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# Wegener's granulomatosis: The current understanding

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Wegener's granulomatosis (WG) is a rare systemic disease characterized by necrotizing granulomatous inflammation of the upper and lower respiratory tract, glomerulonephritis and vasculitis. It occurs as a limited form or generalized form and usually presents with nonspecific symptoms in its early stages, making the diagnosis of this disease more elusive. Strawberry gingivitis is the most common oral manifestation and is characteristic. Prompt recognition of this early manifestation is of utmost importance for the institution of early treatment, thereby avoiding serious complications. The present paper selectively reviews the literature regarding the current status of WG with respect to diagnosis, laboratory features, and treatment. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;100:265-70)**

Wegener's granulomatosis (WG) is a systemic disease characterized by necrotizing granulomatous inflammation of the upper and lower respiratory tract, glomerulonephritis, and vasculitis.[1] The disease was first described as a distinct syndrome by Friedreich Wegener in 1936.[2] The disease may run a course that might vary from indolence to one of rapid progression leading to life-threatening multiorgan failure.[3,4] Of the 2 types of WG, patients with generalized disease are known to have shorter life expectancy than patients with limited WG. Further renal involvement heralds a more severe outcome for the patients.[5] The disease usually develops over a period of time with the mean period from onset of symptoms to diagnosis of WG ranging from 4.7 to 15 months.[3] Without treatment it is invariably fatal; most patients do not survive more than a year after diagnosis.[6] Delay in the diagnosis of WG is mainly due to the nonspecific symptoms that are experienced by the patient during the initial phase of the disease.[3,4]

The most common oral lesion is hyperplastic gingivitis, which is red to purple with many petechiae (strawberry gingivitis), that may remain localized in the oral cavity for unusually long periods of time before multiorgan involvement occurs.[7] Therefore, timely recognition of this often overlooked oral finding can help to establish an early diagnosis of this disease.[4] Management with appropriate therapy produces a good response in most cases, with only occasional relapses.[3] The present paper selectively reviews the literature regarding the current status of WG with respect to diagnosis, laboratory features, and treatment.

## CLINICAL PRESENTATION

WG is a rare disease that usually manifests with pulmonary symptoms such as cough, hemoptysis, and pleuritis. Sinusitis is the most common symptom, seen in 73% of patients, and lung disease will develop in 85% of patients during the course of illness.[3] Serous otitis media, hearing loss may also occur and be the presenting manifestation in 25% of patients.[8] Involvement of the middle ear in this disease can be either a result of primary disease or secondary to involvement of the Eustachian tube.[9]

Renal disease is variedly present in <20% to 80% of patients at the time of initial diagnosis[5] and is usually asymptomatic.[3] During follow-up, 80%-94% of patients invariably develop renal involvement characterized by the presence of crescentic, necrotizing glomerulonephritis on biopsy along with urinary sediment, ie, >5 erythrocytes per high power field or erythrocyte/granular cast.[5]

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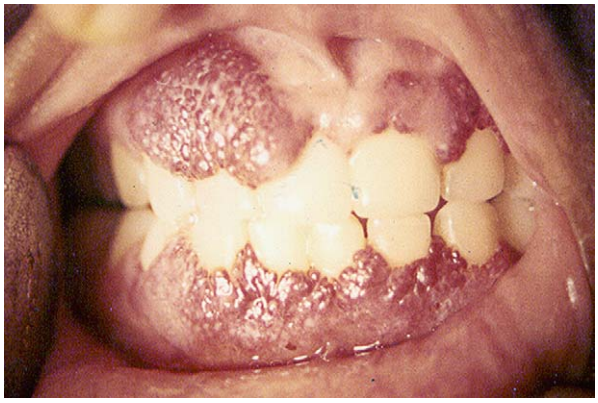

Fig 1. Photograph of oral lesion (strawberry gingivitis) at initial presentation.

## ORAL MANIFESTATIONS

Though oral lesions are reported to occur in 6%-13% of patients, they were an initial presenting feature in only 2% of cases.[8] Strawberry gingivitis is one of the characteristic sign of WG (Fig 1).[2,10,11] This feature, thought to be an early manifestation,[4,7] is extremely rare[4,10] but when present is characteristic.[4,7,11,12]

The oral lesions of microscopic polyangiitis closely resemble the gingival lesions of WG[13] and are difficult to differentiate even by microscopy.[6] However, the American College of Rheumatology (ACR) criteria do not recognize the diagnosis of microscopic polyangiitis and classifies such patients as having WG, Henoch-Schönlein purpura, or hypersensitivity angiitis.[14] Furthermore, with the Chapel Hill criteria (Table I), a patient is considered to have microscopic polyangiitis when there is pauciimmune small vessel vasculitis in the absence of granulomatous inflammation and asthma.[14]

## DIAGNOSTIC CRITERIA

The diagnostic criteria, as defined by the ACR for the diagnosis of WG requires at least 2 of the following 4 criteria[16]: (1) oral ulcers or nasal discharge, (2) the presence of nodules, fixed infiltrate, or cavities on a chest radiograph, (3) nephritic urinary sediment (red cell cast or >5 red blood cell per high power field), and (4) granulomatous inflammation on a biopsy. Although oral ulceration is one of the criteria required by the ACR in the diagnosis of WG, it usually occurs late in the disease. [2,17]

## INITIAL DIAGNOSTIC EVALUATION

If WG is suspected from clinical history and examination of organ systems, investigation should include a complete blood count, erythrocyte sedimentation rate, C-reactive protein, serum creatinine and blood urea nitrogen levels, 24-hour proteinuria, and urinalysis. Chest radiograph and computerized tomography scan are required to detect pulmonary infiltrates or nodules. Additionally, special stains for bacteria and fungus are required to rule out systemic infections.

## ANTINEUTROPHIL CYTOPLASMIC AUTOANTIBODY (ANCA) SEROLOGY

Since the first description in 1982 by Davies et al, antineutrophil cytoplasmic autoantibody has attracted interest as a rapid and noninvasive way to help diagnose WG.[18] The association between WG and ANCA was first confirmed by Van der Woude et al in 1985.[19] Currently, c-ANCA (see below) serves as a sensitive and specific marker of WG.[19-21]

The current recommendation for ANCA testing requires initial screening of all sera by indirect immunofluorescence on ethanol-fixed neutrophils to discriminate 2 main patterns of ANCA: a cytoplasmic pattern (c-ANCA) and a perinuclear pattern (p-ANCA). The pattern obtained should then be confirmed by a more specific ELISA test, specifically for antiproteinase 3 and antimyeloperoxidase.[16,22] Proteinase 3 (PR3) is a 29-kd serine protease found in the azurophilic granules of neutrophils and is the major antigen for c-ANCA.[23] Myeloperoxidase (MPO), a lysosomal enzyme found in the neutrophils, is the major antigen for p-ANCA.[24] The c-ANCA pattern has predominantly been associated with WG,[14,18,22,25] whereas p-ANCA has been more frequently associated with microscopic polyangiitis, other vasculitides, idiopathic necrotizing and crescentic glomerulonephritis, and other diseases.[18]

The combined approach of immunofluorescence and ELISA produces sensitivity of 73% and a diagnostic specificity of 99% in WG.[14,26] However, false-positive c-ANCA test results have been reported in patients with tuberculosis, Hodgkin's lymphoma, human immunodeficiency virus infection, nasal septal perforation, monoclonal gammopathies, and drug-induced Wegener-like disease.[18]

The current recommendation for a mandatory ANCA testing is prudent when there is a strong clinical evidence of signs and symptoms of WG. The positive predictive value in these clinical settings is a useful marker of WG.[26]

## ANCA MONITORING AS A MEASURE OF DISEASE ACTIVITY

Changes in the levels of ANCA in WG generally reflect disease activity,[1,19] with increasing titers being a reliable predictor of relapse.[1] The titers of these antibodies decline during treatment,[19,27] but titers may rise again before a relapse.[27] Although rising titer of c-ANCA is not always followed by active disease,[1,3] persistently positive ANCA titers in patients in clinical

**Table I.** Names and definitions of vasculitides adopted by the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis[15]

| *Name* | *Definition* |
|---|---|
| Medium-sized vessel vasculitis, Polyarteritis nodasa (classic polyarteritis nodasa) | Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules. |
| Small vessel vasculitis, Wegener's granulomatosis | Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels (eg, capillaries, venules, arterioles, or arteries).* Necrotizing glomerulonephritis is common.† |
| Microscopic polyangiitis (microscopic polyarteritis) | Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (eg, capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium-sized arteries may be present.* Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.† |
| Churg-Strauss syndrome | Eosinophil-rich granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels associated with asthma and eosinophila. |
| Henoch-Schonlein purpura | Vasculitis with IgA-dominant immune deposits, affecting small vessels (eg, capillaries, venules, or arterioles).* Typically involves skin, gut, and glomeruli and is associated with arthralgias or arthritis.† |
| Cutaneous leukocytoclastic angiitis | Isolated cutaneous vasculitis without systemic vasculitis or glomerulonephritis |
| Essential cryoglobulinemic vasculitis | Vasculitis with cryoglobulin immune deposits affecting small vessels (eg, capillaries, venules, or arterioles) and associated cryoglobulins in serum.* Skin and glomeruli are often involved.† |

*Essential components.
†Usual but not essential components.

remission have been shown to be a risk factor for eventual relapse.[14,21]

## PATHOLOGY

Traditionally, biopsy is used in patients with suspected WG to confirm the disease and to rule out other entities, such as systemic infections and malignancies.[28] The histopathologic criteria for the diagnosis of WG requires identification of vasculitis, ill defined granulomata, multinucleate giant cells, and necrosis.[11] However, these are usually evident only on thoracoscopic lung biopsy[6] and are notably absent in most biopsy specimens of oral lesions.[11] Rather, it is more common to encounter an intense acute or chronic inflammation with microabscesses, multinucleate giant cells, and pseudoepitheliomatous hyperplasia, which are generally regarded as nonspecific (Fig 2).[2,7,10,11] Although the Chapel Hill definition requires histologic evidence or the presence of clinical features to make a diagnosis of WG,[14,15] it is often difficult to diagnose WG based on microscopic findings alone.[2] However, the histopathologic features mentioned above in combination with strawberry gingivitis are highly suggestive of WG.[2,10,11]

## MANAGEMENT

The standard therapy introduced by Fauci et al[29] remains the gold standard for treating patients with WG.[3] Therapy is aimed at inducing remission with oral prednisone 1 mg/kg and cyclophosphamide 2 to 3 mg/kg. Once remission is achieved, prednisone is usually tapered gradually to alternate days at 3 months and then discontinued, whereas cyclophosphamide is continued for at least a year after remission induction.

If the correct therapeutic decision is taken, most patients respond immediately to treatment within a week. Resolution of oral lesions (Fig 3), clearing of pulmonary infiltrates with evidence of stable scarring, and no further evidence of active renal sediment signifies complete remission. However, remission in some cases may soon be followed by relapse which usually coincides with tapering of immunosuppressive therapy.[3,29]

Though the introduction of standard therapy was clearly a major advance, the improvement in survival has been associated with significant therapy-related morbidity, such as cystitis, bladder cancer, myelodysplastic syndrome (MDS), and severe infections.[3,30] Much of this is related to the doses of cyclophosphamide and prednisolone used.[30] Recently, Reinhold-Keller et al[31] reported the use of daily mesna, as uroprotection, during daily cyclophosphamide therapy. With this therapeutic approach, although only 19% of their patients developed cystitis, the incidence of MDS (8%) was higher than that reported by Hoffman et al.[3] Therapy-related malignancies such as squamous cell

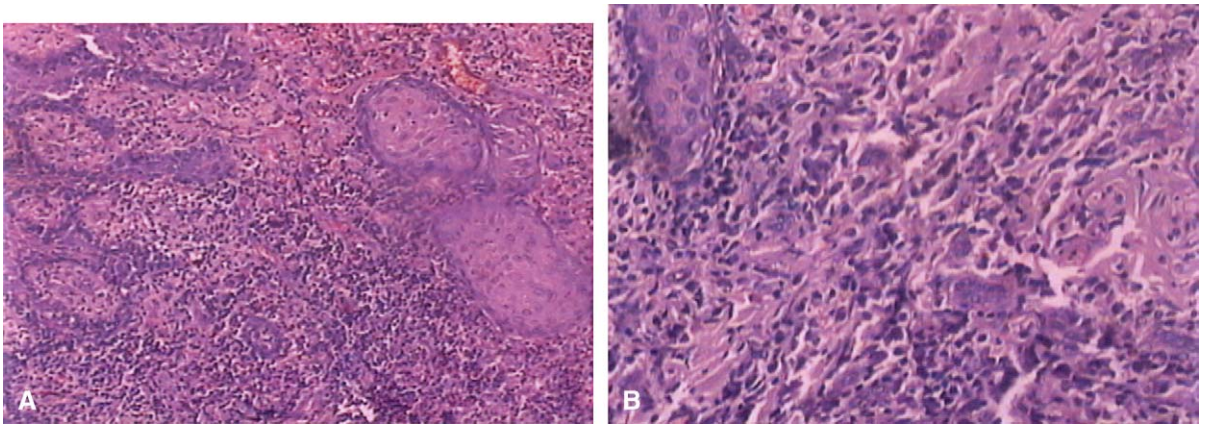


Fig 2. Histopathology showing pseudoepitheliomatous with **A**, chronic inflammatory infiltrate in the underlying connective tissue in (low power) and **B**, chronic inflammatory infiltrate along with multinucleate giant cell (*arrow*) (high power). H & E stain.

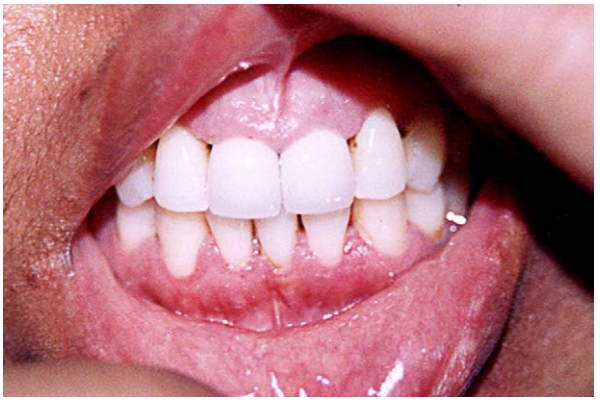

Fig 3. Resolution of oral lesion in Fig 1 following therapy with prednisone and cyclophosphamide.

carcinoma, Kaposi sarcoma, and basal cell carcinoma have also been reported to occur in patients with WG.[5]

## FOLLOW-UP MONITORING DURING INDUCTION THERAPY

Periodic monitoring of blood count during follow-up is critical for proper patient management and secondary complication prevention. Normally with appropriate therapy the leukocyte count is expected to decrease and even result in leukopenia.[29] Persistence or an elevated leukocyte count indicates infection. This may trigger relapse in patients with WG in remission.[32] Monitoring also helps to detect the presence of blast cells (immature myeloid cells) in the peripheral blood that may occur in the course of therapy. The presence of blast cells is a cause for concern as they are usually associated with acute myeloid leukemia (AML) or MDS.[33] These complications in WG is usually seen late in the course of the disease with a mean duration of 60 months between diagnosis and manifestation.[31]

**Table II.** Dental management recommendations for patients with WG

| |
|---|
| **During the period of induction therapy** |
| Emergency care dental treatment only, in consultation with physician/specialist. |
| Daily antibacterial mouth rinses. |
| **During remission/maintenance therapy** |
| Consultation with the physician/specialist. |
| Frequent recall and prophylaxis. |
| Daily antibacterial mouth rinses. |
| Treat all new dental diseases. |
| Avoid nephrotoxic drugs. |
| Consider before any invasive procedure in consultation with physician/specialist: |
| (a) antibacterial prophylaxis. |
| (b) order or obtain laboratory information. |
| (c) monitoring blood pressure before and after surgery. |
| (d) corticosteriod supplementation, if necessary. |
| **During relapse** |
| Refer to specialist immediately, if signs of oral lesion suggestive of WG reappear. |
| Follow recommendations as for induction period. |

Because of the high morbidity associated with standard therapy, intermittent intravenous treatment with cyclophosphamide has been introduced with the intention of reducing treatment-related morbidity.[3] Pulse intravenous cyclophosphamide is probably as effective as oral cyclophosphamide at inducing remission[30] but is known to result in more relapses.[3,5]

A novel method to minimize infection and thereby to prevent relapses had been adopted by Stegeman et al.[32] He reported that the addition of trimethoprim and sulfamethoxazole to therapy with cyclophosphamide and prednisolone resulted in reduction in the relapse rate with fewer incidence of respiratory and nonrespiratory infections.[32] However, neither trimethoprim alone nor trimethoprim combined with low-dose prednisolone sustained remission in generalized WG.[34]

At present, the combination of azathioprine and low-dose prednisolone are mainly used as maintenance therapy.[29,30]

## DENTAL MANAGEMENT

The literature does not provide sufficient documentation that the primary medical care provider who encounters patients with WG during the early phase of the disease—when there are only nonspecific symptoms and/or associated oral signs—often seeks specialist dental opinion. The dental specialist has a relatively high chance of suspecting this systemic vasculitic disorder on the basis of characteristic oral findings, even during the early phase of the disease. This could lead to prompt referral to a rheumatologist, pulmonologist, or nephrologist, providing opportunity for the commencement of early treatment. It is imperative that a referral to the dental care provider be sought before the institution of immunosuppressive therapy, although the disease may run a fatal course if therapy is delayed. Dental evaluation should focus on the identification and removal of a potential source of infections, although no long-term studies have addressed that sepsis originates from dental infections.[3,29] The dental care provider may also encounter these patients during the course of therapy; if this is the case, despite the fact that the literature is replete with specific guidelines for the dental management of patients with WG, it is prudent to follow the recommendations for patients under immunosuppressive therapy[35] (Table II).

## SUMMARY

Although current treatment protocols have changed the outcome for patients with WG from that of an acute systemic disease with high mortality rate to that of a chronic disease with relapse and remission,[30,31] early diagnosis of WG is crucial to prevent organ damage resulting from extension of local disease.[4] Close follow-up with ANCA serology is required to prevent impending complications that might stem from both therapy and disease progression.[36]

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