CASE REPORT
Iran J Allergy Asthma Immunol
June 2006; 5(2): 89-94

Churg Strauss Syndrome after Introducing Oral Steroid to Inhaler - A Report of Three Cases

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Received: 23 August 2005; Received in revised form: 28 January 2006; Accepted: 29 January 2006

ABSTRACT

The tetrad of bronchial asthma, severe sinusitis, nasal polyp, eosinophilia, and systemic vasculitis is the main feature of allergic granulomatosis and angitis (Churg- Strauss Syndrome). This vasculitis is usually seen idiopathic in patients with a long history of asthma; oral steroids using steroid inhalers, vaccination and desensitization might be triggering factors. Drugs such as leukotriene receptor antagonists (LTRAs), penicillin, sulphonamides, anticonvulsants and thiazides have also been implicated. By presenting the cases in this article, the authors suggest that some cases of CSS may be partially or totally suppressed by corticosteroid therapy of asthma for long periods and replacing oral steroid by inhaler will reveal a pathologic condition of CSS, called frustes CSS forms.

We report three subjects with asthma who had been receiving previously multiple corticosteroid courses for control, but when systemic corticosteroids were discontinued or switched over to steroid inhaler, the patients developed a similar syndrome.

Key words: Churg Strauss Syndrome; Corticosteroids; Vasculitis

INTRODUCTION

In 1951 Churg and Strauss described a syndrome, which they termed "Allergic and Granulomatous Angiitis" consisting of allergic rhinitis, pulmonary and systemic small vessel vasculitis together with extravascular granulomas. This description was based on autopsy results.[1] This entity has an incidence of 1-3/100,000 in the United States and 2.5/100,000 in the rest of the world.[2] Death occurs as a result of myocarditis or myocardial infarction due to coronary vasculitis.[3] For several decades, there has been a dispute over Churg Strauss Syndrome (CSS) as a separate entity from other vasculitis, particularly polyarthritis nodosa, Churg Srtauss Syndrome, Wegener's granulomatosis (WG), and microscopic periarteritis nodosa (Microscopic polyangiitis) specific types of vasculitis which are very similar to one another because small and medium sized vessel

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involvement and presence of antineutrophil cytoplasmic antibodies (ANCA), that are common features in all. Like other types of multisystemic uncommon diseases, Churg Strauss syndrome has different diagnostic clinical and pathological characteristics on account of the extensive and variable organ involvements. So, after being first described by Churg and Strauss as a complex of systemic vasculitis and hyper eosiniphilic conditions in patients with asthma and allergic rhinitis,[1] the parameters of this syndrome have greatly changed.[2-3] Thus, in 1990, the American College of Rheumatology confirmed some criteria for the classification of this entity. The experts assessed 20 patients out of 787 patients suffering from vasculopathies and selected 6 criteria out of the previously accepted traditional findings including:

1. Asthma
2. Eosinophilia>10% on differential white blood cell count
3. Mononeuropathy (including mononeuritis multiplex or polyneuropathy).
4. Non-fixed pulmonary infiltration on roentgenography
5. Paranasal sinusitis, and
6. Tissue biopsy containing vascular and extravascular eosinophilia

In 1990, Masi et al indicated that presence of four out of six criteria yielded a sensitivity of 85% and specificity of 99.7% for a clinical diagnosis of Churg Strauss syndrome.[2]

Thus, like other vasculitic syndromes, the diagnosis may be delayed since development of a perfect clinical feature occurs with delay and at the beginning of the disease developing one or more criteria may be interpreted otherwise. This disorder is usually seen in patients with a long history of asthma in whom oral steroids are replaced by steroid inhalers or the ones in whom steroids are replaced by leukotriene anti-receptors. Thus, in addition to the previously described criteria and the other vasculitic conditions, having a history of a steroid dependent allergic asthma with a sudden change in drug and the method of its use may serve as a diagnostic clue to such a rare disease.[4]

In this case series we have explained three different features of CSS which flared-up by corticosteroid withdrawal or conversion of oral form to inhaler.

CASE REPORT

Case 1

The patient was a 42-year-old driver who was admitted because of hypereosinophilia and neuropathy which occurred in right peroneal nerve as well as ulnar and median nerves. One year before admission, he had started bronchodilators and oral steroids for dyspura and wheezing, the later replaced by steroid inhaler 6 months later because of the relative recovery experienced with it. This had been followed by an intractable abdominal pain and hypereosinophilia and consequently oral steroid was re-administered 40 mg/day and resulted in patients' recovery. The drug had been discontinued after two weeks because of relative relief. Then, he experienced swelling in his hands together with paresthesia, weakness of grip strength, loss of bony eminence and loss of skin wrinkles of the fingers and toes. Thus, concerning his weakly positive rheumatoid factor and strongly positive CRP, anti rheumatoid arthritis treatment was started including chlorquin, sulfasalazine, and oral steroids the latter 5 mg daily. About 2 months before admission, he developed neuropathy in both upper and lower extremities. Livedeo reticularis was also noted at the distal end of the fingers and toes.

Upon admission, the WBC count was 12900 with 40% eosinophilia. ESR ranged from 16 to 24, and in chest X-ray a linear atelectasis and parenchymal infiltration was seen at the base of his left lung. Bilateral paranasal sinusitis was present in association with a normal spirogram, and a normal complement value. ANA was negative and biochemical and liver function tests were normal.

On the first day of admission, C-ANCA was negative but P-ANCA was strongly positive. EMG and NCV reported generalised axonopathy and myopathy (demyelinisation).

The patient received methylprednisolon, 1gr per day, for three days and then cyclophosphamide, 800 mg per day, for three successive days.

By administration of cyclophosphamide alternatively, symptoms and signs subsided.

Case 2

A 45-year-old woman was admitted for cough, dyspnea and disseminated maculopapular rash on her hands and feet.

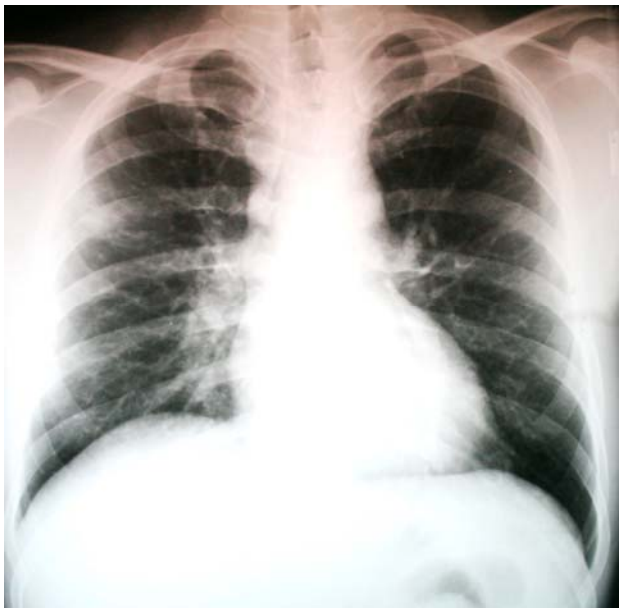

Figure 1. Chest X-Ray showing peripheral distributed parenchymal infiltration.

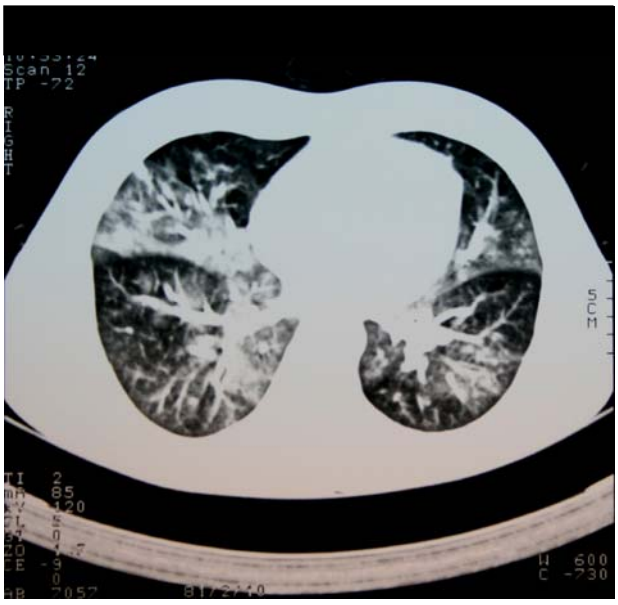

Figure 2. High resolution CT image demonstrates marked peribronchial and perivascular thickening with patchy ground glass opacity.

The patient had a history of bronchial asthma of two years duration along with nasal polyps for many years for which she had undergone two operations. After replacing oral corticosteroid by steroid inhaler and adding methotraxate, she had been experiencing limb weakness. On physical exam, distal motor weakness was observed in addition to the signs of bronchial asthma. Upon admission, the temperature was 38.2°C, ESR=24, WBC=20.000 cells/mm^3 with 81% polymorphonuclear cells and 12% eosinophils. Hgb, Hct, biochemical tests, and liver and kidney functional tests were all normal.

On chest X-ray, the lung markings were coarse at the base of both lungs. Pansinusitis was also observed on roentgenograms. PFT was normal and ANA, C-ANCA, and P-ANCA were all negative. Skin biopsy indicated lymphocytic infiltrate near the small vessels together with eosinophils and also endothelial cell prominence. Administration of oral cyclophosphamides in association with 30mg of prednisolone for ten days resulted in complete recovery and the patient was discharged.

Case 3

A 35-year-old man with a 3-year history of bronchial asthma was admitted to Masih Daneshvari Hospital because of severe dyspnea and wheezing. He had been receiving bronchodilator inhaler and oral corticosteroids before admission. Allergic Broncho Pulmonary Aspergillosis (ABPA) and CSS were both suspected because of eosinophilia. Chest X-ray showed peripheral distributed parenchymal infiltration (Figure 1) and high resolution CT image demonstrates marked peribronchial and perivascular thickening with patchy ground glass opacity (Figure 2).

The patient was discharged with 40 mg / day of prednisolone for two weeks and then advised to switch over to inhaler corticosteroid, but a month later he was admitted again since some of the symptoms such as cough and dyspnea had got aggravated and several skin lesions developed. He had a history of nasal polypectomy several years ago.

The laboratory findings were as follow: ESR=45, WBC= 22000 with 76% polymorphonuclear cells and 3% eosinophils. ANA and C-ANCA were negative and P-ANCA was more than 40 IU/ml, serum IgE=880 IU/ml, sputum test for B.K. detection was negative. Because of his poor health and a strong suggestion of CSS, a pulse injection of 1 gram of methylprednisolon was administered and continued later as oral prednisolone, 50 mg/ day. Biopsy showed small vessel vasculitis together with eosinophilia and subepidermal bulls. A week later, his condition ameliorated

dramatically and he was discharged in a good condition.

DISCUSSION

Churg Strauss Syndrome is a rare entity and up till 1984 only 138 cases had been reported in the literature.[3] The most significant clinical sign of our cases was peripheral neuropathy in different nerves which could well mimic some of the specific etiologies of vasculopathies such as polyarthritis nodosa, cryoglobulinemia, Wegener´s granolomatosis and specially because of the persistent eosinophilia, it might mimic hypereosinophilic syndrome.[5-8]

The presence of mononeuropathy multiplex, especially in the terminal branches of the median, ulnar, and peroneal nerves was the most prominent manifestation and was associated with weakness of grip strength, pain, and paresthesia. The patient had been receiving DMART for a long time because of the positive RF test. Likewise, his manifestations well mimicked rheumatoid arthritis and carpal tunnel syndrome. Motor neuropathy had been interpreted as a side effect of anti-RA drugs such as gold compounds or sulfasalazine.

Churg Strauss Syndrome may be suggested only by the history of bronchial asthma, persistent eosinophilia and peripheral neuropathy, even without taking cutaneous eosinophilic infiltration into consideration.[9,11]

The prominent manifestation was mononeuropathy multiplex, especially in the terminal branches of the median ulnar, and peroneal nerves, which was associated with weakness of grip strength, pain, and paresthesia. Since these manifestations well mimicked rheumatoid arthritis and carpal tunnel syndrome, and because of his positive rheumatoid factor test, he had been receiving DMART for a long time; the motor neuropathy had been interpreted as a side effect of anti-RA drugs such as gold compounds or sulfasalazine. Churg Strauss Syndrome may be suggested only because of the history of bronchial asthma, continuous eosinophilia and peripheral neuropathy (as was mentioned above), even without considering cutaneous eosinophilic infiltration.[9,11]

Of the most important differential diagnosis of Churg Strauss Syndrome is polyarteritis nodosa (PAN); the two diseases may be associated with asthma but the incidence of asthma in PAN ranges from 4% to 54% whereas it is an essential element in CSS.[11,12] The types of the involved blood vessel seem to be different: CSS typically affects small vessels whereas in PAN both small and medium-sized vessels are involved and are usually aneurismal. Cellular infiltrate in PAN is often predominated by polymorphonuclears but there is an eosinophilic predominance in CSS. Extravascular granulomas are specifically seen in CSS. Renal involvement or renal insufficiency in CSS is rare and occurs in one patient out of 30.[13,14] PAN is often associated with evidence of hepatitis B infection.[9] Hypereosinophilic syndrome (HES) encompasses a group of conditions that are associated with eosinophilia greater than 1500/ml for longer than 6 months in the absence of a known cause of hypereosinophilia. Manifestations vary from a skin rash to eosinophilic leukemia. There is also a wide range of cardiac manifestations varying from endomycardial eosinophilic infiltration to thromboembolous complications.[13-15]

Both HES and CSS may mimic the clinical signs of Loeffler syndrome and eosinophilic gastroenteritis.[16]

Histologically, HES is associated with tissue infiltration by masses of eosinophils but unlike CSS, angiitis and granuloma formation are absent.[17] Chronic eosinophilic pneumonia (CEP) is another distinct entity that is often difficult to distinguish from CSS. In pure CEP the systemic expression of vasculitis never appears.[12]

Lack of pathologic criteria usually does not lead to diagnosis. In a study conducted by Lanham et al in 1984, the three prominent signs of CSS were found in only 13% of tissue biopsies in a review of 45 autopsy cases and 37 living patients. In the same study, in only 38% of the tissue biopsies of living patients and in 40% of autopsy cases granuloma was observed. Thus, in this report, the authors tend to emphasize on clinical signs and presence of asthma, hypereosinophilia, and systemic vasculitic manifestations in one or more extrapulmonary organs.[3]

Hypereosinophilia together with hyperleukocytosis, elevated erythrocyte sedimentation rate and elevated serum IgE may be considered as important diagnostic laboratory findings. Complement level is usually normal.[10,11]

Unlike Wegener's granulomatosis, CSS is associated with positive p-ANCA. In a study conducted by Cohen et al in 1991, 67% of patients and in another study conducted by Guillivin et al in 1995, 6o% of

patients exhibited positive P-ANCA titers.[14,15] In a 10-year research conducted at Mayo Clinic, USA, from 1990 to 2000, these patients had a better prognosis than the patients affected by ANCA-positive vasculopathies other than CSS.[16] In another review, 86% of CSS patients had a positive rheumatoid factor.[14] Antinuclear antibody and HBsAg assays were negative. Thus, eosinophilia can be used as an important indicator of the activity about the disease and its responsiveness to treatment[13]. Sural nerve biopsy is the diagnostic procedure indicated whenever there is an evidence of an infectious or immunologic etiology and/or when,in spite of thorough assessments,the final diagnosis cannot be made.[5,17] A skin and/or muscle biopsy is performed when there is an evidence of involvement of these tissues. Concerning the cardinal skin sign of livedeo- reticularis in our first case, skin biopsy was not considered as a diagnostic procedure.[17,18]

We believe that patients with allergic asthma who develop severe allergic rhinitis and nasal polyp may have an underlying hypereosinophilic syndrome. Eosinophil recruitment and activation in the above setting may play a role in mediating both airway hyperactivity and end organ damage which causes the patients to fall within the spectrum of hypereosinophillic syndrome clinically described as Churg Strauss Syndrome.[3,4]

Our observations suggest that some cases of CSS may be partially or totally suppressed by corticosteroid therapy for asthma for very long periods and that asthmatic subjects whose corticosteroid doses are being tapered carefully should be monitored for the development of CSS signs and symptoms.[19,20]

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