

# GRANULOMATOSIS WITH POLYANGIITIS - A CASE REPORT WITH UNIQUE LIVER FUNCTION DE-ARRANGEMENT AND TREATMENT REVIEW

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**ABSTRACT** Granulomatosis with polyangiitis (GPA) is a potentially lethal systemic disorder that is characterized by necrotizing vasculitis of small arteries and veins. The respiratory system is most commonly affected, however upper and lower respiratory system, systemic vasculitis, and necrotizing glomerulonephritis are the essential components of the disease triad. We present a case of a young male adult presenting with symptoms of sinusitis, joint pains, fever with detection of lung lesions on chest x-ray and CT scan who had liver involvement on further investigations with pathological confirmation by antineutrophil cytoplasmic antibody positivity and nasal ulcers. After treatment with corticosteroid and IV Rituximab, the lung findings were entirely resolved with improvement in liver functions.

**KEYWORDS** Cough, Wegener, Granulomatosis

## Introduction

Granulomatosis with polyangiitis was first described by Klinger in 1933, followed by other investigators, including Rossle in 1933, Wegener in 1936 and 1939, and Ringertz in 1947.[1]

Granulomatosis with Polyangiitis (GPA) is a rare multi-system autoimmune disease. It is characterized histopathologically by necrotizing granulomatous vasculitis. The classical clinical triad consists of upper airway involvement (characterized by sinusitis, otitis, nasal mucosa ulcers, bone deformities, and subglottic stenosis), lower respiratory tract involvement (cough, chest pain, hemoptysis) and glomerulonephritis.[2,3]

However, GPA can principally affect any organ in a vasculitic or granulomatous disease pattern. Elevated liver function tests (LFT) are not very often seen. The most common clinical presentation is a mild lesion due to drug exposure, especially NSAID and antibiotic. The actual incidence of liver involvement in GPA is unclear[32]. In clinical practice, even after careful exclusion of

previous treatment with potentially hepatotoxic drugs or coincident viral hepatitis, the question remains whether to classify the patient as having a primary liver disease with associated autoimmune or as having the liver disease as a manifestation of generalised connective tissue disease.

The best treatment approach requires team collaboration between different medical specialties in order to cover the different organs involved by the disease. Traditionally people with GPA who have critical organ system involvement are generally treated with corticosteroids combined with another immunosuppressant such as cyclophosphamide. In patients with less severe GPA, corticosteroids and methotrexate can be used initially.[11,12,13]

Adding cyclophosphamide to corticosteroid therapy altered the prognosis of the disease and resulted in remission and extension of the survival rate.[4] For the past decade, trials confirmed that B cell depletion with Rituximab was comparable to cyclophosphamide as part of induction therapy for active ANCA-associated vasculitis and with possibly superior performance in relapsing disease.[5,6]

## Case report

A 32-year-old man presented to the hospital with joint pain, fever, general fatigue and sinusitis, which he had been experiencing for a month. He was first consulted by a Chest and TB specialist who ordered the Chest X-ray and CT Scan.

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**Figure 1:** Chest X-ray showed a faint, rounded radio-opacity in the right middle zone, on the anterior aspect of 3rd rib as shown below.



**Figure 3:** One month later, the patient presented again to the hospital as there was no improvement in his symptoms and on top of which he started experiencing nasal bleeding for which CT Scan PNS was done. CT Scan PNS revealed right-sided sinusitis. Endoscopy revealed nasal ulcers.



**Figure 2:** Chest CT Scan showed nodular cavitary lung lesion seen in anterior segment of right upper lobe and postero-basal segments of bilateral lower lobes. The largest one is measuring 35x28mm in size in the right lower lobe. The patient was prescribed Antibiotics along with NSAIDs and Nasal Decongestants. Meanwhile, sputum culture acid-fast bacilli and CB NAAT were negative.



**Figure 4:** CT abdomen showed hepatomegaly as shown below.

Rheumatologist made the diagnosis of Granulomatosis with Polyangiitis based on the reports and clinical evaluation. He ordered CBC, c-ANCA ELISA, LFTs, RFTs, CT abdomen, urine routine, viral markers, PTIINR and G6PD profile. Abnormal findings are given below:

|                |                                 |
|----------------|---------------------------------|
| TLC            | 12.6 cells/cmm (neutrophillia)  |
| Platelet count | 639 x 10 <sup>9</sup> per litre |
| SGOT           | 137 units/litre                 |
| SGPT           | 275 units/litre                 |
| S. Proteins    | 8.6 g/dl                        |
| S. albumin     | 3.86 g/dl                       |
| S. globulin    | 4.75 g/dl                       |
| S. Creatinine  | 0.68 mg/dl                      |
| S. potassium   | 5.27 meq/litre                  |
| UPCR           | 0.1                             |
| c - ANCA       | > 100                           |
| ESR            | 38mm at 1hour                   |

At this point, Medicine Specialist was consulted who reviewed the previous reports and ordered ANCA profile, ANA profile, ESR, CBC, Renal function tests and Liver function tests. Results showed PR3 (c-ANCA) = strong positive +++, elevated ESR, leukocytosis, SGOT = 55 units/litre, SGPT = 101 units/litre and RFTs were normal. The patient was then referred to a Rheumatologist.

- In urine examination = no pus cells were seen, and 2-3 RBCs were seen.
- Viral markers = NAD
- G6PD = within normal limits.

During this course, the patient also started experiencing difficulty in breathing and decreased hearing in the left ear. The patient was then started Onmacortil (corticosteroid) 60mg/day along with Syntical (calcium citrate maleate). After one week, fever, joint pain subsided and hearing improved, but there was no improvement in LFTs. (SGOT = 44 units/litre and SGPT = 194 units/litre). So Methotrexate (recommended treatment for Granulomatosis with Polyangiitis) was not started due to the hepatotoxic side effects. At this point, it was suspected that the deranged LFT's could have been due to NSAID's or Antibiotics. So the patient was not given any other drug except Onmacortil for two months. After two months LFT's were repeated, but they were still deranged (SGOT = 45 units/litre and SGPT = 160 units/litre) because of which Methotrexate was not started which was earlier in the plan.

Now, the steroid was reduced to 50 mg/day, and injection Rituximab (1 gm I/V) was administered. There was a drastic improvement, and SGPT came down to 8 units/litre. After a gap of 15 days, again, injection Rituximab (1gm I/V) was administered and Septran DSR 3 tablets/week was started. All the symptoms improved and Chest X-Ray came out to be normal with the disappearance of lung lesions as shown below except that patient experienced weight gain and constipation for which

the following tests were done - RBS, Thyroid profile with anti-TPO antibodies and BP monitoring.

- RBS and BP came out to be normal.
- TSH = 8.710 milliIU/litre
- T3 and T4 = within normal limits
- ANTI-TPO = >1300 IU/ML (normal <35 IU/ML) for which Thyronorm 25 mg was started.

### Further plan

0.5 gm I/V Rituximab (maintenance dose) after every six months for three years with a gradual reduction in steroid dose.

### Discussion

WG is currently characterized as one of the ANCA-associated small vessel vasculitides. It is distinguished clinically by its predilection for affecting the upper and lower respiratory tracts and kidneys and by the histologic presence of necrosis, granulomatous inflammation, and vasculitis.

A limited form of this disease with involvement of the upper respiratory tract and the lungs with renal sparing is frequently seen in women, while the kidneys are involved in the common form frequently seen in men.[6] Sinus and nasal involvement is seen in 70-90% of patients, lung lesions are noted in 80-90% of patients with pleural involvement seen in 25-30% of patients, and renal involvement is seen in 70-80% of patients throughout disease.[7]

The four criteria of diagnosis defined by the American College of Rheumatology (ACR) for Granulomatosis with Polyangiitis are as follows: The presence of two or more of these criteria has a sensitivity of 88% and a specificity of 99%.[7,8]

Another diagnostic system is known as the ELK (E for ears, nose and throat or upper respiratory tract; L for lung; and K for kidney) classification system proposed by DeRemee and colleagues utilize ANCA results[33]. According to this system, any typical manifestation in the E, L or K supported by typical histopathology or a positive cytoplasmic ANCA (c-ANCA) test qualifies for the diagnosis of GPA [34]. ANCA has been recognized to be both sensitive and specific for GPA [35] and is highly associated with GPA, being present in 80-90% of patients with systemic disease. Still, there are some cases of the disease where ANCA is negative[36]. Of all the ANCA associated with GPA, 80-95% of cases are associated with c-ANCA with autoantibodies directed against proteinase three antibodies (PR3) the remainder are p-ANCA directed against myeloperoxidase antibodies (MPO)[37].

Pathologically, Granulomatosis with Polyangiitis is characterized by necrotizing granulomatous inflammation of small vessel walls, resulting in areas of necrosis surrounded by haemorrhage, small microabscesses and granuloma within the lungs. Normocytic anaemia, leucocytosis, elevated erythrocyte sedimentation rate (ESR), positive rheumatoid factor and antineutrophil cytoplasmic antibody (specifically PR3-ANCA) are often shown on serology. PR3-ANCA is positive in 85% of patients with active multi-organ Granulomatosis with Polyangiitis, but this reduces to 30-40% in remission.[8,9]

### CLINICAL MANIFESTATIONS

The classic clinical triad consists of upper airway involvement (characterized by sinusitis, otitis, nasal mucosa ulcers, bone deformities, and subglottic stenosis), lower respiratory tract

Table showing changes in liver enzymes with time.

|      | At initial presentation | Before stopping NSAID's and Antibiotics | After two months | After treatment with Rituximab |
|------|-------------------------|---|------------------|--------------------------------|
| SGOT | 137                     | 44                                      | 45               | 20                             |
| SGPT | 275                     | 194                                     | 160              | 8                              |

| Criterion                            | Definition  |
|--------------------------------------|---|
| Nasal or oral inflammation           | Development of painful or painless oral ulcers or purulent or bloody nasal discharge  |
| Abnormal chest radiograph            | Chest radiograph showing the presence nodules, fixed infiltrates, or cavities   |
| Urinary sediment                     | Microhematuria (>5 red blood cells per high power field) or red cell casts in urine sediment  |
| Granulomatous inflammation on biopsy | Histologic changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole) |

involvement (cough, chest pain, hemoptysis), and glomerulonephritis.[2] Granulomatosis has a broad clinical spectrum ranging from localized disease (predominantly restricted to the respiratory tract) to a severe life-threatening form with the involvement of multiple organs (predominantly the kidneys and lungs). It is believed that the disease begins as localized respiratory tract granulomatosis, which then generalizes into a vasculitis that affects small and medium-sized vessels.[20]

Patient presentation varies and depends on the organ system affected. Some patients present with chronic nasal obstruction, which may be misdiagnosed as chronic sinusitis; others may present with overt acute renal or respiratory failure. Patients with pulmonary involvement often complain of cough with or without hemoptysis, dyspnea, fever, and chest pain.[21]

The renal disease also may be seen as the initial presentation or during the disease. Once present, the renal disease may progress from asymptomatic and mild to fulminant glomerulonephritis within days or weeks, resulting in end-stage renal failure. Even with appropriate therapy, it may lead to chronic renal insufficiency and renal failure.[4]

Ocular manifestations have been reported to occur in 28 to 58% of patients with WG, and they may be part of the initial presentation in 8 to 16% of patients. A complete ophthalmologic examination is an essential part of the diagnostic evaluation. Any compartment of the eye may be affected. Keratitis, conjunctivitis, scleritis, episcleritis, nasolacrimal duct obstruction, uveitis, retro-orbital pseudotumor with proptosis, retinal vessel occlusion, and optic neuritis have all been described. Visual loss has been reported in as many as 8% of patients. CT or MRI of the orbit and sinuses may provide useful anatomic information.[23,24]

### Liver Involvement

Liver involvement in rheumatic diseases, like systemic lupus erythematosus (SLE), primary Sjögren's syndrome, systemic sclerosis, or rheumatoid arthritis has often been reported, most commonly in the form of liver function test (LFT) biochemical changes with predominant cholestatic or hepatocellular patterns. Also, an association of connective tissue diseases with autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC) is well known[25]. The association between autoimmune liver diseases and small-vessel vasculitis is rare but possible[26]. The incidence of liver involvement in GPA is rarely described, mainly in case of series[27,28]. Among the 180 GPA patients of the WGET study[29], no hepatic involvement was described. The Se.Pri.Va. The study group

found elevated liver enzymes in 8–11% of 36 GPA patients and Pavone et al. [30] in 2–25% of AAV patients at the time of diagnosis.

Willeke et al. [31] demonstrated that the liver is frequently affected (49.4%) in patients with active GPA when affection is mirrored by liver test abnormalities. They also detected an association of increased LFT in GPA patients with the BVAS (Birmingham Vasculitis Activity Score), severe disease, and with pulmonary or pulmonary-renal involvement (increased values for  $\gamma$ -GT in GPA patients correlated with the BVAS and were associated with pulmonary involvement, pulmonary-renal syndrome, and a longer time to remission). The biochemical picture during active disease revealed both a cholestatic pattern (i.e. increased  $\gamma$ -GT and ALP) as well as a hepatocellular pattern (with increased ALT and AST). No concomitant autoimmune liver disease and no association with potentially hepatotoxic drugs was observed[31]

### Treatment

Historical systemic treatment included a variety of modalities such as antibiotics, chelating agents and local irradiation.[6] None of these modalities was successful. Corticosteroid treatment was also tried, and it has been shown that corticosteroid alone doubled the life expectancy to about 12 months with a 1-year survival of 34%.[11] Adding cyclophosphamide to corticosteroid therapy altered the prognosis of the disease and resulted in remission and extension of the survival rate.[12] Once remission has been achieved, it is recommended that cyclophosphamide treatment be continued for at least another year before tapering the medication. Both oral and intravenous cyclophosphamide, in combination with corticosteroids, have been used successfully with equal effectiveness.[4]

The prolonged and repeated use of cyclophosphamide is associated with substantial toxicity, which ultimately limits or prohibits its use in some patients. Because of the significant toxicity associated with cyclophosphamide therapy, alternative maintenance therapies have been used. Azathioprine has shown some success, but it is less effective than cyclophosphamide and should only be considered in patients experiencing adverse side effects or when fertility concerns arise.[14] Methotrexate has been used in patients with limited GPA, though it is less likely to achieve and sustain remission.[15,16]

For the past decade, trials confirmed that B-cell depletion with Rituximab was comparable to cyclophosphamide as part of induction therapy for active ANCA-associated vasculitis and with possibly superior performance in relapsing disease.[17,18]

Rituximab is a chimeric monoclonal antibody directed against CD20; a cell surface antigen expressed almost exclusively on cells of B-lymphocyte lineage. Binding of the antibody to CD20 results in selective depletion of B lymphocytes by a variety of different mechanisms. This agent has become an essential component of standard treatment regimens for non-Hodgkin's B-cell lymphoma. Because of the prominent role ascribed to B lymphocytes in autoimmune diseases, Rituximab is increasingly being

investigated as a therapeutic agent for these nonmalignant indications. Neutropenia may develop, for which the patient should be monitored.[5]

## Conclusion

Thus, we conclude that coexistence of liver inflammation with a biochemical profile of anicteric non-viral non-drug-induced hepatitis can coincide with the diagnosis of Granulomatosis with Polyangiitis. Physicians should be aware of the possible occurrence of increased LFT in the active state of vasculitis. Rituximab is a comparable alternative to cyclophosphamide concerning efficacy and safety for the induction of remission of AAV (antineutrophil cytoplasmic antibodies-associated vasculitis). Rituximab should be considered in patients with disease refractory to cyclophosphamide therapy and in relapsing disease, particularly those with anti-PR3 positivity and in young patients who wish to preserve fertility.

## Conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

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