Montelukast and Churg-Strauss Syndrome

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Abstract

A 37-year-old asthmatic presented with arthralgia, dyspnea, hemoptysis, wheezing, abdominal pain, and eosinophilia. He did not receive any corticosteroid therapy previously and five weeks prior to admission Montelukast was started. Transthoracic echocardiography showed severely depressed left ventricular function with an ejection fraction of 20-25%. By the diagnosis of Montelukast-associated Churg-Strauss syndrome with cardiac involvement, the drug was stopped and steroids started. During the follow up period of 3 years, he did not have an other vasculitic episode. Although this is a rare association, the clinicians need to be vigilant in all patients who develop systemic symptoms when starting treatment with leukotriene antagonists.

Keywords: Asthma, cardiac involvement, eosinophilia, Churg-Strauss syndrome, montelukast.

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INTRODUCTION

An association between LTRAs and Churg-Strauss syndrome (CSS) has recently been suggested by a series of published case reports [1-5]. Much of the literature has suggested that the introduction of leukotriene antagonists allowed significant steroid dose reduction, thereby unmasking previously controlled CSS [2-5].

It is a rare systemic vasculitis whose characteristic features include extravascular eosinophil infiltration/vasculitis, peripheral eosinophilia, and asthma. In 1990, the American College of Rheumatology (ACR) developed diagnostic criteria for the syndrome; it is a disease characterized by at least four of the following six features: 1) moderate to severe asthma, 2) peripheral blood eosinophilia (>10%), 3) mononeuropathy or polyneuropathy, 4) pulmonary infiltrates, 5) paranasal sinus abnormality and 6) extravascular eosinophils [6].

We report a case of Churg-Strauss syndrome who did not receive continuous systemic corticosteroid previously. He had asthma, cardiomyopathy, skin manifestations, upper respiratory tract involvement (sinusitis/polyposis/rhinitis), and infiltrates on the chest radiograph.

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CASE REPORT

A 37-year-old man had a history of allergic rhinitis for five years and bronchial asthma for two years. He did not receive any continuous steroid treatment or any drug like Claritromycin or Fluconazole which may provoke the CSS. Five weeks before the admission to our hospital, Montelukast 10mg/day was added to his therapy in an other institution to control asthma. Five weeks after commencing montelukast, he developed general malaise, polyarthralgia, ortopnea, wheezing, hemoptysis, abdominal pain in the right upper quadrane, and purpura on the lower extremities. Then he was referred to our institution for further evaluation. Physical examination revealed inspiratory crackles over both lung bases in addition to generalised expiratory wheeze and 2/6 systolic murmur on the apex of the heart. Laboratory studies showed the following results: leukocytosis of $16.50x10^9$/l with 28% eosinophils, erythrocyte sedimentation rate (ESR) 55mm/h, total IgE level 1136 IU/l. Antinuclear and antineutrophil-cytoplasmic antibodies were not detected. Chest X-ray revealed cardiomegaly and bilateral, perihilar interstitial infiltrates. His spirometric tests showed a Forced Expiratory Volume in 1 second (FEV_1) of 1.56L (39%pred) and a Forced Vital Capacity (FVC) of 1.56L (33% pred). A 12-lead ECG showed sinus tachycardia and non-spesific ST-T wave changes. Transthoracic echocardiography showed a dilated left ventricule and a severely depressed left ventricular function with an ejection fraction of 20-25%. There was a pericardial effusion of 1.4 cm width, mitral regurgitation and a trombus in the left ventricule. Nasal endoscopic evaluation showed allergic mucosal appearance and bilateral polipoid masses limited to the middle meatus.

CT scan of the chest showed bilateral confluent lung infiltrates associated with a ground glass pattern. Coronary angiography was normal. Coronal CT scan of the paranasal sinuses showed mucosal changes consistent with sinusitis in both maxillary and ethmoid sinuses and bilateral soft tissue infiltration limited to middle meatus in the nasal cavity. He could not tolerate flexible fiberoptic bronchoscopic examination. The skin biopsy specimen showed

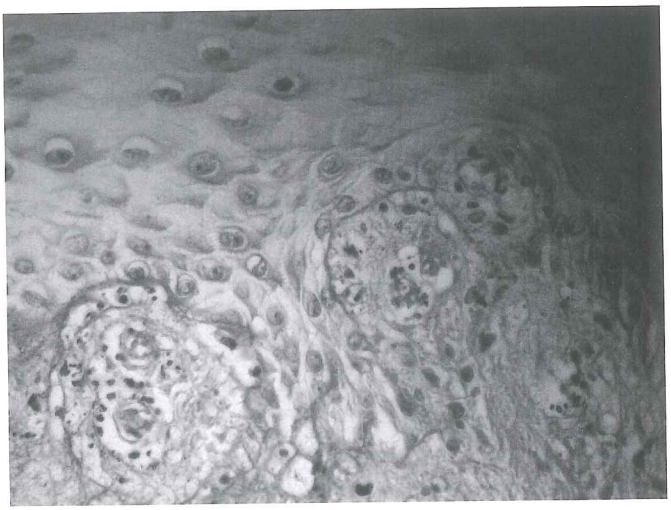

Figure 1. The capillaries show fibrinoid materyal and neutrophils infiltrate around them (leukocytoclasis) (H&EX400).

a leucocytoclastic vasculitis and the biopsy of the nasal masses revealed nasal polyposis (Figure 1). We diagnosed Churg-Strauss syndrome by the four diagnostic criteria of ACR for CSS [8]. Montelukast therapy was discontinued and treatment with prednisone (1mg/kg/day) was initiated. For myocardial and pericardial involvement; Angiotensine Converting Enzyme Inhibitor (ACEI), a nonsteroidal antiinflammatory drug and for the thrombus in the left ventricule warfarin were added.

The patient's condition improved rapidly. The eosinophilia, total IGE levels, ESR and cardiac enzymes returned to normal after initiation of immunosuppression. Pulmonary infiltrates disappeared and left ventricular ejection fraction raised to 40%. After 3 weeks, transthoracic echocardiography did not show any pericardial effusion or thrombus in the left ventricule and warfarin was discontinued. So the dosage of prednisone was slowly tapered over the next 11 months. During the follow-up period of three years, under the therapy of budesonide-formeterol combination, vasculitic reactivation or severe asthma exacerbation did not occured.

DISCUSSION

Churg-Strauss syndrome is an uncommon systemic vasculitis of unknown etiology. Cardiac involvement is a leading cause of mortality and a common clinical manifestation [7]. Cardiac involvement includes eosinophilic endomyocarditis, coronary vasculitis, valvular heart disease, congestive heart failure, hypertension, and pericarditis [8]. Our case presented both with myocarditis and pericarditis.

Allergic rhinitis occurs in about 75% of patients with CSS and like our patient is typically the initial symptom [9]. Recurrent sinusitis, nasal polyps, and nasal obstruction may also be seen [9]. Occassionally, nasal pain, with a purulent or bloody nasal discharge and nasal crusting or septal perforation more typical of Wegener's granulomatosis is seen [9]. In the last largest series, other organs that are commonly affected include peripheral nervous system (74%), paranasal sinus (74%), lung (58%), skin (57%) [10].

It is unclear whether the development of CSS is a direct drug effect or an unmasking of a preexisting condition on withdrawal of steroids for asthma. Tapering of oral steroids did not precede CSS in some patients [4] and like our patient were not on oral steroids at the onset of CSS. First case of Churg-Strauss syndrome associated with montelukast therapy in an asthmatic patient in whom there had been no recent oral corticosteroid use was reported by Tuggey et al. [11]. Even though some authors [12] have indicated that CSS can be masked by oral or inhaled steroids, others [13] think that inhaled steroids are not sufficient to prevent a flare of a non-diagnosed forme fruste of CSS. The blockade of the cysteinyl leukotriene receptors could provoke an imbalance in leukotriene receptor stimulation, leading to an increase in circulating LTB4 [14]. This leukotriene is a strong chemoattractant for neutrophils and eosinophils [15] and could trigger an eosinophilic state, and thereby initiate vasculitic involvement. CSS has also been reported in association with zileuton [2], an inhibitor of 5-lipoxygenase, which also blocks LTB4; this makes the LTB4 chemoattractant hypothesis less likely.

Reviewing the literature between 1966 and 2000, Jamaleddine [16] have found 22 case reports of patients receiving LTAs who developed CSS. In these patients the onset of CSS have occured 2 days to 10 months after starting treatment with LTAs. In our patient this period was 5 weeks.

Churg-Strauss syndrome characteristically evolves through a prodromal phase, a vasculitic phase, and a postvasculitic phase. The duration of each phase varies largely and symptoms may wax and vane. Our patient's past medical history included allergic rhinitis for five years and bronchial asthma for two years.

Although Solans et al. [17] found 28% of the patients had clinical relapse, Rios et al. have not found a single case of vasculitic reactivation. According to Rios et al., Churg-Strauss syndrome usually has only one episode (a "one-shot vasculitis"), because relapses are extremely uncommon [18]. In our patient, during the follow-up period of three years, under the therapy of budesonide-formeterol combination, vasculitic reactivation or a severe asthma exacerbation did not occured.

Our patient was ANCA negative. Data from small series have suggested that ANCA levels correlate with disease activity and Churg-Strauss syndrome has a better prognosis than other ANCA-associated vasculitides[19]. The frequency of ANCA in patients with CSS is 50% to 78% [19, 20], which is as high as for microscopic polyangiitis.

In two case reports from Turkey, among three cases, only in one of them had received montelukast therapy for 2 weeks [21, 22].

CSS does not appear to relate to steroid tapering in our patient. Long-term data on these drugs are lacking and leukotriene's role in vasculitis remains to be elucidated. Cardiac involvement in CSS, may present as a serious course.

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