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Ophthalmic Manifestations in Granulomatosis with Polyangiitis: A Narrative Review

Jasreen Kaur Sandhu*[,1], Gurkaranvir Singh[1], Simrat Kaur Batth[2], Navjot Kaur[1]

Abstract

Granulomatosis with polyangiitis (GPA), a type of vasculitis, is characterized by necrotizing inflammation of small-medium blood vessels and is associated with anti-neutrophil cytoplasmic antibodies (ANCA). While GPA commonly affects the upper respiratory tract, lungs, and kidneys, ocular manifestations can also occur as a part of systemic GPA or isolated GPA involving eyes, the diagnosis of which can be challenging. Ocular involvement in GPA is variable and can present as scleritis, keratitis, conjunctivitis, uveitis, or orbital involvement. This review article briefly explores the etiology of GPA with a focus on the ophthalmic manifestations of GPA, including their clinical features, diagnosis, differentials, and treatment options. Understanding the ocular manifestations can help in early diagnosis, preventing irreversible eye damage and vision loss.

Conclusion: The small blood vessels in almost any organ or tissue can be involved in GPA, the involvement of the eye being one such organ which can present with non-specific signs and symptoms in both generalized and isolated forms. Knowledge of the ocular manifestations of GPA can help catch the disease in its initial stage and prevent irreversible eye damage. Despite being recognized in over half of patients with GPA, ophthalmic signs go misdiagnosed in most patients. The most efficacious strategy for preventing disease mortality and morbidity is having a high level of clinical suspicion, early diagnosis, and commencing immunosuppressive medication early in the disease course.

Keywords: Granulomatosis with polyangiitis (GPA), vasculitis, necrotizing inflammation, small-medium blood vessels, anti-neutrophil cytoplasmic antibodies (ANCA),proteinase 3-anti neutrophil cytoplasmic antibody (PR3 ANCA),antinuclear antibody (ANA), ocular manifestations, clinical features, diagnosis, treatment options, etiology, medications

Introduction

Granulomatosis with polyangiitis (GPA) also known as Wegner's Granulomatosis, is necrotizing Vasculitis involving small-medium blood vessels. It is classified under anti-neutrophil-cytoplasmic-antibody (ANCA) associated vasculitis (AAV). AAV also includes two other pathologies namely microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA or Churg Strauss syndrome) [1]. The clinical presentation of GPA is highly variable. Although GPA classically involves the upper respiratory tract, lungs or kidney [2]; the presentation can be localized or generalized. This variation can lead to a delay in diagnosis and treatment. Studies have reported a range of percentages for ophthalmic manifestations of GPA, from as low as 13% to as high as 50%. However, only 6-18% of

Affiliation:

[1]MBBS, Government Medical College, Amritsar, Punjab, India

[2]Internal Medicine, ICAHN School of Medicine at Mount Sinai/Elmhurst Hospital Center, Queens, New York

***Corresponding author:**
Jasreen Kaur Sandhu, MBBS, Government Medical College, Amritsar, Punjab, India

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GPA presents with ocular manifestation as the first sign [3]. Rarely, it can be the only presenting clinical feature. [4]. These features include (in descending order of frequency) - scleritis (with or without episcleritis or conjunctivitis), retro-orbital pseudotumor and orbital mass, peripheral ulcerative keratitis, compressive neuropathy, retinal vasculitis, and uveal prolapse [3]. The ocular presentation of GPA needs to be differentiated from other common disorders affecting the eye, because the presenting features can be quite similar. Therefore, exclusion can be the only way to diagnose in some cases. This review article discusses in detail the ophthalmic manifestations of GPA and identifies any gaps in existing literature.

Pathoetiology

Although the exact etiology of GPA is not known [4], raised Anti - neutrophilic cytoplasmic antibody (ANCA) has been hypothesized to play the predominant role [5]. The etiology leading to raised ANCA levels, has been suggested to be a combination of factors, including genetics, epigenetics modifications, environmental factors and even some drugs have been found to be causative. PR3 (proteinase 3) - ANCA and MPO (myeloperoxidase) - ANCA are two major serotypes, with the former being more commonly associated with GPA. Serine protease inhibitor 1 (SERPINA 1) gene has been implicated in the pathogenesis of GPA. It encodes for alpha 1 antitrypsin, a serine protease inhibitor which inhibits the expression of PR3 on neutrophils. The null gene SERPINA 1 leads to a decrease in the levels of α1 antitrypsin, and in turn an increase in the expression of PR3. The increased expression leads to an autoimmune response against the neutrophils. Other genes implicated include Proteinase (PRTN) which also encodes for PR3. MHC HLA DP4 (Major Histocompatibility Complex) has been positively associated with increased incidence of GPA. [5-7] Other suspected mutations include CTLA4 (Cytotoxic T lymphocyte associated protein 4) and Fc receptor IIIb [1].

Epigenetic modulation, specifically DNA methylation, holds a pivotal role in orchestrating gene expression, notably within the PRTN3 promoter region. Decreased methylation fuels heightened gene expression, amplifying autoantigens and intensifying autoimmune responses. Notably, reduced methylation during remission poses a greater risk of relapse, whereas heightened methylation post-remission correlates with extended relapse-free periods [8]. Environmental factors, such as seasonal variation, present a debated risk context, with inconclusive study outcomes linking GPA to both winter and summer. Likewise, the potential impact of air pollution, silicon dioxide, vitamin D deficiency, staphylococcus aureus infection, and EBV (Ebstein Barr virus) infection remains uncertain. Medications including hydralazine, phenytoin, antithyroid drugs, sulfasalazine, and allopurinol have also been implicated [9]. Histologically, GPA's autoimmune progression culminates in the formation of neutrophilic microabscesses that evolve into granulomas, subsequently occluding blood vessels and instigating clinical manifestations. The distinctive granulomas in GPA, characterized by ill-defined boundaries, encompass a spectrum of cell types such as giant cells, plasma cells, dendritic cells, and lymphocytes [1]. Diagnosis of GPA hinges on PR3 ANCA detection through immunofluorescence, alongside monitoring serological ANCA levels. Histopathology assists in granuloma identification, with additional diagnostic criteria dependent on the affected organ system. The American College of Rheumatology's diagnostic criteria include parameters like urinary sediment anomalies, chest radiograph abnormalities, oral ulcers or nasal discharge, and granulomatous inflammation on biopsy. Moreover, the ELK criteria incorporate manifestations in the ears, nose, throat, lung, or kidney alongside ANCA positivity to confirm diagnosis [1, 10].

Clinical Features

The clinical presentation for GPA is very varied. It can be limited or generalized. Some of the common system-wise clinical features are:

General - Fever, malaise, weight loss, anorexia [11]

Renal - Crescentic GN, Rapidly progressive glomerulonephritis (RPGN), Pauci-immune glomerulonephritis.

Pulmonary- cough, hemoptysis, dyspnea, pulmonary infiltrates, pulmonary nodules, pleural effusion, pulmonary hemorrhage, subglottic stenosis, bronchial stenosis [1]

ENT- nasal and sinus pain, sinus stuffiness, purulent nasal discharge, nasal ulcerations, epistaxis, and otitis media, mastoiditis, conductive and sensorineural hearing loss [1]

Nervous system- mononeuritis multiplex, Cranial neuropathies, pachymeningitis, seizures, and cerebritis

Cardiac- valvular insufficiency, pericarditis, coronary arteritis

Musculoskeletal- myalgia, arthralgia [1]

Cutaneous - leukocytoclastic vasculitis, purpura, skin infarcts, ulcers, and gangrene [12]

Ophthalmic manifestations and management

Eye manifestations are common and occur in 28–58 percent of cases of generalized GPA [13]. However, rarely in some cases of limited form of disease ocular manifestations may be the only clue to diagnosis [14]. GPA can involve any part of the eyeball, in a range of severity [15]. In some patients it can lead to irreversible damage to the eyes, blindness and even enucleation [13]. Some of the manifestations include scleritis, keratitis, conjunctivitis, uveitis, orbital involvement.

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Table 1: Ocular Manifestations and Management in GPA

Ocular Manifestations	Description	Management
Orbital Inflammation	Swelling, redness, pain around the eyes [19,20]	Systemic corticosteroids (prednisone) with tapering regimen, immunosuppressants such as cyclophosphamide or rituximab as adjunctive therapy [19-21]
Proptosis	Bulging of the eyes	Immunosuppressive therapy, including cyclophosphamide or rituximab; surgical decompression may be considered in refractory cases [20]
Conjunctivitis	Inflammation of the conjunctiva	Topical antibiotics for secondary infection, corticosteroid eye drops to control inflammation [25-26]
Episcleritis	Inflammation of the outermost layer of the eye	Non-steroidal anti-inflammatory drugs (NSAIDs), artificial tears for symptomatic relief [30]
Scleritis	Inflammation of the sclera	Systemic corticosteroids, immunosuppressants like methotrexate or azathioprine [20-21]
Uveitis	Inflammation of the uvea (middle layer of the eye)	High-dose systemic corticosteroids, immunosuppressive agents (cyclophosphamide, azathioprine, methotrexate), biologics (rituximab) [36-37]
Keratitis	Corneal inflammation, leading to pain and blurry vision	Topical corticosteroid eye drops, preservative-free lubricants, bandage contact lenses for corneal protection [15-22]
Sclerokeratitis	Combined inflammation of the sclera and cornea	Systemic corticosteroids in combination with immunosuppressants, tailored to disease severity [21-22]
Optic Nerve Involvement	Can lead to vision loss, eye pain	High-dose intravenous corticosteroids (methylprednisolone), followed by oral corticosteroids; immunosuppressants like cyclophosphamide [46-48]
Orbital Masses	Granulomas or masses in the eye area	Surgical resection for localized lesions, systemic immunosuppressants to prevent recurrence
Periorbital Necrotizing	Tissue death around the eye, urgent treatment required	High-dose intravenous corticosteroids, followed by systemic corticosteroids, plasmapheresis in severe cases [49-51]

Scleritis

Scleritis is a painful inflammatory illness that affects the scleral, episcleral tissue and is characterized by edema and cellular infiltration. [16] Scleritis is the third most common ophthalmic manifestation in GPA behind only ocular pseudotumor and episcleritis. [15] In GPA scleritis is mostly necrotizing and vision threatening, in contrast to scleritis in other autoimmune disorders like rheumatoid arthritis, where the course is benign and insidious [17]. The exact mechanism behind scleritis is not known, but it is thought that the collagen in sclera is targeted by autoantibodies [18]. Scleritis following ocular surgery is also seen in patients with GPA [15]. The clinical features include pain (can be localized or radiating to surrounding regions), nodules (firm, tender, immobile), bluish hue, scleral oedema and congestion in anterior scleritis. In the case of posterior scleritis there may be loss of vision, chorio-retinal detachment. As the disease progresses there may be corneal thinning, leading to staphyloma formation [18, 15]. Episcleritis may or may not be associated with scleritis. It runs a minor and limited course with often quite similar presentation to Scleritis. The eye redness in episcleritis blanches on topical phenylephrine administration, and no such change is seen in Scleritis. The Scleritis associated with GPA also must be differentiated from other infectious causes of scleritis. ANCA serology is the mainstay for diagnosis. Imaging tests that can be done include Optical coherence Tomography for anterior sclera, and B scan ultrasound for posterior scleritis, First line treatment involves topical corticosteroids and non-steroidal anti-inflammatory drugs. If there is no improvement, then the route of corticosteroid administration can be changed to oral or sub conjunctival [18]. Immunosuppressive agents like methotrexate can also be used. [19] Rituximab and Infliximab are emerging and promising treatments for scleritis [20-21].

Keratitis

Keratitis is inflammation of the cornea, particularly the juxta limbal section of the cornea. The central cornea is avascular, while the periphery of cornea receives blood supply from limbal vessels, thus leading to an inflammatory response in this region. It is associated with epithelial dysfunction and stromal lysis [22]. In GPA it is caused by necrotizing vasculitis of limbus arteries and anterior choroidal arteries [15]. Can present as an isolated entity, or along with involvement of nearby structures of the eye. If associated with scleritis then the prognosis is poor. The clinical features include pain, photophobia, watering and red infusion of the eye. The progression of disease can lead to corneal stromal thinning and subsequently perforation, which can be vision threatening [22-15]. The chronic form of the disease can lead to ulceration, scarring, astigmatism, and reduced vision. There is no specific diagnostic test, the only means to a diagnosis is

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finding the underlying GPA, and exclusion of other causes of keratitis. Treatment only with topical corticosteroids is not very effective, unless followed up with systemic immunosuppressive therapy. A combination therapy of oral or intravenous cyclophosphamide (2 mg/kg/day) along with prednisone (1 mg/kg/day) has been found to be effective [23]. Rituximab can be used in case the keratitis is refractory to previous treatment. Amniotic membrane transplant has been found effective in case eyeball reconstruction is needed, in the advanced course of the disease [24]. The differentials for this condition include infectious keratitis (HSV most commonly), exposure keratitis (Bell's palsy), trichiasis, and eyelid anomalies [22].

Conjunctivitis

Conjunctivitis is an inflammation or infection of the conjunctiva, a translucent mucous membrane covering the anterior part of sclera and interior of eyelids. Clinical features include irritation, itching, foreign body sensation, redness, watering or discharge [25-26]. Conjunctiva is located close to lymph nodes and vascular structures, therefore is most active immunologically among external layers of the eye. This makes it more susceptible to antibodies (including ANCA) and inflammatory processes. A link between ANCA and severe/recurrent cases of conjunctivitis has been established [27]. Conjunctivitis commonly has a self-limited course, in case of prolonged course, investigations should be done for an underlying systemic disease [25-26]. In GPA early diagnosis and treatment of conjunctivitis is essential, otherwise this trivial condition could be vision threatening. Conjunctivitis in GPA can present as ulcerative, necrotic and can progress on to be cicatricial conjunctivitis [25-15]. In daily practice conjunctivitis is diagnosed based on clinical features and slit lamp examination. No other routine investigations are done. However, in case of prolonged or severe form of disease it is recommended to undertake scrapings for diagnosis. These samples are undertaken for histopathology(granulomas)and immunofluorescence (ANCA) [28, 29, 26] Prolonged conjunctivitis can involve the cornea leading to corneal perforation. Also, it can be involved along with the disease of surrounding structures like scleritis and keratitis. Cicatrization, symblepharon, trichinosis can also occur. In rare cases it is associated with naso lacrimal duct obstruction and subglottic stenosis. [15]. Treatment primarily involves symptomatic relief using topical steroids, lubricant medication, autologous serum [29]. In case of progressing disease- systemic immunosuppression is done to halt progression. If vision is compromised due to complications- glasses, contact lens, keratic prosthesis can be used [29]. External dacryorhinocystostomy has been found successful in treating overflow symptoms linked to conjunctivitis [30]. Differential diagnosis includes infective conjunctivitis, allergic conjunctivitis, glaucoma, uveitis, trauma, subconjunctival hemorrhage, scleritis, keratitis, corneal ulcer, contact lens, dry eye.

Orbit

Orbit is involved in 45% of ocular manifestations of GPA. In some cases, orbital pseudotumor and upper respiratory tract involvement/glomerulonephritis may be the only clue to diagnosis of GPA. There can be formation of inflammatory pseudotumors. The mass of this tumor can lead to proptosis, diplopia, pain, optic nerve compression. Proptosis can in turn lead to further complications in the form of exposure keratopathy, corneal ulceration [31, 32, 15]. Lid involvement can lead to lid edema, erythema, or its destruction. Nasolacrimal duct can also undergo obstruction or develop mucocele, these manifest clinically as epiphora. Other manifestations include involvement of extraocular muscles, and invasion of surrounding bony (including nose, sinuses) and cartilaginous structures [31, 32, 15]. Though orbital involvement commonly is self-limited, its evolution can be extremely severe prompting enucleation of the eyeball [31, 32]. Proptosis in prolonged cases can develop into enophthalmos due to fibrotic changes [31]. Pseudotumor, proptosis and invasion of surrounding structures can be visualized using CT scan and MRI [33]. Treatment involves two parts, firstly induction of remission and then maintenance. Induction involves use of high dose systemic corticosteroid with cyclophosphamide or Rituximab. Cyclophosphamide is discontinued after induction of remission [32, 31]. Remission involves use of immunological modulators like methotrexate, azathioprine, biologicals, besides the one already used in induction. Along with tapering of the steroids administered [32-31]. An emerging treatment therapy involves only the use of a combination of Rituximab and Infliximab, excluding steroids in the treatment altogether [34]. Surgery can be done to debulk the inflammatory mass, when there is proptosis, optic nerve compression, pain refractory to treatment. Surgery is the last treatment option in orbital involvement in GPA, due to the fear of the disease flaring up [35]. Differentials include thyroid eye disease, orbital lymphoma, metastasis, idiopathic inflammatory pseudotumor, sarcoidosis [33].

Uveitis

Uveitis is inflammation involving the iris, ciliary body, choroid and retina. Anatomical distinction divides it into anterior (iris, pars plicata) intermediate (pars plans) posterior (choroid, retina) and pan uveitis (all of the eye) [36].

Clinical features of uveitis include keratic precipitates, pupillary changes, synechia, redness, pain, blurring of vision, photophobia, and floaters. In intermediate uveitis exudates get organized in the form of “snowballs”. In the case of posterior uveitis there may be no pain or redness [36]. Uveitis in GPA is grouped under autoimmune uveitis. Other autoimmune disorders associated with uveitis include rheumatoid arthritis

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and SLE [37]. Uveitis is reported in 10% of GPA patients. It may be associated with scleritis, keratitis, this association worsens the prognosis of uveitis [15].

There is no direct evidence of autoimmunity, but a link has been established indirectly. This was done by eliciting autoimmune response in animal models. Role of infection producing autoimmune response has also been hypothesized. Retinal antigens have also been implicated in some studies [37]. Complications include retinal detachment, glaucoma, cataract, loss of vision Diagnosis of uveitis is primarily based on clinical features. Confirmation of underlying cause depends on laboratory tests. Treatment involves symptomatic relief measures including dark goggles and NSAIDS. Topical steroids are not useful in controlling disease. Oral prednisolone 20mg/day was quite effective in stopping the inflammatory process, even in preventing relapse [38]. Visual outcome is favorable with use of immunosuppression [37]. Differentials include neovascular glaucoma, conjunctivitis, scleritis, keratitis, foreign body/trauma and other causes of uveitis- infections, trauma, post-surgical, autoimmune (MS, sarcoidosis, Behçet's, rheumatoid arthritis)

Retina and choroid

Retinal and choroidal manifestations in GPA have been reported but are quite rare. [39] The degree of retinal involvement can vary from benign cotton wool spots to venous or arterial occlusion. Retinal manifestations carry poor prognosis for visual acuity [40]. There are several reports on ocular vascular occlusions including CRAO (Central Retinal Artery Occlusion) [40, 41], primarily caused by Vasculitis [40]. Chorioretinitis, a condition simultaneously affecting choroid and retina, has also been reported. It is hypothesized that the primary lesion of GPA involves the proximal part of ophthalmic circulation thus affecting both retinal and choroidal circulation [41]. Histopathology of the choroid has revealed multiple foci of granulomatous inflammation containing epithelioid cells, lymphocytes and multinucleated giant cells. Other findings included infiltration of choriocapillaris by inflammatory cells and blockage by inflammatory debris [42]. At the onset the disease starts at the level of arterioles, venules, and capillaries. It gradually progresses to involve small and medium sized vessels, and ultimately occludes the main artery [43].

Visual symptoms are the clinical indicator of vessel occlusion [41]. These include loss of vision, loss of night vision, pupillary defects. Besides vessel occlusion other manifestations/complications include retinitis, chorioretinitis, macular edema, exudative retinal detachment, retinal necrosis, neo-vascularization, vitreous hemorrhage, phthisis, optic atrophy, optic neuropathy [15]. Clinical examination using fundoscopy is the first step in diagnosis. Indocyanine green angiography helps in exploring the inflammation of choroidal vessels [44] OCT (Ocular Coherence Tomoangiography) allowed us to detect choroidal lesions which are not visible on clinical examination [42]. OCT shows hyperreflectivity of retinal layers [45]. FFA (Fundus Fluorescence Angiography) is the gold standard for the diagnosis of posterior segment inflammation [42]. FFA shows hypo fluorescence, accompanied by leakage of dye in advanced stages [45]. For the treatment of CRAO due to GPA associated vasculitis, steroid therapy for the underlying disease is the preferred treatment. Improvement in visual acuity has been reported post steroid therapy [43] and central serous retinopathy by high dose steroid treatment [39] Choroidal granulomas occur in tuberculosis or sarcoidosis as well, hence, are important differentials [42].

Neuro-ophthalmic manifestations

Three mechanisms of optic nerve damage have been hypothesized in the involvement of optic nerve in GPA

1. vasculitis infarction of vasa nervosum

2. non-vasculitic optic nerve inflammation

3. spread of inflammation from the adjacent sinuses [46]

It can also lead to palsies of oculomotor, abducens and trochlear nerve. Horner's syndrome has been reported in rare cases [15]. Recurrences with further spread of the process may lead to irreversible optic nerve damage and its extension to the superior orbital fissure will eventually lead to full-blown orbital apex syndrome [46] Clinical features include diplopia, reduced visual acuity or sudden visual loss, an afferent pupillary defect, and visual field loss. Complications include permanent loss of vision. For diagnosis_visual acuity and visual field testing must be done. MRI orbit helps to look for change in the optic nerve and surrounding structures, but often in the early stages there may be no detectable changes leading to a diagnostic delay and poor prognosis [46]. Diagnostic sensitivity of nerve biopsy for vasculitis neuropathy is 50–60%. To increase the diagnostic sensitivity, muscle or skin tissues can be simultaneously obtained from the site of the nerve biopsy [47]. The unusual presentation, clinically (no general disease activity of GPA, often associated with apex syndrome) and radiologically, with difficulties to visualize the pathological site (orbital apex) on the initial images [46]. Treatment involves induction and maintenance with steroids and immunomodulators. In refractory or recurrent cases induction with Rituximab and maintenance therapy with azathioprine and low-dose corticosteroids can be done [48]. Decompression surgery may be required in case of the spread of disease from adjoining areas.

Eyelids and lacrimal apparatus

Eyelid involvement can occur in the form of "yellow lid sign" resembling a florid xanthelasma [49]. It can also

present as a mass which can be diagnosed with biopsy, and has shown promising treatment to radiotherapy [50]. Differentials for xanthelasma are high cholesterol and chronic alcoholism. Lacrimal apparatus can be involved in the form of dacryoadenitis, Nasolacrimal duct (NLD) blockage. Dacryoadenitis is characterized by pain, epiphora, edema in orbit, impaired eyeball mobility. NLD blockage can be secondary to the spread of disease from adjacent areas or because of the primary focus of GPA. The main presenting feature is epiphora [15]. It can also lead to ocular sicca syndrome in some cases. Diagnosis of dacryoadenitis is based on serology (for GPA), biopsy, imaging studies (CT, MRI) to look for lacrimal gland enlargement. Primary treatment is steroids [51]. External dacryorhinocystostomy has been found successful in treatment of recurrent dacryoadenitis, and NLD obstruction. There were no reports of recurrent symptoms [30]. Differentials include_benign or malignant neoplasms of lacrimal gland, thyroid eye disease, pre septal cellulitis, and orbital cellulitis [51].

Prognosis

Despite significant advances in prognosis achieved through the introduction of immunotherapeutic interventions in the realm of Granulomatosis with Polyangiitis (GPA), a substantial burden of morbidity persists stemming from intrinsic disease pathology (86%), as well as consequential treatment-associated adversities (42%)," [52]. Empirical data has revealed the predictive significance of previous relapses in foreshadowing future relapse occurrences [53]. The prognosis of ocular outcomes is dependent on the severity and duration of ocular involvement, and generally shows favorable trends when treated with systemic immunomodulatory treatments. The prospect of visual loss or full ocular impairment has been observed in 8-37% of affected persons, particularly when the disease takes a chronic course, generates inadequate treatment responses, or encounters diagnostic delay [54].

Conclusion

The limited ophthalmic manifestations of GPA and its clinical presentation being hard to distinguish from common eye disorders has implications for ophthalmologists, and rheumatologists. Often ophthalmologists may be the one to pick up on this disorder, if an extensive workup is done. It has been established that it is rare for eye manifestations to show up first and be the only manifestation. According to a review of the literature, proteinase 3-anti neutrophil cytoplasmic antibody (PR3 ANCA) is an independent risk factor for ocular involvement, whereas antinuclear antibody (ANA) is associated with optic nerve involvement. Early diagnosis and treatment can not only be vision saving but also lifesaving. There exists a significant gap between the prevalence of ophthalmic manifestations of granulomatosis with polyangiitis and the frequency of its early detection and treatment. There needs to be better coordination of care and interdisciplinary cooperation to decrease the morbidity and mortality associated with GPA.

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