



## Pulmonary involvement in Crohn's disease

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### TO THE EDITOR:

A 34-year-old White nonsmoking male was admitted to hospital with a history of cough and sputum production. The patient had severe intestinal Crohn's disease (CD), which had been diagnosed by colonic biopsy. He presented with gastrointestinal symptoms such as diarrhea, blood in stool, and abdominal pain refractory to 5-aminosalicylic acid therapy, and had been under treatment with infliximab since 2015. His respiratory symptoms (i.e., cough and sputum production) began 2 years later and were treated with amoxicillin/clavulanate for 10 days, without improvement. Two weeks later, the patient developed chest pain, fever, and dyspnea, with no gastrointestinal evidence of a flare-up of CD. At that time, his heart rate was 120 bpm, his SpO<sub>2</sub> was 96%, and his C-reactive protein levels were elevated (190 mg/dL). In addition, he had crackles in the left hemithorax. Blood, sputum, and urine cultures were negative. A CT scan of the chest showed consolidation with air bronchogram and perilesional ground-glass opacities in the left lower lobe (Figure 1A), and a CT scan of the abdomen was suggestive of splenic abscess. Fine-needle aspiration of the spleen was performed, and abscess fluid culture was positive for *Proteus mirabilis*, the patient being started on treatment with ceftriaxone and metronidazole. Bronchoscopy with BAL was performed, and polymerase chain reaction for tuberculosis, direct examination of BAL fluid, and BAL fluid culture were all negative. Given that the splenic fluid collection persisted, drainage was performed, and oral corticosteroid therapy (prednisone at 1 mg/kg per day) was prescribed. Twenty-one days later, the patient had made a full recovery and was therefore discharged to outpatient follow-up. A follow-up CT scan of the chest performed 1 month later showed resolution of the left lower lobe consolidation. The symptoms recurred 3 months later, during corticosteroid reduction. A CT scan of the chest showed splenic abscess and left lower lobe consolidation (Figure 1A). An open lung biopsy revealed fibroblastic plugs within bronchioles, alveolar ducts, and adjacent alveolar spaces. The alveolar septa were thickened by a prominent chronic inflammatory infiltrate associated with type II pneumocyte hyperplasia. In addition to the aforementioned histological changes, there were non-necrotizing granulomas (although not in a lymphatic distribution), consisting of aggregates of epithelioid histiocytes (Figures 1C and 1D). Special stains for microorganisms were all negative. The final diagnosis was aseptic non-necrotizing chronic

granulomatous inflammation associated with organizing pneumonia. The reintroduction of corticosteroid therapy and immunomodulation with azathioprine and infliximab resulted in clinical and radiological resolution of the lung disease (Figure 1B). The splenic fluid collection resolved after 16 weeks of treatment with ciprofloxacin.

Inflammatory bowel disease (IBD) is associated with a variety of extraintestinal manifestations.<sup>(1-3)</sup> Since the original report by Kraft et al.<sup>(4)</sup> published in 1976 and describing six patients with IBD and unexplained chronic purulent sputum, pulmonary involvement in IBD, although rare, has increasingly been reported. Pulmonary complications include airway disease, interstitial lung diseases—particularly bronchiolitis obliterans organizing pneumonia, nonspecific interstitial pneumonia, and sarcoidosis—pulmonary vasculitis, necrotic pulmonary nodules, and serositis.<sup>(1,3,5-10)</sup> Other pulmonary manifestations include toxicity induced by azathioprine, sulfasalazine, mesalazine, and anti-TNF agents, as well as infections (including bacterial, mycobacterial, and fungal infections).<sup>(3)</sup> With regard to noninfectious pulmonary manifestations of IBD, organizing pneumonia is the most common and is usually associated with aseptic non-necrotizing chronic granulomatous inflammation.<sup>(1-3,5,8-10)</sup> In contrast, tuberculosis and nontuberculous mycobacterial infection have been associated with granulomatous bronchiolitis.<sup>(5)</sup>

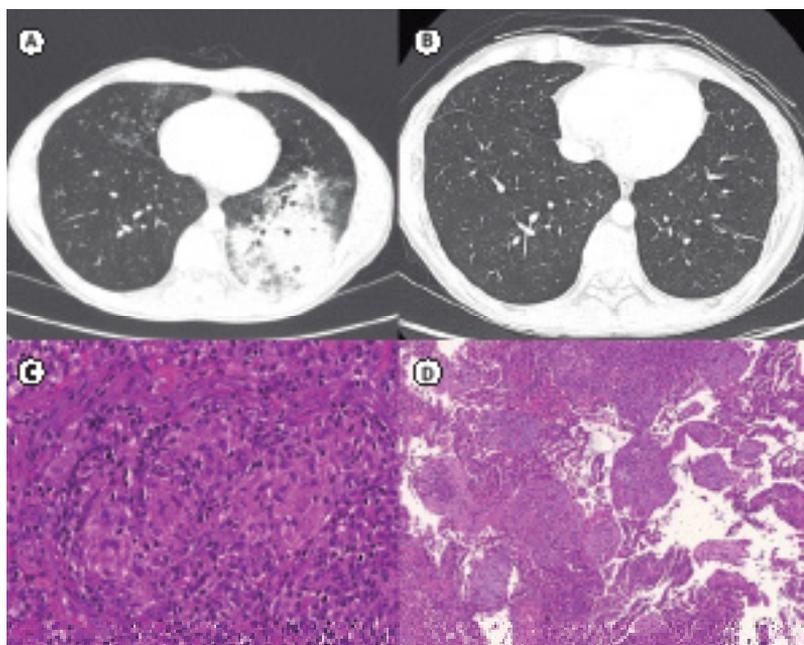
In the case reported here, the final diagnosis was organizing pneumonia with granulomatous inflammation.<sup>(11-14)</sup> Organizing pneumonia is a histological pattern characterized by granulation tissue within alveolar ducts and alveoli, together with chronic inflammation of the adjacent lung parenchyma. Similar lesions are observed in the respiratory bronchioles. The distinction between cryptogenic and secondary organizing pneumonia is important because the treatment of the latter includes the treatment of organizing pneumonia itself and the treatment of the underlying disease or causative agent of organizing pneumonia. Common causes of secondary organizing pneumonia include inhalation injury, infections, drug hypersensitivity, and autoimmune diseases.<sup>(11-14)</sup> In the case reported here, organizing pneumonia was found in association with a granuloma. An epithelioid granuloma, detected on microscopic examination of a biopsy specimen, has been reported to be a reliable marker of CD.<sup>(14)</sup> Necrotizing (or caseating) and non-necrotizing (or noncaseating) lung granulomas are common and can occur either alone or in combination. The terms

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**Figure 1.** In A, CT scan of the chest showing left lower lobe consolidation with air bronchogram and perilesional ground-glass opacities. Note tree-in-bud opacities in the middle lobe. In B, CT scan of the chest showing resolution of the left lower lobe consolidation after treatment. In C, non-necrotizing granuloma, together with a chronic inflammatory infiltrate (H&E staining; magnification,  $\times 40$ ). In D, organizing pneumonia (H&E staining; magnification,  $\times 8$ ).

necrotizing and caseating are sometimes considered to be different from each other. The former is used in order to describe microscopic changes, whereas the latter refers to a gross, cheesy appearance. Infections usually cause necrotizing granulomas or a combination of necrotizing and non-necrotizing granulomas, although some organisms, such as *Cryptococcus* spp. and *Mycobacterium avium* complex, can induce predominantly non-necrotizing granulomas. Conversely, a purely non-necrotizing granulomatous process is more likely to be noninfectious (e.g., sarcoidosis, berylliosis, talc granulomatosis, granulomatosis with polyangiitis, Churg-Strauss syndrome, necrotizing sarcoid granulomatosis, bronchocentric granulomatosis, aspiration pneumonia, and rheumatoid nodules). Given that granulomas in CD are sarcoid-like granulomas, the differential diagnosis between sarcoidosis and CD is particularly important. In the case reported here, mycobacterial infection was excluded because of the absence of caseous necrosis and because no mycobacteria were detected by microbiological

testing, molecular analysis, BAL fluid culture, or lung biopsy. A diagnosis of sarcoidosis was considered but ruled out because the patient presented with a solitary pulmonary lesion, without lymphadenopathy, lymphocytosis, increased CD4/CD8 ratio in BAL fluid, or systemic hyperkalemia.<sup>(5)</sup>

In conclusion, lung disease is a rare complication of IBD, particularly CD. The prognosis of lung disease in patients with CD is generally favorable, with a high response rate to therapy. Corticosteroids are the most common treatment, leading to rapid symptom improvement in up to 90% of patients. However, relapse occurs in 12-30% of patients after corticosteroid tapering or withdrawal, dose increase or drug readministration being required.<sup>(3)</sup> In the case reported here, a patient with CD was found to have organizing pneumonia with granulomatous inflammation, which was successfully controlled with corticosteroid therapy and immunomodulation with azathioprine and infliximab.

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