CASE REPORT

Recurrent pericardial effusion and tamponade in a patient with Erdheim-Chester disease (ECD)

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SUMMARY

Erdheim-Chester disease (ECD) is a rare xanthogranulomatous disorder characterised by the proliferation of lipid laden histiocytes along with infiltration of various organs of the body. Although commonly presenting with bone pains secondary to bony infiltration, cardiac involvement in the form of periaortic fibrosis and pericardial involvement may be seen in a subgroup of patients. We report a case of ECD presenting as recurrent pericardial effusion along with pericardial tamponade.

BACKGROUND

Erdheim-Chester disease (ECD) is a rare xanthogranulomatous disorder belonging to a group of disorders called non-Langerhans cell histiocytosis (NLCH). It is characterised by proliferation of lipid laden histiocytes along with infiltration of various organs of the body. Most commonly, ECD presents with bone pain secondary to bony involvement. Cardiac involvement in the form of periaortic

fibrosis and pericardial involvement is seen in up to 40% of patients.¹ Pericardial involvement can be severe in the form of rapid, recurrent, pericardial tamponade, and can be a cause of increased morbidity and mortality.

CASE PRESENTATION

A 48-year-old man presented to the emergency department due to progressively worsening dyspnoea and non-productive cough, along with reduced appetite and weight loss for a duration of 6 months. He also reported progressively worsening vision involving both his eyes and gradually worsening quadriparesis. His medical history was significant for two previous episodes of worsening of breathlessness in the past 6 months, for which he was diagnosed and treated empirically for bacterial pneumonia and tuberculous pericardial effusion, respectively. At the time of the latest presentation, he had completed 6 months of category I antitubercular therapy without any clinical improvement. In view of persistent worsening of

Figure 1 (A): Chest X-ray of the patient showing large pericardial effusion. (B) ECHO showing large pericardial effusion with right ventricular diastolic collapse. (C) ECG showing low voltage (<0.5 mV) QRS complexes in limb leads.

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Figure 2 CT of the abdomen showing enhancing retroperitoneal soft tissue involving the kidneys, proximal ureters and adrenals bilaterally, along with bilateral moderate hydronephrosis.

pericardial effusion, he had undergone a pleuropericardial shunting 1 month before presentation. He had also been found to have an elevated thyroid stimulating hormone level and was started on thyroxine replacement at that time. His clinical examination revealed a temperature of 98.4°F, heart rate 82 bpm, blood pressure 100/60 mm Hg and respiratory rate 20 breaths/min. General examination revealed presence of yellowish plaques on the bilateral eyelids. Examination of the cardiovascular system showed tachycardia, presence of pulsus paradoxus and muffled heart sounds in the absence of murmurs, rubs or gallops. On examination of his central nervous system (CNS), the patient was found to have bitemporal hemianopia along with bilateral lower motor neuron-type lower limb weakness.

INVESTIGATIONS

Chest radiograph (figure 1A) showed presence of pericardial effusion and the patient's ECG showed low voltage QRS complexes (figure 1C). An urgent echocardiogram showed large pericardial effusion with right ventricular diastolic collapse

(figure 1B). CT of the abdomen (figure 2) showed enhancing retroperitoneal soft tissue involving the kidneys, proximal ureters and the adrenals bilaterally along with bilateral moderate hydronephrosis. CT of the thorax (figure 3A, B) showed gross pericardial effusion with loculations and associated intimal pericardial thickening. The patient's baseline blood counts and biochemical tests showed a mild elevation of liver enzymes, hypoproteinaemia and hypoalbuminaemia along with evidence of hypothyroidism, as shown in table 1. Diagnostic and therapeutic pericardiocentesis was carried out and 2000 mL of fluid was drained. Pleural fluid analysis showed exudative effusion with presence of mesothelial cells and lymphocyte predominant cells (table 1). MRI of the brain (figure 4) showed thickening and hyperintensity involving the optic chiasm along with bulky and hyperintense pontine lesions. A Nerve Conduction Velocity study was suggestive of asymmetric motor sensory polyneuropathy. Bone scan (figure 5) showed osteolytic lesions on the distal ends of both femurs and on the sixth rib. Although the patient's pericardial biopsy and perinephric soft tissue biopsy showed histiocytic aggregates, biopsy of periocular skin lesions was suggestive of xanthogranulomatous disorder along with histiocytic aggregates that showed diffuse positivity to CD68 along with Touton giant cells. Biopsy from soft tissue infiltration of the psoas muscle also showed histiocytic aggregates. The patient's oncogene BRAF 1-activating mutation using PCR technique on skin biopsy specimen was negative. Other causes of recurrent pericardial effusion were ruled out (table 1).

TREATMENT

A diagnosis of ECD was made and the patient was started on interferon therapy along with systemic glucocorticoids. For his bilateral hydronephrosis secondary to extensive soft tissue infiltration, the patient underwent a stenting procedure. His thyroxine replacement dosage was optimised. In view of his premorbid condition, pericardiectomy was withheld.

OUTCOME AND FOLLOW-UP

Despite receiving six doses of pegylated interferon and the previous pleuropericardial window, the patient's clinical condition deteriorated. His hospital stay was complicated by recurrent urinary infections, bilateral papillary necrosis, and *Clostridium difficile* and *Candida* infections. He succumbed to severe sepsis with *Proteus mirabilis*, refractory hypotension and cardiac arrest.

Figure 3 (A and B) CT of the thorax showing large pericardial effusion with intimal thickening.

Table 1 Laboratory profile of the patient during the illness

Test	Result
Haemoglobin (g/dL)	12.9
Total white cell count (per mm ³)	9800
Platelet count (per mm ³)	316 000
Total bilirubin (mg/dL)	0.41
Direct bilirubin (mg/dL)	0.3
Total protein (g/dL)	4.6
Albumin (g/dL)	2.1
Aspartate aminotransferase (U/L)	234
Alanine aminotransferase (U/L)	84
Alkaline phosphatase (U/L)	101
Creatinine (mg/dL)	0.82
Uric acid (mg/dL)	6.4
Calcium (mg/dL)	3.39
Lactate dehydrogenase (U/L)	436
Prothrombin time (s)/international normalised ratio	10.6/0.97
Activated partial thromboplastin time (s)	33.4
Thyroid stimulating hormone (μIU/mL)	37
T4 (μg%)	8.1
FTC (μg%)	1.78
Creatinine kinase MB (ng/mL)	2.88
Troponin T (pg/mL)	50.49
ESR 60 (mm/h)	47
CRP (mg/L)	40.9
ANA	Negative
IGG4 (mg/L)	694
Rapid blood borne virus screen (HIV/HBV/HCV)	Negative
Bone marrow biopsy	Cellular marrow with no specific lesions
ACE (μ/L)	25
XPRT TB PCR	Negative
Mycobacterial culture	Negative
Fungal culture	Negative
Pleuropericardial fluid analysis	
Colour	Haemorrhagic
Protein (g/dL)	1.7
Lactate dehydrogenase (U/L)	183
Glucose (mg/dL)	87
Total white cell count (per mm ³)	642
Differential white cell count (per mm ³)	Polymorphs 48%, lymphocytes 52%
Red blood cells (per mm ³)	67 610
Cytospin study	No malignant cells seen
Cultures	Negative for any growth

ANA, antinuclear antibody; Creatinine kinase MB, Creatinine kinase MB isoenzyme; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; FTC, Free thyroxine concentration; HBV, hepatitis B virus; IgG4, Immunoglobulin G4.

DISCUSSION

ECD, also known as lipid granulomatosis, is a rare multisystemic histiocytic disorder of unknown aetiology.² Histiocytotic disorders have been classified into Langerhans cell histiocytosis (LCH) and NLCH. While LCH has infiltration of characteristic dendritic cells, in NLCH, the infiltration is by lipid laden foamy macrophages. ECD belongs to the NLCH group. To date, around 600 cases have been reported.³ It can affect any organ in the body, most commonly the skeletal system.⁴ It is characterised by uncontrolled proliferation of histiocytes, which are foamy and diffusely positive for CD68 along with touton giant cells. These histiocytes are negative for CD1a, S100 and Birbeck granules in contrast to LCH.^{5 6}

Figure 4 MRI of the brain showing bulky and hyperintense pontine lesions.

Erdheim and Chester's first description of this condition dates back to 1930.⁷ Even though the condition has deposition of lipid laden macrophages, abnormality of lipid metabolism as an aetiology has not been established.^{7 8}

The exact aetiology is unknown; however, recent published studies propose occurrence of oncogene-induced senescence and BRAFV600 mutation.⁹ Recurrent BRAFV600E mutations leading to chronic uncontrolled inflammation have been reported in more than 50% of patients.³ ECD classically affects middle aged people (mean age 57 (16–80) years) and is known to have a slight male predilection (63%).^{10 11} Its clinical manifestations have been varied, from localised disease to severe disseminated disease.³

From a retrospective case study of 59 patients, the most common presentation was identified to be bone pain, followed by exophthalmos and diabetes insipidus.¹⁰ Bone involvement is pathognomonic, occurring mostly in the form of osteosclerotic lesions involving the diaphysis and metaphysis of long bones. Skeletal involvement can be present in more than 70% of patients.^{4 6} Osteolytic lesions can also involve flat bones such as the skull and ribs.¹⁰ Bone scan shows the pathognomonic appearance over the femur, and proximal and distal tibia, and helps in qualitative assessment of osseous involvement.^{4 3} Our patient also had characteristic osteolytic lesions on the distal end of both femurs and on the sixth rib, seen in the bone scan.

Extraskelatal manifestations are protean, involving the CNS, hypothalamus–pituitary axis, thyroid, orbit, gingiva and skin, as well as pulmonary, cardiac, retroperitoneal, hepatic, renal, splenic, testicular, lymph nodal and conjunctive systems.^{5 8} Its

Figure 5 Bone scan showing osteolytic lesions on the distal end of both femurs and on the sixth rib.

progressive systemic involvement along with characteristic skin lesions, described as reddish-brown papules merging into plaques and involving the eyelids, axilla and oral cavity, has been described earlier.¹² Pulmonary involvement can be in the form of progressive dyspnoea and cough, and clinically can have features suggestive of interstitial lung disease. While chest X-ray can show diffuse interstitial infiltrates, CT of the thorax shows patchy fine reticular, centrilobular opacities along with ground glass attenuation and thickening of visceral pleura and interlobular septa.¹³ Evidence of exophthalmos and asymmetric motor sensory polyneuropathy is found in clinical examination. Imaging can show CNS involvement including characteristic lesions in the meninges, brain parenchyma, pons, cerebellum and optic chiasma, and also shows cord compression and progressive paraparesis, as in our patient, who was found to have pons and optic nerve involvement in the brain MRI.^{11 14 15} Renal impairment secondary to ureteric obstruction is common. Dense perinephric fat infiltration is picked up as 'hairy kidney' in CT of the abdomen.³ Retroperitoneal and testicular infiltration along with bilateral adrenal enlargement can also be present.

Cardiac involvement in the form of myocarditis was documented with the help of autopsy studies in 2004.² Most common cardiovascular manifestations are periaortic fibrosis and pericardial diseases. Periaortic disease presents as fibrosis of the aortic adventitial layer and is called 'coated aorta'.^{1 3} Pericardial disease can be in the form of pericarditis, pericardial effusion or pericardial tamponade.³ From a radiological study conducted among 37 patients who had ECD, 26 patients (70%) had abnormal heart imaging; 18 patients (49%) exhibited abnormal infiltration of the right heart, 11 of whom (30%) had a 'pseudo-tumoural' infiltration of the right atrium, whereas 7 (19%) had an infiltration of the auriculoventricular sulcus. Other remarkable findings were pericardial effusion in 9 patients (24%) and pericardial thickening in 5 patients (14%).¹⁵ Myocardial infiltration, myocardial infarction secondary to involvement of the coronary arteries, renovascular hypertension secondary to involvement of the renal artery, involvement of the

interatrial septum, valvular abnormality (aortic and mitral regurgitation) and conduction abnormalities are the uncommon cardiovascular manifestations reported in the literature.^{2 15 16} Cardiovascular involvement has been attributed as a common reason for morbidity and poor outcome.^{1 15}

With its multisystem involvement, differentials to be considered are infiltrative disorders, such as disseminated infections, vasculitis, sarcoidosis, amyloidosis, malignancy, IgG4 disease and LCH. However, characteristic systemic involvement as suggested by the brain MRI and bone scan findings in our patient can be a clue to the diagnosis of ECD.

No guidelines were accepted for diagnosis and treatment of ECD until 2014.³ During this time, various treatment modalities, though not proven, were available, and the most effective treatment was reported to be interferon therapy solely based on reported case series. Based on the 2014 consensus guideline, treatment is advised for all patients. Interferon α (INF α) and pegylated INF (PEG-INF α) have been found to have the largest amount of supportive evidence and continue to be the mainstay of treatment.^{3 17} Other agents such as corticosteroids, chemotherapeutic agents such as cladribine, serine kinase inhibitors, including vemurafenib, imatinib and anticytokine, and directed therapy such as infliximab, tocilizumab and anakinra, have been used in very few patients.³ Surgical decompression, radiotherapy and stem cell transplant have also been tried and are other treatment options available, though with questionable efficacy.³ Predictors of mortality and adverse outcomes have been attributed to CNS involvement and cardiovascular involvement, both of which were present in our patient.^{11 15} There have been very few reports of rapid and recurrent pericardial tamponade secondary to ECD. Thus the management of these is based on anecdotal case reports. Various approaches have been tried, these include repeated pericardiocentesis, failing which there is pericardial window and, finally, surgical pericardiectomy.^{1 18 19} Our patient, in spite of having multiple pericardiocentesis and pericardial window, continued to experience clinical deterioration. Early surgical pericardiectomy can probably be studied in similar patients in the future.

CONCLUSION

ECD is a rare xanthogranulomatous disorder. The last decade has seen increased recognition of this rare condition. Skeletal involvement is the most common manifestation of this multisystemic disorder. Cardiovascular involvement can be either pericardial or aortic. Pericardial involvement is common and is associated with increased morbidity. Rapid and recurrent pericardial effusion in patients with ECD can be life-threatening. INF α has been the mainstay of therapy. Recurrent therapeutic pericardiocentesis, pericardial window and surgical pericardiectomy are therapeutic options in patients with rapidly recurring pericardial tamponade.

Learning points

- Erdheim-Chester disease (ECD) is a rare disease that can present, rarely, with recurrent pericardial effusion.
- Recurrent pericardial effusion in ECD is usually associated with a poor prognosis.

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Competing interests None declared.

Patient consent Obtained.

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REFERENCES

- 1 George OK, Subhendu MS. Recurrent and rapidly occurring pericardial tamponade in Erdheim Chester disease. *Indian Heart J* 2012;64:103–5.
- 2 Loeffler AG, Memoli VA. Myocardial involvement in Erdheim-Chester disease. *Arch Pathol Lab Med* 2004;128:682–5.
- 3 Diamond EL, Dagna L, Hyman DM, et al. Consensus guidelines for the diagnosis and clinical management of Erdheim-Chester disease. *Blood* 2014;124:483–92.
- 4 Spyridonidis TJ, Giannakenas C, Barla P, et al. Erdheim-Chester disease: a rare syndrome with a characteristic bone scintigraphy pattern. *Ann Nucl Med* 2008;22:323–6.
- 5 Sheu SY, Wenzel RR, Kersting C, et al. Erdheim-Chester disease: case report with multisystemic manifestations including testes, thyroid, and lymph nodes, and a review of literature. *J Clin Pathol* 2004;57:1225–8.
- 6 Simiele Narvarde A, Novoa Sanjurjo F, Gómez Rodríguez N, et al. [Erdheim-Chester disease and Langerhans histiocytosis. A fortuitous association?]. *An Med Interna* 2004;21:593–6.
- 7 Gupta A, Kelly B, McGuigan JE. Erdheim-Chester disease with prominent pericardial involvement: clinical, radiologic, and histologic findings. *Am J Med Sci* 2002;324:96–100.
- 8 Schmidt HH, Gregg RE, Shamburek R, et al. Erdheim-Chester disease: low-density lipoprotein levels due to rapid catabolism. *Metabolism* 1997;46:1215–19.
- 9 Cavalli G, Biavasco R, Borgiani B, et al. Oncogene-induced senescence as a new mechanism of disease: the paradigm of Erdheim–Chester disease. *Front Immunol* 2014;5:281.
- 10 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.
- 11 Arnaud L, Hervier B, Néel A, et al. CNS involvement and treatment with interferon- α are independent prognostic factors in Erdheim-Chester disease: a multicenter survival analysis of 53 patients. *Blood* 2011;117:2778–82.
- 12 Caputo R, Marzano AV, Passoni E, et al. Unusual variants of non-Langerhans cell histiocytoses. *J Am Acad Dermatol* 2007;57:1031–45.
- 13 Egan AJ, 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.
- 14 Drier A, Haroche J, Savatovsky J, et al. Cerebral, facial, and orbital involvement in Erdheim-Chester disease: CT and MR imaging findings. *Radiology* 2010;255:586–94.
- 15 Haroche J, Cluzel P, Toledano D, et al. Images in cardiovascular medicine. Cardiac involvement in Erdheim-Chester disease: magnetic resonance and computed tomographic scan imaging in a monocentric series of 37 patients. *Circulation* 2009;119:e597–8.
- 16 Raptis DA, Raptis CA, Jokerst C, et al. Erdheim-Chester disease with interatrial septum involvement. *J Thorac Imaging* 2012;27:W105–7.
- 17 Braithe F, Boxrud C, Esmali B, et al. Successful treatment of Erdheim-Chester disease, a non-Langerhans-cell histiocytosis, with interferon- α . *Blood* 2005;106:2992–4.
- 18 Botelho A, Antunes A, Almeida JC, et al. A rare histiocytosis with severe cardiac involvement: Erdheim-Chester disease. *Rev Port Cardiol* 2008;27:727–40.
- 19 Alharthi MS, Calleja A, Panse P, et al. Multimodality imaging showing complete cardiovascular involvement by Erdheim-Chester disease. *Eur J Echocardiogr* 2010;11:E25.

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