CASE REPORT

An unusual case of interstitial lung disease in a patient with cardiopulmonary syndrome as the initial presentation of Erdheim-Chester disease

Domingo Franco-Palacios,¹ April McDonald,² R Neal Aguillard,³ Allen Berry⁴

¹University of Tennessee Health Science Center College of Medicine, Memphis, Tennessee, USA

²Pulmonary and Critical Care, University of Tennessee, Memphis, Tennessee, USA

³Pulmonary and Critical Care, Methodist University Hospital, Memphis, Tennessee, USA

⁴Department of Pathology, Saint Francis Hospital, Memphis, Tennessee, USA

Correspondence to

Dr Domingo Franco-Palacios, dfrancopalacios@gmail.com

Accepted 21 June 2017

SUMMARY

Erdheim-Chester disease (ECD) is a very rare disorder with only approximately 600 cases reported in the literature. ECD has been recently reclassified as a histiocytic dendritic cell neoplasm. The clinical spectrum ranges from asymptomatic tissue accumulation of histiocytes to invasive tissue infiltration, which can cause fulminant multisystem failure. It typically presents with bone pain and constitutional symptoms. Extrasosseous manifestations are not uncommon. ECD-associated interstitial lung disease has been described in 20%–35% of patients. Diagnosis is primarily by tissue biopsy and immunohistochemistry showing xanthogranulomas composed of foamy histiocytes that stain positive for CD68, CD14 and CD163 and negative for CD1a⁺ and langerin. We report a case of ECD in a young man with cardiopulmonary involvement who presented with haemoptysis and dyspnoea.

CASE PRESENTATION

A 20-year-old man without significant medical history complained of subacute non-productive cough, new-onset orthopnoea and exertional dyspnoea at rest. He was 3 years old when he moved with his family from Mexico to the USA. He works at a warehouse in quality audit and also assists his father in a gas station office. He lives with his parents in Tennessee, an endemic area for histoplasmosis. He otherwise denied exposure to toxins and other environmental hazards and did not have exposure to birds or bird products or recent travel outside the USA. He had never used illicit drugs or tobacco and reported no allergies. Family history was unremarkable. He went to an emergency department and was prescribed with azithromycin, which he took for 5 days without improvement in the respiratory symptoms. He presented to a different hospital where he was admitted for evaluation and treatment of haemoptysis and night sweats without associated fever or other constitutional symptoms.

During this initial hospitalisation at the outside hospital, a chest X-ray showed cardiomegaly. His ECG showed sinus tachycardia with low-voltage QRS without electrical alternans. CT angiography was negative for pulmonary embolism and confirmed the presence of a massive pericardial effusion (figure 1A). The CT chest also revealed an anterior mediastinal mass, left hilar enlarged lymph nodes (figure 1B) and pulmonary nodules but no radiographic findings of pneumonia. Respiratory cultures and blood cultures were negative. A trans-thoracic echocardiogram showed a large pericardial effusion without tamponade. Due to the large pericardial effusion, a pericardial window and biopsy of the pericardium were performed. Two and a half litres of serous pericardial fluid were drained. Microbiological and cytological examinations of the pericardial effusion and biopsy were also negative. He was discharged home clinically stable with resolving respiratory symptoms and on tapering doses of oral systemic steroids (prednisone 60 mg every day) based on pericardial biopsy results of inflammatory pericarditis. He was given instruction to follow up in the pulmonary clinic for possible biopsy of mediastinal and hilar enlarged lymph nodes.

A month later, the patient was readmitted with worsening dyspnoea at rest and cough productive

BACKGROUND

Erdheim-Chester disease (ECD) is a rare, non-Langerhans histiocytic disorder characterised by multi-system infiltration by epithelioid cells and foamy histiocytes that are CD68+/CD1a[−].^{1,2}

It was first described by Drs William Chester and Jakob Erdheim in 1930. Previously considered as a non-neoplastic inflammatory disorder as well as a clonal disorder, ECD was reclassified by the WHO as a haematopoietic neoplasm of histiocytic origin.³ Bone pain is the most common symptom, affecting long bones in a symmetrical distribution. Osteosclerosis is seen in 95% of patients.¹ The most common cardiovascular manifestations are periaortic fibrosis, which sometimes gives a 'coated aorta aspect', and pericardial involvement.² Cases of constrictive pericarditis and tamponade have been described in the literature.^{4–7} The cardiovascular system and central nervous system are involved in 77% and 50%, respectively.

ECD-associated interstitial lung disease (ILD) involves tissues adjacent to lymphatics, vasculature and visceral pleura, and has been described in 20%–35% of patients with ECD. On high-resolution CT (HRCT) scan, interlobular septal thickening, reticular pattern, micronodular ground-glass opacities and pleural effusion are typical findings.^{8,9}

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To cite: Franco-Palacios D, McDonald A, Aguillard RN, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-220659

Figure 1 CT of the chest shows large pericardial effusion (A) and an anterior mediastinal mass (B).

of sputum with streaks of blood. He was afebrile, tachypnoeic, tachycardic and hypoxaemic. His saturation was 92% while breathing a fraction of inspired oxygen of 60% on simple face mask. On examination, his mucosae were intact, no skin lesions were present and the examination of the musculoskeletal system was normal as well. Examination of the cardiovascular system revealed a supple neck without elevated jugular vein distention, regular tachycardia, normal first and second heart sounds, no murmurs, no leg oedema or cyanosis. On chest auscultation there were diffuse bibasilar crackles predominantly in the right base. There were no palpable axillary or inguinal lymphadenopathies or hepatosplenomegaly. He was treated with non-invasive positive pressure ventilation. He was still on prednisone 30 mg daily.

INVESTIGATIONS

The baseline blood counts and biochemical tests were within normal limits. Infectious work-up was negative, including HIV test, and tuberculin skin test and quantiferon gold test were negative. Sputum Gram stain, respiratory and blood cultures were all negative too. A negative histoplasma antigen ruled out endemic histoplasmosis. A complete blood cell count revealed leucocytosis with white blood cell count of $35\,000/\text{cm}^3$ (86% neutrophils) and polycythaemia with haemoglobin of 20 g/dL. Due to the presence of polycythaemia, a JAK2 mutation was checked and it was not detected. Erythropoietin was low at 1.8 (normal 2.6–18.5). Soluble interleukin-2 (IL2) level was 480 units/mL (normal), ferritin was normal, and triglycerides and lactate dehydrogenase (LDH) were slightly elevated at 341 mg/dL and 157 mg/dL, respectively (table 1) antinuclear antibody (ANA) and rheumatoid factors were not detected.

A repeat CT scan of the chest showed ground-glass opacities with interlobular septal thickening in the right middle and lower lobes, a persistent anterior mediastinal mass and more prominent mediastinal lymphadenopathy (figure 2).

A pathology review of the pericardial biopsy performed during the previous hospitalisation showed inflammatory changes with presence of xanthogranulomas and foamy histiocytes (figure 3A). The lesional cells were characterised by oval to spindle-shaped nuclei, some nuclear folding with small variable nucleoli and open chromatin. The cells exhibited abundant foamy and amphophilic cytoplasm and were surrounded by variable amounts of intercellular collagen (figure 3B). A few multinucleated cells were noted. The histiocytes lacked cytological atypia, nuclear hyperchromasia or significant nuclear pleomorphism. Mitotic figures or necrosis were not identified. A background inflammatory infiltrate composed of scattered lymphocytes was seen, with a few cells showing emperipolesis. Immunostains revealed strong positive cytoplasmic staining with CD68 and weakly positive staining for S100 protein and negative staining for CD1a (figure 3C–E).

Table 1 Laboratory profile of the patient during the illness

Test	Results
Total white cell count (thousand/mcL)	35
Segmented neutrophils (%)	86
Haemoglobin (mg/dL)	20.3
Haematocrit	61.8
Platelet count (thousand/mcL)	318
Urea nitrogen (mg/dL)	16
Creatinine (mg/dL)	0.9
Total protein (g/dL)	7.7
Albumin (g/dL)	3.8
Total bilirubin (mg/dL)	0.8
Aspartate aminotransferase (U/L)	27
Alanine aminotransferase (U/L)	47
Alkaline phosphatase (U/L)	66
Calcium (mg/dL)	9.1
Lactate dehydrogenase (U/L)	341
Triglyceride (mg/dL)	157
Ferritin, serum (ng/mL)	121.3
Erythropoietin	1.8
JAK2 V617F mutation	Not detected
JAK2 exon 12 mutation	Not detected
JAK2 exon 13 mutation	Not detected
Femoral bone marrow biopsy	Predominately blood clot with admixed fragments of benign unremarkable bone, marrow elements and skeletal muscle. No abnormal histiocytic features present.

Based on reported findings of the pericardial biopsy, a whole bone scan survey with technetium-99 (Tc-99) was performed. MRI confirmed the presence of small cystic lesions in the left frontal-parietal skull, T8 vertebrae and left femur. A biopsy of the femur was non-diagnostic. Molecular testing for BRAFV600E was negative in serum.

DIFFERENTIAL DIAGNOSIS

Although our patient did not have bone pain, the clinical presentation with cardiopulmonary syndrome in the context of the clinical radiological and pathological findings is supportive of the diagnosis of ECD.¹ All other performed tests were directed to evaluate for possible organ involvement based on the clinical suspicion (symptoms, physical exam, radiographic abnormalities and laboratory results).

Figure 2 CT chest in axial (A) and sagittal (B) sections demonstrate ground-glass airspace opacities with interstitial thickening predominantly in the right middle and lower lobes.

Figure 3 Low-power view shows a sheet-like infiltrate of foamy histiocytes within the pericardium with extension to the visceral pericardial surface (A). High-power view demonstrating xanthomatous histiocytes with oval nuclei with ample foamy cytoplasm (B). CD68 immunostain demonstrating strong cytoplasmic positivity within xanthomatous cells (C). S100 protein immunostain demonstrating weakly positive staining within xanthomatous cells (D). CD1a immunostain demonstrating negative staining within xanthomatous cells (E).

To investigate musculoskeletal involvement which affects most patients with ECD, a whole-body Tc-99 bone scan was ordered in our patient. An avid uptake was demonstrated in the left femur.

Electrolytes and kidney function were within normal limits.

The infectious work-up was negative. A limited autoimmune work-up was not supportive of the presence of collagen vascular disease.

Other differential diagnosis considered in this case includes other histiocytic and non-histiocytic disorders that can present with pericardial effusion, ILD and lymph node involvement.

ILD secondary to histiocytic infiltration can be seen in both Langerhans as well as non-Langerhans types of histiocytosis (eg, Rosai-Dorfman disease (RDD)). RDD, a disease of the lymphoreticular system, is characterised by lymphadenopathies and skin lesions secondary to the proliferation and tissue infiltration by non-Langerhans histiocytes. It can rarely affect the lung parenchyma. On microscopy and immunostain, the histiocytes exhibits emperipolesis (lymphocytophagocytosis) and is positive for CD68 and S100 but negative to CD1A. BRAFV600E is present in more than 50% of cases of ECD but not in RDD.¹⁰ S100 is positive in 20% of cases of ECD.² Electronic microscopy help to differentiate between LHC and non-LHC histiocytosis by demonstrating the presence of Touton cells and absence of Birbeck granules (present in LHC).

The negative staining for CD1a allowed us to exclude Langerhans cell histiocytosis. Cases of overlap syndromes with RDD and Langerhans cell histiocytosis (LCH), RDD and Ig4-RD, ECD and LCH, and ECD and RDD have been described. Whether this case represents a type of overlap syndrome is unknown to us, and we think a biopsy of the mediastinal lymph node could help to make this distinction.

TREATMENT

Broad-spectrum antibiotics were started empirically for suspected pneumonia in the immunocompromised patient based on the presence of tachypnoea, tachycardia, marked leucocytosis with neutrophilia and worsening airspace disease causing hypoxaemia. Bronchoscopy evaluation was deferred due to the patient's severe hypoxaemia. A diagnosis of ECD was made based on clinical presentation of large pericardial effusion, ILD, cystic bony lesions and supporting pathology evaluation of the

pericardium that revealed inflammatory changes with foamy histiocytic infiltration that exhibits the typical pattern in immunostain with positive CD68 and S100 but negative for CD1a.

Immunosuppression was started with administration of intravenous methylprednisolone. Interferon alpha (dose of 3 million units) was initiated on day 2 for treatment of ECD with cardiovascular and respiratory involvement but negative BRAFV600E mutation. The microbiology and serology tests for common bacteria and endemic mycoses remained negative.

Five days after hospitalisation, the patient's respiratory status improved and he was discharged home without oxygen therapy, on tapering doses of corticosteroids and interferon alpha, titrating doses up to 6 million units three times a week.

OUTCOME AND FOLLOW-UP

His hypoxaemic respiratory failure was successfully treated with supportive care and immunosuppressant therapy with steroids and adjuvant interferon alpha therapy. He did not require oxygen therapy on discharge.

In summary, pathology studies of the pericardial fluid and pericardial biopsy in our patient showed chronic pericarditis with prominent xanthomatous reaction and histiocytic infiltrate surrounded by variable amounts of intercellular collagen. Immunohistochemical staining was positive for CD68, weakly positive for S100 and negative for CD1A. The clinicoradiological presentation with typical pathological findings confirmed the diagnosis of ECD. On follow-up visit, 13 months after diagnosis of ECD, he is asymptomatic and doing very well. The anterior

Figure 4 CT scan 8 months after initiation of therapy with interferon alpha with near resolution of interstitial lung disease.

mediastinal and hilar masses are still present. Most of the ILD findings have resolved except for a few bibasilar nodules with a bronchovascular distribution (figure 4). He is on pegylated interferon (PEG-IF) 180 µg weekly.

DISCUSSION

We report a case of ECD in a young man with intrathoracic manifestation of the disease presenting with cardiopulmonary syndrome. Findings on CT of the chest included mediastinal infiltration, pericardial effusion and diffuse parenchymal lung disease.

ECD is an uncommon disorder with 600 cases reported in the literature.

Although the pathophysiology is unknown, it is now considered a histiocytic neoplasm.⁴ A somatic mutation occurs in histiocytes or its immature precursor cells, disrupting the cell growth regulation and division, which leads to overproduction of histiocytes that accumulates in the tissues and organs. One of such somatic mutations is the BRAFV600E mutation seen in more than 50% of cases.⁴ Diagnosis is primarily by tissue biopsy and immunohistochemistry in association with characteristic clinical and radiological findings.¹

The clinical spectrum ranges from asymptomatic tissue accumulation of epithelioid and foamy histiocytes to tissue infiltration, to fulminant multisystem failure. The disease typically presents in adults in their 40s–50s (age range 16–74 years) and has a male predilection (75%). The most common initial symptoms are bone pain in the knees and ankles and constitutional symptoms. Symmetrical and multifocal osteosclerotic lesions of the metaphysis and diaphysis of long bones are the most common findings described in cases of ECD. Extraskelatal tissue infiltration by foamy histiocytes has been reported in about 50% of cases. Diabetes insipidus was seen in 25% of patients in a prospective study of 60 patients.² The most common cardiovascular manifestation in ECD is the presence of soft tissue rounding the thoracic and abdominal aorta and its branches, also known as ‘coated aorta’. Pericardial infiltration is found in 44% of described cases and may lead to constrictive pericarditis or cardiac tamponade.^{2,3} Other patterns of cardiovascular involvement includes myocardial infiltration and infarction (periarterial infiltration of the coronary arteries), abnormal electrical conduction as noted in ECGs, right atrial tumour, valvular heart disease, heart failure and periaortic fibrosis.^{4–7} The prognosis is severe with cardiovascular complications.

Pulmonary involvement in ECD usually affects tissues adjacent to lymphatics, vasculature and visceral pleura. Interlobular septal thickening, reticular pattern, micronodular ground-glass opacities, consolidations, microcystic lesions, thin wall cysts and pleural effusion are typical findings on HRCT scan. ECD-associated ILD has been described in 20%–35% of patients with ECD.^{8,9} The HRCT findings may resemble other pulmonary conditions, particularly idiopathic interstitial pneumonitis, pulmonary Langerhans cell histiocytosis, diffuse pulmonary RRD, pulmonary lymphangitic carcinomatosis, pulmonary malakoplakia and Hermansky-Pudlak syndrome. The presence of a pleural effusion is more commonly seen in ECD compared with Langerhans cell histiocytosis, in which it is extremely rare. If biopsies are taken, microscopic examination reveals sheaths of histiocytic infiltration following a lymphangitic distribution and accompanied by fibrosis. Besides the cardiovascular and central nervous systems, retroperitoneal fibrosis with uropathies and endocrinopathies (eg, diabetes insipidus, hypopituitarism, hypogonadism) has been described.

Predictors of mortality and adverse outcomes have been attributed to central nervous system (CNS) involvement and cardiovascular involvement.^{11,12} Cardiovascular involvement is often asymptomatic. For this reason, many authors recommend an extensive work-up using cardiac MRI, CT scan and echocardiography to rule out involvement of the cardiovascular system.⁶ Central nervous system involvement is an independent predictor of inferior survival and requires aggressive treatment even in asymptomatic or mild disease.¹¹

Prognosis is extremely variable but overall remains poor. In a large series of patients with ECD treated with interferon alpha, the 1-year and 5-year survival rates were 96% and 68%, respectively. Treatment with interferon alpha was an independent predictor of improved survival.^{2,8}

ECD has no standard therapy. The goal is to prolong survival and increase the quality of life of the patients. Therapy consists of use of anti-inflammatory, immunosuppressive and chemotherapeutic agents.^{1,2} Corticosteroids are not considered effective as monotherapy. Corticosteroids in combination with interferon alpha have been shown to improve survival.^{12,14} Conventional or PEG-IF alpha is the first-line therapy for patients with newly diagnosed, symptomatic ECD without BRAFV600E gene mutation.

The benefits of the therapy with vemurafenib in patients with ECD harbouring the BRAFV600E mutation have been described in case series and in a phase 2 ‘basket’ study.¹³ Vemurafenib (used for the treatment of metastatic melanoma) along with Cobimetinib (a selective mitogen-activated protein kinase/extracellular signal regulated kinase (MEK)) are two of the targeted therapies that became part of the armamentarium for treatment of the disease at the molecular level.¹⁵

Cobimetinib has been used in patients with ECD without the BRAFV600E mutation, and its use in combination with vemurafenib needs to be studied.

The use of other agents like cladribine and anakinra is even more anecdotal.^{9,10} Anakinra (an interleukin 1) has been reported in few cases to be efficacious in the treatment of ECD-related bone pain, constitutional symptoms, perinephric infiltrates and skin lesions, but it is not recommended for severe forms of disease such as cardiac or neurological manifestations.^{1,11}

Our patient’s molecular test was negative for BRAFV600E mutation, and therapy with PEG-IF alpha effectively induced a favourable clinical response with significant radiographic improvement. Thirteen months after the index hospitalisation, our patient is asymptomatic and does not have any signs of disease remission, although a full work-up is underway. He is tolerating PEG-IF without reports of side effects.

Learning points

- ▶ Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis of unknown aetiology but classified within the histiocytic neoplasm. Cardiovascular involvement and interstitial lung disease (ILD) are not uncommon extraskelatal manifestations of ECD.
- ▶ Patchy centrilobular opacities and upper lung zone predominance are suggestive of ECD. Pleural effusion is a typical finding in the lung parenchyma of patients with ECD-associated ILD, which help to differentiate from LCH.
- ▶ This entity should be considered in the differential diagnosis of patients with ILD when atypical radiological or musculoskeletal features are encountered.

Contributors DF-P and AM collected the data, drafted and revised the manuscript. RNA is the primary pulmonologist and continues to follow the patient in the clinic. AB is the pathologist who diagnosed the condition. All authors reviewed the supporting reference and participated in the approval of the final version of the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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