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Case Report

Combining Surgery, Radiotherapy, and Topical Chemotherapy to Prevent Primary Orbital Exenteration for Atypical Caruncular Melanoma: A Case Report

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Keywords

Caruncular melanoma · Topical chemotherapy · 5-Fluorouracil · External beam radiotherapy · Case report

Abstract

Introduction: This case report demonstrates the possibility of successful eye and vision-sparing therapy for caruncular melanoma. ***Case Presentation:*** We present an atypical presentation of a caruncular melanoma. After excisional biopsy, residual flat conjunctival melanosis resolved using topical chemotherapy (5-fluorouracil), which was well tolerated. Relapse of the melanoma was treated with external beam radiotherapy, but the tumor grew despite treatment. Eighteen months after complete excision of the relapsed melanoma, the patient remains tumor-free while the eye and its function remain preserved. ***Conclusion:*** This case report suggests that aggressive eye-sparing therapy for caruncular melanoma combining surgery, adjuvant topical chemotherapy, and external beam radiotherapy, can be an alternative for primary orbital exenteration.

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Introduction

The caruncle is an ovoid structure, situated medial to the plica semilunaris in the lacus lacrimalis. Its function is poorly understood. It is supplied by the superior medial palpebral arteries and lymphatics drain into the submandibular lymph nodes. Lesions of the caruncle are not only rare, but as it harbors numerous types of tissue, such as hair follicles, sebaceous glands, sweat glands, and accessory lacrimal tissue, they are diverse, making a clinical diagnosis difficult. The vast majority of caruncular lesions are benign. Melanocytic lesions are common, with nevi accounting for the most of them. Malignant melanocytic caruncular lesions are uncommon [1, 2]. However, we present an atypical caruncular invasive melanoma, successfully treated with surgery, adjuvant topical chemotherapy, and external beam radiotherapy (EBRT). The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000536590).

Case Report

A 69-year-old male Caucasian patient was referred to our clinic because of a growing caruncular lesion of the left eye that easily bled after eye rubbing at night. He was previously diagnosed with basal cell carcinoma of the skin of the thorax, treated with resection with free surgical margins. Ten years earlier, he already underwent a conjunctival biopsy in another center for a pigmented caruncular lesion at the left eye. The pathology result then showed a compound nevus naevocellularis without cytonuclear atypia.

The patient reported no pain or sensitivity. Best-corrected visual acuity was 20/20 in both eyes. Slit lamp examination revealed a round, amelanotic, elevated lesion with yellow crustae and blood on the surface, arising from the caruncle of the left eye and measuring 5 × 4 mm (shown in Fig. 1a). It did not involve the plica or the tarsal conjunctiva. No feeder vessels or pigmentation were noticed in the surrounding conjunctiva. Dilated fundoscopy of both eyes was unremarkable. A clinical diagnosis of keratoacanthoma or papilloma was suspected. An excisional biopsy was performed because of rapid growth of the lesion and the history of bleeding after eye rubbing.

During surgery, conjunctival pigmentation was noticed at the base of the lesion, suggestive of primary acquired melanosis. A “no touch” technique with a 3 mm resection margin was applied to remove the mass, including the pigmented conjunctiva at the base, followed by double freeze-thaw cryotherapy of the conjunctival margins and alcohol application (96% ethanol, 60 s) at the surgical bed [3]. The surface was reconstructed using an amnion membrane transplantation.

Despite a clinically benign and rather inflammatory appearance, an invasive caruncular melanoma (CM) was diagnosed. On microscopy, the CM had a thickness of 4 mm. There was no ulceration or lymphovascular invasion. The mitotic rate was less than six per square millimeter. Immunohistochemical analysis demonstrated reactivity to Melan-A (shown in Fig. 2a) and SOX10. The Ki-67 proliferation index was high (>20%) (shown in Fig. 2b). Immunohistochemistry to PRAME showed weak, focal staining. No BRAF mutations were found on molecular analysis. At the surface, a component of in situ melanoma was noted. The invasive component showed extension into the lateral and deep surgical margins, meaning no complete resection was achieved (shown in Fig. 2c, d). Postoperatively, a small area of flat conjunctival melanosis was clinically noticed in the remnant of the caruncle (shown in Fig. 1b).

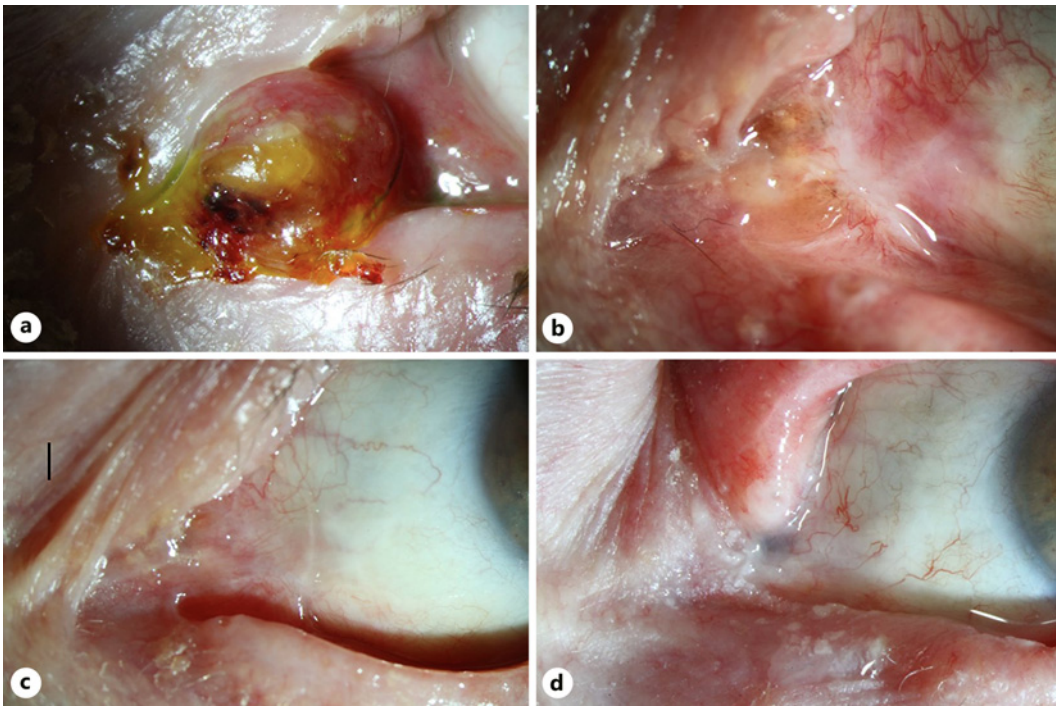

Fig. 1. Slit lamp photography of the left eye at presentation (**a**); 6 weeks after surgery, residual pigmentation (**b**); 8 months after surgery, complete resolution of residual pigmentation 5 months after adjuvant topical chemotherapy with 5-fluorouracil (5-FU) (**c**); 1.5 years after the second surgery, 22 months after external beam radiotherapy (EBRT) (**d**).

Staging by means of a whole-body PET/CT scan revealed no visualization of residual melanoma in the left eye, no adenopathies, and no metastasis. MRI brain and orbit showed no intracranial or orbital metastasis. The caruncular malignant melanoma in our case would be categorized as T2c according to the 8th American Joint Committee on Cancer (AJCC) classification of conjunctival malignant melanomas [4].

Given the incomplete resection, larger excision to achieve tumor-free surgical margins was discussed, but the expected postoperative morbidity was not acceptable to the patient. He did agree to start adjuvant topical chemotherapy; however, due to stock issues mitomycin C (MMC) was unavailable at that time. Instead of MMC, he received three cycles of topical 5-fluorouracil (5-FU) 1% four times daily, with each cycle lasting 1 week followed by two drug-free weeks. 5-FU therapy was well tolerated and no side effects were reported. Three months after completion of 3 cycles topical 5-FU 1% the flat conjunctival melanosis disappeared (shown in Fig. 1c). Nine months after surgery, MRI, and PET/CT showed no signs of malignancy. The risk of tumor recurrence originating from the deep surgical margin was discussed with our patient and the need for close follow-up was emphasized.

However, 13 months after surgery and 11 months after topical chemotherapy, MRI demonstrated a suspected relapse of the tumor inferonasally of the left eye with a diameter of 11 mm without muscle invasion (shown in Fig. 3a). Whole-body PET/CT showed no adenopathies or metastasis. A multidisciplinary discussion led to the initiation of EBRT with 35 sessions of photon-RT over a 2-month period (a total of 70 Gy). The patient developed radiation dermatitis with resultant cicatricial ectropion. Because of persisting tearing despite topical therapy, the patient underwent probing of the tear ducts and implantation of a monocanalicular silicone stent to alleviate the symptoms.

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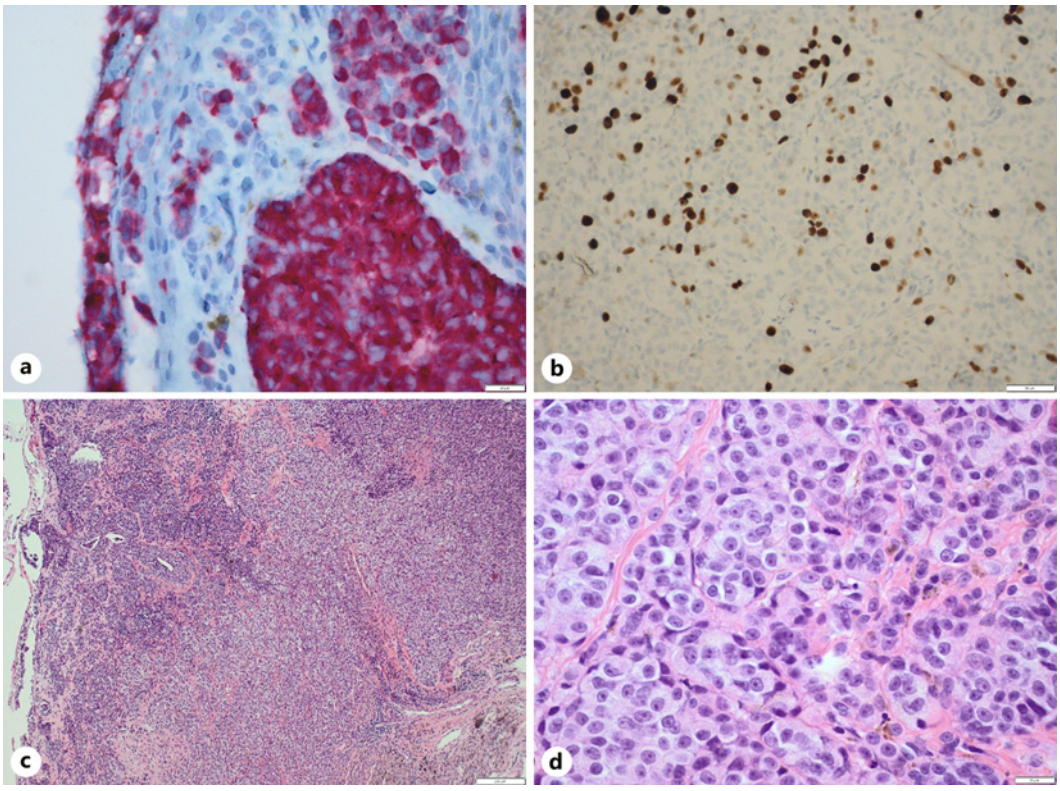

Fig. 2. First excisional biopsy showed staining for Melan-A with strong cytoplasmic staining of the atypical melanocytes, also in the in situ component at the surface (left) (magnification ×40) (**a**); and anti-Ki-67 immunostaining demonstrating an increased proliferation of atypical melanocytes of more than 20% (magnification ×20) (**b**). Biopsy showing atypical melanocytes with enlarged nuclei, varying in shape and size (hematoxylin and eosin, magnification ×5 (**c**) and ×40 (**d**)).

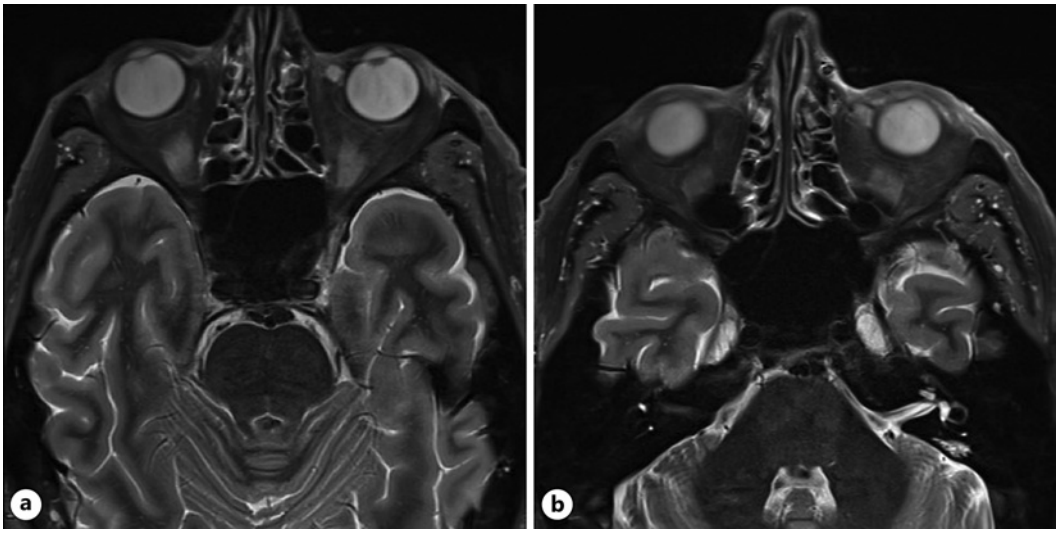

Fig. 3. MRI of the orbits showing the tumor inferonasally of the left eye (T2 weighted, no contrast, slice 11/19) (**a**); and the grown lesion despite EBRT 6 months later (T2 weighted, no contrast, slice 12/19) (**b**).

Because of proximity to the bulbus, prophylactic intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections (off-label use of bevacizumab) were initiated to prevent radiation retinopathy. The Shields protocol for choroidal melanomas was applied, administering anti-VEGF intravitreally every 4 months for the duration of 2 years [5].

Follow-up imaging 3 months after completion of radiotherapy revealed that the lesion had grown despite treatment (shown in Fig. 3b). PET/CT now also showed the recurrence of the melanoma at the inferomedial side of the left eye. Therefore, the patient was advised to undergo a second surgical intervention. An excisional biopsy was performed, and the pathology report confirmed a complete resection of a malignant melanoma. The tumor had a central hemorrhage and showed signs of tumor cell necrosis. No residual tumor was found on postoperative imaging. Thirteen months after the second surgery, PET/CT showed swollen and intensely hypermetabolic lymph nodes in the axilla on the left side. However, in consultation with the oncologist, this was considered to be liaised to a left upper arm COVID vaccination the day before. The subsequent PET/CT 6 months later was unremarkable.

More than 3 years after the diagnosis, the patient continues to have optimal BCVA (fluctuating between 20/25 and 20/20). He only suffers a mild medial ectropion, but without any discomfort (shown in Fig. 1d). Whole-body PET/CT and MRI of the brain and orbit 19 months after complete resection of the melanoma showed no recurrence or metastasis. In addition, fundoscopy and angiography 2 years after the first anti-VEGF injection did not show signs of radiation retinopathy. Clinical follow-up and imaging are continued every 6 months.

Discussion

Caruncular lesions are rare and can be very diverse. Multiple (retrospective) studies show a low clinicopathological correlation (37–53%) [1, 2]. This implies one should be very wary with a clinical diagnosis of a benign caruncular lesion. Because of the low clinicopathological correlation, there should be a low threshold to perform an excisional biopsy to confirm the diagnosis.

Early diagnosis and correct treatment are essential since tumor-related mortality for a conjunctival melanoma after 10 years is reported to be between 23% and 39%, while a caruncular location is an additional risk factor for mortality [6]. Recurrence is one of the greatest risk factors for metastatic spread and mortality [3]. Ten-year recurrence rates for conjunctival melanomas are reported to be as high as 69%, even with intensive treatment and follow-up [7]. Important risk factors for recurrence are a tumor thickness greater than 2 mm, AJCC stage T2 or higher, a non-bulbar location, histologic ulceration, and incomplete resection [3, 6–8].

The patient's presentation was atypical for a CM; the caruncular lesion was rapidly growing and bleeding but without pigmentation and with crustae on the surface. No feeder vessels were present. To the best of our knowledge, only one other similar case report is described in literature by Shields et al. [9]. Histologic ulceration was absent in our case but the non-bulbar location, the tumor thickness of 4 mm, and T2c stage classification were prognostically unfavorable.

Traditionally, management of a conjunctival melanoma implied wide-margin excisional surgery or even exenteration, leading to extensive disfigurement and morbidity [10, 11]. In recent years, there is a trend toward eye-sparing surgery. The current golden standard treatment for a limited conjunctival melanoma (i.e., limited to the epithelium or early deep invasion) consists of surgical excisional biopsy with intraoperative double freeze-thaw cryotherapy of surgical margins and alcoholization of the surgical bed [3, 12]. Extensive conjunctival melanoma with orbital involvement can still be managed by performing

exenteration [12]. However, in case of orbital invasion or a tumor thickness greater than 1.0 mm there is no benefit on survival in these patients, especially in tumors of caruncular origin [11, 12]. Moreover, despite exenteration the melanoma-related mortality rate remains between 33% and 50% in patients with a tumor thickness more than 1 mm [11]. The possibility of having to perform a secondary orbital exenteration in case of future tumor recurrence was discussed with our patient. Research has suggested that early secondary exenteration (i.e., after a number of local recurrences less than or equal to 4) may reduce the occurrence of metastases in conjunctival melanoma [13].

In contrast with the treatment for primary acquired melanosis, treatment with topical chemotherapy for conjunctival melanoma is currently limited to neoadjuvant or adjuvant therapy. MMC and interferon-alpha-2B (IFN-α2B) are most commonly described in studies. Varying initial tumor response rates for adjuvant treatment are reported, ranging between 93–100% and 40–100% for treatment with MMC and IFN-α2B, respectively [14–16]. The preferred adjuvant therapy is MMC, although recurrence rates are as high as 50% (after 12 years of follow-up) [6]. Treatment with topical MMC is reported to have several common (up to 87%), usually transient, adverse effects, including injection, tearing (due to punctal stenosis), irritation, blepharospasm, punctate epithelial keratopathy, and even limbal stem cell deficiency. These potential adverse effects may limit compliance. Regarding topical therapy with IFN-α2B little data are known, but it seems to have a better side effect profile and good effectiveness [4]. More studies are needed to establish the usefulness in clinical practice.

A literature search revealed no studies reporting a beneficial effect on conjunctival melanoma with topical treatment with 5-FU. However, topical 5-FU has been successfully used to treat ocular surface squamous neoplasia [6]. With topical 5-FU, we achieved complete resolution of a residual area of flat conjunctival melanosis 3 months after completion of therapy.

EBRT is commonly used as an adjuvant therapy for head and neck cancers, but the use for conjunctival melanoma is limited to avoid damaging other ocular structures (such as the cornea and adnexa) [4]. It is remarkable that in our case EBRT did not have any effect on the tumor size.

In our patient, the development of radiation retinopathy was expected. Shields et al. [5] demonstrated a benefit in visual outcome after 4 years with prophylactic intravitreal bevacizumab (every 4 months over 2 years) in patients with choroidal melanoma treated with plaque brachytherapy. Data on prophylactic treatment in conjunctival melanoma to prevent radiation retinopathy lack due to sparsity of the tumor. However, to maintain optimal visual function, we applied this protocol to our patient. Although radiation retinopathy has been described up to 5 years after treatment, fluorescein angiography demonstrated absence of any sign during the current follow-up period of over 3 years.

We describe a patient with an atypical presentation of an invasive CM. After a total of 3.5 years of follow-up, of which 1.5 years after the last excisional surgery, our patient has a calm and stable anterior segment, without local or distant tumor recurrence. Both structural and functional integrity were preserved through an extensive treatment combining aggressive surgery, adjuvant topical chemotherapy, EBRT, and prophylactic intravitreal anti-VEGF injections. This is even more remarkable, given the unfavorable prognosis of a T2c CM. Further research is needed to compare long-term morbidity and mortality rates between aggressive conservative treatment versus exenteration in the management of invasive CM.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This study protocol was reviewed and approved by the "Commissie voor Medische Ethiek U(Z) Gent," approval number CR-2023-0004.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors attest that they meet the current ICMJE criteria for authorship. Cédric De Landsheer: conceptualization, methodology, investigation, writing – original draft, visualization. Valentien Merlevede: writing – review and editing. Celine Jacobs: writing – review and editing. Jo Van Dorpe: writing – review and editing. Julie De Zaeytijd: writing – review and editing. Virginie Ninclaus: writing – review and editing. Dimitri Roels: conceptualization, investigation, and writing – original draft.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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