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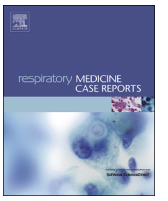

Case Report

A rare pulmonary manifestation of Crohn's disease: Acute fibrinous and organizing pneumonia presenting as multifocal nodules

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ABSTRACT

Acute Fibrinous and Organizing Pneumonia (AFOP) is a rare pulmonary disease, and it has not been recorded in literature as a pulmonary manifestation of Crohn's disease. A 22-year-old individual with an extensive history of Crohn's disease presented to the hospital initially for hematochezia and diarrhea. Computed tomography of her abdomen and pelvis showed multiple pulmonary nodules bilaterally. The patient did not report cough, sputum production, or dyspnea. Autoimmune and infectious workup were overall unremarkable. A CT-guided percutaneous biopsy of a peripheral lung nodule was performed showing features consistent with AFOP. The patient was ultimately treated with a long taper of prednisone and Ustekinumab for Crohn's disease. Follow-up CT-chest showed interval reduction and improvement in lung nodules, which correlated with better control of the patient's Crohn's disease. Pulmonary manifestations of IBD are varied, including pleural disease, bronchiectasis, and organizing pneumonia. Bronchiolitis obliterans organizing pneumonia has been described more frequently in patients with ulcerative colitis compared to Crohn's. Pulmonary nodules are a rare manifestation of IBD and often tend to be granulomatous or necrobiotic. AFOP is a rare entity with no previously reported association with IBD. Secondary AFOP can be caused by autoimmune diseases, drug reactions, infections, or radiation. Treatment of AFOP is usually immunosuppression by glucocorticoids.

1. Introduction

There are many known pulmonary manifestations of inflammatory bowel disease (IBD) of which the most common are airway diseases including bronchiectasis, chronic bronchitis, and lung parenchymal diseases. Pulmonary nodules are infrequently reported in patients with IBD and when discovered have usually been necrobiotic or granulomatous in nature. Here we report a unique case of acute fibrinous and organizing pneumonia (AFOP) associated with Crohn's disease presenting as multiple pulmonary nodules in an asymptomatic patient. AFOP is an uncommon pulmonary disease with a unique histopathologic pattern that can present as a sequela of infection, autoimmune disease, drug reaction, or can be idiopathic. This is the first known report of AFOP associated with Crohn's disease.

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2. Case report

The patient is a 22-year-old female with a long history of Crohn's disease diagnosed at the age of 13 years. Her disease was well controlled with infliximab for 8 years before the current presentation. Due to a lapse in insurance coverage, the patient was unable to get infliximab for two months. She subsequently had hematochezia and diarrhea with up to 15 bowel movements per day. The patient was admitted to the hospital and underwent a colonoscopy. Multiple biopsies obtained from the colon spanning from the ascending colon to the rectum showed active colitis with extensive ulceration and crypt architectural distortion. No granuloma or dysplasia was identified. She was initially treated with intravenous methylprednisolone.

Computed tomography (CT) of her abdomen and pelvis showed incidental findings of multifocal pulmonary nodules in bilateral lung bases. A dedicated CT chest confirmed round, well-circumscribed, non-calcified, solid nodules present in all lobes but with lower lobe and peripheral predominance. Repeat imaging after 3 weeks showed a significant increase in the size of the nodules; for example, a 3 mm nodule has enlarged to 14 mm (Fig. 1). A total of 13 nodules were present. Despite the radiographic changes, the patient did not have any respiratory symptoms such as cough, sputum production, or dyspnea.

To address the possibility of septic emboli, blood cultures (including fungal cultures) were obtained, which were negative. A *trans*-esophageal echocardiogram (TEE) was performed which did not show any evidence of endocarditis. Serum beta D glucan, galactomannan antigen, Cryptococcal antigen, and interferon-gamma release assay were negative. Fungal antibody panel was negative for all including Aspergillus Flavus, Aspergillus Niger, Aspergillus Fumigatus, Blastomyces species, Candida species, Coccidioides, and Histoplasma M-band and H-band. Empiric antibiotics (Vancomycin and Piperacillin-Tazobactam) were stopped by the infectious diseases team.

The pulmonology team was then consulted. An autoimmune workup including rheumatoid factor, myeloperoxidase IgG, proteinase-3 IgG were negative. Anti-nuclear antibody (ANA) was weakly positive at a titer of 1:80. C-reactive protein was 59.8 mg/L (normal <10.0 mg/dL) which was confounded by the active Crohn's flare. A CT-guided percutaneous biopsy of a peripheral lung nodule was performed. Samples were sent for histopathology and cytology and also for bacterial, acid-fast bacillus, and fungal stain and culture. All infectious studies from the biopsy samples were negative.

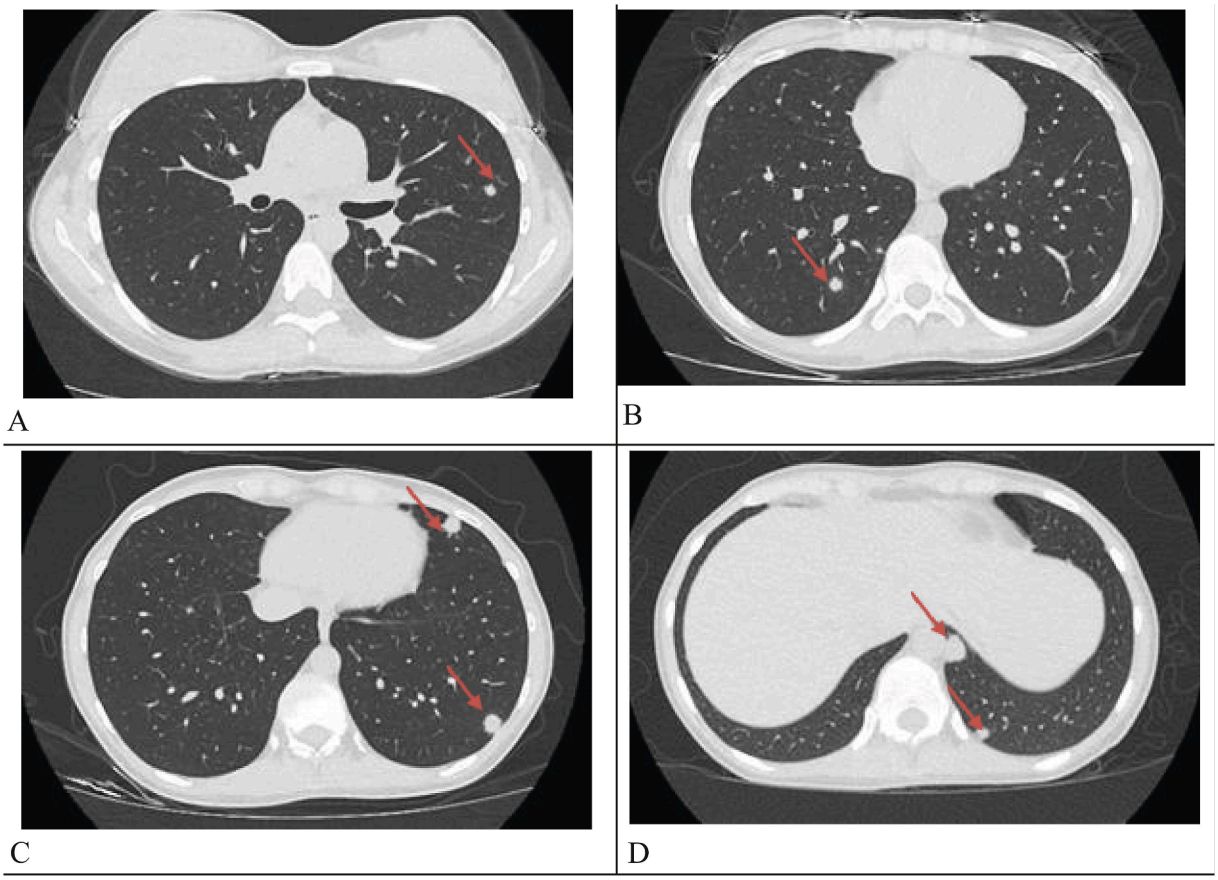

Fig. 1. Representative CT images showing multiple, bilateral, round, well-circumscribed, non-calcified nodules. Specifically, there was a 6-mm nodule within the upper left lobe (A), a pleural-based 9-mm nodules in the lingula (C), a 13-mm nodule in the left lower lobe overlying the aorta (D), and a 10-mm nodule in the right lower lobe (B).

The pathology of the core biopsy revealed fragments of reactive lung parenchyma with alveoli lined with reactive pneumocytes and scattered collections of foamy macrophages. The alveolar lumens were noted to contain “fibrin balls” with the adjacent alveolar septa showing sparse lymphoid infiltrates (Fig. 2). Hyaline membranes, eosinophilic inflammation, pneumonia/abscess, granulomas, vasculitis, or necrosis were not present. The mature fibrotic areas seen in Fig. 2 represent the visceral pleura. The overall histopathologic features were felt to be consistent with AFOP.

Once infectious processes were ruled out and pathology was obtained, monitoring without specific treatment for the nodules was considered. However, given the rate of increase of the size of the nodules and because the patient was having an active exacerbation of Cronh's disease, the decision was made to start immunosuppression. The patient was then treated with prednisone with a long taper over 3 months, dosed at 40 mg (mg) of Prednisone daily for 4 weeks, then 30 mg of daily for 4 weeks, then 20 mg daily for 4 weeks,

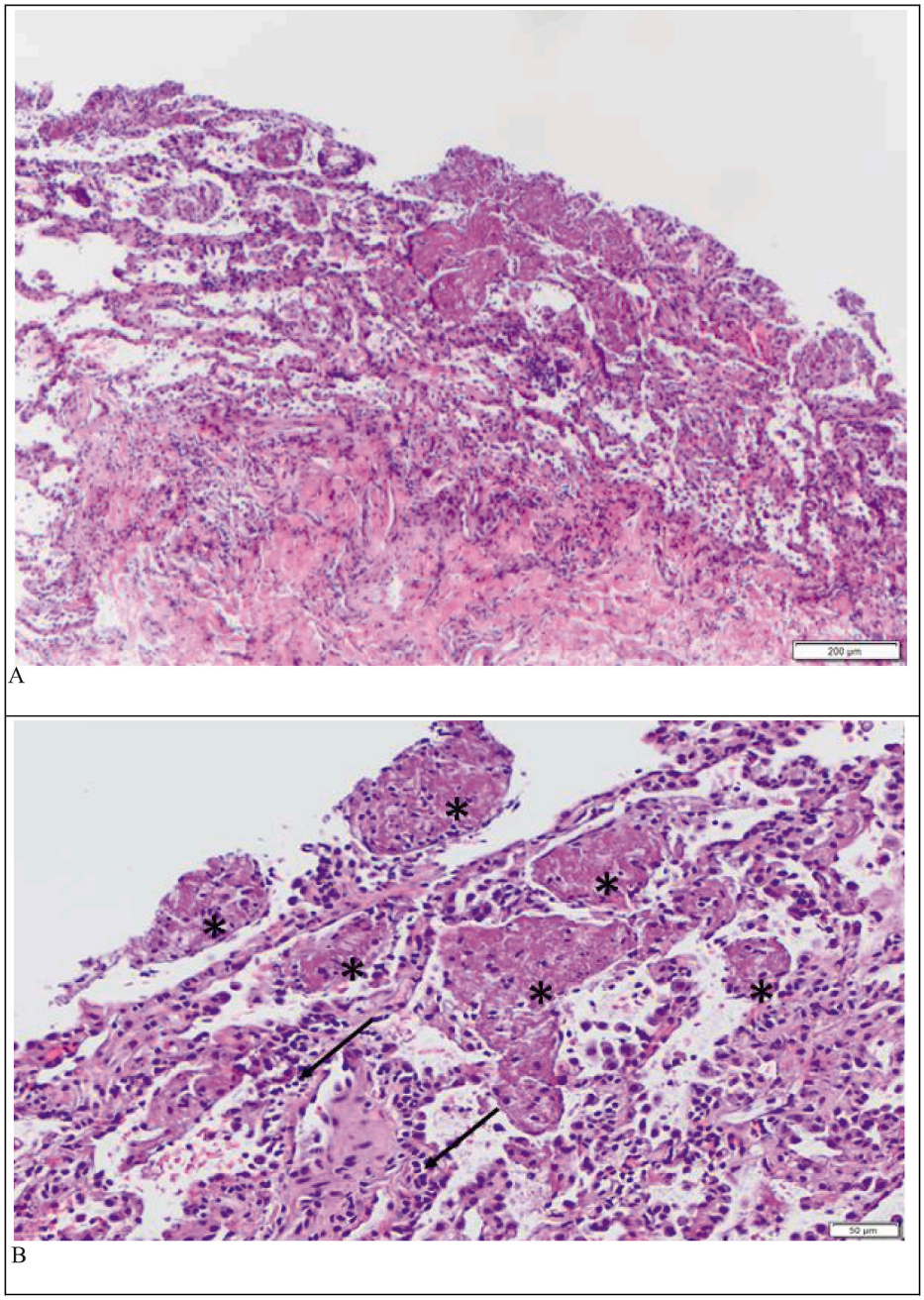

Fig. 2. The histopathologic features of the lung nodule biopsy. The lung parenchyma demonstrates alveoli lined with reactive pneumocytes with patchy filling of alveolar lumens with “balls” of fibrin (marked with *). The alveolar septa adjacent to the intra-alveolar fibrin show sparse lymphoid infiltrates (marked with arrows). No hyaline membrane has been identified. 2A, Hematoxylin and Eosin (H&E) stained section; 40X magnification; 2B 100X magnification.

then 10 mg daily for 2 weeks, and finally 5 mg daily for 2 weeks. She was also started on Ustekinumab (delayed a few weeks until insurance authorization was obtained) to treat Crohn's disease. Follow-up CT of the chest two months after discharge (3 months after initial imaging) showed significant interval decrease in the size and number of bilateral pulmonary nodules, with the largest pulmonary nodule on the right lower lobe measuring 5 mm, and the largest nodule on the left lower lobe measuring 8 mm (Fig. 3). The patient remained asymptomatic from a respiratory standpoint and her Crohn's disease was better controlled.

3. Discussion

Pulmonary manifestations of IBD can vary from pleural disease, airway disease to rarely, lung parenchymal disease, thromboembolic events, and enteric-pulmonary fistulas. The most well-known manifestations are bronchiectasis and organizing pneumonia (OP). Pulmonary sarcoidosis has been rarely known to develop in patients with longstanding Crohn's disease. Airway disease and bronchiectasis have been reported in up to 92% of cases of IBD with higher prevalence in ulcerative colitis (UC) than in Crohn's disease. Similarly, bronchiolitis obliterans organizing pneumonia (BOOP) has been described more frequently in patients with UC than Crohn's [1].

Our case is unique in that the patient was presented with an unusual radiographic and clinical presentation in the setting of Crohn's disease with histopathology compatible with AFOP. The multiple, round, well-circumscribed, non-calcified pulmonary nodules present in our case are rare in both IBD and AFOP. Pulmonary nodules associated with IBD are usually granulomatous or necrobiotic [2]. Our biopsy sections demonstrate subpleural alveolar parenchyma with focal intra-alveolar fibrin deposition. There were no signs of diffuse alveolar damage, and histopathologically, the diagnosis is most consistent with AFOP.

AFOP is a rare entity with previous literature limited to case reports and case series with no prior reported association to IBD. The presentation of AFOP can vary from acute fulminant respiratory failure to subacute dyspnea and cough, but overall carries a poor prognosis. Our patient had an atypical clinical presentation without significant respiratory symptoms and with pulmonary nodules. Other recent reports have indicated that the presentation of AFOP can be cryptogenic without significant symptoms and be responsive

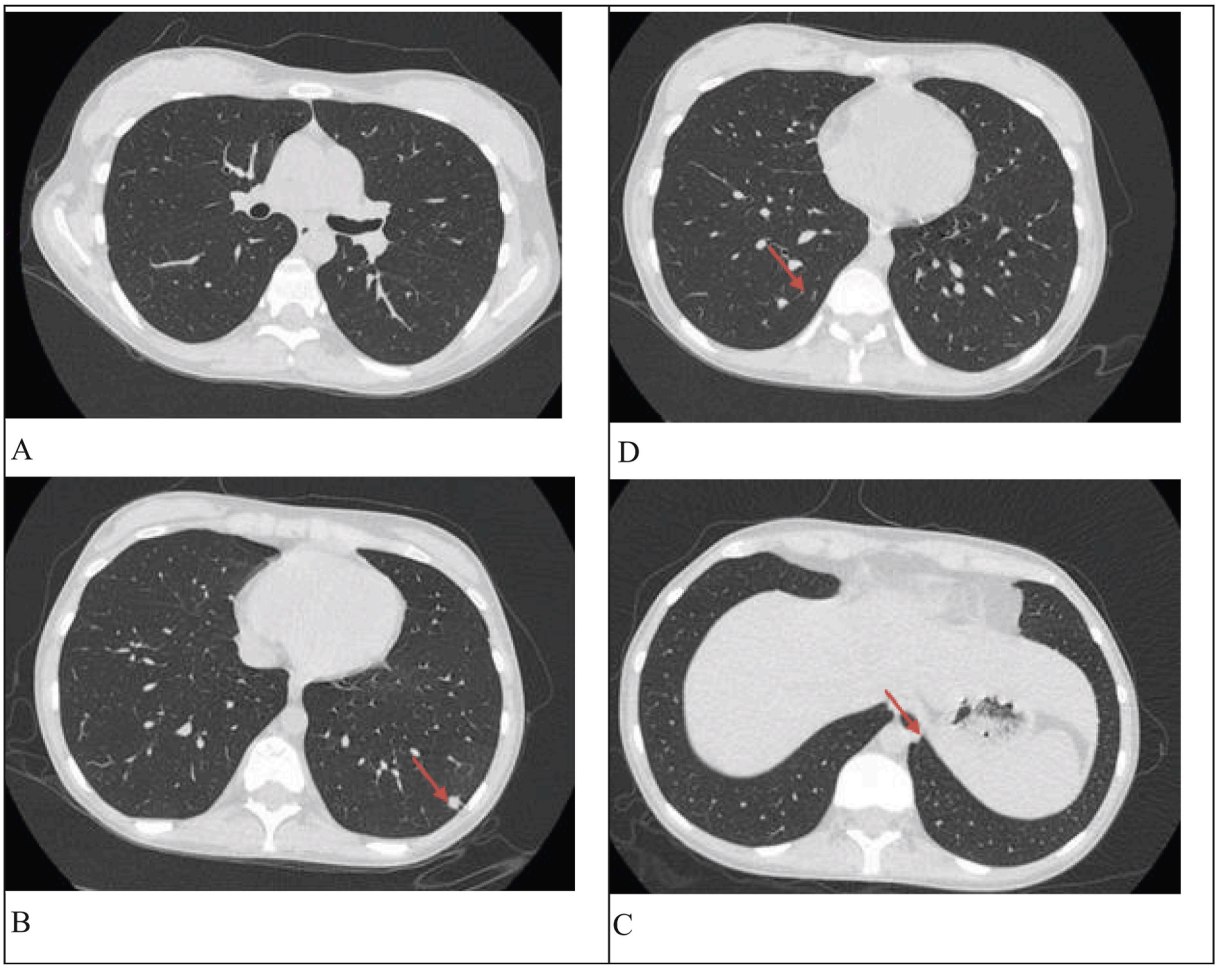

Fig. 3. Representative images from a follow-up CT scan 8 weeks after treatment. The same levels from Fig. 1 are shown here demonstrating significant reduction in the size of most nodules and complete resolution of others.

to glucocorticoids [3]. While severe symptoms associated with AFOP do not improve without treatment, patients who are asymptomatic may be able to be monitored without treatment. The decision was made to treat with glucocorticoids in our patient due to an active Crohn's flare, and because the nodules were expanding in size over the course of a few weeks. Previous reports have noted a variable response to glucocorticoids. Some authors report using other immunosuppressant agents to treat AFOP [7]. This variability may be related to the initial insult leading to AFOP pathology. Our patient was asymptomatic from a pulmonary perspective, and Ustekinumab was initiated for Crohn's disease. No other immunosuppression was considered for the nodules. Resolution of the nodules in our case correlated with better control of the patient's IBD symptoms.

Secondary AFOP can be caused by numerous diseases including autoimmune diseases, infections, drug reactions, or radiation [4]. A common clinical scenario is presumed to be infectious pneumonia, which does not respond to antimicrobials, leading to further investigation resulting in the diagnosis of AFOP. Lu et al. reports a case of AFOP that developed in a patient with Sjogren's syndrome and was treated with corticosteroids [5]. Additionally, a case report discussed by Chen et al. discusses AFOP secondary to systemic lupus erythematosus [6]. An association with IBD, as in our case, has not previously been reported.

Radiographic presentation of AFOP is variable, and published reports typically describe diffuse, but basilar predominant ground-glass to consolidative opacities [7,8]. Nodular infiltrates have been described but are usually present in conjunction with ground-glass opacities (GGO) and more dense consolidation. Isolated well-circumscribed nodules without GGO or other infiltrates, as in our case, have not been previously described.

A confounding factor in cases of IBD-related pulmonary disease is the frequent use of immunosuppressive medications. Tumor necrosis factor alpha (TNF-α) inhibitors used to treat IBD can occasionally cause drug-induced pulmonary toxicity. In a study by Moda et al., among 563 patients with UC, 10 patients (1.8%) experienced organizing pneumonia secondary to drug-induced pathogenesis. The treatment of choice remains glucocorticoids [4]. In our patient's case, the nodules developed when the patient was off infliximab and the timing was concurrent with the flare of Crohn's disease. Moreover, the presence of immunosuppression increases risk of infectious processes that may result in a similar radiographic presentation seen in our patient. We performed a thorough infectious work-up as detailed above, and no evidence of an infectious process was seen.

A primary limitation of our case is the reliance on percutaneous transthoracic needle biopsy (PTNB). This technique can result in sampling of only a small area of the lesion and may not give a true representation of the overall pathology. However, the technique is well established with multiple reports indicating high diagnostic accuracy, sensitivity, and specificity in even subcentimeter peripheral lung lesions [9]. Other series describing AFOP report a significant number of cases diagnosed with PTNB [6]. The nodule biopsied in our case was subpleural in the periphery of the left lung and we had high confidence that a representative sample was obtained. Alternative diagnoses were thoroughly explored, keeping in mind the atypical clinical presentation, but with the histopathological findings described above not meeting criteria for DAD or OP, the diagnosis is most consistent with AFOP.

4. Conclusion

Research regarding the clinical picture, diagnosis, and treatment of secondary AFOP is limited. AFOP is often misdiagnosed as infection, cancer, or other pulmonary manifestations of disease, which may lead to a delay in accurate diagnosis and adequate treatment. While there have been many recorded cases of AFOP in various autoimmune diseases, this is the first reported case with features of AFOP on pathology associated with Crohn's disease.

CRediT authorship contribution statement

Sohi Mistry: Conceptualization, Data curation, Writing – original draft, Writing – review & editing, Validation, Visualization. **Asangi R. Kumarapeli:** Conceptualization, Writing – original draft, Writing – review & editing. **Harsha V. Mudrakola:** Conceptualization, Data curation, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None for all authors.

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