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# Dapsone-Induced Hemolytic Anemia, Severe Acute Liver Injury and Clinically Suspected Methemoglobinemia in a Patient with Hansen's Disease: A Rare Case Report

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## ABSTRACT

**Background**

Dapsone is a key component of multidrug therapy (MDT) for Hansen's disease but is associated with serious adverse effects, including methemoglobinemia, hemolytic anemia, and hepatotoxicity. The simultaneous occurrence of these complications is rare and potentially life-threatening. Early recognition is critical, especially in resource-limited settings where advanced diagnostic tools may not be readily available.

**Case Report**

A 38-year-old female presented with jaundice, fever, and breathlessness approximately one month after initiation of dapsone therapy. Examination revealed pallor, icterus, and edema. Laboratory findings showed severe hyperbilirubinemia (>25 mg/dL), elevated transaminases, anemia (hemoglobin ~8 g/dL), markedly elevated lactate dehydrogenase (1705 U/L), and negative Coombs test, consistent with non-immune hemolysis. Inflammatory markers were elevated, and arterial blood gas analysis indicated metabolic acidosis. Methemoglobinemia was clinically diagnosed by the treating team. Imaging revealed pleural effusion and ascites, suggesting systemic involvement. Dermatology consultation suggested dapsone hypersensitivity syndrome, and dapsone was discontinued. The overall findings were consistent with dapsone-induced multisystem toxicity involving hepatic, hematological, and respiratory systems.

**Conclusion**

This case highlights a rare but severe presentation of dapsone-induced methemoglobinemia, hemolytic anemia, and acute liver failure. Clinicians should maintain a high index of suspicion for dapsone toxicity in patients presenting with jaundice, anemia, and respiratory symptoms shortly after initiation of therapy. Early drug withdrawal and prompt supportive management are essential to prevent life-threatening complications.

***Keywords: Dapsone; Methemoglobinemia; Hemolytic Anemia; Acute Liver Failure; Dapsone Hypersensitivity Syndrome; Hansen's Disease.***



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## INTRODUCTION

Dapsone (4,4′-diaminodiphenyl sulfone) is a synthetic sulfone widely used in the management of dermatological and infectious diseases, most notably as a key component of multidrug therapy (MDT) for Hansen's disease (leprosy).[1] Its antimicrobial action against *Mycobacterium leprae* and anti-inflammatory properties have sustained its relevance in clinical practice for decades. In addition to leprosy, dapsone is employed in conditions such as dermatitis herpetiformis, linear IgA dermatosis, and as prophylaxis against *Pneumocystis jirovecii* pneumonia in immunocompromised individuals. Despite its therapeutic benefits, dapsone is associated with a spectrum of adverse drug reactions ranging from mild and reversible to severe, life-threatening complications.[2]

Among the most clinically significant adverse effects of dapsone are methemoglobinemia, hemolytic anemia, and hepatotoxicity, which may occur independently or in combination. These toxicities are primarily mediated by dapsone's hepatic metabolism via the cytochrome P450 system, leading to the formation of hydroxylamine metabolites that exert oxidative stress on erythrocytes and hepatocytes. This oxidative stress results in the conversion of ferrous iron ($Fe^{2+}$) in hemoglobin to ferric iron ($Fe^{3+}$), producing methemoglobinemia, and simultaneously induces red blood cell membrane damage, leading to hemolysis.[3]

Methemoglobinemia is a condition characterized by elevated levels of methaemoglobin, which impairs oxygen delivery to tissues despite normal oxygen tension. Clinically, patients may present with cyanosis, dyspnea, fatigue, and, in severe cases, altered sensorium and cardiovascular instability.

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Dapsone is one of the most common causes of acquired methemoglobinemia due to its oxidant metabolites, and the risk increases with higher doses, prolonged therapy, and underlying enzymatic deficiencies.[4]

Hemolytic anemia is another well-recognized complication of dapsone therapy. While it is more commonly associated with glucose-6-phosphate dehydrogenase (G6PD) deficiency, hemolysis can also occur in individuals with normal enzyme levels due to oxidative injury. The clinical features include pallor, jaundice, elevated lactate dehydrogenase (LDH), indirect hyperbilirubinemia, and reticulocytosis. The coexistence of hemolysis and methemoglobinemia can further exacerbate hypoxia and clinical deterioration.[5]

Hepatotoxicity, although less common than hematological complications, is a serious and potentially fatal adverse effect of dapsone. It may manifest as asymptomatic elevation of liver enzymes, cholestatic jaundice, or acute liver failure. A particularly severe form is dapsone hypersensitivity syndrome (DHS), which typically occurs within 2–6 weeks of initiating therapy and is characterized by fever, rash, lymphadenopathy, and hepatitis. The syndrome is believed to be immune-mediated and carries significant mortality if not recognized early.[6]

The simultaneous occurrence of methemoglobinemia, hemolytic anemia, and acute liver injury represents a rare but severe form of multisystem dapsone toxicity. Such cases are clinically challenging due to overlapping symptoms, rapid progression, and the need for prompt diagnosis and intervention. In resource-limited settings, where advanced diagnostic modalities such as co-oximetry may not be readily available, clinicians often rely on clinical suspicion supported by laboratory findings.[7]

Hansen's disease continues to be a public health concern in countries like India, where MDT regimens including dapsone are routinely administered under national programs. Although MDT has significantly reduced disease burden, adverse drug reactions remain an important cause of morbidity and treatment interruption. Early recognition of severe reactions such as dapsone toxicity is crucial to prevent complications and ensure patient safety.[8]

This case report describes a patient with Hansen's disease who developed dapsone-induced methemoglobinemia, hemolytic anemia, and acute liver failure, highlighting the importance of early diagnosis, prompt withdrawal of the offending drug, and appropriate supportive management. The case underscores the need for vigilance among clinicians prescribing dapsone and contributes to the existing literature on rare but life-threatening complications of this widely used drug.

## CASE REPORT

A 38-year-old female with a known history of Hansen's disease presented with progressive yellowish discoloration of sclera for 10 days, associated with intermittent fever and acute onset breathlessness. She had been receiving multibacillary multidrug therapy (MBMDT) containing dapsone for approximately one month prior to symptom onset.

At presentation, the patient had progressive yellowish discoloration of sclera for 10 days, associated with intermittent fever and acute onset breathlessness. On general examination, she was found to have pallor, icterus, and pedal edema. Dermatological examination revealed multiple hypopigmented hypoesthetic patches over the lower limbs, consistent with Hansen's disease. A dermatology consultation suggested dapsone hypersensitivity syndrome, and discontinuation of multidrug therapy was advised.

The treating team documented a final diagnosis of acute liver failure with hepatic encephalopathy secondary to dapsone toxicity, along with methemoglobinemia and hemolytic anemia.

Initial hematological evaluation revealed anemia, with hemoglobin levels declining from 9.6 g/dL (pre-admission) to 8.1 g/dL on admission, and persisting around 8.2 g/dL during hospital stay. Total leukocyte count was elevated (14,700 cells/cumm), indicating an inflammatory response. Platelet counts remained within normal limits initially (2.68 lakh/cumm) but showed a mild declining trend during hospitalization.

Peripheral smear examination demonstrated dimorphic anemia with microcytic hypochromic and normocytic normochromic red blood cells. The direct Coombs test was negative, suggesting non-immune hemolysis. Notably, serum lactate dehydrogenase (LDH) was markedly elevated (1705 U/L), supporting ongoing hemolysis.The patient exhibited severe hepatic dysfunction at presentation, which progressively worsened during hospitalization. Pre-admission laboratory values showed total bilirubin 8.91 mg/dL, which increased significantly to 20.1 mg/dL on admission, and subsequently exceeded 25 mg/dL during the hospital course. Direct bilirubin remained markedly elevated, indicating predominantly conjugated hyperbil - irubinemia.Transaminases were significantly elevated, with SGPT rising up to 542 U/L and SGOT up to 545 U/L, indicating hepatocellular injury. Serum albumin levels were reduced (~3.1 g/dL), reflecting impaired synthetic liver function. Coagulation parameters showed prolongation of prothrombin time (16.67 seconds) and mildly elevated INR (1.26).Renal parameters showed mild derangement, with blood urea rising up to 50 mg/dL and serum creatinine up to 1.5 mg/dL during the course of illness. Electrolyte imbalance was notable for persistent hypokalemia (2.6–2.7 mEq/L) (Table 1).

| Parameter | Pre-admission | At Admission | During Hospital Stay | Reference Range |
|---|---|---|---|---|
| Hemoglobin (g/dL) | 9.6 | 8.1 | 8.2 | 12–15 |
| Total Leukocyte Count (cells/cumm) | — | 14,700 | — | 4,000–11,000 |
| Platelets (lakh/cumm) | — | 2.68 | 1.66 | 1.5–4.5 |
| Total Bilirubin (mg/dL) | 8.91 | 20.1 | >25.0 | 0.2–1.2 |
| Direct Bilirubin (mg/dL) | 4.67 | 17.1 | 15.3 | <0.3 |
| SGPT (U/L) | 333 | 542 | 188 | <40 |
| SGOT (U/L) | 545 | 390 | 475 | <40 |
| Serum Albumin (g/dL) | — | 3.1 | 3.1 | 3.5–5.0 |
| Blood Urea (mg/dL) | — | 30 | 50 | 15–40 |
| Serum Creatinine (mg/dL) | — | 1.1 | 1.5 | 0.6–1.2 |
| LDH (U/L) | — | — | 1705 | 140–280 |
| CRP (mg/L) | — | — | 77.2 | <5 |
| ESR (mm/hr) | 45 | — | 30 | <20 |
| Potassium (mEq/L) | — | 4.1 | 2.6–2.7 | 3.5–5.0 |

*Table 1. Serial Laboratory Parameters During Clinical Course.*

This table demonstrates a progressive and severe derangement of hematological and biochemical parameters, consistent with multisystem toxicity. There is a clear decline in hemoglobin levels along with markedly elevated LDH, supporting ongoing hemolysis. Simultaneously, a dramatic rise in total and direct bilirubin levels (>25 mg/dL), along with elevated transaminases and reduced albumin, indicates severe hepatic dysfunction progressing to acute liver failure. The elevated inflammatory markers (CRP, ESR) reflect systemic inflammatory response, while electrolyte imbalance (hypokalemia) and mild renal impairment further signify systemic involvement. Overall, the laboratory trends strongly support the diagnosis of dapsone-induced multiorgan toxicity involving hematological and hepatic systems.Inflammatory markers were significantly elevated, with C-reactive protein (CRP) at 77.2 mg/L and ESR ranging between 30–45 mm/hour, indicating systemic inflammation. Arterial blood gas analysis revealed metabolic acidosis with low bicarbonate levels (~15 mEq/L) and elevated lactate (5.81 mmol/L), suggestive of systemic hypoxia and metabolic stress.Although specific methaemoglobin levels were not available in the records, the diagnosis of methemoglobinemia was clinically documented by the treating team. The presence of acute breathlessness, hypoxia-related symptoms, and concurrent hemolysis in the setting of recent dapsone exposure supported this diagnosis. Ultrasonography revealed bilateral mild pleural effusions and mild ascites, indicating systemic involvement and possible hypoalbuminemia-related fluid accumulation. Pleural fluid analysis showed low cellularity with lymphocyte predominance and no malignant cells, and ADA levels were within non-tubercular range (7.3 U/L).Echocardiography was essentially normal except for sinus tachycardia, thereby excluding cardiac causes of breathlessness. Following the recognition of suspected dapsone toxicity, dapsone-containing therapy was discontinued. Despite supportive management, the patient demonstrated progressive worsening of hepatic dysfunction, persistent anemia, and systemic complications consistent with acute liver failure. The constellation of findings strongly indicated multisystem dapsone toxicity involving hematological, hepatic, and respiratory systems.

## DISCUSSION

Dapsone-induced multisystem toxicity is uncommon, and the simultaneous occurrence of methemoglobinemia, hemolytic anemia, and acute liver failure is particularly rare. The present case highlights a rare but severe manifestation of dapsone-induced multisystem toxicity, characterized by the coexistence of methemoglobinemia, hemolytic anemia, and acute liver failure in a patient undergoing multidrug therapy (MDT) for Hansen's disease. The temporal relationship between initiation of dapsone and the onset of clinical symptoms strongly supports a causal association, further reinforced by clinical and laboratory findings and improvement following drug withdrawal.

Dapsone is metabolized primarily in the liver through N-hydroxylation, producing hydroxylamine metabolites that are responsible for its toxic effects. These metabolites induce oxidative stress, leading to the oxidation of hemoglobin iron from ferrous ($Fe^{2+}$) to ferric ($Fe^{3+}$) state resulting in methemoglobinemia, and also cause damage to red blood cell membranes, precipitating hemolysis. The simultaneous occurrence of these two hematological complications significantly compromises oxygen delivery and contributes to clinical deterioration.[9] In the present case, although direct measurement of methaemoglobin levels was not available, the diagnosis of methemoglobinemia was clinically established which was supported by the presence of acute breathlessness, hypoxia-related symptoms, and concurrent hemolysis in the setting of recent dapsone exposure. Similar observations have been reported in previous studies, where methemoglobinemia was diagnosed clinically in resource-limited settings without co-oximetry confirmation. Dapsone remains one of the most common causes of acquired methemoglobinemia worldwide.[10]

The hematological findings in this patient strongly indicate non-immune hemolytic anemia, as evidenced by declining hemoglobin levels, markedly elevated lactate dehydrogenase (LDH), and a negative direct Coombs test. These findings are consistent with oxidative hemolysis rather than immune-mediated destruction. While hemolysis is classically associated with glucose-6-phosphate dehydrogenase (G6PD) deficiency, it can also occur in individuals with normal enzyme activity due to overwhelming oxidative stress. Similar cases of dapsone-induced hemolysis without G6PD deficiency have been documented in the literature.[11]

The most striking feature of this case is the presence of severe hepatic dysfunction progressing to acute liver failure. The patient demonstrated progressive hyperbilirubinemia, transaminitis, hypoalbuminemia, and clinical features suggestive of hepatic encephalopathy. Dapsone-induced hepatotoxicity is typically idiosyncratic and may present as part of dapsone hypersensitivity syndrome (DHS), which usually occurs within 2–6 weeks of therapy initiation.[12]. The dermatology consultation in this case also suggested DHS, further strengthening the diagnosis.

Dapsone hypersensitivity syndrome is a potentially life-threatening condition characterized by fever, rash, lymphadenopathy, and hepatitis, although incomplete or atypical presentations are not uncommon. The absence of a prominent rash in this patient suggests a variant or incomplete DHS, emphasizing the need for high clinical suspicion even in the absence of classical features. Previous studies have shown that hepatic involvement is a major contributor to mortality in DHS. The coexistence of hematological toxicity and hepatic injury in this case reflects the systemic nature of dapsone toxicity. A retrospective study on adverse drug reactions to MDT in leprosy reported that dapsone was responsible for the majority of hepatic and hematological complications, including hemolysis and toxic hepatitis. Furthermore, a systematic review identified DHS as the most commonly reported severe adverse drug reaction associated with dapsone therapy, with significant mortality rates.[13]

Another important aspect of this case is the presence of metabolic acidosis and elevated lactate levels, which may be attributed to tissue hypoxia resulting from methemo - globinemia and anemia. The combination of reduced oxygen-carrying capacity and impaired hepatic function likely contributed to systemic metabolic derangement.[14]

Radiological findings of pleural effusion and ascites in this patient may be secondary to hypoalbuminemia and systemic inflammation. These findings further indicate the severity of the underlying disease process and the extent of multiorgan involvement.

The diagnosis of dapsone-induced toxicity in this case is supported by standard causality assessment principles, including temporal association, exclusion of alternative etiologies, and clinical judgment. Viral hepatitis markers were negative, and no other clear cause of acute liver failure or hemolysis was identified, strengthening the attribution to dapsone. Management of such cases primarily involves immediate discontinuation of dapsone, along with supportive care.In cases of significant methemoglobinemia, treatment with methylene blue is recommended, although caution is

required in patients with G6PD deficiency. Additional supportive measures may include oxygen therapy, blood transfusion for severe anemia, and intensive care management for acute liver failure.[15]

This case underscores the importance of early recognition and prompt intervention in patients receiving dapsone therapy. Clinicians should maintain a high index of suspicion for dapsone toxicity in patients presenting with jaundice, anemia, and respiratory symptoms, particularly within the first few weeks of therapy. Regular monitoring of liver function and hematological parameters may help in early detection of adverse effects.

## CONCLUSION

This case highlights a rare but severe presentation of dapsone toxicity involving simultaneous hematological and hepatic complications, with clinically significant methemo - globinemia. The case emphasizes the need for vigilance in patients receiving MDT for Hansen's disease and reinforces the importance of early diagnosis, drug withdrawal, and aggressive supportive management to prevent life-threatening outcomes.

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