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First Report of Wegener's Granulomatosis in a 12-year-old Boy in Iran

MH ***MORADINEJAD***, F ***MAHJOUB***, P ***TABATABAEI***, A ***ALIZADEH***

Abstract The aim of this report is to describe the first instance of Wegner's granulomatosis (WG) in a 12-year-old boy at the Children's Medical Center in Tehran University. This report will analyse the variety of clinical manifestations observed in a 12-year-old boy who suffered sinobronchitis for two months before diagnosis. We present a 12-year-old patient who exhibited pathological symptoms of WG prior to diagnosis and treatment. Our patient was monitored for one year after initial therapy through the outpatients department of the Children's Medical Center in Tehran University. One year after treatment, the patient's WG appeared to be in complete remission and he remained entirely well. Although Wegener's granulomatosis is a rare condition in children and can accordingly be confused with more common ailments, accurate and timely diagnosis can be made based on an established record of clinicopathologic features of the disease, and confirmed by biopsy of nasal mucosa.

Key words Sarcoidosis; Sinobronchitis; Tuberclosis; Vasculitis; Wegener's granulomatosis

Introduction

Wegener's granulomatosis (WG) is characterised by granulomatous inflammation of the respiratory tract (upper and lower), necrotising vasculitis affecting small to medium sized arteries, and necrotising glomerulonephritis.[1] Although in its classical form, WG is a multisystem disease with protean manifestations, but clinical manifestations may be mild with limited organ involvement.[2] The disease was first described by Peter McBride in 1897. The pathological-anatomical picture was described by Heinz Karl Ernst Klinger. Detailed description of the disease was given by Friedrich Wegener in 1936 and 1939.[3,4] The four clinical criteria for diagnosis of WG according American College of Rheumatology definition are:

- Nasal or oral inflammation (painful or painless oral ulcers or purulent or bloody nasal discharge)
- Abnormal chest radiograph showing nodules, fixed infiltrates, or cavities
- Abnormal urinary sediment (microscopic haematuria with or without red cell casts)
- Granulomatous inflammation on biopsy of an artery or perivascular area

Although this is a very uncommon disease in children, but up to now it has been reported in a few children with various presentations.[5-7] We present a case of Wegener's granulomatosis in a 12-year-old male admitted to the Children's Medical Center in Tehran University.

Case Report

A 12 year-old boy was referred to the Children's Medical Center because of dyspnoea, cough, nasal congestion and

Departments of Pediatric, Division of Rheumatology, Pathology, Infectious Disease, Otolaryngology, Children's Hospital Medical Center, Tehran University of Medical Sciences, Tehran, Iran

MH **MORADINEJAD** *MD*
F **MAHJOUB** *MD*
P **TABATABAEI** *MD*
A **ALIZADEH** *MD*

Correspondence to: Dr MH **MORADINEJAD**

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post nasal drip enduring 3 weeks. He was admitted to the hospital department of infectious diseases.

In his past history, in January of 2005 (9 months ago) he had an episode of non-febrile generalised tonic clonic seizure during nocturnal sleep followed by 15 minutes of postictal lethargic state. After 2 weeks of Phenobarbital consumption maculopapular skin eruptions appeared and he was admitted with a diagnosis of allergic vasculitis, thus Phenobarbital was discontinued and corticosteroid was begun, dosed at 1 mg/kg/day. Under corticosteroid treatment the boy's symptoms improved and the skin manifestations disappeared and after that corticosteroid treatment was tapered and after 2 weeks discontinued. Four months later he developed conjunctivitis and itching that slowly progressed until it affected the whole body. This condition was accompanied by a dry cough, so again he was admitted to the hospital. This time he was treated with clindamycin with the diagnosis of pneumonia. Shortly however, a rise of liver enzymes were detected (AST: 796 ALT: 440 GGT: 72) and drug induced hepatitis was suspected. Clindamycin was discontinued therefore, whereupon all the patient's symptoms disappeared over the following two months; after 5 months liver enzyme levels were restored to a normal range.

The patient's physical examination notes from his admission to hospital were as follows: fever (Temperature: 39.5 degrees centigrade), nasal discharge, nasal congestion and post nasal drip, fine crepitating rales and bilateral wheezing was heard by auscultation, chest X-ray revealed well defined opacity in right lobe and paracardiac region (Figure 1), and soft tissue mass was detected in paranasal sinus X-ray. Diagnosed this time with sinobronchitis, treatment was started with co-trimoxazole but because of drug hypersensitivity reaction, it was discontinued and changed to intravenous cephalexin at 100 mg/kg/day, combined with ampicillin 100 mg/kg/day for 10 days. Despite antibiotic therapy however, his symptoms failed to improve after one week, so a rheumatological consult was requested. The patient was referred to the rheumatology department with symptoms suggesting any one or combination of Wegener's granulomatosis, immune deficiency syndromes, tuberculosis, and sarcoidosis.

On physical examination by the rheumatologist, the patient was observed to have symptoms confirming WG; these included:

- Nasal crusting and ulceration. Chest auscultation revealed inspiratory stridor.
- Nasoendoscopy showed ulcerations with crusting and bleeding in the nose.
- A computed tomogram of para nasal sinuses that revealed multiple polyps and hypertrophic mucosa (Figure 2).
- A nasal mucosal biopsy which revealed severe infiltration of lymphomonuclear cells (Lymphoplasma cells, macrophages) in the lamina propria and around small blood vessels, which is very diagnostic of Wegener's Granulomatosis. Figure 3 shows microscopic view of WG in vessel wall from the lung.

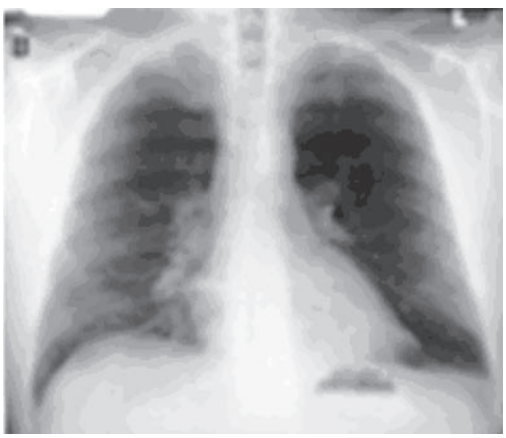

Figure 1 Wegener's granulomatosis chest X-ray.

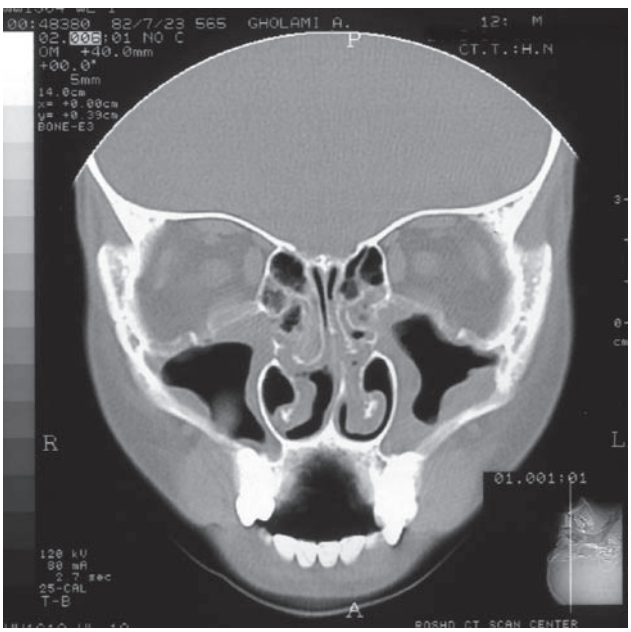

Figure 2 Sinus computed tomography, in computed tomogram of para nasal sinuses multiple polyps and hypertrophic mucosa were seen.

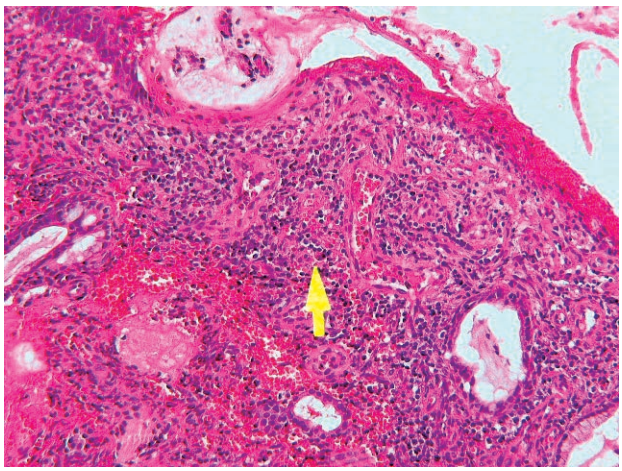

Figure 3 Wegener's granulomatosis, microscopic view, a vessel wall contains an infiltrate of lymphocytes, histiocytes and giant cells (granulomatous vasculitis). There is no necrosis present in this section. The vessel is from the lung.

Laboratory Findings

The Patient's initial laboratory evaluation were as follows: Hb: 6 gr/dl, leukocytosis (total white blood count: 20000), Plt 650000, erythrocyte sedimentation rate (ESR) 140, C-reactive protein (CRP): 3+ positive, and FBS, BUN and Creatinine were normal. Urinalysis revealed 3 red blood cells per high-power field (microscopic haematuria). A 24-hour urine collection revealed a creatinine clearance of 73 mL/min. Rheumatoid factor, ANA, C-ANCA and P-ANCA were negative, while serum ACE level was within a normal range. Because WG was suspected it was decided to go ahead with a biopsy of the nasal mucosa which confirmed the diagnosis.

Upon diagnosis of WG, intravenous methylprednisolone 500 mg/M^2 was prescribed for three days, along with a single intravenous dose of cyclophosphamide at 500 mg/M^2; these were followed by a one-month treatment of oral prednisolone at 2 mg/kg/day and Cyclophosphamide at 2 mg/kg/ day.

The patient responded dramatically to the treatment and respiratory signs and symptoms improved.

Over the next two months the cyclophosphamide dose was gradually decreased to 1 mg/kg every other day.

The patient was re-evaluated 8 months following the therapy. A chest radiograph showed a marked decrease in the size of the patient's pulmonary nodules. Urinalysis results suggested that the disease had become inactive. The patient appeared to achieve a clinical remission. He felt entirely well.

A repeated chest radiograph revealed only minimal residual scarring. Creatinine clearance had normalised to 91 mL/min.

Discussion

The case we report here is demonstrative of how it is possible to miss a diagnosis WG, attributing symptoms of WG to more common – but less harmful – conditions. One reason for this of course, is that WG has been reported quite rare in children and adolescents[8-10] (occurring in only 3.2 individuals among 100,000. This case, for example, is the very first ever documented in Iran. Nevertheless, WG is well characterised, affording diagnosing physicians enough information with which to make a correct diagnosis.[2]

In this case, several notes in the patient's history suggest that an earlier diagnosis of WG could have been made. However, it must be noted that final diagnosis of WG was only confirmed without a doubt after a biopsy of the patient's nasal mucosa.

Nine months before his diagnosis with WG, this patient was admitted to the hospital following an episode of non-febrile generalised tonic clonic seizure during nocturnal sleep, and by 15 minutes of postictal lethargic state. This is consistent with cerebral vasculitis. The maculopapular skin eruptions that appeared shortly after administration of phenobarbital were attributed to drug allergy, but cutaneous manifestations are reported in 14-50% of WG cases in different series and may be the indicative symptom in a significant proportion of cases.[4,11,12] Four months after suffering the masculopapular skin eruptions, our patient was re-admitted with conjunctivitis and itching that slowly progressed until it affected the whole body, and nine months later was admitted to hospital a third time with urticaria, maculopapular rash all over his body. These persistent cutaneous manifestations were strongly suggestive of WG.

This patient's history also notes a dry cough and a rise in liver enzymes. Although the latter was construed at the time to be a side-effect of the drugs used to treat the former complaint.

The triad of paranasal sinus involvement, pulmonary infiltration, and renal disease is characteristic of WG. Pulmonary involvement may be insidious and asymptomatic with pulmonary infiltrates or nodules on chest radiographs, although it may also present with cough, haemoptysis, dyspnoea, and chest discomfort.[3,13] In fact, in our patient, respiratory involvement was in the form of bronchitis and sinusitis that wouldn't respond to common

treatments with various antibiotics.

X-rays to investigate the patient's coughing and shortness of breath showed infiltration and swelling of the lymph nodes in the lungs. The child achieved complete remission however, following standard treatment with corticosteroids and cytotoxic.

Although functional renal impairment is uncommon in the initial stages of the disease's development, a majority of patients (60%) eventually develop glomerulonephritis,[14] with renal impairment usually occurring within the first 2 years of disease onset. Approximately 30% of patients with glomerulonephritis and azotemia prior to initiation of immunosuppressive therapy will progress to end stage of renal disease.[4] Our patient was ultimately observed to have microscopical haematuria and mild proteinuria that throughout the progression of the disease was accompanied by rising BUN and creatinine. Following standard treatment for WG, a complete remission was induced in the patient. Notably, anti-nuclear antibody tests are almost invariably negative, as was the case with this patient.

C-ANCA however, are positive in 88% of patients with active disease and 43% of patients in remission.[3,12,13] An elevated C-ANCA does not however, establish the diagnosis of Wegener's granulomatosis in the absence of the clinicopathologic features of the disease, and the use of C-ANCA as a marker of disease activity in a given patient is controversial.[13] For example, although the C-ANCA test was negative on both occasions it was performed for this patient, because WG was suspected due to the other indicative manifestations noted above, it was decided to go ahead with a biopsy of the nasal mucosa. The pathological findings from the biopsy confirmed the diagnosis of WG, further establishing that while the diagnosis of WG can be based on both the clinical and laboratory findings, it should whenever possible be confirmed without a doubt by a tissue biopsy of nasal or sinus mucosa, or of the bronchial lymphnode. In fact, it is standard practise to obtain a tissue diagnosis before starting treatment, as WG is indicated in nasal or sinus mucosa, or in the bronchial lymphnode severely infiltrated by lympho monuclear cells (Lymphoplasma cells, macrophages) in lamina propria, and around small blood vessels at focus forming giant granulomatoid feature.[15-17]

Our patient's first observable manifestations of the disease were a slowly growing nasal obstruction and discharge, and a productive cough. The characteristic upper and lower respiratory involvement, histopathologic features and the dramatic response to glucocorticoid and cyclophosphamide therapy helped us to confirm the diagnosis. However early presentation of WG in adults is more with kidney involvement and in children with sinobrochitis and Saddle nose is very rare in children.

A study comparing the classical and limited varieties of the disease found that the groups shared many features, particularly their requirement for immunosuppressive therapy, since WG causes major tissue destruction regardless of whether it is a localised or a widespread affliction.[13]

Treatment in Wegener's granulomatosis can be life saving. Treatment should not be delayed if the patient has poor general condition.

Survival has improved with the advent of therapy using cytotoxic agents, currently the eight year survival rate is reported to be about 80%.[17] Up to 90% of patients respond to cyclophosphamide, with three quarters of these achieving complete remission.[17]

Induction treatment is usually given as combined treatment with cyclophosphamide and corticosteroids. Use of corticosteroids alone is associated with a higher relapse rate.[15]

The specificities of induction regimens vary with the drugs used, doses, routes of administration, and duration.[17]

Conclusion

Although Wegener's granulomatosis is a rare condition in children and can accordingly be confused with more common ailments, this first recorded case of juvenile WG in Iran demonstrates that accurate and timely diagnosis can be made based on an established record of clinicopathologic features of the disease, and is confirmed with certainty by biopsy of nasal mucosa.

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