Clinical & Refractive Optometry CRO ONLINE CE A CE JOURNAL FOR OPTOMETRY

Polinsky CB, Prewitt E, Schifanella LL. Necrotizing Anterior Scleritis with Peripheral Ulcerative Keratitis Following Vitreoretinal Surgery. *CRO Journal*. Published online January 27, 2025. doi:10.57204/001c.128647

CE Credit - Case Report(s) & Topic Review

Necrotizing Anterior Scleritis with Peripheral Ulcerative Keratitis Following Vitreoretinal Surgery

Cheryl B Polinsky, OD[1], Ellen Prewitt, OD, FAAO[1], Lisa L Schifanella, OD,MS[1]

[1] Tuscaloosa Veterans Affair Medical Center, Tuscaloosa, AL

Keywords: Necrotizing anterior scleritis, peripheral ulcerative keratitis, scleritis, vitreoretinal surgery, pterygium removal, cataract extraction, necrotizing scleritis with inflammation, rheumatoid arthritis

https://doi.org/10.57204/001c.128647

CRO (Clinical & Refractive Optometry) Journal

Necrotizing anterior scleritis with inflammation (NASI) is a rare form of scleritis characterized by thinning of the sclera and inflammation of the surrounding tissue. This condition is also associated with an increased risk of corneal involvement which can result in vision loss. While autoimmune disorders are present in 30-50% of patients diagnosed with NASI, on occasion it may occur as a complication of ocular surgery. Herein, this report reviews the clinical features, etiologies, and management of a rare case of NASI with peripheral ulcerative keratitis (PUK) secondary to vitreoretinal surgery.

CASE HISTORY

A 73-year-old Caucasian male presented for his initial examination with complaints of redness, irritation, foreign body sensation, and light sensitivity in his left eye. He reported these issues had been present for two months and he denied any associated vision changes. His ocular history included monovision LASIK eighteen years earlier and a vitrectomy in the left eye one year prior to presentation that was performed to clear a vitreal hemorrhage that occurred secondary to vitreous detachment. His medical diagnoses included sleep apnea, hypertension, bradycardia, hyperlipidemia, and osteoarthritis.

Best-corrected visual acuity measured 20/20 in the right eye and 20/30 in the left. Extraocular muscle testing, pupil functions and confrontation visual fields were normal in each eye. Slit-lamp examination revealed a trough of thinning in the left eye extending from the 9 to 11 o'clock position. The area of thinning was approximately 70% of the corneal depth. Sodium fluorescein pooling and stromal staining was noted within the area of thinning with no seidel sign present. Circumlimbal injection of the scleral and episcleral vessels of the left eye was apparent with the greatest injection occurring adjacent to the area of scleral thinning. A mild anterior chamber reaction was also present in the left eye. Anterior segment findings of the right eye were unremarkable and dilated fundus examination revealed healthy optic nerves, maculae and peripheral retinae in each eye. No vitreous cells were noted in the posterior chamber of either eye.

A same day referral was made to a corneal specialist where the patient was diagnosed with necrotizing anterior scleritis with inflammation (NASI) and peripheral ulcerative keratitis (PUK) of the left eye. He was initially treated with 60 milligrams of oral prednisone, topical moxifloxacin six times per day in the left eye, and copious topical lubrication with preservative free artificial tears and ophthalmic ointment. Punctal plugs were also inserted into the superior and inferior left puncta. The patient was ultimately tapered off oral prednisone over a six- month period and was also started on mycophenolate mofetil, an oral immunosuppressant agent, which he continues daily in addition to ocular surface lubrication. Laboratory testing was performed and included: antinuclear antibodies (ANA), rheumatoid factor (RF), human leukocyte antigen (HLA-B27), QuantiFERON-TB Gold Plus (QFT-Plus), hepatitis B and C titers, antineutrophil cytoplasmic antibodies (ANCA) and rapid plasma reagin (RPR). As there was no underlying etiology identified, this presentation was deemed to most likely be secondary to the vitrectomy that was performed the previous year. The patient continues to be followed by a corneal specialist, a uveitis specialist, and a rheumatologist due to the refractory nature of the inflammation.

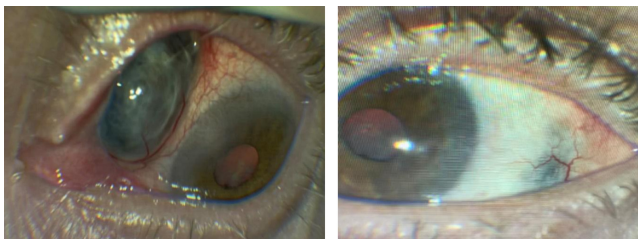

Figure 1. Scleral thinning with visible choroid of the left eye

In this patient's case, his condition was difficult to treat and ultimately resulted in the appearance seen in figure 1 below. The condition has since been stable with his current treatment regimen.

DISCUSSION

Histologically, the sclera is composed of collagen, elastin and proteoglycans which make it prone to inflammation.

The sclera serves as an attachment site for the extraocular muscles, creates a protective barrier for intraocular structures and provides resistance to internal pressure fluctuations associated with aqueous and vitreous humor formation.[1] Two vascular networks nourish the episcleral and scleral tissues: the superficial episcleral plexus and the deep scleral plexus.

Scleritis was initially described in 1702.[2] Limited population-based studies estimate a prevalence of 10,500 cases of scleritis in the United States annually with an incidence of four to six cases per 100,000 persons. Scleritis tends to occur most often in middle-aged individuals with a mean onset of 45-60 years of age. Approximately 60% of cases are diagnosed in women and it is rarely observed in children. No racial or geographical differences have been identified.[2, 3]

Scleritis is broadly defined, and diagnosed clinically, by the extent of inflammation affecting the anterior or posterior segment of the eye. Clinically, anterior scleritis involves inflammation of the sclera from the insertion of the rectus muscles forward and accounts for approximately 98% of all diagnosis of scleritis.[3] Symptoms include mild-to-moderate pain which worsens with eye movements, photophobia, tearing and slightly reduced vision. In daylight or bright illumination, the tissue will exhibit a bluish or violet hue and the deeper vessels will not blanch with 2.5% phenylephrine, helping to differentiate milder cases of scleritis from episcleritis.

Anterior scleritis is classified on the basis of four distinct presentations *(Table 1)*.[3,4] In contrast, the less frequently encountered posterior scleritis presents as inflammation behind the insertion of the rectus muscles and involves the posterior segment of the eye. The most common symptoms of posterior scleritis include: periocular pain, headaches, blurred vision, pain on eye movements and floaters. Anterior scleritis often occurs concurrently. Fundus examination may reveal posterior segment complications including choroidal folds, serous retinal detachments, optic nerve head swelling, and macular edema. Diffuse and nodular forms of posterior scleritis have been identified and can be differentiated with B-scan ultrasonography, CT scans or MRI. Due to the involvement of the posterior segment, there is greater risk for vision loss in cases of posterior scleritis. Less than half of the patients with posterior scleritis will have associated systemic involvement.[5]

Necrotizing anterior scleritis is a rare form of scleritis affecting less than 2% of scleritis patients.[6] There are two broad categories of anterior necrotizing scleritis: necrotizing anterior scleritis *with* inflammation and necrotizing anterior scleritis *without* inflammation. Necrotizing anterior scleritis with inflammation (NASI) is characterized by a red eye with severe, dull, aching pain. The pain present with NASI is the most severe of all the subtypes of scleritis.[7] Peripheral ulcerative keratitis (PUK) and anterior uveitis are the two most common inflammatory features encountered among those diagnosed with NASI.[6]

Among the anterior forms of scleritis, NASI has the greatest likelihood of being associated with systemic disease. Rheumatoid arthritis is the most common cause of necrotizing anterior scleritis with and without inflammation. Granulomatosis with polyangiitis (Wegener granulomatosis) is the second most common cause of NASI and the most common cause of necrotizing anterior scleritis exhibiting corneal involvement.[1] Approximately 90% of patients with NASI and corneal involvement will have an underlying systemic disease.[7] Other systemic etiologies known to be associated with NASI include: lupus, irritable bowel disease, psoriatic arthritis, and ANCA-associated vasculitis. Because of the high association with systemic disease, patients with a known history of ocular surgery or trauma must still be tested for underlying systemic causes.[8]

Patients presenting with NASI without an underlying autoimmune disease who do have a history of surgery or trauma should be evaluated for underlying infectious causes including bacterial, fungal, viral, or parasitic etiologies. A delayed Type IV hypersensitivity response can occur secondary to exposed scleral antigens released during ocular surgery or trauma resulting in NASI.[9] The most common ocular surgeries associated with NASI are pterygium surgery (63.4%) and cataract surgery (17.5%).[7] Vitreoretinal surgery is a rare cause of NASI, accounting for only a small portion of surgically induced cases.

The most common offending organism for infectious scleritis is *Psuedomonas aeruginosa*.[7] *Pseudomonas* produces neutrophil-activated collagenases that break down conjunctival tissue allowing the organism to invade the deeper tissues.[10] Pterygium surgery is the most common precipitating cause of infectious necrotizing scleritis due to the intraoperative use of antimetabolites (mitomycin C) and beta irradiation. These agents break down the integrity of conjunctival vessels and subconjunctival tissue leaving the conjunctiva without epithelium and more susceptible to bacterial infection.[10] Other reported offending organisms include varicella-zoster virus and *Mycobacterium tuberculosis*.[7] Risk factors that increase the chance of developing NASI following ocular surgery include a history of multiple eye surgeries, surgical trauma, and local ischemia caused by the surgery. Sixty-three percent of patients who develop NASI following an ocular surgery will be found to have an associated autoimmune disorder.[11] In these predisposed patients, surgery appears to trigger an influx of immune mediators and complexes at the surgical site via episcleral vessels. The onset of scleritis following surgery varies and can range from one day to many years following the surgery.[7]

NASI with peripheral ulcerative keratitis (PUK) has a poor prognosis for both visual and systemic outcomes as corneal involvement is usually a sign of uncontrolled systemic disease. Among those with uncontrolled underlying systemic conditions, the risk of corneal perforation increases significantly. Patients with corneal perforation tend to have a poor visual outcome, with 65% having vision of counting fingers or worse. There is also a 24% increased risk of mortality in cases of scleritis-associated corneal perforation.[7] The exact mechanism of PUK development in NASI is unknown although it has been theorized that an abnormal T-cell response promotes antibody formation and proliferation. The antibodies then allow the development of

Table 1. Anterior Scleritis Classification[3,4]

Types of Anterior Scleritis	*Clinical Characteristics*
Diffuse	• Most common, occurring in 45% to 61% of all cases of anterior scleritis • Characterized by extensive scleral inflammation and edema with congestion of both the deep and superficial vascular bed • Can be localized or encompass the entire anterior sclera
Nodular	• Characterized by the presence of one or more well-defined, tender, immoveable scleral nodules • Tends to be associated with more localized scleral edema, inflammation and vessel congestion • Approximately 20% of cases will progress to necrotizing scleritis
Necrotizing with inflammation	• Characterized by intense inflammation and vascular congestion • Scleral thinning is marked and can lead to choroidal exposure • Associated pain is often extreme • Often associated with underlying collagen vascular disorders • Inflammation anterior segment is common involving the cornea, ciliary body, or trabecular meshwork
Necrotizing without inflammation	• Characterized by the presence of severe, extensive scleral thinning with visible choroid, in the absence of inflammation or any significant symptoms • Often referred to as *scleromalacia perforans* and most often encountered in patients with rheumatoid arthritis • Reduced acuity may occur secondary to corneal astigmatism caused by the scleral thinning

immune complexes which cause inflammatory cells to invade the stromal layer creating an infiltrate. The epithelium around these immune complexes becomes compromised and eventually ulcerates. The classic presentation of PUK is a peripheral corneal crescent-shaped ulceration with an overlying epithelial defect and infiltrate with overhanging edges. PUK occurs in the periphery of the cornea due to the amount of vascularization present with circulating immune complexes.[12] Symptoms of PUK include redness, photophobia, pain and corneal opacification. Among patients with PUK resulting in corneal perforation, enucleation may be required.

MANAGEMENT

Establishing an accurate diagnosis of anterior scleritis (*Table 2*) is imperative to ensure initiation of appropriate therapy. Due to the association of necrotizing anterior scleritis with systemic causes, a thorough case history, clinical examination, and laboratory testing are foundational components of identifying any undiagnosed underlying etiology (*Table 3*)

Depending on the extent of inflammation, treatment of NASI may require an oral non-steroidal (NSAID), an oral steroid or an immunosuppressive agent. Seventy-percent of patients with NASI will eventually require more aggressive immunosuppressive therapy.[13] Common immunosuppressive agents include: methotrexate, mycophenolate mofetil, and azathioprine.[3,4] Mycophenolate reduces inflammation by inhibiting the proliferation of T and B lymphocytes.[14] In addition to treating NASI, this drug has been shown to be effective in preventing organ rejection, treating autoimmune disorders, and managing recalcitrant uveitis. The SITE study showed that mycophenolate was superior in treating ocular inflammation, including scleritis, when compared to methotrexate and it is currently the first-line immunosuppressive therapy used when treating scleritis.[13]

Table 2. Anterior Scleritis Differential Diagnoses[4]

- Conjunctivitis
  - Allergic
  - Bacterial
  - Viral
- Keratitis
  - Bacterial
  - Viral (Herpes simplex)
  - Fungal
  - Interstitial
- Keratoconjunctivitis
  - Atopic
  - Epidemic
  - Superior Limbic
  - K. Sicca
- Episcleritis
- Pterygium
- Uveitis
- Toxoplasmosis
- Chronic Lymphocytic Leukemia
- Acute Angle Closure Glaucoma

Another class of medication used in the treatment of NASI are calcineurin inhibitors. Cyclosporine-A is the best-known example of a calcineurin inhibitor. In the SITE study, 52% of patients achieved remission of their scleritis while taking oral cyclosporine.[13] Topical cyclosporine-A has also been reported to have been used in the treatment of NASI with only limited success.

One final class of drugs that is relatively new in the management of patients with a diagnosis of NASI are referred to simply as "biologics" and include drugs such as: adalimumab, infliximab, etanercept, and rituximab. This class of medication is commonly used in the treatment of autoimmune disorders such as rheumatoid arthritis, Crohn's disease, and psoriatic arthritis. Adalimumab and infliximab have both shown to improve symptoms of scleritis, whereas Etanercept was not shown to be effective in improving the

Table 3. Evaluation of Anterior Scleritis[3,4]

Laboratory Test	**Systemic Association**
CBC (Complete blood count)	Infectious, inflammation, malignancy
RF (Rheumatoid factor)	Rheumatoid arthritis
ANCA (anti-neutrophil cytoplasmic antibodies)	Wegener granulomatosis
ANA (antinuclear antibodies)	Positive test supports systemic lupus
ACE (Angiotensin converting enzyme)	Sarcoidosis
Serum lysozyme	Sarcoidosis
Serum uric acid	Gout
ESR (Erythrocyte sedimentation rate)	Non-specific (infection and inflammation)
C-RP (C-reactive protein)	Non-specific (elevated in acute stages of inflammation or infection)
RPR (Rapid plasma regain)	Non-specific for syphilis
FTA-ABS (Fluorescent treponemal antibody absorption test	Specific for syphilis. Used to confirm if non-specific RPR test is positive
Lyme titer	Lyme disease
Imaging	
Chest x-ray	Hilar lymphadenopathy and pulmonary infiltrates with sarcoidosis
MRI, CT, B-scan, OCT	Useful in determining if severe cases of anterior scleritis are associated with posterior scleritis

symptoms or ocular manifestations of scleritis. Rituximab was shown to improve scleritis in refractory, non-infective cases.[6]

Like scleritis, the treatment of peripheral ulcerative keratitis depends on the underlying etiology. In the majority of PUK cases, autoimmune disease plays a role. The treatment of the autoimmune disease with oral corticosteroids or immunosuppressive drugs usually results in improvement of the corneal disease. The use of fourth generation fluoroquinolones or fortified cefazolin with fortified tobramycin may be used in cases in which an infectious etiology is possible[15]. Corneal scraping and cytology should be performed in cases of infectious PUK to tailor topical treatment more specifically based on the causative organism. The use of artificial tears and ointment may be of help to lubricate the eye, promote epithelial healing, and wash out immune mediators on the eye[15]. Some studies show that an immunosuppressive drug like cyclosporine A can also be used. Topical steroids and topical NSAIDS increase the risk for corneal perforation and are not widely used in cases of PUK. If corneal perforation does occur, then surgical options must be explored including conjunctival resection, conjunctival flap, lamellar patch flap, amniotic membrane grafting, and penetrating keratoplasty.[2] The use of tissue adhesives can also be used in the case of perforation, which includes cyanoacrylate glue or fibrin glue. Cyanoacrylate glue can be used for corneal perforation less than 3 mm in size, but is non-biodegradable and can cause side effects including irritation, neovascularization, conjunctivitis, and tissue necrosis.[14] Fibrin glue must be used in conjunction with amniotic membrane graft for adhesion and is biodegradable with little to no side effects.[14]

CONCLUSION

It is vital to recognize the clinical signs and symptoms of NASI as this condition is almost always associated with underlying systemic disease and poses a significant risk for severe vision loss. A complete medical history and evaluation should occur to determine if these patients have a history of autoimmune disease, ocular surgery, or ocular trauma. Surgically induced NASI is most often associated with cataract surgery and pterygium surgery but can be precipitated by vitreoretinal surgery in rare instances. Since the majority of NASI patients have an associated systemic condition, even patients with a suspected surgical cause should have laboratory testing performed to rule out potential autoimmune or infectious etiologies. It is also important to look for corneal involvement with NASI as this further increases the risk of a poor visual outcome. Peripheral ulcerative keratitis is the most common corneal condition associated with NASI and the presence of PUK may not only lead to a poor visual outcome but can also be a sign of uncontrolled autoimmune disease, increasing a patient's risk of morbidity. Prompt recognition of this condition in the clinical setting is imperative to increase a patient's odds of a favorable visual outcome.

Submitted: May 24, 2024 EST. Accepted: July 22, 2024 EST.
Published: January 27, 2025 EST.

This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CCBY-NC-4.0). View this license's legal deed at https://creativecommons.org/licenses/by-nc/4.0 and legal code at https://creativecommons.org/licenses/by-nc/4.0/legalcode for more information.

REFERENCES

1. Nevares A, Raut R, Libman B, Hajj-Ali R. Noninfectious Autoimmune Scleritis: Recognition, Systemic Associations, and Therapy. *Current Rheumatology Reports*. 2020;22(4). doi:10.1007/s11926-020-0885-y

2. Srilakshmi SM, Rosenbaum JT. Scleritis. In: *Ocular Disease Mechanisms and Management*. Elsevier Inc.; 2010:642-653. doi:10.1016/B978-0-7020-2983-7.00082-6

3. Lagina A, Ramphul K. *Scleritis*. StatPearls Publishing; 2023. https://www.ncbi.nih.gov/books/nbk499944

4. Gaeta TJ. Scleritis in Emergency Medicine. Practice Essentials, Pathophysiology, Etiology, Medscape. April 2, 2021. http://emedicine.medscape.com/article/809166-overview#showall

5. Vermeirsch S, Testi I, Pavesio C. Choroidal involvement in non-infectious posterior scleritis. *Journal of Ophthalmic Inflammation and Infection*. 2021;11(1). doi:10.1186/s12348-021-00269-9

6. Dutta Majumder P, Agrawal R, McCluskey P, Biswas J. Current Approach for the Diagnosis and Management of Noninfective Scleritis. *Asia-Pacific Journal of Ophthalmology*. 2020;10(2):212-223. doi:10.1097/apo.0000000000000341

7. Sims J. Scleritis: presentations, disease associations and management. *Postgraduate Medical Journal*. 2012;88(1046):713-718. doi:10.1136/postgradmedj-2011-130282

8. Xu T, Reynolds M, Hodge D, Smith W. Epidemiology and Clinical Characteristics of Episcleritis and Scleritis in Olmsted County, Minnesota. *American Journal of Ophthalmology*. 2020;217:317-324. doi:10.1016/j.ajo.2020.04.043

9. Ruiz-Lozano RE, Garza-Garza LA, Davila-Cavazos O, Foster CS, Rodriguez Garcia A. The clinical and pathogenic spectrum of surgically-induced scleral necrosis: A Review. *Survey of Ophthalmology*. 2021;66(4):594-611. doi:10.1016/j.survophthal.2020.12.008

10. Chaidaroon W, Ausayakhun S, Tananuvat N, Upaphong P, Thabsuwan K. Pseudomonas aeruginosa Scleritis following Pterygium Surgery with Mitomycin C or Beta Irradiation: Three-Case Report. *Case Reports in Ophthalmological Medicine*. 2022;2022:1-5. doi:10.1155/2022/8000944

11. Gaonker T, Yadav A, Rastogi A, Bansal P. Surgically Induced Necrotizing Scleritis: An Overview. *Eyenet Magazine*. Published online December 2021:33-35.

12. Cao Y, Zhang W, Wu J, Zhang H, Zhou H. Peripheral Ulcerative Keratitis Associated with Autoimmune Disease: Pathogenesis and Treatment. *Journal of Ophthalmology*. 2017;2017:1-12. doi:10.1155/2017/7298026

13. Abdel-Aty A, Gupta A, Del Priore L, Kombo N. Management of noninfectious scleritis. *Therapeutic Advances in Ophthalmology*. 2022;14:25158414211070879. doi:10.1177/25158414211070879

14. Cuchacovich M, Solanes F, Perez C, et al. Mycophenolate Mofetil Therapy in Refractory Inflammatory Eye Disease. *Journal of Ocular Pharmacology and Therapeutics*. 2016;32(1):55-61. doi:10.1089/jop.2015.0044