Diagnostic Features and Differential Diagnosis of Churg-Strauss Syndrome in the Lung
A Review

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Key Words: Churg-Strauss syndrome; Allergic angiitis and granulomatosis; Eosinophilic pneumonia; Wegener granulomatosis; Eosinophilic lung disease

Abstract

Churg-Strauss syndrome is a rare systemic vasculitis occurring in patients with asthma and blood eosinophilia. Lungs, skin, and nervous system are the most common sites of involvement, although many other organs are affected frequently. The diagnosis often is established from clinical findings or biopsy of extrapulmonary sites, and lung biopsy is performed infrequently. The classic pathologic findings in the lung include a combination of eosinophilic pneumonia, granulomatous inflammation, and vasculitis. All 3 features may not be present in every case, however, and diagnosis often requires careful correlation of the clinical and pathologic findings. The differential diagnosis in the lung includes diseases that are associated with eosinophil infiltrates or a combination of eosinophil infiltrates and granulomatous inflammation. Distinguishing these various diseases from Churg-Strauss syndrome is especially important, since many are more common than Churg-Strauss syndrome, and treatment is usually different.

Churg-Strauss syndrome (also known as allergic angiitis and granulomatosis) is a rare systemic vasculitis that occurs exclusively in people with asthma and is associated with blood and tissue eosinophilia. A recent consensus conference on the nomenclature of the systemic vasculitides defined it as “eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and eosinophilia.”1 Clinical criteria for diagnosis include the combination of asthma, blood eosinophilia greater than 1,500/µL (1.5 × 10⁹/L), and evidence of vasculitis involving 2 or more extrapulmonary organs.2 Biopsies may be performed to confirm the diagnosis and most commonly are from skin, nerve, or muscle. Lung biopsies are performed infrequently.

Clinical Features

Churg-Strauss syndrome occurs mainly in middle-aged adults. The mean age of onset is 38 years, although there is a wide age range, and the disease can affect children and elderly people.3 Overall, there seems to be no sex preference, although a few series have noted a male predominance.4,5 Patients have a history of asthma that is most often of adult onset, usually in the fourth decade. Allergic rhinitis, nasal polyps, and sinusitis are common accompanying features. Some investigators have suggested that there are 3 phases to the disease: a prodromal phase with allergic rhinitis that may be present for years and is followed by asthma, a second phase characterized by blood and tissue eosinophilia with eosinophilic pneumonia or eosinophilic gastroenteritis, and a third phase characterized by systemic vasculitis.2 The disease has been reported in people with asthma treated with
Am J Clin Pathol 2000;114:767-772 © American Society of Clinical Pathologists

leukotriene receptor antagonists, such as montelukast and zafirlukast. It is thought that the decreased corticosteroid dosage needed to control asthma symptoms in patients receiving leukotriene receptor antagonists unmask an underlying vasculitis that previously had been controlled by the corticosteroids.

Systemic symptoms, including fever and weight loss, are observed in most patients at the initial examination. Pulmonary infiltrates, cutaneous lesions, and neuropathy are common manifestations, each occurring in two thirds or more of patients. The most common chest radiographic findings include transient patchy alveolar opacities, while diffuse interstitial infiltrates or nodular densities occur infrequently. Purpura and subcutaneous nodules are the usual skin manifestations, while peripheral neuropathy, especially mononeuritis multiplex, is the characteristic neurologic finding. Other common sites of involvement include the gastrointestinal system with abdominal pain, diarrhea, or bleeding; heart with congestive heart failure, cardiomyopathy, and pericardial effusion; and kidney with focal segmental glomerulonephritis that is generally mild. Blood eosinophilia is present in all patients and is usually extremely high, averaging greater than 1,000/µL (1 × 10⁹/L). Approxi-
mately two thirds of patients have a positive P-ANCA (antineutrophil cytoplasmic autoantibody) test result.

Most patients are treated with corticosteroids, although immunosuppressive drugs, usually cyclophosphamide, may be added in some cases. The prognosis is good, with remission occurring in the majority of patients. Cardiac involvement with myocardial infarction or congestive heart failure is the most common cause of death.

Pathologic Findings

There are surprisingly few detailed pathologic descriptions of the lung findings in Churg-Strauss syndrome. Part of the problem is that tissue biopsy is not necessary for diagnosis in every case, and sites other than lung (especially skin, muscle, and nerve) are sampled more often. For example, only 2 of 39 biopsies in the series reported by Chumbley et al were taken from lung. The original pathologic description by Churg and Strauss was based on the findings in 10 autopsies and 3 skin biopsy specimens. The most detailed histologic description was supplied by Koss et al, who reported the findings in 3 lung biopsy specimens and 1 autopsy.

A spectrum of histologic changes is found in the lung in Churg-Strauss syndrome. As in other organs, classically described findings include the combination of tissue infiltration by eosinophils, necrotizing vasculitis, and extravascular granulomas. Tissue eosinophilia is manifested by areas of eosinophilic pneumonia that are characterized by the accumulation within alveolar spaces of large numbers of eosinophils and macrophages accompanied by alveolar septal expansion by a chronic inflammatory cell infiltrate containing numerous eosinophils and macrophages. Eosinophilic abscesses may occur, and parenchymal necrosis is sometimes prominent. Vasculitis typically accompanies the eosinophilic pneumonia and is characterized by intimal and medial infiltration by chronic inflammation containing numerous eosinophils. It may show granulomatous features or contain numerous giant cells reminiscent of giant cell arteritis and fibrinoid necrosis is sometimes present. Necrotizing granulomas are frequently found in the adjacent parenchyma. They may be composed of large foci of necrosis surrounded by a rim of epithelioid histiocytes, or they may consist of small aggregates of epithelioid histiocytes arranged with their long axes perpendicular to the center, much like the spokes of a wheel (so-called palisaded granulomas).

Although the combination of eosinophilic pneumonia, vasculitis, and granulomatous inflammation is considered diagnostic of Churg-Strauss syndrome, and it was present in the 4 cases described by Koss et al, all 3 histologic lesions often are not found together in 1 organ. The original autopsy study reported by Churg and Strauss for example, described eosinophilic pneumonia-like areas in only one half of the cases, active pulmonary vasculitis in 3 of 10, and extravascular lung granulomas in 2 of 10. Lanham et al further emphasized that the 3 histologic components coincided in a given tissue in only 13% of biopsy specimens and 24% of autopsies. These observations underscore the need for careful clinical and pathologic correlation to establish the diagnosis, especially in cases that do not show the full spectrum of histologic changes.

Differential Diagnosis

The histologic differential diagnosis of Churg-Strauss syndrome in the lung includes disorders associated with a prominent eosinophil infiltrate or a combination of

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Pathologic Diagnosis of Churg-Strauss Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classic diagnostic findings:</strong> Eosinophilic pneumonia, necrotizing vasculitis, and granulomatous inflammation</td>
<td></td>
</tr>
<tr>
<td><strong>Highly suggestive findings (need clinicopathologic correlation):</strong> Eosinophilic pneumonia and necrotizing vasculitis</td>
<td></td>
</tr>
<tr>
<td><strong>Suggestive findings (need clinicopathologic correlation):</strong> Eosinophilic pneumonia and parenchymal necrosis</td>
<td></td>
</tr>
<tr>
<td>Common, but not diagnostic finding (more likely an isolated finding unrelated to Churg-Strauss syndrome): Eosinophilic pneumonia</td>
<td></td>
</tr>
</tbody>
</table>

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Uncomplicated chronic eosinophilic pneumonia is probably the most important lesion to distinguish from Churg-Strauss syndrome, since it is relatively common and usually has less severe clinical implications. It often occurs in people with asthma, and blood eosinophilia may be present, although the degree of eosinophilia is usually not as great as in Churg-Strauss syndrome. Eosinophilic pneumonia is characterized by a mixture of eosinophils and macrophages within alveolar spaces associated with a chronic interstitial pneumonia containing numerous eosinophils. Although there may be eosinophil infiltration of blood vessel walls, this

eosinophils and granulomatous inflammation. Features helpful in the differential diagnosis of these conditions are summarized in Table 3.

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feature is not prominent, and a necrotizing vasculitis is not present. Necrotizing granulomas, likewise, are not a feature. Collections of necrotic eosinophils may be found within air spaces (so-called eosinophilic abscesses), but the necrosis does not extend into adjacent lung parenchyma. It is possible for biopsy specimens in Churg-Strauss syndrome to show only eosinophilic pneumonia, however, and in those cases, the clinical findings as described earlier are necessary to establish the diagnosis. An acute variant of eosinophilic pneumonia was described in which patients develop respiratory failure. It is characterized by areas of diffuse alveolar damage in addition to the eosinophil infiltration.14

Hypereosinophilic syndrome is a rare condition characterized by persistent blood and bone marrow eosinophilia lasting longer than 6 months associated with evidence of tissue infiltration by eosinophils.15 Heart, skin, nervous system, lungs, gastrointestinal tract, liver, and spleen frequently are involved. The most serious complications result from cardiac or central nervous system dysfunction. Most patients respond to corticosteroid therapy, and hydroxyurea or interferon alfa have been used in refractory cases. Although there may be some overlap with Churg-Strauss

### Table 2
Differential Diagnosis of Churg-Strauss Syndrome in the Lung

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>CSS</th>
<th>CEP</th>
<th>HES</th>
<th>BCG</th>
<th>WG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophilic pneumonia (chronic or acute)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hypereosinophilic syndrome</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bronchocentric granulomatosis (allergic bronchopulmonary aspergillosis)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Wegener granulomatosis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Miscellaneous (infections, dirofilarial nodules, eosinophilic vascular infiltration of pneumothorax)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### Table 3
Contrasting Features of Churg-Strauss Syndrome and Major Conditions in the Histologic Differential Diagnosis

<table>
<thead>
<tr>
<th>Feature</th>
<th>CSS</th>
<th>CEP</th>
<th>HES</th>
<th>BCG</th>
<th>WG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood eosinophilia</td>
<td>Yes</td>
<td>Occasionally present</td>
<td>Yes, high</td>
<td>Yes</td>
<td>Rare</td>
</tr>
<tr>
<td>Asthma</td>
<td>Yes</td>
<td>Occasionally present</td>
<td>No</td>
<td>Frequently present</td>
<td>No</td>
</tr>
<tr>
<td>Extrapulmonary involvement ANCA</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Eosinophilic pneumonia</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Necrotizing vasculitis</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Necrotizing granuloma</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ANCA, antineutrophil cytoplasmic autoantibody; BCG, bronchocentric granulomatosis; CEP, chronic eosinophilic pneumonia; CSS, Churg-Strauss syndrome; HES, hypereosinophilic syndrome; WG, Wegener granulomatosis.
syndrome, the absence of asthma clinically and vasculitis and granulomas pathologically distinguishes these 2 conditions.

Bronchocentric granulomatosis is a rare disease with an unknown cause in half the cases, but due to allergic bronchopulmonary aspergillosis in the other half.16 In the latter situation, the patients usually have asthma with blood eosinophilia along with systemic symptoms and pulmonary infiltrates. Lung biopsy shows necrotizing granulomatous inflammation that centers on and replaces bronchioles. Eosinophils are usually prominent in the surrounding parenchyma, and areas of eosinophilic pneumonia may be present. The appearance differs from that of Churg-Strauss syndrome because of the exquisitely bronchocentric location of the granulomatous inflammation and by the absence of a necrotizing vasculitis. Also, many patients with bronchocentric granulomatosis have accompanying mucoid impaction of bronchi. This lesion is characterized by dilated bronchi filled with mucin containing lamellated rows of necrotic eosinophils and Charcot-Leyden crystals (so-called allergic mucin) and often also fungal hyphae. Clinically, blood eosinophilia is usually not as high as in Churg-Strauss syndrome, and extrapulmonary involvement is not a feature.

Rare cases of Wegener granulomatosis have been described in which tissue eosinophilia is a prominent feature in the lung.17,18 Blood eosinophilia has been present in some cases as well, but none of the patients have had asthma. These cases differ pathologically from Churg-Strauss syndrome in that areas resembling eosinophilic pneumonia are not present. Rather, the eosinophil infiltrate is present within and around the granulomatous inflammation. In difficult cases, however, clinical and laboratory findings should help make the distinction, although rare patients with overlapping features of both diseases have been described.19

A number of other conditions may be associated with tissue eosinophilia and granulomatous inflammation and, thus, may enter the differential diagnosis of Churg-Strauss syndrome. Infections are the most important, and coccidioidomycosis, especially, is known to cause this reaction.20,21 A careful search for organisms by using special stains is warranted in all cases and should obviate the problem. Dirofilarial nodules often resemble necrotizing granulomas and may have a surrounding prominent eosinophil infiltrate.22 They are usually solitary nodular lesions, however, and although vascular inflammation may be present, a necrotizing vasculitis does not occur. In addition, the worm should be easily visible within blood vessel lumens in the necrotic zones. A perivascular and interstitial infiltrate of eosinophils has been described in patients with pneumothorax and presumably is related to chest tube placement.23 It is an isolated finding without granulomatous inflammation in a clinical situation that has no features suggestive of Churg-Strauss syndrome. Eosinophils are often prominent in cases of eosinophilic granuloma, but diagnosis should not be difficult, since Langerhans cells constitute the main cellular infiltrate, and true granulomatous inflammation is absent.

References


