OXFORD

*Oxford Medical Case Reports*, 2022, **7**, 261–264
https://doi.org/10.1093/omcr/omac071
**Case Report**

# Cardiac electrical instability in Erdheim-Chester disease: a case report

Andrea Urbani[1,*], Filippo Pensotti[1], Diego Castini[1], Silvia Magnani[1], Pasquale Simone Simeoli[1], Corrado Campochiaro[2], Lorenzo Dagna[2], Alberto M. Cappelletti[3], Carlo Sponzilli[1] and Marco Guazzi[1]

[1]Cardiology Department and Intensive Care Unit, San Paolo Hospital, ASST Santi Paolo Carlo, University of Milan, Milan, Italy
[2]Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR), San Raffaele Scientific Institute, Milan, Italy
[3]Department of Clinical Cardiology and Intensive Care Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

*Correspondence address. Cardiology Department, San Paolo Hospital, Milan, Italy. E-mail: andrea.urbani@unimi.it

## Abstract

**Erdheim-Chester disease (ECD) is a rare multisystemic disorder of non-Langerhans histiocytic cells with a pleomorphic clinical presentation. It affects bones, skin, central nervous system, pituitary gland, ocular tissue, kidneys and perirenal tissue and lungs. Cardiac involvement presents usually with pericardial effusion and right atrial masses, but rarely with conduction system infiltration and subsequent arrhythmic events. Following the discovery of mutations of activating signaling kinase proteins (BRAF, MEK, ALK), the therapeutic landscape has changed to a more precise targeted treatment. Currently vemurafenib is approved for patient with end-organ dysfunction and BRAF-V600E mutation and the prognosis has dramatically improved. Here we present a case of ECD with electrical instability as main clinically relevant manifestation of cardiac involvement.**

## INTRODUCTION

Erdheim-Chester disease (ECD) is a multisystemic non-Langerhans cell histiocytosis with pleiotropic manifestations [1, 2]. Prevalence and incidence of the disease are not precisely known largely due to misdiagnosis. Fewer than 1000 cases are currently described in the published literature [1]. As a multisystemic disease, ECD affects bones, especially of the lower limbs, skin, central nervous system and pituitary gland, ocular tissue, kidneys and perirenal tissue and lungs. Cardiovascular involvement is present in about 50–70% of cases and most commonly described clinical manifestations are pericardial effusion, right atrial pseudotumoral masses, inflammatory coronary artery disease and aortic circumferential infiltration [1, 2]. Here we report a case of ECD with BRAF V600E mutation presented with pericardial effusion and cardiac electrical instability as main clinical manifestations, successfully treated with vemurafenib and anakinra.

## CASE REPORT

A 39-year-old woman presented to the Emergency Department due to an accidental fall causing a lacerated wound in the occipital region. She also reported fatigue, polyuria, polydipsia, episodes of abdominal pain and extreme weight loss during the last months.

On physical examination, blood pressure was 110/60 mmHg and respiratory rate was 16 breaths/min. No murmurs, rubs or gallops were present at cardiac auscultation. Surface electrocardiogram showed 85/bpm sinus rhythm with diffuse low QRS amplitude and QT prolongation (600 ms, calculated with Bazett's formula). White blood cell count was 18 590/mm$^3$ (neutrophils 70% and lymphocytes 24%), CRP was 154 mg/L and procalcitonin was 2.64 ng/ml. She also had elevated serum creatinine value (1.75 mg/dL).

Transthoracic echocardiogram showed a severe pericardial effusion without signs of tamponade (Figs 1 and 2). Moreover, thickening of the right atrial wall and interatrial septum was observed (Fig. 1). Left ventricular systolic function was normal. To investigate the cause of her abdominal pain, the patient underwent a computed tomography (CT) scan of the abdomen that outlined a structural subverting of both kidneys parenchyma triggered by massive bilateral hydronephrosis, thickening of perirenal soft tissue and swelling of the adrenal glands (Fig. 3).

During the first night of hospitalization, the patient reported a polymorphic ventricular tachycardia with Torsade-de-Pointes (TdP) features (Fig. 4). The arrhythmic episode was self-limited and did not cause any symptom or hemodynamic effect. Junctional rhythm with narrow QRS complex and 50 bpm rate was subse-

**Received:** November 29, 2021. **Revised:** March 22, 2022. **Accepted:** May 29, 2022

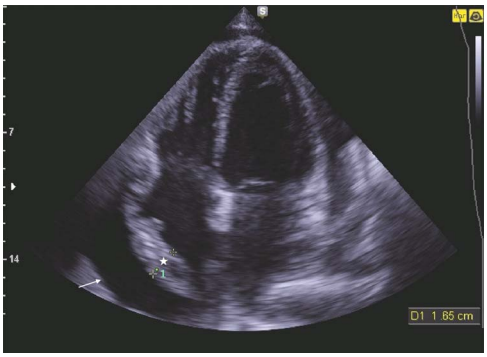


**Figure 1.** Transthoracic echocardiography. Apical four chambers view, large amount of pericardial effusion (white arrow) and thickening of right atrial free wall (white star, 1.65 cm of diameter) and interatrial septum.

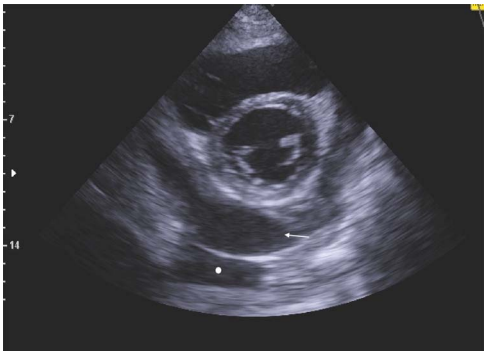

**Figure 2.** Transthoracic echocardiography. Parasternal short axis view, large circumferential pericardial effusion (white arrow) and pleural effusion flap (white dot).

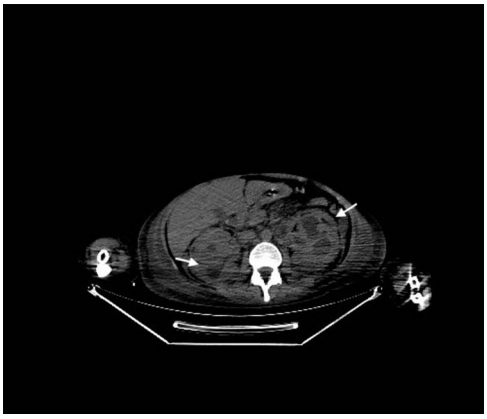

**Figure 3.** Axial abdomen computed tomography-scan image showing bilateral hydronephrosis and bilateral infiltration of perirenal tissue (white arrows).

quently observed at the electrocardiographic monitoring. During the following days, the patient underwent a period of extreme electrical instability with persistent QT interval prolongation and alternation of atrial fibrillation paroxysms with slow ventricular rate, extreme sinus bradycardia, periods of slow junctional rhythm and relapsing episodes of TdP. Therefore, it was decided to place a temporary pacemaker, achieving a stable paced rhythm and the cessation of TdP events. Eventually, an episode of ventricular fibrillation occurred that was successfully treated with external DC shock.

On differential diagnosis, all causes of chronic pericardial effusion were to be considered. On the other hand, the presence of right atrial walls thickening in association with the occurrence of arrhythmic events raised the suspicion of an associated myocardial infiltrative process. Finally, the presence of symptoms suggestive for diabetes insipidus (DI) and the abdomen CT scan findings led to the consideration of a multisystemic disease.

A subxiphoid pericardiocentesis was performed with placement of a pericardial drainage catheter. This allowed the slow drainage of almost 3 L of clear yellow fluid over a 4-day time period. The biochemical fluid analysis was indicative for an inflammatory transudate. No malignant cells were found and bacterial, fungal and acid-fast bacilli cultural tests were negative.

A magnetic resonance imaging (MRI) of the brain was performed showing T2 and FLAIR hyperintensity of the neurohypophysis (Fig. 5), cerebellum and brain stem. This, in association with the clinical response to desmopressin therapy, confirmed the diagnosis of central DI.

Moreover, a total-body $^{18}$F-FDG PET/CT scan was performed demonstrating hypercaptation of the ascending aorta, right atrium (Fig. 6), perinephric tissue, long bones diaphysis and turcic sella (Fig. 7). On the basis of this multiorgan infiltrative involvement, the diagnosis of ECD was suspected. To obtain a diagnostic confirmation, a perirenal soft tissue biopsy was performed. Tissue samples revealed CD68 positive, CD1A and S100 negative histiocytic infiltration with a peculiar xantogranulomatous component in keeping with ECD. BRAF V600E mutation was also detected. The diagnosis of ECD was then confirmed.

According to the diagnosis of ECD with BRAF V600E mutation, the patient started a treatment with vemurafenib and anakinra. The occurrence of life-threatening arrhythmias advised the placement of an implantable cardioverter defibrillator in secondary prevention. Moreover, ureteral stents were implanted to relieve hydronephrosis.

After discharge the patient was referred for outpatient follow-up and a cardiac MRI was programmed to monitor the evolution of myocardial involvement.

The patient is currently in her sixth month of treatment, she is alive and asymptomatic. She did not report any complain regarding her health and was not hospitalized since the discharge.

## DISCUSSION

ECD is a rare multisystemic non-Langerhans cell histiocytosis with pleiotropic manifestations thought to be derived from abnormal proliferation of the monocyte–macrophage cellular lineage [1, 2]. It is strongly associated with somatic mutation of BRAF V600E which enhances cell proliferation and survival by activating the RAS/RAF/MEK/MAPK signaling pathway [3]. Prevalence and incidence of the disease are not precisely known

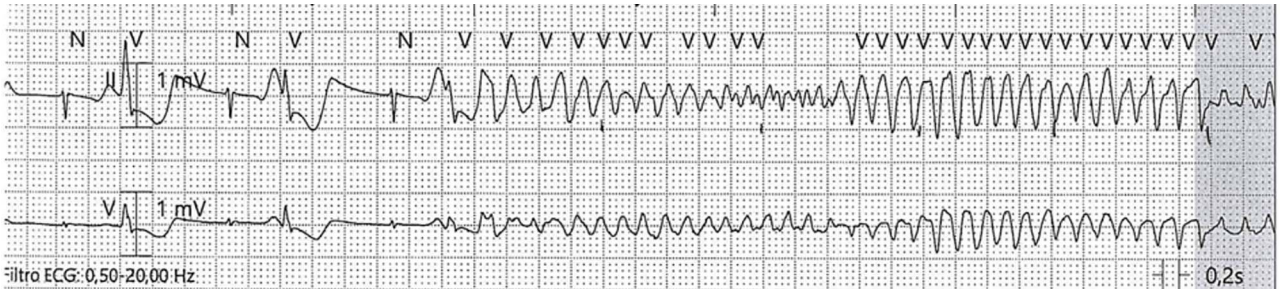


**Figure 4.** Polymorphic ventricular tachycardia with Torsade-de-Pointes features.

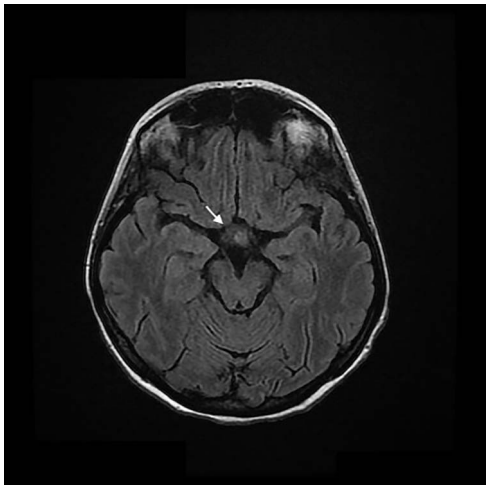

**Figure 5.** Brain-MRI scan. Axial T2-weighted FLAIR sequences reveal an irregular soft tissue intensity of the infundibulum of the pituitary gland (white arrow)

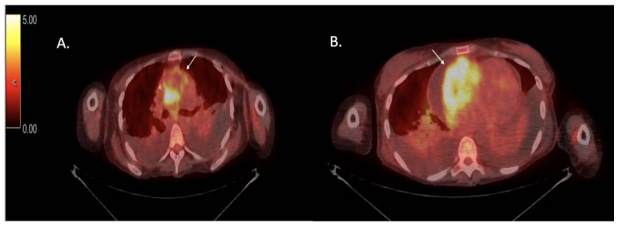


**Figure 6.** (**A**) 18-FDG PET/CT image showing increased fluorodeoxyglucose circumferential uptake of the ascending aorta (white arrow). (**B**) 18-FDG PET/CT image showing increased fluorodeoxyglucose uptake of the right atrium (white arrow).

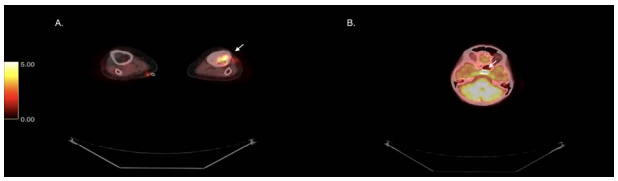


**Figure 7.** (**A**) 18-FDG PET/CT image showing increased fluorodeoxyglucose uptake of the proximal tibia. (**B**) 18-FDG PET/CT image showing increased fluorodeoxyglucose uptake of the sella turcica.

largely due to misdiagnosis. Fewer than 1000 cases are currently described in the published literature [1]. It appears to be slightly predominant in males (male to female ratio of 1.5) and the mean age at diagnosis is 46 years [2].

In most cases the clinical presentation is bone pain due to infiltration of long bones metaphysis and diaphysis, especially of lower limbs. Other localizations are, in order of frequency, perirenal tissue with kidney involvement (65%), large vessels (62%), lungs (52%), central nervous system (CNS) (38%) heart (37%) and skin (25%) [1].

For what concern the cardiac involvement, the most frequent presentations are right atrial masses, myocardial infiltration and pericardial effusion [4]. Infiltration of atrial and ventricular myocardium can determine in rare cases the occurrence of both bradiarrhythmic complications, consisting in pacemaker and conduction system abnormalities, and tachiarrhythmic events. In particular, conduction system involvement is described in only 8% of cases [5]. Periaortic encasement has been described in two-third of patients with the radiological aspect of 'coated aorta' [4].

In a 165 patients cohort, Caro *et al*. identified a cardiac phenotype linked to the BRAF status mainly characterized by right atrial pseudotumor. CNS involvement was also associated with BRAF mutation. The physiopathology of the close link between right atrial pseudotumor and the BRAF $^{V600E}$ mutation remains unclear. In that cohort the three main independent phenotypic features associated with a worse survival were CNS, retroperitoneal and lung involvements [6].

Over the last 5 years after the discovery of activating and signaling pathway mutations (BRAF, MEK, ALK), the therapeutic landscape has changed to a more precise targeted treatment. Currently vemurafenib is approved for patient with end-organ dysfunction and BRAF-V600E mutation based on a phase II trial which demonstrated a 62% response rate using the Response Evaluation Criteria in Solid Tumors criteria and a 100% response rate by FGD-PET evaluation in 22 patients [7].

The most common adverse effects of Vemurafenib documented in literature are arthralgia, maculopapular rash, fatigue, alopecia, skin papilloma and hyperkeratosis, which may lead in around 30% of cases to treatment interruption [7, 8].

Recent data have highlighted a synergic role of the anti-IL1 receptor anakinra in combination with targeted therapies especially in patients with refractory pericardial effusion [8, 9].

In summary, we report a case of a patient with ECD presenting with multiple and severe arrhythmic events

as main clinical manifestation of a multifaceted cardiac involvement. This case report highlights the importance of arrhythmic events recognition in patients with ECD because they might portend a high morbidity and mortality.

## ACKNOWLEDGEMENTS

We are grateful to our patient for giving us permission to write up her case.

## CONFLICT OF INTEREST STATEMENT

None declared.

## FUNDING

No source of funding for this report.

## CONSENT

Patient's consents have been obtained.

## GUARANTOR

Andrea Urbani MD (corresponding author).

## REFERENCES

1. Goyal G, Heaney ML, Collin M, Cohen-Aubart F, Vaglio A, Durham B *et al.* Erdheim-Chester disease: consensus recommendation for evaluation, diagnosis, and treatment in the molecular era. *Blood* 2020;**135**:1929–45.
2. Campochiaro C, Tomelleri A, Cavalli G, Berti A, Dagna L. Erdheim-Chester disease. *Eur J Intern Med* 2015;**26**: 223–9.
3. Diamond EL, Durham BH, Haroche J, Yao Z, Ma J, Sameer A *et al.* Diverse and targetable kinase alterations drive histiocytic neoplasms. *Cancer Discov* 2016;**6**:154–65.
4. Das JP, Xie L, Riedl CC, Hayes SA, Ginsberg MS, Halpenny DF. Cardiothoracic manifestations of Erdheim-Chester disease. *Br J Radiol* 2019;**92**:20190473.
5. Ghotra AS, Thompson K, Lopez-Mattei J, Bawa D, Hernandez R, Banchs J *et al.* Cardiovascular manifestation of Erdheim-Chester disease. *Echocardiography* 2019;**36**:229–36.
6. Cohen-Aubart F, Emile JF, Carrat F, Helias-Rodzewicz Z, Taly V, Charlotte F *et al.* Phenotypes and survival in Erdheim-Chester disease: results from a 165-patient cohort. *Am J Hematol* **93**:E114–7.
7. Diamond EL, Subbiah V, Lockhart C, Blay JY, Puzanov I, Chau I *et al.* Vemurafenib for BRAF V600-mutant Erdheim-Chester disease and Langerhans cell histiocytosis: analysis of data from the histology-independent, phase 2, open-label VE-BASKET study. *JAMA Oncol* 2018;**4**:384–8.
8. Campochiaro C, Cavalli G, Farina N, Tomelleri A, De Luca G, Dagna L. Efficacy and improved tolerability of combination therapy with interleukin-1 blockade and MAPK pathway inhibitors for the treatment of Erdheim-Chester disease. *Ann Rheum Dis* 2019; **0**:1–2.
9. Tomelleri A, Cavalli G, De Luca G, Campochiaro C, D'Aliberti T, Tresoldi M *et al.* Treating heart inflammation with interleukin-1 blockade in a case of Erdheim-Chester disease. *Front Immunol* 2018;**9**:1233.