

# Erdheim-Chester disease: a rare cause of interstitial lung disease

Kong P M, Pinheiro L, Kaw G, Sittampalam K, Teo C H Y

## ABSTRACT

Erdheim-Chester disease is a non-Langerhans cell histiocytosis that is progressive and may lead on to multi-organ involvement. Pulmonary involvement is rare, its presentation is non-specific, and it carries an adverse outcome. Several radiological features, when considered together, may point to the diagnosis. This condition should be considered in the differential diagnosis of interstitial lung disease. We describe a 39-year-old woman who presented with dry cough, malaise and progressive dyspnoea. She was diagnosed to have late stage interstitial lung disease due to Erdheim-Chester disease.

**Keywords:** Erdheim-Chester disease, histiocytosis, interstitial lung disease, lung

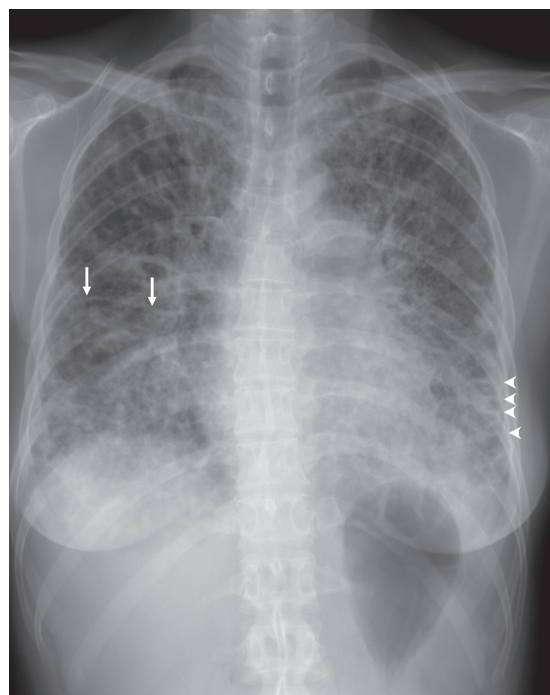
*Singapore Med J 2007; 48(2):e57–e59*

## INTRODUCTION

Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis first described in 1930 as a lipid storage disorder affecting the long bones.<sup>(1)</sup> It is now accepted as a disorder characterised by progressive proliferation of histiocytes with multi-organ involvement. Diagnosis of the condition requires characteristic radiological findings and histological features with histiocytes that stain for CD68 but not CD1a.<sup>(2)</sup> Symmetrical osteosclerosis of the long bones involving the metaphyses and diaphyses but sparing the epiphyses is the most characteristic finding. The disease may also affect the central nervous system, heart, pericardium, lungs, renal, retroperitoneal and retro-orbital tissue. The disease is classically described as presenting in middle age (mean age of 53 years) with bone pain from generalised involvement of the long bones and affecting males over the age of 40. As there is no established treatment, ECD has a mortality rate of 60% while on follow-up.<sup>(3)</sup> Pulmonary involvement is uncommon in ECD but the prognosis is grave and the treatment difficult.<sup>(4,5)</sup> We describe a case of ECD that presented late in the course of illness with pulmonary symptoms.

## CASE REPORT

A 39-year-old Chinese housewife presented with dry cough, malaise and progressive dyspnoea for six



**Fig. 1** Posteroanterior chest radiograph shows diffuse reticular interstitial thickening throughout both lungs with fissural thickening (arrows) and prominent Kerley B lines (arrowheads).

months. Physical examination showed elevated jugular venous pressure, coarse crackles in the lungs and a loud pulmonary component of the second heart sound. She was not on any long-term medications and had no complaints of musculoskeletal pain or fever. Pulmonary function testing showed a restrictive picture with forced expiratory volume at one second (FEV1) of 1.01l (44% predicted), FEV1/forced vital capacity (FVC) of 86% and carbon monoxide diffusion capacity (DLCO) of 7.1 mmol/kPa.min (59% of predicted value). The chest radiograph revealed diffuse reticular interstitial thickening with no zonal predominance and Kerley B lines at the periphery of the left lower lobe (Fig. 1). High resolution (Fig. 2) and conventional computed tomography (CT) with contrast enhancement revealed smooth interlobular septal and fissural thickening, soft tissue thickening around the pulmonary arteries and veins, and areas of ground-glass attenuation. Pericardial soft tissue thickening was also evident. Echocardiography done during the first admission only showed a dilated main pulmonary artery.

Department of  
Respiratory Medicine,  
Tan Tock Seng  
Hospital,  
11 Jalan Tan  
Tock Seng,  
Singapore 308433

Kong PM, MBBS,  
MRCP, FAMS  
Senior Consultant

Department of  
General Medicine

Pinheiro L, MBBS,  
MRCP, FAMS  
Consultant

Department of  
Radiology

Kaw G, MBBS,  
MMed, FRCP  
Consultant

Department of  
Pathology

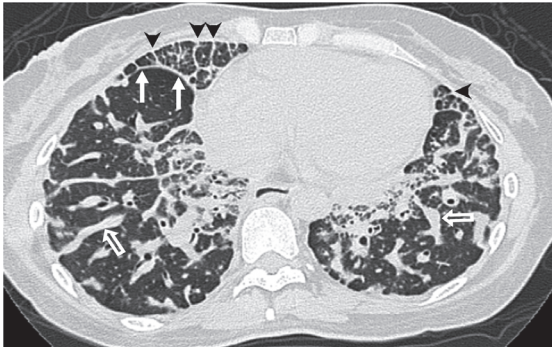
Sittampalam K,  
MBBS, FRCPA  
Consultant

Teo CHY, MBBS  
Registrar

**Correspondence to:**  
Dr Kong Po Marn  
Tel: (65) 6357 7864  
Fax: (65) 6357 7871  
Email: po\_marn\_kong  
@tsh.com.sg

Pulmonary function testing repeated two months later showed significant deterioration. FEV1 was 0.811 (34% predicted) and FVC was 0.971. After initially refusing a diagnostic procedure, the patient consented to a transbronchial lung biopsy. Based on the histological appearance, ECD was considered a possibility although the histochemical stains were inconclusive. Smear and cultures for *Mycobacterium tuberculosis* were negative. Subsequently, radiographs of the long

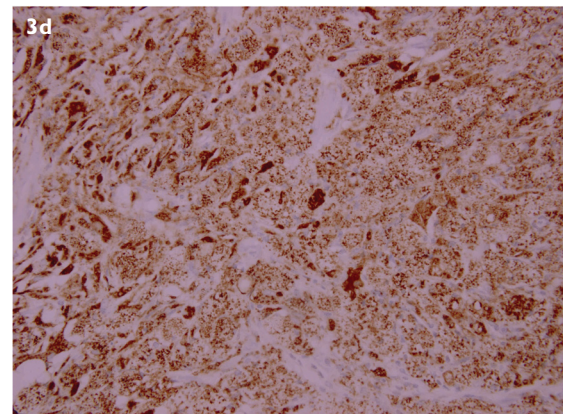
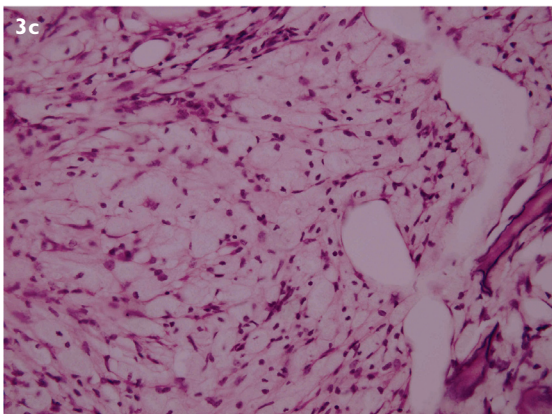
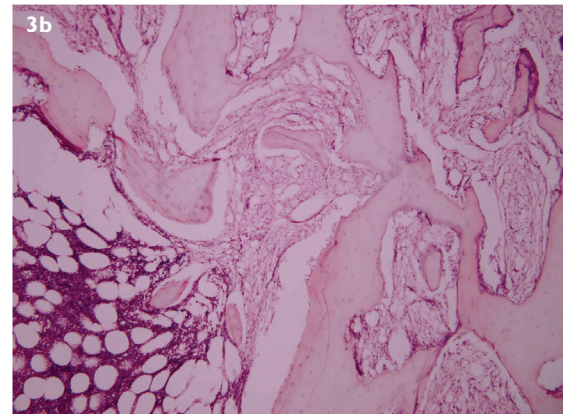
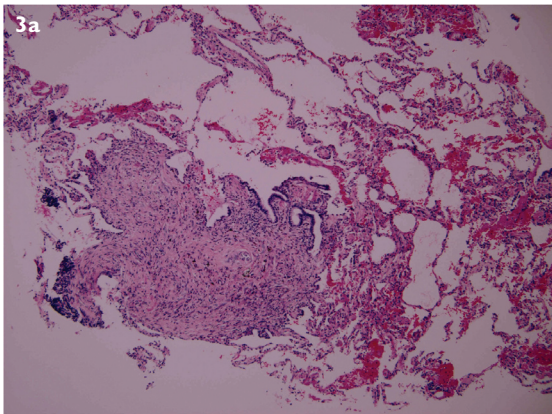
bones were performed which showed sclerotic lesions in the ends sparing the epiphyses. A bone biopsy from the right tibia showed effacement of the normal cellular elements and replacement by sheets of foamy histiocytes containing lipid. These stained positive for CD68 and S-100 but negative for CD1a (Fig. 3), which was consistent with the diagnosis of ECD. The patient deteriorated clinically, and developed pulmonary hypertension and respiratory failure. The patient was started on prednisolone 30 mg daily but passed away soon after.



**Fig. 2** High resolution CT image taken just above the right hemidiaphragm shows interlobular septal thickening (arrowheads), fissural thickening (arrows) and prominent soft tissue thickening around the pulmonary vessels (open arrows).

## DISCUSSION

Pulmonary involvement is rare in ECD. In a literature review of 59 cases<sup>(3)</sup>, only eight cases had pulmonary involvement and there are few reports in current literature. It often presents with non-specific symptoms of dyspnoea and dry cough; typically having been present from several months to one year, and appears to be more common in middle age.<sup>(5-7)</sup> Spirometry shows a restrictive picture with decreased DLCO in most cases. Clinical progression and deterioration of lung function can be rapid.<sup>(4)</sup> The clinical signs are similar to that of other diffuse interstitial lung diseases



**Fig. 3** Photomicrographs show (a) nodular area of fibrosis in the lung with mild chronic inflammation (Haematoxylin & eosin,  $\times 100$ ); (b) sheets of foamy macrophages with destruction of bone and marrow (Haematoxylin & eosin,  $\times 40$ ); (c) foamy macrophages (Haematoxylin & eosin,  $\times 400$ ); (d) positive CD68 immunostain for foamy macrophages (Peroxidase,  $\times 400$ ).

and do not help in the differential diagnosis. Unless the skeletal symptoms and radiological features are looked for, the diagnosis can be missed in cases where pulmonary symptoms are the main complaints and histology from the lungs are not easily available, such as in patients who are unfit for or refuse surgical biopsy. Transbronchial lung biopsies are often not diagnostic.<sup>(4,5,7)</sup>

Histological features in lung biopsies show thickening of the interlobular septa and interstitium at low power microscopy. This is caused by proliferation of large histiocytes as well as fibrosis. The histiocytes have foamy or finely granular cytoplasm and are uniformly positive for CD68 and variably so for S-100 on immunostaining. CD1a is usually negative and Birbeck granules are absent on electron microscopy.<sup>(2,5)</sup> Pulmonary involvement in ECD have several suggestive features such as symmetrical reticular shadows on chest radiographs, interlobular septal thickening on both radiographs and CT, diffuse and localised centrilobular nodular opacities, ground glass opacities and fissural thickening.<sup>(8)</sup> These features suggest the diagnosis of ECD when taken together. Differential diagnoses of the radiological features may include lymphangitic spread of carcinoma, leukaemia, lymphoma, interstitial infiltration associated with amyloidosis, some pneumonias, alveolar proteinosis, sarcoidosis, and even pulmonary oedema.

Treatment of ECD has involved the use of corticosteroids, cytotoxics, interferon, radiation, stem cell transplantation as well as surgery with variable success. The rarity of pulmonary ECD has precluded any standardisation of treatment. The combination of prednisolone and a chemotherapeutic agent appear to

have been successful in anecdotal cases. Bourke et al described a patient treated with cyclophosphamide and prednisolone with documented improvement of pulmonary function and subsequent clinical stability.<sup>(4)</sup> Another described improvement in pulmonary symptoms after combination treatment with cyclophosphamide, VP-16 and prednisolone.<sup>(5)</sup> Overall, pulmonary involvement carries a very poor prognosis, with some cases dying soon after diagnosis.<sup>(5,7)</sup> In summary, ECD with pulmonary involvement appears to be a unique entity with suggestive radiological features and carries a grave prognosis. This entity should be considered in the differential diagnosis of patients with interstitial lung disease when atypical radiological or musculoskeletal features are encountered.

## REFERENCES

1. Chester W. Uber lipoidgranulomatose. *Virchows Arch Pathol Anat* 1930; 279:561-602.
2. Rush WL, Andriko JA, Galateau-Salle F, et al. Pulmonary pathology of Erdheim-Chester disease. *Mod Pathol* 2000; 13:747-54.
3. Veyssier-Belot C, Cacoub P, Caparros-Lefebvre D, et al. Erdheim-Chester disease. Clinical and radiologic characteristics of 59 cases. *Medicine (Baltimore)* 1996; 75:157-69.
4. Bourke SC, Nicholson AG, Gibson GJ. Erdheim-Chester disease: pulmonary infiltration responding to cyclophosphamide and prednisolone. *Thorax* 2003; 58:1004-5.
5. Egan AJM, Boardman LA, Tazelaar HD, et al. Erdheim-Chester disease: clinical, radiologic and histopathologic findings in five patients with interstitial lung disease. *Am J Surg Pathol* 1999; 23:17-26.
6. Devouassoux G, Lantuejoul S, Chatelain P, Brambilla E, Brambilla C. Erdheim-Chester disease: a primary macrophage cell disorder. *Am J Respir Crit Care Med* 1998; 157:650-3.
7. Chung JH, Park MS, Shin DH, et al. Pulmonary involvement in Erdheim-Chester disease. *Respirology* 2005; 10:389-92.
8. Wittenberg KH, Swensen SJ, Myers JL. Pulmonary involvement with Erdheim-Chester disease: radiographic and CT findings. *AJR Am J Roentgenol* 2000; 174:1327-31.