

ENT Manifestations of Wegener's Granulomatosis

M J ASLAM M A ASLAM M I AHMED A BATOOL.

Department of Otorhinolaryngology and Head and Neck Surgery, Pakistan Institute of Medical Sciences hospital, Islamabad
Correspondence: Dr. Muhammad Javed Aslam, ENT Consultant, NESCOM Hospital, H 11/4, Islamabad.

Objectives: The purpose of this study was to find out the presenting features, diagnostic problems, treatment, and prognosis of Wegener's granulomatosis (WG), with special reference to ENT manifestations. **Study Design:** It was a prospective descriptive study. **Study Setting:** The study was conducted at the Department of Otorhinolaryngology and Head & Neck surgery, Pakistan Institute of Medical Sciences (PIMS), Islamabad, from 1st March 1999 to 30th Sep 2001.

Results: The ten patients included in this study comprised of six males and four females, with a male to female ratio of 1.5:1. The age of patients ranged from 16 years to 55 years with an average age of 38.5 years. The most common presentation in our patients was due to nasal involvement of disease. Nasal obstruction, epistaxis, and rhinorrhoea was seen in 80% of patients with WG. Next common symptom was headache (60%) followed by other symptoms. Two patients had ear pain and conductive deafness along with nasal symptoms. One patient in addition to nasal symptoms mentioned presented with saddle nose deformity. One patient presented with hoarseness and progressive stridor, having subglottic stenosis as an isolated finding. **Conclusion:** Most common symptoms in WG localized to ENT region are nasal obstruction, rhinorrhoea and epistaxis. Biopsy and c-ANCA have key role in diagnosis of WG. ESR has a good prognostic relevance

Key words: Wegener's granulomatosis, ENT manifestations, c-ANCA

Wegener's granulomatosis (WG) is a granulomatous disease involving any system of body. Typical histological findings are necrotizing vasculitis with granuloma formation involving upper and lower respiratory tracts along with focal glomerulonephritis. A study was carried out to look into the ENT manifestations of the disease. 10 patients included in the study comprised of 6 males and 4 females, with average age of 38.5 years. Nasal symptoms were the commonest in patients presenting in ENT clinic. c-ANCA and biopsy are to make a diagnosis. Disease activity was best monitored by ESR. Prognosis was better in patients with limited disease. The presentation of disease is discussed along with its diagnosis, treatment, and prognosis.

Results:

The ten patients included in this study comprised of six males and four females, with a male to female ratio of 1.5:1. The age of patients ranged from 16 years to 55 years with an average age of 38.5 years.

The most common presentation in our patients was due to nasal involvement of disease. Nasal obstruction, epistaxis, and rhinorrhoea was seen in 80% of patients with WG. Next common symptom was headache (60%) followed by other symptoms (Table I).

Two patients had ear pain and conductive deafness along with nasal symptoms. One patient in addition to nasal symptoms mentioned presented with saddle nose deformity. One patient presented with hoarseness and progressive stridor, having subglottic stenosis as an isolated finding.

Table 1: Presenting features (n=10)

Presenting features	=n	%age
Nasal obstruction	8	80
Rhinorrhoea	8	80
Epistaxis	8	80
Headache	6	60
Ear pain	2	20
Conductive deafness	2	20
Saddle nose deformity	1	10
Hoarseness	1	10
Stridor	1	10

On examination of nose most patients (80%) had congested nasal mucosa, thickening of mucosa, and granulations (Table II). 60% patients had nasal crusting and ulceration. Two patients had middle ear effusion secondary to nasal obstruction. One patient had septal perforation with saddling of nasal dorsum.

One patient had subglottic stenosis diagnosed clinically and confirmed at direct laryngoscopy and rigid bronchoscopy.

All patients had elevated ESR at initial investigations. In eight patients it was more than 80mm, in remaining two it was more than 60. Two patients showed eosinophilia, 16% eosinophils in differential cell count. Urine examination, renal functions, and chest X ray were normal in nine patients at presentation. c-ANCA was positive in nine patients (90%). Biopsy from nose was taken in nine patients having nasal involvement at presentation. In six patients biopsy revealed typical necrotizing vasculitis with granulomas (60%). In remaining three patients biopsy showed non specific inflammation with granulomas but typical vasculitis was not seen.

Table II: Examination findings (n=10)

Findings	=n	%age
Nasal mucosal congestion	8	80
Nasal mucosal thickening	8	80
Nasal granulations	8	80
Nasal crusting	6	60
Nasal mucosal ulceration	6	60
Middle ear effusion	2	20
Septal perforation	1	10
Subglottic stenosis	1	10

All patients were treated initially with cyclophosphamide, prednisolone, and thrice a week sulphamethoxazole/ trimethoprim, and treatment was continued for one year after induction of remission. Latter in course of disease one patient developed hemorrhagic cystitis as a complication of cyclophosphamide and this drug was discontinued. Methotrexate was started in this patient in dose of 0.3mg/kg/wk and was increased to 15mg/kg/wk. After remission was achieved, the dose was maintained at 10mg/kg/wk for a period of one year.

At presentation 9 patients had limited disease, mostly limited to nose and sinuses and one patient presented with fulminant disease with involvement of upper and lower respiratory tract along with renal failure. This patient was treated in intensive care unit from the beginning, but expired on 13th day of admission due to renal failure and chest infection. Remission was achieved in remaining nine patients initially. Latter in course of disease two patients developed pulmonary involvement and one patient developed renal involvement (Table III). These patients were treated with aggressive cytotoxic therapy and systemic antibiotics. Patients with pulmonary disease recovered while patient with renal involvement died of renal failure around 17 month of presentation.

Reconstruction of nasal dorsum was performed with rib graft in one patient with saddle nose deformity once remission was achieved.

Tracheostomy was required in one patient presenting with hoarseness and stridor. Later direct laryngoscopy and bronchoscopy revealed subglottic stenosis. Repeated dilation was used to treat the problem along with cytotoxic therapy. Decannulation was successful and patient did not require any reconstructive procedure for restoration of a functional air way.

Patients were followed regularly in out patient clinic (Table IV). Longest follow up was of 30 months. One patient died of fulminant disease on 13th day of presentation. One patient was lost to follow up after 6 months; this patient was in remission at last follow up examination. One patient died at 17 month of diagnosis of disease due to renal failure.

Table III: Complications (n=5)

Complication	=n	%age
Rena failure	02	20
Pneumonia	03	30

Table IV: Follow up (n=10)

Duration	=n	%age
06 to 12 mon.	2	20
12 to 24 mon.	4	40
24 to 30 mon.	4	40

Discussion:

Heinz Klinger, a medical student of University of Berlin first reported two patients who died having prolonged sepsis with inflammation of blood vessels. Five years latter, Friedrich Wegner a German pathologist in Breslau described three patients with a syndrome characterized by necrotizing granulomas of upper and lower respiratory tract, a necrotizing systemic vasculitis, and a focal glomerulonephritis. Seven further patients were described in 1954, and at that time definite criteria were established for the diagnosis of Wegener's granulomatosis¹.

Since described by Wegener in 1939, as 'Rhinogenic granulomatosis', the management of disease has progressed a great deal with respect to establishing diagnosis and more importantly treatment of the disease.

Wegener's granulomatosis in the past had got a mean survival of 5 months, with 82% of patients dying within first year, and more than 90% dying within 2 years of diagnosis². Now a days long term remissions can be induced and maintained in extremely high number of patients, because of advent of cytotoxic drugs.

Because of systemic nature of disease and as any organ system may be involved³, the patient may be seen by a wide range of specialists, so that a varying spectrum of clinical involvement may be reported. However, with the predilection of the vasculitis to affect the airway, usually respiratory tract symptoms and signs predominate.

It is a rare disease, and as any organ can be involved patients usually present to different specialist. In our study most patients presented in the out patient department, that is why the number is small.

Males and females are equally affected in most parts of world. In our study this ratio was 1.5:1.

Mean age at presentation in our study was 38.5 years whereas it has been reported mostly in 4th and 5th decade⁴, which is very much as our study depicted.

The common most presentation in our patients, was nasal obstruction, epistaxis, rhinorrhoea, headache.^{3,5} Over 90% patients with Wegener's granulomatosis seek medical attention due to upper and/or lower respiratory tract symptoms⁶.

Two of our patients presented with ear pain and conductive deafness, due to nasal disease. Isolated involvement of ear can take the form of chronic suppurative otitis media, sudden sensorineural hearing loss, tinnitus⁷ or ear problems secondary to nasal disease. Saddle nose deformity is not uncommon ENT manifestation of disease. This is due to septal involvement and destruction of septum⁵.

Subglottic stenosis was diagnosed in one patient who presented with hoarseness and progressive stridor, correlating it with laryngeal involvement. Laryngeal involvement can be during the course of disease or it can be the only manifestation of Wegener's granulomatosis, and high index of suspicion is needed in such cases as other common presenting features are missing^{8,9,10}. In our study subglottic stenosis was an isolated finding on direct laryngoscopy and bronchoscopy carried out to look for case of respiratory obstruction. Latter investigations revealed it to be a case of WG.

Examination of nose revealed nasal mucosal congestion, thickening, and granulation formation in most of the patients (80%) while nasal crusting and ulceration was seen in 60% patients. Most nasal pathology in WG is in the form of mucosal friability, ulceration and thickening^{1,4,5}. Our study depicted mucosal congestion, thickening, and granulations to be the common finding in nasal involvement of disease.

Middle ear effusion in WG secondary to nasal pathology is not uncommon as is saddle nose deformity due to septal perforation.

Subglottic involvement is not rare in WG, most literature reports 20% involvement^{6,8}. In our study this figure was 10% probably due to small number of sample size.

In our patients ESR, blood complete examination, urine complete examination, renal function tests, chest X ray and c-ANCA was carried out in all patients. While nasal biopsy was performed in nine patients presenting with nasal disease.

ESR was raised in all patients, and in all patients it was more than 60mm in first hour. ESR is reported to have good relationship with disease activity and prognosis. Its levels decline with disease progressing in to remission. This fact was very much true in our patients.

Blood complete examination was normal in all but two patients. These patients showed eosinophil count of 16%. This fact has been reported by others¹² but its implication in diagnosis of WG is limited. Eosinophilia is seen in many allergic disorders and worm infestation.

WG is strongly characterized by its association with antineutrophil cytoplasm antibodies (ANCA) which generally have cytoplasmic labeling pattern (c-ANCA)^{13,14}. In our study 80% patients had positive c-ANCA estimations. Many studies report the sensitivity of c-ANCA to be around 70% when there is no renal involvement and in the presence of renal involvement it raises to 90%^{15,16}. Although with the introduction of ANCA¹⁷ diagnosis of WG has become easier but the key to diagnosis even at this time is biopsy of involved tissue. The presence of c-ANCA test should be adjunctive and should not substitute tissue diagnosis. But the fact is that c-ANCA is still being used in isolation in diagnosing and treating WG. This probably is due to the fact that obtaining tissue specimen from lungs and kidneys is demanding one,

and many physicians are not trained to get representative tissue for diagnosis to be established. False results of c-ANCA have been reported in certain infections and neoplasms¹⁶. In evaluating relapse the c-ANCA titers can be misleading. Many patients achieving remission continue to have elevated levels for years.

Most of our patients (90%) presented with limited disease involving nose and sinuses. In ENT clinic most common system involved is nose and sinuses. Nasal biopsy was carried out in all nine patients. Typical necrotizing vasculitis, and granuloma formation¹⁸ was seen in 66.6% cases. The histological findings are patchy in distribution, so large amount of tissue is needed¹⁹, also pathologist need to watch closely for these in a suspected case of WG. All biopsies in our study were taken in operation theatre, with use of local anesthetic. The yield of nasal specimens is lower than biopsy taken from lungs and kidneys. Our study showed better results than reported. This is due to the fact that all of our biopsies were taken by ENT surgeon, after meticulously removing crusts and large tissue was taken in all patients.

Patients in present study were thoroughly investigated for other organ involvement. The disease most commonly involves lungs and kidneys in addition to upper respiratory tract. One patient had renal involvement at presentation, while another patient developed renal involvement during course of disease⁶. Two more patients developed pulmonary involvement latter during course of disease as depicted by chest X ray²⁰.

After the diagnosis of WG confirmed, treatment was instituted using cyclophosphamide and prednisolone²¹, as per recent literature advises. In addition sulphamethoxazole/trimethoprim thrice a week was also added to cytotoxic therapy. The use of sulphamethoxazole/ trimethoprim has shown to decrease the relapse rate, and also that chronic nasal carriers of staphylococcus aureus are associated with high relapse rate of WG²².

Patients were monitored with complete blood examination, ESR, urine complete examination, renal function tests, and chest X ray. These helped to monitor the toxicity of drugs used and also helped to monitor disease activity. More over other organ system involvement was depicted by an abnormality in these investigations. Cyclophosphamide was used for one year after remission of disease. Cyclophosphamide was started in all patients. In one patient it was discontinued due to its adverse effect 'hemorrhagic cystitis'. Methotrexate was started in this patient as an alternative²³. Prednisolone was used till remission was achieved, after wards it was gradually tapered and withdrawn. This regimen remains the most effective treatment of WG in spite of many newer regimens being tried³.

Prognosis was monitored by ESR in all patients in the present study. c-ANCA has been mentioned in the literature for monitoring progression of disease, but it is

not cost effective. More over c-ANCA does not correlate well with disease activity^{24,25}. ESR on other hand has a better correlation with disease activity and is a good prognostic indicator¹¹.

Patients were followed up to 30 months, with an average follow up of 12 months. One patient was lost to follow up at 6 months, he was doing fine on last follow up with disease in remission. Other were regularly followed in the out patient clinic.

This study has many short comings, to highlight are a small sample size and short follow up. Long term follow up is needed to assess the prognosis of disease localized to ENT region.

Conclusions:

- Nasal symptoms predominate in WG localized to Ear Nose and Throat (ENT) region.
- Most common symptoms in WG localized to ENT region are nasal obstruction, rhinorrhoea, and epistaxis.
- Biopsy and c-ANCA have key role in diagnosis of WG.
- Treatment is with cytotoxic drugs, steroids, and sulphamethoxazole/trimethoprim.
- ESR has a good prognostic relevance.

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