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ORIGINAL ARTICLE

A case of Dapsone-induced Haemolytic Anaemia without glucose-6-phosphate dehydrogenase deficiency "mind the bite"

Tiago Ramalho, Diana Rocha, Pedro Andrade, Yuliana Eremina

Introduction: Some drugs induce haematotoxicity as a consequence of increased oxidant stress, especially in susceptible patients, namely those with glucose-6-phosphate dehydrogenase deficiency. Less commonly, it occurs in non-deficient individuals, as we report in this case.

Case report: A patient with a dermatological condition (and multiple comorbidities), being treated with dapsone, is hospitalized due to sepsis with multiorgan dysfunction, including anaemia and thrombocytopaenia. After a good initial response, the haematological dysfunction worsens, suggesting more contributing factors other than the initial septic insult.

Conclusion: It is essential to establish a broad evaluation of each patient, considering a careful review of their past medical history, multiple comorbidities and associated medications. A multidisciplinary discussion can assist in better diagnosis and follow-up of patients. In this particular case, the peripheral blood smear and biochemistry findings were crucial clues to establish the diagnosis.

Tiago Ramalho, MD
Clinical Pathology Department,
Matosinhos Local Healthcare Unit,
Porto, Portugal

Diana Rocha, MD
Medicine Department,
Matosinhos Local Healthcare Unit,
Porto, Portugal
https://orcid.org/0000-0002-1284-2294

Pedro Andrade, MD
Dermatology Department,
Matosinhos Local Healthcare Unit,
Porto, Portugal

Yuliana Olegovna Eremina , MD, PhD
Clinical Pathology Department,
Matosinhos Local Healthcare Unit,
Porto, Portugal
https://orcid.org/0000-0002-3656-7266

Haemolytic anaemia (HA) in a patient with multiple comorbidities and polymedicated should always raise suspicion for drug-related adverse effects.[1] The mechanisms by which drugs can induce haemolysis varies: for example, some antibiotics, non-steroidal anti-inflammatory drugs, analgesics and anti-cancer drugs prompt autoimmune HA, some medications cause thrombotic microangiopathy and other induce an exacerbation of oxidative stress or methaemoglobinemia, in which dapsone is included.[2]

CASE REPORT

We report the case of a 75-year-old female, cognitively intact but with multiple medical comorbidities, namely cardiovascular (essential hypertension with hypertensive heart disease), metabolic (obesity and Type 2 diabetes mellitus, with end-organ damage), renal (nephropathy of diabetic/hypertensive etiology with chronic kidney disease at KDIGO stage 3b) and immunological (euthyroid chronic autoimmune thyroiditis). The patient was originally diagnosed with pemphigus foliaceus in Dermatology consultation. She started lepicortinolone at that time at a dose of 60 mg for 2 weeks, but after initial partial clinical improvement, there was systematic recurrence on weaning. Several months afterwards she developed marked worsening and progression of the lesions to the anterior thorax, abdomen, shoulders, external genital region, face, ears, accompanied by severe itching, marked insomnia, and uncontrollable diabetes secondary to corticosteroid treatment. For these reasons, she came to the emergency department and was hospitalized to complete aetiologic study and have a proper medical approach. On discharge, dapsone was introduced, 100 mg and then 50 mg every other day (after being excluded glucose-6-phosphate dehydrogenase (G6PD) deficit), desloratadine, and prednisolone 40 mg. In baseline analytical terms, she had hemoglobin (Hb) of 12 g/dL (normal (N) 12 – 16), normal liver function tests and serum creatinine of 1.5 mg/dL (N 0.6 – 1.1).

Two weeks after being discharged, she presented to the emergency department with a history of fever and altered mental status in the last two days. After evaluation and study, she was admitted again, with a diagnosis of sepsis starting in acute pyelonephritis, with associated multiorgan dysfunction: volume-refractory hypotension requiring vasoactive agents, need for non-invasive ventilation, acute kidney injury (with a serum creatinine peak of 2.28 mg/dL). Further evaluation revealed elevated inflammatory parameters (c-reactive protein of 361 mg/L (N < 5) and procalcitonin of 25.5 ng/mL (N < 0.5)), anaemia (11 g/dL on admission) and thrombocytopaenia (115 000/uL; N 150 000 – 400 000). Treatment was empirically initiated with piperacillin/tazobactam. The initial blood cultures showed growth of Gram-negative bacilli, identified to be E. coli resistant to amoxicillin/clavulanic-acid, ampicillin and cefuroxime, and sensitive to ceftazidime and piperacillin/tazobactam, so the antibiotherapy was switched to ceftazidime. In the first days, she evolved favorably concerning all the dysfunctions initially presented, except for the haematological one – there was a progressive worsening of the anaemia (up to a minimum Hb value of 7.1 g/dL). In this context, the peripheral blood smear was meticulously reviewed, revealing the presence of keratocytes and "mushroom" cells (Figure 1A and 1B). Given these findings, the analytical study was extended, revealing 5% of reticulocytes (N 0.5 – 2.0), Heinz bodies (Figure 1C and 1D), lactate dehydrogenase of 374 U/L (N 125 – 220), total bilirubin of 2.4 mg/dL (N 0.2 – 1.2) at the expense of nonconjugated fraction and undetectable haptoglobin, findings that favored the hypothesis of haemolytic anaemia. A direct Coombs test was performed, which was negative, excluding autoimmunity as the cause of haemolysis. To perform

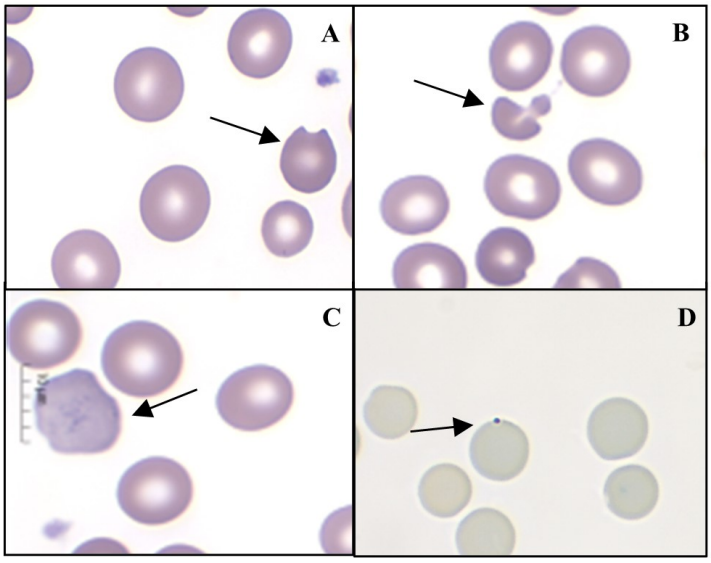

Figure 1 *Blood smear of the patient, x1000, May-Grunwald-Giemsa coloration (A–C) and new methylene blue coloration (D): A – keratocyte (bite cell); B – "mushroom" cell ("pincer" cell); C – polychromatophile; D – Heinz body.*

a biopathological validation of the laboratory results, the clinical file was reviewed, including all the medications she was taking at the time of admission. The hypothesis of an iatrogenic etiology for these haematological findings due to dapsone was placed and, accordingly, methemoglobin was measured – which would be increased (7.1%; N 0.4 -1.5). It was also verified that, besides not having G6PD deficit, the patient did not have a haemoglobinopathy either. Dapsone was discontinued, resulting in an increase in Hb up to 10 g/dL, which also corroborates dapsone being the cause of these haematological alterations.

DISCUSSION

This clinical case reveals the importance of a holistic assessment of each patient. Even though the initial haematological disorders observed could have been justified by the septic condition, the persistent single dysfunction after significant general improvement, motivated the consideration of other etiological factors.

Dapsone is a synthetic sulfone, belonging to the class of antibiotics, used to prevent and treat some infectious and inflammatory diseases. Currently, its use is more related to the treatment of some dermatological conditions and as a second-line option in the prophylaxis of Pneumocystis jirovecii-pneumonia.[2] After being metabolized in the liver by cytochrome p450, its active metabolites (hydroxylamines) are responsible for inducing not only its therapeutic effects but also adverse effects, the most frequent being nausea, loss of appetite, and haematotoxicity (manifested mainly by methemoglobinemia and haemolytic anaemia). Methemoglobinemia occurs in about 15% of patients and haemolysis in about 20%. These effects are dose-dependent.[3]

The main mechanism involved in developing haematotoxicity is oxidative stress, exacerbated in patients with G6PD deficit or Hemoglobin H disease, since they have decreased natural antioxidant defenses, and are, therefore, more sensitive to oxidative processes. Thus, it is always recommended to study the G6PD activity before the initiation of treatment with dapsone. However, there are several described cases in the literature of patients who, even in the absence of a deficit related to the G6PD enzyme or haemoglobinopathies, ended up developing serious cases of haematological dysfunction associated with dapsone therapy, in different clinical contexts.[4-8]

This case also demonstrates how, given certain findings, the clinical process review and a timely extension of the analytical study during the bio-pathological validation of the laboratory results can be beneficial for a patient diagnosis. Thus, clinical-laboratory communication and joint case discussions can help to a quick and efficient confirmation of an eventual hypothesis.

CONCLUSION

When suspecting the presence of HA, it is mandatory to perform a peripheral blood smear for the evaluation of red cell morphology. The findings should give some clues about the possible mechanism of haemolysis. Also, in polymedicated patients, it is crucial to perform a complete review and suspect if any of the drugs could be the cause of haematotoxicity. Even in patients with a plausible etiology for the presence of anaemia, it is important to consider secondary causes that might contribute to the progressive worsening conditions.

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