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Churg–Strauss syndrome in two patients receiving montelukast

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Abstract

Objective. Churg–Strauss syndrome (CSS) has been described in association with the treatment of asthmatic patients with leukotriene receptor antagonist. The main mechanism proposed to explain this condition is the unmasking of CSS after the leukotriene receptor antagonist has allowed corticosteroid tapering. Other hypotheses might be proposed.

Methods. We describe two patients who developed CSS after starting treatment with montelukast, a new antileukotriene drug.

Results. Both patients presented with CSS after 4–5 months of treatment with montelukast. Neither patient received long-term systemic steroids for asthma, but both were on inhaled steroids. One patient had a myocardial involvement and experienced a stroke. Our two patients were treated with systemic steroids and cyclophosphamide.

Conclusions. CSS does not appear to relate to steroid tapering in our patients. The other hypotheses are a coincidence or a direct adverse effect of the antileukotriene. Long-term data on these drugs are lacking and leukotriene's role in vasculitis remains to be elucidated.

KEY WORDS: Churg–Strauss syndrome, Montelukast.

Churg–Strauss syndrome (CSS) is a rare systemic vasculitis associated with asthma and eosinophilia. Several case reports have described the occurrence of CSS in patients who were treated with zafirlukast [1–4] and, more recently, with montelukast [5–10], a new member of the family of leukotriene receptor blockers prescribed for patients with asthma. We report two cases of CSS associated with this drug.

Case reports

Case 1

A 50-yr-old man presented in September 2000 for fever, dyspnoea and asthenia lasting 3 weeks. He had been a heavy smoker since the age of 18 yr. His recent history included asthma that had started 1 yr earlier, for which inhaled salbutamol and beclomethasone were prescribed. In March 2000, oral montelukast (10 mg/day) was started, but was ineffective and shortness of breath increased. Headaches, myalgias, weight loss and asthenia appeared in early July, leading to the discontinuation of montelukast. The patient improved but in August 2000 his asthma became more severe and was thought to be attributable to infectious bronchitis. Bacampicillin was prescribed for 10 days but afforded no improvement.

In September 2000, the patient was hospitalized because of further deterioration of his clinical symptoms, general weakness, persistent fever and chest pain. The physical examination detected neither wheezes nor rhonchi. Cardiovascular, abdominal, neurological, joint and cutaneous examinations were normal. The patient had bilateral temporal headaches; the temporal arteries were palpable and not indurated. Laboratory findings were a white blood cell count of 16.6×10^9/l with 6.8×10^9 eosinophils, and erythrocyte sedimentation rate (ESR) of 116 mm/1st h and C-reactive protein

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(CRP) concentration 27 mg/l. The chest X-ray showed bilateral basal interstitial infiltrates, which were also seen on computed tomography (CT) scanning. The patient underwent fibre-optic bronchoscopy with endobronchial biopsy and bronchoalveolar lavage (BAL). The bronchial biopsy showed interstitial inflammatory infiltration with lymphocytes, neutrophils and a few eosinophils. The BAL fluid was consistent with this finding. Testing for antineutrophil cytoplasmic antibodies (ANCA) was negative.

A diagnosis of CSS was advanced; oral prednisone (1 mg/kg/day) was started and generated rapid improvement. Blood gases improved and the eosinophil count decreased. The patient underwent a temporal artery biopsy because of temporal headaches. Histological examination of the temporal artery showed severe occlusion of the lumen surrounded by a granuloma comprising a lymphocyte infiltrate in the internal lamina elastica, which was slightly fragmented; no giant cells, eosinophils or necrosis were seen. The histological changes indicated an organized thrombus complicating non-giant cell temporal arteritis.

The disease was well controlled with systemic steroids but corticosteroid dependence became evident during tapering at 5 months and asthma recurred. Cyclophosphamide was added 1 month later to facilitate steroid sparing.

Case 2

A 50-yr-old man with a history of insulin-dependent diabetes mellitus and arterial hypertension had been followed for asthma and recurrent sinusitis for 5 yr. In 1998, he underwent nasal meatotomy; the sinus mucosa was diffusely oedematous with associated 20% eosinophil infiltration. For 2 yr the patient received maintenance therapy consisting of inhaled salmeterol and fluticasone. Asthma flares were treated with short-term betamethasone. In June 2000, the patient experienced a more severe and more prolonged asthma exacerbation that required a 10-day course of betamethasone. At that time, montelukast (10 mg/day) was started. In October 2000, he had lost 12 kg over 3 months and presented with asthenia, fever of 38.5°C and dysaesthesias of the lower limbs. He had stage III dyspnoea. Physical examination detected bilateral and diffuse wheezes and rhonchi. He had bilateral hypo-aesthesia of the lower limbs and ankle reflexes were absent. Laboratory findings were a white blood cell count of 21×10^9/l with 9.66×10^9/l eosinophils, ESR 55 mm/1st h, CRP 85 mg/l, fibrin 6.4 g/l, normal creatinine, microscopic haematuria and proteinuria (0.9 g/24 h). Chest X-ray showed bilateral interstitial infiltrates. Fibre-optic bronchoscopy was normal. BAL fluid contained 775 000 cells/ml with 30% eosinophils. An electromyogram showed axonal demyelination polyneuropathy. A neuromuscular biopsy showed severe axonal involvement. Testing for ANCA was negative.

These clinical findings were consistent with a diagnosis of CSS. Montelukast was discontinued and the patient was given an intravenous bolus of 750 mg methylprednisolone, after which he developed acute pulmonary oedema. An ECG showed left atrial hypertrophy and negative T waves. An echocardiogram showed ventricular hypokinesia. This severe congestive heart failure was treated successfully with diuretics. A few days later, he experienced a confusional state with anosognosia and right lateral homonymous hemianopsia. Cerebral CT scanning and magnetic resonance imaging detected an ischaemic stroke in the left posterior cerebral artery region with haemorrhage. Oral prednisone (1 mg/kg/day) was given and the patient improved. The confusional state disappeared but the peripheral neurological disorders persisted. Three months later, at the time of steroid tapering, respiratory symptoms deteriorated. Immunosuppressive therapy combining cyclophosphamide and steroids was prescribed and the patient improved.

Discussion

CSS is a vasculitis of unknown origin that occurs in patients who are usually asthmatic, and triggering factors have been implicated in its development. Desensitization and vaccinations were considered responsible for CSS in 18 of the 96 patients described by our group [11]. CSS arising after treatment with antileukotrienes has also been described.

The role of leukotrienes in asthma has been suspected for many years [12]. The cysteinyl leukotrienes (LTC^4, LTD^4 and LTE^4) have proinflammatory actions, including contraction of the smooth muscles of the airways, increased vascular permeability and mucus secretion, and inflammatory cell infiltration of lung tissue [13]. LTB^4 has been found to be a potent chemoattractant for neutrophils and eosinophils [13].

Developed to treat asthma, the antileukotriene drugs zafirlukast, pranlukast and montelukast are selective competitive antagonists of cysteinyl leukotriene receptors, and zileuton, a 5-lipoxygenase inhibitor, inhibits the synthesis of LTB^4 and the cysteinyl leukotrienes. Antileukotriene drugs may have a steroid-sparing effect, similar to that of salmeterol and theophylline, and may become the best type of drug to combine with inhaled steroids to treat asthma [14]. Leukotriene antagonists are safe and well tolerated in most patients [14]. The most common adverse effects are mild abdominal pain and headaches. Nevertheless, the manufacturers' post-marketing surveillance and several authors [1–10] have reported cases of CSS following antileukotriene treatment.

Most cases of antileukotriene-induced CSS have been reported in association with zafirlukast [1–4]. In early 1998, another leukotriene receptor blocker, montelukast, became available. Although its chemical structure differs from that of zafirlukast, several cases of CSS have been reported in association with it [5–10] and one case associated with pranlukast [15]. The clinical features of the disease are consistent with typical CSS. Most patients have a history of multiple asthma

Table 1. CSS and antileukotrienes: literature review

Patient [ref.]	Age (yr)/ sex	AL/AL–CSS interval	CS at onset SCS–CSS interval	Clinical or biological characteristics											Treatment/outcome
				PI	CMP	NP	Myal	Arthr	Rash	Fever	Sinus	HEP	ESR	Biopsy, EP	
1 [1]	45/F	Zafirlukast/2 m	NR/DC 2 wk earlier	+	+	+	−	NR	+	+	+	+	53	Skin, lung (+)	CYC + SCS
2 [1]	43/F	Zafirlukast/3 d	NR/DC 3 d earlier	+	+	+	+	NR	+	−	+	+	65	Nerve (–)	AL DC/good
3 [1]	59/F	Zafirlukast/4 m	NR/DC 3 wk earlier	+	+	−	+	NR	−	+	+	+	111	Heart (+)	AL DC + SCS/good
4 [1]	36/F	Zafirlukast/3 m	Low doses SCS/ongoing	+	+	−	+	NR	−	+	+	+	NR	Lung (+)	AL DC 2 m before symptoms, SCS/good
5 [1]	21/M	Zafirlukast/2 m	NR/DC 2 wk earlier	+	+	−	+	NR	+	+	+	+	40	Skin, lung (+)	AL DC, CYC + SCS/good
6 [1]	43/F	Zafirlukast/3 m	NR/DC 3 m earlier	+	+	−	+	NR	−	+	−	+	55	Heart (+)	AL DC, SCS/good
7 [1]	48/F	Zafirlukast/3 m	NR/DC 1 m earlier	+	+	−	+	NR	−	+	+	+	60	Pleural fluid (+)	AL DC, SCS/good
8 [1]	23/F	Zafirlukast/2 m	NR/DC 1 m earlier	+	+	−	+	NR	−	−	−	+	NR	Heart (+)	AL DC, SCS/good
9 [2]	47/M	Zafirlukast/1 m	Fluticasone/6 m earlier	+	−	−	NR	+	+	+	+	+	NR	Skin, lung (+)	AL DC, SCS/good
10 [3]	67/M	Zafirlukast/9 m	Fluticasone/NR	+	−	+	−	−	−	−	+	+	NR	Nerve (+)	NR
11 [3]	60/F	Zafirlukast/4 m	Fluticasone/4 m	+	−	−	−	−	+	+	+	−	NR	Lung (+)	NR
12 [4]	53/F	Zafirlukast/7 wk	None/2 m	+	Pericarditis		−	−	+	+	+	+	+	48	Lung (+) AL DC, SCS/good
13 [15]	52/F	Pranlukast/3 m	ICS/2 m	+	−	+	+	−	−	−	+	+	28	Muscle (+)	AL DC, SCS/good
14 [6]	26/M	Montelukast/4 m	Fluticasone/3 m earlier	+	−	+	+	−	−	+	+	+	NR	BALF (+)	AL DC, SCS/good
15 [7]	72/F	Montelukast/10 d	Fluticasone/3 m earlier	+	−	−	−	+	+	+	−	+	NR	NR	AL DC, AZ + SCS/good
16 [8]	25/F	Montelukast/5 m	NR/ > 11 m	−	−	−	−	−	+	+	−	+	75	Lung (+)	AL DC, SCS/good
17 [5]	62/F	Montelukast/3 m	ICS/NR	+	−	+	+	NR	+	NR	+	+	18	NR	AL DC, CYC + SCS/good
18 [5]	43/F	Montelukast/7 m	ICS/2 m earlier	+	+	+	−	NR	+	NR	−	+	100	NR	AL DC, SCS/good
19 [5]	59/F	Montelukast/2 m	ICS/2 m earlier	−	−	−	−	NR	−	NR	+	+	38	NR	AL DC, SCS/good
20 [5]	36/F	Montelukast/6 m	ICS/6 m earlier	+	−	+	+	NR	−	NR	+	+	NR	BALF (+)	AL DC, SCS/good
21 [10]	21/M	Montelukast/2.5 m	Fluticasone/3 m earlier	+	−	−	+	NR	+	NR	+	+	NR	NR	AL DC, SCS/good
22 [9]	43/F	Montelukast/7 m	Prednisone/ongoing	+	+	+	−	NR	−	+/−	−	+	24	NR	AL DC, SCS/NR
23 (this paper)	48/F	Montelukast/4 m	ICS/never	+	−	−	+	−	−		NR	+	116	NR	AL DC, SCS/good
24 (this paper)	23/F	Montelukast/5 m	ICS/5 m (short course)	+	+	+	+	−	−	+	+	+	55	NR	AL DC, CYC + SCS/NR

−, absent; +, present.

AL, antileukotriene; Arthr, arthralgias; AZ, azathioprine; BALF, bronchoalveolar lavage fluid; CCS, Churg–Strauss syndrome; CMP, cardiomyopathy; CS, corticosteroids; CYC, cyclosporin; d, days; DC, discontinued; EP, esosinophils in biopsy; ESR, erythrocyte sedimentation rate (mm/1st h); HEP, hypereosinophilia; ICS, inhaled corticosteroids; m, months; Myal, myalgias; NP, neuropathy; NR, not reported; PI, pulmonary infiltrates; SCS, systemic corticosteroids; Sinus, sinusitis; wk, weeks.

attacks, occurring from 3 days to 9 months after starting treatment (Table 1).

Different mechanisms may be involved in antileukotriene-induced CSS. One possibility is that, because leukotriene antagonists facilitate steroid-tapering, they may unmask underlying CSS. Several cases [1, 5, 10] seem to be consistent with this hypothesis, which was advanced originally to explain cases of CSS associated with other systemic steroid-sparing drugs used in asthma (inhaled corticosteroids [16], theophylline and cromolyns [17, 18]).

Because some cases of antileukotriene-associated CSS have occurred without concomitant oral steroid treatment, other mechanisms are probably involved. Moreover, tapering of oral steroids did not precede CSS in some patients [2–4, 6–8] and other patients, like our two patients, were not on oral steroids at the onset of CSS (Table 1). Indeed, one of our patients (patient 23 in Table 1) had never taken oral steroids and our other patient (patient 24) received only short-term courses of betamethasone for asthma attacks, but both patients were on inhaled steroids. Even though some authors [19] have indicated that CSS can be masked by oral or inhaled steroids, on the basis of our two patients we think that inhaled steroids are not sufficient to prevent a flare of a non-diagnosed forme fruste of CSS.

Although the occurrence of CSS in patients treated with antileukotrienes might be coincidental, this hypothesis can be excluded because of the rarity of CSS, the increased number of cases reported after antileukotriene treatment [5] and the temporal relationship between antileukotriene treatment and systemic vasculitis. A hypersensitivity reaction to leukotriene antagonists is not likely because allergic vasculitides are more often leucocytoclastic than granulomatous. CSS has, nonetheless, been described following administration of macrolides [20], oestrogen replacement therapy [21] and carbamazepine [22]. Finally, the blockade of the cysteinyl leukotriene receptors could provoke an imbalance in leukotriene receptor stimulation, leading to an increase in circulating LTB^4 [23]. This leukotriene is a strong chemoattractant for neutrophils and eosinophils [13] and could trigger an eosinophilic state, and thereby initiate vasculitic involvement. CSS has also been reported in association with zileuton (Food and Drug Administration, Freedom of Information Act, data on file, 1999 [5]), an inhibitor of 5-lipoxygenase, which also blocks LTB^4; this makes the LTB^4 chemoattractant hypothesis less likely.

Respiratory symptoms recurred in both patients, as is often observed when steroids are tapered. This does not reflect, in the absence of concomitant extrapulmonary symptoms, the relapse of CSS. In leukotriene receptor antagonist-induced vasculitis, disease outcome is not different from that observed in other CSS patients, and the majority of patients recover and do not relapse. In case 1, non-giant-cell arteritis was observed on temporal artery biopsy. This biopsy site can be recommended for the diagnosis of necrotizing vasculitis, especially when biopsies of muscle or other organs are negative.

When the role of an antileukotriene is suspected in a patient with CSS, the drug should be withdrawn. However, it is not sufficient merely to control the disease, and steroids should be prescribed, in combination with cytotoxic agents when there are severe manifestations. The outcome of antileukotriene-induced CSS is usually favourable.

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