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A Review of Churg–Strauss syndrome (CSS)

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ABSTRACT

Churg–Strauss syndrome (CSS) is a rare systemic vasculitis of the small and medium sized blood vessels. The triad of asthma, sinusitis and hypereosinophilia is characteristic of CSS. However, it can affect any organ system with predominance for the skin, respiratory, neurological, gastrointestinal and cardiovascular systems. The natural history of the condition has been described in three phases: prodromal, eosinophilic and vasculitic. Diffuse organ involvement of Churg-Strauss syndrome, especially cardiovascular and rare involvement of the CNS and renal system, suggests a poorer prognosis than usual, and can be fatal. The cause of Churg-Strauss syndrome is unknown, but its characteristic histological findings and association with asthma distinguish it from other vasculitides. Such classification criteria can assist in making the diagnosis of CSS and differentiating the condition from other diseases that cause pulmonary infiltrates with eosinophilia including allergic bronchopulmonary aspergillosis, acute and chronic eosinophilic pneumonia, idiopathic hypereosinophilic syndrome, certain parasitic infections and drug reactions. The treatment of patients with CSS must be tailored to individual patients according to the presence of poor prognostic factors. A combination of high-dose corticosteroids and cyclophosphamide is still the gold standard for the treatment of severe cases, but the use of biological agents such as rituximab or mepolizumab seems to be a promising therapeutic alternative.

INTRODUCTION

Churg-Strauss Syndrome (CSS), also known as allergic granulomatosis and angiitis, is a rare autoimmune disorder characterized by inflammation of blood vessels (vasculitis) and the presence of eosinophils (a type of white blood cell). It is part of the spectrum of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides but is distinct due to its strong association with asthma and eosinophilia. [(1)]

However, because individuals often presented with varying combinations of these features, and rarely all 3, more clinically relevant diagnostic criteria were later developed.

Lanham et al proposed a definition based on slightly different characteristics, as mentioned below.

- Bronchial asthma
- Blood eosinophilia of more than 1500 eosinophils per mL
- Vasculitis involving at least 2 extrapulmonary organs [2]

An unintended drawback of these diagnostic criteria was that they often led to delayed diagnosis, as they required the involvement of 2 or more organ systems. This delay in diagnosis was unfavorable because early treatment can prevent complications.

In 1990, the American College of Rheumatology (ACR) proposed new classification criteria for EGPA, requiring the presence of 4 out of 6 features, as mentioned below, for diagnosis. These criteria demonstrated a specificity of 99.7% and a sensitivity of 85% for diagnosis.

- Asthma
- Migratory infiltrates in the lung
- Paranasal sinus abnormalities
- Mono- or polyneuropathy
- Peripheral blood eosinophilia (>10% of total leukocyte count)
- Eosinophilic tissue infiltrates in the biopsy

At the Chapel Hill Consensus Conference in 1994, EGPA was defined as "eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels, associated with asthma and eosinophilia."[3] This definition was significant because it excluded biopsy as a necessity for diagnosis, facilitating the early recognition of cases characterized solely by asthma and eosinophilia in tissue or blood.

Epidemiology

Churg-Strauss Syndrome is a rare disorder, affecting approximately “1 in 20,000 people”globally.

Key epidemiological points include:

- **Age:** Typically occurs in adults aged "40–60 years", though it can affect younger individuals.
- **Sex:** Slightly more common in **males** than females.
- **Geographical Distribution:** No significant geographical variations have been reported, but prevalence may vary based on the incidence of asthma and other risk factors.
- **Prevalence:** Due to its rarity, exact prevalence data are limited, but it is considered one of the least common forms of vasculitis.[4]

Causes

The exact cause of Churg-Strauss Syndrome remains unknown, but it is believed to result from an abnormal immune response.

Key factors include:

- ✓ **Autoimmune Mechanism:** CSS is thought to arise from an overactive immune system that mistakenly attacks the body's own tissues.
- ✓ **Role of Autoantibodies:** While not as prominent as in other ANCA-associated vasculitides, some patients may have detectable autoantibodies.
- ✓ **Genetic Factors:** There may be a genetic predisposition, though specific genes have not been definitively identified.
- ✓ **Environmental Triggers:** Potential triggers include infections, medications, orenvironmental exposures, though evidence is limited.(4)

Reason

The pathophysiology of Churg-Strauss Syndrome involves several key mechanisms:

1. **Eosinophil Activation:** Eosinophils play a central role in CSS. They release toxic proteins and cytokines that cause tissue damage and inflammation.
2. **Vasculitis:** Inflammation of blood vessels leads to narrowing or blockage, impairing blood flow to organs.
3. **Granuloma Formation:** Immune cells aggregate to form granulomas, which can damage affected tissues.
4. **Immune Dysregulation:** Abnormal activation of T cells and other immune cells contributes to the inflammatory process.[5]

Factors Involved for These Causes

Several factors contribute to the development and progression of Churg-Strauss Syndrome:

- **Cytokines and Chemokines:** Substances like interleukin-5 (IL-5) play a critical role in eosinophil recruitment and activation.
- **Enzyme Receptors:** Eosinophils release enzymes (e.g., major basic protein, eosinophil peroxidase) that damage tissues.
- **Signaling Pathways:** Dysregulation of signaling pathways involved in immune cell activation and migration is implicated.
- **Genetic Factors:** Variations in genes related to immune regulation may
- increase susceptibility.[6][7][8]

Pathophysiology

The pathogenesis and clinical phenotype of EGPA follow a dichotomy of either eosinophil-mediated damage or ANCA-induced endothelial injury.

Eosinophils

An initial T_H2-mediated immune response triggers the margination of eosinophils. Their presence in active disease likely results from increased synthesis, enhanced extravasation, and prolonged survival in target tissues. IL-3 and IL-5, produced by T_H2 lymphocytes, are key regulators of eosinophil maturation, release, and survival in the bloodstream. Serum levels of IL-5 consistently correlate with disease activity and decrease with the initiation of immunosuppressive therapy.[9]

Eosinophils release proteins such as eosinophil cationic protein (ECP), eosinophil peroxidases, eosinophil-derived neurotoxins, and eosinophil granule major basic protein, which are directly involved in mediating tissue damage. Histological findings in EGPA typically show eosinophilic infiltrates in the walls of small- and medium-sized blood vessels and in extravascular tissue spaces. During acute pulmonary exacerbations of EGPA, bronchoalveolar lavage fluid is also rich in eosinophils, similar to what is seen in acute or chronic eosinophilic pneumonia. Additionally, extravascular eosinophilic granulomas are often observed, particularly in the gastrointestinal tract.[10]

IL-5 mediates eosinophilic tissue infiltration, as shown by the persistence of tissue major basic protein despite therapy with mepolizumab, which leads to complete downregulation of IL-5 titers. IL-4 and IL-13, other potent cytokines associated with the T_H2 immune response, may also play a significant role in tissue infiltration and degranulation of eosinophils.[24] Peripheral blood eosinophils in EGPA exhibit activation markers such as CD69 and CD25, along with elevated serum levels of IL-5 and ECP.[25][26]

Anti neutrophil cytoplasmic autoantibody

In EGPA, approximately 60% of patients are ANCA-negative, around 35% are MPO-positive, and about 5% are PR3-positive. The presence of ANCA correlates with a higher incidence of glomerulonephritis, mononeuritis, and biopsy-proven vasculitis. Alveolar hemorrhage is also more commonly observed in ANCA-positive patients.[11]

Infusion of anti-MPO-ANCA in wild-type and Rag2 knockout mice resulted in severe necrotizing and crescentic glomerulonephritis. The hypothesis of two clinical subsets in EGPA has been further supported by recent findings showing an increased frequency of HLA-DRB4 in ANCA-positive EGPA patients. Additionally, emerging evidence suggests that T_H17 lymphocytes play a role in the occurrence and maintenance of the vasculitis response, particularly concerning the balance between T_H17 and Treg cells.[28] However, endothelial injury in AAV is primarily mediated by neutrophils through the generation of reactive oxygen species and proteolytic enzymes from cytoplasmic granules.

In their retrospective study of 74 EGPA patients, Keogh and Specks reported an increased prevalence of neuropathy and central nervous system (CNS) involvement in ANCA-positive patients.[12] Since then, increased efforts have been made to identify clinical phenotypes associated with ANCA positivity. Several studies have shown that the presentations of ANCA-positive and ANCA-negative EGPA differ significantly. Patients with ANCA positivity are more likely to have constitutional symptoms, mononeuritis, crescentic glomerulonephritis, and pulmonary capillaritis. Patients who are ANCA-negative are more likely to have higher levels of eosinophilic pulmonary infiltration and cardiac disease (of note, cardiac disease is a primary cause of mortality in patients with refractory EGPA).

Signs and Symptoms

Churg-Strauss Syndrome presents with a wide range of symptoms due to its multisystem involvement.

Common signs and symptoms include:

- ✓ **Respiratory Symptoms:** Asthma or worsening asthma, sinus pain/congestion, nasal polyps.
- ✓ **Skin Manifestations:** Rash, purpura, nodules, or livedoreticularis.
- ✓ **Musculoskeletal Pain:** Joint and muscle pain, arthritis.
- ✓ **Neurological Symptoms:** Peripheral neuropathy (numbness, tingling, weakness), mononeuritis multiplex.
- ✓ **Gastrointestinal Issues:** Abdominal pain, nausea, vomiting, diarrhea, gastrointestinal bleeding.
- ✓ **Cardiovascular Involvement:** Myocarditis, pericarditis, arrhythmias.
- ✓ **Renal Involvement:** Rarely, kidney damage can occur.

Diagnosis

Diagnosing Churg-Strauss Syndrome involves a combination of clinical evaluation, laboratory tests, imaging studies, and sometimes biopsy.

Key diagnostic steps include:

1.Clinical Evaluation:

Assessing symptoms and medical history, particularly the presence of asthma and eosinophilia.

2.Laboratory Tests:

Complete Blood Count (CBC): Elevated eosinophils (>10% or >1.5 × 10^9/L).

Serum Eosinophil Cationic Protein (ECP): Elevated levels indicate active eosinophilic inflammation.

Antineutrophil Cytoplasmic Antibodies (ANCAs): May be

positive in some patients, though not as commonly as in other vasculitides.

3.Imaging Studies:

Chest X-ray/CT Scan: To evaluate lung involvement.

Electromyography/Nerve Conduction Studies: To assess peripheral neuropathy.

4.Biopsy: Confirmatory test showing characteristic findings such as eosinophilic infiltration and granulomatous changes in affected tissues (e.g., skin, lungs, nerves).[13]

Treatment & Management

Treatment for Churg-Strauss Syndrome aims to control inflammation, suppress the immune system, and prevent organ damage.

Key management strategies include:

1. Corticosteroids:

Prednisone: High-dose corticosteroids are the cornerstone of treatment, often used in conjunction with immunosuppressive agents.[14],[15]

Tapering: Gradual reduction of corticosteroids is necessary to minimize side effects.

2. Immunosuppressive Agents:

Cyclophosphamide: Used in severe cases to induce remission.

Methotrexate, Azathioprine, or Rituximab: Alternative options for maintenance therapy or in refractory cases. .[16]

3. Other Therapies:

Monoclonal Antibodies: Biologics like rituximab target B cells and are effective in some patients.

Symptomatic Treatment: Managing asthma with inhaled corticosteroids and bronchodilators.

4. Monitoring:

- Regular follow-up to monitor disease activity and adjust treatment as needed.
- Close monitoring for complications, especially cardiovascular and renal involvement.

Can you live a long life with CSS ?

With effective treatment, you can have a normal life expectancy with CSS. In the advanced stages of the disease, complications like organ failure can affect your life expectancy. But treatment can often stop or reverse organ failure. With treatment, CSS survival rates after five years are over 80%.[17][18]

CONCLUSION

Churg-Strauss Syndrome is a rare but serious autoimmune disorder characterized by vasculitis, eosinophilia, and asthma Early diagnosis and aggressive treatment are crucial to managing the disease and preventing long-term complications. With appropriate therapy, many patients achieve remission and maintain a good quality of life.[19][20]

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