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Review

Churg–Strauss syndrome

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ABSTRACT

Churg–Strauss syndrome (CSS), alternatively known as eosinophilic granulomatosis with polyangiitis (EGPA), was first described in 1951 by Churg and Strauss as a rare disease characterized by disseminated necrotizing vasculitis with extravascular granulomas occurring exclusively among patients with asthma and tissue eosinophilia. EGPA is classified as a small-vessel vasculitis associated with antineutrophil cytoplasmic antibodies (ANCAs) and the hypereosinophilic syndromes (HESs) in which vessel inflammation and eosinophilic proliferation are thought to contribute to organ damage.

Although still considered an idiopathic condition, EGPA is classically considered a Th2-mediated disease. Emerging clinical observations provide compelling evidence that ANCAs are primarily and directly involved in the pathogenesis of AASVs, although recent evidence implicates B cells and the humoral response as further contributors to EGPA pathogenesis.

EGPA has traditionally been described as evolving through a prodromic phase characterized by asthma and rhino-sinusitis, an eosinophilic phase marked by peripheral eosinophilia and organ involvement, and a vasculitic phase with clinical manifestations due to small-vessel vasculitis.

The American College of Rheumatology defined the classification criteria to distinguish the different types of vasculitides and identified six criteria for EGPA. When four or more of these criteria are met, vasculitis can be classified as EGPA.

The French Vasculitis Study Group has identified five prognostic factors that make up the so-called five-factor score (FFS). Patients without poor prognosis factors (FFS = 0) have better survival rates than patients with poor prognosis factors (FFS ≥ 1).

The treatment of patients with CSS must be tailored to individual patients according to the presence of poor prognostic factors. A combination of high-dose corticosteroids and cyclophosphamide is still the gold standard for the treatment of severe cases, but the use of biological agents such as rituximab or mepolizumab seems to be a promising therapeutic alternative.

Contents

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1. Introduction

Churg–Strauss syndrome (CSS) was first described in 1951 by J. Churg and L. Strauss as a form of disseminated necrotizing vasculitis with extravascular granulomas occurring exclusively among patients with asthma and tissue eosinophilia [1]. Called Churg–Strauss syndrome for many years, this condition has now been recognized by the 2012 revised nomenclature for vasculitides as Eosinophilic Granulomatosis with Polyangiitis (EGPA) [2].

The histological lesions observed by Churg and Strauss in most of the affected sites were extremely severe. Most specimens were obtained from autopsy cases; therefore, the samples were large biopsy specimens, which facilitated the detection of the histological markers of EGPA. In addition, glucocorticoid treatment was not available at that time. Glucocorticoids have dramatically changed the prognosis of EGPA. The knowledge of EGPA has recently evolved. Antineutrophil cytoplasmic antibodies (ANCA) have been found in a proportion of EGPA patients; therefore, EGPA has been included in the spectrum of ANCA-associated vasculitis (AAV) together with granulomatosis with polyangiitis (GPA — Wegener granulomatosis) and microscopic polyangiitis (MPA) [3].

EGPA is a disease that charts the crossroads between primary systemic vasculitides [2] and hypereosinophilic disorders [4,5]. Within this dual categorization, EGPA is classified among the small-vessel vasculitides associated with antineutrophil cytoplasmic antibodies (ANCAs) and the hypereosinophilic syndromes (HESs) [4], which are syndromes with accompanying hypereosinophilia [5].

Both vessel inflammation and eosinophilic proliferation are thought to contribute to organ damage, but the clinical presentations are heterogeneous, and the respective roles of vasculitis and hypereosinophilia in the disease process are not well understood.

2. Epidemiology

CSS usually manifests between 7 and 74 years of age, with a mean age at onset of 38 to 54 years [6,7]. A recent review of CSS in the pediatric population identified reports in children as young as four years of age with the disease [8]. The estimated incidence is approximately 0.11 to 2.66 new cases per 1 million people per year, with an overall prevalence of 10.7 to 14 per 1 million adults [9,10]. No gender predominance or ethnic predisposition has clearly been demonstrated in CSS [11].

3. Aetiopathogenesis

Although it is still considered as an idiopathic condition, significant advances have been made recently to aid in the understanding of CSS pathogenesis.

Different environmental factors have been suggested as potential triggers of CSS, including allergens, infections, vaccinations, and medications [12,13]. Among medications, special attention has been placed on the leukotriene receptor antagonists traditionally used to treat asthma. It is now believed that these agents better control the asthmatic component in patients with CSS, allowing a decrease in or discontinuation of the glucocorticoid treatment, which may be controlling the vasculitic component, thus making it clinically evident [14].

Immunogenetic factors may confer susceptibility to EGPA. The HLA-DRB1*04 and *07 alleles and the related HLADRB4 gene are associated with an increased risk of developing EGPA [15,16].

Eosinophil infiltration and ANCA-induced endothelial damage are probably the most important mechanisms of disease pathogenesis.

Eosinophilic granulomatosis with polyangiitis is classically considered a Th2-mediated disease. Peripheral T-cell lines from EGPA patients can produce Th2-associated cytokines such as IL-4 and IL-13 [17]. IL-5 is also up-regulated in active EGPA [18,19] and IL-5 inhibition has been shown to be beneficial in EGPA patients [20]. However, the clinical phenotype of EGPA cannot be explained by an exaggerated Th2 response alone [13].

Consistent with this hypothesis, there is evidence of involvement of Th1 and Th17 cells secreting high amounts of IL-17A in the late stages of EGPA [17,19]. Moreover, regulatory T cells are found in reduced numbers during active disease [21,13].

Eosinophils are abundant both in the periphery and in EGPA lesions. Eotaxin-3 produced by epithelial and endothelial cells might contribute to tissue infiltration by activated eosinophils that constitute the final step of a process that brings the eosinophils out from the bloodstream toward the inflammation site [22,23]. Thanks to animal models, we know that both IL-13 and IL-4, but not IL-5, are strong and synergic promoters of eotaxin synthesis.

Activated tissue eosinophils secrete considerable amounts of eosinophil granule proteins (e.g., eosinophil basic protein, eosinophil-derived neurotoxin), thereby contributing to tissue damage. Moreover, eosinophils in EGPA secrete IL-25, which induces Th2 responses, thereby maintaining a vicious circle [24].

Recent evidence points to B cells and the humoral response as further contributors to EGPA pathogenesis. Not surprisingly, the aforementioned cytokines (i.e., IL-4, IL-13) boost the humoral immune response [13].

CSS is classified among the so-called ANCA-associated systemic vasculitides because of the overlapping clinico-pathological features with the other ANCA-associated systemic vasculitides. However, while ANCA are consistently found in 70–95% of patients with GPA and MPA, their prevalence in CSS is sharply lower (around 40%). The main fluoroscopic pattern is perinuclear with antibodies to MPO [25].

These findings have led to speculation that these antibodies may be an integral part of the inflammatory diathesis that characterizes the disorder [26,27]. They also induce the release of primary granule contents from neutrophils. Thus, antineutrophil cytoplasmic antibodies can cause neutrophil activation and degranulation.

Emerging clinical and in vivo (animal model) observations provide compelling evidence that ANCAs are primarily and directly involved in the pathogenesis of AASVs. [28,29] They are capable of activating neutrophils in numerous ways resulting in the release of reactive

oxygen species, granule proteins, cytokines, chemokines, and adhesion molecules. ANCA-activated leucocytes adhere to the endothelium and cause endothelial damage [28,29].

CSS ANCA-positive patients are more likely than ANCA negative patients to present with the typical clinico-pathological picture of the other small-vessel vasculitis and less likely to suffer from heart and non-hemorrhagic lung involvement. Such reports suggested the hypothesis of the existence of two disease subsets with different clinical manifestations and, possibly, pathogenetic mechanisms [25].

Moreover, a dramatic increase in serum IgG4 has recently been observed in active EGPA cases, which corroborates the notion that robust elevation of IgE levels is common in EGPA [30] and that EGPA may belong to the growing list of IgG4-related diseases. A recent study found increased serum IgG4 levels and IgG4/IgG ratios in active EGPA patients compared to healthy individuals, asthmatic patients, and patients with GPA. Following immunosuppressive treatment, both IgG4 levels and IgG4/IgG ratios are significantly decreased, suggesting that IgG4 is selectively targeted [30]. The main immune mechanisms of EGPA are schematically depicted in Fig. 1.

4. Symptomatology

Clinical manifestations in EGPA tend to segregate into two major disease subsets dominated by vasculitic and eosinophilic manifestations, and ANCA can differentiate between these two subsets. Two large studies demonstrated that ANCA-positive patients had peripheral neuropathy, glomerulonephritis, and purpura (which are due to small-vessel vasculitis) more frequently compared to myocardial involvement, lung infiltrates, and gastrointestinal symptoms that prevailed in the ANCA-negative subset (Fig. 2 [31,32]).

In general, symptom and organ involvement can be related to three major mechanism: (1) the importance of autoantibodies mediated organ involvement, (2) the part of inflammatory mediators in determining specific and aspecific organ damage, and (3) the role of antiphospholipid-related hypercoagulability and thrombosis [33].

EGPA has traditionally been described to evolve through a prodromic phase characterized by asthma and rhino-sinusitis, an eosinophilic phase marked by peripheral eosinophilia and organ involvement, and a vasculitic phase with clinical manifestations due to small-vessel vasculitis [34].

4.1. Prodromal phase

An initial prodromal phase lasting months to years is common and may include arthralgias, myalgias, malaise, fever, and weight loss [35,36]. Asthma is the main manifestation during the prodromal phase and present in 96% to 100% of patients. In this initial phase, upper respiratory symptoms are present in the majority of patients (47%–93%) [9,37]. They include nasal polyps, allergic rhinitis, and recurrent or chronic sinusitis Fig. 2. Lesions observed in granulomatosis with polyangiitis such as nasal or sinus granulomas, hemorrhage, and crusting are quite uncommon, although orbital involvement has been reported [9,37].

Other otolaryngological manifestations include secretive otitis media, chronic ear drainage, sensorineural hearing loss [38,39], and facial nerve palsy [40].

4.2. Eosinophilic phase

The eosinophilic phase is more frequently characterized by peripheral eosinophilia and organ involvement that by lung, cardiac, and gastrointestinal involvement. Involvement of the lung parenchyma occurs in up to two-thirds of EGPA patients [41].

4.2.1. Lung imaging

Migratory infiltrates observed on the chest radiograph is one of the key features of EGPA and was included in the ACR criteria for EGPA classification [42]. Lung computed tomography (CT) scanning has proven to be a more sensitive method to detect parenchymal changes. In a retrospective study [43], 22 patients with active EGPA showed interstitial changes on high-resolution CT but only 64% had abnormal chest radiograph findings. Therefore, high-resolution lung CT should be performed in the diagnostic work-up of eosinophilic asthma, especially when a diagnosis of EGPA is suspected. Neither the lung infiltrates nor any of the other lung imaging changes observed in EGPA is specific because they are also commonly observed in other eosinophilic lung diseases. About 25% of EGPA cases show peripheral nodular opacities. Ground-glass opacities are noted in 86% of active EGPA cases (Fig. 2 [44]) and bronchial wall thickening and bronchiectasis are described in 66% of EGPA cases.

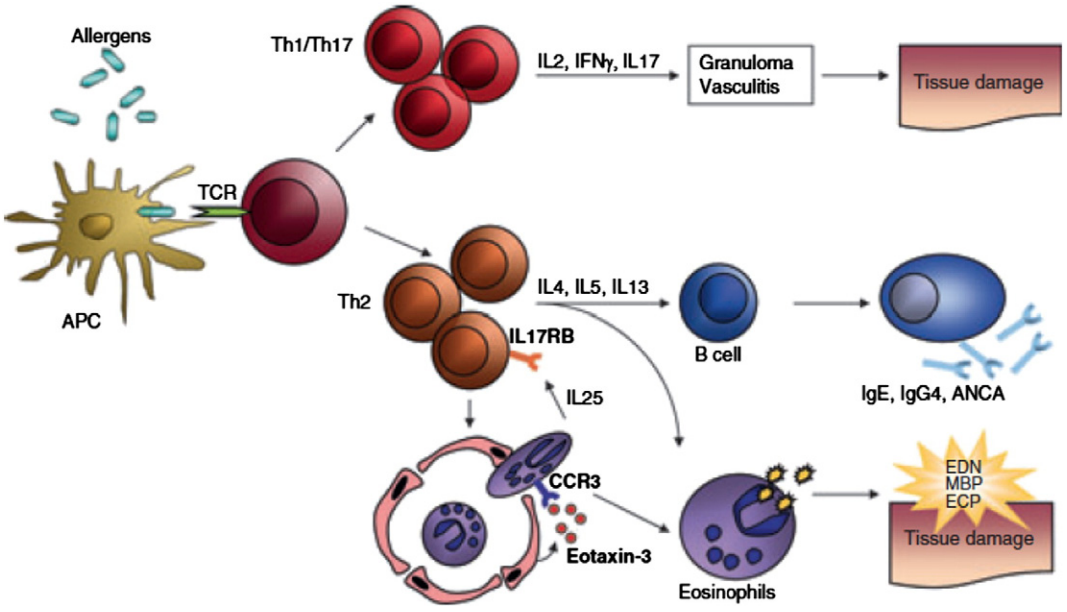

Fig. 1. Pathophysiological events in EGPA.
From: Allergy 2013;68:261–73.

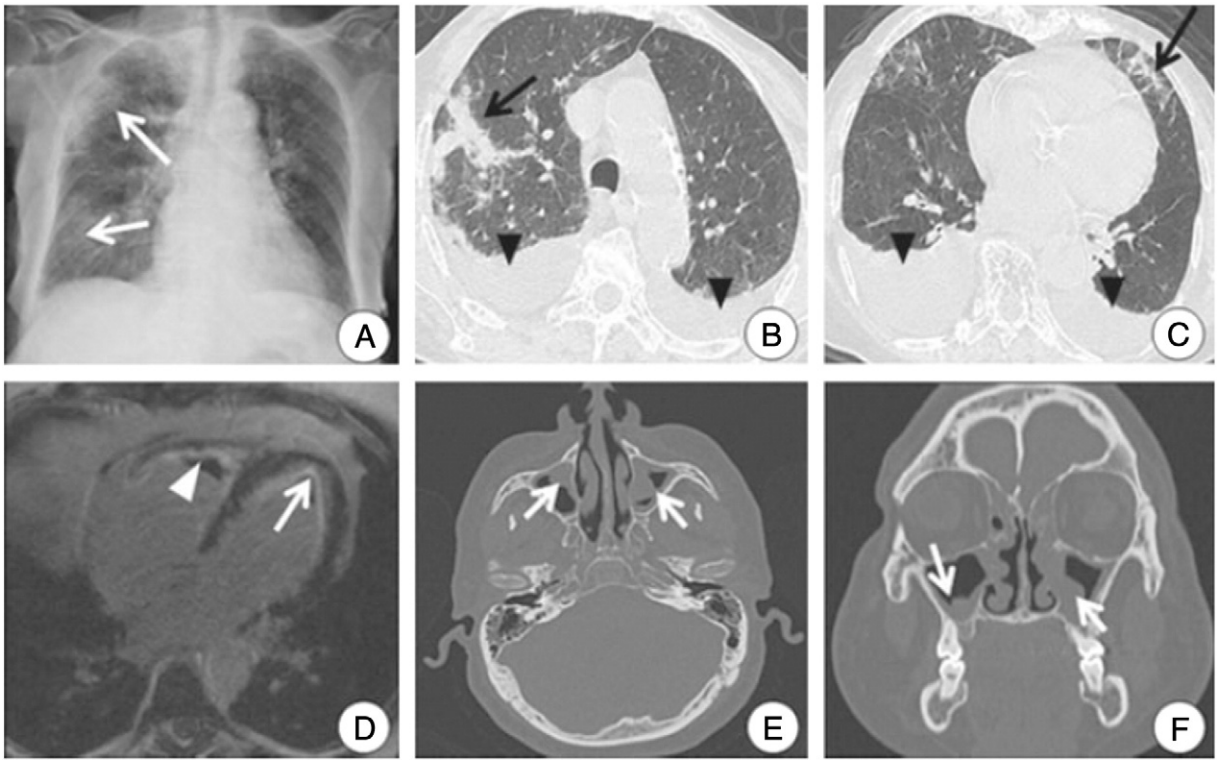

Fig. 2. Representative imaging findings in patients with eosinophilic granulomatosis with polyangiitis (EGPA) (Churg–Strauss). (A) The chest radiograph shows peripheral patchy consolidation in the right lung (arrows). (B, C). High-resolution computed tomography (HRCT) images show peripheral consolidation (arrow) in the right upper lobe, and interlobular septal thickening associated with scarce ground-glass opacity in both middle lobe and lingula (arrows); bilateral pleural effusion (arrowheads) and heart enlargement in a patient with lung and cardiac involvement (cardiac failure due to EGPA-related cardiomyopathy) were also present. (D) T1-weighted contrast-based late enhancement sequence showing endomyocardial late enhancement due to endomyocarditis in the apex of the left (arrowhead) and right ventricle (arrow) with adjacent thrombus formation. (E,F) Both axial (E) and coronal (F) CT reformations of the head show signs of severe sinusitis of the maxillary sinuses (arrows) as well as thickening of the nasal mucosa.
From: Allergy 2013;68:261-73.

4.2.2. Heart disease

Symptomatic cardiac involvement occurs in as many as 27–47% of EGPA cases [45–47] and represents the major cause of early death and poor long-term prognosis [48,49].

Although endomyocardial infiltration (Fig. 2) is the dominant condition, arrhythmia, pericarditis, and valvular defects may also occur [50].

4.2.3. Gastrointestinal involvement

Gastro-intestinal involvement is also often due to eosinophilic infiltration of the gastrointestinal mucosa and more frequently affects the small bowel, and patients presenting with otherwise unexplained abdominal pain and sometimes digestive hemorrhage may continue toward intestinal perforation [1,35,51,52].

4.3. Vasculitic phase

The vasculitic phase is heralded by constitutional symptoms (e.g., fever, weight loss, fatigue) and often by an apparently paradoxical improvement of asthma.

4.3.1. Peripheral neuropathy

Peripheral neuropathy is a cardinal feature of this phase, which affects ~70% of the patients [31,32,53].

Patients may present with multiplex mononeuritis or a mixed sensorimotor peripheral neuropathy. The presence of drop wrist or foot is the typical manifestation of mononeuritis multiplex, and this may be confirmed by nerve conduction studies or sural nerve biopsy, which typically shows inflammation of the vasa nervorum [35,36]. The central nervous system is involved in 25% of cases with neurological involvement. Patients may present with cerebral infarctions and hemorrhage. Although central nervous system involvement is uncommon, some series have it as the second cause of mortality in CSS [27].

4.3.2. Renal manifestations

Although less frequent and severe than in the other ANCA-associated vasculitides, renal manifestations occur in 25% of CSS patients and range from isolated urinary abnormalities to rapidly progressive glomerulonephritis; some patients have chronic renal failure at diagnosis [54]. The most typical picture is pauci-immune focal and segmental necrotizing glomerulonephritis, with or without crescents, which usually involve less than 50% of the glomeruli [55]. Tubulointerstitial nephritis with eosinophilic predominance is found only occasionally; a few patients have mesangial glomerulonephritis or focal segmental sclerosis [56].

4.3.3. Skin lesions

Skin lesions are also a prominent feature of the vasculitic phase [1]. Palpable purpura and nodules, typically located on the limbs and scalp, are the most common skin manifestations. Maculopapular erythematous eruption resembling erythema multiforme, livedo reticularis, vesicles, aseptic pustules, petechiae, ecchymoses and urticarial lesions can also appear at the same time or in different stages of the disease; papular and nodular lesions may undergo a necrotic–ulcerative evolution [57].

5. Histopathology

EGPA was originally described as a pathological triad consisting of eosinophilic infiltration, necrotizing vasculitis and extravascular

granuloma formation [1]. These characteristics were mostly observed on autopsy [1].

The early phase of EGPA is characterized by extravascular tissue infiltration by eosinophils of virtually any organ [58]. Once the disease progresses to the 'vasculitis' phase, pathologic signs of inflammation are observed in small to medium-sized vessel walls. Vasculitis is characterized by fibrinoid necrosis and eosinophilic vessel wall infiltration.

Because of the widespread use of glucocorticoid therapy and/or the small biopsy specimens available for examination, pathology-based identification of granulomas has become infrequent [27,32,45]. Granulomas often involve the arteries, but the more EGPA-specific lesion is the extravascular granuloma, which consists of a core of necrotic eosinophilic material surrounded by palisading lymphocytes and epithelioid and multinucleated giant cells [1,42]. Key histopathological features of EGPA are shown in Fig. 3.

6. Diagnosis

There are no commonly accepted diagnostic criteria for EGPA. Churg and Strauss initially described the syndrome as a necrotizing vasculitis of medium to small sized blood vessels (veins and arteries) associated with eosinophilic infiltration around the vessels and adjacent tissues [1]. The presence of extravascular granulomas was the third criterion in this triad of clinical features, which did not include the presence of either clinical or pathological findings of asthma although all of the patients in the initial description of the syndrome (then named allergic angiitis and granulomatosis) were severe asthmatics.

In 1984, Lanham et al. [35] proposed that patients with EGPA should be characterized by the presence of asthma, eosinophilia, and vasculitic involvement of two or more organs (Fig. 4). In 1990, the American College of Rheumatology (ACR) defined the classification criteria to distinguish between the different vasculitides and identified six criteria for EGPA, namely asthma, eosinophilia >10%, neuropathy, non-fixed lung infiltrates, paranasal sinus abnormalities and extravascular eosinophils on biopsy. When four or more of these criteria are met, vasculitis can be classified as EGPA with a sensitivity of 85% and a specificity of 99.7% [42].

Churg and Strauss (1951)[13]
Pathological material obtained at autopsy
(1) History of asthma
(2) Tissue eosinophila
(3) Systemic vasculitis
(4) Extravascular granulomas
(5) Fibrinoid necrosis of connective tissue

Lanham and colleagues (1984)[6]
Clinical findings with or without pathological material
(1) Asthma
(2) Eosinophila >1·5×10³/L
(3) Evidence of vasculitis that involves at least two organs

American College of Rheumatology (1990)[15]
Clinical findings with or without pathological material; diagnosis probable when four of the six criteria are present
(1) Asthma
(2) Eosinophilia >10%
(3) Neuropathy, mononeuropathy, or polyneuropathy
(4) Pulmonary infiltrates
(5) Paranasal sinus abnormality
(6) Extravascular eosinophil infiltration on biopsy findings

Chapel Hill Consensus Conference (1994)[10]
Pathological and clinical findings
Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotising vasculitis affecting small-to-medium-size vessels and associated with asthma and eosinophilia

Fig. 4. Definitions of Churg–Strauss syndrome.
From: Lancet 2003;361:587-94 and J Allergy Clin Immunol 2001;108:S1-19.

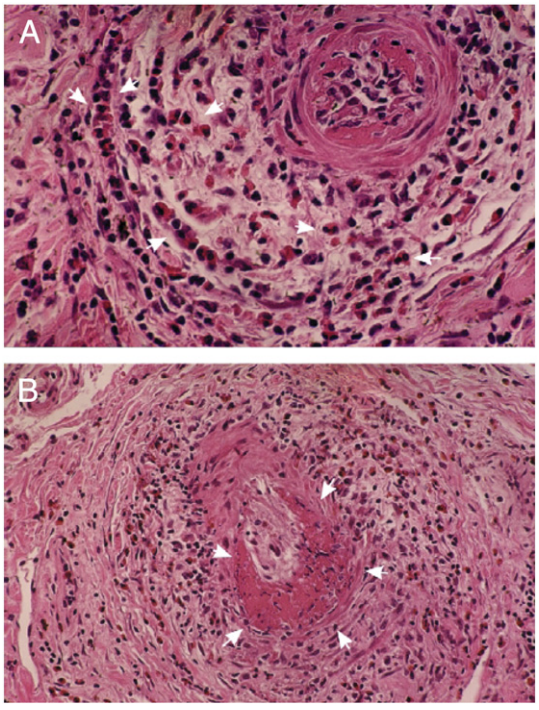

Fig. 3. Tissue biopsy specimens from Churg–Straus patients. (A) Pronounced inflammatory infiltrate consisting of many eosinophils (arrows) with admixed lymphocytes is seen in the media of this small submucosal artery. (B) In addition to great eosinophilic vasculitis, this vessel exhibits striking fibrinoid necrosis of its inner wall (arrows). This appears brightly eosinophilic on haematoxylin and eosin.
From: Lancet 2003;361:587-94 and J Allergy Clin Immunol 1999; 104: 1060–65.

The ACR criteria is the most commonly used set of criteria to diagnose CSA and has not been modified by the Chapel Hill Consensus Conference on the classification of vasculitis in 1994 [3], which calibrated the clinical and histological definitions only (Fig. 4).

6.1. Laboratory findings

Active EGPA is characterized by marked peripheral eosinophilia (usually >1500 cells/μl or >10%).

ANCA may arise several years before the onset of vasculitis [59]. Antineutrophil cytoplasmic antibody-positivity needs to be confirmed by the presence of myeloperoxidase in serum [60].

Although currently there are no validated diagnostic tests for EGPA, new biomarkers are emerging. A recent study demonstrated good diagnostic performance of eotaxin-3, an eosinophil-attracting chemokine, whose serum levels were significantly higher in active EGPA than in a wide range of control groups. At a cut-off level of 80 pg/ml, the sensitivity and specificity of eotaxin-3 for the diagnosis of active EGPA were 87.5% and 98.6%, respectively [22]. This biomarker needs further diagnostic validation but is likely to enter routine clinical practice.

Biopsy of an affected organ is essential to confirm the presence of an eosinophilic inflammatory process or vasculitis. However, characteristic pathological changes need not be present to establish the diagnosis of Churg–Strauss syndrome. To summarize, the diagnosis of CSA is established mainly on clinical grounds.

Eosinophilic granulomatosis with polyangiitis is usually considered a systemic disease. However, 'limited' forms may occur when it is confined to single organs [61], in which case the diagnosis is made on histological grounds.

7. Differential diagnosis

The differential diagnosis of EGPA primarily includes eosinophilic and vasculitic disorders:

- Other forms of ANCA-associated vasculitis (AAV), such as microscopic polyangiitis (MPA) and WG, which share several clinical and histological features with CSA. However, these two diseases differ from Churg–Strauss syndrome clinically by the absence of asthma and pathologically and by the presence of eosinophilia [3,62].

In general, the distinction between EGPA and the other primary systemic vasculitis can be made on the basis of the distinct association of EGPA with asthma and marked blood hypereosinophilia.

Idiopathic hyper-eosinophilic syndrome (HES) is defined as a sustained peripheral blood eosinophilia of unknown origin where eosinophils exceed 1500 cells/mm^3 for more than six consecutive months and are responsible for the development of organ dysfunction and/or damage [63]. Although the organs involved in the two syndromes are similar, HES is characterized by the histological evidence of tissue infiltration by eosinophils, the absence of asthma and vasculitis on biopsy specimens, and ANCA-negative serum [64].

8. Prognosis

In general, CSS has been considered a milder type of systemic vasculitis with lower mortality compared to other types of vasculitis and a remission rate similar to that of GPA but higher than that of MPA [65]. However, if left untreated the mortality of CSS was found to be similar to that of untreated GPA at values approaching 50% at three months [27].

With the introduction of corticosteroid treatment, remission and survival have improved greatly. The French Vasculitis Study Group has identified five prognostic factors, together called the five-factor score (FFS), in patients with necrotizing vasculitis including CSA [66]:

1. elevated serum creatinine levels (>1.58 mg/dl),
2. proteinuria (>1 g per day),
3. gastrointestinal tract involvement,
4. cardiomyopathy, and
5. central nervous system involvement.

In the randomized trial of patients without poor prognosis factors (FFS = 0) [67], survival rates at one and five years were 100% and 97%, respectively. In a trial of patients with poor prognosis factors (FFS ≥ 1) [68], 92% were alive at the 8-year follow-up analysis. Finally, in a recent monocentric retrospective analysis of 150 cases, the 5- and 10-year survival rates were 97% and 89%, respectively [46]. However, disease-related organ damage (e.g., heart failure, chronic neuropathy) may severely impair the quality of life of EGPA patients.

Results of the two studies that assessed long-term outcomes in patients showed that overall remission rates were good and ranged from 81 to 92%. However, 26–28% of patients in remission suffered a relapse [27,69]. and overall mortality in treated patients who relapsed was only 3 · 1% [27].

9. Therapy

The patient's prognostic profile primarily determines the choice of initial therapy. Based on the FFS, the French Vasculitis Study Group has recently conducted two randomized controlled trials, one in patients with poor-prognosis factors (FFS ≥ 1) and the other in patients without poor-prognosis factors (FFS = 0). The results have been published recently [62,63] and can be summarized as follows: patients with an FFS ≥ 1 have a worse prognosis and are usually treated with glucocorticoids and immunosuppressants, whereas glucocorticoid treatment alone is recommended in those with FFS = 0 [67,68].

In CSA patients without poor-prognosis factors (FFS = 0), clinical remission was achieved in 93% of patients with corticosteroid treatment alone [67]. In addition to corticosteroids, medium potent immunosuppressants such as azatioprine or metotrexate may be used for GC sparing and for induction of remission in conjunction with corticosteroids [70].

Corticosteroids are the cornerstone of treatment for Churg–Strauss syndrome. Because these drugs are usually sufficient for treatment of most patients who do not have severe organ involvement, they should be viewed as a first line of therapy without the addition of other immunosuppressive agents.

Usually, 1 mg/kg per day of prednisone or its equivalent is administered orally. Methylprednisolone pulses (15 mg/kg intravenously for three days) may be added in most severe cases. As soon as a clinical response is reached, which is usually in a few weeks, steroids can be tapered off slowly [71].

In patients with poor-prognosis factors (FFS ≥ 1), the addition of 12 cyclophosphamide pulses to corticosteroid treatment was better able to control severe CSA than the six-pulse regimen [68].

On the basis of these results, it has been recommended that CSA patients without poor-prognosis factors (FFS = 0) should be treated with corticosteroids alone [71]. Additional immunosuppressive treatment (azathioprine or cyclophosphamide pulses) is required in case of treatment failure or relapse [71]. Oral cyclophosphamide is given at a dose of 2 mg kg^{-1} day^{-1} for one year in addition to corticosteroids with a monthly intravenous dose of 0 · 6 g/m^2 plus oral corticosteroids [72].

Cyclophosphamide pulses are usually preferable to oral administration because of the lower cumulative dosage. However, the frequency of relapses can be higher with pulses, and it has been shown that oral cyclophosphamide can be efficacious when pulses have failed [71].

In patients with Churg–Strauss syndrome who failed to respond to corticosteroids and immunosuppression, high-dose intravenous immunoglobulins were used in combination with plasma exchange, cyclophosphamide, and glucocorticoids in a pilot trial. All patients achieved remission and the relapse rate was 11% during a follow-up usually exceeding 36 months [73].

Given its ability to halt eosinophil degranulation and Th2 responses in vitro, interferon-a has also been used for EGPA, first in 1998 [74], with promising results.

Mepolizumab, a humanized monoclonal antibody against IL-5, has been used in patients with asthma and eosinophilia. A recent small study of seven patients with steroid-dependent CSS treated with mepolizumab showed that this agent was safe and well-tolerated. It significantly lowered eosinophil counts and enabled patients to significantly decrease the dose of corticosteroids. All patients suffered relapses after the mepolizumab was discontinued [75]. More recently, mepolizumab was used for remission induction in a trial of patients with refractory or relapsing EGPA: eight of the 10 enrolled patients obtained remission and were able to taper glucocorticoid dose below 7.5 mg/day. No patient relapsed during the treatment but the disease flared following mepolizumab withdrawal [20].

Because of the potential side effects of CYC, other alternatives have been explored for the treatment of ANCA-associated vasculitis. The B-cell antagonist monoclonal antibody rituximab seems to be a promising alternative. In theory, this agent could be a therapeutic option for ANCA-positive CSS patients. Although limited to case reports or small case series, there is some evidence that rituximab effectively induced remission in EGPA patients refractory to standard therapy [76,77]. Interestingly, rituximab induced not only clinical remission but also normalization of eosinophil counts and, in one report [78], IL-5 level reduction. Because IL-5 is primarily produced by T cells, this finding implies that B-cell depletion strongly influences T-cell function.

Omalizumab is a recombinant humanized monoclonal anti-immunoglobulin E antibody (IgE) indicated by the Global Initiative for Asthma (GINA) as an add-on therapy in patients with inadequately controlled allergic asthma despite treatment with high-dose inhaled

corticosteroids and long-acting inhaled b2-agonists. Omalizumab inhibits IgE-mediated responses by preventing IgE binding to its receptor on mast cells and basophils, thereby reducing asthma attacks and achieving steroid-sparing results [79,80]. Omalizumab was also successfully used in a CSS patient with residual asthma after the remission of the vasculitic phase [81].

The recent observation that EGPA may respond to Imatinib as well suggests that eosinophilia in EGPA and HES may share pathophysiological mechanisms [82].

However, whether ANCA-positive patients should be treated and/or managed differently from ANCA-negative patients remains to be established.

10. Conclusions

Eosinophilic granulomatosis with polyangiitis is a rare but often severe systemic vasculitis that can affect every organ system. Recently, significant advances have been made in understanding the pathogenesis of Churg–Strauss syndrome. T-cell and B-cell responses along with eosinophil activation play a major role in its pathogenesis, and ANCA is a hallmark of vasculitic disease complications.

CSS is a distinct syndrome that shares many features with other forms of ANCA-associated vasculitis. Based on clinical studies, some authors have suggested that this condition may have two clinical subtypes depending on the presence or absence of ANCA. The first subtype presents with small vessel vasculitic features in ANCA-positive patients. The second subtype presents with peripheral eosinophilia and eosinophil-induced tissue damage in ANCA-negative individuals. The interplay between vasculitis and hypereosinophilia remains enigmatic.

Continued investigation to answer the unresolved questions will lead to better diagnosis, care, and education of patients diagnosed with this potentially debilitating condition.

If appropriately treated, the outcome of EGPA is good. CSS treatment must be tailored to individual patients according to the presence of poor prognostic factors (FFS). A combination of high-dose corticosteroids and cyclophosphamide is still the gold standard for the treatment of severe cases, but the use of biological agents such as rituximab or mepolizumab seems to be a promising therapeutic alternative.

It may be premature to change the therapeutic approach based on the specific clinical subtype of CSS because studies comparing treatment strategies for each group are lacking and the respective global outcomes do not seem to differ significantly. Therefore, it is recommended to treat patients according to the severity of the disease.

Take-home messages

- Churg–Strauss syndrome (CSS) or eosinophilic granulomatosis with polyangiitis (EGPA) is a disseminated necrotizing vasculitis with extravascular granulomas occurring exclusively among patients with asthma and tissue eosinophilia.
- EGPA is still considered an idiopathic condition but is classically considered a Th2-mediated disease. Recent evidence points to B cells and the humoral response as further contributors to EGPA pathogenesis.
- EGPA is thought to evolve through a prodromic phase characterized by asthma, an eosinophilic phase marked by peripheral eosinophilia and organ involvement, and a vasculitic phase with clinical manifestations due to small-vessel vasculitis.
- The American College of Rheumatology identified six criteria for the diagnosis of EGPA: asthma, eosinophilia >10%, neuropathy, nonfixed lung infiltrates, paranasal sinus abnormalities, and extravascular eosinophils on biopsy. Vasculitis can be classified as EGPA when four or more of these criteria are met.
- Patients without poor-prognosis factors are usually treated with glucocorticoids alone, whereas those with a worse prognosis are recommended glucocorticoids and immunosuppressants.

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