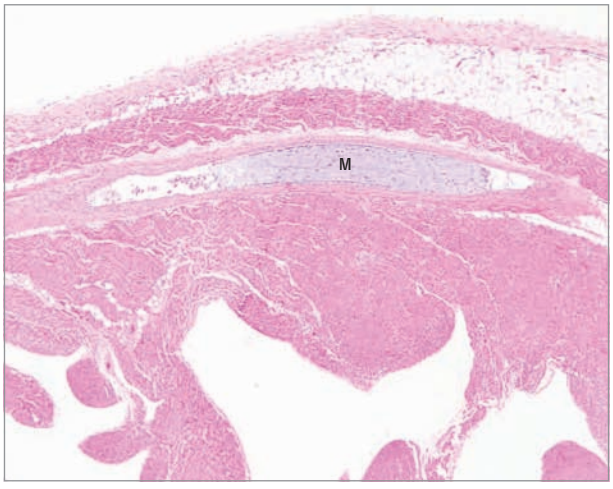
Figure 2. Autopsy Finding



Myxoma (M) embolized to an epicardial coronary artery (hematoxylin-eosin, original magnification ×40).

Discussion | A subset of sudden unexpected pediatric deaths is caused by fatal presentations of unrecognized syndromes.[6] The 8-year-old boy in this case died of sudden cardiac death in the setting of myocardial infarction from embolic cardiac myxoma, owing to CNC caused by a pathogenic *PRKAR1A* variant. The boy died of complications of a rare disease, preceded by subtle indications that received medical attention.

While CNC is rare, penetrance is greater than 95% by age 50 years.[1-3] In CNC, myxomas can develop in mucocutaneous tissue, breast, heart, and elsewhere. Cardiac myxomas occur in up to 50% of affected individuals, including children, with 16% of affected individuals experiencing sudden death or near-death events.[1] Embolization of this boy's cardiac myxoma chronically compromised coronary arterial blood flow, leading to infarction and ultimately sudden cardiac death. In retrospect, his "anxiety" may have been referable to ongoing ischemic heart disease.

Pigmented skin lesions are the most common presenting feature in CNC, reported in 96% of affected individuals.[1-3,5] Ocular lentigines occur in 27% and are frequently brought to an ophthalmologist's attention, typically before signs or symptoms of cardiac myxoma.[5] Both ophthalmologic biopsies showed basal melanocytic proliferation and hyperpigmentation without atypia. Such lesions of the caruncle or semilunar fold are particularly suspicious for CNC, even without additional apparent stigmata.[5]

In retrospect, this boy's congenital chest wall nodule, unsampled at autopsy, was likely an osteochondromyxoma.[4] Considering this together with the lentigines in this boy and his relatives, the possibility of CNC might have been entertained,[2] prompting antemortem genetic evaluation and a cardiology referral, where the myxoma might have been identified.

This case demonstrates that sudden unexpected death in childhood may be a sentinel family event that can identify previously unrecognized familial genetic disease. It highlights the opportunity for clinical detection of pigmented conjunctival lesions to elicit antemortem concern for a syndromic disorder. Although CNC lesions may exhibit no obvious difference from flat nevi in unaffected children, the interpretation of ophthalmic findings in the context of personal and family history, and interdisciplinary care involving ophthalmologist, primary care physicians, and subspecialists like endocrine, cardiology, and genetics professionals, can offer opportunities for life-saving interventions.

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Association of Conjunctival Ulceration With Pembrolizumab

Pembrolizumab and other immune checkpoint inhibitors are an effective alternative to traditional chemotherapy in sensitizing the immune system to combat cancer cells.[1] While effective against malignancies, this mechanism of action can lead to immune-related complications.[2] We present a case of conjunctival ulceration following pembrolizumab therapy for breast cancer.

Figure 1. External Photograph of the Conjunctival Ulceration With Surrounding Vessel Tortuosity

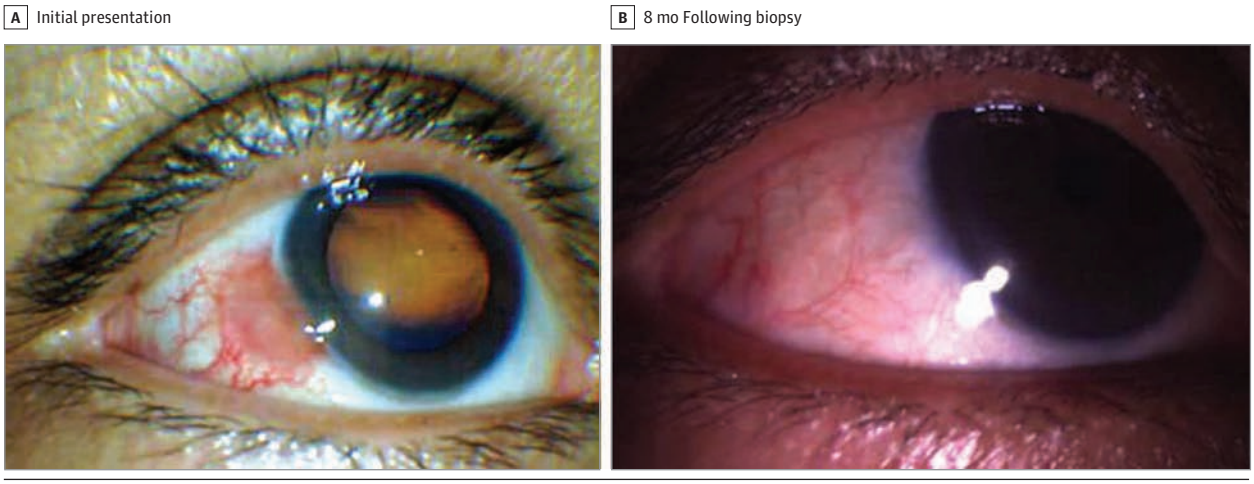
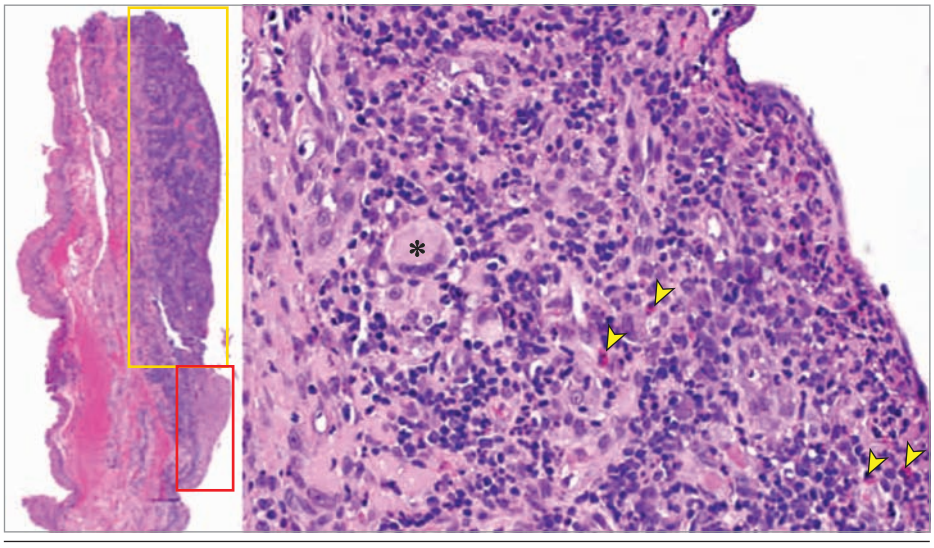


Figure 2. Histopathology Slide



Histopathology slide with hematoxylin and eosin staining at 2X magnification (left) shows denuded epithelium and underlying inflammation (yellow box) with adjacent intact conjunctival epithelium (red box). Hematoxylin and eosin staining at 40X magnification (right) shows acute and chronic inflammation with many neutrophils and lymphocytes interspersed with eosinophils (yellow arrowheads) and a giant cell (asterisk). All special stains for organisms (Brown-Hopps, Brown-Brenn, Groccot methadone silver, and Fite-Faraco) were negative.

Report of a Case | A 57-year-old female individual with no ocular history presented with 1 month of worsening redness and discomfort of the right eye. She had a history of left-sided advanced triple-negative breast cancer, treated with surgery, radiation, and 9 cycles of pembrolizumab-based therapy when symptoms began.

Examination showed a raised pink conjunctival lesion near the temporal limbus (**Figure 1**A). After a negative serologic workup for autoimmune and infectious causes, the patient underwent an excisional biopsy, revealing epithelial ulceration and inflammation (**Figure 2**A). On high-powered magnification, many neutrophils and lymphocytes interspersed with eosinophils were noted, suggesting a potential drug reaction (Figure 2B).

Postoperatively, topical prednisolone acetate was initiated 4 times daily with considerable improvement in symptoms. No further infusions of pembrolizumab were given, as she had completed therapy. After recurrence in symptoms following topical steroid cessation, prednisolone acetate was restarted at 3 times daily and tapered over a 4-month period, without recurrence in symptoms or ulceration (Figure 1B).

Discussion | Immune checkpoint inhibitors work by using the body's immune system to target T cells, blocking their inhibitory processes.[2] This causes increased T cell activation, which leads to cancer cell recognition and elimination by cytotoxic T cells.[2,3] An upregulated immune system helps fight malignancies, but also leaves the cancer patient at risk for autoimmunelike adverse effects. These can affect any organ system, including the eye.[1,2] Most ophthalmic adverse effects are immune-related, including dry eye, uveitis, and ocular myasthenia gravis.[2]

This case of sterile conjunctival ulceration began within days following a ninth and final cycle of pembrolizumab. There was no history of ocular or autoimmune disease and no evidence of such on examination or laboratory workup. Histopathology of the conjunctival lesion revealed an infiltrate consisting of lymphocytes, neutrophils, and eosinophils. The

presence of eosinophils in the tissue, although not pathognomonic, is often associated with drug-induced inflammation.[4] This parallels histopathologic features of cutaneous toxicities associated with immune checkpoint inhibitors, which typically involve a combination of lymphocytic, neutrophilic, and eosinophilic infiltrates.[4]

Given the temporal relationship between immunotherapy and symptoms, a negative laboratory workup, and the histopathology results, we suspect an immune-related adverse event from pembrolizumab. There have only been a few similar reports of ocular toxicities, most involving corneal ulceration.[5,6] One described bilateral corneal perforation in a patient taking pembrolizumab,[6] and the other reported corneal ulceration associated with nivolimumab.[5] Similar to the patient in this case report, these diagnoses were also made based on the association with immunotherapy and symptoms, along with pan-negative diagnostic evaluation.[5,6] Conjunctival involvement is less common, with only few reports of conjunctivitis that responded to topical steroid therapy or sodium hyaluronate eye gel, neither of which required cessation of checkpoint inhibitors.[5,6]

Topical corticosteroids are a successful therapy often used in the setting of immune-related events on the ocular surface.[1] Similarly, the patient in this case report reported improvement in symptoms after starting topical corticosteroids, with return of symptoms after they were tapered. Surgical excision was not likely curative in this instance but did provide valuable diagnostic information. Completion of immunotherapy also likely contributed to the absence of ulcer recurrence.

This case underscores the important role ophthalmologists play in recognizing potential immune-related sequelae of checkpoint inhibitor therapy. As the field of immunotherapy advances, understanding how to report and manage these effects becomes important.

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COMMENT & RESPONSE

Uncertain Diagnostic Accuracy of Self-Monitoring Vision at Home

To the Editor We recently reviewed the article by Korot et al,[1] which reported on enablers and barriers when deploying the My Vision Track vision home-monitoring application (MVT) to patients monitored for anti–vascular endothelial growth factor treatment. We noted that the authors[1] reported sensitivity and specificity estimates for the application of 84.6% and 88.5%, respectively. Although not the focus of the original article, this letter addresses these estimates.

The authors[1] reported these results but not the methods used to calculate them. No reference standard was defined, no flow diagram of participants was included, and no cross-tabulation of index-test against reference standard classifications or precision of diagnostic accuracy estimates reported.[2]

We believe these estimates are incorrectly described as sensitivity and specificity. The estimates appear to have been calculated for a reference standard of active disease among 26 patients whose application results triggered an alert for substantial vision worsening, with 22 assessed as having active disease at a clinic visit where reviewing clinicians presumably knew that attendance had been triggered by an alert.[2,3] The sensitivity seems to be calculated as 22 of 26 and the specificity as 23 of 26, the numerator differing because 1 patient had a retinal detachment rather than active disease. No information in the article[1] allows sensitivity, specificity, or negative predictive value to be calculated; these calculations require numbers of false and true negatives.[4] Many participants may have had active disease, but only 22 were detected by MVT. The estimates could more accurately be termed positive predictive value: the number of patients who had disease as a proportion of all patients who triggered an alert.

The same hospital participated in another study monitoring patients with neovascular age-related macular degeneration, where 69% of patients at the hospital presented with active disease across all monitoring visits.[5] Applying this percentage to the number of "compliant and active" patients in Korot et al[1] (n = 166) gives 115 patients with active disease and 51 with inactive disease, allowing the index test and reference standard results to be cross tabulated (**Table**). Sensitivity and specificity estimates are 22 of 155 (19%) and 47 of 51 (92%).

The discordance between the sensitivity reported by Korot et al[1] and ours seems important to recognize. While it is appropriate for the estimates reported by Korot et al to be used to generate hypotheses, if used to justify widespread imple-