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ARTICLE

Presumed tuberculous sclerokeratouveitis in immunocompetent South African patients

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Abstract

Background/objectives Ocular tuberculosis remains a diagnostic challenge since its clinical presentation is so variable. We describe the clinical characteristics of patients presenting with sclerokeratouveitis secondary to presumed *Mycobacterium tuberculosis* infection.

Method Retrospective analysis of 14 patients presenting with sclerokeratouveitis to Tygerberg Hospital. All patients underwent: (1) detailed ophthalmological evaluation, (2) tuberculin skin test (TST), (3) chest X-ray to assess for systemic disease, and (4) laboratory investigations to exclude other causes of ocular inflammation. Tuberculous sclerokeratouveitis was diagnosed if: (1) clinical findings showed scleritis with adjacent peripheral keratitis and anterior uveitis, (2) TST was positive, (3) other causes of sclerokeratouveitis were excluded, and (4) positive response to tuberculosis treatment without adjunctive anti-inflammatory agents was noted.

Results Seventeen eyes were included. Mean age was 29.1 ± 12.1 years. All patients were females with no history of previous/current pulmonary tuberculosis. Only one patient was HIV positive, but virologically suppressed. All patients had a strongly positive TST result. Scleral involvement was nodular in four patients and diffuse in ten. Corneal involvement manifested as ill-defined peripheral stromal opacities adjacent to the area of scleritis with deep corneal stromal vessels. Corneal sensation was decreased in all involved eyes. All patients responded to tuberculosis treatment with complete resolution of the sclerokeratouveitis.

Conclusions In our highly endemic area, tuberculous sclerokeratouveitis is seen in young, immunocompetent patients, and responds well to tuberculosis treatment without concurrent immunosuppression. Decreased corneal sensation may lead to an incorrect diagnosis of herpetic infection if a high index of suspicion is not maintained for ocular tuberculosis.

Introduction

Tuberculosis (TB) continues to be the leading infectious cause of morbidity and mortality worldwide [1]. According to the World Health Organization (WHO), approximately one-third of the world's population is infected by TB; with 10% of infected people being symptomatic and 90% having latent TB [2]. More than 95% of new infections occur in the developing world, particularly in Africa and South Asia. The increasing number of TB infections has been attributed to factors such as immune suppression resulting from human immunodeficiency virus (HIV) infection, poor socioeconomic conditions, and global migration [2].

TB is the tenth leading cause of death worldwide and is the leading cause of death from a single infectious agent, ranking above HIV/AIDS. Most of these deaths are preventable since the treatment success rate in 2016 was 82% globally in those in whom TB was detected, reported, and treated [1].

According to the 2018 WHO Global TB report, South Africa has the second highest incidence of TB of any country worldwide (567 cases per 100,000) with the highest HIV prevalence amongst the incident TB cases (60%). The report shows that in 2017, the TB mortality rate in South Africa was 39 cases per 100,000 HIV negative patients and 99 cases per 100,000 HIV positive patients.

TB is a multisystem disease that primarily affects the lungs, although it may also have extrapulmonary manifestations affecting other organs including the eye [3]. Ocular TB

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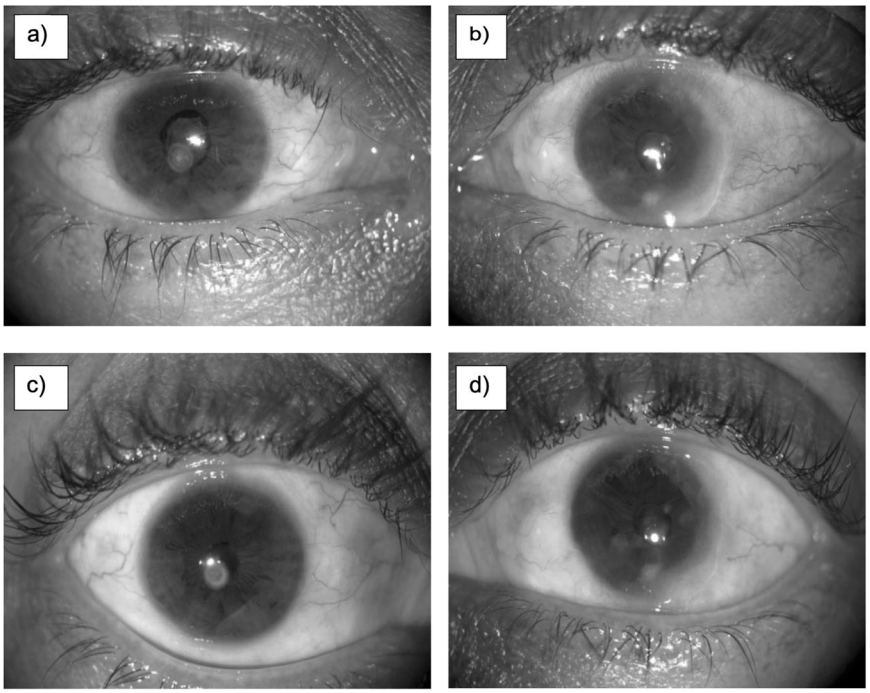

Fig. 1 Chronic bilateral sclerokeratouveitis. a, **b** Right and left eye on presentation. **c**, **d** Right and left eye 1 month after ATT.

is defined as an infection by *Mycobacterium tuberculosis* in the eye, around the eye, or on its surface. It is usually not associated with clinical evidence of pulmonary TB, as up to 60% of extrapulmonary TB patients may not have pulmonary TB [2]. Ocular TB is either primary, in which the eye is the primary port of entry of the mycobacterium into the body, or secondary as a result of seeding by hematogenous spread from a distant site. Primary disease is less common, and includes eyelid, conjunctival, corneal, and scleral lesions, while the uveal tract, retina, and optic nerve are involved in secondary disease. Inflammation of the uveal tract is the most common ocular manifestation of the disease, due to its abundant blood supply [2].

The large variations in clinical presentation and the lack of uniformity in diagnostic criteria make the diagnosis of ocular TB challenging. In most cases diagnosis requires both corroborative evidence, such as a positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA) and/or chest X-ray (CXR), as well as the exclusion of other causes [4]. Gupta et al. proposed a revised classification for ocular TB which lists six clinical signs considered to be highly suggestive of ocular TB [5]. Interestingly enough, sclerokeratouveitis is not one of these signs and we have previously reported that, at least in the South African setting, it should perhaps be added to that list [6].

In this paper we present an illustrative case of sclerokeratouveitis which is followed by, to the best of our knowledge, the largest case series of tuberculous sclerokeratouveitis that responded to antituberculous treatment (ATT) without concomitant use of oral or topical corticosteroids.

Case report

A 31-year-old woman presented initially to the Eye Clinic in 2016 with a 1-year history of ocular discomfort and redness of both eyes associated with gradual loss of vision. She had been seen by several doctors at the Eye Clinic, but a definite cause for her symptoms could not be found.

On examination, she had an uncorrected visual acuity of 0.05 in both eyes, with no improvement with pinhole. Both eyes showed diffuse scleral injection, with a scleral nodule noted in the nasal half of the left eye at the 9 o' clock position (Fig. 1a, b). Her right cornea showed ill-defined areas of stromal scarring extending from 5 o' clock to 9 o' clock with a central defined area of superficial stromal scarring noted just inferior to the visual axis. Deep stromal blood vessels were noted in the 5 o' clock position. Her left cornea showed >270° of ill-defined areas of stromal scarring, with a few patchy areas in the visual axis. Extensive deep stromal vessels were noted from 3 o' clock to 6 o' clock, with irido-corneal touch on the temporal limbus. Both eyes had decreased corneal sensation. She had 2+ cells and 1+ flare in the anterior chamber. Neither Busacca/Koeppe nodules on the iris nor any iris atrophy were noted. Patchy areas of posterior synechiae with no iris bombe and uveitic cataract were noted in both eyes. Fundus examination of both eyes showed no evidence of vitreous condensations, vasculitis, or any subretinal nodules suggestive of granulomas, with cup-to-disc ratios of 0.3 and normal appearance of the maculae.

A clinical diagnosis of sclerokeratouveitis was made and investigations were requested to search for an underlying cause. HIV testing, syphilis serology, full blood count, serum angiotensin converting enzyme, erythrocyte sedimentation rate, rheumatoid factor (RF), antinuclear antibody (ANA), cytoplasmic antineutrophil cytoplasmic autoantibody (cANCA), perinuclear antineutrophil cytoplasmic autoantibody (pANCA) were all normal. No abnormalities were detected on CXR. Due to the negative workup and the presence of decreased corneal sensation, the aetiology was thought to be herpetic and she was started on oral acyclovir 800 mg five times daily for 2 weeks which showed no improvement. During the course of the next year she was treated with topical and oral steroids with no definite improvement.

She defaulted further follow-up visits until presenting again 3 years later with worsening eye symptoms. In addition to a standard diagnostic workup, a TST was performed which showed a 23 mm induration with a blistering reaction. Given the negative workup of other causes of sclerokeratouveitis, as well as the failure to respond to oral acyclovir or topical/systemic steroids previously, it was decided to commence a trial of ATT without topical or systemic corticosteroid use.

On 1-month follow-up, she reported that the redness of both eyes had resolved along with her ocular discomfort. On examination, both eyes appeared white and comfortable, scleritis had resolved, and corneal stromal vessels had started to regress leaving ghost vessels (Fig. 1c, d). The anterior chamber reaction had also subsided. At last follow-up the patient remained free of symptoms and no signs of ocular inflammation were noted even though she had not yet completed 6 months of ATT.

Methods

We retrospectively reviewed the clinical findings of 14 patients with tuberculous sclerokeratouveitis who presented to the Ophthalmology clinic at Tygerberg Hospital in Cape Town, South Africa between January 2016 and March 2019. Informed consent was obtained from all subjects. The protocol was approved by the Health and Research Ethics committee of Stellenbosch University and the study adheres to the principles of the Declaration of Helsinki.

All patients underwent detailed ophthalmological evaluation and CXR to assess for pulmonary disease. Other laboratory investigations requested included HIV testing, CD4+ if HIV+, serum *Treponema pallidum* antibodies, RF, ANA, ANCA, and multiplex PCR for herpes viruses 1–6 on aqueous humour in all cases to rule out other underlying causes.

All patients underwent a TST using a 0.1 mL intradermal injection of 5 IU of purified protein derivative (PPD-S 5TU) to the volar aspect of the forearm and the reaction was measured with a ruler 48–72 h later. TST was considered positive if ≥10 mm in HIV− patients and ≥5 mm in HIV+ patients [4].

The diagnosis of tuberculous sclerokeratouveitis was made based on the clinical findings of scleritis with adjacent peripheral corneal stromal keratitis and anterior uveitis, positive TST and a positive response to a 4-week trial of ATT without anti-inflammatory agents after exclusion of other causes of sclerokeratouveitis. If the trial of treatment was positive, patients were given a four-drug ATT regime (rifampicin, isoniazid, pyrazinamide, and ethambutol) for a total of 2 months (intensive phase) followed by a two-drug ATT regime (isoniazid and rifampicin) for 4 months (continuation phase).

Results

Of the 14 patients assessed as having sclerokeratouveitis 17 eyes were affected. All patients were female and their mean age was 29.1 ± 12.1 years (Table 1). None of the patients had a history of previous/current pulmonary TB and none reported constitutional symptoms of fever, chills, night sweats, anorexia, or weight loss. Only one was HIV positive with a CD4+ count of 615 cells/μL and an undetectable HIV viral load on antiretroviral treatment. Ocular involvement was bilateral in three cases. Scleritis was nodular in four patients and diffuse in ten, while corneal involvement manifested as ill-defined peripheral stromal opacities with deep stromal vessels adjacent to the area of scleritis (Fig. 2a, b). Interestingly, decreased corneal sensation was noted in all 17 affected eyes. Non-granulomatous anterior uveitis with 0.5+ to 2+ cells was documented in all cases with no posterior segment involvement. Despite nine patients having a TST ≥ 20 mm, none had any radiological evidence of pulmonary TB. Tuberculous sclerokeratouveitis was only diagnosed once all other special investigations returned negative results. Based on the decreased corneal sensation noted in all cases, multiplex PCR testing for herpes viruses 1–6 was performed in all 14 included patients to determine whether underlying herpetic infection was present but no positive results were obtained.

Once the diagnosis was made patients were commenced on a 4-week trial of treatment with four-drug ATT as described above without any adjunctive corticosteroid use. Signs of improvement were noted within the first month after initiation of ATT in all cases (Fig. 2c, d) (Fig. 3c, d) and patients continued to show progressive improvement in the signs and symptoms during the period of treatment until complete resolution occurred (Fig. 3e, f).

Table 1 Clinical characteristics of cases assessed as sclerokeratouveitis.

ID no.	Age	Sex	HIV status	Affected eye	VA OD	VA OS	Scleritis	Interstitial keratitis	Corneal senstation	Anterior uveitis	CXR	PPD (mm)
1	23	Female	Negative	OS	1.0	0.5	Nodular	+	Decreased	1+	NAD	21 (blistering)
2	12	Female	Negative	OD	0.05	1.0	Sectoral	+	Decreased	2+	NAD	24
3	33	Female	Negative	OD	0.5	1.0	Sectoral	+	Decreased	2+	NAD	20
4	46	Female	Negative	OD	0.5	0.9	Sectoral	+	Decreased	2+	NAD	21
5	18	Female	Negative	OU	0.5	0.4	Sectoral	+	Decreased	1+	NAD	24
6	31	Female	Negative	OU	0.05	0.05	Nodular	+	Decreased	Trace	NAD	20 (blistering)
7	23	Female	Negative	OD	0.6	0.9	Nodular	+	Decreased	1+	NAD	20
8	21	Female	Negative	OU	0.5	0.6	Sectoral	+	Decreased	Trace	NAD	20
9	53	Female	Positive	OD	0.7	0.9	Nodular	+	Decreased	1+	NAD	15
10	26	Female	Negative	OD	0.4	1.0	Sectoral	+	Decreased	1+	NAD	18
11	34	Female	Negative	OS	1.0	0.7	Sectoral	+	Decreased	Trace	NAD	20
12	29	Female	Negative	OD	0.7	1.0	Sectoral	+	Decreased	1+	NAD	19
13	27	Female	Negative	OD	0.6	0.9	Sectoral	+	Decreased	1+	NAD	17
14	30	Female	Negative	OS	1.0	0.5	Sectoral	+	Decreased	1+	NAD	19

ID no. identification number, *HIV* human immunodeficiency virus, *VA* visual acuity, *CXR* chest X-ray, *PPD* purified protein derivative.

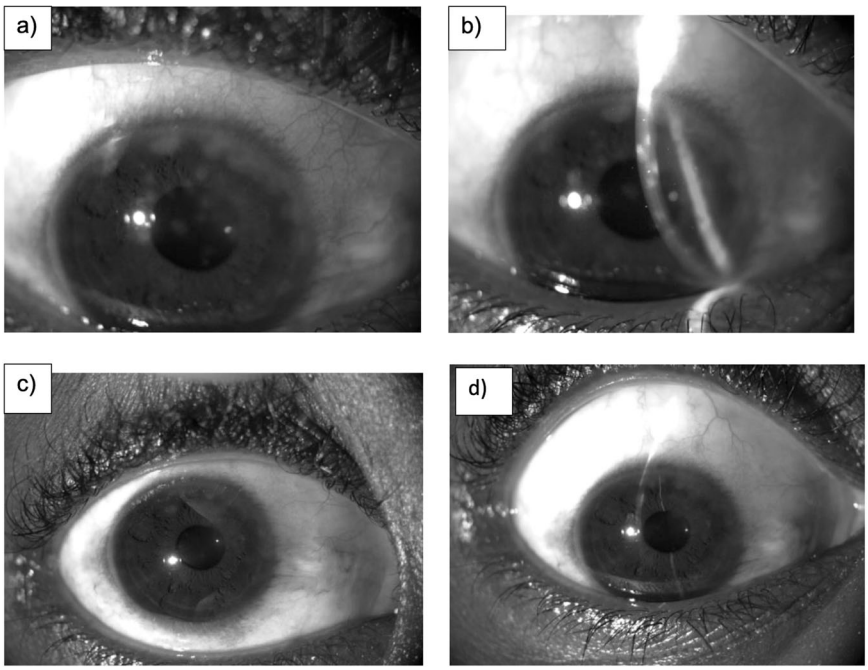

Fig. 2 Right sclerokeratouveitis. **a** On presentation, **b** oblique slit beam highlighting the stromal opacities, **c**, **d** response after 3 weeks of ATT.

Discussion

An extensive literature review revealed a paucity of publications dealing with the topic of sclerokeratouveitis—especially against the backdrop of ocular TB.

Obtaining microbiological or histopathological evidence of *M. tuberculosis*, in the setting of ocular TB, continuous to pose a challenge due to the small sample volumes typically obtained from the eye and the mostly pauci-bacillary nature of the disease. Although culture is regarded as the gold standard for the diagnosis of TB in general, it is seldom utilized on ocular samples due to its very low sensitivity. The long time period required (up to 42 days) for *M. tuberculosis* to grow in culture is also a major drawback in diagnosing ocular TB in routine clinical practice [7].

The case report illustrates the diagnostic challenge clinicians face with ocular TB. As a result of the decreased corneal sensation the diagnosis was initially thought to be herpetic. This highlights the importance of maintaining a high index of suspicion of ocular TB, especially in endemic areas, in cases of sclerokeratouveitis. The positive trial of ATT was valuable in this case, given the negative workup for other causes of sclerokeratouveitis and failure to respond to the other treatment modalities.

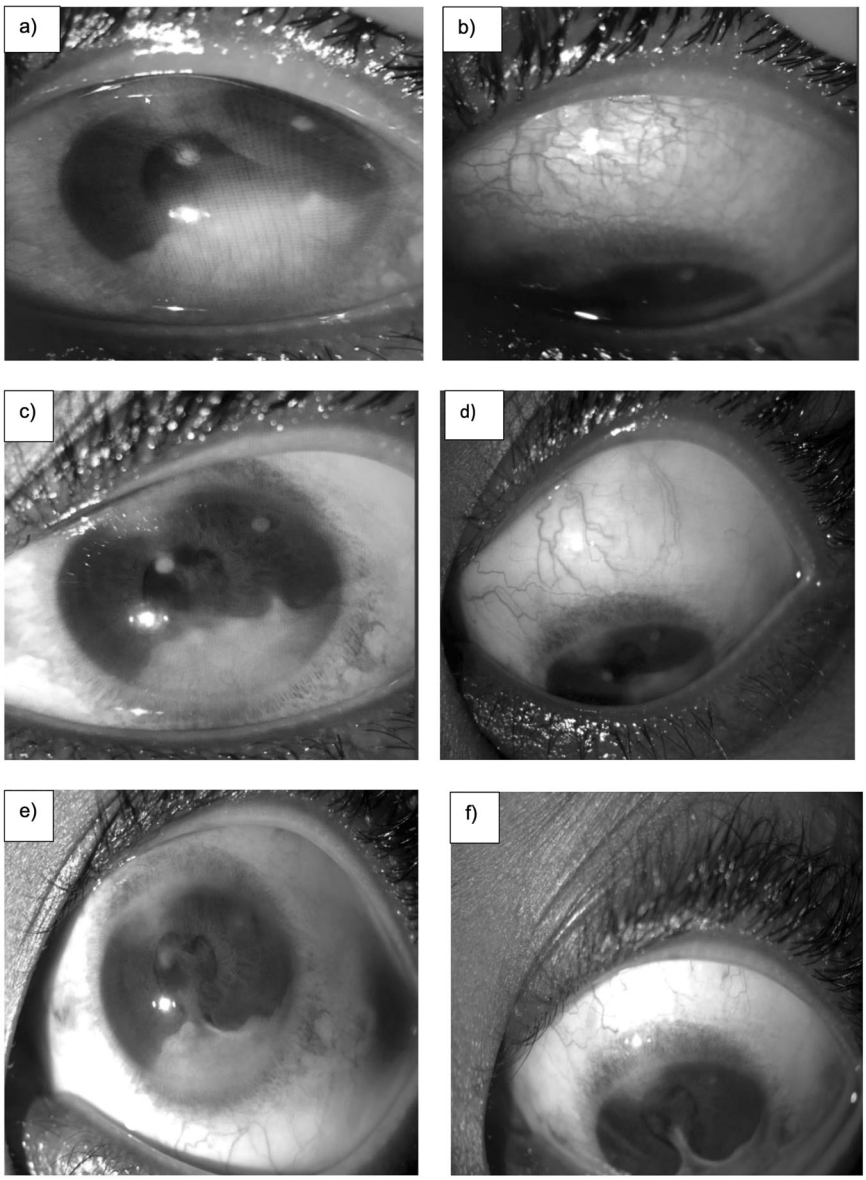

Fig. 3 Left sclerokeratouveitis. **a**, **b** On presentation, **c**, **d** response after 3 weeks of ATT, **e**, **f** response after 6 months of ATT.

It has been well described that TB may cause scleritis, which can occur in isolation or associated with corneal or intraocular involvement [8]. The reported prevalence of infectious scleritis varies between different published retrospective series. Gonzalez-Gonzalez et al. found that of the 500 patients diagnosed with scleritis, the prevalence of infectious scleritis was reported to be 9.4%, with TB accounting for 10.6% of these cases [9]. Tuberculous scleritis may result from either direct scleral invasion by *M. tuberculosis* or an immunological reaction to circulating mycobacterial antigens [3]. The scleral involvement in the patients described in this study was nodular in four and diffuse in ten.

The corneal involvement was adjacent to the area of scleritis, with deep stromal vessels and ill-defined stromal opacities, and all eleven patients had decreased corneal sensation. Upon subsequent treatment with ATT, stromal opacities appeared less dense with residual scarring and regression of deep stromal vessels.

Our patients showed some similarities to those described by Shoughy et al. as having sclerokeratitis [3]. These similarities include a strong female preponderance (seven females and one male), similar age distribution (mean age 29 years), lack of response to corticosteroids, and excellent response to ATT without immunosuppression. A few differences are however also noted in that all their cases were unilateral, they had more patients with nodular scleritis than diffuse scleritis and only 3 of 8 cases had uveitis. In our case series we identified a more detailed pattern of disease that has not been described previously. Our

typical patient: (1) was female, (2) was immunocompetent (all were HIV− except for one who had evidence of immune reconstitution on ARV treatment), (3) had a strong positive TST result, (4) had a negative CXR, (5) had sclerokeratouveitis, (6) had decreased corneal sensation, and (7) either responded poorly to corticosteroid treatment or responded very well to ATT alone or both.

At this point it is probably too early to hypothesize about the reasons behind this pattern. It is unclear why we have only documented it in females. The finding that this pattern was only observed in immunocompetent individuals is also a thought-provoking one. In many variants of ocular TB there appears to be an interplay between direct mycobacterial infection on the one hand and the immunological response to it on the other and one often has to utilize a combination of ATT and immunosuppression to successfully treat these conditions. What is intriguing however is the fact that in this scenario we have documented a marked reduction in ocular inflammation when using ATT without any immunosuppressive drugs, while immunosuppressive drugs alone made virtually no impact on the ocular inflammation. This seems to imply that the sclerokeratouveitis is probably caused by direct infection.

The decreased corneal sensation is also an unexpected finding and warrants consideration. A noteworthy finding was that patients with diffuse scleritis had diffusely reduced corneal sensation whereas patients who only demonstrated sectoral scleritis had reduced corneal sensation corresponding to the inflamed scleral sectors. One possible explanation for this phenomenon might be that the long ciliary branches of the trigeminal nerve which supply corneal sensation have to pass through the inflamed sclera en route to the trigeminal ganglion and that the surrounding scleral inflammation may somehow reduce the conduction along these nerves although further investigation will be required to determine whether this is indeed the case.

In this paper we have described a clinical appearance of presumed ocular TB that appears to follow a fairly distinct pattern in a country where TB is highly endemic. Shoughy et al. [3] described a similar clinical presentation of sclerokeratitis in a small case series from Saudi Arabia; a country also known as a TB endemic area. It is too early to know whether cases in countries with a low TB burden would present in a similar way but hopefully this case series will stimulate greater awareness and surveillance elsewhere. If clinicians are unaware of this pattern, if they do not perform a TST or IGRA to search for the possible presence of TB and if they are misled by the finding of decreased corneal sensation it is quite possible that these patients will be treated with antiviral medication and immunosuppressives without the desired outcome. A high index of suspicion must therefore be maintained if this condition is to be correctly diagnosed and treated.

Summary

What was known before

- The large variations in clinical presentation and the lack of uniformity in diagnostic criteria make the diagnosis of ocular TB challenging.
- It has been well described, especially in endemic areas, that TB may cause scleritis or interstitial keratitis.
- Gupta et al. proposed a revised classification for ocular TB which lists six clinical signs considered to be highly suggestive of ocular TB. Interestingly enough, sclerokeratouveitis is not one of these signs

What this study adds

- An extensive literature review revealed a paucity of publications dealing with the topic of sclerokeratouveitis —especially against the backdrop of ocular TB.
- In this paper we have described a novel variant of ocular TB that appears to follow a fairly distinct pattern in a country where TB is highly endemic.

Author contributions DM was responsible for the review of literature, and preparation of the case series as per journal's requirements. DS was responsible for conceptualization and design of the research and editing of the final article.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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