AIRP Best Cases in Radiologic-Pathologic Correlation: Pulmonary Langerhans Cell Histiocytosis

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History
In 2007, a 47-year-old African American man presented with gradual progressive shortness of breath and recurrent pneumonia. His medical history was significant and included pulmonary hypertension treated with bosentan (Tracleer; Actelion, San Francisco, Calif) and sildenafil citrate (Revatio; Pfizer, New York, NY), as well as coronary artery disease, for which he underwent placement of a right coronary artery stent. He also had a history of heavy smoking, with cessation in 2008 and occasional relapses until he arrived at our center in 2009 for evaluation for lung transplantation. A review of his vital signs revealed a respiratory rate of 15 breaths per minute at rest and resting oxygen saturation of 90% in room air, with desaturation to 72% with short-distance walking despite administration of 6 L of oxygen with a nasal cannula. Mean pulmonary arterial pressure was 30 mm Hg. Computed tomography (CT) of the chest depicted multiple small thin-walled cysts with upper lobe predominance, as well as a few scattered small nodules. Given the patient's clinical history, pulmonary Langerhans cell histiocytosis (PLCH) was suspected, and the patient subsequently underwent double lung transplantation. Pathologic findings confirmed the diagnosis.

Abbreviation: PLCH = pulmonary Langerhans cell histiocytosis

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Figure 1. Chest radiograph shows increased lung volumes and attenuation of vascular markings in the mid and upper lung zones. Reticular areas of increased opacification are also seen, predominantly in the mid and lower lung zones.

Imaging Findings
Initial radiography of the chest demonstrated increased lung volumes and attenuation of the vasculature in the mid and upper lung zones, findings suggestive of emphysema. Fine reticular areas of increased opacification were also seen, predominantly in the mid and lower lung zones (Fig 1). CT of the chest demonstrated multiple enlarged cystic airspaces—some with very thin walls and many with no perceptible walls—that were most pronounced in the mid and upper lung zones. Paraseptal bullae in the right upper lobe and multiple scattered sub-centimeter nodules were also seen, predominantly in the upper lung zones (Fig 2). The central pulmonary artery was dilated, measuring as much as 3.4 cm, a finding in keeping with the patient’s history of pulmonary hypertension.

Pathologic Evaluation
At gross examination, the pleural surfaces of both lungs exhibited anthracosis and small emphysematous bullae, with cobblestoning along the surface of the right lung. Sections demonstrated numerous thin-walled cysts predominantly within the mid and upper lung zones, with foci of bulla formation in the upper lung zones (Fig 3). At microscopic examination, multiple regions of hypocellular stellate scarring were seen, with paracicatricial airspace enlargement, findings consistent with the
fibrotic end-stage of PLCH (Fig 4). Anthracosis was also present, a finding consistent with the patient’s history of smoking, given that he had no occupational exposure to coal (anthracite).

Discussion
Langerhans cell histiocytosis is a disease mediated by histiocytes that are part of the reticuloendothelial system (1–3). It is classified on the basis of whether it is isolated to the lungs (eg, PLCH), a manifestation predominantly seen in adults, or involves multiple organs (eg, Letterer-Siwe disease and Hand-Schuller-Christian syndrome), a manifestation predominantly seen in children (3,4). About 5%–15% of adults who present with PLCH also have extrapleural manifestations, which commonly include cutaneous lesions, pituitary involvement (which leads to diabetes insipidus), and bone lesions (1,4,5).

Langerhans cell histiocytosis primarily affects those in the 3rd–5th decades of life, and both sexes are affected equally (1,5,6). Previously, it was believed that men were more commonly affected than women, likely because of social factors such as smoking, due to higher numbers of male smokers in the past. However, over the past few decades, there has been a rise in female smokers, and no significant difference currently exists between incidences of the disease among the sexes (3). Onset of Langerhans cell histiocytosis is insidious, and as many as 25% of patients are asymptomatic at the time of diagnosis (7–10). Its symptoms are nonspecific and may include cough, dyspnea, fever, and weight loss. Patients may also present with pneumothorax, which is reported as the initial manifestation in 10%–15% of patients (5,9). PLCH occurs almost exclusively in people who smoke, with various articles reporting that among those with the condition, 90%–100% smoke (1,3,5,7).

Given this correlation, PLCH is relatively rare, even among people who smoke. Only about 3%–5% of smokers present with the disease, although this figure may be artificially low because many people in the population may be asymptomatic (3,5,6). Cigarette smoke contains multiple chemicals and is a strong irritant to small airways (5,11). It causes an inflammatory reaction that is mediated by cells such as macrophages, neutrophils, T-cells, and Langerhans cells, which are of particular interest in this disease (1,12). Langerhans cells are a type of dendrite, or antigen-presenting cell (8,12). They are predominantly located within the airway mucosa and lung parenchyma, and they increase in number with exposure to cigarette smoke.
(1,6,13). This proliferation triggers a release of multiple chemokines, proteases, and enzymatic reactions, which produce damaging free radicals that destroy lung architecture and ultimately lead to airway fibrosis and failed wound healing (2,9). Interestingly, proliferation of the multisystemic form of Langerhans cells appears to be clonal in nature, whereas the pulmonary form of Langerhans cells is thought to be polyclonal and nonneoplastic (5,6,8).

Chest radiography often depicts symmetric reticular or micronodular opacities predominantly within the mid and upper lungs, with sparing of the costophrenic recesses (1,6,7). Lung volumes are normal to increased (1,2). A cystic appearance within the lungs may dominate in end-stage disease because of severe lung destruction (5,6,9). CT depicts an upper and mid lung predominance of the disease, with relative sparing of the costophrenic recesses. In the early stages of the disease, only small nodules (usually smaller than 10 mm) may be seen, with a peribronchial distribution (1,6,8,12). Cavitation may be present in as many as 10% of patients (5,9). The classic CT manifestation includes cysts of varying size and thickness, with scattered peribronchial nodules. As the disease progresses, cysts predominate and appear thin-walled, an appearance very similar to that of emphysema, which may complicate its diagnosis in the end stage (3,5). Bronchoscopy and bronchoalveolar lavage may also be used to diagnose PLCH. However, bronchoscopy-guided lung biopsy often has a low yield (10%–20%), and multiple samples are often needed because of the patchy nature of the disease (5). CT findings of peribronchial nodules and cysts are highly conclusive in the appropriate clinical setting and often negate the need for lung biopsy (4,6). Hemoptysis and pleural effusions are rare (6).

Gross evaluation may demonstrate tan-white airway-centered nodules, which are usually well defined with irregular stellate borders and smaller than 1 cm. Intervening lung parenchyma may appear fibrotic, demonstrate cystic changes, or appear normal (6). Histologically, PLCH may have different appearances depending on the stage of the disease. In early stages, lesions are predominantly cellular, with a high concentration of Langerhans cells, eosinophils, and various inflammatory cells (2,3,5,8). Langerhans cell nuclei have a typical folded appearance and are positive for CD1, S-100, and E-cadherin stains (2,6,13). Langerhans cells also contain Birbeck granules, which appear as pentalaminar rods or racquet-shaped inclu-
sions at electron microscopy (6). As the disease progresses, the cellular component decreases and is replaced by collagen, leading to fibrosis and the “burned-out” lesion typically described as a peribronchial stellate scar (2,6,13).

In addition to a progression to end-stage lung disease, complications such as pulmonary hypertension and recurrent pneumothoraces may also occur (2,4,5). Smoking cessation is of paramount importance in treating PLCH, with stabilization occurring in multiple patients and regression occurring in 10%–15% of patients who quit smoking (4,6,7,13). For those in whom the disease progresses, corticosteroid and immunosuppressive therapy may be of use (1,5,10). Ultimately, lung transplantation is a consideration in patients for whom medical therapy is unsuccessful and who progress despite having quit smoking, although recurrent disease has been reported after transplantation (5).

References