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Prevalence, Patterns and Outcomes of Cardiac Involvement in Erdheim-Chester Disease

Short title Cardiac involvement in ECD.

Authors

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1 Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis belonging to
2 the L group of the 2016 revised classification for histiocytosis¹. ECD is characterized by
3 xanthomatous infiltration of various organs with foamy CD68⁺/CD1a⁻ histiocytes. More
4 than 1500 cases have been reported since 1930. Bone pain is the most frequent
5 symptom. About half the patients have extraskeletal manifestations, including
6 exophthalmos, xanthelasma, retroperitoneal “fibrosis” with perirenal or ureteral
7 obstruction, diabetes insipidus, central nervous system and cardiovascular
8 involvements^{2,3}.

9 Cardiovascular manifestations of ECD are frequent but often underdiagnosed⁴. Such
10 manifestations include infiltration of the myocardium (right atrial pseudotumoral
11 masses⁵ and atrioventricular sulcus infiltration), the pericardium (pericarditis and
12 cardiac tamponade), and small and large vessels (coronary infiltration, coated aorta)^{6,7}.
13 The prevalence and long-term outcomes of cardiac involvement in ECD are unknown.
14 Most of the evidence comes from case reports and small series, and to date, no large
15 cohort study has been conducted⁸.

16 We investigated the prevalence, clinical features, imaging features, and prognosis of
17 cardiac involvement by cardiac magnetic resonance (CMR) imaging in a large single-
18 center cohort of ECD patients.

19 **Methods**

20 **Population selection**

21 We retrospectively included patients with a biopsy-proven diagnosis of ECD referred to
22 the internal medicine department of a French tertiary center who underwent CMR
23 imaging between October 2003 and April 2019. In all cases, ECD diagnosis was based on
24 a typical clinical and radiological presentation, with confirmation by typical pathology
25 findings (infiltration with foamy CD68⁺/CD1a⁻ histiocytes). The biopsy samples were

1 reviewed centrally by two trained pathologists, F.C or J.F. E. We screened 262 patients
2 with ECD, 200 of whom were included in the study. A study flowchart is available in the
3 Supplementary material online, *Figure S1*. A comparison between the included and
4 excluded populations is reported in Supplementary material online, *Table S1*.
5 The study was approved by the local ethics committee (*Comité de Protection des*
6 *Personnes d'Ile de France III* [#2011-A00447-34]) and was conducted in accordance
7 with the Declaration of Helsinki.

8 **Evaluation of cardiac involvement by CMR**

9 All patients underwent cardiac imaging. For patients with data from multiple imaging
10 sessions, we assessed the data from the first CMR.

11 **CMR** was performed on a 1.5 T MR scanner (Siemens Aera). MR acquisition was
12 triggered by electrocardiogram, and the protocol included a kinetic study based on
13 steady-state free precession (SSFP) cine MR images along the short axis (8 mm thick, 30
14 phases). Functional studies were performed with this sequence, together with
15 measurement of the right and left ventricular ejection fractions.

16 Morphological studies were performed on vertical long-axis SSFP cine MR images, with
17 8 to 12 horizontal long-axis planes (views of the atrium walls).

18 Short-axis and axial images were acquired 10 minutes after contrast injection (0.2
19 mmol/kg intravenous Gd-DTPA) to check for lesion enhancement. No stress test was
20 performed.

21 All images were re-read blindly by an experienced radiologist (M.B).

22 We identified the types of lesions present (infiltration, pseudomass, effusion, late
23 gadolinium enhancement [LGE]), their localization (pericardial, myocardial, posterior
24 mediastinum, lateral or posterior or medial atrial wall, pattern of LGE) and
25 consequences for cardiac function (alteration of diastolic or systolic functions and

1 tricuspid annular plane systolic excursion [TAPSE]) (Supplementary material online,
2 *Appendix*).

3 Cardiac involvement was defined as an atrial infiltration (abnormal epicardial
4 infiltration of the atria exceeding 3 mm) or a pericardial abnormality (including
5 enhancement, infiltration, or thickening of the pericardium). A pseudomass was defined
6 as an infiltration that exceeded 5 mm in three planes.

7 **Assessment of outcomes**

8 The primary outcome was all-cause mortality. Secondary outcomes were pericarditis,
9 cardiac tamponade, conduction disorders, device implantation, and coronary artery
10 disease (CAD). Outcomes were assessed in all patients.

11 Acute and constrictive pericarditis were defined according to the 2015 European Society
12 of Cardiology Guidelines on pericardial diseases⁹. Cardiac tamponade was defined as
13 symptomatic cardiac compression resulting from the accumulation of pericardial fluid
14 requiring pericardiocentesis. High-degree conduction disorder was defined as a third-
15 degree atrioventricular block (complete heart block [CHB]) or complete sinus node
16 dysfunction [SND] requiring the implantation of a cardiac device. CHB and SND were
17 defined according to the 2018 American College of Cardiology/American Heart
18 Association/Heart Rhythm Society guidelines¹⁰.

19 ECD-related clinical events were defined as the presence of symptomatic, acute or
20 constrictive pericarditis, cardiac tamponade or a high-degree conduction disorder
21 resulting from cardiac infiltration, for which alternative causes had been excluded.

22 CAD was defined as the presence of significant atheromatous lesions (over 50% of the
23 proximal left coronary artery or 70% for the other arteries) on coronary angiogram.

24 Medical charts were thoroughly examined to assess patient outcomes. The secondary
25 outcomes were based on prior medical history and developments after ECD diagnosis.

1 Cardiovascular features, including cardiovascular risk factors and findings from
2 transthoracic echocardiograms, electrocardiograms and coronary angiograms, were
3 collected from the most recent medical charts of the patients when available.

4 ***BRAF* mutational status**

5 All patients underwent testing for codon V600 mutations of *BRAF*. The areas with the
6 highest level of histiocyte infiltration were selected by histological analyses of formalin-
7 fixed biopsy specimens, and DNA was sequentially analyzed by pyrosequencing followed
8 by picodroplet digital PCR, as previously described^{11,12}. Mutation status data were not
9 available for 21 patients (11%).

10 **Phenotype and treatment assessment**

11 All patients underwent a complete physical examination, a computed tomography (CT)
12 scan of the whole aorta, chest, abdomen and pelvis, a **CMR** or CT scan of the brain and
13 the heart, and an 18-fluorodeoxyglucose (FDG) positron emission tomography (PET)
14 scan. Myeloid neoplasms were defined according to the 2016 World Health Organization
15 (WHO) classification¹³. Treatment was left to the physician's discretion. The starting
16 dose of vemurafenib, a BRAF inhibitor, was 480 mg (administered twice daily). The
17 starting dose of cobimetinib, a MEK inhibitor, was 20 mg (administered twice daily with
18 a washout period of one week in every three).

19 **Statistical analysis**

20 Normally distributed continuous variables are expressed as means \pm standard
21 deviations, and non-normally distributed continuous variables are presented as medians
22 with interquartile ranges (IQR). Categorical variables are expressed as frequencies and
23 percentages. Comparisons were performed with χ^2 or Fisher's exact tests for categorical
24 variables and with Student's *t*-tests or Mann-Whitney-Wilcoxon tests for continuous
25 variables. All the reported odds ratios (OR) are crude OR. We first performed a

1 descriptive analysis of the characteristics of the study population, clinical features and
2 CMR imaging data. We then investigated the associations between cardiac involvement
3 and (1) extracardiac phenotype, (2) BRAF mutational status, and (3) outcomes. Finally, a
4 survival analysis was performed to explore the association between cardiac involvement
5 and the prognosis of patients. Kaplan-Meier estimates were used for survival curves.
6 Univariable and multivariable hazard ratios (HR) were estimated using Cox proportional
7 hazards regressions. Confounders to include in the multivariable Cox model (*i.e.*
8 variables both associated with death and cardiac involvement) were identified using
9 directed acyclic graphs (DAGs) and the *adjustmentSets* function of the *daggity* R library.
10 BRAF inhibitor treatment was considered a time-dependent variable. The proportional
11 hazards assumption was tested with Schoenfeld residuals and by inspection of both HR
12 plots and survival curve confidence intervals (CI). The inclusion date was the date on
13 which the histology analysis was performed. The primary endpoint was all-cause
14 mortality. Follow-up was considered to end on the date of death when applicable or on
15 the date of the last medical visit for all other patients. The date on which the last data
16 were collected was May 12, 2021. No more than 2% of the data were missing for the
17 study variables, except for (1) *BRAF* mutational status, which was unavailable for 11% of
18 patients, and (2) cardiovascular features assessed during follow-up. Results were
19 considered statistically significant if $P < 0.05$. All analyses were two-tailed. Statistical
20 analysis was performed with R software, version 3.3.2 (R Project for Statistical
21 Computing).

22 **Results**

23 **Study population**

24 In total, 200 patients were included (70% male). Median age (IQR) at imaging was 63
25 years (54-71 years). Median follow-up was 5.5 years (3.3-9 years). *BRAF*^{V600E} mutations

1 were detected in 117 patients (58%). Median delay between diagnosis and CMR imaging
2 was 5 months (1-20 months). The characteristics of the study population are reported in
3 *Table 1*.

4 **CMR findings**

5 ECD-related cardiac involvement was detected in 96 patients (48%).

6 Seventy-three patients (37%) had right atrioventricular sulcus (RAVS) infiltration. Forty
7 patients (20%) had right atrium free-wall infiltration, 50 patients (25%) had right
8 atrium posterior wall infiltration and 47 patients (24%) had interatrial septum
9 infiltration. Atrial infiltration resulted in a pseudotumoral mass-like appearance in 64
10 patients (32%). Atrial infiltration was well delineated and displayed LGE (*Figure 1*).

11 Pseudotumoral masses could result in coronary stenosis (*Figure 2*).

12 Pericardial involvement was observed in 58 patients (29%) of which 47 (24%) had
13 pericardial effusion, 28 (14%) had pericardial enhancement and 33 (17%) had
14 pericardial thickening (*Figure 1*). **Histological and cytological analyses are shown in**

15 ***Figure 3***. Atrial infiltration and pericardial involvement are displayed in Supplementary
16 material online, *Videos 1 to 3*.

17 LGE lesions were seen in 13 patients (7%), with a sub-endocardial pattern in 5 (3%) and
18 a transmural pattern in 8 (4%).

19 The CMR imaging findings are reported in *Table 2*.

20 **Extracardiac phenotype**

21 Patients with cardiac involvement were significantly more likely to have aortic (83% vs.
22 47%, $P < 0.001$), perirenal (79% vs. 47%, $P < 0.001$), orbital (32% vs. 7%, $P < 0.001$) and
23 maxillary infiltrations (15% vs. 5%, $P = 0.04$) and high C-reactive protein levels (88% vs.
24 64%, $P < 0.001$). Five patients (2.5%) presented with isolated cardiac involvement.

25 Extracardiac clinical features are reported according to cardiac involvement in *Table 1*.

1 ***BRAF*^{V600E} mutational status**

2 Cardiac involvement was observed in 78 patients (67%) with *BRAF*^{V600E} mutations
3 versus in 13 patients (21%) with wild-type (WT) *BRAF* genes (OR 7.4, 95% CI 3.5-16.8,
4 $P<0.001$). Right atrioventricular sulcus infiltration was significantly associated with
5 *BRAF*^{V600E} mutation (OR 13.1, 95% CI 4.8-45, $P<0.001$). CMR findings are reported
6 according to *BRAF* status in *Table 2*.

7 **ECD-related clinical outcomes**

8 In total, 20 patients (10%) suffered from an ECD-related clinical event.
9 Seven patients (3.5%) had acute pericarditis. One patient (0.5%) had constrictive
10 pericarditis, which resolved on treatment (peginterferon alfa-2a). Ten patients (5%) had
11 cardiac tamponade; all had *BRAF*^{V600E} mutations, had never been treated with BRAF
12 inhibitor, and were successfully managed by pericardiocentesis. Three patients (1.5%)
13 had CHB, due to interatrial septum infiltration in all cases. Two patients (1%) had SND,
14 both with right atrium posterior wall infiltration. Clinical illustrations of the conduction
15 disorders observed in the patients are shown in the Supplementary material online,
16 *Figures S2 and S3*. Cardiac involvement, as assessed by CMR, was significantly associated
17 with the presence of an ECD-related clinical event (OR 5, 95% CI 1.5-21.2, $P=0.004$). Two
18 patients (1%) with a normal baseline CMR developed an ECD-related clinical event (1
19 tamponade after 414 days, 1 pericarditis after 417 days).

20 **Coronary artery disease**

21 CAD was observed in 45 patients (23%). One-vessel, two-vessel and three-vessel CAD
22 were observed in 28 (14%), 12 (6%) and 5 (3%) patients, respectively. Thirty-two
23 (16%) patients underwent percutaneous angioplasty, and 7 patients (4%) underwent
24 coronary bypass surgery.

1 No statistically significant associations were observed between CAD and cardiac
2 involvement ($P=0.2$) or between right coronary bed involvement and right
3 atrioventricular sulcus infiltration ($P=0.4$). The cardiovascular features of the patients
4 are reported in the Supplementary material online, *Table S2*.

5 **Survival analysis**

6 None of the patients were lost to follow-up. Overall mortality was 32%, with a median
7 survival of 12 years, and a 5-year survival of 81% (*Figure 4*).

8 On univariable analysis, cardiac involvement was not significantly associated with
9 survival (unadjusted HR 1.5, 95% CI 0.9-2.5, $P=0.1$).

10 Candidate variables for multivariable analysis adjustment are shown in the DAG
11 reported in Supplementary Material Online, *Figure S4*. Confounder variables included in
12 the multivariable model were aortic and central nervous system involvements,
13 hydronephrosis and treatment with BRAF inhibitor. On multivariable analysis, cardiac
14 involvement was not significantly associated with survival (adjusted HR 1.4, 95% CI 0.8-
15 2.5, $P=0.2$).

16 **Discussion**

17 We describe here the prevalence, outcomes and features of cardiovascular involvement
18 in a large retrospective single-center study of patients with ECD. Cardiac involvement is
19 present in nearly half the patients and may lead to pericarditis, cardiac tamponade and
20 conduction disorders¹⁴⁻²⁰ (Structured Graphical Abstract). Atrial infiltration and
21 pericardial effusion are hallmarks of cardiac involvement²¹⁻²³.

22 The frequency of cardiac involvement may be overestimated due to the exclusion of
23 patients who did not undergo CMR. Based on either echocardiograms or cardiac CT
24 scans, 22/58 (38%) excluded patients had ECD-related cardiac involvement. As a result,
25 the true prevalence of cardiac involvement may be between 38% and 48%.

1 Cardiovascular involvement was associated with *BRAF*^{V600E} mutation. There is currently
2 no pathophysiological explanation for this association. Histiocyte infiltration in ECD
3 seems to match the location of white fat in the human body (*i.e.* the epicardial tissue, the
4 bone marrow, the perirenal and retroperitoneal layers)²⁴. Similarly, the sites of cardiac
5 infiltration match the location of epicardial adipose tissues, which have been reported to
6 be located principally in the atrioventricular and interventricular grooves²⁵.

7 Pericardial involvement was frequent and could be either clinically silent or associated
8 with acute pericarditis, cardiac tamponade, or constrictive pericarditis. Cardiac
9 tamponade developed in 5% of the patients and was associated with *BRAF* mutation and
10 absence of treatment with BRAF inhibitor. Constrictive pericarditis has previously been
11 reported as a potential complication in ECD^{21,26,27}. Pericardial thickening was frequent in
12 our series, but constrictive pericarditis was rare and resolved under treatment in one
13 patient. Treatment initiation and close follow-up should be considered in patients with
14 pericardial involvement to prevent clinical complications.

15 ECD-related high-degree conduction disorders were present in 2.5% of patients. Our
16 data suggest that patients with right atrial posterior wall and interatrial septum
17 infiltration should be closely monitored for conduction disorders.

18 CAD was frequent in this series, likely due to the predominance of male patients, the
19 high frequency of clonal hematopoiesis and chronic inflammatory syndrome, and the
20 major burden of classical cardiovascular risk factors^{28,29}. Given the high frequency of
21 CAD in ECD patients, we strongly suggest that any atypical and/or severe myocardial
22 involvement (such as symptomatic heart failure, a decrease in LVEF, LGE lesions or
23 conduction disorders) should prompt physicians to rule out CAD before attributing such
24 manifestations to ECD.

1 CAD may, in some cases, result from a pseudomass coronary compression. A dedicated
2 coronary CT scan could potentially facilitate the identification of coronary compression
3 and/or underlying atheromatous lesions in patients with pseudomasses on CMR. In
4 cases of extrinsic coronary stenosis, BRAF inhibitor treatment, which has been
5 described as a means of treating atrial infiltration, may effectively reduce pseudomass
6 coronary compression^{30,31}.

7 In our series, cardiac involvement was not significantly associated with poorer survival.
8 While previous reports suggested cardiovascular involvement accounts for a significant
9 proportion of deaths in ECD, these studies tended to include only symptomatic patients⁶.
10 However, in our study, patients were systematically screened for cardiac involvement
11 with CMR. In addition to this screening, the identification of *BRAF*^{V600E} mutations and the
12 subsequent use of BRAF inhibitors may explain the discrepancy between our results and
13 previous research. Nevertheless, it is important not to overlook cardiac involvement. In
14 fact, cardiac infiltration was found to be associated with greater morbidity (pericarditis,
15 cardiac tamponade, conduction disorder and potential coronary stenosis).

16 This study has several limitations. It was a retrospective, single-center study, and data
17 for mutational status were not available in all cases. There was a time lag between
18 diagnosis and CMR imaging. Finally, cardiovascular risk factors, transthoracic
19 echocardiograms and electrocardiograms were not available for all patients.

20 However, this study also has several strengths. It is the largest series to date to
21 investigate cardiac involvement in ECD. Cross-sectional imaging results were re-read in
22 a blind fashion. There were few missing data. Finally, survival analysis was based on all-
23 cause mortality.

24 In conclusion, the results for this retrospective single-center cohort highlight features
25 associated with cardiac involvement and the ability of CMR to shed light on cardiac

1 infiltration. Notably, a substantial number of patients with ECD were found to have atrial
2 infiltration, pericardial involvement and CAD. A systematic cardiac evaluation should be
3 performed in all ECD patients.

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6

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9 **Data availability: The data underlying this article will be shared on reasonable**
10 **request to the corresponding author.**

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Figure legends

Graphical Abstract

More than half of ECD patients had evidence of cardiac involvement on CMR, which was associated with a higher risk of clinical events.

Abbreviations: CMR cardiac magnetic resonance; ECD, Erdheim-Chester disease; HR, hazard ratio; OR, odds ratio

Figure 1. Atrial and pericardial infiltration in Erdheim-Chester disease on CMR imaging

A-F. Four-chamber CMR cine images showing atrial infiltration at multiple sites.

A. Right atrioventricular sulcus infiltration in the pericoronary fat of the right coronary artery.

B. Right atrioventricular sulcus pseudomass.

C. Interatrial infiltration.

D. Right, posterior and median right atrial wall infiltration before contrast administration.

E. Right, posterior and median right atrial wall enhancing on late gadolinium enhancement sequences

F. Association of right atrioventricular sulcus and right atrial pseudomasses.

G-I. Mid short-axis cine CMR images.

G. Circumferential pericardial thickening (arrow).

H. Diffuse pericardial effusion (arrow).

Four-chamber cine CMR images demonstrating

I. Pericardial effusion (arrow), and right atrial pseudomasses (arrowheads).

Abbreviations: CMR cardiac magnetic resonance.

Figure 2. Coronary stenosis from left atrioventricular sulcus infiltration on CT scan and CMR imaging

A. Four-chamber CMR cine images showing left atrioventricular sulcus pseudomass.

B, C, D. Cardiac computed tomography images showing a left atrioventricular sulcus pseudomass surrounding the proximal left anterior descending artery.

E. CMR delayed enhancement sequences showing an enhanced left atrioventricular sulcus pseudomass.

F, G. Cardiac CT scan showing thinning of the intraluminal wall of the circumflex artery.

Abbreviations: CMR cardiac magnetic resonance, CT computed tomography.

Figure 3. Histological and cytological samples of cardiac involvement in ECD

A. Explanted heart tissue of a patient with Erdheim-Chester disease (hematoxylin and eosin staining). Proximal right coronary artery (violet arrow) with an atheromatous lesion (*), surrounded by foamy histiocytes adventitial infiltration (square).

B-D. Cytological analysis of pericardial drainage from a patient with cardiac tamponade, showing histiocytes.

B. Staining with hematoxylin and eosin.

C. Staining for CD163.

D. Staining for pERK.

Figure 4. Ten-year survival curves according to cardiac involvement

A. The total population included.

B. Survival according to cardiac involvement on imaging.

Abbreviations: CI confidence interval; CMR cardiac magnetic resonance; HR hazard ratio.