This pattern is defined as thickened interlobular septa and intralobular lines superimposed on a background of ground-glass opacities. Pleural effusion, small lung nodules, cavitation, and lymphadenopathy are very uncommon findings.[2,5,6] These CT findings are not specific to COVID-19; similar results can be obtained for other infectious and non-infectious diseases.[6]

However, two characteristics of the ground-glass opacities may suggest the diagnosis of COVID-19 in the context of the current pandemic. The presence of multifocal nodular (round or oval) ground-glass opacities[7,8] and/or the association of these opacities with reticulation (the crazy-paving pattern)[8–10] should alert the radiologist to the possibility of COVID-19 infection. The latter finding appears particularly when the disease progresses. Our patient presented both findings. We believe that these two findings are important for the diagnosis of COVID-19, although the crazy-paving pattern is less specific; Amorim et al.[11] observed it in 15% of 70 patients with confirmed H1N1 infection.

## Conflicts of interest

The authors have no conflicts of interest to declare.

## References

1. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. Travel Med Infect Dis. 2020:101623, http://dx.doi.org/10.1016/j.tmaid.2020.101623.
2. Xiong Y, Sun D, Liu Y, Fan Y, Zhao L, Li X, Zhu W. Clinical and high-resolution CT features of the COVID-19 infection: comparison of the initial and follow-up changes. Invest Radiol. 2020, http://dx.doi.org/10.1097/RLI.0000000000000674.
3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020, http://dx.doi.org/10.1056/NEJMoa2002032.
4. Zu ZY, Jiang MD, Xu PP, Chen W, Ni QQ, Lu GM, et al. Coronavirus disease 2019 (COVID-19): a perspective from China. Radiology. 2020:200490, http://dx.doi.org/10.1148/radiol.2020200490.
5. Ng M-Y, Lee EY, Yang J, Yang F, Li X, Wang H, et al. Imaging profile of the COVID-19 infection: radiologic findings and literature review. Radiol Cardiothorac Imaging. 2020;2:e200034, http://dx.doi.org/10.1148/ryct.2020200034.
6. Hope MD, Raptis CA, Shah A, Hammer MM, Henry TS, on behalf of six signatories. A role for CT in COVID-19? What data really tell us so far. Lancet. 2020;26, http://dx.doi.org/10.1016/S0140-6736(20)30728-5.
7. Kong W, Agarwal PP. Chest imaging appearance of COVID-19 infection. Radiol Cardiothorac Imaging. 2020;2, http://dx.doi.org/10.1148/ryct.2020200028.
8. Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, et al. CT imaging features of 2019 novel coronavirus (2019-nCoV). Radiology. 2020;295:202–7, http://dx.doi.org/10.1148/radiol.2020200230.
9. Pan F, Ye T, Sun P, et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. Radiology. 2020:200370, http://dx.doi.org/10.1148/radiol.2020200370.
10. Zhou S, Wang Y, Zhu T, Xia L. CT features of coronavirus disease 2019 (COVID-19) pneumonia in 62 patients in Wuhan, China. AJR Am J Roentgenol. 2020:1–8, http://dx.doi.org/10.2214/AJR.20.22975.
11. Amorim VB, Rodrigues RS, Barreto MM, Zanetti G, Hochhegger B, Marchiori E. Influenza A (H1N1) pneumonia: HRCT findings. J Bras Pneumol. 2013;39:323–9, http://dx.doi.org/10.1590/S1806-37132013000300009.

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## 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 reac-

**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 |

tions, 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-$\alpha$ 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/$\mu$L, 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 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.

## References

1. Duarte R, Carvalho A, Ferreira D, et al. Tuberculosis treatment and management of some problems related to the medication. Rev Port Pneumol. 2010;16(4):559–72, http://dx.doi.org/10.1016/S0873-2159(15)30052-0.
2. Akkerman O, Aleksa A, Alffenaar J, et al. Surveillance of adverse events in the treatment of drug-resistant tuberculo-
sis: A global feasibility study. Int J Infect Dis. 2019;83:72–6, http://dx.doi.org/10.1016/j.ijid.2019.03.036.
3. Arbex MA, Varella MC, Siqueira HR, Mello FA. Antituberculosis drugs: Drugs interactions, adverse effects, and use in special situations. Part 1: First- line drugs. J Bras Pneumol. 2010;36(5):626–40, http://dx.doi.org/10.1590/S1806-37132010000500016.
4. Bouchentouf R, Yasser Z, Benjelloune A, Aitbenasser MA. Hypersensitivity reactions to antituberculosis therapy: epidemiology, mechanism and patient management. J Fran Viet Pneu. 2011;2(5):4–8.
5. Verma AK, Singh A, Chandra A, Kumar S, Gupta RK. Rifampicin-induced thrombocytopenia. Indian J Pharmacol. 2010;42:240–2, http://dx.doi.org/10.4103/0253-7613.68432.
6. Pereira J, Hidalgo P, Ocqueteau M, et al. Glycoprotein Ib/IX complex is the target in rifampicin-induced immune thrombocytopenia. Br J Haematol. 2000;1:907–10, http://dx.doi.org/10.1046/j.1365-2141.2000.02299.x.
7. Rifadin 300mg Capsules - Summary of Product Characteristics (SmPC) - (eMC)., Electronic Medicines Compendium. https://www.medicines.org.uk/emc/product/6384/smpc#UNDESIRABLE_EFFECTS. Accessed July 23, 2019.

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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.[1–3] 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.[2–4] 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.[1–3] 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