Wegener’s Granulomatosis: Clinical Manifestations, Differential Diagnosis, and Management of Ocular and Systemic Disease

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Abstract. Wegener’s granulomatosis (WG) is a systemic inflammatory disease whose histopathologic features often include necrosis, granuloma formation, and vasculitis of small-to-medium-sized vessels. WG involves many interrelated pathogenic pathways that are genetic, cell-mediated, neutrophil-mediated, humoral, and environmental. WG most commonly involves the upper respiratory tract, lungs, and kidneys, but has been reported to affect almost any organ. Ophthalmologic involvement is an important cause of morbidity in WG patients, occurring in approximately one-half of patients. The presence of unexplained orbital inflammatory disease, scleritis, peripheral ulcerative keratitis, cicatricial conjunctivitis, nasolacrimal duct stenosis, retinal vascular occlusion, or infrequently uveitis should raise the question of possible WG. A thorough clinical examination, laboratory testing, radiologic imaging, and histologic examination are essential to diagnosing WG and excluding potential mimics. Previously a uniformly fatal disease, treatment with cytotoxic and immunosuppressive agents has greatly improved survival. Treatment-related morbidity is a serious limitation of conventional therapies, leading to numerous ongoing studies of alternative agents. (Surv Ophthalmol 55:429–444, 2010. © 2010 Elsevier Inc. All rights reserved.)

Key words. Wegener’s granulomatosis • vasculitis • ANCA • necrotizing granuloma • sinonasal disease • ocular manifestations of systemic disease

I. Introduction

Wegener’s granulomatosis (WG) is a systemic inflammatory disease whose histopathologic features often include necrosis, granuloma formation, and vasculitis of small-to-medium-sized vessels. Antibodies to neutrophil cytoplasmic antigens (ANCA) are present in about 80–90% of patients and appear to play a role in pathogenesis, but are not likely to be essential to cause disease. WG can affect any organ system, but classically affects the upper and lower respiratory tracts and, in most cases, the kidney. Once a rapidly fatal disease, WG can now be controlled with glucocorticoid and other immunosuppressive therapies.27

Ophthalmologic involvement is an important cause of morbidity, occurring in approximately 50% of WG patients. Although orbital disease is the most common ocular manifestation, WG may involve almost any eye structure.

II. Epidemiology

The annual incidence of WG in the United States is 3 per 100,000. There are about 2,300 newly
diagnosed cases in the United States per year. The average age at the time of diagnosis is about 40–55 years, with no significant sex bias. WG is most common in white patients. African Americans are relatively under-represented, constituting about 2–8% of most studies, although making up 11–14% of the U.S. populations studied.27

III. Etiology and Pathogenesis

Bacteria and other infectious organisms have been implicated as triggers of autoimmune diseases, but none have been proven to play a definite etiologic role in WG. In support of a role for infection, Stegeman et al demonstrated that chronic nasal infestation by S. aureus in patients with WG was associated with a higher rate of relapse than patients without.74 This same group also reported a decrease in the rate of ear, nose, or throat (ENT) (but not renal or pulmonary) relapses in patients receiving chronic antibacterial therapy with trimethoprim-sulfamethoxazole.75 It is not clear whether the ENT “relapses” were truly WG or just a reduction in secondary sinus infections, common in this population.

Laboratory tests that may reflect active WG are non-specific and include anemia, thrombocytosis, leukocytosis, and elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). ANCA are present in several forms of vasculitis. Some authors feel they are pivotal factors in WG, although this remains controversial. About 80–90% of patients with WG are ANCA-positive and, among them, the antibody targets cytoplasmic proteinase 3 (PR3) in 80%, and in up to 20%, the antibody targets cytoplasmic myeloperoxidase (MPO). Only about 65% of patients with milder forms of disease are ANCA-positive.

ANCA is also positive in about 80% of patients with microscopic polyangiitis (MPA), another primary small- and medium-sized vessel disease that often causes glomerulonephritis and pulmonary capillaritis. MPA, unlike WG, does not cause serious ENT complications. In most cases of MPA, the antibody targets MPO, but in up to 20% it may target PR3. ANCA titer are not a reliable guide to disease activity, nor do increases in ANCA titers accurately predict relapse and therefore should not guide therapeutic decision-making.14

Some patients with a well-established diagnosis of WG or microscopic polyangiitis lack detectable ANCA. In the Churg-Strauss syndrome, only about 40% of patients are ANCA-positive. How ANCA could play an essential role in pathogenesis when it may be absent in those diseases that some refer to as ANCA-associated vasculitis or “ANCA-disease” has been difficult to determine. The ANCA story may be taking a new turn with the recent report by Kain and colleagues that antibodies to human lysosomal membrane associated protein 2 (hLAMP 2) are present in 100% of patients with active disease with renal involvement and in 93% of a cohort of 84 patients with either WG, MPA, or “renal limited vasculitis.”34 Injection of these antibodies into rats produced focal necrotizing glomerulonephritis, which was not seen with injection of control human immunoglobulin. Specific epitopes targeted by hLAMP 2 were also shown to target adhesion elements (fimbriae) on gram negative bacteria (E. coli, Klebsiella pneumoniae, and Proteus mirabilis). These exciting observations need to be confirmed, but may link infection and vasculitis through molecular mimicry.

It is unlikely that the pathogenesis of WG will be fully explained by ANCA. There is abundant evidence that aberrant proliferation of Th1 and Th2 lymphocytes and macrophages play a part in promoting disease.42 It is clear that WG is a complex disease that involves many inter-related pathogenic pathways that are genetic, cell-mediated, neutrophil-mediated, humoral, and environmental.

IV. Clinical Manifestations

WG most commonly involves the upper respiratory tract, lungs, and kidneys, but has been reported to affect almost any organ27 (Fig. 1, Table 1).

A. UPPER AIRWAY AND EAR DISEASE

Patients with WG usually have disease affecting the upper respiratory tract. Severe sinonasal disease may cause mucosal thickening, friability, and ulceration, resulting in frequent bleeding. Chronic damage may cause loss of normal mucosal physiologic and immunologic (mucosal immunity) functions. Loss of nasal mucosa and moistening/lubricating functions may cause dryness, crusting and epistaxis, even in the absence of active disease. Recurrent infections of the nose, sinuses, as well as nasolacrimal ducts are common and may be at least in part due to loss of barrier function, duct stenosis/occlusion, and local immune deficiency. Chronic and recurrent inflammation or infections may lead to scarification and neo-ossification of sinus structures (Fig. 2). Occlusion of sinus ostia may require sinus surgery to remove impacted purulent or proliferative inflammatory tissue and facilitate drainage. Following periods of active disease, the mucosa may become friable and is subject to infection or bleeding. Tissue destruction may result
in septal perforation or saddle-nose deformity, which may cause significant functional and cosmetic distress. Chronic otitis media may lead to a perforated and/or scarred, thickened tympanic membrane or fusion of ossicles causing hearing loss. Less often, vasculitis may cause sensorineural deafness. Some form of hearing loss occurs in about 30–40% of patients.

Oral ulcers and gingivitis occur in 10% of patients. Hyperplastic granular gingivitis, described as “strawberry gingivitis” is a rare but characteristic manifestation of WG.

Subglottic stenosis (SGS) affects about a quarter of patients and can cause life-threatening respiratory failure. It may be asymptomatic until 50% tracheal stenosis has occurred and should be considered in the setting of dyspnea in the absence of active pulmonary disease. SGS in one series was associated with tarsal-conjunctival involvement, a relationship that may be significant, but requires confirmation (Table 2).

**B. SYSTEMIC INVOLVEMENT**

During active disease, patients may have non-specific symptoms such as fever, malaise, arthralgias, anorexia, and weight loss. The presence of fever mandates a search for an underlying infection. If fever is not due to WG itself and infection is playing a role, it is most often of the upper respiratory tract. Pulmonary infiltrates or nodules are initially present in about one-half of patients. Clinically, these may present as cough, hemoptysis, dyspnea, or pleuritic or other forms of chest pain. One-third of patients with pulmonary lesions have asymptomatic radiographic abnormalities, usually solitary or multiple pulmonary nodules with or without cavitation and/or less often alveolar opacities. Atelectasis, or segmental or lobar collapse may complicate obstructive endobronchial lesions. Alveolar hemorrhage frequently presents as acute respiratory failure and is the most common reason for ICU admission in WG. Lung disease eventually develops in about 85% of patients. Patients with WG are also at significantly increased risk for venous thrombosis and pulmonary embolism, although the underlying mechanisms are unclear.

Renal involvement occurs in about 80% of WG patients. Only about 20% of patients have features of active glomerulonephritis at presentation; however, if left untreated, renal disease accounts for most of the mortality historically associated with WG. Glomerulonephritis is typically asymptomatic until advanced renal failure develops. It is imperative that the
clinician perform routine screening of the urine and, if blood is present, microscopic evaluations of fresh urine sediment for cellular (RBC or WBC or mixed) casts, signs of glomerulonephritis. WG may also produce mass lesions in any site, including the kidney, where a biopsy is required to make the distinction between renal cell carcinoma and less common renal malignancies.81

A variety of skin lesions may occur in about one-half of patients: palpable purpura, hemorrhagic vesicles, papules, urticaria, subcutaneous nodules, vasculitic ischemic ulcers, livedo, infarction, and digital gangrene.7

Approximately two-thirds of patients complain of musculoskeletal symptoms, for example, arthralgias and myalgias. The most common musculoskeletal feature is migratory polyarthralgias and myalgias. At times, additive symmetrical polyarticular involvement can mimic rheumatoid arthritis (RA). Asymmetric additive patterns and monoarticular pain are uncommon. This arthritis is typically not destructive and does not cause deformities, in contrast to RA. Rheumatoid factor is frequently positive (approximately 60%) and may lead to a false diagnosis of RA if musculoskeletal complaints dominate the clinical presentation. This may be particularly misleading in the presence of active scleritis.

About one-fifth of patients develop nervous system involvement. Central nervous system involvement can manifest as cerebral vasculitis, single or multiple cranial neuropathies, pachymeningitis or mass lesions. Diabetes insipidus may result from damage to the anterior pituitary. Multifocal ischemic nerve lesions may produce mononeuritis multiplex in about 15% of patients. Other organs that are rarely involved include the pericardium, myocardium, breast, parotid gland, pulmonary artery, urethra, prostate, penis, uterus, cervix, and vagina (Table 1).

C. EYE INVOLVEMENT

1. Overview

Ophthalmologic manifestations occur in up to 58% of patients with WG. The largest long-term cohort of WG patients in the literature found 52% of patients developing ophthalmologic disease, with 8% of patients suffering disease-related vision loss.27 WG may affect any part of the eye and may occur alone or, most often, as a component of a multisytem presentation. De novo growth of inflamed tissue or contiguous spread of abnormal tissue from the sinuses may be responsible for orbital disease. Bullen and colleagues noted ocular disease in 29% of cases (40/140). The most common manifestation was orbital disease (18/140, 15%) followed by scleritis (7%)/episcleritis (3.5%), corneal (8%) and nasolacrimal (7%) abnormalities.6 It is critical to recognize that any signs of ocular inflammation in a patient with WG may be a clue to active disease in other organs. This finding should initiate a search to determine the extent of disease.

Patients with WG can present with various ophthalmologic manifestations.61 Hoffman et al reported scleritis as the most common presenting ophthalmologic manifestation, occurring in about 10% of patients.27 Orbital disease and dacroycystitis typically develop after years of continued disease

<table>
<thead>
<tr>
<th>System Involvement</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Upper respiratory and ear</td>
<td>Epistaxis, sinonasal dryness, crusts, obstruction, sinonasal destruction, saddle nose deformity, subglottic stenosis, hearing loss, tinnitus, vertigo</td>
</tr>
<tr>
<td>Lower respiratory</td>
<td>Parenchymal nodules, endobronchial lesions, pulmonary infiltrates and hemorrhage, pulmonary embolism</td>
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<tr>
<td>Renal</td>
<td>Crescentic glomerulonephritis, renal mass lesions</td>
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<tr>
<td>Musculoskeletal</td>
<td>Myalgias, arthralgias, arthritis</td>
</tr>
<tr>
<td>Eyes</td>
<td>Orbital pseudotumor, orbital retraction, conjunctivitis, episcleritis, scleritis, uveitis, retinitis, dacrooadenitis, dacryocystitis, nasolacrimal obstruction</td>
</tr>
<tr>
<td>Skin</td>
<td>Purpura, ulcerations, nodules, nail bed and digital infarction</td>
</tr>
<tr>
<td>Neurological</td>
<td>Cranial nerve abnormalities, CNS mass lesion affects, sensory neuropathy, mononeuritis multiplex, pachymeningitis</td>
</tr>
<tr>
<td>Heart</td>
<td>Conduction abnormalities, pericarditis, myocarditis, cor pulmonale</td>
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TABLE 1

Clinical Manifestations of Wegener’s Granulomatosis

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<tr>
<th>System Involvement</th>
<th>Examples</th>
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activity (Fig. 3). The ophthalmologist may make the initial diagnosis of WG in patients who present with ocular complaints or patients who have undiagnosed systemic involvement in addition to their ocular disease.24

2. Orbit

Proptosis due to orbital involvement occurs in approximately 15–20% of WG patients. Space-occupying orbital lesions can cause extraocular muscle dysfunction leading to diplopia and, in severe cases, may result in optic nerve ischemia and blindness. Proptosis is a helpful clinical sign in the patient with suspected WG, as this finding, in conjunction with upper or lower airway disease or glomerulonephritis, is highly suggestive of the diagnosis.27

The natural history of orbital disease in WG is variable. Orbital disease may begin in the maxillary or ethmoid sinuses and spread to involve the extraocular muscles, nerves, or blood vessels contained in the muscular cone. Alternatively, it can arise de novo intraconally and spread throughout the retrobulbar space. The majority of patients have contiguous disease affecting the nose and sinuses.64 Pronounced proptosis is often complicated by exposure keratopathy and corneal ulceration that may lead to permanent vision loss. Extensive orbital disease may cause destruction of local bony structures or neo-ossification. Bilateral orbital involvement is uncommon.64 Optic nerve compression, infiltration, and blindness are consequences of severe orbital disease.50 Almost one half of patients with infiltrative orbital disease lost vision as a result of optic nerve ischemia in the NIH series reported by Hoffman.
et al. Orbital disease often progresses despite systemic therapy.

Radiographic evaluation of orbital disease in patients with suspected WG is performed using conventional CT and MRI. An advantage of CT is its ability to better evaluate the presence of sinus opacification and osseous invasion, a fairly common finding in patients with WG. MRI is more useful in characterizing the suspected lesion.

Orbital lesions on contrast enhanced CT scans appear as slightly hyperdense relative to nasal mucosa. WG lesions appear hypointense compared to orbital fat in both T1 and T2 modalities on MRI, and typically enhance with IV gadolinium contrast (Fig. 4). Radiologic findings are helpful in distinguishing between WG and other orbital pathology (Table 3). In doubtful cases, orbital biopsy can be performed to differentiate orbital WG from other causes of orbital inflammation.

While orbital inflammation in WG usually causes proptosis, orbital socket contraction may also occur (Fig. 5). One-third of patients with chronic orbital involvement developed orbital contraction with a mean enophthalmos of 2.8 mm by Hertel exophthalmometry. This condition is also associated with restrictive ophthalmopathy, optic nerve disease, and chronic orbital pain that may be unresponsive to immunosuppressive medications. Orbital fistula and infectious orbital abscess may be additional complications.

3. Eyelids

Eyelid involvement may include dacryoadenitis, dacrocystitis, ptosis, lid granuloma, chalazion, florid xanthelasma, and trichiasis (Fig. 5). Nasolacrimal obstruction can be caused by either adjacent sinonasal inflammation or direct involvement of the nasolacrimal system. Eyelid ulceration and fistula formation may also occur (Fig. 6).

4. Conjunctiva

 Conjunctivitis in WG may be ulcerative and necrotic and result in marked cicatricial changes of the ocular surface (Fig. 7). Tarsal-conjunctival disease has been reported by Robinson and colleagues in 16% of patients. Apart from local complications, this finding may also be clinically significant because of a higher than expected association with subglottic stenosis, an association that will need to be confirmed.
5. Episclera and Sclera

Episcleritis usually presents as a red eye without severe pain or visual impairment (Fig. 8). Although typically self-limited in the absence of WG, WG patients often require topical glucocorticoids. In comparison, scleritis can be vision-threatening and result in scleral necrosis and perforation in a matter of days. Clinically, scleritis manifests as severe pain with redness.31 The sclera is often tender and shows intense hyperemia, discoloration, and may progress to ulceration. Necrotizing scleritis, signified by scleral thinning and a bluish appearance from the underlying choroid, may lead to scarring, infection, and, in advanced cases, perforation and phthisis bulbi.46,63,85 (Fig. 9). Hoffman et al reported that scleritis was the third most common ocular manifestation overall and was the most common ocular manifestation reported at the time of disease onset (~10% of cases).27 Scleritis and episcleritis were noted in 7% and 3.5% of 140 patients described by Bullen and colleagues.31

6. Cornea

Corneal involvement is often seen as an associated adjacent corneal infiltrate in active scleritis and has also been described as an isolated phenomenon.31 Corneal disease may also manifest as an interstitial keratitis or peripheral ulcerative keratitis54 (Fig. 10). Peripheral ulcerative keratitis in WG is associated with the presence of autoantibody that is specific against cytokeratin-3.65 Conjunctivalization of the corneal epithelium is a long-standing sequelum of chronic cicatricial disease.

7. Uveitis

Uveitis is not a common manifestation of WG. Uveitis was the least common form of ophthalmologic involvement in 140 patients with WG reported by Bullen et al (4 patients, or 2.9%).6 Anterior, posterior, or pan-uveitis may be present.29,70 Rarely, it may be the initial manifestation.67 Anterior or vitreous inflammation may accompany anterior or posterior scleritis, marginal keratitis, or active inflammation in other surrounding structures. It should be noted that ANCA testing can be positive in up to 30% of patients with uveitis without a history of WG.19 Although it may be possible that these patients with time may develop WG, the positive ANCA immunofluorescence more likely represents a non-specific auto-reactivity against various neutrophil cytoplasmic antigens. Many of these target antigens have been described by Gordon et al.19,20,37,68,75
8. Retina and Choroid

Retinal and choroidal involvement in WG appear to be rare. In Bullen’s series, 4 out of 140 patients (2.9%) had retinitis and one had a branch venous obstruction. A similar percentage of patients with retinal involvement was seen in the NIH series by Hoffman et al. Vasculitis may involve the retina or choroid, be unilateral or bilateral, central or multifocal. Clinically, this is characterized by perivascular sheathing, focal arterial and venous occlusion, retinal whitening or ischemia, intra-retinal hemorrhage, retinal neovascularization, and vitreous hemorrhage. Retinal venous occlusion has been described in the absence of angiographic evidence of vasculitis. This may be related to a general increased risk of venous thrombosis in WG. CMV retinitis should be considered in any patient with WG on immuno-suppressive treatment with a compatible clinical picture.

Sclero-choroidal granulomas may mimic the appearance of a uveal melanoma. Choroidal folds, choroidal effusions, or an exudative retinal detachment may be seen in association with chorioretinal granulomas or posterior scleritis. Vitreous hemorrhage may also occur from a choroidal or ciliary body granuloma. Acute posterior multifocal placoid pigment epitheliopathy has also been described in association with WG.

9. Neuro-ophthalmologic Manifestations

Orbital inflammatory disease may result in compressive optic neuropathy with profound vision loss. Vasculitic involvement of arteries supplying cranial nerves may cause cranial neuropathies and diplopia. Ischemic optic neuropathy may result in sudden, severe visual loss. Optic neuritis may also occur, although appears to be rare. A comprehensive, referenced table of clinical manifestations can be found in the 1998 review of WG by Harman and Margo.

V. Differential Diagnosis

The diagnosis of WG should be suspected in any patients with upper or lower respiratory findings and evidence of glomerulonephritis. The American College of Rheumatology definition is the presence of two out of four of the 1990 criteria for WG, although more recent studies have included a positive ANCA immunoassay result (Table 4).

Orbital disease in WG is often difficult to distinguish from other inflammatory conditions. The differential diagnosis of orbital inflammation is broad and includes infectious, inflammatory, and neoplastic disorders. Graves’ disease is the most common cause of unilateral or bilateral proptosis, which should be evaluated with thyroid function.
testing and anti-thyroid antibodies. Infectious orbital cellulitis should be suspected if there is a history of local trauma or sinus or dental infection or intervention. Accompanying systemic features of infection such as fevers, tachycardia, leukocytosis, and positive blood cultures are also useful in distinguishing infectious from non-infectious inflammation.

Several systemic inflammatory conditions also associated with orbital inflammatory disease include WG, sarcoidosis, idiopathic orbital inflammation (IOI, historically known as orbital pseudotumor), Churg-Strauss syndrome, Erdheim-Chester syndrome, and Tolosa-Hunt syndrome. Sarcoidosis is a multisystem inflammatory disease commonly affecting the lungs, skin, and eyes that is characterized histologically by non-caseating granulomas. Clinical features such as prominent hilar or peripheral lymphadenopathy, pulmonary parenchymal lesions, erythema nodosum, periarthritis, or an elevated serum angiotensin converting enzyme level support the diagnosis.

Churg-Strauss syndrome is a systemic vasculitis that clinically is associated with asthma, allergic rhinitis, and peripheral eosinophilia. Necrotizing vasculitis with granulomatous inflammation and eosinophilia is seen on histologic specimens from affected tissues.

Fig. 6. Sinocutaneous and nasocutaneous fistulae may occur in WG. A: This patient developed an ethmoid-cutaneous fistula after years of disease activity. B: This patient developed underwent bilateral dacryocystorhinostomy surgery for epiphora. This was later complicated by wound necrosis and nasocutaneous fistulae.

Fig. 7. Dystichiasis from cicatricial conjunctivitis in a patient with WG. (Reproduced from Robinson et al66 with permission of Elsevier.)

Fig. 8. Episcleritis from a patient with WG.

Fig. 9. Necrotizing scleritis in a patient WG. Spontaneous perforation is rare, but rupture may occur with minimal trauma.
Orbital involvement in Churg-Strauss, occurring in only one of 96 patients reported in the largest reported series by Guillevin et al. Erdheim-Chester syndrome is a rare systemic granulomatous histiocytic disorder with frequent orbital involvement—around 30% of patients. Diabetes insipidus, retroperitoneal fibrosis, and orbital disease form a unique clinical constellation that points to the diagnosis. Typical sclerotic lesions can be seen on x-ray, and histology shows diagnostic histiocytic cellular infiltrates.

Idiopathic orbital inflammation (IOI) is a common cause of orbital inflammation and is a diagnosis of exclusion after laboratory, radiographic, and, if necessary, histologic evaluation for other causes. Tolosa-Hunt syndrome is a variant of IOI that affects the cavernous sinus, resulting in painful ophthalmoplegia. Its histology is virtually indistinguishable from that of IOI. WG may rarely present as a painful ophthalmoplegia, but systemic and laboratory testing should be sufficient to differentiate it from Tolosa-Hunt.

Neoplastic disorders include rhabdomyosarcoma, the most common orbital malignancy in children, and lymphoma, the most common orbital malignancy in adults. Orbital metastasis from a distant primary source should also be considered.

Conjunctival involvement in WG may be very similar to that seen in ocular cicatricial pemphigoid. The diagnosis can be made by conjunctival biopsy with direct immunofluorescence staining of histologic specimens. Demonstration of linear immune deposit on the basement membrane zone is highly suggestive of the diagnosis of cicatricial pemphigoid; however, there is a report of biopsy-defined ocular cicatricial pemphigoid in a patient with clinical features of active WG.

Scleritis and episcleritis are frequently caused by rheumatoid arthritis and relapsing polychondritis (although an underlying etiology is not identified in approximately 66% of patients with episcleritis and approximately 40% of patients with scleritis). Uveitis is a rare manifestation of WG, and its presence in the absence of concurrent corneal or scleral inflammation should point the clinician towards other causes such as sarcoidosis, Behçet syndrome, inflammatory bowel disease, or infectious causes such as spirochetal or mycobacterial disease.

Ocular disease may be the presenting or dominant symptom in a patient with WG and other systemic illnesses. Thus the ophthalmologist should have a high index of suspicion and inquire about other disease-associated features, which may be symptomatic or asymptomatic. Renal and lung disease are often asymptomatic. Hematuria is usually microscopic, and a urinalysis is a sensitive and cost-effective test to discover glomerulonephritis. Chest CT scans may reveal striking nodular lesions that may not cause symptoms in the absence of involvement of bronchi and pleura. ANCA may be helpful in diagnosing WG when the pre-test probability of disease is moderate to high. However, in cases of WG “limited” to the sinuses and orbits, ANCA may be negative in up to 50% of cases, and biopsy of affected tissue may be required to support the diagnosis and rule out competing illnesses for which treatment may be quite different.

VI. Treatment

Prior to 1970, WG was usually a fatal disease. Only 50% of patients survived 5 months, and mortality was about 80% within 1 year of diagnosis. With glucocorticoids alone, mean survival time was only
1 year. Currently, the combination of glucocorticoids with either cyclophosphamide or methotrexate or azathioprine can lead to disease remission and prolonged survival. WG is now a very treatable, albeit incurable, disease, with survival rates as high as 95% at 5-year follow-up and ~80% after 10 years of follow-up. Unfortunately, treatment-related morbidity remains a challenge with WG. This has led to exploration of numerous alternative therapies, including biologic agents.

A. INITIAL THERAPY

WG is divided into severe and limited disease. Investigators have defined severe disease as WG that threatens the patient’s life or function of a vital organ and limited disease is that which does not. Daily cyclophosphamide and corticosteroids are an effective treatment for severe forms of active WG. However, for some patients with milder forms of illness, cyclophosphamide may not be required at all, and remission may be achieved with methotrexate. In more severe cases, remission can be achieved with cyclophosphamide and treatment can be limited to 3–4 months, thereby markedly reducing the risks of long-term toxicity. After cyclophosphamide and corticosteroids have induced remission, maintenance can be achieved with either MTX or azathioprine. With clinical improvement and sustained remission, prednisone is tapered and discontinued over 6–9 months. Azathioprine for remission maintenance in patients with active severe WG. The results of this study demonstrate similar efficacy of cyclophosphamide and rituximab in achieving disease remission within 6 months. Rituximab appeared to be more effective than cyclophosphamide for inducing remission of relapsing disease compared to new onset WG or MPA (67% versus 42%, P = 0.01). 157 serious adverse events occurred among 197 patients, but these were equally distributed between both groups. Adverse events leading to discontinuation of treatment were similar in both groups (14% versus 17%). The mortality rate, including 9/44 on dialysis, who had either WG, MPA and renal-limited vasculitis for the combined cohort was 1.5% at 6 months follow-up. Because this part of the study focused on induction of remission, follow-up was reported for only six months. Analyses with longer follow-up (minimum follow-up for entire study was 18 months) will reveal if rituximab treatment can reduce the risks of long-term toxicity associated with cyclophosphamide and provide comparable or superior efficacy. The RITUXIVAS study included only patients with renal vasculitis. The investigators compared cyclophosphamide followed by azathioprine maintenance (standard of care) versus rituximab plus cyclophosphamide as 2 or 3 pulse IV infusions (without maintenance therapy). At 12 months, rates of sustained remission (>6 consecutive months of remission) were high (~80%) in both groups, and there was no significant difference in severe adverse events. The high frequency of severe infections and mortality rate of 18% within the first 81 days of the study speaks to the severity of illness in this cohort and the toxicity of each arm of this study. The upshot from these studies is that, first, rituximab appears to be an acceptable alternative to cyclophosphamide for induction of remission in patients with severe disease. Second,
the combination of rituximab and cyclophosphamide as an initial treatment may induce sustained remissions (>6 consecutive months) without the need of maintenance therapy with azathioprine or methotrexate. However, the long-term safety profile of rituximab in these patients remains unclear.

B. MAINTENANCE THERAPY

Initial studies used long-term cyclophosphamide for maintenance of remission. Given its inherent toxicity, other better tolerated therapies have been evaluated. Methotrexate was shown to be equally effective at maintenance of remission in studies by Langford et al with a more favorable toxicity profile. Although rates of relapse were high—53% at 16 months—this was not significantly different from cohorts using long term cyclophosphamide, and it avoided the bladder and hematologic toxicities that may prevent cyclophosphamide use for re-induction of remission following relapse. It is clear that discontinuation of therapy leads to higher relapse rates.

Methotrexate is contraindicated in patients with impaired renal and/or liver function, which limits its use. Azathioprine was evaluated by the European Vasculitis Study Group. Following induction of remission with cyclophosphamide and prednisone, maintenance of remission was attempted with either azathioprine or continuation of oral cyclophosphamide. Relapse rates were ~15% at 18 months in both groups, demonstrating that after a brief period of treatment with cyclophosphamide, alternative therapy with a less risky agent did not sacrificing efficacy. Methotrexate and azathioprine have recently been shown to be equally effective in maintenance of remission.

In looking at the composite of therapeutic interventions for WG one can conclude that: chronic (>3–6 months) cyclophosphamide therapy is unnecessary to induce remission in most patients with severe forms of vasculitis; avoiding cyclophosphamide and using MTX or azathioprine for milder cases of WG, as well as MPA and CSS, is feasible and is as effective as using cyclophosphamide for remission-induction. Limited use of cyclophosphamide for induction of remission, followed by step-down therapy (MTX or azathioprine) has markedly reduced CYC toxicity. Current treatments are not curative and few patients sustain enduring remissions when maintenance therapies are discontinued. Rituximab is an important addition to treatment of these diseases and is particularly relevant to patients in whom there are concerns regarding fertility and prior cyclophosphamide toxicity. Unresolved issues at this time are: what effects does rituximab have on immune competent cells apart from B cells; would rituximab efficacy be enhanced if used with MTX or azathioprine maintenance Rx; and what are the long-term risks of chronic maintenance therapies (e.g. azathioprine, MTX, repeat courses of rituximab) in systemic vasculitis?

C. ALTERNATIVE THERAPIES

Numerous other agents such as rituximab, mycophenolate mofetil, leflunamide, and plasmapheresis have been evaluated in induction and/or maintenance regimens. Despite several case reports and a strong therapeutic rational suggesting a role for TNF-alpha inhibition, a randomized, double-masked, placebo-controlled trial failed to demonstrate efficacy of the TNF-alpha inhibitor etanercept in WG. This trial also demonstrated an increased risk of solid organ malignancy among patients who received concurrent therapy with both etanercept and cyclophosphamide for severe WG.

Timethoprim-sulfamethoxazole has a prominent place in therapy for prophylaxis against pneumocystis infection.

D. TREATMENT FOR EYE DISEASE IN WG

Treatment of ocular involvement in WG is usually in the context of treatment of the underlying disease with systemic corticosteroids and cytotoxic medications. Although it is possible that ocular involvement may occur alone, it is far more likely that it will be seen with more wide-spread disease. Its presence requires a more in-depth evaluation of other organ functions. Consequently, the identification of eye and extra-ocular disease will always require systemic therapy. Adjunctive treatment with topical or local corticosteroids may add benefit. Whereas daily oral prednisone and cytotoxic agents are the mainstay of therapy for most patients with ocular WG, IV pulse corticosteroid therapy may be of value in certain conditions. Intravenous methylprednisolone may lead to dramatic improvement in retrobulbar WG, although in our experience the benefits are not sustained over time.

Successful treatment of ocular disease is usually predicated on the response to systemic therapy. At times, however, surgical intervention is required, both for diagnosis and local control of recurrent or destructive disease. Orbital decompression may be successful in select cases of refractory IOI. In most patients, however, retro-bulbar disease recurs, often leading to worsening diplopia and sometimes blindness. Dacryocystorhinostomy is recommended as a safe and effective treatment for nasolacrimal
duct obstruction in those with well managed nasal-sinus and systemic disease. 41

Treatment of retinal vasculitis consists of systemic therapy with cyclophosphamide and systemic and/or periocular glucocorticoids. Because retinal neovascularization may complicate the management, aggressive panretinal photocoagulation has been suggested as an important component in the treatment of retinal vasculitis. 47

Several case reports illustrate the potential efficacy of rituximab in the treatment of WG patients with ocular involvement refractory to cyclophosphamide, including IOI. 17,38,39,59,69,72 In light of the results from the RAVE study, rituximab appears to be an acceptable alternative as initial treatment or for patients with refractory disease.

Treatment of ocular manifestations of WG is most successful when a multidisciplinary approach is embraced, including ophthalmologists, otolaryngologists, and vasculitis specialists (most often rheumatologists, pulmonologists, or nephrologists). Surgical intervention is indicated in the setting of locally destructive disease or for biopsy for definitive diagnosis. Concurrent systemic immunosuppressive therapy is required for long-term disease control. The choice of systemic therapies depends on the extent of disease, which organ systems are involved, the rate of progression, response to therapy, and side effects.

E. DRUG TOXICITY AND THE EYE IN WG

Ophthalmologic disease may be a result of the morbidity associated with the agents used for treatment. Corticosteroids may cause a rise in intraocular pressure, leading to glaucoma with prolonged use. 18 Corticosteroid use is a risk factor for the development of central serous chorioretinopathy. 22 Corticosteroids compromise host defenses and wound healing, effects that may be clinically relevant in the WG patient.

Corticosteroid-induced cataract formation is dose-and time-dependent. Black and colleagues reported that 70% of patients developing cataracts after 4 years of glucocorticoid therapy with an average equivalent daily dose of prednisone of 10 mg or greater. Among patients followed for less than one year, none developed cataracts. 4 Patients at dosages less than 10 mg daily are also susceptible to cataract formation. 71 Younger patients are thought to develop cataracts faster and at lower doses than adults. 49

Immunosuppressive effects of cyclophosphamide and corticosteroids increase the risk of ocular infections such as toxoplasmosis and CMV retinitis. 3 Immunosuppression may also mask inflammatory features of an orbital abscess; this must be distinguished from retrobulbar infiltration due to WG and should be suspected in cases of worsening proptosis. 13 In general, infectious complications should always be considered in patients with WG on adequate immunosuppression when there are new or worsening symptoms in one area and an absence of other clinical or laboratory evidence of disease relapse in other organs.

VII. Conclusion

WG is a systemic vasculitis that is almost always fatal if untreated. Ophthalmologic involvement is common and may be the initial presenting complaint. Ophthalmologists should have a high index of suspicion for WG in patients who present with unexplained IOI, scleritis, peripheral ulcerative keratitis, cicatricial conjunctivitis, nasolacrimal duct stenosis, or retinal vascular occlusion. Inquiries about the presence of other systemic symptoms, particularly sinonasal disease, hematuria, arthralgias and arthritis, rashes, and constitutional symptoms, may help diagnose WG. In the setting of a moderate to high pre-test likelihood of the diagnosis of WG, ANCA testing with antibodies reactive to PR3 are useful and specific for WG; however, 20% of patients are ANCA-negative. Orbital CT and MRI may help distinguish orbital disease caused by WG from other causes. Although biopsy remains the gold standard, it is usually unnecessary in patients for whom WG is an established diagnosis. Treatment-related morbidity is a serious limitation of conventional therapies, leading to numerous ongoing studies of alternative agents.

VIII. Method of Literature Search

Pubmed was queried with combinations not limited to the following search terms: Wegener’s granulomatosis and eye, orbit, orbital inflammation, conjunctiva, conjunctivitis, sclera, scleritis, uveitis, retina, retinitis, retinal vasculitis, pathogenesis, epidemiology. A review of the search results was performed and relevant articles to the topics of clinical manifestations, differential diagnosis, and treatment were included. Relevant articles to the conditions considered in the differential diagnosis of WG were also included. Case reports without additional value over another report of the same condition were not included. References related to pathogenesis and treatment were selected by a rheumatologist with extensive experience in Wegener’s Granulomatosis (GSH). Relevant articles from bibliographies of selected articles were also included.
References


WEGENER’S GRANULOMATOSIS


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