Clinical Case Report

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Corneal dysplastic melanosis associated with recurrent corneal erosions

A case report

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Abstract

Rationale: Pigmented lesions of conjunctiva and cornea can be observed in various conditions, from the benign nevus to malignant melanoma. Pigmented acquired melanosis (PAM) is one of them, which is a neoplastic proliferation with malignant transformation potential of melanocytes. However, to our knowledge, there has been no report as to a disturbance of corneal barrier function caused by PAM. Here we report a case of corneal PAM which led to recurrent corneal erosions.

Patient concerns: A 60-year-old woman was referred with a 4-month history of intractable recurrent epithelial erosions in the left eye. She denied any history of ocular trauma or surgery. Slit-lamp examination showed small epithelial defects and loose epithelium of overlying pigmented corneal lesions. The pigmentations were scattered in the corneal epithelial layer, from limbus to the central cornea.

Diagnosis: Conservative treatment with therapeutic contact lens and oral doxycycline did not completely cure the corneal erosion. En bloc resection of the pigmented epithelium with cryotherapy and temporary amniotic membrane transplantation were performed. Histopathologic examination demonstrated pigmented melanocytes with mild atypia, scattered mainly in the corneal basal epithelium. Immunohistochemically, the cells were positive for Melan A/MART-1 and negative for CD68 and S100. The Ki-67 proliferation index was low. Therefore, it was diagnosed as primary acquired dysplastic melanosis causing epithelial barrier dysfunction.

Interventions: We performed en bloc resection of the pigmented epithelium with cryotherapy and temporary amniotic membrane transplantation.

Outcomes: After the resection, recurrent corneal erosions and epithelial loosening were completely resolved. Although some pigmented lesions were recurred in the limbal epithelium at 8 o'clock, corneal erosion did not recur during the follow-up for 9 months.

Lessons: Our report suggests that primary acquired dysplastic corneal melanosis may cause epithelial dysfunction resulting in recurrent corneal epithelial erosions.

Abbreviations: BRAF = v-raf murine sarcoma viral oncogene homolog B1, CD68 = cluster of differentiation 68, MART-1 = melanoma antigen recognized by T cells 1, PAM = primary acquired melanosis, RES = recurrent corneal erosion syndrome.

Keywords: corneal melanosis, PAM with atypia, primary acquired melanosis, recurrent corneal erosion

1. Introduction

Pigmented lesions of conjunctiva and cornea can be observed in various conditions, from the benign nevus to malignant melanoma.[1] Primary acquired melanosis (PAM) is one of them, which is a neoplastic proliferation with the potentcy of malignant transformation.[1] However, there has been no report as to a disturbance of corneal barrier function caused by PAM so far. In this case report, we present a corneal dysplastic melanosis which led to recurrent corneal erosions. The patient provided informed consent for publication of the case, and the study was approved by the institutional review board of the Seoul National University Hospital (IRB No. 1711–139–902).

2. Case presentation

A 60-year-old woman was referred to our clinic because of intractable recurrent corneal erosions of overlying corneal pigmented lesions in the left eye. She mentioned that the corneal erosions were initially detected 4 months ago, because of a pain in the eye, blurred vision and photophobia. In spite of wearing therapeutic contact lens, the corneal erosions had recurred several times. The patient denied any underlying disease, including diabetes, ocular trauma, and prior ophthalmic history. The visual acuity was 20/20 in the right eye and 20/25 in the left eye. The intraocular pressure in both eyes was in the normal range. Slit-lamp examination of the left eye showed diffuse coarse pigmentations located in the corneal epithelial layer, scattered at

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peripheral limbus (1–8 o'clock), encroaching to the central cornea threatening visual axis (Figs. 1**A**, **B**). A few small epithelial defects with loose irregular epithelium of overlying the pigmented lesion were observed (Fig. 1**C**). The cornea in the right eye looked clear. Conventional conservative treatment for recurrent corneal erosion syndrome (RES) using a therapeutic contact lens (ACUVUE OASYS; Johnson&Johnson Vision Care, Inc., Jacksonville, FL; Base curve radius 8.80 mm) was initially tried. Gatifloxacin eyedrops (Gatiflo; 0.3% gatifloxacin; Handok, Seoul, Korea) was prescribed 4 times a day for 2 weeks. The 100 mg of oral doxycycline twice a day and 1000 mg of vitamin C 3 times a day were also prescribed. After 2 weeks, corneal epithelial erosions and epithelial loosening were still persistent, although the size of the epithelial defect was decreased (Fig. 1**D**, **E**). To exclude a malignancy, the patient underwent en bloc epitheliectomy of the pigmented lesion followed by cryotherapy to the involved limbus (1–8 o/c) with temporary amniotic membrane transplantation (Fig. 1**F**). During the surgery, all of the epithelium of the pigmentated lesion was very loose and separated easily from the stromal bed without any adhesion. The stroma was clear with no pigmentation. After the epitheliectomy, RES and loosened epithelial area completely subsided (Fig. 1**G**, **H**). The visual acuity was recovered to 20/20. The epithelial surface was maintained smoothly for 9 months. One week after the surgery, the pigmented lesions slightly recurred at 7–8 o'clock of the peripheral cornea involving limbus. However, up to the last visit, the recurred pigmentations were limited to the small peripheral area and did not induce any corneal erosion. (Fig. 1**I**). For the recurred lesion, topical interferon α-2b eyedrops (2 million IU/ml) and additional epitheliectomy with cryotherapy were tried but showed no effect.

In H&E stainings, scattered melanocytes in the basal epithelial layer and free-floating melanin pigmentations were observed. (Fig. 2**A**). Cellular atypia was mild according to the criteria employed in previous reports from the Armed Forces Institute of Pathology (AFIP).[1] In immunohistochemistry staining, Melan A/MART-1 was detected in a few cells (Fig. 2**B**), and Ki-67 proliferation index was low. The S100 and CD68 staining were negative (Fig. 2**C**, **D**). In addition, BRAF gene mutation was not observed. Based on the histopathological findings, it was diagnosed as a corneal PAM with mild atypia. However, given that this case was accompanied with recurrent corneal erosions and loose epithelium, it suggests that PAM may disturb corneal epithelial barrier function. Considering the clinical and histopathologic findings, we finally diagnosed it as a dysplastic corneal PAM which led to epithelial dysfunction.

3. Discussion

The PAM is known to arise from melanocytes in the conjunctival epithelium. Conjunctival PAM is typically observed in the unilateral eyes of middle-aged Caucasians.[1] Melanocytic proliferations in corneal tissue were reported occasionally, mostly in patients with prior history of trauma or conjunctival

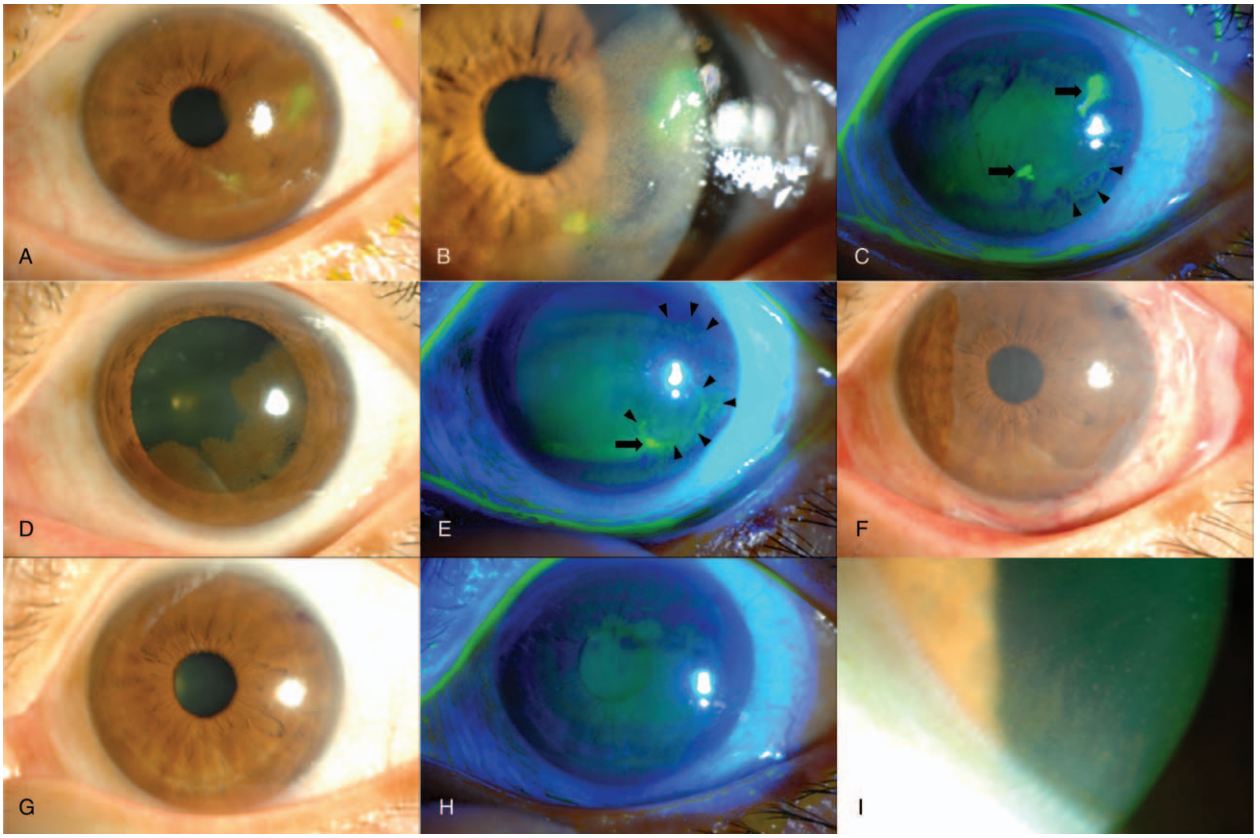

Figure 1. Clinical findings of the anterior segment. (A–B) Anterior segment photographs at initial visit (C) Epithelial defects (arrows) and loose irregular epithelium (arrowheads) observed at initial visit (D) Anterior segment photographs after conservative treatments for two weeks (E) Decreased size of the epithelial defect (arrow), and persistent epithelial loosening (arrowheads) (F) An anterior segment photograph after complete excision of the involved epithelium, followed by cryotherapy and temporary amniotic membrane transplantation (G–H) Healed epithelium after complete excision of the pigmented lesion (I) Recurred pigmentations after 1 week from the excision.

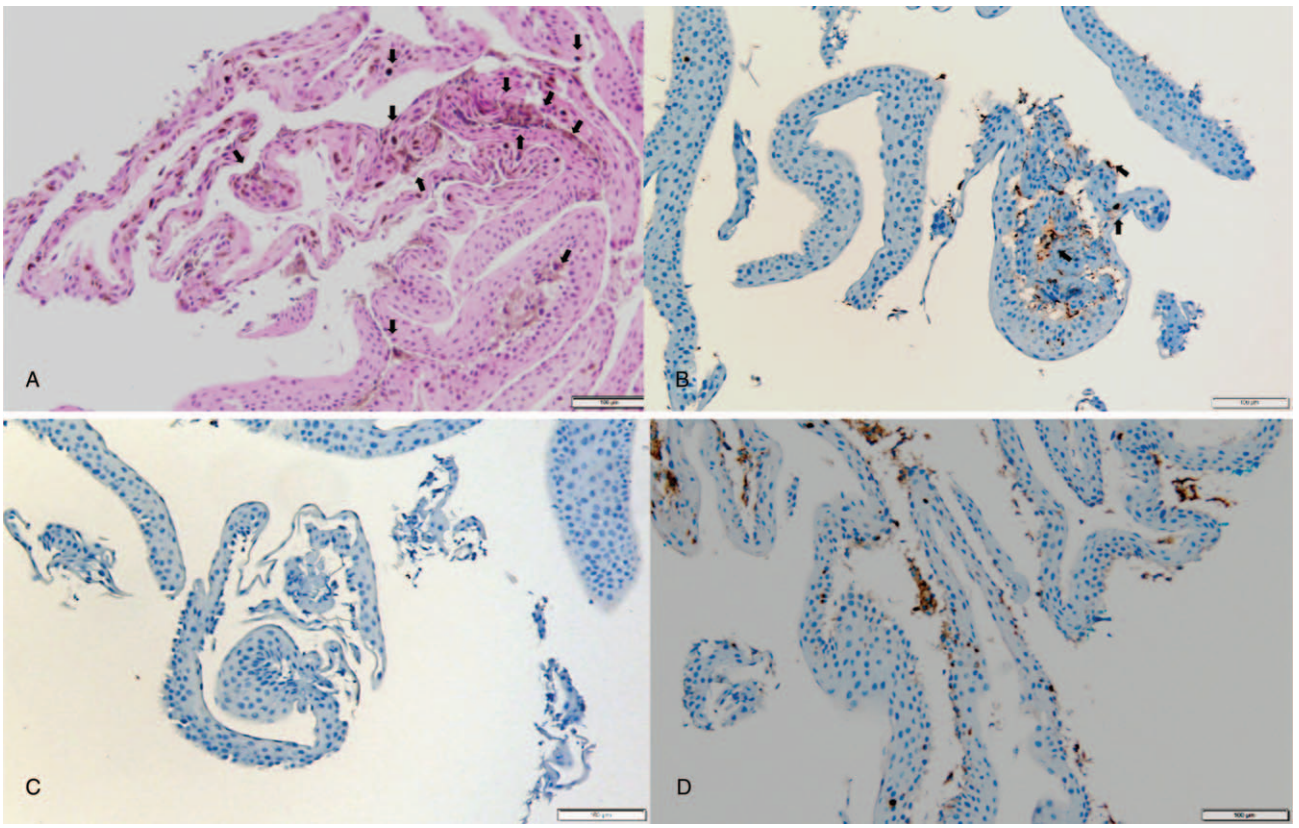

Figure 2. Histopathologic findings. (A) Scattered melanocytes (arrows) in the basal epithelial layer (H&E stain, x200) (B) A few positive cells (arrows) in IHC staining for Melan A/MART-1 (x200) (C) Negative result in IHC staining for S100 (x200) (D) Negative result in IHC staining for CD68 (x200).

PAM or malignant melanoma.[2–4] However, to our knowledge, there has been no report as to a corneal epithelial barrier dysfunction accompanied by corneal PAM. This is the 1st case report of corneal PAM which led to recurrent corneal erosions.

Because the pigmented lesion with epithelial erosions involved almost half of the cornea and 2/3rd of the limbus, we should exclude a malignancy at 1st. Therefore, we biopsied to exclude malignant melanoma. In the histologic examination, surprisingly, it turned out to be PAM with mild atypia. Immunohistochemical stains for S100, Melan A/MART-1, HMB-45, CD68 and Ki-67 were performed to enhance the accuracy of the diagnosis. Melan A/MART-1, HMB-45 and S100 are useful markers to identify cells of the melanocytic lineage and expressed in the majority of benign or malignant melanocytic lesions.[5,6] Immunostaining for CD68 helps distinguish melanophage from melanocytic cells.[6] The Ki-67 proliferation index tends to be high in malignant melanoma.[3,5] For example, Ki-67 was expressed less than 10% in the benign lesion.[3,6] In addition, the detection of BRAF mutation could contribute to the diagnosis of conjunctival melanoma in the early stage.[7] The BRAF mutations were more frequently observed in conjunctival melanoma originating from a nevus (16/27; 57%) than those from PAM with atypia (22/69; 32%) or de novo (1/12; 8%) ($P=.005$).[7] Our case showed positive expression of Melan A/MART-1, and negative expression of CD68. The Ki-67 proliferation index was low (data not shown) and BRAF mutation was not observed, which is not indicative of high grade dysplasia. Additional staining could not be conducted due to a small amount of the tissue.

The PAM with atypia is considered as a premalignant lesion and histopathologic evaluation is essential for predicting prognosis. Conjunctival PAM is divided into 3 subgroups depending on the severity of atypia.[1] When the atypical melanocytes are mostly confined to the basal layer of the epithelium, it is graded as a PAM with mild atypia. If the atypical melanocytes extend into the non-basal epithelium in a pagetoid fashion, it is graded as a PAM with severe atypia. Shields et al[8] reported that 35% of PAM lesions progressed clinically over a 10-year interval and 13% of the eyes with PAM with severe atypia underwent malignant transformation. Not only the histopathologic findings but also the extent of the PAM lesions is highly correlated with the rate of development of malignancy.[8] Therefore, complete surgical excision followed by cryotherapy is generally recommended for the extensive areas of PAM occupying more than 2 clock hours.

To our knowledge, PAM in the subjects without an ocular trauma history has not been reported to cause RES.[3] Nevertheless, given that the corneal epithelial loosening and erosions regressed after the surgical excision of the PAM lesion while the conventional supportive treatment for RES had failed, PAM may be a plausible factor for RES. The defect in the epithelial junctional complex and basement membrane is one of the major causes of RES.[9] However, in this study, we can't determine whether the PAM lesion directly disrupted the epithelial adhesion complexes as the immunostaining for the adhesion molecules was not performed. The other possible explanation for the development of RES is the disruption of epithelial tight junctions, which might be caused by mitotic melanocytes in the PAM lesion. However, due to the lack of experimental data to support this explanation, further evalua-

tions should be performed to reveal the mechanism of the PAM leading epithelial barrier dysfunction or delayed re-epithelization.

Taken together, we found that the clinical findings of this case did not match with the histological findings. There is no definite evidence of malignancy or pre-malignant lesion in the histopathological examination. However, we cannot completely exclude them due to the small size of the resected tissue and low cellularity. Furthermore, given that the pigmented lesion was accompanied by disruption of the epithelial barrier and recurred promptly after the complete excision, we considered this case as a dysplastic PAM with a malignant potency. To detect the possible malignant transformation, the patient should be closely monitored. This case is worthy of notice because it is the 1st reported case of primary acquired corneal melanosis with accompanying functional abnormalities of the corneal epithelial cells leading to recurrent corneal erosions while appearing as histologically benign.

Author contributions

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Supervision: Mee Kum Kim.
Validation: Cheol Lee, Mee Kum Kim.
Visualization: Hyo Kyung Lee, Cheol Lee.
Writing – original draft: Hyo Kyung Lee.
Writing – review & editing: Hyo Kyung Lee, Mee Kum Kim.

References

[1] Shields] JA, Shields CL, Mashayekhi A, et al. Primary acquired melanosis of the conjunctiva: experience with 311 eyes. Trans Am Ophthalmol Soc 2007;105:61–71. discussion 71-62.
[2] Balci M, Yagci R, Guler E, et al. Corneal melanosis successfully treated using topical mitomycin-C and alcohol corneal epitheliectomy: a 3-year follow-up case report. Arq Bras Oftalmol 2015;78:255–6.
[3] Boto-de-Los-Bueis A, Diaz-Valle D, Llorente-Gonzalez S, et al. [Post-traumatic striate melanokeratosis in a Caucasian woman]. Arch Soc Esp Oftalmol 2009;84:213–5.
[4] Ucakhan-Gunduz O, Gunduz K, Karsloglu MZ, et al. Corneal melanoma: report of three cases. Eye Contact Lens 2012;38:341–4.
[5] Jakobiec FA, Bhat P, Colby KA. Immunohistochemical studies of conjunctival nevi and melanomas. Arch Ophthalmol 2010;128:174–83.
[6] Bellido Munoz RM, Dominguez Hidalgo I, Garcia Serrano JL, et al. [Immunohistochemical markers in the diagnosis of pigmented conjunctival lesions]. Arch Soc Esp Oftalmol 2012;87:119–21.
[7] Larsen AC, Dahl C, Dahmcke CM, et al. BRAF mutations in conjunctival melanoma: investigation of incidence, clinicopathological features, prognosis and paired premalignant lesions. Acta Ophthalmol 2016;94: 463–70.
[8] Shields JA, Shields CL, Mashayekhi A, et al. Primary acquired melanosis of the conjunctiva: risks for progression to melanoma in 311 eyes. The 2006 Lorenz E. Zimmerman lecture. Ophthalmology 2008;115: 511-519.e512.
[9] Ramamurthi S, Rahman MQ, Dutton GN, et al. Pathogenesis, clinical features and management of recurrent corneal erosions. Eye (London, England) 2006;20:635–44.