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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Treatment for massive conjunctival malignant melanoma – analysis of two cases

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SUMMARY

Introduction Conjunctival malignant melanoma (CMM) is a highly malignant tumor. Due to its low incidence, atypical early clinical manifestations, and diverse pathological forms, it is easily misdiagnosed or missed in clinical practice, along with extremely poor prognosis. This study aims to report the treatment outcomes of two cases of massive malignant melanoma of CMM to provide insights into clinical diagnosis and treatment strategies.

Outlines of cases Two cases of massive malignant melanoma of the CMM are reported. Both patients presented to our hospital due to black masses in the eyelid, which were diagnosed as malignant melanoma upon examination. After tumor resection, combined treatment with oral administration of temozolomide capsules and intravenous injection of cisplatin was performed, and no recurrence was observed during one year follow-up.

Conclusion This study suggests that although CMM is rare and has subtle early symptoms, timely diagnosis, thorough surgical resection combined with personalized adjuvant therapy (including chemotherapy, targeted, and immunotherapy) can improve patient prognosis. Enhancing awareness among clinicians and patients, and implementing genetic testing-guided precision treatment, are key to improving therapeutic outcomes.

Keywords: malignant melanoma; CMM; chemotherapy; case report

INTRODUCTION

Conjunctival melanoma (CM) is a rare and highly aggressive malignant conjunctival tumor. Its clinical manifestations are easily confused with other ocular diseases, leading to frequent misdiagnosis or neglect. This can subsequently result in severe visual impairment, a significant decline in quality of life, and even death due to distant metastasis. The incidence of this disease is relatively higher among individuals with fair skin. The overall incidence rate is approximately 0.46 cases per 1,000,000 people per year, accounting for about 0.25% of melanomas in all body sites and about 5% of all ocular melanomas [1]. CM is the second most common malignant conjunctival tumor after conjunctival squamous cell carcinoma [2]. Its origin can be traced back to the basal melanocytes in the conjunctival epithelium. According to research statistics, about 70% of CM cases develop from conjunctival melanocytic intraepithelial neoplasia or primary acquired melanosis with atypia, while the remaining cases may arise from malignant transformation of pre-existing nevi or spontaneously [3].

At present, there is no standardized treatment protocol for CM. Commonly used therapeutic approaches in clinical practice include surgical resection with or without adjunctive cryotherapy, topical chemotherapy (such as mitomycin C, 5-fluorouracil, or interferon α-2b), brachytherapy, proton beam radiotherapy, or external photon irradiation. For cases with severe local tissue invasion in the advanced stage, radical orbital exenteration is required [4–7]. However, these treatment methods are associated with a high incidence of postoperative complications and a tumor recurrence rate ranging from 33% to 45% [8, 9]. Therefore, patients need lifelong follow-up monitoring. Although significant progress has been made in the targeted and immunotherapy of cutaneous melanoma in recent years, the relevant research data on applying similar therapeutic strategies (such as anti-*BRAF*, anti-MEK, anti-PDL1, etc.) to the treatment of CM are promising but extremely limited, mostly derived from single-patient cases or small case series of patients with no surgical opportunity before surgery or advanced disease [10, 11, 12].

Given the rarity of CM, its propensity for misdiagnosis, and the limitations of current treatment options, this study aims to provide a detailed analysis of two cases of conjunctival malignant melanoma (CMM) to explore the diagnostic and therapeutic processes. It is hoped that this study will offer clinical physicians more precise diagnostic criteria and more effective therapeutic strategies as a reference, while also providing new ideas and directions for future research on the treatment of CMM.

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REPORTS OF CASES

Patient profile

Patient 1, a 52-year-old man, was admitted to Tangshan People's Hospital on December 4, 2021, due to a black mass on the left palpebral margin. One week prior, a flat black mass was incidentally found on the left palpebral margin and conjunctiva, with ulceration and bleeding but no pain. Orbital computed tomography (CT) showed a thickened, elevated lesion on the left conjunctiva, with no distant metastasis. He had no significant medical history and no abnormalities on full-body examination. Ophthalmic examination revealed diffuse, flat, elevated black masses in the upper palpebral margin, 2/3 of the middle and outer palpebral conjunctiva, central fornix conjunctiva, and upper bulbar conjunctiva of the left eye, with a significant mass in the outer 1/3 of the palpebral margin and scab coverage (Figure 1).

Patient 2, a 74-year-old male, was admitted to our hospital's Ophthalmology Department on May 6, 2020, for a black mass in the right conjunctiva present for 1.5 years. The mass was discovered 1.5 years ago, smooth, painless, and without ulceration or bleeding. He underwent surgical excision at another hospital (details unknown) but received no further diagnosis or treatment. A year ago, the mass recurred and a new mass appeared in the lower fornix of the right eye, which rapidly grew and bled repeatedly after ulceration over the past two months. The ophthalmic examination of the right eye revealed adhesions at the upper and lower eyelid fissures, and a poorly demarcated, purplish-black, elevated mass measuring 1.2 cm × 0.8 cm × 0.6 cm was observed in the central lower fornix (Figure 2).

Ocular color Doppler ultrasound revealed a 1.04 cm × 0.64 cm hypoechoic nodule in the lower eyelid of the right eye with abundant blood flow signals (Figure 3A). Malignant melanoma was suspected in both patients. Orbital CT showed lesions in the lower fornix of the right eye (Figure 3B).

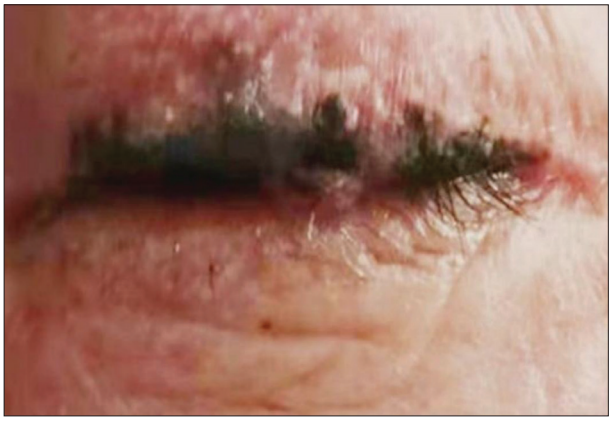

Figure 1. Patient 1: pre-treatment appearance of palpebral margin of malignant melanoma

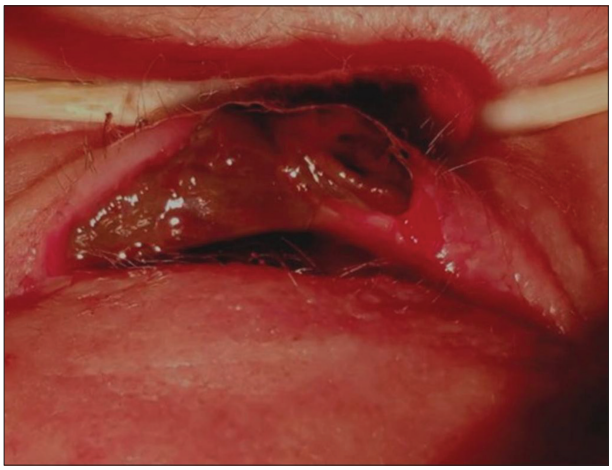

Figure 2. Patient 2: pre-treatment appearance of palpebral margin of malignant melanoma

Surgical methods

After comprehensive imaging assessments, including CT scans of the head, orbit, and chest, and color Doppler ultrasound of the neck, abdomen, pelvis, and urinary system, patient 1 underwent extended resection of the left palpebral margin and CMM, along with blepharoplasty, conjunctival sac reconstruction, and lateral canthoplasty under general anesthesia on December 8, 2021. During the surgery, part of the mass was removed. The patient's oral hard palate mucosa was taken to replace the upper eyelid tarsal plate, with the lower edge of the hard palate mucosa implanted in the lower tarsal sulcus. To reconstruct the damaged tissues, the patient's buccal mucosa (inner cheek lining) was grafted to replace the fornix (the fold between the eyelid and the eyeball) and the upper bulbar conjunctiva (the white part of the eye). This graft helped form a new conjunctival sac to restore normal eye function. Additionally, the lower tarsal plate (the supportive structure of the lower eyelid) was repositioned to repair the defect in the lower palpebral margin, ensuring both functional and aesthetic restoration of the eyelid. Meanwhile, the patient's buccal mucosa was taken to replace the fornix and upper bulbar conjunctiva and form the conjunctival sac, followed by transferring the lower tarsal plate to repair the lower palpebral margin defect. After the lateral canthal angle was formed, the skin tissue defect of the eyelid was covered with a skin flap, completing the eyelid reconstruction and plasty.

Patient 2 underwent extended resection of the right upper palpebral CMM, along with blepharoplasty and resection of the conjunctival mass in the lower fornix of the right eye under general anesthesia on May 18, 2020. The entire layer of the upper eyelid and lateral canthus was removed. The hard palate mucosa was harvested to replace the tarsal plate, with its lower edge implanted in the lower tarsal sulcus. After forming the lateral canthal angle, the eyelid skin defect was covered with a skin flap, completing the reconstruction.

Immunohistochemical results showed: Melan-A (-), Ki-67 (+, 60%), CK (-), HMB45 (+), S-100 (+), Vimentin (+). Genetic testing revealed a *BRAF* V600E mutation, indicating that targeted therapy with *BRAF* inhibitors would be appropriate for this patient. This mutation is significant as it guides the therapeutic approach and helps tailor

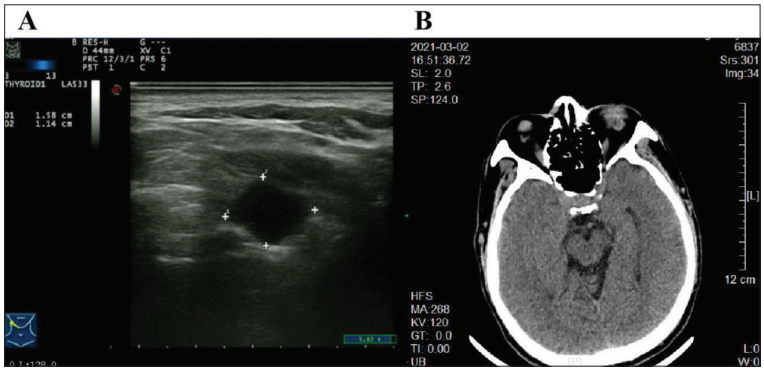

Figure 3. Ultrasound image analysis and computed tomography (CT) scan; A – abundant blood flow signals observed in ocular nodules via conventional ultrasound; B – orbital CT scan showed a lesion in the right lower fornix

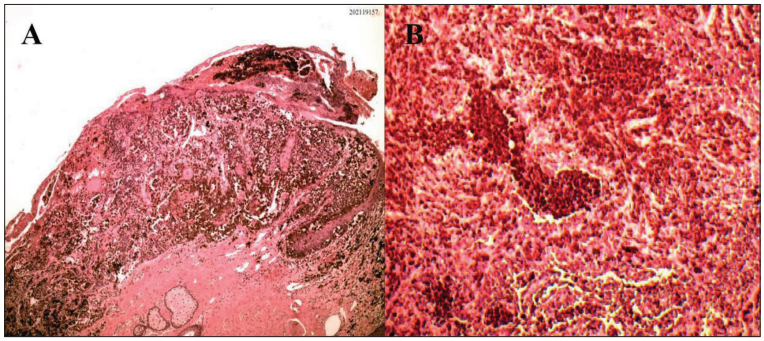

Figure 4. Postoperative histological findings (H&E staining); A – patient 1: postoperative pathological diagnosis: *lentigo maligna* (melanoma) of the conjunctival malignant melanoma; B – patient 2: postoperative pathological examination: malignant melanoma, nodular type; scale = 100μm

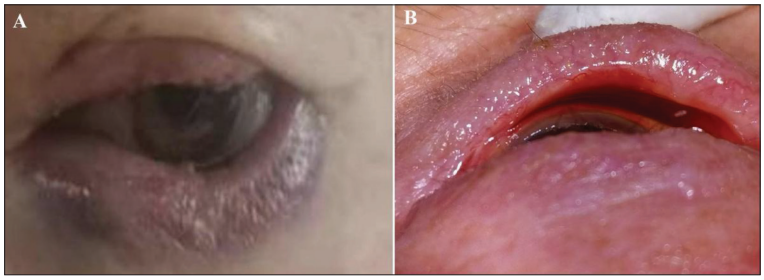

Figure 5. A – healing status of patient 1 three months after conjunctival reconstruction surgery; B – postoperative healing of the right lower fornix in patient 2

personalized treatment strategies, which are crucial for managing CMM.

Pathological and immunohistochemical results

Patient 1: Postoperative pathological diagnosis revealed malignant melanoma of CMM, with 2 mitoses/mm² (Figure 4A). The tumor measured 2.2 cm × 1 cm in maximum area and < 2 mm in maximum thickness. Ulceration and necrosis were present on the mucosal surface, with submucosal invasion. No vascular or nerve invasion was observed, and the lateral resection margin and base were tumor-free, indicating complete excision. No abnormal lymph nodes or metastatic lesions were found. Immunohistochemical analysis confirmed HMB45 positivity, and genetic testing identified a *BRAF* p.V600E mutation, which may influence treatment strategies.

Patient 2: Postoperative pathological examination revealed nodular type malignant melanoma in the vertical growth phase, with 10 mitoses/mm² and no obvious ulceration (Figure 4B). Immunohistochemical examination: Melan-A (-), Ki-60 (+, 60%), CK (-), HMB45 (+), S-100 (+), Vimentin (+). The tumor was nodular with peripheral fibrous tissue (pT3b), no obvious vascular tumor thrombus, and no tumor-infiltrating lymphocytes.

Postoperative chemotherapy regimen

Both patients received a combination systemic therapy regimen consisting of toripalimab and cisplatin. Specifically, toripalimab injection at a dose of 189 mg was administered via intravenous infusion once every two weeks for a total of 12 cycles. Concurrently, cisplatin injection at a dose of 40 mg per day was administered via intravenous infusion for three consecutive days per month, with this cycle repeated every month for a total of six cycles. Three months post-surgery, the eyelid fissure incision, transplanted hard palate mucosa, and buccal mucosa all survived in patient 1, with the formation of a conjunctival sac without adhesion or stenosis.

Meanwhile, the size and movement of the left eyelid move were normal (Figure 5A). As of the most recent follow-up, one year and five months after treatment, the patient remains in good physical condition with no evidence of metastases.

Patient 2 showed no recurrence of purple-black elevated mass in the upper conjunctiva and bulbar conjunctiva of the right eye three months post-surgery, with a smooth surface (Figure 5B). After one year of follow-up post-treatment, the patient was in good physical condition without any abnormal lesions.

Ethics: This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Tangshan People's Hospital. Written informed consent was obtained from the participant.

DISCUSSION

A 52-year-old male patient presented with a black mass on the left eyelid margin, which initially had no ulceration but later showed signs of bleeding. The incidence of this disease increases with age, particularly in individuals over 60, who account for more than 50% of cases, while those under 20 represent only 1%. The disease is more common in elderly males and individuals of Caucasian descent

[13]. The two cases reported in this paper were both male patients, aged 52 and 74 years, respectively. CMM typically occurs unilaterally, with irregular borders and visible pigmentation. It often originates from acquired primary malignant melanoma or, in some cases, from conjunctival nevus pigmentosus. Clinically, it manifests as a slowly enlarging mass on the conjunctiva, with significant variation in initial size, sometimes as small as a grain of rice. Patients may experience occasional eye redness or a foreign body sensation, but usually no vision loss. Some masses may also present with bleeding or exudation [3].

The two cases in this study developed acquired primary malignant melanoma with a history ranging from one week to 1.5 years. Patient 2 discovered a black mass on the right conjunctiva 1.5 years prior to treatment-seeking, which recurred a year ago and rapidly grew over the previous two months, causing repeated bleeding after ulceration.

BRAF gene single-base mutations are the most common genetic variations in malignant melanoma and are a key target for targeted therapy. In China, the *BRAF* mutation rate in malignant melanoma is approximately 25.5%, with 89.1% being the *BRAF* (V600E) mutation [14]. Other rare mutations include V600K, V600R, and V600D [15]. Domestic studies have reported *BRAF* V600E and *c-Kit* mutation rates of 7.7% [16]. In this study, one case of *BRAF* V600E mutation was detected, while no *c-Kit* gene mutation was found.

A 74-year-old male discovered a black mass on the right conjunctiva, present for 1.5 years prior to diagnosis. Initially smooth and non-ulcerated, the mass later grew rapidly and bled recurrently. CMM is rare and morphologically complex, making diagnosis, especially of non-pigmented variants, particularly challenging. It should be differentiated from the following diseases: Conjunctival nevus pigmentosus [17]: commonly found in the bulbar conjunctiva and limbus of the eyelid fissure, it is a benign neuroectodermal tumor. It has a smooth surface, uniform black color, and no ulceration or exudation. The immunohistochemical Ki-67 proliferation index is usually < 10%; p53 and cyclin D1 may show diffuse strong positivity, increasing with disease progression. Melan A can be expressed in both benign nevus cells and malignant melanoma, but its expression in malignant melanoma may decrease with increasing tumor thickness, reduced disease-free survival, and increased mortality. Poorly differentiated squamous cell carcinoma [18]: the most common conjunctival malignancy, it often occurs at the junction of the palpebral margin skin and conjunctiva, the limbus in the eyelid fissure area, and the lacrimal caruncle in the medial canthus, with UV exposure as a key trigger. Some malignant melanomas can mimic this carcinoma with prominent nucleoli. P40, P63, or CK5/6 are positive markers for poorly differentiated squamous cell carcinoma, while HMB-45, MelanA, and S-100 are negative. Poorly differentiated sarcoma [19]: malignant melanoma cells can be spindle-shaped or polygonal, with some having abundant pink cytoplasm and deviated nuclei, resembling rhabdomyosarcoma. Rhabdomyosarcoma cells are positive for myogenin and MyoD1, while S-100, MelanA, and HMB-45 are negative. Tumor cells can also appear in bundles, spindle-shaped or cigar-shaped, resembling leiomyosarcoma. Leiomyosarcoma cells are positive for desmin and SMA, while S-100, MelanA, and HMB-45 are negative. All malignant melanomas are negative for myogenic markers.

Due to minimal early visual impact, some patients overlook CMM, delaying treatment. Improving prognosis and survival depends on understanding the clinical and pathological features of CMM and raising patient awareness for early treatment.

In this study, both patients underwent extensive tumor resection combined with postoperative systemic chemotherapy of toripalimab and cisplatin, achieving favorable local control with no signs of recurrence or metastasis during the short-term follow-up (1–1.5 years). This outcome shows positive significance when compared with larger cohort studies. An international multicenter study involving 288 CMM patients reported that despite receiving surgery combined with adjuvant therapies (such as local chemotherapy or brachytherapy), the cumulative five-year and 10-year local recurrence rates were as high as 19.3% and 36.9%, respectively [20]. The absence of recurrence in our cases within a relatively short follow-up period suggests that the surgical resection combined with immunochemotherapy regimen we adopted may provide additional benefits in controlling local recurrence. Currently, the treatment of CMM is becoming more diversified, and the therapeutic choices in our cases can be cross-referenced with recent literature advances. For patients with high-risk factors after surgical excision, local adjuvant therapy remains a standard option. Apart from the systemic treatment used in our cases, local agents (such as mitomycin C or interferon α-2b) and adjuvant brachytherapy (e.g., iodine-125 plaque) are commonly employed and effective modalities [21]. Particularly for lesions involving the sclera, postoperative adjuvant iodine-125 plaque radiotherapy has demonstrated favorable tumor control rates and potential for vision preservation in medium-term follow-up [22]. Meanwhile, immune checkpoint inhibitors (such as anti-PD-1 agents) have shown promise in the treatment of advanced CMM [23]. The use of toripalimab in this study was based on its established efficacy in melanoma treatment [24], and experience with systemic immunotherapy as postoperative adjuvant therapy for CMM remains limited. The favorable outcome in our cases provides preliminary clinical support for this strategy. Furthermore, the *BRAF* V600E mutation detected in patient 2 offers a critical direction for potential salvage therapy in the future. For advanced melanoma with *BRAF* mutations, combination therapy with *BRAF*/MEK inhibitors has become the standard. Although the incidence of this mutation is relatively low in CMM, once present, targeted therapy represents an important systemic treatment option.

The two cases of CMM reported in this study, despite differences in clinical presentation and disease duration, both achieved good local control and short-term recurrence-free survival through comprehensive imaging evaluation, wide surgical excision, and combined postoperative

systemic chemotherapy. This offers the following insights for the management of similar clinical cases: CMM often presents as a painless pigmented lesion in its early stages, easily overlooked by patients. Clinicians should maintain a high index of suspicion for any new or changing pigmented lesions in the conjunctival region, particularly in middle-aged to elderly males and individuals of Caucasian descent. It is recommended to utilize imaging studies such as orbital CT and color Doppler ultrasound to assess the lesion extent and vascularity, and to perform early pathological biopsy with immunohistochemistry (e.g., HMB45, S-100, Melan-A) for definitive diagnosis. Surgical excision remains the cornerstone for localized disease, aiming for histologically complete resection (negative margins). For extensive or recurrent lesions, wider excision combined with eyelid reconstruction and conjunctival sac formation should be considered. Both patients in this study received postoperative systemic therapy with toripalimab combined with cisplatin, highlighting the potential value of combined immunotherapy and chemotherapy in the adjuvant setting. Furthermore, the detection of a *BRAF* V600E mutation in patient 2 suggests that such patients may benefit from *BRAF* inhibitor-targeted therapy. Therefore, we recommend genetic testing (e.g., for *BRAF*, *c-Kit*, NRAS) for all confirmed patients to guide subsequent targeted or immunotherapy choices. CMM carries a high risk of recurrence and metastasis, necessitating lifelong regular follow-up including ocular examination and systemic imaging. The treatment team should involve ocular oncologists, pathologists, medical oncologists, and radiation oncologists to collaboratively develop and adjust treatment plans for comprehensive disease management.

In summary, the management of CMM should emphasize a comprehensive strategy of early diagnosis, prompt and complete surgical excision, personalized adjuvant therapy, and long-term follow-up. Further prospective studies are needed to establish the efficacy and safety of standardized chemotherapy, targeted, and immunotherapy regimens for this rare malignancy.

Conflict of interest: None declared.

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Лечење масивног малигног меланома конјунктиве – анализа два случаја

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САЖЕТАК

Увод Малигни меланом конјунктиве представља изразито малигни тумор. Због ниске инциденције, атипичних раних клиничких манифестација и разноврсних патолошких облика, у клиничкој пракси се лако погрешно дијагностикује или превиди, а прогноза је изузетно неповољна. Циљ ове студије је приказ исхода лечења два случаја масивног малигног меланома конјунктиве, ради пружања увида у клиничку дијагностику и терапијске стратегије.

Приказ болесника Приказана су два случаја масивног малигног меланома конјунктиве. Оба болесника јавила су се у нашу установу због црних тумефакција на очном капку, које су након испитивања дијагностиковане као малигни меланом. Након хируршке ресекције тумора примењена је комбинована терапија периоралном применом темозоломида и интравенском применом цисплатина. Током једногодишњег периода праћења није забележен рецидив.

Закључак Иако је малигни меланом конјунктиве редак и у раној фази може имати суптилне симптоме, благовремена дијагноза, темељна хируршка ресекција у комбинацији са индивидуализованом адјувантном терапијом (укључујући хемиотерапију, циљану терапију и имунотерапију) могу побољшати прогнозу болесника. Повећање свести код клиничара и болесника, као и примена прецизне терапије вођене генетским тестирањем, кључни су за унапређење терапијских исхода.

Кључне речи: малигни меланом; малигни меланом конјунктиве; хемиотерапија; приказ случаја