Eosinophilic granulomatosis with polyangiitis: an overview

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INTRODUCTION AND EPIDEMIOLOGY

Eosinophilic granulomatosis with polyangiitis (EGPA) is a multisystemic disorder, belonging to the small vessel anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs). According to the 1994 Chapel Hill consensus conference (CHCC), EGPA is defined as an eosinophil-rich and granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium-sized vessels, associated with asthma and eosinophilia. EGPA pathogenesis is not well known: HLA-DRB1*04 and *07, HLA-DRB4 and IL10.2 haplotype of the IL10 promoter gene are the most studied genetic determinants. Among the acquired pathogenetic factors, the exposure to different allergens, infections, vaccinations, drugs, and silica exposure have been involved. Eosinophils are the most characteristic cells in EGPA and different studies have demonstrated their role as effector and immunoregulatory cells. EGPA is considered as a disease with a prevalent activation of the Th-2 cellular-mediated inflammatory response and also humoral immunity plays an important role. A link between B and T inflammatory responses may explain different disease features. EGPA typically develops into three sequential phases: the allergic phase, distinguished by the occurrence of asthma, allergic rhinitis, and sinusitis, the eosinophilic phase, in which the main pathological finding is the eosinophilic organ infiltrations (e.g., lungs, heart, and gastrointestinal system), and the vasculitic phase, characterized by purpura, peripheral neuropathy, and constitutional symptoms. ANCA (especially pANCA anti-myeloperoxidase) are present in 40–60% of the patients. An elevation of IgG4 is frequently found. Corticosteroids and cyclophosphamide are classically used for remission induction, while azathioprine and methotrexate are the therapeutic options for remission maintenance. B-cell depletion with rituximab has shown promising results for remission induction.

Keywords: eosinophilic granulomatosis with polyangiitis, vasculitis, eosinophils, vascular diseases, ANCA-associated vasculitis

PATHOGENESIS

Eosinophilic granulomatosis with polyangiitis pathogenesis is not well known. The disease is probably the result of a complex interaction in which genetically and environmental factors lead to an inflammatory response whose principal players are eosinophils, T, and B lymphocytes (2) (Figure 1).

GENETIC DETERMINANTS

Eosinophilic granulomatosis with polyangiitis is an HLA-associated disease (4). It has been proven that it is associated with HLA-DRB1*04 and *07 (5) and with HLA-DRB4 (6). This contraction of the class II HLA repertoire suggests a strong CD4+ T lymphocyte activation, possibly triggered by allergens or antigens.

It has been also investigated the presence of single nucleotide polymorphisms (SNP) of the gene, which encodes interleukin (IL)-10, an important molecule for the activation of the Th-2 pathway; EGPA ANCA-negative subset has been associated with the IL10.2 haplotype of the IL-10 promoter gene, a condition, which leads to an increased production of IL-10 (7). This is apparently in line with EGPA pathogenesis, which is characterized by an increased Th-2 response and an increase in IgG4 levels, both of which seem to be mediated by IL-10.

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Table 1 | Diagnostic criteria, classification, and nomenclature of eosinophilic granulomatosis with polyangiitis during the last 20 years.

| Lanham diagnostic criteria (1984) | American College of Rheumatology classification criteria (1990) | Revised International Chapel Hill consensus conference nomenclature of vasculitides (2012) |
|----------------------------------|---------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Asthma                           | Asthma                                                       | Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessel, and associated with asthma and eosinophilia. |
| Blood eosinophilia >1500/mm³ or >10% of total WBC | Eosinophilia (≥10% of total WBC)                              | ANCA is more frequent when glomerulonephritis is present. |
| Evidence of vasculitis involving two or more organs | Neuropathy                                                    | |
|                                  | Paranasal sinus abnormalities                                | |
|                                  | Extravascular eosinophils                                     | |

*a All three criteria must be met for a diagnosis of EGPA.
*b The presence of four or more of these six criteria yielded a sensitivity of 85% and a specificity of 99.7% for the classification of vasculitis as EGPA.

WBC, white blood cells.

FiguRe 1 | Eosinophilic granulomatosis with polyangiitis pathogenesis.

ACQUIRED DETERMINANTS

Some environmental triggers have been identified: the exposure to different allergens, infections, vaccinations could trigger the disease. Drugs may also have a pathogenetic role and, among these, the leukotriene receptor antagonists are the most frequently involved more often used as steroid-sparing agents for asthma, their key role in triggering EGPA is still uncertain (8). More recently, also the recombinant anti-IgE monoclonal antibody omalizumab used in patient with asthma has been considered as an EGPA trigger (9–11). According to the most reliable hypotheses, both LTRA and anti-IgE antibody may be involved in EGPA pathogenesis simply unmasking the disease, due to the delayed use of steroids.

A recent review has shown the possible pathogenetic influence of silica exposure in AAVs, including EGPA (12).

EOSINOPHILS

The role of the eosinophils is still uncertain in EGPA but different studies have demonstrated the cytotoxic (13, 14) and pro-coagulant (15, 16) properties of this cell type, which may result in the development of cardiovascular and cerebrovascular complications in patients with any type of hypereosinophilic syndromes including EGPA. Although they are usually considered to be effector cells, they may act as immunoregulatory cells (2); indeed, a cross-talk between T-lymphocytes and eosinophils has been pointed out. In a recent study, high concentrations of IL-25 have been detected in the sera of EGPA patients; eosinophils are the main source of IL-25, which induces T-cells to produce cytokines that stimulate Th-2 and, at the same time, eosinophilic responses (17).

T-LYMPHOCYTES

It has been demonstrated that T-lymphocytes have an important role in the EGPA pathogenesis. T-cells are present in the most of the organ lesions and in some of them, like peripheral neuropathy, they represent the main component. Moreover, serum levels of T-cell activation markers, like IL-2r, are increased during the active phase of the disease (18). T-cells receptors show a restricted repertoire suggesting oligoclonal expansion (19), which is in line with the hypothesis of an antigen-driven disease. Clonal restricted effector CD8⁺ lymphocytes with a proinflammatory profile have been recently described in patients with EGPA (20). Specifically, EGPA is considered as a disease with a prevalent activation of the Th-2 pathway. In keeping with this view, it has been demonstrated that tissue infiltrates in patients with EGPA are rich in T-cells with Th-2 makers such as CD294. Furthermore, EGPA patients CD4⁺ T-cells are able to produce, in vitro, high concentrations of IL-4, IL-5, and IL-13, molecules that hallmark the Th-2 immunorespose.

High-blood concentrations of IL-17 have been found in patients with EGPA, a finding, which suggests that the involvement of Th17 lymphocytes into EGPA pathogenesis; indeed, these lymphocytes are involved in the pathogenesis of other autoimmune diseases (2).

Finally, reduced levels of regulatory CD4⁺ T-cells (Tregs) have been discovered in EGPA patients (21, 22). Tregs usually have a protective role toward the development of autoimmune diseases. Lower numbers of Tregs were found in active EGPA patients than in patients with asthma or with chronic eosinophilic pneumonia; additionally, the percentages of circulating Tregs were lower in active than quiescent EGPA (2).

B-LYMPHOCYTES

The role of the humoral immunity in EGPA seems to be less relevant as compared to other autoimmune diseases. Despite this, EGPA patients often show an abnormal humoral response. ANCA...
Table 2 | Main clinical features in eosinophilic granulomatosis with polyangiitis and their prevalences.

| Clinical features                        | Prevalence (%) | Reference                  |
|------------------------------------------|----------------|----------------------------|
| Mean age at diagnosis (years)            | 50 ± 16        | Comarmond et al. (30)      |
| Asthma                                   | 91–100         | Comarmond et al. (30); Sablé-Fourtassou et al. (31) |
| Ear, nose, and throat involvement        | 48–75          | Comarmond et al. (30); Bacciu et al. (32) |
| Neuropathy                               | 55–72          | Comarmond et al. (30); Sablé-Fourtassou et al. (31) |
| Pulmonary involvement                    | 65–91          | Sablé-Fourtassou et al. (31); Comarmond et al. (30) |
| Cutaneous involvement                    | 40–52          | Comarmond et al. (30); Sablé-Fourtassou et al. (31) |
| Renal involvement                        | 27             | Sinico et al. (33)         |
| Cardiac involvement                      | 27–35          | Comarmond et al. (30); Sablé-Fourtassou et al. (31) |
| Gastrointestinal involvement             | 23–32          | Comarmond et al. (30); Sablé-Fourtassou et al. (31) |
| Central nervous system involvement       | 5–9            | Comarmond et al. (30); Sablé-Fourtassou et al. (31) |
| ANCA positivity                          | 38             | Sinico et al. (34)         |
| pANCA positivity                         | 74 of all ANCA+ patients | Sinico et al. (34) |

ANCA, anti-neutrophil cytoplasmic antibody.
ANCA-negative phenotype, in which the organ is damaged mainly
by an eosinophilic infiltration (e.g., pulmonary infiltrates, car-

The most frequent laboratory findings in EGPA patients
is marked hypereosinophilia, frequently between 5000 and
9000 eosinophils/µL (at least >1500 eosinophils/µL or >10% of
the total white blood cells, according to Lanham criteria (44)),
this is one of the most common signs of EGPA (36). An increase
in non-specific inflammatory markers (ESR, CRP) is often found
(36). The role of the complement is still uncertain. ANCA are
present approximately in 40–60% of the patients; pANCA (perin-
nuclear) is the prevalent pattern, with antibody specificity for MPO
(33, 34, 45).

All these clinical manifestations and laboratory features could
be frequently gathered into two patterns: the vasculitic and
ANCA-positive phenotype, characterized by manifestations result-
ing from small and medium-sized vessel vasculitis (e.g., purpura,
mononeuritis multiplex, glomerulonephritis) and the eosinophilic,
ANCA-negative phenotype, in which the organ is damaged mainly
by an eosinophilic infiltration (e.g., pulmonary infiltrates, car-
diomyopathy) (2). These findings may have pathogenetic implica-
tions, as they suggest that ANCA, as observed in MPO-ANCA
positive patients, which present peripheral eosinophilia, the ANCA speci-
ficity (cANCA PR3-specific, in GPA) and the presence, in GPA, of
eosinophilic pneumonia from EGPA (52).

Eosinophilic granulomatosis with polyangiitis must be distin-
guished from the other AAVs. Granulomatosis with polyangiitis
(GPA) may mimic particular aspects of EGPA, especially in those
patients, which present peripheral eosinophilia, the ANCA speci-
cifiy (cANCA PR3-specific, in GPA) and the presence, in GPA, of
pulmonary cavitated nodules associated with nasal crusting and
nasal and paranasal sinususes erosion, allow clinicians to differentiate
the two vasculitides.

Although microscopic polyangiitis (MPA) could be also charac-
terized by pANCA with MPO specificity, it rarely shows peripheral
eosinophilia, nodules, or eosinophilic pulmonary infiltrates (48).
Finally, EGPA must be differentiated from IgG4-related disease
(IgG4-RD), which may present with allergic manifestations, blood
eosinophilia, pulmonary infiltrates, and sinusitis. However, tissue
biopsies in patients with IgG4-RD show fibrosis and oblitative
phlebitis, without vasculitis or eosinophilic granulomas (53).

**DIFFERENTIAL DIAGNOSIS**

Different conditions have to be considered in the differential
diagnosis, mainly eosinophilic and vasculitic diseases.

Parasitic infections as well as hypersensitivity reactions (e.g., to
drugs) must be excluded. The hyper eosinophilic syndrome (HES) is
characterized by persistent eosinophilia and organ involve-
ment without a reason, which can explain hypoeosinophilia. Car-
diak and pulmonary manifestations are analog to those of EGPA
patients but subjects with HES usually do not have asthma or
vasculitic complication like purpura or glomerulonephritis; fur-
thermore, ANCA are absent in HES (49). A recent revised classi-
fication of HESs has focused on the pathogenesis of many hyper-
eosinophilic disorders: myeloproliferative and lymphocytic forms
of HES should be excluded in all patients. Particularly, Fip1-like-
1(FIP1L1)/platelet-derived growth factor receptor α (PDGFRα)
fusion genes must be investigated (50).

Broncho-pulmonary allergic aspergillosis may mimic pul-
monary involvement in EGPA: differential diagnosis is helped by
finding Aspergillus spp at bronchoscopy lavage or dosing
Aspergillus fumigatus specific serum IgE, which are pathogno-
monic of allergic aspergillosis (51).

Acute eosinophilic pneumonia is featured by pulmonary infiltr-
ates and bronchoscopy lavage rich in eosinophils but usually
originates as an acute illness with fever and dyspnea, without
peripheral eosinophilia or other organ involvement.

Chronic eosinophilic pneumonia diagnosis is more insidious.
Patients may present with asthma, peripheral eosinophilia, and
constitutional symptoms. The absence of other organ manifesta-
tions and the negativity of ANCA may help to differentiate chronic
eosinophilic pneumonia from EGPA (52).

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In our center experience, first level examinations include blood tests and, in particular, complete blood cell count, ESR, CRP, immunoglobulins with their subclasses (especially IgG subclasses), rheumatoid factor, ANCA, eosinophil cationic protein (ECP), serum B12 levels (elevated in myeloproliferative neoplasms), and a screening of renal function and urinalysis. Detection of FIP1L1/PDGFRA fusion genes and stool cultures for ova and parasite examination must be done in the early stages of diagnosis. ANCA are thought to be useful in the differential diagnosis between EGPA and other (especially infectious and hematological) eosinophilic disorders. Likewise, finding fusion genes clearly points toward a diagnosis of myeloproliferative HES. The differential diagnosis with lymphocytic forms of HES is more challenging, as most laboratories do not perform clonal analysis of circulating lymphocyte subsets or their intracellular cytokine production, which could be helpful in these conditions.

Second level examinations include imaging studies such as lung and facial computed tomography (CT), as well as functional studies such as electromyography.

Finally, kidney biopsy and a bronchoscopy with bronchoalveolar lavage are reserved for those patients with severe (and often rapidly progressive) clinical manifestations.

**TREATMENT AND OUTCOME**

Eosinophilic granulomatosis with polyangiitis treatment is a matter of debate because of the lack of large-scale, randomized controlled trials. The five factors score (FFS) may be a guide for clinicians, this score assigns one point to each of the following items, namely, gastrointestinal involvement, CNS involvement, cardiac involvement, proteinuria >1 g/24 h and serum creatinine >141 μmol/L (35). Patients with poor prognosis factors (FFS ≥1) are often treated with both glucocorticoids (classically prednisone at dosage of 1 mg/kg of total body weight/day with a maximum dosage of 75 mg/day, for 1 month and then tapered) and cyclophosphamide (CYC, 2 mg/kg of total body weight/day), while the typical approach for patients with a better prognosis (e.g., FFS of 0) is glucocorticoid therapy alone (54). Recently, a revised FFS has been proposed an age over 65 years, cardiac symptoms, gastrointestinal involvement, renal insufficiency (serum creatinine >150 μmol/L) and absence of ear, nose, and throat manifestations have been pointed out as predictors of 5-year mortality (55).

Classically, used therapies in EGPA remission maintenance are azathioprine or methotrexate (56).

Although primarily used for GPA, the BVAS, a clinical index of disease activity (57), might be useful to better decide when to stop therapy with CYC and introduce maintenance therapy like azathioprine or methotrexate.

Cyclophosphamide toxicity has long been known (58) and, based on our center experience, we recommend not to exceed the dose of 10–15 g of CYC (including both oral and pulse medications). On the other hand, too-short duration of CYC administration has been associated with more relapses (59).

Azathioprine too requires a constant monitoring of liver function, due to the drug-related hepatotoxicity (60).

B-cell depletion adjunct therapy with rituximab has shown promising results for remission induction (61–67).

Interleukin-5, a major survival factor for eosinophils, has been targeted in patients with EGPA using the monoclonal antibody mepolizumab. Use of mepolizumab in refractory cases (68, 69) and steroid-dependent patients (70) has given positive results but EGPA manifestations recurred on drug cessation.

On the assumption of its inhibitory effects on the eosinophil degranulation, interferon-alpha therapy has been tried with positive results in refractory patients, but the severe drug-related toxicity has greatly limited its use (71, 72).

Plasmapheresis may be an adjunctive therapy particularly in patients with rapidly progressive glomerulonephritis, peripheral neuropathy, or alveolar hemorrhage (2).

Eosinophilic granulomatosis with polyangiitis outcomes are well represented in a retrospective study of 383 EGPA patients in the French Vasculitis Study Group cohort. Vasculitis relapse occurred in 97 patients (25.3%), while 72 additional patients experienced asthma flares, sinusitis, and/or increased eosinophilia. Of the 383 patients, 45 (11.7%) died and the major cause of death was attributed to cardiac events. Five-year and 10-year survival rates were, respectively, 88.9 and 78.6%. Vasculitis relapse-free survival rate at 5 years was 64.8%, while at 10 years was 54.4%. ANCA positivity and cutaneous signs were independent predictors of relapse (30).

Another recent analysis of EGPA patients’ long-term follow up has demonstrated that the outcome of EGPA is good with respect to mortality. According to the analysis of 118 patients with EGPA (enrolled in two prospective trials), 108 (91.5%) patients achieved remission (34 of the 108 achieved long-term remission without relapse) and 12 (10.2%) died (only 5 of them died for EGPA-related causes). During relapses, pulmonary symptoms predominated (81%), followed by eye nose and throat signs (38%) and mononeuritis multiplex (36%) (73).

Finally, in a German cohort of 150 EGPA patients, the analysis of the follow-up of 104 of them has evidenced that 70 patients (67.3%) attained remission after conventional therapies, 21 (14%) suffered from major relapses and 42 (28%) from minor relapses. Twelve patients died 94 ± 16 (mean ± SD) months after diagnosis (74).

**PERSPECTIVE FUTURE**

Despite the great levels of knowledge reached, more has to be done to clarify EGPA pathogenesis, a genome-wide association study (GWAS) will probably help to better understand the genetic determinants of the disease. Besides, the environmental factors like silica or any other occupational exposure (e.g., asbestosis) must be studied in depth.

In the future, probably, the distinction between ANCA+ and ANCA− small vessels vasculitides will lead to re-define the current classification criteria with a more simplistic view of all the AAVs.

Despite this, clinicians should keep in mind all the distinctive clinical features and differential diagnosis approaches that make EGPA one of the more characteristic and complex AAV.

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