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NARRATIVE LITERATURE REVIEW

Melanoma metastatic to the orbit: case report and literature review

Melanoma metastático com comprometimento orbital: relato de caso e revisão da literatura

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KEYWORDS:

Melanoma; Orbital neoplasms; Orbit; Histopathology; Immunohistochemistry.

ABSTRACT

The aim of this report is to describe a rare case of melanoma metastatic to the orbit and to emphasize the clinical, imaging, histopathological, and therapeutic findings, as well as to contextualize these observations within a review of the recent literature. This case report includes the clinical presentation, ophthalmic evaluation, imaging studies, histopathology, and immunohistochemistry, along with an integrative discussion based on published evidence. A 66-year-old man presented with headache, eye pain, and progressive swelling of the left eye, which evolved to proptosis and spontaneous ocular bleeding. Computed tomography of the orbit showed diffuse thickening of the lateral and superior rectus muscles, with anteromedial displacement of the globe. Histopathology revealed pleomorphic tumor cells containing melanocytic pigment, and the diagnosis was confirmed by immunohistochemistry, which showed positivity for HMB-45, Melan-A, and S100, along with focal expression of CD56. Systemic staging identified hepatic and lung metastases, consistent with advanced disease and a poor prognosis. The patient was referred for palliative systemic oncologic treatment, highlighting the diagnostic challenges and therapeutic limitations often reported in the literature for this rare entity. Orbital melanoma, particularly in the metastatic context, is a rare and aggressive condition associated with an unfavorable prognosis. Diagnosis depends on a combination of clinical assessment, imaging studies, histopathology, and immunohistochemistry. This case reinforces the need for a multidisciplinary evaluation and highlights the importance of further research to optimize therapeutic strategies in this uncommon clinical scenario.

PALAVRAS-CHAVE:

Melanoma; Neoplasias orbitárias; Órbita; Histopatologia; Imunohistoquímica.

RESUMO

O objetivo é descrever um caso raro de melanoma metastático com acometimento orbitário, enfatizando os achados clínicos, de imagem, histopatológicos e terapêuticos, além de contextualizar essas observações com uma revisão da literatura recente. Relato de caso incluindo apresentação clínica, avaliação oftalmológica, exames de imagem, histopatologia e imunohistoquímica, seguido de discussão integrativa com a evidência publicada. Um homem de 66 anos apresentou cefaleia, dor ocular e edema progressivo do olho esquerdo, que evoluiu para proptose e sangramento ocular espontâneo. A tomografia computadorizada de órbita revelou espessamento difuso dos músculos retos lateral e superior, com deslocamento anteromedial do globo. A histopatologia mostrou células tumorais pleomórficas com pigmento melanocítico, e a imunohistoquímica confirmou o diagnóstico por meio de positividade para HMB-45, Melan-A e S100, além de expressão focal de CD56. O estadiamento sistêmico identificou metástases hepáticas e pulmonares, compatíveis com doença avançada e prognóstico reservado. O paciente foi encaminhado para terapia oncológica sistêmica paliativa, destacando os desafios diagnósticos e as limitações terapêuticas frequentemente relatadas na literatura para essa entidade rara. O melanoma orbitário, especialmente no contexto metastático, é uma condição rara e agressiva, associada a prognóstico desfavorável. O diagnóstico depende da combinação entre avaliação clínica, exames de imagem, histopatologia e imunohistoquímica. Este caso reforça a necessidade de avaliação multidisciplinar e destaca a importância de pesquisas adicionais para otimizar estratégias terapêuticas nesse cenário clínico incomum.

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INTRODUCTION

Orbital melanoma is a rare malignant tumor that presents considerable diagnostic and therapeutic challenges. It can be classified as primary, when originating from ectopic melanocytes within the orbit, or secondary (metastatic), when resulting from the hematogenous spread of cutaneous, uveal, or conjunctival melanoma. Primary orbital melanoma accounts for less than 1% of all orbital tumors, whereas metastatic lesions are more common and usually indicate advanced systemic disease[1,2].

Over the past decades, the global incidence of cutaneous melanoma has steadily increased, along with a growing number of orbital metastases. Most patients are adults in the fifth to seventh decades of life, and there is no clear predominance of either sex[3,4]. Large series describe secondary orbital melanoma as more prevalent than primary disease, typically reflecting disseminated systemic involvement[5,6].

Clinically, orbital melanoma may present with rapidly progressive proptosis, eyelid swelling, diplopia, and orbital pain. However, these manifestations are nonspecific and can mimic other orbital masses, such as meningioma, lymphoma, or cavernous hemangioma, making the initial diagnosis challenging[7,8]. Diagnostic confirmation is based on histopathological evaluation combined with immunohistochemistry, with melanocytic markers such as S100, HMB-45, and Melan-A[9,10] frequently expressed.

The prognosis of metastatic orbital melanoma is generally poor, with the liver being the most frequent site of metastasis, followed by the lungs and the central nervous system. Historical series have reported a median survival ranging from 6 to 12 months after the diagnosis of orbital metastasis[5,11].

In this context, case reports remain important for illustrating uncommon clinical presentations and diagnostic and therapeutic challenges. Here, we describe a rare case of orbital melanoma and highlight the clinical, imaging, and histopathological findings, along with aspects related to disease management.

Recent systematic reviews and institutional cohorts have confirmed the exceptional rarity of orbital melanoma, noting that primary cases are uncommon and often associated with pre-existing melanocytic lesions, whereas secondary cases predominate2,6. Large retrospective series have shown that surgical excision remains the mainstay of local treatment, although complete resection is often limited by tumor extent and orbital anatomy[7].

The therapeutic arsenal for advanced melanoma has expanded considerably over the last decade. In addition to checkpoint inhibitors and tebentafusp, several targeted agents and experimental strategies are under clinical evaluation, particularly for tumors exhibiting uncommon genetic alterations. Early clinical experience suggests that combining immunotherapy with targeted approaches may further enhance treatment efficacy and prolong survival in selected subgroups of patients with orbital involvement[12-16].

Published series on orbital melanoma remain scarce, with most evidence derived from small retrospective cohorts and case reports[1,2,6,7,10]. These studies highlight the heterogeneity of clinical presentation, ranging from indolent lesions confined to the orbit to aggressive tumors with early systemic dissemination. Despite gradual therapeutic advances, the overall prognosis remains poor, underscoring the need for multicenter collaboration and long-term follow-up to better characterize prognostic determinants and optimize therapeutic strategies[8,11,15].

Despite these advances, local recurrence and systemic progression remain common. Long-term follow-up data indicate that, even after radical surgery, overall survival remains unsatisfactory, emphasizing the need for early detection and individualized therapeutic approaches[8,13,16]. Collaborative studies and pooled analyses are essential to better define prognostic factors and refine management algorithms for this uncommon neoplasm.

CASE REPORT

A 66-year-old man was referred to the ophthalmology department with a 1-month history of progressively worsening left-sided headache and ocular pain, followed by eyelid swelling, proptosis, and subconjunctival bleeding. He denied smoking or alcohol consumption. His medical history included diabetes mellitus and hypertension. His ophthalmic history was notable for keratoconus, for which he had undergone penetrating keratoplasty in the right eye approximately 30 years earlier.

At the initial ophthalmic examination, best-corrected visual acuity was 1.3 logMAR in the right eye and 0.69 logMAR in the left eye. Hertel exophthalmometry revealed asymmetrical proptosis, measuring 18 mm in the right eye and 23 mm in the left eye, with a base of 97 mm. Color vision assessment using the Ishihara test was normal in the right eye

(16/16) and markedly reduced in the left eye (3/16). Ocular motility was preserved in the right eye, whereas the left eye showed restricted movement in all directions of gaze. Biomicroscopic examination revealed corneal opacity related to previous hydrops in the right eye and subconjunctival hemorrhage in the left eye. Fundus examination could not be performed in the right eye due to media opacity and was unremarkable in the left eye.

After referral to the Orbital Diseases Unit at Santa Casa de Misericórdia de São Paulo, temporary tarsorrhaphy was performed at the first consultation to protect the ocular surface. On admission, computed tomography (CT) of the orbits was performed in the Emergency Department and showed a diffuse infiltrative process involving the extraocular muscles, with thickening of the superior and lateral rectus muscles and anteromedial displacement of the left globe, resulting in proptosis (Figures 1A–C). The differential diagnosis included IgG4-related disease, orbital vascular disorders, lymphoproliferative disorders, and orbital metastasis.

In view of the initial suspicion of an orbital inflammatory process, empirical treatment with oral prednisone at 1 mg/kg/day was initiated; however, the patient's orbital pain and overall condition progressively worsened, with the development of dyspnea and marked weakness.

Approximately 5 weeks after symptom onset, given the patient's clinical deterioration, a lateral orbitotomy with diagnostic biopsy was performed. Intraoperatively, the lesion exhibited atypical pigmentation and friable tissue, suggestive of a melanocytic neoplasm.

Histopathological examination revealed pleomorphic tumor cells containing melanocytic pigment. Immunohistochemistry showed diffuse positivity for HMB-45 (Figure 2), Melan-A (Figure 3), and S100 protein (Figure 4), along with focal expression of CD56. The tumor cells were negative for AE1/AE3, CD20, CD3, synaptophysin, and p63, consistent with a diagnosis of melanoma.

While awaiting definitive staging, the patient developed acute respiratory failure and rapid clinical deterioration. Systemic evaluation revealed multiple hepatic and pulmonary lesions with a metastatic pattern, consistent with disseminated disease. Despite supportive measures, the patient died during hospitalization before specific systemic oncologic treatment could be initiated.

In the absence of an identifiable primary lesion at presentation, the constellation of clinical, radiological, histopathological, and immunohistochemical findings was consistent with melanoma metastatic to the orbit from an occult primary site.

DISCUSSION

Orbital melanoma remains a rare clinical entity associated with high recurrence and mortality rates. Orbital metastatic involvement, although uncommon, reflects advanced disease progression and may even represent the first clinical manifestation of systemic dissemination[1,2,5,6]. Our patient presented with classic signs of orbital involvement, namely rapidly progressive proptosis, pain, and ocular bleeding, consistent with descriptions in the literature[7,8].

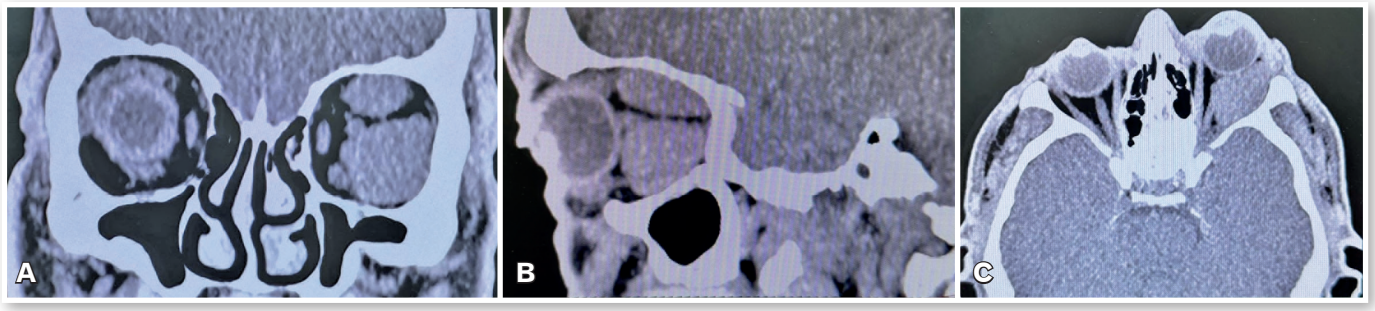

Figure 1. (A) Coronal computed tomography (CT) images showing diffuse thickening of the lateral and superior rectus muscles of the left eye, with anteromedial displacement of the globe, without evidence of bone erosion or optic nerve involvement. (B) Sagittal CT images of the orbit showing diffuse thickening of the lateral and superior rectus muscles of the left eye, with anteromedial displacement of the globe, without evidence of bone erosion or optic nerve involvement. (C) Axial orbital CT images showing diffuse thickening of the lateral and superior rectus muscles of the left eye, with anteromedial displacement of the globe, without evidence of bone erosion or optic nerve involvement.

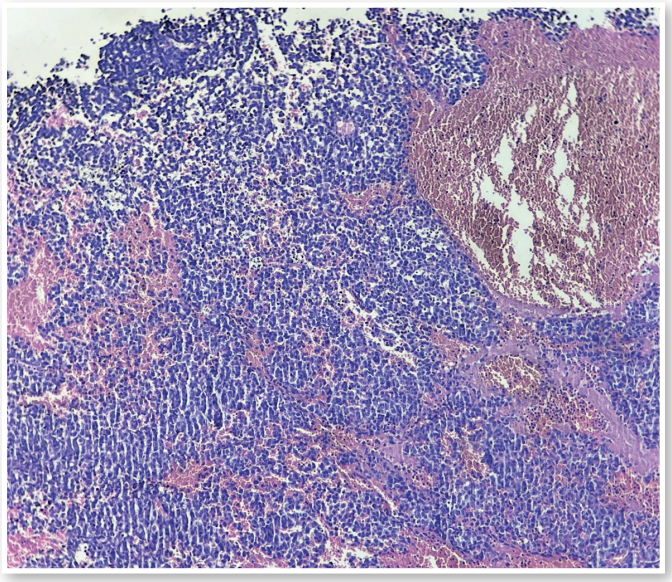

Figure 2. Immunohistochemical staining showing diffuse cytoplasmic positivity for HMB-45 in tumor cells (200×).

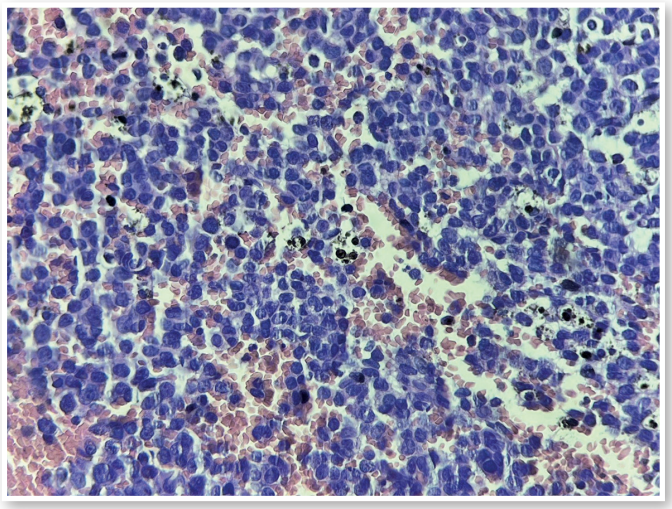

Figure 3. Immunohistochemical staining showing strong cytoplasmic positivity for Melan-A in tumor cells (200×).

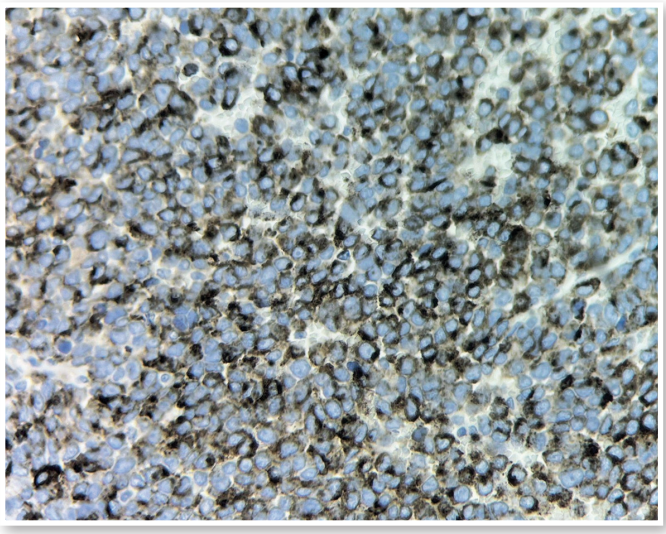

Figure 4. Immunohistochemical staining showing diffuse nuclear and cytoplasmic positivity for S100 protein in tumor cells (200×).

Defining the primary site of the melanoma was challenging in this case. Unlike primary orbital melanomas, which are often associated with precursor lesions such as melanocytosis or blue nevi, and unlike secondary melanomas, which are usually linked to a prior history of cutaneous, uveal, or conjunctival melanoma, our patient had no history of cancer or identifiable cutaneous or ocular lesions. This challenge is not uncommon: in published series, the origin of up to 10%–15% of orbital melanoma cases remains undefined even after systemic investigation[1,2,6].

The lack of molecular analysis was a significant limitation in this case. Evaluation of genetic alterations—such as mutations in GNAQ and GNA11, which are highly prevalent in uveal melanoma, and mutations in BAP1, SF3B1, and EIF1AX, which carry prognostic significance—could have enabled more robust classification. Limited access to these resources highlights ongoing barriers in many centers and does not detract from the clinical and scientific relevance of this report, which exemplifies the complexity of real-world cases[9,11].

Exenteration remains a standard surgical approach for extensive primary cases; however, its role in metastatic disease is controversial, as it has not been shown to confer a survival advantage. Conservative orbitotomy may be considered for localized tumors, while endoscopic approaches are gaining acceptance in selected benign and malignant cases[6,7,15]. Nevertheless, surgery has a limited and predominantly palliative role in orbital metastatic melanoma[5,10].

Radiotherapy may be considered in cases of local recurrence or positive margins. In uveal melanoma, brachytherapy and external beam radiotherapy can provide local control but are associated with significant ocular morbidity. In orbital melanoma, available evidence is limited and largely extrapolated from other anatomical sites[8,9,16].

Recent advances in systemic therapy have reshaped the treatment landscape for melanoma. Immune checkpoint inhibitors (nivolumab, pembrolizumab,

and ipilimumab) have improved survival in metastatic cutaneous melanoma[12]. BRAF/MEK-targeted therapies (dabrafenib/trametinib and vemurafenib/cobimetinib) offer additional benefits in selected patients[14,16]. In uveal melanoma, tebentafusp—an ImmTAC (monoclonal T-cell receptor designed to redirect the immune system against cancer)—demonstrated an overall survival benefit in a phase III clinical trial published in 2021, representing a significant advance for this subtype[13]. However, evidence regarding benefits specifically for orbital disease remains limited to case reports and small series[1,6,10].

Although orbital melanoma is extremely rare, population studies indicate a steady global increase in melanoma incidence, which may indirectly contribute to more frequent detection of orbital metastases[3,4]. Overall prognosis remains poor, with the liver, lungs, and central nervous system being the most common metastatic sites[5,11]. Even in contemporary cohorts, survival following the diagnosis of orbital metastasis rarely exceeds 12 months, highlighting the aggressive nature of this presentation[8,11].

Radiological assessment plays a key role in differentiating orbital melanoma from other benign and malignant orbital masses. CT and magnetic resonance imaging typically show infiltrative lesions involving extraocular muscles or orbital fat; however, these findings are not pathognomonic[7,8]. Therefore, immunohistochemistry remains essential, as the expression of melanocytic markers (S100, HMB-45, and Melan-A) is consistently reported, reinforcing their diagnostic reliability in clinical practice[9,10].

In addition to checkpoint inhibition, ongoing research is exploring combinations of systemic therapies and their integration with locoregional treatments. For example, clinical experience with tebentafusp in uveal melanoma provides proof of concept that immune cell redirection strategies can improve survival even in historically refractory settings[13]. Although extrapolation to orbital melanoma remains speculative, these advances may lead to improved outcomes in the future[12-14].

Given the rarity of orbital melanoma, most available evidence derives from isolated case reports and small institutional series[1,2,6,10]. These studies provide valuable insights into diagnostic challenges, therapeutic decision-making, and real-world outcomes. The present case adds to this body of knowledge by emphasizing the importance of early clinical suspicion, the diagnostic value of immunohistochemistry, and the persistent challenges in accessing molecular testing across many cancer centers worldwide[9,11,16].

This case reinforces the importance of including melanoma in the differential diagnosis of rapidly progressive orbital masses and highlights ongoing diagnostic challenges related to the limited availability of molecular testing. Sharing such experiences enriches the collective understanding of this rare condition and supports further research into improved diagnostic and therapeutic strategies. These findings are consistent with previously published case series[1,2,5,6].

In conclusion, orbital melanoma, whether primary or metastatic, remains a significant diagnostic and therapeutic challenge. Definitive diagnosis relies on histopathology and immunohistochemistry. Although surgery and radiotherapy may be considered in selected cases, patients with disseminated disease typically require palliative systemic management. Emerging strategies—including immunotherapy and molecularly targeted therapies—have shown promising results; however, evidence specific to orbital involvement remains limited. This case underscores the importance of multidisciplinary evaluation and highlights the need for further studies to refine management strategies and improve outcomes in this uncommon disease.

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