Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 3871 - 3875
Received 25 April 2021; Accepted 08 May 2021.

Sever Limbal Stem Cell Deficiency in Refractory Vernal Keratoconjunctivitis: A Case Report

Mitra Akbari[1*]

[1*]Associate Professor of Ophthalmology, Cornea, and Anterior Segment Fellowship.

Eye Research Center, Eye Department, Amiralmomenin Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran.E-mail: mitra.akbari20@gmail.com

ABSTRACT

Purpose: Here we describe a case of severe and steroid-resistant limbal vernal keratoconjunctivitis with limbal papillary hypertrophy, total stem cell deficiency and its pattern of treatment.

Methods: Case report.

Results: The patient was a 21 years-old lady with a complaint of reduced vision, ocular surface burning and photophobia in both eyes since a many years ago. Her complains was aggravated since last year. Her past medical history was unremarkable. According to corneal impression cytology and incisional biopsy of the limbal hypertrophic lesions, the limbal vernal keratoconjunctivitis (VKC) with sever limbal stem cell deficiency had diagnosed. It was resistance to topical steroid therapy, therefore topical tacrolimus 0.05% improved her sign and symptoms and eventually the good visual acuity achieved with penetrating keratoplasty (PKP) and amniotic membrane transplantation (AMT) surgeries.

Conclusion: The limbal mass like hypertrophy with total limbal stem cell deficiency may be the initial manifestation of VKC and should be considered in the differential diagnosis. In severe and refractory VKC,aqueous formulation of topical tacrolimus can be used and enhance graft survival in such complex cases.

KEYWORDS

Vernal Keratoconjunctivitis, Limbal Stem Cell Deficiency, and Topical Tacrolimus.

Introduction

Several ocular surface disorders including vernal keratoconjunctivitis (VKC) are majorly caused by inflammation and hyperactivity of the immune system. The long-term inflammations observed in cases with severe limbal VKC may cause imperceptible loosing of functions corneal limbal stem cells. This occurrence might be due to direct harm to the stem cells by the toxic products of eosinophils and other anti-inflammation cells that infiltrate into the limbus. Partial or total limbal stem cell deficiency (LSCD) can be one of the difficulties of long-standing ocular surface inflammations such as VKC, which can induce severe visual impairments in younger patients. The long-lasting nature of the disorder may be the cause of this secondary ocular surface infection, leading to the clinical manifestation of LSCD.(1)

Corticosteroids are still the major treatment for anterior segment inflammation and are the most commonly used topical anti-inflammatory medications; but, undesirable ocular complications including glaucoma and cataract, usually preclude their application on a regular basis.Medications that inhibit calcineurin such as cyclosporine A and tacrolimus are now majorly used as “steroid-sparing” topical agents for prevention and treatment of diseases with T-cell-mediated pathophysiology, and the majority of the cornea and ocular surface disorders. (2,3)To avoid steroid-related complications, and in resistance cases, immunomodulator drugs such as topical cyclosporine A and tacrolimus have lately been implemented for the treatment of VKC (4). Tacrolimus is an immune system suppressor and is administered to intercept rejection of transplanted organs and have a many application in the ocular surface and corneal chronic inflammations.(2)

In this case report, we present the rare case of severe and steroid-resistant limbal VKC with a severlimbal stem cell deficiency that managed with topical tacrolimus 0.05%and prepared the eyes for surgical procedures such as penetrating keratoplasty (PKP) and amniotic membrane transplantation (AMT)for the patient’s visual rehabilitation.

Case Report

The patient was a 21 years-old lady with a complaint of reduced vision, ocular burning and photophobia in both eyes since many years ago that referred to our cornea clinic. Her complains was aggravated since last year. The medical history of the patient was normal. She was under medical treatment by topical steroids by several physicians that

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 3871 - 3875
Received 25 April 2021; Accepted 08 May 2021.

times but her complains aggravated despite these medications. Her vision was 2 meters finger count in both eyes.

In a slit-lamp examination of eyes, severe corneal haziness, vascularization, and limbal hypertrophy at least 2 corneal quadrants were seen (Figure 1 A, B). Extensive vascularized corneal opacity and unfavorable epithelial integrity (recurrence of epithelial defects) experiencing long-lasting irritation, redness, and tearing, and reduced visual acuity.

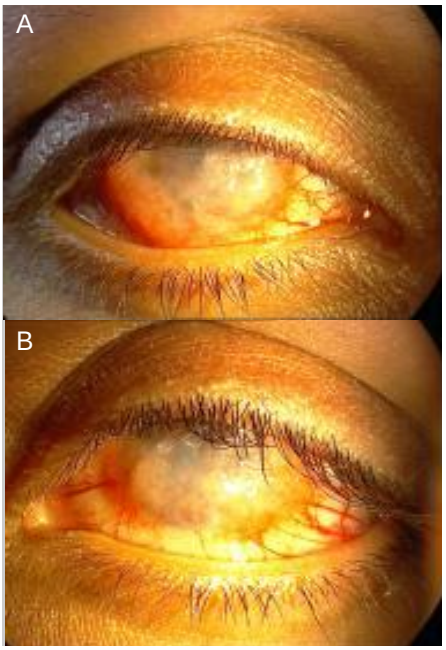

Figure 1. Sever limbal hypertrophy and corneal vascularization in the right (A) and left (B) eye

The differential diagnosis of limbal hypertrophic lesions that we saw in this patient may have many categories of allergic, inflammatory, infectious, and neoplastic diseases.(5) In the first step, our approach for the diagnosis was an obtaining of impression cytology (IC). Many goblet cells and few eosinophils could be seen on IC in some parts of the cornea, according to this finding of IC, limbal stem cells deficiency (LSCD) was confirmed. (6) Small incisional biopsy was obtained from the limbal lesion that in the histopathology exam, many eosinophils seen on the specimen. In the histopathological examination of this lesion, hyperplastic epithelium with eosinophilic permeation and condensed subepithelial stroma of irregular hyperplastic collagenous connective tissue interspersed with multiple eosinophils and inflammatory cells were presented. Limbal pseudoepitheliomatous hyperplasia, the lining epithelium did not show any evidence of dysplasia. According to this report of the pathology, the diagnosis was the limbal vernal keratoconjunctivitis with a hypertrophic limbal papillary reaction. Interestingly there was not any evidence of tarsal conjunctiva papillary lesions.

The diagnosis of LSCD in this patient was performed according to the clinical findings and was confirmed by classic impression cytology. The integrity of the ocular surface epithelium was assessed by fluorescein staining and the pattern of epithelial healing was evaluated. Results were recorded by digital corneal photography (Imagenet; Topcon SL-8Z, Tokyo, Japan) at every follow-up session. All risks and benefits were intelligibly explained, and informed consent was taken from the patient.

This allergic inflammatory reaction was resistant to steroid therapy that previously prescribed and we used for another 6 weeks without any improvement in her conditions. We started the tacrolimus eye drop by 0.05% every 4 hours that continued for 3 months. At that time all signs and symptoms were reduced and the limbal papillary hypertrophy was regressed. After 12 weeks along with decreasing ocular surface inflammation and shrinkage of limbal papillary hypertrophy with the use of topical tacrolimus (Figure 2 A, B), we operated the right eye with penetrating keratoplasty (PKP) and amniotic membrane transplantation (AMT) for her visual recovery (Figure 3). Topical tacrolimus therapy continued for another year after surgery, then the patient was followed for 2 years and visual acuity achieved to 20/30 in the right eye.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 3871 - 3875
Received 25 April 2021; Accepted 08 May 2021.

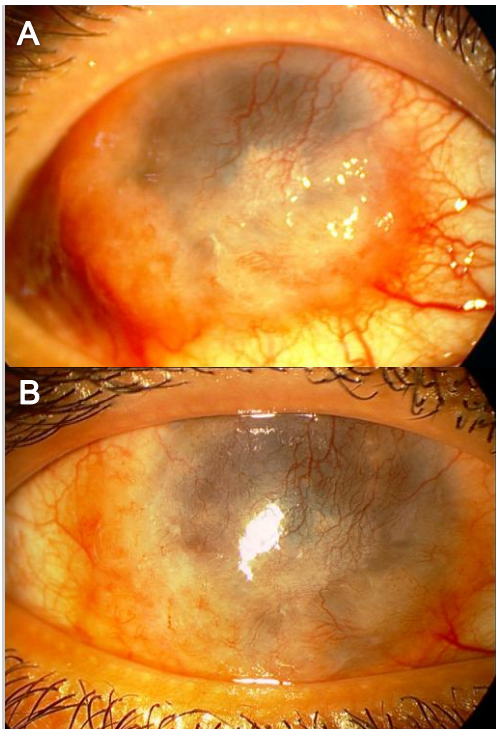

Figure2. Limbal papillary hypertrophy before (A) and its shrinkage (B) 2 months after treatment with topical tacrolimus 0.05% eye drops

Figure 3. Clear graft, 6 months after penetrating keratoplasty and amniotic membrane transplantation

Tacrolimus eye drops preparation: By adding a balanced salt solution to a tacrolimus vial (Prograf, Astellas Pharma Inc., Dublin, Ireland) under a sterile condition, these eye drops were reformed to obtain a 0.05 percent concentration of tacrolimus; following the formation, they were kept at a temperature of 4-degree Celsius.

Discussion

In VKC patients, the disorder may lead to constant visual impairment, and unlike its name, the disease may be constantly present in all seasons of the year. It has been demonstrated that VKC is not singly IgE-mediated and it has multi-factor pathogenesis, which is induced by Th2 lymphocytes, eosinophils, IgE, mast cells, and a mixed network of interleukins and cell mediators. In most cases, the clinical course of VKC is self-limiting and may disappear following puberty. Some VKC patients will face sight-threatening complications, which are mainly due to corneal involvement and LSCD(1,7) such as our patient and iatrogenic damage caused by prolonged corticosteroid treatment.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 3871 - 3875
Received 25 April 2021; Accepted 08 May 2021.

(7)

For treating VKC, various drugs have been administered including antihistamines, mast-cell stabilizers, and non-steroidal anti-inflammatory medications. Topically used steroids are the major therapy for moderate to severe cases with VKC, but some patients, still have the symptoms in spite of the therapy with topical steroids. Extended application of topical steroids can be related to different complications, including glaucoma, cataract, and subordinate infections.In order to prevent these complications in refractory cases, immunomodulators including topical cyclosporine A and tacrolimus have lately been used for treating VKC. (8)Tacrolimus is an immune system suppressor and is administered to intercept rejection of transplanted organs. Tacrolimus is derived from macrolactam and has immunomodulation and anti-inflammation properties. It is constructed by the fungus streptomyces tsukubaensis and represses T cell activation and IL-2 production by attaching to an immunophilin and inhibiting the enzymatic activity of calcineurin. (2, 8) In our case that was resistant to topical steroids, we used the 0.05% concentration of topical tacrolimus eye dropsthat were appropriatelytolerated and subsidedthe inflammation and shrinkage of limbal papillary hypertrophy.

In our patient, the limbal lesion was due to an allergic inflammatory process that was diagnosed according to IC and pathological examination. The limbal lesion was more than a 3-clock hours defect that had required for amniotic membrane transplantation after keratoplasty for proper corneal surface epithelialization. (6) The epithelial defect completely healed after 2-weeks. The cornea was clear one year later without any conjunctivalization.

Amniotic membrane is an appropriate place for remnant stem cells. It helps to proliferate epithelial, decreasing the inflammation of the ocular surface, vascularization of the amount of underlying scar of the cornea, and also increasing the transparency of the cornea. For permanent and stable epithelialization of the ocular surface, a minimum mass of limbal stem cells may be required. (6,9) Our case had a more than 3-clock hours stem cells deficiency but still had enough reserve of viable stem cells that responded to AMT application for graft epithelialization after PKP.

In unmanageable patients with VKC, in whom the symptoms are induced by an elevated mass, surgical incision of the lesion could be a method of treatment, and it may facilitate the improvement of the symptoms that are induced by chronic VKC (10),but in our case the lesion was too extensive that could not be removable and for preservation of limbal stem cells we were not done this procedure.

The present research demonstrated that the 0.05 percent concentration of tacrolimus can be more efficient in the treatment of steroid-resistant VKC. The considerable clinical improvements and reduced density of inflammatory cells in conjunctival impression cytology specimens, were seen in our patient that allow us for further surgical interventions for obtaining a visual recovery. In this case, we observed that topical tacrolimus 0.05% was safe and efficient in improving the signs and symptoms of severe VKC, which was resistant to therapy with topical steroids.

In conclusion, the limbal mass like hypertrophy may be the initial manifestation of VKC and should be considered in the differential diagnosis. In severe and refractory VKC, aqueous formulation of topical tacrolimus can be used and enhance graft survival in such complex cases.

Consent

Written informed consent was taken from the patient before the preparation of this case report.

References

[1] Sangwan VS, Jain V, Vemuganti GK, Murthy SI. Vernal keratoconjunctivitis with limbal stem cell deficiency. *Cornea.* 2011 May;30(5):491-6.

[2] Akbari M, Moghadam RS, Elmi R, Nosrati A, Taghiabadi E, Aghdami N. Adjunctive Tacrolimus for Herpetic Stromal Keratitis. *J Ophthalmic Vis Res*., 2019;14:400–411.

[3] Ghasemi H, Djalilian A. Topical Calcineurin Inhibitors. *J Ophthalmic Vis Res*., 2019;14:398–399.

[4] Chatterjee A, Bandyopadhyay S, Bandyopadhyay SK. Efficacy, Safety and Steroid-sparing Effect of

Topical Cyclosporine A 0.05% for Vernal Keratoconjunctivitis in Indian Children. *J Ophthalmic Vis Res*., 2019;15–21.

[5] Leonardi A, Motterle L, Bortolotti M. Allergy and the eye. *ClinExpImmunol*., 2008; 153(Suppl 1): 17-21.

[6] Tabbara KF. Ocular complications of vernal keratoconjunctivitis.*Can J Ophthalmol*., 1999;34: 88–92.

[7] Kheirkhah A, Zavareh M, Farzbod F, Mahbod M, Behrouz MJ. Topical 0.005% tacrolimus eye drop for refractory vernal keratoconjunctivitis. *Eye (Lond)* 2011;25:872–880.

[8] Akpek EK, Dart JK, Watson S, Christen W, Dursun D, Yoo S, et al. A randomized trial of topical cyclosporine 0.05% in topical steroid-resistant atopic keratoconjunctivitis. *Ophthalmology* 2004;111:476–482.

[9] Sacchetti M, Lambiase A, Mantelli F, Deligianni V, Leonardi A, Bonini S. .Tailoredapproach to the treatment of vernal keratoconjunctivitis. *Ophthalmology*.2010 Jul;117(7).

[10] Kobayashi A, Nagata A, Shirao Y, Kawasaki K, Ohta T, Amaya-Ohkura Y, Nonomura A. Surgical treatment of limbal vernal keratoconjunctivitis by resection of a limbal lesion.*Jpn J Ophthalmol.*, 2002;46(6):679-81.