ISSN: 2641-6360
DOI: 10.33552/WJOVR.2026.05.000625
World Journal of Ophthalmology & Vision Research
Iris Publishers

Case Report

Rheumatoid Associated Scleromalacia Perforans Treated with Disodium Edetate (EDTA)

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Received Date: March 10, 2026

Published Date: June 23, 2026

Abstract

Purpose: To report a case of Scleromalacia perforans (SP) associated with rheumatoid arthritis (RA) treated with disodium edetate (EDTA).

Methods: The patient selected for this case report is an 82-year-old woman with erosive, nodular, seropositive RA who developed scleral melts, despite receiving continuous treatment with different immunosuppressive agents. Her clinical course, characterized by increasingly severe scleral melts and complications, exemplifies the challenges associated with treating this illness. The therapeutic approach necessitated several iterations due to the continuous progression of the disease and development of adverse effects, finally settling on Mycophenolate, Prednisolone and EDTA eye drops.

Results: The patient responded well to the tailored regimen, especially to the EDTA eye drops, which showed promising results in halting disease progression.

Conclusions: This case highlights the difficulties and factors which need to be taken into account when managing SP in the setting of RA. After conducting a literature review on PubMed and Google Scholar using the keywords (Scleromalacia perforans; Rheumatoid arthritis; Disodium edetate) we did not find prior reports of rheumatoid associated SP treated with EDTA with a positive clinical response.

Keywords: Scleromalacia perforans; Rheumatoid arthritis; EDTA; Disodium edetate

Abbreviations: EDTA: Disodium edetate; SP: Scleromalacia perforans; RA: Rheumatoid arthritis

Introduction

Scleromalacia perforans (SP), alternatively termed anterior necrotising scleritis without inflammation, is distinguished by its non-inflammatory nature, manifesting primarily a degenerative process. It was described by van der Hoeve in 1934 as a bilateral disease limited to the sclera, commencing as yellow growths beneath the conjunctiva which progress into necrotic lesions that may coalesce. Subsequently, the sclera undergoes thinning exposing the uvea and ultimately leading to the perforation of ocular globe [1]. It must be noted that senile hyaline scleral plaques may have a resembling clinical picture with hollowed-out grey patches.

Although it is most commonly found in patients diagnosed with RA, SP has been linked to several other pathologies such as systemic lupus erythematosus, limited scleroderma, Behcet's disease, Crohn's disease, granulomatosis with polyangiitis, periarteritis nodosa, graft-versus-host disease, porphyria, and Herpes zoster infection [2]. RA can present with various ophthalmological manifestations including Sjogren syndrome, episcleritis, scleritis and corneal ulcers, with the latter two considered the most severe.

Case Report

An 82-year-old woman, diagnosed with seropositive, erosive, nodular RA at the age of 30, was referred to the ophthalmology clinic on the 3rd of September 2019. The patient was taking Humira and Prednisolone at the time of consultation after suffering adverse effects from Methotrexate and Hydroxychloroquine. Alongside her RA, she was battling osteoporosis and for which she was being treated with Ranitidine, Denosumab, and Vitamin D.

On examination of the anterior segment of the eyes, an area of scleral melt along the inferonasal margin of the right eye was observed, measuring 1.3mm in diameter. In the left eye, three distinct areas of scleral melt were noted in the following regions: superotemporally, measuring 2.0 x 4.0 mm, superonasally measuring 1.5 x 2.5 mm, and another one in the inferotemporal limbal region. Both eyes displayed signs of punctate epithelial erosions on the cornea. At her subsequent follow-up, there was an increase in the size of scleral melt lesions, particularly the one located superotemporally, reaching a size of 6.0 x 7.0 mm, warranting escalated Doxycycline and Prednisolone dosages.

After discussions with her rheumatology team in early 2020, it was decided that she should have six Cyclophosphamide infusions starting from February through May. After finishing the 6 courses in May 2020, it became evident that there were signs of extreme skin fragility and bruising hence Prednisolone was reduced to 5mg per day and Mycophenolate was added to her treatment plan. However, the patient was experiencing loss of appetite and increased fatigue necessitating the discontinuation of Mycophenolate and substitution with Ciclosporin as an alternative anti-rheumatoid drug.

At her ophthalmology clinic visit in June 2020, the slit lamp examination revealed posterior lid margin disease, slightly active nodular scleritis, multiple scleral melts which seemed inactive and punctate epithelial erosions on the cornea. The patient was advised to continue Doxycycline and was started on Tacrolimus 0.1% ointment for 2 months and Dexamethasone 0.1% eye drops for 4 weeks.

Following a month, the RA symptoms in the patient were still uncontrolled with sustained morning stiffness as well as pain and swellings in the metacarpophalangeal and proximal interphalangeal joints of both hands. The rheumatology consultant decided that it was necessary to incorporate Rituximab in the drug regimen she had for her course of action. Unfortunately, the infusions were delayed by a traumatic injury, leading to a severe RA flare in October 2020, affecting her eyes.

The patient reported painful eyes in February 2021 in addition to the size enlargement of a grey area and appearance of a new scleral melt area. As a result, her oral dosage of prednisolone was escalated to 10 mg. SP progressed by March 2021, and the patient reported that cyclosporine was not tolerable, therefore Occ. Cyclosporine 0.2% was prescribed. In the same month, the rheumatology and the ophthalmology teams joined together and decided to start with Mycophenolate 1 g tablets and EDTA eye drops as part of the patient's treatment plan. Her regimen by May 2021 consisted of Mycophenolate 1g; Prednisolone 10 mg; Doxycycline 100mg; occ Cyclosporin 0.2% eye ointment; and EDTA eye drops. Following this revised regimen, the patient reported increased comfort in her eyes and observed improvement in the scleral melt areas.

The patient's current regimen consists of Mycophenolate 1g bd, Doxycycline 50 mg, Prednisolone 5 mg, Carmize 1% eye drops and EDTA 0.37% eye drops.

Results

The SP seemed to have stalled in progression since starting EDTA eye drops. No further flare-ups were reported by the patient. On her last ophthalmology control in February 2024, a specular microscopy count was done, which showed a good cell count, therefore there is no report of corneal endothelial damage so far. The progression and halt of progression of the scleral melt lesions since the patient's first ophthalmology visit until her last can be seen in Figure 1, noting that EDTA was started in May 2021.

Discussion

The ocular presentation in rheumatoid associated SP is explained by the histological similarities between the sclera, cornea and the joints which were initially highlighted by Verhoeff and King [3]. They are avascular structures made of connective tissue rich in elastin, collagen and proteoglycans. The proteoglycans encircle each collagen fibril, run along its length and joins it to the next one. The fibrocytes, also known as sclerocytes, maintain its integrity by interacting with each other [7].

The sclera can be damaged by 3 processes: prolonged local vaso-occlusion, scleral fibrocytes activation, pericellular matrix resorption and inflammatory cell infiltration of the scleral stroma. When the cytokine release triggers sclerocyte activation, it initiates destructive catabolic changes, such as the reduction of the tissue inhibitors of metalloproteinases, leading to the removal of the proteoglycan from the collagen fibril. This exposes the collagen to the immune system, along with increased collagenase levels, ultimately contributing to collagen breakdown [8]. The necrotic process in SP appears to be triggered by arteriolar obstruction caused by a type III hypersensitivity reaction [2-4], which explains the use of immunomodulatory drugs in this condition. In the late stages of the disease patients may develop astigmatism due to changes in the paralimbus, cornea and sclera which can ultimately lead to visual loss or glaucoma caused by structural abnormalities or corticosteroid therapy.

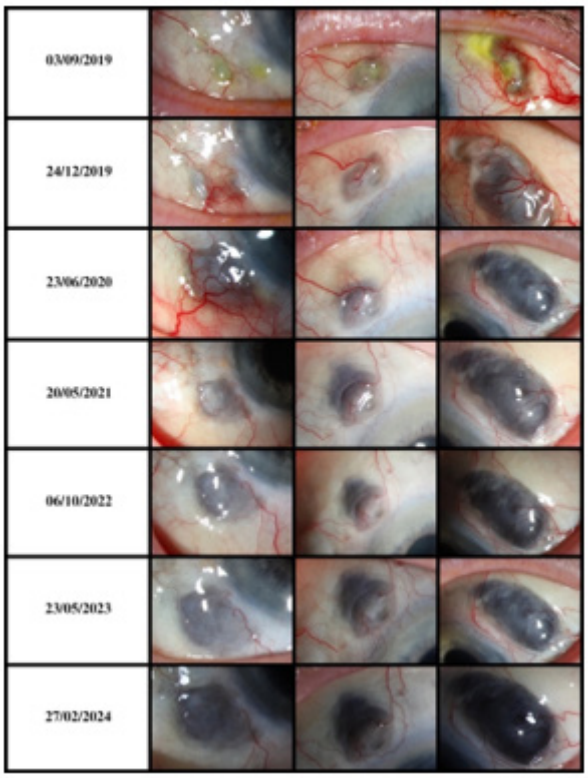

Figure 1: Progression of scleral melt areas.

Therapeutical approaches for SP include steroid therapy, immunosuppressive drugs and sodium versenate [5] for cases that are refractory to the aforementioned drugs. Once the urea is exposed, patch grafting is required [2]. There have been several cases reported since its first description in 1934, however, this is the first report of a rheumatoid associated SP treated with EDTA that resulted in a progression cessation of the lesions. Although EDTA is commonly used for managing heavy metal intoxication, the study conducted by Senoo, et al. have revealed that EDTA prompts corneal endothelial cell proliferation [6].

Based Francois's findings, we know that collagenase is not produced by the epithelium, but rather by the connective tissue cells, such as fibroblasts and microphages. Additionally, the activity of this enzyme relies on two ions: Zinc and Calcium. Notably, the removal of these ions using EDTA abolishes collagenase activity entirely, emphasising their essential role, as previously demonstrated by Mandl in 1972 [5-10].

Furthermore, EDTA also decreases the stimulation of neutrophil migration, which consequently decreases the release of proteinases. However, it is important to mention that EDTA may potentially pose toxicity risks to corneal epithelium in vivo. EDTA effects on cornea were investigated only in concentrations in which it was used as a preservative (0.00001% and 0.015%), much lower than those required for the anticollagenase activity (0.3%, 1% or 2%), therefore further studies are required [11].

In the article written by Evans and Eustace, the following improvements were noted in the eyes after a scleral graft procedure and the use of EDTA eye drops: resolution of conjunctival congestion, filling of the scleral defects and the minimisation of limbal guttering [5]. Based on these findings it was decided to treat this case with EDTA.

Conclusions

This case report highlights the capacity of EDTA to halt the progression of scleral melt areas in SP. Further studies are required to accurately describe the possible toxic effects of this drug on the cornea.

Acknowledgements

The authors would like to thank Dr. Stefania Giulvezan for assistance in obtaining additional clinical images.

Competing Interests

The authors declare no potential conflicts of interests with respect to the research, authorship or publication of this article.

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