Ace in the Hole!

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A 36-year-old woman presented with nonproductive cough and breathlessness on level walking for 6 months. She was a homemaker and did not have any exposure to pets or cigarettes. Her past history was significant for symmetrical upper limb predominant small joint arthritis for 8 years; she had received symptomatic analgesics for several years but had not been evaluated for the etiology of arthritis. General physical examination revealed pallor, swan neck deformity of distal interphalangeal joints and subluxation of metacarpophalangeal joints. Respiratory examination was normal. The hemoglobin level was 9.3 g/dl (normal 12–14), the mean corpuscular volume was 72 fl (normal 86 ± 10), the reticulocyte index was 1.2% and serum ferritin was 300 ng/ml (normal 30–150), consistent with anemia of chronic disease. Urine examination showed dysmorphic red blood cells, with 24-hour urine protein of 560 mg/m²/day (normal <30), and serum creatinine was 1.8 mg/dl (normal 0.8–1). Radiographs were consistent with deforming rheumatoid arthritis (fig. 1b); the serum rheumatoid factor was positive at 1:160 (normal <1:20) by latex agglutination, and anticyclic citrullinated peptides were strongly positive by ELISA. Antinuclear antibody, antineutrophil cytoplasmic antibody, human immunodeficiency virus ELISA and antiglomerular membrane antibody were all

negative. Serum complement levels were normal. A kidney biopsy confirmed the diagnosis of focal segmental glomerulonephritis. Chest radiography showed cystic shadows in the left lower zone (fig. 1a). Spirometry was normal (forced vital capacity of 2.16 liters, 86% predicted) and carbon monoxide diffusing capacity showed moderate reduction (3.32 mmol/min/kPa, 40% predicted). The 6-min walking distance was 512 m at baseline, without significant desaturation (baseline saturation 98% and final saturation at 6 min was 96%). High-resolution computed tomography (CT) showed the presence of multiple thin-walled cysts with no effusion or adenopathy (fig. 2). Ultrasound of the abdomen did not show any angiomyolipomas or lymphadenopathy. Electrophoresis revealed polyclonal hypergammaglobulinemia; Schirmer's test was normal (13 mm bilaterally). Bronchoscopic lavage was lymphocytic by differential count (neutrophils 6%, lymphocytes 56%, monocytes 38%) and was negative for *Pneumocystis jirovecii* cysts by Grocott's staining. Surgical lung biopsy was advised but refused by the patient.

What is your diagnosis and how would you proceed next?

Fig. 1. Composite image with chest radiograph (a) showing evidence of subtle cystic shadows (black arrow). Plain radiograph of the hands (b) shows evidence of juxta-articular osteoporosis, joint space reduction and subluxation (white arrow) of the little finger suggesting the presence of rheumatoid arthritis.

Fig. 2. High-resolution CT showing bilateral multiple 3- to 5-mm thin-walled cysts with occasional centrilobular nodules. The rest of the parenchyma was normal. No evidence of pleural effusion or lymphadenopathy was seen.

Diagnosis: Rheumatoid Arthritis-Associated Lymphoid Interstitial Pneumonia

Transbronchial biopsy was performed. The photomicrographs showed lymphocytic infiltration along bronchioles with germinal center formation (arrow) consistent with lymphoid interstitial pneumonia (LIP) (fig. 3). A diagnosis of rheumatoid arthritis-associated LIP was made.

LIP is an uncommon condition characterized by a diffuse, polyclonal lymphoid infiltrate surrounding the peribronchovascular interstitium [1]. While LIP may be idiopathic, it often occurs associated with several autoimmune diseases and viral infections [2]. Sjögren's syndrome and human immunodeficiency virus infection are the most common associated conditions (table 1) [1]. Controversy exists on the exact status of LIP within the idiopathic interstitial pneumonia group because of its association with other diseases, and some authors have advocated that it be removed from the interstitial pneumonia group [3]. LIP has a female preponderance and usually presents with progressive dyspnea and nonproductive cough. Clubbing and extrapulmonary findings are uncommon [4]. About 80% have associated dysproteinemias, most commonly polyclonal hypergammaglobulinemia. The CT findings include peribronchovascular septal thickening with nodules and ground glass appearance [5]. Cysts are 1–30 mm and are found in 68%;

this may be associated with nodular pulmonary AL amyloidosis and is probably due to the narrowing of the airway as a result of extensive infiltration of the bronchiolar wall by inflammatory cells and a check valve mechanism [6].

LIP is characterized by diffuse polyclonal T-lymphocytic interstitial infiltrates expanding the interlobular and alveolar septae on histopathology. Loosely formed granulomas, lymphoid follicle formation and microcystic honeycombing may be seen. Staining to exclude pneumocystis and viral inclusions (Epstein-Barr virus) and review of the patient's history to exclude hypersensitivity pneumonitis are necessary prior to diagnosis. Radiologically, LIP must be distinguished from other cystic interstitial lung diseases (table 2).

LIP must also be distinguished from pulmonary lymphoproliferative disorders. The presence of cysts and the absence of pleural effusions, large nodules, lymphadenopathy and organomegaly favor the diagnosis of LIP [7].

The diagnosis of LIP requires histopathology; although this is usually achieved by surgical lung biopsy, the lymphocytic infiltration of LIP can also be diagnosed by transbronchial biopsy [8]. Steroids are the mainstay of treatment and a 50–60% response rate is observed. Infectious complications of immunosuppression and malign-

Fig. 3. Low-power view (a, ×100) and high-power view (b, ×400) of the transbronchial lung biopsy specimen showing lymphocyte infiltration along the peribronchovascular interstitium, and occasional germinal center formation was also detected (arrow). No granulomas were seen and stains for acid-fast bacilli, *P. jirovecii* and viral inclusions were negative. Immunohistochemistry showed that the peribronchovascular lymphocytes were positive by CD4, and patchy CD20 positivity in areas of germinal center formation was also observed (not included).

Table 1. Conditions associated with LIP

<i>Idiopathic</i>	<i>Allogeneic bone marrow transplantation</i>
Disease with dysproteinemias	Acquired immunodeficiency syndrome viral infections
Hypogammaglobulinemia	Human immunodeficiency virus
Common variable immunodeficiency	Epstein-Barr virus
Monoclonal or polyclonal gammopathy	Human T-cell lymphotropic virus type 1
Autoimmune diseases	Infections
Sjögren's syndrome	Tuberculosis
Rheumatoid arthritis and juvenile rheumatoid arthritis	<i>Legionella</i> , <i>Mycoplasma</i> and <i>Chlamydia pneumoniae</i>
Chronic active hepatitis	Miscellaneous
Primary biliary cirrhosis	Pulmonary alveolar microlithiasis
Myasthenia gravis	Pulmonary alveolar proteinosis
Hashimoto's thyroiditis	Celiac sprue
Pernicious anemia	Dilantin use
Autoimmune hemolytic anemia	Surfactant protein C deficiency
Systemic lupus erythematosus	

Table 2. Differential diagnosis of cystic interstitial lung diseases

Condition	Characteristic					
	cyst character	cyst size	cyst distribution	associated pulmonary features	associated extra-pulmonary feature	diagnostic requirement
LAM	round to ovoid thin walled	2–5 mm, larger as disease progresses	diffuse, involves lung bases	nodules in TSC-LAM, pneumothorax, pleural effusion and chylothorax	premenopausal women, angiomyolipoma	tissue biopsy or consistent CT and associated condition ¹
Pulmonary Langerhans cell histiocytosis	thin and thick walled	bizarre shape	upper lobe, spares costophrenic angles	nodules, 1–5 mm, cavitation, PHTN	smokers, male predominant, others ²	BALF ³ or tissue biopsy and CD1a positive
Lymphoid interstitial pneumonia (± Sjögren's syndrome)	thin walled	variable sizes	diffuse cysts, peribronchovascular nodules, nodes, calcification (associated amyloidosis), GGO, effusions		associated condition, clubbing	tissue biopsy
Birt-Hogg-Dubé syndrome	thin walled	<5 mm	diffuse cysts, familial condition characterized by triad of pneumothorax, skin lesions and renal tumors			mutations in folliculin gene
Follicular bronchiolitis	thin walled	5–12 mm	peribronchovascular, nodules		RA	tissue biopsy
Light-chain deposition disease	variable large-sized cysts		associated paraproteinemia, lymphadenopathy, pleural effusions			tissue biopsy
Neurofibromatosis	variable-sized cysts (25%) and bullae, upper lobe		type 1 neurofibromatosis, lower-lobe predominant GGO and reticulation			radiology and clinical condition
Metastatic endometrial cell sarcoma	thin walled	1–2 mm	diffuse, small cysts, also seen in metastatic synovial cell sarcoma and leiomyosarcoma			associated primary
Hypersensitivity pneumonitis	thin walled (13%)	<15 mm	GGO, centrilobular nodules, air trapping; occult cysts seen in 13% with subacute hypersensitivity pneumonitis			tissue biopsy
Bronchopulmonary dysplasia	lung cysts can complicate the management of the ventilated patient with bronchopulmonary dysplasia and ARDS; anterior predominant with reticulation					radiology and history
Cystic honeycombing	must be distinguished from cystic ILD; intervening pulmonary parenchyma is normal in cystic ILD; cystic honeycombing can complicate any long-standing ILD, but occurs early in IPF					

LAM = Lymphangioleiomyomatosis; TSC = tuberous sclerosis complex; PHTN = pulmonary hypertension; BALF = bronchoalveolar lavage fluid; GGO = ground-glass opacity; RA = rheumatoid arthritis; ARDS = acute respiratory distress syndrome; ILD = interstitial lung disease.

¹ Angiomyolipomas, tuberous sclerosis or chylothorax. ² Often lung limited in adults. In children, it may be associated with bony lesions, diabetes insipidus and skin lesions. ³ BALF >5% CD1a-positive cells or tissue biopsy.

Fig. 4. Composite image of high-resolution CT at 6 months of treatment showing no fresh cystic lesions and some resolution of the earlier cysts in figure 2.

nant transformation (5–30%) are the most common cause of mortality [2].

The index patient was initiated on 25 mg prednisolone, enalapril, 10 mg methotrexate weekly, supplemental calcium and bisphosphonates. Her joint swelling pain and nephritis resolved by 8 weeks and steroids were tapered over 6 months. Spirometry repeated at 6 months showed no reduction in forced vital capacity (2.08 liters, 84% predicted) and an improvement in carbon monoxide

diffusing capacity (4.94 mmol/min/kPa, 60% predicted). She remains asymptomatic with no progression of cysts on repeat CT (fig. 4) or evidence of active sediments on urine microscopy at 6 months.

Key Words

Lymphoid interstitial pneumonia • Rheumatoid arthritis • Transbronchial lung biopsy • Cystic lung disease

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