

Wegener's Granulomatosis in India: Clinical Features, Treatment and Outcome of Twenty-Five Patients

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ABSTRACT

Objective. To report our clinical experience on Wegener's granulomatosis (WG).

Methods. A retrospective review of case records of all patients with WG in our Rheumatology Clinic during the period July 1988 to June 2000 was carried out and the details of demography, clinical and laboratory data, treatment and outcome were obtained and analysed.

Results. Twenty-five patients (16 females and 9 males) were found eligible for inclusion in the study. The mean age and duration of symptoms at presentation were 33.5 years and 5.5 months, respectively. Two patients had limited WG. Twenty-two patients with generalized WG were treated with standard regimen comprising oral prednisolone (1 mg/kg/day) and oral cyclophosphamide (2 mg/kg/day). Cyclophosphamide was continued for at least one year after the patient attained remission. One patient was treated with intravenous cyclophosphamide regimen. The two patients with limited WG were treated with oral prednisolone and methotrexate (10-12.5 mg as a single dose per week). Remission was achieved in 24 patients after a median time of six months. The median follow-up of patients was five years (range 4 months-11 years). Five patients were lost to follow-up. Eight patients suffered a relapse. The mean time for relapse was 34 months after the initial remission. Seven out of eight patients remitted again after reinstitution of the initial induction regimen. One patient died of diffuse pulmonary haemorrhage despite early institution of therapy.

Conclusion. WG is being increasingly diagnosed in India now because of greater awareness and diagnostic aids. Although remissions are easy to achieve, relapses continue to pose a challenge to the treating physician.

Key words : Wegener's granulomatosis, Cyclophosphamide, Outcome.

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INTRODUCTION

Wegener's granulomatosis (WG) is a necrotising granulomatous vasculitis usually affecting the upper and lower respiratory tracts and kidneys. It belongs to a group of primary systemic vasculitides of unknown etiology, that are associated with antineutrophil cytoplasmic

antibodies (ANCA). Any organ system can be affected and the course is very variable. Antineutrophil cytoplasmic antibody (ANCA)¹ has proved to be a very useful aid to diagnose this aggressive disease in which the two year mortality has been reported to be as high as 90% in untreated cases². With the advent of ANCA as a serological marker, this disease is being

diagnosed at an earlier stage and with a greater degree of certainty in India as shown by Bamberg *et al*³. However, a significant proportion of cases are still being misdiagnosed as tuberculosis, thus leading to a delay in the institution of appropriate therapy³⁻⁵. The present work describes the clinical profile, response to treatment and follow-up of 25 confirmed cases of WG.

MATERIAL AND METHODS

This is a retrospective analysis of the case records of 25 patients seen in the Rheumatology Clinic during the period July 1988 to June 2000. Three cases in this series were published in our earlier series⁴. The diagnosis of WG was suspected when the following constellation of clinical features was present :

1. Upper respiratory tract involvement manifested by paranasal sinus pain with purulent or bloody nasal discharge, nasal blockade, nasal or pharyngeal mucosal ulceration, saddle nose deformity, etc.
2. Lower respiratory tract involvement—either asymptomatic infiltrates or symptoms like cough, hemoptysis and dyspnoea.
3. Renal involvement—in the form of proteinuria, hematuria and various casts (active urinary sediment) and azotemia.
4. Eye involvement—in the form of conjunctivitis, episcleritis, scleritis, uveitis or proptosis due to retro-orbital mass.

Confirmation of the diagnosis by histopathological evidence of granulomatous vasculitis in appropriate biopsy specimens could be obtained in a few patients. In others, a strong clinical suspicion based on the involvement of a characteristic triad—upper respiratory tract, lower respiratory and renal involvement was supported with a positive test for ANCA. The presence of ANCA was detected by using the indirect immunofluorescence method described by van der Woude *et al*¹. The following conditions were carefully excluded: Systemic lupus erythematosus (SLE), Churg

Strauss syndrome, Goodpasture's syndrome, tumours of upper airways and lungs, pulmonary tuberculosis, fungal infections of lungs and midline granuloma.

Twenty-two of the 23 patients with generalised WG were started on a regimen consisting of cyclophosphamide (2mg/kg/day) and prednisolone (1 mg/kg/day) orally. Prednisolone was continued at the same dose for 6-8 weeks and then gradually tapered off over the next 16 weeks. Cyclophosphamide was continued for at least one year after the patient attained clinical remission. One patient received daily oral prednisolone with intravenous pulses of cyclophosphamide (15 mg/kg) at monthly intervals for six months, followed by one pulse every three months for 18 months. Two patients with limited WG were treated with daily oral prednisolone (1 mg/kg/day) and methotrexate (10-12.5 mg as a single oral dose per week). Thereafter, it was gradually reduced.

Relapses were treated with re-introduction of cyclophosphamide and increase in the dose of prednisolone. Remission was defined as per established criteria from the NIH group⁵. Close monitoring of complete blood counts and urine was done to detect the side effects of cyclophosphamide. All patients were instructed to increase their fluid intake and to avoid holding urine to minimise the likelihood of haemorrhagic cystitis. In addition, ESR (Westergren), blood urea, serum creatinine and urine examination were monitored every three months. Chest radiographs were repeated as necessitated by the clinical situation.

RESULTS

The demographic and clinical manifestations of the 25 patients are presented along with a series from USA and a series from India for comparison in table 1. The mean age of patients at the time of diagnosis was 33.5 years (17-60). There was a definite female preponderance in this series (16:9). Other major series in the literature have reported a male predominance^{2,6-8}.

Table 1. Demographic and clinical features of Wegener's granulomatosis

	Hoffman <i>et al</i> (USA, 1992)	Bamberg <i>et al</i> (India, 1992)	Present series (India, 2001)
Patients	158	18	25
M:F	1 : 1	1 : 1	9 : 16
Age (years)			
Mean	41	41.5	33.5
Range	9-78	16-75	17-60
Duration of symptoms Before diagnosis (months)			
Mean	15	8	5.5
Range	0-120	1-36	0.5-30
Clinical Features (%)			
Constitutional	50	89	64
Nose/Paranasal sinuses	84	55	84
Lung	85	78	84
Ear	42	28	40
Eye	52	39	64
Kidney	77	73	72
Joints	67	55	44
Skin	46	39	32
Nervous System	23	28	4
Heart	6	NR	4

NR=not reported.

The classic triad of upper respiratory tract, lung and kidney involvement at the time of diagnosis was seen in 14 patients (56%). There were two patients with limited WG with involvement of only upper respiratory tract, eyes and ears. Sixty-four per cent of patients had constitutional symptoms like fever, malaise, weight loss in addition to specific symptoms referable to the pattern of organ-system involvement.

Upper respiratory tract involvement was seen in 84% of patients. This consisted of nasal, sinus and pharyngeal involvement. Radiographs of the paranasal sinuses revealed evidence of pansinusitis in 20% of patients. Two patients suffered from destructive granulomatous inflammation of the nose culminating in a saddle-nose deformity (Figure 1). Both gave a history of bloody nasal discharge for several months. Nasal mucosal biopsy was done in four

patients. Three of the specimens showed granulomatous lesions and one specimen showed granuloma with vasculitis. Palatal perforation or subglottic stenosis was not seen in any patient.

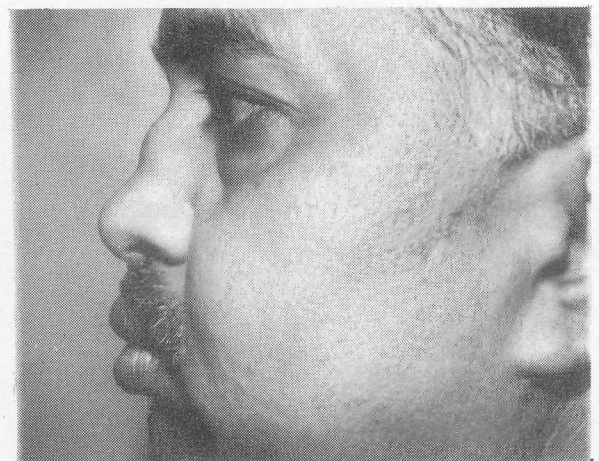


Figure 1. Saddle-nose deformity in a patient with Wegener's granulomatosis.

Ear involvement was seen in 10 patients (40%). The symptoms consisted of earache, hearing loss and tinnitus. The main findings on examination were of serous otitis media and there was sensory-neural involvement in two cases. Most of the patients responded well to immunosuppressive therapy for their disease. Three patients suffered partial hearing loss.

Lung involvement was seen in 84% of patients. Symptoms included cough in 72%, haemoptysis in 36% and dyspnoea in 36 per cent. Physical examination showed paucity of findings in the majority of cases. Features suggestive of consolidation were seen in five and pleural rub was heard in two cases. Chest examination was unremarkable in the remaining patients. The radiological manifestations of lung involvement consisted of cavitating nodules in 9, nodules without cavitation in 5, linear infiltrates in 4 and consolidation in 3 patients. Figures 2a and 2b show the radiological picture in a patient before and after treatment. Ten patients had already taken a trial of anti-tuberculous therapy for 2-4 months without response before referral. Lung biopsy was done in three of the earliest patients (open in two and bronchoscopic in one) to confirm the diagnosis as ANCA estimation was not available at that time. The biopsy showed granulomas consistent with the diagnosis of WG in both the patients.

There was a definite evidence of kidney in-

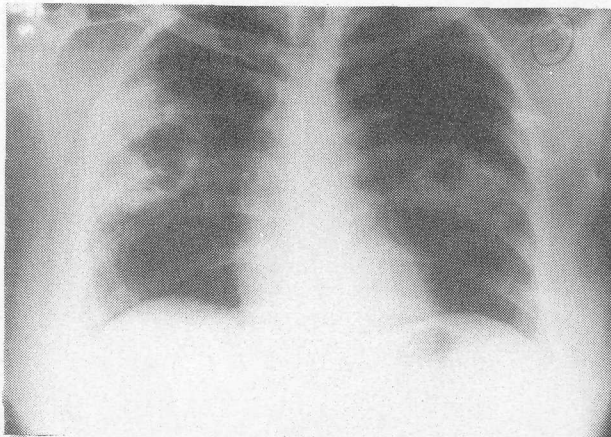


Figure 2a. Chest radiograph of a patient with WG showing two large cavities with surrounding infiltrate before treatment.

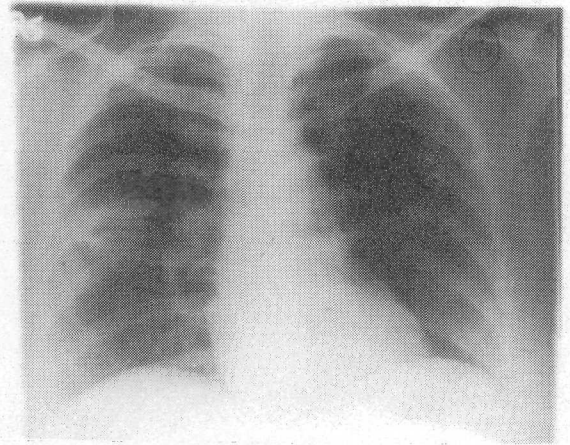


Figure 2b. Chest radiograph of the same patient with marked resolution of the lesions after treatment.

volvement in 18 (72%). Six of these patients had azotemia at the time of diagnosis. Hypertension was present in nine cases. Two patients required hemodialysis support in the first two weeks after presentation (6 cycles and 2 cycles of hemodialysis, respectively). Three out of six patients had residual renal insufficiency after achieving remission. Of the two patients requiring hemodialysis, one patient staged a full recovery with return of normal renal function and the other patient was left with mild stable renal insufficiency. Kidney biopsy was done in eight patients which showed evidence of crescentic necrotising glomerulonephritis in five and focal segmental necrotising glomerulonephritis in three cases.

Eyes were affected in 64% of our patients. The findings consisted of conjunctivitis, episcleritis, scleritis and posterior uveitis. Figure 3 shows



Figure 3. Scleritis in the left eye in a patient with WG.

scleritis in one of the patients. Proptosis was not seen in any patient. Four patients suffered permanent visual loss of varying degrees of severity due to posterior uveitis.

Forty-four per cent of the patients had musculoskeletal involvement. The main complaints were arthralgias and myalgias. Only two patients had objective evidence of arthritis. All the patients responded very well to therapy and none developed joint deformities. Skin involvement in the form of macular rash, purpura and nodules was seen in 32% of patients.

Table 2 shows the results of laboratory investigations. Most of the patients had some degree of anaemia. Leukocytosis was present and ESR was elevated in all the patients at the time of diagnosis. Rheumatoid factor was positive in significant titers in four patients. None of the patients tested positive for anti-nuclear antibody (ANA). ANCA test was performed in 24 patients which revealed typical cytoplasmic pattern of immunofluorescence in 17 patients. None of the samples showed perinuclear pattern of immunofluorescence. Of the remaining eight patients, diagnosis was corroborated with histological evidence in six patients (kidney, lung and nasal mucosa), while in two patients it was based on strong clinical suspicion and subsequent disease course during the follow-up.

Clinical Outcome

Out of the 22 patients, 21 treated with daily prednisolone and cyclophosphamide achieved remission. The only patient treated with daily prednisolone and monthly intravenous cyclophosphamide pulse also attained full remission. Both the patients with limited disease also showed excellent response to therapy. The median time to achieve remission was six months. The median follow-up patients was five years (range 4 months – 11 years). Five patients were lost to follow-up of (not seen in the clinic for more than one year). Adverse effects of therapy included mild, transient leukopenia in two patients and pneumonia in one patient. Gonadal toxicity was not evaluated.

Eight out of 25 patients suffered a relapse, including one patient who had three major relapses. Relapse occurred after a mean of 34 months after initial remission. In this group of eight patients, three patients suffered a relapse limited to the eye (scleritis), four patients had a major relapse with lung and kidney involvement and one had an isolated renal relapse. Two out of three patients with relapse limited to the eye were treated with prednisolone and weekly methotrexate and went into remission on this regimen. One patient was restarted on daily prednisolone and cyclophosphamide with good results. All the four patients with major relapse were restarted

Table 2. Laboratory features in Wegener's granulomatosis

Abnormality	Hoffman <i>et al</i> (% positive)	Bamberg <i>et al</i> (% positive)	Present series (% positive)
Elevated ESR	80	100	100
Anemia	73	91	90
Leukocytosis	NR	64	100
Proteinuria	77	55	72
Hematuria	77	55	72
Rheumatoid factor	NR	25	16
ANF	NR	NR	0
ANCA (cytoplasmic)	88	NR	70

NR=not reported.

on daily prednisolone and cyclophosphamide. Three of these patients attained remission whereas one patient died due to diffuse pulmonary haemorrhage and massive haemoptysis despite early institution of therapy. The status of five patients lost to follow-up remains unknown.

DISCUSSION

To the best of our knowledge, this is the largest series of patients with WG reported from India. It is evident that the disease characteristics and response to treatment are quite similar to those observed all over the world². Our patients with WG were comparatively younger when compared to their western counterparts. This observation holds true for even other rheumatic diseases studied in the Indian population^{8,9}. Most of the reported literature shows either no sex bias or slight male preponderance. However, the present series shows slight female preponderance. This could be an artifact arising from the small sample size. Early diagnosis and institution of treatment is crucial in this life-threatening disorder. The ready availability of diagnostic marker *i.e.*, ANCA, and increased awareness about this disease in present times have changed the outlook of this disease. There is still concern about the significant number of cases being misdiagnosed as having tuberculosis as observed in this study. The situation becomes complex as drug-resistant tuberculosis is frequently encountered among the patients referred to major hospitals. This may lead to a delay in instituting appropriate treatment. ANCA undoubtedly plays a valuable role in the differential diagnosis of such cases.

The present series again illustrates the excellent response to the standard regimen of prednisolone and daily oral cyclophosphamide. Also, the use of less toxic alternatives like methotrexate in combination with steroids in cases of limited WG appears to be a reasonable approach. Intravenous cyclophosphamide pulse therapy was tried in only one patient in the present series and was found to be efficacious.

Both equal and decreased efficacy, when compared to daily oral cyclophosphamide, have been described in patients with WG¹¹⁻¹³. Haubitz *et al*¹⁴ treated 25 patients with conventional oral cyclophosphamide regimen and 22 patients with monthly intravenous cyclophosphamide pulses for one year. They found similar rates of remission, relapse, patient survival and renal outcome in the two treatment groups at three years of follow-up¹⁴. The advantages with intravenous regimen included a 57% reduction in the cumulative cyclophosphamide dose and significant reduction in the incidence of leukopenia, severe infections and gonadal toxicity.

The relapse rate in the present series was 32% (8/25) which is in agreement with previous studies in which the rate has ranged from 20-46 per cent¹⁵⁻¹⁷. It has been reported that most relapses occur within the first year after stopping immunosuppression¹⁵⁻¹⁶. In our series, only one out of the eight patients who suffered a relapse did so in the first year after stopping immunosuppression. Also, the organ involvement in three out of four patients who had a major relapse was similar to their initial presentation. It is to be noted that none of the eight patients suffered a relapse while on immunosuppressive therapy.

Contrary to common knowledge, the risk of serious systemic infections in our patients while on immunosuppressive therapy was surprisingly low. Of particular concern is the significant incidence of side effects reported with cyclophosphamide therapy including cystitis (43%), sterility (57%), bladder cancer (2.8%), myelodysplasia (2%) and lymphoma (0.7%)². While we did not evaluate the reproductive function, none of our patients seems to have developed any of the other toxicities. A longer follow up may be revealing.

Owing to the growing concern about the long-term cumulative toxicity of oral cyclophosphamide, including a 25% incidence of bladder cancer reported after 17 years of follow up in patients with rheumatoid arthritis treated with this drug¹⁸, present opinion favours switching to alternative immunosuppressants

once remission is achieved¹⁹. Two recent studies have used cyclophosphamide as the initial agent to induce remission (a mean treatment duration of only approximately three months) followed by maintenance therapy with azathioprine¹⁹ or methotrexate²⁰. The results at two-year follow up showed that 80% of patients were in remission. In addition, in the azathioprine study, a comparison group treated with daily cyclophosphamide had a similar remission rate to the group treated with azathioprine¹⁹. Considering the available literature, it makes more sense to induce remission with monthly intravenous pulses of cyclophosphamide combined with prednisolone, and switch over to azathioprine or methotrexate for maintenance of remission.

In the present series with a follow up of five years after diagnosis, precise figures for mortality are not available. The worst estimate would be 24% if one assumes that all 5 patients lost to follow up are dead. The 5-year mortality in Hoffman's series was 13 per cent². Bambery *et al*³ reported a mortality of 50% in a case series of 18 patients. However, according to the authors, eight of the nine patients could not receive adequate therapy before death. They had been diagnosed at an advanced stage of disease. To conclude, WG is now being frequently diagnosed because of increased awareness and availability of diagnostic aids. Although current treatment is efficacious, frequent relapses continue to pose a challenge.

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