CASE STUDY

Inhaled corticosteroids and Churg-Strauss syndrome: a report of five cases

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ABSTRACT: Churg-Strauss syndrome is an eosinophil-associated, small vessel granulomatous vasculitis, characterized by late onset asthma, upper airways disease, eosinophilia, and clinical manifestations of systemic vasculitis. Several cases of Churg-Strauss syndrome have been recognized in patients treated with cysteinyl leukotriene-receptor antagonists and weaned off systemic corticosteroids. These cases have led to a general warning on the possible development of Churg-Strauss syndrome after taking cysteinyl leukotriene-receptor antagonists.

The authors report five cases of Churg-Strauss syndrome in severe steroid dependent asthmatics in whom inhaled corticosteroids allowed systemic corticosteroid withdrawal. It is concluded that physicians should monitor patients carefully when severe asthma is controlled with any substance allowing withdrawal from (or even avoidance) of systemic corticosteroids.

Case-control studies should identify more precisely the risk factors of Churg-Strauss syndrome.


Churg-Strauss syndrome is an eosinophil-associated, small vessel granulomatous vasculitis, characterized by late onset asthma, upper airways disease, eosinophilia, and clinical manifestations of systemic vasculitis [1–4]. Extra-pulmonary manifestations include weight loss, myalgia, arthralgia, skin signs, mononeuritis multiplex, gastrointestinal tract involvement, and cardiomyopathy [1–4]. In 1990 the American College of Rheumatology promulgated specific diagnostic criteria for the syndrome [4]. For a diagnosis of Churg-Strauss syndrome to be made patients must present with at least four of the following six features: 1) moderate to severe asthma; 2) peripheral blood eosinophilia (>10%); 3) mononeuropathy or polyneuropathy; 4) nonfixed pulmonary infiltrates; 5) paranasal sinus abnormality; and 6) a biopsy specimen containing a blood vessel with extravascular eosinophils.

Recently, Churg-Strauss syndrome has received much attention because of several reports of the syndrome in patients taking recently approved asthma drugs belonging to the family of the cysteinyl leukotriene (LT)-receptor antagonists (zafirlukast, montelukast, and pranlukast) [5–15]. These cases have led to a general warning on the possible association of Churg-Strauss syndrome with LT receptor antagonists [9, 15]. However, careful analysis of all reported cases suggests that Churg-Strauss syndrome develops primarily in those patients taking these medications who had an underlying eosinophilic disorder that was being masked by corticosteroid treatment and unmasked by novel asthma medication-mediated corticosteroid withdrawal [15]. In the present report, five cases of Churg-Strauss syndrome are described in severe steroid-dependent asthmatics in whom inhaled corticosteroids allowed oral corticosteroid withdrawal.

Case reports

The patients discussed in this paper are detailed in the tables 1–3. They all suffered from severe persistent asthma requiring long-term oral corticosteroids to control their respiratory symptoms (range 3–216 months, mean 67 months). High-dose inhaled corticosteroids were initiated to improve asthma control and decrease systemic corticosteroid therapy on average 33 months before the onset of Churg-Strauss syndrome (range 10–84 months). When high-dose inhaled corticosteroids were started, there was no evidence of an underlying Churg-Strauss syndrome, as defined by the 1990 American College of Rheumatology criteria [4] (one patient had three criteria, two had two, and two had only one). Inhaled corticosteroids allowed the withdrawal of systemic corticosteroids 6–83 months (mean 31 months) before the diagnosis of Churg-Strauss syndrome. No patient received LT modifiers to control their asthma symptoms.

In all patients the diagnosis of Churg-Strauss syndrome could be established according to the criteria of the American College of Rheumatology [4]. Asthma, eosinophilia >10%, and paranasal sinus abnormalities were found in all patients. Neuropathy was identified in three out of five patients. Weight loss and fatigue were always present.
Conversely, cardiac involvement was rarely identified (one pericarditis). Erythrocyte sedimentation rate was elevated in all cases. Positive antineutrophil cytoplasmic antibodies was positive in one case. All patients improved with therapy consisting of systemic corticosteroids in all patients associated with cyclophosphamide in two cases.

Discussion

Glucocorticosteroids (also known as corticosteroids or steroids) are the most effective drugs in the treatment of asthma [16–18]. Oral corticosteroids are still very useful for the control of asthma exacerbations but their chronic use has sharply declined with the introduction of inhaled corticosteroids that give effective asthma control with few systemic side-effects [16–18]. However, a major concern in patients taking oral or high-dose inhaled corticosteroids is still the side-effects associated with long-term maintenance therapy such as increased bone turnover, impaired growth, hypothalamic-pituitary-adrenal suppression, cataract, increased blood glucose, skin bruising, and psychiatric disturbance [16–18]. Therefore much attention has been given to drugs with corticosteroid-sparing effects [19]. Indeed, drugs such as methotrexate, cyclosporin and gold can usefully reduce the dose of oral corticosteroids in some patients [19]. However, these agents can induce severe side-effects and are rarely used in asthma.

The cysteinyl LT LTC4, LTD4, and LTE4 are pro-inflammatory agents that can induce bronchoconstriction, increase vascular permeability, increase mucus production, and induce inflammatory cell infiltration of lung tissue. LT modifiers have recently become available on the market (cysteinyl LT1 receptor antagonists such as zafirlukast, montelukast and pranlukast, as well as the 5-lipoxygenase inhibitor, zileuton). Although these drugs are usually safe and well tolerated, some side-effects have been detected after approval for use in larger population samples [15]. Liver function abnormalities have been reported with zileuton. Moreover, >50 cases of Churg-Strauss syndrome have been published or reported to drug agencies in association with cysteinyl LT1 receptor antagonists in severe steroid-dependent asthmatics who had discontinued oral corticosteroid a few months before development of the syndrome [5–15]. A few cases of the syndrome have also been described after zafirlukast in patients not receiving systemic steroid treatment [12]. The high incidence of such a rare entity [11] during the commercial postmarketing surveillance of cysteinyl LT1 receptor antagonists has led to a general warning that Churg-Strauss syndrome may occur after taking these drugs [9, 15].

There may however, be confusion between a direct drug side-effect and an unanticipated consequence of a decrease in corticosteroid therapy [9, 15]. Interestingly, similar cases have been described with other medications in the past, emphasizing the fact that Churg-Strauss syndrome may be the mere consequence of corticosteroid withdrawal (or avoidance) in patients with an underlying vasculitis using an otherwise effective asthma drug [10, 15]. Indeed, the number of asthmatic people at risk of developing Churg-Strauss syndrome after the introduction of corticosteroid-sparing drugs is substantial, and physicians

### Table 1. – Patient information

<table>
<thead>
<tr>
<th>Sex/age yrs</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/62</td>
<td>M/62</td>
<td>F/53</td>
<td>M/65</td>
<td>M/76</td>
<td></td>
</tr>
<tr>
<td>Duration of oral corticosteroid therapy months</td>
<td>30</td>
<td>60</td>
<td>24</td>
<td>3</td>
<td>216</td>
</tr>
<tr>
<td>Total cumulative and mean daily dose of oral prednisolone mg</td>
<td>23000</td>
<td>13500</td>
<td>5500</td>
<td>1700</td>
<td>16200</td>
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<tr>
<td>Inhaled corticosteroids</td>
<td>Fluticasone</td>
<td>Fluticasone</td>
<td>Fluticasone</td>
<td>Budesonide dipropionate</td>
<td>Budesonide</td>
</tr>
<tr>
<td>Delay between initiation of inhaled corticosteroid and diagnosis of Churg-Strauss syndrome months</td>
<td>10</td>
<td>10</td>
<td>27</td>
<td>84</td>
<td>33</td>
</tr>
<tr>
<td>Dose of inhaled corticosteroid at the time of Churg-Strauss syndrome diagnosis µg</td>
<td>2000</td>
<td>2000</td>
<td>500</td>
<td>1500</td>
<td>1600</td>
</tr>
<tr>
<td>Delay between oral corticosteroid withdrawal and diagnosis of Churg-Strauss syndrome months</td>
<td>7</td>
<td>6</td>
<td>24</td>
<td>83</td>
<td>33</td>
</tr>
</tbody>
</table>

F: female; M: male.

### Table 2. – Churg-Strauss criteria (1990 American College of Rheumatology [4]) at the time of initiation of inhaled corticosteroid therapy

<table>
<thead>
<tr>
<th>Asthma</th>
<th>Peripheral blood eosinophilia &gt;10%</th>
<th>Nonfixed pulmonary infiltrates</th>
<th>Paranasal sinus abnormality</th>
<th>Neuropathy</th>
<th>Necrotizing vasculitis with extravascular eosinophil granulomas</th>
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<td>+</td>
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<td>-</td>
<td>+</td>
<td>NA</td>
</tr>
</tbody>
</table>

Values are presented as percentages and absolute numbers per cubic millimetre. + present; -: absent; NA: not available.
leukotriene receptor antagonists clearly emphasizes the on cases of the syndrome putatively induced by cysteinyl an underlying systemic vasculitis. The recent controversy ation remains that oral corticosteroid withdrawal unmasks ected patient populations. The most widely used explan-

explain the occurrence of Churg-Strauss syndrome in sel-

Churg-Strauss vasculitis with high-dose inhaled corticos-

vasculitis in some patients, indicating possible control of corticosteroids may have a role in triggering an underlying report suggests that discontinuation of high-dose inhaled 
millas 2014; 23: 1330–1336.

Several hypotheses have been proposed in the past to explain the occurrence of Churg-Strauss syndrome in selected patient populations. The most widely used explana-

tions remains that oral corticosteroid withdrawal unmasks an underlying systemic vasculitis. The recent controversy on cases of the syndrome putatively induced by cysteiny1 leukotriene, receptor antagonists clearly emphasizes the need for case-control studies to clarify the respective roles of drugs, steroid withdrawal and other factors in the development of Churg-Strauss syndrome [15, 22].

References

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