

Montelukast and Churg-Strauss syndrome

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Summary

The association of leukotriene receptor antagonists and Churg-Strauss Syndrome (CSS) has been recognised for several years. However, whether these drugs have a direct pathogenic role remains controversial. The present case describes an asthmatic patient, who developed severe obstructive symptoms and progressive heart failure after two sequential exposures to montelukast. As the patient exhibited a markedly raised blood eosinophil count with diffuse infiltrates on chest x-ray and signs of myocarditis, CSS was suspected. The disease was confirmed by open lung biopsy.

The symptoms improved rapidly after administration of high dose immunosuppression with methylprednisolone and cyclophosphamide. This case is noteworthy because the time course of events strongly suggests a direct aetiological role for montelukast in the development of CSS. The pathophysiological mechanism of the association remains unknown.

Keywords: Churg-Strauss syndrome; leukotriene receptor antagonists; eosinophilia; asthma; vasculitis

Introduction

Churg-Strauss syndrome (CSS) is a systemic small vessel vasculitis predominantly involving lungs, skin, heart, peripheral nerves and gastrointestinal tract [1, 2]. The aetiology of CSS is unknown. However, in rare cases CSS is associated with the use of leukotriene receptor antagonists (LRA) such as montelukast, pranlukast or zafir-

lukast [3–5]. Their role in the pathogenesis of CSS remains controversial. A steroid sparing effect of LRA with subsequent unmasking of a latent CSS has been postulated. Here we report a case of CSS in a patient exposed to montelukast during two separate periods.

Case report

A 46-year-old male was admitted to hospital with suspected myocardial infarction. No major cardiovascular risk factors could be detected. The patient's personal history consisted of perennial allergic rhinitis, sinusitis and bronchial asthma since childhood, as well as recent hypersensitivity to aspirin. The asthma had been treated successfully with low doses of inhaled corticosteroids (ICS) and intermittent salbutamol for more than 15 years. Following progressive worsening of nasal obstruction, polypectomy was performed 15 months prior to admission. Up until two months before the operation, the patient had received a first course of montelukast 10 mg per day for two months and a course of oral prednisone tapered from 100 mg per day to zero over two weeks without a lasting benefit for the nasal symptoms. Shortly after the operation, the asthma worsened and oral prednisone was reintroduced followed by tapering to 5 mg per day. To control the asthma symptoms, it had to be increased again gradually to 15 mg per day and was left unchanged for at

least two months prior to admission. Forty days before hospital admission, a second course of montelukast was started. The patient developed increasing dyspnoea and thoracic discomfort on exertion, orthopnoea, dry cough and intermittent abdominal cramps. Three weeks before admission, montelukast was interrupted for one week because of transient urticaria.

The patient was admitted because of worsening respiratory symptoms. On admission, his heart rate was 105

Abbreviations

| | |
|------|----------------------------------|
| CSS | Churg-Strauss syndrome |
| LRA | Leukotriene receptor antagonists |
| ICS | Inhaled corticosteroids |
| ESR | Erythrocyte sedimentation rate |
| LTB4 | Leukotriene B4 |

Table 1

Course of main laboratory and functional characteristics in relation to montelukast and systemic corticosteroid exposure. — = Treatment with systemic corticosteroids
ESR= Erythrocyte sedimentation rate
LVEF= Left ventricular ejection fraction.

| Montelukast exposure (days) | - 630 until - 510 | | - 40 until 0 | | | |
|---|-------------------|-------|--------------|------|----|-----|
| | | | | | | |
| Time from hospital admission (days) | - 660 | - 460 | - 41 | 0 | 7 | 14 |
| Blood eosinophil count (µl ⁻¹) N ≤300 | 332 | 1280 | 560 | 5600 | 30 | 300 |
| C-reactive protein (mg/l) N ≤10 | 2 | | 9 | 108 | 6 | 2 |
| ESR (mm/h) N ≤20 | 5 | | | 82 | 22 | |
| Brain natriuretic peptide (pg/ml) N ≤50.3 | | | 657 | 421 | | |
| Troponin I (µg/l) N ≤2.0 | | | | 30 | 15 | |
| LVEF (%) | | | | 30 | 45 | 50 |

Figure 1

A: Normal chest x-ray forty days before admission.
B: Chest x-ray on admission showing cardiomegaly and bilateral, perihilar, interstitial infiltrates.

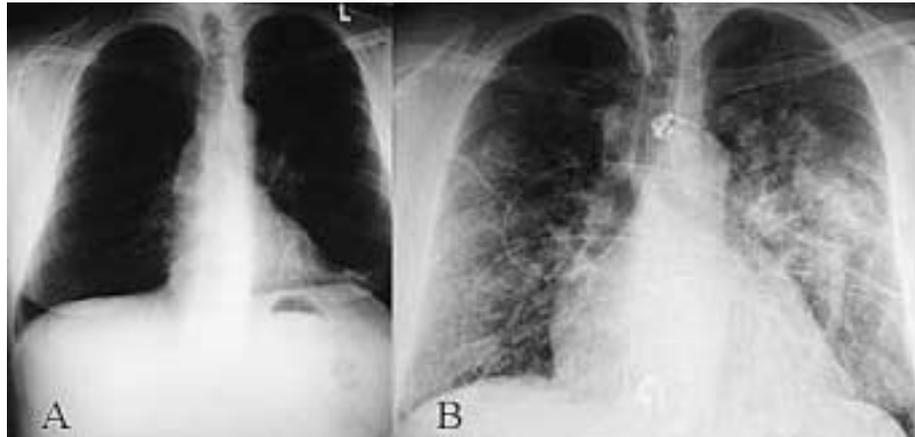
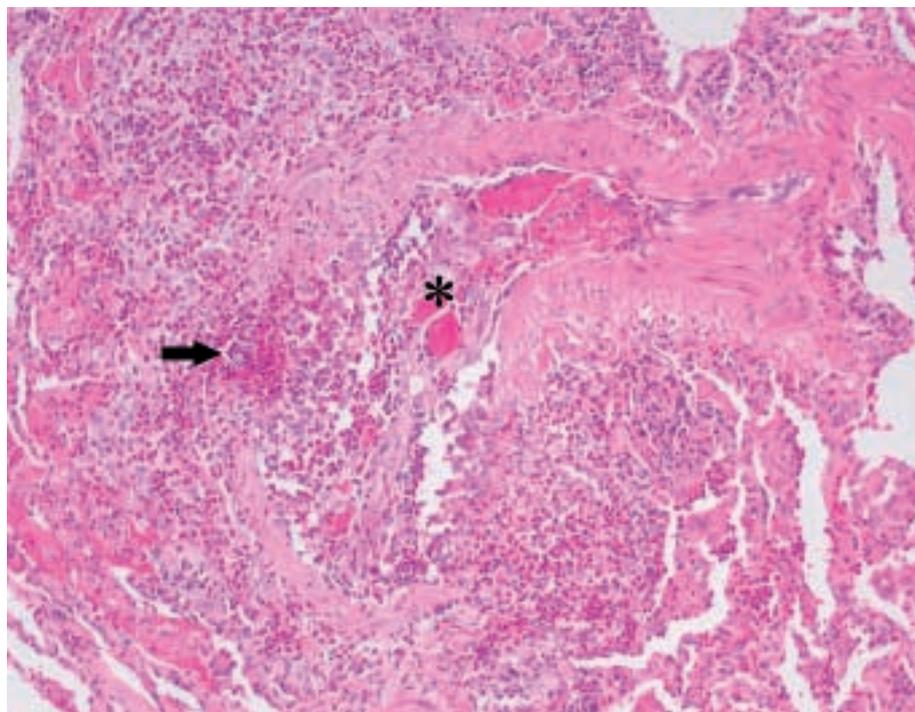


Figure 2

Vasculitis with severe eosinophilic inflammation and partial destruction of the vessel wall (arrow). Inflammatory and thrombotic luminal obliteration (asterix) (× 100).



per minute and blood pressure 110/70 mm Hg. Oxygen saturation was 95% on breathing ambient air and body temperature was 37.0 °C. Physical examination revealed positive hepatojugular reflux and inspiratory crackles. Laboratory studies showed the following results: leukocytosis of $22.44 \times 10^9/l$ ($3.5-10.0 \times 10^9/l$) with 26% eosinophils (0–7.0%), erythrocyte sedimentation rate (ESR) 82 mm/h (0–13 mm/h), CRP 108 mg/l (<10.0 mg/l), albumin 29 g/l (35–52 g/l), creatine phosphokinase 281 U/l (50–200 U/l), troponin I 29.9 µg/l (<2.0 µg/l), lactate dehydrogenase 404 U/l (135–225 U/l) brain natriuretic

peptide 657 pg/ml (<50.3 pg/ml), rheumatoid factor 1:4096 (1:16) (Table). Antinuclear and antineutrophil-cytoplasmic antibodies were not detected. A 12-lead ECG showed Q waves and ST-segment elevations in the anterior leads. Chest x-ray on admission revealed cardiomegaly and bilateral, perihilar interstitial infiltrates. It had been normal 40 days earlier (Figure 1). Transthoracic echocardiography showed a severely depressed left ventricular function with an ejection fraction of 30% without regional wall motion abnormalities (Table). There was a small pericardial effusion and mild mitral regurgitation.

CT scan showed bilateral confluent lung infiltrates associated with a ground glass pattern. Coronary angiography was normal. Bronchoalveolar lavage revealed 78% eosinophils (611 Mio/l). Lung biopsy was obtained by video assisted thoracic surgery. Microscopy revealed wide spread eosinophilic inflammation, focal giant cell granulomas and eosinophilic, necrotising vasculitis (figure 2).

Upon these findings, CSS with myocardial, pulmonary and possibly intestinal involvement was diagnosed. Immunosuppressive therapy was rapidly initiated including three intravenous pulses of 500 mg methylpred-

nisolone followed by daily oral prednisone at 1 mg/kg of body weight and cyclophosphamide pulses of initially 600 mg/m² and later 750 mg/m² given on day 0, 15, 30 and every three to four weeks thereafter for a total of 12 doses.

The patient's condition improved rapidly. The eosinophilia and cardiac enzymes returned to normal after initiation of immunosuppression. Pulmonary infiltrates disappeared and echocardiography confirmed normalised left ventricular function at eight weeks. After 15 months of follow-up, the patient is well under continuous treatment with oral prednisone now tapered to 15 mg per day.

Comment

CSS has been associated with the use of LRA and corticosteroid withdrawal [3, 4]. A steroid sparing effect of LRA with subsequent unmasking of latent CSS was postulated. However, reports of patients developing CSS without concomitant therapy with oral steroids have also been published [5, 6]. Our patient has some unique features in regard to the association of LRA and CSS. Firstly, he had never been treated with systemic corticosteroids prior to his first course of montelukast. At that time his asthma was well controlled with standard inhalation therapy combining a bronchodilator and ICS. Secondly, the first course of montelukast was not given to treat his well controlled asthma, but in an attempt to reduce nasal obstruction due to chronic rhinitis. Respiratory symptoms worsened following montelukast treatment. Only then were oral corticosteroids introduced to treat worsening asthma. Thirdly, blood eosinophil counts rose from normal values to 1280/μl after the first course of montelukast (Table). One year later, when the patient received his second course of montelukast in addition to a constant dose of oral corticosteroids, blood eosinophils increased again tenfold from 560/μl to 5600/μl (Table).

We hypothesise that the first exposure to montelukast triggered initial, unrecognised manifestations of CSS such as deteriorating asthma and eosinophilia leading to the introduction of oral corticosteroids. Severe manifestations of CSS with prominent involvement of several vital organs developed only after re-exposure to montelukast without tapering of corticosteroids. There is a clear correlation of symptoms, blood eosinophilia and radiological changes, with the administration of montelukast on two separate occasions. However, contrary to other reports [4] we do not see any correlation between the administration of corticosteroids and the onset of CSS in our patient. The previously described steroid sparing effect of LRA is controversial [3, 4], since a recent randomised controlled trial revealed that corticosteroids cannot be reduced in patients with persistent, moderate to severe asthma despite administration of LRA [7]. In this report the time course of events with

eosinophilia after the first and the rapid development of severe disease after the second exposure, suggests a causative role of montelukast in the pathogenesis of CSS, as discussed in a recent review by Garcia et al. [8]. The mechanism by which LRA might cause eosinophilic vasculitis remains unclear. Hypersensitivity reactions tend to cause a leukocytoclastic rather than a granulomatous vasculitis. Therefore a hypersensitivity reaction to LRA seems unlikely. Leukotriene B₄ (LTB₄), a powerful chemoattractant of eosinophils, is not inhibited by LRA [9]. This could lead to increased plasma levels of LTB₄ and trigger eosinophilic inflammation. However, CSS has also been reported in association with inhibitors of 5-lipoxygenase (e.g. zileuton), which also block LTB₄ [4].

Almost 150 cases of LRA associated CSS have been reported by the United States Federal Drug Administration [10]. A summary of 24 cases suggested an association of CSS with LRA [5]. In a recently reported series of cases, however, a history of exposure to LRA preceded the CSS related symptoms in only 13 of 23 patients, who received LRA and the time of disease progression from asthma to CSS was not affected by the exposure [11].

LRAs are safe and efficient drugs in most patients with asthma but in rare cases they might contribute to the development of CSS. An as yet unknown direct pathogenic effect of these drugs appears to be possible in light of the presented case. Given the various, inconclusive reports, a controlled study with a large number of patients is needed. In the meantime, clinicians should be aware of this rare but potentially severe complication of LRA.

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