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Cardiac involvement in eosinophilic granulomatosis with polyangitis (Churg Strauss) (RCD code: I-3A.7a)

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Abstract

Eosinophilic granulomatosis with polyangitis – EGPA (previously known as Churg-Strauss syndrome) is a rare, systemic, necrotizing small-vessel vasculitis with accompanying bronchial asthma, eosinophilia and eosinophilic tissue infiltration of various tissues with granuloma formation. The pathognomonic laboratory feature of EGPA is prominent peripheral eosinophilia that commonly exceed 1,500 cells/μl, and the presence in approximately 40% of patients of the antineutrophil autoantibodies (ANCA). EGPA is one of the most common of the systemic vasculitides to affect the heart and if present it deteriorates the prognosis of the disease and increases mortality. Cardiac involvement varies widely ranging from 16–92% and is more common in ANCA negative patients. The cardiac manifestations varies in its clinical presentation. It may present as myocarditis with cardiomyopathy, pericarditis with pericardial effusion (up to 25% of patients), heart failure (18%),varies ventricular and supraventricular arrhythmias, valve involvement and sudden cardiac death. Epicardial coronary arteries involvement is rare, however, coronary angiography should be considered in patients presenting with angina symptoms to rule out important coronary vessels stenosis. Imaging techniques as transthoracic echocardiography (TTE) and cardiac magnetic resonance (CMR) may help in establishing the diagnosis of EGPA. The significance of often detected cardiac damage in CMR without clinical manifestation remains uncertain, however, some preliminary studies suggest that, these patients should be treated more intensively to prevent further cardiac involvement. The main treatment of EGPA consist of corticosteroids and additional immunosuppression in patients with worse prognosis. In differential diagnosis other forms of vasculitides and hypereosinophilic syndromes (HES) that may also affect the heart should be excluded. JRCD 2013; 1 (3): 91–95

Key words: cardiac involvement, EGPA, Churg Strauss, cardiac magnetic resonance

Introduction

Eosinophilic granulomatosis with polyangitis – EGPA (previously known as Churg-Strauss syndrome) is a systemic, necrotizing small-vessel vasculitis with accompanying bronchial asthma, eosinophilia and eosinophilic tissue infiltration of various tissues with granuloma formation [1–3]. It is a rare disease with an annual incidence of 2.4–6.8 cases/1 million inhabitants, and prevalence of 11–14 cases/1 million in the general population [1, 4, 5]. Its frequency is highest at the age of 40–60 years (mean 48) with equal gender and ethnic distribution [6]. The pathogenesis of the disease is still unclear, however, it is often assumed to be an autoimmune disease due to altered immune response [7, 8] and presence of antineutrophil autoantibodies (ANCA) in about 40% of patients [9–11] (Figure 1). As EGPA is a systemic disease, it may affect almost any organ. Most of the patients complain of general symptoms, such as malaise, fatigue, fever, arthralgia and weight loss. The respiratory tract involvement (most characteristic for EGPA) consists of asthma – present in almost all patients [12], and pulmonary infiltrates of patchy and transient character, that usually disappear rapidly after initiation of corticosteroids [13, 14]. Typical for EGPA is also neurological involvement, that can be found in up to 76% of patients, and usually manifest in the form of mononeuritis multiplex (e.g. peroneal paralysis with foot drop), however, peripheral polyneuropathy may also be present [6, 15]. The abdominal pain is the most common presentation of gastrointestinal involvement (present in 50% of patients), however more severe forms of the dis-

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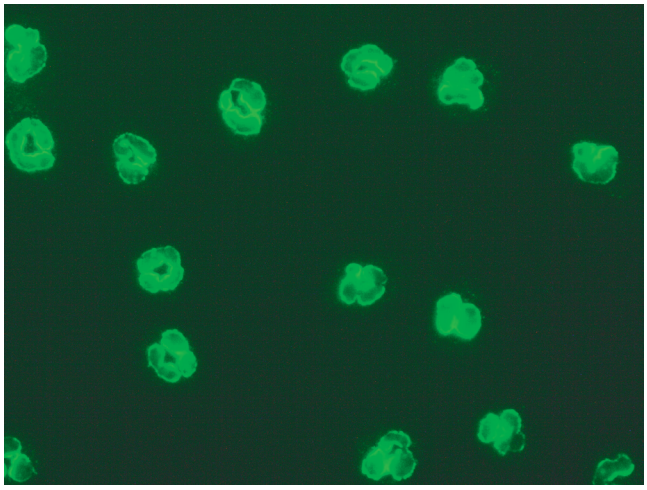

Figure 1. Perinuclear pattern of antineutrophil cytoplasmic antibodies (p-ANCA), which are more common in EGPA. Indirect immunofluorescence staining of ethanol-fixed neutrophils (original magnification, 200x)

ease with life-threatening complications, such as bowel ischemia or necrosis may also be present [1, 16]. Skin changes are present in about 50% of patients and vary in its presentation [17]. Renal involvement is less frequent (25–47%) than in other small-vessel vasculitides, and if present is characterized by pauci-immune focal and segmental necrotizing glomerulonephritis, that may lead to symptoms such as proteinuria, hematuria, or systemic hypertension [6, 11]. Course of the disease usually is divided into three consecutive periods. Prodromal phase with allergic rhinitis and asthma, accompanied by sinusitis and nasal polyposis that evolves into the second phase, where eosinophilia with consequent organ involvement prevails. Finally, the "vasculitis" phase emerges with symptoms associated to small-vessel vasculitis dependent on the affected organ [6]. This sequence of events may, however overlap and establishing the diagnosis may be problematic. The most commonly used criteria for diagnosing EGPA are the one established in 1990 by the American College of Rheumatology [18]. According to them, EGPA is diagnosed (specificity of 99.7% and sensitivity of 85%) if at least four out of the following six criteria are fulfilled: presence of asthma, peripheral blood eosinophilia (>10% of total leucocyte count), mono- or polyneuropathy, paranasal sinus abnormalities, eosinophilic accumulation in tissues demonstrated in biopsy, and migratory lung infiltrates.

Recently two distinct forms/phenotypes emerged inside the EGPA, based on the patients ANCA status [9–11]. In ANCA positive patients the vasculitic pattern of the disease is dominant with more common renal involvement, neuropathy and skin pathology compared to ANCA negative patients. In the latter group, both lung and cardiac involvement are more frequent.

Prognosis and treatment

Historically EGPA without treatment (before the introduction of corticosteroids), was almost inevitably fatal [19], however nowadays the prognosis have substantially improved, and 5-year mortality does not exceed 13.9% [20]. There is no one-line treatment consensus in the induction and maintenance therapy of EGPA, however, most therapeutic schemes are based on the usage of corticosteroids and depending on the severity and prognosis of the disease on adding other immunosupressants. The most commonly used prognostic tool is Five Factor Score (FFS) scale [21]. According to this scale one point is given for each of the following: cardiac involvement, severe gastrointestinal manifestation, central nervous system involvement and renal impairment (proteinuria >1g/24h, or creatinine >140 μmol/l). Patients with a good prognosis have a FFS of 0 points and are treated solely with corticosteroids, while patients with poor prognosis (FFS≥1), or those resistant to corticosteroids, require addition of other immunosuppressants, usually cyclophosphamide [1].

Cardiac Involvement

EGPA is one of the most common of the systemic vasculitides to affect the heart [22], and if present it deteriorates the prognosis of the disease and increase mortality [6, 21, 23]. Approximately 50% of deaths in EGPA patients are related to cardiac diseases, and occur most commonly within the first few months from establishing the diagnosis [24]. Cardiac involvement varies widely ranging from 16–92% and is more common in ANCA negative patients [6, 9, 10, 21, 25–27]. These frequency discrepancies are mostly due to the different diagnostic techniques that have been used. While in the early studies it were mostly clinical presentations and autopsy findings that were evaluated [19], the more recent studies, utilize several imaging technics, including transthoracic echocardiography (TTE) [25, 28, 29] and cardiac magnetic resonance (CMR) [1, 26, 30–32]. These differences depend also on the severity and activity of the disease, with the highest frequencies of cardiac involvement described in the active phase of the disease. According to the treatment scheme based on the FFS prognostic scale [21], cardiac involvement is an indication for adding additional immunosuppression to the corticosteroid treatment. However, it is not yet established, how to define the cardiac involvement, and in most centers this definition is applied only to patients with visible clinical manifestations of cardiac disease. Signs of cardiac damage may be, however, visualized in CMR even in patients in total remission of the disease (and without any clinical symptoms) [31], and impact of this "silent damage" on the disease prognosis remain uncertain. There is an ongoing discussion among the experts in the field of how to treat these patients, especially that there are some growing evidence that additional immunosuppression may reverse the CMR cardiac changes [33]. This important issue need further evaluation in future studies.

Two main mechanism are postulated in the development of cardiac involvement in EGPA patients: vasculitis-related ischemia and eosinophilic infiltration of the myocardium [31, 34].

The cardiac manifestations varies in its clinical presentation. It may present as myocarditis with cardiomyopathy, pericarditis with pericardial effusion (up to 25% of patients), heart failure (18%), varies ventricular and supraventricular arrhythmias, and sudden cardiac death [23, 31, 34–37]. Cardiac valve abnormalities, and cor-

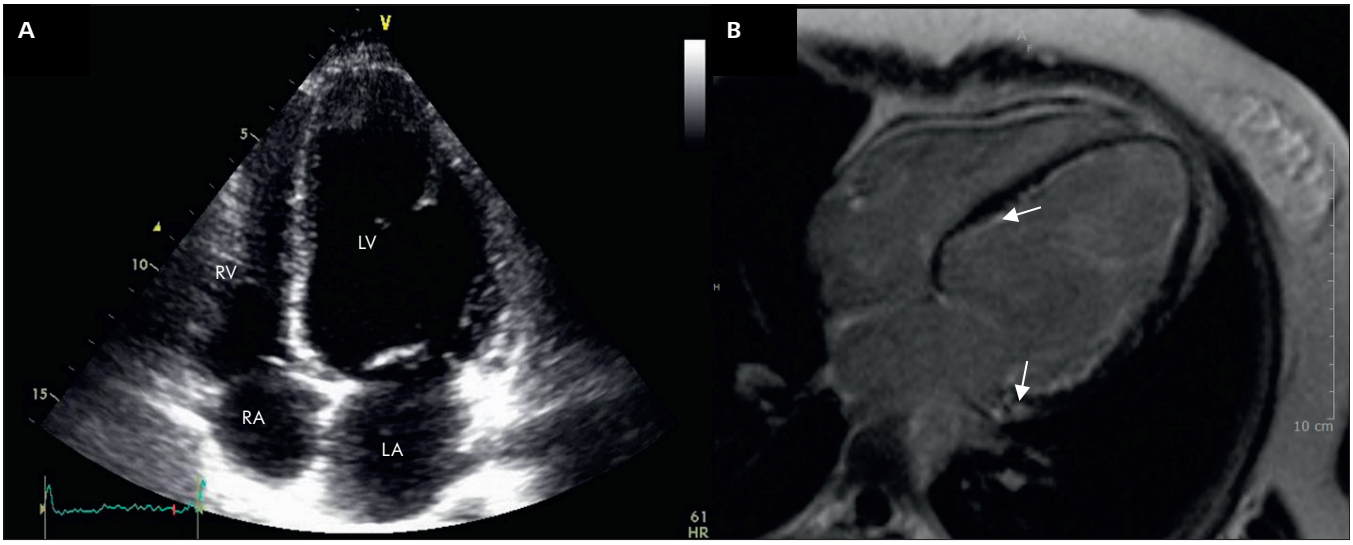

Figure 2. Transthoracic echocardiography (A) and cardiac magnetic resonance (B) in 20 years old female with EGPA with subsequent severe left ventricular systolic wall (arrows). LV – left ventricle, RV – right ventricle, LA – left atrium, RA – right atrium

onary vasculitis leading to myocardial infarction are rare and mostly restricted to single case reports [25]. Ischemia and myocardial infarction in EGPA patients are combined with the inflammatory process and eosinophil accumulation [38], with epicardial coronary arteries rarely demonstrating any changes during the coronary angiography (which should, however, always be considered in EGPA patients presenting with angina pain and typical ECG changes to rule out clinically important vascular stenosis). In some reports, vasculitis of the epicardial arteries have been reported, but it is relatively rare [22].

Diagnostic imaging tests

TTE is the first line imaging modality to assess cardiac involvement in Churg-Strauss syndrome. Subjects with Churg-Strauss syndrome may present with the wide spectrum of cardiac abnormalities, which may be depicted in TTE. TTE may detect a) enlargement of cardiac chambers, especially of left ventricle and atrium, b) diastolic and systolic left ventricular dysfunction (Figure 2A), c) cardiac valve dysfunction, d) pericarditis as well as d) the presence of cardiac thrombus. Importantly, since regional systolic dysfunction does not frequently correspond with epicardial coronary artery supply, TTE may be useful to differentiate between cardiac involvement in Churg-Strauss syndrome and ischemic cardiomyopathy. The two-dimensional speckle tracking strain, strain rate and/or rotational analysis may be used for detailed assessment of myocardial systolic and diastolic dysfunction. Interestingly, systolic left ventricular dysfunction in Churg-Strauss syndrome predominately correlate with decline in global longitudinal and circumferential, but not radial and rotational myocardial deformational parameters, indicating the presence of impaired contraction of inner and middle myocardial layers with preserved function of outer myocardial fiber layer. Moreover, the correspondence between systolic and diastolic deformation parameters suggests the similar impact of pathologic process on systolic and diastolic function in Churg-Straus syndrome [28]. CMR may provide more detailed information about myocardial structure and function when compared to TTE. CMR provides unique characteristics of cardiac morphology including presence of myocarditis and myocardial damage. In addition this new imaging modality may provide thorough insight into presence and extent of pericarditis. The prevalence of myocardial damage as depicted by late gadolinium enhancement (LGE) imaging is frequent in Churg-Strauss syndrome (Figure 2B). LGE lesions, which predominately correspond to myocardial fibrosis are frequently located in subendocardium and may encompass the entire subendocardium resulting in severe systolic dysfunction of left ventricle [31] (Figure 2). The involvement of epicardial layer is rare. The presence of LGE lesions is strongly associated with contractile abnormalities depicted both by visual assessment and feature tracking analysis of myocardial tissue contraction [39]. Importantly, despite normal left ventricular contractile function in TTE, feature tracking analysis may show regional systolic dysfunction in Churg-Strauss syndrome, which might potentially precede development of further systolic abnormalities [39]. CMR is of great value in detection of myocarditis, which may frequently be present in the course of Churg-Strauss syndrome. The prevalence of myocarditis in Churg-Strauss syndrome is not uncommon and may be even present in subjects in total remission [31]. Importantly, the prior reports have shown that immunosuppressive therapy might modulate the activity of myocarditis, as observed by CMR, suggesting the potential role of CMR in the treatment monitoring [40]. Nevertheless, further studies are needed to support this issue.

Pathologic findings

The characteristic histological triad of EGPA consists of: necrotizing vasculitis, eosinophilic infiltration and extravascular granuloma formation, and was originally described in 1951 by Jacob

Churg and Lotte Strauss [19]. The early phase of EGPA is characterized by extravascular tissue infiltration by eosinophils that may occur in almost any organ [41]. In the "vasculitis" phase, pathologic signs of inflammation of the small to medium-sized vessels walls prevails (mostly presenting as necrotizing vasculitis) often accompanied by tissue eosinophilia infiltration. The granuloma formations, are nowadays rarely seen, mostly due to the presence of corticosteroid treatment [6, 41]. As the characteristic, historical triad hardly ever coexist in any given patient in the same time and is not obligatory to establish the diagnosis. The histologic findings varies according to the site where obtained, and are often indistinguishable from other forms of vasculitis diseases, therefore should always be considered in a given clinical setting.

Cardiac pathology may present as endo-myocardial and pericardial eosinophilic infiltration and rarely coronary vasculitis [4]. The cardiac biopsy specimens are often nondiagnostic, and as being high-risk procedures are rarely performed.

Laboratory findings

The pathognomonic feature of EGPA (almost always present on the beginning of the disease) is prominent peripheral eosinophilia that commonly exceed 1,500 cells/μl with more than 10% of eosinophils in the total leukocyte count [1]. It may be diminished by the corticosteroid treatment. Other abnormalities may include: increased serum IgE levels, anemia of chronic diseases, abnormalities of the renal function, and elevation of acute inflammatory markers, e.g., elevated erythrocyte sedimentation rate and C-reactive protein. ANCA are present in approximately 40% of patients in most of the patients showing the perinuclear staining pattern (p-ANCA) mostly directed against myeloperoxidase (anti-MPO).

Differential diagnosis

In the differential diagnosis of the EGPA especially other forms of vasculitides as: granulomatosis with polyangitis (GPA, Wegener's) [42] or microscopic polyangitis (MP) and hypereosinophilic syndromes (HES) should always be ruled out. Especially the latter may present with frequent cardiac involvement [43]. Also symptoms of severe asthma may mimic the cardiac manifestation, and in this clinical setting cardiac imaging is an essential diagnostic tool [36]. The parasitic infections should be considered and excluded.

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