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A rare case of Dapsone-induced agranulocytosis complicated by neutropenic sepsis

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Introduction

Leprosy is a curable disease. The currently recommended treatment regimen consists of three medicines, dapsone, rifampicin and clofazimine; and is referred to as multi-drug therapy (MDT). Dapsone, a critical drug in the MDT for leprosy, contain anti-inflammatory and antimicrobial properties. However, its therapeutic benefits are occasionally overcome by severe adverse effects, such as haemolytic anaemia, methemoglobinemia, and agranulocytosis (1). Agranulocytosis can rarely result in severe effects that lead to neutropenic sepsis due to immunocompromised state (2). Only a few dapsone related cases were reported in Sri Lanka (3). We illustrate a case of neutropenic sepsis due to dapsone, a medical emergency with high mortality unless managed swiftly.

Case presentation

A 38-year-old male with borderline tuberculoid leprosy, on MDT regimen of dapsone, clofazimine, and rifampicin for 2 months, presented with a fever, chills and rigors, sore throat, mouth ulcers, and a progressive decline in consciousness with altered behaviour over the preceding three days.

Further history revealed a low-grade fever for five (5) days with intermittent confusion prior to presentation. Systemic enquiry and travel history were otherwise unremarkable.

On examination, the patient was febrile (103^0 F) and was moderately pale, without icterus. A well-demarcated anaesthetic patch with biopsy scar mark (Figure 1) was noted on the right thigh. Examination of the throat revealed severe bilateral non-pustular tonsillitis with multiple aphthous ulcers (Figure 2).

There were no signs of peripheral neuropathies or lymphadenopathy. Cardio-respiratory examination showed, SpO_2 94% on room air with mild tachypnoea along with Hypotension (BP 90/60 mmHg) and tachycardia (120 BPM). Neurologically, he was confused and agitated with a GCS score of 13/15. Investigations were significant for WBC of 0.74 $\times 10^3/\mu L$ (neutrophils - 0.02), Hb of 8.8 g/dL (blood picture was not suggestive of haemolysis, retic count <1%) and CRP of 426 mg/L. VBG showed lactic acidosis (pH 7.2, HCO_3-17, Lactate: 6.1).

He was diagnosed with severe neutropenic sepsis complicated by possible delirium or meningo-encephalitis. He was Started initially on Intravenous (IV) Piperacillin- Tazobactam 4.5 g/8 hourly, Subcutaneous Granulocyte-Colony Stimulating Factor (G-CSF) 0.3 µg/daily (3 doses), strict monitoring, aggressive fluids resuscitation, nasogastric feeding and barrier nursing. With poor response to antibiotics and persistent fever spikes (Figure 3), he was transferred to the ICU.

The dapsone was discontinued on suspicion of drug-induced agranulocytosis, and he was started on prophylactic oral fluconazole 150mg daily, while rifampicin and clofazimine were continued. On Day-3, he experienced a generalised tonic-clonic seizure which was managed with IV Midazolam (5mg with 2 repeated doses in 5 minutes interval) The aetiology screen revealed only moderate hypocalcaemia (1.9 mmol/L) which was corrected, preventing further seizures. CSF analysis, imaging, extensive investigations, including complete viral panel and cultures, returned non-significant. Hypocalcaemia was thought to be critical illness related. Over five days of care, including a change in antibiotics to IV-linezolid 600 mg/12 hourly, followed by poor response to IV-vancomycin 1 g/12 hourly, his condition improved. By the Day-7, his FBC also improved (WBC - 20.89 $\times 10^3/\mu L$, Hb - 11.3 g/dL, platelets - $499 \times 10^3/\mu L$) with reduction in CRP (64 mg/L). He was discharged after 10 days of antibiotics with plans for follow-up in the dermatology. Early recognition, prompt drug discontinuation and aggressive management, are crucial for preventing life-threatening complications and ensuring patient recovery.

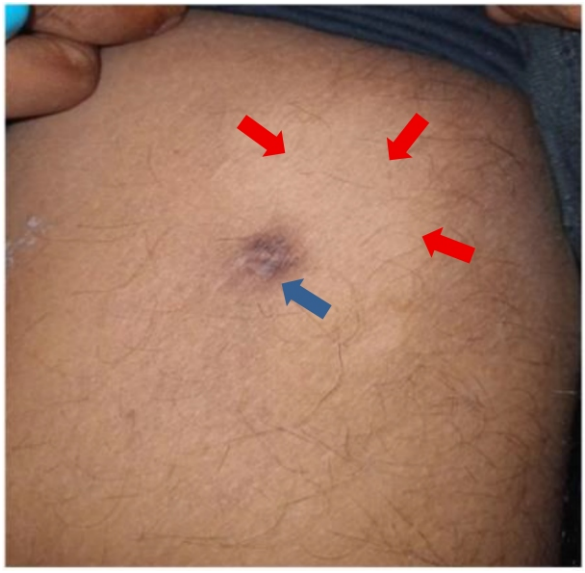

Figure 1: Anesthetic, Hypopigmented patch 7x8 mm (red arrows) with biopsy mark (blue arrow)

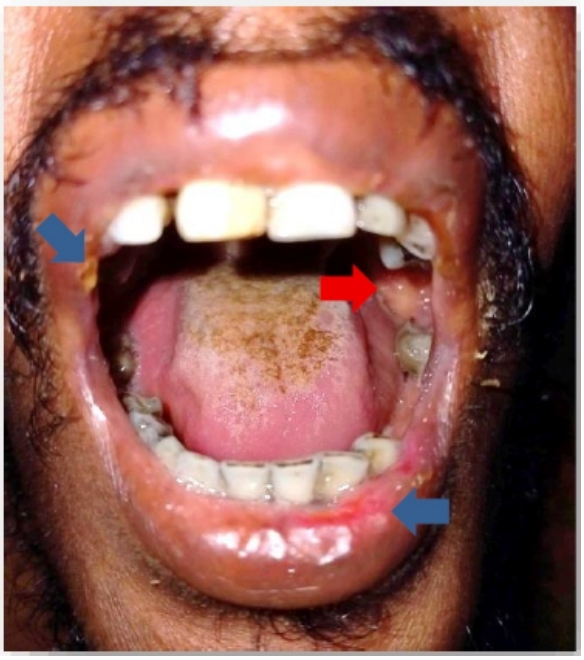

Figure 2: Bilateral non-pustular tonsillitis (red arrow) with multiple aphthous ulcers (blue arrows)

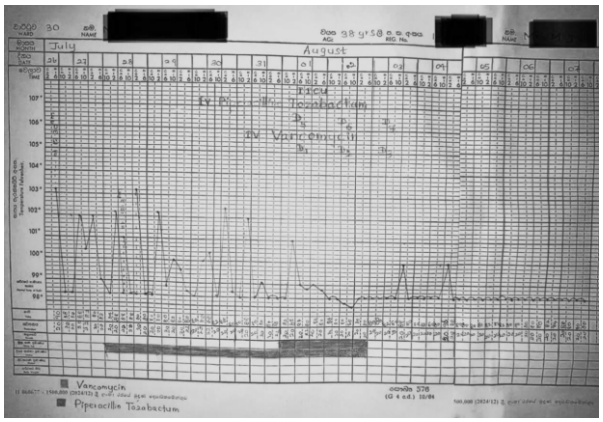

Figure 3: Fever chart of the patient showing fever spikes

Discussion

The initial diagnosis was severe neutropenic sepsis, likely secondary to pharyngitis, complicated by possible meningoencephalitis. On suspicion of drug induced agranulocytosis, the culprit drug has been discontinued.

Therapeutic benefits of dapsone are occasionally overcome by severe adverse effects, such as haemolytic anaemia, methemoglobinemia, and

agranulocytosis (1). Agranulocytosis, defined by an absolute neutrophil count (ANC) of less than 500 cells/μL, can lead to severe immunosuppression. The exact mechanism of dapsone-induced agranulocytosis remains unclear, but immune-mediated destruction of neutrophils with bone-marrow suppression is suspected (4). This is an idiosyncratic reaction may involve the formation of antibodies against neutrophils or their precursors, leading to their rapid depletion. The onset of agranulocytosis can be sudden, often presenting within the first few weeks to months of therapy (5,6). It is a life-threatening condition characterised by fever and severe neutropenia and impairs the immune system's ability to combat infections, particularly bacterial infections depicted in many international case reports (3,7,8). Early recognition, prompt drug discontinuation and aggressive management, are crucial for preventing life-threatening complications and ensuring patient recovery.

In similar cases, Initiation of broad-spectrum antibiotics along with escalation to broader Gram-positive, Gram negative and MRSA coverage signify the aggressive management even in the absence of CSF and blood culture positivity. The seizures in this patient were likely to be multifactorial, yet critical illness hypocalcaemia was considered as the most plausible aetiology which may have resulted from sepsis-induced parathyroid dysfunction, acute kidney injury, and the effects of medications on calcium homeostasis. (9, 10). As in this case, earlier discontinuation dapsone and initiation of granulocyte-colony stimulating factor (G-CSF) were pivotal in reversing the neutropenia and promoting haematologic recovery (11).

Conclusions

Dapsone induced agranulocytosis complicated by sepsis is rare yet fatal and needs early identification, meticulous collaborative management approach for favourable outcomes.

Informed consent has been obtained from the patient to publish this case report with photographs.

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References

1. Pavithran K. Dapsone syndrome. *Indian J Dermatol Venereol Leprol.* 1996;62(2):97-100. https://ijdvl.com/article.asp?issn=0378-6323;year=1996;volume=62;issue=2;spage=97;epage=100;aulast=Pavithran.

2. Coleman MD, Norris RL, Coleman NA. Dapsone toxicity: Some new issues and solutions. *Arch Toxicol.* 1996; **70**(9): 604-609. DOI: 10.1007/s002040050317.

3. Mahesh G, Dissanayake M, Herath P, Rathnayake S, Nuwan R, Perera G. A case of dapsone-induced severe agranulocytosis causing life-threatening skin sepsis in a Sri Lankan child with borderline leprosy: A success story. *Case Rep Med.* 2019;2019:2314379. DOI: 10.1155/2019/2314379.

4. Vora SB, Englund JA. Neutropenia in pediatric patients treated with dapsone. *J Pediatric Infect Dis Soc.* 2015; **4**(3): 259-66. DOI: 10.1093/jpids/piu063.

5. Liangpunsakul S, Jeffers LJ, Reddy KR. Dapsone-induced agranulocytosis in a patient with dermatitis herpetiformis. *Am J Gastroenterol.* 2001; **96**(11): 3335-3337. DOI: 10.1111/j.1572-0241.2001.05352.x

6. Buckley MF, Glare EM, Bourke JF, Glare PA. Dapsone-induced agranulocytosis: Early diagnosis and treatment. *Med J Aust.* 1997; **167**(7): 403-404. DOI: 10.5694/j.1326-5377.1997.tb138726.x

7. Kobe A, Pereira N, Verma S. Severe agranulocytosis induced by dapsone in a patient with leprosy: A case report. *J Med Case Rep.* 2011; **5**: 107. DOI: 10.1186/1752-1947-5-107.

8. Raheem JA, Unnisa A, Iqubal M. Dapsone as a detrimental cause of necrotizing fasciitis with severe resistant neutropenia: A case report. Cureus. 2022; **14**(4): e23076. DOI: 10.7759/cureus.23076.

9. Kelly A, Levine MA. Hypocalcemia in the critically ill patient. *J Intensive Care Med.* 2013; **28**(3): 166-77. DOI: 10.1177/0885066612436618.

10. Sculier C, Gaspard N. Electrolyte disturbances and critical care seizures. In: Seizures in Critical Care: A Guide to Diagnosis and Therapeutics. 2nd ed. Springer; 2017; p. 291-310. DOI: 10.1007/978-3-319-49557-6_18.

11. Ahlawat G, Asthana U, Ahlawat MS, Kshetrapal K, Taxak S, Bansal T. Filgrastim: A saviour in a patient having sepsis with refractory neutropenia in ICU. *J Assoc Physicians India*. 2014; **62**:579-81. https://www.japi.org/w27454/filgrastim-a-saviour-in-a-patient-having-sepsis-with-refractory-neutropenia-in-icu.