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Ocular manifestations of Junctional Epidermolysis Bullosa

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Abstract : Junctional epidermolysis bullosa is an inherited disorder of the basement membrane with cutaneous, ocular and other systemic manifestations. The cutaneous lesions manifest as multiple blisters from birth. Ocular features which develop from the first year of life include recurrent corneal erosions, dry eye and limbal stem cell deficiency. Risk of development of scarring corneal lesions at the age of 25 is 72.2 percentage. Hence early recognition and prompt intervention of this disorder is of utmost importance. This is a case report of a patient who presented with advanced features of complete stem cell deficiency.

Keyword : Epidermolysis Bullosa, corneal neovascularisation, limbal stem cell deficiency

A 15 year old female presented to our institute with the complaints of defective vision in the right eye from childhood and in the left eye for the past 1 year. She complained of watering, foreign body sensation and photophobia in both eyes for the past 1 year. All the above complaints were more severe in the right eye. She had been diagnosed to have Junctional Epidermolysis Bullosa when she developed skin blisters since birth. There were recurrent episodes of dehydration due to repeated and extensive blistering of the skin in the past for which she had been hospitalised several times. She is first born of non-consanguineous marriage and there was no history of similar complaints in the family. She had been treated in a private hospital for skin lesions and the visual problems which were related to multiple erosions in the cornea. She had underwent Amniotic membrane transplantation with fibrin glue for the right eye at the age of 8. On examination, she was thin built and anaemic. Alopecia and perioral ulcers were noted. Multiple blisters in varying stages of healing were noted all over the body with atrophic scarring and thinning of skin (Figure 1). Systemic examination of the cardiovascular, respiratory and nervous systems were normal. Visual acuity in the right eye was 6/60 with -3.00 D sphere and -2.00D cylinder 6/18p and in the left eye 6/24 with -2.00 D sphere 6/9. Slit lamp examination of the right eye revealed 360o vascularisation of cornea sparing only the pupillary area, with loss of palisades of Vogt suggestive of complete limbal stem cell deficiency and conjunctival hyperemia (Figure 2). Pupillary reaction was brisk. Lens appeared clear. Slit lamp examination of the left eye revealed vascularisation of cornea from 1-3 o'clock position, with limbal stem cell deficiency with peripheral keratinisation (Figure 3). Pupillary reaction in the left eye was brisk and lens appeared clear. Fluorescein staining of the cornea showed extensive stippled pattern in the right eye and relatively less stippled pattern in the left eye. On fundus examination, view was hazy due to corneal changes in the right eye, disc and vessels were normal with a normal foveal reflex. In the Left eye, media was clear and fundus appeared normal.

Figure 1. Multiple blisters in varying stages of healing with atrophic scarring and thinning of skin

Figure 2. Right eye showing conjunctivalisation of the cornea

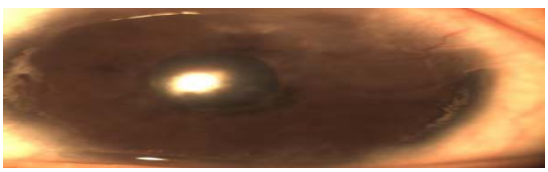

Figure 3. Left eye showing partial limbal stem cell deficiency

Investigations to evaluate dry eye were done. Schirmers II test values were 4mm of wetting in the right eye and 5mm of wetting in the left eye. Tear film break up time (TBUT) in the right eye was 4 sec and in the left eye was 5 sec. The above values were suggestive of severe dry eye (dysfunctional tears syndrome). Blood investigations showed haemoglobin levels to be 8 g/dl. Her total count, differential count and ESR were within normal limits. Dermatology opinion was obtained. She was confirmed to have Atrophic form of Junctional Epidermolysis Bullosa -Non Herlitz type. Hence we report this rare case of Junctional Epidermolysis Bullosa with complete Limbal stem cell deficiency in the right eye and partial limbal stem cell deficiency in the left eye associated with Dysfunctional Tears Syndrome (severe dry eye) in both eyes. Treatment was started with Preservative free Tear substitutes 6 times daily, Lubricating Eye Ointment at Bed time, preservative free 0.05% Cyclosporine eye drops twice a day and Fluromethalone eye drops 0.1% twice a day for both eyes. Limbal stem cell transplantation from a live related donor is planned for the right eye since a limbal autograft from the left eye which already has partial limbal stem cell deficiency is not advisable.

DISCUSSION: Epidermolysis bullosa is a prototype of mechanobullous disease of the stratified squamous epithelium that predominantly affects skin and mucous membrane. The main diagnostic feature is fragility of the skin which manifests as blisters and erosions secondary to minor trauma. The presence of extra cutaneous manifestations adds to the complexity of this disorder. There are three major types which are classified based on the level in the skin at which the blisters develop. Epidermolysis bullosa simplex (EBS) is inherited in autosomal dominant pattern and the line of cleavage is intraepidermal. Junctional Epidermolysis bullosa is inherited in autosomal recessive pattern and the line of cleavage is in the lamina lucida. In the Dystrophic Epidermolysis Bullosa, which is the more severe type, the cleavage occurs in the Sublamina densa level. There are three subtypes of Junctional Epidermolysis bullosa. Herlitz type is the severe form, Non Herlitz type is the atrophic form and the third subtype is associated with Pyloric atresia. The protein that is defective in Junctional Epidermolysis bullosa is laminin 5 which is an essential component of the basement membrane4.

The systemic manifestations of this disorder includes blisters/erosions, atrophic scarring of skin, dystrophic nails, granulation tissue (in perioral region), scarring alopecia, respiratory tract involvement in more severely affected individuals, anemia, growth retardation, malnourishment, Enamel hypoplasia, gastrointestinal tract and ocular involvement5. The Ocular features of Junctional Epidermolysis bullosa are as follows. Corneal blisters which can be intact vesicles or erosions is the most common sign, the frequency of which mirrors the severity of the disease and can start within the first year of life2. 74 % of Dystrophic EB, 47.5 % of Junctional EB Herlitz type, 25% in Non Herlitz type have been documented to have multiple corneal blisters. Other features include corneal scarring, dry eye, Limbal stem cell deficiency, pannus formation, Symblepharon, blepharitis, ectropions and lacrimal duct obstruction. The symptoms of limbal deficiency may include decreased vision, photophobia, tearing, blepharospasm, and recurrent episodes of pain (epithelial breakdown), as well as a history of chronic inflammation with redness. On slit lamp examination, a dull and irregular reflex of the corneal epithelium which varies in thickness and transparency can be noted. Severe deficiency of limbal stem cells may result in an ingrowth of thickened fibrovascular pannus, chronic keratitis, scarring and calcification. Conjunctivalised corneal surfaces are stained abnormally by fluorescein because conjunctival epithelium is more permeable than corneal epithelium and shows a stippled late staining pattern. It is thinner than adjacent normal corneal epithelium, prone to recurrent erosions. Limbal stem cells inhibit fibroblast stimulated angiogenesis and thus maintains an important role in maintaining corneal avascularity. Hence their deficiency leads to corneal neovascularization. Associated tear film abnormalities can further damage the stem cells. Persistent epithelial defects, melting and perforation of the cornea can occur in patients with stem cell deficiency. The diagnosis of limbal stem cell deficiency is essentially clinical, however, it can be confirmed by corneal impression cytology which can demonstrate the presence of goblet cells which is the hallmark of conjunctivalization of cornea1. In vivo Confocal microscopy performed in such eyes show corneal epithelial haze, superficial neovascularization, stromal scarring, and conjunctival hyperemia with loss of palisades of Vogt. Partial Limbal stem cell deficiency can be managed conservatively with ocular lubrication and topical steroid therapy. With increased corneal conjunctivalization repeated scraping of the conjunctivalized epithelium and amniotic membrane transplantation with sutures or fibrin glue as an adjunctive procedure has a high success rate. If there is unilateral complete limbal stem cell deficiency, a conjunctival limbal autograft from the contralateral eye can be done. Though there is no risk for rejection, the contralateral donor eye is at risk for iatrogenic limbal stem cell deficiency. This risk is low when fewer than four clock-hours of limbal tissue are transplanted. Bilateral cases of limbal stem cell deficiency can be managed with keratolimbal allograft from a cadaveric source with systemic immunosuppression since there is risk of rejection. A limbal allograft may be taken from a living related donor who is HLA compatible, thus decreasing rejection risk. Ex vivo growth of stem cells in culture has been used to create grafts recently. The cumulative risks of development of non-scarring and scarring corneal lesions in cases of Junctional Epidermolysis Bullosa at age 5 are 83.18% and 27.08% and at age 25 are 83.18% and 72.22%3. Hence detailed ocular examination and timely intervention is important in the management.

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