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Case Report
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A Unique Case of Cryptogenic Cicatricial Organizing Pneumonia

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Abstract

Organizing Pneumonia (OP) is an inflammatory reaction within the airways, which is classified as cryptogenic or secondary to a known insult. Traditionally this inflammation is responsive to steroid therapy with improvements in patient's symptoms, radiographic findings, and quality of life. However, relapse of the disease is common when steroid doses are reduced or stopped. In the last six years, there has been a new histological pattern discovered, cicatricial organizing pnemonia (CiOP). Histologically, there is scarred parenchyma and dense intraluminal collagen present within the airways, which is not present in OP. It is unclear why this architectural destruction occurs, and unfortunately to date, seems to be less steroid responsive when compared to OP. The prognosis of CiOP is unknown. We highlight this case to bring awareness to a new histologic variant of organizing pneumonia, where there is limited case series to direct potential therapies. There is growing concern that this variant portrays a worse prognosis than OP, although this is not yet proven in clinical studies. Additional studies are warranted for more information for both providers and patients.

Keywords: Cicatricial organizing pneumonia; Fibrosing interstitial pneumonia; Organizing pneumonia

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Introduction

Organizing pneumonia (OP) is an inflammatory reaction defined histologically by the presence of loosely organized fibromyxoid granulation tissue (Masson bodies) in the lumen of small airways, alveolar ducts, and alveoli [1-3]. It is classified as cryptogenic or secondary to a number of known causes including infection, medications, autoimmune diseases, hypersensitivity pneumonitis, or aspiration [1,4]. Clinically patients present with non-resolving respiratory complaints and pulmonary infiltrates usually after a trial of antibiotics, steroids, or both. They may present sub-acutely with a secondary worsening of symptoms most commonly including dyspnea, dry cough, and fatigue after an initial improvement. It can be difficult to diagnose OP based on chest imaging alone as it can present in a variety of patterns including nodules, reticulations, ground glass opacities, consolidative disease with subpleural or peribronchovascular distribution, or crazy paving. There is preservation of background pulmonary architecture without interstitial or dense airspace fibrosis [5]. These radiographic findings are traditionally steroid responsive [1].

Case Presentation

A 65-year-old male with a remote four pack-year smoking history presented to the hospital with four months of progressive dyspnea on exertion with associated chest tightness. Initial evaluation including basic laboratory data, electrocardiogram, and chest radiograph were normal. An echocardiogram revealed a dilated aorta which prompted a chest Computed Tomography (CT). This was abnormal and he was referred to the pulmonary clinic for further evaluation.

He reported MMRC grade 1 dyspnea without cough, sputum production, or chest pain. His symptoms started about four months prior and were progressive in nature. He had no symptoms or clinical manifestations of autoimmune disease and an extensive serum autoimmune work-up was negative. His occupational and social exposures included a remote history of working on a farm and transporting sand crates approximately 45 years prior to presentation. He also endorsed a 25-year exposure during his childhood and as a young adult to wood dust and coal ash with a

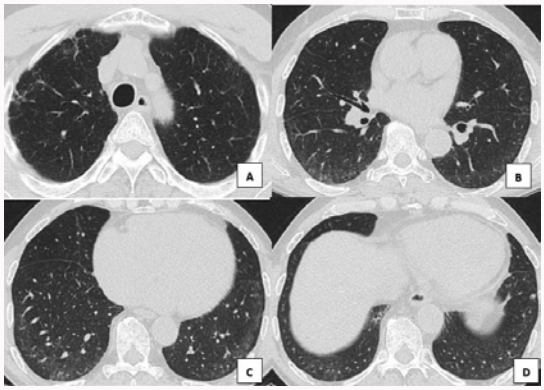

Figure 1: A) Upper lobe with reticular and ground glass opacities. B) Subpleural reticular changes with bronchial wall thickening. C) Middle lung zones with peripherally based reticulations and ground glass opacities. D) Basal lung zones without honeycomb changes.

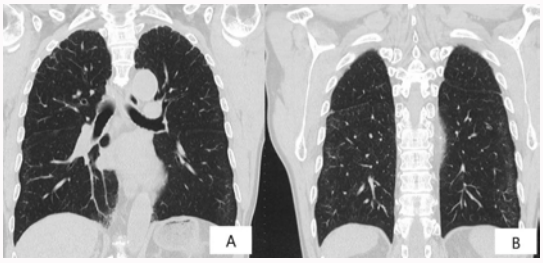

Figure 2A, 2B: Coronal images of the high-resolution chest CT reveal a peripheral distribution with subpleural reticulations, mild traction bronchiectasis and no honeycomb changes.

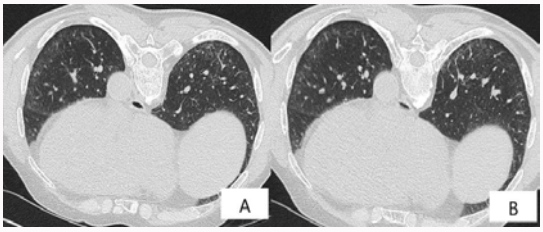

Figure 3A, 3B: High resolution CT prone imaging which reveals persistence of fine reticulations in the bases indicating true fibrotic changes.

coal burning stove at home. His hypersensitivity pneumonitis panel was also negative. His family history was significant for his mother, maternal aunt, maternal uncle, and one maternal cousin who were all diagnosed with idiopathic pulmonary fibrosis. He denied early graying in himself or other family members. Examination revealed dry crackles at the bases bilaterally without additional abnormal findings. He exhibited exertional hypoxia to 85% on a 6-minute walk test, but was able to complete 1,500 feet without significant fatigue. A high-resolution chest CT revealed mild, subpleural, lower lobe predominant ground glass opacities and reticulations without honeycombing (Figures 1A-1D, 2A, 2B), and without complete resolution on prone imaging (Figure 3A, 3B). His pulmonary function tests revealed normal spirometry. His lung volumes revealed a mild restrictive defect (77% predicted), without air-trapping, and moderately reduced diffusion capacity (51% predicted). Given his symptoms, family and exposure history, and imaging findings his case was presented at our multi-disciplinary interstitial lung disease conference and it was recommended he undergo lung biopsy for tissue

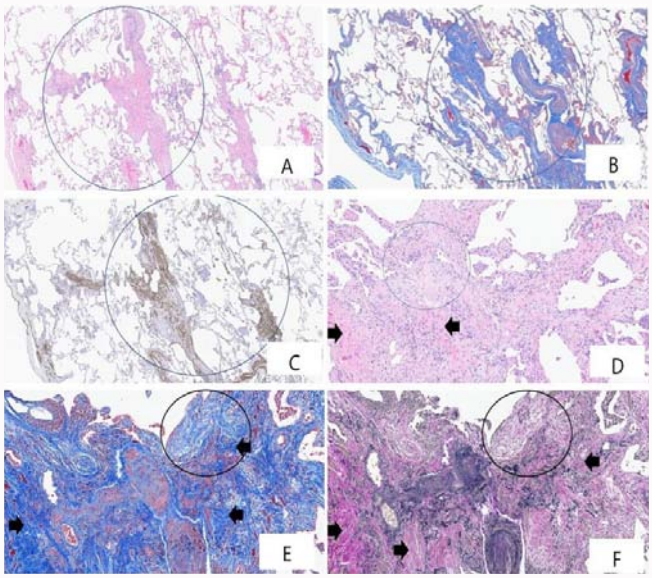

Figure 4: A) Surgical lung biopsy specimen shows the branching polypoidal plugs of organizing pneumonia (circled) (hematoxylin and eosin stain, scanning magnification, 4x).
B) The polypoidal plugs of organizing pneumonia consist of collagen/fibrous tissue highlighted as blue (circled) (Masson Trichrome stain, scanning magnification, 4x).
C) The polypoidal plugs of organizing pneumonia consist of myofibroblasts highlighted as brown (circled) (Smooth muscle actin stain, scanning magnification, 4x).
D) Conventional polypoidal plugs (circled) of organizing pneumonia seen along with the transition to fibrotic areas (arrow) (hematoxylin and eosin stain, low power magnification, 10x).
E) Conventional polypoidal plugs (circled, pale blue) of organizing pneumonia seen along with the transition to fibrotic areas (arrow, deep blue) (Masson Trichrome stain, low power magnification, 10x).
F) Conventional polypoidal plugs (circled, lighter areas) of organizing pneumonia seen along with the transition to fibrotic areas (arrow, magenta) (Elastic Van-Gieson stain, low power magnification, 10x).

sampling. He underwent right sided Video Assisted Thoracoscopic Surgery (VATS) wedge resection. The predominant histologic feature was that of peribronchiolar and subpleural fibromyxoid plugs transitioning into fibrosis (Figures 4A-4F). This airspace organization (Masson bodies) shows varying degrees of fibrosis, demonstrated as deep blueish and light magenta areas on the Masson Trichrome and Elastic Van-Gieson histochemical stains respectively. Smooth muscle actin immunohistochemical stain showed the presence of myofibroblasts. There was also evidence of chronic pleuritis, but no granulomata, food, or foreign material were present. There was no microscopic honeycombing or fibroblastic foci.

Discussion

The term Cicatricial OP (CiOP) was recently introduced within the last six years to describe a histologically discrete subtype of OP [2,4]. First described by Yousem et al. in 2017, there are only a small number of case reports to date reviewing clinical, radiographic and histologic data of this condition [2,4,6-8]. Symptoms are similar to those in OP and range from dyspnea on exertion to dry cough, reported in up to 80% of individuals [2,4,7]. On imaging, findings typical of OP such as subpleural, peribronchial or nodular consolidations, as well as reticulations with associated ground glass are common [4,6,7]. Chronic fibrotic changes, including traction bronchiectasis or honeycombing are uncommon in CiOP [4,7,9,10]. The radiographic similarities between OP and CiOP make it difficult

to diagnose without tissue sampling. Histologically, OP fills the small airways and develops into patchy airspace disease with loose connective tissue, occasionally with mixed fibrin and alveolar filling, without scar or honeycomb formation [4]. A key pathologic finding in CiOP is the presence of scarred lung parenchyma and dense intraluminal collagen within the fibroinflammatory mass [6]. There is distortion but not destruction of the parenchymal architecture because intact septal elastin is drawn inwards toward the central eosinophilic fibrotic tissue. These architectural changes make it appear as if the center of the fibroinflammatory mass is scarred while the periphery of the nodule displays typical loose fibromyxoid buds of connective tissue consistent with OP [4,8]. Cicatricial features are common in OP and can be present more than 50% of the time; however, a cut-off of equal to or greater than 50% cicatricial changes has been proposed to define CiOP [2].

Our patient had greater than 60% cicatricial features on biopsy.

The pathogenesis and development of cicatricial features is unclear. Potentially OP has gone too long under recognized and under treated, or perhaps there is a specific immune mediated reaction within these patients that puts them at increased risk. There is limited data on the prognosis of CiOP, with mixed results to date regarding the effectiveness of steroid therapy [2,4,6-8]. Given the ambiguity of symptoms and lack of characteristic imaging findings, the diagnosis of CiOP requires a lung biopsy. Current potential treatments include oral steroids with doses ranging from 40 mg/day to 120 mg/day for greater than 2 months. Yousem et al. reported 45% of 12 patients had resolution of their radiographic infiltrates and were without symptoms at 110 months of follow up while the remaining 55% had progressive or persistent radiographic disease despite steroids [4]. Similarly, in a Canadian cohort, 60% of patients had radiographic improvement or stability with steroids between 2 and 49 months [7] and in a cohort from Mayo Clinic, 67% of patients were alive after a median follow up of 47 months [2]. Our patient was started on prednisone at 0.5 mg/kg daily; however, after 6 months of treatment, there was no subjective or radiographic improvement in disease; therefore, steroid therapy was discontinued. There was also no worsening of symptoms or CT findings. To date, his pulmonary function testing and imaging findings remain stable, one year after completion of steroid therapy.

Conclusion

Prior to presentation our patient was a very active man, and although his imaging findings were subtle, his new symptoms affected his daily activities. There were no previous imaging studies to compare the chronicity of his CT findings. While he did have a significant inhalational exposure in his distant past, it is unknown if this had any contribution to his current radiographic findings or symptoms. We postulate that given the remote exposure; his disease is more consistent with a cryptogenic entity. He also had a significant family history of reported idiopathic pulmonary fibrosis. He was referred for genetic counseling; however, deferred additional testing at the time. We highlight this case to raise awareness of this histological form of organizing pneumonia which so far seems to be less steroid responsive than traditional OP. CiOP is an increasingly recognized variant of organizing pneumonia, which requires tissue diagnosis. Histopathological findings include those of organizing pneumonia intermixed with the presence of intra-alveolar fibrosis and dense intraluminal collagen, to a degree more than 50%. The treatment of CiOP is not well characterized and neither are the prognostic indicators of a favorable outcome.

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