Seminars in
Arthritis and
Rheumatism

Wegener's Granulomatosis: Ophthalmic Manifestations and Management

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OBJECTIVES **To provide an up-to-date and comprehensive review of Wegener's granulomatosis (WG) as a disease entity, focusing on the ophthalmic manifestations and management options.**

METHODS **A search of Medline was undertaken between 1966 and 2005 regarding WG, systemic vasculitis, and the ocular manifestations of WG. Major ophthalmic and medical textbooks also were reviewed for content, as well as original references.**

RESULTS **Involvement of ocular and orbital structures in patients with WG is common and may be a presenting feature. The ocular manifestations range from mild conjunctivitis and episcleritis to more severe inflammation with keratitis, scleritis, uveitis, and retinal vasculitis. Involvement of the nasolacrimal system and orbital tissues also can occur. Except for some cases of anterior segment inflammation, the ocular involvement will not respond to topical agents, but rather to systemic antiinflammatory and immunosuppressive regimens. Surgical intervention may be of value for obtaining tissue diagnosis, in achieving orbital decompression in cases of significant orbital disease with optic nerve compromise, or in cases of nasolacrimal duct obstruction.**

CONCLUSION **WG is an important clinical entity that needs to be recognized early and treated appropriately. Ophthalmic manifestations are frequently encountered and can result in significant morbidity and even blindness. The management is challenging and often requires a multidisciplinary approach.**

Semin Arthritis Rheum 35:284-292

KEYWORDS **Wegener's granulomatosis, ocular, orbital, ophthalmic, eye, vasculitis**

Wegener's granulomatosis (WG) is a multisystem granulomatous inflammatory disorder of presumed autoimmune origin. It has a predilection for affecting the upper and lower respiratory tracts and kidneys and was initially described in 1931 by a medical student, Heintz Klinger (1). It was not until 1936, however, that Frederick Wegener more clearly distinguished this disorder from that of polyarteritis nodosa (1,2).

The associated vasculitis preferentially affects small-caliber arterial vessels, and to a lesser extent, smaller and larger arteries and veins (3,4). WG is significantly more common in the white population, with a peak incidence in the fifth decade of life (1,3,5-11). The annual incidence is estimated to be between 4.0 and 8.5 cases per million (1,3,5,7,8,12,13).

The reported incidence of ocular involvement in WG varies among different series, but is usually estimated to occur in 50 to 60% of patients (4-6,14-18). The aim of this review was to provide an overview on WG, focusing on the ophthalmic manifestations and the approach to patients presenting with ocular signs and symptoms.

Methods

We reviewed the relevant medical literature by searching "Medline" (1966 and 2005), using the combinations of the following keywords: "Wegener's granulomatosis," "orbit,"

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 0049-0172/06/$-see front matter
doi:10.1016/j.semarthrit.2005.12.003

"ocular," "eye," and "systemic vasculitis." Our search was limited to human studies and preference was given to English-language journals. Articles were included if they emanated from peer-reviewed journals. From these studies and their references, 1276 abstracts were reviewed and those pertinent to our discussion were selected. Major ophthalmic and medical textbooks also were reviewed for content, as well as original references, which were manually searched. Clinical studies were selected if they were randomized controlled trials, single- or double-blind, or interventions with pharmacological therapy compared with placebo, or some other pharmacological agents. Case series and single case reports also were included when reviewing uncommon clinical manifestations and experimental treatments.

Results

WG is defined as a small-vessel idiopathic primary vasculitis and, together with Churg-Strauss syndrome (CSS), microscopic polyangiitis and necrotizing pauci-immune glomerulonephritis, demonstrates a strong association with antineutrophil cytoplasmic antibodies (ANCA) (19,20). Traditionally the diagnostic pathological triad in WG is described as that of parenchymal necrosis, vasculitis, and granulomatous inflammation (21). It is suggested that the demonstration of the classic triad varies according to the tissue sample, being as high as 91% in open lung biopsies (5), and 54% in orbital biopsies (22).

Features on orbital biopsy include fat disruption with areas of focal necrosis, giant cells and free vacuoles, and often active or old fibrosis (23). Coalescence of the neutrophilic microabscesses often produces extensive areas of "geographic necrosis" (24). Sadiq and coworkers reported orbital biopsies consistent with WG in 86% of their patients with orbital disease (25). Orbital biopsy findings can be difficult to accurately interpret; therefore, they should be considered simultaneously with the history, examination, imaging of the orbit and sinuses, and other serological investigations, including ANCA (26).

WG is considered a multisystem disorder and has the potential to affect almost any organ system. Respiratory tract involvement is most commonly seen and is ultimately seen in up to 85% of patients, whereas the renal system is eventually involved in 70 to 80% of patients (5,6,10,11,14,15,27). Ocular involvement in WG is common and reported to occur in up to 50 to 60% of cases and as high as 87% at some time during the patient's lifetime. It may be present at the time of diagnosis or in fact be the presenting feature in 8 to 16% of patients (1,5,6,11,15,17,25,26). Severe ocular morbidity may be a complication in both limited and severe forms of WG (1,14,16,17,27). Frequently, however, the initial signs and symptoms may be rather nonspecific and mimic other less significant illnesses (28). This may delay diagnosis and the initiation of life-saving therapy. Hence referral for ophthalmic evaluation is warranted if there is any suspicion of ocular WG. Given the high rate of ocular involvement in the course of the illness, periodic ophthalmic evaluations may be of value.

Ophthalmic complications may result from a variety of pathologies. These include focal vasculitis of small arterioles veins and arteries, granulomatous inflammation, vascular thrombosis and hemorrhage, or as a consequence of chronic inflammation or ischemia (1). Ocular involvement is varied and may range from mild conjunctivitis to episcleritis, scleritis, granulomatous sclero-uveitis, ciliary vessel vasculitis, retinal vasculitis, nasolacrimal obstruction, dacryocystitis, and retro-orbital mass lesions. The most common reported eye findings are keratoscleritis and orbital disease, manifesting as proptosis (1,14,16,21,23,25,26).

Ocular involvement may also be seen in other systemic vasculitides, although much less commonly than observed in WG, especially as an initial harbinger of the illness. The presence of orbital inflammation and mass effect is particularly uncommon. Ocular complications in microscopic polyangiitis are rare and often limited to scleritis, retinal vasculitis, and eyelid lesions (1,29). Similarly, ocular involvement in polyarteritis nodosa is unusual (29). Ophthalmic manifestations are also very unusual in CSS, with little more than 20 cases reported in the literature (30). Rheumatoid arthritis is more common; however, significant ocular manifestations such as scleritis are typically seen in patients with advanced or longstanding disease (1,29).

Ophthalmic Manifestation

Tarsal-Conjunctival Disease

Conjunctival involvement is uncommon and reported in 4 to 16% of all patients with WG (14,31). Many studies have reported nonspecific conjunctival inflammation without much elaboration (5,15,31). Tarsal-conjunctival disease may be evident by areas of necrosis, active fibrovascular change, or an inactive fibrovascular scar (31). There may also be conjunctival hyperemia and granulomata. The palpebral surface of the eyelids is most commonly involved, and the associated fibro-vascularization may result in entropion and trichiasis (31,32). Hence routine examinations of upper and lower eyelids is recommended in WG patients. A significant association between tarsal-conjunctival disease, nasolacrimal obstruction, and subglottic stenosis has been reported, and hence, referral to an otolaryngologist is also recommended in all patients with tarsal-conjunctival disease (31,33). This association may reflect the fact that all these features are a consequence of mucosal involvement and scarring. It appears that systemic immunosuppression is largely ineffective in the management of these fibrosing manifestations (33).

Episcleritis

Episcleritis also has been described in patients with WG, although it is typically not associated with an underlying systemic disease (1,34). It is characterized by inflammation of the loose episcleral tissue between the conjunctiva and sclera (Fig. 1). Patients complain of pain and watery discharge and on examination a diffuse or localized injection of the bulbar conjunctiva is often present. Complications secondary to episcleritis are much less common compared with scleritis, with anterior uveitis occurring most often (35). Episcleritis is usually self-limiting and resolving in 2 to 3 weeks, and only rarely requiring a short course of topical

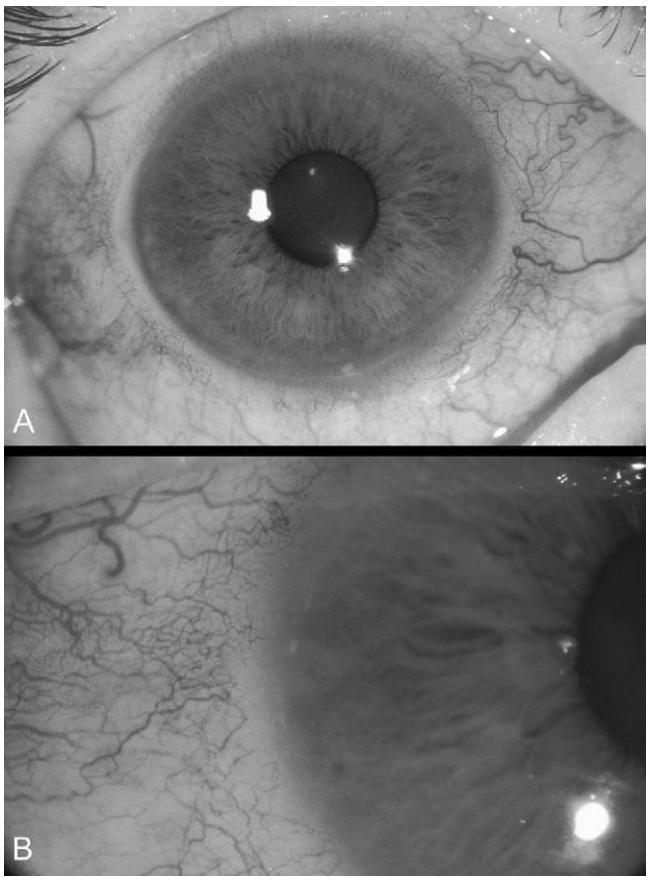

Figure 1 (A, B) Episcleritis of the right eye of a patient with Wegener's granulomatosis. The inflammatory process involves only the superficial episcleral vessels.

steroids or nonsteroidal antiinflammatory drugs (NSAIDs) if symptoms are severe (26).

Scleritis

Scleritis is an inflammatory condition characterized by cellular infiltration and edema of the entire thickness of sclera (28,34) (Fig. 2). It can present with a deep boring pain which may radiate to the temple or jaw and awaken the patient at night, and ocular tenderness (34,36). It is associated with an underlying systemic disorder in up to 50% of cases (26,34). Most common associations are rheumatoid arthritis, WG, inflammatory bowel disease, systemic lupus erythematosus, and relapsing polychondritis (36). A minority of cases may be due to herpes zoster, Lyme disease, or syphilis.

Scleritis is described as anterior (around 98% of cases) or posterior. Anterior scleritis is further classified as diffuse, nodular, or necrotizing (34,36). Necrotizing scleritis is much less frequent, but is often associated with systemic disorders and results in ocular complications in approximately 92% of cases and can lead to permanent blindness (34,37). Scleritis of the necrotizing type is the most common ocular pathology seen in WG, occurring in more than half of patients with ocular WG (2,4,5,12,25,37). The necrotizing process is demonstrated by a black, gray, or brown area surrounded by active inflammation. Progression produces an avascular, white scleral area. Complications of scleritis include keratitis, corneal ulceration, uveitis, ocular hypertension, or glaucoma (38).

Keratitis

Keratitis can be classified as interstitial keratitis or peripheral ulcerative keratitis (also known as marginal keratitis) (26). When it occurs with scleritis, the term sclerokeratitis is used (26). Interstitial keratitis involves inflammation and often vascularization of the corneal stroma but without involvement of the epithelium or endothelium (16). It is frequently a result of an immune response to an infection such as syphilis. Patients present with pain, tearing, and severe blurring of vision, and on examination, there is corneal stromal infiltration and clouding with invading vessels from the limbus. Peripheral ulcerative keratitis, on the other hand, may only produce mild irritation and discomfort and there is breakdown of the overlying epithelium producing ulceration and stromal thinning, which, if left untreated, may result in corneal perforation (26,39). Peripheral ulcerative keratitis associated with WG is often associated with scleritis, and in these patients, eye pain may be pronounced.

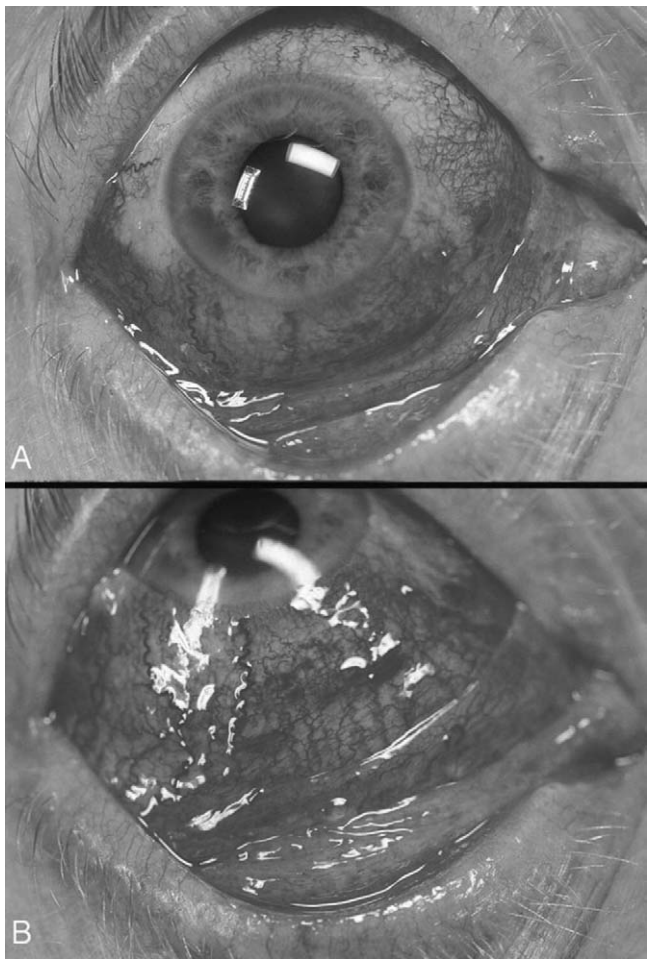

Figure 2 (A, B) Scleritis of the right eye of a patient with Wegener's granulomatosis, The inflammation is intense and involves the deeper layers, including the sclera.

Uveitis

Uveitis, as a primary ocular manifestation of the systemic vasculitides, is uncommon except in Behcet's disease, where it occurs (25) in approximately 2% of patients during the disease course (14). With respect to uveitis in WG patients, it is often due to concurrent scleritis (sclerouveitis), producing secondary intraocular inflammation (26). The occurrence of this phenomenon in the course of scleritis suggests a poorer ocular prognosis (40).

Retinal Disease

Retino-vascular involvement may result in significant morbidity and visual loss. Complications that were reported include retinitis, chorioretinitis, macular edema, exudative retinal detachment, retinal necrosis, retinal vasculitis with central retinal artery or vein occlusion, and vitreous hemorrhage (1,4,7,41,42).

Nasolacrimal Disease

Nasolacrimal obstruction in WG is a result of nasopharyngeal disease and occurs in about 10% of patients. It may be complicated by chronic dacrocystitis and mucocele formation (25,26,42,43). It is generally considered a late manifestation of WG, presenting with chronic epiphora (17). Woo and coworkers reported epiphora due to nasolacrimal outflow obstruction in 52% of their patients with orbital and adnexal WG (44). Approximately half of these patients had lacrimal sac mucoceles. Evidence suggests that lacrimal drainage system disease is a direct consequence of focal WG vasculitis, and not a result of contiguous orbital pathology (15,25,43,44).

Orbital and Adnexal Disease

Orbital disease accounts for a significant proportion of ocular involvement in WG patients. Orbital involvement may be due to primary inflammation (focal disease) or result from extension of disease from adjacent paranasal sinuses or nasopharynx (contiguous disease) (1,15-18,26,42,45). Hence a significant proportion of patients with orbital disease also have signs and symptoms of sinus disease (44). The most common presenting features of orbital disease are ocular pain, epiphora, and injection. Epiphora, however, frequently is a consequence of nasolacrimal disease. There is evidence to suggest that lacrimal drainage system disease may be a direct consequence of focal WG vasculitis, and not a secondary complication of contiguous orbital disease (15,25,43,44).

Orbital disease can manifest as proptosis with or without pain (15,23,44) (Fig. 3). Many patients develop diplopia over the course of the disease, which may be due to the mass effect itself or vasculitis of vessels supplying the extraocular muscles (44). The features of orbital disease are frequently bilateral and constitute a severe risk to useful vision (23,24,44,46). Significant decrease in vision (typically <20/200) is reported in between 20 and 50% of patients as a direct consequence of orbital disease and optic nerve compression (23,25,44). Vision may also be lost as proptosis can be complicated by exposure keratopathy, corneal ulceration, and even corneal perforation (25).

Orbital socket contracture is a more recent sequelae reported in patients with orbital WG (47). It is defined as orbital inflammation with proptosis followed by the development of enophthalmos and radiographic evidence of fibrotic changes in the orbit. This complication likely represents proliferation of fibrous tissue replacing areas of acute inflammation and necrosis. The ensuing contracture can lead to restriction of motility and enophthalmos and can also involve the optic nerve. As with other fibrosing manifestations of WG, socket contracture responds poorly to immunosuppressive medication (47).

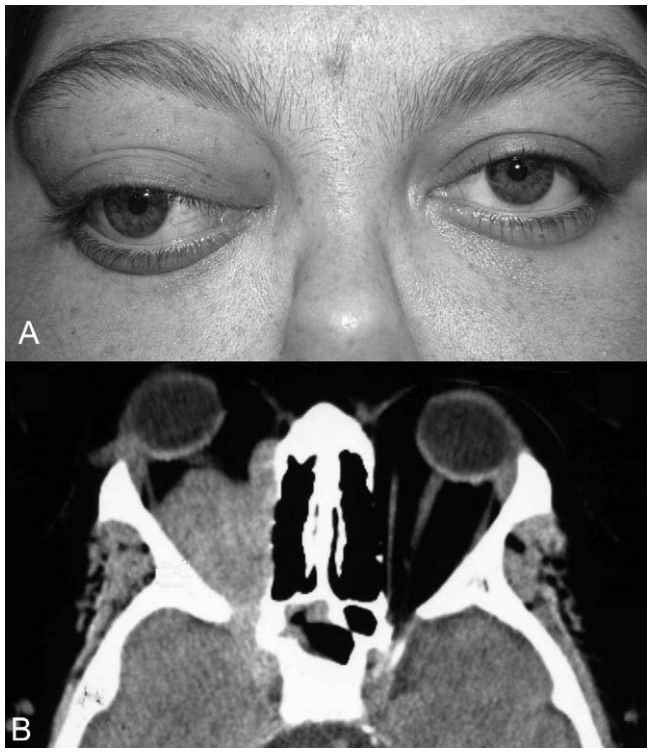

Figure 3 (A) Clinical picture of a 27-year-old patient with right eye proptosis and significant lateral globe displacement secondary to orbital Wegener's granulomatosis. (B) The axial CT scan demonstrates a large right-sided orbital mass that is displacing the globe and also extends posteriorly to the brain.

Biopsy is important for the diagnosis of orbital WG. It has been reported to demonstrate granulomatous inflammation or vasculitis in 75 to 85% of patients (15,23,25,48). However, the classic triad of vasculitis, tissue necrosis, and granulomatous inflammation may only be demonstrated in approximately 50% of cases (22). Once bacterial or fungal causes for a mixed orbital inflammatory infiltration of neutrophils, lymphocytes, plasmocytes, histiocytes, and eosinophils are ruled out, there are few other potential diagnoses. Hodgkin's disease is a rare, but possible differential diagnosis and, if suspected, frozen sections should be obtained (23,48). Immunohistochemical stains are helpful in the diagnosis of lymphoma of the orbit (1). Sarcoidosis may also present with ocular and orbital manifestations. Radiological evidence of pulmonary involvement, the presence of noncaseating granulomas on histology, as well as adjunctive investigations such

as angiotensin-converting enzyme assays, are important in establishing the diagnosis (49).

Thyroid or Graves orbitopathy is the most common cause of orbital inflammatory disease and should always be considered in all patients presenting with orbital inflammation or an orbital mass (49,50). Characteristic ocular manifestations such as eyelid retraction, along with other systemic signs and symptoms of thyroid disease, as well as appropriate investigations looking for thyroid dysfunction, are often diagnostic. Newer and more sensitive assays for thyroid hormone levels are reported to detect hyperthyroidism in the majority of patients with Graves orbitopathy (50).

Acute idiopathic and acute sclerosing inflammatory conditions of the eye have their typical appearances on biopsy and often promptly respond to oral corticosteroids (23,49). Idiopathic orbital inflammation, also known as orbital pseudotumor, is a clinical syndrome characterized by a nonspecific pattern of chronic inflammation manifesting as an orbital mass (1,49). It frequently presents with an abrupt onset of proptosis, pain, and ocular inflammatory symptoms and signs, without an identifiable local or systemic cause. It is a diagnosis of exclusion relying on information obtained from history, physical examination, imaging, and biopsy (49). Treatment with oral steroids is the mainstay of treatment with the use of other systemic immunosuppressants reserved for refractory cases.

Rare Ophthalmic Complications

WG may result in various other ocular pathologies. Optic nerve involvement may manifest as compressive or ischemic optic neuropathy, optic nerve edema, and optic atrophy (1,16,17,23,26). Ophthalmoplegia may occasionally result from vasculitis involving the cranial nerves supplying the extraocular muscles (51).

Laboratory Investigations

Testing for ANCA, by using either immunofluorescence (IF) and/or enzyme-linked immunospecific assay (ELISA), is of significant value in the diagnosis of certain vasculitides. Using ELISA, the c-ANCA pattern is found to react with proteinase-3 (PR3), whereas the p-ANCA pattern typically reacts with myeloperoxidase (MPO) (1,52).

A meta-analysis of c-ANCA testing in WG reported a pooled sensitivity of 91% and specificity of 99% for active WG (53). The sensitivity of p-ANCA/anti-MPO for WG is reported to be around 10 to 12% and hence it is not considered a reliable marker for WG (1,15). It is recommended that both IF and ELISA be utilized when ANCA testing is considered (54). ELISA techniques are more specific, whereas IF has a greater sensitivity (55). An international consensus statement recommends that IF testing be performed on all serum samples of new patients, with positive patients undergoing ELISA testing for PR3-ANCA and MPO-ANCA (56).

As WG is a rare disorder, ANCA testing should only be applied to a population of patients in whom there is a relatively high degree of suspicion of WG (1). With regard to ocular problems, testing can be considered in patients presenting with scleritis or orbital inflammation in whom no apparent other cause is found after a thorough history, examination, and basic laboratory tests (1). There is no clear indication as to whether laboratory results differ significantly in patients with ocular involvement, either as a sole manifestation of WG or as part of a multisystem disorder.

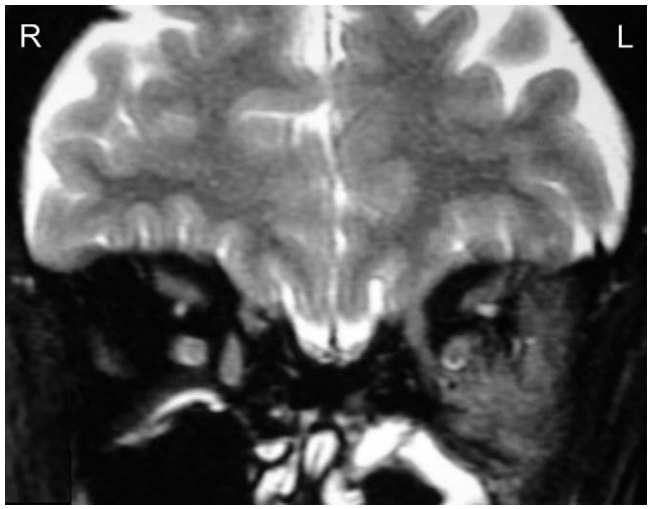

Figure 4 T2-weighted coronal MRI of a patient with Wegener's granulomatosis showing a mass involving the left maxillary sinus and extending into the left orbit.

Radiological Investigations

Computed Tomography (CT)

CT features suggestive of a diagnosis of orbital WG include involvement of the sinus structures and an orbital mass (Fig. 3). There is often obliteration and infiltration of adjacent fat planes that may include osseous erosions (25,57). Most patients demonstrate nonspecific sinus changes that are indistinguishable from chronic sinusitis (58). A more distinctive change is progressive thinning and obliteration of part of the nasal septum. CT can also demonstrate the irregular, ulcerated surface of the lining granulomatous tissue. CT and possibly ANCA in patients with atypical nasolacrimal obstruction is suggested to aid in the earlier diagnosis of WG (45). Lacrimal region CT is helpful in identifying lacrimal sac mucoceles, sinus pathology, gross nasal polyposis, extrinsic tumors, and dacryoliths (59). Demonstrating some of these findings may have implications for patient management.

Magnetic Resonance Imaging (MRI)

More recently, the use of MRI as a diagnostic tool has been highlighted (57,60). Although it may not be fully validated for the vasculitides, it can depict granulomas and better delineate mucosal inflammation and ulceration in the sinuses, nasal cavity, and orbits. In the initial inflammatory phase of WG, MRI may not assist in differentiating mucosal inflammation from granulomatous tissue. However, with gradual granulomatous transformation, granulomas can be illustrated as low-signal-intensity lesions on T1- and particularly T2-weighted sequences in the nasal cavity, paranasal sinuses, and orbits (60,61) (Fig. 4). Unenhanced, non-fat-suppressed T1-weighted sequences may best distinguish WG lesions

from normal structures (62). However, the enhancement characteristics of WG lesions are well appreciated on fat-suppressed T1-weighted images.

Angiography

More recently, the use of indocyanine green angiography has been reported to be of value in the evaluation of choroidal inflammatory vasculopathy and the vasculitic process in anterior scleritis (63). As leakage is demonstrated in scleritis and rarely in episcleritis, indocyanine green angiography may be a useful tool in distinguishing between episcleritis and the more severe scleritis (64).

Treatment

The gold standard treatment for WG and ANCA-associated vasculitis combines glucocorticoids (GC) and cyclophosphamide (CYP) and became popular in the 1970s (65,66). However, it has only recently been validated in randomized trials. Before treatment, the median survival of patients with WG was approximately 5 months, with a 1-year mortality of greater than 80% (67,68). The combination of GC and CYP has repeatedly been demonstrated to achieve remission in the majority if not all patients, often lasting for several years (5,14,69,70). Despite the high rate of remissions, relapse rates remain high following tapering or discontinuation of treatment (15).

There are suggestions from multiple open-label trials that, in cases of limited WG, an alternative regimen of methotrexate (MTX) and GC may achieve remission rates of around 70% (71-73). Although better tolerated compared with CYP, MTX is usually used as a remission-maintaining agent after initial CYP therapy (72,74). The rate of relapse appears to be lower when used in such a manner. Once remission is induced with standard therapy, the substitution of azathioprin (AZA) for CYP is suggested not to increase risk of relapse (13). It may also be considered in patients intolerant to MTX or those with renal impairment (75).

Side effects of standard therapy regimens are significant and are a major cause of morbidity and mortality. In the short term, the risk of opportunistic infections poses a great threat to life, being reported in more than 50% of patients (76).

There are numerous other experimental agents under study in the treatment of WG, in an attempt to minimize exposure to the toxic effects of CYP. The immunosuppressive drug mycophenolate mofetil is very well tolerated as a remission maintenance agent; however, a relapse rate of 43% at a median of 10 months was reported after achieving remission (77). A randomized trial reported good control in many patients receiving cyclosporin after remission induction, despite a higher rate of relapse compared with continued use of CYP. More recently a large randomized, placebo-controlled trial reported that the use of etanercept (a TNF-alpha inhibitor) is not effective for remission maintenance, with high treatment-related complications (78). Smaller studies looking at other immunosuppressive agents such as infliximab (TNF-alpha inhibitor), rituximab (anti-CD20 monoclonal antibody), and 15-deoxyspergualin (DSG) have reported some success in remission induction in WG and antineutrophil cytoplasmic antibody-associated vasculitis, even in patients with refractory disease (79-81).

Management of Patients with Ophthalmic Complications of WG

Medical Management

In general, appropriate treatment of the underlying disease is satisfactory in managing ocular problems. It appears that ocular involvement does not readily respond to topical agents, except in some cases of episcleritis, conjunctivitis, and anterior uveitis, where a short course of topical steroid can be beneficial (16,26). Treatment of keratitis in systemic vasculitides is largely aimed at treating the underlying disorder. The use of topical corticosteroids is considered ineffective and may hasten corneal thinning and even perforation (39,82). In the cases of imminent perforation in peripheral ulcerative keratitis, local measures such as adhesive glue or graft may be necessary (39). In cases of intermediate uveitis, subconjunctival steroid injections may be required, with oral prednisone reserved for chronic posterior uveitis or refractory cases (38).

Patients presenting with scleritis often need to be investigated for underlying systemic disease. The use of indomethacin can be considered as initial management in cases of anterior scleritis. However, oral steroids should be considered if this therapy is ineffective, or in cases of posterior and necrotizing scleritis. In most cases of necrotizing scleritis, the addition of a steroid-sparing immunosuppressant such as CYP is necessary (38,83). Recently, there has been renewed interest in the use of local GC injections in the treatment of anterior scleritis, as earlier concerns regarding the risk of inducing necrotizing scleritis have been refuted. Local GC injection can be very effective and may be considered in resistant cases of scleritis with no active systemic disease (84).

More severe ocular disease is often not responsive to GC alone, and its use may mask disease activity without inducing remission or preventing complications (16,17,23,27,59,85). In a study looking at WG of the orbit, the use of oral steroids alone achieved good control in only 1/10 patients, with 4/10 patients seriously deteriorating (23). The group receiving AZA-GC achieved only partial response. The most dramatic benefits occurred with the use of CYP-GC, with all patients retaining useful vision in at least 1 eye. It is therefore believed that the treatment of choice for significant ocular WG remains the combination of GC and CYP (14,17,23). This combination provides the best chance of retaining useful vision and preventing further visual loss. The use of trimethoprim-sulfamethoxazole (TMP-SMX) and GC may be considered as safe initial therapy if there is no early visual deterioration (23).

Patients with ophthalmologic manifestations of WG are at significant risk of serious systemic disease and hence a collaborative approach among internal medicine specialists/rheumatologists and ophthalmologists is essential to implement prompt diagnosis, treatment, and follow-up (1,4,25,42). Collaboration with the otorhinolaryngologist is also important given the high concurrence of sinonasal disease. Patients should undergo care-

ful questioning and examination with regard to other systemic features. In cases of suspected orbital WG, assistance from an orbital/ophthalmic plastic surgeon is recommended to facilitate tissue diagnosis (25,48). Biopsy can be obtained through an endoscopic transnasal/transethmoidal approach, external ethmoidectomy, and orbitotomy (48). Even patients with very limited disease should be evaluated regularly, as over the course of the disease there is often increasing involvement of organ systems (5,14,86). The occurrence or deterioration of ocular inflammation in a patient with otherwise well-controlled disease may indicate eventual worsening of systemic manifestations (87).

In all cases, treatment should be instituted after confirming the diagnosis of WG, based on the constellation of clinical, hematological, radiological, and biopsy features. A negative ANCA result however should not preclude treatment if there is otherwise strong evidence of a diagnosis of WG. Perry and coworkers suggest that bilateralism, involvement of the upper respiratory tract or sinuses, and scleritis at the time of onset, particularly if associated with corneal infiltrates, should raise the suspicion of a diagnosis of WG (23).

Surgical Management

Surgical interventions in the management of WG are largely limited to those involved with obtaining tissue biopsies for pathological analysis. However, in cases of nasolacrimal duct obstruction, dacryocystorhinostomy (DCR) is effective (88,89). The development of chronic dacryocystitis or mucocele formation may be reasons for considering DCR (43). Surgery for nasolacrimal duct obstruction may be more successful if delayed until upper airway and nasal disease are quiescent, and ANCA titers are low (89).

Although aggressive medical therapy can improve ocular motility and associated orbital symptoms, proptosis associated with orbital WG is often refractory to conventional treatment (26,87). In cases of severe orbital inflammation with proptosis, especially if optic nerve function is compromised, orbital decompression should be considered (26). In other cases of orbital disease, treatment success is based on medical therapy (48). In a study of 15 patients with orbital lesions, there was no difference in outcome between those undergoing initial subtotal excision, as opposed to diagnostic biopsy (48).

Lately, there has been much interest in modalities aimed at delivering high-dose corticosteroids into the eye, through either direct intraocular injections or implantation of slow-release devices (63). Such measures are best reserved for patients with persistent and predominantly ocular involvement, particularly if unilateral, in whom other treatment modalities have failed or are not tolerated. Although often successful at controlling inflammation, cataracts are reported to develop in all patients, and a significant proportion of patients develop open-angle glaucoma, which requires medical or surgical management (90,91). Several large randomized prospective trials are underway looking at the efficacy and safety of intraocular steroid delivery devices for the treatment of uveitis and other retino-vascular diseases.

Prognosis

Since the introduction of combination therapy using CYP and oral GC, death rates have dropped significantly and most patients achieve remission (6,14-16,86). With respect to ocular WG, features are frequently bilateral and can cause significant and often irreversible morbidity if not treated appropriately (46). Significant visual morbidity is reported in 8 to 17% of cases (5,17,25). Visual loss may be a consequence of vascular occlusion, macular edema, inflammatory destruction of neurosensory tissue, and destruction of structural tissue, such as the corneoscleral tunic (1,18,25,42,44). In cases of orbital disease, significant loss of visual acuity is reported in up to half of patients (23,25,44). In all cases of ocular WG, early recognition and referral to an ophthalmologist, accompanied by prompt treatment and periodic follow-up, can significantly decrease the risk of visual impairment.

Discussion

WG is a rare entity that can affect almost any organ system. It can often present with nonspecific symptoms and signs, and hence, may be misdiagnosed. Ophthalmic involvement is relatively common in the course of the disease and may in fact be the initial presenting feature in some patients. It is therefore imperative to consider WG in the differential diagnosis, when more common disorders are ruled out. Even if not initially confirmed, it may be necessary to follow patients on a regular basis using the expertise of various medical specialists, as the disease can evolve and the various diagnostic tests become positive with time. Generally, ophthalmic complications are managed with regimens used to treat systemic disease, as topical therapy and the use of GCs alone are often inadequate. However, in some cases of less aggressive limited disease, alternative and less toxic regimens may be initially considered. Specific surgical options may also be considered in some cases for diagnostic purposes or when the disease involves the orbits and nasolacrimal drainage system. Early diagnosis and an appropriate interdisciplinary approach to management can possibly decrease morbidity and blindness.

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