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CASE REPORT

Lack of Suspicion of Dapsone Hypersensitivity Syndrome in a Leprosy Patient: Case Report with Fatal Outcome

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Background: Dapsone is an antibiotic used in the management of leprosy. Following the worldwide adoption of the dapsone-containing multidrug therapy for treating leprosy, an upsurge in the reported frequency of dapsone hypersensitivity syndrome (DHS) has been observed. DHS is associated with a high fatality rate among patients from low-resourced settings and patients with syndrome-associated hepatitis.

Case Presentation: This is a case of a Ghanaian male who, while being treated for leprosy with the multidrug therapy, developed exfoliative dermatitis and signs of liver damage, 6 weeks after treatment initiation. He was managed for dapsone-related exfoliative dermatitis and infectious causes of liver damage were investigated. However, the patient's condition rapidly deteriorated with a fatal outcome despite discontinuation of dapsone. DHS was only considered as a differential diagnosis postmortem.

Conclusion: This case highlights the importance of having a high index of suspicion for DHS in all patients on dapsone and the need for a thorough workup for all leprosy patients who present with exfoliative dermatitis and signs of liver involvement within the latency period of the syndrome, especially in low resource settings. Furthermore, it stresses the need for prompt and appropriate treatment as DHS can quickly become fatal in such settings.

Keywords: multidrug therapy, exfoliative dermatitis, adverse drug reaction, hepatomegaly, sulfone antibiotic, steroid

Introduction

The sulfone antibiotic, dapsone, is a component of the World Health Organization's recommended multidrug therapy (MDT) for treating leprosy and has been used for this purpose since the mid-20th century.[1,2] While it is most commonly indicated for use in the treatment of leprosy it can also be utilized to treat other conditions.[3] It causes a myriad of adverse reactions[4] including the rare, life threatening Dapsone Hypersensitivity Syndrome (DHS) which has a fatality rate of approximately 10%.[3,5] DHS is characterized by fever, skin rash, lymphadenopathy and multiple organ involvement, predominantly hepatitis.[3,5] This syndrome poses a high mortality risk, especially in patients from low-resource settings and those who consequently develop hepatitis.[3] Some studies suggest an increased incidence of DHS following the introduction of MDT.[6–8] We therefore present a suspected case of DHS in a 35-year-old male Ghanaian patient with leprosy, who presented with fever, exfoliative dermatitis, multiorgan failure, and anemia, which went undiagnosed resulting in a fatal outcome.

Case Presentation

A 35-year-old male with no known past relevant medical or drug history (including alcohol and herbal), was diagnosed with multibacillary leprosy at a leprosy referral hospital in Ghana and was started on the standard MDT on outpatient

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basis. He reported 6 weeks later, while on his second blister, with generalized peeling of his skin, occurring for the first time and which had progressively worsened during the previous 3 weeks before presentation.

The patient was additionally found to be clinically pale, jaundiced, tachypneic (24cpm) and tachycardic (pulse-102 bpm), but had no fever or lymphadenopathy. The liver was palpable but non-tender. The cardiorespiratory system was normal. Examination of the skin showed scaling and shedding on face, trunk and all the limbs, but without evidence of ulceration.

Provisional diagnosis of exfoliative dermatitis secondary to dapsone and severe anemia to query cause were made. Dapsone was immediately discontinued, topical salicylic acid and steroid cream were started, and laboratory tests requested.

Blood work revealed low hemoglobin (HB) of 6.0g/dl (normal range: 11.5–16.0g/dl), deranged liver function: AST >250U/l (upper limit-34U/l), ALT- 216.6U/l (upper limit-50U/l), GGT-189.8U/l (upper limit-36U/l) and ALP>700U/l (upper limit −270U/l), hypoalbuminemia of 19.4g/dl (lower limit-34), hyperbilirubinemia of >342.1 µmol/l (upper limit-25.7µmol/l) with significant elevation of both indirect (360µmol/l; upper limit −17µmol/l) and direct bilirubin (299.63 µmol/l; upper limit −10.3µmol/l); renal function test showed Creatine-130.4µmol/l, Estimated Glomerular Filtration Rate (EGFR)- 57.91mL/min/L (>90mL/min/L), Urea of 15.32mmol/l (upper limit- 7mmol/l) and blood urea nitrogen/creatinine ratio-117 (upper limit −36).

Hepatitis B and C serology, and Human Immunodeficiency Virus (HIV) and malaria rapid tests were negative. Full Blood Count (FBC) was requested following a spot HB test which showed a low hemoglobin level, but this was not done.

The patient was admitted and transfused two units of blood with 100mg intravenous hydrocortisone as premedication. He was given 15mg lactulose twice daily as prophylaxis for constipation during his hospitalization on account of the observed liver derangement. Serially monitored urine showed no cola-like discoloration. He received paracetamol for a low-grade fever of 37.8°C, which developed 2 days after admission, peaking at 39.9°C on the 8th day of admission. Intravenous antibiotics, 1g ceftriaxone twice daily was started on day four of admission at the peak of the fever. He vomited once; vomitus was scanty, predominantly mucoid with some streaks of bright red blood.

An abdominopelvic ultrasound on the 7th day of admission confirmed an enlarged echogenic liver and the main portal vein was 1.5cm dilated. The spleen was sonographically determined to be enlarged but with a homogenous appearance. No focal lesions were observed in either liver or spleen, and the other intra-abdominal organs appeared normal. There was also no ascites or other intra-abdominal masses, and the aorta was normal in size and appearance.

Diagnosis was revised to entertain an underlying chronic liver disease with portal hypertension and likely acute hepatorenal syndrome, complicated by severe anemia (with high possibility of upper gastrointestinal bleeding).

His condition, however, deteriorated over the next 24 hours with the patient noticed to be suddenly gasping for air on the morning of the 8th day, soon after which he ceased breathing. All cardiopulmonary resuscitation efforts were unsuccessful.

In hindsight, the diagnosis of DHS is suspected on account of exfoliative dermatitis, multiorgan involvement (hepatitis, splenomegaly and kidney injury) and fever, in a patient with multibacillary leprosy after 6 weeks of MDT.

Discussion

The syndrome, DHS, is characterized by fever, skin rash, multiple organ involvement (predominantly hepatitis) and lymphadenopathy occurring anywhere from 6 hours to 12 weeks after start of treatment with dapsone.[3,5] However, patients may also present with nausea and vomiting, eosinophilia and leukocytosis, splenomegaly or other complications including pulmonary and cardiac manifestations and anemia.[3–5] DHS may resolve spontaneously or become fatal if not treated appropriately and promptly.[3,5]

In this case, the patient presented with exfoliative dermatitis of 3 weeks duration, evidence of hepatitis (jaundice, deranged liver function, hepatomegaly), splenomegaly, acute kidney injury (elevated blood urea nitrogen to creatinine ratio, mildly reduced EGFR) and severe anemia on admission with antecedent (6 weeks) dapsone history which prompted discontinuation of MDT. Despite the patient reporting for the purpose of collecting the second MDT blister, one week after he first noticed the skin symptoms, the exfoliative dermatitis went unnoticed.

Upon admission, two cardinal signs of DHS (ie, lymphadenopathy and fever, ranging between 37.8–39.9C) were absent, with fever developing later. This is not unusual as approximately 3% and 26% of DHS cases have no associated fever or lymphadenopathy respectively at the time of diagnosis.[3,5] Infections such as HIV, hepatitis B and C, and malaria were ruled out. The absence of the classical symptoms presenting all at once probably diverted attention from considering DHS as the main diagnosis.

Generally, diagnosis of DHS may be difficult because of the heterogeneity of clinical manifestations and laboratory abnormalities, its semblance to other infectious or immunologic diseases,[9,10] its long latency period[11] and the lack of a unified diagnostic tool or criteria.[3,11]

Treatment includes immediate withdrawal of the offending agent and initiation of systemic steroids if there is systemic involvement.[11,12] Although dapsone was immediately withheld on account of exfoliative dermatitis, and an initial 100mg bolus of intravenous hydrocortisone was administered as premedication for blood transfusion, the patient kept deteriorating. In such cases, the recommended dosage of systemic steroid is 1–2mg/kg body weight/day of prednisolone or its equivalent.[11] Also, additional intravenous immunoglobulin may be necessary to manage severe systemic involvement as observed in this patient.

While most patients improve once the culprit drug has been discontinued, some patients may experience worsening of symptoms for 3 to 4 weeks after the start of the reaction,[9] as also seen in this case. Furthermore, following discontinuation of dapsone, organs which were initially involved may deteriorate further while other organs that were previously unaffected may become involved in the reaction.[9]

DHS patients primarily die of liver failure but may also die from sepsis/shock, lung failure, multi-organ failure including bone marrow failure and myocardial infarction.[3,13] The here-presented patient had hepatitis and exfoliative dermatitis eventually covering more than 30% of the body surface area, tachycardia, tachypnoea (Systemic Inflammatory Response Syndrome) – all of which have been identified as poor prognostic factors in DHS.[3,5,11]

The anemia noticed in this patient is likely hemolytic evidenced by low HB, high indirect bilirubin and jaundice and associated with dapsone as well. Unfortunately, the diagnosis cannot be reached conclusively as more specific tests like reticulocyte count, LDH and haptoglobins were not done, in part due to lack of suspicion (normal urine color) and patient's failure to do the recommended test (FBC). Hemolytic anemia is caused by oxidative hemolysis in Glucose-6-Phosphate Dehydrogenase defective patients on dapsone, but has also been implicated in individuals without the defect who are on dapsone, and could therefore have been considered as well.[14,15]

We notice a quick progression of the disease resulting in death in just one week post admission (ie, four weeks after initial symptom). There were missed opportunities to detect exfoliative dermatitis during the review for the second MDT blister at 4 weeks after MDT initiation and to diagnose DHS on admission. The absence of a definitive diagnostic standard and the low awareness of current practicing healthcare workers for this rare yet severe disease may have contributed to these missed opportunities.[5] This case emphasizes the critical importance of timely diagnosis, prompt cessation of dapsone therapy, and initiation of appropriate steroids when necessary, as a delay in these measures can rapidly lead to fatal outcomes in DHS. It also draws attention to the need for a more comprehensive workup and a high index of suspicion in all patients receiving MDT who present with any of the classical symptoms of DHS. It is worth noting that the clinical manifestations described here could possibly also be those of rifampicin hypersensitivity, although this has been largely reported among TB patients on rifampicin and not leprosy patients.[16,17]

Recent studies in China reveal the prospects of HLA-B*13:01 screening in reducing the incidence of DHS.[5,18,19] Remarkably, in a prospective cohort study employing this genetic marker,[18] none of the patients who received dapsone after testing negative for HLA-B*13:01, developed DHS, in contrast to the historical 1% DHS rate observed in the same population without preceding HLA-B*13:01 testing.[19] Adopted as a preventive measure, this screening tool could potentially save lives. However, it remains to be evaluated in how far these findings are applicable to the African population.[5,19]

Conclusion

Early diagnosis is important to reduce mortality associated with DHS. It is therefore necessary to build the capacity of health-care professionals in leprosy care centers for early recognition of adverse reactions to drugs used in MDT,

counseling on potential adverse effects to patients taking dapsone and to provide required laboratory tests to help avoid developments such as those reported here. Some technical guidance and a standardized simple diagnostic criteria or test for DHS would be helpful in aiding the diagnosis of DHS in which symptoms do not occur concomitantly. This may be particularly important at peripheral levels where persons affected by leprosy tend to be treated, with referral systems strengthened to be able to escalate care to higher resource centers.

Abbreviations

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; DHS, dapsone hypersensitivity syndrome; EGFR, Estimated Glomerular Filtration Rate; FBC, Full Blood Count; GGT, gamma-glutamyl transaminase; HIV, human immunodeficiency virus; MDT, multidrug therapy.

Consent for Publication

Written informed consent for publication of the patient's clinical details and/or clinical images was obtained from the relative of the patient. A copy of the consent form is available for review by the Editor of this journal. Institutional approval for publication of case details was given by the management of the Ankaful Leprosy/ General Hospital.

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Disclosure

The authors report no conflicts of interest in this work.

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