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Limbal stem cell deficiency secondary to vitrectomy in the context of an autoimmune polyendocrine syndrome type

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ABSTRACT

Purpose: Autoimmune polyendocrine syndromes (APS) are rare diseases characterized by immunologic activity against multiple endocrine organs. Bilateral keratitis and limbal stem cell deficiency are manifestations described.

Methods: A 28-year-old man presented to our service with discomfort in his left eye. Past medical history included autoimmune polyendocrine syndrome, under hormonal treatment. Ocular history included an idiopathic bilateral peripheral occlusive vascular retinal disease, with areas of non-perfusion, neovascularization, and bleeding, treated with laser photocoagulation. He presented with a vitreous hemorrhage which was treated with a 20-gauge pars plana vitrectomy and endolaser. On review of family history, the patient reported having an older brother also affected by APS, developing the same bilateral retinal affection.

Results: Examination of the anterior segment of the left eye revealed a superior corneal epithelial irregularity. Fundus examination was significant for retinal arteries with segmental blood flow, box-carring, along with peripheral laser scars over previously ischemic areas. Corneal scraping and impression cytology demonstrated goblet cells on the corneal surface epithelium. A diagnosis of limbal stem cell insufficiency was made, and the patient was started on ocular lubricating drops and topical corticosteroids. At follow-up, the patient has been stable.

Conclusions: We describe a case of iatrogenic limbal stem cell insufficiency related to vitrectomy in a patient with autoimmune polyendocrine syndrome, a risk factor for this presentation. We propose that surgical trauma near the limbus and damage to the corneal sub-basal nerve plexus during vitrectomy may result in the development of limbal stem cell deficiency in a predisposed eye, as postulated in this patient with an APS.

1. Introduction

Autoimmune polyendocrine syndromes (APS) are a group of rare diseases characterized by immune activity against more than one endocrine organ. However, non-endocrine organs can be affected due to the loss of immunologic tolerance. APS can be differentiated as polyendocrine syndrome type 1 (APS-1), monogenic and aggressive, and polyendocrine syndrome type 2 (APS-2), polygenic and appearing later in life with more benign forms. APS may present across a broad age spectrum, from infancy to advanced age, with considerable heterogeneity in clinical manifestations and frequency. This variability is influenced by both genetic predisposition and environmental factors, often observed even among individuals within the same family. The pathogenesis is typically insidious, characterized by the presence of circulating autoantibodies and progressive lymphocytic infiltration of target tissues, which may culminate in organ dysfunction and eventual failure.[1,2]

APS-1 is a rare autosomal recessive disease caused by autoimmune regulator gene (*AIRE*) mutations with T-cell–mediated loss of immune tolerance, presenting in some cases with autoantibodies targeting

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proteins with key functions in the affected endocrine organs. It is characterized by a minimum of two of three main components during infancy: chronic mucocutaneous candidiasis, hypoparathyroidism, and primary adrenal insufficiency (Addison's disease). The two most common ocular manifestation of APS-1 include keratoconjunctivitis with dry eye and retinal degeneration.[3,4] Findings within the keratopathy phenotype may vary greatly, and are typically bilateral, ranging from a mild superficial keratitis, to epithelial ulcerations, stromal opacities, and/or severe stromal scarring. One potential complication of this may be the development of a limbal stem cell deficiency.[3,4]In contrast, the retinopathy phenotype is primarily characterized by changes to the retinal pigment epithelium (RPE). Similar to the keratopathy phenotype, retinal findings may vary greatly, from an isolated patchy atrophy of the RPE to pallor of the optic nerve, bone spicules, and attenuated optic atrophy similar to the retinal findings in retinitis-pigmentosa.

Interestingly, the severity of ocular manifestations may not parallel the severity of the affected individuals systemic disease. Management of APS often requires a multi-disciplinary team, with treatment focussed on hormonal replacement and treatment of subsequent complications. Close follow-up is required due to the complexity of APS. A comprehensive clinical evaluation of all family members of APS-1 patients is imperative, given the potential for phenotypic variability within affected families.

Limbal stem cell deficiency (LSCD) is a disorder characterized by loss or the dysfunction of limbal epithelial stem cells, essential components for maintaining a healthy, transparent corneal surface and preventing conjunctival epithelial overgrowth.[5,6] LSCD leads to an unstable and abnormal corneal epithelium, which may result in chronic inflammation, recurrent epithelial breakdown, neovascularization, conjunctivalization with goblet cell invasion, tear film dysfunction, and corneal opacification. Clinically, patients may report symptoms of ocular irritation, photophobia, and decreased vision. Findings on slit-lamp examination may include a hazy epithelium extending centrally, usually from the superior limbus.[5,6] In some cases, the corneal epithelium becomes irregular and forms a whorl-like pattern with a clear line of demarcation between the corneal and conjunctival phenotype of cells. Diagnosis is supported by impression cytology, which may reveal conjunctivalization of the cornea with the presence of goblet cells and immunohistochemical markers of the conjunctiva in the corneal surface. LSCD management depends on the extent and severity of the disease and ranges from conservative treatment with artificial tears or anti-inflammatory agents to surgical options such as an autologous or heterologous limbal stem cell transplant or keratoprosthesis in advanced cases.[5,6]

2. Case description

A 28-year-old man presented to our service with complaints of ocular discomfort in his left eye for 3 months. His past medical history included autoimmune polyendocrine syndrome managed with hormonal treatment. Secondary to APS, he developed chronic mucocutaneous candidiasis, hypoparathyroidism, primary adrenal insufficiency, mental retardation, growth hormone deficiency, short stature, and hypogonadism. Past ocular history included a vitreous hemorrhage, treated with a 20-gauge pars plana vitrectomy. On slit lamp examination, an idiopathic bilateral peripheral occlusive vascular retinal disease was identified with areas of non-perfusion, bleeding, and neovascularization. The origin of this involvement seemed related to the endocrine defects and the patient underwent laser panphotocoagulation. His family history included an older brother also affected by APS, with similar clinical manifestations and ophthalmic disease. Specifically, the brother also developed an idiopathic bilateral peripheral occlusive vascular retinal disease that was managed with laser panphotocolagulation, without surgical intervention.

Systemic workup of the patient revealed a low serum parathyroid hormone (PTH), low serum cortisol, and low serum electrolytes of sodium, calcium and potassium. The patient received replacement hormone therapy with fludrocortisone acetate (a synthetic steroid with potent mineral corticoid and high glucocorticoid activity) and calcium.

The best-corrected visual acuity (BCVA) was 20/30 in both eyes, with an intraocular pressure of 16 mmHg. The anterior segment of the right eye (RE) was normal, and the left eye (LE) had a superior corneal epithelial irregularity with late fluorescein staining. The fundus of the retina showed arterial vessels with segmental blood flow, box-carring, and laser in the periphery on the previously ischemic areas (Fig. 1). Corneal scraping and impression cytology demonstrated goblet cells on the corneal surface epithelium (Fig. 2). Limbal insufficiency was diagnosed, and treatment was initiated with preservative-free lubricants (hyaluronic acid) and topical steroid drops for the ocular surface disease. At one-month follow-up, the patient was comfortable and stable with no corneal epithelial haze, stromal scars, or neovascularization. The steroid drops were discontinued with no further intervention. The patient died after 5 years due to encephalopathy in relation to his condition.

3. Discussion

LSCD is categorized into 2 groups[5]: 1) Acquired: 1.1) Acquired Nonimmune-Mediated to chemical and thermal injury, surgeries, cryotherapies, contact lens wear, or medication toxicity. 1.2) Acquired Primary Immune-Mediated to hereditary Mucous membrane pemphigoid, allergic ocular surface diseases, atopic keratoconjunctivitis, graft-versus-host disease 2) Hereditary: congenital aniridia and autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy/Dysplasia.

LSCD has been described as secondary to previous eye surgery or chronic topical medication with the term of iatrogenic limbal insufficiency.[6] Epitheliopathy in these cases began in the upper periphery at sites of the surgical incision and sites of trauma prior to limbal stem cells and progressed towards the central zone. This suggested that the leading and most probable etiological factor for the development of the limbal insufficiency syndrome was direct surgical trauma to the LSC.[6] Several surgeries affecting the sclerocorneal limbus have been related: intra-and-extracapsular cataract extraction, sutured intraocular lens implantation, penetrating keratoplasty, and multiple pterygium excisions or cryotherapy on the limbal region[6]; still, in some cases, the reason was not apparent. Certain patients may have ocular conditions that could contribute to LSCD, such as rosacea, keratitis, pseudophakic corneal edema, or sustained topical treatment.[6] The number of limbal cells, directly and indirectly, could make them more susceptible to damage from external diseases and pharmacological toxicity.

LSCD has been described as secondary to APS, relating the malfunction of the limbal cells associating keratitis and limbal cell failure[34] to multiple endocrine deficiencies in patients affected by hypoparathyroidism, Addison's disease, or Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) syndrome. The incidence varies from 25 % to 52 %, with dry eye as a common feature[4(p1)]. It begins in childhood, with a mean age of 9.2 years, as the first manifestation in some cases. The diagnosis of APS1 should be suspected in young children with chronic bilateral keratopathy and systemic manifestations.[7] Ocular involvement is typically bilateral of similar severity in both eyes. Often, there is no relationship between the severity of the ocular manifestations and the systemic manifestations.[7] The origin of the dysfunction of limbal stem cells is unclear; however, it has been proposed that there may be a particular corneal autoantigen causing APS1-associated keratopathy[37].

In this case, we believe that the vitrectomy may have been a contributing factor to the development of LSCD in the patient's predisposed eye, although this has not been previously described. The patient had APS, a known cause of LSCD. Despite this, the fellow eye—without prior surgical intervention—remained stable and showed no corneal abnormalities. Similarly, his older brother, who had a comparable APS

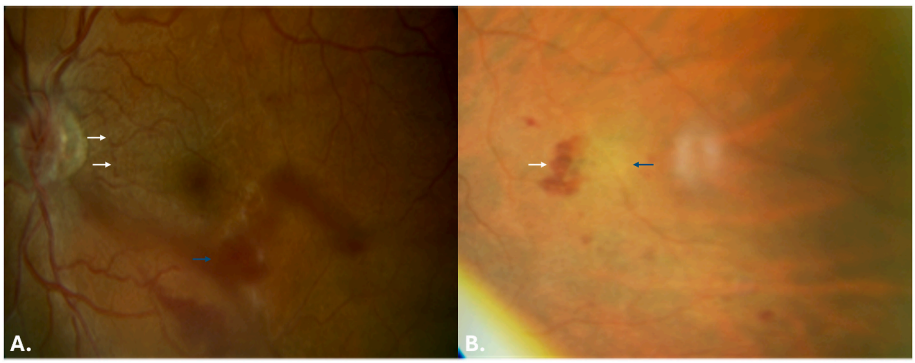

Fig. 1. Fundus photography of the left eye of a patient with autoimmune polyendocrine syndrome. **A.** Fundus image of the optic nerve revealing an idiopathic peripheral occlusive vascular retinal disease, areas of non-perfusion, and subsequent development of neovascularization. Pictured are arterial vessels with segmental blood flow and box-carring (white arrows), as well as a vitreous hemorrhage (blue arrows). Laser is also present in the periphery (not pictured). **B.** Fundus image of the left peripheral retina revealing an intraretinal hemorrhages (white arrow) with an adjacent area of retinal ischemia (blue arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

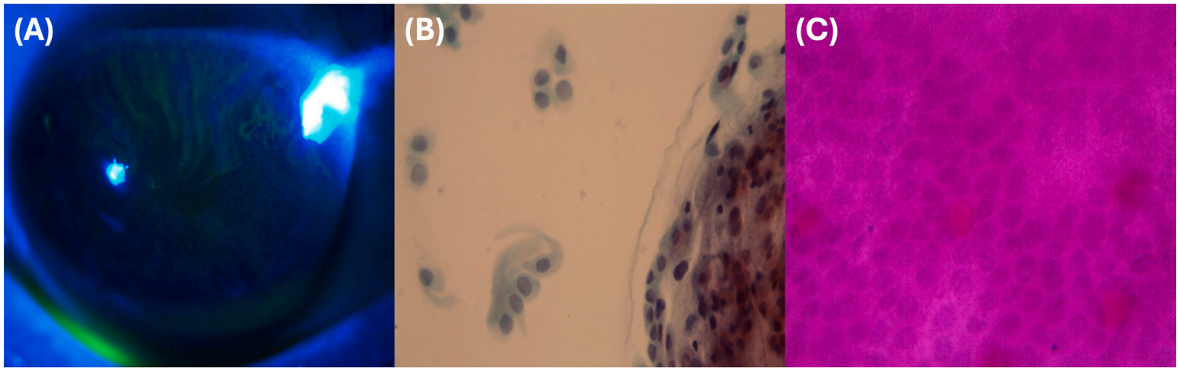

Fig. 2. Slit lamp, corneal scraping, and impression cytology photography of the left eye of our patient with autoimmune polyendocrine syndrome. **A.** Slit lamp photography of the patient's left eye demonstrating a superior corneal epithelial irregularity with late fluorescein staining. **B &. C.** Corneal scraping and impression cytology revealing goblet cells on the corneal surface epithelium.

presentation, exhibited no ocular surface disease in either eye. This suggests that the clinical picture may result from acute surgical damage superimposed on a pre-existing, subclinical stem cell dysfunction associated with APS. The cornea likely harbored a latent defect or impaired limbal stem cell function due to the altered ocular surface microenvironment caused by the underlying endocrinopathy, which became clinically evident following the vitrectomy.

Vitrectomy may compromise the corneal epithelium, resulting in edema or loosening. In the follow-ups, corneal defects are common concerning inflammation factors, the duration of surgery, intraoperative epithelial debridement, intraoperative anterior segment manipulation, previous surgeries, or contact viewing lens systems, affecting especially diabetic patients or with other predisposing factors. The in vivo confocal microscopic findings suggest that the healing process takes a long time to normalize cell morphologic features. In this case, we address surgical trauma over areas close to the limbal region and damage to the corneal sub-basal nerve plexus.

Vitrectomy can damage the limbal region due to trocar insertion through the conjunctiva and sclera near the superior limbus. In this case, a conventional 20-gauge pars plana vitrectomy was performed with the creation of three sclerotomies using a conjunctival peritomy and direct scleral incision. The sclerotomies were placed in standard positions at 4.0 mm posterior to the limbus as the eye was phakic. The infusion cannula was inserted inferotemporally at 8:00 o'clock position, the superotemporal and superonasal sclerotomies were created for the dominant and non-dominant hand instruments, at 10:00 and 1:00 o'clock. The entries were made perpendicular to the sclera to facilitate closure and minimize vitreous incarceration. We used Vicryl sutures to close the wounds, which may have contributed to persistent inflammation. This, coupled with post-operative inflammation in an anatomically or immunologically pre-disposed eye, may have caused extensive inflammation to involve the adjacent sclera and superior limbal cornea, contributing to structural weakening and subsequent corneal insufficiency. LSCD has been reported following multiple intravitreal injections, likely due to repeated surgical trauma in the superonasal limbus.[8] Vitrectomy has also been shown to reduce the density of the corneal sub-basal nerve plexus, resulting in corneal epithelial thinning and decreased corneal sensation—effects attributed to injury of the long ciliary nerves from 360° intraoperative laser treatment. A similar pattern of sub-basal nerve plexus damage has been described after phototherapeutic keratectomy (PTK), though it appears to be more pronounced in patients undergoing vitrectomy.[9,10]

Overall, we describe a case of iatrogenic limbal insufficiency related to vitrectomy in a patient with APS as a risk factor for the presentation. Biomicroscopic findings suggested a clinical diagnosis of limbal insufficiency, confirmed by impression cytology, which revealed goblet cells in the corneal epithelium. Vitrectomy with surgical trauma close to the limbal region and damage to the corneal sub-basal nerve plexus may result in limbal stem cell deficiency in a predisposed eye, for instance, with APS. We hypothesize that the impacts of vitrectomy in the cornea are likely under-reported.

CRediT authorship contribution statement

Francesc March de Ribot: Writing – original draft, Investigation, Data curation, Conceptualization. **Anna March de Ribot:** Writing – original draft, Investigation, Data curation. **Javier Núñez Pérez:** Writing – review & editing, Supervision, Conceptualization. **Joshua M. Huang:** Visualization, Writing – review & editing. **Jordan J. Huang:** Writing – review & editing, Visualization. **Jaime D. Martinez:** Writing – review & editing, Supervision, Resources, Conceptualization.

Patient consent

Consent to publish this case report was obtained from the patient. This report does not contain any personal information that could lead to the identification of the patient.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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