Churg-Strauss syndrome (CSS) is the least common of the antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides, which also include microscopic polyangiitis and granulomatosis with polyangiitis (Wegener’s). CSS has been recently renamed as eosinophilic granulomatosis with polyangiitis (EGPA (Churg-Strauss)) [1].

Everlasting messages from history

The first well-described vasculitis in medical history was periarteritis nodosa in 1866, by Kussmaul and Maier, who reported “a hitherto undescribed peculiar disease of the arteries which is accompanied by Bright’s disease and a rapid progressive paralysis of the muscles” [2]. Thirteen years later, Ehrlich discovered the eosinophil leukocyte [3]. The first published case of EGPA was that of Albert Lamb in 1914 [4] under the heading of polyarteritis nodosa. The 26-year-old patient he reported had asthma, eosinophils up to 7.7 G/L, and he died 1 month after admission to the hospital. Autopsy disclosed especially myocarditis with perivascular eosinophilia and glomerulonephritis with epithelial crescents. Several reports and short series were further published in the following years, until Churg and Strauss [5] eventually reported a well-studied series of 13 cases with extended autopsy in nine. They emphasized the severity of asthma, and the manifestations of cardiac failure, renal damage, and nervous involvement. The characteristic histopathologic features that they described mainly consisted of necrotizing arteritis, eosinophil infiltration, and granulomatosis with giant cells. Up to the 1950s almost all patients with EGPA died and autopsy studies could thus describe the entity in detail.

After corticosteroids had become available, improvement in EGPA was obtained; however it was only in the 1980s that cytotoxic drugs (especially cyclophosphamide and azathioprine) were combined with corticosteroids, and that the prognosis of EGPA eventually improved with long-lasting remission and eventual healing.

Diagnostic criteria: a protracted challenge

Surprisingly, up to now no consensual diagnostic criteria have been established for EGPA. Lanham et al. [6] reported 16 cases and reviewed the literature based on diagnostic criteria including asthma, eosinophils greater than 1.5 G/L, and systemic vasculitis involving two or more extrapulmonary organs. Masi et al. [7] reported the American College of Rheumatology criteria for the classification of CSS which have often inappropriately been used as diagnostic criteria. This was quite inadequate, as for example a patient with idiopathic chronic eosinophilic pneumonia with asthma and paranasal sinusitis could fit such criteria and therefore be called CSS. Furthermore, the Chapel Hill nomenclature was convened as a nomenclature and neither as a classification system nor as a diagnostic system [8].

From nomenclature to diagnostic criteria

The 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides [1] decided to rename CSS as EGPA (Churg-Strauss), a terminology that reminds the user that EGPA is indeed a vasculitis. In recent years, distinct phenotypes have emerged from the largest series of CSS [9,10] with a vasculitic phenotype (with patients having more frequently ANCA, glomerulonephritis, alveolar hemorrhage, and/or biopsy-proven vasculitis) and a tissular phenotype (with patients having more frequently cardiomyopathy, but no ANCA).

Members of the European Respiratory Society CSS-Task Force (listed below as authors) prepared recommendations for the diagnosis of EGPA, including a definition of detailed criteria of vasculitis (or surrogates of vasculitis) in patients with asthma and blood eosinophils greater than 1.5 G/L (box 1). The CSS-Task Force further proposed that patients with asthma and blood eosinophils greater than 1.5 G/L without ANCA, vasculitis, or surrogates of vasculitis be called hypereosinophilic asthma with systemic manifestations (HASM), non-vasculitic (box 2).
Epidemiology and triggers

The prevalence of EGPA in the general population is about 11 to 13 per million inhabitants. There is no sex predominance and the mean age is about 50 years. Drugs, vaccinations, allergic hyposensitization and infectious agents have been reported as possible triggers. More recently, leukotriene-receptor antagonists have been suspected to enhance CSS, however this has not been established.

Clinical manifestations

Data about EGPA mainly result from a limited number of large series, [9–16]. Fatigue, fever, malaise and weight loss are common initial features.

Pulmonary manifestations

Asthma is present in almost all patients (it may occasionally be replaced by severe cough or cough-variant asthma). It usually precedes vasculitis for several years, and is often associated with rhinitis, nasal polyps, or sinusitis. An increase in blood eosinophils is common for months or years before vasculitis develops. High resolution computed tomography (HRCT) features demonstrate pulmonary opacities in a majority of patients. These mainly consist of alveolar opacities (HRCT) features demonstrate pulmonary opacities in a majority of patients. These mainly consist of alveolar opacities.

Box 1

Diagnostic criteria of eosinophilic granulomatosis with polyangitis (EGPA) proposed by the ERS CSS-Task Force

The diagnosis of EGPA requires the presence of asthma, increased blood eosinophils, and vasculitis features and/or surrogates listed below.

1. Asthma (with or without pulmonary opacities on imaging)
2. Blood eosinophils > 1.5 G/L (at least one measurement) or > 10% of leukocytes
3. Vasculitis (or surrogates)
   - Necrotizing vasculitis (biopsy-proven) of any organ
   - Necrotizing glomerulonephritis or crescentic glomerulonephritis (biopsy-proven)
   - Alveolar hemorrhage (defined as bloody bronchoalveolar lavage fluid with compatible opacities on chest X-ray and/or HRCT)
   - Palpable purpura
   - Mononeuritis or mononeuritis multiplex
   - Haematuria associated with red casts or > 10% dysmorphic erythrocytes OR haematuria and 2+ proteinuria on urinalysis (related to the systemic disease, no biopsy) (Watts R et al., Ann Rheum Dis 2007;66:222–7)
   - Myocardial infarction due to proven coronaritis (related to the systemic disease, e.g. non-atheromatous coronary stenosis at coronarography or myocardial infarction without coronary atherosclerosis)
   - MPO-ANCA or PR3-ANCA (Elsa) associated or not with at least one of the following systemic manifestation: myocarditis; pericarditis other than asymptomatic mild pericardial effusion; renal disease other than defined above; peripheral neuropathy; abdominal pain associated with nausea, vomiting, diarrhea; any other organ/system manifestation with significant eosinophilic infiltration at biopsy; any other organ/system manifestation considered to be convincingly related to eosinophilic disease (without biopsy)

Box 2

Diagnostic criteria of hypereosinophilic asthma with systemic manifestations (HASM) proposed by the ERS CSS-Task Force

1. Asthma (with or without pulmonary opacities on imaging)
2. Blood eosinophils > 1.5 G/L (at least one measurement) or > 10% of leukocytes
3. PR3 and MPO-ANCA negative
4. Absence of vasculitis (or surrogates)
5. At least one of the following: myocarditis; pericarditis other than asymptomatic mild pericardial effusion; renal disease other than defined in EGPA; peripheral neuropathy other than mononeuritis multiplex; any other organ/system manifestation with significant eosinophilic infiltration at biopsy; any other organ/system manifestation considered to be convincingly related to eosinophilic disease (without biopsy)

Patients with HASM might eventually develop definite EGPA

Patients with marked biopsy-proven tissular eosinophilia without vasculitis and peripheral blood eosinophilia greater than 0.75 G/L may also be included.
Cardiac manifestations
The cardiac manifestations of CSS mainly consist of myocarditis and pericarditis. Cardiac failure may develop rapidly, with markedly reduced ejection fraction at echocardiography. These may improve very rapidly with corticosteroids, however chronic heart failure may persist as a sequela. Coronary vasculitis is rare and myocardial infarction is unusual.

Nervous manifestations
Mononeuritis multiplex resulting from vasculitic involvement of the vasa nervorum (mostly affecting the common peroneal nerve) is a characteristic feature of systemic vasculitis. Polyneuropathy and central nervous involvement are uncommon and less characteristic of EGPA.

Other manifestations
Skin manifestations may consist of vasculitis (vascular palpable purpura especially), or subcutaneous granulomatous nodules. Gastrointestinal manifestations are occasionally severe with hemorrhage or bowel perforation. Abdominal pain, nausea, vomiting, diarrhea may be present. Renal manifestations are uncommon (less than 20% of cases), however crescentic glomerulonephritis (a typical vasculitis feature) may develop with ensuing acute renal failure. All organs may be involved by CSS including the eye, the urinary tract, etc.

Diagnosis
The diagnosis of EGPA first requires a history of asthma, and the demonstration of a high level of eosinophils in blood cell count (> 1–1.5 G/L). Rarely asthma is not present and replaced by severe cough (cough-variant asthma). Blood eosinophils may drop dramatically after corticosteroid treatment (even within 24 hours), so that blood cell count should always be made before initiation of any corticosteroid treatment (or after stopping corticosteroids if possible).

Antineutrophil cytoplasmic autoantibodies (ANCA) are present in about 40% of patients with CSS, consisting usually of perinuclear antibodies on immunofluorescence, and with anti-myeloperoxidase (MPO) specificity in most cases. Diagnosis usually relies on the characteristic clinical manifestations and ANCA when present. Confirmation by biopsy is necessary in only a minority of patients; biopsies of skin, nerve, and muscle have the best sensitivity.

Treatment and prognosis
Whereas almost all patients died within a few months before corticosteroids were available, these have dramatically changed the prognosis. Cytotoxic drugs (especially cyclophosphamide) have further markedly improved the rate of remission. Maintenance therapy mainly relies on azathioprine. Rituximab for obtaining remission and/or preventing relapses might prove to be a major component of EGPA treatment.

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References
Eosinophilic granulomatosis with polyangiitis: Future therapies

Is EGPA an entity?

Eosinophilic granulomatosis with polyangiitis (EGPA) as the rarest form of ANCA-associated vasculitis (AAV) has several specifics making classification difficult. For good reasons, EGPA is classified amongst the AAVs and it shares features with Microscopic polyangiitis (MPA) and with Granulomatosis with polyangiitis (GPA). However, the prevalence of ANCA is lowest in EGPA and ANCA tend to become negative under therapy much faster than seen in the other AAVs [1,2]. Furthermore, there is substantial evidence that ANCA-negative and ANCA-positive EGPA differ in their clinical presentation, with ANCA-positive patients tending to more “vasculitic” manifestations as glomerulonephritis whereas cardiac-involvement is seen more often in ANCA-negative EGPA [1,3,4]. EGPA and the other AAVs differ also concerning their genetic background. For example, some single nucleotide polymorphisms can be risk factors in GPA but seem to be protective in EGPA [5]. Furthermore, as a relevant portion of its pathology results from tissue hypereosinophilia and most EGPA patients fulfill the “classical” Chusid-criteria for the hypereosinophilic syndromes (HES) [6], according to recent consensus statements EGPA can also be classified as a form of HES [7].

This opening remarks are important when thinking about future therapies in EGPA: it seems likely that with the availability of data from larger cohorts and ongoing genotype and phenotype analysis it will turn out that there is no single entity EGPA but a broad spectrum of conditions ranging from typical AAV-like phenotypes with predominant vasculitic manifestations to forms in which tissue-hypereosinophilia is the leading pathological mechanism as in the HESs. The exact determination of the individual disease phenotype will therefore become important for the choice of the optimal therapy and strategies both from AAV- and from HES-trials may be applied.

New EGPA therapies in the near future

Rituximab

Today, EGPA usually is treated according to the same principles of induction of remission and maintenance of remission using glucocorticosteroids (GC) and conventional immunosuppressants as the other AAVs. In this field, the use of rituximab (RTX) is the most relevant recent development. It is now widely accepted that in the treatment of MPA and GPA, RTX can be used as substitute for cyclophosphamide (CYC), although clear superiority of RTX over CYC as well as the postulated benefits concerning adverse reactions have not been formally proven. In the relevant trials that led to approval of RTX by the FDA, EGPA patients have not been included [8]. However, there are some case reports and some small case series suggesting that RTX might also be effective in EGPA. Most of those reports deal with patients refractory to standard induction of remission. In a few cases, good efficiency has also been demonstrated in non-refractory patients. In the latter the reason for using RTX instead of CYC usually was the wish to conserve fertility [9]. In GPA it has been demonstrated that vasculitic manifestations show a better response to RTX than the granulomatous manifestations [10]. From the available data it might be speculated that comparably in EGPA manifestations due to eosinophilic tissue infiltration respond different than “pure vasculitic” phenomena. Although it is obvious that such observations would lead to a more differentiated use of RTX in EGPA, the current database is not sufficient to support such an approach. It seems likely that RTX will be used for induction of remission in EGPA more often in analogy to the other AAVs, although data from controlled trials will not be available soon. About a possible role of RTX for maintenance of remission, the lack of data is even larger and no data based statements can be made.