An unusual dyspnea in an 87-year old woman affected by Sjögren’s syndrome

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Abstract

Primary Sjögren’s syndrome (pSS) is a progressive autoimmune disease and is characterized by eye and mouth dryness due to lymphocytic infiltration in lacrimal and salivary glands leading to tissue destruction, but it can also present systemic manifestations including lung involvement. Respiratory manifestations in pSS have a prevalence of 9-20% and can be due to airway and/or lung parenchyma involvement, such as in particular in interstitial lung diseases like lymphocytic interstitial pneumonia (LIP). LIP is an inflammatory diffuse parenchymal lung disease, which is almost invariably associated with other conditions, such as autoimmune diseases and immunodeficiency states, and usually affects women with a mean age of 50 years. We described a case of patient with LIP who was referred to our Internal Medicine Unit and the diagnostic issues related to the patient age and comorbidities.

Case Report

An 87-year-old woman with dyspnea and fever was admitted to our internal medicine unit. Her past medical history included hypertensive heart disease with preserved EF, paroxysmal atrial fibrillation (on oral anticoagulant with rivaroxaban), vascular encephalopathy, chronic kidney disease secondary to hypertensive nephrosclerosis, primary Sjögren’s syndrome (pSS), subtotal thyroidectomy and a recent right ankle fracture.

At admission vital signs were normal (BP 125/60 mmHg, HR 85 bpm, T 36.5°C), except for peripheral oxygen saturation (90%), which required supplemental oxygen (FiO2 40%). Physical examination revealed bilateral basal lung crackles and bilateral leg edema.

Arterial blood gas (ABG) analysis on oxygen therapy revealed severe respiratory failure with PaO2/FiO2 of 162.5 and metabolic alkalosis (pH 7.52, pCO2 36 mmHg, pO2 65 mmHg, SaO2 94%, HCO3– 30 mmol/L). Blood tests showed normocytic anemia (hemoglobin 10.7 g/dL, MCV 80 fl, RDW 16.1%), normal white-cell count (7030/µL; neutrophils 83.3% and lymphocytes 10.5%) and platelets (161,000/µL), elevated C-reactive protein (CRP: 10.1 mg/dL) and erythrocyte sedimentation rate (ESR: 103 mm/h) without procalcitonin elevation, no abnormal aPTT and PT, creatinine 0.84 mg/dL (eGFR >60 mL/min), no increase in hepatic cytolysis (ferritin 236 ng/mL, serum iron 26 mcg/dL, transferrin 204 mg/dL, transferrin saturation 9%), vitamin B12 deficiency (137 pg/mL). Autoimmunity testing was positive for rheumatoid factor (RF 63 IU/mL), ANA (1:160), Ab anti-Ro/SSA (590 U/mL) and Anti-La/SSB (1614 U/mL) and consistent with her pSS history. Serial measurements of cardiac troponins were not suggestive of acute coronary syndrome, yet they were compatible with chronic myocardial injury (44-47-35 ng/L). D-dimer was slightly increased (1650 ng/mL) probably due to inflammation. ECG showed a normal sinus rhythm. A chest X-ray evidenced bilateral lung reticular interstitial opacification and hilar enlargement. Upon suspicion of congestive heart failure induced by an airway infection, we administered oxygen, diuretics and antibiotic therapy (piperacillin/tazobactam plus azithromycin), Microbial assays (blood and urine cultures, oropharyngeal swab for respiratory viral and bacterial infections) were all negative. A transthoracic echocardiogram confirmed the presence of hypertensive heart disease (concentric remodeling with an EF of 55%), ruling out new significant cardiac morphofunctional alterations or pulmonary hypertension.

After 3 days the peripheral edema was resolved but, despite the antibiotic treatment, inflammation markers did not decrease and dyspnea showed no improvement. Since the cause of respiratory failure was still unclear, we performed a chest CT angiography which excluded pulmonary embolism and revealed bilateral ground-glass areas in middle-lower sections of the lungs, multiple parenchymal...
micronodular formations, bilateral scattered thin-walled cysts and enlarged hilar and mediastinal lymph nodes (Figure 1A).

The patient also developed symmetrical acute and painful knee swelling, which was not precipitated by mechanical insult (she was bedridden because of respiratory failure). She had no previous history of gout and her uric acid level was within the normal range. Imaging studies demonstrated signs of joint degeneration consistent with the patient history of knee osteoarthritis. However, radiography did not show any tophi, erosions or calcifications of the joint tissues (cartilage, tendons, ligaments, synovia and capsules) and ultrasonography showed no tophaceous deposits, nor double contour sign overlying the surface of cartilage, thus confirming only the presence of bilateral synovial effusion. Although arthrocentesis was not performed, the patient history as well as her clinical, laboratory and radiological features were more indicative of joint involvement in pSS with positive RF, rather than gout or calcium pyrophosphate crystal deposition disease.

Since an immune-mediated etiology of the pulmonary findings was suspected, the patient underwent glucocorticoid infusion (methylprednisolone 1 mg/kg) with progressive dyspnea improvement, weaning from oxygen supplementation, knee synovial effusions decrease with pain resolution and inflammation markers normalization during 7 days of treatment. The patient was discharged from hospital with one month prednisone tapering schedule (starting from prednisone 0.5 mg/kg). After discontinuation of steroid treatment, a second high-resolution computed tomography (HRCT) scan showed almost complete resolution of lung ground-glass areas and reduction in parenchymal micronodular formations (Figure 1B).

The patient history of pSS, clinical presentation, HRCT findings and response to glucocorticoid therapy led to the diagnosis of lymphoid interstitial pneumonia (LIP). In relation to patient age and comorbidities, we decided not to perform further invasive investigations, considering that the collected data were sufficient for diagnosis.

Discussion

Primary Sjögren’s syndrome is a progressive autoimmune disease which is characterized by eye and mouth dryness and lymphocytic infiltration in lacrimal and salivary glands leading to tissue destruction.1,2 Clinical spectrum of pSS can also include systemic manifestations like arthralgia and arthritis (the most frequent articular manifestation is an intermittent symmetrical non-erosive polyarthropathy which can involve small and large joints in similar proportions),3,4 autonomic dysfunction, pancreatitis, vasculitis, renal involvement, increased risk of lymphoma, fatigue and lung (parenchyma and/or airways) involvement.1,2 The disease outcome depends on systemic manifestations, while sicca features affect primarily quality of life, causing local complications.1 Articular man-

Figure 1. A) Pre-therapy HRCT: ground-glass areas in middle-lower sections of the lungs, multiple parenchymal micronodular formations, randomly distributed, bilateral scattered thin-walled cysts, enlarged hilar and mediastinal lymph nodes. B) Post-therapy HRCT: almost resolved lung ground-glass areas and reduction in parenchymal micronodular formations.
ifestations in pSS are associated with other systemic symptoms and with an active immunological profile (hypergammaglobulinemia, anti-SSA antibodies, RF and cryoglobulinemia). Respiratory manifestations in pSS have a prevalence of 9-20% and an annual estimated incidence of 10% 1 year after the diagnosis of pSS, which increases to 20% within 5 years. Respiratory disorders in pSS affecting the Airways include bronchiectasis, bronchiolitis, and hyper-reactive Airways, while lung parenchyma involvement includes nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), lymphocytic interstitial pneumonia (LIP), organizing pneumonia (OP), pulmonary amyloidosis and pulmonary lymphoma (non-Hodgkin’s lymphoma, marginal zone B cell lymphoma, and mucosa associated lymphoid tissue or MALT). Risk factors for pSS associated ILD include older age, Raynaud phenomenon, peripheral arthritis, esophageal involvement, high-titer ANA, anti-SSA and anti-SSB antibodies, hypergammaglobulinemia and RF. Patients with a positive RF are also more likely to develop articular involvement. Pulmonary function testing (PFTs) must be performed in pSS patients with suspected or established ILD to evaluate disease severity, while HRCT is the procedure of choice for the initial evaluation of pSS associated ILD. Lung biopsy is not routinely recommended, but it may be considered in case of neoplastic and non-neoplastic lymphoproliferative disorders, other cancers, amyloid and a suspected infection unresponsive to empirical therapies, if less invasive testing proved nondiagnostic. LIP is an inflammatory diffuse parenchymal lung disease, that is almost invariably associated with other conditions, such as autoimmune diseases (25-39%) including pSS, systemic lupus erythematosus, autoimmune hemolytic anemia, Hashimoto thyroiditis, primary biliary cholangitis, chronic active hepatitis, viral infections (14%) like HIV and EBV and immunodeficiency states (especially common variable immunodeficiency). Adult patients with LIP are usually women with an average age at presentation of about 50 years. LIP related to pSS is characterized by long course of disease, insidious onset, hypergammaglobulinemia with a variety of autoantibodies and generally presents with progressive cough, dyspnea, weight loss, chest pain, fever and arthralgias. Sjögren’s syndrome is associated with one-fourth of reported cases of LIP, which can precede or follow pSS onset. Chest X-ray findings of LIP are nonspecific, usually showing an ILD pattern characterized by fine or coarse reticulonodular shadowing. HRCT major features include: patchy areas of ground-glass opacities, widespread and poorly-defined nodules, broncho-vascular bundles and interlobular septal thickening. Thin-walled cystic Airways can be seen in approximately two-thirds of patients with LIP. Lung consolidation and architectural distortion, rarely evolving in honeycombing, occur in 40% of cases, while mediastinal and hilar adenopathy are present in 65%. Interstitial lung involvement of LIP should be distinguished from that of COVID-19, which is currently much more common than LIP due to the viral pandemic of SARS-CoV-2. A HRCT feature which is present in both diseases is ground-glass opacity, but there are also some differences. Consolidations are rare in LIP patients, and randomly distributed cysts are the hallmark of the disease. Conversely, COVID-19 is characterized by acute onset of respiratory failure, with clinical and radiographic changes occurring rapidly, and the HRCT findings are ground-glass opacities which are typically distributed in peripheral or subpleural spaces, with or without consolidation, while cysts are rare. LIP lung cysts are usually few in number, but randomly and diffusely distributed in both lungs. They generally measure less than 3 cm in diameter and are frequently situated in areas of ground-glass opacity or in subpleural and perivascular spaces. All the HRCT findings of LIP, with the exception of cysts and architectural distortion, are thought to have at least some degree of reversibility after treatment. The majority of patients show improvement or stability, if treated with corticosteroids, but LIP can evolve to honeycombing in some cases. In non-responders or refractory cases, other immunosuppressive agents, such as cyclophosphamide, chlorambucil and azathioprine, have been used with variable results. Differential diagnosis of cystic lung interstitial diseases include: lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH), Birt-Hogg-Dubé syndrome (BHDS), light chain deposition disease (LCDD) and amyloidosis. Cyst mimics (emphysema, honeycombing, cavity, pneumatocele, bronchiectasis) should be ruled out first, because they are much more common than cystic lung diseases. Lymphangioleiomyomatosis (LAM) is characterized by numerous, thin-walled cysts scattered in both lungs and typically affects women of childbearing age. Pulmonary Langerhans cell histiocytosis (PLCH) HRCT findings are multiple thick- and thin-walled bizarre-shaped cysts and centriflobular nodules distributed in middle-upper lung lobes with relative sparing of costophrenic sulci, primarily affecting current or former smokers, more frequently men under 40 years. Birt-Hogg-Dubé syndrome is a rare autosomal dominant disease, linked to a germline mutation in the folliculin gene (FLCN). Its clinical features are lung cysts, spontaneous pneumothorax, renal tumors (both benign or malignant), facial papules (fibrofolliculomas or trichodiscomas) and skin tags (acrochordons). In BHDS lung cysts are predominantly situated in the lower lobes with a disproportionate number of paramediastinal elliptical (flappy) cysts and their diameter can vary from 2 mm to 8 cm. Perivascular cysts are common both in patients with LIP and in patients with BHDS. Pulmonary amyloidosis associated with pSS is rare and can be associated with LIP and cystic lesions, but nodules with or without calcification are the most common HRCT findings. Therefore, for the diagnosis it is usually necessary to perform a surgical lung biopsy, which is also useful to rule out lymphoma. Light chain deposition disease is extremely rare and the majority of patients have an underlying plasma cell dyscrasia. The most commonly affected organs are kidneys, heart and liver, while the lungs are involved only in a few cases. HRCT findings in LCDD most frequently include cysts, which are generally thin-walled and scattered, and nodules that can vary in size from 2 mm to 5 cm. In addition to radiological findings, it is also important to take into account the patient’s symptoms, age, underlying predisposing diseases or conditions like smoking and family history in order to formulate a correct diagnosis. The diagnosis confirmation may require transbronchial or surgical pulmonary biopsy, which on histological examination reveals diffuse interstitial infiltrates of lymphocytes, plasma cells and histiocytes in interlobular and alveolar septae. Lung biopsy may be recommended mainly in patients with an atypical presentation or HRCT patterns or in patients with suspected overlapping systemic diseases. Conclusions

In the diagnostic approach to cystic lung disease, it is important to first rule out cyst mimics that are much more common, and then consider patient characteristics like symptoms of presentation, age,
medical and family history, predisposing diseases, smoking and HRCT features. Healthy individuals under 50 years should not present lung cysts, but with advancing age cysts can occur more frequently. Therefore, in elderly patients experiencing dyspnea it can be more difficult to diagnose a cystic lung disease, also because dyspnea is usually caused by other diseases such as heart failure, infectious pneumonia, COPD or pulmonary embolism which are more common in this setting of patients. Furthermore, in older patients these diseases can frequently overlap making it even more difficult to identify the diagnosis.

The mean age at LIP onset is 50 years, but the disease can be diagnosed in a wide age range, from the young to the elderly. In our case LIP was discovered in an 87-year-old woman affected by pSS, who presented with dyspnea and mild fever, having typical HRCT findings and showing clinical and radiological improvement with glucocorticoid therapy.

Ideally, lung biopsy is essential to confirm the diagnosis and to exclude a lymphoma, but clinicians should take into account all patient characteristics, balancing risks and benefits of every intervention. A lung biopsy would have exposed our patient to an unjustified risk, considering her age and comorbidities. The patient history and clinical and radiological features allowed us to confidently exclude other diseases in the differential diagnosis of cystic lung disease.

Hence, this case report aims to highlight the role of interstitial and cystic lung diseases, including LIP, in the differential diagnosis of dyspnea in elderly patients and the related diagnostic issues. However, the presence of an underlying autoimmune rheumatic disease, such as pSS, should raise a suspicion for ILD.

References