Seminar

Churg-Strauss syndrome

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Churg-Strauss syndrome is a rare diffuse vasculitis that is almost invariably accompanied by severe asthma. Although overall prognosis is good, and treatment with prednisone alone or in combination with immunosuppressive drugs is usually successful, severe asthma typically persists. Diffuse organ involvement of Churg-Strauss syndrome, especially cardiovascular and rare involvement of the CNS and renal system, suggests a poorer prognosis than usual, and can be fatal. The cause of Churg-Strauss syndrome is unknown, but its characteristic histological findings and association with asthma distinguish it from other vasculitides. Controversy surrounds the use of asthma drugs—especially antileukotrienes—and development of the disorder. We review the epidemiological evidence for an association of drug treatment with Churg-Strauss syndrome, the diverse diagnostic and pathological criteria for this syndrome, and treatment options.

Churg-Strauss syndrome presently describes the clinical symptoms of the pathological entity allergic angiitis and granulomatosis, which was identified more than 50 years ago. Patients with this disorder, who may show the pathological findings of a necrotising eosinophilic vasculitis involving nearly all major organ systems, almost invariably also have severe asthma, the onset of which precedes, but rarely follows, development of other clinical manifestations of Churg-Strauss syndrome. Because this disorder is very rare in the general population—ie, in people without asthma—an association and possible causal relation between asthma treatment and Churg-Strauss syndrome has been suggested. In particular, treatments that block cysteinyl leukotriene receptors have been assessed. Although evidence points clearly to a fortuitous association, possibly related to withdrawal of corticosteroids during treatment and unmasking of *forme frustes* Churg-Strauss syndrome, the role of drugs in the cause of the disorder is not entirely resolved.

Diagnosis of Churg-Strauss syndrome can be difficult, because the syndrome may arise at first as a common association between asthma and allergic rhinitis. Because asthma itself might be associated with sinusitis, occasional pulmonary infiltrates (eg, mucus plugging, atelectasis, or intermittent infection), and corticosteroid dependency, a clear diagnosis of Churg-Strauss syndrome might not be made until the abdominal viscera, heart, or nervous system become involved, which may be fatal in the latter two systems. The association of Churg-Strauss syndrome with antineutrophil cytoplasmic antibodies has facilitated diagnosis of this disease. A careful balance between assessment of the clinical manifestations and available pathophysiological evidence allows for timely treatment of Churg-Strauss syndrome, which may prevent serious morbidity or death.

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Successful treatment of this rare syndrome needs prompt differentiation of Churg-Strauss syndrome from asthma alone, and staging of the severity of the disorder is required for appropriate immunosuppressive therapy. Because the disorder is rare, only corticosteroids and some common immunosuppressive treatments have been assessed under controlled situations for Churg-Strauss syndrome. For patients in whom the complications of the disorder are refractory to these therapies, various less well-tested regimens have been prescribed.

Pathophysiology

The cause of Churg-Strauss syndrome is unknown. Asthma and atopy are closely linked, and both are associated with blood eosinophilia. An infectious agent or foreign antigen, which might be inhaled, could initiate allergic inflammation in a genetically susceptible individual, resulting in rhinosinusitis and asthma. Blood and tissue eosinophilia then arise, with infiltrative eosinophilic pneumonia or gastroenteritis in some patients. Vascular inflammation may result from endothelial-cell adhesion and leucocyte activation, with subsequent necrotising vasculitis in several organ systems, especially the lung, heart, peripheral nervous system, skin, and gastrointestinal tract. Vascular inflammation in various organ systems results in the most lethal phase of the disease. Cardiac involvement accounts for many deaths. These three distinct clinical phases—asthma, tissue eosinophilia, and vasculitis—take place in many, but not all, patients with Churg-Strauss syndrome. These phases, and the varied pathological findings, suggest that the pathophysiology of the disorder might evolve over time.

Search strategy and selection criteria

Papers were selected for review by Medline search with relevant cross-referenced topics. Keywords used were Churg-Strauss syndrome; vasculitis and drugs; small vessel vasculitis; asthma and vasculitis; and we searched English language articles. In selected cases, further review of cited papers was obtained directly from the references of papers initially reviewed in search. Non-peer-reviewed publications or single case reports were not included in this review. Abstracts not yet published as peer-reviewed publications also were excluded.

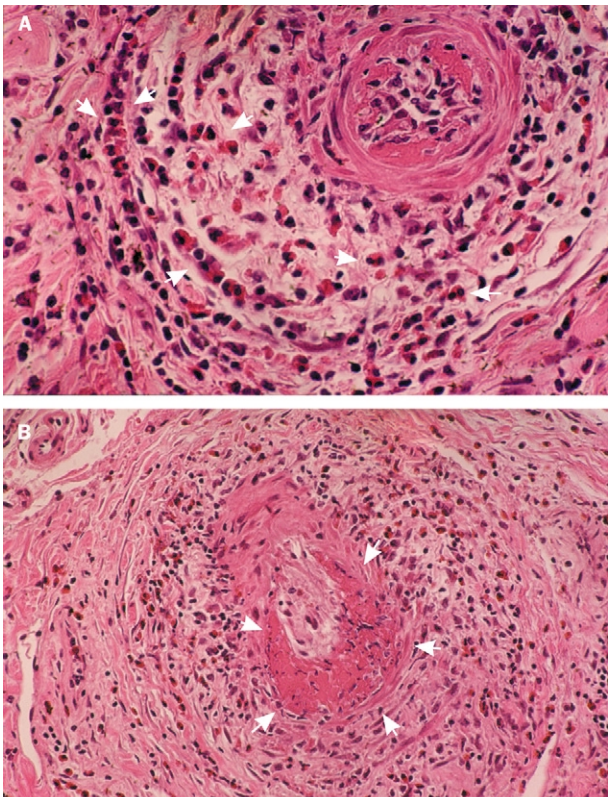

Figure 1: **Tissue biopsy specimens from Churg-Strauss patients**
(A) Pronounced inflammatory infiltrate consisting of many eosinophils (arrows) with admixed lymphocytes is seen in the media of this small submucosal artery (original magnification ×350). (B) In addition to great eosinophilic vasculitis, this vessel exhibits striking fibrinoid necrosis of its inner wall (arrows). This appears brightly eosinophilic on haemoxylin and eosin (original magnification ×350). Reprinted with permission, from *J Allergy Clin Immunol* 1999; **104:** 1060–65.

Results of studies suggest that Churg-Strauss syndrome is an autoimmune process involving leucocytes, in particular eosinophils, endothelial cells, and lymphocytes.[1,2] Impairment of CD95 ligand-mediated apoptosis of lymphocytes and eosinophils has been noted, associated with oligoclonal T-cell expansion.[3] Increases in concentrations in serum of eosinophilic cationic protein (suggesting eosinophil activation), soluble interleukin 2 receptor (suggesting T-cell activation), and soluble thrombomodulin (indicating endothelial-cell damage) have been described in patients with Churg-Strauss syndrome.[4] Results of a study of the clinicopathological features of neuropathy associated with the disorder showed that CD8+ and CD4+ T cells outnumber eosinophils in neuronal biopsy specimens.[5] Increased concentrations of IgE have been noted in patients during the vasculitic phase of the disorder, which may return to normal during periods of disease remission.[6]

The finding of antineutrophil cytoplasmic antibodies in 48–66% of patients with Churg-Strauss syndrome has led to speculation that these antibodies may be an integral part of the inflammatory diathesis that characterises the disorder.[7,8] Antineutrophil cytoplasmic antibodies in sera and purified immunoglobulins lead to release of reactive oxygen species from human neutrophils in vitro.[9] They also induce release of primary granule contents from neutrophils. Thus, antineutrophil cytoplasmic antibodies can cause neutrophil activation and degranulation. However, although they might amplify inflammation, they are not generally viewed as the primary cause of the disease, since about a third of patients with Churg-Strauss syndrome do not have these antibodies in their serum.

Analysis of tissue biopsy specimens from patients with Churg-Strauss syndrome shows an eosinophil-rich inflammatory infiltrate with granuloma formation in connective tissue and blood-vessel walls (figure 1). Necrotising vasculitis with fibrinoid changes arises in small-to-medium sized vessels. Because the primary vessels involved are arterioles, venules, and capillaries, some researchers have classified Churg-Strauss syndrome as a small-vessel vasculitis, similar to Wegener's granulomatosis and microscopic polyangiitis. However, these two diseases differ from Churg-Strauss syndrome clinically—by the absence of asthma—and pathologically, by the presence of eosinophilia.[10,11]

Development of Churg-Strauss syndrome after allergic hyposensitisation, vaccination, exposure to certain drugs, corticosteroid withdrawal, and association with pulmonary infections suggests that in some patients, these events could initiate an inflammatory cascade.[6,8,12]

Diagnostic criteria

Syndromes are a constellation of symptoms or pathological findings, which vary in accordance with the diagnostic criteria that are applied. Churg-Strauss syndrome is especially complicated in this respect, since asthma—which is itself a syndrome of reversible airflow obstruction and inflammation—almost always is a component of the disorder. Because Churg-Strauss syndrome occurs rarely, prospective diagnosis in a large series of patients is difficult.

Churg and Strauss initially described the syndrome as a necrotising vasculitis of medium-to-small sized blood vessels (veins and arteries), associated with eosinophilic infiltration around the vessels and adjacent tissues.[13] The presence of extravascular granulomas was the third

Panel 1: Definitions of Churg-Strauss syndrome

Churg and Strauss (1951)[13]
Pathological material obtained at autopsy
(1) History of asthma
(2) Tissue eosinophila
(3) Systemic vasculitis
(4) Extravascular granulomas
(5) Fibrinoid necrosis of connective tissue

Lanham and colleagues (1984)[6]
Clinical findings with or without pathological material
(1) Asthma
(2) Eosinophila >1·5×10^9/L
(3) Evidence of vasculitis that involves at least two organs

American College of Rheumatology (1990)[15]
Clinical findings with or without pathological material; diagnosis probable when four of the six criteria are present
(1) Asthma
(2) Eosinophilia >10%
(3) Neuropathy, mononeuropathy, or polyneuropathy
(4) Pulmonary infiltrates
(5) Paranasal sinus abnormality
(6) Extravascular eosinophil infiltration on biopsy findings

Chapel Hill Consensus Conference (1994)[10]
Pathological and clinical findings
Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotising vasculitis affecting small-to-medium-size vessels and associated with asthma and eosinophilia

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criterion in this triad of clinical features, which did not include presence of either clinical or pathological findings of asthma, although all patients in the initial description of the syndrome (then named allergic angiitis and granulomatosis) were severe asthmatics. Subsequently, Reid and co-workers[14] identified all three of these pathological criteria to be present in under a fifth of patients diagnosed with the disorder. Accordingly, pathological progression of the lesion of Churg-Strauss syndrome, which may not correspond temporally with all clinical manifestations, is now recognised to take place.

This finding has resulted in decreased reliance on pathological criteria alone for diagnosis of the disorder and to clinical redefinition of Churg-Strauss syndrome. Lanham and colleagues[6] at the Hammersmith Hospital, London, UK, have defined the disorder as a syndrome including: (1) a history of asthma; (2) blood eosinophilia (>1500 cells/μL); and (3) systemic vasculitis involving two or more organs. Panel 1 lists the different categories of diagnostic criteria for the disorder.[6,10,13,15]

A critique of these criteria by a special workshop of the US National Institutes of Health elucidated some difficulties in their application;[1] eosinophilia in peripheral blood can vary, and Churg-Strauss syndrome arises in some patients who do not have this clinical feature. The historical diagnosis of asthma as a requisite for the syndrome allows for considerable subjectivity, especially since vasculitis may precede asthma in rare cases of the disorder.[16–20] The involvement of more than two organs is difficult to assess without doing a biopsy—an invasive procedure in patients who may be very ill and need initiation of aggressive systemic corticosteroid treatment.

Frequency of Churg-Strauss syndrome

For reasons given above, the prevalence of Churg-Strauss syndrome in the population varies between reports. In patients in the general population, the frequency of the disorder has been estimated at 2·4–6·8 per 1 000 000 patient-years (panel 2).[21,22] In a 10-year study in the UK, the annual frequency of Churg-Strauss syndrome was 2·7 per 1 000 000 patient-years.[22] Watts and colleagues[23] reported a significant difference in incidence of the disorder between Spain and the UK.

Relation of antiasthma treatments to Churg-Strauss syndrome

In 1998, Wechsler and colleagues[24] published a provocative report of an association between Churg-Strauss syndrome and antileukotriene treatment for asthma patients taking zafirlukast, an antagonist of the cysteinyl-leukotriene-receptor. Subsequent associations were reported for montelukast by Franco and Wechsler[25,26] and for pranlukast by Kinoshita and co-workers.[27]

Stirling and Chung,[28] citing evidence of development of Churg-Strauss syndrome after treatment with azithromycin and other macrolide antibiotics, oestrogen replacement therapy, and carbamazepine, also suggested that the disorder might be caused by "an idiosyncratic or hypersensitivity reaction to [leukotriene receptor agonists]". They also considered the notion that *forme fruste* Churg-Strauss syndrome could exist at initiation of leukotriene-receptor-agonist therapy. Indeed, development of the disorder is frequently associated with taper of oral corticosteroid treatment, suggesting unmasking of Churg-Strauss syndrome that was previously suppressed by systemic corticosteroid therapy. This explanation could be true for development of Churg-Strauss syndrome in patients receiving fluticasone or budesonide,[24,29] which have been shown to reduce the need for oral corticosteroid therapy.

Panel 2: **Estimated frequency of Churg-Strauss syndrome**

Reference	Population	Frequency (cases/10^6 patients per year)
22	General population	2·4
14	General population	3·3
21	General population	6·8
21	Population without asthma	1·8
21	Population with asthma	64·4

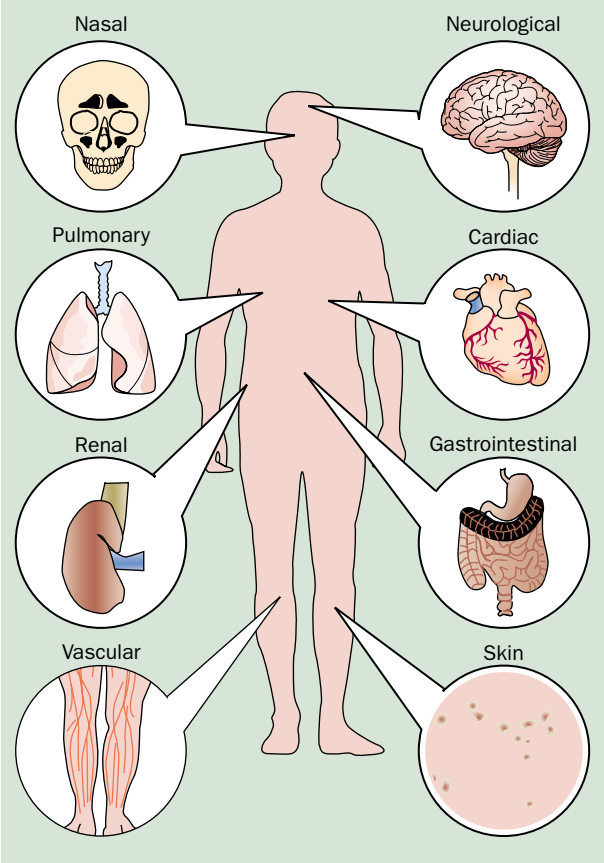

Figure 2: **Systemic distribution of vasculitis in Churg-Strauss syndrome**

Pulmonary infiltrates have been identified with concomitant use of sodium cromoglicate—a mast-cell stabilising drug with no structural homology to any of the above drugs—in patients with asthma.[30] Nonetheless, some concern remains that antileukotriene therapy might block actions of cysteinyl-leukotrienes in the lung and in extrapulmonary tissues. Researchers have not yet established whether cysteinyl-leukotrienes are useful in modulation of inflammatory reactions or regulation of migration of dendritic cells to lymph nodes with consequent differential effects on T-helper cells—eg, the balance between T-helper-1 cells and T-helper-2 cells.[31,32]

In their report to the US National Institutes of Health panel,[1] representatives of the Adverse Events Reporting System of the US Food and Drugs Administration noted development of Churg-Strauss syndrome in 165 patients who met two or more American College of Rheumatology criteria for the disorder. Of these, 126 (76%) had a history of previous oral corticosteroid use, and of those for whom adequate information was available, 88% developed

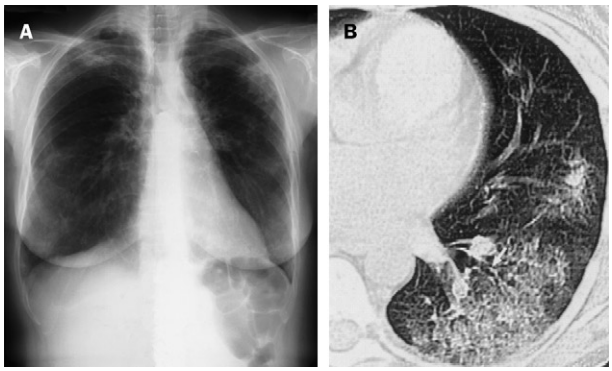

Figure 3: **Typical imaging findings in a patient with Churg-Strauss syndrome**
(A) Posteroanterior radiograph showing bilateral multifocal areas of consolidation in a peripheral and patchy non-segmental distribution. (B) CT scan showing peripheral ill-defined parenchymal opacities in the left lower lobe. (A) Courtesy of Eugene Geppert, University of Chicago. (B) Reprinted with permission, from Levin D, *Eur J Radiol* 1999; **29:** 149–51.

Churg-Strauss syndrome during a period of tapering corticosteroid use.[1] 12% of patients had a history of leukotriene-receptor-agonist use but no history of use of oral corticosteroids. From this finding, the researchers concluded that no one class of drug was associated with Churg-Strauss syndrome and that antiasthma drugs associated with the disorder are safe.

The strong association between corticosteroid taper and absence of structural homology of drugs associated with Churg-Strauss syndrome strongly suggest that many cases of the disorder in patients with asthma are either unrecognised or develop during taper of systemic steroid treatment, and that unmasking during withdrawal of oral corticosteroids may result in emergence of the disorder. Specifically, the incidence of Churg-Strauss syndrome is no greater in people with asthma receiving antileukotriene therapies than in those not receiving these drugs.

Diagnosis

Despite the continuous redefinition of diagnostic criteria for Churg-Strauss syndrome (see above), diagnosis remains a clinical one. Pathological confirmation of eosinophilic tissue infiltration or vasculitis is desirable whenever possible. Diagnosis of Churg-Strauss syndrome is suggested when a previously healthy individual presents with adult-onset allergic rhinitis or recurrent sinusitis associated with asthma and followed by signs and symptoms of systemic vasculitis. Diagnosis, however, is typically missed initially, because asthma and associated sinus disease are very common, and these symptoms can precede onset of vasculitis by many years (mean latency 8 years, range 0–61, SD 10·86).[8,33]

Diagnosis of Churg-Strauss syndrome should be considered in patients with asthma if there is either a raised peripheral-blood eosinophil count or pulmonary infiltrates are present. Although asthma is typically associated with eosinophilia, eosinophil counts of greater than 800 cells/μL are unusual in asthma, and counts greater than 1500 cells/μL or greater than 10% of the total white-cell-count should prompt consideration of Churg-Strauss syndrome. Furthermore, although fleeting pulmonary infiltrates can occur in asthma from associated atelectasis or mucus plugging, they are unusual in asthma and should prompt further assessment.

Clinical features by organ system

Churg-Strauss syndrome can affect virtually any organ system in the body, though occasionally one organ system is predominantly affected (figure 2).[34,35] Systemic symptoms are prominent. Fever was present in all initial cases described by Churg and Strauss.[13] Weight loss is often great and might herald onset of the vasculitic phase, as do fatigue and malaise.[6] Arthralgias might arise, but frank arthritis is rare.

Pulmonary involvement is nearly universal in Churg-Strauss syndrome. Most patients (96–100%) have asthma that typically arises early in the course of the disease.[36] Severity of asthma increases over time and, paradoxically, may improve with onset of the vasculitic phase.[6] Asthma persists in at least 80% of patients after treatment and remission of the vasculitis.[8] Rarely, asthma will arise after onset of systemic vasculitis.

Pulmonary infiltrates are present in most patients with Churg-Strauss syndrome but are often fleeting and non-specific in nature.[6] The most common abnormality shown on chest radiograph in one series was bilateral multifocal consolidation in a patchy non-segmental distribution (figure 3).[37] Infiltrates can be symmetrical and have a peripheral distribution characteristic of eosinophilic pneumonia. Diffuse reticulonodular opacities, interlobular septal thickening, bronchial-wall thickening, and hilar adenopathy are sometimes seen on thin-section CT scans of the chest (figure 3).[37] Pulmonary nodules can occur, but, unlike those in Wegener's granulomatosis, they rarely cavitate. Diffuse alveolar infiltrates should suggest possibile alveolar haemorrhage, which happened in 4% of patients in one series.[8] Pleural effusions arise occasionally.

Allergic rhinitis occurs in about 75% of patients with Churg-Strauss syndrome and is typically the initial symptom.[6,13,36] Recurrent sinusitis, nasal polyps, and nasal obstruction are also seen.[6] Occasionally, nasal pain, with a purulent or bloody nasal discharge and nasal crusting or septal perforation more typical of Wegener's granulomatosis, is seen.[6]

Peripheral neuropathy is common in patients with Churg-Strauss syndrome (65–75%); mononeuritis multiplex is the most frequent finding.[6,36] When mononeuritis multiplex is seen in a patient with asthma and eosinophilia, the diagnosis of Churg-Strauss syndrome is almost certain. CNS involvement may include palsies of the cranial nerves (ischaemic optic neuritis), cerebral haemorrhage or infarction, convulsions, coma, and psychosis, but these occurrences are much less typical.[6,13] When it occurs, cerebral infarction is a great cause of morbidity and mortality from Churg-Strauss syndrome.[6,36]

Gastrointestinal involvement arises often in Churg-Strauss syndrome. Abdominal pain is the most usual complaint. An eosinophilic gastroenteritis with bloody diarrhoea may be followed by intestinal perforation.[6,13] Eosinophilic peritonitis with ascites may arise. Pancreatitis and cholecystitis also have been reported.

Cardiac involvement is a leading cause of mortality and a common clinical manifestation.[38] Cardiac involvement includes eosinophilic endomyocarditis, coronary vasculitis, valvular heart disease, congestive heart failure, hypertension, and pericarditis.[13,36]

Skin lesions are common and variable.[13] They include erythematous, maculopapular, or pustular lesions. Non-thrombocytopenic palpable purpura is typical. Nodules have been noted on the head, trunk, and extremities (arms and legs). Biopsy findings show a leucocytoclastic vasculitis, which may result from small-vessel vasculitis in the skin.[11]

Renal involvement is fairly typical, but unlike other necrotising vasculitides such as Wegener's granulomatosis or microscopic polyangiitis, renal failure is rare. In a series by Guillevin and colleagues,[8] 26% of patients with

Panel 3: **Differential diagnosis by phase of Churg-Strauss syndrome**

Allergic phase
(1) Allergic bronchopulmonary aspergillosis
(2) Sarcoidosis

Eosinophilic phase
(1) Simple pulmonary eosinophilia from drug or parasite
(2) Chronic eosinophilic pneumonia
(3) Hypereosinophilic syndrome
(4) Hypersensitivity pneumonitis
(5) Eosinophilic gastroenteritis
(6) Rheumatoid arthritis

Vasculitic phase
(1) Wegener's granulomatosis
(2) Microscopic polyangiitis
(3) Polyarteritis nodosa

Churg-Strauss syndrome had some manifestation of renal involvement, including proteinuria, hypertension, glomerulonephritis, renal insufficiency, and renal infarction. A report of 19 patients with Churg-Strauss syndrome noted renal involvement with microscopic haematuria in 13 (68%) patients and proteinuria in 12 (63%).[39] Renal biopsy findings showed focal segmental glomerulonephritis in most patients.[36,39,40] The characteristic glomerular lesion is a focal segmental glomerulonephritis with necrosis, crescent formation, or both.[36] Immunohistochemical staining does not show characteristic immunological deposits—ie, glomerulonephritis in Churg-Strauss syndrome is pauci-immune (no detectable antibodies on immunological staining).

Laboratory and imaging diagnostic findings

Abnormal laboratory findings in patients with Churg-Strauss syndrome include anaemia, leukocytosis, increased peripheral blood eosinophil count, and a raised erythrocyte sedimentation rate.[1,13] Rarely, eosinophilia is not present, and wide-ranging and rapid changes in eosinophil counts happen.[6] Use of corticosteroids to treat asthma may result in failure to detect eosinophilia in a patient with undiagnosed Churg-Strauss syndrome. Blood chemistry and urinalysis findings might show occult renal disease. Antineutrophil cytoplasmic antibodies are present in more than half of patients with a perinuclear staining pattern.[1,7] Antineutrophil cytoplasmic antibody-positivity needs to be confirmed by demonstration of myeloperoxidase in serum.[38] Eosinophilia might be noted in bronchoalveolar lavage fluid.[36]

CT scans of the sinuses and chest can confirm presence of sinusitis and pulmonary infiltrates. Cardiac abnormalities can be seen on electrocardiogram and echocardiogram.

Biopsy of an involved organ should be done to confirm the presence of an eosinophilc inflammatory process or vasculitis. However, characteristic pathological changes need not be present to establish diagnosis of Churg-Strauss syndrome. In a series of 16 patients with the disorder diagnosed by Lanham and colleagues,[6] 14 had positive tissue biopsy specimens but two had non-diagnostic findings. Necrotising vasculitis was seen in five skin, three renal, and two muscle biopsy specimens. Granulomas were present in the kidney in one sample. Eosinophilic tissue infiltration was noted in three skin, three renal, and one lung biopsy specimen.

Differential diagnosis

Differential diagnosis of Churg-Strauss syndrome depends on the stage at which disease is suspected (panel 3). In patients with asthma that is difficult to control and associated sinus disease, in whom a diagnosis of limited or *forme frustes* Churg-Strauss syndrome is being considered, sarcoidosis, allergic bronchopulmonary aspergillosis, and other causes of severe obstructive lung disease should be thought about. When eosinophilia, pulmonary infiltrates, or both are present, differential diagnosis includes drug and parasitic causes of simple eosinophilic pneumonia, chronic eosinophilic pneumonia, idiopathic hypereosinophilic syndrome, allergic bronchopulmonary aspergillosis, and hypersensitivity pneumonitis.[41] Asthma is not typically present in patients with simple eosinophilic pneumonia, hypereosinophilic syndrome, or hypersensitivity pneumonitis. Although patients with hypereosinophilic syndrome might have cardiac involvement and mononeuritis multiplex similar to Churg-Strauss syndrome, absence of vasculitis on tissue biopsy specimens suggests the disorder is not present.

Prognosis

Prognosis for Churg-Strauss syndrome is generally good. Early assessments of prognosis included this disorder with polyarteritis nodosa, thus attenuating projected expectations of remission and cure. However, the disorder has a better rate of long-term remission than polyarteritis nodosa.[42–44] With the introduction of corticosteroid treatment, remission and survival have improved greatly. Patients with limited organ involvement respond well to systemic corticosteroids alone. Those needing additional immunosuppressive therapy—eg, cyclophosphamide—are mainly those with substantial organ involvement and those who do not respond adequately to systemic corticosteroids alone.

Results of two studies that assessed patients' long-term outcomes showed that overall remission rates were good, ranging from 81–92%. However, 26–28% of patients in remission relapsed.[8,34] Relapses seemed to arise in a bimodal (early and late) distribution, with 40% of patients relapsing within the first year of treatment.[8,34] However, overall mortality in treated patients who relapsed was only 3·1%.[8]

Solans[34] has reported that 40% of patients with Churg-Strauss syndrome need oral steroids only and do not require additional treatment. Of those not responding or who relapsed after treatment with corticosteroids alone, many responded to the addition of immunosuppressive therapy with cyclophosphamide. Not surprisingly, patients with the poorest outcomes did not respond also to multimodal treatment with prednisone and cyclophosphamide followed by further initiation of rescue therapy with unproven treatments (see below).

To establish which patients have the poorest prognosis and hence may need the most aggressive treatment, Guillevin[8] analysed, by univariate and multivariate analysis, 96 people with Churg-Strauss syndrome. Of those who died, severe end-organ vasculitis was the most frequent cause, followed by cardiac disease. Echocardiography usually showed a hypokinetic septum with normal thickness.[45] The two most meaningful predictors for a poor outcome were cardiac involvement—shown as vasculitis, cardiomyopathy, or congestive heart failure—and severe gastrointestinal disease leading to bleeding, perforation, or necrosis. Other elements associated with poor prognosis included proteinuria greater than 1 g/day; the number of patients with renal involvement was small. Guillevin concluded that treatment should be initiated according to disease severity at presentation. Patients with life-threatening

Panel 4: Treatment regimens by prognostic categories

Patients with indicators of good prognosis

Corticosteroids alone

Prednisone 1 mg kg^{-1} day^{-1} for 1 month or until no evidence of disease is present. Gradual taper over the course of a year should follow with reinstatement of prednisone if disease activity reoccurs

Patients with systemic involvement or indicators of poor prognosis

Corticosteroids as outlined above plus

Cyclophosphamide concurrent with steroids

Oral 2 mg kg^{-1} day^{-1}

Intravenous pulse 0·6 g/m^2 monthly

Alternative (unproven) therapies

Intravenous immunoglobulin 400 mg/kg for 5 days monthly

Ciclosporin 150 mg orally every 12 h

Interferon alfa

Mycophenolate mofetil

Azathioprine

organ involvement should receive corticosteroids and other immunosuppressive drugs, whereas patients with less complicated Churg-Strauss syndrome have good remission rates with monotherapy with oral corticosteroids.[8,35]

Treatment

Corticosteroid therapy

Corticosteroids are the cornerstone of treatment for Churg-Strauss syndrome. Because these drugs are usually sufficient for treatment of most patients who do not have severe organ involvement, they should be viewed as first-line therapy, without addition of other immunosuppressive agents. Frequent complications of treatment include iatrogenic Cushing's syndrome, steroid-induced diabetes, corticosteroid-induced myopathy, steroid psychosis, osteoporosis with vertebral fractures,[46] avascular necrosis, gastrointestinal haemorrhage, and infectious complications.[34]

Corticosteroid-induced loss of bone-mineral density is another treatment-related side-effect in patients with Churg-Strauss syndrome.[38] When this loss happens, secondary causes should be excluded. Hypogonadism from cyclophosphamide is typical in patients with Churg-Strauss syndrome.[34] Bisphosphonates are the most effective primary and secondary preventive agents.[38]

Modifications in management can usually be made to adjust for the side-effects of systemic corticosteroids. The recommended dose of prednisone is 1 mg kg^{-1} day^{-1} for 1 month, with a gradual taper up to 1 year.[8] With acute multiorgan involvement, 1 g intravenous methylprednisolone for 3 days, followed by 40–60 mg of prednisone daily, has been advocated.[47] Treatment is continued until no evidence of disease is present and then gradually tapered (panel 4).

During treatment, patients with Churg-Strauss syndrome should be followed up expectantly for reduction in severity of vasculitic symptoms and markers of inflammation, including the erythrocyte sedimentation rate. Antineutrophil cytoplasmic antibodies, although a marker of disease, may not reliably correspond with disease activity, and hence might not be valuable in assessment of disease remission in all patients. Results of a study in three patients with Churg-Strauss syndrome showed that eosinophilia in sputum and blood corresponded with exacerbations.[48] Successful treatment is indicated by resolution of end-organ symptoms, (eg, mononeuritis multiplex), and pulmonary infiltrates should also abate. However, it is not uncommon for the symptoms of asthma to persist both during treatment and after conclusion and remission of disease.[8] Often, inhaled corticosteroids or low-level oral systemic steroids are needed as continued treatment for asthma.

Adjuvant treatment with cyclophosphamide

Cyclophosphamide can be added to the treatment regimen when patients with Churg-Strauss syndrome relapse, and this drug has improved prognosis in those with severe necrotising vasculitis.[49] This occurrence has led to recommendation of cyclophosphamide as adjuvant therapy in patients who have substantial vasculitic end-organ involvement and in those who have not proven responsive to corticosteroids. The primary efficacy seems to be in rapidity and rate of remission. However, no evidence, as yet, lends support to improved 10-year survival from combination therapy.

Treatments for Churg-Strauss syndrome can potentially have toxic effects. The adverse effects of cyclophosphamide include haemorrhagic cystitis, bladder fibrosis, bone-marrow suppression, ovarian failure, and neoplasm.[50] The overall rate of infection may increase by as much as 10%.[51] This infection could be reduced in patients at highest risk by prophylactic use of trimethoprim plus sulfamethoxazole three times a week. Perhaps the greatest concerns are for haemorrhagic cystitis, which arises in 9–17% of patients.[52,53] The risk of this side-effect is associated with the cumulative dose of cyclophosphamide, but may happen with as little as 100 mg of the drug. One approach to prevention of cyclophosphamide-induced cystitis consists of extensive hydration and administration of mesna before and after each infusion.[8]

Risk of urological malignancy in patients with Churg-Strauss syndrome is 15–45 times greater than in the population at large.[54–57] This risk results from accumulation of the urotoxic metabolite acrolein in the bladder, which is caused by administration of cyclophosphamide. The dose of cyclophosphamide should probably be reduced in patients presenting with renal insufficiency.[58] Substitution of cyclophosphamide with mycophenolate mofetil or azathioprine as corticosteroid-sparing agents after 4–6 months has been used as standard practice in many centres.[38,59] However, no results from prospective trials lend support to this practice.

The benefit of pulse intravenous administration of cyclophosphamide versus oral regimens is debatable. A small clinical study of 25 patients with Churg-Strauss syndrome compared oral cyclophosphamide 2 mg kg^{-1} day^{-1} for 1 year plus oral corticosteroids with a monthly intravenous dose at 0·6 g/m^2 plus oral corticosteroids.[60] Efficacy was comparable in both groups of patients; however, the power of the study was a limiting factor. Nonetheless, the side-effect profile was twice as great in the group receiving continuous oral administration. Side-effects specifically attributable only to cyclophosphamide—eg, alopecia, neutropenia, and haemorrhagic cystitis—were seen only in this group of patients. Use of pulse cyclophosphamide allows a lower cumulative dose to be given, which is advantageous in avoiding long-term side effects—eg, the likelihood of subsequent malignancy. In view of the decrease in side-effects and apparent equal efficacy between groups of patients, the researchers on this study recommended pulse over daily oral therapy for Churg-Strauss syndrome.[60]

Rescue and alternative therapeutic options

Case reports of rescue or alternative therapies are plentiful; evidence-based support for their use unfortunately is not. Plasma exchange has been reported anecdotally to be successful in treatment of refractory Churg-Strauss syndrome.[61] However, in a series of studies, Guillevin did not show the value of plasma exchange in patients with polyarteritis nodosa or Churg-Strauss syndrome.[62] Although addition of cyclophosphamide improved the rate of remission (but did not improve 10-year survival), results of repeated randomised studies have not shown efficacy of plasma exchanges in patients with either polyarteritis nodosa or Churg-Strauss syndrome.[8,62]

Several case reports also note successful administration of intravenous immunoglobulin for systemic vasculitides.[63,64] In one, this drug was successfully used to treat Churg-Strauss syndrome (400 mg/kg for 5 days monthly).[65] However, no randomised controlled studies have been done of intravenous immunoglobulin to treat this disorder.

Tatsis and colleagues[66] reported use of interferon alfa in four patients with Churg-Strauss syndrome with cardiac involvement who failed to respond to corticosteroids and immunosuppression or could not be weaned from corticosteroids. Patients received 3–10 million units of the drug three times a week. Dosage was titrated to clinical results and peripheral blood eosinophil counts. Discontinuation of cyclophosphamide and reduction of dose of prednisone was achieved in all four cases. The researchers concluded that interferon alfa might offer a less toxic substitute for adjuvant therapy in patients who are difficult to treat.[66] It is noteworthy that this drug has been associated with cardiac toxic-effects such as arrhythmia, ischaemic heart disease, and cardiomyopathy and therefore warrants a thoughtful approach before initiation of treatment.[67]

Conclusions

There is no one set of criteria for accurate diagnosis of Churg-Strauss syndrome. Confirmation by biopsy of vasculitis is complicated by the unpredictable and often sequential onset of manifestations of the disease in the various organs it involves, and by its incomplete evolution even in organs that are affected. Clinical diagnosis alone is difficult in early stages of Churg-Strauss syndrome because of the substantial overlap between the disorder and the usual symptoms of severe asthma. However, onset of severe asthma in an adult that is associated with gastrointestinal manifestations, renal disease, cardiac manifestations, pulmonary infiltrates resembling allergic alveolitis, or mononeuritis multiplex should alert doctors to the probable emergence of Churg-Strauss syndrome, especially in patients who are being or have been withdrawn from a previous course of systemic corticosteroids.

The major differentiating factor of Churg-Strauss syndrome from other vasculitides is its almost invariable association with asthma, although no pathogenetic mechanism for this association has been established. The emergence of Churg-Strauss syndrome in many asthma patients is probably due to withdrawal from immunosuppressive corticosteroids for severe asthma rather than being attributable to induction by various unrelated compounds that have been coincidentally associated with the disorder. However, because this issue remains unresolved, caution should be exercised when initiating a new treatment in patients with severe asthma.

Treatment for Churg-Strauss syndrome begins with recognition of the association of asthma with vasculitis, and therapy is staged according to severity of involvement. In non-complex cases, a minimum of 1 year of oral corticosteroid therapy is sufficient. In patients in whom organ involvement is extensive or refractory to treatment, other immunosuppressive agents—eg, cyclophosphamide—are needed in addition to oral corticosteroids. Even on completion of successful treatment, patients with Churg-Strauss syndrome might need continuous observation and further therapeutic intervention, and asthma generally remains persistent and difficult to manage.

Conflict of interest statement

In the past 3 years, ARL has served on the advisory board for Merck and IN has been part of a speaker's bureau for Intermune, GlaxoSmithKline, and Merck. MES and IN are Director and co-Director, respectively, of Respiratory Clinical Research at the University of Chicago and have participated in multicentre clinical research studies with many pharmaceutical companies that make drugs used in the treatment of asthma, some of which are mentioned in this Seminar.

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