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RESEARCH ARTICLE

Unusual Corneal Sarcoidosis Manifestations

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ABSTRACT

Aim: To document atypical presenting forms of ocular sarcoidosis at the corneal level.
Methods: Case report.
Results: A 63-year-old woman presented multiple uncommon unilateral primary corneal conditions as manifestation of ocular sarcoidosis, including peripheral ulcerative keratitis, sterile corneal infiltrate (corneal granuloma), and sterile infiltrates related to a corneal foreign body, requiring medical and surgical management to control the inflammatory symptoms and to preserve the integrity of the eyeball. An excisional biopsy of a nodule in the temporal conjunctiva was performed under topical anesthesia. Histological analysis revealed a non-caseating granuloma, confirming the diagnosis of ocular sarcoidosis.
Conclusion: When thinking of ocular involvement in patients with ocular sarcoidosis, it is essential to remember that manifestations such as peripheral ulcerative keratitis, sterile corneal infiltrate, and sterile foreign body-related infiltrates may be presentations of this disease.

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Corneal granuloma; corneal surgery; ocular sarcoidosis; sarcoidosis; ulcerative keratitis

Sarcoidosis is a multisystem granulomatous disease whose pathophysiology is not entirely clear. It can affect almost any organ, but involvement of the mediastinal lymphatic system, lungs, skin, and eyes are prevalent. A definitive diagnosis of sarcoidosis requires histopathological confirmation of non-caseating granulomas.[1]

Ophthalmologic involvement has been documented in 20 to 50% of sarcoidosis cases, and it is the first manifestation in up to 20%. Virtually any portion of the globe can be affected, but the most frequent ocular manifestation is uveitis which can be anterior, intermediate, posterior, or panuveitis, usually bilateral and chronic.[2] Ocular surface involvement is not uncommon and may appear as aqueous tear deficiency, lacrimal gland infiltration, infiltration of the ocular surface, episcleritis, conjunctival nodules, or conjunctival scarring. Conversely, primary corneal involvement is sporadic, but secondary corneal involvement can be caused by keratitis sicca due to lacrimal gland infiltration and the development of band keratopathy as a consequence of chronic uveitis.[1,3]

In this publication, we document a challenging corneal case of atypical sarcoidosis ocular manifestations through several years with multiple unilateral primary corneal conditions, including peripheral ulcerative keratitis, sterile corneal infiltrates (corneal granuloma), and sterile infiltrates related to a corneal foreign body. We also described the interventions and therapeutic recommendations for approaching each of these corneal manifestations.

Case report

A 63-year-old female patient came to our cornea service for the first time five years ago, showing ocular inflammation of the right eye. By then, ophthalmologic examination revealed the presence of nasal and temporal peripheral ulcerative keratitis (PUK) of the right eye without uveitis, requiring management with lubricants, topical steroids, and conjunctival recession (Figure 1a). In addition, conjunctival biopsy reported the absence of vasculitis, and systemic studies were initiated in search of an infectious or rheumatologic pathology that could explain PUK.

Our patient had a history of type 2 diabetes mellitus controlled with insulin, hypertension, medium effort dyspnea studied for ten years by pneumology without chronic obstructive pulmonary disease criteria nor evidence of neoplasia by imaging (X-ray and CT scan) classified for several years as adult asthma, coronary vasospasm under follow-up by cardiology with two negative catheterizations for ischemia, rosacea under management by dermatology and knees and elbows chronic pain under management with analgesics by orthopedics.

The studies searching for the origin of PUK included: hemoleukogram (normal), c-reactive protein and erythrocyte sedimentation (normal), renal function (normal), electrolytes including calcium (normal), liver function tests (normal), urinalysis (normal), venereal disease research laboratory (VDRL), and fluoresscent treponemal antibody-absorption (FTA-Abs) (non-reactive), tuberculin purified protein derivate (PPD) (6 mm), rheumatoid factor (negative), antinuclear antibodies (positive 1:80 homogeneous pattern), extractable nuclear antigens (negative), antineutrophil cytoplasmic antibodies (negative) and chest X-ray which evidenced chronic central bronchial-interstitial inflammatory changes. With these results, the patient was evaluated by internal medicine and rheumatology, but no findings suggestive of inflammatory joint or connective tissue pathology could explain PUK.

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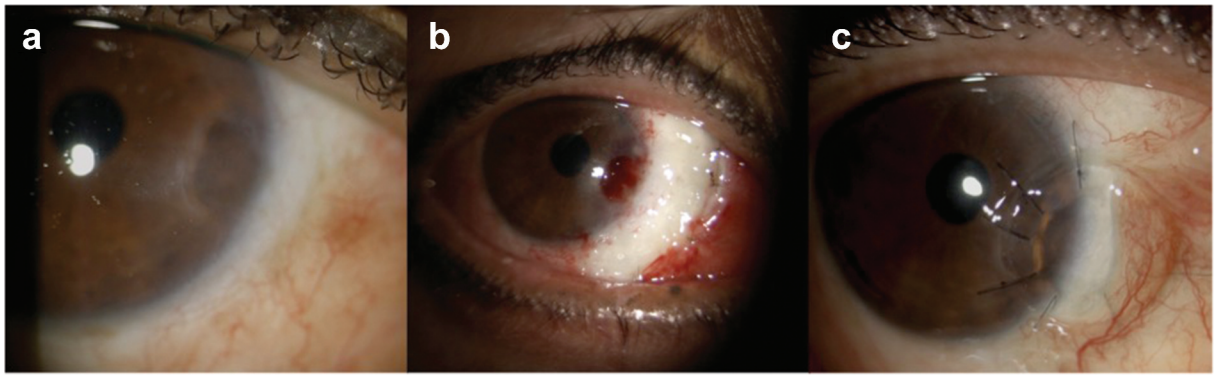

Figure 1. a) Slit-lamp photography showing the right eye with an area of residual nasal thinning secondary to nasal PUK 4 months postoperatively. b) Slit-lamp photography showing nasal conjunctival recession required in one of the inflammatory reactivations. c) Slit-lamp photography showing nasal eccentric lamellar corneal graft one month postoperatively.

The patient was observed closely for approximately three years, showing various inflammatory relapses of nasal and temporal PUK and requiring prolonged management with lubricants, steroids, and two other conjunctival recessions (one nasal and one temporal) (Figure 1b). During one of the inflammatory relapses, mild anterior uveitis (+1 cellularity, no synechiae or hypopyon) most likely secondary to the ocular surface inflammation was evident and responded rapidly to steroid management. One nasal PUK reactivation included a very severe thinning that reached 85% depth; after cooling the acute inflammation response, management with nasal eccentric lamellar corneal graft was performed to avoid corneal perforation in a possible future reactivation (Figure 1c).

During the fourth year of follow-up, the patient presented an inflammatory reactivation of temporal PUK associated with a deep corneal infiltrate of progressive and slow growth in the inferotemporal quadrant (Figure 2a). Cultures of the infiltrate were negative, and empirical moxifloxacin 0.5% administration (Vigamoxi-Alcon Laboratories, Inc. Fort Worth, Texas - United States) was started. However, after one month of

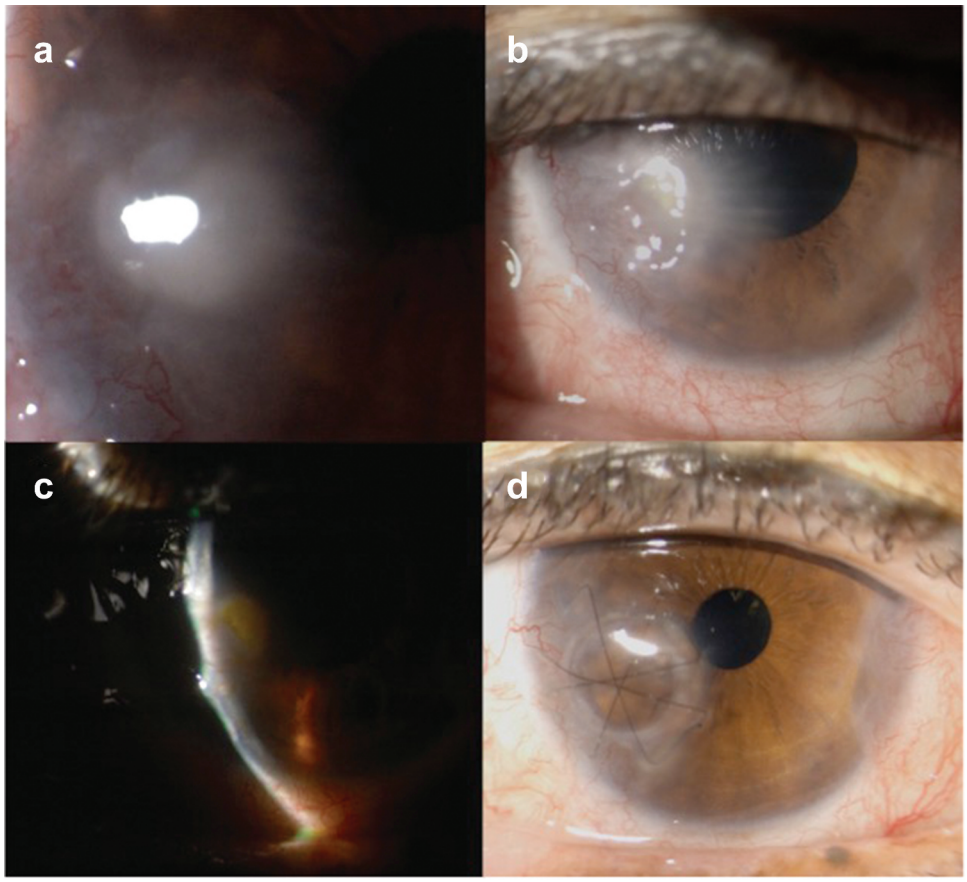

Figure 2. b) Slit-lamp photography showing the right eye with deep corneal infiltrate located in the inferotemporal quadrant. b) Corneal infiltrate after one month with antibiotic treatment. c) Slit image of corneal infiltrates after one month with antibiotic treatment showing deep involvement. d) Slit-lamp photography showing one month postoperative deep corneal biopsy with a 3 mm punch and a corneal graft at this level.

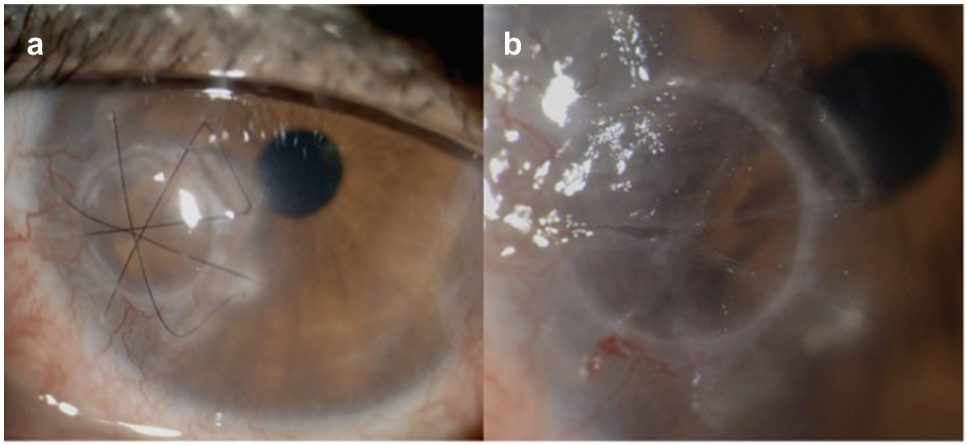

Figure 3. a) Slit-lamp photography showing the right eye with infiltrates in the corneal graft sutures path. b) Close-up of corneal infiltrates immediately after sutures removal.

antibiotic treatment, the infiltrate persisted and became deeper (Figure 2b,c), so fortified antibiotics were prescribed. After two months of antibiotic treatment without satisfactory response, a deep corneal biopsy was performed with a 3 mm punch and a corneal plug graft was placed at that level (Figure 2d). The resected corneal tissue was divided into two fragments; one destined for culture (aerobic, anaerobic, mycobacteria, superficial and deep mycoses) and the other for biopsy. All cultures were negative, and the biopsy reported an insufficient sample for histopathological analysis.

The patient evolved well initially, showing no recurrence of the infiltrate; however, after two months, multifocal corneal infiltrates related to the path of the sutures were evidenced (Figure 3a). Therefore, sutures were removed, and topical moxifloxacin 0.5% administration started (Vigamoxi-Alcon Laboratories, Inc. Fort Worth, Texas -United States). Microbiological cultures of the removed sutures were performed, with negative results (Figure 3b). Consequently, due to the negative results and the absence of response to antibiotics, administration of prednisolone 1% drops three times a day was started (Pred F - Allergan Pharmaceuticals, Waco, Texas - United States), showing an excellent response within 1 week.

Six months later, the patient reported intermittent irritation of the temporal conjunctiva; no PUK reactivation was evidenced, but a 2x2mm temporal conjunctival nodule was found (Figure 4a). Furthermore, the patient reported the appearance of erythematous and pruritic skin lesions of hands and forearms dorsum that improved with sun exposure. A directed biopsy for the temporal conjunctival nodular lesion of the right eye was performed and, histopathological analysis revealed a conjunctival mucosa with granuloma at the lamina propria level, composed of epithelioid histiocytes and some multinucleated giant cells with minimal adjacent lymphocytic infiltrate, without areas of necrosis or suppuration (Figure 4b). This histopatological findings added to the spectrum of eye and systemic clinical manifestations supported the diagnosis of sarcoidosis. Additionally, an online dermatological assessment of the skin lesions was performed, clinically suspecting granuloma annulare, but a skin biopsy was pending.

With the diagnosis of sarcoidosis, the patient was referred back to rheumatology to re-evaluate multisystem involvement (pulmonary, cardiovascular, cutaneous, among others) and for considering systemic management of her

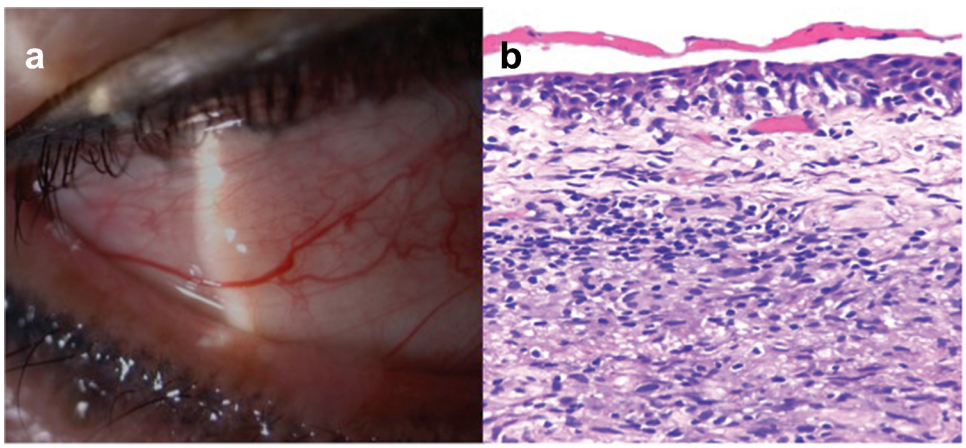

Figure 4. a) Slit-lamp photography showing the right eye temporal conjunctival nodule. b) Histological characterization, hematoxylin-eosin (H&E) staining at 10X: Granuloma composed of epithelioid histiocytes and some multinucleated giant cells without necrosis or suppuration. Minimal adjacent lymphocytic infiltrate.

pathology. However, this assessment was not possible, nor was a biopsy of the skin lesions due to the patient's death from COVID-19.

Discussion

Primary corneal involvement in ocular sarcoidosis is infrequent, with only a few case reports in the world literature.[4–6] The case presented in this article describes different types of unilateral corneal involvement over five years of follow-up as the primary manifestation of ocular sarcoidosis.

Peripheral ulcerative keratitis usually occurs due to infectious and immunologic causes, and is common in patients with rheumatoid arthritis; its pathophysiology usually involves the deposition of immune complexes with microangiitis at the level of the limbar vascular arcade.[7] Currently, there are only two case reports of PUK in patients with sarcoidosis as underlying systemic disease; however, the pathophysiological connection between these two conditions is not entirely clear since systemic vasculitis has been described in patients with sarcoidosis, but it is infrequent.[4,5] Moreover, PUK is more uncommon in patients with sarcoidosis than other pathologies frequently associated with systemic vasculitic processes such as rheumatoid arthritis and granulomatosis with polyangiitis. PUK was the primary ocular manifestation of the disease in our patient, showing multiple inflammatory reactivations both nasal and temporal and requiring medical and surgical management. Biopsies of the resected conjunctiva in the conjunctival recessions performed failed to demonstrate the presence of active vasculitis.

The development of interstitial keratitis and corneal infiltrates related to sarcoidosis is very unusual and might be granulomatous. So far, only one case of sarcoidosis-related keratitis has been described; it consisted of multifocal sub-epithelial lesions in a 3-year-old girl whose diagnosis of sarcoidosis was confirmed one year after the keratitis episode through renal biopsy; the described infiltrates responded satisfactorily to steroid treatment.[6] Conversely, our patient showed a deep, single focus corneal infiltrate first thought to be infectious; however, it was sterile, as confirmed by the negative culture results and poor response to antibiotic therapy. Thus, although we suspected it could have been a granulomatous infiltrate (intrastromal corneal granuloma) due to its excellent response to steroids, histopathology could not confirm it because the sample was insufficient. Furthermore, there are no reports of interstitial keratitis, corneal infiltrates, or corneal granulomas similar to the clinical presentation in our patient.

Sterile infiltrates related to corneal sutures were another corneal manifestation in our patient; negative cultures revealed their sterile character, besides the poor response to antibiotic therapy and excellent response after suture removal and steroid management. Commonly, several biological tissues can develop foreign body reactions, involving the development of an inflammatory reaction with the formation of a granuloma composed of proteins, macrophages, and multinucleated giant cells in response to a foreign body. Therefore, we believe that it is not a coincidence that sarcoidosis is a granulomatous disease, and there may be a greater predisposition in the patients experiencing it to develop granulomatous sterile infiltrates in reaction to corneal foreign bodies (sutures).[8]

It is critical to mention that this case is difficult to classify as definitive, presumed or probable ocular sarcoidosis according to the latest published criteria for the diagnosis of ocular sarcoidosis, since these ocular sarcoidosis categories are based on diagnostic criteria that include, as ocular manifestations the most commonly observed findings at the ocular level, especially granulomatous uveitis and findings in the posterior pole. The primary corneal findings described in this case are rare and therefore are not part of these criteria. The uveitis presented by the patient was a mild non-granulomatous anterior uveitis, which we consider to be secondary to recurrent ocular surface and cornea inflammation and not a primary uveitis. The direct conjunctival biopsy suggestive of sarcoidosis added to the ocular findings and to the diagnostic studies carried out, led to the diagnosis of sarcoidosis, that we considered to be definitive because it was supported by histopathological findings.[9] This is why it is very important to take directed conjunctiva biopsies, as they have a greater chance of showing granulomatous infiltration.

Finally, even though primary corneal involvement is rare in patients with ocular sarcoidosis, it is important to consider that manifestations such as PUK, sterile corneal infiltrates, and sterile foreign body-related infiltrates can be infrequent presentations of sarcoidosis.

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Disclosure statement

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References

1. Salah S, Abad S, Monnet D, et al. Sarcoidosis. *J Fr Ophthalmol.* 2018;41(10):e451–e467. doi:10.1016/j.jfo.2018.10.002.

2. Hwang DK, Sheu SJ. An update on the diagnosis and management of ocular sarcoidosis. *Curr Opin Ophthalmol*. 2020;31:521–531. doi:10.1097/ICU.0000000000000704.
3. Yang SJ, Salek S, Rosenbaum JT. Ocular sarcoidosis: new diagnostic modalities and treatment. *Curr Opin Pulm Med*. 2017;23 (5):458–467. doi:10.1097/MCP.0000000000000409.
4. Siracuse-Lee D, Saffra N. Peripheral ulcerative keratitis in sarcoidosis: a case report. *Cornea*. 2006;25:618–620. doi:10.1097/01.ico.0000183486.93259.c9.
5. Harthan JS, Reender RE. Peripheral ulcerative keratitis in association with sarcoidosis. *Cont Lens Anterior Eye*. 2013;36:313–317. doi:10.1016/j.clae.2013.07.013.
6. De Boer JH, Sijssens KM, Smeekens AEFN, et al. Keratitis and arthritis in children with sarcoidosis. *Br J Ophthalmol*. 2009;93 (6):835–844. doi:10.1136/bjo.2007.134601.
7. Gupta Y, Kishore A, Kumari P, et al. Peripheral ulcerative keratitis. *Surv Ophthalmol*. 2021;66:977–998. doi:10.1016/j.survophthal.2021.02.013.
8. Anderson JM, Rodriguez A, Chang DT, et al. Foreign body reaction to biomaterials. *Semin Immunol*. 2008;20:86–100. doi:10.1016/j.smim.2007.11.004.
9. Mochizuki M, Smith JR, Takase H, et al. Revised criteria of International Workshop on Ocular Sarcoidosis (IWOS) for the diagnosis of ocular sarcoidosis. *Br J Ophthalmol*. 2019;103 (10):1418–1422. doi:10.1136/bjophthalmol-2018-313356.