

Multiple arterial thrombosis and pericarditis revealing histiocytosis successfully treated with MEK-inhibitor cobimetinib

Sirs,

Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis characterised by long bone and peri-nephric involvement ("hairy-kidney") associated with compatible histology. Vascular sheathing involving adventitia of vessels ("coated-aorta") is described and is usually non symptomatic. Cardiac involvement includes pericarditis, atrium pseudo-tumour or coronary infiltration.

A 71-year-old man suffered from lower limb pain and arthritis of the ankles and knees for three years. He had medical history of hypertension and prostatic hypertrophy. He had no smoking or drinking habits and no coronary heredity. Imaging (x-ray/magnetic resonance imaging) showed no fracture or arthritis. Repeated laboratory investigations were normal except elevated C-reactive protein (CRP) between 20 and 40 mg/L (n<10mg/L). Patient described fatigue, pain and dyspnea. Physical examination showed a wound of the third toe of the right foot.

Laboratory examinations including lipid tests were unremarkable except CRP level at 45 mg/L and platelets at 555 G/L (n: 150-450 G/L). Body computed tomography (CT) showed multiple thrombosis – popliteal artery at his origin, right anterior tibia artery, left superficial femoral artery – stenosis of coeliac trunk and renal arteries. Other abnormalities – infiltration of peri-nephric fat, right ureter dilatation, mesenteric enlarged lymph nodes – were present on the CT. Cardiac echocardiography showed left ventricle ejection fraction at 30% with abundant pericardial effusion. Pericardial puncture appeared as exudate made of 82% of neutrophils. Malignant cells were absent and culture for infectious agents was negative. Coronary angiography showed a 70% stenosis of left anterior descending artery requiring percutaneous coronary intervention. The patient also underwent urgent femoral and popliteal angioplasty. Due to pericardial effusion, multiple thrombosis and stenosis, the main diagnosis suspected was neoplasm. ¹⁸Fluorodeoxyglucose positron emission tomography (¹⁸FDG-PET) showed radiotracer uptake on vessels, heart, and peri-nephric fat. Bone scintigraphy showed radiotracer uptake of metaphyseal/diaphyseal region of long bones suggestive of ECD. Peri-nephric

fat biopsy was infiltrated by Cd68⁺, Cd1a⁺ and S100⁺ foamy histiocytes surrounded by fibrosis. *BRAF*^{V600E} mutation was positive on biopsy samples. Bone marrow biopsy showed essential thrombocythaemia (TE) with mutation on *JAK2* gene. Due to cardiovascular involvement and association with myeloproliferative neoplasm, patient received cobimetinib (MEK-inhibitor). The metabolic response was good on bones, vessels and heart at 6 months. Platelets counts became normal under cobimetinib.

Erdheim-Chester disease is a rare non Langerhans-cell histiocytosis affecting adults. Diagnosis is based on clinical/imaging presentation and typical histology (1). Imaging shows long bones involvement (bilateral symmetric metaphyseal/diaphyseal osteoclerosis of legs), infiltration of peri-nephric fat ("hairy kidney") and vascular sheathing. Adventitia of aorta is the preferential site of infiltration (*i.e.* "coated aorta") but it can affect all vessels and might lead to stenosis/thrombosis at ending stage. Pericarditis, right-atrium pseudo-tumour and coronary infiltration are described in ECD (2). It is usually asymptomatic and diagnosis is mostly performed with imaging (MRI or CT or US) (3). Coronary occlusion is exceptional. Main predicting factor of aortic/

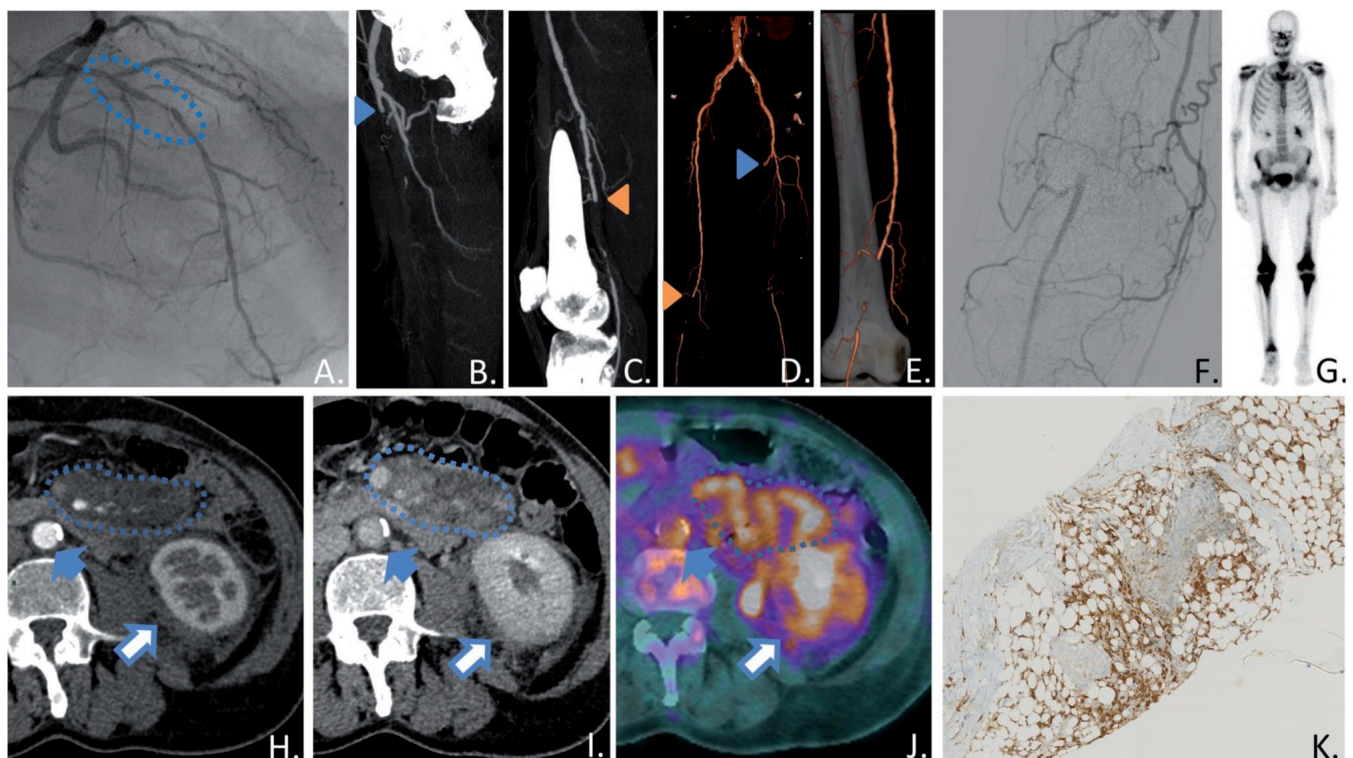


Fig. 1. Images of features of Erdheim-Chester disease.

A: Coronary angiography showing stenosis of left anterior descending artery.

B-C-D-E: Maximum Intensity Sagittal and angio3D projection showing vascular occlusion. Orange arrow shows occlusion of the left superficial femoral artery. Blue arrow shows occlusion of the supraarticular popliteal artery.

F: Arteriography showing occlusion of the left superficial femoral artery and of the supraarticular popliteal artery.

G: Bone scintigraphy showing radiotracer uptake on metaphyseal/diaphyseal region of long bones suggestive of ECD.

H: CT scan at the arterial phase and at the portal phase (**I**) showing circumferential thickening of the aortic wall enhanced at portal time (blue arrow) and peri-nephric fat (white arrow)

J: Axial ¹⁸FDG Positron Emission Tomography showing radiotracer uptake on aortic wall and peri-nephric fat.

K: Guided tissue biopsy of peri-nephric fat showing histiocytes Cd 68+.

coronary infiltration is BRAF^{V600E} mutation present in 60% of patient (4, 5).

Tissue biopsy is mandatory to confirm infiltration of Cd 68⁺, Cd1a⁺ and S100⁺ histiocytes, to rule out differential diagnosis (lymphoma, solid tumour, vasculitis, hyper-IgG4 syndrome or other histiocytosis), and identify somatic mutations in MAP-kinase pathway gene present in almost 80% of patients (mostly *BRAF* and *MAP2K1*) (5). From those findings, ECD is now considered as a myeloid neoplasia (6). Co-occurrence of myeloproliferative neoplasm confirm the myeloid origins of cells in ECD (7, 8). This presentation also confirms the MEK-inhibitors efficiency in Erdheim-Chester disease (associated with TE) (9, 10).

To conclude, this case highlights the diagnosis of Erdheim-Chester disease presenting as multiple stenosis, thrombosis associated with pericarditis and efficiency of Mek-inhibitor.

J. RAZANAMAHERY¹, MD
A. MALAKHIA², MD
B. GUILLON³, MD
S. HUMBERT¹, MD
N. MAGY-BERTRAND¹, MD PhD

¹Department of Internal Medicine, ²Department of Radiology, ³Department of Cardiology, University Hospital, Besancon, France.

Please address correspondence to:
Dr Jerome Razanamahery,
CHRU Besancon,
3 boulevard Alexander Fleming,
25000 Besancon, France.
E-mail: jrazanamahery@chu-besancon.fr

Competing interests: none declared.

© Copyright CLINICAL AND
EXPERIMENTAL RHEUMATOLOGY 2020.

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, 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.
3. 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: e597-98.
4. COHEN-AUBART F, GUERIN M, POUPPEL L *et al.*: Hypoalbuminoproteinemia and BRAFV600E mutation are major predictors of aortic infiltration in the Erdheim-Chester disease. *Arterioscler Thromb Vasc Biol* 2018; 38: 1913-25.
5. EMILE J-F, ABLA O, FRAITAG S *et al.*: Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. *Blood* 2016; 127: 2672-81.
6. HAROCHE J, COHEN-AUBART F, ROLLINS BJ *et al.*: Histiocytoses: emerging neoplasia behind inflammation. *Lancet Oncol* 2017; 18: e113-25.
7. PAPO M, DIAMOND EL, COHEN-AUBART F *et al.*: High prevalence of myeloid neoplasms in adults with non-Langerhans cell histiocytosis. *Blood* 2017; 130: 1007-13.
8. DURHAM BH, ROOS-WEIL D, BAILLOU C *et al.*: Functional evidence for derivation of systemic histiocytic neoplasms from hematopoietic stem/progenitor cells. *Blood* 2017; 130: 176-80.
9. COHEN AUBART F, EMILE J-F, MAKSDUD P *et al.*: Efficacy of the MEK inhibitor cobimetinib for wild-type BRAF Erdheim-Chester disease. *Br J Haematol* 2018; 180: 150-53.
10. DIAMOND EL, DURHAM BH, ULANER GA *et al.*: Efficacy of MEK inhibition in patients with histiocytic neoplasms. *Nature* 2019; 567: 521-24.