Case Report

Churg-Strauss Syndrome after the Use of Montelukast in a Patient with Asthma

Ming-Chi Luk, Man-Yee Lee and Emily Kun

Abstract: Churg-Strauss syndrome (CSS) is an uncommon disease of unknown etiology. We reported a patient who developed CSS after treatment with Montelukast. There is currently no evidence to suggest that Montelukast causes CSS directly. Patients with moderate or severe asthma, who are able to discontinue or avoid oral corticosteroids, constitute a group that is at risk for the manifestation of CSS. Close monitoring is necessary.

Keywords: Churg-Strauss syndrome, Cysteinyl leukotriene type I antagonist, Montelukast, Pancarditis

Case Report

A 44-year-old woman, nonsmoker, was admitted to the hospital in August 1999 because of a submandibular swelling for 2 months.

She had been diagnosed to have allergic rhinitis and asthma since March 1998. Her asthma was difficult to control despite therapy with inhaled long acting $\beta_2$-agonist and high dose inhaled steroid. She had five episodes of moderate asthmatic attacks within a year, requiring hospitalization and short courses of oral steroid. However, she had not been given continuous oral steroid for her asthma. Her chest X-ray was normal. There was one episode of transient eosinophilia with an eosinophil count of 2.6 x $10^9$/L (NR 0-0.5 x $10^9$/L) in September 1998. Montelukast was added to her treatment regimen in early March 1999. The asthmatic symptoms improved dramatically. Her peak flow rate increased from around 300L/min to 400L/min. The dose of inhaled Budesonide was reduced from 400 mcg bid to 200 mcg bid in early July 1999.

Two months before this admission, she started to notice a submandibular swelling, which gradually increased in size. She had generalized neck and shoulder pain. She also had subjective body weight loss and poor appetite, with low grade fever for a few days before admission.

On admission, her temperature was 37°C, with a pulse rate of 86/min and blood pressure of 120/77 mm Hg. Urine dipstick test for red blood cell and protein were negative. Physical examination revealed a soft and mildly tender swelling in the submandibular region. There was no regional lymphadenopathy. Heart sounds were normal with a soft ejection systolic murmur heard over the apex. Respiratory, abdominal and nervous systems examination were unremarkable. The complete blood picture revealed marked eosinophilia of 35.7%. The chest X-ray, renal and liver biochemistry were normal. She developed low-grade fever and hoarseness of voice 2 days after admission. Splinter hemorrhages were noted on her fingers with vasculitic lesions over both palms and feet. Echocardiogram was performed and showed no vegetation and an ejection fraction of 60%. ANA and ANCA were negative. Immunoglobulin E level was grossly elevated 778 IU/ml (normal range <100 IU/ml). Fine needle biopsy of the submandibular mass was done.

On day 8 of admission, she developed transient unconsciousness, hypotension and desaturation. Chest X-ray showed pulmonary edema. ECG showed complete heart
block. A repeat echocardiogram revealed moderate mitral regurgitation and tricuspid regurgitation with an ejection fraction of 40%. She was intubated and transferred to intensive care unit. Transcutaneous cardiac pacing was performed. Rheumatology consultation was sought. Churg-Strauss syndrome (CSS) complicated by coexisting bacterial infection was suspected clinically. Intravenous antibiotics and pulse methylprednisolone were given. Her blood pressure did not improve with fluid resuscitation and inotropic infusion. She finally succumbed 7 hours after ICU admission.

Postmortem examination revealed features of CSS with allergic granulomatosis, coronary vasculitis and eosinophilic pancarditis. Multi-organ involvement was found, including pulmonary vasculitits, focal segmental necrotizing and crescentic glomerulonephritis, vasculitis, eosinophilia and granuloma formation in the submandibular soft tissue.

Discussion

Churg-Strauss syndrome (CSS), or eosinophilic angiitis, was first described by Churg and Strauss. They reported allergic angiitis, granulomas and polyarteritis nodosa in the autopsy study of a group of patients with long history of asthma. It is a systemic disease affecting variable organs. Similar to other distinct primary vasculitis syndrome, CSS has characteristic dominant organ involvement. The skin, respiratory and peripheral nervous systems are the most common organs to be affected. Cardiac and gastrointestinal involvements are also frequent. Contrary to Wegener’s granulomatosis and microscopic polyangitis, renal failure is uncommon in CSS, but its presence is associated with higher mortality rate. There is no single diagnostic test for CSS. Diagnosis is based on clinical grounds and pathologic findings (Table 1).

The clinical course of CSS can be roughly divided into 3 phases: the prodromal phase characterized by prominent allergic history such as allergic rhinitis, sinusitis and asthma; the eosinophilic phase with tissue infiltration by eosinophil; and the vasculitic phase with multisystem involvement, often the lung, the heart, the gastrointestinal tract and the nervous system. The duration of different phases can be variable and indistinct. Asthma may precede the development of systemic vasculitis by up to 30 years (A mean interval of 6.6 years between onset of asthma and vasculitis). The onset of the vasculitic phase is often sudden. Most patients appear to develop the cardinal manifestations suddenly (such as foot drop, palpable purpura, or pulmonary infiltrate) without a perceptible prodrome. The natural clinical course of CSS is modified by corticosteroids, particularly systemic therapy that is administered for the control of asthma symptoms.

The exact incidence or prevalence of the CSS is unknown due to the long prodromal phase and lack of a single diagnostic test. It is thought to be a rare disease with the incidence estimated around 1.5 to 3.7 cases million patient-years (MPY) in the general population in a study undertaken in UK.

The cysteinyll leukotriene type I (CysLTI) antagonists, zafirlukast, montelukast and pranlukast, have been associated with the onset of CSS. In one literature review using Medline from February 1966 to October 2000, twenty-two case reports of patients receiving LTAs who developed CSS were identified. There was a temporal relationship. The onset of CSS occurred from 2 days to 10 months after starting treatment.

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<tr>
<th>Study</th>
<th>Criteria</th>
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<td>Churg and Strauss¹</td>
<td>1) Necrotizing vasculitis of small and medium-sized arteries and veins; 2) eosinophil infiltration around involved vessels and in tissues; and 3) extravascular granulomas</td>
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<tr>
<td>Hammersmith²</td>
<td>1) history of asthma; 2) peak blood eosinophilia &gt;1500 eosinophils/mm³; and 3) systemic vasculitis involving 2 or more extrapulmonary organs</td>
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<td>American College of Rheumatology³</td>
<td>Four or more of the following 6 criteria: 1) asthma; 2) &gt;10% blood eosinophilia; 3) mononeuropathy (including multiplex) or polyneuropathy; 4) nonfixed pulmonary infiltrates on chest radiography; 5) paranasal sinus abnormalities; 6) extravascular eosinophils</td>
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<td>Chapel Hill Consensus Conference 1994⁴</td>
<td>Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium sized vessels and associated with asthma and eosinophilia</td>
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with CysLTI antagonist. The incidence rate is also high, approximately 56 to 74 cases MPY, among patients with asthma using either zafirlukast or montelukast.7

The incidence of CSS is higher among the asthmatic population than that in the general population. The estimated incidence is of 60 MPY in patients with asthma not receiving CysLTI antagonist.8 CSS has been reported in patients receiving new anti-asthmatic such as zileuton (a 5-lipoxygenase inhibitor), fluticasone dipropionate (inhaled corticosteroid) and salmeterol xinafoate (long acting β2-agonist) based on data from the Adverse Events Reporting System of the FDA.9 The majority of patients who developed CSS after using these anti-asthmatic medications had history of prior systemic corticosteroid usage. Most developed CSS on tailing down their corticosteroid dose. It is unlikely that the use of CysLTI antagonists causes CSS directly. Since steroid is the mainstay treatment for CCS, the tapering of the steroid dose, made possible with the use of the new anti-asthmatic medications, may have unmasked the clinical manifestations of the incipient CCS.

CSS is a potentially fatal disease. Fifty percent of untreated patients die within three months of the onset of vasculitis. The extent of organ involvement is important. Guillemin et al10 identified a 5-factor score to evaluate the severity of vasculitis. The 5 factors that were associated significantly with a poor outcome included myocardial involvement, the presence of proteinuria (>1 g/d), renal insufficiency (plasma creatinine concentration >1.6 mg/dL), central nervous system involvement and gastrointestinal diseases, which were defined as intestinal bleeding, perforation, pancreatitis, or laparotomy. The 5-factor score was significantly associated with a high risk of death when it is greater than or equal to 2. A short duration of asthma, severe GI and cardiac involvement were also poor prognostic factors. A score of 0 correlated with an 88% survival rate.

Lanham et al3 found systemic steroids alone useful in the treatment of CSS. With treatment, the remission rate is high (90% to 95% remission within 1 year of treatment), although 30% to 40% of patients may experience relapse.11 When corticosteroid therapy does not cause remission (as either corticosteroid sparing or corticosteroid failure) and other significant life-threatening organ involvement exists, the use of cytotoxic therapy is indicated. Like polyarteritis nodosa and microscopic polyangiitis, CSS responds to cyclophosphamide. Cyclophosphamide with corticosteroid therapy significantly prolongs survival for patients with a 5-factor score of greater than or equal to 2.12,13 Methotrexate or azathioprine may be used instead. However, they may not be as efficacious as cyclophosphamide in inducing remission. Isolated case reports suggest the effectiveness of other alternative treatments including high dose intravenous immunoglobulin, plasma exchange, and α-interferon therapy.

Our patient illustrates a typical scenario, in which features of CCS evolve with the background history of allergic rhinitis and asthma after treatment with montelukast. She did have poor prognostic factors including short duration of asthma and cardiac involvement. Unfortunately, she did not respond to the treatment.

Conclusions

To date, there is no evidence to suggest that Montelukast causes CSS directly. Physicians should be alerted to the possible development of CCS in patients with severe to moderate asthma when their steroid dose is tapered on administration of steroid sparing medications. Close monitoring and a high index of suspicion is needed.

References

8. Weschler ME, Drazen JM. Leukotriene modifiers and Churg-
CHURG-STRASS SYNDROME AFTER THE USE OF MONTELUKAST