Comment. Topical interferon was first described by Maskin in 1994 as being effective in the treatment of ocular neoplasia. A limited number of cases in the literature also show the cytostatic effect of ATRA on ocular surface dysplasia.4

Our early experience with topical ATRA alone was consistent with early reports of effectiveness, with no response occurring in certain patients. Our early experience with topical interferon alfa-2b demonstrated a more consistent clinical response, and recent studies have documented an 80% treatment efficacy using topical interferon alfa-2b.2 Mitomycin C and fluorouracil are alternative topical therapies for ocular surface dysplasia. However, interferon has fewer ocular adverse effects compared with these topical chemotherapeutic agents.2 Retinoic acid is known to irritate the conjunctiva in higher doses.4

In our patient, neither ATRA nor interferon alfa-2b alone was effective in slowing growth of the ocular lesion. Longer treatment with interferon alfa-2b may have led to a better response. The rapid clinical response to the combined treatment with topical interferon alfa-2b and ATRA seems remarkable. However, previous studies have described the synergistic effects of interferon alfa-2b and ATRA in combination, both in vitro and in vivo. These same studies, although not of an eye or eye model, reported that ATRA can permit growth inhibition by interferons in interferon-unresponsive cells.3

Prospective studies with more patients and longer follow-up are needed to confirm the treatment efficacy and safety profile of this combination therapy as a well-tolerated alternative to topical mitomycin C and fluorouracil. Appropriate further studies may reveal a benefit for both dysplastic and neoplastic lesions.

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Financial Disclosure: None reported.


Prostaglandin E Receptor 4 Expression in Human Conjunctival Epithelium and Its Downregulation in Devastating Ocular Surface Inflammatory Disorders

Prostaglandins are a group of lipid mediators that form in response to various stimuli, including prostaglandin (PG) D2 (PGD2), PGE2, PGF2α, PGI2, and thromboxane A2. There are 8 types of prostaglandin receptors that are conserved in mammals ranging from mice to humans: the PGD receptor, 4 subtypes of the PGE receptor (EP1, EP2, EP3, and EP4), the PGF receptor, the PGI receptor, and the thromboxane A receptor.1 In regard to PGE receptor subtype EP4, it was reported that EP4 messenger RNA was present in the intestinal epithelium2 and that EP4 maintained intestinal homeostasis and downregulated immune response.3 Like the intestine, the ocular surface is also one of the mucosa that are in contact with commensal bacteria. In this study, we examined the expression of EP4 in human conjunctival epithelium and compared its expression between various ocular surface diseases.

Methods. This study was approved by the Institutional Review Board of Kyoto Prefectural University of Medicine, Kyoto, Japan. For reverse transcription–polymerase chain reaction assay, we obtained human conjunctival epithelial cells from healthy volunteers by brush cytology using previously described methods.4 The primers were (forward) 5' - ACC ATG CCT ATT TCT ACA GCC ACT ACG -3' and (reverse) 5' - AGG TCT CTA ATA TTC GCA AAG TCC GTA G-3' for human PTGER4 and (forward) 5' - AGG TCT CCA TCT TCC AGG AG-3' and (reverse) 5' - CCT GCT TCA CCA CCT TCT TG-3' for human GAPDH. For immunohistochemistry, we used nearly normal bulbar conjunctival tissues obtained during surgery for conjunctivochalasis as a control, and human conjunctival tissues were also prepared from samples obtained during surgery to reconstruct the ocular surface such as treatment for various ocular surface diseases including Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), ocular cicatricial pemphigoid (OCP), and pterygium. For EP4 staining, we used the rabbit polyclonal antibody to EP4 (Cayman Chemical Co, Ann Arbor, Michigan).

Results. The presence of PTGER4 messenger RNA and EP4 protein in human conjunctival epithelium was examined by reverse transcription–polymerase chain reaction and immunohistological analysis, respectively. The PTGER4 messenger RNA was detected in normal human conjunctival epithelium (Figure, A). The sequences obtained from these polymerase chain reaction products were identical to the human PTGER4 complementary DNA sequence. The EP4 protein was also detected in the nearly normal conjunctival epithelium obtained from the patients with conjunctivochalasis (Figure, B). Next, we examined the conjunctival tissues with various ocular surface diseases. The EP4 protein was detected in conjunctival epithelium from patients with pterygium as well as in the conjunctival epithelium from...
control patients with conjunctivochalasis. However, we did not detect EP4 immunoreactivity in the conjunctival epithelium from patients with SJS/TEN or OCP (Figure, C). Our results showed that EP4 is strongly downregulated in the conjunctival epithelium of tissues with devastating ocular surface disorders such as SJS/TEN and OCP, although it is usually expressed in human conjunctival epithelium.

**Comment.** To our knowledge, this is the first documentation regarding downregulation of EP4 expression in human conjunctival epithelium in tissues with devastating ocular surface inflammatory disorders, although there were reports of expression of EP receptors in ocular tissues. Kabashima et al\(^3\) reported that EP4 deficiency impaired mucosal barrier function and aggregation of neutrophils and lymphocytes in the colon and that administration of an EP4-selective agonist to wild-type mice ameliorated severe colitis; they concluded that EP4 maintains intestinal homeostasis. On the other hand, Yao et al\(^6\) recently reported that PGE2 acts on its receptor EP4 on T cells and dendritic cells and promotes immune inflammation.

In human conjunctival tissues, the EP4 protein was detected in only epithelial cells but not infiltrating cells into subconjunctival tissues. Because there is mucosal inflammation on the ocular surface even in patients with chronic-phase SJS/TEN or OCP, we suspect that the downregulation of EP4 expression in conjunctival epithelium might be associated with the ocular surface inflamm-
mation in patients with SJS/TEN or OCP and that there is a possibility that EP4 in human normal conjunctival epithelium suppresses the ocular surface inflammation.

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Financial Disclosure: None reported.

Funding/Support: This work was supported in part by grants-in-aid for scientific research from the Japanese Ministry of Health, Labour, and Welfare (Research on Intractable Diseases), the Japanese Ministry of Education, Culture, Sports, Science, and Technology, a research grant from the Kyoto Foundation for the Promotion of Medical Science, the Intramural Research Fund of Kyoto Prefectural University of Medicine, a Shiseido Female Researcher Science Grant, and a research grant from the Japan Allergy Foundation.

Additional Contributions: Chikako Endo provided technical assistance.


**Subconjunctival Mycetoma as an Unusual Cause of Tears With Black Deposits**

Ocular mycosis is a rare condition that is usually related to ocular trauma, preexisting ocular disease, or immunocompromised states. We report a case of subconjunctival mycetoma secondary to *Exophiala dermatitidis* in a healthy middle-aged woman with recalcitrant ocular inflammation and black deposits in her tears.

Report of a Case. A 44-year-old woman had recurrent discharge from her right eye and black deposits in her tears for 2 years. Her symptoms persisted despite the use of topical antibiotics, steroids, and antihistamine. She was otherwise healthy and was not receiving any systemic or other topical medication. She denied any history of ocular trauma or surgery. She did not use contact lenses or eye makeup.

On examination, her general condition was excellent. Her visual acuity, intraocular pressure, and fundi were all normal. There was no eyelid swelling or erythema. On everting the right upper eyelid, some subconjunctival black deposits were noted (Figure, A). During biopsy, the conjunctiva was incised and multiple black, mulberry-like concretions extruded with mucoid discharge (Figure, B). Topical chloramphenicol, 0.5%, with dexamethasone sodium phosphate, 0.1%, eyedrops were prescribed postoperatively. Histopathological evaluation of these concretions showed large amounts of fungal hyphae (Figure, C and D) with chronic inflammation over the conjunctiva. The diagnosis was subconjunctival mycetoma. Initial culture results for fungal growth were negative, but further evaluation with 28S ribosomal RNA gene sequencing identified the causative organism as *Exophiala dermatitidis*. At subsequent follow-up visits, the patient had complete resolution of symptoms. Topical antifungal treatment was not given as she was asymptomatic and there was no recurrence of mycetoma at month 3 after debridement.

Comment. Tears with black deposits are extremely rare. In our case, we initially thought the black deposits were either foreign bodies or adrenochrome deposits, but they proved to be shedding from the subconjunctival mycetoma. Patients with tears with black deposits should therefore be evaluated for the presence of subconjunctival mycetoma. A similar clinical entity termed *melanodacryorrhea* (black tears) is caused by extracocular extension of uveal melanoma.

In immunocompetent subjects, fungal infection can remain superficial and localized as illustrated in our case. Subconjunctival mycetoma has been reported after subtenon corticosteroid injection in an immunocompromised host and in an immunocompetent woman with no risk factors, similar to our patient. The *Exophiala* species are dematiaceous mold commonly recovered from soil, plants, water, and decaying wood materials. This strain of black yeasts has been reported to cause subconjunctival mycetoma. They are related to ocular trauma, preexisting ocular disease, or immunocompromised states. We report a case of subconjunctival mycetoma secondary to *Exophiala dermatitidis* in a healthy middle-aged woman with recalcitrant ocular inflammation and black deposits in her tears.

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