Eosinophilic Granulomatosis with Polyangitis (EGPA) and IgG4 related disease presenting as overlap Syndrome: Case report of unusual case and literature review

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Declaration of conflicting interests

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ABSTRACT

EGPA is an Anti-neutrophilic Cytoplasmic antibody (ANCA) associated vasculitis which consists of small vessel vasculitis and hypereosinophilia.[1] There are heterogeneous presentations of EGPA, and sometimes boundaries with other hypereisophilic syndromes with respect to clinical presentation, in particular IgG4-Related disease (IgG4-D) is not clear.

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Introduction

EGPA is an Anti-neutrophilic Cytoplasmic antibody (ANCA) associated vasculitis which consists of small vessel vasculitis and hypereosinophilia.[1] There are heterogeneous presentations of EGPA, and sometimes boundaries with other hypereisophilic syndromes with respect to clinical presentation, in particular IgG4-Related disease(IgG4-D) is not clear.

IgG4 related disease is multi system disease which like EGPA can present with upper and lower respiratory systems with peripheral eosinophilia.[2] In some rare cases both diseases can co-exist in same patient.

Case Report

47 old Saudi female, non-smoker, who is known asthmatic for 5 years, presented to us because of worsening of her asthmatic symptoms over last 8 months.

On admission, patient had persistent shortness of breath with cough.

On Systemic inquiry, she has no fever, weight loss, no joint pain, rash or oral ulcers.

Past history was significant for decreased hearing in both ears and she underwent myringotomy 5 years back. She also has history of intermittent nasal blockage.

On general examination, patient was vitally stable, except she was desaturating upto 88% on room air.

Chest investigation revealed bilateral brhonchi.

Investigation revealed-Hb 9.9 g/dl, Total leucocyte count of 8.5 x109/L with eosinophil count of 2.1x109/L (24%).PLT count567x109/L.

Liver and renal functions were within normal limits.

ESR 54 mm/h and CRP87 mg/dl. ANCA was negative

X-ray chest was significant for scattered nodular opacities, more prominent on right middle and lower zone dominance.

CT chest at admission revealed scattered areas of ground glass densities and nodular opacities in peribronchial areas. (Figure 1)

Brochoalveolar lavage, showed mixed inflammatory cell with significant eosinophils (40%) while it was negative for culture .

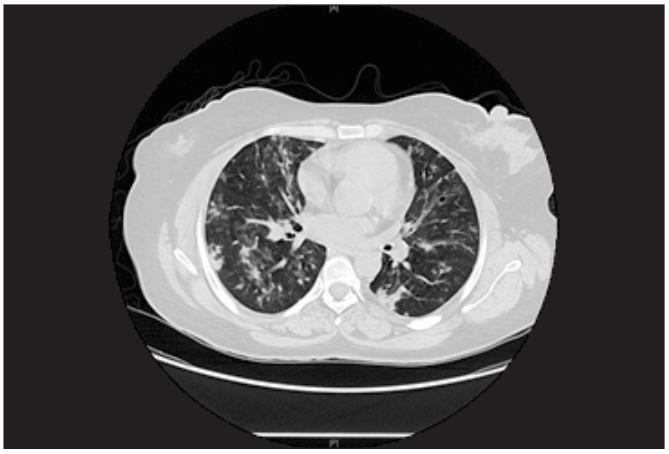

Figure 1: High resolution CT scan of Chest showing scattered patches of peribronchovascular ground glass infiltrates and nodular densities in both lungs.

Patient underwent ,open lung biopsy which showed marked reactive lympho plasmacytic infiltration. There was focal eosinophilic infiltration with Masson bodies. In one section of biopsy, a branch of pulmonary artery revealed vasculitis (fig 2).

Immunohisto chemistry stain, was positive for IgG 4 (Figure-2) and Serum IgG4 was160 mg/dl(normal level 8-140 mg/dl). PFT showed restrictive pattern with DLCO 60%.

CT sinuses was suggestive of chronic sinusitis while CT abdomen was unremarkable.

Hospital Course

Patient was diagnosed as a case of EGPA overlap with IgG4-related disease(IgG4-RD), .She was started on 2 lite oxygen through nasal cannula and her saturation improved to 96%. After ruling out active infection she was given pulse steroid of 1 gram 3 doses ,she was also started on monthly intravenous cyclo phosphamide.

Patient underwent uneventful recovery and continued

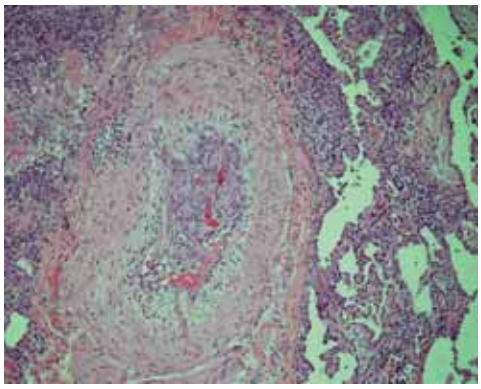

Figure 2: Large pulmonary arteriole showing organzing and obliterative thrombus associated with vasculitis. Note the presence of focal wall infiltration by inflammatory cells.Hematoxylin and eosin stain(9X200)

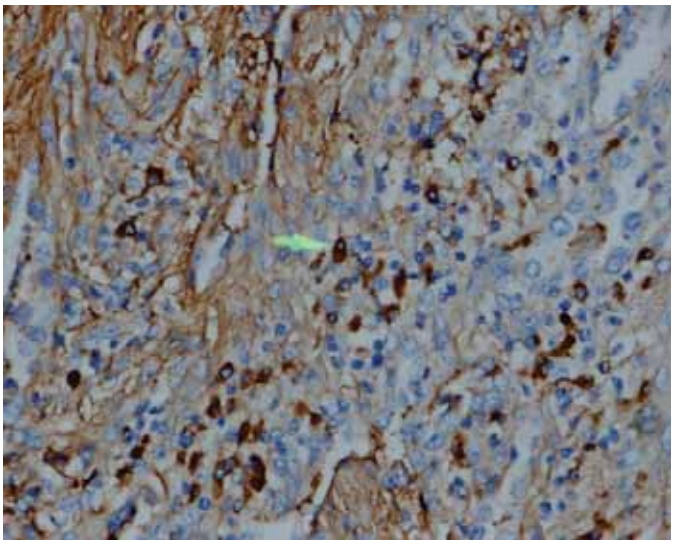

Figure 3: This photomicrograph of lung biopsy, shows IgG4 containing plasma cells (arrow) (IgG immunostain ,original magnification X400)

to improve during 3 months of follow up.

Discussion

EGPA is a multisystem disorder, characterized by allergic rhinitis, asthma, and prominent peripheral blood eosinophilia.[1] EGPA is classified as a ANCA associated vasculitis of the small and medium sized arteries, although the vasculitis is often not apparent in biopsy in the initial phase of the disease.

ANCA especially anti-myeloperoxidase type(P-ANCA) is present in 40–60% of the patients with EGPA while in remaining patients it not helpful in making the diagnosis.[3] My patient was negative for ANCA.

The exact pathogenesis of EGPA is unknown. The disease can be triggered by exposure to allergens or drugs, but an association with HLA-DRB4 has also been recognized. Th2 immunity is heightened, with up-regulation of cytokines like IL-4, IL-13, and IL-5.

The histopathologic findings include extra vascular tissue infiltration by eosinophilic with granuloma formation. In about half of patients there is vasculitis of small arteries, arterioles, venules and occasionally capillaries.

Serum IgG4 levels are elevated in active EGPA and correlate with the number of organ manifestations and disease activity. Tissue analysis did not show an increased IgG4 plasma cell infiltration in EGPA biopsies.[4,5]

It is important that EGPA must be differentiated from IgG4-RD, which may present with findingsconsistent with both an autoimmune disorder and an allergic disorder. It is a systemic fibro inflammatory disease which presents with manifestations, of blood eosinophilia, pulmonary infiltrates, and sinusitis.

Pathogenesis of IgG4-RD involves an allergic mechanism, as Th2 cells are active with expression of Th2 related cytokines like IL-4, IL-13, and IL-5.4 So in both EGPA and IgG4 disease Th-2 cells has central role in pathogenesis.

In IgG4 disease serum IgG4 should around or more than 135 mg/dl .It has a 97% sensitivity and 79.6% specificity in the diagnosis of IgG4-RD,6 while IgG4 levels are moderately elevated in EGPA, as seen in our patient .

To add to complexity, in a sizeable minority of patients may have normal serum IgG4 concentrations, but they have classical histopathologic features in tissue biopsy.

It is recently suggested that in the correct clinical setting, the diagnosis can be established by histological features highly suggestive of IgG4-RD.It requires at least two histopathologic features, which included dense lymphoplasmacytic infiltrate, stori form fibrosis , and obliterative phlebitis.[6]

A positive ANCA test does not exclude the diagnosis of IgG4-RD; confirmation through immunoenzymatic assays of the ANCA specificity, clinical-pathological correlation, and histopathological evaluation remain crucial steps for the differential diagnosis between AAV and IgG4-RD.

In rare cases, there can be clinical and histological features of both diseases.6In such cases histological examination reveals small vessel vasculitis is associated with lymphoplasmocytic infiltrate rich in IgG-4 positive plasma cell. (figure.2)

Regarding management of such patients, they are usually treated with cyclophosphamide while patients with refectory,7or relapsing disease, rituximab is an alternate treatment option.7Patient in above mentioned case report responded well to cyclophosphamide .

In conclusion, I think that association between EGPA and IgG4 related is possible, and represent a peculiar entity and it responds well to cyclophosphamide.

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