

Seven cases of complete and incomplete forms of Churg-Strauss syndrome not related to leukotriene receptor antagonists

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Background: Various forms of Churg-Strauss syndrome have been reported in association with the use of leukotriene receptor antagonists in asthmatic patients.

Objective: Our purpose was to increase awareness that different forms of the Churg-Strauss syndrome occur in patients not receiving leukotriene modifiers.

Methods: We searched for all the cases of Churg-Strauss syndrome that were seen in the University of Rochester Medical Center, New York, in the past 4 years.

Results: We identified 7 patients, 6 of whom fulfilled the American College of Rheumatology criteria for the classification of Churg-Strauss syndrome. None of them used leukotriene receptor antagonists. All had asthma and sinus disease. The duration and severity of their asthma varied considerably. In the majority of the patients the features of Churg-Strauss syndrome became obvious as the systemic corticosteroid dose was being tapered or discontinued, although 3 patients had not been receiving maintenance oral corticosteroids at disease onset. Three patients had positive antineutrophil cytoplasmic antibodies test result (perinuclear pattern). There was histologic documentation of vasculitis in 4 patients. Five of 7 patients responded to high-dose corticosteroid treatment.

Conclusion: Our 7 cases are similar to the various forms of Churg-Strauss syndrome that have been reported in association with the leukotriene receptor antagonists. Complete or incomplete forms of this syndrome can become apparent in asthmatic patients as systemic corticosteroids are being tapered but can also occur in patients with mild asthma of short duration who use only inhaled corticosteroids. (*J Allergy Clin Immunol* 1999;104:1060-5.)

Key words: Churg-Strauss syndrome, leukotriene receptor antagonists, asthma, eosinophilia, vasculitis, corticosteroids, case series

Churg-Strauss syndrome (CSS) is a disorder characterized by pulmonary and systemic small-vessel vasculitis, extravascular granulomas, and hypereosinophilia. Since the report of the 13 cases by Churg and Strauss in 1951,¹ various forms of the syndrome have been described, and the terms “formes-frustes” (incomplete)² or “limited”^{3,4} CSS have been used to describe forms that lack some of

Abbreviations used

ACR:	American College of Rheumatology
ANA:	Antinuclear antibodies
ANCA:	Antineutrophil cytoplasmic
BUN:	Blood urea nitrogen
CRP:	C-reactive protein
CSS:	Churg-Strauss syndrome
ESR:	Erythrocyte sedimentation rate
FEF 25%-75%:	Forced expiratory flow 25%-75%
FVC:	Forced vital capacity
LRA:	Leukotriene receptor antagonists
p-ANCA:	Perinuclear pattern ANCA
qd:	Daily
SPEP:	Serum protein electrophoresis
WBC:	White blood cell count

the prominent features of the syndrome. In 1990 the American College of Rheumatology (ACR) developed classification criteria that include (1) asthma, (2) eosinophilia >10%, (3) mononeuropathy or polyneuropathy, (4) nonfixed pulmonary infiltrates, (5) paranasal sinus abnormality, and (6) biopsy specimen containing a blood vessel with extravascular eosinophils. Four of these 6 criteria are required for the classification of CSS.⁵

Recently, CSS has received attention because of a reported association with leukotriene receptor antagonists (LRA).⁶⁻¹⁰ As part of this renewed interest, we report 7 cases of newly diagnosed complete and incomplete forms of CSS at the University of Rochester Medical Center, New York, NY, in the past 4 years (1995-1999). None of our patients used LRA. Our objective is to increase awareness of early symptoms and signs of CSS in asthmatic patients regardless of LRA use.

METHODS

Seven cases of CSS were diagnosed by the allergy, immunology, and rheumatology clinical group in the past 4 years. To identify additional cases, the hospital's computerized inpatient database was searched using the codes “vasculitis,” “Churg-Strauss syndrome,” “asthma,” and “hypereosinophilia” for the period of January 1, 1995, to April 30, 1999. The list of the potential candidates was reviewed by the attending physicians of record. No additional cases were identified. The diagnosis was mainly based on the 1990 ACR criteria⁵ with clinical judgment applied on individual patients.¹¹ The diagnosis of asthma was based on history or spirometry. Sinus disease was documented by sinus radiography, computed tomography, or biopsy.

RESULTS

All patients were white. The mean age at diagnosis was 59 years (27 to 70 years). The patients' characteris-

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Received for publication Feb 22, 1999; revised July 19, 1999; accepted for publication Aug 2, 1999.

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0091-6749/99 \$8.00 + 0 1/1/101987

TABLE I. Characteristics of 7 patients with complete and incomplete Churg-Strauss syndrome not receiving LRA

Patient	1	2	3	4	5	6	7
Age (y)/sex	70/F	69/M	61/F	61/M	54/M	69/F	27/F
Race	W	W	W	W	W	W	W
Asthma (y)*	20	20	1	14	7	3	3
Sinusitis	+	+	+	+	+	+	+
Eosinophilia (%)	55	4.4	21	40	25	64	27
Total WBC (μ L)	20,200	13,600	27,100	14,700	21,300	44,100	12,900
Presenting symptoms of syndrome	MM	Pericarditis	Fever, rash, parotid enlargement	MM	MM	Fleeting pulmonary infiltrates	Pericarditis
Subsequent symptoms (in order of appearance)	Progressive MM	Cholecystitis, rash	Pulmonary infiltrates	ICH, CNS involvement†	Progressive MM	Palpable purpura, arthritis	Polyneuropathy, digital infarcts
Other		Allergic rhinitis	MI‡	Chronic lung changes	Allergic rhinitis		Allergic rhinitis
ESR (mm/h)	21	62	127	37	27	78	35
ANCA	p-ANCA	p-ANCA	Negative	Negative	p-ANCA	Negative	Negative
Vasculitis on biopsy specimen	Yes (sural nerve)	Yes (gallbladder)	No (sinus, skin, lung, sural nerve)	No (sural nerve, quadriceps muscle)	Yes (peroneus brevis muscle)	LCV (skin)	No (sinus)
ACR criteria§	5/6	3/6	5/6	4/6	5/6	4/6	4/6
Steroids at syndrome onset	Oral	Inhaled	Inhaled	Oral	Oral	Inhaled	Inhaled
Improvement with high-dose steroids	Partial	Yes	Yes	Yes	Partial	Yes	Yes
Immunosuppressives	CYC	CYC	AZA	No	CYC, IVIG	No	No

F, Female; M, male; W, White; +, present; WBC, white blood cell count; MM, mononeuritis multiplex; ICH, intracranial hemorrhage; CNS, central nervous system; MI, myocardial infarction; ESR, erythrocyte sedimentation rate; ANCA, antineutrophil cytoplasmic antibody testing (fluorescence); p-ANCA, perinuclear pattern ANCA; LCV, leukocytoclastic vasculitis; CYC, cyclophosphamide; AZA, azathioprine; IVIG, intravenous immunoglobulin.

*Years of asthma before onset of the syndrome.

†Happened 4 years later and cyclophosphamide was added to prednisone at that time.

‡Happened 9 months later and was thought to be unrelated to the syndrome.

§At least 4 of 6 criteria (asthma, eosinophilia, neuropathy, nonfixed pulmonary infiltrates, paranasal sinus abnormality, and extravascular eosinophils) are required for classification of Churg-Strauss syndrome.¹

||This patient needed oral corticosteroids but they were discontinued because of history of positive tuberculin skin test.

TABLE II. Medications of 7 patients with complete and incomplete Churg-Strauss syndrome at disease onset

Patient	Medications
1	Prednisone 4 mg qd, beclomethasone dipropionate (MDI), amoxicillin, metoclopramide, calcitonin, estradiol
2	Beclomethasone dipropionate (MDI), ipratropium bromide (MDI), chromolyn sodium (MDI), verapamil, aspirin
3	Fluticasone propionate (MDI), amoxicillin/clavulanic acid, aspirin, medroxyprogesterone, conjugated estrogens, acetaminophen
4	Prednisone 15 mg qod, flunisolide (MDI), theophylline, terbutaline
5	Prednisone 10 mg qd, triamcinolone hexacetonide (MDI), ipratropium bromide (MDI), nedochromil sodium (MDI), salmeterol (MDI), theophylline, amitriptyline, ranitidine, propoxyphene
6	Triamcinolone hexacetonide (MDI), propoxyphene, erythromycin
7	Triamcinolone hexacetonide (MDI), ipratropium bromide (MDI), fluticasone propionate (nasal spray), oral contraceptives

All patients used inhaled albuterol sulfate as needed. qd, Daily; MDI, metered-dose inhaler; qod, every other day.

tics are summarized in Table I. Medications at the onset of the disease are shown in Table II. The relationship of corticosteroid use to the onset of the disease is shown in Table III. Three of the patients are described in detail. Patient 1 is described as having classic CSS. Patient 2 has an incomplete form of CSS with eosinophilic vasculitis without peripheral eosinophilia (see Discussion section). Patient 3 clearly meets the ACR criteria for CSS, but there was no histologic documentation of vasculitis despite multiple tissue biopsies.

Patient 1

A 70-year-old white woman had a history of allergic rhinitis, chronic sinusitis (documented by sinus radiography), and asthma for 20 years. She had been receiving inhaled corticosteroids and short prednisone bursts for 10 years. In February 1996 the asthma became more severe and oral prednisone was started. The dose was gradually increased to 60 mg daily (qd), and, after control was achieved, it was quickly tapered to 4 mg qd in 1 month. At that time numbness and pain developed in the right

TABLE III. Relationship of corticosteroid use to disease onset in 7 patients with complete and incomplete Churg-Strauss syndrome not receiving LRA

Patient	1	2	3	4	5	6	7
Time inhaled steroids started before onset of syndrome (y)	10	10	1	13	4	3	3
Inhaled steroids tapered or discontinued	No	No	No	No	No	No	No
Time oral steroids started before onset of syndrome	6 mo*	AD	AD	13 y*	6 mo*	4 mo*	AD
Oral steroids tapered ^a or discontinued ^b before onset of syndrome	1 mo	NA	NA	5 mo	1 mo†	1 mo	NA

AD, At diagnosis of syndrome; NA, not applicable.

*For asthma control.

†This patient needed oral corticosteroids, but they were discontinued because of history of positive tuberculin test.

hand at the thumb, index, middle finger, and thenar area and 5 days later left foot drop developed that were consistent with mononeuritis multiplex of the right median and left peroneal nerves. There was also a recent 10-pound weight loss. Medications on admission are shown in Table II. Laboratory evaluation revealed a white blood cell count (WBC) of 20,200/ μ L with 55% eosinophils and an erythrocyte sedimentation rate (ESR) of 21 mm/h. The anti-neutrophil cytoplasmic antibody (ANCA) test was positive by fluorescence at a titer of 1:160 with a perinuclear pattern (p-ANCA). Blood urea nitrogen (BUN), creatinine, and urinalysis were normal. The antinuclear antibody (ANA) test was positive at a titer of 1:160 (homogeneous pattern) and serum protein electrophoresis (SPEP) showed no paraproteins. Chest radiography was normal. Stool examination for parasites was negative. Nerve conduction studies were consistent with left peroneal axonal neuropathy. The left sural nerve biopsy specimen demonstrated axonal degeneration as well as intramural eosinophilic, mononuclear, and lymphocytic infiltrate with thrombosis of adjacent vessels (Fig 1). The patient was started on intravenous methylprednisolone, 250 mg twice daily, and the next day the eosinophil fraction dropped to 1% (total WBC 10,600/ μ L). The patient was subsequently placed on prednisone 60 mg qd. With that dose the neurologic symptoms remained stable and the asthma was controlled. Pulmonary function testing showed normal forced vital capacity (FVC) and FEV₁. The ESR was 12 mm/h and the C-reactive protein (CRP) value was 1.0 mg/dL (normal <0.5 mg/dL). In 2 weeks the prednisone was decreased to 50 mg qd, and a week later paresthesias with sensory loss developed in the dorsum of the left hand, consistent with radial nerve sensory neuropathy. At the same time the ESR increased to 36 mm/h and the CRP level to 3.9 mg/dL. Cyclophosphamide was started at 50 mg (1.4 mg/kg) qd and prednisone was increased to 60 mg qd. The cyclophosphamide dose was gradually raised to 100 mg qd (2.8 mg/kg). Each time that a decrease in the prednisone dose was attempted, new neurologic deficits, which were all preceded by an increase in the ESR and the CRP level, developed. The eosinophil count remained normal throughout. The patient had serious steroid complications, including progression of osteoporosis, steroid myopathy, and cataracts. In March 1997 she had dyspnea, hypoxia, and bilateral pulmonary infiltrates caused by *Aspergillus fumigatus*. She died in April 1997 despite aggressive treatment with itraconazole and broad-spectrum antibiotics. Autopsy was not performed. Up to the

time of death, although the patient was severely immunosuppressed, the CSS was only partially controlled.

Patient 2

A 69-year-old man had asthma that started in childhood but had become more severe over the past 20 years. He also had a history of long-standing allergic rhinitis and chronic recurrent sinusitis. He was initially treated with oral corticosteroids but for the past 10 years was been maintained only on inhaled corticosteroids with good control of the asthma. In January 1999 pericarditis and a supraventricular tachycardia developed, which responded to verapamil. In March 1999 the patient had acute cholecystitis and underwent cholecystectomy. Medications at the time are shown in Table II. Histologic examination of the gallbladder showed marked eosinophilic vasculitis involving numerous submucosal vessels. In addition, fibrinoid necrosis of the arterial wall was present in more than half of all the vessels identified (Fig 2, A and B). At the same time an erythematous papular rash developed on the lower extremities that appeared vasculitic according to the referring physician (biopsy was not performed). The WBC was 13,600/ μ L with 4.4% eosinophils (peak). The ESR was 62 mm/h. BUN and creatinine values were slightly elevated in a prerenal pattern that responded to hydration. Urinalysis was normal. p-ANCA was positive by fluorescence at a titer of 1:640. Hepatitis B surface antigen was negative. Preoperative chest radiography was normal. The patient was started on prednisone 60 mg qd with rapid clearing of the rash and was subsequently transferred to our hospital. Spirometry while receiving prednisone showed an FVC of 2.87 L (69% predicted), an FEV₁ of 1.89 L (57% predicted), and a forced expiratory flow 25% to 75% (FEF 25%-75%) of 1.05 (32% predicted). Cyclophosphamide 100 mg qd was added. The patient continues to do well and the prednisone dose is currently 15 mg qd, which is being further decreased.

Patient 3

A 61-year-old woman had a history of mild asthma that was diagnosed in August 1997 on the basis of history and spirometry that revealed an FVC of 2.34 L (70% predicted), an FEV₁ of 1.33 (50% predicted), and an FEF 25%-75% of 28% predicted. At the same time she was treated for recurrent episodes of sinusitis that responded partially to antibiotics. In January 1998 she had bilateral maxillary anastomosis and ethmoidectomy. Biopsy specimen exami-

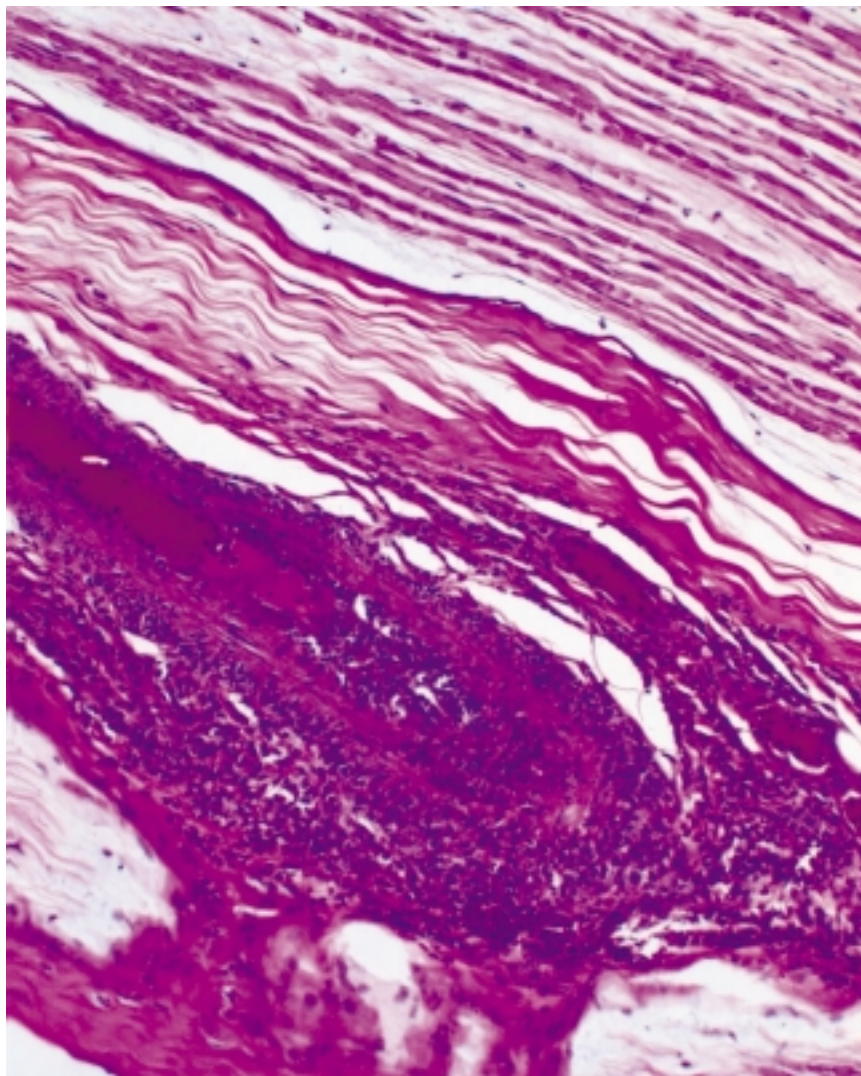


FIG 1. Mixed eosinophilic, mononuclear, and lymphocytic infiltrate involving vascular wall. Upper portion of photograph shows peripheral nerve tissue. (Hematoxylin and eosin stain, original magnification $\times 200$.)

nation of the ethmoid contents showed severe chronic sinusitis with lymphoid follicle formation and with admixed eosinophils. There was no evidence of vasculitis or granulomas. The patient was maintained on inhaled fluticasone with good control of the asthma. In May 1997 she had fever, cough, expiratory wheezing, and a generalized erythematous maculopapular pruritic rash. Parotid enlargement was noted. Medications at the time are shown in Table II. The WBC was 27,100/ μ L with 21% eosinophils. The ESR was 127 mm/h. The BUN, creatinine, and urinalysis were normal. ANCA, ANA, and cryoglobulins were negative and SPEP showed no paraproteins. Stool examination for parasites was negative. A skin biopsy specimen revealed dermal infiltration with eosinophils and lymphocytes without evidence of vasculitis. In a few days bilateral pulmonary interstitial infiltrates and hypoxia developed. The WBC peaked at 72,900/ μ L with 35% eosinophils. A wedge lung biopsy specimen revealed eosinophilic pneumonia. Histologic sections showed alveolar spaces and

some respiratory bronchioles filled with eosinophils and alveolar macrophages. The alveolar septa were thickened with an inflammatory infiltrate of eosinophils, lymphocytes, and plasma cells. There was no evidence of vasculitis with either hematoxylin and eosin or elastic tissue stain. The patient was started on prednisone 60 mg qd with rapid resolution of the rash, adenopathy, parotid enlargement, pulmonary infiltrates, and eosinophilia. However, as the prednisone dose was slowly tapered, neuropathic pain and sensory deficits developed in both feet consistent with sensory polyneuropathy, which was confirmed by nerve conduction studies. A sural nerve biopsy specimen demonstrated axonal neuropathy without evidence of vasculitis. She was placed on azathioprine 50 mg qd, which was gradually increased to 100 mg qd. Subsequent prednisone tapering was successful without disease flares. The patient had a non-Q-wave myocardial infarction in December 1998, documented by elevated troponin I levels. Coronary risk factors included hypertension, hypercholesterolemia,

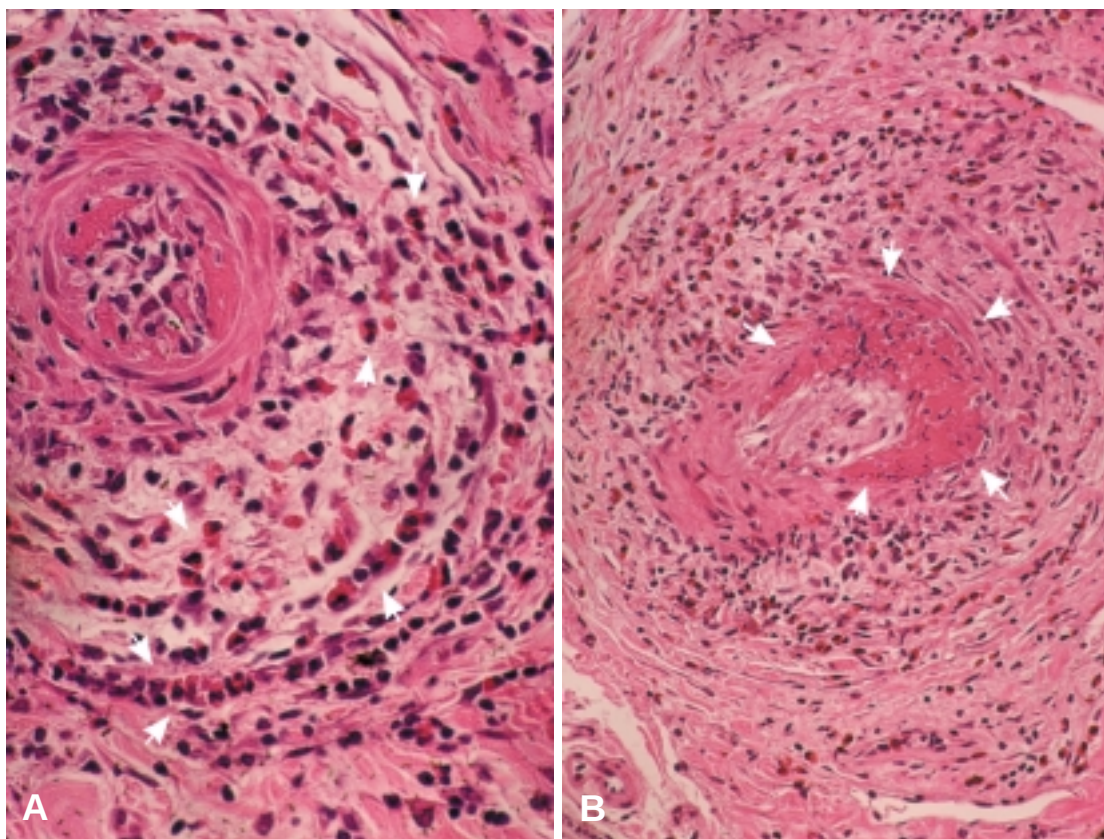


FIG 2. **A**, Pronounced inflammatory infiltrate consisting of numerous eosinophils (arrows) with admixed lymphocytes is seen in the media of this small submucosal artery. (Original magnification $\times 350$.) **B**, In addition to marked eosinophilic vasculitis, this vessel exhibits striking fibrinoid necrosis of its inner wall (arrows). This appears brightly eosinophilic on hematoxylin and eosin stain. (Original magnification $\times 200$.)

and history of smoking. Cardiac catheterization showed only mild coronary artery disease. There was no evidence of vasculitis in the coronary vessels. Echocardiogram showed anterior apical septal wall motion abnormalities with an ejection fraction of 55%. The eosinophil count was normal and there were no signs of systemic vasculitic activity. This event was thought to be unrelated to the CSS and the prednisone dose was not raised. The patient remains symptom free except for occasional left facial tenderness. The prednisone has been gradually tapered to 7.5 mg qd while the azathioprine has been kept at 100 mg qd.

DISCUSSION

The etiology of CSS is unknown. In a recent report Wechsler et al⁶ described a syndrome resembling CSS with pulmonary infiltrates, eosinophilia, and cardiomyopathy in association with the LRA zafirlukast. After that, 4 cases of CSS in patients receiving zafirlukast have been reported.⁷⁻⁹ In addition, a letter from Merck & Co, Inc to physicians in December 1998 indicated that signs and symptoms of CSS have been reported with the use of another LRA, montelukast. Pranlukast, an LRA not available in the United States, was reported in association with CSS in Japan.¹⁰

The significance of this association is not clear. A

plausible explanation is that the introduction of the LRA improved the asthmatic, leukotriene-mediated component of pre-existing CSS and allowed reduction of the systemic corticosteroid dose, unmasking other manifestations of the syndrome. Churg et al² and Churg and Churg¹² reported cases of formes frustes CSS that followed the reduction of the systemic corticosteroid dose. This explanation is further supported by a letter from GlaxoWellcome, Inc to physicians in January 1999 stating that "in rare cases, patients on inhaled fluticasone propionate may present with eosinophilic conditions and clinical symptoms consistent with CSS, possibly due to a reduction of the systemic steroid dose." Reduction of the oral corticosteroid dose, however, did not precede the CSS in all LRA-associated reported cases. Four patients receiving zafirlukast were not on maintenance oral corticosteroids at the time of onset.⁷⁻⁹

Asthma and sinus disease were the unifying features in our cases. The duration of asthma before the onset of CSS was variable from 1 to 20 years. The severity of asthma was also variable as assessed by history, spirometry, and oral corticosteroid requirements. The only medication that was common in all 7 patients was inhaled corticosteroids. The duration of inhaled and oral corticosteroids before disease onset was variable and 4 patients were receiving maintenance oral corticosteroids for asthma control at dis-



FIG 3. Vasculitic digital infarcts in patient 7.

ease onset (Table III). Patient 6 required oral corticosteroids for asthma control, but they were discontinued 1 month before disease onset because of concerns regarding a history of a positive tuberculin skin test. Histologic documentation of vasculitis was established in 4 patients (patient 6 had leukocytoclastic vasculitis). Patient 7 had no evidence of vasculitis on sinus biopsy but had vasculitic digital infarcts as shown in Fig 3. Patients 3 and 4 had axonal neuropathy with no evidence of vasculitis on the sural nerve biopsy specimen.

Six of our patients met at least 4 of the ACR criteria for the classification of CSS (Table I). The absence of eosinophilia in patient 2 is intriguing. This patient has allergic asthma and chronic sinusitis and pronounced eosinophilic vasculitis on the biopsy specimen, which is consistent with CSS.¹³ Although peripheral eosinophilia is considered one of the primary diagnostic features of CSS, there are reports of forms of the syndrome without it.^{3,4} In addition, flares of CSS can occur while corticosteroids are being tapered without peripheral eosinophilia, as shown by the clinical course of patient 1. We believe that patient 2 had an incomplete form of CSS. Patient 3 probably had an incomplete form as well because there was no histologic documentation of vasculitis despite the presence of eosinophilic pneumonia and tissue eosinophils in the sinuses and skin. This patient has several similarities with one of the patients in the original report of the formes frustes CSS.² It is important to note that, in that report, all patients were receiving oral corticosteroids, which were thought to be masking some of the features of the syndrome. Patients 2 and 3 were not taking oral corticosteroids at disease onset.

Our patients are similar to those reported in association with zafirlukast treatment, except that none of them had been receiving LRA. Similar to 4 of those cases,⁷⁻⁹ 3 of our patients were not receiving maintenance oral corticosteroids for treatment of asthma at the onset of the syndrome. In addition, one of the patients who was reported in association with zafirlukast had only borderline peripheral eosinophilia of 9% despite eosinophilic vasculitis on the lung biopsy specimen.⁸ Information regarding ANCA is available only in 5 of the reported cases in association with zafirlukast.⁶⁻⁹ Two of them had positive ANCA of a perinuclear pattern (40%). This is

similar to our findings (43%) but lower than reported in other series (67%).¹⁴ Several of the reported cases in association with zafirlukast had biopsy specimens that showed eosinophilic vasculitis or granulomas,⁶⁻¹⁰ but detailed biopsy information is not available in all.⁶

In patient 7 the diagnosis was delayed despite the early neuropathic symptoms and the vasculitic digital lesions. This indicates that the spectrum of CSS may be often underdiagnosed because of the low reported incidence¹⁵ and because incomplete forms of the syndrome may remain unrecognized.⁴

Our 7 cases are being reported because of the recent interest in LRA-associated CSS to emphasize that the disease, either in complete or incomplete forms, occurs without these agents. The practicing physician should be aware of the possibility that steroids may be masking a form of CSS and that this syndrome can occur in patients with mild to moderate asthma of short duration who are using only inhaled steroids.

We thank Drs Roger Cass, John Leddy, Stephen Rosenfeld, and Ignacio Sanz for providing permission to report the individual patients. We also thank Dr Robert Schwartz for reviewing the manuscript.

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