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REVIEW

Eosinophilic cardiac disease: Molecular, clinical and imaging aspects



Cardiopathie à éosinophiles : aspects moléculaires, cliniques et en imagerie

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Summary Eosinophilia may be responsible for cardiac injuries of widely varying severity, from acute myocarditis to endomyocardial fibrosis. In this review, we present both the molecular mechanisms that are responsible for these lesions and their clinical and paraclinical aspects. Numerous aetiologies can lead to severe eosinophilia, but these are mainly represented by hypersensitivity reactions, rheumatological diseases and hypereosinophilic syndrome. Because cardiac involvement may be extremely severe, echocardiography should be always performed in the context of eosinophilia and appropriate therapeutics should be started rapidly in order to limit the progression of the disease.

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Abbreviations: CT, computed tomography; DRESS, drug rash with eosinophilia and systemic symptoms; ECG, electrocardiography; ECP, eosinophil cationic protein; ECPA, eosinophilic coronary periarteritis; EDN, eosinophil-derived neurotoxin; EMF, endomyocardial fibrosis; EPO, eosinophil peroxidase; FP, FIP1L1-PDGFR α ; GM-CSF, granulocyte macrophage colony-stimulating factor; HES, hypereosinophilic syndrome; Ig, immunoglobulin; IL, interleukin; L-HES, lymphocytic hypereosinophilic syndrome; MBP, major basic protein; MRI, magnetic resonance imaging.

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MOTS CLÉS

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Myocardite à
éosinophiles ;
Syndrome DRESS

Résumé Une hyperéosinophilie peut être responsable de lésions cardiaques dont la sévérité est très variable, allant de la myocardite aiguë jusqu'à la fibrose endomyocardique. Nous présentons, à travers cette revue de la littérature, les mécanismes moléculaires qui entraînent ces différentes lésions ainsi que leurs aspects cliniques et paracliniques. Si de nombreuses étiologies peuvent être responsables d'hyperéosinophilie, les réactions d'hypersensibilité, les maladies rhumatologiques et le syndrome d'hyperéosinophilie en sont les principales causes. Parce que l'atteinte cardiaque peut être extrêmement sévère, une échocardiographie doit être systématiquement réalisée en cas d'hyperéosinophilie et un traitement approprié doit être débuté rapidement afin de limiter la progression des lésions.

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Introduction

Eosinophilic cardiac disease is a relatively rare condition that was first described in 1936 by Wilhelm Löffler, who called it 'fibroplastic parietal endocarditis with blood eosinophilia' [1]. Also known as Löffler's endocarditis, eosinophilic endomyocardial fibrosis (EMF) is an uncommon cause of restrictive cardiomyopathy. In fact, several types of cardiac damage may be encountered in the context of eosinophilia, from acute myocarditis to EMF. All result from toxicity of infiltrating eosinophils into cardiac tissue. The aim of this review is to present both the mechanisms that underlie these lesions and their clinical aspects, imaging features and specific treatments.

Physiology and pathophysiology of eosinophils

Eosinophils are normally found in the blood and in certain tissues. These granulocytes are involved in normal antimicrobial immunity [2]. They have surface proteins for immunoglobulin (IgE) binding to IgE antigen complexes by which phagocytosis and release of granules is triggered. Indeed, when stimulated, eosinophils possess the ability to elaborate substances that are toxic to a wide variety of parasites that are too large to phagocytose [3]. Their usual location in the body (respiratory tract, gastrointestinal tract and skin) is therefore explained by this antiparasitic activity. They measure 12–15 μm in diameter and are characterized by a bilobed nucleus and numerous eosin-staining specific granules in their cytoplasm [4]. These granules contain high concentrations of hydrolases and cationic and basic proteins [5,6] (Fig. 1 [7]).

Production and kinetics

Along with the other polymorphonuclear leukocytes, eosinophils are produced by the bone marrow, where they represent up to 6% of the resident nucleated cells [8]. Under the influence of several cytokines, the haematopoietic stem cells gradually differentiate into eosinophilic myelocytes and then into mature eosinophils (Fig. 1). This maturation

process takes approximately 8 days. The main cytokines responsible for the increase in eosinophil number are granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-3 and IL-5. IL-5 – produced by T helper 2 lymphocytes – is specific for the production of eosinophils and is considered to be their major growth factor [9]. It is also involved in survival, chemotaxis and degranulation. Eosinophils remain in the peripheral blood for 8–12 hours before migrating preferentially to certain tissues where they are concentrated: the respiratory tract, the gastrointestinal tract, the skin and the urogenital tract (in females). Eosinophils survive for 1–2 weeks unless apoptosis is prevented by cytokines (GM-CSF, IL-3, IL-5) [8].

Composition

The cytoplasm of eosinophils is filled with many eosin-staining specific and non-eosinophilic granules. As eosinophils are involved in the inflammation process and in innate and adaptive immunity, the specific granules are capable of inducing tissue damage and dysfunction by degranulation following activation by an immune stimulus. They contain cationic proteins: major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN) and eosinophil peroxidase (EPO) [9] (Fig. 1). These proteins have several effects including production of free radicals, cell necrosis and apoptosis induction. These eosinophilic constituents are very deleterious to the endothelial cells and are capable of activating platelets and impairing the anticoagulant effects of thrombomodulin [10]. Finally, the endocardium appears to be very sensitive to the release of these cardiotoxic agents, especially MBP and ECP [11].

Definition of eosinophilia

Eosinophils are present in the blood in small numbers: the normal count of circulating eosinophils is $\leq 350/\text{mm}^3$, for both adults and children. Mild eosinophilia is defined by a level of 500–1500 eosinophils/ mm^3 . A count of 1500–5000 eosinophils/ mm^3 is considered as moderate and > 5000 eosinophils/ mm^3 is a significant eosinophilia [8].

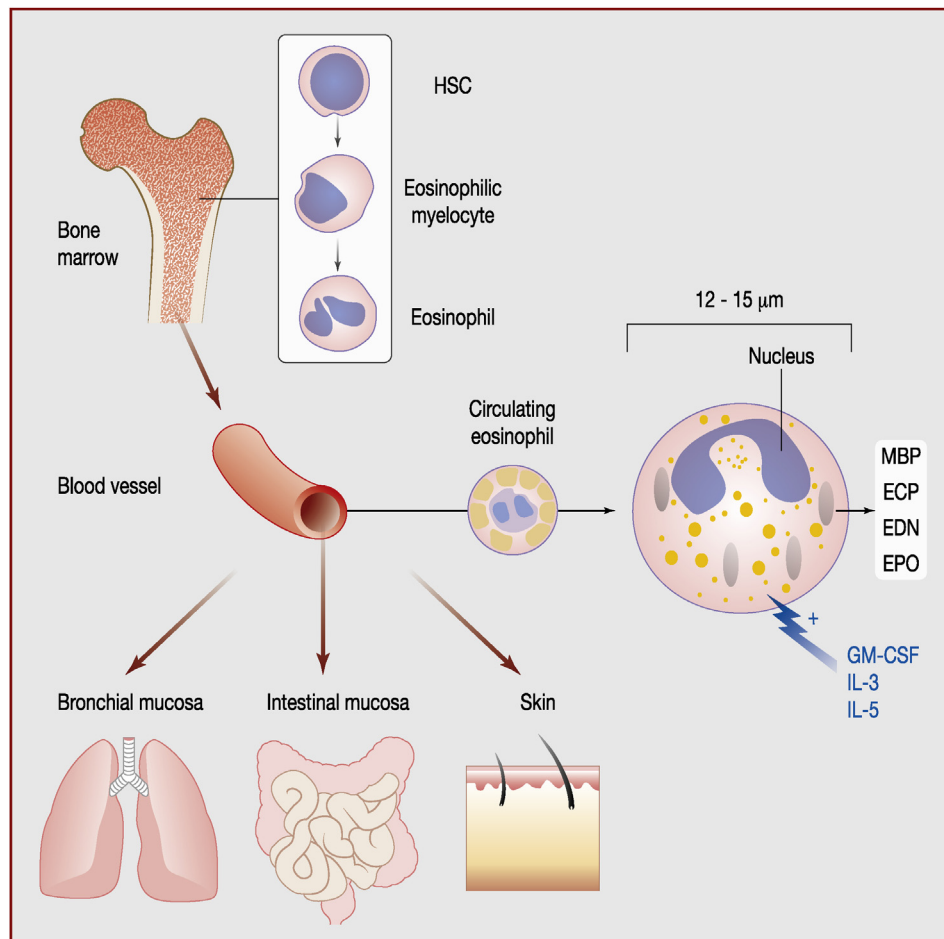


Figure 1. Eosinophil characteristics and normal kinetics. After production in the bone marrow, eosinophils remain in the peripheral blood for a few hours before migrating to specific organs that are involved in antimicrobial immunity. Circulating eosinophils contain numerous red-orange granules in their cytoplasm. These granules are composed of various cationic proteins, cytokines and lipid mediators. The cationic proteins – especially major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN) and eosinophil peroxidase (EPO) – are potent mediators of antimicrobial immunity. These proteins are extremely toxic to heart cells. The production of eosinophils is stimulated by cytokines such as granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-3 and IL-5. Reproduced with permission from Séguéla and Acar [7].

Cardiac toxicity

The degree of damage associated with eosinophilic infiltration of tissue appears to be related to the stimulus attracting the eosinophils, the duration of eosinophilia and the degree of eosinophil activation. Indeed, deleterious effects on tissues, particularly on the heart, are more common in cases of profound eosinophilia ($> 5000/\text{mm}^3$). According to Gottdiener et al. [12], three phases are classically described. The first stage is due to eosinophilic infiltration into the tissues and leads, after the release of granular proteins, to cells necrosis. When biopsies are performed, they consistently show deposits of MBP, ECP and EPO. The second phase is represented by thrombosis formation. Because the cationic proteins of eosinophils bind to the anion-binding exosite of thrombomodulin, the complex thrombomodulin-thrombin cannot form and it loses its anti-thrombotic role. Indeed thrombomodulin, by binding to the circulating thrombin, is a potent physiological inhibitor of coagulation (Fig. 2 [7]). The third stage corresponds to fibrotic scarring. In the final stage, cardiac endothelium and valves become fibrotic and

thickened, resulting in a non-compliant ventricle, initially defined as Löffler's fibroplastic endocarditis [1].

Causes of eosinophilia

Many diseases may be responsible for eosinophilia but not all cause profound eosinophilia. The most common aetiologies are reported in Table 1. The first step is to exclude reactive eosinophilia [13]. Indeed, some drugs (anticonvulsants, non-steroidal anti-inflammatory drugs, antimicrobial agents, sulfonamides) are well known to trigger an abnormal production of eosinophils. Eosinophilia may be the sole manifestation of a drug-induced hypersensitivity reaction. When a drug-related eosinophilia is associated with a morbilliform eruption and severe tissue damage, this condition is called drug rash with eosinophilia and systemic symptoms (DRESS) syndrome [14]. Withdrawal of the offending drug usually results in normalization of the eosinophil count within 7–10 days [8]. Cases of post-vaccination eosinophilic myocarditis (after smallpox or diphtheria/tetanus/pertussis vaccines)

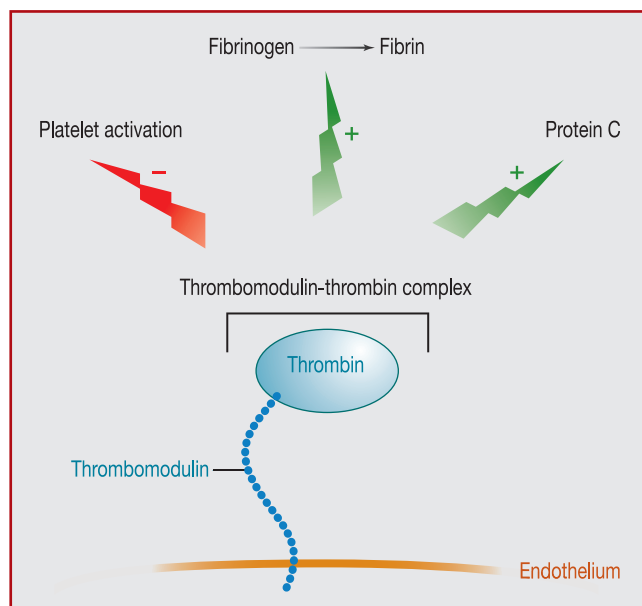


Figure 2. Actions of thrombomodulin. Thrombomodulin, a cell surface protein of the endothelium, normally binds to thrombin to form the complex thrombomodulin-thrombin. This complex inhibits platelet activation, activates the conversion of fibrinogen to fibrin and activates protein C, which is a major physiological anticoagulant. By binding to the extracellular anionic domain of thrombomodulin, the cationic proteins of eosinophils prevent the formation of the complex and cause thrombosis. Reproduced with permission from Séguéla and Acar [7].

Table 1 Major causes of chronic eosinophilia > 1500/mm³.

Reactive eosinophilia
Drugs (hypersensitivity)
Anticonvulsants
Non-steroidal anti-inflammatory drugs
Antimicrobial agents
Sulfonamides
Infections
Helminths
Human immunodeficiency virus
Human T-lymphocyte virus I
Tuberculosis
Allergic diseases
Systemic diseases
Crohn's disease
Churg-Strauss syndrome
Wegener's granulomatosis
Polyarteritis nodosa
Rheumatoid arthritis
Cholesterol crystal embolism
Malignancies
Hodgkin lymphoma
Non-Hodgkin lymphoma
Acute leukaemia
Systemic mastocytosis
Hypereosinophilic syndrome
Lymphocytic variant
Myeloproliferative variant

have also been reported [15,16]. Thereby, in the presence of significant eosinophilia, an empirical anti-helminthic drug therapy should be started immediately. Other aetiologies are mainly represented by systemic diseases, malignancies and hypereosinophilic syndrome (HES).

Hypereosinophilic syndrome

HES is a heterogeneous group of rare haematological disorders characterized by unexplained and sustained blood eosinophilia. Chusid et al. [17] defined HES as an eosinophilia > 1500/mm³ for longer than 6 months, without any secondary cause and with evidence of organ involvement. HES is consecutive to a clonal proliferation of myeloid precursor cells. It occurs in several myeloproliferative disorders associated with tyrosine kinase mutations or translocations. Although more common between 20 and 50 years of age, this entity is sometimes encountered in children and is more common in males [18–20]. Whereas dermatological, pulmonary and gastrointestinal involvement seems to be more common, the involvement of the cardiovascular system represents the major source of morbidity and mortality [19]. In children, HES is commonly associated with chromosomal abnormalities. A new classification, introducing the concepts of variants, was recently proposed [21]. As their clinical presentations, treatments and prognoses are different, two subtypes of HES must be recognized: a lymphocytic variant of HES (L-HES) and a myeloproliferative variant or chronic eosinophilic leukaemia. Bone marrow cytogenetic analysis and fluorescent in-situ hybridisation are essential for their diagnosis. Indeed, an FIP1L1-PDGFR α (FP) fusion gene, created by an 800-kb deletion at the 4q12 locus, was discovered in the majority of myeloproliferative variants [22]. Thus, patients with FP mutation are likely to have the myeloproliferative variant of HES as opposed to L-HES. The product of this fusion gene is a constitutively active protein-tyrosine kinase capable of transforming haematopoietic cells into eosinophil precursors. It explains the fact that a well-known tyrosine kinase inhibitor, imatinib, is completely effective in 88% of FP-positive patients [22,23]. However, some patients with myeloproliferative variant are FP-negative and therefore do not respond to imatinib. The L-HES variant is characterized by a deregulation of the lymphocyte homeostasis, resulting in an increased secretion of cytokines (IL-5). In this case, corticosteroids are the first-line therapeutic agents. For the resistant forms, an anti-IL-5 therapy (mepolizumab) is recommended [23]. Whereas the L-HES variant is less deleterious for the heart, the transformation into acute leukaemia seems to be more common, especially for children [18].

Eosinophilic cardiac injuries

The heart is one of the most frequently involved organs in cases of sustained eosinophilia [17,18]. In the Löffler's post-mortem examination of two patients with chronic eosinophilia, cardiac involvement was characterized by fibrosis that obliterated the ventricles [1]. It is now recognised that EMF is the ultimate form of eosinophilic cardiac disease. Classically, cardiac injuries of eosinophilia are

divided into three chronological phases: eosinophilic infiltration, thrombosis and fibrosis [12].

Endomyocardial injuries: three successive phases

Eosinophilic myocarditis (acute necrotic stage)

The early phase is characterized by an eosinophilic endomyocarditis with eosinophil and lymphocyte infiltration [23]. When infiltrating cardiac tissues, eosinophils degranulate and release toxic cationic proteins, thus inducing necrosis and apoptosis. However, patients generally have no cardiac symptoms during this stage and they may present only non-specific signs [24]. Clinical and in vivo recognition of eosinophilic myocarditis is infrequent, whereas it accounts for up to 0.5% of unselected myocarditis autopsy series [25]. Electrocardiography (ECG) may show sinus tachycardia, supraventricular tachycardia, non-specific ST-segment anomalies or conduction delays, but is often unremarkable. Echocardiography reveals an increased left ventricular wall thickness because of interstitial myocardial oedema (Fig. 3A, Video 1). Endomyocardial biopsy is necessary to make the diagnosis and to differentiate eosinophilic myocarditis from other types of myocarditis. Indeed, histological sections show eosinophilic infiltration of the endocardium and subendocardial interstitium, evidence of myocardial necrosis and sometimes eosinophilic granulomas (Fig. 4) [25,26]. At this stage of the disease, the aim of treatment is to rapidly lower the eosinophil count in order to limit myocardial necrosis.

Acute narcotising eosinophilic myocarditis represents the most severe form of acute eosinophilic heart disease and may be rapidly fatal without early diagnosis and appropriate treatment [24,27]. Patients present acute heart failure symptoms or may have cardiogenic shock immediately. ECG shows conduction abnormalities and diffuse ST-segment elevation. The level of troponin is elevated, mimicking acute myocardial infarction [28,29]. Echocardiography shows a left ventricular systolic dysfunction with wall motion abnormalities. In this context, cardiac magnetic resonance imaging (MRI) seems to be very efficient for depicting the endomyocardial involvement [30]. Indeed, the endocardial inflammation is well detected by the use of delayed-enhancement sequences (Fig. 3B) showing extensive eosinophilic infiltrates and, sometimes, a patchy distribution of gadolinium enhancement. Moreover, cine sequences can accurately assess ventricular function.

Eosinophilic myocarditis resulting from a hypersensitivity mechanism may present with normal or mildly elevated peripheral eosinophil counts. In all, 50% of patients have no eosinophilia at the onset of disease. It results from the migration of circulating eosinophils into the tissue, while bone marrow cannot respond immediately with increased production [31]. Thus, repeated white blood count examinations are important in case of myocarditis with initially absent eosinophilia. Symptoms of congestive heart failure have to be treated with conventional drugs. Because corticosteroid therapy inhibits the degranulation of eosinophils, it has been proposed as a first-line treatment for eosinophilic myocarditis in order to limit myocardial necrosis. However, the efficacy of corticosteroids remains controversial [32,33].

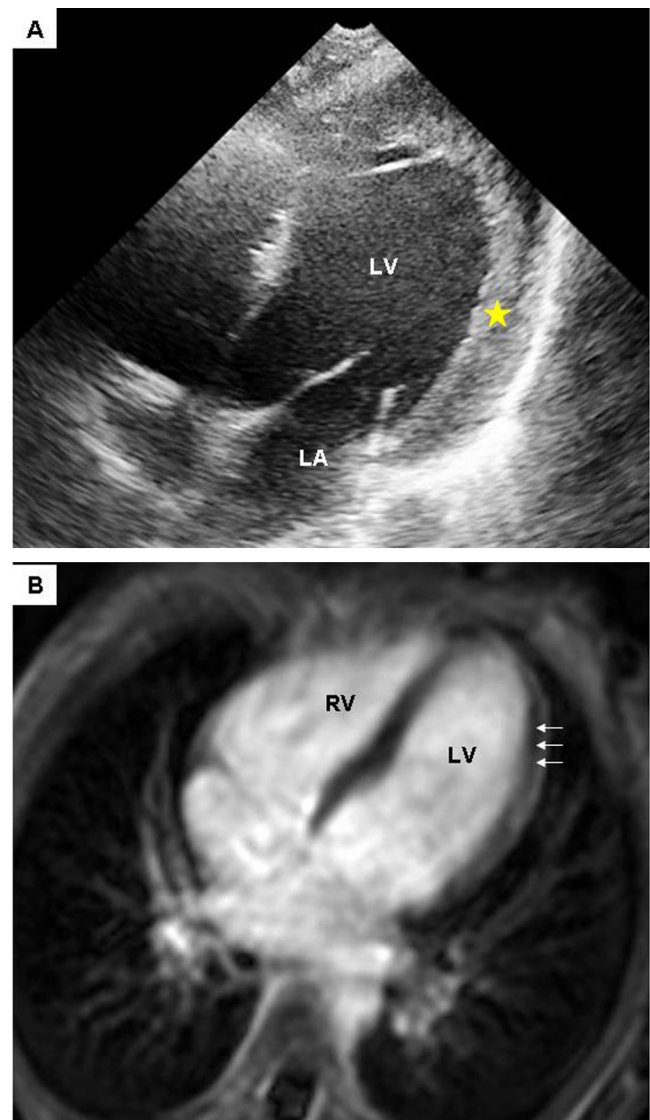


Figure 3. Echocardiographic and cardiac magnetic resonance imaging (MRI) features of eosinophilic myocarditis in a 5-year-old child with reactive eosinophilia (hypersensitivity reaction to antibiotics): (A) transthoracic echocardiographic apical four-chamber view showing the thickened free wall of the left ventricle (LV) (yellow star) due to interstitial myocardial oedema resulting from a profound infiltration of eosinophils; (B) MRI delayed-enhancement image in the four-chamber view showing diffuse subendocardial enhancement (arrows) of the free wall of the LV. LA: left atrium; RV: right ventricle.

In case of fulminant heart failure, mechanical support may be necessary.

Thrombotic stage

As the eosinophilic activation continues, patients may present the second stage of the disease, with formation of mural thrombi along the damaged endocardium. Several mechanisms have been proposed to explain this thrombosis. As previously mentioned, eosinophilic proteins can bind to thrombomodulin, thus impairing the anticoagulant property of the endothelial membrane [34]. Furthermore, factors of coagulation may be activated by the granular proteins of

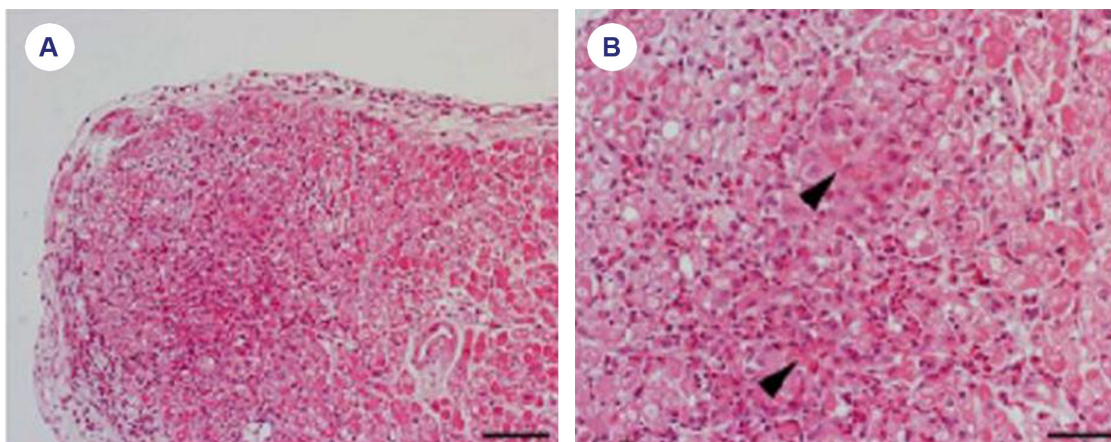


Figure 4. Endomyocardial biopsy of eosinophilic myocarditis: (A) extensive eosinophilic infiltrate involving the endocardium and the myocardium (haematoxylin and eosin); (B) subendocardial granulomas consisting of central amorphous granular material (arrowheads) surrounded by histiocyte-like elements and a marked eosinophilic infiltrate with signs of myocyte necrosis (haematoxylin and eosin). Reproduced with permission from Corradi et al. [26].

eosinophils [23]. Thrombi most commonly involve both ventricles at the apex and may extend to the ventricular outflow tracts, the subvalvular regions and occasionally the atrium. Mural thrombi are well recognized both by echocardiography (Fig. 5, Video 2) and cardiac MRI. Nevertheless, cardiac MRI seems to be more sensitive and specific for the detection of ventricular thrombi than echocardiography [35].

Thromboembolic events have been reported to occur in 4–29% of adult patients with idiopathic eosinophilia [17,36,37]. Thus, in cases of organized thrombi, oral anticoagulation therapy appears to be legitimate [38,39]. To prevent embolic events, the best target international normalized ratio value seems to be 3.0. Antiplatelet therapy has also been proposed to prevent the formation of thrombi at the stage of eosinophilic myocarditis. However, no study has

been conducted to evaluate the effectiveness and modalities of these treatments.

Fibrotic (scarring) stage

Finally, the formation of thrombi is followed by the fibrotic stage, which corresponds to scarring of the endomyocardium. Fibrosis, an irreversible damage, involves the two ventricles (Fig. 6 [40]) and may include subvalvular apparatus of both mitral and tricuspid valves [41,42]. In their echocardiographic series, Gottdiener et al. [12] found mitral regurgitation in 43% of patients with HES. Indeed, the accumulation of thrombofibrotic material between the mural endocardium of the left ventricular free wall and the ventricular aspect of the posterior mitral leaflet limited the posterior mitral leaflet motion (Fig. 7) [43]. In addition to these valvular attachments, EMF is responsible for restrictive cardiomyopathy of very poor prognosis. EMF may also alter the cardiac conduction system leading to severe ventricular arrhythmias [44].

At this stage, echocardiography allows visualization of atrioventricular valve regurgitation; and spectral Doppler flow patterns across the mitral valve and pulmonary veins are consistent with restrictive filling. Echocardiographic criteria have been proposed to assess the severity of EMF (Table 2 [35]). Endomyocardial biopsy shows marked EMF, classically in the absence of any residual eosinophilic infiltrate [40] (Fig. 6). EMF is well depicted by cardiac MRI, and cine sequences are useful to demonstrate diastolic dysfunction [45–48] (Fig. 8). On cardiac catheterization, the typical haemodynamic feature is the dip-and-plateau, or square root, sign [49,50]. This restrictive filling pattern can also be well analysed by strain echocardiography [51].

Surgery is often the only efficient treatment at this stage of the disease. Endocardial decortication provides acceptable results by prolonging survival [52–54]. Indeed, after endomyocardectomy, 70% of patients have revealed improvements of symptoms [55]. When valvular regurgitation is important, valvular surgery may be considered, and bioprosthetic valve replacement is commonly preferred to mechanical prosthesis [56,57]. Indeed, recurrent



Figure 5. Transthoracic echocardiography of a 50-year-old woman with Wegener's disease. Apical four-chamber view showing an apical mural thrombus (arrows) of the two ventricles. End-diastolic volumes are small because of the apical masses. LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle.

Table 2 Criteria for the diagnosis and assessment of severity of endomyocardial fibrosis.

	Score ^a
Major criteria	
Endomyocardial plaques > 2 mm thickness	2
Thin (≤ 1 mm) endomyocardial patches affecting > 1 ventricular wall	3
Obliteration of the right or left ventricular apex	4
Thrombi or spontaneous contrast without severe ventricular dysfunction	4
Retraction of the right ventricular apex	4
Atrioventricular valve dysfunction due to adhesion of the valvular apparatus to the ventricular wall	1–4 ^b
Minor criteria	
Thin endomyocardial patches localized to one ventricular wall	1
Restrictive flow pattern across mitral or tricuspid valves	2
Pulmonary valve diastolic opening	2
Diffuse thickening of the anterior mitral leaflet	1
Enlarged atrium with normal-sized ventricle	2
M-movement of the septum and flat posterior wall ^c	1
Enhanced density of the moderator or other bands	1

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^a A definite diagnosis of endomyocardial fibrosis can be made in the presence of two major criteria or one major criterion associated with two minor criteria. A total score < 8 indicates mild endomyocardial fibrosis, 8–15 moderate disease and > 15 severe disease.

^b The score is assigned according to the severity of atrioventricular regurgitation.

^c M-movement of the interventricular septum refers to a pattern of movement observed on M-mode echocardiography that is thought to be due to obliteration or restriction of the left ventricular apex combined with mitral regurgitation.

thrombotic events are more common with the use of mechanical valves [58]. Ultimately, orthotopic heart transplantation should be considered, providing good results [40]. In any case, it is necessary to control eosinophilia by medical treatments before considering any surgical therapy.

Pericardial injury

Endomyocardial involvement is often associated with pericardial effusion, thus characterizing myopericarditis. However, isolated acute eosinophilic pericarditis has also been reported [59,60], as well as eosinophilic cardiac tamponade [61]. Finally, pericardial involvement of eosinophilia may occur as constrictive pericarditis [62].

Coronary lesions

Eosinophilic coronary periarteritis (ECPA), also described as 'isolated eosinophilic coronary arteritis', 'eosinophilic arteritis', 'eosinophilic coronary arteritis', 'limited form of Churg-Strauss syndrome', 'hypersensitivity-associated acute coronary syndromes' and 'Kounis syndrome', is a rare ubiquitous disease affecting patients of any age, and classically diagnosed at post-mortem examination [63]. Almost all patients with ECPA have anginal pain for several weeks or years before sudden death [64]. Vasospastic angina mainly appears from the evening to the early morning (Prinzmetal's vasospastic angina), and patients usually die in the early morning. Despite the fact that bronchial asthma or drug allergy is generally not found, ECPA is believed to be a distinct coronary disease due to a localized inflammatory reaction rather than a limited form of a primary vasculitis [64,65]. At autopsy, epicardial coronary arteries (from the main stem to their large branches) are grayish-white in

colour and elastically hard. ECPA is reported to frequently be accompanied by spontaneous coronary arterial dissection in the affected wall, especially in women [64]. Histological examination shows a severe inflammatory infiltration, mainly eosinophils, of the adventitia and periadventitial soft tissue. The intima and media are usually intact. In comparison, coronary lesions of Churg-Strauss syndrome are characterized by the presence of fibrinoid necrosis and/or granulomatous inflammation. Only a few cases of the isolated cardiac form of polyarteritis nodosa have been described so far, and for all of them, coronary arteritis was distributed, not only in epicardial large coronary arteries but also in intramyocardial small arteries. Furthermore, in polyarteritis nodosa, the infiltration of inflammation cells was throughout the vascular wall with fibrinoid necrosis [66,67]. Thus, ECPA must be differentiated from medium-sized arteritis with eosinophilic infiltration due to primary vasculitis. Because diagnosis of ECPA is very difficult to make at the clinical examination stage, vasospastic angina associated with eosinophilia and/or asthma and/or allergy should suggest ECPA, leading to corticoids therapy.

Tropical endomyocardial fibrosis

Tropical EMF is the most common cause of restrictive cardiomyopathy worldwide [68]. As Davies was the first to describe the clinico-pathological features of tropical EMF in 1948 [69], this cardiomyopathy is sometimes called Davies disease. Tropical EMF is endemic in tropical and sub-tropical areas, especially in Africa. Because the cardiac lesions are similar to those observed in eosinophilic EMF, some authors have suggested that the two diseases have a common pathogenesis involving eosinophilic toxicity [70–72].

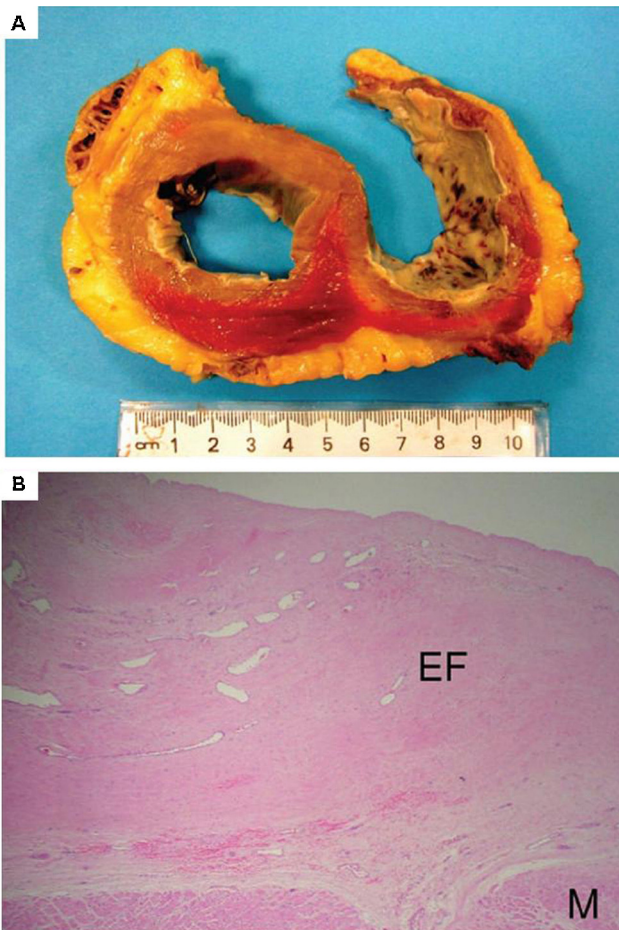


Figure 6. Gross anatomy and endomyocardial biopsy of endomyocardial fibrosis in a 48-year-old male with myeloproliferative neoplasm (FIP1L1-PDGFR α rearrangement): (A) cross section of an expanded heart with marked left ventricular hypertrophy and endocardial fibrosis with multiple superficial haemorrhages. The patient had a hypereosinophilic syndrome and was positive for the FIP1L1-PDGFR α gene rearrangement; (B) gross endocardial fibrosis (EF) with no cellular infiltrates. M: myocardium. Reproduced with permission from Korczyk et al. [40].

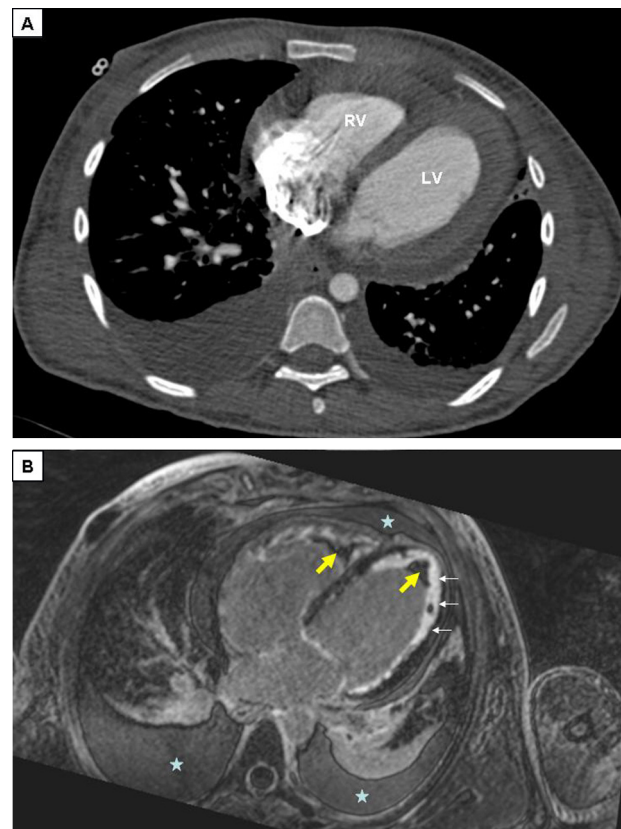


Figure 8. Features of endomyocardial fibrosis in a 20-year-old man with Epstein-Barr virus-associated lymphoma: (A) four-chamber computed tomography (CT) scan image showing thickened walls of the two ventricles; (B) magnetic resonance imaging (MRI) high-resolution delayed-enhancement four-chamber view showing a 'three-layered' appearance of the ventricular walls: the middle layer (thin white arrows) shows hyperenhancement secondary to fibrosis; the innermost layer consists of non-enhancing endocardial thrombus (thick yellow arrows) and mainly affects apices; pericardial and bilateral pleural effusions are also well depicted (blue stars). LV: left ventricle; RV: right ventricle.

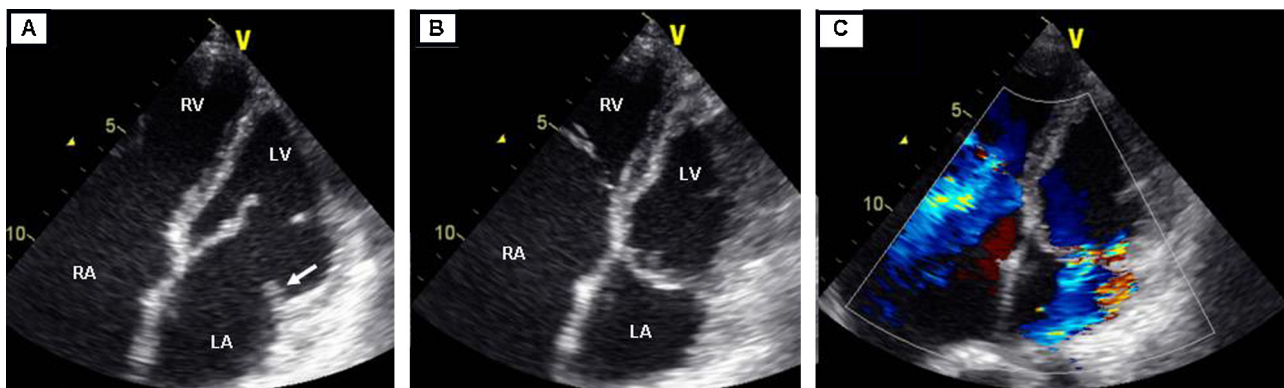


Figure 7. Transthoracic echocardiography of mitral regurgitation resulting from endomyocardial fibrosis: apical four-chamber view demonstrating the mechanism of mitral regurgitation in (A) diastole and (B) systole; the posterior mitral leaflet (arrow in A) has a restrictive motion because of abnormal attachments to the left ventricular wall; (C) colour Doppler mode showing the severity of mitral regurgitation; a severe tricuspid regurgitation reflects high filling pressures (restrictive cardiomyopathy). LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle.

Indeed, the high prevalence of parasitic infections in the tropics was assumed to be the cause of a transient or sustained eosinophilia, leading to the cardiac lesions. This hypothesis was supported by observations of visitors to subtropical regions who developed tropical EMF [73]. However, the variable association with eosinophilia and the frequent absence of eosinophils on endomyocardial biopsies, even in the early stages, are arguments against this assumption [68–74]. Thus, exact mechanisms of tropical EMF remain unknown. A new hypothesis involves an infective trigger in genetically susceptible individuals [74].

Conclusions

Mechanisms that explain why, in sustained eosinophilia, the heart is particularly targeted by eosinophils are not well understood. Nonetheless, a profound eosinophilic infiltration of the interstitial compartment is very deleterious to cardiac tissues. Clinical and echocardiographic signs of eosinophilic cardiac disease may vary widely. As early treatment can limit irreversible damage, echocardiography should be systematically performed in cases of eosinophilia, especially if it is prolonged. In the absence of aetiology, first-line treatment should include anti-helminthic therapy, corticosteroid therapy and anticoagulant therapy. The goal of these therapeutics is to rapidly lower the eosinophil count and prevent thromboembolic events. As second-line treatment, specific treatment of eosinophilia must be conducted depending on the cause. Finally, surgery may be necessary at the fibrotic stage of the disease, before considering heart transplantation for the most severe cases. Eosinophilic coronary periarteritis is a rare isolated eosinophilic injury localized to epicardial coronary arteries, which is responsible for vasospastic angina. For all of these lesions, prognosis is related to the severity of cardiac injuries but also to the cause of eosinophilia.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.acvd.2015.01.006>.

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