

Consecutive Conjunctival Melanoma and Extranodal Marginal Zone B-Cell Lymphoma of MALT Type in an Adult Patient

Lymphoma of mucosa-associated lymphoid tissue (MALT) has been estimated to represent about 8% of all non-Hodgkin lymphomas (NHLs) and was categorized among the extranodal marginal zone B-cell lymphomas in the 2001 World Health Organization classification. Although extranodal marginal zone B-cell lymphoma of MALT type occurs most frequently in the stomach, it has also been described in

various nongastrointestinal sites such as the conjunctiva. Conjunctival melanoma represents only 1.6% of all ocular tumors. Herein we report the case of a patient with consecutive melanoma and extranodal marginal zone B-cell lymphoma of MALT type of the conjunctiva, questioning a relationship between both rare entities.

Report of a Case. A 38-year-old man was referred to the ocular oncology unit for a pigmented conjunctival lesion of his left eye. The lesion was situated at the limbus at the 12-o'clock position, measured 15 mm at the largest basal diameter, and showed progression. There was no sign of primary acquired melanosis.

A complete excision showed conjunctival malignant melanoma (**Figure 1**) and was followed by contact radiation therapy of the resected tumor scleral bed. Four months later, a nodular relapse of melanoma developed at the margin of the radiation field. Surgery was successful and follow-up was uneventful for 3 years, at which point a conjunctival thickening of the nasal bulbar conjunctiva (3 mm) in the same eye was observed at the margin of the radiation field, questioning a possible relapse of the melanoma. There was no clinical evidence of lymphadenopathy, organomegaly, or systemic lymphoma-related symptoms. Resection of the lesion was performed, and the his-

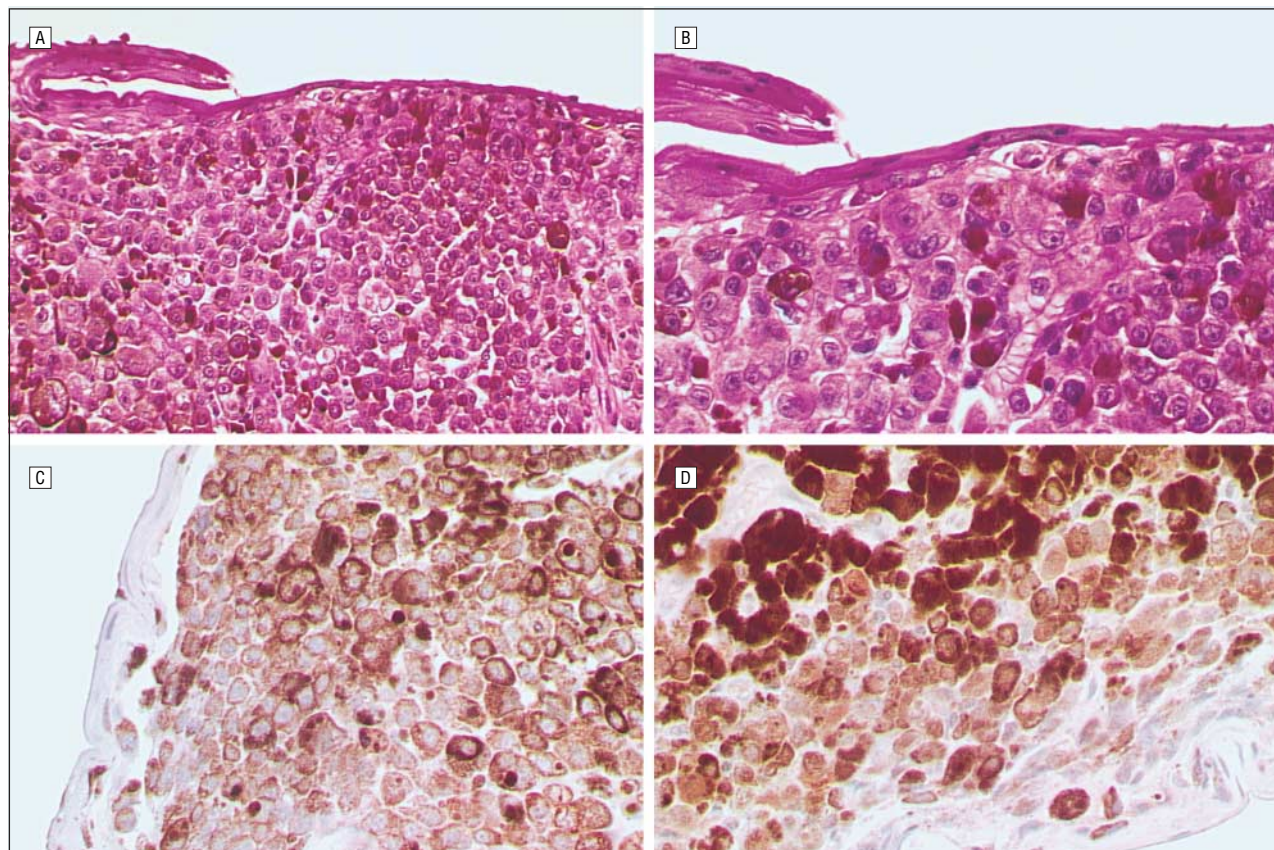


Figure 1. A, Conjunctival malignant melanoma with a diffuse pattern of infiltration of the conjunctiva (hematoxylin-eosin-saffron, original magnification $\times 10$). B, The tumoral cells appear large and epithelioid with atypical nuclei and large nucleoli with no mitotic figure. The epithelium of the conjunctiva is thinner and infiltrated with tumoral cells (hematoxylin-eosin-saffron, original magnification $\times 40$). C and D, Immunostainings with the anti-HMB-45 (C) and anti-PS100 (D) antibodies showing intraintracytoplasmic positivity of the tumoral cells (original magnification $\times 40$).

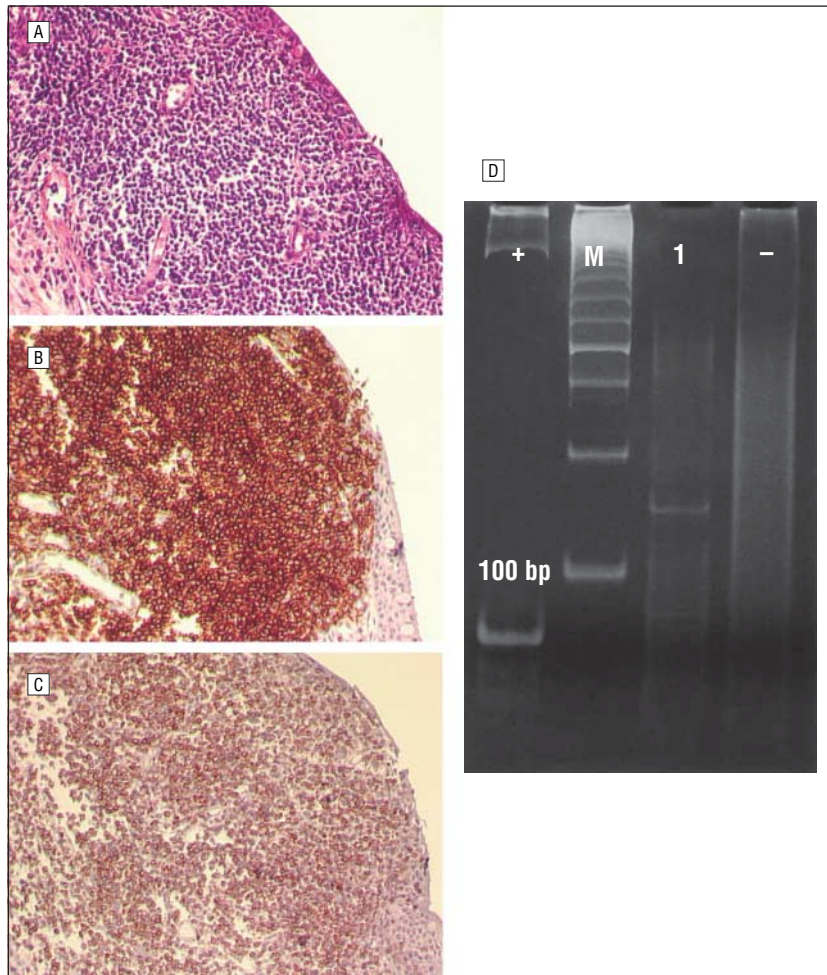


Figure 2. A, Mucosa-associated lymphoid tissue lymphoma composed of small lymphomatous cells with round nuclei and dense chromatin. The tumoral cells show a diffuse pattern of infiltration and focally infiltrate the conjunctival epithelium (hematoxylin-eosin-saffron, original magnification $\times 20$). The lymphomatous cells are CD20 positive (B) and *Bcl-2* positive (C). B, Immunostaining showing a membranous positivity with the anti-CD20 antibody (original magnification $\times 20$). C, Immunostaining showing intracytoplasmic positivity with the anti-*Bcl-2* antibody (original magnification $\times 20$). D, IgH gene rearrangement studies by polymerase chain reaction (PCR) at the *FR3* locus on polyacrylamide gel. Lane 1 corresponds to the PCR with DNA extracted from paraffin-embedded conjunctival biopsy. A band in lane 1 between 100 and 150 base pair (bp) assesses the presence of a monoclonal B-cell population. Plus sign indicates positive control; M, bp marker; 1, patient; and minus sign, negative control.

tologic examination revealed extranodal marginal zone B-cell lymphoma of MALT type. Immunohistochemical analyses showed CD20 positivity, CD3 negativity, and *Bcl-2* positivity (Figure 2A-C). Polymerase chain reaction analysis of paraffin-embedded tissue was performed and detected a clonal rearrangement of the immunoglobulin heavy-chain gene at the *FR3* locus (Figure 2D). No local recurrence of the melanoma was observed. The staging of the disease, including magnetic resonance imaging of the orbit, computed tomography of the chest and abdomen, bone marrow biopsy, and gastric endoscopy, found an exclusive conjunctival localization with good perfor-

mance status and a normal serum lactate dehydrogenase level. Because of the complete resection of the lesion and previous irradiation, no complementary treatment was necessary. After follow-up of 24 months, the patient remains in complete remission.

Comment. Until now, few patients with both cutaneous melanoma and lymphoproliferative disease have been described in the literature. To our knowledge, the association of a conjunctival melanoma with an NHL of the same localization has never been described until now. A significantly elevated risk of NHL among survivors of cutaneous melanoma and of cutaneous melanoma among survi-

vors of NHL has been reported, supporting the hypothesis of shared genetic or etiologic factors such as immunosuppression, UV radiation, and genetic factors.^{1,2} The *p16* gene, which inhibits cyclin-dependent kinase and was reported to be mutated or deleted in melanoma and lymphoma, has been proposed as a potential candidate for the common pathogenesis of both neoplasms.³

Our observation is noteworthy for the occurrence of 2 different malignant diseases in the same tumor localization. All previously mentioned explanations could be proposed; MALT-type lymphomagenesis is now well described. The lymphomatous process could be a local inflammatory reaction induced by previous irradiation of the conjunctiva; a deregulation of the Fas/CD95/APO-1 pathway, inducing tumor cell tolerance⁴; and/or an inhibition of the apoptotic process through the *Bcl-10* or *HIAP-1* (human inhibitor of apoptosis protein 1) genes.^{5,6} In this patient it could be speculated that a dysregulation of apoptotic function, in particular the CD95 pathway, was the mechanism for both melanoma and lymphoma.

This peculiar observation further underlines the need for continued observation in patients treated for a conjunctival malignancy to detect relapses of the initial disease and assess the presence of associated diseases that could arise, as well as the need for additional studies to detect any associated genetic abnormalities.

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Tadalafil Associated With Anterior Ischemic Optic Neuropathy

Tadalafil (Cialis; Eli Lilly, Indianapolis, Ind) is used to treat erectile dysfunction.¹ Sildenafil (Viagra; Pfizer, New York, NY), a similar medication, has been associated with nonarteritic anterior ischemic optic neuropathy (NAAION).^{2,3} We describe a patient who developed NAAION after he took tadalafil.

Report of a Case. A 59-year-old man with prostate cancer and erectile dysfunction underwent uncomplicated laparoscopic prostatectomy. His only other medical problem was depression, treated with bupropion hydrochloride. The immediate postoperative hematocrit measured 25.2%. The patient was ambulating and hemo-

dynamically stable on postoperative day 1 and that evening took 20 mg of tadalafil. Fifteen hours later, he reported dizziness lasting several minutes. Blood pressure and pulse measured 126/61 mm Hg and 99 bpm, respectively. The episode resolved spontaneously. Forty-five hours after ingesting tadalafil, he noted sudden, persistent “graying” in the inferior visual field of the left eye. The next day, he took 20 mg of tadalafil. The graying did not change.

Examination 6 days later revealed acuity of 20/20 OU, with a left relative afferent pupillary defect. Perimetry (Swedish Interactive Threshold Algorithm Standard 24-2) was normal in the right eye and showed inferior altitudinal loss in the left eye (**Figure 1**). The fundi were normal except for 2 cotton-wool spots in the macula right eye, left optic disc edema, and nerve fiber layer hemorrhage (**Figure 2**). The right optic disc was crowded. The remainder of the examination results were normal. Hematocrit measured 30.2%. Erythrocyte sedimentation rate and C-reactive protein levels were normal. He had no symptoms of temporal arteritis. Six weeks later, acuities and fields were unchanged in each eye, the left optic disc edema was resolving, and no cotton-wool spots were seen.

Comment. Nonarteritic anterior ischemic optic neuropathy developed 45 hours after taking tadalafil. Tadalafil, a phosphodiesterase type 5 inhibitor, enhances erection through

smooth muscle relaxation and increased blood flow in the corpus cavernosum. Forty-five hours is within 2.5 half-lives for a drug that is effective for at least 36 hours, the latest time point tested in clinical trials.¹ In this case, crowded optic discs and postoperative anemia were concurrent risk factors for NAAION.⁴ However, the patient was mobile and asymptomatic prior to taking tadalafil.

Pomeranz et al³ published a case series of NAAION associated with sildenafil, another phosphodiesterase type 5 inhibitor. Sildenafil lowers systemic blood pressure, which could contribute to NAAION. The authors proposed that sildenafil might also contribute to NAAION by vasodilation of the optic disc circulation and interference with vascular autoregulation. Tadalafil acts similarly but is more specific for phosphodiesterase type 5 (found in the corpus cavernosum) and has a longer half-life; also, tadalafil did not lower systemic blood pressure in clinical trials.¹ Nonarteritic anterior ischemic optic neuropathy associated with tadalafil would more likely be due to a local effect on optic disc circulation.

Pomeranz et al³ suggested that patients with a history of unilateral NAAION not use sildenafil. No definite association between tadalafil and NAAION can be made on the basis of the current case. Similarly, the cotton-wool spots might have been related to anemia, tadalafil, or both. However, this case should heighten

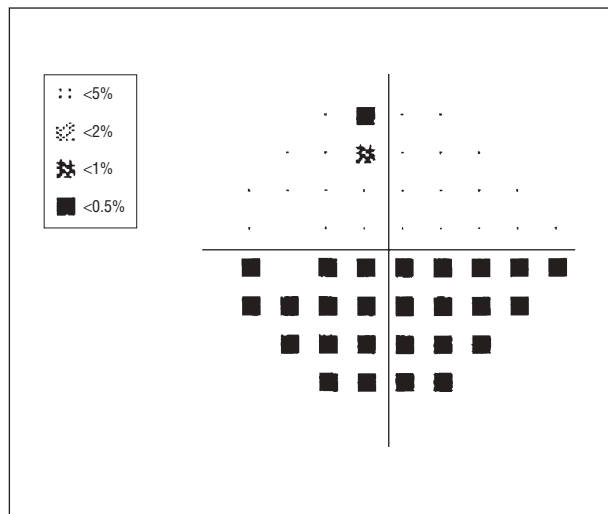


Figure 1. Swedish Interactive Threshold Algorithm Standard 24-2 pattern deviation plot of the left eye. There is inferior altitudinal visual field loss.



Figure 2. Left optic disc. There is edema and a superior nerve fiber layer hemorrhage.