Case Report

A rare case of drug-induced agranulocytosis: A challenging diagnosis and management approach

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ABSTRACT

Agranulocytosis is a severe adverse drug reaction characterized by a significant decrease in the number of neutrophils, making patients highly susceptible to infections. I present a rare case of drug-induced agranulocytosis in a 45-year-old male patient who presented with a sudden onset of fever, sore throat, and severe fatigue. Infectious and autoimmune etiologies were ruled out by thorough examinations. A thorough medication history indicated that a new drug for the treatment of hypertension had just been started (chlorthalidone). The patient was immediately placed on broad-spectrum antibiotics and granulocyte colony-stimulating factor after the medication was rapidly stopped. The patient's neutrophil count gradually increased with prompt management, and he displayed clinical improvement. This instance emphasizes the value of prompt diagnosis and treatment of drug-induced agranulocytosis to avert potentially fatal consequences.

Key words: Agranulocytosis, Antibiotics, Chlorthalidone, Infections, Neutrophil count

Drug-induced agranulocytosis is a rare but potentially life-threatening condition characterized by a severe decrease in the number of circulating neutrophils, resulting in a compromised immune system. It is most commonly caused by medications such as antithyroid drugs, antiepileptic drugs, and non-steroidal anti-inflammatory drugs [1]. The clinical presentation of drug-induced agranulocytosis can mimic other infectious or inflammatory conditions, making diagnosis challenging.

In this case report, a rare case of chlorthalidone-induced agranulocytosis is discussed, highlighting the diagnostic challenges and the importance of appropriate management strategies [2,3]. The reported incidence of chlorthalidone-induced agranulocytosis is low, approximately 0.8–1% of patients treated with chlorthalidone have experienced agranulocytosis, with case reports and small studies forming the current body of evidence. However, due to underreporting and the potential for misdiagnosis, the true incidence might be underestimated [4,5].

CASE PRESENTATION

A 45-year-old male presented to the emergency department with a 3-day history of fever, sore throat, and severe fatigue. The patient was prescribed chlorthalidone 25 mg daily as a new antihypertensive drug and had been taking it for 2 weeks. The patient had a 3-year history of essential hypertension.

Physical examination revealed fever documented at 38.5°C and pharyngeal erythema without tonsillar exudates. Pulse was recorded at 110 bpm, respiratory rate was 24 breaths/min, blood pressure was 150/95 mmHg, and oxygen saturation was 96% on room air.

Laboratory investigations showed a significantly reduced neutrophil count of 230 cells/mm^3, consistent with agranulocytosis while other blood parameters were within normal limits. Throat culture and serological tests for common viral and bacterial pathogens were negative.

Given the recent initiation of chlorthalidone and the absence of other identifiable causes, chlorthalidone-induced agranulocytosis was suspected. To assess the likelihood of chlorthalidone being the offender, the Naranjo algorithm was employed. Based on the algorithm's criteria, chlorthalidone scored 7, indicating a probable cause of agranulocytosis in this case. There were no observable changes in the monocyte count, but neutropenia was increasing and more pronounced on days 5 and 7, reaching a value of 40 neutrophils per mm^3 (Table 1).

The patient was started on broad-spectrum antibiotics. The medications used by the patient were intravenous amoxicillin/clavulanic acid, paracetamol, and omeprazole. However, bacterial

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Table 1: Changes in blood cell types from day 1 to day 14

Cells/mm^3	Days of treatment							
	Day 1	Day 3	Day 5	Day 7	Day 9	Day 11	Day 13	Day 14
Leukocytes	13.770	11.000	7.420	4.890	4.430	3.450	3.600	8.440
Neutrophils	230	180	60	40	80	210	330	620
Lymphocytes	1.880	1.410	1.710	1.420	3.030	2.120	2.100	2.180
Monocytes	870	850	720	790	840	1.160	1.380	1.190

culture was found to be negative. Giemsa stained blood smear showed the absence of granulocytes from the peripheral blood smear (Fig. 1), and the bone marrow evaluation revealed that the antecedents of the three series were normal.

Using indirect immunofluorescence, atypical positive antineutrophil cytoplasmic antibody (ANCA) (title 1/80) was found during the neutropenic period. Chlorthalidone was withheld and the patient was started on amlodipine for control of his hypertension. Granulocyte colony-stimulating factor (G-CSF) of 60 MU was recommended in two subcutaneous doses and was given to the patient. On day 14 of chlorthalidone withdrawal, the granulocyte count was normalized. After the event, 2 months later, the ANCA finding was negative.

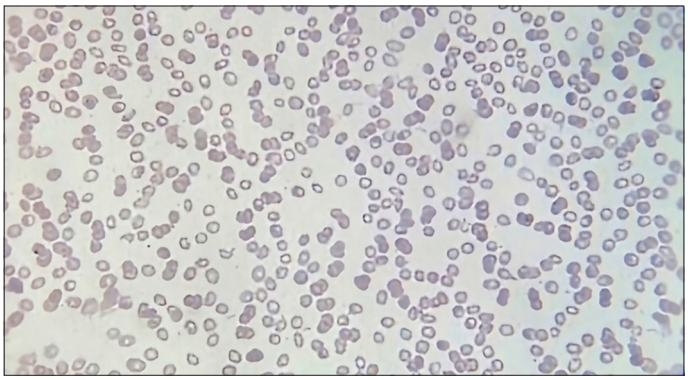

Figure 1: Giemsa stained blood smear – absent granulocytes

DISCUSSION

Chlorthalidone, a thiazide-like diuretic, is commonly prescribed for the management of hypertension and edema due to its potent antihypertensive and diuretic effects [6]. While it is generally considered safe and well tolerated, rare but severe adverse reactions, such as agranulocytosis, have been reported in the literature [7,8]. Chlorthalidone is a widely prescribed thiazide diuretic for hypertension. While generally well tolerated, it can cause a spectrum of adverse effects, with agranulocytosis being a rare but documented complication.

The exact mechanism of chlorthalidone-induced agranulocytosis remains unclear. Proposed mechanisms include direct bone marrow suppression: Chlorthalidone might directly affect bone marrow precursors, leading to reduced neutrophil production; immune-mediated destruction: The drug may trigger an immune response that destroys mature neutrophils; idiosyncratic reactions: Individual susceptibility may play a role, with certain patients having a predisposition to developing DIA with chlorthalidone. The pathophysiology underlying chlorthalidone-induced agranulocytosis remains elusive. It is postulated to involve immune-mediated mechanisms, possibly triggered by a hypersensitivity reaction to the medication. Drug-induced immune-mediated destruction of granulocyte precursors leads to a rapid decline in neutrophil counts, predisposing patients to severe bacterial infections and sepsis.

Patients with chlorthalidone-induced agranulocytosis may present with a variety of symptoms, including, fever, chills, mouth ulcers (stomatitis), sore throat, fatigue, malaise, and signs of infection (depending on the affected area). These symptoms can be non-specific, making diagnosis challenging. A complete blood count revealing a neutrophil count below 500/μL is crucial for diagnosis. Other blood tests might be necessary to rule out other causes of neutropenia and identify potential infections [6].

The cornerstone of managing chlorthalidone-induced agranulocytosis is immediate discontinuation of the drug. Supportive measures include (a) antibiotic prophylaxis or treatment: Broad-spectrum antibiotics are often prescribed to prevent or treat infections in neutropenic patients, (b) growth factor therapy: G-CSF can stimulate the bone marrow to produce more neutrophils, potentially accelerating recovery, and (c) supportive care: Measures to prevent complications and improve comfort, such as maintaining good hygiene, managing fever, and providing adequate hydration and nutrition. The recovery time for chlorthalidone-induced agranulocytosis is variable, usually ranging from 7 to 14 days after drug discontinuation. Close monitoring of blood counts is essential to track neutrophil recovery [7].

Early recognition of agranulocytosis is crucial for initiating prompt management and preventing complications. Patients may present with non-specific symptoms such as fever, sore throat, and malaise, which can easily be overlooked or attributed to other causes. Therefore, clinicians should maintain a high index of suspicion and perform regular hematological monitoring in patients receiving chlorthalidone therapy [9]. On suspicion of agranulocytosis, immediate discontinuation of chlorthalidone is imperative to halt further hematological toxicity. Supportive care, including broad-spectrum antibiotics and prophylactic antifungal agents, should be initiated promptly to prevent opportunistic infections. In addition, administration of G-CSF can stimulate neutrophil production and accelerate recovery [10].

Although the prognosis of chlorthalidone-induced agranulocytosis is generally favorable with timely intervention, the potential for life-threatening complications underscores the importance of vigilant monitoring and proactive management

strategies. Furthermore, clinicians should exercise caution when rechallenging patients with chlorthalidone or structurally related medications to avoid the recurrence of agranulocytosis [11].

Moreover, differential diagnosis is crucial in evaluating patients presenting with hematological abnormalities while on chlorthalidone therapy. Other potential causes of neutropenia, such as viral infections, autoimmune disorders, and bone marrow disorders, should be carefully considered and ruled out to avoid misdiagnosis and inappropriate management [12].

In addition, pharmacovigilance plays a vital role in identifying and monitoring rare adverse drug reactions, including chlorthalidone-induced agranulocytosis. Health-care professionals should report suspected cases to regulatory authorities and adverse event reporting systems to contribute to ongoing surveillance and enhance the understanding of drug safety profiles [13]. Patient education is another key aspect of managing chlorthalidone therapy and mitigating the risk of adverse reactions. Patients should be informed about the signs and symptoms of agranulocytosis and advised to seek immediate medical attention if they experience any concerning symptoms, such as fever, sore throat, or unusual bruising [14]. Furthermore, interdisciplinary collaboration among health-care providers, including physicians, pharmacists, and hematologists, is essential in the holistic management of patients with chlorthalidone-induced agranulocytosis. Close communication and shared decision-making facilitate optimal patient care and minimize the risk of adverse outcomes [15].

CONCLUSION

This case emphasizes the importance of considering drug-induced agranulocytosis as a potential cause of neutropenia in patients presenting with fever and sore throat, especially in the context of recent medication changes. Health-care professionals should be vigilant in monitoring patients for adverse drug reactions and promptly intervene to prevent life-threatening complications.

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