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 hist-

Figure 1. A, Conjunctival malignant melanoma with a diffuse pattern of infiltration of the conjunctiva (hematoxylin-eosin-saffron, original magnification ×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 ×40). C and D, Immunostainings with the anti-HMB-45 (C) and anti-PS100 (D) antibodies showing intracytoplasmic positivity of the tumoral cells (original magnification ×40).
tologic examination revealed extra-
nodal marginal zone B-cell lym-
phoma of MALT type. Immuno-
histochemical analyses showed CD20 
positivity, CD3 negativity, and 
Bcl-2 positivity (Figure 2A-C). Polymer-
ase 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 ob-
served. The staging of the disease, 
including magnetic resonance imag-
ing of the orbit, computed tomogra-
phy of the chest and abdomen, bone 
marrow biopsy, and gastric endos-
copy, found an exclusive conjuncti-
val localization with good perfor-
mance status and a normal serum lac-
tate dehydrogenase level. Because of 
the complete resection of the lesion 
and previous irradiation, no comple-
mentary treatment was necessary. Af-
ter follow-up of 24 months, the pa-
tient 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 con-
junctival melanoma with an NHL of 
the same localization has never been 
described until now. A significantly 
elevated risk of NHL among survi-

dors of NHL has been reported, sup-
porting the hypothesis of shared ge-
netic or etiologic factors such as 
immunosuppression, UV radiation, 
and genetic factors. The p16 gene, 
which inhibits cyclin-dependent ki-
nase and was reported to be mutated 
or deleted in melanoma and lym-
phoma, has been proposed as a po-
tential candidate for the common 
pathogenesis of both neoplasms.

Our observation is noteworthy for 
the occurrence of 2 different malig-
nant diseases in the same tumor lo-
calization. All previously men-
tioned explanations could be 
proposed; MALT-type lymphoma-
genesis is now well described. The 
lymphomatous process could be a 
local inflammatory reaction in-
duced by previous irradiation of the 
conjunctiva; a deregulation of the 
Fas/CD95/APO-1 pathway, induc-
ing tumor cell tolerance; and/or an 
inhibition of the apoptotic process 
through the Bcl-10 or HIAP-1 (hu-
man inhibitor of apoptosis protein 
1) genes. In this patient it could 
be speculated that a dysregulation of 
apoptotic function, in particular the 
CD95 pathway, was the mech-
anism for both melanoma and 
lymphoma.

This peculiar observation fur-
ther underlines the need for contin-
ued observation in patients treated 
for a conjunctival malignancy to de-
tect relapses of the initial disease and 
assess the presence of associated dis-
eses that could arise, as well as the 
need for additional studies to de-
tect any associated genetic abnor-
malities.

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Tadalafil Associated With Anterior Ischemic Optic Neuropathy

Tadalafil (Cialis; Eli Lilly, Indianapolis, Ind) is used to treat erectile dysfunction. Sildenafil (Viagra; Pfizer, New York, NY), a similar medication, has been associated with nonarteritic anterior ischemic optic neuropathy (NAAION). 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 hemodynamically 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 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. The fundi were normal except for 2 cotton-wool spots in the macula right eye, left optic disc edema, and nerve fiber layer hemorrhage. 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. In this case, crowded optic discs and postoperative anemia were concurrent risk factors for NAAION. However, the patient was mobile and asymptomatic prior to taking tadalafil.

Pomeranz et al 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. Nonarteritic anterior ischemic optic neuropathy associated with tadalafil would more likely be due to a local effect on optic disc circulation.

Pomeranz et al 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 awareness of the potential for tadalafil to cause NAAION.

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.