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Review Article

Eye a Window to Granulomatosis with Polyangiitis: A Review

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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, ranging from 28% to 58% of cases. Ocular involvement in GPA can present as scleritis, keratitis, conjunctivitis, uveitis, or orbital involvement. Prompt diagnosis is crucial as ocular manifestations can lead to irreversible damage and vision loss. This review article discusses the ophthalmic manifestations of GPA, including their clinical features, diagnosis, and treatment options. Additionally, it explores the etiology of GPA, including genetic and epigenetic factors, environmental risk factors, and medications associated with the disease. The article aims to provide a comprehensive understanding of ocular manifestations in GPA and identify gaps in the existing literature for further research.

Methodology: PubMed was used and source of information, and articles pertaining to ("GPA"AND"Ophthalmological manifestations"), ("GPA"AND"Ophthalmic manifestations"), ("GPA"AND"Eye") were found. Initially only latest publications were considered (up to 5 years old), but if all information was not available then previous publications were also taken.

Keywords: Granulomatosis with Polyangiitis (GPA); Vasculitis; Necrotizing inflammation; Small-medium blood vessels; Anti-Neutrophil Cytoplasmic Antibodies (ANCA); 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 [1]. 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).

The clinical presentation of GPA is highly variable. Although GPA classically involves the upper respiratory tract, lungs or kidney; 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 GPA presents ocular manifestation as the first sign. Rarely, it can be the only presenting clinical feature. These features include (in a 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.

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 [2].

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LITERATURE REVIEW

This review article discusses in detail the ophthalmic manifestations of GPA and identifies any gaps in existing literature.

Etiology

Although, the exact etiology of GPA is not known, raised ANCA (Anti-Neutrophilic Cytoplasmic Antibody) has been hypothesized to play the predominant role. 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 [3]. PR3-ANCA and MPO-ANCA are two major serotypes, with the former being more commonly associated with GPA.

Genetics: *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 PRTN which also encodes for PR3. MHC HLA DP4 has been positively associated with increased incidence of GPA. Other suspected mutations include CTLA4 and Fc receptor IIIb [4].

Epigenetics: DNA Methylation is known to modify gene expression in the region of PRTN3 promoter. Hypomethylation leads to an increased expression of the gene, increased autoantigens and increased autoimmune response. DNA Hypomethylation is also associated with a greater chance of relapse in patients who were in remission. Whereas increase in methylation after remission is associated with more chance of a relapse free period.

Environmental risk factors: Seasonal variation has been a hypothesized risk factor, with different studies showing different results. Studies have shown a positive link between GPA and winter season, also with summer, while some studies have been inconclusive to show any link between GPA and seasons [5]. Other proposed risk factors include air pollution, silicon dioxide, low vitamin D levels, infection with staphylococcus aureus, EBV. Again, contrasting results are there for the association of these risk factors with GPA.

Drugs: Hydralazine, phenytoin, antithyroid medications, sulfasalazine, and allopurinol have been implicated.

Pathogenesis

Increased expression of PR3 on the surface of neutrophils is the main culprit behind the autoimmune reaction. The etiological factors discussed above act to increase PR3 expression. TNF α and C5a are also known to increase PR3 expression [6]. Besides this the expression is also increased by cell death, apoptosis, and NETs.

Histology

The autoimmune process leads to formation of neutrophilic microabsecess, which ultimately turn into granulomas. These granulomas occlude blood vessels leading to the manifestations of the disease. The granulomas in GPA have ill-defined boundaries, and consist of giant cells, plasma cells, dendritic cells, lymphocytes.

Diagnosis

It is based on detection of PR3 ANCA, using immunofluorescence. Serological ANCA levels can also be used for therapeutic monitoring. Histopathology is also used to look for granulomas. The rest of the tests for diagnosis are based on the organ system involved [7].

Diagnostic criteria

- The American College of Rheumatology criteria include a) Urinary sediment showing red blood cell casts or more than five red blood cells per high power field, b) Abnormal findings on chest radiograph, c) Oral ulcer or nasal discharge, and d) Granulomatous inflammation on biopsy. The presence of two or more of the above-mentioned criteria is diagnostic.
- The ELK (E stands for ears, nose, and throat or upper respiratory tract, L for lung, and K for kidney). Any one of these manifestations along with ANCA positivity is diagnostic.

Clinical features

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

General: Fever, malaise, weight loss, anorexia.

Pulmonary: Cough, hemoptysis, dyspnea, pulmonary infiltrates, pulmonary nodules, pleural effusion, pulmonary hemorrhage, subglottic stenosis, bronchial stenosis.

ENT: Nasal and sinus pain, sinus stuffiness, purulent nasal discharge, nasal ulcerations, epistaxis, and otitis media, mastoiditis, conductive and sensorineural hearing loss.

Nervous system: Mononeuritis multiplex, cranial neuropathies, pachymeningitis, seizures, and cerebritis.

Cardiac: Valvular insufficiency, pericarditis, coronary arteritis Musculoskeletal-myalgia, arthralgia.

Cutaneous: Leukocytoclastic vasculitis, purpura, skin infarcts, ulcers, and gangrene.

Opthalmic manifestations

Eye manifestations are common and occur in 28–58 percent of cases of generalized GPA. However, rarely in some cases of limited form of disease ocular manifestations may be the only clue to diagnosis [8].

GPA can involve any part of the eyeball, in a range of severity. In some patients it can lead to irreversible damage to the eyes, blindness and even enucleation. Some of the manifestations

include scleritis, keratitis, conjunctivitis, uveitis, orbital involvement.

Scleritis

Scleritis is a painful inflammatory illness that affects the scleral, episcleral tissue and is characterized by edema and cellular infiltration. Scleritis is the third most common ophthalmic manifestation in GPA. 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. The exact mechanism behind scleritis is not known, but it is thought that the collagen in sclera is targeted by autoantibodies. Scleritis following ocular surgery is also seen in patients with GPA.

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 sclerites there may be loss of vision, chorio-retinal detachment. As the disease progresses there may be corneal thinning, leading to staphyloma formation. 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. Immunosuppressive agents like methotrexate can also be used. Rituximab and Infliximab are emerging and promising treatments for scleritis [9].

Keratitis

Keratitis is inflammation of 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. In GPA it is caused by necrotizing vasculitis of limbus arteries and anterior choroidal arteries.

Can present as an isolated entity, or along with involvement of nearby structures of eye. If associated with scleritis then the prognosis is poor. The clinical features include pain, photophobia, watering and red infusion of eye. The progression of disease can lead to corneal stromal thinning and subsequently perforation, which can be vision threatening [10].

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 finding the underlying GPA, and exclusion of other causes of keratitis.

Treatment only with topical corticosteroids is not very effective, unless followed up with systematic 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. 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 advanced course of the disease.

The differentials for this condition include infectious keratitis (HSV most commonly), exposure keratitis (Bell's palsy), Trichiasis, and eyelid anomalies.

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 [11].

Conjunctiva is located close to lymph node and vascular structures, therefore is most active immunologically among external layers of 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. Conjunctivitis commonly has a self-limited course; in case of prolonged course investigations should be done for an underlying systemic disease.

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.

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).

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.

Treatment primarily involves symptomatic relief using topical steroids, lubricant medication, autologous serum. In case of progressing disease-systematic immunosuppression is done to halt progression. If vision is compromised due to complications-glasses, contact lens, Keratic prosthesis can be used [12]. External dacryorhinocystostomy has been found successful in treating overflow symptoms linked to conjunctivitis.

Differential diagnosis includes infective conjunctivitis, allergic conjunctivitis, Glaucoma, uveitis, trauma, subconjunctival hemorrhage, scleritis, keratitis, corneal ulcer, contact lens, dry eye.

DISCUSSION

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 pseudo tumor [13]. 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.

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.

Though orbital involvement commonly is self-limited, its evolution can be extremely severe prompting enucleation of eyeball. Proptosis in prolonged cases can develop into enophthalmos due to fibrotic changes. Pseudotumor, Proptosis and invasion of surrounding structures can be visualized using CT scan and MRI.

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. Remission involves use of Immunological modulators like methotrexate, azathioprine, biologicals, besides the one already used in induction. Along with tapering of the steroids administere [9]. An emerging treatment therapy involves only the use of a combination of Rituximab and Infliximab, excluding steroids in the treatment altogether.

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.

Differentials include thyroid eye disease, orbital lymphoma, metastasis, idiopathic inflammatory pseudotumor, sarcoidosis.

Uveitis

Uveitis is inflammation involving iris, ciliary body, choroid and retina [14]. Anatomical distinction divides it into anterior (iris, pars plicata) intermediate (pars plans) posterior (choroid, retina) and pan uveitis (all of eye).

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.

Uveitis in GPA is grouped under autoimmune uveitis. Other autoimmune disorders associated with uveitis include rheumatoid arthritis and SLE. Uveitis is reported in 10% of GPA patients. It may be associated with scleritis, keratitis, this association worsens the prognosis of uveitis.

There is no direct evidence of autoimmunity, but a link has been established indirectly. This was done by elicitin autoimmune response in animal models. Role of infection producing autoimmune response has also been hypothesized. Retinal antigens have also been implicated in some studies. Complications include retinal detachment, glaucoma, cataract, loss of vision.

Diagnosis of uveitis is primarily diagnosed based on clinical features. Confirmation of underlying cause depends on laboratory tests [15].

Treatment involves symptomatic relief measures including dark goggles and NSAIDS. Topical steroids are not useful in controlling disease. Oral prednisolone 20 mg/day was quite effective in stopping the inflammatory process, even in preventing relapse. Visual outcome is favorable with use of immunosuppression.

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. 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 [16].

There are several reports on ocular vascular occlusions including CRAO (Central Retinal Artery Occlusion), primarily caused by Vasculitis. 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.

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. 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.

Visual symptoms are the clinical indicator of vessel occlusion. 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.

Clinical examination using fundoscopy is the first step in diagnosis. Indocyanine green angiography helps in exploring the inflammation of choroidal vessels.

OCT (Ocular Coherence Tomoangiography) allowed us to detect choroidal lesions which are not visible on clinical examination. OCT shows hyperreflectivity of retinal layers. FFA (Fundus Flourescence Angiography) is the gold standard for the diagnosis of posterior segment inflammation. FFA shows hypo fluorescence, accompanied by leakage of dye in advanced stages.

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. Central serous retinopathy by high dose steroid treatment. Choroidal granulomas occur in tuberculosis or sarcoidosis as well, hence, are important differentials [17].

Neuro-ophthalmic manifestations

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

- Vasculitis infarction of vasa nervosum.
- Non-vasculitic optic nerve inflammation.
- Spread of inflammation from the adjacent sinuses.

It can also lead to palsies of oculomotor, abductees and trickle at nerve. Horner's syndrome has been reported in rare cases. 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 [18].

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.

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.

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.

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. Decompression surgery may be required in case of the spread of disease from adjoining areas [19].

Eyelids and lacrimal apparatus

Eyelid involvement can occur in the form of "yellow lid sign" resembling a florid xanthelasma.

It can also present as a mass which can be diagnosed with biopsy, and has shown promising treatment to radiotherapy. 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 primary focus of GPA. The main presenting feature is epiphora. 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. External dacryorhinocystostomy has been found successful in treatment of recurrent dacryoadenitis, and NLD obstruction. There were no reports of recurrent symptoms. Differentials include benign or malignant neoplasms of lacrimal gland, thyroid eye disease, pre septal cellulitis, and orbital cellulitis [20].

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. But early diagnosis and treatment can not only be vision saving but also lifesaving.

REFERENCES

1. Garlapati P, Qurie A. Granulomatosis with polyangiitis. 2022.
2. Trimarchi M, Sinico RA, Teggi R, Bussi M, Specks U, Meroni PL. Otorhinolaryngological manifestations in granulomatosis with polyangiitis (Wegener's). Autoimmun Rev. 2013;12(4):501-505.
3. Dammacco R, Biswas J, Mohanan-Earatt A, Lisch W, Zito FA, Rubini G, et al. The eye is a common site of granulomatosis with polyangiitis. A collaborative study. BMC Ophthalmol. 2023;23(1):26.
4. Trandafir CM, Balica NC, Horhat DI, Mot IC, Sarau CA, Poenaru M.Granulomatosis with Polyangiitis (GPA)-A Multidisciplinary Approach of a Case Report. Medicina. 2022;58(12):1837.
5. Kronbichler A, Lee KH, Denicolo S, Choi D, Lee H, Ahn D, et al. Immunopathogenesis of ANCA-associated vasculitis. Int J Mol Sci. 2020;21(19):7319.
6. Lyons PA, Rayner TF, Trivedi S, Holle JU, Watts RA, Jayne DR, et al. Genetically distinct subsets within ANCA-associated vasculitis. N Engl J Med. 2012;367(3):214-223.
7. Hadzik-Blaszczyk M, Zdral A, Zielonka TM, Rozy A, Krupa R, Falkowski A, et al. *SERPINA1* gene variants in granulomatosis with polyangiitis. Adv Exp Med Biol. 2018:9-18.

9. Muller A, Krause B, Kerstein-Stahle A, Comduhr S, Klapa S, Ullrich S, et al. Granulomatous inflammation in ANCA-associated vasculitis. Int J Mol Sci. 2021;22(12):6474.

10. Greco A, Marinelli C, Fusconi M, Macri GF, Gallo A, de Virgilio A, et al. Clinic manifestations in granulomatosis with polyangiitis. Int J Immunopathol Pharmacol. 2016;29(2):151-159.

11. Nwannunu CE, Shah R, Limmer AL. Management of Primary Small-Vessel Vasculitis. Skin Therapy Lett. 2020;25(3):5-8.

12. Orazbekov L, Issergepova B, Assainova M, Ruslanuly K. Granulomatosis with polyangiitis with ocular manifestations. Case Rep Ophthalmol. 2021;12(1):98-104.

13. Rogaczewska M, Puszczewicz M, Stopa M. Exclusively ocular and cardiac manifestation of granulomatosis with polyangiitis-a case report. BMC Ophthalmol. 2019;19:1-5.

14. Sfiniadaki E, Tsiara I, Theodossiadis P, Chatziralli I. Ocular manifestations of granulomatosis with polyangiitis: A review of the literature. Ophthalmol Ther. 2019; 8:227-234.

15. Majumder PD, Sudharshan S, George AE, Ganesh SK, Biswas J. Antineutrophil cytoplasmic antibody-positive scleritis: Clinical profile of patients from a tuberculosis-endemic region. Indian J Ophthalmol. 2018;66(11):1587-1591.

16. Murthy SI, Sabhapandit S, Balamurugan S, Subramaniam P, Sainz-De-La-Maza M, Agarwal M, et al. Scleritis: Differentiating infectious from non-infectious entities. Indian J Ophthalmol. 2020;68(9):1818-1828.

17. Lagina A, Ramphul K. Scleritis. 2022.

18. Murthy SI, Shah S, Bagga B, Dudam R. Rituximab therapy combined with methotrexate for severe necrotizing scleritis in a case of granulomatosis with polyangiitis. Indian J Ophthalmol. 2020;68(9):1981-1983.

19. Ng CC, Sy A, Cunningham ET. Rituximab for non-infectious Uveitis and Scleritis. J Ophthalmic Inflamm Infect. 2021;11:1-5.

20. Valor-Mendez L, Kleyer A, Rech J, Manger B, Schett G. Sustained clinical remission under infliximab/rituximab combination therapy in a patient with granulomatosis with polyangiitis. Auto Immun Highlights. 2021;12:1-3.