



## CASE PRESENTATION

### Conjunctival melanoma: a case study and literature review

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#### ABSTRACT

**Introduction:** conjunctival melanoma is a rare but highly aggressive ocular neoplasm, characterized by high recurrence and risk of systemic metastasis.

**Objective:** to present the diagnosis and treatment of a clinical case of conjunctival melanoma in an elderly patient.

**Case presentation:** an 82-year-old male patient, resident of ambato, with no relevant medical history, presented with rapidly growing conjunctival tumor in the right eye. Biopsy revealed non-keratinized stratified squamous epithelium with nests of hyperchromatic polygonal cells, severe pleomorphism, and brown pigment, confirming malignant conjunctival melanoma with compromised margins. Treatment consisted of surgical removal of the eyeball, due to tumor extension and resection involvement. Histopathological analysis showed melanocytic proliferation with a high mitotic index and presence of melanophages. Post-surgical evolution was favorable, although the risk of recurrence and metastasis remains high.

**Conclusions:** this case highlights the importance of timely diagnosis through biopsy and the need for radical treatments in advanced lesions. Surgical excision remains the most effective option to reduce recurrences and preserve survival.

**Keywords:** Conjunctiva; Clinical Diagnosis; Melanoma; Conjunctival Neoplasms; Eye Neoplasms.

## INTRODUCTION

Conjunctival malignancies are a rare type of pathology, but they are among the most aggressive malignant neoplasms of the eye and require early therapeutic intervention to prevent blindness or loss of the ipsilateral eye and tumor-related death. Primary conjunctival malignancies are of greater relevance to oncologists; these include squamous cell carcinoma, malignant melanoma, and malignant lymphoma.<sup>(1)</sup> Conjunctival melanoma is a rare tumor with a high probability of recurrence and a high mortality rate of approximately 30 % in the early stages.<sup>(2)</sup>

This condition arises from melanocytes, most frequently in sun-exposed skin. It represents 1,6 % of all non-cutaneous melanomas, and less frequently, melanoma originates in other tissues such as the uvea, rectum, mouth, and respiratory tract. Conjunctival melanoma typically presents with a tumor size of approximately 13 mm in transverse diameter and 3 mm in thickness. It affects the bulbar region in 97 % of cases, the forniceal region in 30 %, the tarsal region in 28 %, or the caruncular region in 11 %, often with corneal involvement in 54 % and rarely with orbital involvement in 4 %.<sup>(3)</sup>

Conjunctival melanoma (CM) resembles cutaneous melanoma in terms of pathogenesis and molecular characteristics, unlike melanoma occurring in other mucosal sites or uveal melanoma. The depth of invasion and the degree of ulceration, among other factors, are important prognostic indicators in CM. This necessitates the integration of pathological and clinical findings, which are essential in this instance. Anatomical location is also sensitive in determining appropriate clinical management.<sup>(4)</sup>

It is essential that healthcare professionals possess the necessary skills for the diagnosis and treatment of chronic malnutrition (CM) due to the complications that arise when it is uncontrolled. Therefore, this research was conducted with the objective of presenting the diagnosis and treatment of a clinical case of CM in an elderly patient.

## CASE REPORT

An 82-year-old male patient, residing in Ambato, Tungurahua Province, Ecuador, with no significant medical history, presented with a rapidly growing conjunctival tumor in his right eye. A sample of the tumor was examined under a microscope, revealing two irregular, white-blackish fragments, unmarked, measuring 0,4 x 0,3 x 0,1 y 0,5 x 0,4 x 0,1. These fragments were not sectioned; instead, the entire sample was processed (Figure 1).



**Fig. 1** Taking the sample from the right eye with MC.

Upon receiving the results, it was shown that the sample fragments had a surface covered with non-keratinized stratified squamous epithelium. The underlying stroma showed nests and solid areas of polygonal and spindle-shaped cells with hyperchromatic nuclei exhibiting severe pleomorphism, prominent eosinophilic nuclei, and three mitoses counted in 10 high-power fields (40x). These were accompanied by brown pigment with coarse granules and scattered melanophages with congested blood vessels. The resection margins were compromised by the lesion.

The final diagnosis revealed a melanoma of the right eye, confirmed by a previously performed incisional biopsy. This melanoma tested positive for malignancy, with resection margins compromised by the lesion. The case was resolved by surgical removal of the eyeball (Fig. 2).



**Fig. 2** Right eye with post-surgical MC.

## DISCUSSION

Numerous studies have shown melanocyte mutations, evaluating the expression of p16, SOX10, HMB45, and Ki-67, which are associated with the development of melanomas and conjunctival nevi. In conjunctival melanocytic lesions (CM), the most predictive expression parameters are HMB45 (45 %), followed by p16 (25 %) and Ki-67 (12 %). Therefore, the role of p16 in the diagnosis and prognosis of conjunctival melanocytic lesions, in the context of clinical and immunohistochemical parameters, is essential for their early detection.<sup>(5)</sup>

Mucosal melanoma (MM) is characterized by BRAF-V600E (305) and BF1 (17 %) mutations. Programmed cell death ligand 1 (PD-L1) showed a significant sixfold overexpression in MM compared to other mucosal melanomas.<sup>(6)</sup> An association exists between CD8, PD-1, and PD-L1 expression in MM, in addition to the BRAF and NRAS molecular profile, as well as some clinicopathological criteria. PD-L1 expression was detected in tumor-infiltrating immune cells in 87 % and in tumor cells in 34 %. In infiltrating cells, it correlated with a higher pTNM stage, and in tumor cells, with worse disease survival.<sup>(7)</sup>

There is a degree of pigmentation in recurrences of carcinoma in situ (CCIS), as it is similarly related to the clinical outcome. That is, 71 % of patients present with recurrences with low pigmentation of the primary lesions, but recurrences can occur with any degree of pigmentation. There is a correlation between the pigmentation of recurrences and iris color in 27 %. Therefore, CCIS implies a risk of metastasis and death associated with tumor pigmentation.<sup>(8)</sup>

Globally, melanoma is the second most aggressive type of cutaneous melanoma and the third with the highest mortality rate. It has an incidence of 1,2 % per 1000 inhabitants and a prevalence of 1,8 % per 1000 inhabitants. In European countries, this incidence is reduced to 0,8 % and the prevalence to 1,5 % per 1000 inhabitants.<sup>(9)</sup>

Factors influencing the incidence of ocular melanoma include sex, age, laterality, race, and ethnicity. In the United States, the risk of ocular melanoma is associated with ultraviolet radiation in 95 % of cases. This incidence is higher in non-Hispanic white individuals. In comparison, in Latin America, sun exposure also accounts for 98 % of the risk of developing ocular melanoma.<sup>(10)</sup>

The most frequent presentation is unilateral, located in the bulbar or limbal conjunctiva, ranging in color from red to brown or even black, with a maximum diameter of 4-20 mm.<sup>(11)</sup> That is, it is a keratinized lesion at the limbus and a pigmented lesion in the bulbar conjunctiva with multiple pigmented bulbar conjunctival lesions and a keratinized limbal nodule. The location may affect the orbital bone, extraocular muscles, optic nerve or paranasal sinuses as a consequence of the cell growth of the tumor.<sup>(12)</sup>

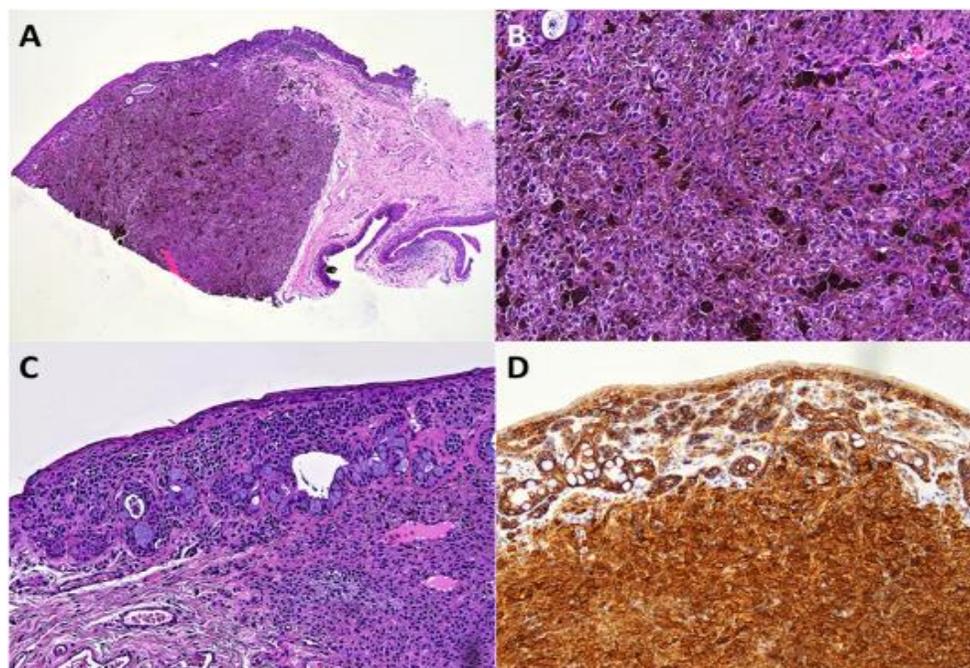
Among the clinical characteristics according to the age of presentation in MC, the highest percentage of cases occurs in young patients. Although the risk of developing it encompasses a median age of 46-69 years, and in older patients  $\geq 70$  years, the disease is more extensive and therefore they have a higher risk of loss of visual acuity and local tumor recurrence.<sup>(13)</sup>

The conjunctiva is the only ocular tissue in which lymphatic vessels exist. Therefore, the tumor cell easily accesses the lymphatic vessel and spreads to the lymph node.<sup>(14)</sup> Melanoma recurrence affects 82 % of patients who presented with melanoma. The increase in lymph node metastasis related to melanoma was expressed at 7 % after each recurrence observed in patients. According to the eighth edition of the American Joint Committee on Cancer (AJCC) classification for

melanoma, the 10-year risk by category increased significantly in the case of visual acuity loss >3 lines, recurrence, new tumor, exenteration, melanoma-related locoregional and systemic metastasis, and death.<sup>(15)</sup>

The most appropriate diagnosis is biopsy, as it allows confirmation of MC by observing the squamous neoplasm of the ocular surface and the conjunctival intraepithelial melanocytic neoplasm-2 and also the MC in situ.<sup>(16)</sup> Early recognition and appropriate management are essential due to its high malignant and metastatic potential: Due to its frequent recurrences, knowledge and use of intra- and postoperative adjuvant treatment modalities and regular follow-up are necessary.

Conjunctival melanocyte carcinoma (CM) is a dermal-based, deep-spreading melanocytic proliferation, sometimes wedge-shaped, with histological features including a variable degree of cytological atypia. It arises in the conjunctiva and, under microscopic examination, demonstrates a predominantly subepithelial melanocytic proliferation with a biphasic appearance (Fig. 3). It involves central and deep involvement with a nodular expansion of clusters and nests of large epithelial melanocytes with round to oval nuclei, small nucleoli, and moderately abundant anophylic cytoplasm with relatively diffuse but variable melanin pigmentation.<sup>(17)</sup>



**Fountain:** Hohnen H, Singh S, Lam G, Mesbah Ardakani N. Conjunctival combined deep penetrating naevus: a clinicopathological report. *Pathology*. 2023;55(5):721-723. doi:10.1016/j.pathol.2023.01.008

**Fig. 3** Microscopic images of the lesion.

**Grades:** A (Low magnification view shows deep subepithelial melanocytic proliferation [Hematoxylin and Eosin]). B (The central and deep portions of the lesion were composed of sheets and nests of epithelioid melanocytes, with enlarged nuclei and abundant pink cytoplasm with melanin pigmentation and mixed clusters of melanophages [Hematoxylin and Eosin]); C (A conventional nevus cell component was present in the superficial aspect of the lesion associated with reactive proliferation of the conjunctival crypts [Hematoxylin and Eosin]); D (Immunohistochemistry for  $\beta$ -catenin showed diffuse nuclear and membranous staining in the DPN component [Immunohistochemistry])

It can frequently involve pre-existing stromal structures, such as nerve bundles and vessels, with invasion of the lymphatic space. Pathological findings include nests of undifferentiated carcinoma with significant infiltration of reactive lymphocytes and plasma cells. Tumor cells are also positive for pancytokeratin (CK-pan), epithelial membrane antigen (EA), tumor protein 40 (p40), and tumor protein 63 (p63), with a cell proliferation index (Ki-67) greater than 80 %. Group 20 (CD20), CD3, and CD8 lymphocytes were positive.<sup>(18)</sup>

Ocular and orbital melanoma are extremely serious pathologies due to the degree of metastasis they can develop. The most common sites are the uvea (73 %), followed by the conjunctiva (22 %), the lacrimal sac (4 %), and the orbit (2 %). Most patients with melanoma have a higher incidence of liver metastases (89 %) compared to lymph nodes (16 %). Similarly, the overall survival rate for these patients is 18 %, provided they are treated with targeted therapies to control the affected organ.<sup>(19)</sup>

Basic characteristics include age, sex, tumor size, cell type, location, and TNM stage. Prognostic values include disease-free interval, local recurrence, distant metastasis, and survival. Therefore, patients aged 50 to 60 years are associated with a 56% higher risk compared to younger patients. Tumor thickness is also a prognostic factor, as tumors larger than 8 mm are associated with a 45 % higher risk of mortality.<sup>(20)</sup>

As a rare disease, MC requires personalized treatment in most cases. Treatment may be based on surgery, topical chemotherapy, radiotherapy, cryotherapy, and other emerging treatment modalities. It is essential to be aware of the most recently introduced treatment options, along with advances in molecular biology related to this particular disease, to enable early intervention.<sup>(21)</sup>

Cid-Bertomeu,<sup>(22)</sup> states that surgical excision is the treatment of choice for neoplasms. Although topical therapy is also useful for patients with MC. Among the chemotherapeutic drugs used, topical interferon alpha 2b (IFN- $\alpha$ 2b) is one of the most common.  $\alpha$ 2b) is the recommended choice due to its low toxicity. Furthermore, IFN-  $\alpha$ 2bse has been successfully applied to melanocytic tumors refractory to other treatments, such as cryotherapy and topical mitomycin C. Some research demonstrates the efficacy of IFN- $\alpha$ .  $\alpha$ 2b to prevent local recurrence and distant metastases.

Another option is the treatment of the YAP/TAZ pathway in melanoma. YAP/TAZ activation in melanoma and the susceptibility of cell lines to YAP/TAZ inhibition by verteporfin (VP) are related to the tumor's genetic background. Niels J. Brouwer explains its effectiveness at the cell line level, which includes the mutational background and cell growth rate. He indicates that BRAF/NRAS proliferation decreases due to the significant response to YAP/TAZ inhibition by VP.<sup>(23)</sup>

## CONCLUSIONS

Mycosis colliculus (MC) is a rare but potentially devastating ocular neoplasm, as it can compromise vision and even the patient's survival if not diagnosed and treated promptly. Its incidence is influenced by various risk factors such as race, sex, age, and, notably, sun exposure, which is a preventable factor. Diagnosis is based on a biopsy, which allows for confirmation of the lesion's malignancy through microscopic examination. Regarding treatment, the most effective option is surgical excision of the eyeball, a strategy that aims to reduce the risk of recurrence and prevent metastatic spread to other target organs.

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