

Cutting Edge Issues in the Churg–Strauss Syndrome

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Abstract Churg–Strauss syndrome (CSS) is a rare systemic small-vessel vasculitis that develops in the background of bronchial asthma, which is characterized by eosinophilia and eosinophilic infiltration of various tissues. It belongs to the group of antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides. The triggering factors and pathogenesis of CSS are still unknown. The possible role of eotaxin-3 and CCR4-related chemokines in selective recruitment of eosinophils to the target tissues in CSS has been recently suggested, but the role of eosinophilic inflammation in the development of vasculitic lesions is not completely understood. From the clinical view, two distinct phenotypes of the disease are slowly emerging depending on the ANCA-positivity status. Glucocorticoids are still the mainstay of treatment; however, data are accumulating regarding the beneficial role of novel immunosuppressants and biologic compounds, especially in patients with poorer prognosis.

Keywords Churg–Strauss syndrome · Pathogenesis · Vasculitis · Eosinophils

Introduction

Churg–Strauss syndrome (CSS) is a systemic necrotizing small-vessel vasculitis, with accompanying bronchial asthma,

eosinophilia, and eosinophilic infiltration of various tissues resulting in granuloma formation [1–3]. Initial descriptions of this disease appeared during the early 1940s among patients thought to be suffering from polyarteritis nodosa, who at the same time exhibited symptoms of allergy, asthma, pulmonary infiltrates, and prominent eosinophilia [4]. However, it was Jacob Churg and Lotte Strauss who in 1951 distinguished a new entity based on 13 autopsy cases and named it allergic granulomatosis and angiitis [5]. The disease is rare, with the annual incidence ranging from 2.4 to 6.8/1 million in the general population [1, 6] and up to 34.6–67/1 million in asthmatic patients [7, 8]. Its frequency is the highest at the mean age of 48 (range 40–60) with equal gender distribution [9], with no demonstrable ethnic or familial predisposition. CSS shares several clinical and pathological similarities with other vasculitides as Wegener's granulomatosis (WG), microscopic polyangiitis (MP), and renal-limited vasculitis. Due to the presence of antineutrophil cytoplasmic autoantibodies (ANCA) in these diseases, they are often referred to as ANCA-associated vasculitides (AAV) [10].

Diagnosis

The natural course of CSS usually consists of three successive phases; firstly, a prodromal period, characterized by allergic rhinitis and accompanying asthma, sinusitis, and nasal polyposis. In the second stage, peripheral blood eosinophilia prevails with eosinophil tissue infiltrations, which may evolve into the third phase—a life-threatening vasculitis [11]. Establishing a diagnosis is not easy. During the early stages, differentiation from other phenotypes of asthma may be problematic, while the later stages of CSS share similarities with hypereosinophilic syndromes and

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other vasculitides. Any delay in diagnosis may predispose the patient to serious complications during the vasculitic phase and limit the effectiveness of treatment [12].

The classic recognition of CSS proposed by Churg and Strauss [5] was based on pathological findings and required the presence of all three of the following features: necrotizing vasculitis of small- and medium-sized vessels, eosinophilic infiltration, and extravascular granuloma formation. As this triad hardly ever coexists at the same time in any given CSS patient [3], a need for more practical diagnostic criteria was raised by Lanham et al. [11]. They proposed to define the syndrome as the coexistence of asthma, blood eosinophilia ($>1,500$ eosinophils/ μl) and evidence of vasculitis involving at least two extrapulmonary organs. The main disadvantage of this set of criteria is the requirement of two sites of vasculitic involvement, as it can exclude patients in the beginning phase of CSS and delay potential treatment. Furthermore, the level of blood eosinophilia can fluctuate during the course of the disease, while asthma may occasionally begin only after the appearance of vasculitis [9, 13]. Because of these limitations, in 1990, the American College of Rheumatology (ACR) proposed new classification criteria for CSS which defined six key features of the disease [14]. The presence of four of the following six criteria, namely: asthma, peripheral blood eosinophilia ($>10\%$ of total leukocyte count); mono- or polyneuropathy; paranasal sinus abnormalities; eosinophilic accumulation in tissues revealed by biopsy; and migratory infiltrates in lungs, makes diagnosis highly probable (specificity 99.7%; sensitivity 85%). However, these criteria were established on the basis of already recognized cases of CSS, for the purpose of standardizing the clinical definition for use in research studies. Unfortunately, their application in diagnosing new cases has not been particularly effective [15]. Nevertheless, they remain the most frequently used criteria for diagnosing CSS. In 1994, at the Chapel Hill Consensus Conference, an international group of experts established new classification criteria for CSS [10]. According to the revised guidelines, CSS was defined as: “eosinophil-rich and granulomatous inflammation involving respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels associated with asthma and eosinophilia”. The Chapel Hill definition of CSS has often been criticized for including biopsy as a requirement for establishing diagnosis, as well as the relative lack of specificity when compared to earlier definitions [13]. Additionally, the need for confirmation of CSS in biopsy specimens is problematic, as the three characteristic histology features hardly ever coexist [16], which can significantly delay diagnosis. This issue is of crucial importance during the early phases of the disease, where isolated tissue eosinophilia is usually the most common and only finding [16].

Pathogenesis of Churg–Strauss Syndrome

The cause of CSS remains unknown. It is believed that an unknown infectious agent, foreign antigen, or auto-antigen may initiate a Th2-type immune response in predisposed individuals, resulting in rhinosinusitis and asthma. This response then initiates eosinophilia, followed by infiltration of tissues by eosinophils. The end result is formation of eosinophilic granulomas and subsequent necrotizing vasculitis in several organs.

Several putative agents that trigger CSS have been suggested. The most significant are nearly all classes of anti-asthmatic medications [3], especially leukotriene receptor antagonists [17–20], which are noted as having the strongest association with CSS development. The published case studies and case series suggested that implementation of newer asthma controlling drugs allowed for significant reduction of glucocorticoid dose and unmasking previously existing vasculitis; however, this hypothesis has not been confirmed in recent systematic review focusing on the relation between CSS development and steroid use in asthma [19].

The characteristic feature of the disease, distinguishing CSS from other small-vessel vasculitides is profound blood and tissue eosinophilia. Histological findings in CSS usually include eosinophil-rich infiltrates in walls of small- and medium-sized vessels and surrounding tissues. Another common finding is vasculitis with fibrinoid necrosis, while extravascular eosinophilic granulomas may be observed less frequently (Fig. 1a, b) [9, 21]. Numerous eosinophils can also be seen in broncho-alveolar lavage fluid (BALF), especially in CSS patients with acute exacerbations of lung symptoms (Fig. 1c).

This close relationship of disease activity with evidence of blood and tissue eosinophilia indicates that eosinophils are crucial in the pathogenesis of the disease. It is believed that proteins secreted by activated eosinophils, once deposited in affected tissues, are responsible for tissue injury and contribute to CSS symptoms (e.g., myocardial infarction and neuropathy) [22–24]. Increased concentrations of eosinophil cationic protein have been reported in sera from CSS patients during disease exacerbations [25, 26] as well as in tissue biopsies [27], induced sputum [28], and BALF, sampled from patients with pulmonary active CSS [29]. Similarly, the increase in concentration of soluble thrombomodulin, during the active phase of CSS, is likely a consequence of endothelial cell damage mediated by eosinophil toxic proteins [25]. Additionally, it has been found that the peripheral blood eosinophils in CSS expresses surface markers of activation (CD69, CD25), most notably in subjects with active disease and concomitant increases in serum IL-5 [30, 31].

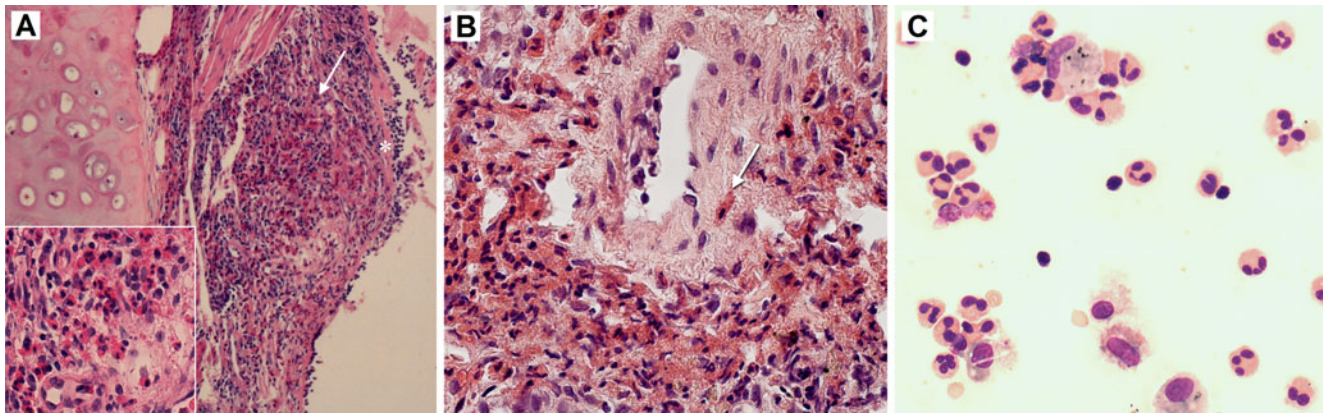


Fig. 1 Tissue biopsy findings in Churg–Strauss syndrome (CSS). **a** The endobronchial biopsy of the lung in active disease. Massive inflammatory infiltrate (*arrow*) forms unspecific granulation tissue, with numerous eosinophils (see the *inset*) and mononuclear cells, which entirely occupies all subepithelial part of mucosa and submucosa. Basal membrane of severely damaged respiratory epithelium is markedly thickened (*asterisk*). Hematoxylin and eosin (HE) staining (original

magnification $\times 100$, *inset* $\times 200$). **b** Active stage of CSS arteritis. The wall of an arteriole and surrounding perivascular space are infiltrated with eosinophils, some of them invading deeply the wall of the vessel (*arrow*). HE, ($\times 200$). **c** Cytopspin preparation of broncho-alveolar lavage fluid cells sampled from Churg–Strauss syndrome patient with lung symptoms. Marked increase in the number of eosinophilic granulocytes and lymphocytes. May–Grünwald–Giemsa ($\times 200$)

The accumulation of eosinophils during active stage of the disease is likely a consequence of increased eosinopoiesis, enhanced extravasation, and prolonged survival in target tissues. The maturation and release of eosinophils is regulated by interleukin-3 (IL-3), granulocyte-macrophage colony stimulating factor and, most importantly, interleukin-5 (IL-5) [32]. Produced predominantly by activated Th2-lymphocytes, IL-5 is capable of activating mature eosinophils and prolonging their survival. Indeed, elevated levels of serum IL-5 were found in patients with active CSS and correlated with clinical markers of disease activity [30, 33, 34]; they also decreased upon administration of immunosuppressive therapy [35–37]. Impaired eosinophil apoptosis has been suggested as a cause of CSS eosinophilia [38]; however, it is likely a consequence of IL-5 action in vivo, as circulating eosinophils become sensitive to apoptosis when deprived of growth factors in culture [31].

Resident cells in affected tissues (e.g., epithelial and endothelial cells) can also contribute to eosinophilia, for they secrete eosinophil-specific chemokines when activated by Th2-type cytokines. It has been reported that both eotaxin-3 (CCL26) [39] as well as CCR4-active chemokine (CCL17, CCL22) levels were elevated in sera of patients with active CSS; their concentration correlated with disease activity and decreased markedly upon introduction of immunosuppressive therapy [37, 40]. In a recent study, serum levels of CCL26 were found to be a reliable marker for active CSS [41]. Additionally, both CCL26 and CCL17 were found to be expressed in resident cells of affected tissue [39, 40]. These results suggest that eotaxin-3 and chemokines acting on the CCR4 receptor facilitate the selective recruitment of eosinophils and

effector Th2 cells to the target tissue, thus amplifying the inflammatory response.

T cells are usually found within granulomas and CSS-related lesions [22, 42]. Additionally, markers of T cell activation, such as serum soluble interleukin-2 (IL-2) receptor and sCD26, were markedly increased in active disease [25, 43]. Recently, two independent research groups found an association between an HLA locus and CSS. The frequencies of HLA-DRB1*04 and HLA-DRB1*07 alleles, and HLA-DRB4 gene were higher in CSS patients, indicating the presence of restricted MHC class II repertoire and highlighting the pathogenetic role of T cells in the development of the disease [44, 45]. Such a hypothesis is supported by the presence of clonally expanded subpopulations of T cells in CSS [38, 46].

Interestingly, peripheral blood lymphocytes from CSS patients seem to secrete significantly higher amounts of both Th2 (IL-4, IL-13) and Th1 (IFN γ) cytokines [47]. Similarly, expression of Th1 and Th2-type cytokines was found in biopsies from CSS lesions [48]. Activated Th2-effector cells are considered to be the main source of IL-5, which is undoubtedly the key cytokine responsible for eosinophil differentiation and activation. However, studies analyzing the capacity of stimulated mononuclear cells to produce IL-5 are inconsistent. Some authors detected significantly higher IL-5 secretion in CSS when compared to healthy controls [49], while others found only moderate production of this cytokine in vitro [47, 50] despite concomitant increase in its plasma concentration [37]. The discrepancy between in vivo and in vitro data suggests that other cells can contribute to the IL-5 secretion (e.g., eosinophils) or that tissue-specific factors can modulate the function of Th2 cells at the site of inflammation. In

consequence, the production of IL-5 is probably restricted only to the CSS-related lesions. Indeed, larger amounts of IL-5 were found in BALF sampled from active CSS patients [30] (unpublished data—Jakiela B). This hypothesis has been supported by results of Terrier et al. [50], who found that eosinophils in CSS patients expressed higher amounts of IL-25, capable of enhancing the production of Th2-type cytokines (including IL-5) by activated lymphocytes. Such a growing body of evidence indicates that eosinophils may participate in the development of Th2 responses in target tissues of CSS.

The development of adaptive immune responses is also modulated by immunoregulatory cytokines. For example, IL-10, which is produced mainly by activated macrophages and regulatory T cells, inhibits Th1-type responses, thus favoring differentiation of Th2 cells. Serum IL-10 levels were significantly higher in both active and inactive CSS as compared to healthy controls [43]. Additionally, ANCA-negative CSS has been linked with the IL10.2 haplotype of IL10 gene that has been associated with increased expression of IL-10 [51].

Apart from reciprocal interactions between Th1 and Th2 axes, the development and function of effector T helper cells is tightly controlled by regulatory T lymphocytes (Treg). Treg are a subset of CD4⁺ lymphocytes expressing transcription factor FoxP3, which are capable of inhibiting effector T cell responses in a receptor-mediated manner or by secreting anti-inflammatory cytokines (e.g., IL-10). It has been suggested that CSS could develop in patients with asthma if the numbers of Tregs are low or their secretory function is impaired [52]. Decreased percentages of CD4⁺ FoxP3⁺ cells were found both in active CSS and in patients in remission when compared to healthy controls [37, 53]. It's tempting to speculate that deficiency in Treg cells entails sustained activation of effector T cells, leading to the development of chronic inflammation.

The pronounced Th2 response and subsequent accumulation of eosinophils do not explain, by itself, the development of vasculitis in the course of CSS. Accordingly, vasculitic lesions are not present in other diseases with significant tissue eosinophilia (e.g., hypereosinophilic syndromes). It has only recently been demonstrated that Th17 lymphocytes, which produce large amounts of proinflammatory cytokines (e.g., IL-17A, IL-17F, and IL-22), are involved in the pathogenesis of vasculitic disorders [54]. Two independent groups have described higher numbers of circulating lymphocytes capable of producing IL-17A in CSS [31, 55] and corresponding increases in Th17/Treg ratio, which correlated positively with markers of disease activity. Collectively, these results suggest that increased activity of Th17 cells, when not properly controlled by Treg, could be responsible for maintaining the inflammatory reaction, vasculitic symptoms, or granuloma

formation in CSS. However, the actual role of Th17 cells in the background of Th2-dominated inflammation, awaits further elucidation.

Recently published data make the current pathogenic model of CSS much more complex than previously thought. It seems that multiple lineages of effector T cells, including Th2, Th17, and probably Th1 cells participate in CSS inflammatory response. Both infiltrating lymphocytes and activated resident cells secrete eosinophil-acting mediators, which contribute to eosinophilic inflammation and tissue damage (see Fig. 2 for details). Nevertheless, factors triggering different stages of CSS have not been identified so far, and data explaining development of vasculitis in the background of eosinophilic inflammation are scarce.

Clinical Features

During the course of the disease, the vast majority of patients complain of general symptoms, such as fever, malaise, fatigue, diffuse arthralgia, and weight loss; these symptoms may worsen before the vasculitic phase appears [11]. The systemic nature of CSS implies that it can affect virtually any organ; however, the involvement of the respiratory tract with asthma and pulmonary infiltrates remains a hallmark of the disease.

Respiratory System

Asthma, present in almost all CSS patients [9, 56, 57], precedes vasculitic symptoms for many years (mean 8 ± 10 years) [58]. The disease begins usually during adulthood, is difficult to control, and often corticosteroid-dependent [57, 59]. It is in most cases accompanied by rhinitis, sinusitis, and nasal polyposis [59, 60]. Taken together, these symptoms resemble a common asthmatic phenotype of aspirin-intolerant asthma [61]. However, association of aspirin-induced asthma with vasculitis is rare [62, 63] and CSS patients tolerate aspirin well [64]. Allergic background is common in CSS and ranges from 31.4% to 64% depending on the time of testing during the course of the disease and corticosteroid use [11, 65, 66]. Asthma usually worsens before the vasculitic phase and requires systemic corticosteroids to achieve remission [11, 59].

The presence of pulmonary infiltrates accompanying asthma makes the diagnosis of CSS highly likely. These infiltrates have a patchy, transient character on chest X-ray, occasionally with non-necrotic nodules lacking specific distribution (Fig. 3a). They disappear rapidly after initiation of corticosteroid treatment [66]. Several recent case studies presented the analysis of high resolution computed tomography chest scans which revealed that pulmonary changes

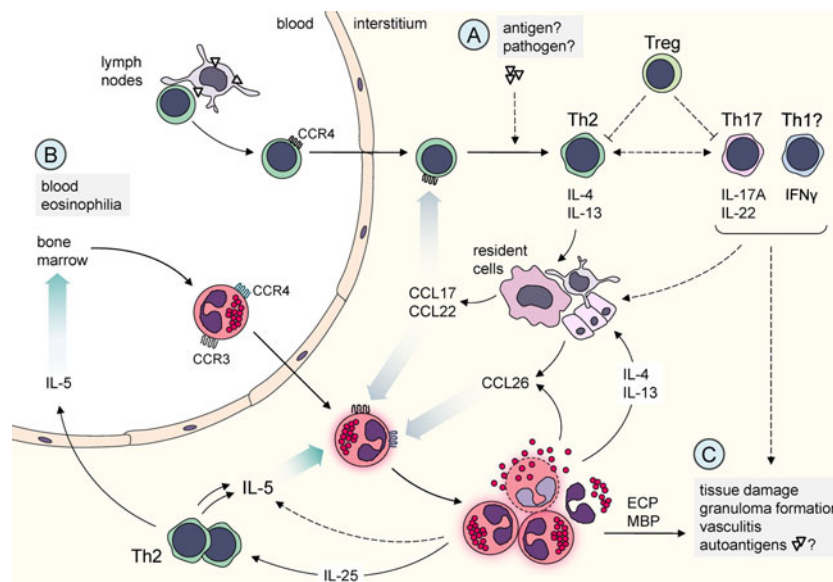


Fig. 2 Putative model of the CSS-related inflammation. **a** Unknown antigens are presented to Th-cells by antigen presenting cells. Effector Th2 cells secrete IL-4 and IL-13, which activate resident cells to produce CCL26, CCL17 and CCL22. **b** IL-5 and eosinophil-acting chemokines promote eosinophil expansion. **c** Activated eosinophils secrete IL-25, favoring Th2-cell activation, and mediate tissue damage by releasing granule proteins and inflammatory mediators. Th17 cells

(and probably Th1) can further activate resident cells and contribute to granuloma formation and vasculitis. *Dashed lines* depict the interactions which have not been studied in detail. Abbreviations: CCR3, CCR4 (C-C chemokine receptor type 3, -4), CCL17, CCL22, CCL26 (C-C motif chemokine 17, -22, -26), Th (T helper cells), Treg (regulatory T cells), IFN γ (interferon- γ), IL-4, -5, -13, -17A, -17F, -25 (interleukin-4, etc.)

can be found in a majority of CSS patients and are present in almost all at the time of initial diagnosis [67–71]. The most frequently described lesions in CT were interstitial ground-glass opacities and bronchial wall thickenings (Fig. 3b); however, the small number of patients in these studies and variability of lesions did not allow for the determination of a characteristic pattern of pulmonary changes. The typical paranasal sinus abnormality revealed by CT scans is the thickening of sinus and nasal cavity mucosa without evident bone erosions (Fig. 3c).

Cardiovascular System

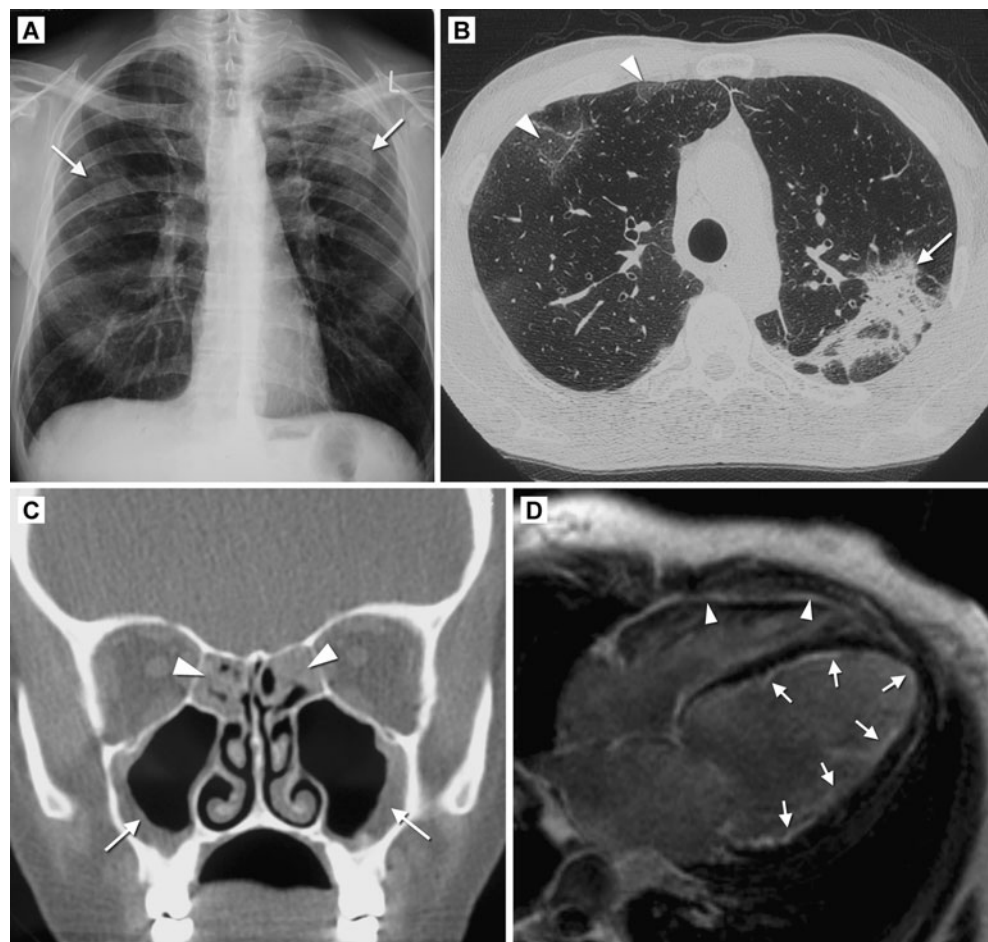
Cardiac involvement in CSS seems to be highly prevalent. Depending on a study and methods of detection, its frequency varies widely (16–92%) [9, 72–75]. It has been suggested that cardiac changes are associated with poor prognosis and high mortality if left untreated [76]. Two possible mechanisms of heart involvement in CSS were postulated: vasculitis-related ischemia [77] and eosinophilic infiltration of the myocardium [78]. The former is now being questioned as heart involvement is less common in the ANCA-positive patients [58], and furthermore, it seems to be more frequent in CSS patients with high eosinophil count at the time of initial diagnosis [74, 75]. Varied forms of cardiac involvement have been described in CSS,

including myocarditis, pericarditis, cardiomyopathy, arrhythmias, intraventricular thrombi, valvular disease, coronary arteritis, and sudden cardiac death [9, 76, 79–81]. Differences in both frequency and character of heart lesions may be partially explained by the diverse examination techniques used. While early reports were based mainly on clinical manifestations and autopsy findings [5], those more recent utilize both echocardiography [82, 83] and cardiac magnetic resonance imaging (CMR) [73–75]. The differences may also depend on the activity of the disease. Although the highest frequency of myocardial damage is observed during the active phase of the disease, patients in remission have detectable MRI changes characteristic for both non-reversible chronic fibrosis (see example in Fig. 3d) and active inflammation [75]. The significance of this clinically silent heart involvement, detected by CMR, and its implications for changes in treatment remains uncertain. In one small study, intensification of immunosuppression led to the improvement of CMR changes in both symptomatic and asymptomatic patients [84].

Neurological Involvement

Neurological manifestations may be found in up to 76% of CSS patients [85]. They usually manifest as an axonal neuropathy, mainly mononeuritis multiplex with sudden weakness, asymmetric foot or wrist drop, and sensory

Fig. 3 Typical radiology imaging findings in CSS.
a Chest X-ray showing peripherally distributed areas of consolidations (*arrows*).
b Chest CT-scan demonstrating ground-glass opacities (*arrowheads*) and consolidations (*arrows*). **c** CT-scan of the paranasal sinuses showing thickened maxillary sinus mucosa (*arrows*) and homogenous tissue occupying ethmoidal sinuses (*arrowheads*).
d Cardiac magnetic resonance in a Churg–Strauss syndrome patient. Late gadolinium enhancement in the four-chamber apical view shows extensive subendocardial fibrosis of left ventricle (*arrows*). The subendocardium of right ventricle is also involved (*arrowheads*).
 Courtesy of Dr. Piotr Grzanka and Tomasz Miszański-Jamka



deficits (Fig. 4a). Peripheral polyneuropathy may also be present [86]. The most commonly affected nerves are peroneal, median, tibial, and ulnar [9]. Their dysfunction may be proved by electrophysiological studies [87]. Central nervous system involvement is less common and affects between 10% and 39% of patients. It includes palsies of muscles innervated by cranial nerves, cerebral hemorrhages or ischemic strokes, seizures, coma, and psychosis [1, 85]. Some preliminary reports suggest also the dysfunction of

parasympathetic nervous system, which may contribute to arrhythmias in CSS patients [88].

Other Organ Involvement

Skin changes are present in about one half to two thirds of patients [9, 89] and are variable. The most common finding is nonthrombocytopenic palpable purpura

Fig. 4 CSS symptoms visible on physical examination.
a Mononeuritis multiplex presenting as left peroneal paralysis. **b** Palpable purpura



(Fig. 4b), but subcutaneous nodules, petechiae, urticarial rashes, livedo of trunk and limbs, and papules can also be present [1, 9, 90]. Skin biopsy may reveal an unspecific condition, such as leukocytoclastic vasculitis [21, 91], or more diagnostic lesions, like extravascular necrotizing granulomas and eosinophilic infiltration of the dermis [92].

Gastrointestinal tract involvement may accompany CSS syndrome in up to one half of patients [89]. The most common complaint is abdominal pain. However, vasculitic symptoms and eosinophilic infiltration may lead to acute abdomen and life-threatening complications, such as bowel ischemia and necrosis, hemorrhage, perforation or bowel fistulas, mucosal ulcerations, and obstructive symptoms [93, 94]. Occasionally, it may affect visceral organs other than intestines and cause pancreatitis or cholecystitis [94].

The most common manifestation of renal involvement is a pauci-immune focal and segmental necrotizing glomerulonephritis that may lead to hematuria, proteinuria, and systemic hypertension [11]. Renal involvement is seen in about 25–47% of patients [9, 11, 66]; however, in contrast to other AAVs, it rarely causes renal failure and may be overlooked.

Laboratory Abnormalities

The main abnormality, often obscured by corticosteroid treatment, is prominent peripheral blood eosinophilia, which regularly exceeds 1,500 cells/ μ l, or according to ACR criteria, more than 10% of the total leukocyte count [14]. It is almost always present during the initial diagnosis and correlates with exacerbations of the disease [9, 11]. Total serum IgE levels are elevated in most CSS patients; however, the IgE lacks specificity for common allergens [65]. During the course of the disease, most patients experience anemia of chronic diseases and elevation of acute inflammatory markers, e.g., elevated erythrocyte sedimentation rate and C-reactive protein [58]. Urinalysis and serum renal function parameters may reveal renal dysfunction. Antineutrophil cytoplasmic antibodies (ANCA) detected by immunofluorescence are present in about 40% of the patients. Among ANCA-positive patients, up to 90% show a perinuclear staining pattern (p-ANCA) (Fig. 5), while the remaining have a cytoplasmic pattern (c-ANCA) [58, 72]. Most of the detectable p-ANCA antibodies are directed against myeloperoxidase (anti-MPO).

Two Distinct Phenotypes of the Disease

Recently, two parallel studies have hypothesized that two distinct phenotypes of CSS could be identified depending

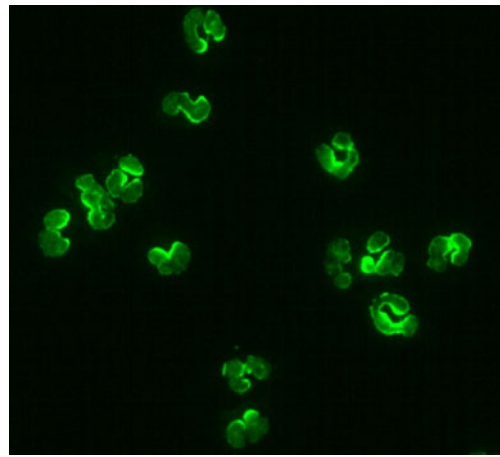


Fig. 5 Perinuclear pattern of antineutrophil cytoplasmic antibodies (p-ANCA). Indirect immunofluorescence staining of ethanol-fixed neutrophils (original magnification, $\times 200$)

on the presence or absence of ANCA antibodies [58, 72]. The ANCA-positive patients predominantly display the vasculitic pattern of the disease with higher incidence of renal involvement, neuropathy, alveolar hemorrhage, and purpura. On the other hand, the ANCA-negative patients tend to suffer from heart and lung disease more often (with the exclusion of alveolar hemorrhage). Additionally, histopathological findings differ within these two subtypes, with fibrinoid degeneration/necrosis being more prevalent in the ANCA-positive group [58, 95].

Prognosis and Severity of CSS

Historically, the prognosis of CSS was inevitably fatal, with mortality rates up to 50% within 3 months from vasculitic phase appearance [11, 66, 96]. With the advent of glucocorticoid treatment, survival rates have substantially increased, and the 5-year mortality does not currently exceed 13.9% [97].

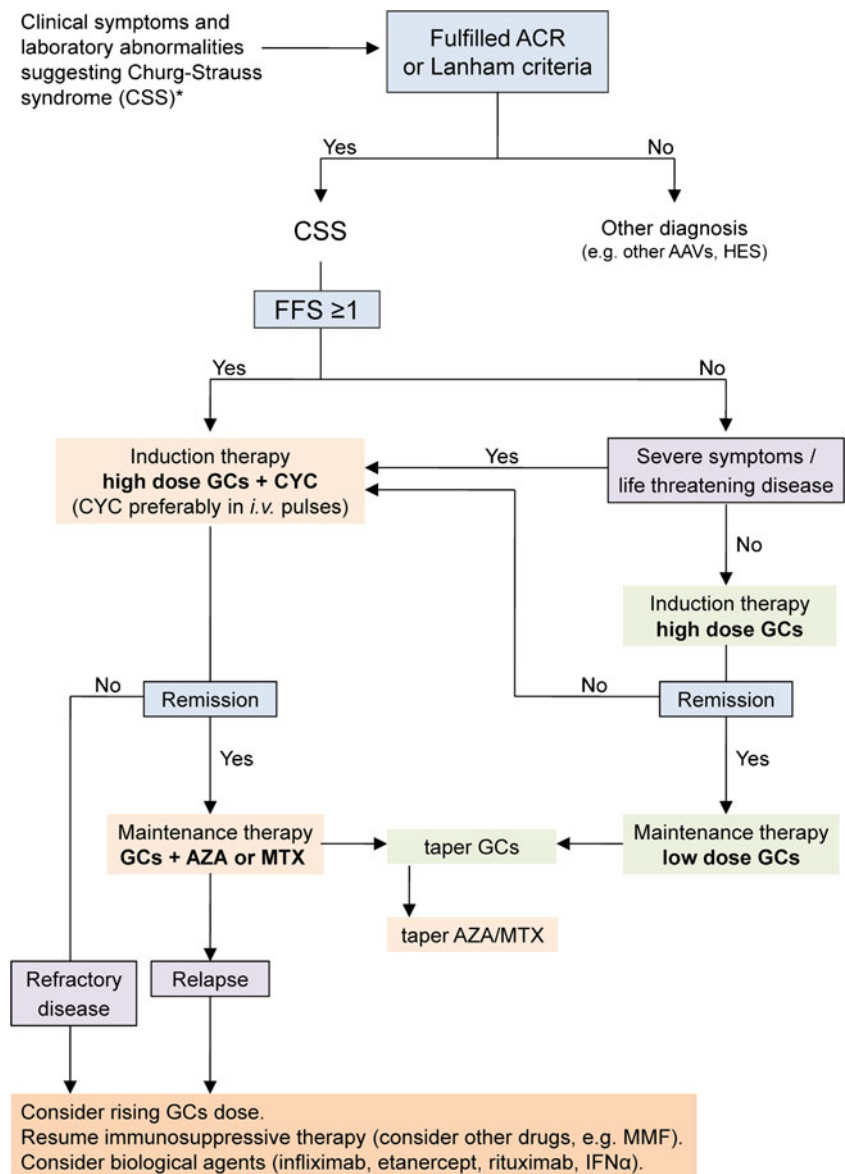
Several objective scoring systems are now available to assess levels of disease activity and organ damage [98]. These include the Birmingham Vasculitis Activity Score (BVAS) [99]; the vasculitis damage index (VDI) [100]; and the five-factor score (FFS) [12]. BVAS serves to assess disease activity by analyzing detailed organ involvement. It is based on nine organ systems and includes 66 questions concerning clinical features attributed to active vasculitis. It has been widely used and validated in many clinical trials. VDI assesses accumulated organ damage due to either disease process or treatment. It illustrates sustained damage and correlates with both morbidity and mortality rates [101]. FFS is a prognostic tool, which distinguishes five features which influence prognosis, namely cardiomyopathy, severe gastrointestinal manifestation, central nervous

system involvement, and kidney impairment (two factors: proteinuria >1 g/24 h or creatinine >140 $\mu\text{mol/l}$). Each of these features has a value of 1 point. Patients with a good prognosis have a FFS of zero. Recently, the FFS has been revised by Guillevin et al. [97] and now comprises of four factors indicating poorer prognosis (age >65 years, cardiac symptoms, gastrointestinal involvement and renal impairment counted as stabilized peak creatinine >150 $\mu\text{mol/l}$), and one connected with a good outcome—the ear, nose, and throat (ENT) involvement (lack of ENT symptoms = +1 point). The main differences between these two versions of the FFS include the introduction of age as a poor prognostic factor, exclusion of central nervous system involvement, and inclusion of ENT involvement as a positive outcome factor. However, this new FFS requires further clinical validation.

Treatment and Outcomes

Systemic glucocorticoids remain the mainstay of CSS treatment. Initial dosage is high, either a 1 mg/kg/day equivalent of methylprednisolone or, in more severe patients, higher doses in intravenous pulses—up to 15 mg/kg/day [89]. Patients with good prognosis (FFS=0) are treated solely with corticosteroids, while patients with poor prognosis (FFS $\geq$ 1) or those resistant to corticosteroids, require additional induction therapy with other immunosuppressants such as cyclophosphamide (CYC) [12, 102]. Initially, CYC is preferably administered as an intravenous pulse regimen, as it may act more rapidly with lower accumulative dose and less side effects [103, 104]. After achieving remission (defined as low and stable peripheral eosinophil count, decreased acute inflammatory

Fig. 6 Suggested therapeutical scheme for patients with Churg–Strauss syndrome. CSS Churg–Strauss syndrome, ACR American College of Rheumatology, AAVs ANCA-associated vasculitides, HES hypereosinophilic syndromes, FFS five factor score, GCs glucocorticosteroids, CYC cyclophosphamide, AZA azathioprine, MTX methotrexate, MMF mycophenolate mofetil, IFN- α interferon-alpha. *other causes of high eosinophilia excluded



phase parameters and no clinically active vasculitis), maintenance therapy is introduced, generally with less toxic immunosuppressants, such as methotrexate (MTX) or azathioprine (AZT). This therapy, together with corticosteroids is then gradually decreased over the course of 18 to 24 months [2]. In most cases, a low dose of maintenance corticosteroid therapy is maintained in order to control asthma [9, 105]. Remission can be achieved in as many as 90% of CSS patients (with FFS=0) but relapses do occur in more than one third of these cases [105]. Relapsing patients should be treated with increased doses of corticosteroids and resumption of immunosuppression [105, 106]. In refractory cases (up to 10% of patients do not respond to standard treatment) and/or often relapsing and severe disease, other immunosuppressants such as mycophenolate mofetil [106] or new biological compounds should be considered. In the latter group, rituximab [36], interferon-alpha (IFN- α) [107], infliximab, and etanercept [108] have shown promising results among a small group of patients, but their role in CSS treatment needs to be further elucidated by large clinical trials.

Patients should be screened for side effects of treatment, and appropriate preventive therapy must be administered [103]. Possible treatment options are shown in Fig. 6.

Summary

A rare systemic small-vessel vasculitis, Churg–Strauss syndrome (CSS) belongs to the group of antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides (AAV). Unique features of CSS include prominent blood and tissue eosinophilia with co-occurrence of bronchial asthma. The etiology of CSS is unknown and its pathogenesis is not completely understood. The possible role of eotaxin-3 and CCR4-related chemokines in selective recruitment of eosinophils to the target tissues has been recently suggested. From the clinical standpoint, two distinct phenotypes of the disease are slowly emerging depending on the presence or absence of ANCA. Steroids are still the mainstay of treatment; however, data are accumulating regarding the beneficial role of novel immunosuppressants and biologic compounds, especially in patients with poorer prognosis.

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