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Case Report

Pulmonary Langerhans Cell Granulomatosis with Extrapulmonary Involvement

Pulmonary Langerhans cell granulomatosis is defined as an abnormal Langerhans cells infiltration in the lungs. Multifocal involvement is unusual, however. We report 3 cases of pulmonary Langerhans cell granulomatosis combined with either rib, thyroid or hypothalamus involvement.

Pulmonary Langerhans cell granulomatosis (LCG), previously known as eosinophilic granuloma, is a localized proliferative disorder of Langerhans cells in the lungs distinct from disseminated forms such as Letterer-Siwe disorder (LS) and Hand-Schuller Christian syndrome (HSC).[1,2] Pulmonary LCG with extrapulmonary involvement is occasionally encountered.[2-5]

We report 3 cases of pulmonary LCG. All had extrapulmonary involvement of either the rib, hypothalamus or the thyroid glands. The imaging findings of pulmonary LCG and manifestations of LCG are rarely reported simultaneously.

CASE REPORTS

Case 1

A 25-year-old male smoker presented with chest pain, body weight loss and productive cough for more than 4 months. The past history was unremarkable. Pulmonary function tests (PFT) showed moderate restrictive ventilatory impairment with moderate reduction of gas exchange. The initial chest radiograph showed nodular and cystic lesions in both upper lungs with abnormality of the left 7th rib (Fig. 1A). Gallium scan and whole body bone scan demonstrated radioactivity of the left 7th rib. High-resolution computed tomography (HRCT) of the thorax showed diffuse nodular and cystic pattern with cavitary nodules, predominantly in the upper lobes, and expansile cystic lesion in the left 7th rib (Fig. 1B, 1C) Pulmonary LCG was diagnosed.

Wedge resection on right upper lobe was performed and histopathology demonstrated fibrotic lung tissue infiltrated with chronic inflammatory cells and macrophages. Nodular aggregations of Langerhans cells dem-

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onstrated positive stains for S-100 protein consistent with LCG (Fig.1D). The left 7th rib was presumed as LCG involvement.

Case 2

A 10-year-old boy was brought to our hospital for suspected right thyroid malignancy. He had been well except for a right pneumothorax presenting 6 months before, as well as a chest surgery for an unknown condition. Physical examination revealed a 4X5 cm, fixed, non-tender mass over the right neck and multiple papules in the scalp. Thyroid sonogram revealed bilateral hypoechoic pattern with a heterogeneous mass in the right lobe (Fig. 2A). The chest radiograph showed minimal reticular interstitial process in both upper lobes and surgical stitches over the right upper lobe. Technitium 99 thyroid scan showed huge non-functional mass in the right thyroid. The thyroid function tests were normal. Needle aspiration of the thyroid gland was inconclusive but malignancy cannot be ruled out. A right thyroidectomy was performed and pathologic diagnosis was LCG. Immunohistochemical staining for S-100 protein was positive and Birbeck granules were found by electron microscopy (EM). Scalp lesion biopsy also suggested LCG.

Corticosteroid was prescribed, but the patient instead took herbal medications against advice. Six months later, another pneumothorax developed lead-

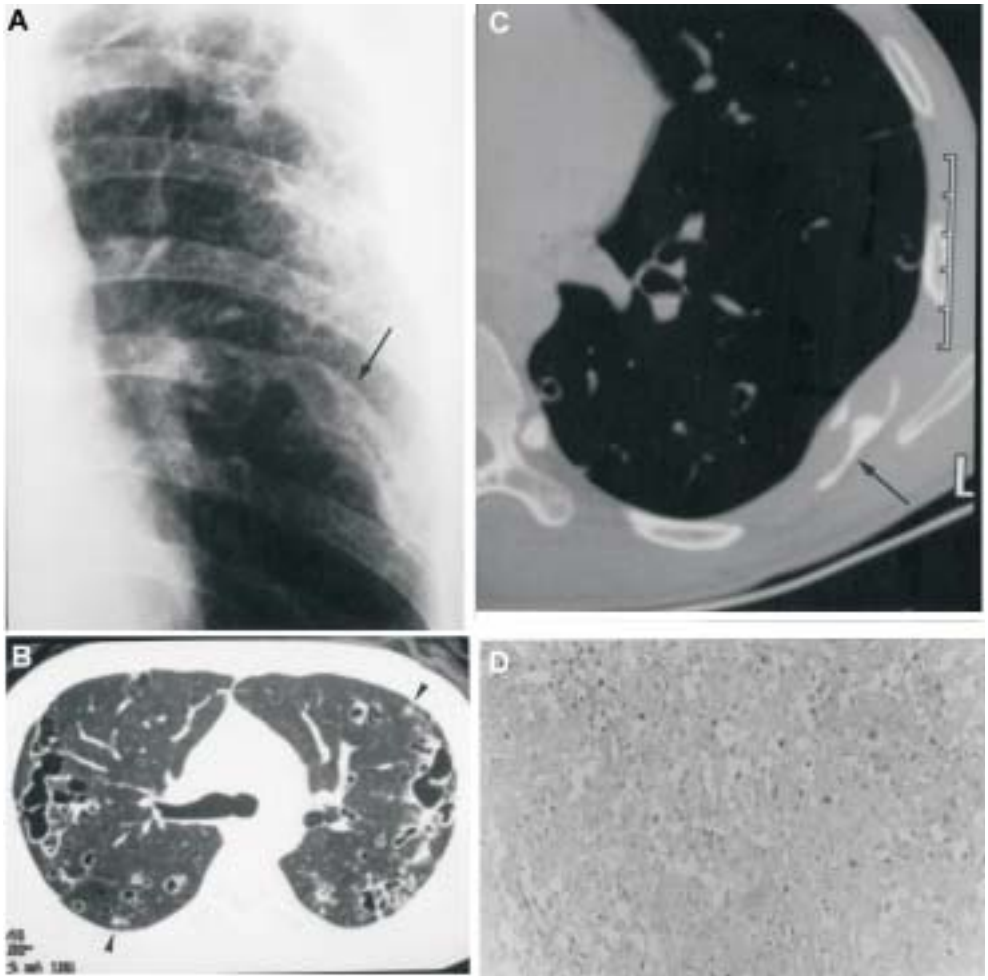

Fig. 1. Langerhans cell granulomatosis with lung and rib involvement in a 25-year-old male smoker. (**A**) Magnified chest PA radiograph shows cystic lesions in upper lobe, a bubble-like change with sclerotic margin in the left 7th rib (arrow). (**B**) HRCT of the lung at carinal level demonstrates multiple thin- and thick-walled cysts. Scattered nodules (arrow head) are also noted. (**C**) CT scan with bone window shows bubble-like appearance of left 7th rib (arrow). (**D**) Histopathology shows nodular aggregation of Langerhans cells and some eosinophils in pulmonary parenchyma (Hematoxylin & eosin stain, ×200).

ing to readmission. Aside from a left pneumothorax, diffuse reticulonodular interstitial changes mixed with cystic lesions in both lungs were found on the chest radiograph. Absence of the right thyroid and enlargement of the left thyroid with attenuated density was also noted (Fig. 2B). HRCT and contrast enhanced CT of the thorax showed multiple cystic lesions of bilateral lungs and left pneumothorax (Fig. 2C). After correlation with the previous sonography, nuclear medicine and pathological findings, LCG of the left thyroid was suggested.

He received pulmonary wedge resection on the left upper and lower lobe and histopathology revealed histiocytes and macrophages in the alveoli. Immunohistochemical staining for S-100 protein was strongly positive (Fig. 2D), and LCG was confirmed. One and a half years later, he died of respiratory failure.

Case 3

A 37-year-old male non-smoker suffered from polyuria and polydipsia for a year and amnesia for 2 weeks. He had 5 episodes of pneumothorax in the past 18 years. Six years prior to the development of the above-mentioned symptoms he had received complete treatment for tuberculosis. In addition, he had received steroids for dermatitis of the hands. The PFT disclosed mild restrictive ventilatory impairment with moderate reduction of gas exchange. Water deprivation test suggested central diabetes insipidus (DI). Audiometry, visual field and optic fundus examinations were normal. Initial chest radiograph revealed diffuse retiulonodular interstitial changes bilaterally. Radiographs of the long bones and the skull were normal. HRCT of the thorax showed multiple variable-sized cystic lesions in both lungs with thickening of interlobular septa suggesting

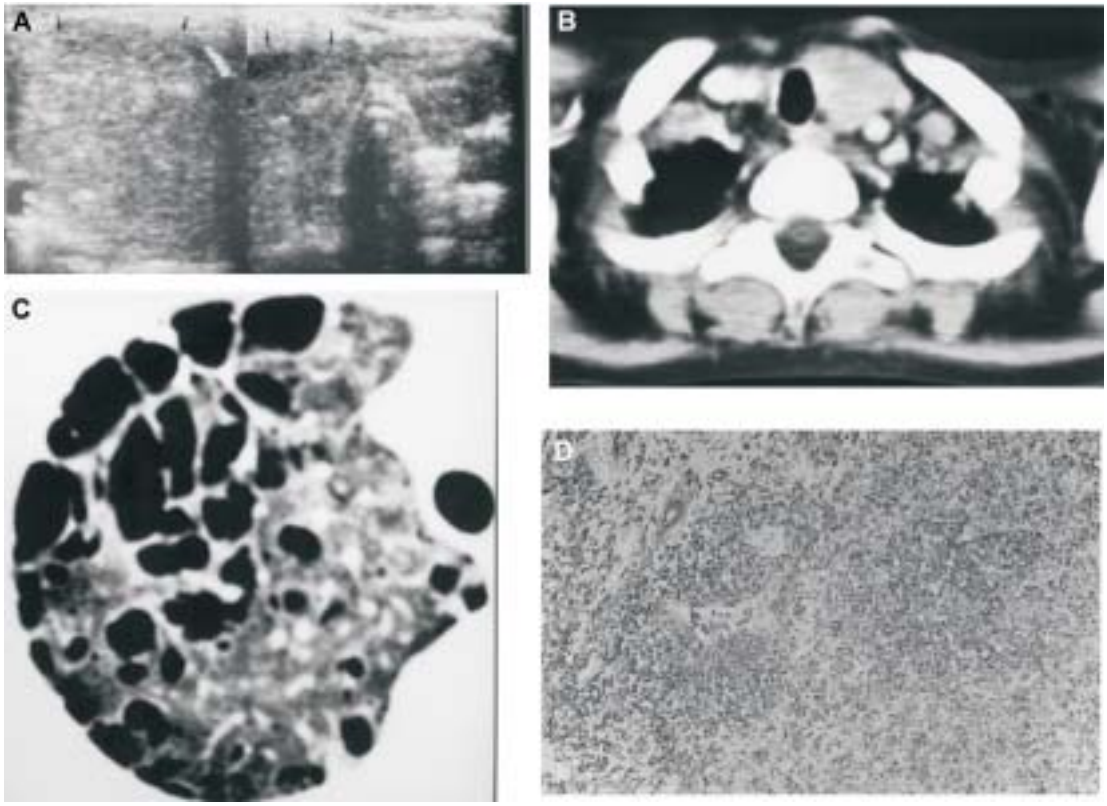

Fig. 2. A 10-year-old boy with pulmonary Langerhans cell granulomatosis associated with thyroid involvement. (**A**) Sonography depicts diffuse enlargement of the thyroid glands with decreased echogenicity and mixed with some echogenic spots, more prominently in the right lobe (left panel, arrows). Color Doppler ultrasound shows decreased color flow signals in the enlarged thyroid (right panel, arrows). (**B**) Six months after right thyroidectomy, contrast enhanced CT shows diffuse hypodensity in enlarged left thyroid with no regional lymph node. (**C**) Magnified HRCT of right upper lobe of lung shows multiple variable-sized cystic lesions. (**D**) Histopathology reveals aggregation of Langerhans cells in pulmonary parenchyma. The Langerhans cells are positive for S-100 protein on immunohistochemical staining. (Immunostaining for S-100 protein, ×100).

LCG (Fig. 3A). Gallium scan and bone scan showed no radioactivity in bilateral femoral heads, compatible with previous avascular necrosis post hip arthroplasty changes. Brain CT scan was performed due to DI and showed abnormal enhancement in the suprasellar region (Fig. 3B) which was further confirmed to be a hypothalamic tumor by MRI (Figs. 3C, 3D, 3E). Mild elevation of liver function tests prompted suspicion of LCG involvement. Hence, imaging exams including sonography and CT scan of upper abdomen and liver biopsy were performed which cleared the doubt. However, the patient refused further bronchoscopy, open lung biopsy or brain biopsy. LCG was diagnosed based on clinical presentation and imaging findings. Radiotherapy to the suprasellar region was also refused. Four months later, progression of symptoms prompted readmission but the patient was lost to follow-up after discharge.

DISCUSSION

LCG, also known as eosinophilic granuloma or histiocytosis X, was first described in the early 1940's.[2,3] It is a rare disorder of unknown etiology and characteristically displays an abnormal proliferation of X-body containing Langerhans cells (LCs) with granuloma formation. Three different clinical entities have been noted: LS, HSC and eosinophilic granuloma (EG).[4-8]

LS presents most in the infantile age group as diffuse histiocytic infiltration of the liver, skin and bone and has a 70% mortality rate.[5,6,9] HSC is a chronic disseminated form and often presents with the classic triad of DI, exophthalmos and lytic skull lesions.[6,9] Multifocal involvement, with a predilection for bone plus skin, liver, spleen, lungs, hypothalamus and lymph node, are usually seen in children.[5] EG is the most common form of LCG occurring at any age and is characterized by

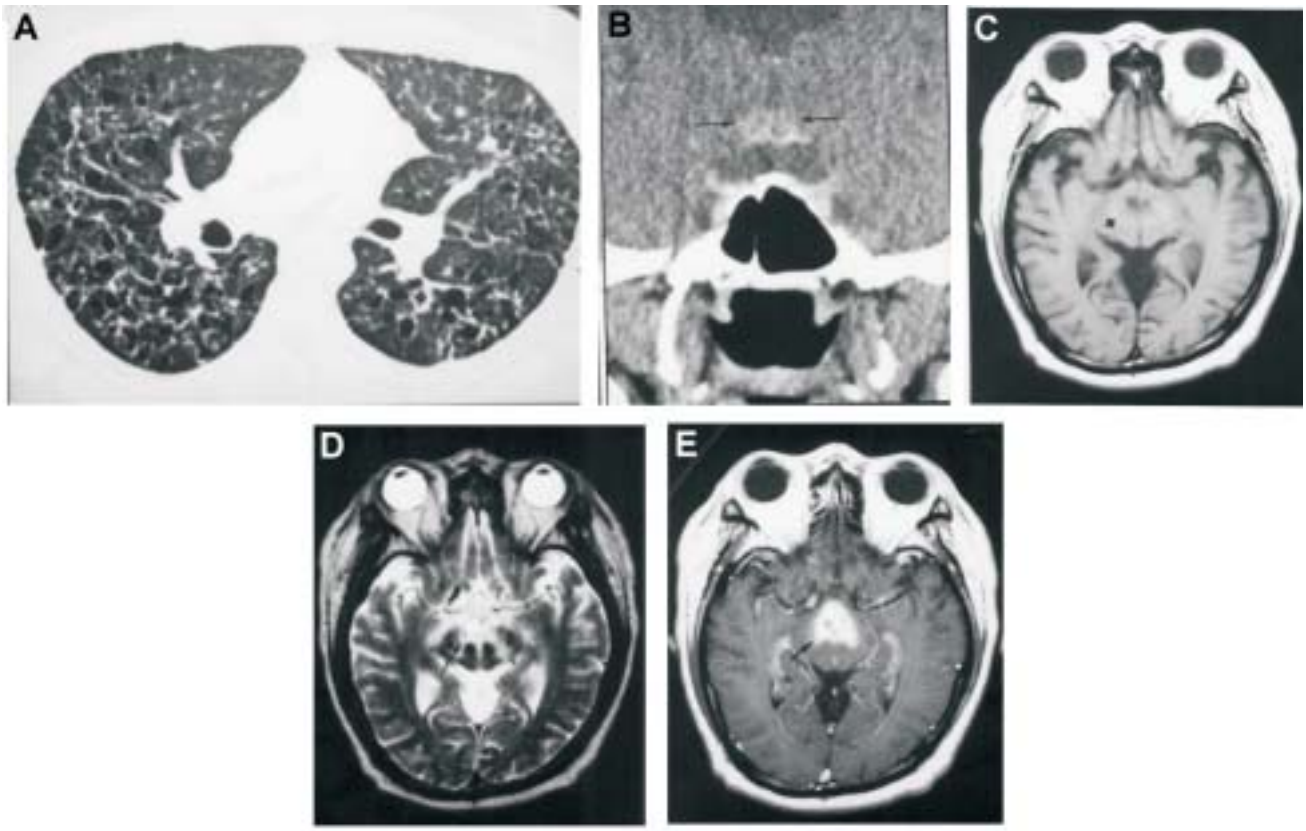

Fig. 3. A 37-year-old male non-smoker, diagnosed as Langerhans cell granulomatosis. He had typical pulmonary HRCT images and diabetes insipidus. (**A**) HRCT of lung through the subcarinal level shows multiple cystic lesions in both lungs and thickened interlobular septa. (**B**) Contrast enhanced coronal CT of brain discloses abnormal enhancement in the suprasellar region (arrows). (**C**, **D**, **E**) MRI reveals an infiltrating hypothalamus mass (arrow) with mixed signal on T1WI (TR/TE = 550/10/axial), hyper-intense on T2WI (TR/TE/450/25/axial) and contrast enhancement on T1WI (TR/TE/450/25/axial).

well-defined expanding bony lesions in flat bones, long bones and vertebra.[3] LS and HSC are regarded as pluritissular forms of LCG. Pulmonary LCG, known as localized form, may develop systemic involvement in time, therefore, some spiculated that the multifocal or pluritissular form of pulmonary LCG may be a late manifestation of HSC.

LCs are histiocyte-like cells derived from bone marrow stem cells and travel via the circulation to various tissues to initiate an immune response.[3,5] LCs contain a unique cytoplasmic inclusion body, X-body also known as the Birbeck granule, seen under EM.[4,6,8,10] Presence of a S-100 protein on the surface of LC differentiates it from the histiocyte.[1] Immunohistochemistry nowadays has largely replaced EM as a diagnostic tool.[1] On the other hand, the diagnosis of LCG can be made only based on light microscopic findings by experienced pathologist.[10]

The early stage of pulmonary LCG is characterized by multiple granulomatous lesions in the interstitium, close to the terminal or respiratory bronchioles.[1,3-5, 8, 9, 11] Cellular infiltrates with findings of clusters of LC are important diagnostic clues. The middle and late stages of disease show progressive lung destruction with cavitation, fibrotic changes and cystic changes.[3,5,10] The mechanism for cystic changes varies from bronchiolar check valve, paracicatricial emphysema or traction bronchiectasis.[5,7,12-14]

Pulmonary LCG is a disease of young and middle-aged adults, with age ranging from 3 months to 69 years,[8] and peaks at 21-40 years old. [4,5,9,12,14] There is a male predominance [4,5,12,15] or both sexes may be equally affected.[9] Young male adults with pulmonary LCG tend to have more severe disease compared with women and elderly patients.[2]

Pulmonary LCG was thought to be related to smoking[1-6,14,15] and 90-97% of patients had a positive smoking history.[2,15] The inhaled substance was thought to initiate LC response similar to type 4 hypersensitivity reaction.[4] A possibility of genetic mutation has been cited[4,6] but lacks confirmation.

The clinical presentation of pulmonary LCG is variable. Cough, dyspnea, fatigue, weight loss, fever, pneumothorax, hemoptysis, bony lesions and DI are encountered. Twenty-three percent of patients are however, asymptomatic.[4] The incidence of bone lesions in pulmonary LCG is roughly 8%, but the actual incidence is difficult to estimate due to differences of patient classification. Cystic bone lesions are commonly found in the skull, rib and pelvis.[2,4,11,15] Pulmonary LCG should be suspected when bone lesions are present in diffuse interstitial lung disease[10] although metastatic lesions are also possible.[2] In case 1, the correlation of rib lesions with HRCT findings and the absence of malignancy suggest pulmonary LCG with bone involvement.

DI may be seen in pulmonary LCG [2,4,11,15] with an incidence of 5-7%.[2,4] Suprasellar or hypothalamic abnormality of LCG and sarcoidosis are however, not distinguishable by MR or CT. Age may aid to differentiate these two conditions, as LCG occurs in children, while sarcoid granulomas in adults.[16] The chest radiographic features are non-specific and is insufficient to differentiate LCG from sarcoidosis. The HRCT of both pulmonary LCG and sarcoidosis may show diffuse nodular shadows with thickening of interstitium. Enlarged mediastinal and hilar nodes are important findings of sarcoidosis but cystic lesions are not.[7,10] The HRCT of case 3 showed reticular and cystic changes, favoring LCG more than sarcoidosis.

Rarely involved tissues are the kidneys, meninges, parotid glands, lymph nodes and thyroid.[3,17] Case 2 initially presented with bilateral thyroid enlargement, and was suspected for malignancy, but right thyroidectomy proved LCG.[17] Later in the disease course, enlarged left thyroid seen on HRCT suggested left thyroid gland involvement.

The majority of patients with multifocal LCG that have typical bone lesions are often associated with skin, lung and bone marrow involvement, but multifocal LCG with skin or lung involvement may not have bone lesions. Pluritissular LCG may represent a spectrum of disease of varied activity. Typically, multifocal LCG remains active for years but in the majority of patients is followed by remission.[3]

Multifocal LCG with or without pulmonary involvement has a worse prognosis than pulmonary LCG. Cutaneous lesions and recurrent pneumothorax indicate a worse prognosis.[4]

Pneumothorax incidence is about 11-20%[2,4,8,10,14] and accounts for 2-25% of deaths in pulmonary LCG.[4] Respi-

ratory failure, sepsis secondary to pulmonary or cutaneous lesion and development of malignancy in the later disease course are the most common causes of death.[3] Malignant lymphoma and carcinoma, usually lung cancer are know to be associated with pulmonary LCG. Whether LCG is benign, pre-malignant or malignant remains unresolved.[1,3,8]

The most important treatment for pulmonary LCG is smoking cessation. Other therapeutic options include irradiation therapy, corticosteroids, antibiotics, surgery and cytotoxic agents.[3,4,11,12]

Diagnostic modalities utilized for the diagnosis of pulmonary LCG include, transbronchial lung biopsy, although open lung biopsy is usually required to obtain sufficient tissues for a definitive diagnosis.[3,12] Advocates of bronchial alveolar lavage claim identification of X-bodies in LC.[1,4]

Imaging plays an important role in the diagnosis of pulmonary LCG. Emphysema, reticular, nodular, reticulonodular patterns with presence of cavitary nodules and cystic lesions predominantly in the upper and middle lobes are usually found in plain chest radiographs. Alveolar opacities, pleural effusion and hilar lymphadenopathy are unusual.[2,4,8,10,12,13] The absence of hilar adenopathy, presence of pneumothorax and characteristic nodular and cystic changes predominantly of both upper lobes make the diagnosis of LCG more likely.[4] Extrapulmonary conditions such as DI or bone lesions also point to LCG as a possible diagnosis.

Differential diagnosis based on chest radiograph includes tuberculosis, histoplasmosis, cancer metastasis, occupational disease, lymphangiomyomatosis, sarcoidosis, bullous disease, hypersensitivity lung, idiopathic pulmonary fibrosis, septic emboli, cystic bronchiectasis and collagen vascular disease.[4,10,12,13]

CT scan of thorax permits a more confident distinction of the different conditions and is more sensitive than chest radiograph in revealing structural change and detecting of cyst and nodules.[7,10,12-14] HRCT shows nodules, cavitary nodules, thin or thick-walled cysts, ground-glass opacities, reticulation, emphysematous changes, lung distortion, mosaic or expiratory air-trapping with an upper lobe predominance.[7,8,10,12,13,15] The findings of nodular lesions combined with cystic changes are important diagnostic signs of pulmonary LCG.[7,9,10,12,13] Cystic, reticular or honeycombing lesions without nodules in bilateral lobes favor IPF, rheumatoid arthritis (RA), collagen vascular disease and LAM. Nodular or large cavitary lesions in lower lobes are more often seen in metastasis, septic embolization, Wegener's granulomatosis and RA. Sarcoidosis rarely presents as cystic or cavitary lesions and often has prominent mediastinal and hilar lymphadenopathy, infrequently seen in pulmonary LCG. The absence of complete cystic walls differentiates centrilobular emphysema from pulmonary LCG. No history of occupational exposure often excludes pneumoconiosis.[7,10,12,13] Additional CT evidence of extrapulmonary foci of disease, as in our cases, in the parasellar region, ribs and thyroid glands provided further support of LCG.

In conclusion, it is important to understand pulmonary LCG, its varied clinical entities and its clinical presentation so as to be able to keep a high index of suspicion for the possibility of multiple extrapulmonary involvement which should be correlated with the radiographic, especially with the CT imaging findings as to facilitate diagnosis and prognostication of this rare disease.

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