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Case Report

A Case of Conjunctival Melanoma Presenting as a Squamous Cell Carcinoma

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Keywords
Conjunctival melanoma · Squamous cell carcinoma · Conjunctival tumor

Abstract
Introduction: Conjunctival melanoma (CM) is a rare but potentially lethal ocular malignancy that arises from melanocytes in the conjunctiva. Its clinical presentation can mimic other more common conjunctival lesions, such as squamous cell carcinoma (SCC), leading to diagnostic challenges. ***Case Presentation:*** We present a case of CM initially misdiagnosed as conjunctival SCC due to overlapping clinical features. ***Conclusion:*** CM presenting as nonpigmented, conjunctival tumor is a diagnostic challenge. Clinicians should maintain a high index of suspicion for conjunctival melanocytic or amelanotic lesions, particularly those with atypical features.

Introduction

Conjunctival melanoma (CM) is a subtype of mucosal melanoma that arises from atypical melanocytes in the basal layer of the conjunctival epithelium and represents 2% of ocular tumors [1]. Like the incidence of cutaneous melanoma, but unlike that of other mucosal melanomas, the incidence of CM is rising, likely due to increased UV exposure [2]. Incidence of CM increases with age and is found to be more common in older individuals. The mean age at presentation is between 55 and 65 years, while it is extremely rare in those younger than 20 years of age [3]. The 5- and 10-year local recurrence rates were 26% to 60% and 31% to

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66.4%, respectively. The 5- and 10-year related metastasis rates were 17% to 52% and 27% to 57%, respectively. The 5- and 10-year tumor-related mortality rates were 5% to 30.5% and 14% to 37.4%, respectively [4, 5]. With a high rate of local recurrence and metastasis, CM has a significant mortality that makes it a life-threatening disease [6].

The preferred management of all resectable CM is total surgical excision with tumor-free margins of 2 to 4 mm combined with cryotherapy [7]. The adjuvant cryotherapy is administered to the surgical margins with the conjunctiva raised to avoid scleral damage [8]. In case of corneal involvement, alcohol corneal epitheliectomy is performed [7]. The aim of these adjuvant treatments is to destroy clinically undetectable tumor cells that may persist along the margin of resection and thus prevent dissemination of viable cells [9].

The clinical presentation of CM varies widely [1]. Typically, CM presents as painless, pigmented nodules on the bulbar, palpebral, forniceal, or limbal conjunctiva [6]. The diagnosis of CM can be challenging since it is often mimicking other more common ocular surface lesions such as conjunctival squamous cell carcinoma (SCC) [10]. Here, we present a case of CM initially misdiagnosed as conjunctival SCC due to its clinical presentation, highlighting the importance of considering melanoma in the differential diagnosis of conjunctival lesions.

Case Report

A 75-year-old woman presented with a lesion on the temporal aspect of the conjunctiva of her right eye. She reported noticing the lesion since 1 year prior to presentation and gradual increase in size. She denied any trauma, bleeding, visual disturbances, or ocular discomfort. The patient in the anamnesis does not take any medication and has no known illnesses, although she has never actually been to a doctor before and generally refuses to undergo medical visits. On examination, a well-defined, exophytic, painless, minimally and very locally pigmented lesion was observed on the temporal bulbar conjunctiva (Fig. 1). The lesion exhibited irregular borders, a bi-lobed, pink aspect with prominent intrinsic and extrinsic vasculature and feeder vessels without invasion of the lower fornix (Fig. 2). There were no signs of intraocular involvement or lymphadenopathy. On ultrasound biomicroscopy, a thickness of 1.29 mm without scleral infiltration could be visualized (Fig. 3).

Given the clinical appearance suggestive of conjunctival SCC, an excisional biopsy was performed. Histopathological examination revealed nests of ulcerated pigmented epithelioid cell tumor with numerous tumor-infiltrating lymphocytes and melanosis with severe atypia providing the diagnosis of CM. Immunohistochemically, the tumor cells were strongly positive for the melanocytic markers Melan A and SOX 10. Following the diagnosis of CM, evaluation with orbital imaging was performed revealing no local invasion or distant metastasis. The patient underwent wide local excision of the lesion with cryotherapy to the surrounding conjunctival margins. Adjunctive treatment with topical chemotherapy (mitomycin C 0.04% four times daily for 7 days after excision and cryotherapy) was initiated to reduce the risk of local recurrence (Fig. 4). The patient refused further imaging such as PET and CT scans at the time. Regular follow-up examinations were scheduled to monitor for disease recurrence or metastasis.

Discussion

CM is a rare malignancy, accounting for approximately 5% of all ocular melanomas. It typically presents as a pigmented lesion of the bulbar conjunctiva, often near the limbus. Clinical features such as irregular borders, growth rate, and vascularization may mimic other

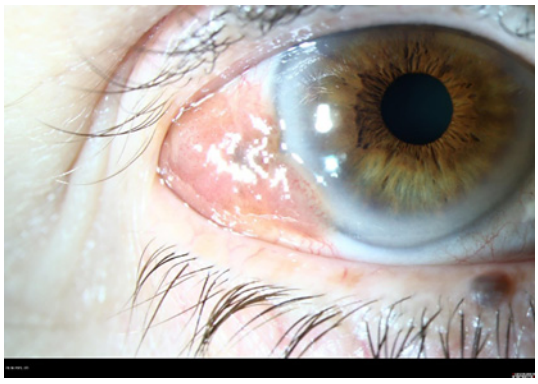

Fig. 1. Color anterior segment photograph of the right eye of a 75-year-old woman, with an exophytic temporal conjunctival lesion.

malignant conjunctival lesions, including SCC, leading to misdiagnosis. In 70% of cases, CM presents as a pigmented, thickened, conjunctival tumor with enlarged feeder vessels, while in the remaining cases there is a minimally elevated and nonpigmented or mildly pigmented lesion, thus making clinical diagnosis challenging [11].

Conjunctival SCC is an epithelial malignant tumor in the spectrum of ocular surface squamous neoplasia (OSSN), and its main differential diagnosis includes conjunctival intraepithelial neoplasia, papilloma, and granuloma. It is usually present as a gelatinous, nonpigmented vascularized mass, located more frequently in the interpalpebral area, and possible infiltration of the adjacent corneal epithelium [12].

When comparing OSSN and amelanotic CM, it is essential to consider their clinical presentation, histopathological features, and imaging characteristics. OSSN typically presents as a pink or red mass, often with well-defined borders and slower growth. It often appears as a fleshy, warty, or nodular growth. It may be exophytic or have a papillomatous, wart-like appearance [13]. Amelanotic CM appears as a pale or reddish mass with irregular borders and more aggressive growth. It usually presents as a darkly pigmented, irregularly shaped lesion [14]. It can be nodular or flat, with potential for ulceration. OSSN features atypical squamous cells with varying degrees of dysplasia and potential invasion. Key characteristics of OSSN include keratinization and leukoplakia. Histologically, leukoplakia is associated with epithelial hyperplasia and dysplasia, where cells appear atypical and may exhibit varying degrees of keratinization [15]. Amelanotic CM presents with atypical melanocytes without pigmentation and may show deeper invasion into the stroma [16]. The lesion of this case reported had clinical features suspicious for OSSN such as lack of vast pigmentation, a papillomatous architecture, an intrinsic vascularity, and the presence of feeder vessels [17]. However, neither keratinization nor leucoplakia is pathognomonic for OSSN lesions and not seen in CM [18]. Due to the clinical overlap between these two conjunctival tumors, histopathology remains the gold standard for the diagnosis [19].

The histopathologic confirmation of CM diagnosis is reliant on the identification of atypical melanocytes. These cell alterations manifest with pleomorphic nuclei, large nuclear size, prominent nucleoli, mitotic activity with atypical mitoses, and abundant cytoplasm [20]. Other histological features of the CM include pagetoid growth, radial extension of the intraepithelial component, patchy or bandlike inflammation of the basal layer of the lesion, decreased maturation of basal cells, and invasion of sclera or cornea [21].

Differentiating CM from SCC is crucial due to differences in management and prognosis. While SCC is primarily treated with surgical excision and occasionally adjuvant therapies, CM requires wide local excision with meticulous removal of all involved tissues to reduce the risk of recurrence and metastasis [22]. Additionally, imaging studies such as CT scans, PET scans, or MRI play a vital role in the management of patients with CM by providing essential

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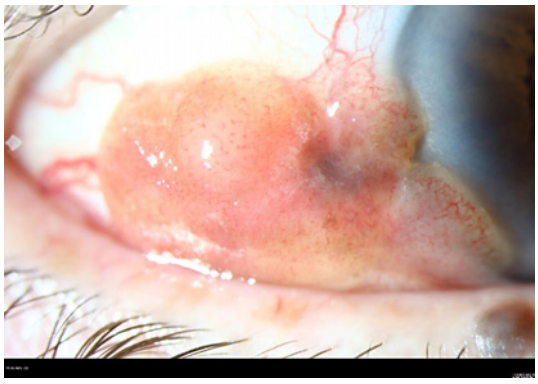

Fig. 2. A bi-lobed, slightly pigmented conjunctival lesion with wide feeder vessels.

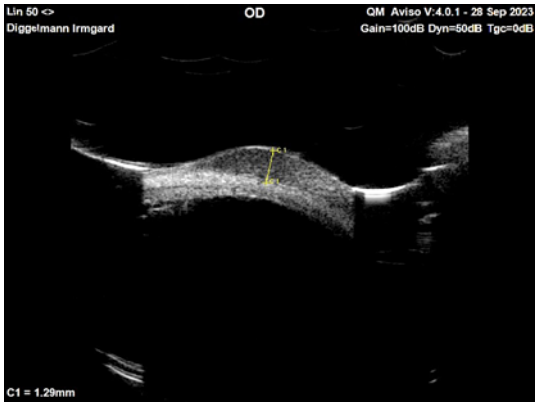

Fig. 3. UBM of the 1.29-mm-thick conjunctival lesion showing no scleral infiltration. UBM, ultrasound biomicroscopy.

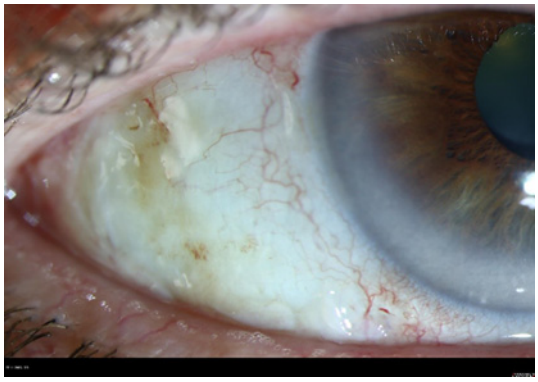

Fig. 4. Color anterior segment photograph of the right eye of the patient after the tumor excision.

information about the tumor's extent, local invasion, lymph node involvement, and potential distant metastases [23]. In cases of CM, orbital involvement is a significant concern due to the potential for local invasion and spread of the tumor beyond the conjunctiva. Orbital findings in CM can range from localized swelling and mass formation to more significant issues such as bone erosion and metastatic spread [24]. Follow-up recommendations for patients with CM are essential for monitoring disease recurrence, progression, and managing potential complications [6]. The follow-up strategy should be individualized based on the initial stage, treatment received, and any specific risk factors [9]. Regular clinical examinations should be performed every 3–6 months at initial phase in the first 1–2 years and annually after 2 years.

Imaging studies should be performed every 6–12 months at initial phase, especially if there is a high risk of recurrence or metastasis. After 2 years, based on individual risk, typically imaging may be performed annually or as clinically indicated [25].

Metastases most often appear in the preauricular or submandibular lymph nodes, lung, and brain. Physical examination should include palpation of the head and neck lymph nodes. Annual chest X-rays and brain magnetic resonance imaging are recommended [26]. Several clinical risk factors for recurrence of CM have been reported, including location in the tarsal region or in the conjunctival fornix, eyelid margin involvement, incomplete excision, and involvement of margins on histopathology [27]. Further, tumor-associated lymphangiogenesis identified histopathologically appears to increase the risk of local recurrence [28].

Generally, first-line treatment for local CM is wide local surgical excision followed by cryotherapy to the surgical margins [9]. In cases in which local tumors are extensive or persistently recurrent, exenteration or enucleation may be necessary to prevent tumor metastasis or invasion into nearby structures such as the globe or orbit [29]. Various adjuvant therapies are often utilized after excision due to the high recurrence rates. Topical therapies applied to excision sites include mitomycin C and interferon (IFN)-α-2b [30]. Depending on the study, the dose of MMC varies between 0.002% and 0.04% for desired responses, at the cost of some adverse side effects [31–33]. Topical mitomycin C 0.04% appears to be a safe and effective therapy for conjunctival or corneal SCC, even when there is extensive recurrent tumor [34]. A recent review confirmed the effectiveness of topical mitomycin C 0.04% chemotherapy in the management of ocular surface neoplasia [35]. However, in case of topical mitomycin used in the management of CM, it also reported recurrence rates of 33–100% for primary treatment and 0–66% for adjuvant treatment [36]. Reported complications of topical mitomycin chemotherapy range from common transient self-limiting problems such as local irritation, hyperemia, epiphora, allergy, keratoconjunctivitis, and corneal abrasion [37] to longer lasting problems such as punctal stenosis, cataract, persisting keratoconjunctivitis, and among the most serious ones limbal stem cell deficiency [38], being present in up to 12% of patients [39]. Topical IFN-α-2b has shown to be effective as a single agent or as an adjunct therapy agent after surgery, and since it has not been associated with limbic stem cell damage, it could be an excellent alternative treatment [40].

Radiotherapy is another adjunct treatment of CM and can be in the form of brachytherapy or external beam radiation therapy [41]. No standard therapy regimens exist for treatment of metastatic CM. However, given the molecular and pathophysiological similarities between CM and cutaneous melanoma, drugs used to treat metastatic disease in cutaneous melanoma patients may benefit patients with metastatic CM [42].

Relapse of CM after 6–12 months requires a comprehensive approach involving diagnostic evaluation, restaging, and targeted treatment [43]. Surgical management is often the primary approach, supplemented by adjuvant therapies such as topical chemotherapy with mitomycin C, and systemic treatments as necessary such as chemotherapy, targeted therapy, or immunotherapy may be indicated [44]. Options include immune checkpoint inhibitors (e.g., pembrolizumab, nivolumab) or targeted agents depending on the molecular profile of the melanoma [45]. Enhanced follow-up and patient education are critical to managing the disease effectively and ensuring early detection of any further issues.

The successful treatment of CM depends on the extension of the tumor. Important rules of CM surgery are to use the no-touch technique and to let the ocular surface dry until the tumor is completely removed so as to not seed the malignancy [46]. After excision, it often remains the large epibulbar defects which may require reconstruction. Large defects, more than 1 cm in diameter, can result in unsatisfactory direct closure, and the result may be the scarring or

the restriction of eye movements, or a foreign body feeling that led to discomfort for the patient [47]. Conjunctival defect might be closed either primarily or with conjunctival flap, a graft from the opposite conjunctiva, oral mucosa, or amniotic membrane (AM), depending on the defect size [48]. All these methods have both advantages and disadvantages [49]. Several reports informed about the success of using the AM in the surgery for reconstruction defects after conjunctival tumor excisions [50]. The good success and efficacy of AM for ocular surface reconstruction are due to enhanced epithelization, anti-inflammatory, antifibrotic, and antiangiogenic effects [51]. Mild limbal stem cell deficiency, subclinical symblepharon, and rarely local tumor recurrence were observed as long-term complications [47]. AM may provide a more generous amount of tissue for conjunctival reconstruction in especially extensive CM [46].

Conclusion

CM presenting as nonpigmented, conjunctival tumor is a diagnostic challenge. Clinicians should maintain a high index of suspicion for conjunctival melanocytic or amelanotic lesions, particularly those with atypical features. Prompt diagnosis, appropriate management, and long-term surveillance are essential to optimize patient outcomes and minimize the risk of recurrence and metastasis.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. 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/10.1159/000541860).

Conflict of Interest Statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author Contributions

Feliciana Menna: design of the work, acquisition, and analysis of data for the work. Markus Tschopp: review of the work and ensuring questions related to the accuracy or integrity of any part of the work. Peter Meyer: review of the work. Anthia Papazoglou: review of the work and final approval of the version to be published.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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