

# Acute Cardiac Tamponade in a 77-year-old Italian Woman with Erdheim-Chester Disease

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Doi: 10.12890/2016\_000451 - European Journal of Case Reports in Internal Medicine - © EFIM 2016

Received: 20/06/2016

Accepted: 25/08/2016

Published: 19/09/2016

**How to cite this article:** Kyriakopoulou M, Decaux G, El Mourad M, Casado-Arroyo R. Acute cardiac tamponade in a 77-year-old Italian woman with Erdheim-Chester disease. *EJCRIM* 2016;3:doi:10.12890/2016\_000451.

**Conflicts of Interests:** The Authors declare that there are no competing interests.

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## ABSTRACT

Erdheim-Chester disease (ECD) is a non-Langerhans' histiocytosis and a very rare multisystemic disease of unknown aetiology, with skeletal involvement of the long bones and in more than 50% of cases with extraskeletal involvement. The disease was described in 1930 by the anatomopathologist Jakob Erdheim and his student William Chester. More than 500 cases have since been reported. We report the case of a 77-year-old Italian woman with ECD who was admitted to hospital for acute cardiac tamponade. The patient presented with simultaneous cutaneous, retro-orbital, skeletal, cerebral and cardiovascular manifestations and was successfully treated with corticosteroids followed by interferon.

## LEARNING POINTS

- Erdheim-Chester disease (ECD) is a non-Langerhans' histiocytosis and a very rare multisystemic disease that is thought to be associated with cytokine disturbances.
- ECD has a variable prognosis but is poorer in those with heart involvement.
- First-line treatment involves the administration of interferon alpha.

## KEYWORDS

Erdheim-Chester disease, tamponade, BRAF, interferon alpha

## INTRODUCTION

Erdheim Chester disease (ECD) typically presents in 40–60-year-old adults and has a male predominance. The natural history of the disease varies from asymptomatic to multisystemic, life-threatening forms. The diagnosis of ECD is based on histological and radiological criteria. The characteristic histological image is a xanthomatous or xanthogranulomatous infiltration of tissues by spumous histiocytes, surrounded by fibrosis. ECD can be distinguished from Langerhans' cell histiocytosis by the immunohistological and microscopic characteristics of the histiocytes. ECD patients are positive for CD68 and negative for CD1a and have no Birbeck granules. Extra-skeletal involvement may include the skin, kidneys, retro-orbital tissue, central nervous system, heart, lungs, liver, thyroid, testicles, breast or ganglions<sup>[1]</sup>.

## CASE REPORT

A 77-year-old Italian woman with a medical history of diplopia and glaucoma was admitted to our hospital for dyspnoea, orthopnoea and lower extremity oedema. She had a 4-month history of bilateral exophthalmos, orbital xanthogranuloma and fatigue (Fig. 1). Her medical history included Barrett's oesophagus, hepatic steatosis, vesicular lithiasis, haemorrhoids, hypovitaminosis D, spine fractures, cataract, bladder prolapse, sacrocolpopexy, hysterectomy and ovariectomy. She was allergic to penicillin. She was taking a collyrium with carteolol once per day, calcium once per day and vitamin D once per week. She was a lifelong non-smoker, did not consume alcohol, had not travelled abroad recently and had never used illicit drugs.

On physical examination she had a temperature of 36°C, heart rate of 85 beats/minute and blood pressure of 125/75 mmHg. She was dyspnoeic (NYHA III b) and orthopnoeic. She presented with remarkable bilateral painless exophthalmos, palpebral oedema, orbital xanthogranuloma and jugular turgescence. The cardiovascular examination showed normal S1 and S2 with no added sounds. The respiratory examination showed diminished breath sounds at the bases of the lungs and decreased fremitus. She also had bilateral lower extremity oedema.

Emergent cardiac echography (Fig. 2) revealed a circumferential pericardial effusion with an anterior predominance, compression of the right ventricle, septal shift and variations of 50% in mitral and aortic flow, all signs of acute cardiac tamponade. Urgent pericardiocentesis was carried out and 1300 ml of serous liquid was removed. The patient was then admitted to the intensive heart unit for further monitoring. The clinical evolution was excellent and on the fifth day she was transferred to the department of internal medicine so diagnostic investigations could be continued.



Figure 1. Bilateral exophthalmos and xanthogranuloma

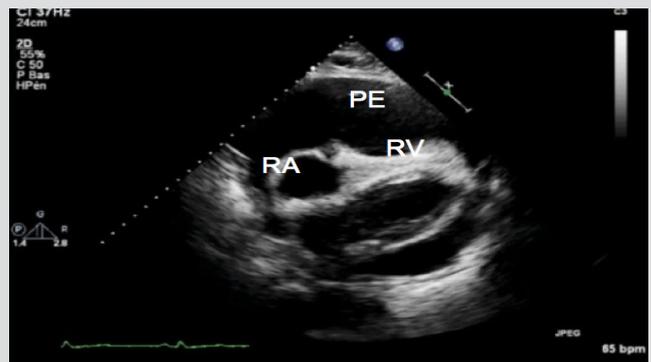


Figure 2. Cardiac echography

(PE, pericardial effusion; RA, right atrium; RV, right ventricle)

Laboratory tests showed lymphopenia 755/mm<sup>3</sup> (normal 1340–3950/mm<sup>3</sup>), elevated CRP 59 mg/l (normal < 10 mg/l), normal renal and liver function, and low albumin 29 g/l (normal 32–46 g/l). Chest radiography (Fig. 3) showed cardiomegaly and mild bilateral pleural effusion. ECG showed sinus rhythm with right bundle branch block. The particular phenotype of the patient with bilateral exophthalmos and orbital xanthogranuloma of recent onset with the combination of dyspnoea and pericardial and pleural effusion suggested that this case was not an ordinary cardiac tamponade of idiopathic, infectious, autoimmune or metabolic aetiology. We therefore considered multisystemic disease. Analysis of the pericardial liquid showed spumous histiocytes, anti CD 68+, anti CD 1a- and anti S100-. PET CT (Fig. 4) showed orbital, humeral, radial, trochanteric, femoral, colic and pleural FDG uptake. There was also FDG uptake by the thoracic aorta, the pericardium, the right atrioventricular orifice and the left breast. Femoral biopsy showed spumous histiocytes, anti CD 68+, anti CD 1a-, anti S100- and Touton giant cells. There was no BRAF mutation, but mutation of kit M541L was found. Cardiac MRI (Fig. 5) showed pericardial thickening associated with delayed enhancement, delayed enhancement at the atrioventricular orifices, and circumferential non-transmural enhancement of the thoracic aortic wall (at the adventitia, sparing the muscular layer). Cerebral MRI showed pachymeningitis with a multifocal pseudo-tumoural character and bilateral orbital infiltration.

After histological diagnosis of ECD with multi-organ involvement, treatment with intravenous corticosteroids (500 mg methylprednisolone once per day) was administered for 3 days followed by subcutaneous interferon alfa-2b (3 million units twice per week for 1 week and then 6 million units three times per week). The patient was discharged from the hospital 2 weeks later. After almost 1 week she visited her doctor and interferon alfa-2b was changed to peginterferon alfa-2a (135 units once per week) with better tolerance but with



moderate fatigue and a spike in temperature (38°C) on the day of injection. The patient is still alive 1 year later, and the exophthalmos has partially regressed.



Figure 3. Chest radiogram showing cardiomegaly and mild bilateral pleural effusion

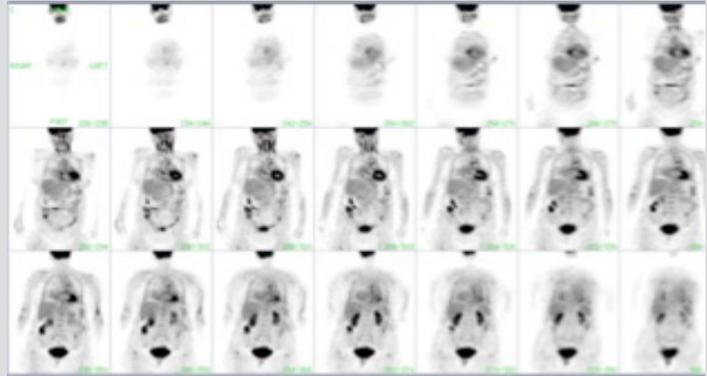


Figure 4. PET CT showing orbital, humeral, radial, trochanteric, femoral, colic and pleural FDG uptake and FDG uptake by the thoracic aorta, the pericardium, the right atrioventricular orifice and the left breast

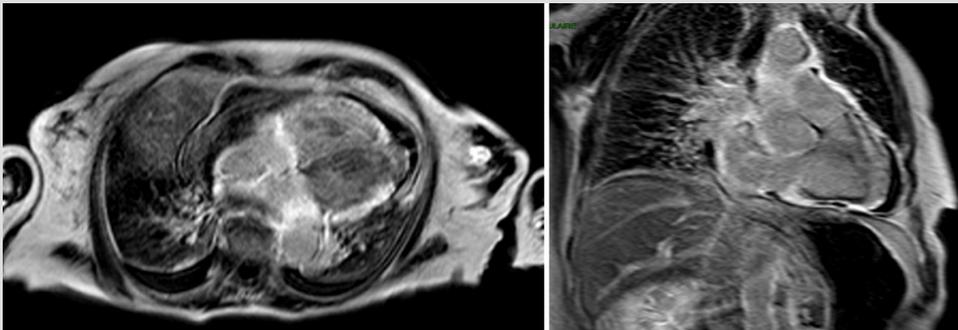


Figure 5. Cardiac MRI showing pericardial thickening associated with delayed enhancement, delayed enhancement at the atrioventricular orifices, and circumferential non-transmural enhancement of the thoracic aortic wall (at the adventitia, sparing the muscular layer)

## DISCUSSION

We described the case of a 77-year-old Italian woman with ECD who was admitted to hospital for acute cardiac tamponade, presented with simultaneous cutaneous, retro-orbital, skeletal, cerebral and cardiovascular manifestations and was successfully treated with corticosteroids followed by interferon. We diagnosed ECD based on clinical, radiological and histological findings.

The aetiology of ECD is unknown but it is thought to be associated with cytokine disturbances. Elevated levels of interferon alpha, interleukin (IL)-7, IL-12, monocyte chemo attractant protein-1 and decreased levels of IL-4 found in ECD patients support an associated systemic immune Th-1 oriented perturbation. Recent findings of mutations in the BRAF proto-oncogene in >50% of ECD cases clearly add further complexity to the pathophysiology of ECD<sup>[2,3]</sup>.

The differential diagnosis of ECD includes Langerhans' cell histiocytosis, Rosai-Dorfman disease, Takayasu vasculitis, Wegener's granulomatosis, primary hypophysitis, chronic recurrent multifocal osteomyelitis, malignancy and sarcoidosis.

There are no consensus guidelines for the treatment of ECD because no large studies have been performed. However, different treatments have been used individually with various levels of success. These include systemic corticosteroids, immunotherapy (interferon) and chemotherapy.

First-line treatment involves the administration of interferon alpha for all forms of ECD with higher doses required on a long-term basis for those with CNS and cardiac involvement. Second-line therapies include anakinra, vemurafenib, imatinib and cladribine. Salvage therapies include vincristine, vinblastine, cyclophosphamide, methotrexate and doxorubicin.

Palliative therapies include prednisolone and bisphosphonates. Other treatments used include infliximab, tocilizumab, mycophenolate and stem cell transplantation. Recently, infliximab and vemurafenib have been used with some success; vemurafenib seems to be promising for patients with a BRAFV600 mutation, but new prospective trials are needed<sup>[1,2,4,5]</sup>. It is important to emphasize that while these treatments may control the symptoms and delay evolution of the disease, there is as yet no cure for ECD.

## CONCLUSION

ECD has a variable prognosis which is poorer in those with central nervous system and heart involvement. Before interferon alfa became available, mean survival after diagnosis was 19.2 months. Now, with interferon alfa treatment, the mortality rate is only 26% and 5-year survival is 68%. The main cause of death is heart, respiratory or renal failure<sup>[2,3]</sup>.

ECD is a very rare disorder and often difficult to diagnose. It may be months or even years after symptom onset before patients are finally diagnosed and properly treated. Cardiovascular involvement in particular, is common but often asymptomatic and underdiagnosed. Consequently, physicians must be very vigilant when there is clinical suspicion of ECD.

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