Case Report

Isolated pulmonary involvement in Erdheim-Chester disease

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ABSTRACT

Erdheim–Chester disease is a rare non-Langerhans cell histiocytic disorder. It is primarily a disease of the long bones. Pulmonary involvement in systemic disease is detected in about half the reported cases. Isolated lung involvement is extremely rare with no clear recommendations for treatment. A 52-year-old caucasian male was evaluated for 1.9 cm × 1.6 cm spiculated nodule in the right upper lobe. Pulmonary function testing and bronchoscopy with endobronchial ultrasound, transbronchial biopsy, and microbiology were inconclusive. Positron emission tomography–computed tomography (PET-CT) was significant for the avidity in same lung nodule along with mediastinal and hilar adenopathy but no bone involvement. Wedge resection with histopathology and immunohistochemistry reported a fibrohistiocytic infiltrate in bronchovascular distribution which was positive for CD68 and negative for CD1A, S100, and BRAF V600E mutation. Magnetic resonance imaging brain ruled out central nervous system involvement. The rarity of the condition along with the complex pathology makes it difficult to diagnose and hence intervene appropriately.

KEY WORDS: CD68, Erdheim–Chester, histiocytic, non-Langerhans, pulmonary

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INTRODUCTION

Erdheim–Chester disease (ECD) is a very rare disorder with only about 500 cases reported so far. It commonly presents as sclerotic bone lesions with cardiac, pulmonary, and central nervous system involvement in a setting of systemic disease. Our patient had isolated symptomatic pulmonary disease which is an atypical presentation. Management remains a challenge due to rarity of the disease itself and lack of convincing literature on efficacy of treatment for pulmonary involvement.

CASE REPORT

A 52-year-old white male was seen in pulmonary clinic with complaints of chronic dyspnea, nonproductive cough, and right-sided chest discomfort for 6 months. He was a nonsmoker with medical history significant for asthma in childhood and occupational exposure to silica. He did not complain of bone pain and review of symptoms was otherwise negative. Pulmonary examination revealed normal respiratory effort without any adventitious sounds. He recently had a normal myocardial perfusion scan and an echocardiogram with ejection fraction of 60%. Pulmonary function testing depicted normal flow volume loops, forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) - 82%, FVC - 69%, FEV1-66%, and diffusion capacity of carbon monoxide - 118%.

A CT chest revealed a 1.9 cm × 1.6 cm nodule located peripherally in the right upper lobe (RUL) in posterior segment, anterior inferior mediastinal lymphadenopathy,

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and obstructed right middle lobe (RML) bronchus with atelectasis of involved segment [Figure 1].

Endobronchial ultrasound of collapsed RML and transbronchial needle aspiration was inconclusive. The transbronchial lung biopsy failed to isolate any lung parenchyma and showed normal bronchial epithelium with mild chronic anthracosis in subepithelium without features of malignancy or granuloma. Cytological analysis of bronchoalveolar washing demonstrated normal bronchial and mixed inflammatory cells with alveolar macrophages but no malignant cells. Cultures were negative for fungal and mycobacterium species and showed normal respiratory flora. He underwent a PET-CT which confirmed previously noted lung mass and extensive hypermetabolic hilar and mediastinal lymphadenopathy [Figure 2] but did not reveal any abnormal bone uptake.

Patient underwent a mediastinoscopy which showed extensive adenopathy in superior mediastinum and hard sclerotic right paratracheal node which was benign on frozen section. This was followed by video-assisted thoracoscopic surgery (VATS) which revealed a lesion in posterior segment of RUL (benign on frozen section). RML was noted to be completely dysfunctional and indurate with inflammation. Wedge resection of RML and RUL showed a fibrohistiocystic infiltrate in bronchovascular distribution. Pulmonary arteries were noted to have myointimal thickening in an asymmetrical pattern but without any features of vasculitis. Immunoperoxidase studies were positive for CD 68, CD 163, and lysozyme highlight consistent with a histiocytic infiltrate but negative for S100 and CD1A [Figure 3].We ruled out Langerhans cell histiocytosis, Histiocytic sarcoma and IgG4 with special stains. These findings were consistent with ECD. Magnetic resonance imaging (MRI) brain was done to rule out neurologic disease and showed no dural-based masses, ventriculomegaly, or any pathologic enhancement. The patient also tested negative for BRAF V600E mutation. A bone scan failed to demonstrate any bone lesions either.

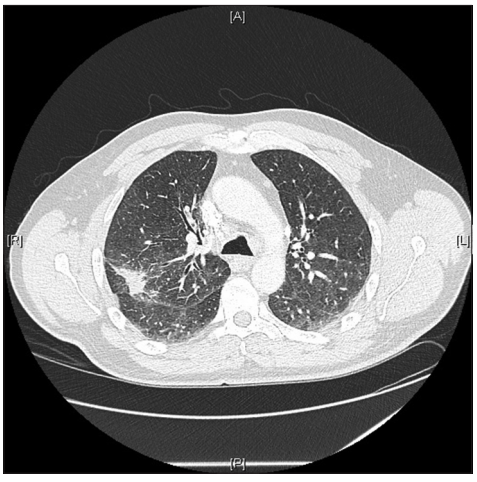

Figure 1: Computed tomography chest showing 1.9 cm × 1.6 cm nodule in the right upper lobe in transverse section

DISCUSSION

ECD is a rare non-Langerhans cells histiocytic disorder which was first described in 1930 by Erdheim and Chester.[1] Since then, only about five hundred cases have been reported in literature.

The etiology is undetermined; however, an association with genetic or infectious etiology is unlikely. The most common clinical presentation is that of bone pain in a median age of 53 years with a slight male predominance.[2] Osseous involvement is primarily bilateral and symmetrical and is seen in the form of cortical osteosclerosis of diaphysis or metaphysic of long bones, although periostitis and epiphyseal involvement is also seen. These can be visualized on conventional radiograph as well as CT or MR.[3] Bone involvement can be asymptomatic, but it is pathognomic and is present in virtually all reported cases, even as a silent radiological finding.[2]

Extraosseous involvement can manifest in the form of cardiovascular, pulmonary, neurological, retroperitoneal, and less commonly cutaneous or constitutional symptoms.[2] Neurological or cardiac involvement is seen in the aggressive form of disease and is associated with poor prognosis.[4-6] Anterior pituitary involvement can manifest as diabetes insipidus and less commonly as prolactinemia and somatotropic deficiency.[7] Visual disturbances, pyramidal, and extrapyramidal syndromes are also prevalent. Cardiac involvement can present as pericardial infiltration, myocardial involvement, conduction defects,

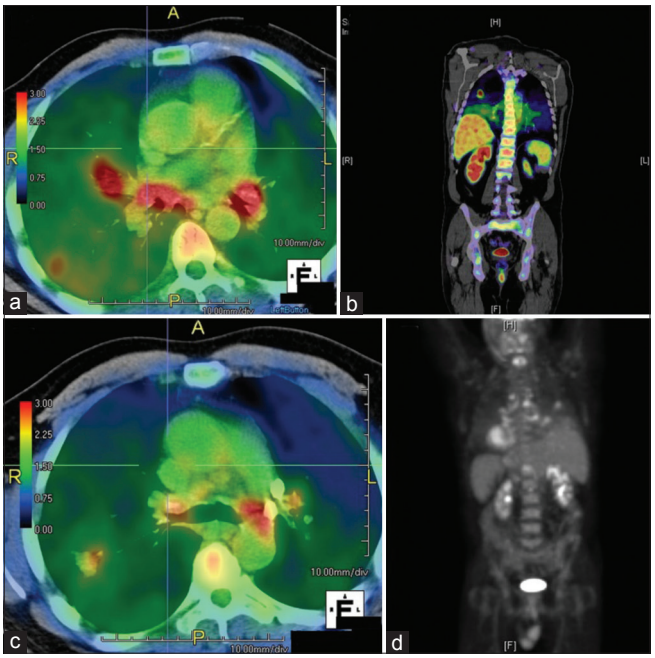

Figure 2: Positron emission tomography images demonstrate extensive hypermetabolic mediastinal and hilar lymphadenopathy in transverse section (a), avidity of 1.8 cm nodule in coronal section (b) and transverse section (c). There is no pathological bone involvement in three-dimensional whole body format (d)

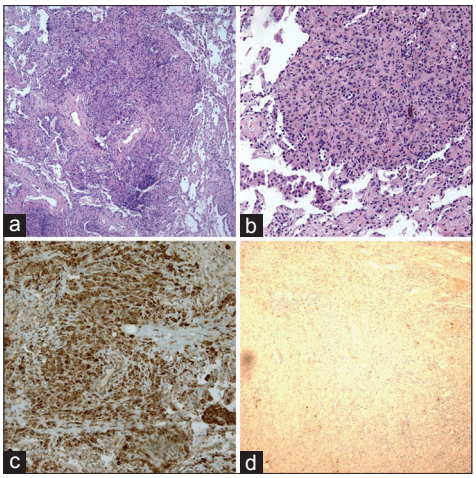

Figure 3: Lung wedge biopsy with hematoxylin and eosin stain depicting a histiocytic infiltrate effacing the normal lung architecture (×10) (a). Histiocytic cells with epithelioid to spindled morphology mixed with a lymphoplasmacytic infiltrate (×20) (b). Immunohistochemical stains show marked positivity of the histiocytes with CD68 (×20) (c) and negative staining pattern with S100 (×10) (d)

and valvulopathy.[6] Coated aorta appearance is evident in late stage due to periaortic infiltration extending from ascending to abdominal aorta.[5]

Pulmonary disease is seen in about half the cases, and the presentation may range from being asymptomatic to progressive dyspnea over month to years, with or without cough.[8,9] Clinically, it may mimic interstitial lung disease, Langerhans cell histiocytosis, or interstitial pneumonitis. In one large case series of 34 cases, pulmonary involvement was not an independent predictor of survival and had little impact on overall prognosis.[8] However, there is evidence that advanced lesions with extensive fibrosis can lead to cardiopulmonary failure, which is a major cause of morbidity and mortality.[10] Therefore, it should be sought out in a known case of ECD. Spirometry may be normal or restrictive with reduced diffusion capacity.[8]

Radiological evidence of pulmonary disease is nonspecific but always precedes clinical manifestations. CT chest can show lymphangitic infiltration concentrated around bronchovascular bundle or as interlobular septal and pleural thickening or effusion.[8,9,11,12] Pleural involvement if present is mainly visceral rather than parietal and reflects histiocytic infiltrate with fibrosis.[6,12] Less commonly, mediastinal infiltration, centrilobular nodular opacities, and ground glass opacities or lung cysts distributed in apical, anterior, and peripheral segments are also described.[9] Thoracic imaging may also show bone involvement. Clavicle involvement was mostly bilateral and symmetrical while rib involvement can be asymmetrical.[13] However, the most appropriate method to identify bone lesions is CT/MRI or more accurately bone scintigraphy. PET-CT is equally efficacious and beneficial. Organs known to be affected should be evaluated with dedicated imaging after confirmed diagnosis.

A tissue biopsy is required for diagnosis of ECD. Bronchoscopy and TBLD with or without navigational approach should be attempted first as a lesser invasive modality for the lesions that are accessible. This will also allow nodal sampling especially when workup for malignancy as a differential is underway. Bronchoalveolar lavage may contain macrophages and foamy histiocytes.[8] Failure to obtain diagnostic sample with TBLD warrants lung biopsy with VATS after consideration of associated risks. Pathology will show histiocytic infiltrates in lymphangitic pattern with associated fibrosis and lymphoplasmacytic inflammatory infiltrates.[9] Interspersed inflammatory cells and multinucleate giant cells (Touton cells) with admixed and surrounding fibrosis can be seen. Immunohistochemical staining is typical and will express the CD 68, CD 163, and Factor XIIIa but not the CD1a.[8,9] S100 may or may not be expressed in ECD.[9,11] Bony specimens if present should undergo BRAF V600E analysis for targeted therapy in patients who have failed the first-line treatment.[14]

Treatment is indicated for symptomatic disease, neurological involvement, and ongoing or impending organ dysfunction. Pulmonary involvement is not an indication for treatment unless symptomatic. Conventional or pegylated interferon (IFN) is the preferred modality and can be used until disease progresses or side effects appear.[4,5] Glucocorticoids have no survival benefit but can be employed as a second line if IFN is not tolerated or if the symptoms are mild.[8] Alternatively, systematic chemotherapy with Vinblastine, Etoposide, or radiation therapy for local palliation can be used. There is limited evidence of cladribine use for treatment of neurological disease.[14] BRAF inhibitor vemurafenib can be used when mutation is present and in those who fail conventional therapy.[14,15] Surgery is another option to relieve obstruction in mechanical complications. Even though IFN and corticosteroids are the treatment of choice for ECD, their efficacy is noted to be insignificant in cardiac or pulmonary involvement.[8,15,16]

FDG-PET is recommended every 3–6 months for all patients after initiation of therapy. Organ-specific imaging is recommended every 3 months initially which can be increased to every 6 months after disease stabilization.[11] Pulmonary follow-up is recommended each year with careful review using a low-dose CT.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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