RHEUMATOLOGY ADVANCES IN PRACTICE

Letter to the Editor (Case report)

Rheumatology Advances in Practice 2021;0:e1–e3
doi:10.1093/rap/rkab047
Advance Access Publication 27 July 2021

Erdheim–Chester disease presenting as acute ischaemic cardiomyopathy and aortitis in a *BRAF* V600E-negative patient

Key message

- Cardiovascular manifestations are diverse in Erdheim–Chester disease and can constitute the primary clinical presentation of a patient.

Dear Editor, We describe a case of a previously healthy middle-aged male who presented with severe acute ischaemic cardiomyopathy in the setting of an apparent large vessel vasculitis. The patient was ultimately diagnosed with Erdheim–Chester disease (ECD).

A 54-year-old man with no past medical history presented to an outside hospital for stuttering sub-sternal chest pain that began while chopping wood and escalated over 3 days. The chest pain was described as squeezing, radiating to the back, worsened by exertion and associated with dyspnoea and lightheadedness.

Physical examination was notable for sinus tachycardia and moderate hypervolaemia. ECG showed ST elevations with associated Q waves in leads V2–V5, I and aVL. Initial laboratory tests were significant for a neutrophil-predominant leucocytosis of 20 K/uL, troponin I 5.23 ng/mL, erythrocyte sedimentation rate (ESR) 23 23 mm/h, C-reactive protein (CRP) 14.9 mg/L, aspartate aminotransferase (AST) 197 units/L, alanine aminotransferase (ALT) 75 75 units/L. Chest CT angiogram demonstrated circumferential mural thickening throughout the entire length of the aorta, extending past its bifurcation and involving both iliac arteries with no evidence of dissection.

Left heart catheterization showed complete occlusion of the proximal left anterior descending coronary artery and ectasia of the right circumflex artery and lateral circumflex artery consistent with a vasculitic process *vs* atherosclerosis. No stents were placed. Transthoracic echocardiogram revealed mild left ventricular dilatation, increased wall thickness, apical aneurysm without thrombus, anteroseptal and apical akinesis, mildly reduced right ventricular systolic function, left ventricular ejection fraction of 10%, moderate-sized pericardial effusion with no signs of tamponade and no evidence of valvulopathy. He was transferred to our hospital for further medical management of a late-presentation myocardial infarction, acute decompensated systolic heart failure and work-up of a possible large vessel vasculitis.

On arrival to our cardiac intensive care unit, he was free of chest pain and endorsed only anxiety on full review of systems. History was negative for recent illness, travel, sick contacts or significant occupational exposures. Family history was non-contributory. In-house laboratory tests were significant for troponin I 50.00 ng/ml, ESR 91 mm/h, CRP 166.79 mg/L, Lactate dehydrogenase (LDH) 926 units/L, B-type natriuretic peptide (BNP) 1662 pg/ml.

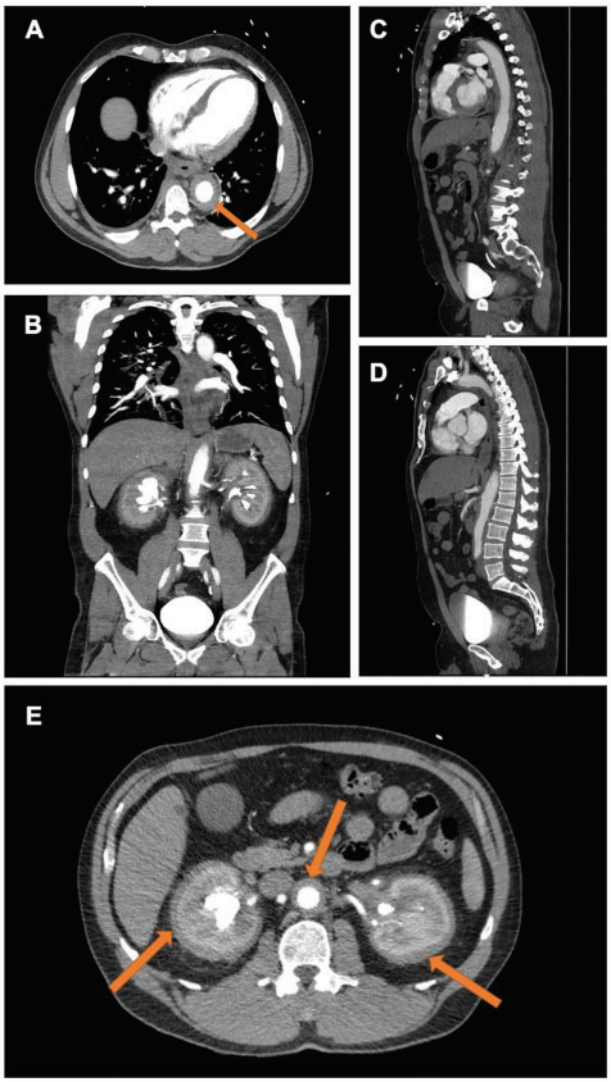
A broad differential diagnosis of infectious and non-infectious aetiologies for aortitis was considered. An extensive work-up that included blood cultures, FTA-ABS, Quantiferon-TB Gold, β-D-glucan, *Aspergillus* galactomannan, HBV and HCV serology, ANA, ENA panel, ANCAs, IgG subclasses and RF was unrevealing. The patient's CT images were obtained from the outside hospital and reviewed with in-house radiology. Our radiology team corroborated reports of extensive soft tissue thickening that involved the thoracic aortic arch, the major aortic branch vessels and the common iliac arteries (Fig. 1). However, imaging also revealed extensive bilateral perinephric thickening (Fig. 1). This constellation of findings raised suspicion for ECD.

After 1 week of hospitalization, the patient required emergency pericardiocentesis with drain placement for treatment of cardiac tamponade secondary to a large haemorrhagic pericardial effusion. The patient was stabilized, and a repeat echocardiogram showed no interval changes. An oncology consultation was requested owing to growing suspicion for ECD. Bone scan and kidney biopsy were planned, but the patient suffered a fatal ventricular fibrillation cardiac arrest before these tests could be carried out. The patient's family consented to an autopsy, which revealed evidence of systemic fibrosis and diffuse infiltrative xanthomatous histiocytosis consistent with ECD (Supplementary Figs S1 and S2, available at *Rheumatology Advances in Practice* online).

ECD is a rare systemic disorder characterized by the infiltration of multiple organs with xanthomatous $CD68^{+}$/$CD1a^{-}$ histiocytes and an overproduction of fibrous connective tissue [1]. The aetiology is unknown, with evidence pointing to ECD being a form of histiocytic neoplasm where ∼50% of affected individuals have a mutation in the *BRAF* V600E gene [1, 2]. The condition predominantly affects bone, although the clinical presentation varies depending on the extent and pattern of organ involvement [1, 3]. Of note, our patient presented without any constitutional symptoms or bone pain. There was evidence of extensive organ involvement in our patient, including the aorta, coronary vessels, prostate, testes, renal arteries and retroperitoneal tissue encasing both kidneys and adrenal glands. Histological examination for alternative pathologies, including IgG4-related disease (IgG4-RD), was negative. Immunohistochemistry for the *BRAF* gene mutation was also negative in our patient.

The spectrum of potential cardiovascular manifestations in ECD is broad and includes peri-aortic fibrosis,

Fig. 1 CT of chest, abdomen and pelvis



(**A**) Transverse view showing circumferential aortic wall thickening. (**B**) Coronal CT image demonstrating bilateral perinephric thickening. (**C**, **D**) Sagittal images showing coated appearance of the aortic wall extending from thorax to abdomen. (**E**) Hairy kidney sign, with another demonstration of circumferential aortic wall thickening.

coronary infiltration and myocardial infarction, pericardial effusion, valvular disease and restrictive cardiomyopathy [4, 5]. Although the prognosis of ECD is guarded [1], there have been several reports of small numbers of patients showing positive responses to varied drug regimens, often including IFN-α [6].The emergence of targeted therapies has advanced the treatment of ECD. The US Food and Drug Administration approved kinase inhibitor, vemurafenib, has been used for patients with the *BRAF* V600E mutation [7]. In patients without the *BRAF* V600E mutation, the inhibition of downstream mitogen-activated protein kinase kinase 1 (MEK1) and mitogen-activated protein kinase kinase 2 (MEK2) kinases by cobimetinib has shown promise [8].

Acknowledgements

The authors would like to thank Stephen P. Naber, MD, PhD for providing the anatomical pathology and histology images and Eugene I. Tikh, MD, PhD for providing the radiology images.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no conflicts of interest.

Ethics approval: Not applicable as per Tufts Medical Center IRB case report policy. Written consent was

obtained from the patient's family, because the patient (subject of case report) is deceased.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary data

Supplementary data are available at *Rheumatology Advances in Practice* online.

Anthony J. Nicolas[1] and Steven C. Vlad[1]
[1]*Division of Rheumatology, Tufts Medical Center, Boston, MA, USA*
Accepted 14 July 2021
Correspondence to: Anthony Nicolas, Division of Rheumatology, Tufts Medical Center, 800 Washington Street, #599, Boston, MA 02111, USA.
E-mail: nicolasaj@upmc.edu

References

1 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.

2 Haroche J, Charlotte F, Arnaud L *et al.* High prevalence of *BRAF V600E* mutations in Erdheim-Chester disease but not in other non-Langerhans cell histiocytoses. Blood 2012;120:2700–3.

3 Cavalli G, Guglielmi B, Berti A *et al.* The multifaceted clinical presentations and manifestations of Erdheim–Chester disease: comprehensive review of the literature and of 10 new cases. Ann Rheum Dis 2013; 72:1691–5.

4 Haroche J, Amoura Z, Dion E *et al.* Cardiovascular involvement, an overlooked feature of Erdheim-Chester disease: report of 6 new cases and a literature review. Medicine (Baltimore) 2004;83: 371–92.

5 Quinaglia-Silva T, Medina F, Ramos CD, Coelho-Filho OR. Cardiac involvement in Erdheim-Chester disease. Circ Cardiovasc Imaging 2018;11:e008531.

6 Munoz J, Janku F, Cohen PR, Kurzrock R. Erdheim-Chester disease: characteristics and management. Mayo Clin Proc 2014;89:985–96.

7 Oneal PA, Kwitkowski V, Luo L *et al.* FDA approval summary: vemurafenib for the treatment of patients with Erdheim-Chester disease with the *BRAF*V600 mutation. Oncologist 2018;23:1520–24.

8 Diamond EL, Durham BH, Ulaner GA *et al.* Efficacy of MEK inhibition in patients with histiocytic neoplasms. Nature 2019;567:521–4.