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Resolution of Autoimmune Polyglandular Syndrome–Associated Keratopathy With Keratolimbal Stem Cell Transplantation:

Case Report and Historical Literature Review

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Abstract

Purpose— To describe the presentation and treatment of a case of autoimmune polyglandular syndrome type 1 (APS1)–associated keratopathy and to review the associated literature.

Methods— A 23-year-old man with decreased vision secondary to APS1-associated keratopathy was treated with systemic immunosuppression and keratolimbal allograft (KLAL) stem cell transplantation.

Results— The patient maintains excellent vision 27 months after KLAL and systemic immunosuppression.

Conclusions— An underlying etiology of APS1-associated keratopathy is stem cell deficiency, which can be treated effectively with KLAL and systemic immunosuppression.

Keywords

polyglandular; autoimmune; keratopathy; stem cell; keratitis; keratolimbal allograft; multiple endocrine deficiency

In 1929, Thorpe and Handley¹ described the case of a 4.5-year-old girl with chronic tetany secondary to parathyroid deficiency and chronic intractable oral mycelial infection. The authors also described “a slight opacity of both corneas” that later developed “large cornea ulcerations.” Since that time, the described syndrome has been well documented. However, the associated keratopathy has been poorly understood and not effectively treated.

Autoimmune polyglandular syndrome type 1 (APS1) is a rare autosomal recessive polyendocrinopathy with variable combinations of mucocutaneous candidiasis, autoimmune destruction of endocrine glands, and ectodermal dystrophy. Specific endocrine dysfunction can include hypoparathyroidism, Addison disease, hypothyroidism, and diabetes. This syndrome is also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). Ocular manifestations are often disabling and include keratoconjunctivitis, dry eye, iridocyclitis, cataract, retinal detachment, and optic atrophy.²

Keratopathy has been associated with APS1 since its original description in 1929 and is considered to be an essential feature of the syndrome. In 1962, Gass published the first extensive review of APS1-associated keratoconjunctivitis.³ He reported that keratoconjunctivitis occurred in 50% of patients with APS1 and was often one of the earliest manifestations of the syndrome. The keratitis was thought to be phlyctenular and possibly

related to monolithiasis. Two cases were suspected to be compatible with Salzmann nodular dystrophy. Visual acuity was as poor as 5/200 in 1 case.

Since then, several reports have further described the keratopathy in APS1. Stieglitz et al⁴ described 2 cases that were later included in a case series by Wagman et al⁵ in 1987. Four of 16 patients with APS1 manifested a self-limited, bilateral keratitis. The age of onset ranged from 2 to 9 years. In 2 of the 4 patients, the keratitis preceded the onset of any endocrinopathy. Wagman et al did not believe that the keratitis was a hypersensitivity reaction to *Candida*. Instead, he suggested that the cause may be a defect in suppressor T-lymphocyte function. However, the laboratory studies of Wagman et al did not show an autoimmune etiology for the keratitis.

These results corresponded well to a later long-term review of 69 patients with APS1 by Merenmies and Tarkkanen² published in 2000. In this series, 17 patients (25%) had chronic bilateral keratitis. In 13 patients, the first symptoms occurred before the age of 4 years, and in 3 patients, keratitis was the presenting sign before any systemic disease. The final visual acuity of the better eye in the 17 patients with APS1-associated keratitis was 0.6 (20/80) or more in only one third of the patients. Keratitis was again not thought to be secondary to candidiasis, but no alternate etiology was proposed and remained unknown. Without a basic understanding of the cause of the keratopathy, previously attempted surgical treatments have had poor results.

In this report, we discuss our hypothesis that APS1-associated keratopathy is secondary to limbal stem cell deficiency. In the past impression cytology has been used to show limbal stem cell deficiency in 2 patients with APS1.⁶ Furthermore, Tseng et al⁷ has reported the use of ex vivo expanded allogenic limbal stem cells on amniotic membrane to treat limbal stem cell deficiency in a patient with multiple endocrine deficiency. The following is the first case of bilateral APS1-associated keratopathy effectively treated with keratolimbic allograft (KLAL) stem cell transplantation and superficial keratectomy.

CASE PRESENTATION

A 23-year-old man with APS1 presented to our cornea service. Systemic disease included Addison disease, hypothyroidism, hypoparathyroidism, and history of oral candidiasis. He was taking hormone replacement therapy. Oral medications included the following: cortisol, thyroid hormone replacement, calcium, and vitamin D. The patient complained of poor vision that was deteriorating and photophobia. He also reported occasional dry, itchy, red, and irritated eyes but was doing well on the day of examination. On further questioning, the patient reported that his vision was excellent until age 15, when the vision in 1 eye “suddenly dropped,” followed by the second eye a few weeks later. Previous ocular treatment included punctal plugs in both lower puncta and artificial tears.

Eye Examination

On initial presentation, best-corrected visual acuity (BCVA) was 20/200 in the right eye and 20/200 in the left eye. No afferent pupillary defect (APD) was present. Visual fields were full to confrontation. Schirmer at 5 minutes without anesthetic was 17 mm in the right and 16 mm in the left. Intraocular pressure was 7 in both eyes. All 4 puncta were open. Lids were normal. Conjunctiva was white with no inflammation. Corneal examination showed extensive limbal neovascularization, loss of palisades of Vogt, subepithelial/anterior stromal fibrosis, diffuse epitheliopathy, and diffuse late staining with fluorescein from the limbus to the center of the cornea except for the small clear area inferior to the visual axis. Anterior chamber was deep and quiet. Lens was clear. Dilated fundus examination showed a poor view secondary to the cornea, but it was grossly normal (Figs. 1 and 2).

Treatment

Our impression was total limbal stem cell failure that was probably related to APS1. The patient was started on cyclosporin twice a day OU, vitamin A ointment every 4 hours OU, loteprednol twice a day OU, and oral doxycycline 50 mg 4 times a day. After 3 months, the patient was more comfortable. However, the corneal examination was essentially unchanged. The decision was made to begin systemic immunosuppression and perform KLAL with superficial keratectomy as described by Holland and associates.^{8–12} Systemic immunosuppression consisted of the following regimen: tacrolimus 4 mg twice a day, mycophenolate 500 mg twice a day, and prednisone 30 mg 4 times a day. After KLAL on the right eye, topical moxifloxacin 4 times a day, cyclosporin 4 times a day, prednisolone 1% 4 times a day, and artificial tears every hour were applied. A prophylactic dose of valacyclovir 500 mg 4 times a day was also prescribed. The cornea reepithelialized, no rejection episodes occurred, and visual acuity improved. An identical procedure was performed on the left eye 9 months later. Again, the patient did well postoperatively. The systemic immunosuppression did not seem to affect the primary endocrine disease. With the exception of the steroids, hormone replacement doses did not change.

The corneal specimen disclosed a thin corneal limbus with irregular and flattened epithelial cells. There were rare goblet cells with condensed cytoplasm. Bowman layer and superficial stroma were replaced by loose and uneven collagen fibrous tissue. Many small neovascular lumens were observed (Fig. 3). The lack of inflammation, neovascularities, and stratified epithelial cells suggest possible limbal stem cell deficiency.

On the most recent examination, 27 months after right eye surgery and 18 months after left eye surgery, the patient's BCVA was 20/25+ in both eyes. The conjunctiva had no inflammation. The KLAL graft had good epithelium with no signs of rejection. The cornea was essentially clear with only minimal anterior stromal scarring (Figs. 4 and 5). Lens examination shows a trace posterior subcapsular cataract. The patient is slowly being tapered off immunosuppressive therapy and is currently taking tacrolimus 2 mg in the morning and 1 mg in the evening, mycophenolate 500 mg twice a day, valacyclovir 500 mg 4 times a day, loteprednol 3 times a day OU, cyclosporin 3 times a day OU, and artificial tears as needed.

DISCUSSION

Although the association of keratopathy with APS1 is well established, its etiology has been elusive because limbal stem cell theory was previously unknown. We suggest that keratopathy associated with APS1 is secondary to limbal stem cell deficiency.

In 1 representative case, Gass reported "the peripheral 75% of the cornea was hazy and heavily vascularized. Several irregular, slightly raised, confluent, grayish nodular corneal opacities were present in the midperipheral zone. The lower portion of the cornea was clear." Wagman described the keratitis as "superficial vascularization" and "anterior stromal scarring" often with "diffuse punctate staining."⁵

These previous corneal descriptions and our presented case are almost identical to aniridic corneas with stem cell deficiency. There is a superficial neovascularization at the limbus often beginning superiorly and eventually involving the entire limbus and extending centrally. The palisades of Vogt are lost. There is also diffuse subepithelial scarring that can often become severe enough to resemble subepithelial nodules. The central or paracentral cornea can remain clear for many years, but eventually this area also becomes vascularized and develops subepithelial scarring. Furthermore, in our presented case, late staining with fluorescein characteristic of stem cell deficiency was present.

Because the etiology of the keratitis was not previously understood, surgical treatment could not be directed at the cause of the problem. Prior surgical approaches have been attempted but with poor results. Superficial keratectomy was reported by Stieglitz et al.⁴ Visual acuity decreased from 20/20 before the onset of keratopathy to 20/100 preoperatively. After superficial keratectomy, there was an initial increase in visual acuity to 20/30. However, abnormal, vascularized tissue regrew over the cornea by 27 months, and vision dropped to 20/200.

Similarly, corneal transplantation has had less than desired results. Penetrating keratoplasty was attempted by Svane-Knudsen¹³ in 1959 for a patient with idiopathic hypoparathyroidism and good vision until the age of 11–12 years, when vision began to deteriorate and a “superficial vascular invasion superiorly” was noted. Preoperatively, the eye had a large corneal leukoma and acuity of hand motion at 0.5 m. Initially, the result was excellent (no visual acuity was given in the publication), but the graft slowly opacified over the next several months, and vision was reduced to light perception.

Later, Tarkkanen and Merenmies¹⁴ performed penetrating keratoplasty in 4 eyes of 2 patients with APS1-associated keratitis. Initially, there was an improvement in visual acuity, but all 4 eyes experienced rejection episodes. However, the rejection episodes were able to be controlled with steroids. Nonetheless, all 4 corneas redeveloped vascularization and loss of visual acuity to below preoperative levels. Interestingly, histology from the excised host corneal buttons showed that only the anterior cornea (epithelium, Bowman layer, and anterior stroma) was affected. The posterior cornea (posterior stroma, Descemet, and endothelium) was normal. In our specimen, the pathology also showed irregular epithelia and marked neovascularization in the superficial limbal cornea, similar to the description by Tarkkanen and Merenmies.¹⁴

The pathologic findings in our case and others show that the affected corneal layers are the same as those of limbal stem cell disease from a variety of causes: aniridia, chemical/thermal burns, Stevens–Johnson syndrome, and ocular cicatricial pemphigoid. Of these many causes of stem cell deficiency, our patient’s ocular surface most closely resembles that seen in aniridia, where the conjunctiva is typically quiet with no inflammation early in the disease, but secondary inflammation can occur late in the disease.

Previous publications have reported keratitis and keratoconjunctivitis with APS1. Our patient had only mild subjective complaints of occasional itching, redness, irritation, and dryness on initial presentation. However, APS1 keratopathy is not primarily an inflammatory disease. These inflammatory changes are secondary effects that occur later in the disease. Therefore, we prefer the term keratopathy to keratitis or keratoconjunctivitis. Stem cell deficiency is possible as the original cause of the abnormal corneal surface, which leads secondarily to inflammation by chronic irritation. APS1 keratopathy may have recurrent erosions, leading to inflammation on the corneal surface similar to that seen in later stages of aniridic keratopathy. In the final disease stages, corneal ulceration, chronic pain, and ultimately leukoma can develop in both types of keratopathy. Topical steroids and nonsteroidal anti-inflammatory drugs have been offered as effective treatment.^{15,16} They can decrease the secondary inflammation and lead to a more comfortable eye. They can thus be of valuable preoperatively to reduce inflammation and reduce the chances of rejection postoperatively. However, they will not improve visual function or treat the fundamental problem of stem cell deficiency.

Late stages of APS1 keratopathy, similar to aniridic keratopathy, will lead to significant anterior stromal scarring and loss of vision. The loss of vision can be significantly greater for the patients with APS1 because there is not the associated foveal and optic nerve hypoplasia often seen with aniridia. Our patient maintained excellent visual acuity until he was 15 years old. Once stem cell deficiency begins, we recommend performing stem cell transplantation

early in the course of APS1-associated keratopathy, before anterior stromal scarring occurs. This will prevent the need for a secondary penetrating keratoplasty to clear the visual axis.

ASP1 is directly associated with mutations in the autoimmune regulator (AIRE) gene and functions as a transcription factor.^{17–20} *AIRE* was found only in the lymphoid related tissues such as thymus, spleen, and lymph node. Recently Adamson et al²¹ have reported that *AIRE* is expressed in immunologically relevant tissues and in a restricted number of extraimmunologic tissues in the adult. They have detected *AIRE* protein in extrathymic embryo tissue, of particular interest, the expression seen in immune-privileged sites of testis and brain. We may presume a role of *AIRE* in limbal stem cells, although it remains to be elucidated.²²

In summary, we believe APS1 keratopathy occurs secondary to limbal stem cell deficiency. This case shows that KLAL, superficial keratectomy, and systemic immunosuppression can provide excellent visual recovery.

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FIGURE 1.
Preoperative photo of the right eye. Total limbal deficiency with subepithelial fibrosis.

FIGURE 2.
Preoperative photo of the left eye. Total limbal deficiency with subepithelial fibrosis.

FIGURE 3.

Photomicrograph showing the limbus with many different sized capillaries in the superficial stroma. The stratified epithelial cells are flattened and Bowman layer is absent. (PAS, original magnification, left $\times 50$, right $\times 100$).

FIGURE 4.
Postoperative appearance of the right eye. Epithelium is normal. Note well-healed KLAL tissue at limbus.

FIGURE 5. Postoperative appearance of the left eye. Epithelium is normal. Note well-healed KLAL tissue at limbus.