J Bras Pneumol. 2023;49(3):e20220467
https://dx.doi.org/10.36416/1806-3756/e20220467

Fulminant organizing pneumonia in a patient with ulcerative colitis on mesalamine and infliximab: striving to identify the cause!

Lídia Gomes[1], Maria Alcide Marques[1], Pedro Gonçalo Ferreira[1]

TO THE EDITOR:

Pulmonary involvement in inflammatory bowel disease is uncommon and often occurs secondarily to drug-induced toxicity or as an extraintestinal manifestation (EIM) of the underlying disease.[1]

We describe the case of a patient with ulcerative colitis (UC) on immunosuppressive therapy that developed fulminant interstitial lung disease (ILD) with severe hypoxemic respiratory failure. Written informed consent for publication of clinical details and images was obtained from the patient. In addition, we discuss the etiological investigation carried out.

This report relates to a 38-year-old Caucasian male who had been diagnosed with UC 2 years earlier and had been on treatment with mesalamine and infliximab for 17 and 5 months, respectively. He was a former smoker (20 pack-years), with no other relevant exposures or previous chronic respiratory disease, and was admitted with a 3-week history of worsening dyspnea, fever, and pleuritic chest pain.

On physical examination, he was polypneic, with an Spo_2 of 90% on room air and decreased breath sounds over the lung bases. Blood gas analysis showed hypoxemic respiratory failure (Po_2/FIo_2 = 232) with normal lactates. He tested negative for SARS-CoV-2. A blood panel revealed C-reactive protein of 12.9 mg/dL (normal range, < 0.5) with procalcitonin and white cell count (including eosinophils) within the normal range. A chest x-ray showed bilateral alveolar opacities (Figure 1A). Given an initial clinical suspicion of opportunistic pneumonia with ARDS, the patient was placed on broad-spectrum antibiotics with piperacillin-tazobactam and linezolid. Despite a good initial response to conventional oxygen therapy (FIo_2 = 0.35; Po_2/FIo_2 = 195), there was overall clinical worsening with persistent high fever and increasing FIo_2 demand (FIo_2 = 0.60; Po_2/FIo_2 = 148), even with CPAP. Chest CT angiography excluded pulmonary embolism and showed multifocal consolidations with a peribronchial component suggesting rapidly progressive organizing pneumonia (OP; Figure 1B). The patient underwent bronchoscopy with a comprehensive microbiological workup for viruses, bacteria, mycobacteria, and fungi, the results of which were negative. Given the progressive clinical worsening and the possibility of drug-induced acute lung injury, systemic corticosteroid therapy was initiated (methylprednisolone 125 mg/day for 3 days and then methylprednisolone 60 mg/day for 8 days, with further progressive tapering) and resulted in partial clinical and radiographic improvement. Colonoscopy excluded active UC.

Lung function testing revealed an FVC of 57% predicted and a single-breath D_{LCO} of 41% predicted. A significant oxyhemoglobin desaturation (nadir Spo_2 of 78%) was evident during the six-minute walk test, which was interrupted after four minutes (six-minute walk distance = 150 m). Reassessment with chest HRCT showed improvement of consolidations, with persistent areas of mosaic and ground-glass pattern (Figure 1C). The patient was referred for video-assisted thoracoscopic surgical lung biopsy. Histological analysis showed key features of OP, accompanied by a giant-cell reaction and chronic bronchiolitis. Given the absence of active UC, both infliximab and mesalamine were permanently discontinued, and, regarding ILD treatment, the patient was discharged on prednisolone (30 mg/day with a progressive weaning protocol) and was started on mycophenolate mofetil (target dose of 3 mg/day) and ambulatory oxygen.

After a multidisciplinary discussion of all complementary test results available and a thorough literature review, a provisional high-confidence diagnosis of mesalamine-induced lung disease (rapidly progressive OP with giant-cell reaction) was made. The case had a score of 5 on the Naranjo Adverse Drug Reaction Probability Scale and a score of 6 on the Karch-Lasagna modified algorithm ("probable adverse drug reaction").[2]

At 2-month follow-up, the patient had improved remarkably, with a normal chest X-ray, an FVC of 84% predicted, a D_{LCO} of 71% predicted, and no desaturation during the six-minute walk test (six-minute walk distance = 475 m, 75% predicted). The 6-month HRCT revealed complete resolution of the previous consolidation and patchy areas of ground-glass opacity (Figure 1D).

In our case, the final diagnosis was based on clinical presentation, imaging abnormalities, elusive lung histological features, and the exclusion of possible etiologies, including opportunistic infection. The timing of respiratory symptom onset is variable, and no clear-cut temporal association between mesalamine initiation and subsequent lung disease has been found.[3] On the other hand, most cases of infliximab-induced lung toxicity occur early after treatment initiation.[4] Pulmonary EIM was excluded based on endoscopic remission of UC and the patient's level of immunosuppression, as well as on the absence of other organ involvement. Above all, histological findings were strikingly consistent with a drug-related hypersensitivity reaction.[2] Although rare cases of OP secondary to infliximab have also been reported, there are in the literature cases of mesalamine-induced lung disease showing histological patterns of OP with focal areas of granulomatous/giant-cell reaction and

1. Serviço de Pneumologia, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.

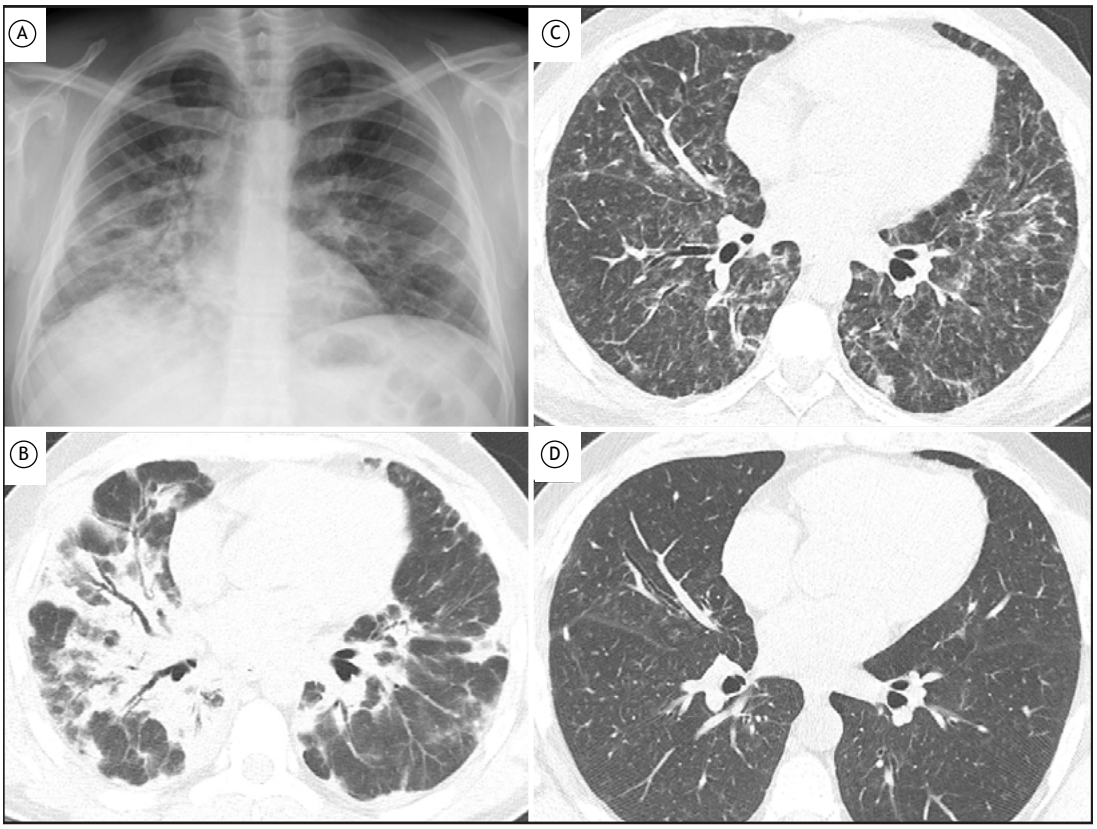

Figure 1. In A, chest X-ray showing bilateral alveolar opacities. In B, chest CT angiographic image showing multifocal consolidations with a peribronchial component. In C, chest HRCT scan showing improvement of consolidations, with persistent areas of mosaic and ground-glass pattern. In D, 6-month HRCT scan showing complete resolution of the previous consolidation and patchy areas of ground-glass opacity.

chronic bronchiolitis, which is perfectly in line with our findings.[2,3,5] Sequential drug rechallenge was not performed due to high risk.

The treatment for mesalamine-induced lung disease includes prompt discontinuation of the drug and, in severe forms, adjuvant anti-inflammatory therapy.[3] There are less than 20 case reports of histologically proven mesalamine-related OP in the literature, few of which were severe enough to require noninvasive positive airway pressure support.[3,5-7]

Overall, our case highlights the challenge of diagnosing rapidly progressive ILD in patients with UC on specific immunomodulatory maintenance therapy. Early suspicion of drug-induced lung disease in these patients, with timely exclusion of other etiologies, is crucial. Infection should be excluded at the highest possible priority (particularly if the patient is on anti-TNF agents). Differentiating a pulmonary EIM of UC from drug toxicity remains challenging; however, the absence of other EIMs, as well as remission of UC as evidenced by upper gastrointestinal endoscopy findings and patient-reported clinical information, can almost exclude pulmonary EIMs.[6] Lung biopsy can be useful in selected patients, and a thorough multidisciplinary discussion is mandatory to establish a confident diagnosis, enable early treatment, and thus avoid complications.[2]

AUTHOR CONTRIBUTIONS

LG: drafting of the manuscript.

MAM and PGF: critical review of the paper.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Harbord M, Annese V, Vavricka SR, Allez M, Barreiro-de Acosta M, Boberg KM, et al. The First European Evidence-based Consensus on Extra-intestinal Manifestations in Inflammatory Bowel Disease. J Crohns Colitis. 2016;10(3):239-54. https://doi.org/10.1093/ecco-jcc/jjv213
2. Tejeda Taveras N, Rivera Martinez A, Kumar R, Jamil A, Kumar B. Pulmonary Manifestations of Inflammatory Bowel Disease. Cureus.

2021;13(3):e14216. https://doi.org/10.7759/cureus.14216

3. Foster RA, Zander DS, Mergo PJ, Valentine JF. Mesalamine-related lung disease: clinical, radiographic, and pathologic manifestations. Inflamm Bowel Dis. 2003;9(5):308-15. https://doi.org/10.1097/00054725-200309000-00004
4. Caccaro R, Savarino E, D'Inca R, Sturniolo GC. Noninfectious interstitial lung disease during infliximab therapy: case report and literature review. World J Gastroenterol. 2013;19(32):5377-80. https://doi.org/10.3748/wjg.v19.i32.5377
5. Casey MB, Tazelaar HD, Myers JL, Hunninghake GW, Kakar S, Kalra SX, et al. Noninfectious lung pathology in patients with Crohn's disease. Am J Surg Pathol. 2003;27(2):213-9. https://doi.org/10.1097/00000478-200302000-00010
6. Huang PH, Kuo CJ, Lin CW, Cheng YM, Hu HC, Lin CY, et al. Mesalazine-related lung disease in a patient with ulcerative colitis: A case report. Medicine (Baltimore). 2018;97(48):e13242. https://doi.org/10.1097/MD.0000000000013242
7. Oi H, Suzuki A, Yamano Y, Yokoyama T, Matsuda T, Kataoka K, et al. Mesalazine-induced lung injury with severe respiratory failure successfully treated with steroids and non-invasive positive pressure ventilation. Respir Med Case Rep. 2020;31:101157. https://doi.org/10.1016/j.rmcr.2020.101157