A Case of Interstitial Pneumonia with Features of Autoimmunity

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ABSTRACT

We present a case of a 61-year-old woman with several months of gradually worsening shortness of breath, requiring multiple hospitalizations with acute hypoxemic respiratory failure. She was initially treated for eosinophilic pneumonia presumed to be secondary to medications or rheumatoid lung without much improvement. Her subsequent chest CT showed honeycombing and diffuse ground-glass opacities, and she was found to have elevated rheumatoid factor (RF) and anti-CCP antibody titers without extrathoracic features of rheumatoid arthritis. This clinical scenario was suggestive of an interstitial lung disease (ILD) due to occult underlying connective tissue disorder (CTD), along the lines of the recently proposed entity interstitial pneumonia with autoimmune features (IPAF). She continued to deteriorate rapidly and passed away after experiencing recurrent exacerbations. As there is limited evidence to explain the clinical course of such patients, there is a need for prospective research to develop tailored regimens to prevent progression or even reverse the disease process.

KEYWORDS: interstitial pneumonia with autoimmune features, undifferentiated connective tissue disorder with interstitial lung disease

ABBREVIATIONS: **Anti-CCP**, Anti-cyclic citrullinated peptide; **BAL**, bronchoalveolar lavage; **AE-IPF**, Acute exacerbation of Idiopathic Pulmonary Fibrosis; **CTD**, Connective tissue disorder; **CTD-ILD**, Connective tissue disease-associated interstitial lung disease; **CT**, Computed tomography; **CHF**, Congestive Heart Failure; **COPD,** Chronic Obstructive Pulmonary Disease; **FVC**, Forced vital capacity; **HRCT**, High resolution computed tomography; **IIP**, Idiopathic interstitial pneumonias; **IPAF**, Interstitial pneumonia with autoimmune features; **IPF**, Idiopathic Pulmonary Fibrosis; **ILD**, Interstitial lung disease; **IVIG**, Intravenous immunoglobulin; **NSIP**, Nonspecific interstitial pneumonia; **RA-ILD**, Rheumatoid Arthritis related Interstitial Lung Disease; **RF**, Rheumatoid Factor; **UCTD-ILD**, Undifferentiated connective tissue disorder with interstitial lung disease; **UIP**, Usual interstitial pneumonia.

CASE REPORT

A 61-year-old woman with a long standing history of arthralgias due to osteoarthritis, as well as coronary artery disease, hypertension, hyperlipidemia, and a 46-pack-year smoking history, presented with dyspnea on exertion which was gradually worsening over a few months, myalgias and cough with white sputum production.

She was initially treated for pneumonia, presumed COPD, and possible acute CHF secondary to ischemic heart disease. Given her lack of improvement, further workup was performed. The CT scan of the chest showed diffuse bilateral ground-glass opacities (**Figure 1**). She underwent a bronchoscopy that revealed 29% eosinophils on bronchoalveolar lavage (BAL), raising concerns for eosinophilic pneumonia presumed to be due to hydrochlorothiazide or bupropion, two of her home medications. These medications were discontinued, and the patient was discharged on oxygen along with a course of oral steroids. She was readmitted several weeks later with hypoxemia. She was found to have an elevated rheumatoid factor (RF) of 844 IU/ml and anti-cyclic citrullinated peptide (Anti-CCP) antibodies at >200 units, raising a concern for rheumatoid lung. She denied a history of

Figure 1. CT scan of the chest shows diffuse bilateral ground-glass opacities.

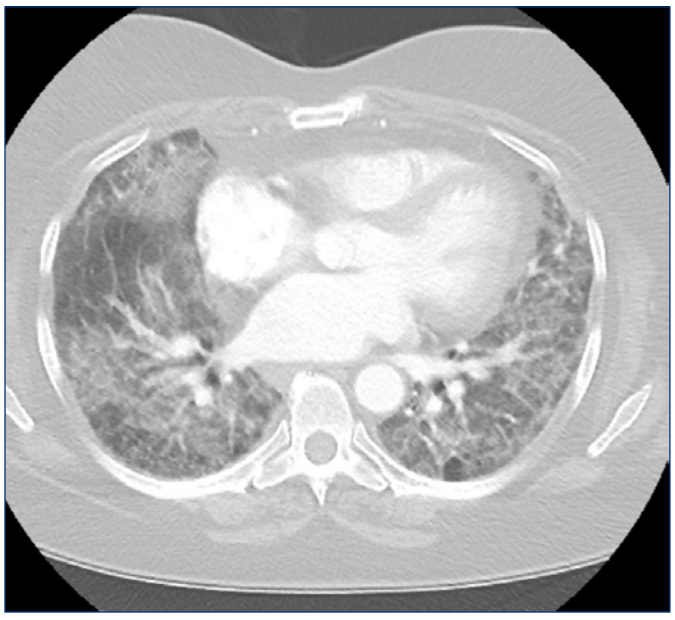
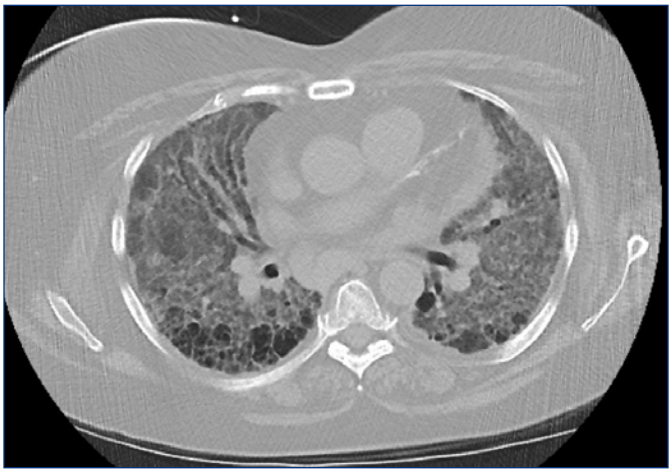


Figure 2. A high resolution chest CT showed diffuse ground-glass opacities, extensive sub-pleural reticulation, traction bronchiectasis, and areas of honeycombing.



morning stiffness and had a remote history of knee effusion with no current joint pain. All other autoimmune workup, including an extended myositis antibody panel, was negative except an initial elevated serum creatine kinase (CK) level at 1,005 IU/L. She eventually was stabilized with high-dose intravenous steroids and mycophenolate after consulting with an interstitial lung disease (ILD) specialist and rheumatologist. Shortly after, the patient had another exacerbation, requiring noninvasive ventilatory support in the intensive care unit where she received intravenous immunoglobulin (IVIG) and was discharged on an increased dose of mycophenolate and oral steroids after a prolonged hospitalization. Since she was at an increased risk of complications from a surgical lung biopsy, she was clinically treated for an occult connective tissue disorder with primary lung involvement.

During her subsequent admission with hypoxemic respiratory failure, a high resolution computed tomography (HRCT) of the chest showed persistent diffuse ground-glass opacities, now with extensive sub-pleural reticulation, traction bronchiectasis, bronchiolectasis, and areas of radiographic honeycombing, suggestive of rapid disease progression (**Figure 2**). She had a prolonged hospital stay where she received IVIG, mycophenolate, steroids, rituximab, and cyclophosphamide. Her hypoxemia progressed and she died approximately 8 months after her initial presentation to the hospital for respiratory symptoms.

DISCUSSION

Up to 30% percent of patients with a new diagnosis of ILD may have a known diagnosis of systemic autoimmunity, yet it is not uncommon to present with lung findings as the primary manifestation of an underlying undiagnosed connective tissue disorder.[1,2] As most patients with connective tissue disease-associated ILD (CTD-ILD) experience better clinical outcomes than idiopathic interstitial pneumonias (IIP), identification of the etiology of ILD is essential for its impact on prognosis and management.[1]

The current European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines exclude patients with known CTD from the diagnosis of idiopathic interstitial pneumonias (IIP).[3,4] However, some patients have a unique phenotype of underlying undifferentiated connective tissue disorder with otherwise unclear etiology of interstitial lung disease (UCTD-ILD).[2] As per the European Respiratory Society and American Thoracic Society in 2015, a consensus-derived nomenclature interstitial pneumonia with autoimmune features (IPAF) was formed to classify and further study such patients.[1,2]

To be classified as interstitial pneumonia with autoimmune features (IPAF), patients must show interstitial pneumonia on lung HRCT and/or surgical lung biopsy, be unable to meet connective tissue disease (CTD) diagnostic criteria, exclude alternative etiologies, and satisfy criteria from two of the following three domains: clinical, serologic, and morphologic. Clinical criteria include physical manifestations of CTDs; serologic criteria include elevated levels of various auto-antibodies, and morphologic criteria include specific patterns of ILD as suggested by lung HRCT or determined by surgical lung biopsy.[1]

Our patient had significantly elevated RF and anti-CCP serum titers without any symptoms or physical exam findings of defined CTD. Apart from her previous smoking history and a remote history of jewelry washing, she had no environmental exposures or medication use likely to explain the presence of ILD. There is increasing evidence of an association between higher levels of anti-CCP antibodies in patients who do not meet the diagnostic criteria for rheumatoid arthritis and the development of Interstitial Lung Disease.[5] Tobacco smoking can cause Anti-CCP antibody production with site-specific citrullination in the lungs which could predate arthritis. RA-ILD has a poor prognosis, especially with extensive lung involvement.[6] On the initial BAL fluid analysis, our patient had an eosinophil level of 29%. Though remarkably elevated levels of BAL fluid eosinophil percentage (≥25%) is more often found in eosinophilic pneumonia than in Idiopathic Pulmonary Fibrosis (IPF), a modest increase in the percentage of eosinophils in the BAL fluid is one of the predictors of acute exacerbation of IPF (AE-IPF) and has been also associated with a poor prognosis in fibrosing ILDs.[7,8]

She had lung HRCT findings of diffuse ground-glass attenuation with sub-pleural reticulation along with honeycombing and traction bronchiectasis without apicobasal gradient. This HRCT pattern was not felt to be diagnostic of any specific entity but could have represented fibrosing nonspecific interstitial pneumonia (NSIP) or usual interstitial pneumonia (UIP) patterns of disease. A tissue diagnosis would have been beneficial to better classify this patient, but transbronchial lung biopsy is usually of a low yield in fibrotic ILD, and a surgical lung biopsy can be a high-risk procedure in certain patient populations. In a retrospective study, in-hospital mortality post non-elective surgical lung biopsy in ILD patients was 16% and even higher in patients with diffuse ILD and acute hypoxemic respiratory failure.[9,10]

As the proposed criteria for IPAF is yet to undergo validation, management plans for these patients are not well-established and instead are made on a case-by-case basis with involvement of a multidisciplinary team.[10] In patients with

known CTD-ILD, oral steroids and/or immunosuppressive therapy have long been the cornerstone of the treatment.[11,12] While there are no randomized controlled trials supporting the efficacy of immunosuppressive treatment for IPAF, one retrospective study found that mycophenolate treatment was associated with improvement in forced vital capacity (FVC) in patients with CTD-ILD or IPAF.[13] Rituximab treatment has been associated with stability of lung function in refractory IPAF in one case series.[14] Cyclophosphamide treatment has been associated with improvement in FVC in patients with steroid-refractory unclassifiable idiopathic interstitial pneumonias, particularly those patients meeting the criteria for IPAF.[15]

Pulse dose steroid therapy has been used in rapidly progressing IPF as well as fibrosing NSIP.[11] There are a few reported cases where IVIG has been used in myositis-associated ILD and refractory cases of other forms of ILD.[16] Most studies suggest that patients with IPAF have survival benefit as compared to non-IPAF IIP patients.[17] Various studies suggest benefit from lung transplantation in patients with severe CTD-ILD, though there are no guidelines on lung transplantation in IPAF.[18]

CONCLUSION

Our patient was treated with prednisone, mycophenolate, rituximab, IVIG and cyclophosphamide, but her disease continued to progress during 7 hospitalizations, including 2 ICU admits, and the majority of her hospital-free time in a rehabilitation facility, ultimately leading to her death in less than one year after her initial hospital presentation with shortness of breath. It remains unclear if her ILD did in fact represent IPAF, and there is still very little known about the underlying mechanisms driving this entity (or entities). Given the limited data, further studies are needed to refine the IPAF classification criteria, validate the appropriate treatment plans, and understand the trajectory of this disease.

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