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WEGENER GRANULOMATOSIS;
DIAGNOSIS & MANAGEMENT

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ABSTRACT... Objective: To highlight the different clinical features, parameters of diagnosis and to see the effect of chemotherapy and steroids on this disease. **Setting:** Department of Otolaryngology Head & Neck Surgery Jinnah Hospital Lahore. **Period:** From Dec 1998 to July 2001. **Methods:** Five cases of Wegener Granulomatosis were studied during the study period. Three patients had limited disease while two patients had generalized disease with renal involvement. All patients were started on azathiopurine (2mg/Kg/day) or cyclophoshamide (1-2mg/km/day) along with steroids. After a months time the dose of steroid was reduced to alternate day. Weekly monitoring of white blood cell count with urine examination for RBCs or protein casts was done. Any patient with haematuria or TLC reduced to less than 3500 were immediately taken off from cyclophoshamide and azathiopurine was started. Patients having classic disease , dose of cyclophoshamide had to be increased from two to four milligram / per Kilogram per day to achieve a good response. The response to treatment was measured by noticing the resolution of pulmonary infiltrates reduced ESR and negative C-ANCA. **Results:** We found nasal symptoms like nasal obstruction and epistaxis to be the most common symptom followed by fever, cough and deafness. Crusting, granulations and occasional perforation were usually found on nasal examination. Conductive deafness was most common ear finding. History, clinical examination, ESR, C-ANCA and a representative biopsy were all essential in diagnosing this condition. Azathiopurine and cyclophosphamide were the main chemotherapeutic agents used with prednisone to cause remission in all our patients except one who died two weeks after having been admitted in our institution. Surprisingly in contrast to the normal cause of high mortality reported in international literature in this disease to be renal failure, our patient died due to respiratory failure. Four out of five patients went into remission a year after regular treatment with this regime. The major complications occurring during hospital stay and their treatment were nausea, vomiting, sudden fall of TLC, and oral thrush. **Conclusion:** The common presentation of patient with Wegner's Granulomatosis is of upper respiratory tract symptoms like nasal obstruction and epistaxis followed by lower respiratory symptoms like cough, fever and Haemoptysis. A representative biopsy with positive C-ANCA and high ESR are hallmarks of diagnosing this condition. The most effective medical regime till today is cyclophosphamide and azathiopurine with alternate day prednisone for inducing remission.

INTRODUCTION

Wegener Granulomatosis is a systemic vasculitis with preferential involvement of respiratory tract. It is named after Sir Freidrich Wegener who in 1939 detailed the clinical course of this condition Ataman-et-al[1] 1994 gave the Classic description of Wegener's Granulomatosis consisting of a triad of Necrotizing inflammation with granulomas in the respiratory treat.

A systemic small vessel vasculitis.
A focal glomerulonephritis.

Initially it was viewed as a disease that presented as a classical triad of upper airway, pulmonary and renal involvement. We now know that this is not the case and understand that limited forms can also occur. The limited form of disease presents with Ear nose and throat and chest involvement without renal involvement, while the generalized or classic form depends upon involvement of the kidney. The disease diagnosed in its early stage and treated gives excellent results and prevents from life threatening complications but on the other hand if not diagnosed in time or in adequately treated leads to grave consequences, which include death as well.

Aim of our study was to reveal this relatively uncommon disease presenting features and also to highlight the treatment used for this disease

In our set up the patient usually presents with moderately advanced stage of disease but still are managed well if therapy is started on time

In our study three patients had limited and two patients had generalized disease. Four patients went into remission after a year long treatment but one died of respiratory failure due to extensive chest involvement

We found the most effective treatment regime in inducing long time remission was either cyclophosphamide or azathiopurine together with alternate prednisilone therapy. Azathiopurine may be effective in maintaining remission induced with cyclophosphamide when it is prematurely discontinued for reasons of toxicity such as patient who develop neutropenia or cystitis.

An unusual thing was that one of the patient died of aggravated lower respiratory tract infection rather than renal failure which is most common cause reported in literature to cause death in Wegener Granulomatosis. Chest infection inpatients of Wegener should not be taken lightly.

MATERIAL AND METHODS

This study was conducted at department of Otolaryngoogy Head and Neck Surgery Jinnah Hospital Lahore, during the period from December 1998 to July 2001. Five consecutive cases of Wegener Granulomatosis with different age groups were admitted and treated with chemotherapy and steroids .All cases had moderately advanced disease. A thorough history was taken especially regarding nasal obstruction, nasal discharge, haemoptysis, burning micturation and haematuria .All the patients filled the following questionnaire which helped in making a baseline renal, respiratory cardiac and hepatic, metabolic and haematological profile for each patient before the therapy was started.

Table-I.
Pretreatment Profile
Does the patient have polydypsia or does he work
Does the patient have haematuria or burning micturation at night?
Has the patient taken any of the chemotherapeutic agent before?
Does he get multiple attacks of infection repeatedly?
Does he have wheeze, haemoptysis or severe attacks of dyspnoea?
Does he have heart burn, retro sternal or epigastric pain?
Did he ever develop swelling in axilla or groin?
Did he ever have jaundice or hepatitis?

The clinical examination included ear, nose and throat, respiratory and General physical examination. The radiological examination included plain x-Ray chest (PA or lateral view) and sinus (waters view).The most

important role in diagnosis and management of the disease was the use of ESR and C-ANCA. Both the markers helped in determining the severity and prognosis of the disease. The second most important aid was made by biopsy which confirmed the diagnosis. Urine examination for red blood cells, proteins and casts pointed to a more generalized type of picture.

Patient base line investigations like haemoglobin, total-leucocyte count, differential count along with ESR was done. Particular attention was made to haemoglobin and total leucocyte count. Patients having anemia and with low total leucocyte count were potentially bad candidates for starting cyclophosphamide as chemotherapeutic agent. A count of less than three thousand WBC declared the patient unfit for receiving cyclophosphamide.

Depending on the extent of the disease and the base line profile the patients were started on azathiopurine (2mg/kg/day) or cyclophosphamide (1-2mg/kg/day) along with steroids. After a months time the dose of steroids were reduced to alternate day therapy. Weekly monitoring of white blood cell count was done along with urine examination for RBCs or protein casts. Any patient whose urine report started showing even microscopic haematuria or blood picture having TLC reduced to less than 3500 were immediately weaned off from cyclophosphamide to azathiopurine till that time when the haematuria reduced and TLC became more than 5000cumm.Only then cyclophosphamide was resumed again.

Patients with classic form of disease were started on cyclophosphamide 2 mg/kg /day along with steroids, if the patient did not show a good response this was increased to 4mg /kg /day, but not more than that.

Patients also had to be put on antacids to prevent stress ulcers due to steroid intake. Cases having haematuria and not responding to cyclophosphamide had to be given azathiopurine, patient with poor oro dental hygiene and nasal crusting had to do nasal douching with saline four times a day and were given pyodine or diluted hydrogen peroxide gargles.

Remission was set in when patients had resolution of pulmonary infilterates, reduced ESR, and negative C-ANCA. The patients were discharged and were advised to continue the drug at least a year after C-ANCA became negative. Patient had monthly chest X-Ray and ESR done along with 6 monthly C-ANCA test done. During their treatment they were advised for monthly, 3, 6 monthly and yearly follow up.

RESULTS

All patients were divided into two main groups. Three patients had limited disease and two had classic disease with involvement of the kidneys 60% patients were male and 40% were female. Majority of our patients belonged to lower middle class and were mostly males. Age and Gender range noted in our study is shown in table II and III.

Table-II. Age Group (n=5)

Age (Years)	No of pts	%age
0-35	2	40
36-59	2	40
60-80	1	20

Table-III. Gender Group (n=5)

Sex	No of pts	%age
Male	3	60
Female	2	40

As far as duration of disease was concerned 40 % of our patients had symptoms for 8 months while another 40% had symptoms for 6 months and 20% had symptoms for 12 months as shown in table IV.

Table-IV. Disease duration (n=5)

Duration (Months)	%age
6 months	40
8 months	40
12 months	20

The most common presenting feature in our study of 5 patients were epistaxis (80%).Nasal obstruction, fever and cough were other important features.

Epistaxis was bright red in colour, moderate in amount and had sudden onset of action .It was aggravated by physical stress. Nasal obstruction was mostly alternating but in one case it was persistently unilateral. Excessive accumulation of nasal crusts with foul smelling discharge was the common cause of nasal obstruction.

Three of our patients had limited disease while two patients came to us with renal involvement thus they had generalized disease. Different presenting features and their percentage involvement is shown in table V.

Table-V. Presenting Features (n = 5)

Features	%age
Epistaxis	80
Nasal Obstruction	60
Fever	60
Cough	60
Deafness	40
Sore throat	20
Swelling submandibular area	20
Haemoptysis	20

On nasal examination one patient had an ulcer on the anterior part of septum while one had a perforation 3x2.5cm dimension filled with crust. Lacerations were found on the septum in all patients.

Table-VI. Nasal findings (n=5)

Nasal Findings	Number	%age
Granulations	2	40
Perforation	1	20
Ulcer	1	20
Laceration	5	100

Lacerations were found on the septum in all patients and two of the 5 patients had granulations on both side of septum Table VI shows the clinical findings and their percentage involvement .

Fever was moderate to high grade in three patients while it was mild to moderate in two patients. The cough was productive and foul smelling in patients who had acute involvement of the chest. The cough was associated with chills and rigors.2(40%) of patients had history of weight loss which was of short duration.

One (20%) of patient had haemoptysis and another (20%) had swelling in left sub-mandibular gland. One (20%) patient had a fatal outcome due to respiratory failure. This patient had bilateral infiltrates in the chest on plain X-Ray, with reduced vital capacity and forced expiratory volume on spirometry. The other patients had mixed findings as shown in table VII.

Table-VII. Chest Findings (n=5)

Chest Findings	Number	%age
Dull percussion note	2	40
Crepitation	1	20
Ronchi	1	20
Harsh vesicular breath sounds	2	40

The various ear problems and their percentage involvement is shown in table VIII.

Table-VIII. Percentage of Ear findings (n=5)

Findings	Number	%age
Conducting hearing loss	3	60
Retracted TM	2	40
Congested	1	20

Three patients had to under go multiple trials of biopsy to reach the diagnosis. The trial had to be conducted 2-3 times.

Two of the patients who had generalized disease with

renal involvement had high ESR between 110 -140 mm. The other three patients who had limited disease had their ESR ranging between 50-80mm.Table 9 shows the level of ESR in our patients:

Table-IX. Level of ESR (n=5)		
ESR value	**Number**	**%age**
50-70	1	20
91-140	2	40
70-90	2	40

During the treatment our patients had to face the following complications which are listed in table 10 .Most of these were due to the therapy itself.

After six months of therapy the level of ESR dramatically declined in all four patients except for the one who died. This decline matched with the decline in C-ANCA titers and improvement in their clinical condition.

Table-X. Complications of occurring hospital stay (n=5)		
Complications	**Number**	**%age**
Nausea and vomiting	5	100
Generalized weakness	5	100
Oral cavity infections	1	20
Chest infections	1	20
Neutropenia	3	60
Hair thinning	2	40
Acidity and heart burn	2	40
Death	1	20

Initially all our patients were started on cyclophosphamide but after three weeks due to rapid fall in TLC, two patients dose had to be adjusted where one patient was shifted on azathiopurine for a months time till the TLC came to normal.

All our patients had to be given antiemetics as most of them developed nausea and vomiting three weeks after start of their treatment. Patients had to be given pain killers for generalized body aches and vitamin supplements during their therapy.

One patient receiving cyclophosphamide developed oral thrush and his treatment had to be stopped and was replaced by azathiopurine and he was started on nilstat gargles. The patient was relieved in two weeks time.

Unfortunately one patient died of aggravated respiratory tract infection. This patient initially presented to us with episodic fever, bouts of breathlessness and foul smelling discharge. His X-Ray showed left lung collapse with pneumothorax and cavities in right lung. With the help of pulmonology department left chest intubation was done. This patient went into further complications as he developed rapidly expanding surgical emphysema which aggravated with bouts of coughing and another chest tube had to be put on right side. The left chest tube was removed after a weeks time but his chest wound started discharging as a broncho-pleural fistula followed by empyema was diagnosed . Patient was shifted to ICU where he was managed on a ventilator , nebulized but after 12 hours he failed to sustain life and was declared dead due to respiratory failure.

All three patients who had limited disease went into remission one year after therapy and the classic patients took one year to go into remission. Remission set in when C-ANCA became negative, clinically symptoms and sign improved as the granulations and infiltrates resolved and ESR became low. The patients were followed three and six monthly thereafter.

DISCUSSION

Wegner Granulomatosis is an uncommon and rare condition. The incidence is in range of one for every fifty two thousand of population in most European and American countries .It is extremely rare in blacks than whites. Males to females ratio is 3:2.The peak age in which it occurs is early thirties and forty.

DeRemee[2] proposed the ELK classification depending upon the extent of different organ involvement: ELK stands for E stands for ear .nose and throat

involvement, L stands for Lung involvement, K stands for Kidney involvement.

Wegener Granulomatosis is an auto immune mediated disease with antibody directed against intracytoplasmic component of leucocytes. C-ANCA is specific and sensitive marker for diagnosing Wegener Granulomatosis ,while rising ESR and C-ANCA are prognostic and relapse determining markers.

In 1958 Sir Walton[3] suggested that the primary lesion of disease occurred in the respiratory tract and the generalized form occurred later and he pointed that subsequent to primary lesion an Arthus phenomenon took place followed by widespread hypersensitivity reaction.

In 1982 Davies et al reported about C-ANCA when he studied a group of patients who had necrotizing glomerulonephritis with no immune deposits but had clinical evidence of systemic disease

Vander Woude[4] and coworkers in 1985 reported the presence of these antibodies in patients of Wegener Granulomatosis.

For the diagnosis at least two organ systems should be involved out of three. Repeated biopsies of lesions searching for fibrinoid necrosis sometimes have to be taken to reach the diagnosis

A representative biopsy which is deep and devoid of nasal crusts is required to avoid granulation tissue to allow search for fibrinoid necrosis in a vessel wall to make a diagnosis of Wegener Granulomatosis.

ESR is a good diagnostic and prognostic marker in this disease. It tells us about the severity of the disease and at the same time its increasing and decreasing level tell us whether the patients clinical condition is deterioting or improving.

As stated by Mc Donald[5] in 1990In more severe form of Wegener Granulomatosis laboratory test will be abnormal, highly elevated ESR(above100 mm in first hour),marked anemia and a C-ANCA test with a very high titer"

In differential diagnosis Poly Arteritis Nodosa and Mid line granuloma are considered important categories. According to Hellquist[6] three main histological features should be found in Wegener Granulomatosis:

1 Pyogenic tissue with fibrin and acute inflammatory cells
2 Granulomas of Epitheloid type
3 Small vessel vaculitis.

Clinically it is difficult to differentiate between Poly Arteritis Nodosa and Wegener but non respiratory granulomatous vasculitis that only effects small and medium size arteries and P-ANCA are diagnostic of poly arteritis nodosa. Their is disruption of vessel wall especially internal elastic lamina, followed by healing and fibrosis

In Wegener there is respiratory Granulomatosis along with generally small vessel involvement .

The midline structures like palate ,nose and chest are effected in Midline Granuloma. On histopathology these show mostly atypical T lymphocytes cells having angiocentric predilection with infilteration of vessel wall, helping us to distinguish it from Wegener.

Fungal infections usually present with clinical features of rhino sinusitis not responding to conventional antibiotic treatment. Mostly the cause is Aspergillus or Mucor mycosis. In mucor mycosis black necrotic tissue along with septal and palatal perforations are found.

Blitzer and Lawson[7] have described the histopathological changes and have described the fungal organism as angioinvasive ,which attacks the internal elastic lamina causing thombosis formation in vessel wall causing ischaemic infarction and haemorrhagic necrosis. Necrosis and septate hyphae are found in aspergillosis while non-septate are found in mucor mycosis.

In the past untreated, this disease was rapidly fatal with

a mean survival rate of five months. Various therapies like antibiotics and chelating agents and even local medications were given. Despite these measures patients died from haemorrhage, secondary infection and most commonly from renal disease . Radiation was one mode of therapy which was tried on in early sixties. The response was temporary regression of disease but it was not considered effective for generalized form of disease.

In 1954 Fahey et al[8] suggested that cytotoxic drugs are effective either alone or in combination with corticosteroids.

In 1962 Aungst and Lessman[9] reported their experience with alkylating agents. The first successful documented use of alkylating agent with steroids was done in 1967. Fauci et al[10] in 1985 achieved a remission rate of 93% using cyclophosphamide with alternate day prednisone.

CONCLUSION

Wegener Granulomatosis is a disease of wide spectrum .It can involve all organ systems in the body. In our set up majority of the patients present with either upper or lower respiratory tract symptoms. For the diagnosis at least two organ systems should be involved out of three and a representative biopsy with high ESR and a positive C-ANCA is required. In limited disease ESR is low while in generalized disease the ESR is high. The most effective medical regime till today is cyclophosphamide or azathiopurine with alternate day prednisone for inducing remission. Lower respiratory tract symptoms should not be taken lightly and benefits of cyclophosphamide should be weighed against its hazards.

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