EOSINOPHILIC GRANULOMATOSIS WITH POLYANGITIS

(CHURG STRAUSS SYNDROME)

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Eosinophilic Granulomatosis with Polyangitis (EGPA), earlier known as Churg Strauss syndrome, is the least common form of antineutrophil cytoplasmic antibody (ANCA) – associated vasculitis (AAV)[1,2]. Very few cases are reported from India till date. EGPA is currently defined as eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium size vessels and associated with asthma and eosinophilia. Nasal polyps are common. ANCA is more frequent when glomerulonephritis is present. Granulomatous and nongranulomatous extravascular inflammation, such as nongranulomatous eosinophil-rich inflammation of lungs, myocardium, and gastrointestinal tract, is also common. Many patients with otherwise typical EGPA do not have glomerulonephritis. Limited expressions of EGPA confined to the upper or lower respiratory tract may occur [3].

Aetiopathogenesis

This small and medium vessel vasculitis (SVV/MVV) is a peculiar form of immune mediated disease involving autoimmune as well as allergic (eosinophilic) pathogenesis. Eosinophils, T and B cells as well as epithelial and endothelial cells are actively involved in the disease process. ANCA activate neutrophils which in turn release chemokines, cytokines, adhesion molecules, etc. Th2 immune response is predominant in EGPA though Th1 and Th17 responses may also contribute to pathogenesis. Eosinophils release eosinophilic cationic protein and neurotoxin which contribute to cardiac and neuropathic manifestations respectively.

Diagnosis of EGPA is usually delayed as its main features (rhinitis and asthma) are extremely common, use of glucocorticoids can suppress clinical disease and extrapulmonary manifestations occur in later stage of the disease. Mean age of clinical manifestation is around 40 years. There is no gender predominance. 40-60% cases of EGPA are p-ANCA (myeloperoxidase MPO) positive. Though the disease does not have any familial preponderance, HLA DR4 appears to be the main genetic risk factor. It appears that ANCA-negative and ANCA-positive patients may have a different genetic background.

Environmental factors in a genetically predisposed individual lead to MPO-ANCA associated disease. Vaccinations, desensitizations and certain drugs are implicated as triggering factors. Drugs implicated include erythromycin and other macrolides, quinine, carbamazepine, plant solution (1 case report), leukotriene receptor antagonists (LTRA) such as montelukast and zafirlukast and omalizumab (monoclonal anti IgE antibody). Glucocorticoid tapering and withdrawal following use of LTRA and omalizumab may unmask latent EGPA in such cases.

Clinical Features

EGPA evolves over years with a wide variety of clinical characteristics [4]. The American College of Rheumatology (ACR) classification criteria (Table 1) are not diagnostic especially in clinical situations where biopsy proof of vasculitis is not available. 3 phases of disease, often overlapping, are as follows:

1. Prodromal – Atopic disease, allergic rhinitis, asthma.

2. Eosinophilic – Peripheral eosinophilia and eosinophilic infiltration of multiple organs especially lungs and gastrointestinal tract.

3. Vasculitic – MVV and SVV manifests as constitutional and systemic features and is associated with granulomatosis (vascular and extra vascular)

Upper respiratory symptoms such as atopy, allergic rhinitis, sinusitis and nasal polyps are common in early stages of disease. Rhinorrhoea, purulent nasal discharge, crusting, epistaxis and otitis may also occur. Half of the patients undergo surgery for their sinonasal problem.

Asthma, a cardinal feature of EGPA, is present for 8-10 years before the onset of vasculitic phase and is poorly controlled on mild to moderate doses of inhaled glucocorticoids. EGPA should be suspected in all cases of late onset asthma especially if it follows chronic upper respiratory symptoms. Lungs are usually involved in EGPA. Transient, symmetric peripheral pulmonary opacities due to eosinophil-rich pulmonary infiltrates with necrotizing granuloma can be seen on radiological examination. These manifest as worsening of asthma. Haemoptysis is rare. Pulmonary manifestations of EGPA need to be differentiated from a few ANCA-negative conditions such as idiopathic hyper-eosinophilic syndrome (absence of asthma), allergic bronchopulmonary aspergillosis (no involvement of other systems) and chronic eosinophilic pneumonia (granulomas are rare).

Peripheral nerve involvement can be due to ANCA related vascular effect (axonal ischaemia) or to neurotoxin secreted by eosinophils. 75% patients suffer from peripheral nerve involvement in the form of mononeuritis multiplex (ANCA induced) and symmetric or asymmetric polyneuropathy (Eosinophil neurotoxin related). Severe pain may accompany peripheral nerve disease.

Fever, malaise, myalgia, polyarthralgia, lymphadenopathy, anorexia and weight loss are general features that can occur at the onset of vasculitic phase. Cutaneous involvement (Fig. 1) can be of various patterns including maculopapular rashes, tender papulonodular lesions on lower extremities, palpable purpura which can become necrotic and haemorrhagic lesions that may turn into extensive ecchymosis. Biopsy of skin nodules can reveal eosinophilic granuloma in 10% cases.

Clinical features of involvement of other organ systems are listed in Table 2. Of particular interest is cardiovascular involvement which occurs in 15-50% patients, may not be symptomatic and carries worse prognosis.

Investigations

Peripheral eosinophilia (> 10%; >1500/cumm) is cardinal feature of EGPA. This is associated with increased IgE levels. ESR and CRP are nonspecific inflammatory markers. Serum creatinine, creatinine kinase and routine urine examination should be obtained in all cases. MPO-ANCA (earlier known as p-ANCA) are positive in 40-60% cases. ANCA negative cases show hypereosinophilic manifestations such as fever, livedo, pleuritis, pulmonary infiltrates, tissue infiltration by eosinophils and cardiac

disease whereas ANCA positive cases develop mononeuritis multiplex, purpura, alveolar haemorrhages, neuropathy, central nervous system disease and glomerulonephritis. Though prognostic value of ANCA is not established, ANCA positive patients are known to have more severe disease. Reappearance of ANCA in a controlled patient may indicate possible recurrence of vasculitis.

Results of pulmonary function tests are consistent with asthma (airflow obstruction) Parenchymal involvement is suggested by decreased vital capacity and also by reduction in diffusion capacity. Chest X-ray and HRCT need to be obtained in suitable cases. Bronchoalveolar lavage (BAL) is a useful investigation to differentiate between eosinophilia (> 30% eosinophils in BAL fluid), infection, haemorrhage and malignancy. Cardiac assessment (ECG, Echocardiography) is necessary in all cases.

Attempts are underway to find reliable markers for disease activity such as eosinophil cationic protein, IL-5 and TARC (thymus and activation-regulated chemokine).

Treatment

Decision for use of drugs is based on Five Factor Score (FFS-Revised) which includes the following [4]:

1. Severe vasculitis-related gastrointestinal involvement
2. Cardiac involvement
3. Serum creatinine level > 150 µmol/L (1.697 mg/dl)
4. Age older than 65
5. Absence of ear, nose, and throat (ENT) symptoms

5 year mortality increases with increasing FFS (9% for 0 and 40% for ≥2).

Management of EGPA includes glucocorticoids (GCs) and immunosuppressants [5]. All patients should be given GC (Prednisolone 1 mg/kg or equivalent) to start with. More severe cases need intravenous pulse methylprednisolone (15 mg/kg) for 3 days followed by oral GC. Most patients with 0 to -1 FFS will respond to GCs alone. Dose of GC should be gradually tapered over next 12-18 months after adequate control of disease. Concomitant therapy for prevention of gastrointestinal adverse reactions, osteoporosis, and infections should be administered to all patients receiving aggressive immunosuppression.

Patients with FFS ≥ 1 should be administered intravenous pulse cyclophosphamide (CYC) (along with mesna to prevent urinary bladder toxicity) in the dose of 15 mg/kg. Initial 3 pulses are administered at fortnightly intervals and further 3-6 pulses every 3 weeks (every 4 weeks later if required). Oral CYC is not recommended in view of possible toxic effects of high cumulative dose. Dose of CYC should be appropriately reduced in patients above age of 60 years and in those with

impaired renal function. Methotrexate (20-25 mg/week oral or parenteral) is suggested as an alternative to CYC in induction treatment of EGPA.

Rituximab (RTX) appears to be an effective agent for induction in relapsing and refractory cases irrespective of ANCA status [6]. Relapses can occur with equal frequency after CYC as well as RTX and can be effectively controlled with retreatment.

Plasmapheresis should be attempted in ANCA positive seriously ill cases not responding to standard therapy. The efficacy of intravenous immunoglobulin and interferon alpha is yet to be established.

Use of azathioprine or methotrexate along with GC is advocated as maintenance therapy on achieving remission after 6-12 months. These drugs should be continued in lowest effective dose for about 18-24 months.

Meprolizumab (humanized monoclonal IL-5 antibody) and omalizumab (anti IgE monoclonal antibody) are currently being studied for use in EGPA.

References

1. Pagnoux C. Churg-Strauss Syndrome: Evolving Concepts. Discov Med 2010;9(46):243-252
2. Sinico RA, Bottero P. Churg–Strauss angitis. Best Practice & Research Clinical Rheumatology 2009; 23:355–366.
3. Jennette JC, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis & Rheumatism 2013;65 (1):1-11
4. Comarmond C, et al. Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss) - Clinical Characteristics and Long-Term Follow up of the 383 Patients Enrolled in the French Vasculitis Study Group Cohort. Arthritis & Rheumatism 2013;65(1):270-281
5. Mukhtyar C, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis 2009;68:310-317
6. J.Thiel J, Hässler F, Salzer U, Voll RE, Venhoff N. Rituximab in the treatment of refractory or relapsing eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). Arthritis Research & Therapy 2013;15:R133

Table I

ACR classification criteria for Churg-Strauss syndrome (1990)

	Feature
1	Asthma
2	Eosinophilia > 10%

3	Neuropathy, mono or poly
4	Pulmonary infiltrates, nonfixed
5	Paranasal sinus abnormality
6	Extravascular eosinophils

At least 4 of these 6 criteria need to be positive for classification purpose. The presence of any 4 or more of the 6 criteria yields a sensitivity of 85% and a specificity of 99.7%.

Table 2

Systemic involvement in EGPA

	Organ-system	Features
1	Renal	Proteinuria, microscopic haematuria, nephrotic syndrome, necrotizing glomerulonephritis
2	Abdominal	Abdominal pain, acute abdomen, cholecystitis, pancreatitis, ascitis, eosinophilic gastroenteritis, colitis, diarrhea, bleeding, mesenteric vasculitis, bowel ischaemia, perforation
3	Cardiac	Endomyocarditis, arrhythmia, impaired LV function, heart failure, mild valvular insufficiency, coronary vasculitis
4	Cerebrovascular	Meningitis, arachnoid haemorrhage, diffuse brain damage, cranial neuropathy (trigeminal, glossopharyngeal)

Foetal morbidity is slightly high in EGPA pregnancies. Effect of vasculitis on placenta is not known. Concomitant malignancies reported but their incidence is not higher than that expected in general population.

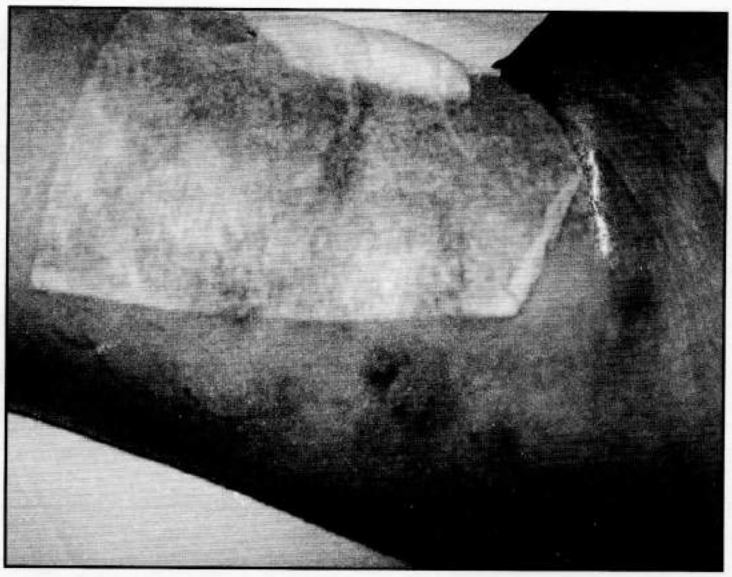

Fig. 1

Cutaneous involvement in EGPA

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For Private Circulation Only
Monograph on Vasculitis

Published by
Dr. Gumdal Narsimulu

On behalf of
Indian College of Physicians
Academic Wing of Association of Physician of India
Unit 6 & 7, Ground Floor, Turf Estate, Off Dr. E. Moses Road
Near Mahalakshmi Station (W), Mumbai 400 011.
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Printed at :
Bangalore, India.

December, 2014

ASSOCIATION OF PHYSICIANS OF INDIA
INDIAN COLLEGE OF PHYSICIANS

MONOGRAPH

ON

VASCULITIS

EDITOR
DR. G. NARSIMULU