CASE REPORT

WEGENER'S GRANULOMATOSIS

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ABSTRACT: Wegener's granulomatosis is an uncommon multisystemic disease, characterized by necrotizing granulomatous inflammation of the upper and lower respiratory tracts and general focal necrotizing vasculitis (Commonly known as "Wegener's triad"). We are reporting a case of 42 years male, who was admitted to Pulmonology Department Lady Reading Hospital (LRH) Peshawar on November 21, 2008 with the four months history of dry cough, partial bilateral nasal obstruction, Sore throat, fever and pain in both ears for the last two months; and he was also complaining of intermittent hemoptysis for the last one month. Finally diagnosed and successfully managed as a case of Wegener's Granulomatosis.

KEY WORDS: Wegener's Granulomatosis; ANCA; Vasculitis; Biopsy

INTRODUCTION:

Wegener's Granulomatosis (WG) is an uncommon disease that affects about 1 in 20,000 to 1 in 30,000 people. It involves inflammation of blood vessels (vasculitis). Symptoms are due to inflammation that can affect many tissues in the body, including blood vessels (vasculitis). It is also considered a disease of abnormal immune function[1].

A more specific blood test used to diagnose and monitor Wegener's granulomatosis is the antineutrophil cytoplasmic antibody (ANCA test), which is frequently elevated when the disease is active. The diagnosis of Wegener's granulomatosis is established by detecting both abnormal cellular formations, called Granuloma and vasculitis in a biopsy of tissue involved with the inflammatory process. For example, an open lung, nasal mucosal biopsy or a kidney biopsy is generally used in making a diagnosis of Wegener's granulomatosis. Management is directed toward stopping the inflammation progression by suppressing the immune system[2].

Wegener's granulomatosis is an uncommon type of inflammation of small arteries and veins it characteristically involves inflammation of the arteries that supply blood to the tissues of the lungs, the nasal passages (sinuses), and the kidneys, referred to as generalized Wegener's granulomatosis. "Incomplete" forms exist that only involve one of these parts is sometimes referred to as limited Wegener's granulomatosis [4].Wegener's granulomatosis typically affects young or middle-aged adults. The cause of Wegener's granulomatosis is not known[3]**.**

We are reporting a case of 42 years male, Private Religious Scholar by profession from North Waziristan Agency, which is one of the southern Agencies of Federally Administrated Tribal Areas (FATA), located **140** miles from the south of Peshawar, the capital of Khyber Pakhtunkhwa. He was married having **11** kids and was admitted to Pulmonlology Department Lady Reading Hospital (LRH) Peshawar on November 21,2008 with the four months history of dry cough, partial bilateral nasal obstruction,

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Sore throat, fever and pain in both ears for the last two months; and he was also complaining of intermittent hemoptysis for the last one month.

CASE REPORT:

The patient was having bilateral partial nasal obstruction for the last four months associated with dry cough. For the relief of these complaints, surgical operation of nose (SMR) was done three months back by an ENT Surgeon, but unfortunately these symptoms were not relieved. Cough is gradually increasing and irritates the patient and associated with low grade intermittent fever without rigors and chills for the last two months. The fever was occurring at any time of the day and was associated with headache but no sweats. During these two months duration he had sore throat, and pain and discharge from both ears.

History of weight loss was present and severity of nasal obstruction had been increased. For the last one month he was complaining of intermittent hemoptysis, which was mild in quantity. All these symptoms are associated with generalized bodyachs and malaise. There was no history of tuberculosis in the past and no history of exposure to pigeon and parrots. He was not having any history of oral ulcerations or thrush and there was no history of hoarseness of voice He was having Type-2 Diabetes Mellitus and Bronchial Asthma for the last twenty years. He was using 2 inhalers Salbutamol and Beclomethasone on regular basis and Oral hypoglycemic drug Glebenclemide 10mg daily and his blood sugar levels were controlled. He had also used short courses of different classes of antibiotics during the last four months for these complaints, but not proven to be effective and useful. He had also used short courses of oral steroids for his asthma exacerbations, but for not more than seven days duration. His socioeconomic history was poor. There was no history of Tuberculosis, Asthma or any such type of ailment in his family members. He was hospitalized for the first time for this illness. He was married having 11 kids, 3 male and 8 female. He was not addicted to anything. Sleep and appetite was decreased and bowel habits are also abnormal. General Physical Examination, He was lying in his bed comfortably, with intravenous line maintained on left arm. Blood Pressure was 130/80, Pulse90/minute and is regular, Peak Flow was 320 L/Minute, and Oxygen Saturation was 92 % at room air. He was anemic and there was enlarged right cervical Lymph Node which is non tender and mobile. Clubbing is absent. ENT Examination of his nose was showing crusts bilaterally and septal and lateral wall erosion was also noted. Throat was congested and right ear containing mild wax and left ear having dull tympanic membrane. Chest examination was showing bilateral wheezes with end inspiratory crackles. Epigastrium was tender, with no viscromegally.Cardiovascular and central nervous system examinations were also found to be unremarkable.Ophthalmoscopic and slit lamp examination of the eyes were also normal.

Chest X-ray at the time of presentation showed bilateral diffuse ill defined cavitating shadows scattered throughout both lung fields (Figure I) & X/ray PNS were showing hazy maxillary and sphenoid sinuses with hypertrophied bilateral nasal turbinate ,more pronounced on the right side (Figure II) . At that time we made differential diagnosis of

Bronchial Asthma and Diabetes Mellitus Type-2 with; (1) Pulmonary Tuberculosis (2) Vasculitides; Churgh Straus syndrome, Wegener's Granulomatosis and Microscopic Polyangiitis. (3) Allergic bronchopulmonary Aspergillosis. (4) Superadded Fungal Infection. (5) Metastatic Lung Disease. Laboratory investigations were carried out, showing low Hemoglobin: 8.2g/dl, PCV: 24.9%, TLC: 9100/cmm, with normal neutrophil, lymphocytes and eosinophile count, but C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR) was markedly raised and ESR was estimated at 125-150 in 1st hour. Rheumatoid factor (RA) was Positive. Urine routine examination was showing Albumin: ++, Red cells: Numerous Pus cells: 25 –30 & Granular casts: ++. All other Laboratory investigations including Liver function tests, serum electrolytes and renal function tests were within normal limits. Sputum examinations for Acid Fast Bacilli and Fungal Hyphae for aspergillus fumagatous were done 3 times, but came out to be negative (Table I). Bronchospy was also performed, which was showing indurated and inflamed mucosa. Bronchial biopsy was inconclusive and bronchial wash for AFB and Malignant Cells was also negative. Pulmonary Function Tests were performed showing moderate reversible airflow obstruction. 24 Hours urinary protein: 1312mg/minute and 24 hours total volume: 2917ml and Creatinine Clearance: 76ml/min (N: 95-60).

Ultrasonography of abdomen was normal. CT Scans of thorax & abdomen, PNS and Brain were also done and reported as Bilateral Pulmonary cavitatory nodules, consolidations and infiltrates with fractures of ribs on right side, which was traumatic in nature because of fall on chest by the patient 2 months back (Figure III, IV). Mucosal Thickening in both maxillary sinuses and Sphenoid sinuses were noted (Figure V). CT brain and abdomen were normal. So at this time our differential diagnoses were narrowed to only to Wegener's Granulomatosis & Fungal Infection. Audiometery was also done, report was showing right ear moderate to severe more conductive with BC down at 4000Hz & Left ear moderate to severe more conductive with BC down at 400Hz. We had planned Nasal mucosal biopsy and the same time ANCA levels were also sent to Laboratory. Nasal Biopsy was reported as Microscopic Examination reveal fragments of tissue exhibiting respiratory epithelial lining. Focal areas of ulceration are identified in the mucosa. Stroma shows moderate acute and chronic inflammatory cell infiltrate along with multinucleated giant cells and areas of necrosis. The vessels show marked thickening of the wall. Special stains carried out for fungus were Negative. Diagnosis was suggestive of Necrotizing Granulomatous Inflammation. At the same time, we had liaison with nephrologists for renal biopsy and they had done that. Results were No granulomata were seen, may be because of prolong steroids use by the patient in the Unit. Two (2) glomeruli out of 20 were globally sclerosed with thickening of the GB membranes. IMF showed focal deposit of C3. While, IgG, IgA, IgM and C1q were negative. Light microscopic and IMF features are of healed Focal Necrotizing GN, IMF pattern and C-ANCA positivity suggest Wegener's Granulomatosis.

C-ANCA and P-ANCA levels were measured on dated January 06, 2009 (Table I)**.**

P-ANCA:-1.68U/ml

(Abnormal value greater than 6U/ml)

C-ANCA:-5.84U/ml

(Abnormal value greater than 2U/ml)

Our Final tissue and ANCA based diagnosis was WG.

We had started patient on Cyclophosphamide Pulse Therapy and steroids orally. The patient gradually started improving and after three months follows up to the outpatient department, his chest x-ray was crystal clear, ESR was 30 and Urine examination was showing no RBCs or Casts. No side effects of drugs had been observed. He was then switched to oral methotrexate, instead of cyclophosphamide pulse therapy of 6 cycles one month apart for first 6 months and steroids were continued, but tapered it. He was sent home with the treatment combination of Methotrexate and Oral prednisolone.Before starting on methotrexate his renal and liver functions were checked and were Normal. He was cured and went into complete remission with this regimen.

TABLE I: LABORATORY INVESTIGATIONS

HAEMATOLOGICAL INVESTIGATIONS	**OTHERS INVESTIGATIONS**
Full Blood Count: **Hb:** 8.2g/dl **TLC:** 9100/cmm **N:**75% **L:**20% **E:**03% **Platelet Count:** 382000/cmm **ESR:** 125-150 mm is 1st hour **PCV:**24.9% **LFTs:** **SGPT:** 21 U/L **SBR:**0.2mg/dl **ALP:**407U/L RFTs: **Urea:**58mg/dl **Creat:**1.03mg/dl **S-Na:**138 mEq/L **S-K:** 4 mEq/L **S.Cl:** 102 mEq/L **RA Factor**: **Positive** **ANF** : Negative R**BS** : **168 mg/dl** **FBS on 22/12/2008: 60mg/dl** **S-Calcium:**8.5mg/dl	**Urine R/E:** Albumin:++ Red Cells: Numerous Pus Cells:25 –30 Granular casts:++ **Sputum for AFB** was negative three times. **Sputum for Fungal Hyphae** were negative three times. **C-ANCA and P-ANCA** levels were measured on dated January 06, 2009. **P-ANCA:-1.68U/ml** (Abnormal value greater than 6U/ml) **C-ANCA:-**5.84U/ml (Abnormal value greater than 2U/ml) **24 Hours urinary protein:** 1312mg/minute **24 hours total volume:** 2917ml and **Creatinine Clearance:** 76ml/min (N: 95-60). **CRP:** very raised **Ultrasonography** of abdomen was normal.

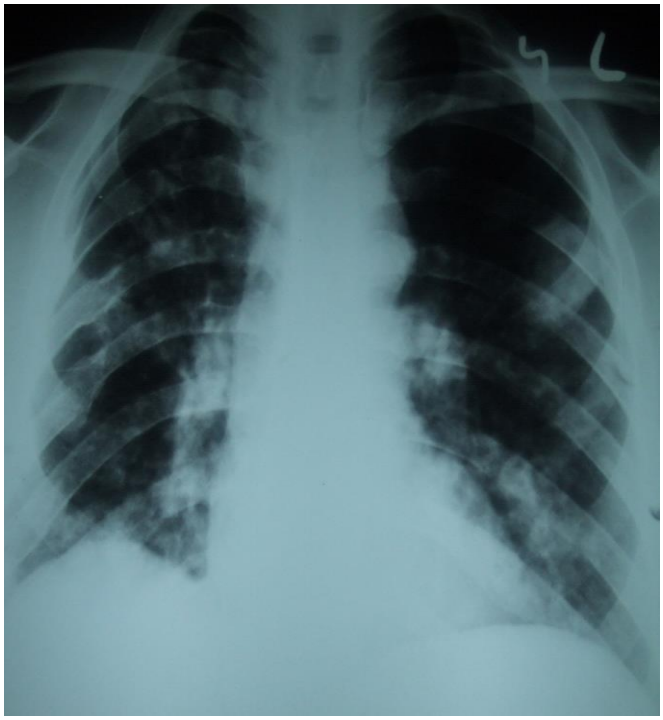

FIGURE I: Chest X-Ray showing bilateral diffuse ill defined nodular and cavitatory shadows Scattered all over the lung fields more on the right side.

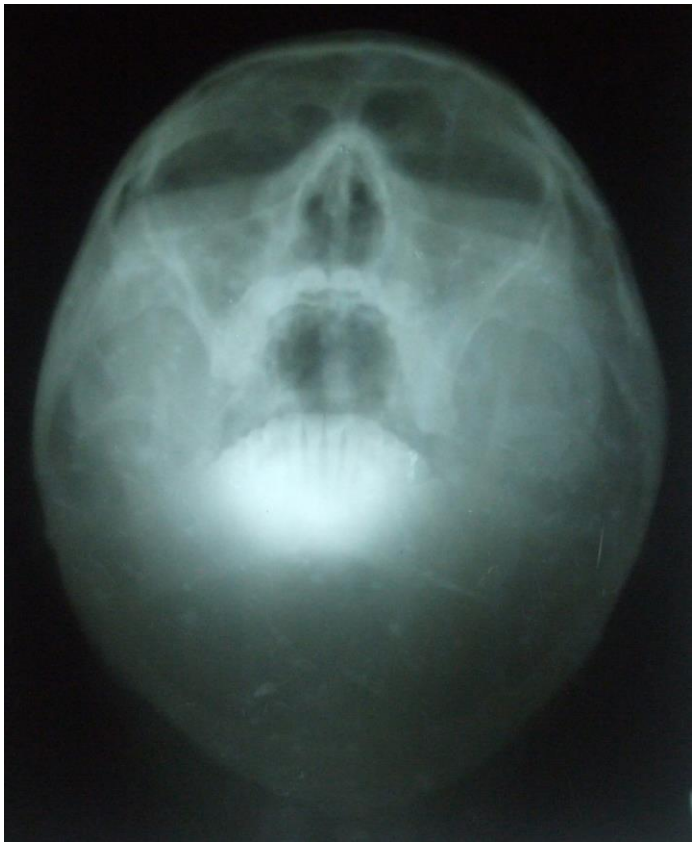

FIGURE II: Both Maxillary and sphenoid sinuses are Hazy, and bilateral hypertrophied Nasal turbinate seen, more on the right side.

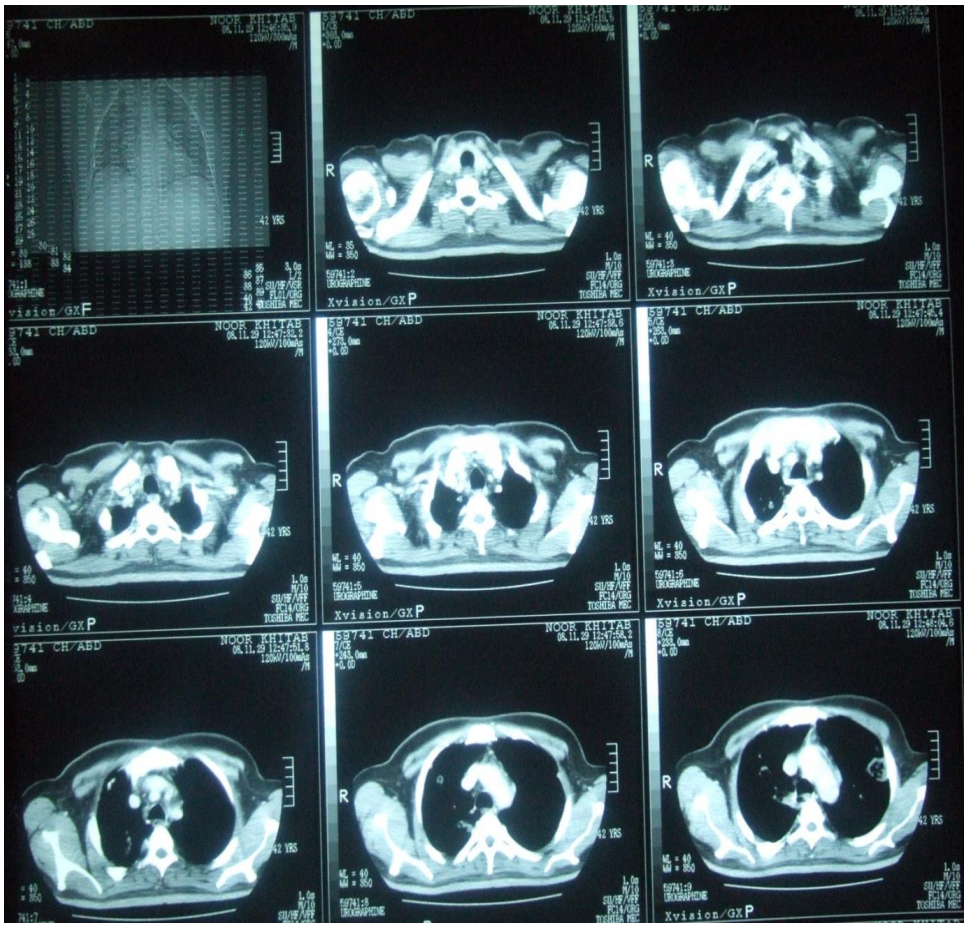

FIGURE III: CT THORAX (Mediastinal window**)**, showing Bilateral Pulmonary nodules, consolidations and alveolar infiltrates are seen bilaterally and there are fractures of ribs on right side due to secondary to fall of the patient few months back. It is not pathological fractures. No mediastinal abnormality seen and there is no signs of Pleural effusion.

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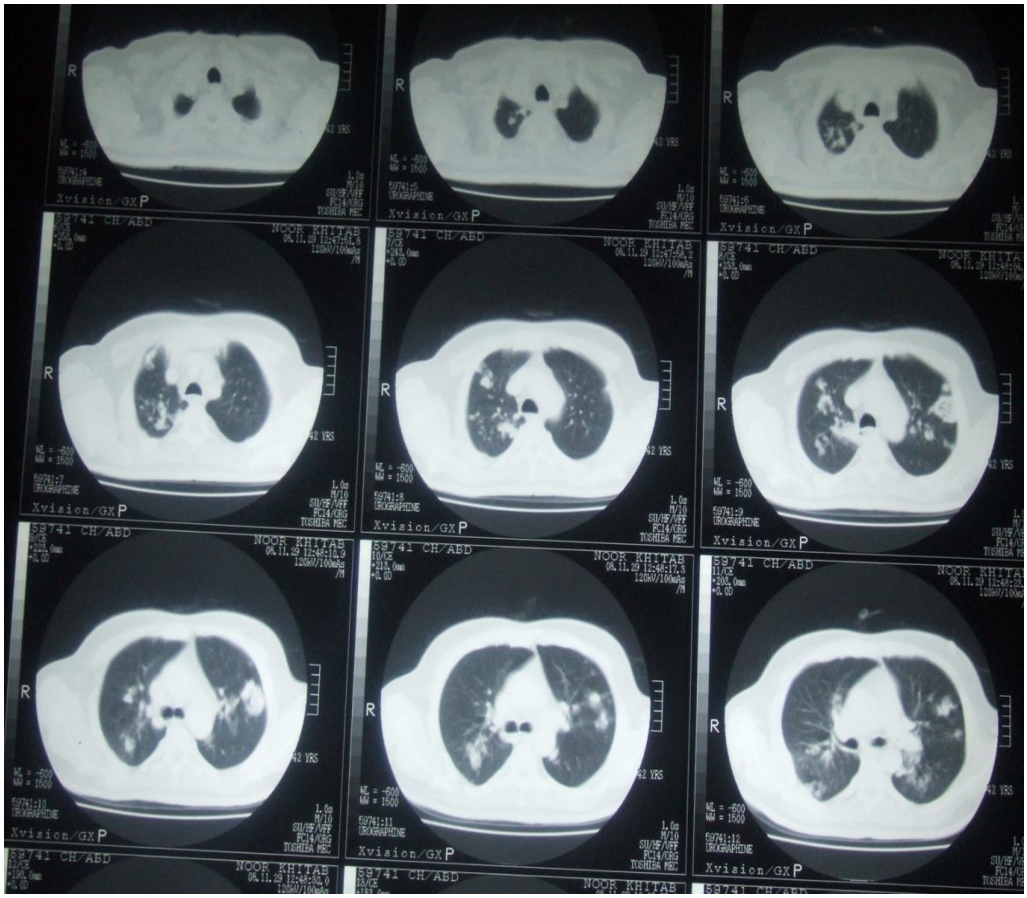

FIGURE IV: CT THORAX (Lung window**)**, showing Bilateral Pulmonary nodules some are cavitatory, consolidations and alveolar infiltrates are seen bilaterally and there are fractures of ribs on right side due to secondary to fall of the patient few months back. It is not pathological fractures.

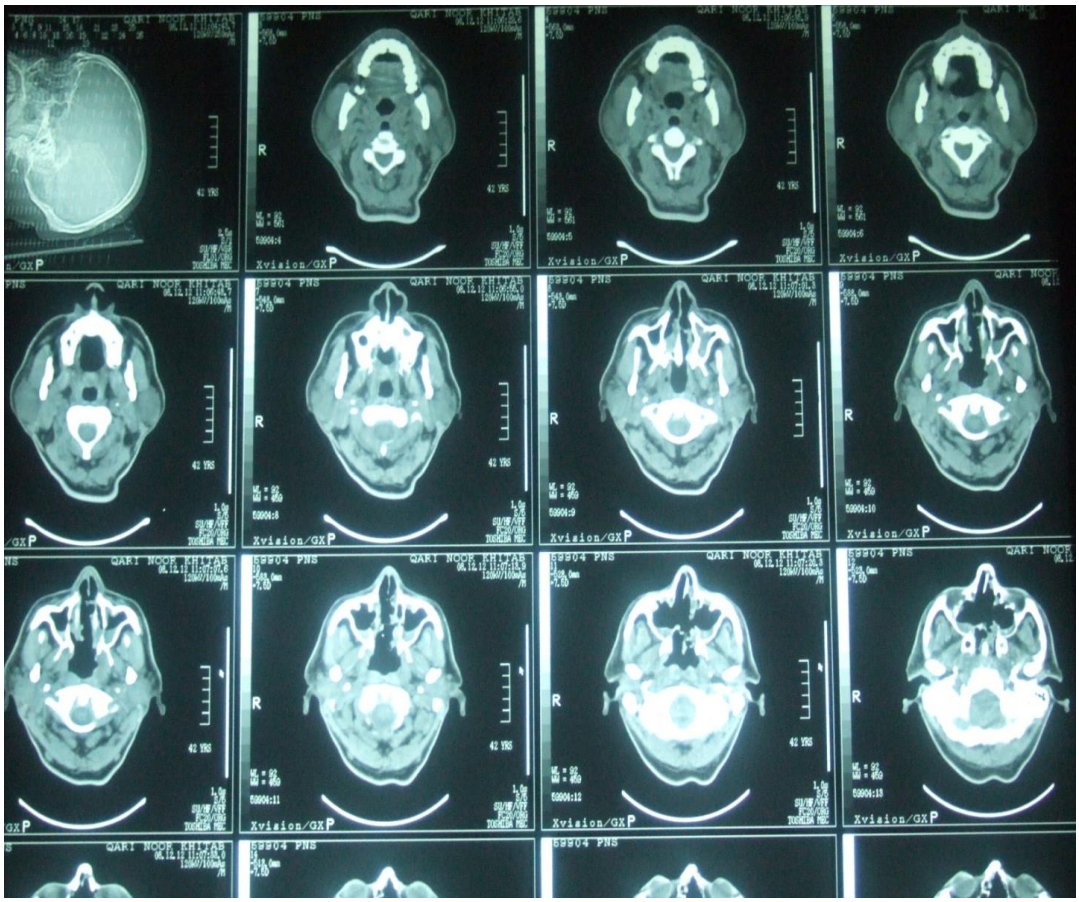

FIGURE V: Computed Tomography (CT) scan of the Para Nasal Sinuses (PNS) shows, Mucosal Thickening in both maxillary sinuses and Sphenoid sinuses. Differential diagnosis includes (1) Wegener's Granulomatosis (2) Fungal Infection.

DISCUSSION:

WG is classified as ANCA positive vasculitis, generally localized on the small and medium-sized blood vessel. It frequently affects the upper and lower respiratory airways and kidneys and the lungs are affected in 90 % of patients [5, 6]. Pulmonary involvement takes place in 45% of patients at presentation and 87% during the course of the disease. Cough, hemoptysis, and pleuritis are the most widespread pulmonary symptoms. The most universal radiographic findings include pulmonary infiltrate (67%) and nodules (58%). Classic radiological presentations of the lung involvement are multiple, bilateral, nodular infiltrations, with or without cavities. These radiological features were very typical in this case. According to several data, in 20-50% of patients it is manifested with pleural effusion[6]. Uncommon presentations are interstitial lung disease, hilar mass or pneumothorax [7, 8]. WG is at present characterized as one of the ANCA-associated small

vessel vasculitides. It is renowned clinically by its predilection for affecting the upper and lower respiratory tracts and kidneys and by the histological existence of necrosis, granulomatous inflammation, and vasculitis. There is a strong and specific involvement with autoantibodies directed against proteinase 3, a component of neutrophil azurophilic granules.The existence of such antibodies is a strong marker for a diagnosis of WG, but should not be used in place of a tissue diagnosis. The presence of ANCA is not compulsory to make a diagnosis of WG by either the American College of Rheumatology (ACR) or the Chapel Hill Consensus Conference (CHCC) definitions. Infrequently, patients with infections, neoplasms, inflammatory bowel disease, sclerosing cholangitis and additional rheumatologic diseases develop ANCA, but these are predominantly perinuclear ANCAs or reveal an atypical staining pattern[9].

2Occasionally, patients with infection, inflammatory bowel disease, rheumatic disease, neoplasm develop ANCA[10]. Toyoshima et al[12] presented a case of good curative response and restitution of granuloma after the applied antituberculosis therapy which extremely bizarre. However, in our case, therapy response was obtained after the applied immunosupressive therapy. After three months of therapy, the patient was stable, devoid of any symptoms of WG. The three-month follow-up was recommended.

Sex distribution of the disease is equal but mostly in white people. Age of presentation is wide but majority presents in the fifth decade, which is also consistent with this case. Clinical presentation can be so diverse that the list of differential diagnoses is vast, ranging from infection, neoplasm, tuberculosis, malignancy, other forms of vasculitis [11]. Though Ocular symptoms were not present in this case, but Ocular manifestations have been reported to happen in 28 to 58% of patients with WG, and they may be part of the preliminary presentation in 8 to 16% of patients[11, 12]. A complete ophthalmologic examination is a significant part of the diagnostic evaluation. Any compartment of the eye might be affected. Keratitis, conjunctivitis, scleritis, episcleritis, nasolacrimal duct obstruction, uveitis, retro-orbital pseudotumor with proptosis, retinal vessel occlusion, and optic neuritis have all been described. Visual loss has been reported in as numerous as 8% of patients' or magnetic resonance imaging of the orbit and sinuses may provide useful anatomic information.

Unexplained constitutional symptoms are often part of the early presentation. Fever and weight loss may be reported at the onset of the disease and more frequently during the course of the illness. The upper airway disease is the mainly frequent presenting feature of WG. This includes sinusitis, oral lesions (ulcer, gingivitis), otitis media, hearing loss, epistaxis, and saddle nose deformity; sinusitis is the most frequent initial presentation in about half to two thirds of patients with WG. In this case epistaxis, fever, weight loss, hearing defects, otitis media and sinusitis were the most well-known features. Further unusual presentations of WG include salivary gland, cutaneous, gastrointestinal, and cardiac involvement. Renal disease also may be seen as the initial appearance or during the course of the disease. Once renal is present, disease may progress from asymptomatic and mild to fulminant glomerulonephritis within days or weeks, resulting in end-stage renal failure. Even with appropriate therapy, it may show the way to chronic renal insufficiency and renal failure[13].

In our case, the patient began therapy with monthly intravenous cyclophosphamide pulse therapy along with oral steroids (Prednisolone). The use of monthly intravenous pulse therapy is primarily to lower the overall cumulative dose of cyclophosphamide and thereby avoid some of the toxic side effects of the oral regimen. Our patient responded to intravenous pulse cyclophosphamide therapy and steroids with marked improvement in his urinalysis, decreased numbers of red blood cells per high power field, improvement in his serum creatinine level, Erythrocyte sedimentation rate and improvement of his inflammatory symptoms. He received a total of 3 months of intravenous pulse therapy, which he tolerated quite well, and has so far not had any signs of relapse. Prednisone alone is not a recommended therapy for WG[16]. However, in patients who have limited or non life threatening disease, monthly intravenous cyclophosphamide pulse therapy can be effective and can lessen some of the side effects. Pulse therapy is given in conjunction with prednisone, regularly starting at 1 mg/kg/day and given at this dosage for at least 1 month, then tapering by 5 to 10 mg per week until prednisone is stopped or the patient is placed on maintenance therapy of 5 to 15 mg every other day[19]. Mortality, on the other hand, can be drastically reduced with the beginning of a cyclophosphamide-corticosteroid treatment combination[20].

Additional treatments for WG include methotrexate and prednisone, which is an additional substitute for patients with active but not instantly life-threatening disease and normal or near-normal renal function. This particular course of therapy may be pretty in patients who have insufficient bone marrow reserve from past cyclophosphamide therapy or a history of cyclophosphamide-induced bladder injury. In those with severe disease at presentation, pulmonary hemorrhage, or declining disease despite immunosuppressive management plasmapheresis may be indicated. There is not much clinical information to deal with the long-term outcome in patients who go through plasmapheresis for WG[17, 18].

CONCLUSION:

Even though, classified in the group of rare pulmonary diseases, early diagnostics and the timely beginning of clinical management may considerably influence the further course of disease. Therefore, the application of supplementary diagnostic tests may be crucial for the prognosis of disease. The mean time to complete remission is 12 months, with occasional patients requiring treatment for more than 2 years before all symptoms have resolved. As a result, patients should not be considered non- responders until they have been monitored on this regimen for more than several months. This treatment has been quite effective in inducing remission in more than 90% of patients who adhere to this course of therapy; approximately 75% experience absolute remission. Response to this course of therapy is defined as a lessening or resolution of the inflammatory manifestations and at least the three-month follow-up of the patient is recommended. For the clinical management, early recognition of disease is of particular importance for prognosis in the patients with Wegener's granulomatosis.

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