Ocular Hypertension Concomitant to Periocular Imiquimod 5% Cream Therapy

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A 54-year-old male physician was referred by his dermatologist for biopsy-proven actinic keratosis (AK) of the right upper eyelid, for which he was to start topical imiquimod 5% cream (Aldara, Graceway Pharmaceuticals). The lesion was close to the lid margin, therefore, serial ocular exams were scheduled throughout the treatment course. During initial exam, there was a 1mm² erythematous, hyperkeratotic papule near the medial canthus, abutting the lid margin. The rest of the anterior segment exam was benign. Ocular pressure was not obtained in that visit, but six months earlier his pressure was 17 and 18, respectively. There was no family or personal medical history of ocular hypertension or glaucoma. The patient had declined surgical excision for the lesion, and elected to proceed with imiquimod 5% treatment, being fulling aware that direct ocular application was to be avoided. Imiquimod 5% was applied once every other day, directly to the lesion. The patient reports that he was meticulous in avoiding the ocular surface.

Ten days later, he presented with a two-day history of pain and swelling over the right upper lid. He denied ocular pain or photophobia. Blistering of the lesion and vision were stable. Eye pressure was 27 in the right, and 20 on the left, confirmed with repeated applanations on two separate slit lamps. In the right eye, there was minimal conjunctival irritation. The cornea was thin, clear, and without any uptake. The anterior chamber was deep and quiet. Gonioscopic exam showed a wide open angle without any synechiae or pigmentation. An undilated fundus exam was also normal, including a healthy optic nerve with 0.2 cup-to-disc ratio. The lesion had adequately responded to imiquimod; in light of his unexplained rise in introcular pressure imiquimod 5% cream was suspected. Four days later, he returned with the lesion healed and free of any discomfort. His ocular pressures had returned to 17 and 19, respectively. The anterior chamber remained quiet. Since the initial presentation, the patient’s eye pressures have returned to baseline and no abnormalities were identified.

Discussion

Imiquimod 5% cream is an immune response modulator used to treat a variety of dermatological conditions, including AK, Bowen's disease, basal cell carcinoma, and melanoma.1 It allows for local control of disease in the periocular region in several reports, showing promise as an alternative or adjunct to resection.2,3 Most common ocular side effect is ocular surface irritation. There has been no previous report of ocular hypertension related to imiquimod 5%, nor has any intraocular inflammation been associated with this drug. While it it far from proven that imiquimod 5% was the definite culprit in the ocular pressure rise, the close proximity of the episodes makes it plausible.

There are several possible mechanisms for imiquimod 5% cream to induce ocular pressure rise. First, it may act similarly to corticosteroids, which can induce cytoskeletal rearrangement in the trabecular meshwork that may lead to outflow obstruction. Imiquimod 5% cream is known to induce immune cell migration, e.g. Langerhan’s cells, possibly via a similar mechanism.4 It is conceivable that it may induce cytoskeletal rearrangement of the trabecular meshwork, as well. Kwon, et al. reported a case of acute ocular hypertension associated with systemic interferon-α therapy.5 There was no sign of ocular...
inflammation, and pressure returned to normal upon cessation.

Secondly, imiquimod is pro-inflammatory. It is known to induce cytokines, such as interleukins in the skin, involving its TLR activity. A crucial ocular surface pro-inflammatory protein, the corneal epithelial-derived thymic stromal lymphopoietin, shares certain ligands with TLRs. Potentially this activity may induce uveitis if applied to the eye, giving rise to intraocular pressure. However, no cell or proteinaceous flare was observed in this patient.

Lastly, it is possible that imiquimod 5% cream may cause myopic shift and angle closure, similar to topiramate. Again, there was no evidence of this on our exam of this patient.

Conclusion
Immunomodulators such as imiquimod 5% may offer a promising alternative for the treatment of periorcular tumors, allowing disease control while preserving precious periorcular tissue. This case emphasizes the importance of close ophthalmic monitoring whenever imiquimod therapy is applied close to the eye. Ocular hypertension may be a previously unknown, yet potentially serious side effect of imiquimod 5% cream. In order to detect further correlations between intraoc-

ular hypertension and imiquimod 5% cream a clinical trial is needed.

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