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Case Series

Clinical Spectrum of Granulomatosis with Polyangiitis-Wegener's Granulomatosis: A Case Series

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Abstract

Granulomatosis with polyangiitis is a multi-organ system disease of unknown etiology, characterized by granulomatous inflammation, tissue necrosis, and variable degrees of vasculitis in small- and medium-sized blood vessels. It is rare and commonly missed. Here, we present three cases who have been followed for 1-3 years.

Key words: Granulomatous inflammation, Necrotizing vasculitis, Polyangiitis-Wegener's

INTRODUCTION

Granulomatosis with polyangiitis is a granulomatous necrotizing vasculitis characterized by a predilection to affect the upper and lower respiratory tracts and, in most cases, kidneys.[1] The disease was first described in 1931 by Heinz Klinger, a German medical student.[2-4] In 1936 and 1939, Friedrich Wegener, a pathologist, provided detailed information about three patients with a similar illness. It has been subsequently redesignated as granulomatosis with polyangiti.[5] It is classified as anti-neutrophil cytoplasmic antibodies (ANCA) positive vasculitis mostly localized on the small and medium- sized blood vessel.[1,6] Although distinctive patterns of organ involvement exist in Granulomatosis with polyangiitis, any organ system can become affected.[1,7]

It has a predilection for causing destructive lesions in the upper respiratory tract, including nasal septal perforation, "saddle-nose" deformity, erosive sinusitis, middle ear damage, and subglottic stenosis.[8,9] Classic lung lesions are pulmonary nodules with a tendency to cavitation, alveolar hemorrhage and non-specific infilterates.[10,11] Glomerulonephritis that leads to crescentic and segmental, necrotizing lesions, is often associated with rapidly progressive glomerulonephritis.[12,13] Migratory oligoarthralgias and oligoarthritis are common[1,8] Granulomatosis with polyangiitis cases, particularly those with severe, widespread disease, are associated with anti-neutrophil cytoplasmic antibodies.[6,11] The sensitivity of proteinase 3 (PR3-ANCA) is about 90% in active WG and 40% when the disease is in remission. The specificity of PR3-ANCA in the diagnosis of WG exceeds 95%.[14,15,1,12] For patients with limited WG, defined as the absence of an immediate threat to either the function of a vital organ or the patient's life, 30% or more lack ANCA.[16-18] Immunosuppressive therapy is effective in the induction of disease remissions in most cases. Untreated systemic WG had a dismal prognosis, with a mean survival of approximately 5 months.[12,19] Not much data is available on the epidemiology of WG in India. A study conducted at AIIMS, New Delhi detailed 23 cases of WG between 1988 and 2000. 16 of the patients were male and 7 were female.[20] In another study conducted at KEM Mumbai 25 patients of WG were diagnosed over a period of 4 years. There were 23 cases where generalized WG two cases of limited WG.[21]

Here, we present a case series comprising of three cases which reflects the wide spectrum of clinical presentation of this disease.

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CASE SERIES

Case 1

A 43-year-old female presented with 4 months history of fever, polyarthritis, purulent ear discharge, hemoptysis, parotitis, scleritis of left eye, and decreased urination. Patient was treated for chronic sinusitis, and otitis media elsewhere but the condition did not improve. On the day of admission the patient was conscious afebrile, her pulse was regular 86/min, BP was 130/86 mm of Hg. She had severe pallor, nodular scleritis of left eye, non-foul smelling discharge from right ear, and symmetrical polyarthritis. Audiometry revealed B/L sensorineural deafness. Examination of cardiovascular and respiratory system was normal. Gastrointestinal (GI) system and central nervous system (CNS) were normal. On the 4th day of admission, patient developed anuria and received hemodialysis. She developed hypertension during the course of her stay in the hospital which was controlled by calcium channel blockers and diuretics.

X-ray of chest was normal. Computed tomography (CT) thorax showed multiple nodules in left upper and right lower lobes, diffuse ground glass opacity, with septal thickening in B/L perihilar region. Cavity was present in left upper lobe along with B/L pleural effusion. All these findings were suggestive of WG. USG abdomen and pelvis revealed B/L acute medical renal disease along with moderate ascites.

A diagnosis of generalized granulomatosis with polyangiitis was made based on involvement of lungs, upper respiratory tracts, kidneys, positive ANCA, and anti-PR-3 antibody (>200 Ru/ml) (Table 1).

Following the confirmation of diagnosis patient was given 1 g methyl prednisolone bolus daily for three days followed by tab prednisolone 1 mg/kg body weight. She was also started on tab cyclophosphamide 2 mg/kg, with a starting dose of 50 mg/day. It was increased to 75 mg/day with dose modification based on her serum creatinine levels. She received four sessions of hemodialysis and was given four units of blood transfusion. Patient was discharged with cyclophosphamide 75 mg/day, prednisolone 50 mg/day, anti-hypertensives, and calcium supplements. At the time of her discharge her hemoglobin (HB) was 8 g%. Renal function had improved. Her serum creatinine was 2.6 mg/dl and serum urea was 86 mg/dl. She requested to be discharged was asked to report after 1 months but failed to return.

8 months later she was readmitted with complaints of generalized weakness and swelling of feet. Her HB was 6.5 g%, serum creatinine was 4.6 mg/dl, serum urea was 126 mg/dl. Her thin layer chromatography 9800/cmm, DC-N-86% L 11% E 2% L 1%, Random blood sugar (RBS) 100 mg/dl. Liver function was within normal limits. Urine contained traces of albumin, plenty of red blood cells, 20-30 pus cells/HPF, there was no scleritis, ear discharge, polyarthritis, or fever. Her X-Ray showed no lesions. She was given 3 bolus doses of methylprednisolone of 1 g each along with mycophenolate mofetil, 1 g/day and advised to increase the dose to 2 g over 2 weeks period since she was unable to afford Rituximab for financial reason.

Table 1: Investigations of case 1

TLC	23180/cm²
DC	N 90% L9% E1%
HB	4.3 g/dl
TPC	5,20,000
ESR	155
Serum urea	83
Serum creatinine	5.9
S.NA	125
S. K	5.9
Serum bilirubin (T)	1.2
Serum bilirubin (D)	0.4
SGPT	48
SGOT	48
ALP	185
Urine pus cells	15-20/HPF
Urine RBC	>100/HPF
Urine albumin	Trace
Urine sugar	Absent
C-ANCA	Positive
Anti PR-3	>200 Ru/ml
	(0-20) Ru/ml

TLC: Thin layer chromatography, RBS: Random blood sugar, HB: Hemoglobin, Anti PR-3: Anti proteinase 3

She had already received 13 g of oral cyclophosphamide and therefore mycophenolate was preferred to avoid toxicity in the background of deteriorating renal function renal function. The patient requested a discharge and was asked to follow up a month later. However, the patient never returned.

Case 2

A 48-year-old male presented with 4 years history of chronic sinusitis, and polyarthralgia. He gave history of epistaxis and nasal discharge for which he was treated by the ENT specialist. A nasal growth was observed for which he underwent a biopsy. Histopathological examination showed evidence of chronic inflammation. Subsequently, he was admitted in the unit of clinical immunology for prolonged cough, fever and hoarseness of voice. On examination patient was afebrile, pulse rate 84/min BP 116/70 mmHg examination of the lungs revealed basal crepitation. Examination of upper respiratory tract revealed maxillary sinusitis. He had a saddle shaped nose, congested, and swollen vocal chords were found in the laryngoscopic

examination. Cardiovascular (CVS) examination was normal. GI and CNS examination revealed no abnormality. His HR CT thorax showed sub pleural nodules. He was diagnosed as a case of limited Wegner's granulomatosis based on involvement of upper respiratory tract, saddle nose deformity, lung involvement in form of sub pleural nodules and positive anti-MPO autoantibody. He put on 1 mg/kg of oral prednisolone which was tapered after 6 weeks. He was lost to follow-up for 3 years and readmitted for fever, cough and hoarseness of voice. He was put on antibiotics and the dose of steroid was hiked to 0.5 mg/kg and methotrexate 7.5 mg/week was added and advised to increase the dose by 2.5 mg monthly. He came back after 3 months and. At this juncture, patient was asymptomatic; however, his renal functions were deranged His serum creatinine was 1.5 mg/dl. He was now diagnosed as a case of classical Wegner's in view of renal dysfunction and was started on tab cyclophosphamide 2 mg/kg body weight for 6 months. He was also given pneumocystis carinii prophylaxis with tab cotrimoxazole DS once a day. After 6 months, the patient was in complete remission. Cyclophosphamide was discontinued and tab methotrexate 7.5 mg/week was started and increased by 2.5 mg weekly up to 15 mg/week. Oral prednisolone 5 mg was given as a maintenance dose. Now after a follow-up of 1½ years, patients symptoms have resolved and he is currently on tab Methotrexate calcium supplements (Table 2).

Case 3

Our third case was 54-year-old women who presented with 6 years history of chronic sinusitis, headache, hoarseness of voice and non-productive cough. There was no history of hypertension or type 2 DM On examination the patient was febrile. Her pulse was 100/min, BP was 136/70. She had tender sinusitis left sided lid edema, palpable purpurae on lowerlimb suggestive of cutaneous vasculitis. ENT examination revealed laryngeal edema. Abdomen was soft and non-tender. CVS and CNS examination was normal. X-Ray paranasal sinuses (PNS) revealed pansinusitis, X-Ray chest was normal. High resolution CT thorax showed lower lobe infiltrations. CT scan of PNS showed several maxillary sinusitis. Her C-ANCA was negative and anti-PR-3was negative. She was diagnosed as case of limited form of granulomatosis with polyangiitis based on the involvement of upper respiratory tracts, lungs, and cutaneous vasculitis. She was started on antibiotics for sinusitis, and prednisolone 1 mg/kg body weight.

A drainage of PNS was planned but deferred. When the patient was readmitted for PNS drainage, routine investigation revealed RBS of 300 mg/dl. Her HBA1C was 8.1, FBS was 286 and PPBS was 312. She also had lobar pneumonia. Patient was started on regular insulin and broad spectrum antibiotics.

Subsequent biopsy of PNS showed evidence of chronic inflammation. She was discharged after the infection subsided and blood sugar was stabilized. She was on maintenance dose of prednisone (7.5 mg/day) methotrexate (10 mg/day) and cotrimoxazole prophylaxis. After 1 year, the patient has remained relatively asymptomatic (Table 3 and Figures 1-3).

DISCUSSION

Granulomatosis with polyangiitis (Wegener's) is an uncommon disease with an estimated prevalence of 3/100,000.[22] It is extremely rare in blacks compared with whites; the male-to-female ratio is 1:1.[22] 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.[22] Involvement of the upper airways occurs in 95% of patients with granulomatosis with polyangiitis (Wegener's).[23] Patients often present with severe upper respiratory tract findings such as paranasal sinus pain and drainage and purulent or bloody nasal discharge, with or without nasal mucosal ulceration.[8,10,11] Nasal septal

Table 2: Laboratory investigations of case 2

HB	14.4 g%
TLC, ESR	24,300, 90
DC	N85, L 11, E4
RBS	105
Serum urea, serum creatinine	40mg/dl 1.3mg/dl
Serum bilirubin T Serum bilirubin D	1.2 md/dl 0.4 mg/dl
SGOT	38
SGPT	48
ALP	116
Anti MPO	28.9 (N≤9)
ANCA, Anti PR3	NEGATIVE

Anti PR3: Anti proteinase 3, TLC: Thin layer chromatography, RBS: Random blood sugar, ANCA: Anti-neutrophil cytoplasmic antibodies, HB: Hemoglobin

Table 3: Laboratory investigations of case 3

HB	12.6
TLC, DC	18,600 N 89%, L10% E 1%
TPC	20,6.000
ESR	101
Serum urea	27 mg/dl
Serum creatinine	0.9 mg/dl
Bilirubin (t)	1.0 mg/dl
Bilirubin (d)	0.4 mg/dl
SGOT	32
SGPT	26
ALP	126
RBS	100 mg/dl
CRP	30 mg/dl

PR3: Proteinase 3, TLC: Thin layer chromatography, RBS: Random blood sugar, HB: Hemoglobin

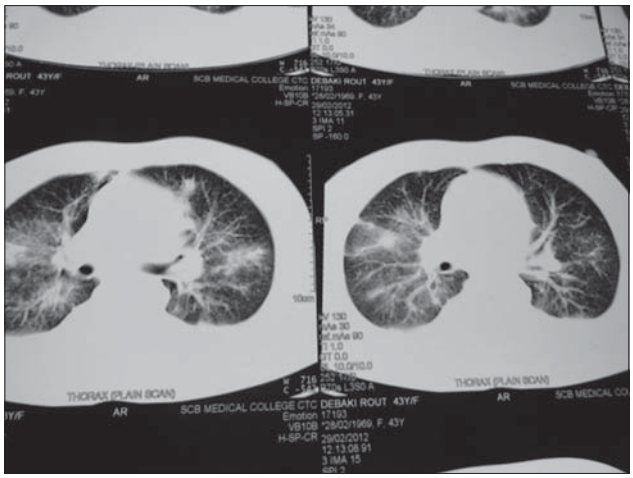

Figure 1: Computed tomography thorax showing bilateral nodular lesions, ground glass opacity and cavity left upper lobe in granulomatosis with polyangitis (Case 1)

Figure 2: Saddle shaped nose of case 2

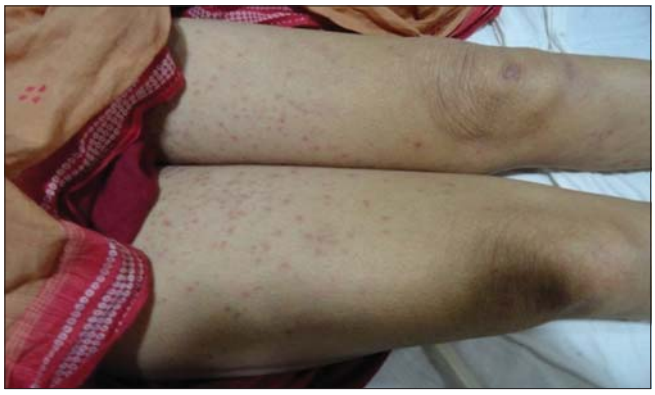

Figure 3: Cutaneous vasculitis of case 3

perforation may follow, leading to saddle nose deformity. Serous otitis media may occur as a result of Eustachian tube blockage.[8] Subglottic tracheal stenosis resulting from active disease or scarring occurs in 16% of patients and may result in severe airway obstruction.[8,23] Pulmonary involvement may be manifested as asymptomatic infiltrates or may be clinically expressed as cough, hemoptysis, dyspnea, and chest discomfort.[23,10,11] It is present in 85-90% of patients. Eye involvement (52% of patients) may range from a mild conjunctivitis to dacryocystitis, episcleritis, scleritis, granulomatous sclerouveitis, and ciliary vessel vasculitis. Renal disease (77% of patients) generally dominates the clinical picture and, if left untreated, accounts directly or indirectly for most of the mortality.[24,9,12] Cutaneous manifestations have been reported in 40-50% of patients with WG and may be part of the initial presentation in 13-25% of cases. The cutaneous manifestations of WG include ulcers, palpable purpura, subcutaneous nodules, papules, and vesicles.[22] Prior to the introduction of effective therapy, granulomatosis with polyangiitis (Wegener's) was universally fatal within a few months of diagnosis.[19,25]

In 1990, the American College of Rheumatology (ACR) established the criteria for the classification of WG as nasal or oral inflammation, radiologically demonstrated pulmonary infiltrates, abnormal urinary sediment (red cell cast, hematuria), granulomatous inflammation on biopsy.[16] Patients are diagnosed with Wegener's granulomatosis if 2 of these 4 criteria are present.[16,13] The presence of autoantibodies to proteinase 3/cANCA is not required for diagnosis of WG, by either ACR or Chapel Hill consensus Conference definition.[16,13,26]

Glucocorticoids alone led to some symptomatic improvement, with little effect on the ultimate course of disease.[27] 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%.[19,15,21] After 3-6 months of induction treatment, cyclophosphamide should be stopped and switched to another agent for remission.[21] The agents with which there has been the greatest published experience are methotrexate and azathioprine In the absence of toxicity, maintenance therapy is usually given for a minimum of 2 years past remission, after which time consideration can be given for tapering over a 6-12 month period until discontinuation.[27,28] In two recent randomized trials that enrolled ANCA positive patients with severe active granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis, rituximab 375 mg/m^2 once a week for 4 weeks in combination with glucocorticoids was found to be as effective as cyclophosphamide with glucocorticoids for inducing disease remission.[27,28]

In our case report, we have shown the wide spectrum of clinical presentation of the disease. Two of the patients were female and one was male. The mean age at

presentation was 48 years. All the three case had upper respiratory tract involvement in the form of chronic sinusitis. One of our patients had sensorineural hearing loss. Cutaneous vasculitis and saddle nose deformity were also found. Lung involvement was present in all three of the patients. All three of them showed different forms of lung involvement each of which has been described in WG. Our first case is the classical case of granulomatosis with polyangiitis. In the second case, the spectrum gradually changed from limited granulomatosis with polyangiitis to classical variety. The third case has remained in limited form. In our set up the main drawback is late presentation with delayed diagnosis. All these patients were treated for chronic sinusitis and were given Non-steroidal anti-inflammatory drug (NSAIDS)/antibiotics in view of the high leukocyte count. NSAID may precipitate renal failure or aggravate an already dysfunctional kidney.

CONCLUSION

Granulomatosis with polyangiitis has wide spectrum clinical manifestations. It should always be considered as differential diagnosis in patients with intractable sinusitis, deafness and otitis media. Since renal involvement at times can be subtle utmost caution should be exercised while prescribing NSAIDS to these patients.

REFERENCES

1. Godman GC, Churg J. Wegener's granulomatosis: Pathology and review of the literature. AMA Arch Pathol 1954;58:533-53.
2. Klinger H. Grenzformen der periarteritis nodosa. Frankfurt Z Pathol 1931;42:455.
3. Wegener F. Über eine eigenartige rhinogene granulomatose mit besonderer beteiligung des arterien systems und der nieren. Beitr Pathol Anat Allg Pathol 1939;102:36-68.
4. Fauci AS, Wolff SM. Wegener's granulomatosis: Studies in eighteen patients and a review of the literature. Medicine (Baltimore) 1973;52:535-61.
5. Wegener F. Über eine generalisierte, septische of gefäberkrankungen. Verh Dtsch Pathol Ges 1936;29:202.
6. Jennette JC, Falk RJ, Bacon PA, Basu N, Ferrario MC, Flores-Suarez LF, *et al*. Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides Arthritis & Rheumatism. Vol. 65. American College of Rheumatology, January, 2013; 2012. p. 1-11.
7. Specks U, Wheatley CL, McDonald TJ, Rohrbach MS, DeRemee RA. Anticytoplasmic autoantibodies in the diagnosis and follow-up of Wegener's granulomatosis. Mayo Clin Proc 1989;64:28-36.
8. Murty GE. Wegener;s granulomatosis: Otorhinolaryngological manifestations. Clin Otolaryngol Allied Sci 1990;15:385-93.
9. Anderson G, Coles ET, Crane M, Douglas AC, Gibbs AR, Geddes DM, *et al.* Wegener's granuloma. A series of 265 British cases seen between 1975 and 1985. A report by a sub-committee of the British Thoracic Society Research Committee. Q J Med 1992;83:427-38.
10. Kuhlman JE, Hruban RH, Fishman EK. Wegener granulomatosis: CT features of parenchymal lung disease. J Comput Assist Tomogr 1991;15:948-52.
11. Walton EW. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). Br Med J 1958;2:265-70.
12. Andrassy K, Erb A, Koderisch J, Waldherr R, Ritz E. Wegener's granulomatosis with renal involvement: Patient survival and correlations between initial renal function, renal histology, therapy and renal outcome. Clin Nephrol 1991;35:139-47.
13. Sørensen SF, Slot O, Tvede N, Petersen J. A prospective study of vasculitis patients collected in a five year period: Evaluation of the Chapel Hill nomenclature. Ann Rheum Dis 2000;59:478-82.
14. van der Woude FJ, Rasmussen N, Lobatto S, Wiik A, Permin H, van Es LA, *et al.* Autoantibodies against neutrophils and monocytes: Tool for diagnosis and marker of disease activity in Wegener's granulomatosis. Lancet 1985;1:425-9.
15. Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP, *et al.* The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 1990;33:1101-7.
16. Carrington CB, Liebow A. Limited forms of angiitis and granulomatosis of Wegener's type. Am J Med 1966;41:497-527.
17. Cassan SM, Coles DT, Harrison EG Jr. The concept of limited forms of Wegener's granulomatosis. Am J Med 1970;49:366-79.
18. Kerr GS, Fleisher TA, Hallahan CW, Leavitt RY, Fauci AS, Hoffman GS. Limited prognostic value of changes in antineutrophil cytoplasmic antibody titer in patients with Wegener's granulomatosis. Arthritis Rheum 1993;36:365-71.
19. Regan MJ, Hellmann DB, Stone JH. Treatment of Wegener's granulomatosis. Rheum Dis Clin North Am 2001;27:863-86, viii.
20. Kumar A, Pandhi A, Menon A, Sharma SK, Pande JN, Malaviya AN. Wegener's granulomatosis in India: Clinical features, treatment and outcome of twenty-five patients. Indian J Chest Dis Allied Sci 2001;43:197-204.
21. Pradhan VD, Badakere SS, Ghosh K, Almeida A. ANCA: Serology in Wegener's granulomatosis. Indian J Med Sci 2005;59:292-300.
22. Carlson JA, Cavaliere LF, Grant-Kels JM. Cutaneous vasculitis: Diagnosis and management. Clin Dermatol 2006;24:414-29.
23. Cordier JF, Valeyre D, Guillevin L, Loire R, Brechot JM. Pulmonary Wegener's granulomatosis. A clinical and imaging study of 77 cases. Chest 1990;97:906-12.
24. Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: Prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med 1983;98:76-85.
25. Hollander D, Manning RT. The use of alkylating agents in the treatment of Wegener's granulomatosis. Ann Intern Med 1967;67:393-8.
26. Falk RJ, Gross WL, Guillevin L, Hoffman G, Jayne DR, Jennette JC, *et al*. Granulomatosis with polyangiitis (Wegener's): An alternative name for Wegener's granulomatosis. Ann Rheum Dise 2011;70:704
27. De Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, *et al.* Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52:2461-9.
28. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, *et al.* Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221-32.

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