ORIGINAL RESEARCH PAPER

Rheumatology

KEY WORDS: Granulomatosis with polyangiitis (GPA), Wegener granulomatosis, anti-neutrophil-cytoplasmic-antibody (ANCA) associated vasculitides (AAV), pulmo-renal syndrome, small vessel necrotizing vasculitis, pauci-immune complex vasculitis, PR3 ANCA positive vasculitis.

CASE SERIES OF PR3 ANCA POSITIVE VASCULITIS PATIENTS:

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ABSTRACT

Granulomatosis with polyangiitis (GPA) is a rare vasculitis affecting small vessels. Hallmark features include necrotizing granulomas and pauci-immune complex vasculitis, which most commonly affects the upper respiratory tract, lungs, and kidneys. In these patients, we must initiate early treatment to prevent irreversible organ damage and death. Here, we describe three cases that were treated at tertiary care teaching hospital in Gujarat, India.

INTRODUCTION:

Wegener granulomatosis, renamed as granulomatosis with polyangiitis, is a small vessel necrotizing vasculitis, which is a component of a anti-neutrophil-cytoplasmic-antibody (ANCA) associated vasculitides (AAV). AAV includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA or Churg Strauss syndrome). Among the three ANCA-associated vasculitides, GPA is the most common.This classification on the Modern Nomenclature of Systemic Vasculitides was laid down at the Chapel Hill Consensus Conference in 2012.(1)

The first case was described by a German medical student named Heinz Klinger in 1931. Five years later, in 1936, a German pathologist, Friedrich Wegener, described three cases of peculiar small vessel vasculitis with granulomatous inflammation and identified the disorder as a distinct form of vasculitis. In 1954, Godman and Churg published a review of 22 cases, and the disease was universally known as Wegener's granulomatosis.(2)

Granulomatosis with polyangiitis is an uncommon disease with an estimated prevalence of 3 per 100,000. It is extremely rare in blacks compared with whites; the male-to-female ratio is 1:1. The disease can be seen at any age; ~ 15% of patients are < 19 years of age, but only rarely does the disease occur before adolescence; the mean age of onset is ~40 years.(3)

Case 1

A 46 - year - old female presented with redness in both eyes associated with blurring of vision , bilateral ear discharge with hearing loss for 2 months. Red blisters over extensor surface and deviation of mouth toward right with drooping of saliva from left side for 1 month. The patient experienced progressive dyspnea associated with chest pain and dry cough for 10-15 days. the patient didn't have any significant past medical history. On examination the patient had left sided LMN palsy. Lab investigations showed normocytic normochromic anemia,thrombocytosis with raised inflammatory markers and urine microscopic examinations showed hematuria(blood+1) and 8-10 red cells. PR3 ANCA was positive and skin biopsy suggestive of neutrophilic infiltration in superficial dermal vessels and subepidermal tissue with foci of necrosis. Immunofluorescence showed granular staining in dermal blood vessels which was negative for IgG,IgA and IgM. HRCT was suggestive of consolidations with few necrotic areas in apicoposterior and anterior segment of left upper lobe (possibility of : 1.Necrotising pneumonia 2. Lung abscess). Patient was treated with immunosuppressive therapy (pulse methylprednisolone, rituximab) and antibiotics. Patient's symptoms improved with treatment. She is currently on maintenance therapy (rituximab and steroid).

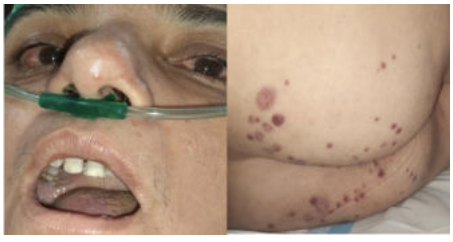

Figure 1. Redness of eye
Figure 2. Red blister over skin

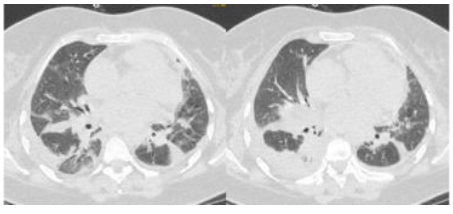

Figure 3. HRCT images of case 1

Case 2

A 48 - year - old male presented with a cough with yellowish, foul smelling, and occasionally bloody expectoration, associated with low grade fever and nasal blockage. He also had rashes over the trunk , Proximal parts of all 4 limbs for 1 month. Patient had painless oral ulcer on gingivobuccal sulcus,palate and buccal mucosa for 1 month, and bilateral hearing loss with whitish discharge from ear for 1 month. Patient did not have any significant past medical history. Lab investigations showed normocytic normochromic

anemia,thrombocytosis with raised inflammatory markers, and urine microscopic examinations showed hematuria(blood+1) and 8-10 red cells. PR3 ANCA was positive. 24 hr urinary protein was 1107 (normal range 0-100). Nasal endoscopic biopsy showed inflammatory exudates. Punch biopsy of Lower lips ulcer and right thigh ulcer specimen showed neutrophilic infiltration in superficial dermal vessels and subepidermal tissue with foci of necrosis (leukocytoclastic vasculitis). HRCT was suggestive of large nodules with internal cavitation in the bilateral lung field. Patient was treated with immunosuppressive therapy (pulse methylprednisolone, rituximab) and antibiotics. Patient's symptoms improved with treatment. He is currently on maintenance therapy (rituximab and steroid).

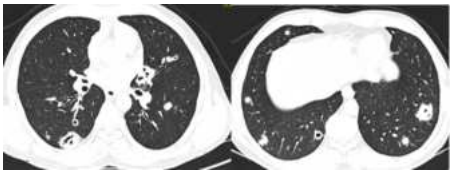

Figure 4. HRCT images of case 2

Case 3

A 46 - year - old female presented with redness in both eyes, not associated with blurred vision, and ear discharge with hearing loss for 1 month. The patient then developed a high - grade fever with chills and rigor, associated with dry cough and gradually progressive breathlessness for 1 week. On examination, the patient had right eye ptosis. She is a known case of hypothyroidism and on regular treatment. Laboratory investigations showed normocytic normochromic anemia with raised inflammatory markers, and urine routine showed proteinuria (albumin : trace) and hematuria (blood+2) with 14-16 red cells. PR3 ANCA was positive. Chest X-ray suggested air space opacity in bilateral lung fields , indicating the possibility of consolidation. MRI of the orbit did not show any lesion. Patient was treated with immunosuppressive therapy (pulse methylprednisolone, rituximab) and antibiotics. Patient's symptoms improved with treatment. She is currently on maintenance therapy (rituximab and steroid).

Investigations table of all 3 cases:

Investigation	Case 1			Case 2			Case 3		
	Day 1	Day 3	Day 7	Day 1	Day 3	Day 7	Day 1	Day 3	Day 7
Hemoglobin (13-16 g/dL)	9.7	10.3	9.6	10.3	10.8	10.7	7.7	8.7	9
WBC (4000-11000 microliter)	8300	14000	8580	7980	14870	13160	17610	9400	6920
Platelet (150000-4500000 microliter)	617K	811K	808K	687K	659K	613K	362K	273	288K
N/L ratio (49-75% / 26-46%)	80/14	87/11	80/15	82/11	92/5	80/14	80/14	84/07	85/8
Eosinophil (0-5%)	2	0	1	1	1	1	1	1	1
MCV (83-101 fL)	87	85	84	82	83	86	92	94	92
SGPT (10-49 U/L)	26	30	31	93	122	95	28	–	22
SGOT (0-34 U/L)	39	59	58	67	74	24	34	–	30
Creatinine (0.5-1.1 mg/dL)	0.43	–	0.38	0.47	0.59	0.67	0.76	0.61	0.65
CRP (>5 positive)	307	178	45.8	134	71	–	160.97	–	55.3
ESR (0-20 mm/hr)	120	–	–	102	–	–	96	–	–

DISCUSSION:

Granulomatosis with polyangiitis (GPA) is characterized by a pulmo-renal syndrome associated with otorhinolaryngologic manifestations. Cytoplasmic-ANCA (c-ANCA) with autoantibodies directed against proteinase 3 antibodies is seen in approximately 90% of the cases with GPA, and the remaining are perinuclear-ANCA (p-ANCA) directed against myeloperoxidase antibodies. (3)

The formation of the granulomas in GPA starts with the formation of neutrophilic microabscesses. Partial or total occlusion of blood vessels occurs due to granulomas formed by GPA.Granulomas of tuberculosis and sarcoidosis are well formed but in GPA, granulomas are not well-formed. These granulomas consist of giant cells surrounded by plasma cells, lymphocytes, and dendritic cells. These cells can damage the submucosa and penetrate the surrounding tissues, cartilage, or bone, resulting in necrosis and permanent deformities. (4)

Approximately 95 % of patients have upper respiratory involvement, with sinusitis and nasal diseases being common. 85-90% of patients have pulmonary involvement in the form of pulmonary infiltrations or pulmonary nodules. Subglottic stenosis and bronchial stenosis are also potentially serious complications of GPA. Approximately 77% of patients have renal involvement, which, if left untreated, directly or indirectly accounts for most of the mortality in this disease. (3) Eye involvement is common and is seen in more than half of the people with the disease, with scleritis and conjunctivitis being most commonly observed. Hearing loss and otitis media are seen in 42% and 44% of patients, respectively, throughout the course of the disease. Dermatologic involvement is reported in approximately 46% of the patients with GPA, presenting with purpura, vesicles, ulcers and subcutaneous nodules; biopsy reveals vasculitis, granuloma, or both. Nervous system involvement is seen in about 23% of the patients, with peripheral neuropathies being the most common. Neuropathy could lead to mononeuritis multiplex. Cardiac involvement (8% of patients) manifests as pericarditis, coronary vasculitis, or rarely, cardiomyopathy. (3)

The ELK (E stands for ears, nose, and throat or upper respiratory tract, L for lung, and K for kidney) proposed by DeRemee utilizes ANCA to diagnose. Per these criteria, any typical manifestation involving the ELK along with positive c-ANCA or typical histopathological finding qualifies for a diagnosis of GPA. (5)

The treatment of GPA involves the use of immunosuppressive agents in various combinations. Treatment is classified into two phases: the induction phase and the maintenance phase. Commonly used agents for induction therapy are cyclophosphamide, glucocorticoids, rituximab, and plasmapheresis if indicated. Cyclophosphamide, in combination with glucocorticoids, has been proven effective in treating life- or organ-threatening disease. Pulse steroids for 3 days before initiating oral glucocorticoids are frequently used. The choice is based on patient preference, clinician preference, and the adverse effects associated with each. According to the Rituximab versus Cyclophosphamide for Induction of Remission for ANCA-associated Vasculitis trial (RAVE trial). (6) It was concluded that rituximab was not inferior to daily cyclophosphamide for induction of remission and may be superior in relapsing disease. (3) In patients without severe disease and no contraindication to methotrexate, methotrexate in combination with glucocorticoids is used. Indications for plasmapheresis include rapidly declining kidney function, the presence of

positive anti-glomerular basement membrane antibodies, or pulmonary hemorrhage complicated by respiratory compromise that does not respond to intravenous glucocorticoids. Maintenance therapy is initiated after induction of remission is achieved (usually within 3-6 months). Patients are transitioned to maintenance therapy to avoid relapses. Methotrexate, azathioprine, and rituximab are effective. The preference for one of these agents depends on whether the patient has been newly diagnosed or has experienced more than one relapse. Other factors that influence the choice of the maintenance agent include a prior history of toxicity or comorbidity that increases the risk of toxicity to a particular agent. The duration of maintenance therapy is usually 12-36 months after remission has been induced. In patients who are at high risk of relapse, maintenance therapy is continued indefinitely.

The average life expectancy for a patient with GPA without any treatment is 5 months, with a 1-year survival rate of less than 30%. In recent times, more than 80% of treated patients are alive for at least eight to nine years. Although the prognosis of GPA has significantly improved with the introduction of immunosuppressive agents and biologics, there is significant morbidity from the disease itself (86%) or due to side effects from the treatment (42%). Patients with severe renal involvement have a guarded prognosis and a higher rate of mortality. (7)

CONCLUSION:

Granulomatosis with Polyangiitis (GPA), is a complex autoimmune disorder characterized by inflammation of the blood vessels, which can lead to damage in various organ systems, most notably the respiratory tract and kidneys. Early diagnosis and prompt treatment are crucial for improving patient outcomes and preventing severe complications. Advances in immunosuppressive therapies have significantly enhanced the management of GPA, offering patients improved quality of life and survival rates. Continuous monitoring and multidisciplinary care remain pivotal in the effective management of this chronic condition.

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