Churg–Strauss syndrome

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CASE PRESENTATION

A 51-year-old Caucasian man was hospitalized because of myalgia and fever. He had been suffering from chronic rhinitis since the age of 18 years and from asthma since the age of 45 years. Three months before hospitalization, he had received an influenza vaccine. On admission, he also complained of fatigue and paresthesias involving the lower limbs, and reported the recent onset of palpable purpura at both legs (Figure 1a). Laboratory tests are summarized in Table 1. The patient's HLA-DRB1 genotype was positive for *04–*07 alleles, both belonging to the HLA-DRB4 gene. Chest computed tomography (CT) scan was normal, whereas head CT showed diffuse sinusitis (Figures 1c and d). Electroneurography disclosed sensorimotor polyneuropathy with signs of axonal damage affecting the right peroneal and left sural nerves. A biopsy of the purpuric lesions was performed, and histology showed leukocytoclastic vasculitis (Figure 1b). As an antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis was suspected and urinary abnormalities persisted, renal biopsy was performed. On light microscopy (Figure 2), the biopsy specimen included 24 glomeruli, 3 of which were obsolescent. Segmental necrosis was found in 30% of the glomeruli, whereas four showed extracapillary proliferation. The tubulointerstitium, arterioles, and venules were normal, with no eosinophilic infiltration. Immunofluorescence showed no immune deposits. Churg–Strauss syndrome (CSS) was diagnosed on the basis of histological findings showing vasculitis and the presence of asthma, eosinophilia, sinusitis, and polyneuropathy. Prednisone therapy (initial dose 1 mg/kg/day) induced rapid symptom remission, normalization of the eosinophil count, and urinary abnormalities. Prednisone was stopped 9 months later but was resumed soon after withdrawal because of relapsing asthma.

DEFINITIONS AND CLASSIFICATION CRITERIA OF CSS

Churg–Strauss syndrome is characterized by small-vessel vasculitis, eosinophil-rich inflammation, vascular and/or extravascular granulomas, and peripheral eosinophilia occurring in patients with asthma and often allergic rhinitis or sinusitis.[1] Since the seminal study by Churg and Strauss,[2] who described the syndrome as a condition of 'allergic granulomatosis and angiitis,' a number of definitions and classification criteria have been proposed. The American College of Rheumatology (ACR) criteria were established to distinguish the individual forms of vasculitis from each other; thus, they must be used for the classification and not for the diagnosis of vasculitis, and should ideally be applied only when histological evidence of vasculitis is available. The ACR criteria for CSS include asthma, eosinophilia >10%, peripheral neuropathy, pulmonary infiltrates, paranasal sinus abnormalities, and extravascular eosinophils; the presence of at least four of these six criteria yields a sensitivity of 85% and a specificity of 99.7% for the classification of vasculitis as CSS.[3] The Chapel Hill consensus conference generated mutually exclusive definitions for the different vasculitides, and defined CSS as an 'eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small-to-medium-sized vessels, associated with asthma and eosinophilia.'[4]

EPIDEMIOLOGY

The prevalence of CSS is 11–14/1,000,000 inhabitants and its annual incidence is 2.7/1,000,000 patients.[5] It frequently occurs in patients aged 40–60 years, the mean age at diagnosis being ~48 years;[1] however, as asthma and allergic rhinitis or sinusitis are frequent, and may precede the vasculitic manifestations of many years, there is often a delay between initial symptoms and diagnosis. There is no clear gender predominance, ethnic predisposition, or familial clustering.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

The clinical course of CSS usually evolves through three phases: the prodromic, 'allergic' phase, hallmarked by asthma, allergic rhinitis, and sinusitis; the second, 'eosinophilic' phase, with

peripheral eosinophilia and clinical features due to tissue eosinophilic infiltration (for example, eosinophilic gastroenteritis); the third, also called 'vasculitic,' with manifestations of
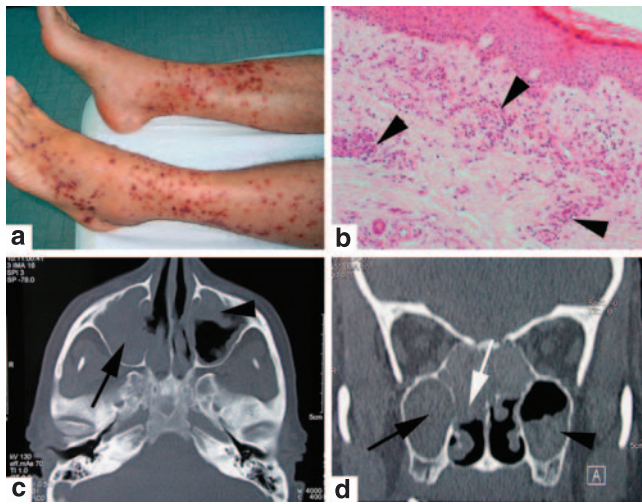

Figure 1 | Clinical and imaging findings on admission to hospital. (**a**) Purpura of the lower limbs. (**b**) Low-power magnification appearance of a skin biopsy of the purpuric lesions seen in panel a, showing an inflammatory infiltrate mainly involving the dermal vessels (arrowheads) with aspects of leukocytoclastic vasculitis. The epidermal epithelium is normal. Hematoxylin and eosin staining, original magnification ×4. (**c**, **d**) Computed tomographic scans of the head showing diffuse signs of sinusitis; an isodense and homogeneous tissue occupies completely the right (black arrow) and partially the left (arrowhead) maxillary sinuses; the nasal mucosa also appears markedly thickened (white arrow). No bone erosions are evident. (**c**) Axial and (**d**) coronal views.

Table 1 | Results of laboratory tests

	On admission to hospital	Normal values
White-cell count (cells/mm^3)	23,000	4000–11,000
Eosinophils (%)	52	2–8
Erythrocyte sedimentation Rate (mm/h)	40	2–30
C-reactive protein (mg/l)	11.2	0–5
Creatinine (μmol/l)	124	44–124
Urinalysis	Dysmorphic hematuria	
Proteinuria (mg/24 h)	960	<150
ANCA	1/80 (perinuclear pattern)	Negative
Anti-MPO antibodies (EU/ml)	100	<6

ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase.

necrotizing vasculitis (for example, peripheral neuropathy and purpura).[1]

Churg–Strauss syndrome can involve almost any organ. The frequencies of its clinical features are reported in Table 2.[6–8] Asthma precedes the systemic symptoms of a mean of 8–12 years;[9,10] it often has an adult onset and may paradoxically improve when vasculitic symptoms develop. In addition to typical nasal/paranasal sinus manifestations, purulent bloody nasal discharge and nasal crusting may also occur, although they are more typical of Wegener's granulomatosis. Other otolaryngological manifestations include otitis media and sensorineural hearing loss.[10] Lung involvement shows two fairly distinct patterns on CT: an 'airway' pattern, with bronchial wall thickening or dilatation, small centrilobular nodules and tree-in-bud signs, and an 'airspace' pattern, with ground-glass opacities, consolidation, and poorly defined infiltrates. Airway and airspace patterns are, respectively, associated with obstructive and restrictive pulmonary function test results.[11] Unlike in Wegener's granulomatosis, CSS nodules seldom cavitate.

Peripheral neuropathy, characterized by axonal damage on electrophysiological studies, most frequently affects the peroneal, median, tibial, and ulnar nerves.[9,12] The small bowel is more frequently involved than the large bowel, with most cases showing eosinophilic gastroenteritis or ischemic lesions.[13]

Renal disease is often an overlooked feature of CSS. Although less frequent and severe than in the other ANCA-associated vasculitides, renal manifestations occur in 25% of CSS patients.[14] The most typical picture is pauci-immune focal and segmental necrotizing glomerulonephritis, with or without crescents, which usually involve <50% of the glomeruli. Tubulo-interstitial eosinophilic nephritis is found only occasionally; a few patients have mesangial glomerulonephritis or focal segmental sclerosis. Finally, obstructive uropathy due to ureteral involvement has also been reported. Renal disease is an adverse prognostic factor for CSS patients; the largest study accurately assessing renal involvement in CSS showed a (although not statistically significant) higher 5-year mortality rate in patients with renal involvement than in those without;[14] previous studies also showed that proteinuria >1 g/24 h was a particularly strong predictor of mortality in CSS.[1,9]
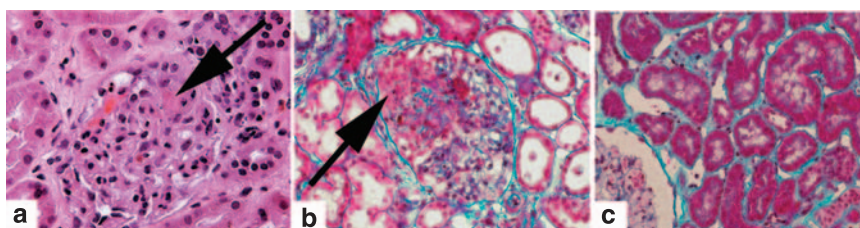

Figure 2 | Renal biopsy findings. (**a**) Segmental necrosis (arrow) in an otherwise normal glomerulus. Hematoxylin and eosin staining, original magnification ×40. (**b**) Glomerular extracapillary proliferation: part of the glomerulus is occupied by a cellular crescent (arrow), which confines the capillary tuft against Bowman's capsule. Masson's trichrome staining, original magnification ×40. (**c**) The tubules and the interstitium do not show remarkable abnormalities. Masson's trichrome staining, original magnification ×40.

Table 2 | Frequencies of the main clinical manifestations of Churg–Strauss syndrome in three large series of patients

	Keogh and Specks[6] 91 patients	Sinico et al.[8] 93 patients	Sablé-Fourtassou et al.[7] 112 patients	Main clinical features by organ system
Asthma	99%	96%	100%	
Nasal and paranasal sinus involvement	74%	77%	62%	Rhinitis, sinusitis, nasal polyps
Lung involvement	58%	51%	Infiltrates, 65%; pleural effusion, 22%; alveolar hemorrhage, 7%	Migratory pulmonary infiltrates, pleural effusion, alveolar hemorrhage
Constitutional symptoms[a]	NA	68%	Weight loss, 8%; fever, 45%; arthralgia, 37%; myalgia, 54%	
Skin manifestations	57%	53%	52%	Purpura, nodules, urticarial lesions
Peripheral nervous system involvement	76%	65%	72%	Mononeuropathy, mononeuropathy multiplex, distal symmetric polyneuropathy
Gastrointestinal manifestations	31%	22%	32%	Abdominal pain, digestive hemorrhage, diarrhea
Kidney involvement	25%	27%	16%	Urinary abnormalities, rapidly progressive renal failure
Heart involvement	Endomyocardial, 13%; pericardial, 8%	16%	35%	Cardiomyopathy, pericarditis
Central nervous system involvement	11%	14%	9%	Cranial nerve palsy, cerebral infarction or hemorrhage

NA, not available.
[a]Constitutional symptoms include weight loss, fever, fatigue, diffuse arthralgia, and myalgia.

Cardiac manifestations, often severe, include left ventricular or global heart failure, conduction abnormalities, myocardial infarction (due to coronary vasculitis), and pericarditis.[9]

Laboratory tests show peripheral eosinophilia >1500 cells per µl in ∼90% of patients;[15] undetected eosinophilia often results from oral corticosteroid treatment for asthma. High C-reactive protein levels and sedimentation rates are common, as well as inflammatory disease-related anemia.[7] Total serum IgE levels are high in ∼90% of cases, but IgE specific to common allergens is positive in <30%, thus implying that putative unidentified allergens are involved in CSS.[15] ANCAs are positive using immunofluorescence in 38% of the patients, 74–90% of whom have a perinuclear-ANCA (P-ANCA) and <10% a cytoplasmic pattern (C-ANCA);[7,8] a few cases show 'atypical' patterns (C + P) or C-ANCA without the usual interlobular accentuation ('C-ANCA atypical').[8] On ELISA, almost all P-ANCAs are anti-myeloperoxidase, whereas C- or atypical ANCAs are either anti-myeloperoxidase, anti-proteinase 3, or undetermined.[8]

HISTOPATHOLOGY
The typical histopathological elements of CSS are extravascular granulomas, small-to-medium-sized-vessel vasculitis, and tissue eosinophilia. Extravascular granulomas show a center of necrotic eosinophils surrounded by palisading lymphocytes and multinucleated giant cells.[2,3] Vasculitis involves arteries, arterioles, and, less frequently, venules, and often includes eosinophil-rich infiltrates;[3] it is characterized by vessel wall fibrinoid necrosis and may or may not be granulomatous.

These key features are concomitantly found in only a minority of cases; in addition, some lesions underlie specific histopathological abnormalities and specific sites commonly lack eosinophilic infiltration. For instance, purpura is usually due to leukocytoclastic vasculitis (without fibrinoid necrosis or eosinophils), and pulmonary hemorrhage is due to alveolar capillaritis (without granulomas).[9] Eosinophilic infiltrates are also rare in CSS glomerulonephritis.[14] Similarly, peripheral nerve histology shows epineural vasculitis but almost never eosinophils.

Other affected sites have a broader range of histological pictures.[9] Gastrointestinal lesions may be characterized by tissue eosinophilia, as in cases presenting with eosinophilic gastroenteritis, or mesenteric vasculitis, which causes small- or large-bowel ischemia; in some cases, granulomas, vasculitis, and tissue eosinophilia coexist.[13] Cardiac lesions range from eosinophilic coronary vasculitis to transmural eosinophilic granulomatous myocarditis; pericarditis may also occur, with pericardial biopsies often disclosing necrotizing vasculitis and eosinophilic infiltrates.[9] Lung manifestations other than alveolar hemorrhage also encompass different lesions, which in some cases are similar to those of eosinophilic pneumonia, whereas in others they show granulomas and necrotizing vasculitis; bronchial wall thickening is often due to eosinophilic and lymphocytic infiltration.[11]

DISTINCT CLINICAL SUBSETS: THE 'ANCA DICHOTOMY'
That CSS represents a spectrum of diseases rather than a single entity had already been proposed by Churg and Strauss, who reported 'other allergic syndromes (Löffler, Zuelzer, Silk) may represent the more benign forms of allergic granulomatosis, while angiitis is its most malignant expression.'[2] Two recent studies have shown that ANCAs may help differentiate CSS subsets, as ANCA positivity is associated with a higher frequency of renal involvement, peripheral

neuropathy, alveolar hemorrhage, and purpura (all manifestations of necrotizing vasculitis), whereas ANCA negativity is associated with heart and lung disease (other than alveolar hemorrhage).[7,8] Interestingly, histological signs of vasculitis were more frequent in ANCA-positive than in ANCA-negative patients.[7] These findings suggest the presence of two separate subsets, one ANCA associated, with features of small-vessel vasculitis, and one ANCA negative, in which organ damage is mainly mediated by eosinophilic infiltration. It can be noted that this dichotomy has an immunogenetic basis, as the frequency of the CSS-associated HLA-DRB4 gene is higher in CSS patients with vasculitis symptoms.[16]

PATHOGENESIS

It has been shown that CSS is associated with the HLA-DRB4 gene and particularly with its HLA-DRB1*04 and *07 alleles.[16] A restricted HLA repertoire points to an antigen-driven, T-cell-dependent disease,[16] a view supported by the presence of T-cell clones with similar T-cell receptor specificities in CSS patients.[17]

Both CD4+ and CD8+ T cells are found in CSS lesions, and soluble interleukin (IL)-2-receptor serum levels (suggestive of T-cell activation) are high in CSS patients. Peripheral T-cell lines from CSS patients show a predominance of CD4+ cells producing not only T-helper (Th)2 (for example, IL-4, IL-13) but also Th1 cytokines (for example, interferon-γ (IFN-γ)). In addition, peripheral mononuclear cells secrete high levels of IL-5, which promotes eosinophil

activation and adhesion to endothelium.[18] Variations in the Th1/Th2 cytokine ratio potentially account for the heterogeneous CSS phenotype, which can range from a predominantly Th1-mediated granulomatous vasculitis to Th2-mediated systemic hypereosinophilia.[18]

Eosinophils may cause tissue damage by releasing cytotoxic granule proteins (for example, eosinophil cationic and major basic protein) or by inducing apoptosis of target cells,[19] and can also function as antigen-presenting cells.[18] Prolonged eosinophil survival may be regulated by T cells through the CD95–CD95 ligand (CD95L) apoptotic pathway: CSS peripheral lymphocytes exhibit a switch from the membrane-bound CD95 isoform to its soluble splice variant, which protects eosinophils and T cells themselves from CD95L-mediated apoptosis; consequently, the T-cell–eosinophil crosstalk may promote both sustained eosinophilia and T-cell clonal expansion.[17]

Endothelial cells also contribute to CSS eosinophilia by producing eotaxin-3, a chemokine with strong chemotactic activity on eosinophils; its serum levels correlate with the degree of eosinophilia and disease activity in CSS patients.[20]

B cells can function as antigen-presenting cells and be precursors of ANCA-producing plasma cells; ANCAs may ultimately cause vasculitis through different mechanisms (for example, neutrophil activation and reactive oxygen metabolite production). The pathogenetic role of ANCAs in CSS is uncertain, although their high frequency in CSS patients with vasculitic manifestations strengthens the hypothesis that they
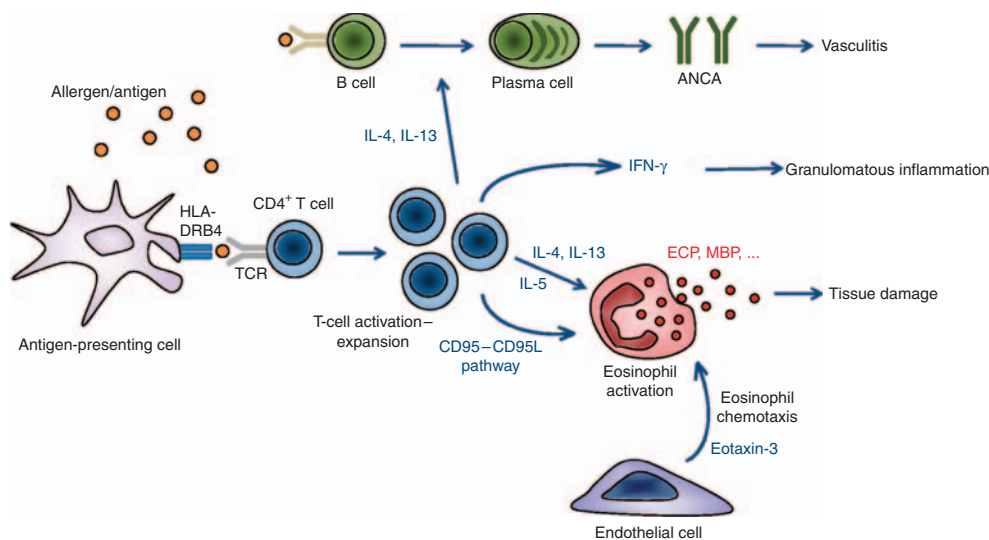

Figure 3 | Pathogenetic model proposed for Churg–Strauss syndrome, based on available experimental evidence. Hypothetical allergens or antigens may be uptaken by antigen-presenting cells and presented to CD4+ T cells, leading to T-cell activation and expansion. Antigen-presenting cells (which can be of different cell types, for example, dendritic cells, monocyte macrophages, and eosinophils) have a restricted HLA repertoire and often express HLA-DRB4. Once activated, CD4+ T cells secrete IFN-γ, which promotes granulomatous inflammation, and also drive eosinophil activation and expansion through the secretion of IL-4, IL-5, and IL-13, or by means of the CD95–CD95 pathway. Eosinophils mediate tissue damage mainly by secreting granule proteins such as ECP and MBP. Endothelial cells may also contribute to tissue infiltration by eosinophils by releasing eotaxin-3, a chemokine with strong chemotactic activity on eosinophils. B cells are also likely to play a pathogenetic role: activated on antigen encountering and 'helped' by T-helper 2 cytokines such as IL-4 and IL-13, they may become mature plasma cells and then produce different autoantibodies, including ANCA, which may in turn mediate vasculitis. ANCA, anti-neutrophil cytoplasmic antibodies; CD95L, CD95 ligand; ECP, eosinophilic cationic protein; IFN-γ, interferon-γ; IL(-4, -5, -13), interleukin(-4, -5, -13); MBP, major basic protein; TCR, T-cell receptor.

mediate vascular injury and inflammation.[1] The efficacy of B-cell-depleting agents in some refractory CSS cases further supports a pathogenetic role of B cells.[21]

Finally, different agents may trigger CSS, such as allergens, vaccinations, and drugs. Numerous reports showed a temporal correlation between the use of anti-leukotrienes for asthma and the development of CSS; however, these drugs allow steroid tapering, which can unmask incomplete forms of CSS.[1] Figure 3 depicts an immunopathogenetic model of CSS.

TREATMENT AND PROGNOSIS

Current views indicate that the treatment of CSS should be tailored on the basis of patient prognosis. Five factors are considered to be strong prognostic predictors (five-factor score, FFS), namely, heart, gastro-intestinal, and central nervous system involvement, proteinuria $>1 g/24 h$, and creatinine $>140 \mu mol/l$ (each factor is given 1 point). Patients with $FFS = 0$ should receive corticosteroids alone, whereas those with $FFS \geqslant 1$ should also receive cytotoxic agents (for example, cyclophosphamide, CYC) as first-line therapy.[1,22–25]

High corticosteroid doses (usually 1 mg/kg/day of pre-dnisone) are used as initial therapy, with corticosteroid pulses before oral treatment in severe cases. Steroid tapering should begin when acute-phase reactants or eosinophil counts normalize. CYC is added to steroids also in the case of steroid-resistant, steroid-dependent, or frequently relapsing disease.[1,22] As for the duration of induction therapy, it has been shown that patients given CYC for 4–6 months have higher relapse rates than those treated for 1 year.[22] Once remission is achieved, a switch from CYC to the less toxic azathioprine is recommended. The duration of maintenance therapy should be at least 6 months; however, steroids are usually continued for asthma, which often persists despite vasculitis remission. The therapeutic recommendations based on FFS should be taken with caution and critically considered case by case, as they carry the risk of overtreating patients with minor complications (for example, proteinuria slightly higher than 1 g/day) and, on the other hand, undertreating those with severe disease manifestations (for example, severe peripheral neuropathy).

Up to 10% of CSS patients are refractory to conventional treatment. The anti-CD20 monoclonal antibody, rituximab, has been effective in refractory CSS, also by inducing a decrease in eosinophil counts, ANCA, and serum IL-5 levels.[21] Mycophenolate mofetil has also been reported to be effective.[22] Other agents for refractory CSS include IFN-α, whereas no evidence yet supports the use of anti-IL5 or anti-IgE-antibodies; notably, CSS developed in asthmatic patients receiving the anti-IgE, omalizumab, probably because this allows (as do anti-leukotrienes) steroid tapering.[1]

The outlook of CSS is usually good. Remission can be achieved in ∼90% of patients,[22,24] but 35–74% of them relapse; relapses are often heralded by increased peripheral eosinophilia and usually respond to raised corticosteroid doses or resumption of immunosuppressants.[6,22,24]

CONCLUSIONS

CSS has a heterogeneous clinical spectrum, ranging from a predominantly eosinophilic/allergic disorder to systemic vasculitis. ANCAs, being correlated with CSS vasculitic manifestations, may help differentiate these clinical subsets. Although CSS often responds to steroids and immuno-suppressants, more selective therapeutic approaches are needed to reduce exposure to immunosuppression and for refractory cases. Future studies are warranted to elucidate the genetic and immune-mediated pathogenetic mechanisms.

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