

SHORT COMMUNICATION

Limbal stem cell deficiency in the context of autoimmune polyendocrinopathy

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PURPOSE. *To report two sisters with bilateral progressive visual loss and photophobia secondary to stem cell deficiency due to multiple endocrine deficiency.*

METHODS. *Case reports and review of medical literature.*

RESULTS. *The younger sister had severe photophobia and decreased visual acuity since May 2000. Despite multiple outpatient visits no definite cause was found and conservative treatments failed. On slit lamp examination severe meibomian gland dysfunction, loss of eyelashes, decreased tear meniscus, diffuse corneal vascularization, and delayed punctate fluorescein staining of corneal epithelium were detected. She also had episodes of hypotension, oral candidiasis, and seizures. Her systemic workup revealed multiple endocrine deficiency (Addison's disease and hypoparathyroidism). Hormone replacement therapy with fludrocortisone and oral calcium accompanied by punctual occlusion led to significant clinical recovery. The older sister showed a similar pattern but interestingly the onset was later and the signs and symptoms were milder.*

CONCLUSIONS. *In the pediatric age group with diffuse corneal vascularization and no definite cause, systemic workup should be done to rule out multiple endocrine deficiencies. The therapy consists of hormone replacement therapy and management of dry eye. (Eur J Ophthalmol 2006; 16: 870-2)*

KEY WORDS. *Limbal stem cell deficiency, Autoimmune polyendocrinopathy, Multiple endocrine deficiency*

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INTRODUCTION

Multiple endocrine deficiency (MED), recently renamed autoimmune polyendocrinopathy, is an immune mediated disorder that involves multiple organs including parathyroid and adrenal glands and ectodermal tissues (nails, skin, enamels) and may also cause keratitis secondary to stem cell deficiency (1, 2).

Corneal vascularization has a diverse etiology including longstanding ocular surface inflammation or infection, stem cell deficiency, and immune mediated disorders. Normally, the limbal stem cells of the cornea inhibit conjunctival vessels to invade the cornea, however, any pathologic condition that alters this natural barrier may eventually lead

to some degree of corneal vascularization and subsequent haziness that limits the visual acuity (2, 3).

We report two sisters with bilateral superior corneal vascularization with different severity (regarding the delayed onset of disease in the older sibling) and dry eyes concomitant with impression cytology proven stem cell deficiency due to autoimmune polyendocrinopathy.

Case reports

Case 1

An 8-year-old girl was referred to our care in May 2000. She had been followed elsewhere for some months for photophobia and decreased vision and conservative man-

agement with lubricants and artificial tears was used but no significant recovery occurred. She had multiple episodes of seizures and oral candidiasis. Her general examinations revealed nail dystrophy. On her first ocular examination, her visual acuity was 20/40 in both eyes. The eyes were injected and the patient could not open her eyes completely secondary to severe photophobia. On slit lamp examination, severe meibomian gland dysfunction and decreased tear meniscus was detected.

Corneal vascularization that was more prominent in the superior part of the cornea (Fig. 1) and punctual epithelial erosions were seen in both eyes. Delayed diffuse punctate fluorescein staining of the corneal epithelium was also noted. Other ocular examinations including anterior chamber, iris, lens, vitreous, retina, and intraocular pressure were unremarkable. Corneal impression cytology revealed goblet cells on the corneal surface epithelium (Fig. 2). She also had episodes of hypotension and seizures due to imbalance of serum electrolytes. Her systemic work-up revealed low levels of adrenal hormones (cortisone 3 mg/dL [normal range 5–23 mg/dL]) and disturbance in serum electrolytes (low sodium and calcium and high potassium levels). Serum parathormone (PTH) level was 4 pg/mL (normal range: 9–65 pg/mL). Our impression was of a multiple endocrine deficiency (Addison's disease and hypoparathyroidism) which caused stem cell deficiency by altering the stroma of the limbus (stem cell niche) and caused dry eyes, corneal vascularization, and haziness, which resulted in visual loss and photophobia.

The patient received replacement hormone therapy with fludrocortisone acetate (a synthetic steroid with potent mineral corticoid and high glucocorticoid activity) and elemental calcium and the puncti were occluded by cauterization. After 1 year significant clinical improvement occurred.

Case 2

Her 15-year-old sister showed the same picture of the disease with much milder symptoms in January 2005. She experienced attacks of dizziness and fainting but to lesser extent and duration than her younger sister. Her systemic workup showed similar but milder electrolyte imbalance (low sodium and calcium and high potassium levels). Her vision was 20/25 in both eyes. On slit lamp examination, severe meibomian gland dysfunction and decreased tear meniscus was detected. Mild corneal vascularization was more prominent in superior part of the cornea (Fig. 3).

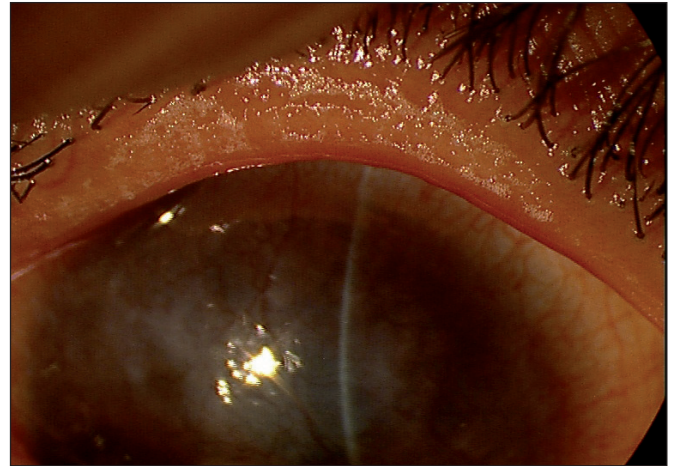


Fig. 1 - Superficial corneal vascularization and corneal haziness (mostly in superior part of cornea) due to stem cell deficiency (Case 1).

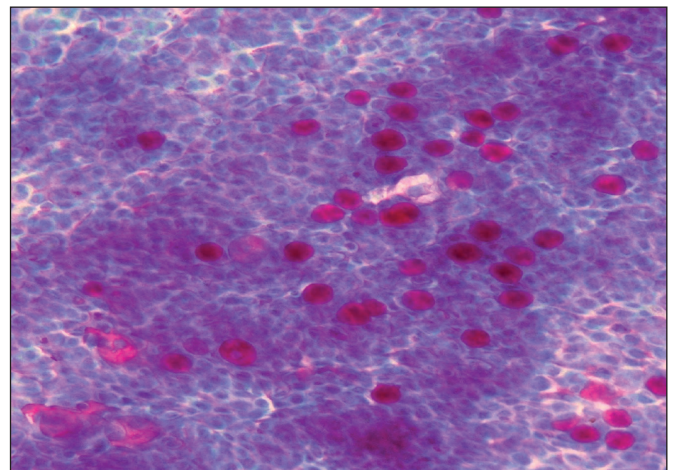


Fig. 2 - Impression cytology showing goblet cells on the corneal epithelium (Case 1).

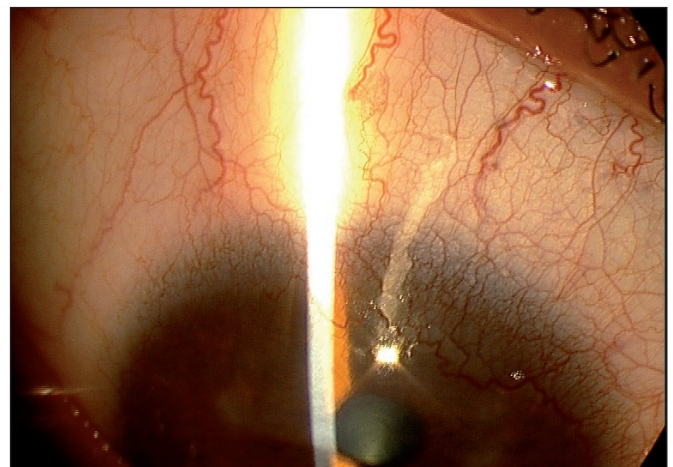


Fig. 3 - Milder superficial corneal vascularization and corneal haziness (mostly in superior part of cornea) due to stem cell deficiency (Case 2).

DISCUSSION

Keratitis associated with multiple endocrine deficiency was first reported by Gass (3) in 1962. He reported a syndrome of keratoconjunctivitis, superficial moniliasis, idiopathic hypoparathyroidism, and Addison's disease. Afterwards, Wagman et al (4) reported a series of 14 patients with an autosomal recessive syndrome characterized by hypoparathyroidism, Addison's disease, chronic mucocutaneous candidiasis, and immune disorders. Four of them had a self limited bilateral keratitis in which the age of onset ranged from 2 to 9 years. Keratitis preceded the onset of any endocrinopathy in two of four patients and was among the first signs of the syndrome. Our cases differ from theirs as the keratitis was not self limiting and led to significant dry eye and corneal vascularization that decreased vision. They also had nail dystrophy, which altogether indicates the diagnosis of autoimmune polyendocrinopathy/candidiasis/ectodermal dystrophy (APECED) syndrome (2), which is a subgroup of MED.

Interestingly, keratitis is usually the first manifestation of disease. It may cause vascularization and scarring of anterior corneal stroma. The corneal involvement usually starts from the superior part of the cornea and the corneal epithelium becomes irregular and forms a whorl-like pattern (4).

The cause of the corneal vascularization is not well recognized but it seems that deficiency of limbal stem cells, a natural barrier that prevents the conjunctival tissue to migrate to the corneal surface and warrants the corneal avascular nature, is the main reason (4-9).

On impression cytology (5), migratory goblet cells are found on the corneal surface. Histopathology findings of limbal area consist of destroyed stem cells, limbal inflammation, and progression of conjunctival goblet cells on the corneal surface. The treatment of keratitis associated with MED is conservative and supportive and includes hormone replacement therapy and management of dry eye by lubricants, artificial tears, or punctal occlusion (6).

The interesting issue regarding our cases is the later onset and milder presentation in the older sibling that is compatible with genetic expression and penetration in cases with multiple alleles and polygenic autosomal inheritance, i.e., the heavier the genetic load, the earlier and more severe presentation of the disease. This fact has not yet been mentioned in the literature for these patients.

In conclusion, in any child with diffuse corneal vascularization accompanied by dry eye and meibomian gland dysfunction without any definite cause, systemic work-up for endocrine deficiency may be helpful and hormone replacement therapy together with measures that improve dry eye status may restore the vision and relieve the symptoms.

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