Activation of tubercular scleritis after local immune suppression

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ABSTRACT

Introduction: This article describes the challenge to diagnose and manage a case of treatment-refractory scleritis in the postoperative setting after routine trabeculectomy for uncontrolled glaucoma. Case Report: This case features a 63-year-old veteran who presented after trabeculectomy with perioperative use of mitomycin C (MMC) with unresolving scleritis refractory to topical and oral steroid treatment. Infectious and inflammatory work-up was negative except for detection of tuberculosis (TB) on Quantiferon Gold test. The patient was sent to infectious disease clinic, where it was elucidated that he was high risk for Mycobacterium tuberculosis reactivation and had been previously treated with single agent isoniazid. He was started on multidrug anti-TB therapy and his scleritis resolved quickly thereafter. Concurrent management of his glaucoma required special considerations and we elected for a minimally invasive approach, given the complications anticipated by operating on an eye with active infection. Conclusion: We hypothesize that this is the first documented case of localized immunosuppression caused by the use of MMC and/or local steroid use, leading to reactivation of latent TB. Management of the infection and of the concurrent uncontrolled pressures in the eye posed a unique challenge.

Keywords: Glaucoma, Mitomycin C, Scleritis, Tubercular scleritis

INTRODUCTION

Scleritis is a painful ocular inflammatory process that can lead to vision loss, or worse if not promptly diagnosed and treated [1]. Due to its potential serious risk of vision loss, scleritis should be promptly diagnosed when a typical clinical history is corroborated by characteristic ophthalmic exam findings: pain, deep injection of the sclera, and decreased vision [1].

Fifty percent of scleritis cases emerge in the setting of an associated systemic illness, commonly an autoimmune condition or infectious disease [2].

Immune suppression is a known risk factor for reactivation of latent TB. This includes patients with human immunodeficiency virus (HIV) (10–110 times higher risk), organ transplantation with immunosuppressive therapy.
denied shortness of breath, night sweats, fever, and disease clinic for concern of TB uveitis-scleritis. He reactivation and was promptly referred to the infectious TB exposure. He was deemed to be high risk for TB had close contact with inmates, many of whom had (INH) for one year. He also noted a ten-year period been exposed to TB during his military service in Japan volunteered additional information. He had previously the Quantiferon-TB Gold. At this point, the patient treatment, autoimmune and infectious uveitis work-
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increases 2.8- to 7.7-fold [7].
This case highlights an interesting HIV-negative patient who we believe developed a postoperative scleritis, due to reactivation of TB in the setting of possible local immune suppression. Intraoperatively, he was given MMC, an antimetabolite that affects wound healing, with known complications that include infection due to immunosuppression [8, 9].

CASE REPORT

The patient is a 63-year-old African American male with medical history of hyperlipidemia and hypertension, and with ocular history of advanced primary open angle glaucoma in both eyes. He has previously undergone phacoemulsification and trabeculectomy with MMC of the right eye a month prior and presents with painful red eye and blurry vision.

On previous exam, four months prior to ocular surgery, visual acuity was 20/25 in the right eye (OD) and 20/30 in the left eye (OS). Tonometry measured 19 mmHg OD and 14 mmHg OS, respectively (pachymetry 572/560), with good compliance on brimonidine 0.2% three times a day in both eyes, dorzolamide-timolol twice daily in both eyes, and latanoprost every night bilaterally.

After noting elevated intraocular pressure (IOP) and visual field progression in the right eye, the decision was made to proceed with cataract extraction with intraocular lens placement and trabeculectomy with MMC. The surgery was uncomplicated. A 0.2 cc of 0.4 mg/mL MMC was injected subconjunctivally 30 minutes prior to the start of the surgery.

Over the course of the next several months, patient had repeat flares of scleritis with a waxing and waning course. Symptoms were temporarily controlled with topical steroids, but would worsen when the dosage or frequency were decreased. Given persistent inflammation and worsening scleritis resistant to steroid treatment, autoimmune and infectious uveitis work-up was commenced. All tests were negative except for the Quantiferon-TB Gold. At this point, the patient volunteered additional information. He had previously been exposed to TB during his military service in Japan in the 1970s and was treated at the time with isoniazid (INH) for one year. He also noted a ten-year period during which he worked as a correctional officer, having had close contact with inmates, many of whom had TB exposure. He was deemed to be high risk for TB reactivation and was promptly referred to the infectious disease clinic for concern of TB uveitis-scleritis. He denied shortness of breath, night sweats, fever, and recent weight loss. His physical exam at this time was unremarkable except for eye findings. Liver panel and serum chemistry were within normal range. His chest X-ray did not show any focal consolidation or lesion. The diagnosis of tubercular scleritis was made clinically based on history and laboratory findings, given the risks and difficulty of obtaining intraocular biopsy as well as lack of confirmatory testing with such samples. He was referred to the Baltimore City Health Department for initiation systemic TB therapy which included isoniazid 300 mg daily, rifampin 1200 mg daily, and vitamin B6 100 mg daily. Within three months of initiating therapy, there was complete resolution of the scleritis and the patient was tapered off topical steroids without recurrence of symptoms. Prior to this, the patient had failed all taper attempts off topical anti-inflammatory agents and had persistent, symptomatic inflammation. Steroids were discontinued after initiation of anti-TB treatment and this was the first time that the patient also endorsed a subjective improvement in symptoms of pain and photophobia.

His eye pressure, however, throughout this course, continued to remain elevated into the mid 30s mmHg on maximally tolerated medical therapy. The patient's active scleritis posed an interesting challenge for surgical management. The scleritis had involved most of the superior sclera. Therefore, if the patient were to undergo aqueous drainage implantation, it would have to be in the less-preferred infero-nasal quadrant. Additionally, it was unclear if implantation of a foreign object in a “hot eye,” i.e., an eye with active infection and inflammation, could worsen the underlying scleritis. The decision was made to pursue a minimally invasive surgical therapy with the understanding that the patient could undergo a more definitive treatment after complete treatment of secondary TB. He underwent four clock hours of goniotomy with the Kahook dual blade (New World Medical, Rancho Cucamonga, CA). Vigorous heme reflux and episcleral venous blanching were noted during the procedure confirming good connection with the downstream collector channels.

Following TB treatment, steroid discontinuation, and goniotomy, his IOPs remain stable in the low teens and visual field testing has not shown any progression. The patient has also not experienced any recurrence of the scleritis over the last nine months, which was the total duration of his TB therapy, and has been quiescent for the following two years without recurrence of the scleritis.

We hypothesize that the scleritis is a result of localized immunsuppression induced by the intraoperative MMC in combination with postoperative steroid use, which led to the reactivation of latent TB. We were led to this diagnosis in light of other negative infectious and/or inflammatory work-up, and in considering the complete resolution of symptoms with TB therapy, after months of uncontrolled recurrence with other attempted therapy. Other items on the differential here include: prolonged postoperative inflammation, although as previously
mentioned there was no resolution of this inflammation over the course of several months, with either topical or oral steroid therapy. The rapid definitive resolution of inflammation, with no recurrence, with antitubercular rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE) therapy suggests underlying mycobacterium activation as the cause of the scleritis.

**DISCUSSION**

Ocular TB is a rare cause of scleritis among the more common infectious and immune-mediated etiologies. Past cases of ocular TB largely consist of patients from endemic regions, with varying reports of incidences between 0.6% and 20.6% among patients with known TB, depending on the region, time period, and patient population [10]. Risk factors that predispose patients to extrapulmonary TB include age greater than 40, female sex, and HIV infection; rates of ocular TB in patients with or without HIV are variable, though some studies suggest increased incidence of ocular TB among the HIV population [10–12].

It is suggested that the acid fast bacilli travel hematogenously to the intraocular region; infection can also occur via direct local extension from adjacent tissue or hypersensitivity immune response from infection elsewhere with absence of mycobacterium in the eye [11, 13]. The most common presenting subtype is uveitis, with posterior uveitis being more common than anterior, accounting for 35–42% of all intraocular TB [4, 11]. It is hypothesized that the choroid and ciliary body are most typically infected due to the high regional oxygen tension of these tissues [11, 13]. Intraocular TB, however, can manifest as phycytenular keratoconjunctivitis, interstitial keratitis, cataract (secondary to ongoing inflammation), scleritis, choroidal tubercles, chorioretinitis, retinal lesions and vitreal opacification, retinal vasculitis, endophthalmitis, globe rupture, orbital infection, infection of the eyelid, and with neuro-ophthalnic uveititis-scleritis, as the structures involved are delicate and difficult (or impossible) to biopsy or culture [21]. This literature reinforces the difficulty of diagnosing TB and its latency-scleritis, as the structures involved are delicate and difficult (or impossible) to biopsy or culture [21]. This fact, along with the invasiveness of the biopsy procedure, led us to elect not to biopsy the sclera.

Regarding cases related to patients with tubercular scleritis specifically, a recent review of the literature cites a 1976 study done in the United States which found that, of 301 patients with scleritis, only four were diagnosed with active TB (1.3%) [14]. In another study out of Sri Lanka, of 2130 patients with TB, ocular TB was diagnosed in 23 patients (1.1%), among whom sceral nodule/episcleritis was found in 1 patient (0.05%) [15]. Though scleritis is itself rare and TB scleritis more rare still, focal necrotizing scleritis is the most common manifestation, presenting as dark red discoloration of the sclera with chronic granulomatous inflammation and caseous necrosis [10, 16, 17].

Patients typically present with unilateral pain, red eye, and decreased or blurry vision, though cases have been reported that include additional symptoms of excessive lacrimation and photophobia with associated ipsilateral headache, ear pain, and nausea/vomiting [18–20]. Patients often present with multiple episodes of scleritis despite treatment with nonsteroidal anti-inflammatory drugs and topical steroids prescribed at every episode [19]. Of the cases reviewed, none of the patients identified associated fevers, night sweats, weight loss, shortness of breath, or any other signs of systemic illness [18–20].

Two reported patients had history of ocular surgery; one had remote history of cataract surgery two years prior [18] and another report presents a patient status post-drainage tube placement for open angle glaucoma [20]. In the latter report, mycobacterium abscesses was isolated after topical antibiotic treatment proved ineffective [20]. Though in this case, nontuberculous mycobacterium was isolated, it was postulated that postoperative immune suppression with topical corticosteroids may have been the risk factor for infection [20].

We therefore would like to propose that this is a rare case of localized immunosuppression caused by the disruption to the local environment by surgical manipulation, and use of MMC and/or local steroid use, which led to reactivation of latent TB. On the patient’s initial presentation, the differential diagnosis for his scleritis included the more common diagnosis of postoperative scleritis. His course, however, of persistent unremitting inflammation, despite repeated courses of steroid, necessitated a more inclusive work-up. Upon the initiation of antitubercular therapy, his scleritis imminently resolved and did not recur. Given his previous resistance to standard treatment and the definitive resolution of scleritis with RIPE therapy, in combination with the patient’s risk factors (serving overseas and as a prison correctional officer) and his positive Quant Gold testing, we were led to the conclusion that his scleritis was most likely due to mycobacterium infection.

Regrettably, no histopathology was obtained; the literature reinforces the difficulty of diagnosing TB uveitis-scleritis, as the structures involved are delicate and difficult (or impossible) to biopsy or culture [21]. This fact, along with the invasiveness of the biopsy procedure, led us to elect not to biopsy the sclera.

Though no reports have shown reactivation of latent TB due to mitomycin, it is well-established that immune suppression constitutes a “high” risk factor for TB reactivation [22]. It has been suggested that mitomycin, an antifibroblast and antitumor alkylating agent that inhibits DNA synthesis, has immune suppressant properties that may contribute to postoperative infection, though the evidence establishing infection risk is variable [8]. Mitomycin C is commonly used in trabeculectomy to delay wound healing through inhibition of fibroblast proliferation. It is not without complications, however; these include corneal astigmatism, thin atrophic blebs, bleb infection, endophthalmitis, and hypotony [9]. It has also been reported that MMC, itself, can be associated with scleritis after glaucoma surgery, though each reported case resolved with steroids [23]. One study that
evaluated the histology of monkey eyes after use of MMC during a glaucoma procedure found that the filtration site in four of five eyes was completely acellular—with no fibroblast proliferation [24]. The benefit of its use to prevent bleb scarring is apparent, but we postulate that, in the rare event that there is latent infection contained by immune cells in the eye, MMC may act as an insult to immune cells akin to anti-tumor necrosis factor (TNF) agents that pose TB reactivation risk.

Complications due to scleritis include scleral perforation and vision loss, and for this reason, prompt diagnosis and treatment initiation is imperative. Though tuberculous scleritis is rare, it should be considered in patients with a positive purified protein derivative (PPD) or chest radiograph results in cases of refractory scleritis resistant to initial treatment. Clinical suspicion must be high, especially in patients from endemic areas or who have other risk factors, since there is no uniform or typical presentation. Detailed history is essential and appropriate testing should be expedited, including PPD, chest radiography, and Quantiferon-TB Gold. Histology, if obtained, may show caseating granulomatous lesions and cultures may show mycobacterium; however, diagnosis can be made in absence of these specimens if there is the appropriate clinical context, followed by rapid resolution of symptoms with the initiation of anti-TB treatment [25–27].

As mentioned, no photographs were taken at the time, due to Veterans Affairs (VA) privacy regulations. Biopsy was considered, but due to the invasive nature of the procedure in combination with the established difficulty of culturing mycobacterium in ocular tissue, the decision was made to pursue a clinical diagnosis in collaboration with our infectious disease colleagues. We recognize that this poses a limitation to our case.

**CONCLUSION**

Treating ocular TB may not only be sight-saving, but can also serve as the heralding flag to initiate systemic treatment in a patient who may otherwise suffer consequences of reactivated TB at a later junction. High clinical suspicion and inter disciplinary approach to treatment is key to a successful outcome. In particular, when treating populations, such as veterans, who have extensive travel history to endemic regions or are originally from endemic regions, it may be useful to include questions about TB history in a preoperative assessment.

**REFERENCES**


Author Contributions
Erin Lanzo – Conception of the work, Design of the work, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ramya Swamy – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.

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