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Review

Dividing the Janus vasculitis? Pathophysiology of eosinophilic granulomatosis with polyangitis☆

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ABSTRACT

Eosinophilic granulomatosis with polyangitis (EGPA) is a rare small- and medium-sized vessel vasculitis belonging to the group of anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV). It is commonly divided into two phenotypes depending on the presence of ANCAs targeting myeloperoxidase (MPO). MPO-ANCAs are present in 31% to 38% of patients and are associated with a vasculitis phenotype of the disease, whereas patients without MPO-ANCA are at risk of cardiac involvement. Despite significant advances in understanding the overall pathogenesis of the disease, the explanation for this dichotomy is still unclear. In this review, we synthesize our knowledge of the pathogenesis of EGPA and attempt to i) distinguish EGPA from other diseases including other AAVs, asthma, allergy and hypereosinophilic-associated conditions and ii) speculate about the preponderant mechanisms, which could explain the two disease phenotypes.

Contents

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1. Introduction

From its first description in 1951, by Jacob Churg and Lotte Strauss, until the revision of the Chapel Hill nomenclature in 2012, allergic granulomatosis and angiitis was called Churg–Strauss syndrome [1]. Its name was recently changed to eosinophilic granulomatosis with polyangitis (EGPA) to reduce the use of eponyms [2]. EGPA is a rare small- and medium-sized vessel vasculitis belonging to the group of anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAVs). The American College of Rheumatology diagnostic criteria are asthma, eosinophilia, mono-polyneuropathy, pulmonary infiltrates, non-fixed paranasal sinus abnormalities and extravascular eosinophils; four of six criteria are needed for a diagnosis [3]. EGPA includes features of allergy, asthma, hypereosinophilic diseases and AAVs, but we have few data for understanding its pathophysiology [4].

Specific features of the disease are needed for characterizing it. Why are ANCAs detected in only 31% of 38% of patients in a disease belonging to the group of AAVs [5–7]? How do we explain the formation of granulomas in a T-helper (Th) 2-mediated non-parasitic disease? Moreover, we have limited evidence supporting the central role of eosinophils in EGPA, so should we assume their key position in the pathogenesis of the disease? Finally, should we consider splitting the disease [8]?

This review synthesizes current knowledge of the pathogenesis of EGPA. In the first part we consider EGPA at a crossroads of AAV, hypereosinophilic-associated conditions, asthma and allergy. Then, we speculate about the two disease phenotypes, which are the vasculitis-phenotype, which is associated with the presence of myeloperoxidase (MPO)-ANCAs and the non-vasculitis-phenotype, which is mainly characterized by cardiac involvement.

2. EGPA at a crossroads of different diseases

2.1. EGPA and AAV

2.1.1. AAV revised classification

The revised international Chapel Hill Consensus Conference nomenclature of vasculitides classified systemic AAVs by the presence or absence of granuloma and asthma (Table 1) [2]. EGPA was classified as systemic vasculitis with granulomatosis, asthma, and blood eosinophilia, microscopic polyangiitis (MPA) as vasculitis without asthma or granuloma, and granulomatosis with polyangiitis (GPA) as evidence of granulomatosis without asthma. Such classification helps in bedside diagnosis but not in understanding the entire specificity of the disease pathogenicity of EGPA that is necessarily different from the other two AAVs.

2.1.2. Genetic predisposition

Our understanding of vasculitides has benefitted from genetic studies. A British genome-wide association study (GWAS) showed a genetic component in AAV pathogenesis with both human leukocyte antigen (HLA) and non-HLA associations. The strongest associations related to autoantigens of the vasculitis, not the clinical syndrome. PR3 ANCAs were linked to the HLA-DP subtype and the genes encoding α1-antitrypsin or PR3, whereas MPO-ANCA presence was associated with HLA-DQ [9]. Although informative, this study involved only GPA and MPA patients, not EGPA patients.

Still, genetic susceptibility/predisposition has been suggested for EGPA from associations between EGPA and HLA. A positive association was found for HLA DRB1*04 and HLA-DRB1*07 twice, whereas a protective effect was reported with HLA-DRB3 and HLA-DRB1*13 [10,11]. Of note, a study of the HLA-DRB1 locus in 403 patients with GPA and 103 with EGPA linked the extended interleukin 10 (IL-10)-3575/-1082/-592 TAC haplotypes with ANCA-negative EGPA [12]. Even though IL-10 level was reported to be elevated in EGPA, we lack a post-transcription analysis of the haplotypes [13].

Genes related to the costimulatory molecule CD226 (DNAX accessory molecule 1), the intracellular signaling-involved molecule PTPN22 and eotaxin-3 single nucleotide polymorphisms were investigated but were not associated with EGPA [14–16].

Exome sequencing has led to significant understanding in the field of vasculitis, especially in polyarteritis nodosa in which a mutation in CERC1, the gene encoding adenosine deaminase 2, was found in multiple affected families of Georgian, Jewish or German descent [17]. Exome sequencing and GWAS studies are still needed in EGPA.

2.1.3. Granuloma

As recalled in the new classification, an important aspect of the immune response is the formation of a granuloma, originally described as an “allergic granuloma”. A granuloma consists of a palisade of giant cells or epithelioid histiocytes surrounding necrotizing eosinophils [1]. Pathology descriptions also showed fibrinoid necrosis, eosinophil infiltration, lymphocytes, and exceptional vascular localization. Thus, EGPA granulomas are specific because they contain eosinophils, exhibit necrosis and are associated with both vasculitis and Th2-related cytokine production.

Such specificity has been a matter of debate because granulomas are found in various rheumatic diseases such as systemic vasculitides or connective tissue diseases (systemic lupus erythematosus or rheumatoid arthritis), as well as lymphoproliferative diseases and common variable immunodeficiency, and even bacterial endocarditis, or chronic hepatitis [18,19]. Indeed, granulomas can be found in other rheumatic pulmonary diseases, but mainly Th1-related inflammatory conditions,

Table 1
EGPA at a crossroads of hypereosinophilic associated conditions and ANCA-associated vasculitides.

Hypereosinophilic associated-conditions [79]		ANCA-associated vasculitides [2]		
Eosinophilic disorders	Reactive causes of eosinophilia	EGPA	MPA	GPA
- Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRα, PDGFRβ, or FGFR1 - Chronic eosinophilic leukemia - Idiopathic hypereosinophilic syndrome	- Infections, particularly tissue-invasive parasites - Allergy/atopy and hypersensitivity conditions - Drug reaction - Collagen-vascular diseases - Pulmonary eosinophilic diseases - Allergic gastroenteritis - Metabolic conditions - Non-myeloid malignancies - Rare conditions[a]	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present.	Necrotizing vasculitis, with few or no immune deposits, affecting small vessels. Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent.	Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels. Necrotizing glomerulonephritis is common.

ANCA: anti-neutrophil cytoplasm antibody, EGPA: eosinophilic granulomatosis with polyangitis, MPA: microscopic polyangiitis, GPA: granulomatosis with polyangiitis, PDGFRα: platelet-derived growth factor receptor alpha, PDGFRβ: platelet-derived growth factor receptor beta, FGFR1: fibroblast growth factor receptor 1, IgE: immunoglobulin E.

[a] Rare conditions include familial eosinophilia, hyper IgE syndrome, Omenn syndrome, Gleich's syndrome, and eosinophilia-myalgia syndrome.