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Paracentral Corneal Ulceration in Secondary Sjogren Syndrome Successfully Treated with Fibrin Glue and Cenegermin: A Case Report

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Abstract

An 84-year-old woman came to our attention, complaining of decreased visual acuity. The patient was affected by Sjogren syndrome secondary to rheumatoid arthritis for 15 years and developed a paracentral corneal ulcer. The treatment consisted of covering and filling the ulcer with fibrin glue and placing a soft contact lens. Furthermore we started topical treatment with cenegermin eye drop and prophylactic topical antibiotic. In two weeks, we achieved a significant improvement in stromal thickness and resolution of the epithelial defect. After four weeks, we observed an improvement in sensitivity, evaluated with confocal microscopy, which returned to normal after eight weeks. Cenegermin is a powerful therapy aimed at increasing corneal sensitivity and promoting the healing process in severe neurotrophic ulcers also combined with surgical corneal repairing techniques.

Introduction

Sjögren syndrome is a multisystemic autoimmune disease characterized by mononuclear infiltration of exocrine glands. The salivary and lacrimal glands' inflammation and destruction lead to dry eye manifestation, namely Keratoconjunctivitis Sicca (KCS) and oral dryness xerostomia.[1]

Diagnostic criteria of Sjögren syndrome are based on the American College of Rheumatology/European League Against Rheumatism (ACR-EULAR) classification.[2]

Sjögren syndrome-related dry eye is a chronic progressive condition with a significant negative impact on the patient's life quality.[3] Patients can experience blurred vision, difficulty in reading despite a normal visual acuity. Paradoxically, a subset of patients can experience more visual disturbances than ocular discomfort due to

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the reduced ocular sensitivity caused by the severe ocular surface disease and inflammation decreasing corneal innervation.[4,5]

The treatment of Sjögren syndrome-associated dry eye aims at interrupting inflammation and symptomatic relief to avoid damage to the ocular surface and cornea and improve ocular dryness signs.[6] Dry eye disease refractory to treatments can lead to severe ocular complications ranging from corneal abrasion to infection, ulceration, melting, and perforation, requiring urgent surgical treatment to prevent further devastating complications.[7] Numerous treatment options for corneal ulcer and perforation are available, ranging from temporizing measures such as glue to corneal transplantation. The size, location, and etiology of the perforation can guide the surgeon in choosing the technique.[8] The decreased corneal innervation and the subsequent decreased corneal sensitivity in Sjögren syndrome can be targeted with a medication belonging to the recombinant human Nerve Growth Factor (rhNGF) class of drugs (Cenegermin).[9,10]

Case Description

An 84-year-old woman came to our attention, complaining of decreased visual acuity.

The patient was affected by Sjogren syndrome secondary to rheumatoid arthritis for 15 years. At slit lamp evaluation the left eye presented a roundish central corneal ulcer of 2.45 millimeters width. Best-Corrected Visual Acuity (BCVA) was hand motion in the affected eye.

Anterior segment evaluation showed a deep, quiet, anterior chamber. Corneal and conjunctival staining with fluorescein and lissamine green was performed. The score was recorded according to SICCA Ocular Staining Score.[11]

The staining score was graded as 6 for corneal staining and 6 for conjunctival staining. Tear film Break Up Time (T-BUT) was 1 second. The Ocular Surface Disease Index (OSDI) was evaluated and resulted in 45.

The Schirmer test I (without anesthesia) was performed with a standardized Schirmer strip placed over the lower lid in the temporal angle, and it showed the result of 2 millimeters at 5 minutes.

Besides, corneal sensitivity was tested in the affected eye by using Cochet-Bonnet aesthesiometer in temporal, nasal, inferior, and superior quadrants of the cornea at 3 millimeters (mm) from the corneal limbus. Furthermore, the conjunctival sensitivity was tested in the nasal and temporal quadrant at 3 mm from the limbus. The sensitivity was tested as well in the contralateral eye, including the central quadrant of the cornea.

Anterior Segment Optical Coherence Tomography (AS-OCT) corneal map, performed with Optovue® (software version:2018,1,0,37), highlighted a deep ulcer with the loss of the epithelium and stroma in to and the preserved integrity of the Descemet membrane - endothelium complex (Figure 1). Confocal microscopy (HEIDELBERG CORNEAL MICROSCOPY) examination was performed.

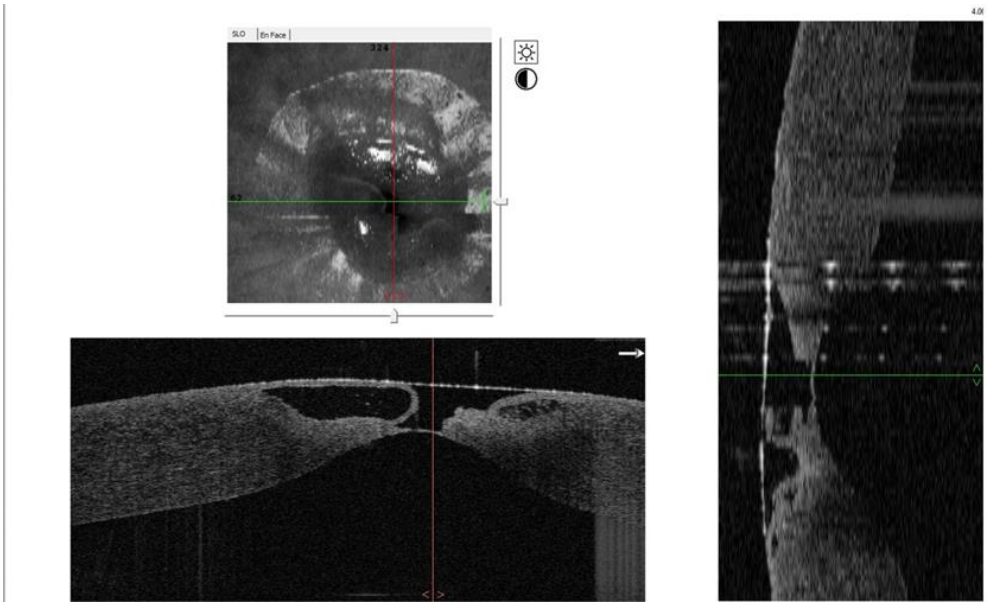

Figure 1: Day 0 OCT-A showing a very deep ulcer with loss of epithelium and stroma, while Descemet's membrane and endothelium remain intact.

The informed consent was explained and then signed by the patient.

Topical anesthesia with oxybuprocaine chlorhydrate 4% was performed. In an aseptic environment, periocular tissues disinfection was performed with iodopovidone solution at 10% concentration for 5 minutes. A sterile drape and blepharostat were applied. The cornea was dried accurately using sponges, and fibrin glue (TISSEEL®) was applied inside the ulcer and on the perilesional tissue. Eventually, a soft contact lens (Pure Vision® Bauch & Lomb) was applied. Four times a day, topical moxifloxacin has been instilled. We prescribed cenegermin (Oxervate®) for the left eye only, one drop every 2 hours, six times a day. Every two days, an ophthalmological check was performed. One month later, the ulcer stroma recovered to a thickness of 180 micrometers at the thinnest point (Figure 2 and 3). We checked corneal and conjunctival sensitivity with Cochet Bonnet esthesiometer. We noted that the ocular surface sensitivity has improved in the right eye too; the patient admitted having instilled excess eye drops in the contralateral eye, three times daily.

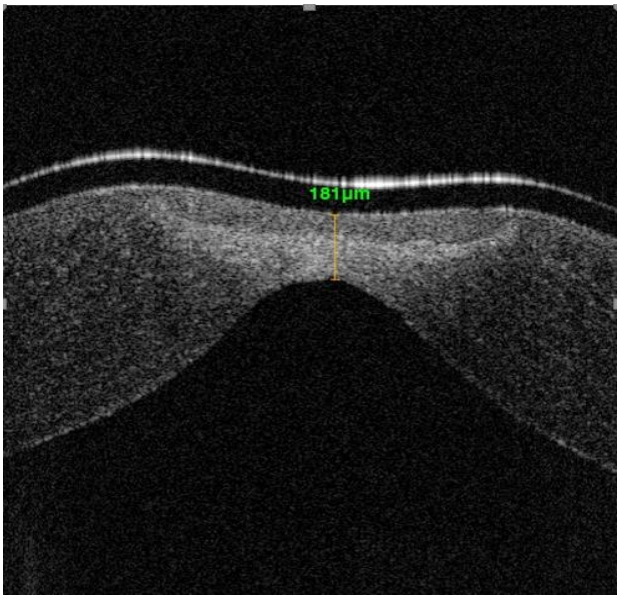

Figure 2: OCT-A after 4 weeks of cenegermin treatment showing stromal thickness of 181 µm and complete resolution of epithelial defect.

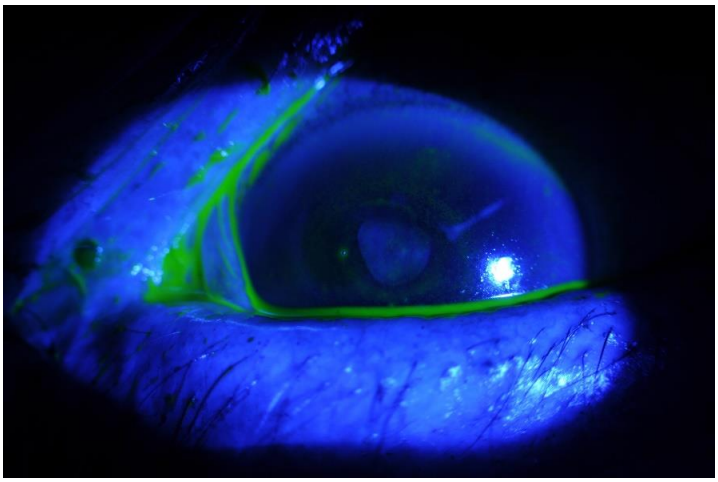

Figure 3: Slit lamp view, after 4 weeks of cenegermin, showing complete resolution of the epithelial defect.

After one year of follow-up, complete resolution of the epithelial defect is maintained, the anterior chamber is quiet, and the stroma has a thickness of 450 microns (Figure 4).

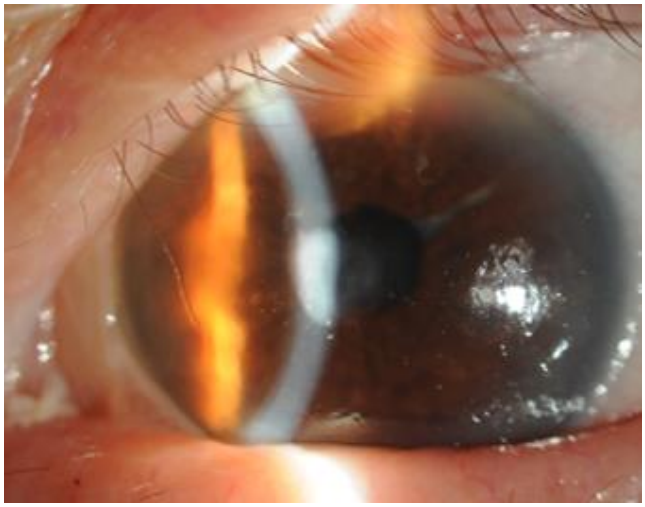

Figure 4: Slit lamp view after 1 year of follow-up showing complete resolution of the epithelial defect, with persistent paracentral leukoma.

Results of in vivo confocal microscopy are summarized in (Table 1).

Table 1: Confocal microscopy

	Left Eye			Right Eye		
	pre Oxervate	4 weeks	8 weeks	pre Oxervate	4 weeks	8 weeks
Confocal microscopy						
Dendritic cells	138±8	136±8	70±6	31±4	38±4	64±6
Nerves (fiber/mm2)	32±4	44±5	56±6	25±3	45±5	50±5
Fiber number	5	6	6	4	7	7
Fiber lenght (micron)	1374,16	1784,75	2063,18	1426,21	2250,18	2602,4

Day 1st: confocal microscopy showed increased presence of Langherans'cells and a decreased nerve fiber concentration.

Two weeks after cenegermin treatment the epithelium healed. Sensitivity and ocular staining score before and after cenegermin treatment are summarized in (Table 2). Final left BCVA was 2/5 (0.4).

Table 2

	Left Eye			Right Eye		
	pre Oxervate	4 weeks	8 weeks	pre Oxervate	4 weeks	8 weeks
Corneal sensitivity						
temporal	0	4	6	0	1	6
superior	0	3	6	0	2	6
nasal	0	4	6	0	2	6
inferior	0	3	6	0	2	6
Conjunctival sensitivity						
temporal	0	2	3	0	2	3
superior	0	1	3	0	2	3
nasal	0	2	3	0	2	3
inferior	0	1	3	0	1	3
Ocular Staining Score						
Cornea	3	2	1	2	1	1
Conjunctiva						
temporal	3	2	1	2	2	1
inferior	3	2	1	2	2	1
Total	12	7	4	7	6	3

Discussion

Sjögren syndrome is an autoimmune disease of the exocrine glands, and it is one of the leading causes of aqueous deficient dry eye disease. Dye eye disease is a multifactorial disease of the ocular surface, characterized by loss of ocular surface homeostasis.

Corneal perforation management can be achieved by using different procedures. According to ulcer size and depth can be used bandage contact lens, fibrin glue tissue or cyanoacrylate, amniotic membrane patch graft, and tectonic keratoplasty, if necessary, associated with partial or total tarsorrhaphy.[12]

According to the integrity of the Descemet-endothelial complex and the ulcer's size, we decided to use fibrin glue adhesive and cenegermin.

The fiber number and fiber length increased progressively from cenegermin treatment until the last follow up. The corneal sensitivity score increased, and ocular staining decreased, showing the improvement of the staining score. The contralateral eye showed an increase in the considered parameters with half of the recommended cenegermin dosage, and this confirms the efficacy of cenegermin, even at an inferior dosage.

The dendritic cells decreased from the start of the treatment, along with the inflammation decrease.[13]

The severe ocular surface disease and inflammation of SS lead to decreased corneal innervation,[4,5] and cenegermin is a therapy available targeting the decreased corneal sensitivity of SS-dry eye.

Conclusion

In case of impending perforation or ulcer with micro-perforations, associated with chronic severe dry eye, cenegermin is a valuable supportive therapy to fibrin glue. It effectively promotes an improvement in corneal sensitivity, thereby facilitating epithelial regrowth and increasing stromal thickness.

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