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Wegener's granulomatosis: Case report and review of the literature*

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SUMMARY

The clinical manifestations of Wegener's granulomatosis (WG) may be varied and easily overlooked. Awareness of distinguishing signs and symptoms allows early recognition and appropriate management. The body of literature dealing with the various facets of this disorder has grown in the past few years. Development of new diagnostic markers and successful therapies has rekindled interest in this disease. To assure early diagnosis and optimal prognosis the physician must maintain a high index of suspicion for WG. Although introduction of immunosuppressive therapy has dramatically improved the course of this disorder, treatment-related morbidity is often profound.

Key words: Wegener's granulomatosis, ethmoid, parotid

INTRODUCTION

Since its initial description by Klinger (1931) and Wegener (1939), Wegener's granulomatosis (WG) has become to be recognized as a distinct clinico-pathological entity. Wegener, between 1936-1939, reported 3 cases of a systemic granulomatous small-vessel vasculitis and identified the classic triad of necrotizing granulomatous inflammation of the upper and lower respiratory tract, systemic vasculitis of small arteries and veins, and focal necrotizing glomerulonephritis (Wegener, 1939). However, it was not until 1954 that Fahey and co-workers published a comprehensive description of this syndrome. Subsequently in 1973, Fauci and Wolff provided a detailed account of the clinical and pathological features of this disease, and reported their experience with the use of cyclophosphamide in the management of WG.

For many years WG was considered uniformly fatal, with five months being the mean duration of survival from the time of diagnosis (Gross, 1989). However, considerable variability is known to exist in both the extent of the involvement and rapidity of disease progression. In 1966, Carrington and Liebow introduced the concept of limited (renal-sparing) WG in which the clinical onset and the pulmonary lesions were identical to generalized classic WG, except for the absence of typical renal involvement and a longer survival. Nevertheless, it is currently widely accepted that WG begins as a localized process, which if untreated may progress with unpredictable velocity to classic aggressive disease with features of a systemic necrotizing vasculitis (Carrington and Liebow, 1966). This article is intended to report a case of WG and update our knowledge of the diverse manifestations of this disorder.

CASE REPORT

A 24-year-old male presented with a 6-month history of headache, nasal stuffiness, recurrent episodes of epistaxis and weight loss. Physical examination revealed a blood pressure of 100/70 mm Hg, regular pulse rate of 84 beats per min, and respiratory rate of 14 per min. Anterior rhinoscopy showed diffuse crusting on both sides of the nose. Removal of the crusts disclosed a friable mucosal surface underneath. There was a small septal perforation posteriorly. Biopsy of the nasal mucosa revealed vasculitis, necrosis, and granulomatous inflammation. An infectious cause was ruled out by special stains and cultures for fungi and Mycobacteria of tissue specimen. Sinus roentgenograms disclosed complete opacification of maxillary and ethmoid sinuses. Chest X-rays were unremarkable. Urine analysis, serum creatinine, and creatinine clearance test results were within normal limits. Pertinent laboratory findings were as follows: Hb: 120 g/l; white blood cell count: 15.900 × 10/l; erythrocyte sedimentation rate: 86 mm/h; CRP3+, VDRL and FTA-ABS were non-reactive.

An audiogram revealed bilateral, moderate conductive hearing loss. On the basis of clinical and pathological findings tentative

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diagnosis of limited WG was made and the patient was treated with prednisone (60 mg/day) and trimethoprim (160 mg b.i.d.) and sulfomethoxazole (800 mg b.i.d.; De Remee et al., 1985; West et al., 1987; Israel, 1988). The diagnosis was corroborated by a positive result of the cytoplasmic-antineutrophil cytoplasmic auto-antibodies (C-ANCA) test before treatment, with a titer of 1:64. Four weeks later, while still on therapy, the patient developed loss of vision and proptosis in the left eye and swelling in the right parotid area. Fundoscopic examination revealed papilledema in the left eye. Urine analysis disclosed microscopic haematuria and red blood cell casts. A CT scan of the orbita showed an ethmoid mass extending into the retro-orbital area, destroying the medial wall of the orbita (Figure 1). Biopsy of the right parotid mass disclosed granulomatous vasculitis and necrosis (Figure 2). The patient was subsequently treated with cyclophosphamide (2 mg/kg/day) and prednisone (1 mg/kg/day). His general condition improved dramatically. Proptosis and papilledema resolved and urinary sediment abnormalities disappeared. Immunosuppressive therapy was continued for one year after induction of remission. At his follow-up visit 6 months later, the patient was completely free of symptoms. Physical examination revealed a saddle-nose deformity and slight nasal crusting, but no evidence of active disease.

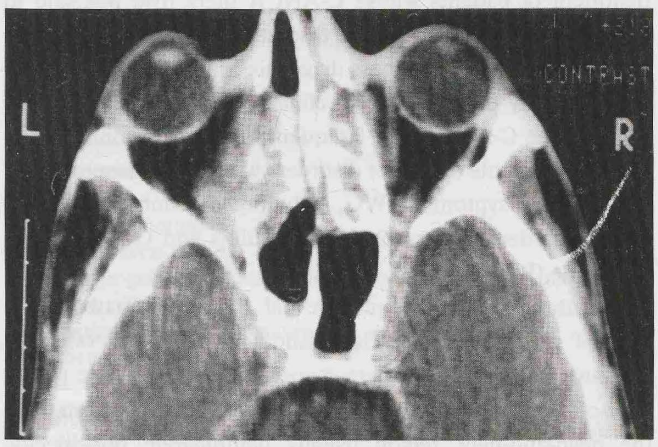

Figure 1. CT scan of the orbit showing an ethmoid mass extending into the retro-orbital area, destroying the medial wall of the orbit.

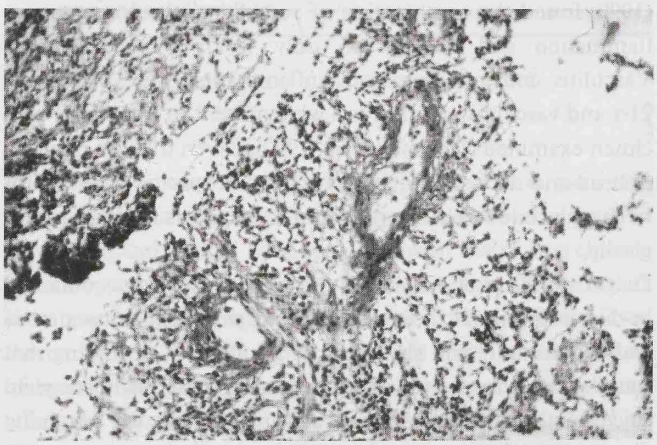

Figure 2. Lightmicroscopical section showing granulomatous vasculitis (Hematoxylin-eosin × 120).

His erythrocyte sedimentation rate had dropped to 24 mm/h, and the C-ANCA test was negative.

DISCUSSION

WG is a rare disease of obscure aetiology. No geographical or occupational exposure factors have been associated with the disease (Haynes, 1977). An association exists between WG and HLA-B8, HLA-DR2 antigens, perhaps indicating some familial predisposition (Gross, 1989). WG probably represents an aberrant hypersensitivity reaction to an unknown antigen, possibly one that enters through the upper respiratory tract (Fauci and Leavitt, 1989). This disorder can affect any age group (age range: 3 months to 75 years), but the mean age of the patients at the time of diagnosis is 40 years (Fauci and Wolff, 1973). The male-to-female ratio is 3:2 (Haynes, 1977). The disease may be present in a variety of organ systems (Figure 3). A recent review reported ENT involvement as the major organ system affected by WG. Nasal, sinus, tracheal, and ear abnormalities were presenting symptoms in 73% of the patients and eventually occurred in 92% of the patients (Hoffman et al., 1992). Involvement of upper respiratory tract may be manifested as purulent nasal discharge, nasal crusting, epistaxis, sinus pain, nasal stuffiness, saddle nose deformity, and secretory or chronic otitis media. Nasal crusts are often large and tend to form casts of the nasal cavity (McCaffrey, 1990).

According to the same series, tracheal stenosis was present in 16% of patients leading to shortness of breath which in some patients required emergency tracheotomy (Hoffman et al., 1992). Subglottic stenosis was reversible in a minority of cases and most patients required surgical intervention to restore subglottic patency. Another relatively rare manifestation of WG in the head-and-neck region is involvement of the salivary glands (Kovarsky, 1978; Specks et al., 1991). Specks et al. (1991) reported a series of patients with WG presenting initially with major salivary gland involvement. They also suggested that WG should be an important consideration in the differential diagnosis of salivary gland swellings. The presented case is yet another example of a major salivary gland involvement which occurred,

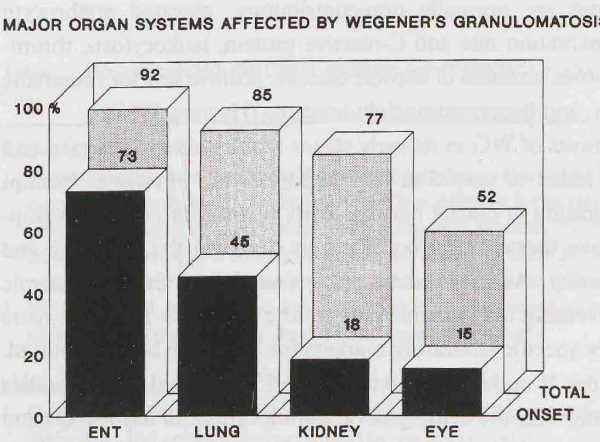

Figure 3. Disease manifestations.

during the course of the illness. Oral manifestations are frequently overlooked but may be the first clue to the diagnosis of WG.

Gingival hypertrophy in the form of a "strawberry gum" (gum enlargement with scattered petechial flecks) has been considered to be pathognomonic of WG (Cohen and Meltzer, 1981). Moreover, WG should be suspected in all healthy individuals that present with gum hypertrophy of recent onset (Nand et al., 1991).

Lower respiratory tract disease may be asymptomatic and only suspected when abnormal findings are present in routine chest X-rays (Haynes, 1988). Chest roentgenograms characteristically demonstrate bilateral nodular infiltrates which usually cavitate. Pulmonary involvement may also manifest as dry cough, hemoptysis, dyspnoea, and postobstructive pneumonia (Haynes, 1988). However, cases of massive pulmonary haemorrhage have been reported.

Renal involvement occurs late in the course of the disease and is the most important determinant of clinical outcome (Haynes, 1988). It may manifest itself as microscopic haematuria, red blood cell casts, proteinuria, and pedal oedema as the glomerulitis progresses. If untreated, rapidly progressing (crecentic) glomerulonephritis and death ensue (Haynes, 1988).

WG has been reported to affect nearly every organ system. Ocular manifestations are particularly common and may be the presenting feature of the disease (Haynes, 1988; Hoffman et al., 1992). Proptosis, which is frequently painful, is the most diagnostically helpful ocular finding and, when present in the setting of upper and lower airway disease and/or glomerulitis, is strongly suggestive of WG (Hoffman et al., 1992). Fifteen per cent of the patients are reported to develop proptosis at some stage of their illness (Hoffman et al., 1992). Other ocular manifestations include: conjunctivitis, cornea-scleral ring ulcers, episcleritis, scleritis, visual loss due to optic nerve ischaemia, and diplopia resulting from entrapment of extraocular muscles (Haynes, 1988). Less frequent systemic manifestations include: migrating arthralgias, non-deforming arthritis, mononeuritis multiplex, cranial nerve dysfunction, spontaneous subarachnoid or intracerebral haemorrhage (Venning et al., 1991), seizures, diabetes insipidus, pericarditis, coronary vasculitis and ischaemia, and cutaneous eruptions (Hoffman et al., 1992). Laboratory findings are normally non-contributory: elevated erythrocyte sedimentation rate and C-reactive protein, leukocytosis, thrombocytosis, anaemia of chronic disease, positive test for rheumatic factor, and hypergammaglobulinaemia (Haynes, 1988).

Diagnosis of WG in its early stages require clinical acumen and high index of suspicion on the part of the physician. Prompt recognition is crucial because early institution of immunosuppressive therapy may considerably decrease the mortality and morbidity. As the disease progresses the pattern of systemic involvement may provide clues to the diagnosis. In recent years highly-specific laboratory markers for WG have been identified. Van der Woude and co-workers (1985) reported on antibodies reacting with the cytoplasm of granulocytes and monocytes and their strong association with WG. Presently termed neutrophil cytoplasmic auto-antibodies, they demonstrate two staining patterns with immunofluorescence: perinuclear-antineutrophil cytoplasmic auto-antibodies (P-ANCA) and cytoplasmic-antineutrophil cytoplasmic auto-antibodies (C-ANCA; Specks and De Remee, 1990). The specificity of C-ANCA for WG has been confirmed in several large studies. Nölle et al. (1989) showed that the sensitivity of C-ANCA depends on disease activity and extent; it is positive in 67% of the patients with active limited disease, and in 96% of the patients with active generalized disease. Consequently, a negative C-ANCA test does not rule out a diagnosis of WG (Nölle et al., 1989). In contrast, due to its high specificity, a positive C-ANCA test can be of decisive diagnostic value, especially in the situations where the clinical manifestations are somewhat atypical or when the histological features do not allow a confirmed diagnosis (Nölle et al., 1989). Only recently, the C-ANCA antigen has been identified as the third neutral serum protease (proteinase 3) localized in the azurophilic granules of neutrophils (Kao et al., 1988; Lüdeman et al., 1990). Therefore, it is conceivable that highly specific enzyme-linked immunosorbent assays will replace the immunofluoresence techniques currently in use.

Furthermore, titers of C-ANCA have been shown to correlate closely with the disease activity, and thus measurement of C-ANCA titers may also be used to monitor therapeutical response and disease activity in patient follow-up. A rise in C-ANCA titers seems to predict clinical relapse and early treatment of patients whose C-ANCA titers rose was said to forestall exacerbations in the disease (Tervaert et al., 1990). Despite its clinical usefulness diagnosis of WG can not be established solely on the basis of clinical features and a positive result of the C-ANCA test. Frequent histological confirmation is required to rule out other disorders which may closely mimic the signs and syptoms of WG, including infections, connective tissue disorders, hypersensitivity vasculitis and Goodpasture's syndrome (Klinger, 1931).

Histopathologically, specimen reveal the classic pathological triad of granulomatous inflammation, necrosis and vasculitis (Devaney et al., 1990). Whereas open lung biopsy is the procedure of choice with the highest diagnostic yield, specimen from the head-and-neck region usually demonstrate non-specific pathological changes (Devaney et al., 1990; Haynes, 1988). In an analysis of 126 head-and-neck biopsy specimen, Devaney et al. (1990) found the combination of vasculitis, granulomatous inflammation and necrosis in only 16% of the specimen. Vasculitis and granulomatous inflammation were present in 21% and vasculitis and necrosis were present in 23% of the specimen examined (Devaney et al., 1990). Given that the majority of head-and-neck specimen may show non-specific inflammatory changes one rarely can rule out the diagnosis of WG histologically.

Diagnostically useful tissue in the upper airways was obtained in decreasing order of frequency from paranasal sinuses, nose and subglottic region (Hoffman et al., 1992). The finding that samples taken from the sinuses had the highest diagnostic yield suggests that the sinuses are an optimal site for obtaining diagnostic tissue from the head-and-neck region when radiographical involvement is present (Devaney et al., 1990).

The differential diagnosis of WG may be quite extensive (Table 1). However, it is of particular importance from the otolaryngologist's perspective in distinguishing between WG, idiopathic midline granuloma, and polymorphic reticulosis. These are all destructive lesions which involve the midfacial structures (Haynes, 1988). Idiopathic midline granuloma, once believed to be a localized form of WG, may be differentiated by its extremely destructive extension into the facial soft tissue and palate. The lesion predominantly involves the nose, paranasal sinuse and palate (Fauci et al., 1983; Haynes, 1988). Biopsies frequently demonstrate a combination of necrosis and acute or chronic inflammation with or without granuloma (Fauci et al., 1983; Haynes, 1988). It is of utmost importance to recognize and appropriately diagnose this lethal disorder, since local irradiation has been found to result in dramatic long-term remissions in the majority of cases (Fauci et al., 1976).

Table 1. Differential diagnosis of Wegener's granulomatosis.

1. Neoplastic diseases:
   - polymorphic reticulosis
   - non-keratinizing squamous cell carcinoma
   - nasopharyngeal lymphoma
   - primary and metastatic lung carcinoma
2. Infectious diseases:
   - tuberculosis
   - syphilis
   - rhinoscleroma
   - Leishmaniasis (Espundia)
   - Histoplasmosis
   - Blastomycosis
   - Coccidioidomycosis
   - leprosy
3. Vasculitic syndromes:
   - polyarthritis nodosa
   - allergic granulomatous angiitis (Churg-Strauss syndrome)
   - giant cell arteritis
   - systemic lupus erythematosis
   - rheumatoid arthritis
4. Miscellaneous:
   - idiopathic midline granuloma
   - atrophic rhinitis
   - cocaine abuse
   - acute necrotizing ulcerative mucositis (Noma)
   - Goodpasture's syndrome
   - relapsing polychondritis

Polymorphic reticulosis is a T-cell lymphoma that has been given various names, e.g. "lymphoid granulomatosis" (Devaney et al. 1990) and "mixed lymphoma" (Gnepp, 1988). It is characterized by a rapid onset of ulcerative, destructive lesions within the upper respiratory tract (Greene et al., 1991). In some cases there may be a prolonged course of nasal symptoms consisting of nasal crusting, bleeding and pain. Systemic disease may affect the lungs, kidneys, skin, and gastrointestinal tract. The disease may be difficult to differentiate from WG. This requires careful examination of adequate tissue by an experienced haematopathologist. Histologically, there is an invasion of atypical mononuclear cells which infiltrate the tissue in an angio-invasive and angiocenteric pattern. Treatment consists primarily of radiotherapy. However, combination chemotherapy may be necessary when there is multisystem involvement (Greene et al., 1991).

Syphilis is still the great masquerader, and may sometimes mimic the clinical features of WG. It can be distinguished from WG by serologic tests for reaginic antibodies (VDRL, RPR) and more specific tests (FTA-ABS, MHATP). Frequently, sarcoidosis may give rise to a clinical picture resembling WG. In sarcoidosis, however, the granulomas are classically non-caseating and well-formed (Gibbs et al., 1987; Devaney et al., 1990). Although necrotizing granulomas have been reported, this form of sarcoidosis only rarely produces extra-thoracic lesions. Serum angiotensin-converting enzyme is a widely used serologic marker for sarcoidosis and is not affected by WG (Gibbs et al., 1987).

Prior to the introduction of immunosuppressive drugs, WG was associated with a mortality rate of 93% after 2 years (Specks and De Remee, 1990). However, the introduction of cyclophosphamide in the 1960s vastly improved the outlook for the patients with WG. In 1983, Fauci and co-workers reported a 93% remission rate in 85 patients with cyclophosphamide and prednisone (Table 2). Although treatment with this regimen has been lifesaving, extended follow-up has led to recognition of a greater frequency of disease relapse, morbidity and drug toxicity than had been previously appreciated (Hoffman et al., 1992). A recent report demonstrated a relapse rate as high as 50% in patients receiving cyclophosphamide plus prednisone (Hoffman et al., 1992). However, caution should be employed to distinguish true clinical relapse from secondary infections. Most patients with WG and serious sinonasal involvement develop secondary infections of these tissues, almost surely because of mucosal damage and the subsequent impairment of host defenses (Fauci and Leavitt, 1989). *Staphylococcus aureus* is the predominant organism cultured from the nose and sinus of infected patients. Treated patients in complete remission often have apparent relapse because of increased sinus symptoms together with an elevation of erythrocytes sedimentation rate. Careful evaluation shows, however, that the symptoms and the

Table 2. Recommended treatment regimen for Wegener's granulomatosis.

Active multi-organ disease:
1. Cyclophosphamide (2 mg/kg/day); leukocyte count is used to guide dosage adjustments. Cyclophosphamide is continued for at least one year after complete remission and eventually tapered by 25-mg decrements every 2-3 months until discontinued or until a maintenance dose is found necessary to prevent flame-up of the disease.
2. Prednisone (1 mg/kg/day) for four weeks; it is changed over 1-3 months to 60 mg on alternate days and tapered gradually.

Fulminant disease:
1. Cyclophosphamide may be given i.v. at a dose of 4 mg/kg/day, for three days and subsequently changed to the lower oral dose regimen.
2. Prednisone may be given at a dose of 2-15 mg/kg/day.

elevation of the erythrocyte sedimentation rate are usually related to upper airway infection and both respond promptly to antibiotics, with or without drainage procedure. This observation is important because increasing or re-instituting immunosuppressive therapy under these circumstances is obviously contra-indicated (Fauci and Leavitt, 1989).

In the past decade, the search for safer and effective alternative therapies has resulted in the emergence of various therapeutic regimens, i.e. intermittant high-dose intravenous "pulse" cyclophosphamide (Sessoms and Kovarsky, 1984), trimethoprim/sulfomethoxazole (TMP-SMX; De Remee et al., 1985; West et al., 1987; Israel, 1988), and low-dose weekly methotrexate (Hoffman et al. 1992). The interest in intravenous "pulse" cyclophosphamide stemmed from its successful application in the treatment of systemic lupus erythematosis with nephritis (Sessoms and Kovarsky, 1984). However, despite its efficacy in inducing remission, intravenous "pulse" cyclophosphamide is associated with a higher long-term relapse rate (Hoffman et al., 1992). A therapeutic benefit of TMP-SMX in this disease was reported by De Remee et al. (1985). Subsequently, their result was corroborated by West et al. (1987) and Israel (1988). However, the anecdotal nature of these reports, the tenuous nature of diagnosis in some cases, the use of concurrent immunosuppressive therapy and failure to rule out infection for which TMP-SMX may be effective as antimicrobial: all cast some doubt on purported efficacy (Hoffman et al., 1992). In a recent study, TMP-SMX achieved prolonged improvement in only one out of nine patients with active biopsy-proven disease (Hoffman et al., 1992).

Based on current experience, standard therapy with daily cyclophosphamide and steroids is currently the best-known means of achieving remission and minimizing disease. However, drug toxicity associated with such treatment is substantial (Hoffman et al., 1992) and requires continued effort to better understand disease pathophysiology and to identify effective alternative, less toxic therapy.

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