

Relapsing Granulomatosis with Polyangiitis with Severe Lung Involvement-A Case Report

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Abstract

Case Report

Introduction: Granulomatosis polangitis is a granulomatous vasculitis involving small vessels, the diagnosis is by circulating antibodies against cytoplasmic component of neutrophils (c-ANCA) which have been detected in more than 90% patients with active GPA and histopathological hallmark of the disease small vessel vasculitis. Since the introduction of steroids and cyclophosphamide as a standard immunosuppressive regimen, survival of patients diagnosed with GPA has improved considerably. Despite the ability to successfully induce remission, 50–70% of remissions are later associated with one or more relapses. **Case report:** 48 year old male was diagnosed with GPA on histopathology and c-ANCA titres, and was treated with steroids and cyclophosphamide for 18 months and Azathioprine for 3 yrs of maintenance therapy and treatment was stopped gradually. After 2 and ½ years off treatment, patient was diagnosed as Relapse of GPA, and as per guideline recommendations, we started our patient on cyclophosphamide with combination of glucocorticoids. **Conclusion:** Granulomatosis with polyangiitis is a chronic relapsing disease. Its relapse rate rises from 20% at 12 months to almost 60% after 5 years [2]. Each relapse may result in further morbidity; hence recognition of a relapse is essential. In our patient, on follow up after 3 months of treatment, there was significant clinical and radiological improvement of the disease on cyclophosphamide along with glucocorticoids and hence the use of Rituximab can be preserved for refractory cases of relapse not responding to cyclophosphamide.

Keywords: Granulomatosis with polyangiitis, Lung involvement, Relapse, Cyclophosphamide.

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INTRODUCTION

Granulomatosis with polyangiitis (Wegener's) is a distinct clinicopathologic entity characterized by granulomatous vasculitis of the upper and lower respiratory tracts together with glomerulonephritis. In addition, variable degrees of disseminated vasculitis involving both small arteries and veins may occur [1].

The histopathological hallmarks of GPA include small vessel vasculitis, geographic necrosis, hemorrhagic infarcts, a mixed inflammatory cellular infiltrate, and a granuloma formation, which may be either intravascular or extravascular. Circulating antibodies directed against cytoplasmic component of neutrophils (c-ANCA) have been detected in more than 90% of patients with active GPA [1].

Despite the ability to successfully induce remission, 50–70% of remissions are later associated with one or more relapses. The determination of relapse

should be based on objective evidence of disease activity, taking care to rule out other features that may have a similar appearance such as infection, medication toxicity, or chronic disease sequelae.

Relapse rate rises from about 20% at 12 months to about 60% at 5 years [2]. Since the introduction of steroids and cyclophosphamide as a standard immunosuppressive regimen, survival of patients diagnosed with GPA has improved considerably. Mortality rates, previously exceeding 80% in 1 year, have been reduced to 20% in 5 years [3], but still it is a chronic disease, significantly lowering the quality of the patient's life.

CASE REPORT

A 48 year old male presented in March 2010 with complaints of cough with blood tinging of sputum, running nose, nasal blockade, epistaxis, and bilateral joint pain in ankle, knee joint.

On physical examination there was a large ulcer measuring 2.5 X 2.5cm on right side nasal septum cartilaginous portion. Chest x-ray showed opacity in right mid zone and lower zone s/o patches of consolidation. Sputum for AFB- negative, RFTs revealed BU-49, S. creatinine 1.2.

CT thorax report revealed multifocal areas of consolidation in the anterior and posterior segments of the right upper lobe, the medial segment of the right middle lobe and in the superior segment of the lingula, with multiple peribronchial nodules, and few small mediastinal nodes, lung picture was suggestive of cryptogenic organising pneumonia or could be a lung manifestation of a systemic disorder like collagen vascular disease or polyarthritis. Other reports were CRP- negative, RA Factor- negative, C-ANCA strongly positive 1:640 titre PR3 ANCA >200 positive, C3 & C4 were normal values. Renal ultrasound was normal. Nasal septal biopsy was done and report revealed sections showing fibrocollagenous tissue with areas of necrosis, the tissue also encloses small and medium sized vessel showing presence of acute and chronic inflammatory infiltrate in the wall of blood vessels, necrotizing inflammation associated with vasculitis highly suggestive of granulomatosis with polyangiitis.

A diagnosis of GPA was made and started on tab prednisolone 50mg/day and tab cyclophosphamide 100mg/day. RFTs and WBC counts were monitored on treatment. Treatment with cyclophosphamide and steroids was continued for 18 months. After 18months of treatment repeat CT thorax revealed fibrotic lesions in right upper and middle lobe and left lingular segment.

Treatment with cyclophosphamide was stopped in view of remission of disease and patient was changed to tablet azathioprine 500mg OD and oral

steroids as maintenance therapy for 3 years and gradually stopped as patient response. Patient remained asymptomatic for 2 and 1/2years off treatment.

Patient again presented to OPD in April 2018 with complaints of cough with expectoration for 15 days associated with blood tinging of sputum since 15 days and also complaints of low grade fever on and off since 15 days, chest x-ray was suggestive of consolidation and cavitary lesion in the right and left mid zone. Laboratory investigations revealed Hb 10.9g%, total counts 16,900 cells/cumm with neutrophil 80% lymphocytes 20%, sputum for AFB smear-Negative, s. creatinine 1.1 Blood urea 25, LFT's were normal. Patient was given course of antibiotics and chest x-ray was repeated which did not show resolution instead lesions were increased.

CT thorax was done report revealed consolidation with cavitation and nodular lesions noted in right upper lobe and middle lobe and also in left upper lobe and lingula. A thin rim of pleural effusion noted in left side. A few enlarged mediastinal nodes are seen in pre and para tracheal regions, these findings of pulmonary changes were consistent with relapse of Granulomatosis with polyangiitis, C-ANCA PR3 antibodies were >100u/ml- positive, CRP- Positive. No renal and cardiac involvement. Patient is started on treatment with Cyclophosphamide 100mg OD orally and Prednisolone 50mg in two divided doses orally. Patient was diagnosed early and considered for initiation of treatment according to EULAR recommendations⁴. He was started on treatment with a combination of cyclophosphamide and glucocorticoids and response to treatment was evaluated, currently he has finished treatment for 3 months durations and shows clinical and radiological improvement following treatment. He has tolerated the treatment well.



Fig-1: CT Thorax at diagnosis of relapse of GPA showing bilateral thick walled multiple cavitary lesions

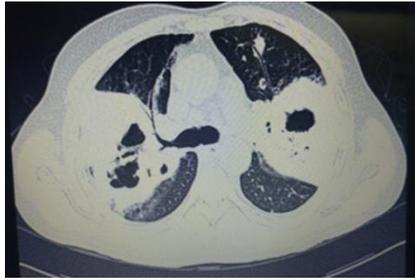


Fig-2: CT Thorax at diagnosis of relapse of GPA showing bilateral multiple cavitary lesions in transvers section of CT thorax



Fig-3: Chest X-ray PA view showing bilateral thick walled cavitary lesions and consolidation at the time of diagnosis of Relapse



Fig-4: Chest X-ray PA view after 3 months of treatment with cyclophosphamide + prednisolone significant resolution seen



Fig-5: CT Thorax after 3 months of treatment showing improvement



Fig-6: CT Thorax after 3 months of treatment showing resolution of cavitary lesions

DISCUSSION

Granulomatosis with polyangiitis is an uncommon disease with an estimated prevalence of 3 per 100000. The disease can be seen in any age group, the mean age of onset is 40years, the male: female ratio is 1:1[1]. GPA is the most common form of vasculitis to involve the lung. Granulomatosis with polyangiitis (Wegener's) is a distinct clinicopathologic entity characterized by granulomatous vasculitis of the upper and lower respiratory tracts together with glomerulonephritis. However, it is important to recognize that GPA is a systemic disease that can affect almost any organ. The most frequently involved sites are upper respiratory tract, lower respiratory tract and kidneys [1].

Over 90% of patients with GPA first seek medical attention for symptoms arising from either upper airway or lower airway. Nasal and sinus disease is characterized by congestion and epistaxis due to mucosal friability, ulceration and thickening.

GPA involving the lower airways can affect the pulmonary parenchyma, the bronchi and rarely the pleura. Presenting features of parenchymal involvement may include cough, dyspnea, chest pain and hemoptysis. The most common form of pulmonary involvement in GPA is that of nodules or mass lesions, which may cavitate. These lesions are caused by necrotizing granulomatous inflammation. The lung nodules of GPA have very characteristic histopathological features. Small necrotizing microabscesses appear to be the earliest lesion. The necrotic centre is surrounded by palisading histiocytes and scattered giant cells. Occasionally the necrosis may be bronchocentric. When this type of necrotizing granulomatous inflammation extends into the walls of small vessels it is referred as granulomatous vasculitis.

The most common findings are discrete focal opacities that vary in size and appearance, from diffuse consolidation to nodular masses. The latter may increase up to 10cm in diameter but are usually 2-4cm. they show no zonal predilection, are usually multiple, are rounded or oval in shape. Nodules often occur concurrently with consolidation, and commonly resolve spontaneously, with or without scarring. On HRCT ground glass shadowing may surround the nodules which may be due to hemorrhage [5].

A definitive diagnosis is obtained by establishing the presence of necrotizing granulomatous vasculitis, often in association with glomerulonephritis on renal biopsy specimens [5]. The decision as to which site the biopsy sample should be taken from should be based on individual factors including the severity of illness, invasiveness of the procedure, likelihood of a positive yield is based on data from literature, and urgency of beginning treatment[6].

Antineutrophilic cytoplasmic antibody (ANCA) has a high degree of association with GPA. Since their description, two main immunofluorescent staining patterns of ANCA have been found i.e. cytoplasmic pattern and perinuclear pattern. The c-ANCA has been found in 0-90% of patients with active GPA while p-ANCA has been observed in 5-10% of patients with GPA. The sensitivity of ANCA for GPA has been reported to range from 28-92% [7].

Prior to the introduction of effective therapy, granulomatosis with polyangiitis (Wegener's) was universally fatal within a few months of diagnosis. Glucocorticoids alone led to some symptomatic improvement, with little effect on the ultimate course of the disease. The development of treatment with cyclophosphamide dramatically changed patient outcome such that marked improvement was seen in >90% of patients, complete remission in 75% of Patients, and 5-year patient survival was seen in over 80% [1].

Despite the ability to successfully induce remission, 50-70% of remissions are later associated with one or more relapses. The determination of relapse should be based on objective evidence of disease activity, taking care to rule out other features that may have a similar appearance such as infection, medication toxicity, or chronic disease sequelae. The ANCA titer can be misleading and should not be used to assess disease activity. Many patients who achieve remission continue to have elevated titers for years. Results from a large prospective study found that increases in ANCA were not associated with relapse and that only 43% relapsed within 1 year of an increase in ANCA levels. Thus, a rise in ANCA by itself is not a harbinger of immediate disease relapse and should not lead to reinstitution or increase in immunosuppressive therapy.

Reinduction of remission after relapse is almost always achieved; however, a high percentage of patients ultimately have some degree of damage from irreversible features of their disease, such as varying degrees of renal insufficiency, hearing loss, tracheal stenosis, saddle nose deformity, and chronically impaired sinus function [1].

Considering all new data, in 2016, the European League Against Rheumatism (EULAR) with the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) have published an update of 2009 EULAR recommendations with the focus on the management of ANCA-associated vasculitis[8]. The treatment differed according to clinical presentation of the disease. For remission-induction of new-onset organ-threatening or life-threatening AAV, treatment with a combination of glucocorticoids and either cyclophosphamide or rituximab is recommended. For patients with AAV refractory to remission-induction therapy, switching from cyclophosphamide to rituximab or from rituximab to cyclophosphamide is recommended [8].

CONCLUSION

Granulomatosis with polyangiitis is a chronic relapsing disease. Its relapse rate rises from 20% at 12 months to almost 60% after 5 years [2]. Each relapse may result in further morbidity; hence recognition of a relapse is essential. Since the introduction of steroids and cyclophosphamide as a standard immunosuppressive regimen, the survival of patients diagnosed with GPA has improved considerably. Our patient developed relapse after two and half years of treatment and as per guideline recommendations, we started our patient on cyclophosphamide with combination of glucocorticoids.

In our patient, on follow up after 3 months of treatment, there was significant clinical and radiological

improvement of the disease on cyclophosphamide along with glucocorticoids. The use of Rituximab can be preserved for refractory cases of relapse not responding to cyclophosphamide.

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