Recurrent bilateral lung infiltrates in a patient with ulcerative colitis

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In all cases of ILD in patients with UC, drug-induced pneumonitis should be excluded. In patients who receive both anti-TNF-α and mesalazine and develop drug-induced pneumonitis, it is quite difficult to differentiate which is the actual causing agent. https://bit.ly/3AnNJNN

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A 61 year-old male with a history of coronary artery disease presented in the emergency department with a 10-day history of dyspnoea in mild physical activity. He was diagnosed with ulcerative colitis (UC) 3 years ago, and 6 months earlier he started treatment with anti-tumour necrosis factor (TNF)-α (he had received two doses of infliximab, the first dose 2 months ago and the second dose 1 month ago) and mesalazine. 1 month after the last dose of anti-TNF-α and 6 months after the initiation of therapy for UC he was hospitalised due to fever and severe respiratory failure (arterial oxygen tension/inspiratory oxygen fraction: 212) in the gastroenterology department. Chest computed tomography (CT) revealed limited emphysema, bilateral ground-glass opacities and mosaic attenuation; thus, anti-TNF-α induced interstitial pneumonia was suspected (figure 1a, b).

Task 1

What would be the next step in the management of this patient? Choose as many as apply.

a) Flexible bronchoscopy
b) Initiate empiric treatment with antibiotics for community-acquired pneumonia (amoxicillin/clavulanate plus azithromycin or moxifloxacin)
c) Discontinue anti-TNF-α
d) Initiate treatment with corticosteroids

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Due to the severe respiratory failure it was decided that the patient was not fit to undergo bronchoscopy. He was treated with moxifloxacin, systemic corticosteroids with gradual tapering over 2 months and anti-TNF-α was discontinued. The patient's condition improved significantly and he continued receiving mesalazine. In the meantime, he underwent a follow-up chest CT with no ground-glass opacities (figure 2a, b), and he did not present with symptoms compatible with exacerbation of UC.

1 month after the gradual withdrawal of corticosteroids, the patient presented with shortness of breath and low oxygen saturation without symptoms from other systems. On examination, the patient was in mild distress, afebrile (temperature 36.6°C), tachypnoeic (respiratory rate 20 breaths per min), without tachycardia (heart rate 80 beats per min) and with a room air oxyhaemoglobin saturation of 86%. Physical examination revealed bilateral end-expiratory crackles and was otherwise normal. The leukocyte count was normal, while C-reactive protein and erythrocyte sedimentation rate were mildly elevated at 22 $mg \cdot L^{-1}$ (upper normal limit 6 $mg \cdot L^{-1}$) and 41 $mm \cdot h^{-1}$, respectively. Arterial blood gases on room air revealed pH of 7.39, oxygen tension of 62.8 mmHg (8.37 kPa), carbon dioxide tension of 33.5 mmHg (4.46 kPa), bicarbonate of 21.4 $mmol \cdot L^{-1}$ and serum lactate of 1.40 $mmol \cdot L^{-1}$.

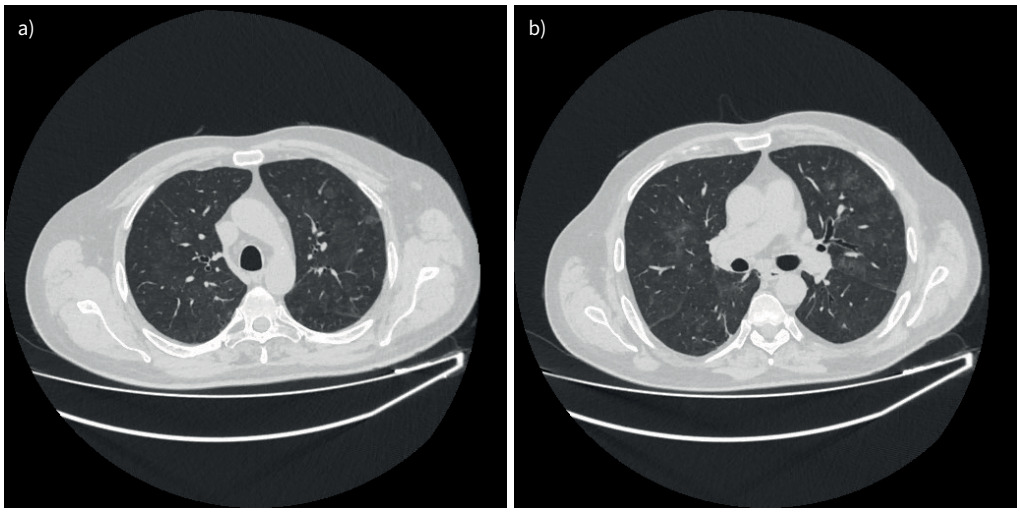

FIGURE 1 a, b) Chest computed tomography 6 months after mesalazine initiation and 1 month after the last dose of anti-TNF-α: limited emphysematous lesions, ground-glass opacities and mosaic attenuation.

Task 2

Which of the following investigations would you order now? Choose as many as apply.

a) Blood cultures
b) Sputum cultures for common pathogens
c) Chest CT
d) Coronavirus disease 2019 (COVID-19) PCR test

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CT scan revealed deterioration of bilateral ground-glass opacities and mosaic attenuation with mediastinal lymph nodes <1 mm (figure 3a, b), while pulmonary function testing revealed a restrictive disorder (total lung capacity (TLC) 74% and forced vital capacity (FVC) 2.89 L (69% predicted)) and severe impairment of diffusing capacity for carbon monoxide (D_{LCO}; 46% predicted) (table 1). Other laboratory examinations were unremarkable. Blood cultures, sputum culture for common pathogens, tuberculous and

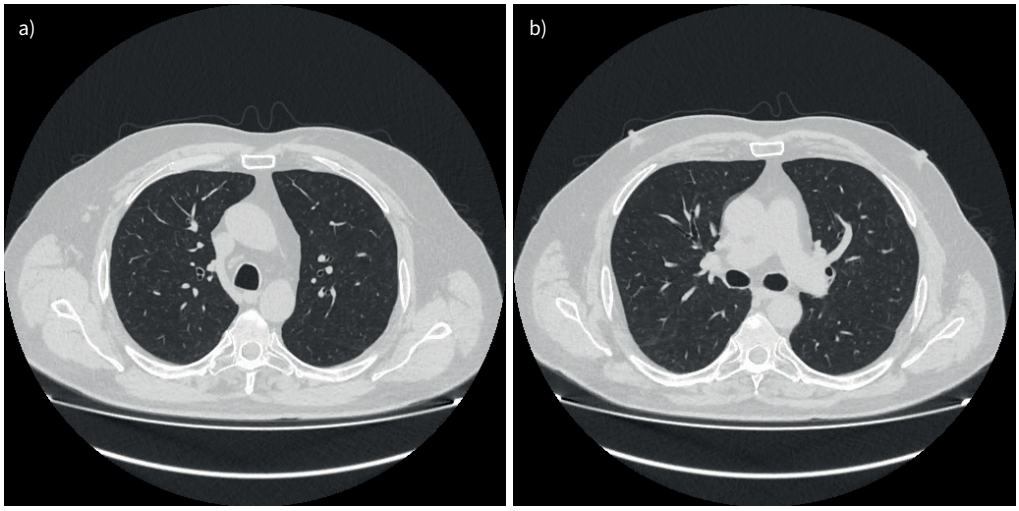

FIGURE 2 a, b) Follow-up chest computed tomography (after 1.5 months of treatment with corticosteroids and anti-TNF-α discontinuation): resolution of ground-glass opacities and mosaic attenuation.

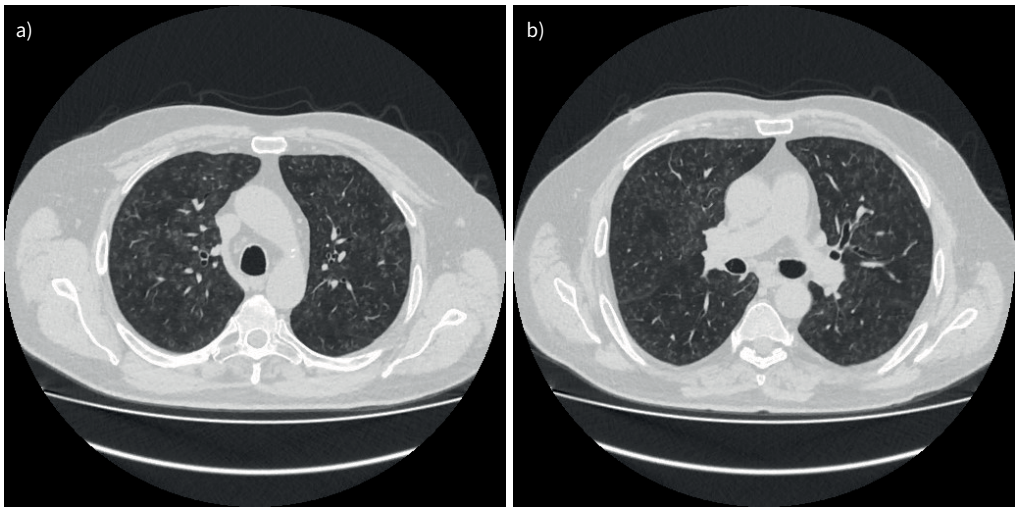

FIGURE 3 a, b) Chest computed tomography 1.5 months after the images shown in figure 2 (1 month after the gradual withdrawal of corticosteroids): extensive bilateral ground-glass opacities, small centrilobular nodules and mosaic attenuation.

nontuberculous mycobacteria and urine culture were negative. Nasopharyngeal swab PCR analysis for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and other viruses, including respiratory syncytial virus (RSV) and influenza, was negative. A serological panel including rheumatoid factor (RF) and antinuclear antibodies (ANCA) was normal. Serum angiotensin-converting enzyme was 20 $U \cdot L^{-1}$.

Task 3

What would be the next step in the management of this patient?

a) Flexible bronchoscopy
b) Initiate treatment with antibiotics
c) Lung biopsy
d) Colonoscopy

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The patient underwent bronchoscopy and bronchoalveolar lavage (BAL). Lavage samples demonstrated lymphocytosis (lymphocytes 68%, macrophage 20%, neutrophils 12%); flow cytometry of the BAL did not reveal abnormal findings, demonstrating a CD4 to CD8 ratio <1. PCR analysis for SARS-CoV-2 was negative. Bacterial, fungal including *Pneumocystis jirovecii*, and mycobacterial smear special stains and

TABLE 1 Pulmonary function tests, D_{LCO} and TLC on the day of admittance, at 7 days after treatment initiation and after 6 months

Parameter	On admittance	7 days after treatment initiation[#]	After 6 months[#]
FEV_1, L	1.96	2.60 (+31%)	2.83 (+44%)
FEV_1, % pred	59	80 (+33%)	87 (+47%)
FVC, L	2.89	3.42 (+19%)	3.83 (+32%)
FVC, % pred	69	82 (+18%)	92 (+33%)
FEV_1/FVC, %	89	100 (+13%)	97 (+9%)
$FEF_{25–75\%}$, % pred	31	55 (+76%)	58 (+87%)
D_{LCO}cSB, %	46	67 (+43%)	68 (+48%)
D_{LCO}cSB/V_A, %	65	81 (+25%)	83 (+28%)
TLC, % pred	74	85 (+15%)	85 (+15%)

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25–75\%}$: forced expiratory flow at 25–75% of FVC; D_{LCO}cSB: single-breath diffusing capacity for carbon monoxide corrected for haemoglobin; V_A: alveolar volume; TLC: total lung capacity. [#]: values in parentheses are the percentage changes compared with the day of admittance.

cultures for common pathogens were also negative. Additionally, there was no evidence of pulmonary haemorrhage. Cytological analysis was also negative. To exclude the possibility of lung involvement due to UC, a colonoscopy was performed that demonstrated no findings compatible with disease exacerbation.

Task 4

Based on the medical history and BAL findings, which is the most probable diagnosis?
a) Infection (atypical, viral pathogens)
b) Drug-induced pneumonitis
c) Acute respiratory distress syndrome
d) Cryptogenic organising pneumonia
e) Inflammatory bowel disease-related interstitial lung disease

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Based on the facts that the patient had a new onset of interstitial lung disease (ILD), the last dose of anti-TNF-α was administered 4 months ago, while he was still receiving mesalazine, and the lymphocytic cellular pattern in BAL, mesalazine-induced interstitial pneumonia was the most probable diagnosis.

Task 5

What would be your treatment approach? Choose as many as apply.
a) Initiate antibiotics (macrolides)
b) Initiate systemic corticosteroids
c) Discontinue mesalazine

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Mesalazine was discontinued and methylprednisolone at a dose of 1 $mg \cdot kg^{-1}$ prednisolone equivalent was administered. The clinical condition of the patient improved gradually, with a concomitant improvement of pulmonary functional tests (D_{LCO} 67%, TLC 85% and FVC 3.42 L (82% pred)) (table 1) at 7 days after treatment initiation. He was discharged 1 week after hospitalisation and received oral methylprednisolone with gradual tapering over 3 months with no evidence of residual lung disease in the follow up CT (figure 4a, b). The patient was also reassessed after 6 months, remaining asymptomatic and without evidence of drug-induced pneumonitis relapse or pulmonary functional tests deterioration (table 1). After multidisciplinary discussion with the gastroenterology department, it was decided not to administer any treatment for UC, which was in full remission at present time.

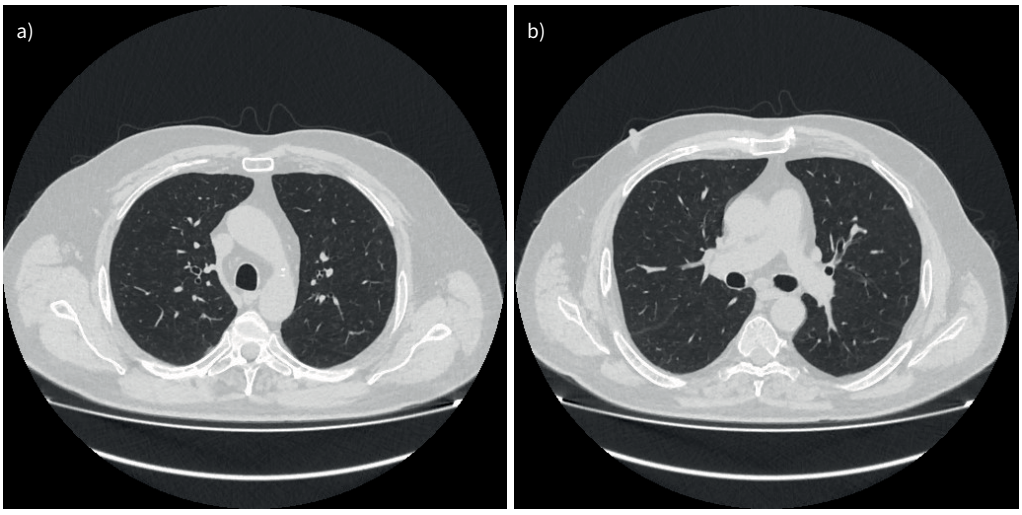

FIGURE 4 a, b) Follow-up chest computed tomography 3 months after the images shown in figure 3 (3 months after mesalazine discontinuation): complete resolution of bilateral ground-glass opacities, small centrilobular nodules and mosaic attenuation.

Discussion

Bronchopulmonary disease is a rare extrapulmonary manifestation of UC, the true prevalence of which is unknown. Interstitial pneumonia associated with inflammatory bowel disease (IBD) has been described, the most common form being organising pneumonia. Patients may also present with diffuse parenchymal infiltrates induced by medication used for the management of UC (aminosalicylates, methotrexate, thiopurines, anti-TNF-α) or by opportunistic infections caused by these treatments [1]. In this specific case of a patient with UC presenting with acute respiratory failure, drug-induced pneumonitis was finally attributed to mesalazine treatment.

Although mesalazine is usually well tolerated, associated toxicity has been rarely described with eosinophilic, cryptogenic organised or nonspecific interstitial pneumonia as the more typical patterns of respiratory involvement [2, 3]. The duration of treatment with mesalazine before the onset of symptoms varies between 1 month and several years (up to 8 years) [4, 5]. Likewise, anti-TNF-α treatment is infrequently associated with drug-induced pneumonitis [6–10]. The onset of anti-TNF-α induced lung injury can emerge between 2 and 6 months after the introduction of the drug, with rare cases occurring up to 44 months after the initial medicine administration [8, 11]. In this case, the relapse of the disease despite the discontinuation of anti-TNF-α and receiving therapy with corticosteroids after the first manifestation of drug-induced pneumonitis 3 months ago, led to the investigation of alternative causes.

Drug-induced pneumonitis is a diagnosis of exclusion, based on clinical suspicion, exposure to a pneumotoxic drug and exclusion of other causes of ILD [12]. In general, clinical, laboratory, radiological and histological features of drug-induced ILD (DI-ILD) are nonspecific and variable even with the same offending drug. The disease may have acute, subacute or chronic onset and the main symptom is worsening of dyspnoea. Patients with suspected DI-ILD should undergo bronchoscopy not only to rule out alternative diagnoses such as opportunistic infections, but also to help define histopathological features based on BAL findings. BAL of DI-ILD is usually a lymphocytic alveolitis with CD4/CD8 <1 ratio [13–15]. High-resolution CT findings are also nonspecific, but they can indicate the extent of the disease. Histological confirmation is not mandatory; however, it provides useful data that should be integrated with clinical and radiological findings to support the diagnosis of DI-ILD. In addition, morphological abnormalities of lung tissue, obtained usually by transbronchial biopsy, vary from acute/subacute interstitial pneumonia to established fibrosis and any histological pattern may be caused by a number of different drugs [16–18].

ILD in IBD reflects a spectrum of diseases, such as organising pneumonia, nonspecific interstitial pneumonia, desquamative interstitial pneumonia (typically in smokers), eosinophilic pneumonia, and usual interstitial pneumonia [19, 20]. In this case ILD could not be attributed to UC as there were no manifestations of UC in other organs and more specifically the large intestine, and ground-glass opacities resolved, despite the discontinuation of the two UC-targeted therapies, anti-TNF-α and mesalazine.

Conclusion

In all cases of ILD in patients with UC, drug-induced pulmonary disease should be excluded. Both anti-TNF-α and mesalazine have been implicated in inducing ILD. In patients who receive both of these medicines and develop drug-induced pneumonitis, it is quite difficult to differentiate which one is the actual causing agent. In this case, the withdrawal of anti-TNF-α after the first incident of drug-induced pneumonitis and the relapse 6 months after the initiation of therapy, while still receiving mesalazine, led to the discontinuation of mesalazine as the pneumonitis-provoking agent.

Answer 1

a, b and c.

<< Go to Task 1

Answer 2

a, b, c and d.

<< Go to Task 2

Answer 3

a.

<< Go to Task 3

Answer 4

b.

<< Go to Task 4

Answer 5

b and c.

<< Go to Task 5

Conflict of interest: None declared.

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