Case Report

Churg-Strauss Syndrome in a Group of Patients Receiving Fluticasone for Asthma

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ABSTRACT. Churg-Strauss syndrome (CSS) is a rare primary systemic vasculitis associated with marked eosinophilia. Reports have described patients with asthma who developed a systemic illness similar to CSS following treatment with leukotriene receptor antagonists. Over a 14 month period we encountered an unusual cluster of 6 patients who developed CSS. Only one patient received a leukotriene receptor antagonist prior to disease onset. However, common to 5 of 6 patients was the reduction or discontinuation of oral corticosteroids after the introduction of inhaled corticosteroids (fluticasone). This suggests an unmasking of underlying CSS by this therapeutic strategy. (J Rheumatol 2002;29:2651–2)

Key Indexing Terms:
CHURG-STRAUSS SYNDROME LEUKOTRIENE ANTAGONISTS CORTICOSTEROIDS

Churg-Strauss syndrome (CSS) is a rare systemic vasculitis that develops in patients with asthma[1]. Recent reports have suggested a possible association between the use of leukotriene receptor antagonists and the development of CSS[2-5]. The American College of Rheumatology classification for CSS requires at least 4 of the following 6 criteria for the diagnosis: asthma, eosinophilia > 10% on white blood cell differential count, mononeuropathy or polyneuropathy, nonfixed pulmonary infiltrates, paranasal sinus abnormality, and biopsy showing accumulations of eosinophils in extravascular areas[6]. Over a 14 month period we encountered an unusual cluster of patients with asthma in whom CSS was diagnosed.

The characteristics of these 6 patients are shown in Table 1. Patients 1, 2, and 6 rapidly developed severe symptoms requiring hospitalization, while symptom onset in the others was insidious. All had a history of moderate to severe asthma, and all but Patient 6 required treatment with oral corticosteroids (prednisone). Prior to the development of CSS symptoms, all the patients had started using inhaled fluticasone. Prednisone was tapered or discontinued in the 5 patients receiving prednisone; the schedule of prednisone taper is shown in Table 1. Only Patient 4 received prior treatment with a leukotriene antagonist (zafirlukast).

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All patients presented with increasing dyspnea and marked eosinophilia (Table 1). At presentation, Patients 4 and 5 had raised, nonpruritic, blanching, irregular erythematous plaques over the trunk and extremities, and Patient 2 had stellate purpura of the palms and soles. Patients 4 and 5 had mild inflammatory arthritis involving the wrists, proximal interphalangeal joints, knees, and ankles.

Testing for antineutrophil cytoplasmic antibody (ANCA) and allergic bronchopulmonary aspergillosis was negative in all patients. A sural nerve biopsy and lower extremity angiogram in Patient 1 were consistent with vasculitis. An endomyocardial biopsy from Patient 2 showed inflammation and eosinophilic infiltrates. The pleural fluid from Patient 4 had a white blood cell count of 3225 cells/mm^3 with 40% eosinophils.

With the exception of Patient 5, who had only 3 criteria, the other patients fulfilled 4 or more criteria for CSS. However, only Patients 1 and 2 had what could be considered a classic or typical CSS presentation.

All patients were initially treated with moderate doses of prednisone (range 40–80 mg per day), which resulted in improvement in pulmonary symptoms and a rapid reduction in peripheral blood eosinophilia. The subsequent course of these patients was variable, although all are currently stable taking low dose prednisone. Patient 1 had improved leg function after a 6 month course of monthly intravenous cyclophosphamide and is stable taking prednisone 10 mg per day. The cardiac ejection fraction of Patient 2 is stable at 31%, and asthmatic symptoms are controlled with prednisone 5 mg every other day plus fluticasone and montelukast. Patients 3 and 5 remain stable taking prednisone 5 mg per day and inhaled fluticasone. Patient 4 failed a 4 month course of oral cyclophosphamide, but has been stable taking 15 mg per week methotrexate and 5 mg per day

Table 1. Patient characteristics.

Patient	Age/sex	Asthma Duration, yrs	Rate of Prednisone Taper Prior to CSS Symptoms, mg/day	Clinical Characteristics	Eosinophils, %/Absolute count
1	40 M	35	12 to 5 mg over 6 mo	Fever, pulmonary infiltrates, pericardial and pleural effusions, mononeuritis, leg vasculitis	49/7000
2	36 M	1	5 two-week pulses over 7 mo	Fever, pulmonary infiltrates, sinusitis, purpura, cardiomyopathy	43/3200
3	40 F	18	10 mg to 0 over 5 mo	Pulmonary infiltrates, recurrent otitis media, Raynaud's phenomenon	46/4900
4	44 M	30	10 mg to 0 over 1 yr	Fever, pulmonary infiltrates, pleural and pericardial effusions, sinusitis, rash, arthritis	14/1800
5	46 F	24	10 mg to 0 over 6 mo	Sinusitis, rash, arthritis	26/3200
6	64 M	5	No prednisone	Pulmonary infiltrates, sinusitis, pleural effusions	57/13,000

prednisone. Patient 6 is stable taking prednisone 5 mg per day and montelukast.

CSS is a rare disease with an annual incidence in the United Kingdom calculated to be 2.4 per million[7]. Based on our referral population of roughly 600,000, and the collective experience of our group over the last 10 years of less than one new patient with CSS per year, this group of 6 patients is quite unusual. These patients and other patient clusters that have been reported[2-5] raise the possibility that the incidence of CSS may be increasing. However, other factors may be contributing to this perceived increase, and analysis of these patients may provide insight into these factors. We were unable to identify a pattern of environmental factors that might have played a role in the development of CSS in these patients.

The cysteinyl leukotriene type I receptor antagonists (zafirlukast, montelukast, pranlukast) have been in use since 1996, and there are reports of patients developing eosinophilia, pulmonary infiltrates, and other features of systemic inflammation while using these agents[2-5]. However, the evidence from our patients and those reported by another group[8] does not support a potential association between CSS and the leukotriene receptor antagonists. Before onset of eosinophilia and systemic disease, all our patients were receiving inhaled fluticasone, and in 5 of 6 patients oral corticosteroids were tapered or discontinued. We suspect that some of these patients with severe asthma had an underlying disorder that was effectively suppressed by low dose oral prednisone. The control of asthmatic symptoms was improved with the use of inhaled fluticasone, allowing the reduction or discontinuation of oral corticosteroids. The term "formes frustes of Churg-Strauss syndrome" has been used to describe patients who develop vasculitis when oral corticosteroid doses are tapered[9]. The use of inhaled steroids and leukotriene inhibitors in place of oral corticosteroids could be unmasking CSS in these patients. Leukotriene inhibitors do not appear to have a causative role in the development of CSS. Indeed, 2 of our patients are currently receiving leukotriene antagonists as an asthma treatment with no ill effects. The clusters of patients that have been reported could represent the population that was at risk for developing CSS when potent inhaled corticosteroids and leukotriene antagonists became more widely utilized. As inhaled corticosteroids and leukotriene antagonists are increasingly used as a substitute for oral corticosteroids in patients with asthma, clinicians will need to be vigilant in assessing patients with a history of asthma who present with atypical symptoms.

REFERENCES

1. Churg J, Strauss L. Allergic granulomatosis, allergic angiitis and periarteritis nodosa. Am J Pathol 1951;27:277-301.
2. Wechsler ME, Garpestad E, Flier SR, et al. Pulmonary infiltrates, eosinophilia, and cardiomyopathy following corticosteroid withdrawal in patients with asthma receiving zafirlukast. JAMA 1998;279:455-7.
3. Holloway J, Ferriss J, Groff J, Craig TJ, Klinek M. Churg-Strauss syndrome associated with zafirlukast. J Am Osteopathol Assoc 1998;98:275-8.
4. Knoell DL, Lucas J, Allen JN. Churg-Strauss syndrome associated with zafirlukast. Chest 1998;114:332-4.
5. Kinoshita M, Shiraishi T, Koga T, Ayabe M, Rikimaru T, Oizumi K. Churg-Strauss syndrome after corticosteroid withdrawal in an asthmatic patient treated with pranlukast. J Allergy Clin Immunol 1999;103:534-5.
6. Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990;33:1094-100.
7. Lanham JG, Elkon KB, Pusey CD, Hughes CR. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. Medicine 1984;63:65-81.
8. Bili A, Condemi JJ, Bottone SM, Ryan CK. Seven cases of complete and incomplete forms of Churg-Strauss syndrome not related to leukotriene receptor antagonists. J Allergy Clin Immunol 1999;104:1060-5.
9. Churg A, Brallas M, Cronin SR, Churg J. Formes frustes of Churg-Strauss syndrome. Chest 1995;108:320-3.