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LETTER TO THE EDITOR

Severe rifampicin-induced thrombocytopenia in a patient with miliary tuberculosis

Tuberculosis is a potentially treatable infectious disease caused by *Mycobacterium tuberculosis* Complex. Pulmonary presentation is the most frequent, with non-pulmonary forms being more commonly observed in children and immunocompromised patients. Tuberculosis remains a major public health problem in Portugal, although its incidence has been decreasing (15,6 cases/100,000 inhabitants, according to the Portuguese National Statistical Institute, 2017). Newly diagnosed tuberculosis patients are empirically treated with a combination of four drugs: isoniazid, rifampicin, pyrazinamide and ethambutol.[1] No antituberculous drug is free of risk, and the World Health Organization (WHO) recommends monitoring and reporting suspected or confirmed adverse drug reactions (ADR) caused by antituberculous drugs.[2] Most ADR are benign, result from inherent toxicity to the drug and can be minimized by dosage adjustment, exposure duration reduction or by vitamin supplementation.[3] Less frequently, ADRs are immune-mediated and can present as cutaneous, hematological or systemic manifestations. These are rarer and more unpredictable, imposing both diagnostic and therapeutic challenges.[4] Rifampicin, one of the most important antituberculous agents, is a well-tolerated and effective drug. Most frequent adverse reactions to rifampicin (Table 1) include gastrointestinal effects, cutaneous reactions, hepatotoxicity and flu-like syndrome. Immunological reactions, such as hemolytic anemia, agranulocytosis and thrombocytopenia, are less frequent.[3] Immune-mediated thrombocytopenia induced by rifampicin, first described in 1970, is a potentially fatal ADR. It is characterized by rapid platelet destruction following drug administration in susceptible individuals and occurs more frequently in situations of intermittent administration or reintroduction after a period of discontinuation.[5]

The authors report a clinical case of a 60-year-old male patient with ulcerative colitis who maintained active disease, even after corticosteroid and azathioprine therapy. Biological therapy with an anti-TNF-α was started, after exclusion of latent tuberculosis. Approximately 4 months later he presented anorexia, night sweats and weight loss. Laboratory results showed hemoglobin 10,4 g/dL, lymphocytes 300/μL, sodium 132 mEq/L, lactate dehydrogenase 426 U/L, C-reactive protein 153 mg/L, negative IGRA test and HIV serology. CT-scan showed scattered micronodules in the pulmonary parenchyma, a necrotic mediastinal adenopathic conglomerate, a necrotic hilar adenopathy and homogenous hepatosplenomegaly. As the patient presented no cough, a bronchoalveolar lavage was collected, which was positive for acid-fast bacilli. The nucleic acid amplification test detected the presence of *Mycobacterium tuberculosis* Complex and a definitive diagnosis of miliary tuberculosis was established. First-line antituberculous drugs (isoniazid, rifampicin, pyrazinamide, ethambutol) were initiated, with good tolerance. On the 15th day of therapy, laboratorial findings showed increased transaminases (AST 329 U/L, ALT 270 U/L) and hyperbilirubinemia (total bilirubin 2,15 mg/dL), which determined the temporary suspension of the antituberculous agents. After normalization, antituberculous drugs were sequentially reintroduced according to the following scheme: amikacin, levofloxacin and pyrazinamide; subsequently introduced ethambutol, with suspension of amikacin; subsequently added rifampicin. About 6 days after rifampicin reintroduction, an abrupt drop of platelet count from $241 \times 10^3/\mu L$ to $2 \times 10^3/\mu L$ occurred, with associated epistaxis. The antiplatelet antibody test was negative and other possible causes of thrombocytopenia were excluded. Severe thrombocytopenia induced by rifampicin was assumed and the drug was discontinued. After platelet transfusion and methylprednisolone pulses, the platelet count returned to normal values. The patient was discharged to the Center for Pneumological Diagnosis, medicated with levofloxacin, ethambutol, pyrazinamide and isoniazid. After that, *Mycobacterium tuberculosis* Complex isolated from the sputum cultural exam showed resistance to isoniazid and pyrazinamide, and the therapeutic regimen was changed to levofloxacin, ethambutol, cycloserine and clofazimine, for 12 months.

Immunocompromised patients and intermittent treatment, as was the case of this patient, are predisposing factors for hypersensitivity reactions to antituberculous agents.[4] The mechanisms responsible for it are not yet fully identified, but it is known that they are based on an immunological mechanism: rifampicin is thought to bind non-covalently to the platelet membrane glycoproteins, causing conformational changes in the glycoprotein Ib/IX complex, and increasing the affinity of pre-existing natural antibodies (present in low concentrations and with low affinity in the absence of this drug), with consequent platelet

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Table 1 Frequency of the adverse events to rifampicin (Adapted).[7]

System organ class	Frequency	Adverse events
Infections	Unknown	Pseudomembranous colitis; Influenza
Blood system disorders	≥1% and <10%	Thrombocytopenia
	≥0,1% and <1%	Leukopenia
	Unknown	Disseminated intravascular coagulation; Eosinophilia; Agranulocytosis; Hemolytic anemia
Immune system disorders	Unknown	Anaphylactic reaction
Nervous system disorders	≥1% and <10%	Headache; Dizziness
Eye disorders	Unknown	Tear discoloration
Vascular disorders	Unknown	Shock; Flushing; Vasculitis; Bleeding
Respiratory disorders	Unknown	Dyspnea; Wheezing; Sputum discolored
Gastrointestinal disorders	≥1% and <10%	Nausea, vomiting
	≥0,1% and <1%	Diarrhea
Hepatobiliary disorders	Unknown	Hepatitis; Hyperbilirubinemia
Skin and subcutaneous tissue disorders	Unknown	Erythema multiforme; Stevens-Johnson syndrome; Toxic epidermal necrolysis; Drug reaction with eosinophilia and systemic symptoms; Pruritus
Musculoskeletal disorders	Unknown	Myopathy; Bone pain
Renal and urinary disorders	Unknown	Acute kidney injury

destruction.[6] The mechanism of hypersensitivity is type II (cytotoxic hypersensitivity, antibody-dependent) according to the classification of Gell and Coombs.[4] There is no definitive diagnostic method to confirm the responsibility of rifampicin in this type of hypersensitivity. In the absence of laboratory confirmation, the diagnosis can be corroborated by the normalization of the platelet count after suspension of the drug in question. Although it is a diagnosis of exclusion, a high degree of suspicion is necessary for a rapid diagnosis.

This case is highlighted by its rarity and severity, with the occurrence of multiple adverse reactions to the antituberculous drugs in an immunocompromised patient with miliary tuberculosis. The WHO recently published the initial results of a pilot study about the surveillance of antituberculous agents' adverse events, named aDSM (active tuberculosis Drug Safety Monitoring and management), which demonstrates monitoring is feasible.[2] The authors also wish to emphasize that, although uncommon, the occurrence of rifampicin-induced thrombocytopenia is a potentially serious and fatal ADR, which imposes its suspension and contraindicates its reintroduction.

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Ethical disclosures

Protection of human and animal subjects: The authors declare that no experiments were performed on humans or animals for this study.
Confidentiality of data: The authors declare that they have followed the protocols of their work center on the publication of patient data and that all the patients included in the study received enough information and gave their written informed consent to participate in the study.
Right to privacy and informed consent: The authors declare that no patient data appear in this article.

Conflict of interest

None.

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