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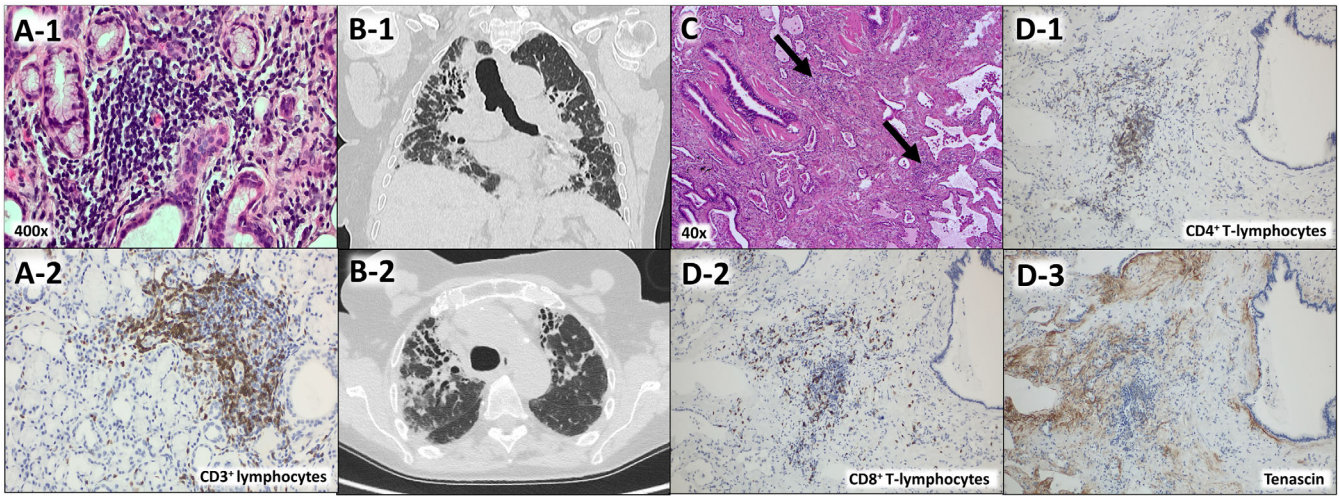
Clinical Images: Severe interstitial lung disease in Sjögren disease — What happens in the lungs? Inflammation or fibrosis?



The patient, a 66-year-old woman, was first diagnosed with idiopathic pulmonary fibrosis (IPF) in 2015, and therapy with nintedanib was initiated. In 2020, the patient presented to our clinic for differential diagnosis. The laboratory tests revealed an elevated antinuclear antibody titer as well as anti-Ro/SSA and anti-La/SSB antibodies. Lip mucosal biopsy revealed findings of lymphoplasma cellular infiltration of the salivary glands consistent with Sjögren disease (SD) (**A-1** and **A-2**). High-resolution computed tomography (HRCT) of the lungs showed marked bronchiectasis, subpleural and basal reticulations, and peripherally basally accentuated ground-glass opacities, but no significant honeycombing (**B-1** and **B-2**). According to the international IPF guideline, the pattern could be classified as "probable usual interstitial pneumonia (UIP)" (1,2). Because of the patient's poor general health condition, an invasive diagnostic was not possible. Based on these findings, the diagnosis of SD with severe interstitial lung disease (ILD), not responding to nintedanib, was confirmed. We then initiated an immunosuppressive induction therapy with cyclophosphamide and glucocorticoids, followed by a switch to mycophenolate mofetil. Due to the rapid and severe pulmonary deterioration, a single lung transplantation was performed.

Microscopically, the central and peripheral lung parenchyma revealed a patchy fibrous proliferation with an extensive fibrosis pattern and lymphohistiocytic infiltration, especially peripheral with bronchiolization and scattered fibroblastic foci (**C**, partial lymphocytic infiltration [arrow]), $CD4^+$ and $CD8^+$ lymphocytic infiltrates (**D-1** and **D-2**), and increased level of tenascin as extracellular marker of fibrosis (3) (**D-3**), compatible with the diagnosis of ILD in SD. The histologic pattern corresponded to the fibrotic subtype in nonspecific interstitial pneumonia (fibrotic pattern) with partial inflammatory superimposition, although aspects of a typical UIP pattern (bronchiolization, fibroblastic foci, peripheral predominance) were also evident.

The present case demonstrated the relevance of a rheumatological (interdisciplinary) evaluation even at the initial diagnosis of IPF. Castelino et al showed a switch from IPF to ILD in connective tissue disease (CTD) in up to 28% of the patients after an interdisciplinary evaluation (4). Moreover, the change of diagnosis was associated with a modification of the therapy in 80% of the patients with CTD-ILD (4). Even pulmonary asymptomatic patients with CTD can show ILD, making structured screening essential (5,6). That is why all patients with CTD should receive pulmonary function testing including the quantification of diffusing capacity for carbon monoxide (DLCO) at initial diagnosis. In case of reduced DLCO (<80%) or other risk factors, HRCT should be performed to verify CTD-ILD (5,6). Immunologic bronchoalveolar lavage or cryobiopsy may be considered useful to verify differential diagnosis of CTD-ILD (6).

ILD in SD can include active inflammatory changes in addition to fibrotic components. As inflammatory changes can be amenable to immunosuppressive treatment, the importance of early recognition of ILD in SD should be emphasized (7). For a few years antifibrotic drugs (eg, nintedanib) were used for treatment of the fibrotic component (8). Currently, no guideline is available for the treatment of SD-ILD, although reviews recommend immunosuppressive therapy (eg, cyclophosphamide and mycophenolate mofetil) (9). In systemic sclerosis, a reduced progression rate of ILD was observed in the combined immunosuppressive and antifibrotic treatment (10). In this

context, the early combination of antifibrotic and immunosuppressive drugs should be discussed and will be given a higher priority in the future (9).

In summary, this case highlighted the need of a structured rheumatological screening in IPF regarding inflammatory rheumatic diseases. The treatment strategy of SD-ILD should include immunosuppressive and antifibrotic drugs to address the inflammatory as well as fibrotic component.

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