

REVIEW ARTICLE

Eosinophilic granulomatosis with polyangiitis (Churg–Strauss): state of the art

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Abstract

Eosinophilic granulomatosis with polyangiitis (Churg–Strauss, EGPA) is a systemic small-vessel vasculitis associated with asthma and eosinophilia. Histology of EGPA shows tissue eosinophilia, necrotizing vasculitis, and eosinophil-rich granulomatous inflammation. EGPA commonly presents with upper airway tract and lung involvement, peripheral neuropathy, cardiac and skin lesions. Antineutrophil cytoplasmic antibodies (ANCA) are positive in ~40% of the cases and more often in patients with clinical manifestations due to small-vessel vasculitis. The pathogenesis of EGPA is multifactorial: the disease can be triggered by exposure to allergens or drugs, but a genetic background has also been recognized, particularly an association with HLA-DRB4. Th2 responses are prominent, with up-regulation of IL-4, IL-13, and IL-5; however, Th1 and Th17 responses are not negligible. Eosinophils are activated, have a prolonged lifespan and probably cause tissue damage by releasing their granule proteins; their tissue recruitment can be regulated by chemokines such as eotaxin-3 and CCL17. Humoral immunity is also dysregulated, as demonstrated by prominent IgG4 and IgE responses. EGPA promptly responds to glucocorticoid therapy, although combinations of glucocorticoids and immunosuppressants (e.g., cyclophosphamide, azathioprine) are eventually required in most cases. Newer therapeutic options include the anti-IL5 antibody mepolizumab, whose efficacy has been described in small clinical trials, and the B-cell-depleting agent rituximab, reported in several case series.

In 1951, Churg and Strauss (1) first described a syndrome characterized by asthma and a 'strikingly uniform clinical picture' with 'fever and eosinophilia, and symptoms of cardiac failure, renal damage and peripheral neuropathy resulting from vascular embarrassment in various systems of organs'. Histology of the 13 cases examined by Churg and Strauss (1) was quite similar: in most organs, they found tissue eosinophilia, necrotizing and granulomatous vascular lesions and extravascular granulomas. These features identified a syndrome that could be distinguished from classical polyarteritis nodosa and also by granulomatosis with polyangiitis (Wegener's, GPA). Named Churg–Strauss syndrome for many years, this entity has now been recognized by the 2012 revised nomenclature for vasculitides as eosinophilic granulomatosis with polyangiitis (Churg–Strauss, EGPA) (2).

The histological lesions observed by Churg and Strauss in most of the affected sites were extremely severe; it must be considered that most were autopsy cases, and thus, large biopsy specimens were obtained, facilitating detection of the histological hallmarks of EGPA; in addition, glucocorticoid treatment was not available at that time. Glucocorticoids have dramatically changed the prognosis of EGPA; most patients receive glucocorticoids before diagnosis, which may also account for the apparently lower severity of the histopathological lesions we observe today (1, 3).

The knowledge on EGPA has recently evolved: antineutrophil cytoplasmic antibodies (ANCA) were found in a proportion of EGPA patients, and therefore, EGPA has been included in the spectrum of ANCA-associated vasculitis (AAV) together with GPA and microscopic polyangiitis (MPA) (4), and multiple attempts have been made to provide

classification criteria. Several studies have elucidated the role of immune mechanisms (5, 6) and identified genetic associations such as that with HLA-DRB4 (7, 8). New potential diagnostic biomarkers (e.g., eotaxin-3) and predictors of outcome have been recognized (9–11). Finally, treatment approaches have been refined, thanks to the use of immunosuppressants and newer biologic therapies. The B-cell-depleting agent rituximab has been used in single patients, while the anti-interleukin (IL)-5 antibody mepolizumab has proven efficacious in two pilot trials (12).

We here provide an overview of EGPA, particularly focusing on recent advances in pathogenesis, diagnosis, and treatment.

Classification criteria and definitions for EGPA

There are no commonly accepted diagnostic criteria for EGPA. In 1984, Lanham et al. (13) proposed that patients with EGPA should have asthma, eosinophilia, and vasculitic involvement of two or more organs (Table 1). In 1990, the American College of Rheumatology (ACR) defined the classification criteria to distinguish the different vasculitides and identified six criteria for EGPA, namely asthma, eosinophilia >10%, neuropathy, nonfixed 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% (14). However, as the ACR criteria were established for classification (and not diagnostic) purposes, they can only be used in patients with a diagnosis of vasculitis to define the type of vasculitis. In 1993, the Chapel Hill consensus confer-

ence produced mutually exclusive clinico-pathological definitions for primary vasculitides (4) (Table 1).

Epidemiology

Eosinophilic granulomatosis with polyangiitis is a rare disease, with an annual incidence of 0.5–4.2 cases/10⁶ inhabitants (15), which has been reported to be stable in the past years (16), and a prevalence of 11–14 cases/10⁶ inhabitants (17, 18). EGPA usually arises in people aged 40–60 years, the mean age at diagnosis being 49 years (19); pediatric cases have also been reported (20). No gender predominance, familial clustering, or ethnic predisposition have clearly been demonstrated (21).

Genetic and environmental factors

Immunogenetic factors may confer susceptibility to EGPA. The HLA-DRB1*04 and *07 alleles and the related HLA-DRB4 gene are associated with an increased risk of developing EGPA (7, 8). The finding of a skewed HLA repertoire, as in other autoimmune conditions, supports the hypothesis of an antigen-driven disease. Interestingly, the ANCA-negative subset of EGPA was found to be associated with the IL10.2 haplotype of the *IL10* gene promoter, which functionally translates into an increased IL-10 expression (22). Other single nucleotide polymorphisms showed only little or no effect on the susceptibility to EGPA (23–25).

Eosinophilic granulomatosis with polyangiitis was long suspected to be triggered by exogenous factors including environmental agents, infections, vaccinations, and drugs. Exposure to particulate silica was a risk factor for EGPA, as it was for other AAVs, although patient numbers were small (26). The role of infections and vaccinations in EGPA is still elusive, and no single infectious agent or type of vaccination proved to have a causal role. Numerous studies have described the development of EGPA following treatment with different drugs, such as macrolide antibiotics (27) and particularly leukotriene receptor antagonists (LTRAs) (28).

Different hypotheses have been made to explain how LTRAs can induce EGPA in patients with asthma: (i) they can unmask smouldering forms of EGPA because their use allows steroid tapering; (ii) they have a direct pathogenetic role or cause an allergic, idiosyncratic reaction; (iii) the association between LTRAs and EGPA, although temporarily related, may be simply coincidental, and the progression from asthma to full-blown EGPA may reflect the phasic nature of the disease, which initially shows allergic manifestations and subsequently eosinophilic and vasculitic complications (29). A reduction in steroid dose surely provides a feasible causal link between LTRAs and EGPA; this is also supported by the observations that other steroid-sparing drugs used for asthma such as theophylline, cromolyns (30), and the anti-IgE antibody omalizumab (31) apparently precipitate EGPA. An elegant case-crossover study by Hauser et al. (32) further confirms this hypothesis. However, in a recent analysis of suspected drug-induced EGPA registered in the FDA Adverse Event Reporting System database, EGPA

Table 1 Classification criteria and definitions commonly used for eosinophilic granulomatosis with polyangiitis (Churg–Strauss, EGPA): Lanham's criteria, ACR classification criteria and Chapel Hill definition

Lanham et al. (13)

Asthma

Eosinophilia >1.5 × 10⁹/l

Clinical or pathological evidence of vasculitis involving at least two organs

ACR 1990* (14)

Asthma

Eosinophilia >10%

Neuropathy (mono- or poly-neuropathy)

Non-fixed pulmonary infiltrates

Paranasal sinus abnormalities

Extravascular eosinophil infiltration on biopsy

Chapel Hill Consensus Conference 1994 (4)

Eosinophil-rich and granulomatous inflammation involving the respiratory tract, necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and eosinophilia.

*At least four of the six ACR criteria are required to classify vasculitis as EGPA.

ACR, American College of Rheumatology

emergence did not follow—in most patients—glucocorticoid tapering or withdrawal (33).

Pathogenesis

Although the events starting the disease process are poorly understood, recent research improved our understanding of the pathophysiology of the eosinophilic and vasculitic responses in EGPA. The asthmatic and eosinophilic components clearly suggest an activated and skewed T-cell balance. Indeed, T-cell activation and (oligo-)clonal expansion was identified in active EGPA (34).

Eosinophilic granulomatosis with polyangiitis is classically considered a Th2-mediated disease. Peripheral T-cell lines from EGPA patients can produce Th2-associated cytokines (e.g., IL-4, IL-13) (35); IL-5 also seems to be up-regulated in active EGPA (36, 37), additionally evidenced by beneficial effects of IL-5 inhibition in EGPA patients (38). T cells positive for the Th2 marker CD294 were found to be abundant in EGPA paranasal sinus biopsies (5), and cells obtained from broncho-alveolar lavage (BAL) fluid of patients with active EGPA also showed a Th2-skewed functional profile, given their high transcript levels of Th2 cytokines (particularly IL-4, IL-5, IL-10) (36). Tissue recruitment of Th2 cells is likely to be mediated by specific chemokines such as CCL17, most likely produced by dendritic cells (5); interestingly, CCL17 serum levels strongly correlate with peripheral eosinophil counts (39). However, the clinical phenotype of EGPA cannot be explained by an exaggerated Th2 response alone. For instance, asthma often paradoxically improves in

the full-blown vasculitic phase of the disease. Well fitting, there is evidence of involvement of Th1 and also Th17 cells secreting high amounts of IL-17A in the late EGPA phases (35, 37). Moreover, regulatory T cells are diminished during active disease (40). Whether these cells are localized in the affected tissues or act systemically is yet unknown.

Eosinophils are abundant both in the periphery and in EGPA lesions. Eotaxin-3, produced by epithelial and endothelial cells, might contribute to tissue influx of eosinophils (11, 41). 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 (6).

Recent evidence points to B cells and the humoral response as further contributors to EGPA pathogenesis. First evidence came from the observation of myeloperoxidase (MPO)-specific ANCA in ~40% of the patients. Also, the B-cell-depleting agent rituximab has shown promising results in small patient series (42, 43). Further, strong elevation of IgE levels is common in EGPA, and recently, a dramatic increase in serum IgG4 in active EGPA became evident (44). Not surprisingly, the aforementioned cytokines (i.e., IL-4, IL-13) boost the humoral immune response and especially IgG4 production. IgG4 antibodies cannot sufficiently activate the complement and weakly bind to Fc γ receptors, and therefore, their pathogenic role is currently unclear.

The main immune mechanisms of EGPA are schematically depicted in Fig. 1.

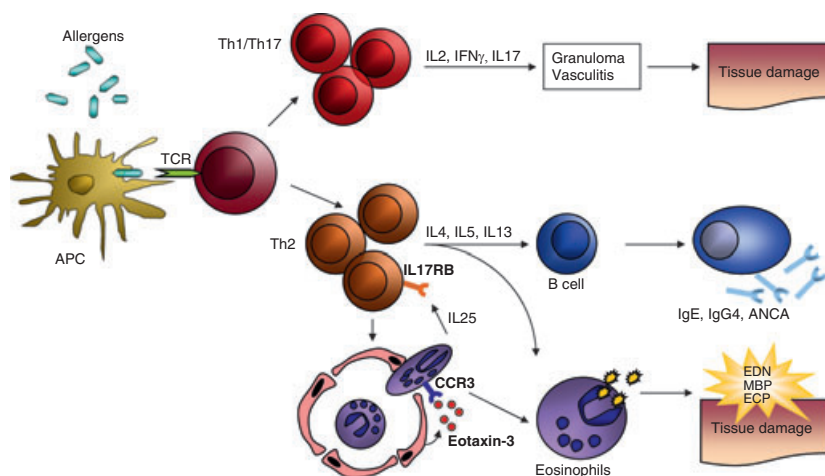


Figure 1 Simplified scheme of pathophysiological events in eosinophilic granulomatosis with polyangiitis (EGPA) (Churg–Strauss). Hitherto unidentified allergens elicit an adaptive immune response in EGPA patients. T cells secrete Th1- (IFN- γ), Th17- (IL-17) and Th2- (IL-4, IL-13, IL-5) associated cytokines and activate eosinophils. The strong Th2 immune response precipitates a B-cell response resulting in IgG4, IgE and antineutrophil cytoplasmic antibodies (ANCA) production. Increased

expression and secretion of eotaxin-3 guides eosinophils to the endothelium and tissues. Eosinophils in turn maintain a vicious circle of T-cell activation by secreting IL-25. Local degranulation of activated eosinophils finally causes damage, necrosis and fibrosis to tissues and vessels. APC, antigen-presenting cell; TCR, T-cell receptor; ANCA, anti-neutrophil cytoplasmic antibody; EDN, eosinophil-derived neurotoxin; MBP, major basic protein; ECP, eosinophilic cationic protein.

Clinical manifestations and laboratory findings

Eosinophilic granulomatosis with polyangiitis is traditionally described to evolve through a prodromic, allergic phase characterized by asthma and rhino-sinusitis, a eosinophilic phase hallmarked by peripheral eosinophilia and organ involvement, and a vasculitic phase with clinical manifestations due to small-vessel vasculitis (45). These phases partially overlap and may not appear in such a defined order, although asthma and rhino-sinusitis only rarely arise after the vasculitic manifestations (46).

The typical case that should raise suspicion of EGPA is that of a patient with adult-onset asthma and a history of rhino-sinusitis, who develops pronounced eosinophilia and lung infiltrates. Eosinophilia may occur in asthmatic patients but is usually mild (<10%); likewise, lung infiltrates due to bronchial plugging by mucus and superimposed infection may complicate asthma, but they remain uncommon (46).

Main clinical manifestations

Eosinophilic granulomatosis with polyangiitis is usually considered a systemic disease; however, 'limited' forms may occur when it is confined to single organs (47); in such

cases, the diagnosis is made on histological grounds. Asthma is found in 95–100% of patients and may precede the systemic disease manifestations of many years. It generally arises in adulthood, and its severity varies (45); unlike in classical bronchial asthma, in EGPA, it does not show the typical seasonal exacerbations (48). Allergic rhinitis, recurrent sinusitis, and nasal polyposis also hallmark the prodromic EGPA phases (Fig. 2) (49); nasal polyps affect 50% of the patients and systematically recur after surgery in patients not receiving immunosuppressive therapy (50). Other otolaryngological manifestations include secretive otitis media, chronic ear drainage, sensorineural hearing loss, and facial nerve palsy.

The eosinophilic phase is characterized by lung, cardiac, and gastrointestinal involvement. Involvement of the lung parenchyma occurs in up to two-thirds of EGPA patients (51). Chest X-ray abnormalities generally consist of mainly peripheral, patchy, and migratory infiltrates. On high-resolution CT, they appear as ground-glass opacities or poorly defined areas of consolidation (Fig. 2), which often coexist with abnormalities due to lower airway involvement, such as tree-in-bud signs, bronchial wall thickening and small centrilobular nodules (52). Alveolar hemorrhage affects 3–8% of the patients (53, 54). Pleural effusion, secondary to

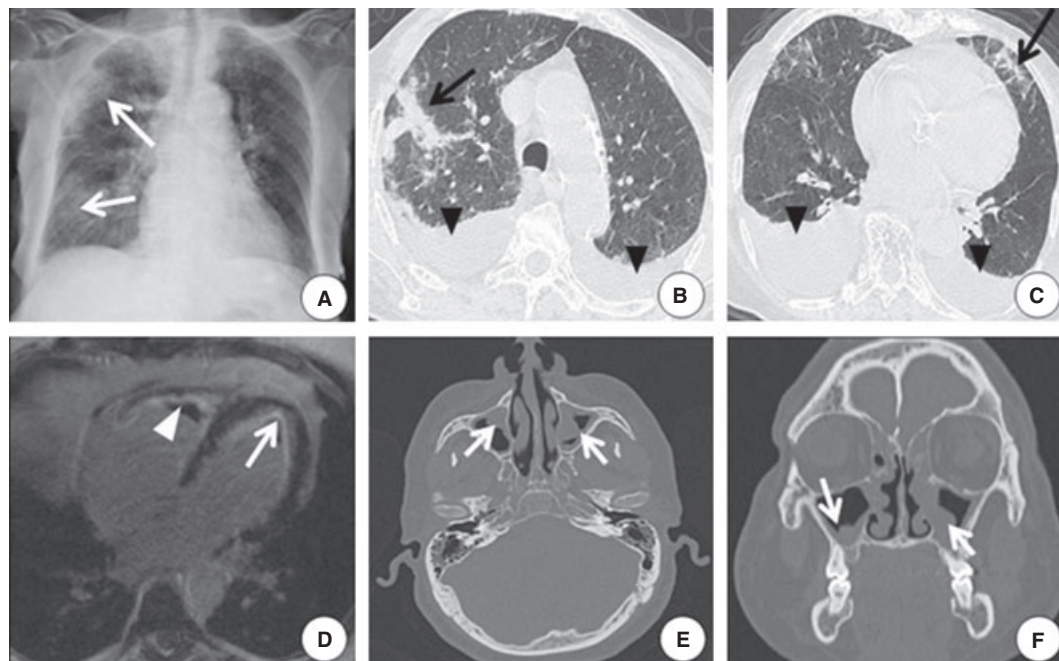


Figure 2 Representative imaging findings in patients with eosinophilic granulomatosis with polyangiitis (EGPA) (Churg–Strauss). (A) The chest radiograph shows peripheral patchy consolidation in the right lung (arrows). (B,C). High-resolution computed tomography (HRCT) images show peripheral consolidation (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.

eosinophilic pleuritis or eosinophilic cardiomyopathy-related congestive heart failure, may also be found (Fig. 2).

Heart involvement, particularly when clinically evident, is a well-known adverse prognostic factor (19, 55). In a retrospective analysis of 49 patients, 22 (45%) had clinical evidence of cardiac disease; of these, 13 had MRI or histological proof of endomyocarditis, which was associated with impaired cardiac function and occasionally intra-cardiac thrombus formation (56). Peripheral eosinophilia is more pronounced in patients with cardiac damage: early lesions, dominated by eosinophilic infiltration, likely progress to fibrotic changes with consequent restrictive cardiomyopathy. Although endomyocardial infiltration is the dominant picture (Fig. 2), coronary vasculitis, pericarditis, and valvular defects may also occur (57). Additionally, patients with EGPA are at increased risk of venous thrombo-embolic events, such as deep venous thrombosis and/or pulmonary embolism (58). Gastro-intestinal involvement is also often due to eosinophilic infiltration of the gastrointestinal mucosa and more frequently affects the small bowel; patients present with otherwise unexplained abdominal pain, and sometimes digestive hemorrhage. In rare cases, acalculous cholecystitis is the dominant manifestation (59–61).

The vasculitic phase is heralded by constitutional symptoms (e.g., fever, weight loss, fatigue) and often by an apparently paradoxical improvement of asthma. Peripheral neuropathy is a cardinal feature of this phase, affecting 70% of the patients (54, 60, 62). It is characterized by axonal damage on electrophysiological studies and frequently affects the peroneal, tibial, ulnar, and median nerves; the most common pattern is mononeuritis multiplex, often complicated by asymmetric foot or wrist drop, but it may also evolve as a symmetric or asymmetric polyneuropathy (63); sensory deficits and neuropathic pain are also frequent (63, 64).

Renal manifestations are found in 25% of the patients, and range from isolated urinary abnormalities (i.e., microscopic hematuria, proteinuria) to rapidly progressive glomerulonephritis. Histology shows crescentic necrotizing pauci-immune glomerulonephritis, which is often less severe than that observed in the other AAVs (3). Skin lesions, particularly purpura, are also a prominent feature of the vasculitic phase; purpura occurs in 25% cases and usually involves the lower limbs. Nodules, urticaria, livedo, and skin ulcers are also reported (3, 60).

The vasculitic or generalized phase of the disease does not necessarily include only the aforementioned organ manifestations. For instance, cardiac involvement also frequently occurs in this phase; its prognostic impact is deep, in fact EGPA-related heart failure was the strongest predictor of mortality in a large retrospective cohort (19).

Disease subsets

The clinical phenotype of EGPA is varied. However, its clinical manifestations tend to segregate into two major disease subsets, dominated respectively by vasculitic and eosinophilic manifestations. ANCA can differentiate these two subsets. Two large studies demonstrated that ANCA were positive in

38% of EGPA patients and that ANCA-positive patients more frequently had peripheral neuropathy, glomerulonephritis, and purpura (which are due to small-vessel vasculitis), whereas endo-myocardial involvement and lung infiltrates prevailed in the ANCA-negative subset (54, 60) (Table 2). A more recent study, performed on EGPA cases reported in the adverse event database of the US Food and Drug Administration, compared ANCA-negative EGPA patients and EGPA patients positive for anti-MPO-ANCA, providing results comparable with those of the previous two studies (65) (Table 2). These observations raise the question as to whether ANCA contribute to the development of vasculitis in EGPA. Further studies are needed to determine the prognostic role of ANCA and whether treatment needs to be tailored on the ANCA status.

Laboratory findings

Active EGPA is characterized by marked peripheral eosinophilia (usually >1500 cells/ μ l or >10%). Eosinophilia correlates with disease activity, and relapses are often heralded by its increase (66). C-reactive protein and erythrocyte sedimentation rate are also high in the active phase. Serum IgE levels are elevated in most patients but lack specificity for common allergens (48). Recent data show that serum IgG4 are high in 75% of active EGPA patients and that they correlate with disease activity better than IgE do (44). ANCA may arise several years before the onset of vasculitis (67); a perinuclear immunofluorescence pattern (P-ANCA) is found in 74–90% of ANCA-positive EGPA cases and usually corresponds—using ELISA—to anti-MPO antibodies; the remaining cases have cytoplasmic-ANCA (C-ANCA) that correspond to anti-proteinase-3 antibodies or mixed (C + P) patterns (54).

Although there are no validated diagnostic tests for EGPA, new biomarkers are emerging. A recent study demonstrated a good diagnostic performance of eotaxin-3, a eosinophil-attracting chemokine; its serum levels were significantly higher in active EGPA than in a wide range of control groups [e.g., AAVs, hypereosinophilic syndromes (HESs)]. Importantly, all patients with HES investigated in this study had active disease at the time of blood sampling. At a cut-off level of 80 pg/ml, the sensitivity and specificity of eotaxin-3 for the diagnosis of active EGPA were, respectively, 87.5% and 98.6% (11). This biomarker needs diagnostic validation but is likely to enter routine clinical practice.

Pathology

The key histological features of EGPA are tissue eosinophilia, necrotizing vasculitis, and extravascular eosinophilic granulomas. Vasculitis is characterized by fibrinoid necrosis and eosinophilic vessel wall infiltration. Granulomas may 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, 14). The pathology of EGPA, however, varies at different sites. Lung lesions may show all the aforementioned features, whereas

Table 2 Major organ manifestations and ANCA status in three published series of patients with EGPA (Churg–Strauss).

	Sablé-Fourtassou et al. (60)			Sinico et al. (54)			Healy et al. (65)		
	ANCA+ (n = 43) (%)	ANCA– (n = 69) (%)	P-value	ANCA+ (n = 35) (%)	ANCA– (n = 58) (%)	P-value	MPO-ANCA+ (n = 15) (%)	ANCA– (n = 55) (%)	P-value
Asthma	100	100	ns	97	95	ns	100	100	ns
Sinusitis	76	53	0.01	77	78	ns	60	64	ns
Lung involvement, all kinds	56	71	ns	34	60	0.02	40	76	<0.01
Alveolar hemorrhage	7	7	ns	20	0	0.001	na	na	na
Heart involvement	12	49	<0.001	6	22	<0.01	0	38	<0.01
Gastrointestinal involvement	42	26	ns	20	22	ns	0	14	0.03
Skin involvement, all kinds	53	51	ns	60	48	ns	67	62	ns
Purpura	39	20	0.03	26	7	0.02	53	40	ns
Peripheral neuropathy, all kinds	84	65	0.03	71	60	ns	73	42	0.02
Mononeuritis multiplex	na	na	na	51	24	0.01	na	na	na
CNS involvement	12	7	ns	17	12	ns	20	13	ns
Renal involvement, all kinds	35	4	<0.001	51	12	<0.001	33	16	ns
RPGN/biopsy-proven GN	19	0	<0.001	29	5	<0.01	na	na	na
Vasculitis on biopsy	79	39	<0.001	76	32	<0.001	81	61	ns

ANCA, anti-neutrophil cytoplasmic antibodies; MPO-ANCA, myeloperoxidase-ANCA; CNS, central nervous system; RPGN, rapidly progressive glomerulonephritis; GN, glomerulonephritis; ns, not significant; na, not available; EGPA, eosinophilic granulomatosis with polyangiitis.

cardiac pathology usually shows endo-myocardial and pericardial eosinophilic infiltration and only rarely coronary vasculitis; likewise, gastrointestinal involvement histologically shows eosinophilic gastroenteritis and, in some cases, mesenteric vasculitis leading to bowel ischemia (45, 59). Conversely, kidney lesions show focal crescentic glomerulonephritis but only rarely eosinophilic infiltration or granulomas (45). Peripheral neuropathy also features epineural lymphocytic vasculitis with rare eosinophils, and purpura is due to leukocytoclastic vasculitis of dermal vessels but usually lacks granulomatous or eosinophilic reactions. Key histopathological features of EGPA are shown in Fig. 3.

Differential diagnosis

The differential diagnosis of EGPA essentially includes eosinophilic and vasculitic disorders. The HESs are characterized by persistent and pronounced eosinophilia (generally >1500/ μ l), organ involvement and absence of 'reactive' forms of eosinophilia (particularly parasitic and viral infections, drugs, allergy, neoplasms, autoimmune, or immune-mediated diseases) (68). A recent pathogenesis-driven classification of the HESs subdivides them into the following main groups: (i) myeloid and lymphoid neoplasms with eosinophilia and associated abnormalities of *PDGFRA*, *PDGFRB* or *FGFR1* (e.g. the *FIP1L1-PDGFRFA* fusion gene); (ii) chronic eosinophilic leukemia or other myeloid neoplasms associated with eosinophilia that lack recognized genetic abnormalities; (iii) lymphocytic variant of HES (where a lymphocyte clone

abnormally produces eosinophil hematopoietins such as IL-5 or IL-3); (iv) idiopathic HES (68, 69). Therefore, a careful hematologic and molecular work-up is needed to distinguish these forms. They (in particular idiopathic HES) may substantially overlap with EGPA: cardiac and pulmonary manifestations may be similar in idiopathic HES and EGPA, while idiopathic HES patients rarely have asthma or polyps (39) and vasculitic complications (e.g., purpura, glomerulonephritis, neuropathy); tissue biopsies do not show vasculitis in idiopathic HES and ANCA are typically negative (70). Particularly challenging is the differentiation of ANCA-negative EGPA and HES. In a recent study comparing patients with ANCA-negative EGPA and *FIP1L1-PDGFRFA*-negative HES, none of the tested serum biomarkers (sIL2R, IL-5, IL-6, IL-8, IL-10, CCL17, eotaxin-1) could differentiate the two patient groups (39). As cited above, we found that eotaxin-3 might indeed differentiate active EGPA from various forms of HES as well as other allergic or immune-mediated diseases associated with eosinophilia (11, 41).

Allergic bronchopulmonary aspergillosis (ABPA) may mimic a respiratory tract-limited EGPA; isolation of *Aspergillus* spp. on BAL or sputum and high serum levels of *Aspergillus fumigatus*-specific IgE are diagnostic of ABPA (71). Acute eosinophilic pneumonia is also hallmarked by pulmonary infiltrates and a eosinophil-rich BAL fluid, but usually presents as an acute febrile illness with respiratory failure, lacks peripheral eosinophilia and other organ manifestations (72). Chronic eosinophilic pneumonia is more insidious and patients may have asthma, peripheral eosinophilia and

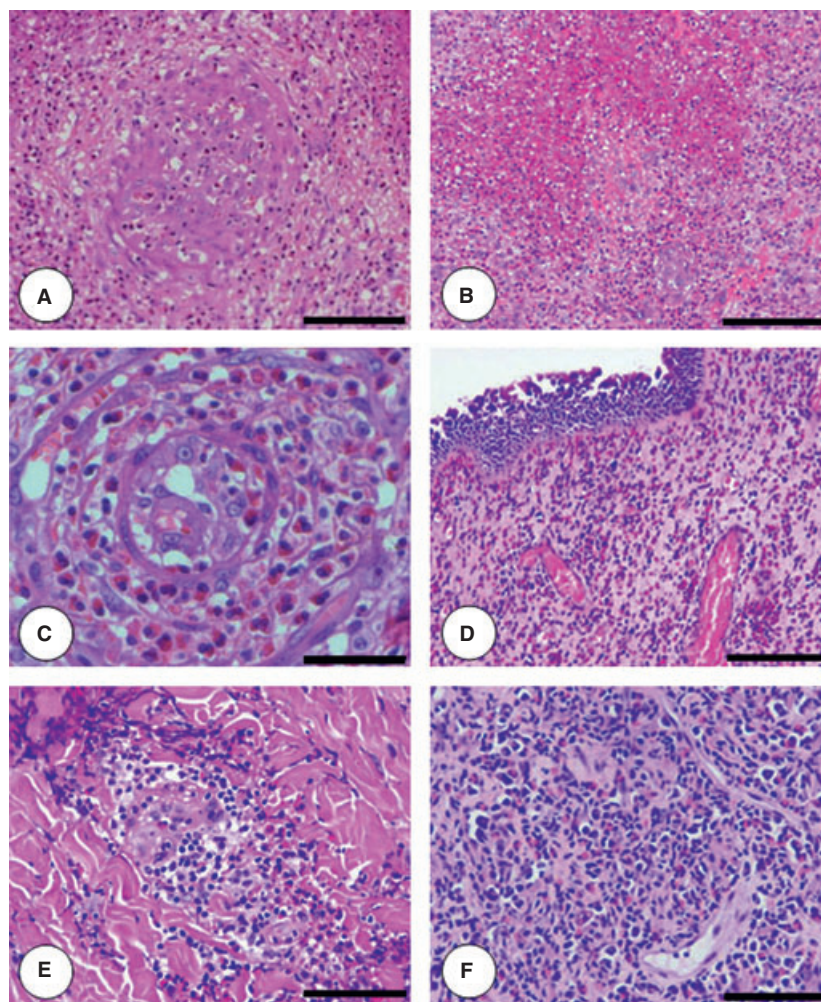


Figure 3 Representative histological findings in patients with eosinophilic granulomatosis with polyangiitis (EGPA) (Churg–Strauss). (A) Granulomatous necrotizing vasculitis with intense eosinophil infiltration (intestinal biopsy). (B) Massive eosinophilic infiltration with a large area of geographic necrosis (intestinal biopsy). (C) Vasculitis of a small artery showing transmurial eosinophil infiltration (intestinal biopsy). (D) Marked eosinophil infiltration

of the nasal mucosa in a patient with EGPA-related nasal polyposis. (E) Lympho-monocytic vasculitis with sparse eosinophils in a patient with cutaneous vasculitis. (F) Diffuse lympho-monocytic and eosinophil dermal infiltration in a patient with skin nodules. A through F: hematoxylin and eosin. Original magnification: A, $\times 20$; B, $\times 10$; C, $\times 40$; D, $\times 10$; E, $\times 20$; F, $\times 20$. Bar is 100 μm in (A, E, F), 200 μm in (B, D), and 50 μm in (C).

systemic symptoms such as weight loss, night sweats and fever. The absence of other organ manifestations and of ANCA may help differentiate it from EGPA (72). Among eosinophilic disorders, those secondary to parasitic infections and drug hypersensitivity also need to be ruled out.

Eosinophilic granulomatosis with polyangiitis must be differentiated from other small-vessel vasculitides. GPA may indeed overlap with EGPA, particularly in cases with eosinophilia: differential features include ANCA specificity (C-ANCA/proteinase-3 ANCA being more frequent in GPA) and the presence, in GPA, of lung cavitated nodules, nasal crusts and nasal and paranasal sinus bone erosions (45). MPA, although usually associated with P-ANCA/MPO-ANCA as is EGPA, rarely shows pronounced eosinophilia

and upper airway tract involvement, whereas its renal complications are often more severe than those of EGPA.

Finally, given the recent observation of raised IgG4 in EGPA, its differential diagnosis should also include the so-called IgG4-related disease, which may present with allergic manifestations, eosinophilia, lung infiltrates and sinusitis. Tissue biopsies in the IgG4-related disease reveal storiform fibrosis, obliterative phlebitis, in absence of vasculitis or eosinophilic granulomas (73, 74).

Treatment and outcome

There is no consensus regarding the use of a staged, remission-induction and remission-maintenance approach in

EGPA. The patient's prognostic profile primarily determines the choice of the initial therapy; the Five-Factor Score (FFS), the most widely used prognostic score in EGPA, includes heart, gastro-intestinal and central nervous system involvement, proteinuria >1 g/24 h, and creatinine >140 μ M/l (10). As patients with an FFS ≥ 1 have a worse prognosis, they are usually treated with glucocorticoids and immunosuppressants, whereas glucocorticoids alone are recommended in those with FFS = 0 (75, 76). This approach, however, has been challenged by other authors, who recommend the use of combination of immunosuppressants and glucocorticoids as first-line therapy also for patients with peripheral neuropathy and eosinophilic alveolitis or alveolar hemorrhage (19).

Cyclophosphamide has been successfully used for remission induction in patients with FFS ≥ 1 in a randomized controlled trial comparing six and 12 cyclophosphamide pulses given along with glucocorticoids; the two regimens were equally effective in inducing remission, but relapses (especially minor) prevailed in the 6-pulse group (75). Methotrexate has also been used for induction in a non-randomized trial: remission was achieved in 73% of the cases, but it was maintained in only 50% of those included in the long-term follow-up analysis (77). In keeping with these data, a more recent study showed that $>50\%$ of patients (previously treated with mepolizumab) relapsed while on methotrexate maintenance (78).

In a trial of patients with FFS = 0, remission was obtained with glucocorticoids alone in $>90\%$ cases but relapses occurred in 35% of them during glucocorticoid tapering; patients with treatment failures or relapses randomly received azathioprine or cyclophosphamide as adjunctive therapy, with no significant differences in outcome (76).

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 (79).

Given its ability to halt eosinophil degranulation and Th2 responses *in vitro*, interferon- α has also been used for EGPA, first in 1998 (80), with promising results. In a more recent pilot trial of seven patients with refractory disease, all achieved remission after 3 months of interferon- α therapy (81). These patients were included with an additional seven in a long-term follow-up study evaluating interferon- α as maintenance treatment: after a median follow-up of 64 months, only three patients were still receiving interferon- α whereas the remaining ones had discontinued it due to lack of efficacy and/or adverse events (82).

Recent trials have demonstrated that targeting IL-5, the major survival factor for eosinophils, significantly reduces exacerbations in asthmatic patients with sputum eosinophilia and allows glucocorticoid tapering in HES patients without *FIP1L1-PDGFR α* mutation (83). These results prompted the use of anti-IL5 therapy in EGPA. Initially reported to be effective in a refractory EGPA case (84), the anti-IL5 antibody mepolizumab was given in a small trial to seven steroid-dependent patients (85): mean eosinophil counts

decreased by 75% and glucocorticoids were safely reduced (from a mean dose of 18.8 to 4.6 mg) in all seven subjects. However, EGPA manifestations recurred on drug cessation; the drug tolerability and safety were good. 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 treatment, but again disease flares followed mepolizumab withdrawal (38).

B-cell depletion with rituximab effectively induces remission in the AAVs. Rituximab was given to EGPA patients refractory to standard therapy, although most studies are limited to case reports or small case series (42, 86); in these cases rituximab effectively induced remission, and in only two patients the treatment course could not be completed because of bronchospasm. Rituximab was also used for EGPA-related renal disease in a pilot trial of three patients, all of whom achieved remission (42). Interestingly, rituximab induced not only clinical remission but also normalization of eosinophil counts and, in one report (43), IL-5 level reduction. As IL-5 is essentially produced by T cells, this finding implies that B-cell depletion strongly influences T-cell function.

The main clinical trials conducted in EGPA are summarized in Table 3. It is important that the trial results be interpreted in light of the selection criteria used for enrollment, which are briefly summarized in the same table.

The outcome of EGPA is good with respect to mortality. In the randomized trial of patients without poor prognosis factors (76), survival rates at 1 and 5 years were respectively 100% and 97%; in the trial including patients with poor prognosis factors (75), 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 (19). However, disease-related organ damage (e.g. heart failure, chronic neuropathy) may severely impair the quality of life of EGPA patients. Immunosuppressive treatment can also contribute to morbidity, particularly favouring malignancies and infections. In the aforementioned retrospective analysis of 150 patients, followed for a median of 53 ± 5 months, the authors reported seven solid organ malignancies and four non-melanoma skin cancers, along with 31 infections requiring hospitalization (e.g. bacterial pneumonia, *Pneumocystis jiroveci* pneumonia, CMV infection). Interestingly, the glucocorticoid dose was identified as a major risk factor for infection (19). Other glucocorticoid-related complications such as osteoporosis, cataract and diabetes were also frequent, which underscores the importance of investigating new treatment strategies able to achieve complete and durable remission and to reduce exposure to glucocorticoids.

Conclusions

Eosinophilic granulomatosis with polyangiitis is a rare but often severe systemic vasculitis which can affect almost every organ system; T-cell and B-cell responses along with

Table 3 Clinical trials performed in patients with EGPA (Churg–Strauss)*

Author, Year (ref)	Treatment(s)	Study design	Enrollment criteria	No. of patients	Study objective(s)	Main outcomes
Metzler et al., 2004 (77)	MTX (0.3 mg/kg/week) + PDN (variable dose)	Prospective, open-label trial	Newly diagnosed or relapsing patients with no immediately critical organ-threatening disease	11 (remission induction) and 23 (remission maintenance)	Induction of remission and remission maintenance	73% (8/11) patients achieved remission, 48% (11/23) relapsed while on maintenance treatment
Danieli et al., 2004 (79)	IVIg (2 g/kg) synchronized with PEX (6 monthly cycles followed by 3 bi-monthly cycles) + CYC (2 mg/kg/day) + PDN (initial dose, 1 mg/kg/day)	Prospective, open-label trial	Newly diagnosed patients	9	Induction of remission and long-term follow-up	100% (9/9) patients achieved remission, 11% (1/9) relapsed during treatment
Cohen et al., 2007 (75)	GCs (3 MP pulses followed by PDN at initial dose of 1 mg/kg/day) + CYC (6 or 12 pulses of 0.6 g/m ²)	Randomized controlled trial	Newly diagnosed patients with ≥ 1 poor prognosis factors†	48	Comparison of 6 vs 12 CYC pulses in induction of remission and prevention of relapses	Non-significant difference in remission induction rates (91% in the 6-pulse and 84% in the 12-pulse group); more frequent relapses in the 6-pulse (86%) than in the 12-pulse (62%) group
Ribi et al., 2008 (76)	PDN (1 mg/kg/day) alone for induction, plus CYC iv pulses or oral AZA for maintenance	Randomized controlled trial	Newly diagnosed patients without poor prognosis factors†	72	Induction of remission with PDN alone, and comparison of CYC vs AZA as adjunctive therapy for failure or relapse	93% (67/72) patients achieved remission, 35% (25/72) relapsed during treatment; 19 were randomized to either AZA ($n = 10$) or CYC ($n = 9$) with no significant outcome differences
Metzler et al., 2008 (81)	IFN- α (3×10^6 IU thrice weekly)	Prospective, open-label trial	Patients refractory to standard therapy with GCs plus CYC or MTX	7	Induction of remission	100% (7/7) patients achieved remission and were able to taper GCs
Jones et al., 2009 (86)	Rituximab (375 mg/m ² /week $\times 4$ weeks or 1 g $\times 2$)	Retrospective multicentre survey	Patients with refractory disease	5	Induction of remission	5/5 achieved remission with 4/5 relapsing within 24 months

Table 3 (continued)

Author, Year (ref)	Treatment(s)	Study design	Enrollment criteria	No. of patients	Study objective(s)	Main outcomes
Metzler et al., 2010 (82)	IFN- α (3×10^6 IU thrice weekly)	Prospective, open-label trial	Patients in stable remission taking PDN ≤ 10 mg/day	13	Remission maintenance in EGPA treated for induction with IFN- α (Ref. 71) or conventional immunosuppressants	77% (10/13) patients relapsed; treatment was discontinued in 69% (9/13) patients due to lack of efficacy, adverse events or both
Kim et al., 2010 (85)	Mepolizumab (4 monthly iv doses of 750 mg) on top of ongoing GC therapy	Prospective, open-label trial	Patients with steroid-dependent disease (taking PDN ≥ 10 mg/day $\pm$ other immune-suppressive drugs)	7	GC tapering	100% (7/7) patients were able to taper GCs, with a mean dose reduction of 64%; after mepolizumab withdrawal, EGPA relapsed requiring GC bursts
Moosig et al., 2011 (38)	Mepolizumab (9 monthly iv doses of 750 mg) on top of ongoing GC therapy	Prospective, open-label trial	Patients with active refractory or relapsing disease despite PDN ≥ 12.5 mg/day plus immune-suppressive drugs	10	Induction of remission and PDN tapering (to a dose <7.5 mg/day)	80% (8/10) patients achieved remission and tapered PDN to <7.5 mg/day; 50% (5/10) relapsed following switch from mepolizumab to MTX
Hermann et al., 2012 (78)	MTX (0.3 mg/kg/week) on top of ongoing GC therapy	Prospective, open-label trial	Patients who achieved remission with mepolizumab in the trial Ref. (38)	9	Maintenance of remission	33% (3/9) patients were in remission at the end of follow-up; 3 major and 7 minor relapses occurred in 3 and 5 patients respectively

*Only trials enrolling 5 or more patients are reported.

†Poor prognosis factors denote the items included in the Five-Factor score (heart, gastro-intestinal and central nervous system involvement, proteinuria >1 g/24 h, and creatinine >140 μ M). MTX, methotrexate; PDN, prednisolone; IVig, intravenous immunoglobulins; PEX, plasma exchange; CYC, cyclophosphamide; GC, glucocorticoid; MP, methylprednisolone; AZA, azathioprine; IFN- α , interferon- α ; EGPA, eosinophilic granulomatosis with polyangiitis.

eosinophil activation play a major role in its pathogenesis, and ANCA hallmark the vasculitic disease complications. If appropriately treated, the outcome of EGPA is good; recent data suggest that biologic agents such as the anti-IL5 mepolizumab and possibly rituximab are promising treatment options.

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Conflict of interest

The authors have no conflict of interest with the publication of this article.

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