

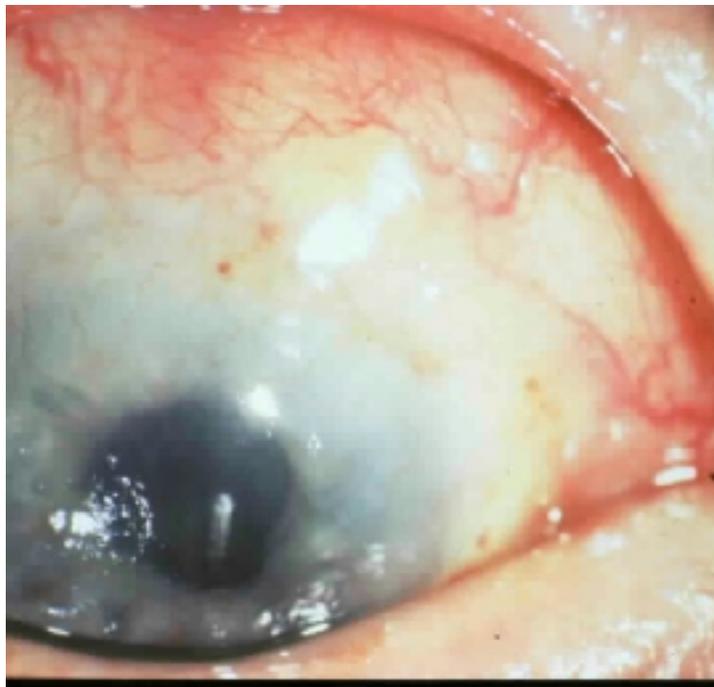
A Case of Very Limited Wegener's Granulomatosis and Scleritis

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Case Presentation:

The patient is a 75 year old man who underwent cataract extraction of the right eye in March 93. The surgery was uneventful. A year and half later, the patient developed a large, rapidly advancing conjunctival mass medially in the right eye. Biopsy of the lesion revealed chronic inflammation. The right eye was treated with topical dexamethasone/neomycin/polytrim without any improvement. The patient was referred in August this year.

The past medical history was significant for hypertension. Review of systems was significant for fatigue. On examination, the visual acuity was counting fingers at 3 ft OD, and 20/30 OS. The biomicroscopic examination showed a large conjunctival mass superonasally as seen below.



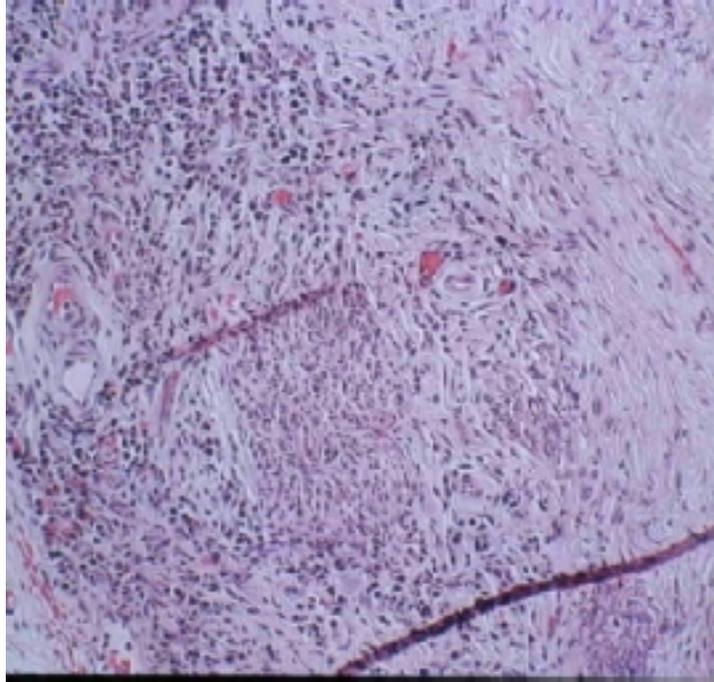
There was diffuse conjunctival injection and inflammation. Conjunctiva inferotemporally also appeared to be elevated as seen in the figure below.



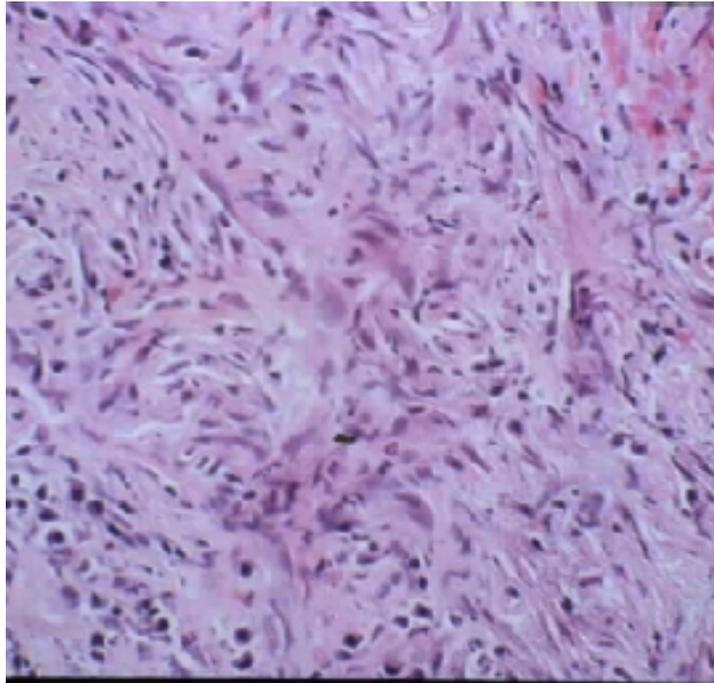
Superiorly, a corneal pannus was also noted. The rest of the exam and the exam of the left eye was unremarkable.

An immunologic workup included a negative ANCA, an erythrocyte sedimentation rate of 65, mildly elevated soluble IL-2 receptor level at 894, and ANA with rat liver substrate of 1:80. Urinalysis was positive for glucose, but negative for RBC. The rest of the workup including a chest X-ray, CBC, FTA-abs, RPR, rheumatoid factor, and immune complex assays were all negative.

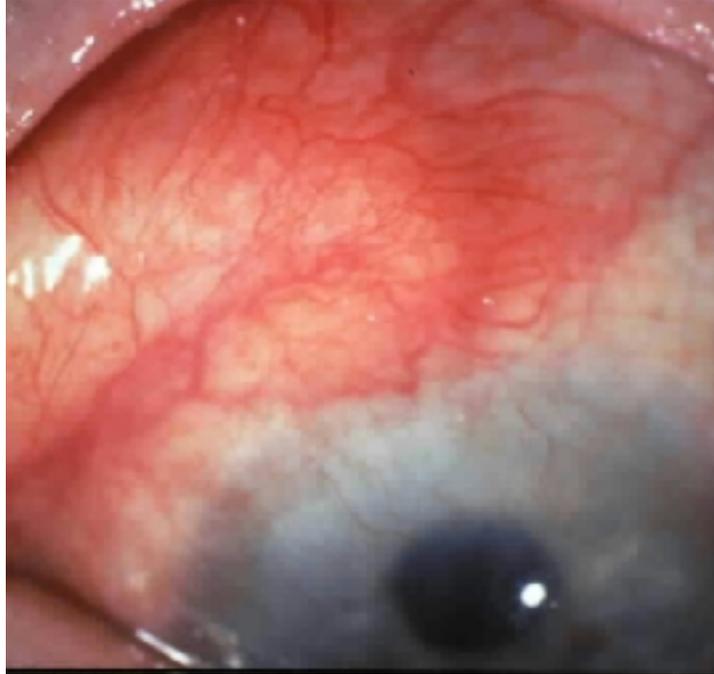
The patient underwent conjunctival and scleral biopsy of the right eye. Intraoperatively, after the conjunctiva was lifted, multiple scleral nodules were noted. Histopathology of the specimen revealed probable vasculitis with micro-abscesses, seen below,



with epithelioid cells and eosinophils seen further below,



suggestive of Wegener's granulomatosis. Postoperatively, the patient was treated with 1% rimexolone four times a day. The vision in the right eye gradually improved to 20/30. Trimethoprim-sulfamethoxazole was added. However a month later, the nodular scleritis in right eye persisted, (See figure below)



and cyclosporine 100 mg per day was started. Two months later, the scleritis appeared worse. Trimethoprim-sulfamethoxazole and cyclosporine were stopped, and cyclophosphamide was initiated.

Discussion:

Wegener's granulomatosis (WG) was first established as a distinct clinical entity in 1936 by Wegener, a German pathologist. It is a systemic disease of unknown etiology and is characterized by granulomatous inflammation of the upper and lower respiratory tract, necrotizing vasculitis, and nephritis.

It is a rare disease that typically occurs in patients in their fourth to sixth decades, although it has been reported in patients with age range from 7 to 75.¹ There is a slight male preponderance with a male to female ratio of up to 1.5 to 1. Although it has been reported in blacks and Hispanics, the disease occurs most commonly in Caucasians.

The classical triad of WG consists of necrotizing granuloma of the upper and lower respiratory tract, typically with mucosal inflammation and ulceration; necrotizing vasculitis involving both arteries and veins; and nephritis which is a focal necrotizing glomerulitis with thrombosis of capillary loops. WG is classified into three forms: a generalized form that correlates with the classic triad; a limited form which is more indolent and typically involves the respiratory tract but spares the kidneys; and a very limited form, as in our patient, with only ocular or orbital disease.

The onset of active or generalized disease is characterized by malaise, fatigue, fever and weight loss.¹⁻⁶ Respiratory tract abnormalities are the most common manifestations, with pulmonary infiltrates and sinusitis being the two most common presenting signs of WG. Upper airway abnormalities include sinusitis, hemorrhagic rhinitis, nasal mucosal ulcerations and otitis media. Characteristic lower respiratory tract symptoms are cough, hemoptysis, dyspnea and pleuritic pain. Chest X-ray may show multiple, bilateral nodular infiltrates with a tendency toward cavitation.

Renal disease usually occurs after upper and lower airway disease. It may manifest as mild, focal and segmental glomerulonephritis with minimal urinary sediment abnormalities; or it can be a fulminant diffuse necrotizing glomerulonephritis. Renal disease may progress rapidly and is associated with a poor prognosis.

Other manifestations include arthralgias and nondeforming arthritis, and skin lesions such as papules, vesicles, palpable purpura, ulcers, and subcutaneous nodules. Neurological abnormalities such as peripheral neuropathy or cranial nerve palsies may be present. Cardiac involvement includes pericarditis, and congestive cardiomyopathy.

Ocular disease occurs in 58% of patients with WG,¹ and can be divided into 2 categories: contiguous and focal.⁷ Contiguous disease arises from the extension of granulomatous sinusitis of long duration and results in orbital pseudotumor, orbital abscess or cellulitis, or nasolacrimal duct obstruction. Orbital inflammation with proptosis is the most common ocular manifestations in WG.⁷⁻⁹ Focal disease is defined as a focal vasculitis involving the anterior, posterior or both segments of the eye and possibly the orbit. Of the focal diseases, conjunctivitis, scleritis, episcleritis, and keratitis are the most common. Other focal ocular manifestations of WG are ischemic optic neuropathy, retinal artery occlusion, uveitis, chorioretinal ischemia and infarction.

Scleritis occurs in 7-11% of patients with WG, and often parallels systemic symptoms and may be the presenting sign of a systemic exacerbation. The scleritis may be diffuse, nodular, or necrotizing. Necrotizing scleritis and peripheral ulcerative keratitis (PUK) are the most malignant ocular manifestations of WG, and can result in ocular perforation. PUK develops after breakdown of the peripheral corneal epithelium and progresses centrally and circumferentially. It may appear similar to Mooren's ulcer, except that in Mooren's ulcer the sclera is not involved; in contrast scleritis is invariably present in peripheral ulcerative keratitis associated with WG.

Until recently, there was no specific diagnostic test for WG. Nonspecific laboratory findings include normocytic anemia, leukocytosis, thrombocytosis, elevated erythrocyte sedimentation rate, positive rheumatoid factor, elevated C-reactive protein, and circulating immune complexes.

In 1985, antineutrophil cytoplasmic antibodies (ANCA) were found to be a specific test for WG,¹⁰ with specificity as high as 99% by indirect immunofluorescence techniques and 98% by ELISA.¹¹ The sensitivity of ANCA depends on disease activity: the sensitivity is 32% for patients with WG in full remission after limited disease, 67% for patients with active limited disease, and 96% for patients with active generalized disease.

There are two types of ANCA staining, the classic granular cytoplasmic staining pattern, and the perinuclear staining pattern. The cytoplasmic staining pattern, or C-ANCA is specific for myeloperoxidase, which is a neutrophil protease referred to proteinase 3.^{12,13} C-ANCA is highly specific for WG.^{10,14} The perinuclear staining pattern, or P-ANCA, is specific for various lysosomal enzymes such as myeloperoxidase, cathepsin G, human leukocyte elastase, and lactoferrin.¹² P-ANCA is a specific marker of idiopathic necrotizing and crescentic glomerulonephritis, a disease frequently associated with microscopic polyarteritis, and occasionally with WG. It is thought that WG, microscopic polyarteritis, and idiopathic necrotizing and crescentic glomerulonephritis are part of the spectrum of one disease process. Although C-ANCA is typically the ANCA associated with WG, both C-ANCA and P-ANCA can be found in generalized, limited and very limited WG.¹⁵

A study from the Massachusetts Eye & Ear Infirmary showed that ANCA is highly specific and sensitive for WG in patients with scleritis.¹⁶ Of the 23 patients with scleritis, all 7 patients with positive ANCA titers had limited or generalized WG, and none of the 16 patients with negative titers had WG.

According to the diagnostic criteria established by the American College of Rheumatology, the presence of 2 or more of the following four criteria is associated with a sensitivity of 88% and a specificity of 92% for WG: abnormal urinary sediment, abnormal chest X-ray, oral ulcers or nasal discharge, and granulomatous inflammation.¹⁷ ANCA is an important test in the diagnosis of WG, because of its high specificity and sensitivity. However, since ANCA is only positive in 67% of patients with limited disease and 32% of patients in remission, a negative ANCA does not exclude the diagnosis.

Pathological findings of necrotizing granuloma in involved extraocular tissues confirms the diagnosis of WG in the presence of compatible systemic clinical findings with or without positive ANCA. If necrotizing granuloma is found in conjunctiva and/or sclera in association with complete and limited clinical features the diagnosis of WG is confirmed even if the ANCA is negative. A study from the Mass Eye & Ear Infirmary by Niffenegar, Jacobiec and others described the diagnosis of very limited WG based on histopathologic findings and a positive ANCA.¹⁸ The histopathologic findings include granulomatous foci, collagen necrosis, and infiltration with neutrophils and eosinophils.

WG can be fulminant and fatal without cytotoxic therapy. The 2 year mortality rate is 90% in patients with generalized disease. A study from NIH reported that with combined cyclophosphamide and corticosteroid therapy, remission was induced in 93% of cases, with a survival rate of 88% at a mean followup of 51 months.¹⁹ In the NIH protocol, cyclophosphamide is administered at a dose of 2 mg/kg/day. Oral prednisone is administered at 1 mg/kg/day until the immunosuppressive effects of cyclophosphamide are apparent. Prednisone is then tapered.

A number of reports have suggested that trimethoprim-sulfamethoxazole may be beneficial in the treatment of WG. In a case report from the infirmary by Soukiasian and Jakobiec, a patient with limited WG and scleritis was successfully treated with trimethoprim-sulfamethoxazole with normalization of ANCA titers.²⁰ The patient remained disease-free during a follow-up of 20 months. However a recent study compared the efficacy of trimethoprim-sulfamethoxazole, with and without prednisone, in maintaining remission in patients with generalized WG to that of methotrexate.²¹ The study revealed that 91% of patients received methotrexate and prednisone remained in remission. In the group that received trimethoprim-sulfamethoxazole alone only 58% of patients remained in remission. In contrast all the patients who received both trimethoprim-sulfamethoxazole and prednisone experienced a relapse within 14 months. They concluded that trimethoprim-sulfamethoxazole should not be used for the maintenance of remission in patients with generalized WG.

In general C-ANCA titers are not a sensitive marker of relapse. However a study by Power et al showed that in patients with WG and scleritis or peripheral ulcerative keratitis, the serum ANCA level did not revert to normal during remission in 4 of the 5 patients who had relapses; however ANCA converted to normal in all 3 patients who remained in remission.²² Therefore failure of ANCA titers to revert to normal levels may be associated with the potential for relapse.

References:

1. Fauci AS, Haynes BF, Katz P, Wolff SM: Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med* 98:76, 1983.
2. Walton EW: Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). *Br Med J* 2:265, 1958.
3. Fahey JL, Leonard E, Churg J, et al: Wegener's granulomatosis. *Am J Med* 17:168, 1954.
4. McDonald TJ, DeRemee RA: Wegener's granulomatosis. *Laryngoscope*. 93:220, 1983.
5. Pinching AJ, Lockwood CM, Pussell BA, et al: Wegener's granulomatosis: Observations on 18 patients with severe renal disease. *Q J Med* 52:435, 1983.

6. Brandwein S, Esdaile J, Danoff D, et al: Wegener's granulomatosis. Clinical features and outcome in 13 patients. *Arch Intern Med* 143:476, 1983.
7. Straatsma BR: Ocular manifestations of Wegener's granulomatosis. *Am J Ophthalmol* 44:789, 1957.
8. Haynes BF, Fishman ML, Fauci AS, Wolff SM: The ocular manifestations of Wegener's granulomatosis. Fifteen years experience and review of the literature. *Am J Med* 63:131, 1977.
9. Bullen CL, Liesegang TJ, McDonald TJ, et al: Ocular complications of Wegener's granulomatosis. *Ophthalmology* 90:279, 1983.
10. van der Woude FJ, Rasmussen N, Lobatto S, et al: Autoantibodies against neutrophils and monocytes: Tool for diagnosis and marker of disease activity in Wegener's granulomatosis. *Lancet* 1:425, 1985.
11. Nolle B, Specks U, Ludemann J, et al: Anticytoplasmic autoantibodies: Their immunodiagnostic value in Wegener granulomatosis. *Ann Intern Med* 111:28, 1989.
12. Falk RJ, Jennette JC: Antineutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis. *N Engl J Med* 318:1651, 1988.
13. Niles JL, McCluskey RT, Ahmad MF, et al. Wegener's granulomatosis autoantigen is a novel neutrophil serine protease. *Blood* 74:1888, 1989.
14. Ludemann G, Gross WL: Autoantibodies against cytoplasmic structures of neutrophil granulocytes in Wegener's granulomatosis. *Clin Exp Immunol* 69:350, 1987.
15. Cohen Tervaert JW, Elema JD, Kallenberg CGM: Clinical and histopathological association of 29kD-ANCA and MPO-ANCA. *Acta Pathologica Microbiologica et Immunologica Scandinavica (Suppl 19)* 98:35, 1990.
16. Soukiasian SH, Foster CS, Niles J, et al: Diagnostic value of antineutrophil cytoplasmic antibodies (ANCA) in scleritis associated with Wegener's granulomatosis. *Ophthalmology* 99:125, 1992.
17. Leavitt RY, Fauci AS, Bloch DA, et al: The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. *Arthritis Rheum* 33:1101, 1990.
18. Nifennegger JH, Jakobiec FA, Raizman MB, et al: Pathological diagnosis of very limited (ocular or orbital) Wegener's granulomatosis. (In Press)
19. Fauci AS, Haynes BF, Katz P, Wolff SM: Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med* 98:76, 1983.
20. Soukiasian SH, Jakobiec FA, Niles JL, et al: Trimethoprim-sulfamethoxazole for scleritis associated with limited Wegener's granulomatosis: Use of histopathology and antineutrophil cytoplasmic antibody (ANCA) test. *Cornea* 12:174, 1993.
21. DeGroot K, Reinhold-Keller E, Taxis E, et al: Therapy for the maintenance of remission in sixty-five patients with generalized Wegener's granulomatosis. *Arthritis & Rheum* 39:2052, 1996.
22. Power WJ, Rodriguez A, Neves RA, et al: Disease relapse in patients with ocular manifestations of Wegener's granulomatosis. *Ophthalmology* 102:154, 1995.

Questions for Wegener's Granulomatosis: Pathogenesis and Management

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1. The classic diagnostic triad of Wegener's granulomatosis (WG) includes:
 - a. Granulomatous inflammation of the upper and lower respiratory tract
 - b. Necrotizing vasculitis

- c. Nephritis
- d. All of the above

2. Antineutrophil cytoplasmic autoantibodies (ANCA) was first described by:

- a. Davis et al
- b. Hall et al
- c. Godman and Churg
- d. Van der Woude et al

3. All are true for patients with ANCA-associated diseases Except:

- a. Have high incidence of a prodromal flu-like illness
- b. There is a seasonal variation in onset of disease
- c. An infectious illness is known to reactivate WG
- d. ANCA are secondary autoantibodies

4. Most common ocular manifestation of Wegener's granulomatosis is:

- a. Orbital inflammation with proptosis
- b. Conjunctivitis
- c. Scleritis and peripheral ulcerative keratitis
- d. Episcleritis

5. American college of Rheumatology criteria for diagnosis of WG includes the following:

- a. Abnormal urinary sediment (red-cell cast or 5 RBC/hpf)
- b. Abnormal findings on chest radiograph (nodules, cavities or fixed infiltrates)
- c. Oral ulcers or nasal discharge

d. Granulomatous inflammation (in the vessel wall, perivascular, or extravascular ocular and orbital tissues)

e. All of the above

6. Diagnosis of a very limited WG can be made based on:

a. Only ocular or orbital disease

b. Histopathologic findings and a positive ANCA

c. No renal or respiratory disease

d. All of the above

7. Following is true about ANCA-associated diseases

a. P-ANCA occurs most frequently with renal limited disease

b. C-ANCA occurs most frequently with lung and sinus involvement

c. Both a and b

d. None of the above

8. According to NIH protocol, which are the most effective treatment for WG

a. Cyclophosphamide (2mg/kg/day)

b. Oral prednisone (1mg/kg/day)

c. Cyclosporine A

d. Both a and b

9. Which drug is the least effective for treatment of WG

a. Cyclophosphamide

b. Prednisone

c. Trimethoprim-sulfamethoxazole

d. Azathioprine

e. Methotrexate

ANSWERS

1.d (Ref 2,3)

2.d (ref 10)

3.d (ref 21)

4.a (ref 41, 42)

5.e (ref 45)

6.d (ref 13)

7.c (ref 56)

8.d (ref 15)

9.c