EDITORIAL

Fibrotic or nonfibrotic interstitial lung disease in patients with primary Sjögren syndrome

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Primary Sjögren syndrome (pSS) is a heterogeneous disease that impairs the quality of life (QoL), mainly because of dryness of the mouth and eyes, fatigue, and joint pain; it presents with systemic manifestations in 30% to 40% of patients, including the pulmonary involvement.[1] Pulmonary manifestations of the disease are heterogeneous but they represent a leading cause of morbidity and mortality, particularly when interstitial lung disease (ILD) associated with pSS (pSS-ILD) is diagnosed.[2]

The term ILD refers to a broad category of more than 200 lung diseases encompassing a variety of illnesses with diverse causes, treatments, and prognoses. These disorders are grouped together because of similarities in their clinical and radiographic presentations, and physiological features leading ultimately to pulmonary fibrosis in a great proportion of cases.[3] A specific ILD category may occur among various connective tissue diseases (CTD-ILD), including pSS.[4] The only available classification of CTD-ILD mirrors the histologic classification of idiopathic interstitial pneumonias.[3] Due to difficulties and potential risks associated with obtaining lung biopsies, clinicians often use radiographic patterns on high-resolution computed tomography (HRCT) as proxy of the disease severity and underlying processes.[5] The most common pattern in pSS-ILD is nonspecific interstitial pneumonia (NSIP), followed by usual interstitial pneumonia (UIP), and subsequently organizing pneumonia and lymphocytic interstitial pneumonia. A combination of different imaging patterns can also be observed.[6]

In this issue of *Polish Archives of Internal Medicine*, Li and colleagues[7] retrospectively studied 151 patients affected by pSS, and compared the patients with fibrosing ILD with those without this presentation. Their analysis showed that the fibrosing ILD was more frequent among men and presented with a greater frequency of dry cough, shortness of breath, and fever than nonfibrosing ILD. Additionally, the fibrosing ILD group had a shorter median duration of the disease and lower frequency of the mouth and eyes dryness. This group showed also higher leukocyte count, levels of C3 and C-reactive protein, together with a lower frequency of positive anti-Ro52 and anti–Sjögren-syndrome–related antigen A antibodies. Other markers, such as C4, rheumatoid factor levels, antinuclear antibody and anti–Sjögren-syndrome–related antigen B antibody positivity rates were similar in both groups.

Analyzing the HRCT findings, the authors[7] reported an asymmetrical appearance, distributed in the basal and lateral regions of both lower lobes in 48 patients with fibrosing ILD, together with reticular characteristics consistent with pulmonary fibrosis. Surprisingly, the fibrosing ILD group included significantly more patients with ground-glass opacities, mediastinal lymphadenopathy, bronchial wall thickening, interlobular septal thickening, subpleural lines, bronchiectasis, consolidation, and pleural thickening, while micronodules were more prevalent in the nonfibrosing ILD group. The patients in both groups were followed-up for a median time of 11.5 months. During this period, they underwent a mean of 2 chest examinations, and most of them received both steroid and immunosuppressive treatment with different results. No significant differences were detected on the final radiological assessment between the 2 groups.

In a multivariable regression analysis, dry cough and shortness of breath were the only independent predictive factors of pulmonary fibrosis in the patients with pSS.

The predictive value of symptoms for the disease progression has been characterized in other ILDs, particularly idiopathic pulmonary fibrosis (IPF). In IPF, cough was shown to be an independent predictor of the disease progression, and could be used to predict time to death or lung transplantation.[8] Similarly, it was shown that

changes in dyspnea score over 6 and 12 months were predictive of survival time in IPF.[9]

Nevertheless, in the discussed study,[7] the group of fibrosing pSS-ILD patients included individuals with a UIP pattern (prototypical progressive fibrotic phenotype), and other fibrosing patterns, such as NSIP, organizing pneumonia with concomitant interstitial fibrosis, and pleuro-parenchymal fibroelastosis on the original HRCT.[10] The definition used by Li et al[7] is interesting, since it aims to respect the fact that, in addition to IPF, a proportion of other chronic fibrosing ILDs develop a progressive fibrosing phenotype characterized by increasing fibrosis on HRCT, worsening of pulmonary function and symptoms, leading to impaired QoL and early mortality.[11] Therefore, early recognition of symptoms and signs of pulmonary involvement is paramount to prevent disability and death in these patients.[12] Unfortunately, the retrospective design of the study performed by Li et al,[7] together with the lack of pulmonary function data and a short follow-up, did not allow them to find out if pSS-ILD patients, particularly those in the fibrosing group, showed a progressive phenotype, impacting QoL and survival.

Moreover, the study did not report any information on potential episodes of acute exacerbation among the included patients. Exacerbation is defined as an acute worsening or development of dyspnea associated with new bilateral ground-glass opacities and/or consolidations on HRCT, superimposed on a background pattern consistent with ILD.[13] They are characterized by very poor prognosis, with in-hospital mortality of 50% to 100% and with over 90% mortality in the patients requiring ventilatory assistance, observed also in the patients with CTD-ILD.[14] It is known that exacerbations are more likely in CTD-ILD with a fibrotic phenotype;[14] therefore, it would have been important to consider these dramatic events in the present study.

Furthermore, another limitation of the study is insufficient reporting of ongoing treatments and their effects: the study highlights a radiological improvement in the subgroup of pSS-ILD patients treated with steroids and immunosuppressants, but no data are available on the use (and effect) of antifibrotic drugs,[15] currently approved for progressive fibrosing ILDs other than IPF,[11] and therefore also for fibrotic, progressive pSS-ILD.

In conclusion, this study suggests that the patients with fibrosing pSS-ILD present with a specific phenotype, characterized by a higher white blood cell count, more aggressive presentations with shorter disease course, lower frequency of mouth and eye dryness, and higher frequency of dry cough and shortness of breath than the patients with a nonfibrosing pSS pattern. Cough and shortness of breath were also independent predictors of pulmonary fibrosis in pSS. These results need to be interpreted with caution mainly due to the retrospective design. Confirming these findings with prospective well-designed studies would be important to validate the results of Li et al[7] and to offer new robust screening tools for fibrotic pSS-ILD.

ARTICLE INFORMATION

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