Case report

Autoimmune epithelitis beyond the exocrine glands: an unusual case of anti-Ro/La and Scl-70 lymphocytic interstitial pneumonia

O.D. Argyropoulou¹, L.G. Chatzis¹, D. Rontogianni², A.G. Tzioufas¹

¹Department of Pathophysiology, School of Medicine, National and Kapodistrian University of Athens, Greece; ²Department of Pathology, Evangelismos Hospital, Athens, Greece.

Ourania D. Argyropoulou, MD
Loukas G. Chatzis, MD
Dimitra Rontogianni, MD
Athanasios G. Tzioufas, MD

Please address correspondence to: Prof. A.G. Tzioufas,
Department of Pathophysiology,
School of Medicine,
National and Kapodistrian University of Athens,
75 Mikras Asias str.
11527 Athens, Greece.
E-mail: agtzi@med.uoa.gr

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ABSTRACT

Objective. Interstitial lung disease is a life-threatening complication of many systemic autoimmune diseases with diverse clinical and histopathological features. Among them, lymphocytic interstitial pneumonia (LIP) is mainly associated with primary Sjögren’s syndrome (pSS). A case of a middle-aged man with LIP, anti-Ro/La, anti-Scl70 autoantibodies and overlapping histopathological features of pSS and systemic sclerosis (SSc) is presented and discussed.

Methods. A 65-year-old man complaining for easy fatigue and dry cough was evaluated. Physical examination revealed bibasilar crackles on auscultation. Imaging tests showed areas of centrilobular nodules with tree-in-bud sign on the medial lobe of the right lung. Pulmonary function tests demonstrated small airways disease. Laboratory evaluation revealed elevated ESR and CRP, ANA titre >1/320, positive Ro52, Ro60 and La autoantibodies but also, weakly positive anti Scl70 autoantibody.

Results. Right lobe lung biopsy showed diffuse fibrosis with altered alveolar architecture and diffuse infiltration of alveolar septa by lymphocytes and mast cells. Ectopic germinal centres were disclosed, adjacent to the small bronchi causing lumen obstruction and validated after the demonstration of CD23 expression, specific for follicular dendritic cells. Biopsy of minor salivary glands revealed intense periductal fibrosis with limited round cell infiltrates, not fulfilling the histopathological criteria for pSS. The diagnosis of LIP was established and the patient received corticosteroids with poor response. Subsequently he was treated with rituximab with satisfactory results.

Conclusion. This case with LIP and disease-specific autoantibodies for pSS and SSc teaches the complexity and overlapping nature of both diseases, extending from autoimmune epithelitis with ectopic germinal centres to fibrosis-related SSc. It points out the significance of the affected tissue biopsy, which may uncover the different disease phenotypes. To this end, treatment with anti-CD20, acting at the crossroads of the pathogenetic mechanisms of both diseases may serve as a first choice therapy.

Introduction

Interstitial lung diseases (ILDs) constitute a large and heterogeneous group of parenchymal lung disorders associated with significant morbidity and mortality. In systemic autoimmune rheumatic diseases and with varying frequencies, the lung is a possible target in the form of ILD. Although non-specific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP) and organising pneumonia (OP) are the most common ILD patterns, lymphocytic interstitial pneumonia (LIP), acute interstitial pneumonia (LIP), acute interstitial pneumonia (AIP)/diffuse alveolar damage (DAD), and rarely desquamative interstitial pneumonia (DIP) have been also observed (1).

LIP is a benign lymphoproliferative disease with female preponderance and is considered as a reaction of the bronchus-associated lymphoid tissue (BALT) to various external stimuli (2). Progressive dyspnea and non-productive cough in the setting of bilateral reticulonodular infiltrates or thin-walled cysts on imaging tests should raise the suspicion for the disease. It may be idiopathic or occur in the context of a systemic autoimmune disease most commonly, primary Sjögren’s syndrome (pSS), rheumatoid
arthritis (RA), systemic lupus erythematosus (SLE), thyroiditis Hashimoto, Myasthenia Gravis or infections mainly HIV and EBV. The clinical course ranges from spontaneous resolution to lymphoma transformation, progressive respiratory failure and death. LIP is a corticosteroid responsive disease, but other immunosuppressive agents (e.g. azathioprine, rituximab) have also been used with variable results (3). Hereafter, we present a case of a middle-aged man with LIP and triple autoantibody activity (anti-Ro/La and anti-Scl70) presenting in the affected tissues both phenotypes of pSS and systemic sclerosis (SSc).

Patient and methods
A 65-year-old man, non-smoker and without any occupational exposure to toxic substances, presented with a 1-month history of easy fatigue and dry cough. He had a history of surgical papillary thyroid carcinoma and ankylosing spondylitis in complete remission (managed only with NSAIDs). The latter was diagnosed on the basis of low back pain in association with mild erosions on plain radiographs, whereas the patient didn’t present signs of peripheral arthritis (RA-like). Pulmonary auscultation revealed bibasilar crackles whereas the remainder of the physical examination was normal. Chest radiograph showed bilateral reticular opacities extending predominantly on the right medial lobe. High resolution chest computed tomography (HRCT) was obtained and revealed areas of centrilobular nodules with a linear branching pattern (tree-in-bud sign) on the medial lobe of the right lung, and a hypodermic tissue developing between the sub-segmental branches of the right pulmonary artery and extending to the parenchyma at the posterior inferior surface of the right upper lobe along the peribronchovascular tissue (Fig. 1a). Pulmonary function tests (PFTs) revealed small airways disease as attested by the significant reduction of MMEF 75/25 (40.8% of the predicted value). Laboratory evaluation revealed elevated ESR and CRP, ANA titre >1/320 with fine speckled nuclear fluorescence pattern (detection by immuno Fluorescence, NOVA Lite HEp-2 ANA kit, Inova Diagnostics, San Diego, USA), positive Ro52, Ro60 and La autoantibodies but also, weakly positive anti Scl70 autoantibody (as detected by immunoblot using the ENA ProfilePlus1 kit, Euroline, Euroimmun, Lübeck, Germany). The patient was negative for HIV and EBV. Schirmer’s test was within normal limits and Rose Bengal staining was negative. A minor salivary gland biopsy and lung biopsy were performed. The content of inflammatory cells were evaluated by Haematoxylin & Eosin (H&E) staining, whilst ectopic germinal centres were demonstrated by H&E staining along with CD23 positivity mainly disclosed by the follicular dendritic cells. The patient gave written consent for the publication of the haematological, imaging and histopathological findings related to his disease.

Histopathological results
Diagnostic thoracoscopy and right lobe biopsy was performed. The histopathological examination showed diffuse fibrosis with altered alveolar architecture and diffuse infiltration of the alveolar septa by lymphocytes and mast cells. Active germinal centres adjacent to the small bronchi, causing lumen obstruction were observed in Haematoxylin Eosin staining (Fig. 1B). The formation of germinal centres was further verified by immunohistochemical staining with the CD23 marker of follicular dendritic cells (Fig. 1C). Thickening of artery walls with interstitial hypertrophy and perivascular fibrosis was also noticed. Minor salivary gland biopsy was performed and revealed profound periductal fibrosis with limited inflammatory cell invasion, not fulfilling the histopathologi-

Fig. 1. Imaging and histopathological features.
A: High-resolution computed tomography (HRCT) of the lungs, showing areas of centrilobular nodules with a linear branching pattern (tree-in-bud sign) on the medial lobe of the right lung (arrow). B: Staining with Haematoxylin eosin x 10 of the medial lobe of the right lung showing diffuse infiltration of alveolar septa by lymphocytes and mast cells. Active germinal centre (thin arrow), adjacent to the bronchial epithelium (wide arrow), causing luminal obstructive effects.
C: Immunohistochemical staining with Haematoxylin eosin x 10 of the medial lobe of the right lung, showing CD23 overexpression on follicular dendritic cells in the germinal centre near the bronchioli (arrow).
D: Staining with Haematoxylin eosin x 10 of minor salivary glands, exhibiting periductual fibrosis with limited cell infiltrates (arrow).

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cal criteria for pSS (Fig. 1D). The diagnosis of LIP was established and the patient was started on corticosteroids. Three months later and due to poor response, worsening of imaging findings and taking into consideration the previous history of papillary thyroid carcinoma, PET/CT was performed and was negative for thyroid or other neoplastic disease. Rituximab was then administered at a dose of 1g/2weeks (2 cycles) with satisfactory results. Indeed, the patient became asymptomatic and PFTs significantly improved, since MMEF 75/25 was increased to 51.1% (improvement more than 10%).

Discussion

This is a very interesting case of LIP with triple specific autoantibody reactivity. Indeed, the complex of Ro and La autoantibodies is necessary for the classification of pSS while, anti-ScI70 associates with SSC. Double tissue phenotyping of the patient disclosed ectopic germinal centres (EGCs) in the lung, adjacent to bronchial epithelium, a finding connoting pSS and fibrotic changes in salivary glands and the lungs, similar to those observed in SSC associated with pSS (4). The overlap features of this case highlight the complexity of systemic autoimmune diseases and suggest some possible common pathways operating for their development.

The most common form of lung involvement in pSS is small airways disease, with peribronchial infiltrates, similar to those observed in salivary glands (5). NSIP, UIP, OP and LIP have also been described in some patients (6). On the other hand, patients with SSC and anti-ScI70 autoantibodies are at higher risk for ILD development with 40–75% presenting with PFTs abnormalities (7). As noted in the opening lines of the manuscript in complex cases like this, one should consider interacting disease pathways, operating in parallel. “Autoimmune epithelitis” is used as the aetiological term for pSS (8) that essentially describes the ability of the epithelial cell to behave as a key player for the initiation and perpetuation of the autoimmune lesion, through mechanisms such as antigen presentation; expression of both costimulatory molecules and the intracellular autoantigens Ro/SSA and La/SSB on their membranes, providing signals for lymphocyte activation, apoptosis, chemokine production and germinal centre formation (9). The latter was the dominant microscopic feature of our case and may very well explain the anti-Ro/La positivity, since B-cells in EGCs may contain intracytoplasmic immunoglobulins with anti-Ro/SSA and anti-La/SSB activity (10, 11).

But how can we address the concomitant fibrotic phenotype in our case? This can be explained in two ways. First, by the direct action of certain cytokines which are produced in the EGCs. As such, the synergistic action of IL-17 and IL-22 on the epithelial cell has previously been described, thus altering its phenotype to a mesenchymal cell with pro-fibrotic properties, via the induction of TGFβ (12). Notably, all these cytokines are found in abundance in the tissue lesion of pSS (13). Second, the association of the extensive fibrotic lesions in both lungs and salivary glands and the poor response to corticosteroids may suggest that beyond inflammation, another route may be implicated. As such, it could be proposed the “epithelial/fibroblastic route”, which is considered to operate as a linking mechanism in ILD of SSC. According to this theory, endothelial cell injury with subsequent vascular damage and alveolar epithelial cell injury are the key initial insults that precede fibrosis. Upon injury, the release of various mediators along with a potential disturbance in tissue remodeling by the transition of epithelial cells to myofibroblasts, contribute eventually to accelerated fibrosis (14).

To conclude, although our patient had LIP and disease specific autoantibodies he did not fulfil classification criteria for pSS or SSC, thus pointing out the complexity and overlapping nature of both diseases. The presentation of this case teaches that, a) LIP in certain cases may have the appearance of autoimmune epithelitis, b) tissue biopsy may disclose different disease phenotypes, pointing that diseases overlapping with Sjögren’s syndrome should be also extended at tissue level, and c) anti CD20 monoclonal antibodies may serve as an alternative therapy for steroid resistant patients.

References