Granulomatosis with Polyangiitis (GPA) Mimicking Tuberculosis

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Abstract
Granulomatosis with Polyangiitis (GPA) is a rare disease with varied clinical manifestations. We present a case of GPA which manifested initially with symptoms suggestive of meningeal tuberculosis. High index of suspicion and collective review of all clinical features helped in the correct diagnosis. Treatment of this case with rituximab provided significant symptomatic relief.

Introduction
Granulomatosis with Polyangiitis (GPA) is a rare autoimmune disease, characterized by necrotizing vasculitis, leading to the classic triad of granulomatous inflammation of the respiratory tract, necrotizing glomerulonephritis, and systemic vasculitis predominantly affecting the small vessels.1 Being a rare disease, with non-specific symptoms, early diagnosis of GPA is difficult.2 Due to the involvement of respiratory tract, and the high prevalence of multi-drug resistant tuberculosis in India, many patients are initially misdiagnosed as having tuberculosis.3

Here, we present a case which manifested initially with symptoms suggestive of meningeval tuberculosis. However, the patient did not respond to antitubercular therapy and in view of the patchy meningitis, other symptoms, laboratory investigations and previous history, a diagnosis of GPA was made. This case report underlines the need for a high index of suspicion and continuous treatment monitoring in GPA to diagnose and manage non-responders.

Case Report
A 32 year female presented with complaints of right-sided throat pain. Endoscopic examination of the throat revealed suspected granulomatous lesion at the junction of the eustachian tube and nasopharynx. Laboratory investigations revealed elevated C-reactive protein (CRP)-10 mg/dl and erythrocyte sedimentation (ESC) rate=30mg /1st hour (ESR). The antineutrophil cytoplasmic antibodies (C-ANCA) were strongly positive in high titer (38 IU/dL; normal range: 0-5 IU/dL). Computed tomography (CT) scan of the paranasal sinuses was normal. Magnetic resonance imaging (MRI) of brain did not reveal any abnormality in the brain and brainstem. She was suspected to have an upper respiratory tract limited (ANCA associated) vasculitis (Granulomatosis with Polyangiitis). A biopsy of the lesion was planned; however, the patient refused. Since patient was symptomatic, she was started on low dose steroid (methyl prednisolone 5 mg daily) for 2 weeks with significant improvement. Since her ESR and CRP were still high and she required steroids to reduce the pain, methotrexate (10 mg/week) was started as steroid sparing medicine for 2 months. The patient improved; however, later she discontinued the medications and lost for follow up.

Six months later, the patient returned with severe pain in the throat, along with severe headache, dysphagia, dysphonia and pain in the ear. She had leukocytosis and, elevated ESR and CRP levels. An MRI of the brain revealed patchy meningitis in the basal region with obstructive hydrocephalus. (Figure 1) Left otitis media and mastoiditis were also noted. Her cerebrospinal fluid (CSF) analysis showed few lymphocytes with 1 gm of protein. With all the neurological features, a working diagnosis of tuberculosis was made as it is the most common cause for basal meningitis. She was started on antitubercular drugs (ethambutol hydrochloride, isoniazid, pyrazinamide and rifampcin), along with steroids. A ventriculoperitoneal (VP) shunt was placed for obstructive hydrocephalus. Even after one month of treatment with antitubercular drugs, steroids and post placement of VP shunt, her symptoms (dysphagia, dysphonia and headache) persisted.

A repeat MRI revealed similar findings. With a previous history of c-ANCA positivity, the ANCA was repeated which was strongly positive in high titer (34 IU/dL). Patient was diagnosed as having ANCA positive central nervous system vasculitis. She was started on intravenous cyclophosphamide (750 mg every two weeks) with pulse methylprednisolone (1 g daily for 3 days), followed by 50 mg/day oral methylprednisolone. Dysphagia and dysphonia improved within 2 weeks; however, she continued to have severe headache, which responded only to intravenous methylprednisolone (125 mg) intermittently. Since the patient continued to have symptomatic...
headache even after 4 doses of cyclophosphamide and oral steroids, rituximab (1 g) was added to 3-day pulse methylprednisolone therapy. After two doses of rituximab therapy, 15 days apart, the patient showed significant response. Her symptoms, especially severe headache, reduced substantially, along with reduced requirement of steroids. Notable improvements were also found in the MRI findings, as shown in Figure 2. At present, the patient is on methyl prednisolone (2.5 mg on alternate days) and is clinically asymptomatic. At the last visit, inflammatory parameters were normal but C-ANCA was still positive, the titers, however, were reduced.

**Discussion**

GPA is a rare disease with an estimated prevalence of 3 per 100,000. In India, about 40-50% of patients with GPA are reported to be initially misdiagnosed as tuberculosis. Many of the patients with GPA are treated with antitubercular drugs initially. At the time of second presentation, the patient had symptoms associated with upper respiratory tract, ears, and eyes, along with elevated ESR and CRP. There was a high suspicion of tuberculosis due to a high prevalence of tuberculosis in the region. Further, on the basis of MRI reports indicating patchy meninitis and hydrocephalus, the diagnosis of tubercular meningitis was made.

Vasculitis conditions are often misdiagnosed as infective disorders, notably tuberculosis, in India. It has been suggested that a diagnosis of vasculitis must be considered in ‘unproven’ cases of tuberculosis in case the response to anti-tubercular therapy is not achieved in 1-2 months.

Despite the clinical history and examination indicating the possibility of GPA, investigations should always be conducted to rule out other diseases with a similar clinical picture, including connective tissue disease, malignancy, sarcoidosis, interstitial lung disease, infections, and drug toxicity. A careful assessment of the clinical course of disease, radiological characteristics, laboratory tests (including c-ANCA) and careful review of the results of the histological examination of the involved tissue can help establish the correct diagnosis.

Management of ANCA positive vasculitis consists of remission induction with initial immunosuppressive therapy, followed by maintenance immunosuppressive therapy to prevent relapse and control the disease. Cyclophosphamide and prednisolone are most commonly employed drugs for remission induction in patients with systemic or severe disease. Shifting to methotrexate or azathioprine can be considered for maintenance of remission, in order to avoid the side effects of continued cyclophosphamide therapy.

Once the diagnosis of ANCA positive vasculitis was made in this case, treatment was initiated with cyclophosphamide and prednisolone. However, even after four cycles of cyclophosphamide therapy, the patient had no improvement in symptoms. Rituximab was thus used as an alternative, to which the patient had significant response.

About 15-20% of patients with GPA have been reported to be refractory to standard treatment. Rituximab is now being increasingly used for various refractory autoimmune diseases, including refractory ANCA associated vasculitis or in patients with a contraindication to cyclophosphamide. A retrospective study that included 66 patients with GPA, treated with rituximab and glucocorticoid for remission induction, showed that 78.8% patients achieved response in 6 months. Low dose rituximab, when used for maintenance of remission, was associated with low rates of relapse (11.2 per 100 patient years) and was also safe. Further, it does not have infertility concerns or bladder toxicity associated with cyclophosphamide.

**Conclusion**

Granulomatosis with Polyangiitis, with its varied and non-specific manifestations, is often a missed diagnosis and confused with TB. Since the disease can be fatal if untreated, one should always keep a high clinical suspicion for a timely diagnosis of this rare disease. Once the diagnosis is established, patients should be closely monitored for treatment response, as identifying non-responders at an early stage can help save crucial time of disease progression. Promptly shifting the non-responders to the next line of treatment can help bring in substantial symptomatic relief, induce remission and reduce complications.

**References**