A 36-Year-Old Man With Seizures and Multiple Cystic Pulmonary Nodules

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A 36-year-old Hispanic man presented to an outside institution with new onset simple partial motor seizures, which were characterized by clonic twitching and tonic activation of the left lower face, with gradual deviation of the head to the left. The seizures would develop either spontaneously or with left facial stimulation and were often preceded by perioral tingling. They would last 30 to 60 s and occur as frequently as every 15 to 30 min.

Because of difficulty controlling his seizures with antiepileptic therapy, he was referred to our institution. He complained of fatigue and dizziness and noted dyspnea for the previous 2 months. He had no prior health problems and took no medications. He was a one pack/d smoker, and he denied ethanol and illicit drug use.

Physical Examination

Vital signs revealed BP of 115/71 mm Hg, pulse 68 beats/min, respiratory rate 16 breaths/min, and temperature 36.5°C. Physical examination noted a man in mild acute distress. Cranial nerves II to XII were grossly intact; left cranial nerve V testing was avoided because of concern about eliciting a seizure. Strength and deep tendon reflexes were normal. Lungs were clear to auscultation, heart was regular without mur-

murs, and abdomen was benign without hepatosplenomegaly. No lymphadenopathy was appreciated.

Laboratory Findings

Laboratory tests revealed a leukocyte count of 8.5×10^9 (normal, $3.5\text{--}10.5 \times 10^9$). Cerebrospinal fluid analysis showed 89 total nucleated cells (normal, 0–5) with 35% neutrophils and 39% lymphocytes, RBC count of 152, glucose level of 57 mg/dL (corresponding serum level of 90), and protein level of 42 mg/dL (normal, 0–35 mg/dL). Vancomycin, ceftriaxone, and acyclovir were initiated empirically for possible infectious meningitis, although subsequent extensive investigations for infection were all negative. MRI of the brain showed increased T2 signal in the bilateral frontal and parietal sulci, consistent with leptomeningeal inflammation. EEG showed focal rhythmic spike discharges in the right frontocentral region that

FIGURE 1. CT scan of the thorax. Multiple cavitating pulmonary nodules.

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FIGURE 2. Histology of lung biopsy. Histiocytes and eosinophils (hematoxylin and eosin, original magnification $\times 400$).

became obscured by rhythmic clonic muscle artifact bilaterally.

Over several days, seizures were refractory to escalating antiepileptic drugs. The seizures began to extend to the left arm and leg. The patient was intubated for airway protection. Out of concern for a systemic cause of seizures, further imaging was obtained. CT scanning of the chest showed multiple cystic pulmonary nodules, primarily in the upper lobes (Fig 1). CT scanning of the pelvis and abdomen was unrevealing. The patient subsequently underwent video-assisted thorascopic surgery. A histopathology slide is shown in Figure 2. Further, immunochemical staining was positive for S100 and CD1A.

What is the diagnosis?

DISCUSSION

Langerhans cell histiocytosis (LCH) is a rare diagnosis that can be difficult to recognize because of a variety of presenting manifestations. Langerhans cells, a specific type of dendritic cell, are distributed beneath the epithelial lining of the tracheobronchial tree. After exposure to an inhaled antigen, activated Langerhans cells stimulate lymphocyte proliferation. Additionally, the interaction between Langerhans cells and T cells results in cytokine secretion and features of chronic inflammation. It is hypothesized that neurologic damage is due to CD8⁺ lymphocyte infiltration and cytokine production in the CNS.

A common site of LCH in adults, and typically the most involved location, is the respiratory system. Pulmonary LCH should be considered in young to middle-aged cigarette smokers with an upper lobe predominance of small nodules associated with thin- or thick-walled cysts on high-resolution CT scans. The cysts are usually <1-cm thick and irregularly shaped. Presenting symptoms can include cough, exertional dyspnea, and spontaneous pneumothorax. Often, there are no symptoms, and imaging findings are incidental. Pulmonary function tests classically show reduced diffusing capacity. In some instances, lung biopsy is needed for confirmation. If history and radiologic findings are consistent, then biopsy may not be required. Because cigarette smoking is thought to play a causative role in pulmonary LCH, smoking cessation is the most important intervention.

LCH is associated with a diverse range of neurologic symptoms, depending on the location of disease. The classic site of involvement is the hypothalamic-pituitary axis, often resulting in diabetes insipidus. Involvement of the anterior pituitary has been described. LCH can also affect the choroid plexus and meninges, giving rise to clinical features of leptomeningitis. Cerebrospinal fluid outflow obstruction can lead to increased intracranial pressure and hydrocephalus. MRI is nonspecific and can include white- and gray-matter lesions with varying enhancement, extraparenchymal involvement, and, with chronic disease, atrophy. Seizures are a clinical manifestation of LCH, classically in the setting of space-occupying lesions (not evident in this case). Untreated, LCH can cause progressive neurodegeneration, resulting in cognitive and/or motor dysfunction. Treatment of CNS disease may include surgery, radiation, chemotherapy, and/or corticosteroids.

Clinical Course

A skeletal survey was performed and did not show evidence of lytic lesions. A bone marrow biopsy specimen revealed normocellular marrow with normal trilineage hematopoiesis and no involvement of LCH. A brain biopsy was considered but ultimately deemed excessively risky.

Over the two ensuing weeks, the patient's seizures became increasingly responsive to antiepileptic medication. He was discharged on phenytoin, levetiracetam, lacosamide, and clonazepam and with instructions for smoking cessation.

At 1-month outpatient follow-up (nearly 8 weeks since smoking cigarettes), the patient was seizure free. CT scanning of the chest showed resolution of the pulmonary nodules and cysts. MRI of the brain showed reduced leptomeningeal enhancement.

CLINICAL PEARLS

1. LCH can affect multiple organ systems, with pulmonary, cutaneous, and bone manifestations common.
2. Pulmonary LCH is classically associated with upper-lobe-predominant cystic nodules on CT scanning.
3. Treatment of LCH depends on the site of involvement and severity of the disease. For pulmonary disease, tobacco cessation is a crucial element.
4. CNS manifestations are diverse. Diabetes insipidus due to pituitary involvement is a classic finding. Seizures can occur in the absence of space-occupying lesions.

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