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 antitubercular drug is free of risk, and the World Health Organization (WHO) recommends monitoring and reporting suspected or confirmed adverse drug reactions (ADR) caused by antitubercular drugs.2 Most ADRs 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 antitubercular agents, is a well-tolerated and effective drug. Most frequent adverse reactions to rifampicin (Table 1) include gastrointestinal effects, cutaneous reac-

tions, hepatotoxicity and flu-like syndrome. Immunological reactions, such as hemolytic anemia, agranulocytosis and thrombocytopenia, are less frequent. 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.

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 adenopathie 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 × 10^9/μL to 2 × 10^9/μL 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. 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 destruction. The mechanism of hypersensitivity is type II (cytotoxic hypersensitivity, antibody-dependent) according to the classification of Gell and Coombs. 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 antituberculosis drugs in an immunocompromised patient with miliary tuberculosis. The WHO recently published the initial results of a pilot study about the surveillance of antituberculosis agents’ adverse events, named aDSM (active tuberculosis Drug Safety Monitoring and management), which demonstrates monitoring is feasible. 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.

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Conflict of interest

None.

References


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The effect of alcohol consumption in the treatment of nontuberculous mycobacteria

To the editor:

Nontuberculous mycobacteria (NTM) are considered opportunistic pathogens. They are widely distributed in the environment, and several species are associated with a wide range of infections, most commonly affecting the lung. The increasing number of immunocompromised patients and predisposing diseases – such as chronic obstructive pulmonary disease (COPD), silicosis and bronchiectasis—as well as the increasing life expectancy of patients with cystic fibrosis, are factors contributing to a rising incidence of NTM disease. However, patients can develop NTM disease without any apparent underlying cause. This suggests that NTM disease is a multifaceted disease, and the genetic background or environmental exposures could also, increase susceptibility to infection. Population-based studies across Europe report a steady increase in NTM isolation and related lung disease over time. In Portugal, epidemiological studies are scarce but are in line with