with moderate systolic dysfunction. Transesophageal echocardiography revealed an aortic valve vegetation measuring 11 × 7 mm and a mitral valve vegetation measuring 3 mm (Figures 1 and 2), confirming the diagnosis of native valve infective endocarditis complicating preexisting valvular disease.

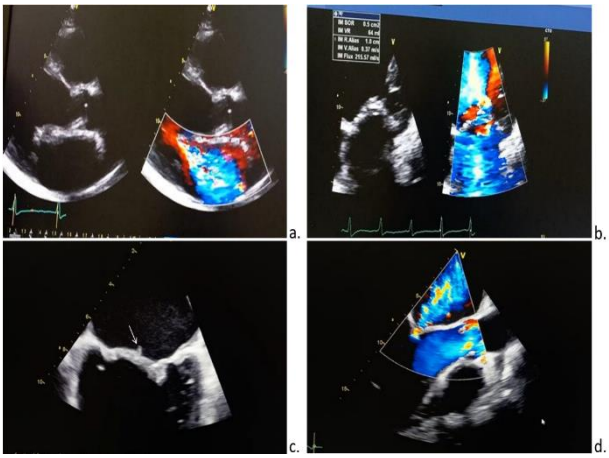

Figure 1. A and B, Transthoracic echocardiographic (TTE) images showing severe mitral regurgitation. C, Transesophageal echocardiography (TEE) image showing a 3-mm vegetation on the mitral valve (white arrow). D, TEE image showing mitral regurgitation extension

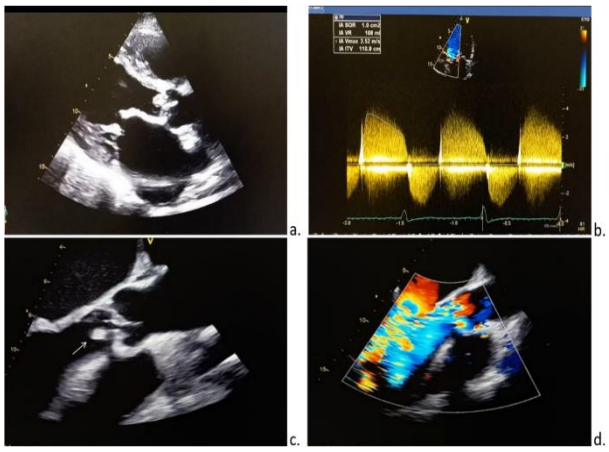

Figure 2. A, Transthoracic echocardiographic (TTE) image showing vegetation on the aortic valve. B, TTE image showing quantification of severe aortic regurgitation. C, TEE image showing an 11-mm vegetation on the aortic valve (white arrow). D, TEE image showing aortic regurgitation extension and accelerated left ventricle filling through the mitral stenosis.

The patient was started on intravenous ceftriaxone (2 g/d) combined with gentamicin (5 mg/kg per day for 15 days) on the day blood cultures became positive (day 1). Blood cultures remained positive for 9 days, with the first negative culture documented on day 9 of therapy. In light of the delayed clearance of bacteremia, the severity of underlying rheumatic valvular disease, and anticipated surgical management, the duration of antimicrobial therapy was discussed in a multidisciplinary meeting involving infectious diseases, cardiology, and cardiac surgery teams, and a 6-week antibiotic course was decided preoperatively. Clinical and biological improvement was observed during the first 4 weeks, with defervescence and a decrease in inflammatory markers.

During the fifth week of treatment (day 30), the patient developed recurrent fever, accompanied by a rise in C-reactive protein from 19mg/L to 96mg/L. Complete blood count revealed severe agranulocytosis, with a neutrophil nadir of 0.1×10^9/L, after a cumulative ceftriaxone dose of 60g. The evolution of hematologic parameters is summarized in (Table 1). Bone marrow biopsy showed hypoplasia of the neutrophil lineage, with no evidence of malignant infiltration or infection.

Ceftriaxone was immediately discontinued and replaced with teicoplanin (600mg/d). The patient received filgrastim (recombinant human granulocyte colony-stimulating factor [rhG-CSF]). Three and seven days after treatment modification, leukocyte counts recovered to 3×10^9/L and 9×10^9/L, respectively (Figure 3). In the absence of alternative causes and based on the temporal relationship, cumulative dose, and rapid recovery after drug withdrawal—corresponding to a Naranjo adverse drug reaction probability score of 6 (probable)—ceftriaxone-induced agranulocytosis was diagnosed in consultation with the hematology team (Figure 4).

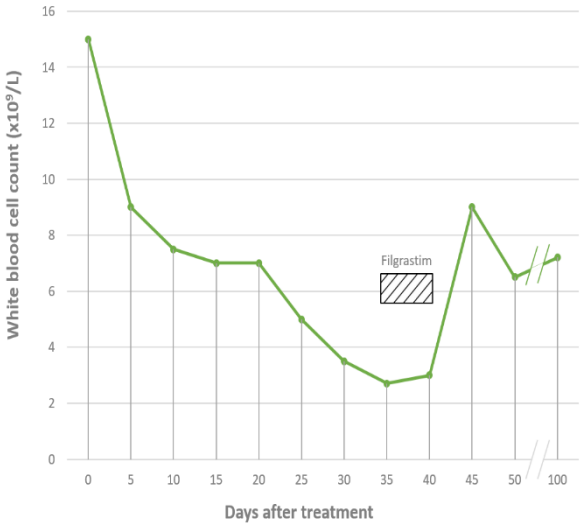

Figure 3. Evolution of white blood cell count

Table 1. The evolution of complete blood count

Parameter	Baseline	Neutrophil Nadir	After Recovery
WBC ($\times10^9$/L)	15.15	**2.74**	9.0
Neutrophils ($\times10^9$/L)	13.16	**0.10**	6.36
Lymphocytes ($\times10^9$/L)	1.61	1.93	1.98
Monocytes ($\times10^9$/L)	0.18	0.21	0.36
Eosinophils ($\times10^9$/L)	0.17	0.45	0.22
Basophils ($\times10^9$/L)	0.05	0.05	0.06
Hemoglobin (g/dL)	8.9	9.0	9.7
Platelets ($\times10^9$/L)	459	432	342

A follow-up transesophageal echocardiographic examination performed 3 weeks after initiation of antibiotic therapy, while the patient was still receiving preoperative treatment, revealed that the mitral vegetation had resolved, whereas the aortic vegetation remained unchanged. The severity of both mitral and aortic valvulopathy was stable. The patient was referred for surgery and underwent double valve replacement with mechanical prostheses. Intraoperatively, a spontaneously debrided periannular abscess involving the mitral-aortic

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trigone was identified. Valve tissue cultures were not available. Postoperatively, according to current European Society of Cardiology and American Heart Association guidelines,[6,7] antimicrobial therapy with teicoplanin was continued and completed for a total duration of 6 weeks. This decision was guided by operative confirmation of periannular extension and abscess formation in the absence of valve tissue culture data. The patient was discharged in good condition, with stable white blood cell counts and no evidence of relapse during follow-up.

A timeline summarizing the key clinical events of this case is presented in (Table 2).

Table 2. Timeline of the key clinical events of our case

Time Point	Clinical Events
Day 0 (Admission)	Fever and worsening dyspnea. Hemodynamically stable. Systolic and diastolic murmurs at the mitral area, with a diastolic murmur at the aortic area.
Initial Investigations	C-reactive protein, 50 mg/L; white blood cell count, 15 × 10^9/L; hemoglobin, 8.9 g/dL. Blood cultures positive for penicillin-susceptible *Streptococcus mitis*.
Imaging	Transthoracic and transesophageal echocardiography: severe mitral and aortic regurgitation; severe mitral stenosis; aortic vegetation, 11 × 7 mm; mitral vegetation, 3 mm.
Diagnosis	Native valve infective endocarditis complicating preexisting valvular disease.
Treatment Initiation	Intravenous ceftriaxone (2 g/d for 6 weeks) and gentamicin (5 mg/kg per day for 15 days).
Weeks 1–4	Clinical improvement with defervescence and decreasing inflammatory markers.
Week 3	Follow-up transesophageal echocardiography: mitral vegetation resolved; aortic vegetation persisted; valvular severity stable.
Week 5	Recurrent fever; C-reactive protein increased to 96 mg/L. Severe agranulocytosis (neutrophils, 0.1 × 10^9/L) after a cumulative ceftriaxone dose of 60 g.
Diagnostic Workup	Bone marrow biopsy: neutrophil lineage hypoplasia; no evidence of malignancy or infection.
Management of Agranulocytosis	Ceftriaxone discontinued; teicoplanin (600 mg/d) initiated; filgrastim administered.
Day 3	Leukocyte count 3 × 10^9/L.
Day 7	Leukocyte count, 9 × 10^9/L; ceftriaxone-induced agranulocytosis confirmed.
Surgery	Debridement of periannular abscess involving the mitral-aortic trigone; successful double valve replacement with mechanical prostheses.
Postoperative Period	Teicoplanin continued for 6 weeks; leukocyte counts remained stable.
Outcome	Discharged in good clinical condition.

Discussion

Ceftriaxone-induced agranulocytosis is a rare but potentially life-threatening adverse reaction, despite ceftriaxone being widely used and generally considered safe. A systematic review of nonchemotherapy drug-induced agranulocytosis identified 492 cases classified as probable or definite, with only six related to ceftriaxone, none of which had ceftriaxone considered the definite cause.[1] Another study reviewed 50 β-lactam–induced neutropenia cases, six of which involved ceftriaxone.[8]

This adverse reaction is dose-dependent and typically occurs after high cumulative exposure or prolonged courses. In our patient, agranulocytosis developed after a cumulative ceftriaxone dose of 60 g on day 30 of therapy. Similar to previously reported cases, this timing falls within the 16th to 29th day range described in the literature,[5,9] and the cumulative dose was slightly higher than the mean dose reported by Neftel et al[8] (51 g [SD, 29 g]).

The pathogenesis of ceftriaxone-induced agranulocytosis is not fully understood, but two main mechanisms have been proposed: an immunologic mechanism, involving an autoimmune response, and a nonimmunologic mechanism, involving direct toxicity to myeloid precursors.[4] Drug-induced agranulocytosis is often detected during routine monitoring of complete blood cell counts, especially in patients receiving prolonged courses, because patients may remain asymptomatic.[4]

The Naranjo adverse drug reaction probability scale is commonly used to assess causality.[10] In our case, the patient scored 6, corresponding to a probable adverse drug reaction (Figure 4). Given the severity of presentation and the availability of an alternative antibiotic, several items of the scale were not tested, as it was deemed unethical to do so solely for causality assessment.

NARANJO Score		Yes	No	Unknown – not done
1-	Are there previous conclusive reports on this reaction?	1	0	0
2-	Did the adverse event occur after the suspected drug was administred?	2	-1	0
3-	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administred?	1	0	0
4-	Did the adverse reaction reappear when the drug was readministered?	2	-1	0
5-	Are there alternative causes (other than the drug) that could have on their own caused the reaction?	-1	2	0
6-	Did the reaction reappear when a placebo was given?	-1	1	0
7-	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	1	0	0
8-	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	1	0	0
9-	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0
10-	Was the adverse event confirmed by any objective evidence?	1	0	0
	TOTAL	***6*** **Probable** adverse drug reaction		

Figure 4. Naranjo score used to assess the likelihood of an adverse drug reaction by assigning the total score to a probability category.
Interpretation:

- ≥9 → Definite
- 5–8 → Probable
- 1–4 → Possible
- 0 → Doubtful

For our patient: total score of 6 → Probable adverse drug reaction.

Bone marrow biopsy is generally reserved for persistent or atypical cases or when no alternative explanation is identified and can help predict recovery, as a complete absence of myeloid precursors is associated with slower recovery.[4] Given our patient's clinical context and after discussion with the hematology team, bone marrow biopsy was performed to exclude peripheral destruction due to severe sepsis, confirming neutrophil lineage hypoplasia. To our knowledge, cases of ceftriaxone-induced agranulocytosis confirmed by bone marrow biopsy in the context of infective endocarditis remain exceedingly uncommon.

Prompt recognition and immediate discontinuation of the causative antibiotic are key to management.[5] A broad-spectrum antibiotic from a different pharmacologic class should be initiated to treat the underlying infection and prevent secondary infections. Moreover, rhG-CSF, such as filgrastim, has shown promising results, enabling faster neutrophil recovery and improved clinical outcomes.[2,11,12] In our patient, ceftriaxone was promptly discontinued and replaced with teicoplanin, and filgrastim was administered, leading to improvement in the white blood cell count beginning on day 3, with complete recovery observed on day 7—consistent with prior reports.

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This case reinforces that even commonly used antibiotics such as ceftriaxone can rarely cause life-threatening agranulocytosis. As in previously reported cases, prolonged exposure and high cumulative doses increase the risk, highlighting the importance of routine CBC monitoring. Early discontinuation of the causative agent, combined with supportive therapy including rhG-CSF, led to rapid recovery, and bone marrow biopsy may be considered in atypical cases to clarify the mechanism and guide management.

Conclusions

Ceftriaxone-induced agranulocytosis is an extremely rare but life-threatening adverse reaction. It typically occurs after prolonged courses or high cumulative doses of ceftriaxone; therefore, routine blood tests should be performed regularly in these patients. Although the exact mechanism remains unknown, causality can be assessed using the Naranjo score. Management is critical and requires the triad of prompt withdrawal of ceftriaxone, broad-spectrum antibiotic coverage if neutropenic fever is present, and administration of rhG-CSF (eg, filgrastim) to accelerate neutrophil recovery.

Patient Perspective

The patient reported that the prolonged hospitalization and isolation during the agranulocytosis phase were challenging but understood the necessity of these measures for his safety. He remained compliant with all treatments and supportive care and expressed relief as his condition improved.

Declarations:

Ethical Approval

Ethical approval for this case report was obtained from the Ethics Committee of the Military Hospital, Mohamed V University, Rabat, Morocco. The committee does not issue reference numbers. Written informed consent to participate was obtained from the patient.

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Conflict of Interest

The authors declare no conflict of interest.

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