

ASTHMA THERAPIES AND CHURG-STRAUSS SYNDROME

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The pulmonary vasculitides are a group of rare but serious disorders that require early recognition, accurate diagnosis, and effective therapy. Churg-Strauss syndrome (CSS) is classified as small vessel vasculitis. Four different definitions for the diagnosis of CSS have been developed: (1) the pathologic criteria put forth by Churg and Strauss, (2) the criteria based on clinical grounds from Lanham and colleagues, (3) the criteria based on clinical grounds from the American College of Rheumatology, and (4) the criteria from the Chapel Hill Consensus Conference, which closely concur with the Churg and Strauss definition. It is apparent that cessation, diminution, or even a switch from low-dose systemic to inhaled corticosteroid therapy can precipitate the appearance of CSS. The term *forme fruste* has been used to indicate that the signs and symptoms of CSS were (inadvertently) suppressed by cortico-

steroids. The clinical risk factors for CSS are moderately severe or severe asthma, chronic sinusitis, or reductions in systemic corticosteroid therapy. Differential diagnosis, treatment, and ongoing monitoring of CSS therapeutic responses are reviewed. The introduction of leukotriene modifiers and high-potency inhaled corticosteroids have allowed control of asthma symptoms, which results in avoidance or reduction in oral corticosteroid use. The advent of these agents has been associated with reports of CSS appearing in patients with asthma. The available data regarding the association of CSS and antiasthma agents are most consistent with the unmasking of a previously contained pathologic condition (*forme-fruste* CSS) or disease that progresses because systemic corticosteroids were avoided. Early recognition and immunosuppressive therapy are the keystones of successful treatment of this rare disorder (*J Allergy Clin Immunol* 2002;109:S1-20).

Key words: Churg-Strauss syndrome, vasculitis, asthma, asthma therapy, leukotriene modifiers, β -agonist, corticosteroids, *forme fruste*

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The pulmonary vasculitides are a group of rare but serious disorders that require early recognition, accurate diagnosis, and effective therapy. Churg-Strauss syndrome (CSS) is classified as small vessel vasculitis and is of particular interest to allergists because it occurs in patients with sinusitis and asthma. The original report of CSS in 1951 allowed the syndrome to be recognized earlier in its clinical course, and advances in the treatment of allergic diseases have changed the recognized clinical features of CSS. This shift in the clinical and pathologic features can be dated to the advent of the wider use of corticosteroid therapy for refractory asthma and is thought to be related to the therapeutic effects of corticosteroids on CSS. The clinical features of CSS continue to evolve with asthma therapy. The availability of higher potency inhaled corticosteroids and leukotriene modifiers, which allow the control of (allergic) symptoms in the absence of oral corticosteroids, has also altered the features of CSS. We present a historical review of the CSS, a pathologic description of the disease, a review of the alternative case definitions and the clinical presentation and course of the disease, effective and practical methods of diagnosis, the reported epidemiologic factors, and effective treatment strategies for CSS. A case presentation approach is used to review the association of CSS with fluticasone, zafirlukast, montelukast, and budesonide/fluticasone/salmeterol, with a focus on specific clinical features that are relevant to the issue of cause and effect. The mechanisms by which adverse drug reactions occur are reviewed.

Abbreviations used

ACR:	American College of Rheumatology
ANCA:	Antineutrophil cytoplasmic antibody
c-ANCA:	Cytoplasmic ANCA
CSS:	Churg-Strauss syndrome
CT:	Computed tomography
ESR:	Erythrocyte sedimentation rate
HES:	Hypereosinophilic syndrome
MPA:	Microscopic polyangiitis
MPY:	Million patient-years
NSAID:	Nonsteroidal anti-inflammatory drug
PAN:	Polyarteritis nodosa
p-ANCA:	Perinuclear ANCA
WBC:	White blood cell
WG:	Wegener's granulomatosis

HISTORICAL PERSPECTIVE AND PATHOLOGIC FEATURES

Historical description of CSS

Vasculitis was first recognized in 1866 by Kussmaul and Maier¹ in the form of polyarteritis nodosa (PAN). For many years all types of vasculitis, regardless of clinical or pathologic findings, were simply called PAN. Classic PAN involved large elastic arteries and was characterized by the formation of macroscopic aneurysms. In the mid 1930s the lesions of Wegener's granulomatosis (WG) were recognized and were described 2 decades later.² Churg and Strauss³ reported "allergic angiitis, granulomatosis, and polyarteritis nodosa," now recognized as CSS. In a 1954 article, Godman and Churg⁴ codified the typical distribution (upper respiratory tract, lower respiratory tract, and kidney) and microscopic appearance of WG lesions. They further noted that WG, CSS, and microscopic polyangiitis (MPA) all seemed to affect the same sizes and types of vessels and had pathologic similarities, which led them to the accurate notion that these entities might somehow be related. Today, CSS, WG, and MPA are all classified as "small vessel vasculitis." They exhibit similar patterns of vascular involvement, generally similar types of microscopic appearances in affected vessels, and frequent occurrence of antineutrophil cytoplasmic antibody (ANCA) reactivity in the serum; they all require a similar therapeutic approach.

CSS case definitions

Developing guidelines for diagnosing CSS has proved somewhat elusive. Table I depicts 4 different definitions. It should be noted that the original descriptions of Churg and Strauss were based on autopsy material from the pre-corticosteroid age and thus reflect untreated disease of generally marked severity. In contrast, current cases have virtually always been treated with corticosteroids before diagnosis, and some cases display relatively mild disease. The criteria put forth by Churg and Strauss³ were essentially a combination of asthma, eosinophilia, and a systemic necrotizing vasculitis. Their definition consistently involved pathologic samples, but diagnosis is now

possible in most cases on clinical grounds with the use of either the criteria of Lanham and colleagues⁵ or the American College of Rheumatology (ACR)⁶ criteria shown in Table I (the common themes are asthma, eosinophilia, and vasculitis). The advantage of the ACR scheme is that it enables the recognition of disease in the early stage of eosinophilic infiltration without evidence of vasculitis. Notably, all classic pathologic features (tissue eosinophilia, eosinophilic vasculitis, fibrinoid necrosis, and necrotizing granulomas) rarely occur together and are simultaneously visible in only a few biopsy samples.⁵ Jennette et al⁷ also concur closely with the definition set forth by Churg and Strauss.

Approximately 70% of CSS cases are ANCA positive. However, none of the classification schemes incorporates testing for ANCA, which involves the application of serum from a patient to normal alcohol-fixed neutrophils and observation of the pattern of fluorescence (perinuclear [p]-ANCA vs cytoplasmic [c]-ANCA). Most p-ANCA reflects antibodies that are directed against myeloperoxidase; c-ANCA shows antibodies that target neutrophil proteinase 3. In a patient with 1 of the diagnostic schemes shown in Table I, positive ANCA offers strong support for the presence of CSS.

Pathologic features of CSS

Biopsy and autopsy materials from patients with CSS evince a variable combination of several different features. Eosinophilic tissue infiltration is almost a universal finding that varies histologically by site and often simply appears as large numbers of eosinophils in an organ in which none would be expected (eg, a lymph node or salivary gland). In the lung, eosinophilic infiltration appears as chronic eosinophilic pneumonia (Fig 1). Frequently, infiltrated organs are enlarged and fine-needle aspirates of such organs, such as a lymph node, may reveal only eosinophils. In a patient with asthma and blood eosinophilia, this finding is adequate to make a diagnosis of CSS.

Vasculitis in CSS is also characterized by eosinophilic infiltration of vessel walls (Fig 2, A), sometimes with eosinophilic necrosis (Fig 2, B). In general, the vessels involved are small arteries, veins, arterioles, venules, and capillaries. Capillaritis in the lung correlates with diffuse pulmonary hemorrhage. Involvement of capillaries and venules in the skin is associated with palpable purpura, whereas pathologic conditions of other sizes and types of vessels produces significantly variable effects that range from no obvious clinical lesions to typical vasculitis symptoms, such as mononeuritis multiplex. It is difficult to be certain about the frequency even of vasculitis. In a recent large series, necrotizing vasculitis was present in no more than 50% of biopsy specimens from cases accepted as CSS.⁸ Alveolar hemorrhage thought to reflect capillaritis was seen in 3 of 96 patients.

The original description by Churg and Strauss emphasized the presence of granulomas with necrotic centers and giant cells arrayed around the necrotic foci (Fig 3). Such granulomas are uncommon; in a tabulated review of the literature, Lanham et al⁵ reported granulomas in only 40% of

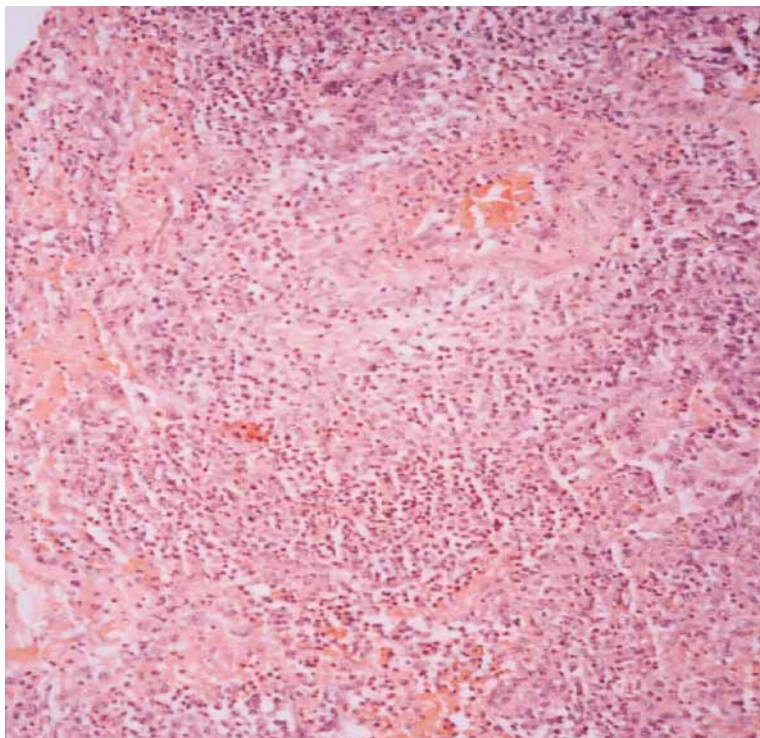


FIG 1. Microscopic image (medium power) of the lung shows a pattern of eosinophilic infiltration (eosinophilic pneumonia) and mild vasculitis in a small pulmonary artery branch.

TABLE I. Definitions of CSS

Churg and Strauss 1951 ³ (autopsy pathologic material)
History of asthma
Tissue eosinophilia
Systemic vasculitis
Extravascular granulomas
Fibrinoid necrosis of connective tissue
Lanham et al 1984 ⁵ (clinical with or without pathologic condition)
Asthma
Eosinophilia, $>1.5 \times 10^9/L$
Evidence of vasculitis that involves at least 2 organs
ACR 1990 ⁶ (clinical with or without pathologic condition; diagnosis likely when 4 of the 6 criteria are present)
Asthma
Eosinophilia, $>10\%$
Neuropathy, mononeuropathy, or polyneuropathy
Pulmonary infiltrates
Paranasal sinus abnormality
Extravascular eosinophil infiltration on biopsy
Chapel Hill Consensus Conference 1994 ⁷ (pathologic/clinical)
"Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels and associated with asthma and eosinophilia"

cases. Tissue necrosis may be found in the absence of granulomas, especially in chronic eosinophilic pneumonia-like foci in the lung.

Correlations of pathologic findings and stage of disease in CSS cases tend to progress through a series of stages. In large series, the earliest manifestation is allergic rhinitis, followed by the onset of asthma, and culminating in overt CSS.⁵ There is also pathologic progres-

sion.⁹ The earliest cases involved only tissue infiltration by eosinophils without vasculitis. These patients frequently responded to high-dose corticosteroids alone. Once overt vasculitis developed, a combination of corticosteroids and an immunosuppressive agent, such as cyclophosphamide, was required; but these agents sometimes failed to induce remission. The detection of CSS at the stage of eosinophil infiltration therefore increases the

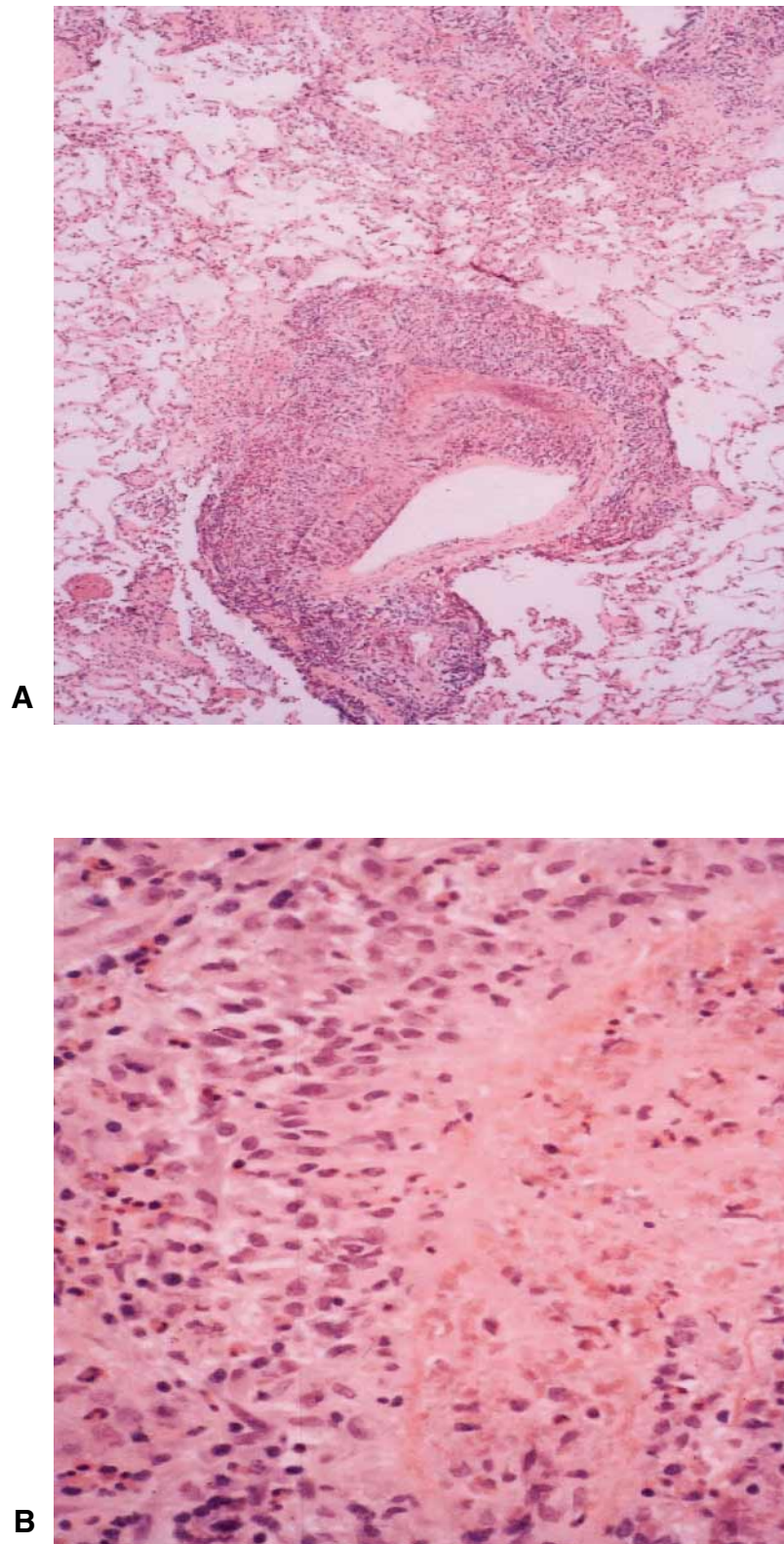


FIG 2. Microscopic images at low (**A**) and high (**B**) power show vasculitis in a pulmonary artery branch. Note the eosinophilic necrosis visible in the high-powered image (**B**).

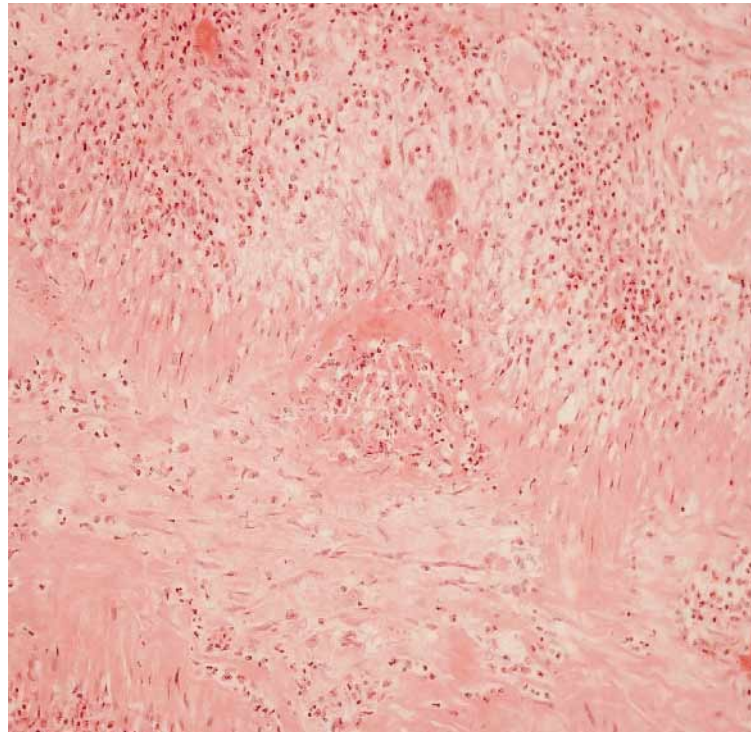


FIG 3. High-powered view of an early Churg-Strauss granuloma that is forming around a necrotic focus in the wall of a small artery in the kidney.

likelihood of successful treatment. It is important to note that this is not always a straightforward process; tissue infiltration and vasculitis commonly coexist, and neither clinical observation nor biopsy is 100% effective in detecting vasculitis.

Formes frustes of CSS

Before the wide use of oral corticosteroids for severe asthma, most cases of CSS simply appeared to arise without warning in patients with asthma and, often, allergic rhinitis. It has now become apparent that cessation of corticosteroid therapy, diminution of corticosteroid therapy, or even a switch from low-dose systemic to inhaled corticosteroid therapy can precipitate the appearance of CSS. Originally, 4 such cases were reported,¹⁰ and it was suggested that they be termed *formes frustes* of CSS to indicate that signs and symptoms of CSS were (inadvertently) suppressed by corticosteroids. These formes frustes cases ranged from tissue infiltration (eosinophilic lymphadenopathy) without overt vasculitis to very severe diffuse vasculitis. None of the patients had received corticosteroid-sparing drug therapy (such as leukotriene receptor antagonists) before the emergence of disease. Pathologically, they did not seem to differ from other CSS cases, although the number of samples that were examined was relatively small. Increasing numbers of cases are now being reported in which modifications of corticosteroid therapy alone coincide with overt CSS.¹¹

Patterns of organ involvement and prognosis in CSS

CSS is a systemic disease with widespread but quite variable organ involvement that includes the heart, lungs, gastrointestinal tract, cerebral vessels, joints, muscles, skin, and nerves. Cardiac and gastrointestinal involvement is frequent in CSS and can have symptoms related to these organs. These 2 types along with central nervous system involvement are associated with higher mortality rates.^{5,8,12} Lanham et al⁵ concluded that cardiac disease accounted for approximately 50% of deaths. However, definitions of CSS that require pulmonary involvement (such as the Chapel Hill Consensus Conference⁷) will result in significant underdiagnosis, because approximately 30% of cases in the summarized series of Lanham et al⁵ did not exhibit such involvement. As opposed to WG and MPA (the overlap form of PAN), renal failure is uncommon in CSS.

CLINICAL PRESENTATION, DIAGNOSIS, AND ASSESSING DISEASE ACTIVITY

CSS develops in patients with a history of upper airway disease and asthma. Asthma may precede the development of systemic vasculitis by up to 30 years; however, a shorter duration of asthma before the onset of vasculitis is associated with a poorer prognosis (a mean interval of 6.6 years between onset of asthma and vas-

TABLE II. Clinical manifestations of CSS in 4 series

Manifestation	Lanham et al ⁵ (%)	Chumbley et al ¹³ (%)	Guillevin et al ⁸ (%)	Reid et al ¹⁶ (%)
Rhinitis/sinusitis/ Upper airway disease	75	70	61	52
Lower respiratory, not including asthma	63	27	36	48
Lower respiratory, including asthma	100	—	100	96
Cardiac, not including hypertension	25	—	22	26
Cardiac, including hypertension	75	—	22	26
Gastrointestinal	44	17	33	17
Renal	69	20	33	57
Muscle/joint	69	20	54	57
Dermatologic	56	27	49	26

culitis).¹³ Patients with CSS will most often be seen by internists, general practitioners, allergists/immunologists, pulmonologists, and otolaryngologists because of the strong association of CSS with asthma and its predilection for adults. CSS is rare in pediatric populations; reported cases have occurred primarily in older children or adolescents. The reduction of systemic corticosteroids is a common, although not essential, event before the development of CSS.^{14,15} Although the reduction in systemic corticosteroid therapy may be due to spontaneous improvement of asthma, reduction is often associated with symptom control in the context of inhaled corticosteroid therapy or systemic noncorticosteroid therapy. The clinical risk factors for CSS are moderately severe or severe asthma, chronic sinusitis, and a recent reduction in systemic corticosteroid therapy.

The allergic features of CSS are often but not always dominant, and patients with CSS may be seen by neurologists, dermatologists, cardiologists, hematologists, and nephrologists. The frequencies of the clinical features of the disease are presented in Table II.^{5,8,13,16} The neurologic manifestations of the disease are of particular interest because peripheral neuropathy or mononeuritis multiplex is an important clinical finding that indicates the onset of the vasculitic phase of the disease and can suggest the diagnosis. The cardiac evaluation of CSS is also of interest, because reports describe initial evaluation as cardiomyopathy with eosinophilia.¹⁷⁻¹⁹ Cardiac involvement is relevant to advanced disease because terminal cardiac events have been reported in 50% of autopsy cases.⁵

Clinical diagnosis

The diagnosis of CSS is complicated by the absence of a single confirmatory, easily obtainable laboratory test. Rather, the diagnosis depends on the association of the features of the disease with its histologic hallmarks. Tissue eosinophilia is essential; blood eosinophilia is almost always present, and p-ANCA is often detectable. The absence of blood eosinophilia or ANCA does not exclude CSS but significantly reduces the probability. The diagnosis of CSS rests on histologic evidence of vasculitis that affects variably sized vessels with eosinophil infiltration. All other information is support-

ive. This does not mean the diagnosis cannot be made without histologic confirmation, but the diagnosis is never as secure without histologic evidence. The clinical challenge is the recognition of the earliest signs of the disease or the need for tissue biopsy.

CSS should be seriously considered in a patient with asthma who has any of the following features: new-onset foot drop (mononeuritis multiplex); palpable purpura (small vessel vasculitis of dermal blood vessels with hemorrhage); migratory pulmonary infiltrates that resemble pneumonia (eosinophilic infiltration of the lung); or cardiac enlargement with or without failure. These findings are generally associated with significant malaise. Other potential concomitant symptoms include a decrease in appetite, subjective fever, paresthesias, headache, dyspnea, and arthralgias. Concomitant findings of increased asthma may or may not be paramount, although most affected patients have a history of moderate to severe asthma. Less frequent clinical findings include abdominal pain, diarrhea, proteinuria or hematuria, progressive lymphadenopathy, or worsening sinusitis.

A diagnostic biopsy should generally be performed on the most accessible affected tissue. Ideally, variably sized blood vessels affected by vasculitis are needed for a definitive diagnosis, and this requirement may limit the value of a skin biopsy or transbronchial lung biopsy. The biopsy of sites that are not affected clinically (referred to as a blind biopsy) is of limited value and therefore discouraged. Suggested biopsy sites include sural nerve or affected muscle with foot drop, skin biopsy with palpable purpura, thorascopic or open or transbronchial lung biopsy with migratory pulmonary infiltrates, pleural biopsy with pleural effusion, intestinal mucosal biopsy with diarrhea or abdominal pain, or lymph node removal with lymphadenopathy. Endomyocardial or renal biopsy is less frequently indicated but should be considered if data suggest organ involvement (eg, cardiac decompensation, proteinuria, hematuria, or decreased renal function). Fine-needle aspirate of a lymph node, nasal/sinus mucosal biopsy, thoracentesis, or pericardiocentesis may demonstrate eosinophils and, under some circumstances, can be diagnostic. Tissue eosinophilia is a necessity for CSS, but histologically similar tissue eosinophilia may occur in other

conditions, including hypereosinophilic syndrome (HES), eosinophilic gastroenteritis, allergic bronchopulmonary aspergillosis, hyperplastic rhinosinusitis with nasal polyposis, fungal hypersensitivity sinusitis, eosinophilic pneumonia, parasitic disease, and drug allergy. Thus, tissue eosinophilia without vasculitis is not, with rare exception, adequate to support the risk of immunosuppressive agents other than prednisone. Peripheral eosinophil quantification is a useful initial step in the differential diagnosis of CSS. Other relevant laboratory data include ANCA, erythrocyte sedimentation rate (ESR), urinalysis, quantitative C-reactive protein, and chest radiograph. Serum complement or immune complex studies are not likely to be helpful. Allergic bronchopulmonary aspergillosis and allergic fungal sinusitis can have features similar to CSS; therefore, aspergillus or other mold skin testing, aspergillus precipitins (immunoglobulin G that is specific for aspergillus), and total serum immunoglobulin E can help distinguish these possibilities. Parasitic disease is an important consideration in patients who are at risk; infestation with ascaris and strongyloides can be detected by stool examination. Other considerations include HES, WG, tuberculosis (associated with false positive ANCA), MPA, PAN, and lymphoma or other malignancy. Arteriography is not usually helpful for the diagnosis of CSS but can distinguish it from medium-sized vessel vasculitides, including PAN.

Clinical course and disease monitoring

The clinical course of CSS is variable. Although the onset of the vasculitis phase is often sudden, the duration of the prodromal phase can be difficult to precisely identify. Most patients appear to experience suddenly the development of the cardinal manifestations (such as foot drop, palpable purpura, or pulmonary infiltrates) without a perceptible prodrome. Most likely, blood and tissue eosinophilia develop over extended time but are unrecognized. Acute-phase reactants and ANCA also probably become detectable during the preclinical phase, but for most patients this is conjecture because these tests are not routinely obtained for asthma treatment. The natural clinical course of CSS is modified by corticosteroids, particularly systemic therapy that is administered for the control of asthma symptoms.

The assessment of treatment response and follow-up of affected patients is limited by the modest understanding of the natural history of the disease. The essential pathophysiologic feature is tissue eosinophilia, but repeated tissue biopsy is not practical. Blood eosinophilia is a surrogate but not always a reliable marker of tissue eosinophilia. Nevertheless, the monitoring of blood eosinophil counts is generally a useful strategy to facilitate decision making for changes in therapy. Reductions in blood eosinophil counts coupled with the improvement of clinical findings (such as skin lesions, foot drop, and chest radiograph findings) provide reassurance that the treatment is effective.

An additional consideration is monitoring acute-phase reactants (such as platelet count, ESR, C-reactive protein

levels, or quantified ANCA). Increased or detectable levels before therapy suggest that the improvement or exacerbations of CSS would correlate with decreases or increases in these parameters.

The frequency of monitoring for any laboratory value depends on the clinical situation. A general recommendation is to assess blood eosinophil counts and acute-phase reactants every few days during the initiation of therapy, weekly to triweekly during the stabilization of the disease, and every few weeks to every few months during long-term care. Repeat ANCA testing may be helpful when discordant laboratory or clinical findings occur or after clinical control of the disease (to establish a new baseline value).

Increases in ANCA, peripheral eosinophil counts, and/or acute-phase reactants may presage clinical exacerbation. Increasing therapy before clinical worsening probably results in reduced morbidity and mortality rates and the total medication required for disease control. Exacerbation or relapse may occur after prolonged periods of apparent disease inactivity; therefore, extended clinical and laboratory monitoring is encouraged. The lack of detectable disease activity for more than 18 to 24 months would mitigate the value of ongoing laboratory follow-up, but relapse should be considered indefinitely. Clinical acumen and judicious use of the laboratory are essential in following CSS.

TREATMENT FOR CSS

Although rare, CSS is a serious disease that requires early and aggressive intervention. Making the diagnosis of CSS places the clinician in a position to consider effective treatment options that can be adapted to reflect the clinical evaluation. Treatment with systemic corticosteroids can be considered for patients who are carefully monitored early in the course of the disease without poor initial prognostic signs (evidence of impending organ dysfunction). For most patients, especially those patients with evidence of active vasculitis, treatment with corticosteroids and immunosuppressive agents (cyclophosphamide) is considered first-line therapy.

CSS is 1 of several diagnoses that should be considered when moderate-to-severe asthma is progressive or difficult to control. CSS should be especially considered when HES, corticosteroid resistance, vocal cord dysfunction, sinusitis, and gastroesophageal reflux disease have been excluded.^{10,11,19,20-23}

The criteria and guidelines for making a CSS diagnosis are established but may not be conclusive when adequate tissue is not available.^{6,8,24} A characteristic of CSS is its association with asthma and eosinophilia, and the presence of asthma in the face of vasculitis is an important differentiating factor for CSS. Other differentiating factors include the presence or absence of positive p- or c-ANCA; the percentage of positivity differs among the vasculitides. For example, the c-ANCA is positive in about 80% of patients with WG, although it is positive in only approximately 10% of patients with CSS. The p-

ANCA is positive in 60% of patients with CSS, but in only 14% of patients with WG. In MPA, p- and c-ANCA positivity are nearly equivalent, 45% to 50% respectively. Finally, patients with PAN vasculitis have 5% to 15% positivity for p-ANCA and lack positivity for c-ANCA.²⁵ Although these autoantibody tests are correlative, they generally do not predict response to treatment, and many false positives and false negatives exist in the classification of these illnesses, according to ANCA titer.

Distinguishing CSS (a vasculitis) from HES is critical because different treatment approaches are indicated. Cardiomyopathy is important and may differentiate HES from CSS, because HES can cause a restrictive endomyocardial fibroelastosis. Although CSS may have some general cardiac and/or vascular effects in terms of coronary artery vasculitis, it does not cause restrictive cardiomyopathy.

Once CSS has been distinguished, it is critical to determine the extent of organ dysfunction to establish the appropriate intensity of anti-inflammatory treatment. Guillevin et al^{8,24} identified a 5-factor score in which the severity of vasculitis was evaluated. The 5 factors that were associated significantly with a poor outcome included heart disease; myocardial involvement; the presence of proteinuria (≥ 1 g/d); severe gastrointestinal symptoms that are defined as intestinal bleeding, perforation, pancreatitis, or laparotomy; and a short duration of asthma. The 5-factor score was significantly associated with a high risk of death when ≥ 2 . In this analysis, severe gastrointestinal tract and myocardial involvement were also poor prognostic factors. A score of 0 correlated with an 88% survival rate.^{8,24}

When corticosteroid therapy does not cause remission in CSS (as either corticosteroid sparing or corticosteroid failure) and other significant life-threatening circumstances exist, the use of immunosuppressive cytotoxic therapy is indicated. Eosinophilia with other vasculitis, including WG, PAN, or MPA, all respond to cytotoxic therapy as the major therapy. The standard treatment for CSS includes cyclophosphamide, with or without corticosteroids, in varying dosages that are continued for 1 year into remission. Other cytotoxic agents, which include methotrexate or azathioprine, may be used; however, they may not be as efficient as cyclophosphamide in inducing remission. Generally, there is 90% to 95% remission within 1 year of treatment, although 30% to 40% of patients may experience relapse and require continued therapy, which is essentially a repeat of prerenal treatment.⁸ More than 50% of patients with systemic necrotizing arteritis, including CSS, show long-term cure. A small percentage (5% to 6%) of patients have no response to therapy, and the overall mortality rate is 20% to 25% over 5 to 10 years.

The immunologic mechanism of action of cyclophosphamide and other immunosuppressive agents involves the inhibition of T cells, B cells, and monocyte macrophages. Hence, the immunosuppressive protocol can suppress the induction of newly developed cell-mediated immunity and may suppress the ability to generate new antibodies in response to sensitization. In addition, this

therapy has been shown to suppress numerous *in vivo* and *in vitro* immunologic functions. The complications of therapy include decreased bone marrow reserve, leukopenia, and hemorrhagic cystitis. Hematopoietic and bladder malignancies are seen rarely. Finally, infertility occurs in approximately 15% to 20% of the patients who undergo intense cyclophosphamide therapy.

The reduction of elevated immunoglobulin levels and normalization of sedimentation rate in C-reactive protein are important correlates of effective therapy. Alternative forms of treatment for systemic vasculitis, in particular CSS, have been used successfully.

1. The trimethoprim/sulfamethoxazole combination prevents superinfection and may have a direct therapeutic effect on WG.
2. Intravenous pulse cyclophosphamide, as opposed to daily oral use, has been demonstrated in the treatment of lupus nephritis and other autoimmune diseases.
3. Intravenous immunoglobulin has been shown to be an effective treatment in systemic vasculitis and, in isolated case reports, as a corticosteroid and cytotoxic drug-sparing agent.
4. Experimental therapies include the use of soluble TNF receptor decoy therapy and monoclonal antibodies to TNF, which have been used in other rheumatic diseases.
5. α -interferon therapy improves the symptoms of CSS.

Recently, it has become clear that α -interferon therapy may be an important adjunct in the treatment of vasculitides, in particular CSS, and in HES.²⁶⁻²⁸ The true value of α -interferon therapy in circumstances in which there is excess eosinophil production is now becoming fully appreciated. Evaluation of the use of these more significant and costly therapies for primary vasculitis syndromes will be important for comparison with the standard therapy established over the past 30 years.

EPIDEMIOLOGIC FACTORS

In the past, CSS reports focused primarily on the incidence of this disorder in the general population. However, recent studies have examined the incidence of CSS in asthmatic populations, particularly in patients with asthma who received various forms of therapy.

In 1995, Watts et al²⁹ reviewed the records of patients with systemic vasculitis who visited the Norwich (United Kingdom) Health Authority between 1988 and 1994. Data capture was accomplished by a review of pathology and discharge records, with independent confirmation by expert review of individual records. Within this stable and homogeneous patient population of approximately 413,500 individuals who are relatively isolated in the eastern part of the United Kingdom, 6 cases of CSS were found by the Lanham criteria⁵ (2.4 cases per million patient-years [MPY]) but only 3 cases of CSS were found by the more stringent ACR criteria (Table I).⁶ A subsequent study of CSS epidemiologic factors in the general population was a 10-year study undertaken by Watts et al,³⁰ who again reviewed the Norwich Health

TABLE III. CSS: incidence from various sources

Source	Population	Incidence/period prevalence (cases per MPY)
Watts et al ^{29,30}	General population	2.4-3.7
Kurland et al ³¹	General population	4
Reid et al ¹⁶	General population	3.3
Estimates	Asthmatic population (assuming 5% to 8% of population with asthma)	30-74
Martin et al ³²	General population	6.8
	Nonasthmatic	1.8
	Asthmatic	64.4
Wechsler & Drazen ²¹	Zafirlukast + montelukast (asthmatic)	56-74

Authority for changing CSS incidence between 1988 and 1997.¹³ Of the 82 cases of systemic vasculitis that were identified, 11 subjects met the ACR criteria for CSS. Although the overall incidence was estimated to be 2.7 cases per MPY (3.4 cases per MPY by Lanham criteria), the incidence more than doubled from the first 5 years (1.5 cases per MPY) to the latter 5 years of the study (3.7 cases per MPY). The authors concluded that this increase may have resulted from better case recognition, which may have in part resulted from the introduction of ANCA testing (Table III).^{13,16,21,29,31,32}

Assuming that asthma occurs in 5% to 8% of the general population, it could be estimated that the rate of CSS in a population of patients with asthma would be 12.5 to 20 times that of the general population (ie, 30 to 74 cases per MPY). CSS incidence rates in this range have been reported in asthmatic cohorts in the United Kingdom. A retrospective analysis of a prescription-event monitoring database of the Drug Safety Research Units in Northhampton (United Kingdom) by Martin et al³² has corroborated this estimate. The Drug Safety Research Unit collects anonymous demographic and prescription information from physicians who report on "any new diagnosis, unexpected deterioration, or other complaint sufficient to enter in the patient's notes." Of the 622,294 patients who were observed during 58 prescription-event monitoring studies performed between 1985 and 1994, the investigators identified 4 cases of CSS, yielding a rate of 6.8 cases per MPY. When studies of the 3 new asthma drugs (nedocromil, bambuterol, and salmeterol) were considered, among the 35,799 individuals reported, CSS developed in 3 patients (64.4 cases per MPY); this falls within the range calculated earlier. However, only 1 case of CSS (in a patient receiving paroxetine therapy) was noted in the other 55 drug cohorts, yielding a rate of 1.8 cases per MPY in the general population. Of note, all 4 patients in whom CSS developed were taking oral or inhaled corticosteroids in the 3 months before the diagnosis of CSS.

Given the increased number of CSS reports since the introduction of leukotriene modifiers in 1996, Wechsler and Drazen²¹ sought to estimate the incidence of CSS in association with these drugs. They compared these estimates with those in general and asthmatic populations to determine whether the incidence of CSS that was associ-

ated with these drugs was different. Adverse event report forms for zafirlukast and montelukast were obtained between September 1996 and July 1999 from the Food and Drug Administration through the Freedom of Information Act. Reports were reviewed for potential CSS and other eosinophilic conditions, and extensive Medwatch case reports were studied for further details. Individual cases were classified as probable on the basis of the presence of 4 or more ACR criteria, and numbers of confirmed cases were obtained from Zeneca Pharmaceuticals and Merck Pharmaceutical. The incidence range was calculated by dividing the number of confirmed or probable cases by estimates of drug exposure (in patient-years) that were obtained from the respective drug companies. In association with these drugs, CSS was estimated to occur in 56 to 74 cases per MPY. This rate was strikingly similar to the estimates that were calculated earlier for patients with asthma and to the rate determined by Martin et al³² for patients who undergo asthma therapy. Furthermore, the mean age and gender of patients with CSS that is associated with leukotriene modifier use were similar to that reported by Guillemin et al,⁸ with respect to the general population (mean age, 48 years; female, 54%). In addition, the number of suspected cases with both of these leukotriene modifiers was similar.

Estimated rates of CSS in association with leukotriene modifiers are similar to rates in the asthma population that were observed before the introduction of these therapies; therefore, the available epidemiologic data does not appear to support the notion that there is a causative role for these drugs in CSS pathogenesis.

CASE REPORTS OF DRUG-ASSOCIATED OCCURRENCE

Leukotriene modifiers are the newest class of asthma therapy and include both cysteinyl leukotriene receptor antagonists (such as zafirlukast, montelukast, and pranlukast) and 5-lipoxygenase inhibitors (such as zileuton). The introduction of this class of agents and the availability of high-potency inhaled corticosteroids have allowed an alternative approach to asthma treatment. One of the advances that is associated with the introduction of higher potency inhaled corticosteroids and leukotriene modifiers is the ability to limit the use of oral corticosteroids

for patients whose condition requires frequent pulses of the drugs or continuous therapy. The positive outcome is the potential for decreasing the long-term side effects of systemic corticosteroids. The advent of these agents has been associated with reports of CSS in treated asthmatic patients. Most authors conclude that the most plausible mechanism of the occurrence of CSS is an unmasking of either a previously contained pathologic condition or the clinical declaration of a *forme fruste* as the result of withdrawal or avoidance of systemic corticosteroid therapy that is made possible by newer antiasthma drugs. The exact relationship between the appearance of this rare severe syndrome and antiasthma therapies is the subject of considerable interest. The following cases were selected for evaluation to explore the relationship between various antiasthma therapies and CSS.

Case 1: Fluticasone-associated CSS

A 39-year-old man who immigrated to the United States in 1992 was examined in the emergency department in July 1996 with 2 weeks of dyspnea, wheezing, and nonproductive cough. He denied a history of asthma, sinusitis, allergic rhinitis, or other chronic respiratory conditions. A chest radiograph demonstrated indistinct bronchovascular markings in the lingula and right middle lobe. Despite treatment with nebulized albuterol and a trimethoprim/sulfamethoxazole combination, he returned with similar complaints to the emergency department 2 more times over the subsequent 6 weeks. A 10-day course of erythromycin and an albuterol metered-dose inhaler were prescribed. During a subsequent 3-month stay in the Balkans, he experienced progressive dyspnea and wheezing and was treated with oral antibiotics and systemic corticosteroids. He was asymptomatic for several months. In February 1997 he was examined again for dyspnea, frontal headache, nonproductive cough, and wheezing. Spirometry revealed mild, reversible airflow obstruction. A course of oral prednisone and antibiotics was prescribed, and he began therapy with 440- μ g fluticasone, twice daily, by metered-dose inhaler. One month later, he was asymptomatic, with significantly improved spirometry and a normal chest radiograph; but a limited computed tomography (CT) scan of the sinuses documented pansinusitis (1 completely obscured maxillary sinus, with partial, mild-to-moderate involvement of the remaining sinuses). In May 1997 he experienced severe chest tightness, wheezing, and dyspnea with spirometric evidence of airflow obstruction after taking naproxen, with a resolution of symptoms after stopping the drug. He was treated with prednisone, antibiotics, and salmeterol by metered-dose inhaler and noted a modest reduction in his symptoms over several weeks.

On September 12, 1997, he experienced mild exertional dyspnea and was found to have fleeting basilar rales on examination, with a normal chest radiograph. On September 22 he was examined for a 5-day history of painful, purple spots on fingers and toes, along with a "feverish" feeling. A systolic murmur and a third heart tone were detected. Chest radiograph revealed bilateral infiltrates

and cardiomegaly. White blood cell (WBC) count was 12,000 with 43% eosinophils (Fig 4), and ESR was 36 mm/h. He was admitted to the hospital where blood cultures were sterile and an echocardiogram failed to reveal lesions of endocarditis. His WBC count was elevated to 13,000, with 47% eosinophils; his antinuclear antibody and ANCA were negative. Cardiac catheterization revealed normal coronary vessels, with an ejection fraction of 31%. Cardiac biopsy documented striking eosinophilic infiltrates that involved both the endocardium and myocardium. Myofibril necrosis and dense eosinophilic inflammation were noted around the arteries in the biopsy specimen. He was treated with a daily course of 60-mg prednisone and was discharged with a prescription for fluticasone, prednisone, carvedilol, and lisinopril.

By September 30 his spirometry and peripheral eosinophil count had returned to normal, but a sinus CT scan documented pansinusitis, with complete obliteration of all sinus cavities. In the summer of 1998, his prednisone doses were decreased, and a daily regimen of 10 mg montelukast was started. In September 1998 a small right upper-lobe nodule was found on radiograph and was confirmed by CT scan along with several micronodules. In the setting of a positive purified protein derivative tuberculin skin test, a course of isoniazid was given. He underwent endoscopic sinus operation in September 1999. As of June 2001 he was asymptomatic except for mild fatigue, worked full time, and played soccer. He was maintained on a regimen of fluticasone and carvedilol.

Over the 14 months from 1997 to 1998, we encountered 6 patients with a history of asthma in whom CSS developed. On the basis of our referral population of approximately 600,000 patients and our collective experience over the last 10 years of fewer than 1 new patient with CSS per year, this group of 6 patients was quite unusual. Only 1 patient received a leukotriene antagonist before disease onset. However, common to all patients was the reduction or discontinuation of oral corticosteroids after the introduction of inhaled corticosteroids (fluticasone), which suggests an unmasking of underlying CSS (S. Cooper, MD, unpublished data, 2001). Including our 6 patients, fluticasone-associated CSS was reported in at least 23 cases, with only 10 of these patients concurrently taking leukotriene receptor antagonists.^{11,17,18,23,33-36}

Although the available evidence does not suggest that fluticasone is the causative agent of CSS in asthmatic patients, there is a reason for vigilance in patients with upper and lower respiratory tract disease in whom oral corticosteroids are reduced or eliminated through the use of potent inhaled corticosteroids. CSS tends to occur in patients with moderate-to-severe asthma with concomitant sinus disease; intermittent systemic corticosteroids are occasionally required to treat these at-risk patients. The increased frequency of CSS in patients with asthma and sinus disease is suggested by a recent review of the natural history of aspirin-sensitive asthma in which biopsy-documented CSS was reported in 5 of 500 patients.³⁷ The ability of agents that allow systemic corticosteroids to be withdrawn or withheld

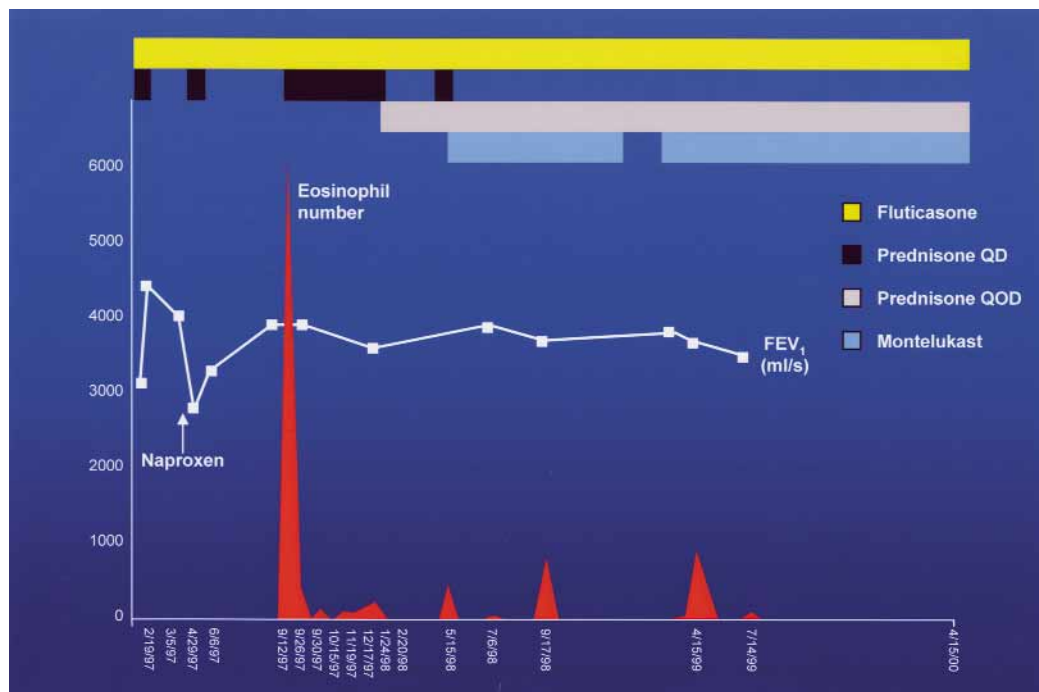


FIG 4. Graphic representation of eosinophil counts (shaded red areas; numbers on the y-axis represent absolute eosinophil counts/ μ L) and FEV₁ (white line; numbers on the y-axis represent milliliters per second) as a function of time (x-axis). There were no FEV₁ measurements taken during the hospitalization. Horizontal bars at the top of the figure correspond to the drugs that were used at the respective time. From top to bottom: fluticasone (yellow), daily prednisone (black), alternate-day prednisone (gray), and montelukast (blue). QOD, Every other day; QD, daily.

allows the underlying vasculitis to become manifest in the forme-fruste CSS paradigm. This can occur not only when systemic cortico-steroids are withdrawn from patients with CSS, but also when systemic corticosteroids are avoided because of the availability of agents that allow symptom control without systemic corticosteroids.

Case 2: CSS associated with switching from oral corticosteroids to the combination of the inhaled corticosteroids and long-acting β_2 -agonists

A 56-year-old woman with a history of hypothyroidism and chronic rhinitis, sinusitis, nasal polyposis, and aspirin intolerance was treated for many years with thyroxine. In 1991 asthma developed with severe symptoms, which required repeated hospitalizations. During the following years, she received treatment with oral glucocorticoids, theophylline, low doses of budesonide, and short-acting inhaled β_2 -agonists but was still hospitalized repeatedly for severe asthma exacerbations. In 1995 she was given the combination of high doses of inhaled corticosteroids (initially 400- μ g budesonide, 4 times daily, and subsequently 1-mg fluticasone, twice daily) and the long-acting inhaled β_2 -agonist, salmeterol (50 μ g to 100 μ g twice daily). The severe asthma exacerbations and hospitalizations gradual-

ly decreased in frequency, and treatment with oral corticosteroids could be reduced to courses of tapered oral methylprednisolone. In 1996 she received 1 2-week course of oral methylprednisolone. Otherwise, she was free of symptoms and had a normal spirometry.

In September 1997 her asthma worsened, and she received oral methylprednisolone (32 mg for 7 days and 16 mg for 7 days). One month later she was hospitalized and diagnosed with CSS. Her symptoms were fever (39°C), daytime and nocturnal dyspnea, joint pain, diffuse wheezing, basal crepitations, and multiple purpuric lesions. Radiography showed an enlarged heart and basal pulmonary infiltrates. Computerized axial tomography showed the presence of pleural fluid, pericardial fluid, and pulmonary infiltrates.

Laboratory tests revealed an elevated sedimentation rate and an increased number of eosinophils (59% of the WBCs). The ANCA was negative; the antinuclear factor was strongly positive, and there were elevated cardiac enzyme levels. Lung biopsy revealed eosinophilic pleuritis, eosinophilic vasculitis, focal alveolitis, and interstitial infiltration with eosinophils. Treatment was started with methylprednisolone, cyclophosphamide, and continuation of salmeterol and fluticasone. She recovered completely over a period of 2 months. In December 1997 cyclophosphamide-induced hemorrhagic cystitis

developed. The cyclophosphamide was then replaced by oral azathioprine (150 mg per day). There was no relapse in vasculitis, and the asthma remained under control. However, she had severe side effects from the corticosteroid treatment, which included weight gain (approximately 20 kg) and myopathy. These led to a progressive and slow reduction of oral corticosteroid doses. Oral corticosteroids have now been eliminated from her regimen, and her only treatment is azathioprine, salmeterol, and fluticasone. She returned to her previous weight; her laboratory tests are normal, and her asthma is well under control.

This case was associated with adult onset of asthma. The asthma was severe from the beginning, and the patient was treated with oral corticosteroids. In 2 other similar cases, which are not detailed here, patients received salmeterol and fluticasone, which allowed the interruption of oral corticosteroid use. The CSS appeared suddenly and without warning, although the asthma seemed to be under control. There was considerable lag time between the discontinuation of the oral corticosteroid therapy and the appearance of the CSS. This prolonged lag time might be related to the systemic effects of high doses of inhaled corticosteroids.³⁸

Case 3: Zafirlukast and CSS (adapted from Wechsler et al¹⁹)

A 45-year-old woman with a history of severe sinusitis and asthma since the age of 40 years required multiple systemic corticosteroid tapers for asthma control. On the initiation of therapy with zafirlukast in November 1996, she began to notice marked improvement in her symptoms and was able to exercise vigorously for the first time in more than 5 years. She was able to taper her systemic corticosteroids by the beginning of January 1997 and continued to do well until late January when a rash developed on her forearm and she experienced weakness and malaise. Her primary care physician discontinued zafirlukast therapy and started oral corticosteroid therapy, but within 48 hours she experienced the development of a fever of 101°F and a leukocytosis of 18,800 with 36% eosinophilia and was referred to the hospital emergency department for admission. On examination, she had diffuse wheezes and radiographs showed diffuse patchy alveolar infiltrates. In addition to bronchodilator therapy, treatment with both systemic intravenous corticosteroids and antibiotics were initiated. On her second hospital day, the wheezes persisted, and bilateral rales and jugular venous distension developed. An echocardiogram was obtained that revealed global biventricular hypokinesis, with a left ventricular ejection fraction of 35% to 40%. Subsequently, a unilateral foot drop developed that was suggestive of mononeuritis multiplex. P-ANCA was detected and was confirmed pathologically when a skin biopsy revealed perivascular lymphocytic infiltrates with eosinophils and thrombi; thorascopic lung biopsy demonstrated organizing pneumonitis with necrotizing eosinophilic vasculitis.

Six of the features of CSS manifested, including asth-

ma, sinusitis, eosinophilia, pulmonary infiltrates, mononeuropathy, and extravascular eosinophils, as well as cardiomyopathy. Initial treatment was intravenous methylprednisolone (180 mg/d) and cyclophosphamide (100 mg/d). Eosinophilia resolved within 48 hours, and respiratory symptoms resolved within 2 weeks of therapy initiation. Pulmonary function returned to baseline; chest radiographs were normal; the echocardiogram improved, and the neuropathy resolved.

She was tapered off cyclophosphamide after a few months and continued to do well until attempts to taper and discontinue the systemic corticosteroid therapy. On low-dose prednisone, she experienced a recurrence of rash and increased wheezing that necessitated continuation of systemic corticosteroid therapy.

In clinical trials that led to its approval, more than 6000 patients received zafirlukast, which accounted for approximately 2500 patient-years of exposure. All adverse effects were minimal and similar in occurrence to placebo. In these patients, there were no cases of CSS or systemic eosinophilic disease. After 6 months of zafirlukast availability and approximately 40,000 patient-years of exposure, 8 patients who received the drug in the setting of systemic corticosteroid withdrawal were noted to have experienced the development of pulmonary infiltrates, cardiomyopathy, and eosinophilia that are characteristic of CSS.¹⁹

Through July 1999, after 1.7 MPY of exposure to zafirlukast, at least 42 confirmed cases of CSS and 80 cases of systemic eosinophilia were reported in association with this drug.²¹ Furthermore, several other case reports have been reported in the literature.^{34,35,39} Although not all of these reported cases had documented systemic corticosteroid withdrawal that is characteristic of forme-fruste CSS as a prominent feature, all cases to date have had courses that were compatible with the natural history of CSS, including "indolent allergic disease that evolves into asthma, with multiple exacerbations that may progress to eosinophilia and, finally, multiorgan systemic eosinophilic vasculitis."⁵

Case 4: Montelukast and CSS (adapted from Wechsler et al¹⁷)

A 62-year-old woman with a history of adult-onset asthma and chronic sinusitis had received treatment with high doses of inhaled corticosteroids (up to 880- μ g fluticasone, daily). Her condition had required multiple courses of systemic corticosteroids during the preceding few years. In March 1998, she began treatment with montelukast for asthma symptoms; this resulted in improved symptoms, and within 6 weeks the dose of fluticasone was reduced from 440 to 220 μ g daily. On many days, she felt so good that "she did not take her fluticasone at all." Over the next 2 months, she started to feel progressive pain, weakness, and sensory loss in both her upper and lower extremities. In August 1998, she was admitted to the hospital with worsening upper and lower extremity polyneuropathy and was found to have a WBC count of 21,300 cells, with 49% eosinophilia. She had

diffuse wheezes on lung examination, but chest radiography revealed no infiltrates. She was noted to have an ill-defined rash on her arm, and skin biopsy later revealed perivascular infiltration of eosinophils that was suggestive of small vessel eosinophilic vasculitis. Myopathy and neuropathy work-up included electromyography, which suggested mononeuritis multiplex; a biopsy of the gastrocnemius muscle confirmed the presence of eosinophilic vasculitis that was consistent with CSS. An echocardiogram revealed normal cardiac function.

She was treated with a high dose of methylprednisolone (80 mg, 3 times daily), which resulted in the prompt resolution of the eosinophilia and the skin lesions. However, although the asthma symptoms stabilized with high doses of inhaled corticosteroid therapy (220- μ g puffs twice daily), neurologic sequelae persisted, and she continued to have bilateral lower extremity weakness.

Montelukast was approved for use in the United States in March 1998 after approximately 2600 patients (2100 patient-years of exposure) received the drug without significant adverse events and without the occurrence of CSS. However, through July 1999, after 2 MPY of exposure, more than 65 cases of CSS or systemic eosinophilia were reported to the manufacturer and to the Food and Drug Administration.²¹ Of these, there were no case reports in children. Most patients were middle-aged and shared many of the common risk factors that are characteristic for CSS.⁸

There have been several case reports of CSS in association with montelukast use,^{17,33,40} which share similarities with one another and with the cases reported with zafirlukast. In all of these cases, CSS occurred in patients with long histories of difficult-to-control asthma and after patients had either tapered systemic or high doses of inhaled corticosteroids or had advancing disease despite increasing doses of inhaled corticosteroids. CSS developed after corticosteroid withdrawal as a result of, or concomitant with, leukotriene modifier use in patients who had what was perceived to be severe asthma, but what was likely CSS masked by corticosteroids (former-frustrate CSS).¹⁰ A second mechanism is typified by patients who have not been tapered from systemic corticosteroids. These patients have worsening underlying asthma symptoms as the heralding sign of incipient CSS. Although in the past, systemic corticosteroids would have been used to treat this worsening prodromal allergic asthma phase, the recent availability of high-dose inhaled corticosteroid therapy and leukotriene modifiers has led to a decrease or delay in systemic corticosteroid prescription for these patients. Although inhaled corticosteroid therapy may temporarily mask the syndrome because of adequate systemic corticosteroid absorption or local airway effects, as the disease progresses, it does not effectively treat the systemic vasculitis; even systemic corticosteroids are often not effective, and cytotoxic therapy is required. Similarly, leukotriene modifiers may be initially added in lieu of corticosteroids for the treatment of signs of airway obstruction because the disease is not recognized as CSS (Fig 5).

MECHANISMS OF ADVERSE DRUG REACTIONS

The World Health Organization defines an adverse drug reaction as any response to a drug that is noxious and unintended and that occurs at doses used for prophylaxis, diagnosis, or treatment.⁴¹ These adverse reactions generally can be classified into 1 of several established categories, such as pharmacologic, hypersensitivity, idiosyncratic, or pseudoallergic or a drug interaction (Table IV). If, in fact, CSS is a drug-induced disease, then it should fit into 1 of these categories.

For most drugs, there is an identifiable component of the chemical structure that explains its pharmacologic actions; this is called a *pharmacophore*. For example, each of the β_2 sympathomimetics contains a phenylethylamine nucleus (Fig 6). These drugs may differ in β_2 selectivity, potency, oral bioavailability, and duration of action because of differences in side chains or functional groups on the phenylethylamine nucleus. However, the pharmacophore that is common to each and responsible for the stimulation of β_2 receptors is the phenylethylamine nucleus.⁴² This pharmacophore is responsible for adverse reactions that result from an extension of the drug's pharmacologic effects, such as hypokalemia and tremors.

Similarly, a common pharmacophore can be identified in drug-induced immunoglobulin E-mediated hypersensitivity reactions. Cross-reactivity among penicillins and cephalosporins is related to a common 4-member β -lactam ring (Fig 7).⁴³ In the case of penicillin, the second 5-member thiazolidine ring removes electrons from the β -lactam ring, which decreases the stability of the nitrogen-carbon bond. This, in turn, allows a protein to attach to the carbon-oxygen component of the β -lactam to form a hapten. Other antibiotics are cross-reactive with penicillin, depending on the stability of the nitrogen-carbon bond. In the case of cephalosporins, there is only 5% cross-reactivity because the 6-member thiazine ring removes fewer electrons and the nitrogen ring is more stable than in the penicillin molecule⁴⁴; therefore, it has greater difficulty forming a hapten with a protein. Carbapenems such as imipenem have a 50% cross-reactivity because of the poor stability of the nitrogen-carbon bond.⁴⁵ In contrast, monobactams such as aztreonam have virtually no immunoglobulin E-mediated cross-reactivity with penicillins because there is no ring attached to the lactam ring to withdraw electrons⁴⁶; therefore, the nitrogen-carbon bond remains stable.

CSS has been associated with the leukotriene receptor antagonists, montelukast,¹⁷ pranlukast,¹⁵ and zafirlukast,¹⁹ and the inhaled corticosteroid, fluticasone.⁴⁷ In addition, erythromycin,⁴⁸ cocaine,⁴⁹ and carbamazepine⁵⁰ have been associated with CSS. However, each of these compounds has a distinct chemical structure without an identifiable common pharmacophore (Fig 8). Even the 3 leukotriene receptor antagonists are structurally dissimilar. Thus, it is extremely unlikely that these drugs induce CSS through a common pharmacologic or hypersensitivity mechanism.

Image available in print only

FIG 5. **A**, After chronic asthma and sinusitis, leukotriene modifiers are added in lieu of systemic corticosteroids for worsening asthma symptoms (*Sx*). Although asthma symptoms may be adequately treated, systemic vasculitis that requires corticosteroid treatment becomes manifest. **B**, *Forme-fruste* CSS occurs when leukotriene modifiers, which are used for what is perceived to be severe asthma, allow systemic corticosteroids to be tapered and the underlying CSS to be unmasked. (**B**, from Wechsler ME, Pauwels R, and Drazen JM. Leukotriene modifiers and Churg-Strauss syndrome: Adverse effect or response to corticosteroid withdrawal? *Drug Safety* 1999;21:241-51. With permission.)

Moreover, a pharmacologic adverse reaction common only to the leukotriene modifiers is implausible. If, theoretically, cysteinyl leukotrienes protect blood vessels from inflammation, antagonizing their effects at the receptor could lead to a decrease in the protective effect. This effect

would be analogous to the adverse pharmacologic effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on gastric mucosa or renal blood flow (Table IV). However, there are no data to support the notion that leukotrienes exert this or any other protective effect in the body (ie, there are no

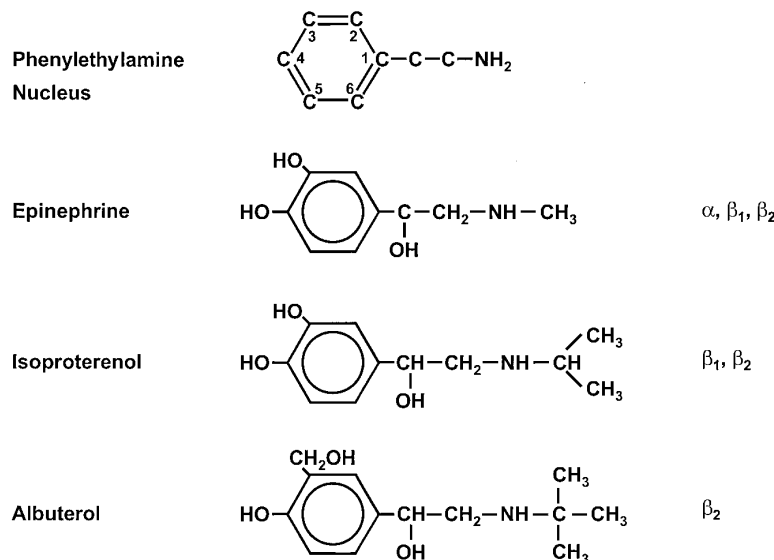


FIG 6. Structure and function of selected sympathomimetic amines with increasing β_2 selectivity. Each of these compounds contains a common pharmacophore, a modification of the phenylethylamine nucleus. Adrenergic receptor activity is indicated by the conventional α , β_1 , and β_2 designations.

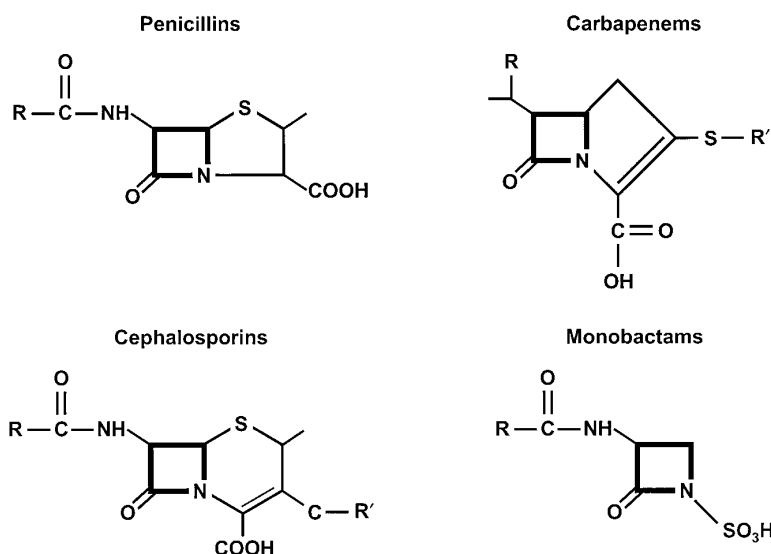


FIG 7. Chemical structures of selected β -lactam antibiotics. Each contains a 4-membered β -lactam ring (*bold portion*) that is capable of forming a hapten with a protein and thus producing an immunoglobulin E-mediated hypersensitivity reaction. The greater the instability of the β -lactam ring, the greater the cross-hypersensitivity with penicillin: carbapenems, 50%; cephalosporins, 5%; and monobactams, 0%.

known beneficial effects from physiologic production of leukotrienes, only deleterious effects).

In viewing all of the mechanisms of adverse drug reactions listed in Table IV, the only category to which a leukotriene receptor antagonist might conceivably induce CSS is by an idiosyncratic reaction. These reactions are rare, occur in a predisposed patient, and may involve a specific genotype.⁵¹ For example, the antimalarial primaquine induces hemolytic anemia only in patients with the glucose-6-phosphate dehydrogenase-deficient geno-

type. Idiosyncratic adverse reactions would be expected to be limited to 1 or a small number of agents in the same class of drugs. The observation that CSS is associated with not only all of the leukotriene receptor antagonists but also an inhaled corticosteroid, an anticonvulsant, an antibiotic, and a topical anesthetic makes an idiosyncratic reaction implausible.

With similar logic, it is unlikely that this diverse group of drugs can induce CSS through either pseudoallergic or drug interaction mechanisms. Most pseudoallergic reac-

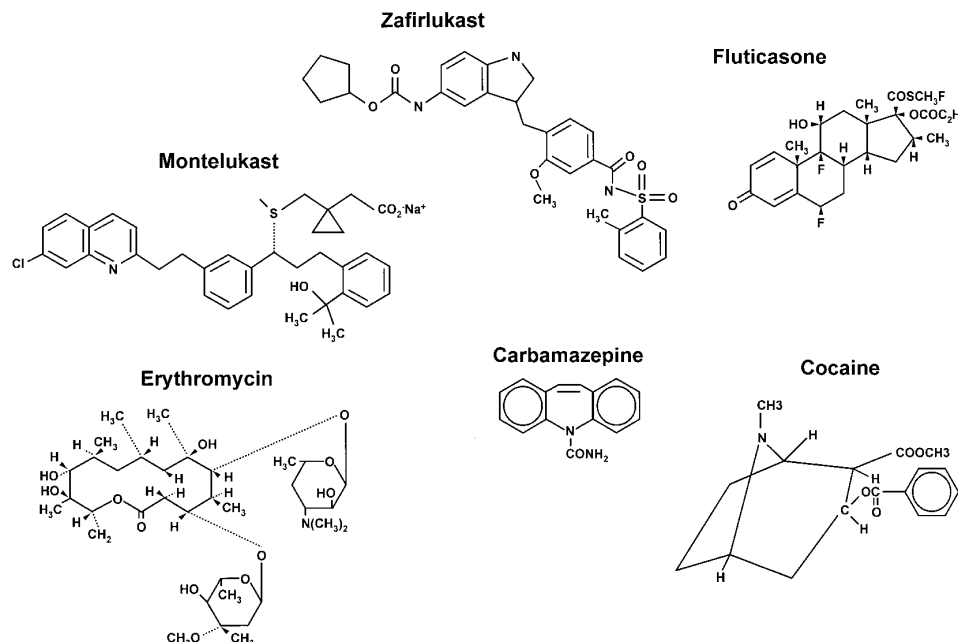


FIG 8. The chemical structure of 6 drugs for which there are case reports of CSS in patients who underwent therapy with these drugs. The structures are all distinct, and there is no identifiable common pharmacophore among them.

tions involve a final common pathway, such as the non-immunologic stimulation of mast cell release of mediators (eg, radiocontrast products or vancomycin). Drug interactions require either a common metabolic pathway or competition for metabolic products. With the latter mechanism, the inhibition or stimulation of the metabolism of 1 drug results in an increase or decrease of the pharmacologic effects of another drug (Table IV). Because CSS is not thought to be a dose-related pharmacologic effect of any of the drugs that have been associated with the syndrome, it is unlikely that a pharmacologic drug-drug interaction is responsible. Although a nonpharmacologic adverse interaction among asthma therapeutic agents is difficult to exclude, no distinct combination of these agents has been uniquely linked to CSS.

Because none of the established mechanisms of adverse drug reactions provides a plausible explanation for CSS, it is unlikely that this syndrome is a drug-induced disease.

CONSENSUS STATEMENT

CSS is a rare but important disease that requires early recognition, accurate diagnosis, aggressive treatment, and vigilant monitoring. Patients with moderate-to-severe asthma who are able to discontinue or avoid oral corticosteroids constitute a population at risk for the manifesta-

tion of CSS. Thus, any therapeutic agent that facilitates corticosteroid dose reduction in asthma could be associated with CSS. On the basis of the available clinical and epidemiologic data, almost all of the CSS cases can be accounted for by the following 3 paradigms: The first paradigm is an unmasking phenomenon (ie, the progression of clinical symptoms when oral corticosteroids are withdrawn). The second paradigm is a systemic corticosteroid avoidance phenomenon in which the vasculitic phase occurs when systemic corticosteroid therapy is avoided because asthma symptoms can be controlled by other means. The third paradigm is the aggressive disease paradigm in which vasculitis progresses despite systemic corticosteroid therapy. The data reviewed did not suggest or support alternative explanations. The best available information does not suggest a causal relationship between any antiasthma therapy and CSS. The possibility that antiasthma drugs trigger the appearance of the vasculitic phase of CSS was seriously considered. A comparative analysis of the drug-associated cases was helpful for deeming antiasthma drug triggering of CSS unlikely. Patients treated with fluticasone who manifest CSS did not appear to have a CSS exacerbation when subsequently treated with montelukast. Likewise, patients who manifest CSS while being treated with leukotriene modifiers did not have a CSS exacerbation when subsequently treated with an inhaled corticosteroid. There is no evidence of

TABLE IV. Classifications of adverse drug reactions

Category	Subcategory	Mechanism	Example
Pharmacologic	Same organ or system	Extension of the pharmacologic action of the drug on the target organ or system	Bradycardia from a β -blocker used to treat angina or hypertension
	Different organ or system	Extension of the pharmacologic action on an unintended organ	Growth suppression in a child being treated for asthma with an inhaled corticosteroid
	Antagonizing a physiologic effect	Pharmacologic action of the drug inhibits a physiologic protective effect	NSAID used to treat arthritis decreases protective effects of prostaglandins on gastric mucosa or renal blood flow
Hypersensitive immunologic reaction	Type 1: anaphylactic	Immunoglobulin E antibodies to a drug attached to surface of mast cell or basophil	Urticaria or anaphylactic shock; penicillin
	Type 2: cytotoxic	Binding of immunoglobulin G or M to cell-bound antigens resulting in the activation of the complement system	Methicillin-induced interstitial nephritis; methyldopa-induced hemolytic anemia
	Type 3: Arthus	Immunoglobulin G-, M-mediated immune complex formation	Serum sickness; drug fever
	Type 4: delayed	Sensitized lymphocytes	Contact dermatitis from topical application of neomycin, antihistamines, and benzocaine
Idiosyncratic		Occurs rarely in a subpopulation of genetically predisposed patients; may involve a specific genotype	Primaquine-induced hemolytic anemia in patient with G6PD deficiency, chloramphenicol-induced aplastic anemia
Pseudoallergic (anaphylactoid)		Does not involve an immunologic reaction but may produce similar effects through a common final pathway	Aspirin- and NSAID-induced bronchospasm; anaphylactoid reaction to radiocontrast products; vancomycin-induced red man syndrome
Drug interaction	Inhibited metabolism	One drug inhibits the metabolism of a second drug, resulting in an extension of the second drug's pharmacologic effects	Cimetidine inhibition of theophylline metabolism, producing theophylline-induced seizures
	Enhanced metabolism	One drug decreases the efficacy of a second drug by enhancing its metabolism	Rifampin enhancing the metabolism of estrogen in a patient taking an oral contraceptive, resulting in pregnancy

G6PD, Glucose-6-phosphate dehydrogenase.

precipitation of a vasculitic phase by either class of agent for patients at highest risk.

The concept of unmasking CSS is relevant to antiasthma drug development. The release of a new agent that would control asthma symptoms and substantially reduce the number of patients who require oral corticosteroids would be expected to unmask CSS cases in a manner similar to that described for fluticasone, montelukast, and zafirlukast. The availability of high-potency inhaled corticosteroids and leukotriene modifiers, which can be effective therapeutic alternatives to oral corticosteroids, is expected to reduce the number of patients with asthma who are at risk for CSS in whom underlying vasculitis is suppressed by oral corticosteroids that are given for asthma control.

One challenging aspect of studying this syndrome relates to difficulties in obtaining accurate estimates of the

population frequency of this rare syndrome and of the number of individuals who have been exposed to various therapeutic agents for asthma. More accurate measurements are highly desirable, not only to prevent the misperception that antiasthma therapy may be causing vasculitis but also to provide basic epidemiologic, and perhaps even mechanistic, information that is relevant to the pathogenesis of CSS vasculitis. A drug that would allow the withdrawal of oral corticosteroids in patients with moderate-to-severe asthma, without unmasking CSS, could do so by interrupting an essential pathway for the expression of vasculitis. Such an agent may be of benefit in the treatment of CSS. There are substantial deficits in our understanding of the pathobiologic factors of CSS, along with an urgent need for a coordinated study approach and a better mechanistic understanding of this rare syndrome.

Our current understanding of CSS allows us to identify a population of patients with moderate-to-severe asthma (who are able to withdraw from or avoid oral corticosteroids) who are at risk for the development of CSS. The possibility of CSS should be considered when these patients have abdominal discomfort, diarrhea, headache, paresthesias, dyspnea, cough, fever, or significant weight loss. A review of systems is an appropriate screening tool for at-risk patients who are receiving a new therapy or being withdrawn from oral corticosteroids. Patients with suggestive symptoms should be examined for mononeuritis multiplex and palpable purpura. Initial laboratory evaluation should include a chest radiograph, urinalysis, ANCA, ESR, and eosinophil count. The diagnosis is confirmed by biopsy of the most accessible affected tissue.

In the absence of randomized clinical trials, recommendations for therapy are based on expert opinion. The intensity of treatment for CSS should correspond to the certainty with which the diagnosis is made. There are circumstances in which CSS will respond effectively to oral prednisone alone, and this approach is worth trying early in the disease when organ compromise is not imminent. Patients who have pathologic evidence of vasculitis and serious organ involvement should be considered for cytotoxic therapy. Vigilant monitoring of the treatment response and for the potential toxicities of immunosuppressive therapy is required. Although most patients will enjoy a durable remission, the monitoring of patients for recurrent CSS when therapy is tapered is essential. A substantial minority will have recurrent episodes, which can occur many years after the onset of the vasculitis.

In summary, CSS is a serious vasculitis syndrome that occurs in the setting of difficult asthma and requires early recognition and effective treatment. Patients with moderate or severe asthma who are able to discontinue or avoid oral corticosteroids constitute a group that is at risk for the manifestation of CSS. The available data regarding the association of CSS and therapeutic agents for asthma are most consistent with an unmasking phenomenon (ie, progression of clinical symptoms when oral corticosteroids are avoided, withdrawn, or withheld). Early diagnosis and initiation of effective therapy are the responsibility of all those clinicians who care for patients with allergic diseases.

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