Wegener's Granulomatosis: Pathogenesis and Management
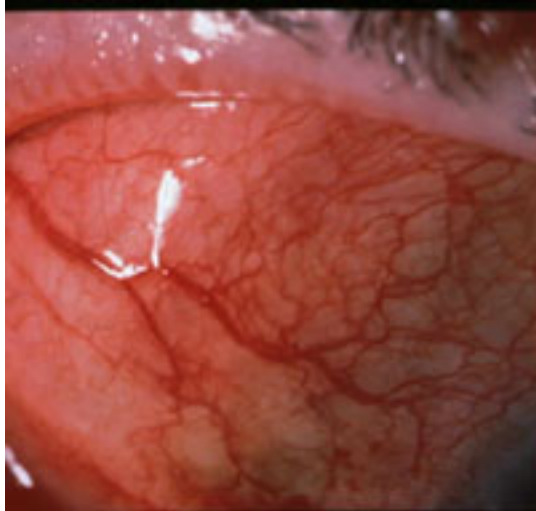
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Case Report

A 71 years white female was referred to us, on 8/17/95, with a history of episcleritis in her right eye for four months. She complained of some discomfort and pain on the right side of forehead. She gave a history of diabetes mellitus controlled on diet and some sort of arthritis involving hand and arm. Her family history was significant for a brother with retinal detachment and daughter with diabetes mellitus. Her past medical history was significant for carcinoma of the colon, kidney stones, Bell's palsy and polymyalgia rheumatica. She is allergic to sulfa drugs. She was taking Sulindac 150 mg orally and using Voltaren eye drops in her right eye twice daily. On examination her visual acuities (VA) were 20/30 in right eye (OD) and 20/20 in left eye (OS). External examination was significant for mild rosacea changes. She had two patches of true scleritis, OD, with tenderness to palpation. Rest of her anterior segment examination, including intraocular pressure (IOP) and dilated fundus examination was with in normal limits. We began the patient on Naprosyn, 500 mg PO BID, and launched a limited battery of noninvasive serologic studies.

Her laboratory work up was positive for cytoplasmic pattern of antineutrophil cytoplasmic antibodies (c-ANCA) at a titer of 17 units (> 5 units considered positive); angiotensin converting enzyme (ACE) level was 39 units (reference range 5-33). Her erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA) (Rat substrate and HEP2 cells), rheumatoid factor (RF), complete blood count (CBC), urine analysis (U/A), soluble interleukine-2 receptor (sIL-2r), serum lysozyme, HLA-B27 were all with in normal limits. Repeat ANCA was positive, ACE was 43, and chest and sinus X-ray were normal.
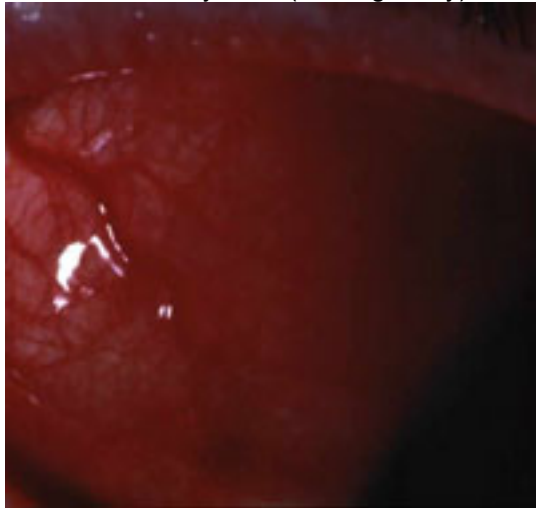
Based on her scleritis and positive ANCA, a diagnosis of limited Wegener's granulomatosis was made. The patient was offered treatment with Cytoxan and oral steroid, but she refused Cytoxan because of her past experience with treatment of colon carcinoma. She was begun on 20 mg prednisone orally per day. She could not tolerate this much steroid and complained of nervousness, leg cramps and difficulty in sleeping. Therefore the prednisone was reduced to 10 mg per day.

On subsequent follow up visit (on 10/26/95), methotrexate 7.5 mg per week was added to her program for non responsive nodular scleritis in the right eye. On 11/14/95, she felt better ocularly, but complained of shortness of breath and fatigue. Her scleritis was felt to be improved with the rest of the examination unchanged, therefore methotrexate (MTX) was boosted to 10 mg per week. One month later, she said things were better, but she could not tolerate methotrexate. The scleritis improved with reduction of ANCA levels to 10 units from 17 units on 8/95. At this point MTX was discontinued due to her intolerance, although we expected her scleritis to recur. On 1/20/96, in consultation with Dr. Foster, her rheumatologist added weekly intramascular injection of 7.5 mg MTX, to her program of 5 mg prednisone. She returned to our clinic, on 2/8/96, with 2+ scleritis in the OD. Her methotrexate was boosted to 10 mg per week and Vexol eye drops OD QID was added. Two months later, on 4/4/96, she felt that drops had helped her. Examination revealed 3+ scleritis in the right eye (Fig 1) with the rest of examination unchanged. At this point, subconjunctival (s/c) injection of steroids (Decadron) was given in the right eye. A week later (on 4/11/96), her scleritis improved but she was very negative about continuing methotrexate. Her methotrexate was discontinued.

Figure 1

She came one month later, on 5/14/96, with complaints of pain and swelling around the right eye. On evaluation, her acuities were 20/30 in the OD and 20/20 in the OS, 3+ to 4+ scleritis with 2+ edema of conjunctiva in the OD (Fig 2) and rest of her examination was with in normal limits. Her ANCA was 16 units (10 units on 12/95), CBC & sIL-2r were within normal limits. We convinced her to take oral Cytoxan (150 mg a day).

Fig 2

 Two months later, on 7/2/96, the patient presented with no pain in the eye and improvement in the scleritis but complained of chills, nose bleeds and dizziness. She blamed these symptoms to the Cytoxan. We told her the positive effect of Cytoxan on the scleritic process and boosted the dose of Cytoxan to 200 mg per day. She could not tolerate this dosage, so reduced it back to 150 mg. A week later, on 7/10/96, she complained of pain, tearing, and light sensitivity in the right eye. She felt very weak and depressed. She was taking 150 mg Cytoxan per day and vexol eye drops twice daily in the right eye. She had 2+ scleritis and her leukocyte count was 4100. Her Cytoxan was discontinued because of intolerance.

Three months later, on 10/18/96, she came with scleral perforation and choroidal show (Fig 3).
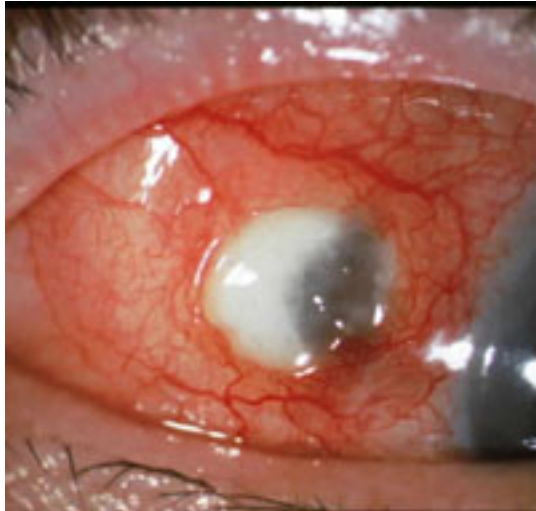
Fig 3

Her acuities were 20/30 in the right eye and 20/20 in the left eye and rest of the examination was essentially normal. Her ANCA level was 192 units (was 16 units on 5/96), urinanalysis was significant for cloudiness, with some blood, repeat chest & sinus x-rays, CBC, ANA, creatinine, C1q immune complex and BUN all were normal. She was given 1 gram Cytoxan intravenously (IV) and a scleral patch graft was planned after giving her two to three cycles of IV Cytoxan to control the ongoing inflammation. A month later, on 11/21/96, she complained of sore throat, chills earache and had lost weight (7-12 lbs). Her clinical examination was unchanged from the last visit. Her ANCA were 374 units (192 on 10/18/96) and 1 gram IV Cytoxan was given.

On 12/12/96, the patient complained of pain in the right eye and she believed that Cytoxan was not helping her. She also complained of blood in stools, chills every night, blisters in her mouth and 12 lbs weight loss. She believed she was sick because of the Cytoxan. At this point a renal consult was obtained from the Massachusetts general hospital. Laboratory evaluation showed ANCA 340 units (374 on 11/21/96), urine analysis revealed 1+ protein, 15-20 RBC per high power field (HPF), 5-10 WBC/HPF and 3+ calcium oxalate, differential leukocyte count showed 91% segmented neutrophils (Normal 50-70%) and urine & stool cultures were negative. The patient was diagnosed as having the systemic form of Wegener's granulomatosis and she was given pulse IV Solumedrol, 500 mg and IV Cytoxan 750 mg. This resulted in a marked improvement. Subsequently three more pulses were given and the patient was then switched to oral prednisone 60 mg and Cytoxan 100 mg per day.

The patient underwent scleral patch graft in the right eye on 1/6/97. Postoperatively, she has been doing very well. On her most current visit, on 4/22/97, she felt much stronger, no fever, no oral ulcers; she had gained weight. She was taking 100 mg Cytoxan PO, prednisone 12.5 mg PO daily and vexol eye drops four times a day in the right eye. On examination the scleral graft was intact, her acuities were 20/40 improving to 20/30 in the right eye and 20/25/in the left eye. She developed steroid-induced high blood pressure and diabetes, which are treated with atenolol and oral hypoglycemic agents respectively.

Summary:

To summarize, this is a very sensitive patient who was intolerant to multiple medications. She had a serious, life-threatening disease. It is critical to distinguish between side effects of medication and the symptoms of progression of disease. In this case, seeking an independent expert opinion helped considerably. (Fig 4)
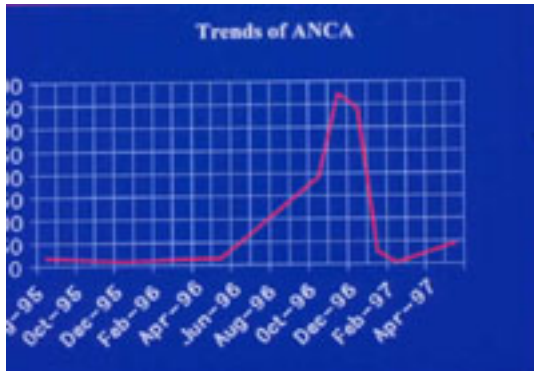
Fig 4

Wegener's granulomatosis: Pathogenesis and management

History and Introduction

Wegener's granulomatosis (WG) is a systemic disease of unknown etiology characterized by granulomatous inflammation of the upper and lower respiratory tract, necrotizing vasculitis, and nephritis. Klinger first described this disease as a special form of polyarteritis nodosa in 1931(1). WG was established as a distinct clinicopathologic entity later in that decade by Wegener, a German pathologist (2, 3) The classic criteria for the diagnosis of WG are based on the pathologic findings of Godman and Churg in their paper of 1954 (4). The disease was almost always fulminant and fatal until the introduction of cytotoxic therapy (5, 6). A preliminary report on a prospective study of patients with WG at the National Institutes of Health (NIH) in 197 (37). established the effectiveness of cyclophosphamide therapy in inducing remission in this disease, although the disease itself remains poorly understood.

Discovery of Antineutrophil Cytoplasmic Auotantibodies (ANCA):

In 1982, Davis et al (8) described eight patients with segmental necrotizing glomerulonephritis following an arbovirus infection, in whom routine assays for autoantibodies were negative. All patients had a serum factor that stained the cytoplasm of neutrophils by the indirect immunofluorescent (IIF) method. The fluorescent staining activity decreased or disappeared following successful treatment with prednisone and cyclophosphomide, but the antineutrophil factor reappeared after relapse of the disease. Hall et al(9) reported four more patients in 1984, and using IIF, they also described cytoplasmic staining of ethanol-fixed human neutrophils. The four had evidence of multisystem disease, and renal biopsies revealed segmental necrotizing lesions for three of the four patients. Two of the four responded favorably to steroids and cyclophosphamide or azathioprine. These papers (8,9) did not attract much attention until Van der Woude et al (10) in 1985, in a study of 41 patients with WG, reported for the first time "an autoantibody specific for this disease". They described antibodies that reacted with the cytoplasm of ethanal-fixed neutrohils and monocytes, initially called anticytoplasmic antibodies and later changed to antineutrophil cytoplsmic antibodies (ANCA). Using a large number of patients (222 with biopsy-proven WG and 1657 controls), Nolle et al (11) tested the specificity of ANCA for WG and the sensitivity of the assay for isolated organ involvement and disease activity with IIF technique. Of the WG patients, 168 (76%) were positive by IIF and 160 (72%) were positive by ELISA. Their findings suggested that testing for ANCA had great differential diagnostic potential and was highly specific for WG, generally distinguishing WG from other vasculitic and rheumatic diseases.

Definition and classification

WG, as the pathology was defined by Godman and Churg,(4) is a fulminant systemic disease involving multiple organ systems. Clinical observation since that time suggests that the disease exists in two forms: an indolent form called limited, initial, or locoregional WG, (5, 8-10) and a fulminant form called active, generalized, or disseminated WG. The latter form correlates with the classically defined disease of Godman and Churg. Godman and Churg's classic diagnostic triad of morbid pathologic findings (4) are listed in Table 1.
Table 1

CLASSIC DIAGNOSTIC TRIAD FOR WEGENER'S GRANULOMATOSIS

1. Necrotizing granuloma of the upper or lower respiratory tract	**Typically, mucosal inflammation and ulceration in the respiratory tract; mucosal inflammation characterized by foci of epithelioid cells, multinucleated giant cells, and fibrillar organization with secondary necrosis of fibrillar tissue; tissue eosinophilia common**
2. Vasculitis	Involves both arteries and veins and is of a focal, necrotizing variety; is granulomatous in nature, featuring multinucleated giant cells; typically seen in lung tissue and variably present elsewhere
3. Nephritis	Focal, necrotizing glomerulitis with fibrinoid necrosis and thrombosis of capillary loops, sometimes extending beyond Bowman's capsule; neutrophils usually present; granulomatous inflammation with giant cells only occasionally seen

There are no established diagnostic criteria for the limited form of WG, although typically the respiratory tract is involved, and the kidneys are spared. Necrotizing granulomatous inflammation and vasculitis are seen in the involved tissue. Limited disease usually takes the form of pulmonary infiltrates or cavitating lesions, chronic hemorrhagic rhinitis, sinusitis, otitis, ulcerations in the oral cavity, nasolacrimal duct obstruction, orbitopathy, conjunctivitis, keratitis, scleritis, or uveitis.8-13

Epidemiology

WG is a rare disease. A study of the population in Norfolk, United Kingdom revealed an incidence of 8.5 per million(14). The disease typically manifests in the fourth and fifth decades, although its occurrence at ages ranging from 7 to 75 has been reported (15,16). The disease can affect either sex, with some of the larger series revealing a preponderance of males in a ratio as high as 1.5:1.5 (15,17). WG occurs most commonly in white patients but has been reported in blacks and Hispanics (15).

A higher frequency of HLA-DR1 in patients with WG was reported (18). Recently a study from the Netherlands reported a significant decrease in the frequency of HLA-DR13/DR6 among patients

with WG in comparison to controls (19).

PATHOGENESIS

The cause of WG is unknown. It is considered to be a hypersensitivity disorder because granulomatous inflammation, tissue eosinophilia, vasculitis, and glomerulonephritis are all characteristic of hypersensitivity states. This concept of hypersensitivity as a pathogenic factor is supported by a study of prevalence of allergies in patients with systemic vasculitis, which revealed that 45 of 60 patients (73%) had a history of at least one type of allergy, which was significantly higher compared to controls (20).
Role of ANCA in pathogenesis of WG is not known. However following findings suggest a possible role:

- The tight correlation of ANCA titers with active systemic disease suggests that ANCA may be involved in pathogenesis (21)
- Patients may have either one or the other of the two types of ANCA but virtually never both types (21). If the antibodies were secondary to the disease, some patients would be expected to have both types.
- In addition, the rise in antibody titer frequently found preceding flares of disease suggests that the antibodies are not merely secondary(26).
- In vitro, TNF- and IL-8 are shown to act synergistically to induce a translocation of PR3 from the intragranular loci to the cell surface of neutrophils (28). When these primed neutrophils are exposed to ANCA, they undergo respiratory burst and degranulation, releasing toxic oxygen species and noxious lytic enzymes.
  It is interesting to hypothesize that, in patients with circulating ANCA, these antibodies interact with neutrophils that have been primed by an infection or other inflammatory process (29). *Clinical support for this theory drives from the follwing observations:*
- Patients with ANCA-associated disease have high incidence of a prodromal flu-like illness
- There is a seasonal variation in onset of disease (30)
- Infectious illness is known to reactivate WG (31)
  Postulated pathogenetic mechanisms can be summarized as follows (Fig 5)
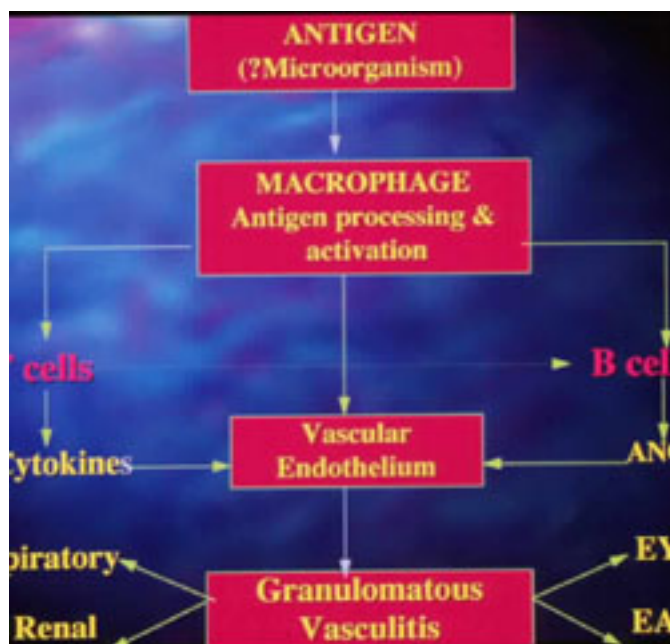

Fig 5

Mayet and colleagues were able to induce an increased PR3 expression in the cytoplasm, as well as a transient translocation into the membrane of human umbilical endothelial cells (HEC) after treatment of HEC with IL-1(25). The expression of PR3 on endothelial cell membrane provides a possible role of ANCA-endothelial interactions in the pathogenesis of ANCA-associated vasculitis. Furthermore, C-ANCA from the sera of patients with WG significantly inhibits the proteolytic activity of PR3, as well as the complexing of PR3 with its major physiologic inhibitor, alpha-1-antitrypsin (1-PI) (26-28). The C-ANCA, in interfering with the normal physiological control of activated PR3 by 1-PI, may be factor in the vasculitis of WG. After formation, PR3-1-PI complexes are apparently are not reversible, but PR3-ANCA complexes appear to be reversible. The inhibitory effects of C-ANCA on PR3-alpha-1-antitrypsin complexation correlates with clinical disease activity, while the ANCA titers may not correlate with disease activity (28). Other evidence for a role of ANCA in the pathogenesis of WG is its induction of granulocyte activation. Mice immunized with human ANCA develop anti-anti-ANCA (mouse ANCA). Mouse ANCA induces adhesion of neutrophils to fibronectin and activates the respiratory burst in neutrophils (29).

Elevated immunoglobulins, elevated circulating immune complexes, and deposited immune complexes are seen in some patients with WG, but these features are not characteristic of the disease (7,32,33). The predominance of T cells and monocytes in the pulmonary vasculitic and glomerulonephritic cellular infiltrates (34,35). suggests that the disease may be one of T-cell activation rather than immune complex deposition. The antigenic specificities of the T cells remain unknown. However peripheral blood mononuclear cells from patients with WG have the capacity to proliferate in response to the antigen-specific stimulation by PR3 (36,37). This response to PR3 indicates that autoreactive PR3-specific T cells are present in patients with WG. Other evidence of the role of cell-mediated immunity and particularly of activated macrophages in the pathogenesis of the disease is the finding of elevated serum neopterin concentrations in patients with WG (38).

Systemic Features:

Early reports on the clinical manifestations of WG were based on small series of patients in which the clinical findings were correlated with pathologic findings in the criterion organ systems of Godman and Churg (5,6). In fact, WG is a systemic disease to which every organ system is vulnerable. A review of the systemic manifestations of WG is provided in Table 2. It is useful to inspect the NIH prospective review of 85 patients followed over 21 years, (13) which is the only large series in the literature reporting presenting signs and symptoms and organ system involvement

Table 2

Pulmonary

- Interstitial infiltrates
- Hemoptysis
- Cavitating lesions
- Pleural effusion
- Subglottic stenosis
- Cough
- Shortness of breath

Upper Airway

- Sinusitis
- Epistaxis
- Rhinitis
- Saddle nose deformity

Otologic

- Otitis
- Tinnitus
- Eustachian tube dysfunction

Most patients initially presented to their physicians with upper airway illnesses. Pulmonary infiltrates and sinusitis, reported in 71 and 67 percent of patients, respectively, were the two most common presenting signs or symptoms. Arthralgia or arthritis, fever, otitis (usually related to eustachian tube obstruction), and cough were a presenting sign in at least 25 to 50 percent of patients. There was ocular inflammation in 16 percent of patients at presentation; 7 percent of patients had proptosis as a presenting sign. Functional renal impairment was a presenting sign in only 11 percent of patients. In the NIH and other series (5,6,11,15,32,33) malaise, fatigue, fever, and weight loss are characteristic of the onset of active or generalized disease.

Over the course of the disease in the NIH patients, lung disease or upper airway disease (that is sinusitis, hemorrhagic rhinitis, or otitis media) were each present in 94 percent of patients, and all patients had one or the other (15). The characteristic and typical lung findings are multiple, bilateral nodal infiltrates with a tendency toward cavitation and evanescent areas of atelectasis. Pleural effusions were present in approximately 20 percent of patients; it is notable that hilar adenopathy was not seen and that pulmonary calcifications were extremely rare. Subglottal stenosis of the airway can occur. The authors of the NIH study point out that although severe upper airway disease in WG can cause erosion through the walls of the sinuses, none of the NIH patients had erosion through the skin of the face or nose, and most importantly, no patient had perforation of the palate. They point out that either of these findings would strongly indicate another localized midline destructive disease such as midline granuloma or a midline neoplasm. Secondary infection was extremely common in patients with upper airway disease, Staphylococcus aureus being the predominant organism in every case (15).

In the NIH group, 85 percent of patients eventually had renal disease that ranged in severity from mild, focal, and segmental glomerulonephritis with minimal urinary sediment finding or functional impairment to fulminant, diffuse, necrotizing glomerulonephritis with proliferative and crescentic changes. Renal disease, once present, may progress rapidly and is associated with poorer prognosis despite cytotoxic therapy (32).

Arthralgias and nondeforming arthritis are common in WG, eventually occurring in 67 percent of patients. Skin involvement occurs in 45 percent of patients and can take the form of papules, vesicles, palpable purpura, ulcers, or subcutanous nodules Some of these findings can be triggered by seemingly trivial local trauma, as can the rheumatoid nodules found on extensor surfaces in rheumatoid arthritis. Nervous system disease in the form of mononeuritis multiplex or cranial nerve abnormalities is not uncommon. Acute pericarditis was the most common form of cardiac disease with carditis and dilated congestive cardiomyopathy also seen.

There seems to be a seasonal variation in the onset of symptoms, with a higher frequency of onset of symptoms in winter, lower in summer, and intermediate for the other seasons (14,39).

Ophthalmic Features:

The first review of the ocular manifestations of WG was by Straatsma in 1957 (40). He found documentation of ocular involvement in 19 of 42 (43 percent) cases in which the diagnosis of WG was confirmed at autopsy. In the NIH series, 58 percent of patients ultimately had eye or orbital involvement (15). The ocular manifestations of WG can be divided into two categories: contiguous and focal (40). Contiguous disease arises from contiguous granulomatous sinusitis of long duration and results in severe orbital pseudotumor, orbital abscess or cellulitis, or nasolacrimal duct obstruction. Focal disease in WG is defined as focal vasculitis, involving the anterior, posterior, or both segments of the eye and possibly the orbit, unrelated to any upper airway disease.

Similar patterns of ophthalmic disease were found in Straatsma's series (40) in an early NIH report on 29 patients (41) in the NIH review of the literature (41) and in a review of 140 patients from the Mayo Clinic with biospy-proven WG (42). In all of these series, the most common ophthalmic manifestation of WG was orbital inflammation with proptosis. Of the focal manifestations of WG, conjunctivitis and episcleritis are most common. Although the conjunctivitis and episcleritis of WG are often recurrent and bothersome to patients, these are benign processes.

Corneal or scleral involvement is not benign and takes the form of peripheral ulcerative keratitis or scleritis. The scleritis may be diffuse, nodular, or necrotizing. Peripheral ulcerative keratitis and necrotizing scleritis are the two most malignant ocular manifestations of WG; each can result in ocular perforation, leading to blindness and possibly to loss of the eye. Localized conjunctivitis or episcleritis usually occurs before the onset of peripheral ulcerative keratitis or scleritis. The corneal component begins with the development of intrastromal, peripheral, corneal inflammatory infiltrates. Pain may be mild or severe. The crescentic peripheral corneal ulcer progresses both centrally and circumferentially. Scleral involvement is invariably present in peripheral ulcerative keratitis associated with WG, which may be helpful in differentiating it from Mooren's ulcer. Ischemic optic neuropathy and retinal artery occlusion are other types of focal eye involvement that can occur in WG. Chorioretinal ischemia and infarction (43) and keratoconjunctivitis sicca (44) are also part of the ophthalmic spectrum of this disease.

Given that ocular signs and symptoms are often part of the presentation of WG, the patient may first seek medical attention from an ophthalmologist. It is notable that it is not unusual for the active, generalized phase of WG to be heralded by an episode of "red eyes".

DIAGNOSIS:

Clinicopathologic Criteria

The diagnosis of WG is generally based on the clinicopathologic findings of upper and lower respiratory tract inflammation, renal disease, and variable degrees of disseminated vasculitis involving other organ systems. In 1983 the NIH group recommended that to establish a definitive diagnosis of WG, a patient should have clinical evidence of disease in at least two of three areas-upper airways, lung, and kidney-and that biopsy results should show disease in at least one and preferably two of the organ systems (15). More recently, the American College of Rheumatology established criteria for the classification of WG by studying the sensitivity and specificity of various findings that distinguish patients with WG from patients with other systemic vasculitides (45). They report that the presence of two or more of the following four criteria was associated with a sensitivity of 88.2 percent and a specificity of 92 percent for WG:

1. Abnormal urinary sediment (red-cell casts or 5 red blood cells per high power field)
2. Abnormal findings on chest radiograph (nodules, cavities, or fixed infiltrates)
3. Oral ulcers or nasal discharge

4. Granulomatous inflammation (in the vessel wall, perivascular, or extravascular)
Ocular and Orbital Tissues

Ocular and orbital tissues rarely show classic necrotizing, granulomatous vasculitis (46). Nevertheless, ocular and orbital tissues can provide pathologic support fo rthe diagnosis without incurring the potential morbidity of open thoracotomy. In cases of ocular inflammation, biopsy of involved sclera is most likely to be diagnostic of underlying WG. Involved conjunctiva typically is not diagnostic, because the conjunctival substantia propria usually contains only the nonspecific findings of lymphocytes and plasma cells. Neutrophils and eosinophils are sometimes seen. If intrascleral vessels have been obtained in a scleral specimen, true necrotizing vasculitis with inflammatory cell infiltration into the vascular wall and fibrinoid necrosis may be seen (47). Granulomatous inflammation of the iris and ciliary body have been observed in association with necrotizing scleritis in WG. Occlusive necrotizing vasculitis of the anterior ciliary arteries within the rectus muscles and sclera has been observed and postulated as the mechanism for marginal corneal ulceration (47,48). Biopsy of orbital tissue in cases of proptosis from retrobulbar mass lesions in patients with WG can show acute and chronic inflammation with or without granulomatous vasculitis (15,49).

At the Massachusetts Eye and Ear Infirmary, we have been able to make a diagnosis of very limited WG in patients with only ocular or orbital disease on the basis of a constellation of histopathologic findings and a positive ANCA test (13). Early diagnosis of WG on this basis, with no respiratory or renal involvement, allows prompt institution of immunosuppressive therapy that may further reduce morbidity and mortality in this destructive disease.

In a study from the Massachusetts Eye and Ear Infirmary, conjunctival and scleral tissues from patients with WG and a history of scleritis were examined for eosinophil activation. By using immunohistochemical analysis, markers for eosinophil granule proteins (eosinophil major basic protein and eosinophil cationic protein) were tested (50). Markers for these eosinophil granule proteins were not detected in patients with inactive scleritis. Markers were detected in a patient with active scleritis whose disease progressed a month later to the complete form of WG; and were not present in a patient with active scleritis whose disease did not progress. From this study, one may hypothesize those activated eosinophils in conjunctiva or sclera may be a harbinger of disease progression.

Laboratory:

ANCA staining of neutrophils occurs in two patterns. There is the classic granular cytoplasmic staining pattern, sometimes called C-ANCA, which is specific for myeloblastin, a serine protease (54,55). C-ANCA is highly specific for WG (Fig 6 C-ANCA) (51,52) but not all patients positive for C-ANCA can be identified as having WG by the classic criteria (56).
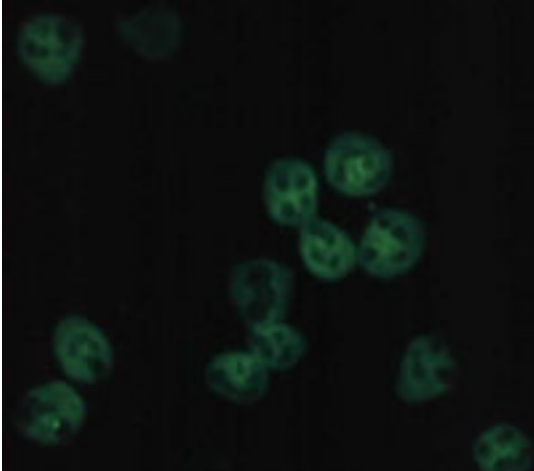
Fig 6

There is also a perinuclear staining pattern, sometimes called P-ANCA (Fig 7), which is specific for myeloperoxidase and is associated with idiopathic necrotizing and crescentic glomerulonephritis (54).
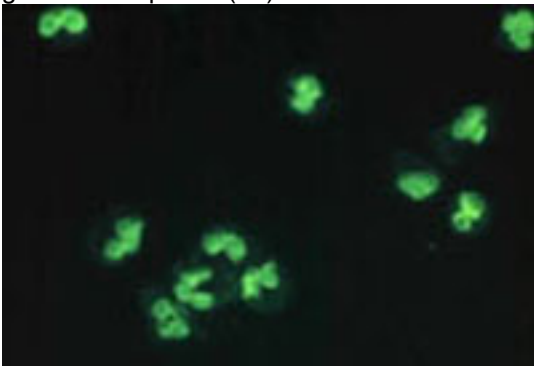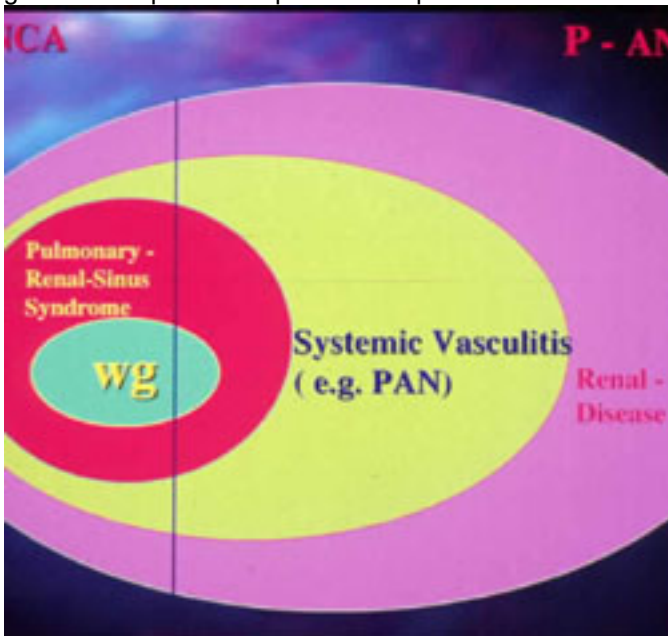

Fig 7

Although the classification of these vasculitides remains a subject of debate, most clinicians and researchers agree that WG, microscopic polyarteritis, and idiopathic necrotizing and crescentic glomerulonephritis are part of the spectrum of one disease process (Fig 8).

Fig 8

In a series of patients with ANCA-associated glomeruloneophritis, with and without systemic vasculitis, it was observed that P-ANCA occurs most frequently with renal-limited disease and C-ANCA with lung and sinus involvement (56). In patients with clinically suspected WG, antibodies to the C-ANCA antigen were associated with upper respiratory tract involvement, whereas antibodies to the P-ANCA antigen were associated with alveolar hemorrhage (57). Although C-ANCA is typically the ANCA associated with WG, there are cases in the literature that meet the classic criteria for WG and are characterized by the P-ANCA pattern of staining (58).

It is important to include an ANCA test in the diagnostic evaluation of patients with ocular or orbital inflammation suggestive of systemic vasculitis. Pulido and associates (59) found positive ANCA in six patients who had eye findings in the setting of systemic vasculitis; in two of these patients, it was the ocular findings that prompted systemic work-up for vasculitis. Four patients had systemic WG, one had microscopic polyarteritis, and one had systemic vasculitis with no specific histologic diagnosis. Ocular findings included ptosis, bilateral lacrimal gland masses, proptosis, choroidal folds, episcleritis, iritis, periphlebitis, retinal hemorrhage, keratoconjunctivitis sicca, and bilateral central scotomas from occipital lobe infarction.

At the Massachusetts Eye and Ear Infirmary, we have found elevated ANCA titers to be highly specific and sensitive for WG in patients with scleritis (60). Of 24 patients with scleritis in which ANCA titers were obtained, all 7 with positive titers had clinical and pathologic evidence of limited or generalized WG. In none of the 16 patients with scleritis and negative ANCA titers was a diagnosis of WG made. The etiology of the scleritis in half of these patients remains unknown, so the exact specificity and sensitivity of the ANCA test in scleritis remains undetermined. Either type of ANCA can be found in patients with limited or generalized WG with ophthalmic involvement (59,60).

The correlation and prognostic value of ANCA titers with disease activity is still under debate. It has been suggested that ANCA titers decrease with decreasing clinical disease activity; (61) and a rise in ANCA titer may represent subclinical disease(62). However a study of serial C-ANCA levels in a large group of patients with WG indicated that C-ANCA titer changes were not a sensitive marker of disease activity (63). Although a positive C-ANCA was a sensitive (88%) indicator of active WG, changes in serial titers temporally correlated with a change in disease status in only 64% of patients. Furthermore, an increase in the C-ANCA titer preceded clinical exacerbation of disease in only 24% of patients who had been in remission. These findings are supported by a similar study that showed ANCA titers were not correlated with the severity of vasculitis in a group of 44 patients with WG (64).

In a study of 8 patients with ocular manifestations of WG, either scleritis alone, or scleritis combined with peripheral ulcerative keratitis, serial ANCA levels were followed (65). ANCA level failed to revert to normal during remission in 4 of 5 patients who had relapses. The ANCA level for all 3 patients who remained in remission converted to normal. Therefore failure of ANCA titers to revert to normal may be associated with relapse.

Serum thrombomodulin (sTM), a marker of endothelial cell injury, is released into the circulating blood following endothelial cell damage. STM has been shown to be elevated in patients with active WG, and not elevated in patients in remission (66). A study of 197 sera of 102 patients with WG of different disease activity revealed that sTM was significantly elevated in patients with limited active WG; was further elevated in patients with generalized WG (67). Sera of patients with limited and generalized WG in complete remission did not have elevated levels of sTM. STM is therefore a promising serological marker of disease activity.

Recently a study of 32 patients with WG reported elevated antiendothelial cell antibodies (AECAs) in all patients with active disease (68). AECA titers correlated with disease activity, showing a decrease in patients entering remission and an increase in patients having a relapse. Normal AECA levels were seen only in patients with inactive disease.

There have been reports of elevated soluble interleukin-2 receptor (sIL-2R) levels in patients with active disease and in patients experiencing relapses.69-71 The sIL-2R levels correlated with severity of clinical disease. One of these studies indicated that sIL-2R was significantly higher in patients in remission who later developed relapses (69).

Serum levels of soluble adhesion molecules, including intercellular adhesion molecule 1, vascular cell adhesion molecule 1, and E-selectin were followed serially in a study of patients with WG. Significantly elevated levels of intercellular adhesion molecule 1 and vascular cell adhesion molecule 1 were found in active WG, and the levels correlated with disease activity (72). However the sensitivity and specificity of elevated serum levels of these adhesion molecules are not clear.

TREATMENT:

Agents
The use of cytotoxic agents in WG was first reported in 1954 in the case of a patient whose disease went into remission with nitrogen mustard (6). A prospective review in 1973 of cyclophosphamide therapy in 18 patients with WG at the NIH demonstrated this agent's extraordinary efficacy in WG (7) In 1983 this NIH group reported their 21 yr of experience with 85 patients who underwent combined cyclophosphamide and corticosteroid therapy. Remission was induced in 79 of 85 patients (93 percent). Mean follow-up was 51 months. The NIH report and other studies found azathioprine to be less effective (74,75) and have established cyclophosphamide as the drug of choice for WG. Azathioprine (76), chlorambucil, (73,77) and methotrexate (78) have been effective in some cases.
In the NIH protocol, (15) 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 the cyclophosphamide are apparent. At this point, the prednisone is switched to alternate day therapy and is tapered. Cyclophosphamide is administered for 1 full yr after remission has been achieved and then is tapered. In fulminant cases, oral cyclophosphamide in doses of as much as 3 to 5 mg/kg/day may be required. Alternatively, intravenous pulse therapy of cyclophosphamide may be considered. In pulse therapy, cyclophosphamide 15mg/kg is given in a single intravenous pulse dose every 4 to 6 weeks, with timing of subsequent doses based on recovery from the myelosuppressive effects of therapy. Some patients who cannot tolerate daily oral cyclophosphamide therapy may respond to and tolerate intravenous pulse therapy, which significantly reduces the total monthly dose.
Cyclophosphamide is a bone marrow suppressant; throughout therapy, the leukocyte count is monitored every 2 days to 2 wk, and the dose is adjusted as disease activity and leukocyte count allow. Patients should be monitored for hematuria, because hemorrhagic cystitis is a potentially devastating but usually preventable complication of cyclophosphamide therapy. Other potential complications of cyclophosphamide therapy include immunosuppression and opportunistic infections, gonadal dysfunction, and neoplasm. Patients who are treated with this cyclophosphamide-prednisone regimen are also susceptible to all the risks associated with prolonged steroid therapy. Responsibility for the detailed management of the chemotherapeutic aspects of patient care in WG must rest with an individual who is, by virtue of training and experience, an expert in the field of chemotherapy.
Azathioprine is sometimes used to maintain remission in patients who have developed toxicity to cyclophosphamide. Methotrexate is used as an alternative to cyclophosphamide in patients whose illness is not immediately life-threatening or in whom cyclophosphamide treatment is not tolerated. Methotrexate treatment has been shown to achieve remission in 69-71%of patients (79,80). Cyclosporin A is sometimes used in patients who could not tolerate cyclophosphamide therapy. In initial doses of up to 5 mg/kg/day, cyclosporin A showed efficacy, but when lowered to 1-2 mg/kg/day mild disease flares occurred (81). Trimethoprim-sulfamethoxazole has been advocated for indolent or localized WG, as maintenance therapy, and as a sparing agent for cyclophosphamide and corticosteroids in the treatment of active disease (82-85). Whether trimethoprim - sulfamethoxazole is effective as an immunosuppressant, on the basis of folic acid antagonism, or as an antibiotic remains unclear. The efficacy of trimethoprim-sulfamethoxazole in preventing relapses in patients with WG in remission was tested in a prospective study. Eighty

two percent of 41 patients remained in remission at 24 months, as compared with 60% of patients in the placebo group (86). However in a recent study comparing the efficacy of low-dose intravenous (IV) methotrexate and trimethoprim-sulfamethoxazole in maintaining remission, low dose methotrexate was found to be superior to trimethoprim-sulfamethoxazole (87). In the group of patients who received methotrexate and low dose prednisone, 91% remained in remission. In contrast, all patients received trimethoprim-sulfamethoxazole and prednisone experienced a relapse after a median of 14.5 months. In the group that received trimethoprim-sulfamethoxazole without prednisone, 58% remained in remission, compared to 86% of the patients who received methotrexate alone

The use of intravenous immunoglobulin has been reported to result in significant clinical improvement, with a decrease of ANCA levels (89-92). The observed clinical effects of intravenous immunoglobulin may be explained by the idiotypic regulation of ANCA, since intravenous immunoglobulin is known to contain antiidiotypic antibodies to ANCA. Blinded, randomized, placebo controlled trials are necessary to assess intravenous immunoglobulin as a therapeutic option in the treatment of WG.

Guidelines for Management and Referral of Wegener's Granulomatosis with Ophthalmic Involvement:

Therapy for WG with ophthalmic involvement depends on the type and extent of the ophthalmic involvement.

- Patients with orbital cellulitis or pseudotumor related to contiguous sinus disease require antibiotics and appropriate drainage procedures and should be treated in conjunction with an otolaryngologist.
- These cases and WG complicated by orbital pseudotumor with no contiguous sinus disease should be monitored for optic neuropathy. Patients with proptosis may require orbital decompression to preserve optic nerve function or for the treatment of secondary diplopia. The NIH group found that proptosis in some patients persists even after systemic remission has been induced (15).
- The ophthalmologist should be aware that conjunctivitis or red eyes in a patient with a diagnosis of limited or inactive WG, can signify activation of generalized disease. Such patients should be referred to an internist or rheumatologist for systemic evaluation and monitoring.
- Scleritis, particularly if necrotizing, peripheral ulcerative keratitis, anterior or posterior uveitis, and retinal or optic nerve vasculitis are sight-threatening processes that often correlate with generalized disease activity; the use of systemic cyclophosphamide and prednisone in such cases, even in the absence of generalized disease activity, is warranted.
- Necrotizing scleritis may occur after recent local ocular trauma or surgery in the absence of activation of systemic disease. Systemic cyclophosphamide and prednisone therapy are warranted in these cases, because this process is sight-threatening.
- Tectonic scleral grafting is indicated in cases of impending perforation of the globe.
- Therapy with trimethoprim-sulfamethoxazole in our experience is not helpful in patients with necrotizing eye disease or posterior pole vasculitis.
- Elective surgery such as cataract extraction is contraindicated in patients with active disease, because catastrophic wound-healing problems are likely to ensue.
- Patients in remission, off cyclophosphamide, may undergo elective surgery, but these patients probably require perioperative cyclophosphamide and prednisone to prevent activation of necrotizing disease.

PROGNOSIS

Before the introduction of cyclophosphamide, WG was rapidly fatal, particularly once there was functional renal impairment. The mean survival of patients with untreated WG was 5 mo, with a 1-yr mortality rate of 82 percent and a 2-yr mortality rate of 90 percent (5). Corticosteroids improved the average survival time to 1 yr but did not decrease mortality (73). In the NIH group, (15) the standard cyclophosphamide and prednisone therapy described previously induced remission in 93 percent of patients. In 21 yr of follow-up on 85 patients in the NIH series, 6 died with active disease and 4 died in remission from other causes. Of note, 25 of the 79 patients who achieved remission suffered a relapse, usually as cyclophosphamide was tapered. In all but one of these patients, remission was promptly reinduced with cyclophosphamide and prednisone therapy. The mean duration of remission for living patients was 48.2 mo. Twenty-three patients were stable off all therapy for a mean duration of 35.3 mo. Patients were warned of the premonitory signs of relapse such as elevation of the sedimentation rate, arthralgia, malaise, and skin lesions, and relapses were noted and treated early, thus avoiding significant organ damage. Although the NIH group had an overall mortality of only 12 percent, 1-yr mortality from WG has been reported in the 30 to 50 percent range, despite the use of cyclophosphamide (32,33) in other smaller series, particularly if the disease is defined by the presence of renal involvement.

The visual prognosis in WG is generally good except in cases of catastrophic vision loss from retinal or optic nerve vasculitis, or in the event of perforation from necrotizing scleritis or peripheral ulcerative keratitis.

CONCLUSIONS:

WG, although no longer routinely fatal, is nevertheless a disease with significant morbidity. The ophthalmologist may play a role in the diagnosis of WG, since ocular involvement often signals systemic disease activity. Early diagnosis and treatment with cyclophosphamide appears to be the key to avoiding irreversible end-organ damage such as renal failure, ocular perforation, cardiomyopathy, and subglottal stenosis of the airway. The management of cytotoxic therapy in patients with WG is neither formulaic nor straightforward and calls upon both medical art and science. Some of the complications of therapy, such as opportunistic respiratory tract infection and hematuria, can be manifestations of the disease itself. Deciding if hematuria, for example, represents nephritis or cyclophosphamide toxicity presents a significant challenge to the physician, with serious consequences for the patient.

The discovery of ANCA as a specific and sensitive index of generalized disease in WG is likely to improve the prognosis for patients with this disease by facilitating earlier diagnosis and detection of relapse. Although the etiology of WG remains unknown, the recent discovery of these disease-specific antibodies may help to elucidate the pathogenetic mechanisms involved in this destructive disease.

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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 drugs is the least effective for treatment of WG

a. Cyclophasphomide

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