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Churg-Strauss syndrome

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A syndrome comprising asthma, allergic rhinitis, pulmonary and systemic small-vessel vasculitis, and extravascular granulomas was described in 1951 by Churg & Strauss, mainly from autopsied cases (1). Clinical studies of patients with polyarteritis nodosa, associated asthma, pulmonary infiltrates, and eosinophilia had been reported previously (2–5). Churg & Strauss described the pathologic lesions and distinguished this entity from polyarteritis nodosa. They described basic anatomic changes consisting of “widespread vascular lesions of the type seen in polyarteritis nodosa, and of characteristic tissue alteration in the vessel wall and in the extravascular system. This tissue alteration ... comprised necrosis of eosinophilic exudate, severe ‘fibrinoid’ collagen change, and granulomatous proliferation of epithelioid and giant cells.” Churg & Strauss considered it to be a distinct histopathologic entity which they termed “allergic granuloma”.

Classification

Many attempts have been made to classify the vasculitides, based on pathologic and/or clinical features (6–13). Liebow (14) described the group of pulmonary angiitis and granulomatosis, a broad group encompassing disorders characterized by cellular infiltration of the blood vessels with neutrophil or eosinophil leukocytes (angiitis) and destruction and necrosis of the pulmonary parenchyma with a peripheral, chronic, cellular reaction (granulomatosis). Churg-Strauss syndrome (CSS), the least common variety of angiitis and granulomatosis, was later included in this group (10, 15).

The 1992 Chapel Hill International Consensus Conference agreed on a set of names and definitions for most

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systemic vasculitides (16). CSS was defined by the presence of an eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small- to medium-sized vessels, and associated with asthma and blood eosinophilia. The presence of conspicuous eosinophils in inflammatory infiltrates was not included in the definition because it was not a distinguishing feature from other types of vasculitis (16). This definition is limited in its practical use, as it is biopsy dependent (17), and has been criticized (12).

Classification criteria had been previously developed by the American College of Rheumatology (Table 1), by comparing 20 patients who had this diagnosis to 787 control patients with other forms of vasculitis (18). Thus, documented vasculitis was a prerequisite for inclusion in the study. These classification criteria included manifestations that are characteristic of CSS and occur with less frequency or are absent in other vasculitides. The presence of any four or more of the six classification criteria yielded a sensitivity of 85% and a specificity of 99.7%. A classification tree was also constructed in the same study (18), with three selected criteria: asthma, eosinophilia of >10% on differential white blood cell count, and a history of documented allergy other than asthma or drug sensitivity. For example, patients with eosinophilia and a documented history of either asthma or allergy are classified as having CSS. The sensitivity of this tree classification was 95% and its specificity 99.2%. Asthma was the most discriminative in segregating the cases and controls. These classification tree criteria are very simple and might be advantageous in patients with well-documented systemic vasculitis (18). They provide a way to

standardize the definition of the disease in groups of patients, for the purpose of clinical or epidemiologic studies (13) or differential diagnosis (19). However, they are not appropriate for diagnosis of the individual patient (13), and their performance as diagnostic criteria is poor (20).

Pathology

Since the diagnosis of this rare systemic vasculitis has been often made by biopsy of extrapulmonary tissues, the pathologic features of the CSS in the lung have been described in only a few studies (1, 21–27). The gross findings in the lung include lesions of varying size, some of them with necrosis and cavitation. Vascular thrombi and foci of hemorrhage may also be seen, as well as scarring at later stages (28). Histologically, the main characteristic of CSS in the lung is the combination of granulomatous necrotizing vasculitis of small- to medium-sized vessels and eosinophilic pneumonia (11). In patients who have not been on steroid therapy, the latter lesion is often the most obvious histologic finding, with massive eosinophil infiltration of the air space, and interstitial and perivascular eosinophilic infiltrates. The necrotizing granulomatous inflammation affects mainly the extravascular areas, but may also involve the vessel walls. The granulomas are characterized by palisading epithelioid histiocytes surrounding a central necrotic zone rich in eosinophils, which may contain debris from the eosinophils, including Charcot-Leyden crystals (29). Intramural and interstitial non-necrotizing sarcoid-like granulomas may also be seen. The associated vasculitis is characterized by a cellular inflammation of the vessel walls, which is rich in eosinophils and giant cells. It mainly affects the small arteries, but the veins may also be involved. Transmural fibrinoid necrosis or scarring may also be seen.

Bronchial and bronchiolar abnormalities characteristic of chronic asthma are often present, consisting of eosinophilic infiltration and edema of the submucosa, smooth-muscle hypertrophy, goblet cell metaplasia in the bronchiolar mucosa, thickening of the epithelial basement membrane, and mucostasis in the small airways. Interstitial infiltration by lymphocytes and plasma cells may also be present, as well as intra-alveolar histiocytes.

Open lung biopsy is usually recommended in order to obtain sufficient material for pathologic analysis (15). The efficacy of transbronchial biopsy has been recently assessed in six patients with CSS and evidence of active pulmonary disease but without parenchymal lesions easily accessible by radiologically guided biopsy (30). Transbronchial biopsy

Table 1. American College of Rheumatology 1990 criteria for classification of Churg-Strauss syndrome (traditional format classification) (adapted from ref. 18)

Criterion	Sensitivity (%)	Specificity (%)
Asthma	100	96.3
Eosinophilia >10%	95	96.6
Neuropathy, mono- or poly-	75	79.8
Pulmonary infiltrates, nonfixed	40	92.4
Paranasal sinus abnormality	85.7	79.3
Extravascular eosinophils (biopsy including vessels)	81.3	84.4
Sensitivity and specificity were calculated in 20 patients with Churg-Strauss syndrome vs 787 patients with other defined vasculitis syndromes. Patient is classified as having Churg-Strauss syndrome if at least four of these six criteria are positive. Presence of any four or more of six criteria yielded sensitivity of 85% and specificity of 99.7%.		

provided a diagnostically helpful histopathology in four of six cases. Biopsies from the upper respiratory tract were positive in five out of six cases. CSS may also be diagnosed by biopsy of extrapulmonary tissues, such as skin, muscles, or nerves. Typical features include the presence of an eosinophil-rich vasculitis of the small vessels (28). The presence of extravascular necrotizing granulomas is highly suggestive. The cutaneous and subcutaneous lesions, called CSS granulomas, lack diagnostic specificity (31, 32).

The differential diagnosis of CSS with Wegener's granulomatosis, hypereosinophilic syndromes, polyarteritis nodosa, and microscopic polyangiitis is rarely difficult when the clinical features are taken into account. However, the pathologic lesions of CSS may resemble those of the other vasculitides, highlighting the possible overlaps between these entities (32, 33). In addition, the three lesions characteristic of CSS, namely, necrotizing vasculitis, eosinophilic pneumonia, and extravascular granulomas, which rarely coexist temporally or spatially in biopsy specimens from patients with CSS, are found together in a minority of cases, and are not pathognomonic (25, 31). Eosinophilic infiltration of the air spaces, and necrotizing and eosinophilic extravascular granulomas are usually not seen in Wegener's granulomatosis, whereas the extensive and destructive parenchymal necrosis characteristic of the latter disorder is not a feature of CSS (32, 34, 35). Extravascular granulomas are also absent in polyarteritis nodosa, a disorder in which lung involvement is less frequent, and microscopic polyangiitis (31, 36).

Distinguishing CSS from chronic eosinophilic pneumonia may be more difficult pathologically, since the eosinophilic infiltration of the lung is similar in these disorders. Moreover, a moderate vasculitis (37, 38) and small extravascular eosinophilic granulomas (15) may be found in chronic eosinophilic pneumonia. Thus, the diagnosis of CSS should be restricted to patients in whom the necrotizing granulomatous vasculitis is prominent, and associated with clinical features of vasculitis (15).

Clinical features

Natural history

Three phases have been described by Lanham et al. in the natural history of CSS, although they do not always appear successively (25). Typically, it begins with allergic rhinitis, which is often complicated by nasal polyposis, allergic rhinitis, allergic sinusitis, and asthma. This first phase may

last for years, and is followed by a second phase with the onset of blood and tissue eosinophilia, with chronic eosinophilic infiltration of the lung and/or eosinophilic gastroenteritis. Spontaneous or treatment-induced remission of the disease can occur at this stage, but recurrence is frequent. The third stage is defined by the emergence of symptoms of systemic vasculitis. The mean delay between the onset of asthma and of the vasculitis is 3 years, but longer delays (up to 58 years) have been reported (39). On the other hand, asthma and vasculitis can occur simultaneously. A short interval between the onset of asthma and the appearance of systemic symptoms may indicate an unfavorable prognosis (22).

CSS mainly affects adults with a mean age of about 40–45 years (range 7–74 years) at the onset of asthma (31), although an older mean age (50 years) has been reported in more recent series (18). The vasculitis may not be present until the fifth decade of life (25). The male to female ratio ranges from 1 to 3, depending on the clinical series (13, 22, 25, 40–42) (reviewed in ref. 31). The annual incidence of the disease has been estimated to be 2.4/million/year, which is less than the estimated incidence for Wegener's granulomatosis (8.5/million/year) or systemic rheumatoid arthritis (12.5/million/year) (43).

Asthma

Asthma is always present in CSS (22, 25, 40–42). As compared to common asthma, it appears later in life, is more severe, and requires more frequent use of corticosteroids, although it initially seems quite typical. The clinical manifestations of airways disease increase in frequency and severity, until the vasculitis appears (25). Improvement or even remission of the asthma has been reported after the vasculitis is present (22). Fever and weight loss become prominent in patients developing systemic symptoms of vasculitis, and their presence in patients with asthma is evocative of CSS (31). Endobronchial granulomas macroscopically visible at bronchoscopy have been described (44), but are seldom seen in CSS, in contrast to Wegener's granulomatosis.

Pulmonary infiltrates

Asthma is accompanied by pulmonary infiltrates in two-thirds of the patients (22, 25, 40–42), and this association is very suggestive of the diagnosis. The infiltrates can also appear later in the history of the disease and coexist with the vasculitis. Roentgenographic features are characterized by

transient and patchy infiltrates which lack lobar or segmental distribution (45), and disappear rapidly after corticosteroid treatment. The infiltrates may be peripheral and symmetric and similar to chronic eosinophilic pneumonia (46). Nodular bilateral opacities may occasionally be seen but rarely cavitate, in contrast to Wegener's granulomatosis (35, 45, 47). A diffuse interstitial infiltrate can also be seen, but is less common than it is in Wegener's granulomatosis (47). Hilar lymph node enlargement has been occasionally reported. Rarely, diffuse alveolar opacities reveal diffuse alveolar hemorrhage (48, 49). Remarkably, the chest radiograph is often normal throughout the course of the disease (22, 42, 50).

The pulmonary abnormalities of CSS have been recently studied by high resolution and conventional CT of the chest (51, 52). The predominant CT findings consist of parenchymal consolidation and/or ground-glass opacities (10 out of 17 patients) (52). Parenchymal opacification was predominantly peripheral in distribution in six patients (then mimicking the CT abnormalities seen in chronic eosinophilic pneumonia) and patchy in four patients. Pulmonary nodules, bronchial dilation, thickening of the bronchial walls or of the interlobular septa, and bronchiectasis were also noted in some patients. One patient had multiple cavitating nodules. Interestingly, the chest CT was normal in two (out of 17) patients. Enlarged, irregular, and stellate-shaped arteries have been described by high-resolution CT in a patient with CSS (53). These radiologic findings correlated with enlargement and eosinophilic infiltration of the vessel walls on histologic examination. Similarly, small (0.5–1.5 mm) fluffy densities with a centrilobular and perivascular distribution have been described in children with pulmonary involvement of various vasculitides including CSS (54). Although not specific, this pattern was thought to correspond to an angiocentric inflammatory process with some associated hemorrhage, and correlated with the clinical progression of symptoms.

Pleural abnormalities are relatively common (about 30%) in patients with CSS (55). Specific manifestations of the vasculitis must be distinguished from pleural infections, which may be secondary to the iatrogenic immunosuppression. Pleural effusions associated with CSS tend to be small (52) and manifest occasionally as pleurisy or dyspnea. When done, the pleural biopsy shows a chronic pleuritis with eosinophilic infiltration (55). The effusion is an exudate with a notably high eosinophilia. Phrenic nerve paralysis has also been reported in CSS (56).

Rhinitis and sinusitis

Allergic rhinitis is observed in about three-quarters of the patients (25, 57). Nasal eosinophilic polyposis, nasal mucosal crusting, and chronic or recurrent eosinophilic sinusitis are common during the evolution of CSS (58). Since the necrosis is much less common than in Wegener's granulomatosis, complications of the rhinitis are rare. Nevertheless, perforations of the nasal septa have been reported (57, 58).

Laboratory abnormalities

Peripheral blood eosinophilia is an essential feature of CSS, and usually exceeds $1.5 \times 10^9/l$ in the peripheral blood, a diagnostic criterion proposed by Lanham et al. (25). All the 20 patients described by Masi et al. (18) had eosinophilia on white blood cell differential counts that was $>10\%$ (range 11–77%) in either present or past hospital admissions, and all but two patients had absolute eosinophil counts of $>1.5 \times 10^9/l$. The association of high eosinophilia and asthma in the context of systemic vasculitis is highly suggestive of CSS (18). The peripheral eosinophil count usually drops very rapidly after the onset of the corticosteroid treatment, and rises if the disease relapses (25, 59). Eosinophilia is also present in bronchoalveolar lavage fluid, with eosinophilia on white cell differential counts often greater than 60%, the mean percentage being around 30% (50, 55, 60–62). The alveolar eosinophilia can persist under corticosteroid treatment, even after clinical and radiologic abnormalities have disappeared (61). Marked pleural eosinophilia is also common in patients with pleural effusion (55).

Antineutrophil cytoplasmic antibodies (ANCA) are present in 55–67% of the patients with CSS, depending on the technique used (63). The ANCA are mainly perinuclear ANCA of antimyeloperoxidase specificity, but cytoplasmic ANCA are also possible (64, 65). The presence of ANCA is not specific for CSS, but is also associated with Wegener's granulomatosis (mainly cytoplasmic ANCA with antiproteinase 3 specificity) and microscopic polyangiitis (mainly perinuclear ANCA), but not polyarteritis nodosa (35, 66). Thus, the classification of a given case between the above-mentioned vasculitides should not be based on the specificity of ANCA, but rather on the presence of distinctive clinical or pathologic features (67).

Very high IgE levels are common in CSS but lack specificity (22, 25, 42, 50). For example, IgE values were elevated in all of the five patients tested in the series of Masi

et al. (18), and six of the eight patients tested in the series of Lanham et al. (25). Other nonspecific biologic abnormalities have been reported, including increase of the erythrocyte sedimentation rate, anemia, positive rheumatoid factor, and immune complexes (25).

Systemic vasculitis

The systemic vasculitis of CSS resembles that of polyarteritis nodosa, but severe renal disease is less common. The onset of the vasculitis is suspected when myalgia, arthralgia, and general symptoms (fatigue, weight loss), appear in an asthmatic patient. The systemic vasculitis accounts for most of the deaths from CSS. In their review of the literature, Lanham et al. (25) showed that the main causes of death in CSS were heart failure (48%), renal failure (18%), cerebral hemorrhage (16%), and gastrointestinal perforation or hemorrhage (8%), whereas status asthmaticus and respiratory failure caused the death of only 8% and 2% of the patients, respectively.

Cardiovascular disease occurs in about half the patients suffering from CSS (25, 41, 42), and may be the first manifestation of CSS (68, 69). The clinical spectrum of cardiac abnormalities in CSS ranges from asymptomatic electrocardiographic abnormalities to sudden death (68, 69). Although all cardiac structures may be involved, granulomatous eosinophilic infiltration of the myocardium and coronary vessel vasculitis are the most common lesions, leading to coronary disease (68, 70, 71) and severe congestive heart failure (72). Five of the 13 patients initially reported by Churg & Strauss (1) had heart failure. The myocardial dysfunction may be improved by a therapy combining steroids (73) and cyclophosphamide (74). Heart, or heart and lung transplantation has been proposed (72, 75), but the lack of control of the systemic vasculitis may lead to the recurrence of the disease in the transplanted heart (76). Mitral regurgitation is common in CSS, since it was present in half the cases in a series of 12 patients who were tested echocardiographically (77); it could be observed even when the ventricular function was well preserved, and might have been caused by diffuse myocardial fibrosis (77). Pericardial effusions are common and usually moderate (18, 42), but occasionally can be hemodynamically significant (78–80) or lead to pericardial fibrosis (78). Endomyocardial involvement is rare but can lead to endomyocardial fibrosis (81–84).

Neurologic involvement is present in over 60% of the patients with CSS (22, 25, 31, 85). It usually manifests as peripheral neuropathy: mononeuropathy multiplex, distal symmetric polyneuropathy, or sometimes asymmetric

polyneuropathy (85–88). Sural nerve biopsy contributes to the diagnosis when vasculitis is found pathologically (89). Immunohistochemical studies of sural nerve biopsies have shown the infiltration of epineural vessels with CD4-positive and, to a lesser extent, CD8-positive lymphocytes; immunoglobulins G, M, A, and notably, E, as well as complement factors and light chains, were also reactive in these biopsies, supporting the concept that nerve obstruction or destruction of the vasa nervorum by the vasculitis, immunologic abnormalities through IgE, and/or a primary T-cell-mediated process against epineural vessels may play a pathogenic role in the peripheral neuropathy of CSS (90, 91). Less commonly identified peripheral manifestations include radiculopathies (92), ischemic optic neuropathy, and trigeminal neuropathy (85). Reports of central nervous system involvement are less frequent (25%) (93); it ranges from psychiatric disturbances to myelopathy (94), cerebral infarctions (85), cerebral hemorrhage (95, 96), epilepsy, and coma (50, 82). In addition, patients with CSS receiving corticosteroids and a cytotoxic agent are at increased risk of developing central nervous system infection or lymphoma, the clinical manifestations of which may be indistinguishable from those of the systemic vasculitis (97).

Renal involvement is present in 16–49% of the patients, but is generally considered to be mild, as opposed to the severe necrotizing glomerulonephritis with segmental thrombosis which is the hallmark of polyarteritis nodosa (31). However, hematuria, proteinuria, or systemic hypertension (25) may be present, and a marked renal impairment has been described (40, 98, 99). The frequency of severe lesions may be underestimated since renal impairment accounted for 18% of the deaths from CSS in the series of Lanham et al. (25), and 14% of the deaths in the series of Guillemin et al. (100). When performed, the renal biopsy typically shows focal segmental glomerulonephritis with possible necrotizing features including crescents, often associated with p-ANCA (31). Eosinophilic interstitial infiltrates, granulomas, and vasculitis are also possible but uncommon (31, 98, 101).

The gastrointestinal tract may be affected by CSS, the mesenteric vasculitis and/or the eosinophilic infiltration of the bowel wall causing ischemia (102), small-bowel perforations (103, 104) or necrosis (105), fistulas (106), mucosal ulceration (103, 106), hemorrhage (107), or obstructive symptoms (108). Pancreatitis and acute acalculous cholecystitis have also been reported (100, 109, 110). The involvement of the gastrointestinal tract can appear before the asthma (111). It accounted for 31% of the deaths from CSS in the series of Guillemin et al. (100).

Cutaneous lesions are present in about two-thirds of the patients (31) and may be the initial manifestation of the disease (112). The main lesion encountered is a palpable purpura of the lower extremities (25, 112, 113). Subcutaneous nodules of the limbs and scalp are seen in about 30% of the patients (22, 25). Although suggestive, these lesions are not pathognomonic, and do not distinguish CSS from the other vasculitis syndromes (18). Their biopsy may show only leukocytoclastic vasculitis, or more specific lesions such as extravascular necrotizing granulomas or eosinophilic infiltration of the dermis (112, 114, 115), therefore contributing to the diagnosis of CSS. Skin infarction (114), livedo reticularis (31, 116), erythematobullous lesions (116), macular erythema (114), papular erythema (112), and urticaria (116) may also be seen. The cutaneous involvement generally parallels the systemic course of the disease.

Polyarthralgias and arthritis are present in 28–51% of the patients (31), especially during the onset of the vasculitis. Myalgias are also common, but polymyositis is rare (117). Muscle biopsy often contributes to the diagnosis of CSS (88, 118). Osteonecrosis has been described (119).

Ophthalmologic complications of CSS are rare, but ischemic optic neuritis can lead to blindness (120–122). Third nerve palsy (123) and orbital pseudotumor have also been described (124).

Occasional patients have had allergic granuloma involving the lower urinary tract and the prostate (125, 126). These rare lesions may lead to bilateral ureteral stenosis, secondary obstructive uropathy, and anuria (127).

Autoimmune hemolytic anemia (128) has been occasionally described in the course of CSS. The occurrence of thromboembolism may be triggered by the vasculitis or by the activation of thrombosis by eosinophil products (129).

CSS has been reported during childhood (130, 131). It is especially rare in women of reproductive age, although, when present, it may be associated with fetal mortality in pregnancy (132). However, successful pregnancies of patients with CSS in remission at the beginning of the pregnancy have been reported (132–134). Recurrence of the CSS may be triggered by the pregnancy (133, 135).

Diagnosis

Diagnostic criteria

Since CSS lacks pathognomonic features, the diagnosis relies on the presence of a combination of clinical and

laboratory manifestations (13). Three diagnosis criteria for CSS have been proposed by Lanham et al. (25):

- 1) asthma
- 2) eosinophilia exceeding $1.5 \times 10^9/l$
- 3) systemic vasculitis of two or more extrapulmonary organs.

These criteria have proven useful for the purpose of diagnosing CSS in a given patient. However, they were defined before detection of ANCA was available. The presence of ANCA should now probably be considered a major diagnostic criterion when present (136), obviating the need for biopsy in typical cases.

Concept of “formes frustes” of CSS and overlapping syndromes

The diagnosis of CSS may be difficult since it may occur with a variety of clinical presentations. The initial description made by Churg & Strauss (1) was based on a pathologic study of untreated patients who had died of the disease. They all presented severe asthma and systemic vasculitis lesions. Since then, many variant forms of the disease have been described in which one of the main diagnostic criteria of the disease is missing (25, 138). Such cases have been described as “formes frustes” of CSS (137), and seem to occur particularly in patients who have been treated with corticosteroids for a diagnosis of asthma. Alternatively, some patients exhibit a form of the disease limited to a particular organ, with pathologic lesions highly suggestive of CSS. For instance, a case of Churg-Strauss syndrome with eosinophilic vasculitis localized to the colon and the gallbladder has been reported (102). However, such cases of CSS presenting without asthma are exceptional (138, 139).

The limits of CSS from the other vasculitides and other hypereosinophilic disorders may be difficult to delineate (136). The lesions of CSS may overlap with those of many other disorders, as discussed above. Moreover, occasional cases of clinical overlap syndromes have been described. For example, the association of typical clinical features of CSS and temporal arteritis with jaw claudication has been reported (140–142). Similarly, chronic eosinophilic pneumonia may progress to CSS (143–146). Overlap syndromes between CSS and Wegener's granulomatosis have been reported (147). Some cases may also be difficult to classify as either CSS or idiopathic hypereosinophilic syndrome (136).

Pathogenesis

Infections

The relationship between vasculitis syndromes and infection is complex, and was the focus of several recent reviews (148–150). Briefly, the induction or exacerbation of vascular injury may be triggered by immune complexes containing bacterial or viral antigens, by pathogens which directly invade the endothelial cells, or by circulating cytokines or autoantibodies related to a systemic infection. It has been hypothesized that bacterial infections might upregulate the surface expression of autoantigens such as proteinase-3 via reactive cytokines, thus enhancing autoimmune inflammation (148). The effectiveness of antimicrobial therapies in the prevention of relapses during Wegener's granulomatosis or Behçet's disease is compatible with the participation of bacterial agents in the pathogenesis of systemic vasculitides (151, 152). Several vasculitides have long been associated with a variety of persistent viral infections, particularly hepatitis B virus (linked to 7–36% of the cases of polyarteritis nodosa [153]), hepatitis C virus (associated with most cases of mixed cryoglobulinemic syndrome and many autoimmune disease manifestations [148, 154]), and human immunodeficiency type-1 virus (HIV-1) (associated with a wide variety of rheumatic and autoimmune complications [155]). Due to the rarity of CSS, the association between this disorder and viral infections has not been thoroughly investigated. However, the onset of CSS has been reported in a patient with HIV-1 infection who also had antibodies to hepatitis B virus (156). In such a case, the vasculitis may occur as a result of a direct pathogenic effect of HIV-1 infection on vascular tissues, or as a consequence of one of the many coinfections accompanying HIV-1 infection in immunocompromised patients (148). Alternatively, it could be merely a coincidence of two independent disorders.

ANCA

ANCA are a group of autoantibodies directed against various cytoplasmic constituents of polymorphonuclear leukocytes: proteinase 3 or bactericidal permeability-increasing protein for cytoplasmic ANCA, myeloperoxidase, and much less often elastase, cathepsin G, lysozyme, lactoferrin, azurocidin, and other yet to be identified constituents of neutrophils for perinuclear ANCA (35, 157). ANCA have been associated with vasculitides (158). They may also participate in the pathogenesis of these disorders in which extravascular structures are a common site of injury, by triggering the

release by neutrophils of toxic granule proteins and oxygen radicals (159), and increasing the expression of adhesion molecules by endothelial cells (160). Some support for this concept has come from the demonstration of a relationship between the presence of serum ANCA and the activity of the disease (161). On the other hand, serum anti-endothelial cell antibodies are associated with both active and inactive phases of CSS. They are likely to reflect endothelial cell damage (like elevated levels of soluble thrombomodulin), but may not participate in the pathogenesis of the vasculitis (161). Although pulmonary disease appears at some time during the course of disease in many patients with ANCA-associated vasculitis, no histologic lesion of the lung could be found to be specific for perinuclear or cytoplasmic ANCA (162).

Little is known about the mechanisms leading to the development of ANCA. Exposure to silicon-containing compounds has been associated with the presence of ANCA of myeloperoxidase specificity (163). Recent evidence has shown that proteinase 3, one of the main ANCA antigens, is constitutively expressed on the surface of a subset of resting normal neutrophils. The formation of ANCA may be favored by a genetic predisposition, such as a genetically determined severe α_1 -antitrypsin deficiency (which also inhibits proteinase-3), or genetic heterogeneity of the ANCA antigen itself (157). Also favoring the genetic predisposition of systemic vasculitis are the link between systemic vasculitis and particular human leukocyte antigen molecules, and the animal model of spontaneous granulomatous arteritis in mice carrying a hereditary deficit in *Fas*-mediated apoptosis (157). Interestingly, resistance of peripheral blood lymphocytes to *Fas*-induced apoptosis has been described in a patient with CSS (164).

Allergy, drugs, and immunizations

A number of systemic vasculitides including CSS may have an allergic component, although the specific allergens have not been identified. This hypothesis is based on the higher prevalence of allergies among the families of patients suffering from systemic vasculitis (45–73%) than in controls (41, 165). In CSS, allergic-type rhinitis is part of the clinical spectrum of the disease (25).

However, a precise precipitating factor is difficult to establish, since reintroduction of the suspected agent is hazardous and ethically questionable. In a retrospective study of 43 patients with systemic necrotizing angitis and asthma, Guillemin et al. (41) showed that 19 patients had a history of desensitization and five of vaccination in the 4

weeks preceding the onset of the disease, suggesting that these events may have provided an antigenic stimulus to precipitate the vasculitis. The repetitive exposure to airborne antigens is considered a possible precipitating factor for CSS (41). The concern about an etiologic role of *Aspergillus* species has also emerged after the observation of a patient with demonstrated allergic bronchopulmonary aspergillosis, in whom the disease progressed to typical CSS after a latent period of 17 years (166). Similarly, inhaled organic antigens (*Actinomyces*) have been suspected to initiate the pathogenesis of the disease in a patient who developed CSS after exposure to pigeons (167). The clinical course of the vasculitis was also closely related to smoking cocaine in a woman with relapsing CSS (168). Other reported cases might suggest the possible triggering role of *Ascaris* infection or hepatitis B virus vaccination (169, 170). Altogether, these reports argue for the possible triggering role of various agents in susceptible patients. However, they have remained isolated so far.

A possible association between treatment with leukotriene modifiers and CSS has been suggested recently, after several patients developed a clinical syndrome indicative of CSS, consisting of pulmonary infiltrates, peripheral blood eosinophilia, and cardiomyopathy, while receiving zafirlukast (171, 172). Zafirlukast, a novel, orally administered, competitive cysteinyl leukotriene type-1 receptor antagonist, was recently approved for the treatment of mild to moderate asthma (173). Although its use was safe during initial clinical trials, its increase in use may have unmasked an uncommon adverse effect. The eosinophilic syndrome developed while the patients discontinued or tapered oral corticosteroid treatment, so it is unclear whether zafirlukast itself or the tapering of corticosteroid was responsible for the onset of the syndrome. Interestingly, all the patients had findings sufficient for the clinical diagnosis of CSS, but their presentation was atypical in that all patients had acute dilated cardiomyopathy, and the airway obstruction symptoms were attenuated (171). This may reflect the altered activation of eosinophil leukocytes in the presence of the drug. The adverse effect may be secondary to an imbalance in leukotriene receptor stimulation, since zafirlukast opposes the action of cysteinyl leukotrienes C₄, D₄, and E₄, but not of B₄ (174). Notably, all eight patients who developed the syndrome had been dependent on steroids. The most plausible hypothesis proposed by the authors is that zafirlukast reduced the airway symptoms and facilitated a reduction of the corticosteroid dose in patients suffering from a pre-existing eosinophilic syndrome such as a forme fruste of CSS (137, 175), which in turn was

unmasked by the tapering of the corticosteroids (171). However, two similar cases have been described in patients who had not been taking corticosteroids recently (176, 177). Thus, a causal relationship between zafirlukast and CSS cannot be ruled out.

Other cases of drug-induced granulomatous angiitis (178–185) and ANCA-positive non-CSS vasculitides (186) have been reported but are a very rare occurrence.

Eosinophils

It is generally accepted that eosinophil leukocytes play a role in the pathogenesis of a variety of diseases, including asthma (187–190). Although their specific role in the pathogenesis of systemic vasculitides has been less studied than that of neutrophils, one can suspect a particular role of eosinophils in CSS (191). Hence, they have been shown to release specific proteins contained in their cytoplasmic granules, as well as oxygen-free radicals, eicosanoids, sulfido-peptide leukotrienes, platelet-activating factor, and a number of cytokines and growth factors (192–194). Of particular interest, the granule-derived proteins are released by activated eosinophils, which present a specific phenotype (hypodense eosinophils) (195, 196). These include major basic protein, eosinophil cationic protein (ECP), eosinophil peroxidase, and eosinophil-derived neurotoxin/protein X (EDN). These cationic proteins have been shown to have cytotoxic properties for airway epithelium (197–199), to activate coagulation and complement cascades (200–203), to induce the release of a variety of inflammatory factors and cytokines (193, 204), to upregulate the expression of adhesion molecules (205, 206), and to increase vascular permeability (207), bronchial reactivity to methacholine (208), and bronchoconstriction *in vivo* (209). These various effects have been implicated in the pathogenesis of asthma, and are likely to be also involved in that of CSS, although specific evidence is lacking. Activated eosinophils have also been implicated in the pathogenesis of endomyocardial fibrosis, through activation of coagulation and stimulation of fibroblast proliferation (210), and they may participate as well in the endocardial and myocardial fibrotic lesions seen in CSS (211).

Hypodense eosinophils have been observed by ultrastructural studies in the bronchoalveolar lavage of patients suffering from CSS (59), although this phenotype was not as prominent as it was in chronic eosinophilic pneumonia (195). Initially described in a patient with chronic eosinophilic pneumonia (212, 213), urinary EDN excretion is thought to reflect ongoing *in vivo* eosinophil degranulation

Table 2. Predictive mortality value of five-factor score in patients with polyarteritis nodosa and Churg-Strauss syndrome, from references 31, 226

FFS	Five-year survival (%)	Relative risk	No. of patients (n=336)
0	88.1	0.62	218
1	74.1	1.35	81
≥2	54.0	2.40	37

The five-factor score (FFS) was defined as number of factors present in patient: proteinuria greater than 1 g/day, renal insufficiency (creatininemia greater than 140 $\mu\text{mol/l}$), cardiomyopathy, and gastrointestinal tract or central nervous system involvement. Five-year survival rate was 77.6% for polyarteritis nodosa group and 78.9% for Churg-Strauss syndrome.

(60). Hence, high levels of urinary EDN excretion were described in patients with CSS, suggesting that eosinophil degranulation occurs *in vivo* in this disorder (59, 60). Interestingly, different kinetics was observed between the delayed decrease in urinary EDN excretion, and blood eosinophil counts, which rapidly dropped to a normal value after the onset of corticosteroid treatment (60). Thus, measurement of urinary EDN excretion may be a useful indicator of a sustained eosinophil degranulation *in vivo* and of disease activity in CSS. Large amounts of ECP and EDN were also found in the granulomas of necrotic lesions (214), demonstrating that eosinophil degranulation actually takes place in the active lesions of CSS. A high level of serum ECP has been described in a patient with CSS, the level declining in the remission stage (215). In a recent study conducted in patients with CSS, markedly increased levels of serum ECP indicative of eosinophil activation were found during the active phase of the disease, but not during remission (161). Interestingly, high levels of soluble interleukin-2 receptor were also present during active disease, indicating that T-cell activation also takes place in CSS. Similarly, the serum interleukin-5 level was elevated upon admission of a patient with CSS, and normalized under corticosteroid treatment (216), suggesting that interleukin-5 may be involved in the recruitment, priming, and/or activation of eosinophils in CSS. Taken together, these findings suggest a role for eosinophil leukocytes in the pathogenesis of CSS.

Cytokines and adhesion molecules

Cytokine production has been studied in patients with CSS. Elevated levels of serum tumor necrosis factor- α , transforming growth factor- β , interleukin-2, interleukin-5, interleukin-6, interferon- α , and interleukin-2 receptor were shown (161, 216–220). Interestingly, transforming growth factor- β , a cytokine known to stimulate angiogen-

esis and inflammatory cell chemotaxis, is a potent inducer of the translocation of the lysosomal enzyme proteinase 3 to the cell surface of polymorphonuclear neutrophils (220), and might play a crucial role in the genesis of ANCA-associated disorders.

Several studies have reported increased expression of adhesion molecules on circulating leukocytes and, *in situ*, on endothelial cells in vasculitic lesions (221). This upregulation of adhesion molecules reflects the activation of endothelial cells and polymorphonuclear leukocytes, and promotes the activation and recruitment of neutrophils and probably eosinophils and monocytes to sites of active inflammation (157).

Integrating the pathogenesis of CSS

Like most forms of vasculitides, the occurrence of CSS is likely to require a combination of inherited risk determinants and environmental triggering factors, including antigens and/or infections, which by themselves are insufficient to cause vasculitis complications (222). Prolonged or unusual surface expression of ANCA antigens related to infections or other antigenic stimulation, in the context of a susceptible genetic background, may lead to the immune presentation of ANCA antigens to circulating leukocytes and then to the production of ANCA (157). The ANCA may then mediate the activation and adherence of neutrophil and eosinophil polymorphonuclear cells to the endothelium, and the release of toxic components, thus damaging the endothelium and initiating the vasculitis process. A deficiency in the phagocytic removal of apoptotic neutrophils and eosinophils by macrophages may increase the inflammatory phenomenon. The increase in permeability of the endothelium to monocytes/macrophages would allow the amplification of the inflammatory process, through the generation of a variety of cytokines and chemokines and the expression of adhesion molecules. The actual pathogenesis of the disease, however, remains an enigma.

Treatment and prognosis

As in other systemic vasculitides, the mortality rate in CSS is high if left untreated. Glucocorticoids have largely improved patient outcome in this disorder, and continue to be the basis of the treatment. They are usually started at the dose of 1 mg/kg/day of prednisone, and tapered progressively after 1 month over a 9–12-month period, with

careful survey of the clinical status, blood eosinophil cell count, and erythrocyte sedimentation rate. Although very few data are available, the persistence of ANCA after clinical remission does not adequately reflect disease activity, and should not be the basis for therapeutic intensification (223). After the inflammatory disease is controlled, an alternate-day regimen should be preferred whenever possible in order to reduce the risk of infection (224). Stopping the corticosteroids can be difficult after vasculitis has been controlled, because of the residual asthma.

Although initial reports suggested that glucocorticosteroids could be used alone as the initial therapy for CSS (22, 25), in a proportion of patients, a combined therapy with a cytotoxic agent (cyclophosphamide, azathioprine) and glucocorticoids seems to be required in order to control the disease. Due to the rarity of the disorder, most of the therapeutic trials studying CSS also included patients with polyarteritis nodosa. Since it remains unclear whether these vasculitides are similar enough to justify identical therapeutic strategies in all cases, one should be cautious when applying their results to CSS. Nevertheless, several trials showed the efficacy of both glucocorticoids and glucocorticoids plus cyclophosphamide (100, 225, 226). The addition of cyclophosphamide to corticosteroids and plasma exchanges mainly improves the quality of the initial clinical response to therapy, and reduces the incidence of relapses (225). However, this treatment is associated with major side-effects, and the dose should be kept as low as possible (227). Monthly intravenous pulse cyclophosphamide therapy (0.6 g/m² for 1 year, adapted to renal function, adjusted downward as needed to avoid total leukocyte counts lower than 3×10⁹ cells/l, and given with intense hydration, and together with the protective agent mesna), should be preferred to oral daily cyclophosphamide (2 mg/kg per day or less for 1 year in combination with corticosteroids), because it allows a lower cumulative dose, would be less toxic, is at least equally effective at controlling disease activity, and is more rapidly effective than the daily oral regimen (31, 227, 228). Therefore, oral cyclophosphamide has been proposed as a second-line rescue treatment for patients with CSS or another severe systemic vasculitis in whom the disease is not controlled by corticosteroids and a monthly pulse regimen of cyclophosphamide (229).

High-dose methylprednisolone pulses (15 mg/kg per day intravenously over 60 min for 1–3 days) have become widely used at the initiation of therapy when a life-threatening condition requires a rapid action treatment (6, 31). High-

dose intravenous immunoglobulin may also be helpful (230). The combination of plasma exchanges with either corticosteroids alone, or corticosteroids and cyclophosphamide, has been demonstrated not to improve the cumulative survival rate, even for patients with factors of poor prognosis or glomerulonephritis (231–233). Therefore, plasma exchanges should not be systematically proposed for initial treatment of CSS. Interferon- α , which has been successful in treating patients with the hypereosinophilic syndrome, may be an effective treatment for CSS, since it suppresses the proliferation of eosinophil colony-forming bone-marrow cells and inhibits the release of eosinophil granule proteins (234); indeed, interferon- α treatment led to remission of disease in two patients who had attained incomplete remission with corticosteroids and cyclophosphamide or methotrexate (235). Cyclosporin A might be beneficial in some patients (236).

Since the outcome of CSS is dependent on systemic organ involvement and disease activity, it has been suggested that the first-line treatment be based on prognostic factors (100). Cardiac or renal involvement impairs the survival of patients with systemic necrotizing vasculitis (237). In a prospective study, Guillevin et al. (226) identified five conditions that were significantly associated with a poor prognosis: proteinuria greater than 1 g/day, renal insufficiency (serum creatinine greater than 140 μ mol/l), cardiomyopathy, and gastrointestinal tract or central nervous system involvement (Table 2). The five-factor score (FFS) was defined as the number of these factors present in a patient. Although a high FFS was associated with a higher mortality rate, similar survival rates were obtained in this study regardless of the therapy tested prospectively (31, 226). Thus, the relevance of choosing first-line treatment regimens according to prognostic factors has yet to be proven. A prospective study is currently being conducted (L. Guillevin, J.-F. Cordier, coordinators) to test this approach. However, it is usually believed that cyclophosphamide is indicated in patients with factors of poor prognosis FFS $\geq$ 1 (31).

The combined treatment of CSS with corticosteroids and cyclophosphamide has dramatically improved the prognosis of this disorder. More than 75% of the patients with CSS or polyarteritis nodosa are still alive after 5 years (Table 2), and the survival in CSS has been shown to be similar to that of polyarteritis nodosa (100, 226, 238), although this is controversial (23, 239). As more patients survive with the disorder, it becomes apparent that this regimen may cause acute as well as long-term toxicities. The major side-effects of cyclophosphamide include

hemorrhagic cystitis, bladder fibrosis, bone-marrow suppression, severe infections, ovarian failure, bladder cancer, and hematologic malignancies (224). The recognition of infections in these patients is difficult, because their clinical manifestations are often diminished by immunosuppressant therapy and are indistinguishable from the symptoms of the underlying disease (pulmonary infiltrates), and because the spectrum of potential pathogens is large (97). Hence, early diagnosis and treatment of infection is critical in these patients. The most frequent serious infection is pneumonia (240). Prevention of opportunistic infections such as that of *Pneumocystis carinii* is recommended in all patients who are on a regimen combining daily corticosteroids and a cytotoxic agent: trimethoprim 160 mg plus sulfamethoxazole 800 mg three times a week in non-sulfa-allergic patients; or monthly inhaled pentamidine in patients with sulfa allergy (97, 224). Azathioprine has been proposed to maintain remission in patients with CSS (25, 241), especially after they have developed cyclophosphamide-related toxicities (224), but treatment with azathioprine may also cause significant bone-marrow suppression (97).

In conclusion, the current therapeutic approach to CSS is rather similar to that of Wegener's granulomatosis, polyarteritis nodosa, and microscopic polyangiitis, although it is still controversial: any patient who has severe disease manifestations (i.e., immediately life-threatening, cardiac, gastrointestinal, renal, or central nervous system involvement) should probably receive both glucocorticosteroids and

a cytotoxic agent as initial therapy (242). Further studies may lead us to refine treatment strategies based on the anatomic distribution and the intensity of disease activity, and to identify less toxic regimens.

Concluding remarks

CSS is distinguished from the other systemic vasculitides by the presence of asthma. Involvement of the myocardium, peripheral nerves, gastrointestinal tract, and skin is common. Perinuclear ANCA of antimyeloperoxidase specificity are present in most patients, and have provided new insights into the pathogenesis of this disorder. They should be considered as a major diagnostic criterion when present, but have not proven useful for follow-up purposes. In patients with CSS treated with a combination of corticosteroids and a cytotoxic agent, iatrogenic infections associated with the immunosuppression are an initial life-threatening complication. The physician should always be vigilant to detect infection, the manifestation of which may be clinically indistinguishable from that of vasculitis.

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