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CHURG–STRAUSS SYNDROME: A REVIEW

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ABSTRACT

Churg–Strauss syndrome (CSS) is a rare diffusive granulomatous necrotizing small vessel vasculitis characterized by the presence of asthma, sinusitis, and hypereosinophilia. The cause of this allergic angiitis and granulomatosis is unknown. Other common manifestations are pulmonary infiltrates, skin, gastrointestinal, and cardiovascular involvement. No data have been reported regarding the role of immune complexes or cell mediated mechanisms in this disease, although autoimmunity is evident with the presence hypergammaglobulinemia, increased levels of IgE and Antineutrophil cytoplasmic antibody (positive in 40%). Th2 response is of special importance in the up regulation of different interleukins such as IL-4, IL-13, and IL-5. Th1 and Th17 responses are also of significance. Activated eosinophils have a prolonged survival and probably cause tissue damage by releasing eosinophil granule proteins, while their tissue recruitment can be regulated by chemokines such as eotaxin-3 and CCL17. The aim of this review is to find out the possibility of new therapeutic approaches to Churg- Strauss Syndrome.

KEYWORDS: *Churg–Strauss syndrome, allergic angiitis, hypereosinophilia and asthma, sinusitis, Antineutrophil cytoplasmic antibody.*

INTRODUCTION

Churg–Strauss syndrome (CSS) is a rare diffusive small and medium vessel vasculitis characterized by eosinophilic infiltration of organs with necrotizing vasculitis and interstitial and perivascular granulomas. Three phases have been described in the natural history of the disease (prodromal, eosinophilic, and vasculitic phases) although they do not always occur successively. Initial records show CSS is a condition highly responsive to steroids.

In a study American College of Rheumatology (ACR) has proposed six criteria for CSS—four being necessary for CSS to be diagnosed with 85% sensitivity and 99.7% specificity. Even though allergic asthma, rhinosinusitis and eosinophilia is a part of CSS, most reports consider this vasculitis a disease by itself or a variant of asthma which occurs from immune system interference such as with the use of medications such as leukotrienes or inhaled corticosteroids—both conditions resulting from sudden withdrawal of oral steroids in chronic severe asthma. The condition must be distinguished from aspirin-induced asthma (AIA), mould-induced allergy allergic bronchopulmonary aspergillosis (ABPA), allergy to drugs (such as minocycline) and parasitic infections.[1]

The knowledge and understanding of EGPA has evolved in recent years. Since anti-neutrophil cytoplasmic antibodies (ANCA) have been found in a proportion of patients, EGPA has subsequently been included in the spectrum of ANCA-associated vasculitis (AAV), along with GPA and microscopic polyangiitis (MPA).[4] Several studies have elucidated the role of immune mechanisms, identifying genetic associations with HLA-DRB4 while recognizing new diagnostic and follow-up biomarkers (e.g., eotaxin-3).

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History

In a case series of 13 patients in 1951, Jacob Churg and Lotte Strauss first described the entity based on autopsy findings. They all had a familiar pattern of illness with severe asthma, fever, blood eosinophilia and autopsy evidence of granulomatous necrotizing vasculitis.[2] They named the disease allergic granulomatosis and angiitis. Their classic definition and diagnosis of the disease shows all 3 features of:

- Eosinophilic infiltration
- Necrotizing vasculitis of small- and medium-sized vessels
- Extravascular granuloma formation

However, as individuals presented a wide variance of these features, rarely with the presence of all 3 features, more clinically relevant diagnostic criteria became necessary.

Lanham et al. proposed a definition based on.

- Bronchial asthma
- Vasculitis involving at least 2 extrapulmonary organs
- Blood eosinophilia more than 1500/microliter

American College of Rheumatology proposed new classification criteria in 1990 where 4 out of 6 features needed to be identified in CSS:

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

It rendered a 99.7% specificity and 85% sensitivity for diagnosis.

The Chapel Hill consensus conference in 1994 came up with a definition of EGPA as "eosinophil-rich and granulomatous inflammation involving respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels associated with asthma and eosinophilia." Impotance of above definition was its exclusion of biopsy as a necessity for diagnosis and therefore its ability to recognize early cases with only asthma and tissue and blood eosinophilia.[3]

Etiology

There have been efforts in recent years to sub-classify clinical phenotypes of eosinophilic granulomatosis with polyangiitis based on the presence or absence of vasculitis, somewhat counterintuitive to the nomenclature itself.

Patients who are ANCA positive (reported around 40% of all patients with EGPA) tend to have a vasculitic phenotype and are more common to have myalgia, migrating polyarthralgia, weight loss, mononeuritis multiplex, and renal involvement either as crescentic or necrotizing glomerulonephritis.

Conversely, patients without ANCA positivity tend to have an eosinophilic phenotype with a higher incidence of myocarditis. The presence of ANCA alone, however, is not the absolute correlate to vasculitis. About 47% of patients in a study by Cottin et al. had vasculitis without seropositivity for ANCA, while 29% were positive for myeloperoxidase ANCA without the presence of vasculitis.

The rest of the patients will fall into the eosinophilic asthma phenotype. It is important to recognize that subgroup early, particularly in the presence of myocarditis with no other evidence of vasculitis. Overly depending on the presence of vasculitis to diagnose EGPA may result in missing those patients with eosinophilic asthma who may otherwise benefit from early targeted therapy. The primary trigger in pathogenesis in cellular level seems to be an aberrant T-helper cell pathway.[4]

Pathophysiology

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

Eosinophils

TH2-mediated immune response provokes the margination of eosinophils. Eosinophilic presence in active disease is likely a consequence of increased synthesis, enhanced extravasation as well as prolonged survival in target tissues. IL-3 and IL-5, produced by TH-2 lymphocytes, are the key regulators in maturation and release of eosinophils, as well as their survival in blood. Serum levels of IL-5 correlate consistently with disease activity and go down with the initiation of immunosuppressive therapy.

Epithelial and endothelial cells, when activated by Th-2 type cytokines, also secrete eosinophil-specific chemokines like eotaxin 3(CCL26), CCL17, and CCL22.

They act on CCR4 receptors to facilitate the recruitment of eosinophils and effector Th2 cells to the end organs– thus amplifying the immune response. Martorana et al. demonstrated serum levels of CCL26 as a reliable marker for disease activity in CSS.

Eosinophils, in turn, release the cationic proteins like eosinophil cationic protein (ECP), eosinophil peroxidases, eosinophil-derived neurotoxins, and eosinophil granule major basic protein which is directly involved in mediating tissue damage.

Eosinophils also secrete cytokines like IL- 1, IL-3, IL-5, TGF- beta, and vascular endothelial growth factor. IL-5, in turn, plays in an active role in maturation, differentiation, and survival of eosinophils. Histological findings in EGPA are characterized by eosinophilic infiltrates in walls of small and medium-sized blood vessels as well as extravascular tissue spaces. In EGPA with acute pulmonary exacerbations, Bronchoalveolar lavage fluid is also rich in eosinophils, similar to acute or chronic eosinophilic pneumonia. Extravascular eosinophilic granulomas are also observed, particularly in the gastrointestinal tract.

IL- 5 is not the only mediator of eosinophilic tissue infiltration, as has been evidenced by the persistence of tissue. Major Basic Protein (MBP) in spite of therapy with mepolizumab causing complete downregulation of IL5 titers. IL-4 and IL-13 are two other potent cytokines of Th-2 profile immune response and may play an important role in tissue infiltration and degranulation of eosinophils. Peripheral blood eosinophils in EGPA express surface markers of activation like CD69 and CD25 along with a concomitant increase in serum IL-5, and ECP.[5]

Anca

p- ANCA levels increase with antibodies in a perinuclear pattern are seen in approximately 40% of patients with EGPA. Rarely a cytoplasmic pattern with specificity for neutrophil proteinase 3 (c- ANCA) is seen. The presence of ANCA correlates with an increased incidence of glomerulonephritis, mononeuritis, and biopsy-proven vasculitis. Alveolar hemorrhage is also found more often in this group of patients.

Infusion of MPO- ANCA in wild-type and Rag2 knockout mice resulted in severe necrotizing and crescentic glomerulonephritis . The 2 subset hypothesis in clinical phenotyping of EGPA has been further substantiated by a recent demonstration of increased frequency of HLA- DRB4 in EGPA patients with ANCA positivity. There has been some recent evidence of the role of Th17 lymphocytes in the occurrence and maintenance of vasculitis response in the disease, particularly with regards to the balance between Th17 and Treg cells.

Endothelial injury in ANCA associated vasculitis is, however, neutrophil-mediated with the generation of reactive oxygen species and proteolytic enzymes from cytoplasmic granules.[6]

Diagnosis

Conditions that need to be considered in the differential stems from the 2 principal phenotypes of EGPA – eosinophilic lung disease and systemic small and medium vessel vasculitis.

Eosinophilic Lung Diseases Acute and chronic eosinophilic pneumonia, Allergic bronchopulmonary aspergillosis, Bronchocentric granulomatosis, Loffler's syndrome, Idiopathic hypereosinophilic syndrome.

Small and Medium Vessel Vasculitis Granulomatosis with polyangiitis, Polyarteritis nodosa, Microscopic polyangiitis.

Most of the eosinophilic lung diseases are distinguished from EGPA by lack of multisystem involvement except idiopathic hypereosinophilic syndrome, where peripheral eosinophilia more than 1500/cubic mm is a chronic phenomenon lasting beyond 6 months. ANCA is completely absent in hypereosinophilic syndrome, and late-onset asthma is very uncommon. Molecular genetic testing has helped in identifying mutations specific to idiopathic hypereosinophilic syndromes, for example, FIP1-like 1-platelet-derived growth factor receptor–alpha or T-cell antigen receptor rearrangements.

As far as differentiation from other small and medium vessel vasculatures is concerned, renal involvement is much more common in granulomatosis with polyangiitis (GPA), as is evidence of cavitary lung lesions or necrotizing upper airway lesions. Septal nasal perforation often reported in GPA does not occur in EGPA.[7]

Treatment / Management

Early recognition and ability to use corticosteroids and immunosuppressants have significantly changed the natural history of EGPA, improving prognosis and overall survival.

Corticosteroids help in reduction of eosinophil burden in blood and tissues and inhibit the prolongation of eosinophil survival in extravascular tissues. While the initial dose of therapy for a non-severe disease has been 1 mg/kbw of oral prednisone, induction of remission in severe disease is often better achieved with pulse dose methylprednisolone with or without cyclophosphamide.

Refractory Disease

Treatment strategy for frequent relapse or severe refractory disease somewhat depends on end-organ involvement.

Plasmapheresis is effective and preferred in rapidly progressive glomerulonephritis or alveolar hemorrhage.

Intravenous immunoglobulin, on the other hand, is considered in neuropathy or cardiomyopathy refractory to conventional therapy.[8]

Based on smaller case series and well-evidenced success with other ANCA-associated vasculitis, rituximab (anti CD 20) and tumor necrosis factor inhibitors (TNF) are considered as an alternative option.

There has also been some success with interferon-alfa, for induction of remission in seven CSS patients refractory to cyclophosphamide. It down-regulates expression of IL-5 (known to have an increased titer in CSS) and IL-13, apart from modulating eosinophil activating cytokines in CSS. However, it was unable to reduce the rate of relapses after one year of follow-up.

There have also been recent reports of successful use of mepolizumab–an anti-IL-5 monoclonal antibody as well as omalizumab (recombinant humanized monoclonal anti-IVIG E antibody) in refractory EGPA. Both drugs have already been in use for moderate to severe persistent asthma with allergic phenotypes.

The challenge, as evident in multiple studies, is to maintain remission with a high incidence of relapses. Although agents of choice have been well established, the ideal duration of treatment, and which drugs to stop first is still not well standardized.[9]

Treatment Strategies for Eosinophilic Granulomatosis with Polyangiitis

Induction of Remission

Without Poor Prognosis

- Oral prednisone: 1 mg/kg daily for 3 weeks, then tapering 5 mg every 10 days to 0.5 mg/kg. Then taper 2.5 mg every 10 days to the minimal effective dosage, or until definite withdrawal.
- Intravenous methylprednisolone pulse (15 mg/kg) followed by oral prednisone as above.

Relapse

- Oral azathioprine 2/mg/kg daily for at least 6 months.
- Cyclophosphamide pulses (600 mg/m2) every 2 weeks for 1 month, then every 4 weeks.

With Poor Prognosis

- Three consecutive methylprednisolone pulses (15 mg/kg) on day 1 to 3 plus oral prednisone.

Plus

- Either 12 cyclophosphamide pulses (600 mg/m2) every 2 weeks for 1 month then every 4 weeks after that.

Or

- Short-course of cyclophosphamide (oral 2 mg/kg) for 3 months or 6 cyclophosphamide pulses (600 mg/m2) every 2 weeks for 1 month, then every 4 weeks after that, followed by azathioprine 2 mg/kg for 1 year or more.[10]

Maintenance of Remission

- Methotrexate (10 to 25 mg per week)
- Cyclosporin A (1.5 to 2.5 mg/kg per day)
- Azathioprine (2 mg/kg per day)

Refractory Disease

- Plasma exchange
- IVIG (0.4 g/kg per day for 5 days)
- Interferon-alfa (3 million IU 3 times per week subcutaneously)
- TNF inhibitors: infliximab, etanercept, adalimumab
- Rituximab (325 mg/m2 for 4 consecutive weeks).[11]

DISCUSSION

Churg–Strauss syndrome was first described in 1951 by Churg and Strauss.
It is a rare systemic vasculitis (2.5 cases/100 000 adults/year) occurring exclusively in people with asthma and is associated with blood and tissue eosinophilia. The most commonly involved organ is the lung followed by the skin. CSS, however, can affect any organ system of the body.

The clinical features develop in several sequential phases.

1. Prodromal phase: Characterized by atopic disease, allergic rhinitis and asthma.
2. Eosinophilic phase: Peripheral blood eosinophilia and eosinophilic infiltration of many organs and commonly lung, seen.
3. Vasculitic phase: Can have life-threatening sequelae and heralded by constitutional symptoms. Skin involvement common.[12]

Asthma is the cardinal feature of CSS and precedes vasculitic phase. It presents as a chronic severe form and requires frequent or long-term courses of systemic steroids. Upper airway abnormality in the form of allergic rhinitis, recurrent sinusitis, and nasal polyposis is fairly common.

Involvement of skin is a frequent feature of the vasculitic phase and presents as tender subcutaneous nodules, palpable purpura and hemorrhagic lesions. Cardiac and neurological involvement is often seen; cardiac complications in form of infarction and arrythmias are responsible for 50% of deaths. Early diagnosis and treatment prevents organ damage and mortality. However confirming the diagnosis is difficult as individual manifestations occur in isolation and lung parenchymal involvement is not universal. The laboratory abnormalities are nonspecific and includes eosinophilia, high IgE, raised acute phase reactants, hypergammaglobulineamia.[13]

CONCLUSION

It is a rare systemic vasculitis (2.5 cases/100 000 adults/year) occurring exclusively in people with asthma and is associated with blood and tissue eosinophilia. The present study mainly focused on the therapeutic approaches. Early diagnosis and treatment prevents organ damage and mortality. However confirming the diagnosis is difficult as individual manifestations occur in isolation and lung parenchymal involvement is not universal. The challenge, as evident in multiple studies, is to maintain remission with a high incidence of relapses. Although agents of choice have been well established, the ideal duration of treatment, and which drugs to stop first is still not well standardized. Further standardization for new treatment methods is very important for future study.

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