Review

Cardiovascular manifestations of Erdheim-Chester disease

A. Berti[1,2], M. Ferrarini[3], E. Ferrero[3], L. Dagna[1,2]

[1]Vita-Salute San Raffaele University, Milan, Italy;
[2]Department of Medicine and Clinical Immunology, IRCCS San Raffaele Scientific Institute, Milan
[3]Department of Oncology, IRCCS San Raffaele Scientific Institute, Milan, Italy.

Alvise Berti, MD
Marina Ferrarini, MD
Elisabetta Ferrero, MD, PhD
Lorenzo Dagna, MD

Address correspondence and reprint requests to:
Dr Alvise Berti,
Unit of Medicine and Clinical Immunology,
San Raffaele Scientific Institute and San Raffaele University,
Via Olgettina 60, 2
0132 Milan, Italy,
E-mail: berti.alvise@hsr.it

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ABSTRACT

Erdheim-Chester disease (ECD) is a rare inflammatory disorder of unknown etiology, characterised by diffuse organ infiltration of CD68-positive, CD1a-negative, S100-low/negative foamy histiocytes. It is a non-Langerhans cell histiocytosis which invariably involves bones (96% of cases). Extraskeletal involvement is observed in about 50% of cases. Cardiovascular involvement affects more than 20% of patients and associates with poor prognosis, conferring a reduced response to treatment. Frequent findings are pericardial effusion (24% of patients), "coated aorta", a perivascular circumferential thickening of the aorta, and pericardial thickening. Other typical features include right atrial mass with pseudo-tumoural appearance and histiocytes' infiltration of right atrial walls, atrioventricular sulcus and interatrial septum.

After the recent introduction of cardiac cine MRI in the clinical assessment of patients affected by ECD, a growing body of case reports and retrospective data showed that cardiovascular involvement is present more frequently than previously thought and that it is relatively often asymptomatic. Hence, clinicians should systematically screen ECD patients for occult cardiovascular involvement by means of highly sensitive imaging tools. Despite these recent novelties, comprehensive literature reviews focusing on ECD cardiovascular involvement and its imaging assessment in the last decade are lacking.

Introduction

Erdheim-Chester disease (ECD) is a systemic disorder of unknown aetiology, characterised by diffuse xanthomatous or xantho-granulomatous tissue infiltration with CD68-positive, CD1a-negative, S100-low/negative foamy macrophages (1). It is a rare form of non Langherans histiocystosis with more than 500 cases described from the first report by Jakob Erdheim and William Chester in 1930.

Since the foamy histiocytes can virtually infiltrate all organs, ECD has a wide clinical spectrum of signs and symptoms (1, 2). ECD almost invariably affects bones (3). Extra-skeletal disease is observed in about 50% of the patients and leads to a significant worsening of prognosis, in particular when certain organs are involved, such as heart, lungs, and central nervous system (1, 2, 4).

In decreasing order of frequency, clinical manifestations of ECD at onset include bone pain due to skeletal and neurological involvement, diabetes insipidus, constitutional symptoms, retroperitoneal infiltration with possible ureteral obstruction, pulmonary, cutaneous, cardiovascular, and endocrine involvement (1, 2). Although less common at presentation, the overall frequency of pulmonary, retroperitoneal and cardiovascular involvement, among others, substantially increases over the course of the disease (2).

Clinical severity ranges from asymptomatic to life threatening, with a 5-year mortality of about 30–40%. ECD is a chronically debilitating disease and treatments are still unsatisfactory (5).

Novel insights in the pathogenesis

In the last decade, remarkable progress has been made in understanding ECD pathogenesis. Our group first demonstrated that proinflammatory cytokines/chemokines are produced by ECD histiocytes (6) and may be responsible for histiocyte recruitment, activation and differentiation into the pro-inflammatory (M1) phenotype (7). Local cytokines/chemokines production is paralleled by systemic Th1-pattern mediators release, especially interleukin (IL)-1beta, IL-6, CCL2, CCL5, CXCL8, TNF-alpha, and interferon (IFN)-gamma (6, 8-10). More recently,

a variable fraction of intralesional macrophages from the majority of patients affected by ECD (from 38% to 68%) was found to harbor the oncogenic $BRAF^{V600E}$ mutation (11, 12). Moreover, by the use of an ultrasensitive approach called locked nucleic acid polymerase chain reaction-(PCR)/pyrosequencing assay we were able to detect $BRAF^{V600E}$ mutation in ECD histiocytes and also in a minor fraction of circulating monocytes in all patients (18/18) from our cohort (13), suggesting that the reported frequency of BRAF mutation may be underestimated. $BRAF^{V600E}$ mutation confers to these cells the activation of the mitogen-activated protein kinase signalling. Although the association of $BRAF^{V600E}$ and ECD does not imply pathogenic causality, the presence of the mutation in nearly 100% of affected patients supports the hypothesis of its primary role in the pathogenesis of the disease. Moreover, other oncogenic NRAS and PIK3CA mutations were reported in ECD patients with and without $BRAF^{V600E}$ mutation, highlighting the pivotal role of RAS-RAF-MEK-ERK kinase pathway activation in ECD (14).

Whether ECD should be considered an inflammatory or a neoplastic/clonal disorder is still matter of debate. The link between these two sides of the same coin is probably the oncogene induced senescence (OIS), a protective mechanism against oncogenic events (5, 13, 15). The $BRAF^{V600E}$ and other activating mutations in theMAPK-kinase pathway are well-known inducers of OIS (16). Cells carrying the mutated oncogene arrest the cell cycle, thus reducing the risk of neoplastic transformation (15, 16). OIS is characterised by the expression of cell cycle suppressor proteins, such as $p16^{INK4a}$ and $p21^{CIP1/WAF1}$, and by the activation of a proinflammatory response (16). OIS-induced cytokines and chemokines (the so called senescence-associated secretory phenotype or SASP) are responsible for leukocyte recruitment and differentiation in cells expressing a senescent phenotype, secreting cytokines and chemokines which in turn have been shown to act in an autocrine and paracrine manner (13, 17). Notably, we found evidence of OIS in intralesional histiocytes of ECD $BRAF^{V600E}$-postive patients (13), similarly to what described in other disorders harbouring $BRAF^{V600E}$ mutation, such as melanoma, papillary thyroid carcinoma and hairy-cell leukaemia (16, 18).

Clinical features

ECD mostly affects middle-aged individuals, affecting almost equally males and females (1, 3). The disease is characterised by a broad spectrum of clinical manifestations, since foamy histiocytes can infiltrate virtually any organ (5). Skeletal involvement is almost invariably present (96% of patients) and can be asymptomatic (up to 50%) (1). Bone pain, commonly manifesting around the knees and ankles, is the most frequent symptom of disease at presentation (about 26%) (1, 2). Femur, tibia and fibula and less frequently humerus, radius and ulna are typically involved (1). Classical imaging findings are a cornerstone of the diagnosis. Plain x-rays typically show bilateral and symmetric cortical osteosclerosis of the long bone extremities (diaphyseal and metaphyseal regions), whereas epiphyseal regions and axial skeleton are usually spared (1, 12, 19). 99mTc bone scan usually shows a symmetric and abnormally increased tracer uptake in the distal ends of the long bones (Fig. 1D) (1, 12).

Extraskeletal disease is observed in about 50% of the patients and accounts for a more severe prognosis, in particular when certain organs are involved, such as heart, lungs, and central nervous system (CNS) (1, 4). Neurological involvement and diabetes insipidus are two prominent features of ECD, the second and the third disease manifestations at onset respectively (2). CNS involvement varies from 25% to 50% (2, 3), and it is an independent predictor of death, accounting for 29% of all death of ECD patients (4). Lesions may be both intra or extra-axial and are mainly nodular masses, leading to a wide range of clinical deficits, from a mild deterioration of the cognitive function to severe focal symptoms and gait disturbance (20). In decreasing order of frequency, diabetes insipidus, exophthalmos, cerebellar ataxia, panhypopituitarism and papilledema are the main neurological manifestations (3, 20). Diabetes insipidus is the most commonly overlooked condition at presentation, with a median diagnostic delay of 5 years (range, 0–34) (2).

Constitutional symptoms are common at presentation (more than 20% of patients), and consist of weight loss, fatigue, weakness and fever (1) and rarely night sweats (21). Incidence tends to decline during the course of the disease or after treatment, sometimes recurring with disease relapse or progression (2). Retroperitoneal involvement, with possible ureteral obstruction, accounts for more than 30% of disease manifestations even if not particularly represented at onset (14%), probably because frequently asymptomatic in the initial phase and thus unnoticed (2). The "hairy kidney" due to histiocytes perirenal infiltration, hydronephrosis and renovascular hypertension due to renal artery stenosis, are among the most frequent manifestations (Fig. 1C) (1, 22). Pulmonary involvement, with interstitial fibrosis and pleural effusion, is only moderately present at onset, albeit increasing during the course of disease (2). Cardiovascular involvement is uncommon at presentation (less than 7%), and develops in up to 22% of ECD patients over the course of the disease (2. 23). Common features include pericardial effusion (2, 24), right atrial wall infiltration (25), and the "coated aorta", a circumferential thickening of the aorta which is considered a typical finding at computerised tomography (CT) scan (26, 27). Finally, xanthoma and periorbital xanthelasma are the cutaneous lesions most often reported (2, 28).

Laboratory findings are unspecific for the diagnosis of ECD. These may reflect an inflammatory status, such as increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) serum levels and normochromic and normocytic anaemia; or an increased bone turnover, as indicated by raised levels of alkaline phosphatase (3). Laboratory studies are also useful for the assessment of renal insufficiency (by means of creatinine and azotemia), an imbalance of the hypothalamic-pi-

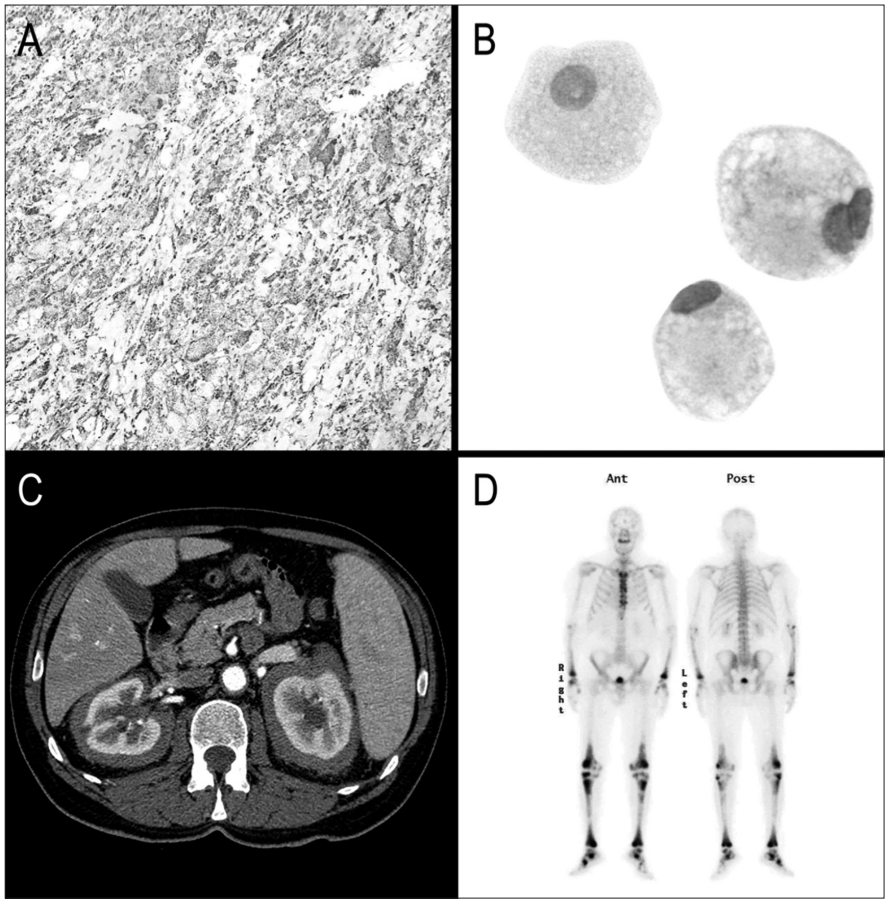

Fig. 1. **(A)** Immunohistochemical study of a paracardiac mass biopsy revealing that infiltrating histiocytes are positive for CD68 (immunostaining, 100×), but negative for the dendritic cell markers CD1a, CD207 and S100 (not shown). **(B)** Foamy histiocytes isolated from pericardial fluid of a patient with ECD-related pericardial effusion. **(C)** Contrast-enhanced CT scan study showing retroperitoneal histiocytes' infiltration of the perinephric fat ('hairy kidney'), often determining hydronephrosis and/or renovascular hypertension. **(D)** 99mTc bone scan showing a symmetrical and abnormally increased uptake of the radiotracer in the distal extremities of femur and radius, proximal and distal extremities of tibia, and ankles.

tuitary axis (increased prolactin levels and decreased LH, FSH, ACTH, GH, TSH levels) or for the diagnosis of diabetes insipidus (high serum osmolality, positive water deprivation test) (3).

Diagnostic approach

ECD classically manifests with bone pain, diabetes insipidus, neurological and/or constitutional symptoms at presentation (2). When disease is suspected, a complete radiological evaluation at baseline is recommended (12, 26). In fact, many disease sites could be silently involved, thus explaining the importance of a complete assessment of disease burden in all patients (12). A whole body CT-scan with contrast, a 18-fluorodeoxyglucose-positron emission tomography (FDG-PET) of the entire body including brain and distal extremities, a gadolinium-enhanced cardiac and brain magnetic resonance imaging (MRI) are recommended in all patients (12). Although 99-tecnectium bone-scan is typically used for the detection of skeletal involvement, the recent demonstration of high sensitivity of PET scan for extra-skeletal disease, has made this imaging tool the elective study for both skeletal and extra-skeletal evaluation (29-31).

Biopsy of the tissue affected and its histological analysis is mandatory to confirm diagnosis (12). In fact, diagnosis is made by identifying distinctive histopathological findings in the appropriate clinical and radiologic context (1, 32). CD68-positive, CD1a-negative and CD207(Langerin)-negative is the characteristic immunostaining of ECD histiocytes, whereas positivity for S100 has been rarely observed (Fig. 1A) (12). $BRAF^{V600E}$ mutation of should be accurately researched in tissue samples, given its potential therapeutic implications (11-13).

Cardiovascular manifestations

A recent systematic review of the literature performed by our group showed that cardiovascular involvement develops in up to 22% of ECD patients over the course of the disease, whereas it is uncommon at onset, resulting less than 7% of all presenting symptoms (2). Incidence of cardiac manifestations at presentation varies in different ages of life, reaching its peak in older patients (2). However, cardiovascular manifestations of ECD probably remain still underestimated (23). Together with CNS (4), cardiovascular involvement associates with poor prognosis and confers a reduced response to treatment (2, 33, 34). Hence, patients affected with ECD should be systematically screened for cardiac disease, even if asymptomatic (12, 25).

Common features of cardiovascular involvement include right atrial wall infiltration (Fig. 2 B-C and 3 B-D) (25, 35), pericardial disease, often accompanied with effusion (Fig. 3A) (24, 25) and sometimes leading to cardiac tamponade (24), and circumferential thickening of the aorta, a condition called "coated aorta" (Fig. 2 A-D) (26, 27). Based on data available in the literature, 75% of patients with ECD-related cardiovascular disease have heart involvement (25). The frequency of pericardial disease, the most frequent cardiovascular manifestation overall, is 44%, whereas myocardial infiltration accounts for 31% and periaortic fibrosis for 56%, with half of these presenting with a "coated aorta" aspect (25). Other less frequent manifestation are right atrial tumour (8%), symptomatic valvular heart disease (8%), aortic and mitral regurgitations with equal distribution); heart failure (26%), myocardial infarction (8%) (25). Among patients with retroperitoneal fibrosis, almost 30% develop renovascular hypertension due to ostial stenosis of renal arteries (2). Usually it ameliorates upon angioplasty and stenting of the stenotic renal artery, but

disease tends to recur in the absence of a specific medical therapy (3, 22). Finally, ECD-associated venous involvement is rather uncommon (23). Case reports describe deep vein thrombosis and pulmonary embolism (23, 36), sagittal sinus thrombosis (37), obstruction of the superior vena cava (23), and coronary sinus involvement (23).

Pericardial infiltration

Pericardial involvement is the most frequent cardiovascular manifestation of ECD (Fig. 3A). Pericardial effusion is usually circumferential and may vary among patients from minimal to massive effusion, rarely leading to pericardial tamponade (24, 33) or requiring pericardiocentesis (38). The incidence of pericardial effusion in reported around 24% of patients with cardiovascular involvement (25). A comprehensive review of the literature published in 2013 reported that pericardial effusion is the most common presenting manifestation (80%; 12 out of 15 patients) among patients with cardiovascular involvement as initial complaint (2).

Cytological analysis of the pericardial fluids reveals the presence of a wide range of inflammatory cells, foamy macrophages (Fig. 1B), and mesothelial cells (39, 23). Pro-inflammatory cytokines/chemokines can also be detected (10). Given the pivotal role of proinflammatory cytokines in ECD (6, 8, 10, 40), we hypothesised a potent local inflammatory response as the leading cause of pericardial effusion. Our group demonstrated that TNF-alpha in pericardial fluid is responsible for the increased permeability and dysfunction of endothelial cells, likely leading to exudate formation (9), supporting the use of the anti-TNF-α infliximab as a rational strategy for treating ECD patients with cardiac involvement (38).

Increased pericardial thickness may be associated with pericardial effusion, and it is reported in 14% of patient with cardiovascular manifestation (Fig. 3C) (25). A thickened pericardium may inconstantly appear enveloped by fibrosis (35). Although with different sensitivity, trans-thoracic echocardiography, CT-scan and cardiac-MRI are all able to detect pericardial effusion and increased pericardial thickness (23, 25, 31, 33, 35, 41).

Myocardial infiltration and cardiac valve disease

Myocardium is involved in at least one-third of patients with cardiovascular ECD, and it is frequently asymptomatic or paucisymptomatic (23, 25, 33). Myocardial hypertrophy and thickening due to the presence of fibrotic tissue and histiocytes infiltration are typical (33, 42). Foamy histiocytes infiltration seems to start from subepicardial fatty tissue and to progress into the myocardium (23, 42).

Cardiac sites often affected by the disease are ventricular and atrial walls. In particular, histiocytes' infiltration may be diffuse or have a pseudo-tumoural appearance (23, 43, 44) possibly involving either interatrial septum (45) and right atrioventricular sulcus (Fig. 2 B-C and 3 B-D) (23). By means of cardiac-MRI, right atrial masses may be incidentally detected in a considerable number of patients, even if asymptomatic for cardiac involvement (25, 33). Although rare, valvular dysfunctions or conducting abnormalities secondary to right atrial masses have been described (23). Aortic and mitral regurgitations in the context of ECD with cardiac involvement have been reported (23, 33), as well as coronary artery disease leading to myocardial infarction (46-48). Heart failure represents the natural evolution of myocardial infiltration in the absence of causal therapy, eventually leading to death (almost half of the patients with heart failure, as reported in literature) (1, 23).

ECG abnormalities are present in at least 60% of patients with cardiovascular involvement, but are largely unspecific, including short PR, sinus bradycardia (sometimes requiring pacemaker), left ventricular hypertrophy, Q-wave abnormalities (sometimes without clinical history of acute coronary syndromes), and ST-T abnormalities (without clinical history of pericarditis) (3, 25).

Aorta and its branches involvement

The perivascular histiocytes' infiltration of the aorta and its primary branches lead to a characteristic appearance on CT-scans, which is commonly referred to as "coated aorta" (Fig. 2 A-D-E) (1, 26, 35). Its presence should increase the suspicion of ECD in the appropriate clinical setting, such as in a patient with a history of diabetes insipidus, unexplained exophthalmos or gait disturbance, or with a typical bone scintigraphy (12, 26).

Anatomical sites of periaortic infiltration may vary among patients. Thoracic (25% of cases), abdominal (25% of cases) or the whole aorta (50% of cases) may be involved (23). Among thoracic sites, descending aorta (75%) and aortic arch (68%) are more frequently reported than ascending aorta (43%) (35). Perivascular sheathing is typically circumferential, regular, without clear stenosis. Fibrosis is mainly located to the adventitia, but sometimes may infiltrate the vascular walls until the intima (23, 49). Autoptic or surgery samples, showed that this pathological finding is due to perivascular foamy histiocytes' infiltration (26, 49).

Large branches of the aorta are frequently involved, in particular brachiocephalic trunk, left common carotid artery and left subclavian artery, pulmonary trunk, celiac trunk, superior mesenteric artery, and renal arteries (23, 35). Often, perivascular involvement remains clinically silent until advanced disease. However, renal arteries may develop ostial stenosis in the context of retroperitoneal fibrosis, leading to activation of renin-angiotensin pathway and renovascular hypertension (1, 3). As mentioned before, angioplasty and stenting temporary normalise blood pressure, but specific medical therapy for ECD is needed to avoid restenosis (22).

Infiltration around coronary arteries are relatively frequently observed (25, 47). Some monocentric retrospective studies reported the right coronary artery as the most frequently sheathed by the fibrosis (23, 25, 35) (Fig. 2 B-C). Fibrosis around the left anterior descending and circumflex arteries were also noted, although far less commonly (35).

Eventually, multiple anatomical sites affected described above may be variably associated. A singular but extremely clear example of pan-cardiac involve-

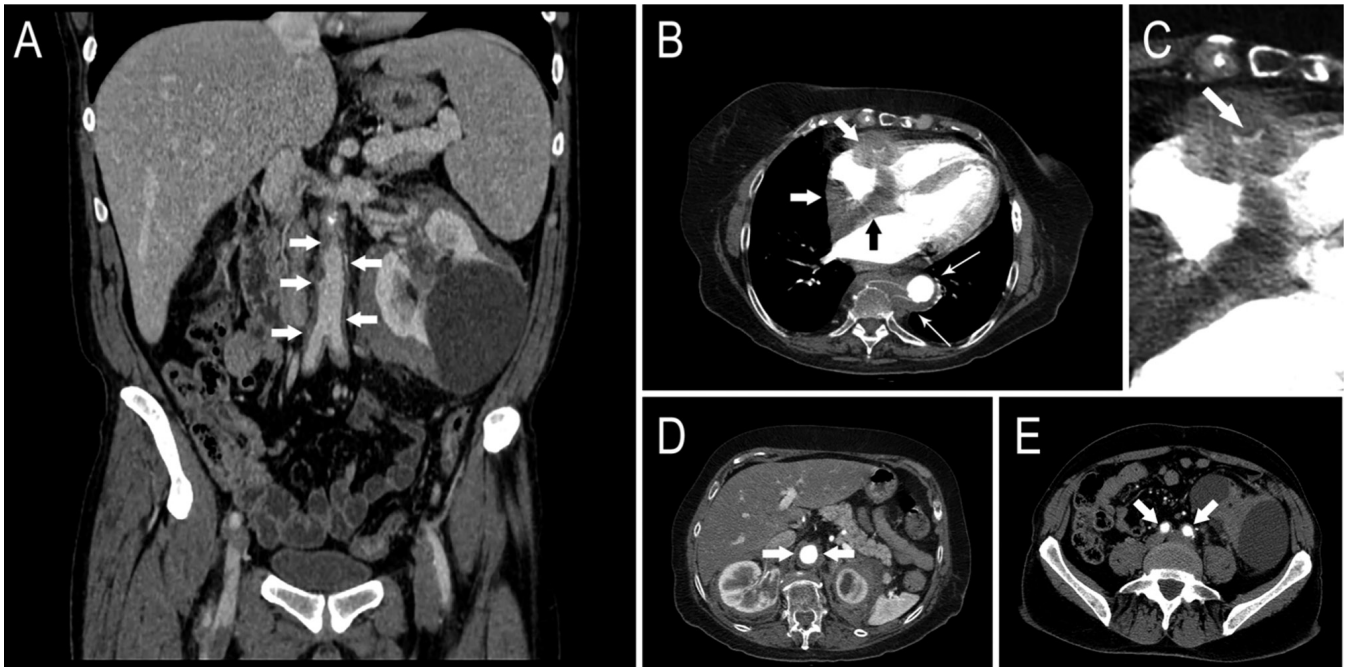

Fig. 2. ECG-gated, contrast-enhanced CT scan. **(A)** Contrast enhanced, coronal CT scan of the abdomen showing circumferential thickening of the abdominal aorta and both common iliac arteries, with a "coated aorta" appearance (white arrows). In addition, the presence of perinephric fat histiocytes' infiltration and a large, benign parenchymal cyst in the left kidney **(B)** Irregular and nodular thickening of the walls of the right atrium (white fat arrow) and inter-atrial septum (black arrow), infiltrating the coronary sulcus (white fat arrow). Moreover, periaortic circumferential fibrosis of the descending thoracic aorta ("coated aorta") could be noted, surrounding the intercostal arteries (white thin arrows). **(C)** Detail of the panel B, showing infiltration of the right coronary sulcus surrounding the opacified lumen of the right coronary artery (white arrow) **(D, E)** Coated aorta appearance of the abdominal aorta and of the common iliac arteries (white arrows).

ment has been described (33), involving pericardium, myocardium, atria, right ventricle, thoracic and abdominal aorta.

Venous involvement

Venous involvement was anecdotally reported. Deep vein thrombosis with pulmonary embolism (36, 23), sagittal sinus thrombosis (37, 23), superior and inferior vena cava obstruction, especially the superior vena cava outlet (23, 50), coronary sinus involvement (23), and a case of fibrosis around the superior vena cava with thrombosis of the right internal jugular vein (23) were described.

Cardiovascular imaging in Erdheim-Chester disease

As mentioned before, the poor prognosis conferred by cardiovascular involvement should lead clinicians to screen and strictly follow-up each patient affected by ECD (2, 33, 34). To date, several imaging techniques are mainly used to evaluate ECD patients for cardiovascular involvement: cine cardiac MRI (Fig. 3 A-D), trans-thoracic echocardiography (TTE) and CT-angiography (Fig. 2 A-E).

Recently, cardiac MRI was found to be highly sensitive for the evaluation of cardiac morphology, functional parameters and tissue viability, leading to its wide employment for cardiac study (41, 51-54). TTE is generally used as a first-line imaging technique for the detection of cardiac involvement, but systematic use of cardiac-MRI allowed to show silent cardiac involvement missed at TTE evaluation in a considerable number of patients (12). Although studies directly comparing the role of TEE and cardiac MRI in evaluating ECD cardiac involvement are lacking, the latter technique is probably able to localise more accurately pathological tissue and to offer a more detailed description of it. As written before, typical cardiac ECD-lesions are atrioventricular sulcus infiltration, right atrial mass yielding pseudo-tumoural appearence, heart encasement by enhanced pathological tissues, pericardial thickness (Fig 2-3) (2, 23, 25, 33). Indeed, ECD-specific features could be detected at cardiac MRI by means of the study of tissue oedema, perfusion and (late) gadolinium enhancement highlighting the degree of tissue infiltration (25, 33, 41, 52, 53). ECG and respiratory-gated cardiac cine MRI also apprises clinicians of functional parameters, such as stroke volume, left and right ventricular end-diastolic and end-systolic volumes (53, 54). In addition to its intrinsic less sensitivity and specificity for the detection of ECD-cardiac involvement, TTE is an operator-dependent technique.

Although less informative than cardiac-MRI, ECG-gated cardiac-CT may be used for the detection of pericardial effusion and pericardial thickening, myocardial infiltration, right atrial masses, perivascular coronary arteries involvement and diffuse mediastinal fat infiltration (35). However, ECG-gated CT-scan is less specific than cardiac MRI in differentiating between pericardial fluid and thickened pericardium (35, 53, 54).

Thoraco-abdominal CT-scan angiography is particularly useful for the detection of large vessel involvement (12, 25, 35), particularly the above-

mentioned, "coated aorta" appearance, that is almost pathognomonic to ECD (26). Moreover, it may be helpful in evaluating renal arteries' ostial stenosis due to perivascular infiltration (12, 22). Besides the imaging representation of the cardiovascular system, contrast enhanced CT-scan is still mandatory at baseline in order to screen for the presence of other ECD lesions, such as retroperitoneal, mediastinal and lung involvement (12).

Since FDG-PET is able to depict at the same time all metabolically active ECD lesions in a patient, PET-CT may have a role in evaluating global disease burden and for follow-up (29-31). However, it is not particularly sensitive for the characterisation of cardiovascular lesions.

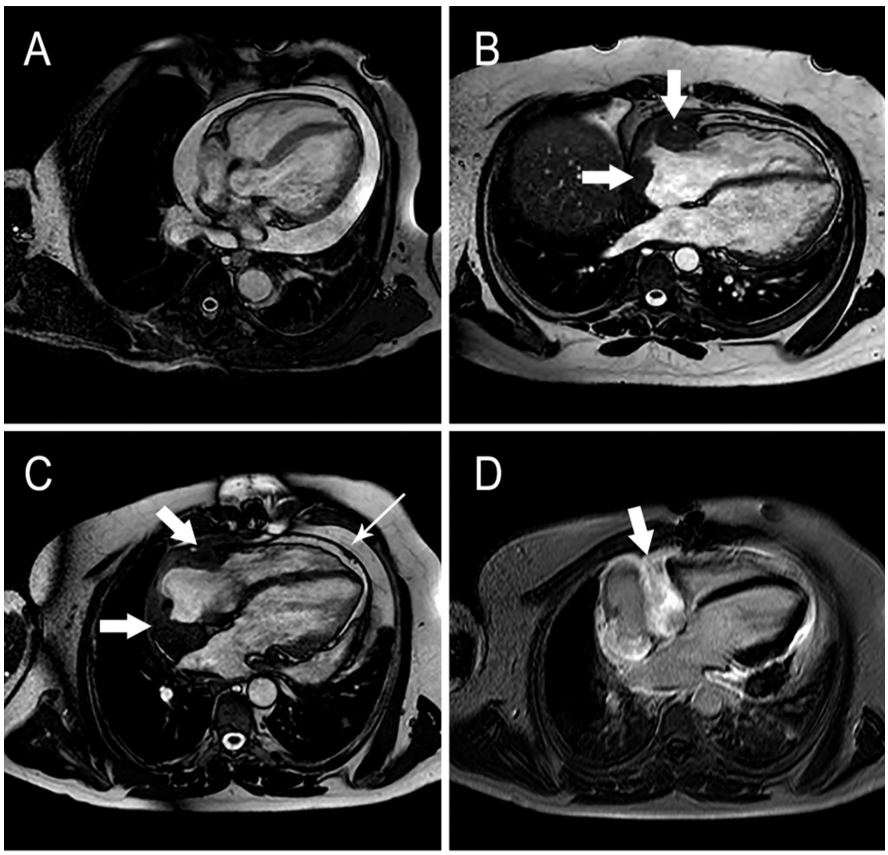

Fig. 3. Horizontal long axis of cardiac MRI. **(A)** Circumferential pericardial effusion with diffuse and marked thickening of right atrial walls and interatrial septum **(B)**. Two prominent right atrial masses (white arrows), one of these surrounding the right coronary artery **(C)** Nodular thickening of the right atrial free wall (white fat arrows), infiltrating the atrioventricular sulcus, with a diffusely thickened pericardium (3 mm) (white thin arrow). **(D)** Late-enhancement cardiac MRI of the patient in panel C, showing strong enhancement of the right atrioventricular sulcus mass (white arrow).

Differential diagnosis

The diagnosis of ECD may be challenging since clinical manifestations are largely unspecific and may overlap with other inflammatory and neoplastic conditions. Hence, the current guidelines for the diagnosis of ECD lay on the identification of characteristic histological features, largely similar across the wide range of organs affected, in the appropriate clinical setting (12). The presence on tissue sample of CD68-positive, CD1a-negative non Langerhans histiocytes, with foamy cytoplasm and lacking Birbeck granules confirm the diagnosis.

Most of the vascular symptoms are unspecific and common to other inflammatory conditions, such as large vessel vasculitis or idiopathic periaortitis (55, 56). Indeed, Takayasu arteritis, Behçet's disease, giant cell arteritis and polyarteritis nodosa might present with acute-phase reactant levels, fever, fatigue, weight loss and vascular inflammation (57-60). Periaortic infiltration with its collaterals involvement may be seen in Takayasu arteritis, a condition that usually affects young women. However, differently from ECD, Takayasu arteritis usually involves the entire vessel wall, from adventitial to intimal layer (57, 61). Moreover, stenosis, occlusions and sometimes aneurysms are typically present in a considerable proportion of patients affected by Takayasu arteritis, while they are fairly uncommon in ECD. Chronic idiopathic aortitis in the context of idiopathic retroperitoneal fibrosis is a rare condition characterised by a systemic inflammatory state (constitutional symptoms, elevated levels of ESR and CRP, etc.) with evidence of abdominal aortic aneurysms and perianeurysmal retroperitoneal fibrosis (55, 56). In this clinical scenario, retroperitoneal fibrosis is usually not circumferential as in ECD, but rather involves lateral and anterior sides of the aorta, usually sparing the posterior one (55, 56). Another difference with ECD is that inferior vena cava might be involved in idiopathic retroperitoneal fibrosis (56). IgG4-related disease may manifest with retroperitoneal fibrosis and acute inflammatory response; hence, it should be taken into consideration in differential diagnosis (62, 63). Pancreas and retroperitoneum are among the more frequently affected anatomical sites, and aorta, its branches and the surrounding tissues may be involved (62, 64). An extra-vascular radiological clue highly suggestive for ECD in differential diagnosis is the presence of perinephric fat infiltration ("hairy kidney"), absent in other conditions presenting with retroperitoneal fibrosis.

Heart involvement may be present in up to 60% of patients affected by Takayasu arteritis, and as for ECD is often silent or paucisymptomatic (58). Pericarditis might be virtually present in all forms of small, medium and large-sized vasculitis, but it is rarely clinically significant, whereas myocarditis is sometimes seen in ANCA-associated vasculitis (particularly in eosinophilic granulomatosis with polyangiitis) and in Takayasu arteritis (58, 60, 61). Coronary angiitis is relatively common in Takayasu arteritis, Behçet's disease and polyarteritis nodosa (58, 59).

Differential diagnosis of right atrium pseudotumoural masses includes mainly tumours originating in this heart chamber, as cardiac myxoma and angiosarcoma (3, 44, 65). Although cardiac myxoma may be associated with constitutional symptoms and thus mimicking a systemic condition as ECD, it is more often localised in left atrium (86% of cases) (66). Also, the typical radiological picture of coated aorta, hairy kidneys or symmetric osteosclerosis of the long bones should address the diagnosis of ECD.

Treatments and therapeutic novelties

Many treatments for ECD have been proposed, including corticosteroids (67), chemotherapy drugs (67-70), IFN-alpha-2a (71-75), different biological drugs (36, 38, 76), kinase inhibitors (34), autologous stem cell transplantation (12), and bisphosphonates (40) with a variable response. Usually, initiation of therapy is recommended after appropriate diagnosis, with the rare exception of patients with a cutaneous-dominant disease or a minimal or asymptomatic bone disease (12).

IFN-alpha has been shown to have an impact on ECD and is currently considered the fist-line treatment for the disease (71-75). However, response to IFN-alpha dramatically varies among patients and according to sites of disease involvement, being unsatisfactory in the case of CNS and cardiovascular lesions (74). In a prospective, nonrandomised, observational cohort study, treatment with IFN-alpha and CNS involvement were demonstrated to be independent prognostic factors in ECD. Usual dose for subcutaneous IFN-alpha-2a is 3 million IU 3 times/week (or 135 micrograms SC weekly), but it has been demonstrated that higher doses of interferon-alpha-2a or pegylated interferon-alpha-2a had greater efficacy in case of severe disease, with CNS and cardiac involvement (75).

If patient is unresponsive or if interferon treatment is contraindicated/not tolerated, a relatively wide range of second line treatments or clinical trials is available. Evidence is accumulating that the selective block of an inflammatory cytokine shown to be involved in ECD pathogenesis should be a reasonable option. Anti-IL-1-receptor antagonist anakinra is, among biologicals, the one with most clinical evidence (77). Successful treatment of a patient with cardiac disease was reported (76). Two patients were successfully treated with infliximab, with clinical and radiological improvement of cardiovascular involvement documented at serial imaging evaluations. In both cases there was reduction or disappearance of pericardial effusion, together with a significant reduction of the pathologic tissue surrounding the heart (38). Recent data showed that IL-6 is strongly expressed in ECD lesions and increased serum levels of IL-6 have been implicated in the systemic manifestations observed in ECD (40). Hence, a clinical trial aim in evaluating the efficacy and safety of a 6-month course of the IL-6 receptor inhibitor tocilizumab is actually ongoing (NCT01727206). A clinical trial with Sirolimus and Prednisone is also ongoing (ACTRN12613001321730). Monotherapy with corticosteroids is not a treatment of choice, because of their scarce therapeutic efficacy, even if they may reduce oedema acutely. Cladribine has been used as a second line agent, given its use in systemic Langherans cells histiocytosis, albeit with limited benefits (78). Imatinib mesylate treatment in 7 patients led to variable outcomes, resulting a rational approach only when other therapeutic strategy have failed (34).

After the recent discovery of the $BRAF^{V600E}$ mutation in ECD histiocytes, the potential therapeutic implications changed dramatically. Indeed, the use of the inhibitor of $BRAF^{V600E}$ vemurafenib showed an astonishing improvement in three patients treated (75). Recently, a considerable improvement or stabilisation of the disease, including cardiac and aortic infiltration, was demonstrated in eight patients treated with a median follow up of approximately 10 months (79). A clinical trial with vemurafenib in ECD (NCT01524978) is currently ongoing. However, given the limited clinical experience with BRAFV600E inhibitor vemurafenib and the high rate of its potential severe side effects, the development of safe and effective alternative treatments is desirable.

Conclusion

Clinicians should be aware of ECD, and this rare clinical entity should be considered in the differential diagnosis of several systemic, inflammatory diseases. Skeletal involvement is almost invariably present in ECD, whereas extra-skeletal manifestations are observed in about 50% of patients affected. Cardiovascular involvement affects more than 20% of patients and associates with poor prognosis, conferring a reduced response to treatment. Patients affected with ECD should be systematically screened for cardiac disease, even if asymptomatic. Among patients with ECD-related cardiovascular disease, 75% have heart involvement. Classical findings are pericardial effusion, present in 24% of patients, pericardial thickening, and "coated aorta", a circumferential perivascular fibrosis of the aorta. "Coated aorta" appearence is one of the most suggestive radiological findings, which should increase the suspicion of ECD in the appropriate clinical setting, as in patients with bilateral symmetric diametaphyseal osteosclerosis of long bones. Other typical cardiovascular findings include pseudotumoural right atrial mass and histiocytes' infiltration of right atrial walls, interatrial septum, and atrioventricular sulcus.

Cardiovascular involvement is frequently asymptomatic. Indeed, thanks to the novel imaging tools such as cardiac-MRI and high-resolution CT-scan, cardiovascular involvement in ECD has been shown to be more frequent than previously suspected. Further studies are needed in order to shed new lights on the driving pathogenic mechanisms and to identify new therapeutic strategies.

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