Interstitial pneumonitis with autoimmune features: 2 case reports and review of literature

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Abstract

The classification of interstitial pneumonia with autoimmune features (IPAF) is used to categorize patients with an autoimmune substrate and pulmonary interstitial involvement, who do not meet the classification criteria for any specific connective tissue disease. These patients seem to have a better clinical course than patients with IPAF. The diagnosis of IPAF is of paramount importance and *a window of opportunity* to identify and to treat forms of early onset of pulmonary interstitial disease without any established damage and to recognize incomplete forms of connective diseases preventing complete clinical manifestation.

Introduction

Many patients with idiopathic interstitial pneumonia (IIP) have clinical features that suggest an underlying autoimmune process, but do not meet the standard criteria for a connective tissue disease (CTD).[1] The *European Respiratory Society/American Thoracic Society Task Force on Undifferentiated Forms of Connective Tissue Disease associated Interstitial Lung Disease* proposes the term *interstitial pneumonia with autoimmune features* (IPAF) and offers classification criteria organized around the presence of a combination of features in three domains: a clinical domain consisting of specific extra thoracic features, a serologic domain consisting of specific autoantibodies, and a morphologic domain consisting of specific chest imaging, histopathologic or pulmonary physiologic features. A designation of IPAF should be used to identify individuals with IIP and features suggestive of a suspected CTD.[2]

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Case Reports

Case #1

A 68-year-old man was referred to our clinic for a suspected connective tissue disease. He did not report symptoms of Raynaud phenomenon, sicca syndrome, strength deficit, arthralgia; he complained of an irritating dry cough. Ex-smoker for 20 years, he denied exposure to pneumotoxic substances or allergies or familiarity with respiratory diseases. He had an history of revascularized ischemic heart disease and a previous episode of paroxysmal atrial fibrillation treated with pharmacological cardioversion and followed by oral anticoagulant therapy. His previous therapy with cordarone was stopped for pulmonary interstitial disease. In particular, he developed a persistent dry cough in May 2016 and had spirometry which was within the normal limits. However, high-resolution computed tomography (HRTC) showed a fine reticular mantle framework at the bases and the ventral segments of the upper lobes. Initial interface images from distortion were fibrotic with no honeycombing [fibrosing non-specific interstitial pneumonia (NSIP) pattern]. Doppler echocardiography revealed the presence of a post-ischemic dilated cardiomyopathy with hypokinesia (fraction of ejection FE 38-40%). The rheumatological physical examination showed the presence of *Mechanic hands* characterized by distal digital fissuring and cracking of the skin. Puffy hands or Raynaud phenomenon or digital ulcers or sclerodactyly were absent. There were not strength deficit or peripheral synovitis or impotence in the limbs. Thoracic physical examination showed fine bi-basal crackles, while the cardiac examination showed the known arrhythmia. Blood tests in multiple determinations documented a positivity for anti Pm SCL 75, while the remaining autoantibodies were negative [standard anti extractable nuclear antigens (ENA), anti-nucleus antibodies (ANA), anti cytrullinated proteins (CCP), anti-muscles antibodies related to myositis (antiMI 2 antiKu, antiPM Scl 100 antiJo 1 antiPL 7 PL 12 EJ, OJ)]. Muscle necrosis enzymes were normal

(aldolase, creatikinase CPK and transaminase GOT normal). A spirometry with carbon monoxide diffuse (DLCO) was performed: forced vital capacity (FVC): 80% of predicted, total lung capacity (TLC): 79% of predicted, DLCO/Va: 75% of predicted. 6 minutes walking distance (6MWD): 560 m (Nadir SpO_2 93%). Test for tuberculosis (quantiferon) was negative. Patient performed a capillaroscopy and electromyography of the 4 limbs that were normal. Due to the heart cardiac comorbidity, bronchoscopy with broncho wash has not been done. On the basis of the pulmonary HRCT scan (confirmed in several CT), a multidisciplinary (pneumologist, radiologist and rheumatologist) diagnosis of fibrosing NSIP with IPAF characteristics was made (positivity for Pm Scl 75 mechanic's fingers). It was decided in agreement with pulmonologists to start a steroid therapy to scale with prednisone 25 mg day for 1 month and to follow gradual tapering.

Case #2

The patient was a 64-year-old woman with a history of gastroesophageal reflux disease developed years earlier (with previous gastric fundoplication surgery) and familiarity for Sjögren (sister) and pulmonary fibrosis (father). She was diagnosed with Morphea in 2015 and treated with topical therapy. She had autoimmune blood tests which were positive for the antiphospholipid antibodies (lupus anticoagulant, antibeta 2 glycoprotein I GPI) with a high titer positivity of the rheumatoid factor. The remaining rheumatological autoimmunity and muscle enzyme tests were normal. Tuberculosis test was negative and acute phase reactants were normal. For reported dysphagia, she performed esophageal manometry with evidence of hypokinetic changes in peristalsis compatible with a connective tissue disease. A digestive X ray confirmed esophageal hypokinesia, while a pH impedance measurement did not show any reflux. The patient underwent capillaroscopy that excluded any disease with a scleroderma pattern. She reported no symptoms of Raynaud phenomenon, sicca syndrome, strength deficit, arthralgia and only complained of an irritating dry cough. HRCT showed a thickening of the interstitium at the bases and thickened septa, many ground glass areas, panel compatible with NSIP (Figures 1 and 2). Also esophageal dilation was reported. Bronchoscopy was performed with bronchoalveolar lavage and revealed mild lymphocyte infiltrate, desquamation of endoalveolar macrophages and the presence of some giant cells. Spirometry was normal, while capillary alveolar diffusion was slightly reduced. The rheumatological physical examination showed Morphea in the lower third of the right leg and in the lower right abdominal quadrants. She had no of puffy hands or digital ulcers or microstomy or skin calcifications and no synovitis. The thoracic physical examination showed fine bi-basal crackles. Spirometry with DLCO showed FVC: 80% TLC: 79% DLCO/Va: 55% 6MWD: 385 m (Nadir SpO_2 90%). Also, in this case a multidisciplinary approach was adopted. According to pulmonologists, she was diagnosed with NSIP with IPAF (morphea, relaxation of esophagus of the esophagus, antiphospholipid antibodies and rheumatoid factor positive, 1 sister with Sjögren). We decide to start azathioprine 50 mg day and prednisone 25 mg day to escalate quickly.

Discussion

Interstitial pneumonias are a large group of diseases mainly characterized by an excessive deposition of extracellular matrix in the alveolar interstitium, which can lead to lethal respiratory failure. They can be idiopathic or secondary to smoking, environmental exposures or autoimmune diseases.[3] The term *interstitial pneumonia with autoimmune features* was proposed to classify patients with an interstitial lung disease (ILD) associated with clinical or serological characteristics of autoimmune diseases, but who do not meet fully the classification criteria for specific connective tissue dis-

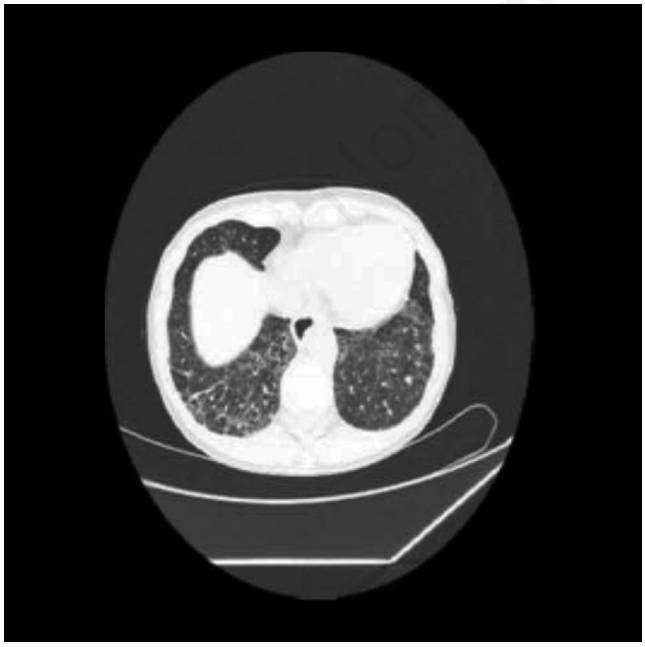

Figure 1. High-resolution computed tomography image suggesting nonspecific interstitial pneumonia. Note the ground glass areas at the lung bases bilaterally and thickening of the septa.

Figure 2. High-resolution computed tomography image suggesting nonspecific interstitial pneumonia. Note the ground glass areas at the lung bases bilaterally.

eases.[4] The proposed classification criteria for IPAF are described in by Fisher *et al*.[2] The proposed criteria reflect the expert panel opinion and will need to be validated on the basis of prospective research studies. The presence of interstitial pneumonia on HRCT imaging and/or in surgical lung biopsy is necessary for the classification of IPAF. An additional condition required for the classification of IPAF is the exclusion of known causes for interstitial pneumonia. Furthermore, patients should not meet criteria for a defined CTD.[2] The classification criteria revolve around three central domains: a clinical domain consisting of specific extra-thoracic features, a serologic domain consisting of specific circulating autoantibodies, and a morphologic domain consisting of specific chest imaging features, histopathologic features or pulmonary physiologic features. To be classified as having IPAF, the patient must meet all of the aforementioned criteria and have at least one feature from at least two of the domains**.** In the clinical domain, specific clinical features suggestive of an underlying CTD are included. Some features, such as Raynaud's phenomenon, palmar telangiectasia, distal digital tip ulceration and digital oedema, are specific signs for systemic sclerosis that can be highlighted during the clinical visit .[5,6] Other specific features, such as digital fissuring (*mechanic hands*) and persistent rash on the digital extensor surfaces (Gottron's sign), are indicative of anti-synthetase syndrome or systemic sclerosis-myositis overlap associated with PM-Scl antibody positivity.[7,8] The use of nailfold microscopy is helpful to identify capillary loop abnormalities that can be predictive of CTDs.[9] Peripheral joint synovitis, but not joint pain alone, is included as an IPAF criterion, while other non-specific features, such as alopecia, photosensitivity, oral ulcers, weight loss, sicca symptoms, myalgia or arthralgia, are not included. In the serologic domain, less specific serologic markers, such as low-titer ANA, low-titer rheumatoid factor (RF), erythrocyte sedimentation rate, C-reactive protein or creatine phosphokinase, are not included. ANCA panel positivity is not included in the serologic domain, because it positivity is related with vasculitides are associated with the vasculitides rather than the CTD-ILD spectra of disorders. Low-titer ANA positivity with a diffuse, homogeneous or speckled staining pattern is excluded, because weak ANA positivity is present in many non-rheumatic patients and even in *healthy* control populations .

Similarly, low titre positivity for RF, which is often present, for example, in otherwise healthy elderly subjects, was excluded.[2] In particular, it is necessary to have a titer of ANA diffuse or homogeneous or speckled staining pattern, positivity at least 1:320 and an high-titer RF values (defined as greater than or equal to twice the upper limit of normal) to meet IPAF inclusion criteria.[10,11] Instead ANA positivity, with either a nucleolar or centromere-staining pattern, is included as an IPAF criterion regardless of the titer, because of a strong association with systemic sclerosis.[10] In accordance with current guidelines for ANA testing, the preferred method for the ANA assay is indirect immunofluorescence, because the ELISA assay for ANA testing could give false negatives in subsets of patients with systemic sclerosis.[12,13] For the other autoantibodies, any value above the upper limit of normal is considered positive. It is known that serologic testing may be repeated for various reasons, such as when an autoantibody titer is borderline positive. However, for the purposes of IPAF criteria, serologic testing does not need to be repeated, if positive**.** The patterns commonly found in CTD-ILD and that suggest an underlying autoimmune process are NSIP, organizing pneumonia (OP), NSIP with OP, and lymphoid interstitial pneumonia (LIP).[14] A radiologic pattern of usual interstizial pneumonia (UIP) is most frequently associated with rheumatoid arthritis;[15] therefore a radiologic UIP pattern is associated to IPAF only in the presence of at least one feature from the other two domains (a clinical feature or a serologic feature) or another morphologic feature. NSIP's ongoing CT alterations are characterized by basal predominant reticular abnormalities with traction bronchiectasis, peri-bronchovascular extension and subpleural sparing, frequently associated with ground-glass attenuation.[16] OP's ongoing CT alterations are characterized by bilateral patchy areas of consolidation with a subpleural and lower lung zone predominance,[17] while HRCT findings suggestive of LIP are defined as predominantly peri-bronchovascular cysts, with or without ground glass opacities or reticular abnormalities. A NSIP pattern is histologically characterized by interstitial inflammation and alveolar wall fibrosis with a uniform appearance.[16,17] A cellular NSIP pattern demonstrates a mild to moderate interstitial chronic inflammatory infiltrate with little fibrosis, while the fibrosing NSIP pattern is mainly characterized by interstitial thickening with uniform fibrosis and little cellular inflammation.[17] Histologically, the OP pattern is a patchy alveolar filling process characterized primarily by tufts of fibroblastic organization involving alveolar ducts and alveoli with or without bronchiolar intraluminal polyps. Histologically, LIP is characterized by polyclonal and inflammatory cellular infiltrates, which may be diffuse and interstitial and/or which may form nodular lymphoid aggregates with or without germinal centres.[17] In addition to interstitial pneumonia, the presence of several concurrent thoracic manifestations is another characteristic often encountered among patients with CTD.[2] Although the IPAF criteria classification needs to be revisited, recognizing patients with IPAF is of paramount importance and *a window of opportunity* to identify and treat forms of early onset of pulmonary interstitial disease without established damage as well as recognize incomplete forms of connectivopathies preventing a complete disease manifestation.

Conclusions

A designation of IPAF should be used to identify individuals with IIP and features suggestive of suspected CTD. The collaboration between rheumatologists and pneumologists is very important to recognize this interstitial pneumonia. As shown in the literature, IPAF patients compared to IIP tend to be younger, predominantly females and with NSIP pattern, but especially they achieve better performance in pulmonary function tests and need less O_2 support.

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