CASE REPORT

Dapsone-induced agranulocytosis presenting as neutropenic sepsis in borderline tuberculoid leprosy

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Abstract

Dapsone, a core component of multidrug therapy (MDT) for leprosy, can rarely cause life-threatening haematologic toxicity. We report a 66-year-old woman with borderline tuberculoid leprosy, receiving multibacillary MDT (MDT-MB), who developed fever, sore throat, and malaise seven days into her second monthly blister pack. Laboratory evaluation revealed severe neutropenia (absolute neutrophil count [ANC] 0.1 × 10^9/L) and markedly elevated C-reactive protein (CRP 230 mg/L), consistent with dapsone-induced agranulocytosis. Neutropenic sepsis was clinically suspected. Peripheral blood smear showed haemolytic changes. Blood and urine cultures were sterile.

Dapsone was immediately discontinued, and she received empiric intravenous cefuroxime, supportive care, and packed red blood cell transfusion for haemolysis-related anaemia. The fever resolved within 48 hours, and the ANC recovered over five days. Following complete haematologic recovery confirmed by periodic blood count monitoring, MDT-MB was resumed without dapsone, with continuation of rifampicin and clofazimine. This case underscores the importance of regular haematologic monitoring, early recognition, and prompt withdrawal of the offending agent. Timely supportive care and empiric antibiotics are essential to prevent potentially fatal complications.

Keywords: Dapsone; agranulocytosis; leprosy; neutropenic sepsis; oxidant haemolysis

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Introduction

Leprosy remains a public health challenge in Sri Lanka, a high-burden country reporting approximately 2,000 new cases annually. Despite intensified case-finding and surveillance efforts, detection rates remain high.[1] Multidrug therapy (MDT), as recommended by the World Health Organization, comprises rifampicin, clofazimine, and dapsone. Dapsone (4,4′-diaminodiphenylsulfone) is a cornerstone of MDT but is associated with potential haematologic toxicities, including haemolytic anaemia and methaemoglobinaemia, as well as rare hypersensitivity reactions.[2] Among these, agranulocytosis is an idiosyncratic and uncommon adverse effect (reported in 0.2–0.4% of cases) that can be fatal, particularly when complicated by sepsis.[3] We report the case of 66-year-old Sri Lankan woman with leprosy who developed dapsone-induced agranulocytosis complicated by sepsis and subsequently achieved full recovery following prompt drug withdrawal and supportive care.

Case Presentation

A 66-year-old woman with borderline tuberculoid leprosy, managed with the multibacillary multidrug therapy (MDT-MB), presented with systemic symptoms seven days into her second blister pack. She reported fever and sore throat for five days, vomiting for four days, and cough with dyspnoea for three days, along with generalized malaise.

On admission, she was febrile. Physical examination revealed a palpable left cervical lymph node, while respiratory and abdominal examinations were otherwise unremarkable.

Laboratory Investigations: Initial laboratory evaluation revealed severe neutropenia with a marked inflammatory response. The total white blood cell (WBC) count was 2.73 × 10⁹/L, with an absolute neutrophil count (ANC) of 0.10 × 10⁹/L (3.5%) and lymphocytes of 2.27 × 10⁹/L (83%). Haemoglobin was 10.2 g/dL, platelet count 403 × 10⁹/L, and C-reactive protein (CRP) 230 mg/L. Table 1 presents the temporal changes in haematologic and biochemical parameters from baseline through pre-event and on Days 1, 3, and 5 of hospitalization, alongside reference ranges.

By day 3 of hospitalization, haemoglobin had declined to 7.5 g/dL with an LDH of 683 U/L. Peripheral blood smear showed normocytic, normochromic erythrocytes with bite and blister cells, consistent with oxidant stress–induced haemolysis, along with leukocyte changes suggestive of bacterial infection. Blood and urine cultures were sterile, and chest radiography was unremarkable. Total bilirubin was elevated on Day 1, with indirect predominance, further supporting oxidant stress – induced haemolysis.

Table 1. Haematologic and Biochemical Parameters in Dapsone-Induced Agranulocytosis

Test	Normal Range	Baseline	Pre-event	D1	D3	D5
WBC (×10⁹/L)	4.0–11.0	9.33	8.67	2.73	5.41	5.54
ANC (×10⁹/L)	2.0–7.0	3.36	2.93	0.10	0.96	0.91
Haemoglobin (g/dL)	12.0–15.0	13.4	11.2	10.2	7.5	9.7
Platelets (×10⁹/L)	150–450	324	270	403	448	602
CRP (mg/L)	<5	–	–	230	–	–
LDH (U/L)	135–225	–	–	–	683	255
Total bilirubin (µmol/L)	5–21	–	–	37.3	–	14.5
Direct bilirubin (µmol/L)	0–5	–	–	11.2	–	7.8

Values at baseline (before MDT), Pre-event (one week before admission), and on Days 1, 3, and 5 of hospitalization (D1, D3, D5), with reference ranges. CRP values on Day 2 and Day 4 were 175 mg/L and 73 mg/L, respectively, and are not shown in the table. Brewer's test was negative at baseline and is not shown in the table. Abbreviations: ANC, absolute neutrophil count; CRP, C-reactive protein; LDH, lactate dehydrogenase. "–" denotes test not performed or result unavailable.

Diagnosis and Management: A working diagnosis of dapsone-induced agranulocytosis complicated by neutropenic sepsis was made. Dapsone was immediately discontinued, and the entire MDT-MB blister pack was withheld. The patient was admitted and commenced on empiric intravenous cefuroxime along with supportive care.

Fever resolved within 48 hours of antibiotic therapy, and by day 3 of hospitalization, constitutional and upper respiratory symptoms had regressed, with a reduction in cervical lymphadenopathy. Laboratory parameters on the same day demonstrated improving leukocyte counts with ongoing haemolysis, and one unit of packed red blood cells was transfused in accordance with standard thresholds.

Haematologic recovery was observed over five days, with the ANC rising from 0.10×10^9/L on Day 1 to 1.18×10^9/L by Day 5, accompanied by a progressive decline in CRP, paralleling clinical improvement.

Outcome and Follow-up: The patient was discharged after six days of hospitalization. She was counselled regarding the risk of recurrence, the importance of regular haematologic monitoring, and the need to seek prompt medical attention for febrile illness. Weekly complete blood counts were obtained. Following full haematologic recovery, MDT-MB was resumed without dapsone, consisting of rifampicin and clofazimine, thereby minimizing the risk of recurrent haematologic toxicity.

Discussion

Dapsone-induced agranulocytosis is a rare idiosyncratic adverse reaction characterized by severe neutropenia, typically defined as an absolute neutrophil count (ANC) $< 0.5 \times 10^9$/L. The reaction is associated with reactive metabolite formation: hepatic N-hydroxylation generates dapsone hydroxylamine, which may impair granulocyte precursor survival and suppress granulopoiesis. Reactive metabolite–protein binding has also been proposed as a mechanism contributing to immune-mediated neutrophil or precursor cell destruction, although direct evidence specific to dapsone remains limited.[2,4]

Early clinical manifestations, such as fever, sore throat, or mucosal ulcers, may represent the first indicators of neutropenia.[5] An absolute neutrophil count (ANC) below 0.5×10^9/L confers a high risk of infection. Baseline complete blood counts with differential are recommended before initiating dapsone therapy, followed by weekly monitoring for the first month, every 2 weeks for the next 2 months, and subsequently at longer intervals once counts are stable.[2]

Neutropenic sepsis generally warrants prompt empiric broad-spectrum antibiotic therapy, often including antipseudomonal coverage. In this case, however, the patient was clinically stable and considered low risk for complications based on clinical assessment; she responded favourably to cefuroxime under close observation without requiring escalation of therapy.

In febrile neutropenia, microbiologic confirmation is often lacking even when clinical features suggest serious infection: positive blood cultures are identified in only a minority of cases, and many patients remain culture-negative despite fever and neutropenia.[6] Sterile cultures do not exclude neutropenic sepsis, and current guidelines support prompt empiric antibiotic therapy when clinical suspicion is high, without awaiting microbiologic confirmation. In this case, although both blood and urine cultures were negative, the presentation was consistent with neutropenic sepsis, highlighting the importance of early empiric therapy in patients with dapsone-induced agranulocytosis.

Although granulocyte colony-stimulating factor (G-CSF) can accelerate neutrophil recovery and shorten the duration of neutropenia, its routine use in drug-induced agranulocytosis is not supported by current evidence and should be reserved for high-risk patients.[7] Indications include profound neutropenia (ANC $< 0.1 \times 10^9$/L), ANC $< 0.5 \times 10^9$/L with fever or sepsis, and elderly or multimorbid patients at increased risk of infectious complications. In this case, G-CSF was not required, as the fever resolved within 48 hours and neutrophil counts improved spontaneously following drug withdrawal, consistent with endogenous marrow recovery.

In addition to agranulocytosis, the patient developed haemolytic anaemia due to oxidant stress, further highlighting the spectrum of dapsone-related

haematologic toxicity. Dapsone should not be reintroduced following severe haematologic toxicity, and the therapeutic regimen should be modified to prevent recurrence.

Case reports have described severe neutropenia following dapsone use in patients treated for leprosy, with manifestations ranging from neutropenic sepsis and life-threatening skin sepsis to fatal infections, underscoring the potential severity of this reaction.[3,5,8,9,10] Management has differed. Some patients, including the present case, recovered with supportive care without G-CSF, whereas responses to G-CSF were variable, with at least one report showing limited efficacy.[8] These observations underscore the importance of close monitoring, early recognition, prompt drug discontinuation, and individualized management in all patients receiving dapsone.

Conclusion

Dapsone-induced agranulocytosis, although rare, can be life-threatening. Prompt recognition, immediate discontinuation of the drug, and timely supportive care are essential to prevent serious complications and ensure patient safety.

Ethics statement

Written informed consent was obtained from the patient for publication of this case report and accompanying laboratory data. Patient anonymity has been preserved.

Author contributions

AW was responsible for patient management, data collection, literature review, and manuscript drafting. ASR provided clinical supervision and was involved in the literature review and substantial revision of the manuscript. KA and ND contributed to data interpretation and patient care. SN assisted with medical management and patient care. All authors read and approved the final manuscript.

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