Review

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Granulomatosis with polyangiitis (Wegener's disease): An updated review of ocular disease manifestations

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Summary **Granulomatosis with polyangiitis (GPA) is a potentially lethal systemic disorder that is characterized by necrotizing vasculitis of small arteries and veins. The respiratory system is most commonly affected in limited forms of the disease, however upper and lower respiratory system, systemic vasculitis, and necrotizing glomerulonephritis are the characteristic components of the disease triad. The peak incidence is observed at 64-75 years of age, with a prevalence of 8-10 per million depending on geographic location. In this review we focus on the ocular manifestations of the disease which occur in nearly in one third of the patients. In addition we describe the neuro-ophthalmic complications which occur in up to half of cases. We also discuss the current systemic treatment options including corticosteroids, cyclophosphamide, azathioprine, and the available biologic response modifiers including rituximab. The disease remains difficult to diagnose due to the generalized symptomatic presentation of patients with GPA. As a result, several sets of diagnostic criteria have been developed which include clinical, serological, and histopathological findings to varying extents. Early diagnosis and multi-specialty collaboration among physicians is necessary to adequately manage the disease and the potential complications that may result from drugs used in the treatment of the disease. Despite recent advances, more research is necessary to prevent the high rates of mortality from the disease itself and from therapeutic side effects.**

Keywords: Granulomatosis with polyangiitis, Wegener's, vasculitis, ocular complications, granuloma

1. Definition

Granulomatosis with polyangiitis (GPA) is a systemic disorder that is characterized by necrotizing vasculitis of small arteries and veins (*1,2*). The classic diagnostic criteria for GPA were based on the initial detailed clinical and pathologic findings as described by Godman and Churg in 1954 (*3,4*). This includes a triad of necrotizing granulomas of upper and lower respiratory system, systemic vasculitis, and necrotizing glomerulonephritis. An incomplete or limited form of GPA in which the kidneys are usually spared has been reported (*5-8*). The respiratory system is the most common organ to be involved in limited GPA, although any other organ system can be involved. A very limited form of the disease, with clinical involvement of a single organ such as the eye, has also been described with any ocular structure being affected (*9*). GPA is a complex and potentially lethal disease with high mortality rate if left untreated. Eearly detection of the disease and the introduction of immunosuppressive therapy has resulted in improved prognosis and decreased mortality rate.

2. History

Although GPA was first described by Klinger as a form of polyarteritis nodosa (PAN) (*10*), the unique nature of the disease was recognized earlier by Wegener (*11*).

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The term GPA was first introduced into the English literature in 1954 by Godman and Churg (*4*) This term, as opposed to Wegener's granulomatosis, describes the main pathologic feature (granulomatous inflammation) and reflects the vasculitic involvement of multiple types of vessels (polyangiitis).

3. Epidemiology

The incidence of GPA is estimated to be 8-10 cases per one million depending on geographic location (*12*). It has been suggested that the incidence of GPA is increasing, however this may simply reflect the availability of new diagnostic modalities and serologic tests such as anti-neutrophil cytoplasmic antibodies (ANCAs) that allows a more frequent diagnosis (*13*). The age of symptoms onset has a wide distribution with a peak incidence at 64-75 years of age (*12,14,15*).

Previous studies showed that GPA can occur in children with 8-15% of cases occurring in patients age 19 or younger (*14-16*). Although slight male predominance has been reported in few case series (*17,18*) a recent study including 158 patients showed no sex predilection (*19*). GPA is most frequently reported in white Caucasian patients but can be seen in all racial and ethnic groups (*12,15,18,19*).

4. Systemic manifestations

Classic GPA, as detailed by Godman and Churg in 1954 (*4*), includes the triad of necrotizing granuloma of upper and lower respiratory system, systemic vasculitis, and necrotizing glomerulonephritis. The kidneys are usually spared in the limited form of GPA. Classic GPA can sometimes begin with limited organ involvement and then convert to a more generalized form with nose, lung and kidney being affected (*20*). Patients with GPA usually present with nonspecific symptoms of generalized systemic illness including fever, malaise, weight loss, arthralgia, and myalgia (*18*) .

The earliest complaints, which are also the most common reasons for seeking medical attention, are usually related to upper respiratory tract problems including sinus pain, purulent nasal discharge, epistaxis, nasal ulceration, and serous otitis media. The presence of clinical signs such as suppurative otitis, mastoiditis, a saddle-nose defect, and hearing loss should alert the physician for GPA (*7*). It has been shown that over 90% of patients with GPA have upper respiratory tract involvement (*19*) A large number of patients present with pulmonary symptoms (cough, hemoptysis, dyspnea and less commonly, pleuritic chest pain and tracheal obstruction). Bilateral or unilateral pulmonary infiltrates are present in nearly 50% of patients initially, with lung disease eventually developing in 85-90% of patients. Pleural effusion has also been reported in 12% of cases (*21*). GPA can cause significant morbidity and mortality secondary to diffuse pulmonary hemorrhage (*22*).

Although renal involvement is clinically evident in only 11–20% of cases at presentation, glomerulonephritis eventually develops in 77–85% of patients, usually within the first two years of disease onset (*18,19*). Dermatologic involvement has been reported in about 50 % of patients with GPA with purpura involving the lower extremities being the most common finding (*19*). Less commonly, ulcers, vesicles, papules, subcutaneous nodules and lesions resembling those of pyoderma may be seen. Arthralgia and myalgia are seen in 70% of patients (*19*). Nervous system involvement is seen in about one-third of patients with peripheral neuropathies being the most common (*23*). Cranial neuropathies, external ophthalmoplegia, seizures, cerebritis and stroke syndromes are also important findings. Diabetes insipidus may occur when granulomas extend from the sinuses into the pituitary gland (*23*). Cardiac involvement is rare, with pericarditis being the most frequent complications (6%).

5. Ocular manifestations

In a survey of 701 North American patients with GPA, 30% of patients were reported to have ocular involvement (*15*). Other studies have reported similar findings, with ocular involvement in about 50% of the patients (*19,24*). Ocular disease can be the presenting or even the only clinically apparent manifestation of GPA (*25*). Straatsma classified the ocular involvement as contiguous or noncontiguous based on the presence or absence of direct extension from the adjacent involved sinuses (*26*).

Severe ocular morbidity with vision loss or total blindness may be seen in 8-37% of patients, especially if there has been a delay in diagnosis, or if the disease has been inadequately treated (*24*).

6. The orbit

The orbit is one of the most frequently involved ocular structure in GPA, and is more often secondary to extension of sinus pathology (*19,24,27*). Manifestations of orbital disease include proptosis, lid edema, diplopia, and decreased vision. Orbital pain was present in only 30% of patients in an Australian cohort (*28*). Of patients with orbital involvement, 14-30% have bilateral disease (*27*). Damage to ocular structures may result from mass compression, vascular occlusion or spread of an orbital cellulitis. Proptosis occurs in up to one-third of cases (*19*). GPA can present as an orbital mass leading to cranial nerve involvement and entrapment of extraocular muscle resulting in diplopia (*29*). Also, orbital involvement may result in blindness from a compressive ischemic optic neuropathy (*19*). In a recently published National Institutes of Health (NIH) report, a group of 158 patients with GPA were evaluated and about one-half of patients

with retro-orbital involvement lost vision (*19*). Orbital involvement has also been reported in children (*30*).

7. The eyelids

Eyelid changes in GPA may include edema, entropion, trichiasis, and xanthelasma. Woo *et al.* found that some of their patients with lid edema had an orbital mass and recommended consideration of GPA as a potential diagnosis in atypical lid edema (*28*).

8. The lacrimal system

Inflammation of the lacrimal gland (dacryoadenitis) has been reported as a presenting sign of GPA (*31*). This presents with pain and edema of the anterior orbit in the superior-temporal region with swelling of the eyelid and discomfort with eye movement. Nasolacrimal duct obstruction is a late finding and is usually associated with nasal involvement (*32*). Sicca syndrome with positive single strand A/ single strand B (SS-A/SS-B) auto-antibodies has also been reported.

9. The conjunctiva

Conjunctival involvement includes chronic inflammation, sometimes with granuloma formation or ulceration (*33*). Ulcerative conjunctivitis may result in conjunctival cicatrization. The conjunctiva serves as a useful biopsy site if a granuloma is present or as a proxy in those with scleritis or peripheral ulcerative keratitis (PUK) (*34*).

10. The episclera and sclera

Both scleritis and episcleritis have been previously reported in patients with GPA (*35*). GPA can result in nodular, diffuse, or necrotizing scleritis with tendency toward a more severe scleritis compared to other etiologies (*36*). Necrotizing scleritis can lead to significant ocular morbidity with severe vision loss and blindness if not adequately treated. Complications include globe perforation requiring enucleation (*37*). In necrotizing scleritis, an area of the inflamed sclera becomes avascular and ischemic, often secondary to occlusive vasculitis. Hoffman *et al.* (*16*) reported scleritis to be the third most common ocular manifestation of GPA following orbital and nasolacrimal involvement. Necrotizing scleritis has been reported following routine cataract surgery in patients with GPA. In some patients, it has been the presenting sign of GPA, while in others, it occurred despite being in remission (*38*).

11. The cornea

PUK is the most significant corneal complication of GPA. On histopathology, there is an immune-mediated occlusive necrotizing vasculitis of the anterior ciliary arteries. These arteries supply the anterior segment of the eye including the sclera, conjunctiva and the peripheral cornea. Concentration of this hematologic inflammatory milieu in the peripheral cornea leads to ulceration of the peripheral corneal proteoglycans and collagen. This can progress concentrically and/ or centrally and is often bilateral. Owing to the shared blood supply, PUK is often accompanied by scleritis (usually necrotizing) (*39*). It has been proposed that necrotizing scleritis with PUK may characterize systemic vasculitis (*40*). While PUK is the prototypical corneal complication in GPA, many other corneal manifestations have also been described. In some cases, the adjacent scleral inflammation leads to an exudative peripheral keratitis without ulceration. Stromal (interstitial) keratitis, is a rarely described feature of GPA (*41*).

12. The uvea

Although uncommon in isolation, intraocular inflammation has been described in patients with GPA. The uveitis associated with GPA is nonspecific, unilateral or bilateral and can be anterior, intermediate, or posterior with or without vitritis (*8,24,26*). An analysis of a large cohort of patients with anti-neutrophil cytoplasmic antibodies (ANCA) positive vasculitis found an incidence of 17.9% for uveitis: 70% anterior uveitis, 10% intermediate uveitis, and 20% posterior uveitis. The authors noted that 50% of patients with anterior uveitis had a coexisting scleritis (sclera-uveitis), suggesting that often uveitis was a secondary phenomenon (*42*). Also a granulomatous panuveitis has been described as the initial manifestation of GPA (*43*).

13. The retina and choroid

Retinal and choroidal involvement are uncommon manifestations of GPA with vessel involvement (with or without clear vasculitis) being the most common manifestation. Bilateral arterial occlusions of the retinal and choroidal circulations as well as vitreous hemorrhage have been previously reported (*8,44,45*). Bullen and colleagues identified four patients with retinal vasculitis manifesting as retinal hemorrhages and edema, cotton-wool exudates and choroidal thickening (*46*). Choroidal folds with uveal thickening and chorioretinal ischemia with infarction presenting clinically as single or multiple, white or creamy lesions at the level of the retinal pigment epithelium have also been reported (*47*). Central retinal vein occlusion has also been reported in younger people with GPA, although the mechanism remains unclear (*48*). Significant angiopathy and retinal hemorrhages could be the presenting sign of GPA (*49*). Although many chorioretinal manifestations are of vasculitic origin,

there are reports of choroidal granulomatous lesions. Inflammatory sclero-choroidal masses have simulated ocular neoplasms (*50*) .

14. Neuro-ophthalmic

In a large Australian cohort with orbital GPA, binocular diplopia occurred in half of the patients at some point during the study (*28*). Granulomatosis can cause an adjacent mass effect, or directly involve the oculomotor nerves or extraocular muscles. In addition vasculitis can interrupt the nerve's blood supply (28). In a report by Hoffman *et al.*, 50 % of their GPA patients lost vision due to compressive optic neuropathy secondary to orbital granuloma. In another study, Holle *et al.* (*27*) found that of the 25 optic nerves encircled by granulomatous tissue, only six showed signs of compressive optic neuropathy. Retro-bulbar optic neuritis due to adjacent granulomatosis has been described (*51*). Takazawa reported optic perineuritis that caused by granulomatous infiltration in two patients (*52*). Both anterior ischemic optic neuropathy (AION) and posterior ischemic optic neuropathy (PION) have been described in patients with GPA secondary to vasculitis disrupting the blood supply to the optic nerve (*31,53*).

15. Diagnosis

The diagnosis of GPA is difficult and often delayed due to the wide range of clinical presentations. Historically, the diagnosis of GPA has been made following the criteria of granulomatous involvement of upper and lower respiratory tract, glomerulonephritis and varying degrees of systemic vasculitis (*4*). In an effort to diagnose GPA, Fauci and colleagues at the NIH came up with definitive diagnostic criteria for GPA. According to these criteria, a patient should have clinical evidence of disease in at least two of three areas (upper airways, lung and kidney), and biopsy results that show disease in at least one and preferably two of these organ systems (*18*).

The American College of Rheumatology has established the following criteria for the diagnosis of GPA in order to distinguish the disease from other vasculitides: *i*) a urinary sediment containing red blood cell casts or more than five red blood cells per high-power field, *ii*) abnormal findings on the chest radiograph, *iii*) oral ulcers or nasal discharge and *iv*) granulomatous inflammation on biopsy (*22*). The presence of two or more of these four criteria was associated with an 88% sensitivity and 92% specificity.

Another diagnostic system known as the ELK (E for ears, nose and throat or upper respiratory tract; L for lung; and K for kidney) classification system proposed by DeRemee and colleagues utilizes ANCA results (*54*). According to this system, any typical manifestation in the E, L or K supported by typical histopathology or a positive cytoplasmic ANCA (c-ANCA) test qualifies for the diagnosis of GPA (*55*). ANCA has been recognized to be both sensitive and specific for GPA (*56*) and is highly associated with GPA, being present in 80-90% of patients with systemic disease. Still, there are some cases of the disease where ANCA is negative (*57*). Off all the ANCA associated with GPA, 80-95% of cases are associated with c-ANCA with autoantibodies directed against proteinase 3 antibodies (PR3) the remainder are p-ANCA directed against myeloperoxidase antibodies (MPO) (*58,59*).

In patients with limited form of the disease, ANCA is found in 50-80% of cases (*60,28,34*) . In both limited and systemic GPA cases, PR3-ANCA is more common than MPO-ANCA (*57*). Whether ANCA-negative GPA represents a detection issue or different mechanisms that do not involve ANCA is yet to be known (*25*). GPA patients with MPO-ANCA tend to have less severe disease and a more favorable course (*57*).

Despite clinical remission, elevated ANCA titers may still persist in up to 40% of patients, and ANCA titer changes with disease activity in only 64% of patients (*19,61*). A recent study suggested that the presence of MPO-ANCA may be associated with more treatment resistance, and the presence of PR3-ANCA might be a predictor of disease relapse (*62*).

Other Laboratory findings at the time of diagnosis such as leukocytosis, anemia, and thrombocytosis are generally nonspecific (*16*). Although both erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are elevated in patients with GPA, ESR correlates better with disease activity than does CRP (*19*). All immunoglobulins levels may be elevated, especially IgE (*63*).

Rheumatoid factor (RF) has been reported to be elevated in more than 50% of patients (*19*). The presence of abnormal urinary sediment, proteinuria, and abnormal creatinine clearance should raise the suspicion of glomerular involvement.

Biopsy of orbital or ocular tissue can be performed. Perry *et al*. (*64*) reviewed orbital biopsies in patients with GPA and found that common elements included changes in orbital fat (necrosis, lipid-laden macrophages and giant cells), micro abscesses, and granulomatous inflammation. Necrotizing vasculitis was uncommon (*64*). Typical findings on scleral biopsy include: granulomatous foci, polymorphous inflammation (plasma cells, lymphocytes and neutrophils), collagen necrosis and vasculitis (*34*).

Lung tissue is the most commonly biopsied site. A renal biopsy, may show a necrotizing glomerulonephritis (*60*).

Radiologic evaluation of the lungs, trachea, sinuses and orbits can be used to identify additional areas of involvement (and potential biopsy sites).

16. Etiology/pathophysiology

Although the exact etiology of GPA is unknown. It

is believed that the onset of the disease is triggered by an initial insult (infectious or environmental) in a genetically susceptible individual. Furthermore, various allergies are reported to be more common in patients with GPA (*65*). It is possible that infectious agents, such as parvovirus B19 and Staphylococcus aureus, may play a role through providing an antigenic primer especially since some relapses are associated with a preceding or concurrent infection (*66,67*). GPA has been observed in siblings and a higher frequency of certain human leukocyte antigen (HLA) markers (B2, B8, DR1, DR2 and DqW7) has been reported without a consistent relationship to the disease (*68,69*).

The granulomatous and vasculitis features of the disease appear to have separate mechanisms that are being unraveled. There are contributions from both cell-mediated and humoral arms of the immune system where granuloma formation is felt to be a cell-mediated process that could represent an early manifestation of the disease (*70,71*). The vasculitis in GPA is pauci-immune with a predilection for small vessels. Proposed mechanisms for the vasculitis include pathogenic B and T lymphocytes and possibly ANCA autoantibodies themselves which may be compounded by an increase in regulatory T cells (*71*). Presently, GPA-associated vasculitis cannot be fully explained by ANCA alone. Evidence for a direct pathogenic role of ANCA is strongest for MPO-ANCA where animal models for MPO-ANCA induced vasculitis exist in literature (*72*). Additionally, there are two case reports of human infants being born with circulating maternal MPO-ANCA antibodies who developed glomerulonephritis and alveolar hemorrhage that improved with plasma exchange (*73*). The evidence for a direct pathogenic role of PR3-ANCA is less conclusive, and the presence of PR3-ANCA itself has not been found to be pathogenic in mice models. However, the combination of PR3-ANCA and a genetic susceptibility (NOD gene mutation) does lead to vasculitis in mice (*72*). Until today, there is no single animal model that has reproduced both the vasculitic and granulomatous features of GPA (*74*). Given the different mechanisms by which MPO-ANCA and PR3-ANCA incite vasculitis, it is likely that there is more than one pathway leading to the GPA clinical phenotype (*70,72*).

17. Treatment

17.1. *Systemic Treatment*

The average life expectancy for a patient with GPA without treatment is only 5 months, with a 1-year survival rate of less than 20% (*2,17-19*). It is a common misconception that the presence of an ocular manifestation in the absence of systemic manifestations represents a quiet disease. It should be noticed that ocular manifestations, particularly necrotizing scleritis, can be an indicator for both morbidity and mortality unless appropriate systemic treatment is initiated (*37,75*).

The best treatment approach requires team collaboration between different medical specialties in order to cover the different organs involved by the disease. Because of the importance of systemic therapy, a brief overview of current regimens will be discussed. Historical systemic treatment included a variety of modalities such as antibiotics, chelating agents and local irradiation (*17,76*). None of these modalities were successful. Corticosteroid treatment was also tried and it has been shown that corticosteroid alone doubled the life expectancy to about 12 months with a 1-year survival of 34% (*77*). Adding cyclophosphamide to corticosteroid therapy altered the prognosis of the disease and resulted in remission and extension of the survival rate (*33*). Once remission has been achieved, it is recommended that cyclophosphamide treatment to be continued for at least another year before tapering the medication. Both oral and intravenous cyclophosphamide, in combination with corticosteroids, have been used successfully with equal effectiveness (*61,78,79*). Because of the significant toxicity associated with cyclophosphamide therapy, alternative maintenance therapies have been used. Azathioprine has shown some success, but it is less effective than cyclophosphamide and should only be considered in patients experiencing adverse side effects or when fertility concerns arise (*80*). Methotrexate has been used in patients with limited GPA, though it is less likely to achieve and sustain remission (*81,82*). Recently, trials confirmed that B cell depletion with rituximab were comparable to cyclophosphamide as part of induction therapy for active ANCA-associated vasculitis and with possibly superior performance in relapsing disease (*83,84*). Rituximab is a monoclonal antibody that targets the CD20 antigen on B cells and clears circulating B cells from the circulation, without affecting plasma cells which may be important in disease relapse (*84,85*). Neutropenia may develop, for which the patient should be monitored. Studies on the long-term effectiveness of rituximab are still in progress. The rituximab in ANCA-Associated Vasculitis (RAVE study) (*83*), a double-blind, randomized, multicenter trial, showed that rituximab is a non-inferior alternative to cyclophosphamide for induction. Following this, Holle *et al*. (*86*) reported that rituximab was effective for vasculitic manifestations refractory to cyclophosphamide but was less effective for granulomatous manifestations. There are case reports of success treatment with infliximab as an adjuvant therapy to cyclophosphamide and methotrexate in the treatment of two adults with necrotizing scleritis and one child with non-necrotizing scleritis (*87,88*).

Other therapies demonstrating some efficacy for induction and/or maintenance of remission have included mycophenolate mofetil, plasmaphereses, cyclosporine, intravenous immunoglobulin (IVIG), and protein A immunoadsorption (*89*). Trimethoprim-

sulfamethoxazole has been reported to be beneficial in patients with the limited form of GPA, where there is no renal involvement (*90*).

Given the success of rituximab in GPA, other B lymphocyte targeting medications are being under investigations. There is currently a clinical trial underway to determine if a monoclonal antibody against B Cell Activating Factor can prevent relapse (*91*). Therapies to modulate the memory T cell (Th17) pathway are in development, though no studies specific to GPA are yet in progress (*91*). Given the presumed role of T lymphocytes in granuloma formation, it remains hopeful that therapies directed against T lymphocytes may benefit patients with refractory orbital granulomatous inflammation (*74*). An inhibitor to the activated complement molecule c5a is being studied as an induction agent in patients with GPA (*81,91*).

17.2. *Local treatment (medical/surgical)*

Local corticosteroid therapy can be used for the treatment of some non-vision threatening ocular manifestation of GPA such as conjunctivitis and episcleritis, with careful monitoring of severe ocular complications that might appear during the course of the disease. These complications such as scleritis, PUK, uveitis and retinal and optic nerve vasculitis usually fail to respond to local therapy alone and require the use of systemic immunosuppressive therapy as soon as possible (*92*). Of note, orbital granulomas are more prone to relapse and many authors have found that these granulomas may only be partially responsive to cyclophosphamide or rituximab (*86,93*). Of the 40 patients with orbital granulomas reported by Holle *et al.*, 41% of cases were refractory to cyclophosphamide induction (*27*). Despite intensive immunosuppression, 72% developed some form of visual impairment and 19% suffered blindness secondary to optic nerve compression. Surgery is of limited benefit and is reserved for grave situations. Orbital decompression with de-bulking of the granuloma can be done in cases of compressive optic neuropathy. In cases of severe pain and complete blindness, retro-bulbar alcohol injection or enucleation can be used as palliative measures (*27,94*). In cases of nasolacrimal duct obstruction, surgical creation of a new outflow (dacryocystorhinostomy) is required to bypass obstruction and relieve epiphoria for resolution of these symptoms, though it is not without risk. Postoperative wound necrosis and naso-cutaneous fistula have been reported (*95*). The rate of adverse events is improved with preoperative and postoperative control of the underlying disease (*28,96*).

Necrotizing scleritis and PUK can progress with resultant globe perforation. At this point, conjunctival resection, Tectonic scleral grafting, and cyanoacrylate glue are all used as temporizing measures while the systemic disease is brought under control (*39*). Even after remission is achieved, patients with corneal or scleral thinning can perforate with minor trauma and the use of polycarbonate safety glasses are highly recommended.

Cataract and glaucoma are common in patients with GPA and are secondary to the chronic inflammation and corticosteroid treatment rather than the GPA itself. It is recommended that no surgery should be done during active disease, and even when the patient is in remission, the patient needs to be monitored closely during the post-operative period.

18. Prognosis

Although the prognosis of GPA has dramatically improved with the introduction of immunotherapy, there is still significant morbidity from the disease itself (86%) or side effects from the therapy (42%) (*19*). It has been shown that the presence of prior relapses is a predictor of future relapses (*72*).

The visual prognosis depends on severity and chronicity of the eye disease and, in general, is good when treated appropriately with systemic immunotherapy. Vision loss or total blindness may be seen in 8-37% of patients, especially if the disease has been long-standing or inadequately treated, or when there has been a delay in diagnosis (*19,24*).

Major causes of vision loss in the setting of GPA are compressive optic neuropathy, retinal and optic nerve vasculitis, and globe perforation from necrotizing scleritis and peripheral ulcerative keratitis. Holle *et al.* (*27*) showed that the risk of blindness is higher with longer time to remission, higher number of relapses or the presence of refractory disease. In general, the prognosis for limited GPA is better than for the complete form. Despite systemic immunotherapy, patients with severe renal disease have a guarded prognosis with higher mortality rate (*97*).

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