What Is Your Diagnosis?

Respiration 2011;82:212–216
DOI: 10.1159/000327239

Ace in the Hole!

Srinivas Rajagopala\textsuperscript{a} Smrita Swamy\textsuperscript{b} Anoop Kumar\textsuperscript{a} Pritilatha Rout\textsuperscript{c}

Departments of \textsuperscript{a} Chest Diseases, \textsuperscript{b} Radiodiagnosis and \textsuperscript{c} Pathology, St. John’s Medical College Hospital, Bengaluru, India

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 \textit{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.
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 idiopathic 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 hypergamma-globulinemia. 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 malig-
Table 2. Differential diagnosis of cystic interstitial lung diseases

<table>
<thead>
<tr>
<th>Condition</th>
<th>Characteristic</th>
<th>Associated Pulmonary Features</th>
<th>Associated Extra-Pulmonary Feature</th>
<th>Diagnostic Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAM</td>
<td>round to ovoid thin walled</td>
<td>2–5 mm, larger as disease progresses</td>
<td>nodules in TSC-LAM, pneumothorax, pleural effusion and chylothorax</td>
<td>premenopausal women, angiomyolipoma tissue biopsy or consistent CT and associated condition1</td>
</tr>
<tr>
<td>Pulmonary Langerhans cell histiocytosis</td>
<td>thin and thick walled bizarre shape</td>
<td>upper lobe, spares costophrenic angles</td>
<td>nodules, 1–5 mm, cavitation, PHTN smokers, male predominant, others2</td>
<td>BALF3 or tissue biopsy and CD1a positive</td>
</tr>
<tr>
<td>Lymphoid interstitial pneumonia (± Sjögren’s syndrome)</td>
<td>thin walled</td>
<td>variable sizes</td>
<td>diffuse cysts, peribronchovascular nodules, nodes, calcification (associated amyloidosis), GGO, effusions</td>
<td>associated condition, clubbing</td>
</tr>
<tr>
<td>Birt-Hogg-Dubé syndrome</td>
<td>thin walled &lt;5 mm</td>
<td>diffuse cysts, familial condition characterized by triad of pneumothorax, skin lesions and renal tumors</td>
<td>mutations in folliculin gene</td>
<td></td>
</tr>
<tr>
<td>Follicular bronchiolitis</td>
<td>thin walled</td>
<td>5–12 mm peribronchovascular, nodules</td>
<td>RA</td>
<td>tissue biopsy</td>
</tr>
<tr>
<td>Light-chain deposition disease</td>
<td>variable large-sized cysts</td>
<td>associated paraproteinemia, lymphadenopathy, pleural effusions</td>
<td></td>
<td>tissue biopsy</td>
</tr>
<tr>
<td>Neurofibromatosis</td>
<td>variable-sized cysts (25%) and bullae, upper lobe</td>
<td>type 1 neurofibromatosis, lower-lobe predominant GGO and reticulation</td>
<td></td>
<td>radiology and clinical condition</td>
</tr>
<tr>
<td>Metastatic endometrial cell sarcoma</td>
<td>thin walled</td>
<td>1–2 mm</td>
<td>diffuse, small cysts, also seen in metastatic synovial cell sarcoma and leiomyosarcoma</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity pneumonitis</td>
<td>thin walled (13%) &lt;15 mm</td>
<td>GGO, centrilobular nodules, air trapping; occult cysts seen in 13% with subacute hypersensitivity pneumonitis</td>
<td></td>
<td>tissue biopsy</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>lungs can complicate the management of the ventilated patient with bronchopulmonary dysplasia and ARDS; anterior predominant with reticulation</td>
<td></td>
<td></td>
<td>radiology and history</td>
</tr>
<tr>
<td>Cystic honeycombing</td>
<td>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</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

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.
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

**References**


