Autoimmunity Reviews xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Churg–Strauss syndrome

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ARTICLE INFO

Article history:
Received 20 November 2014
Accepted 7 December 2014
Available online xxxx

Keywords:
Churg–Strauss syndrome
Eosinophilic granulomatosis with polyangiitis
ANCA-associated vasculitis
Hypereosinophilic syndromes
Asthma
Wegener granulomatosis

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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http://dx.doi.org/10.1016/j.autrev.2014.12.004
1568-9972/

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

Please cite this article as: Greco A, et al, Churg–Strauss syndrome, Autoimmun Rev (2014), http://dx.doi.org/10.1016/j.autrev.2014.12.004