Prevalence, patterns and outcomes of cardiac involvement in Erdheim–Chester disease

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

Cardiovascular manifestations of ECD are frequent but often underdiagnosed[4]. Such manifestations include infiltration of the myocardium (right atrial pseudotumoral masses[5] and atrioventricular sulcus infiltration), the pericardium (pericarditis and cardiac tamponade), and small and large vessels (coronary infiltration, coated aorta)[6,7]. The prevalence and long-term outcomes of cardiac involvement in ECD are unknown. Most of the evidence comes from case reports and small series, and to date, no large cohort study has been conducted[8].

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

Methods

Population selection

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

reviewed centrally by two trained pathologists, F.C or J.F. E. We screened 262 patients with ECD, 200 of whom were included in the study. A study flowchart is available in the Supplementary material online, *Figure S1*. A comparison between the included and excluded populations is reported in Supplementary material online*, Table S1.*

The study was approved by the local ethics committee (*Comité de Protection des Personnes d'Ile de France III* ([#2011-A00447-34]) and was conducted in accordance with the Declaration of Helsinki.

Evaluation of cardiac involvement by CMR

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

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

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

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

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

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

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

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

Assessment of outcomes

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

Acute and constrictive pericarditis were defined according to the 2015 European Society of Cardiology Guidelines on pericardial diseases[9]. Cardiac tamponade was defined as symptomatic cardiac compression resulting from the accumulation of pericardial fluid requiring pericardiocentesis. High-degree conduction disorder was defined as a third-degree atrioventricular block (complete heart block [CHB]) or complete sinus node dysfunction [SND] requiring the implantation of a cardiac device. CHB and SND were defined according to the 2018 American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines[10].

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

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

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

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

BRAF mutational status

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

Phenotype and treatment assessment

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

Statistical analysis

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

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

Results

Study population

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

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

CMR findings

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

Seventy-three patients (37%) had right atrioventricular sulcus (RAVS) infiltration. Forty patients (20%) had right atrium free-wall infiltration, 50 patients (25%) had right atrium posterior wall infiltration and 47 patients (24%) had interatrial septum infiltration. Atrial infiltration resulted in a pseudotumoral mass-like appearance in 64 patients (32%). Atrial infiltration was well delineated and displayed LGE (*Figure 1*). Pseudotumoral masses could result in coronary stenosis (*Figure 2*).

Pericardial involvement was observed in 58 patients (29%) of which 47 (24%) had pericardial effusion, 28 (14%) had pericardial enhancement and 33 (17%) had pericardial thickening (*Figure 1*). Histological and cytological analyses are shown in *Figure 3*. Atrial infiltration and pericardial involvement are displayed in Supplementary material online, *Videos 1 to 3*.

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

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

Extracardiac phenotype

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

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

BRAF^{V600E} mutational status

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

ECD-related clinical outcomes

In total, 20 patients (10%) suffered from an ECD-related clinical event.

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

Coronary artery disease

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

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

Survival analysis

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

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

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

Discussion

We describe here the prevalence, outcomes and features of cardiovascular involvement in a large retrospective single-center study of patients with ECD. Cardiac involvement is present in nearly half the patients and may lead to pericarditis, cardiac tamponade and conduction disorders[14–20] (Structured Graphical Abstract). Atrial infiltration and pericardial effusion are hallmarks of cardiac involvement[21-23].

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

Cardiovascular involvement was associated with *BRAF*^{V600E} mutation. There is currently no pathophysiological explanation for this association. Histiocyte infiltration in ECD seems to match the location of white fat in the human body (*i.e.* the epicardial tissue, the bone marrow, the perirenal and retroperitoneal layers)[24]. Similarly, the sites of cardiac infiltration match the location of epicardial adipose tissues, which have been reported to be located principally in the atrioventricular and interventricular grooves[25].

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

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

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

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

In our series, cardiac involvement was not significantly associated with poorer survival. While previous reports suggested cardiovascular involvement accounts for a significant proportion of deaths in ECD, these studies tended to include only symptomatic patients[6]. However, in our study, patients were systematically screened for cardiac involvement with CMR. In addition to this screening, the identification of *BRAF*^{V600E} mutations and the subsequent use of BRAF inhibitors may explain the discrepancy between our results and previous research. Nevertheless, it is important not to overlook cardiac involvement. In fact, cardiac infiltration was found to be associated with greater morbidity (pericarditis, cardiac tamponade, conduction disorder and potential coronary stenosis).

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

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

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

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

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Data availability: The data underlying this article will be shared on reasonable 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.