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Clinical Case

Methemoglobinemia as an adverse effect of the treatment for leprosy: case report

Metemoglobinemia como efeito adverso do tratamento para hanseníase: relato de caso

Metahemoglobinemia como efecto adverso del tratamiento de la lepra: informe de caso

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Abstract

Introduction: Leprosy treatment consists of a multidrug therapy regimen with the following drugs: Rifampicin, Dapsone, and Clofazimine. Among the side effects, methemoglobinemia results from the use of Dapsone and requires special attention, as it leads to the need to discontinue the medication and, in severe cases, hospitalization. It is a rare complication, on which there is hemoglobin anomaly, which makes it impossible to capture and release oxygen. It is caused by the action of Dapsone when administered in doses and duration beyond the recommended ones. The presence of cyanosis, low oxygen saturation, and dyspnea on exertion stand out as signs and symptoms, although the PaO_2 is within the reference values. The diagnosis of methemoglobinemia is performed by co-oximetry. Patients with cyanosis or symptoms of hypoxemia, with sufficiently high PaO_2, are highly suspicious. **Case presentation:** A case of methemoglobinemia identified in Primary Health Care (PHC) during a treatment for leprosy is presented, which required meticulous management, culminating in the suspension of multidrug therapy, with resolution of the adverse event. **Conclusions:** The strict clinical follow-up by the PHC during the treatment of leprosy allows the early recognition of possible adverse effects of multidrug therapy as well as the adoption of the necessary measures.

Keywords: Leprosy; Dapsone; Methemoglobinemia; Adverse event; Case reports.

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Resumo

Introdução: O tratamento da hanseníase consiste em um regime de poliquimioterapia com as seguintes drogas: Rifampicina, Dapsona e Clofazimina. Entre os efeitos colaterais, a metemoglobinemia decorre do uso da Dapsona e requer atenção especial, pois enseja a necessidade de suspensão da medicação e, em casos graves, de internação hospitalar. Trata-se de uma complicação rara, na qual ocorre uma anomalia da hemoglobina, que impossibilita a captação e a liberação de oxigênio. É provocada pela ação da Dapsona, quando administrada em quantidade e em duração além das recomendadas. Destacam-se como sinais e sintomas a presença de cianose, baixa saturação de oxigênio e dispneia aos esforços, embora a PaO_2 esteja de acordo com os valores de referência. O diagnóstico da metemoglobinemia é realizado pela co-oximetria. Pacientes com cianose ou sintomas de hipoxemia, com PaO_2 suficientemente alta, apresentam elevada suspeição. **Apresentação do caso:** Apresenta-se um caso de metemoglobinemia identificado na Atenção Primária à Saúde (APS) durante um tratamento de hanseníase, que exigiu condução minuciosa, culminando na suspensão da poliquimioterapia, com resolução do evento adverso. **Conclusão:** O acompanhamento clínico rigoroso pela APS durante o tratamento da hanseníase possibilita o reconhecimento precoce de eventuais efeitos adversos da poliquimioterapia, bem como a adoção das devidas medidas.

Palavras-chave: Hanseníase; Dapsona; Metemoglobinemia; Evento adverso; Relatos de casos.

Resumen

Introducción: El tratamiento de la lepra consiste en un régimen de poliquimioterapia con los siguientes fármacos: Rifampicina, Dapsona y Clofazimina. Entre los efectos secundarios, la metahemoglobinemia resulta del uso de Dapsona y requiere atención especial, ya que conlleva la necesidad de suspender la medicación y, en casos graves, la hospitalización. Es una complicación rara, en la que existe una anomalía de la hemoglobina, que imposibilita la captación y liberación de oxígeno. Es provocada por la acción de la Dapsona, cuando se administra en cantidad y duración superiores a las recomendadas. Los signos y síntomas son cianosis, baja saturación de oxígeno y disnea a mínimos esfuerzos, aunque la PaO_2 está dentro de los valores de referencia. El diagnóstico de metahemoglobinemia se realiza por cooximetría. Los pacientes con cianosis o síntomas de hipoxemia, con PaO_2 suficientemente elevada, presentan alta sospecha. **Presentación del caso:** Se presenta un caso de metahemoglobinemia identificado en Atención Primaria de Salud (APS) durante un tratamiento por lepra, que requirió una conducta exhaustiva, culminando con la suspensión de la poliquimioterapia con resolución del evento adverso. **Conclusiones:** El estricto acompañamiento clínico por parte de la APS durante el tratamiento de la lepra permite el reconocimiento precoz de los posibles efectos adversos decurrentes de la poliquimioterapia, así como la adopción de las medidas necesarias.

Palabras clave: Lepra; Dapsona; Metahemoglobinemia; Evento adverso; Informes de casos.

INTRODUCTION

Leprosy is an infectious disease caused by *Mycobacterium leprae*, primarily affecting the skin and peripheral nerves.[1] The clinical spectrum varies depending on the individual's immune response to the etiologic agent.[2] This disease has a global impact and is increasingly becoming a significant public health concern in Brazil, ranking second in the world for the number of cases, second only to India.[3] Also known as Hansen's Disease (HD), the disease has, among its classifications, a simplified version proposed by the World Health Organization (WHO) for therapeutic purposes. This classification, based on bacillary load and number of lesions, divides the disease into paucibacillary (PB), when there are no bacilli in the skin smear and the presence of only one to five skin lesions, and multibacillary (MB), when there are more than five lesions, nerve involvement, or proven presence of bacilli in a skin smear.[4]

The treatment recommended by the WHO for the disease consists of a polychemotherapy (PQT) regimen containing three drugs: Rifampicin, Dapsone, and Clofazimine. The duration of treatment depends on its classification: six months for patients with paucibacillary HD (PB-HD) and 12 months for multibacillary cases (MB-HD).[4] Although adverse events to PQT are not frequent and, when present, are well tolerated by users,[5] it is important that health teams be aware of them, so that there can be early identification and intervention. Among the side effects, the presence of methemoglobinemia, resulting from the use of

Dapsone, must be promptly identified, as this condition may lead to the need to discontinue the medication or, even in severe cases, to be referred to hospital admission.[5]

The present report describes the case of a patient being treated for leprosy, experiencing adverse effects to Dapsone, and the subsequent conduct of the health team responsible for her care.

There are limited reports in the literature regarding complications associated with leprosy treatment in Primary Health Care (PHC), underscoring the need to share noteworthy cases to facilitate knowledge dissemination.

CASE PRESENTATION

V.S.P., a 57-year-old woman, attended an appointment in June 2021 with her family doctor (FD), who had recently joined the Family Health team that assisted her, to follow up on her leprosy treatment.

The patient reported having been diagnosed with HD ten months earlier at a dermatology reference center. Since then, she had been under treatment and has completed ten supervised doses of the therapeutic regimen, with the plan to fulfill the total of 12 doses as outlined in the MB-HD schedule.

The patient had a single hypochromic and hypoesthetic macule on her right scapular region, which was biopsied at the time of diagnosis.

During the appointment, the patient mentioned experiencing dyspnea on exertion, particularly when ascending mild slopes. However, she denied experiencing any other associated symptoms such as cyanosis, cough, or chest pain. In addition, she reported no other morbidities or allergies. Regarding medications, she stated that she only uses PQT.

Upon physical examination, the patient was pale (+/4+), acyanotic, eupneic, with no signs of respiratory distress, no changes in heart and lung auscultation, and no nail clubbing. She had a blood pressure of 120×80 mmHg, a pulse of 80 bpm and a peripheral oxygen saturation (SpO_2) of 90% in ambient air (measured on a nail without enamel, with the patient's extremities heated, using two different pulse oximeters, with appropriate plethysmographic waves). At the time she had a suspicion of hypoxemia.[6]

She brought tests collected two days before treatment, whose results were: hemoglobin (Hb)=10.5 g/dL; hematocrit (Ht)=32.9%; mean corpuscular hemoglobin (MCH)=32 pg; mean corpuscular volume (MCV)=100 fL; degree of anisocytosis (red cell distribution width – RDW)=16.5%; leukocytes=8.100/μL; platelets (Pt)=257,000/μL; creatinine (Cr)=0.83 mg/dL; glutamic oxaloacetic transaminase (GOT)=25.7 U/L; glutamic pyruvic transaminase (GPT)=24 U/L; thyroid-stimulating hormone (TSH)=3.71 μIU/mL. According to the tests, the patient had macrocytic anemia (Hb<12 g/dL for women and MCV>98 fL).[7]

In light of this, her FD requested other tests for the causal investigation of macrocytic anemia and to confirm hypoxemia. Furthermore, the patient was asked to provide all documents issued and/or tests conducted at the time of diagnosis. This request aimed to understand the rationale behind undergoing treatment for MB-HD, particularly considering that the patient presented with only one skin lesion and lacked peripheral nerve involvement, which would typically suggest a treatment approach such as PB.

The patient returned for another appointment after four days, carrying everything that had been requested.

The tests performed at the request of the FD were collected two days before the return, the results of which were: Hb=9.4 g/dL; Ht= 30.3%; MCH=30.8 pg; VCM=99.3 fL; RDW=16.4%; leukocytes=5,380/μL; Pt=254,000/μL; total bilirubin=0.65 mg/dL; direct bilirubin=0.28 mg/dL; indirect bilirubin=0.37 mg/dL; erythrocyte sedimentation rate (ESR)=15 mm; reticulocytes=127,000 /μL (corrected reticulocyte

count=3.18%); ferritin=605 ng/mL; iron=125 mcg/dL; transferrin saturation index (TSI)=58.11%; folic acid=6.87 ng/mL; vitamin B12=150 pg/mL; arterial blood gas test: pH=7.38; $PaCO_2$=36.2 mmHg; PaO_2=102 mmHg; BE=-3.9 meq/L; HCO_3=20.8 mEq/L; SaO_2=94.7%.

Based on the new tests, anemia worsened (Hb decreased from 10.5 to 9.4 g/dL), associated with an increase in the absolute number (>100,000/μL)[8] and the relative number of reticulocytes (>2%)[9], which demonstrates hyperproliferative anemia. There was also a reduced dosage of vitamin B12 (<200 pg/mL).[7] As there were no clinical signs of acute blood loss and laboratory signs of iron deficiency, the main causal hypothesis for hyperproliferative anemia was hemolysis. The evidenced macrocytosis could be caused both by hemolysis and by a deficiency of B12.

The arterial blood gas test showed slightly reduced arterial oxygen saturation (normal SaO_2 ≥95%) with blood oxygen pressure as expected (adequate PaO_2 ≥80 mmHg).[10] The divergence between the oxygenation values measured by arterial blood gas test and pulse oximetry and the presence of signs and symptoms of hypoxemia with normal blood oxygen raised the suspicion of methemoglobinemia.[11]

The patient also brought an intradermal scraping bacilloscopy performed at the time of diagnosis, which had a bacilloscopic index (BI)=00, and the histopathological evaluation of the skin lesion, performed in August 2020, which demonstrated a mononuclear inflammatory infiltrate with the formation of subepidermal and perianexial epithelioid granulomas, with a negative test for mycobacteria using the Fite-Faraco histochemistry method, which does not rule out paucibacillary forms of leprosy.

Based on the test results and the clinical features presented by the patient, the doctor diagnosed her with PB-HD. This diagnosis was further supported by a counter-referral from the Dermatology Department, where the diagnosis was initially made in October 2020. The document provided by the patient explained the diagnosis of tuberculoid leprosy and proposed a paucibacillary treatment lasting six months.

Due to the patient's suspected development of hemolytic anemia and methemoglobinemia due to Dapsone, coupled with the assurance that she had completed the requisite treatment for PB-HD (six supervised doses), it was then decided to discontinue PQT and formally discharge the patient, indicating successful completion of leprosy treatment. In response, B12 and folic acid replacements were prescribed and control tests were requested.

Upon returning, three months later, the patient presented no complaints, referring to the resolution of the dyspnea on exertion. The physical exam was unchanged, with SpO_2 of 97%. The complementary tests, taken one week before the appointment, showed Hb=13.6 g/dL; Ht= 41.3%; MCH=28.2 pg; MCV=85.7 fL; RDW=15.1%; reticulocytes=87,200/μL (1.8%); vitamin B12=400 pg/mL.

DISCUSSION

PHC serves as an individual's initial interface with the health system, providing comprehensive and highly effective care for major health issues. Therefore, it plays a crucial role in the strategy for leprosy care.[12]

Thus, PHC professionals must be able to recognize the signs and symptoms of the disease, define its classification, indicate the appropriate therapeutic regimen, and monitor the response to treatment and the side effects of PQT.[12]

Therefore, it is essential that these professionals observe the proposed changes in the management of HD cases such as those that had occurred recently in Brazil.[13]

Although the WHO[4] has recommended treatment for both forms of HD with Rifampicin, Dapsone, and Clofazimine since 2018, in Brazil this standardization only occurred as of 2021.[13] Previously, treatment

for PB was performed with only two drugs (PQT-PB) and for MB, with three drugs (PQT-MB). The change in the treatment of PB-HD, currently carried out with three drugs, may have confused the attending health team, who believed it was PQT-MB due to the use of a triple scheme. Professionals should then be aware of the updated recommendations to prevent iatrogenesis, as in the presented case.

The treatment for leprosy in adults currently recommended by the Brazilian Ministry of Health[5] involves the administration of Rifampicin 600 mg once a month; Clofazimine 300 mg once a month and 50 mg once a day; and Dapsone 100 mg once a day (PQT-U). Treatment time varies depending on the presentation of the disease: six months for cases of PB-HD, with six supervised doses administered up to nine months; and 12 months for MB, with 12 doses up to 18 months.[5] Pharmacovigilance after the introduction of PQT-U is essential to ensure the monitoring of adverse events.[4]

Among the range of side effects described for these drugs, Azulay[14] cites the following: for Rifampicin, hepatitis, flu-like syndrome, thrombocytopenia, skin rash, shock, and kidney failure; for Clofazimine, skin and mucosal pigmentation, skin dryness that may progress to ichthyosis, abdominal pain and decreased peristalsis; and for Dapsone, gastritis, acrocyanosis, hemolytic anemia, methemoglobinemia, photodermatitis, Stevens-Johnson syndrome, exfoliative dermatitis, erythroderma, sulfone syndrome, and peripheral motor neuropathy.

Dapsone is the drug in the regimen that requires the most attention from health professionals, as it has potentially serious adverse effects.[15] Its metabolites can lead to oxidative stress[16] and, consequently, hemolysis.[17] According to the Ministry of Health,[15] if patients using Dapsone have bleached mucous membranes, with weakness and tachycardia, they are likely to have hemolytic anemia. In such cases, tests are required to confirm the diagnosis, and the administration of folic acid and complex B is recommended, as was the case in the reported scenario.

Another dreaded effect of Dapsone is methemoglobinemia, which should be suspected in patients who experience symptoms such as shortness of breath and cyanosis of the extremities during its use.[15]

Methemoglobinemia is characterized as a clinical syndrome caused by an increase in the concentration of methemoglobin (MetHb) in the blood, occurring both due to congenital changes and exposure to various chemical agents. MetHb is an aberrant state of hemoglobin, in which the ferrous ions (Fe^{++}) of the heme are oxidized to the ferric state (Fe^{+++}), making these molecules unable to bind reversibly to oxygen. This is an unusual and potentially serious condition.[18]

The acquired form of methemoglobinemia is the most common, provoked by agents that cause significant oxidative stress in the cells. Drugs, such as lidocaine, benzocaine, amyl nitrate, sulfonamides, and chloroquine, as well as environmental agents (industrial nitrates and pesticides), are examples of triggers.[19]

The diagnosis of methemoglobinemia should be considered in patients with central cyanosis and a low SpO_2 reading. The arterial blood analysis shows a sufficiently high PaO_2, with normal SaO_2, at values above those indicated by the pulse oximeter,[20] as the latter method is unable to capture hemoglobin in its oxidized form.[11] The gold standard for the diagnosis of methemoglobinemia is co-oximetry, capable of measuring the concentration of different types of blood hemoglobins using spectrophotometry.[20]

Treatment in asymptomatic patients may consist only of simple measures such as removing the triggering agent. Conversely, in symptomatic patients, the administration of supplemental oxygen and methylene blue may be indicated.[19]

Despite the strong clinical suspicion of methemoglobinemia at the PHC level, the gold standard for diagnosing this pathology was not available, which weakened the case report.

Conversely, the case urges the reader to seek updates on the therapeutic changes of the most prevalent diseases in PHC while advising them on the identification of adverse effects of the treatment of these pathologies, increasing the resolution of this level of care.

CONCLUSIONS

The present report reinforces the importance of PHC and the FD in the care of the main health conditions, including diseases such as leprosy.

PHC, as the primary level of care emphasizing continuity and relationship-building, facilitates early identification and effective treatment of complications, thereby minimizing risks for patients.

The FD, through the integration of health promotion, protection, and recovery efforts, prioritizes a person-centered approach and cultivates strong doctor-patient relationships. As a distinctive professional within the realm of PHC, the FD provides care with a high level of quality and problem-solving capacity.

CONFLICT OF INTERESTS

Nothing to declare.

AUTHORS' CONTRIBUTIONS

HPL: Conceptualization, Data Curation, Methodology, Project administration, Supervision, Writing – review & editing. FLOA: Formal analysis, Investigation, Visualization, Writing – original draft. MSB: Formal analysis, Investigation, Visualization, Writing – original draft. TAS: Formal analysis, Investigation, Visualization, Writing – original draft. MMC: Formal analysis, Investigation, Visualization, Writing – original draft. RAO: Formal analysis, Investigation, Visualization, Writing – original draft. MMN: Formal analysis, Investigation, Visualization, Writing – original draft. All authors approved the final version and agreed to report on all aspects of the study.

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