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Overcoming Barriers: Diagnosis of High-Grade Melanoma: Perspective from a Clinical Case

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ABSTRACT

We present the case of a 30-year-old male patient with loss of visual acuity in the left eye. The imaging study detected a lesion of high suspicion of tumor in the left eye. Enucleation of the left eye was performed, confirming the diagnosis of choroidal melanoma by histopathological study. Subsequently, the disease progressed with neoplastic activity in the lungs, liver, lymph nodes and central nervous system. A case description is provided along with a bibliographic review, focusing on the approach and prognostic factors in patients with metastatic disease.

KEYWORDS: Uveal melanoma, Choroid, Enucleation, Radiotherapy, Immunotherapy, Central nervous system

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I. INTRODUCTION

The uveal tract is formed anteriorly by the iris and the ciliary body and posteriorly by the choroid. The choroid is located between the sclera and the retina, uveal tumors arise from the melanocytes of the uveal tract. (1,2)

Choroidal melanoma is considered the most frequent primary malignant intraocular neoplasia, with the eye being the second most common site of presentation of melanoma. (1,2) Clinically, it is characterized by progressive deterioration of visual acuity. Diagnosis is clinical and is supported by multiple noninvasive techniques (indirect ophthalmoscopy, ultrasound, fluorescent angiography) and invasive ones. Invasive methods are reserved when the diagnosis has not been established or for therapeutic purposes. There are multiple factors that directly affect the prognosis such as age, tumor size, histological characteristics along with the presence of metastasis. (1,2) It has been reported that up to 50% of patients with choroidal melanoma present with metastasis despite adequate initial management and close monitoring. (2)

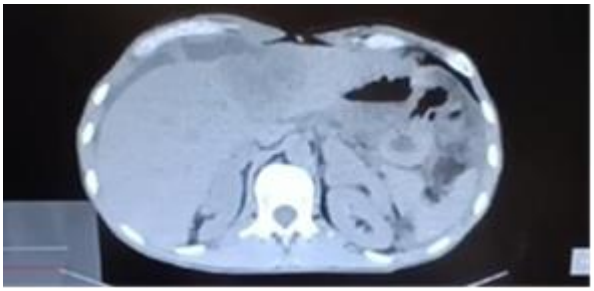
II. CLINICAL CASE PRESENTATION

30-year-old male, with no known comorbidities. His condition began in November 2022 with eye pain, headache, and decreased visual acuity in the left eye (LE). He was evaluated by the ophthalmology service, who performed a fundus examination of the left eye and found pigmented nodules in the retina. An ultrasound of the LE was performed with a report of a subretinal lesion with regular edges associated with retinal detachment. An MRI of the skull was performed (12/16/2022), finding a solid-looking image of 12.32 mm, defined margins, and reinforcement with the administration of contrast in the LE. In April 2023, he presented with worsening pain, orbital edema, and further deterioration of left visual acuity. Due to suspicion of tumor origin, enucleation was performed on 04/04/23.

Histopathological study reported choroidal melanoma of 1.6 cm diameter and 1.1 cm thick with infiltration of the optic nerve, classified as T4 and clinical stage IIIA. The immunohistochemical study reported: Melanoma Cocktail positive in cytoplasm, S100 protein positive in diffuse and nuclear cytoplasm and CKAE1/E3: Positive.

In August 2023, extension studies were carried out without the presence of metastatic activity. He was evaluated by medical oncology who proposed adjuvant radiotherapy, 17 sessions were granted, completed in October 2023. A thoracoabdominal tomography was performed (08/02/24) with a report of tumor activity at the lung, liver and adrenal. In March 2024, he debuted with seizures, a cranial tomography was performed with evidence

of tumor progression at the central nervous system. He was re-evaluated by medical oncology, who indicated palliative whole-cranial radiotherapy and was considered a candidate to continue with immuno-oncological therapy with Nivolumab and Ipilimumab. He is currently continuing with chemotherapy sessions scheduled to complete 4 cycles.



Simple abdominal tomography.

III. DISCUSSION

Uveal melanoma is a rare disease, representing 3-5% of melanomas, with choroid tumor being the most common (90%). In the USA, an annual incidence of 6-7.5 cases per million patients is reported, which may vary by country, sex, and race. Choroidal melanoma occurs more frequently in men, with a higher incidence between the fourth and fifth decades of life. Fifty percent of cases die from metastatic disease. (1–3)

Uveal melanoma has few genetic aberrations, these are associated with its metastatic potential and survival, it has been reported that the loss of chromosome 1q occurs in cases with metastasis, on the other hand, the loss of chromosome 3 is related to a decrease in long-term survival. (1) Among the risk factors associated with this tumor, it has been described that it affects people with fair skin, light eyes, freckles, tans, outdoor activities, oculo-dermal melanocytes and multiple abnormal cutaneous nevi (Ota nevus and dysplastic nevi). (2)

The clinical presentation is usually broad and nonspecific; however, the most frequent findings are visual acuity impairment, photopsia and visual field defects, the first is a consequence of tumor infiltration of the fovea, exudative retinal detachment with macular involvement or contact of the tumor with the lens. Other data that are presented less frequently are severe ocular pain, except in cases of inflammation, extraocular extension or neovascular glaucoma. During examination, the correct performance of indirect ophthalmoscopy is essential for the detection of choroidal melanoma, the classic findings are: a dome-shaped or button-shaped tumor, with superficial vasculature and a pigmented tumor, usually orange, however, they can vary from a dark color to being amelanotic, tumors with a thickness greater than 4 mm are associated with exudative retinal detachment. (1,2)

Ocular ultrasound and optical coherence tomography are the initial studies for the evaluation of ocular tumors. Ocular ultrasound with A and B mode is the most important auxiliary test during the approach, it helps to evaluate the intraocular extension of the neoplasia; in B mode, 3 suggestive characteristics of choroidal melanoma are observed: acoustically silent zone within the melanoma, choroidal excavation and shadows in the orbit. In optical coherence tomography, melanomas show subretinal fluid with or without serous retinal detachment and photoreceptor integrity. Optical coherence tomography angiography identifies superficial and deep retinal and choroidal structures in a noninvasive manner, giving greater detail of the underlying lesion. Fluorescence angiography and indocyanine green angiography are capable of detecting the microcirculation of choroidal melanomas. (1,2,4)

Choroidal melanomas are classified according to size, cell type and TNM staging system. According to ‘’The Collaborative Ocular Melanoma Study (COMS)’’, it proposes the classification by size as follows: small (4-8 mm in diameter and/or 1- 2.4 mm in height), medium (6-16 mm in diameter and/or 2.5- 19 mm in height) and large (>16 mm in diameter and/or > 10 mm in height). According to cell type, they are epithelioid, fusiform and mixed. (2,5)

The therapeutic goal of uveal melanoma is to preserve vision and reduce the risk of metastatic disease. The therapeutic strategy depends on the tumor size, visual acuity and extraocular involvement. Small and medium choroidal melanomas can be treated with radiotherapy, laser therapy and resection of the localized lesion. Episcleral brachytherapy, which favors tumor regression, is the most recommended for preserving vision, but is associated with complications from radiotherapy, such as the development of neovascular glaucoma. Enucleation is considered the primary therapeutic strategy in cases of large melanomas associated with glaucoma, vision loss and/or extraocular invasion, as in the case of the patient who reported invasion of the optic nerve. (1,2,6)

Up to 50% of patients with choroidal melanoma develop metastasis despite adequate initial management and close monitoring. Uveal melanoma spreads through the hematogenous route, with the liver being the most common site of metastasis (90%), followed by the lung (24%), brain and bone (16%). The risk of spread depends on multiple factors such as tumor size at diagnosis; large tumors have a 49% risk of metastasis at 10 years, medium-sized tumors have a 26% risk and small tumors have a 12% risk. (2,4)

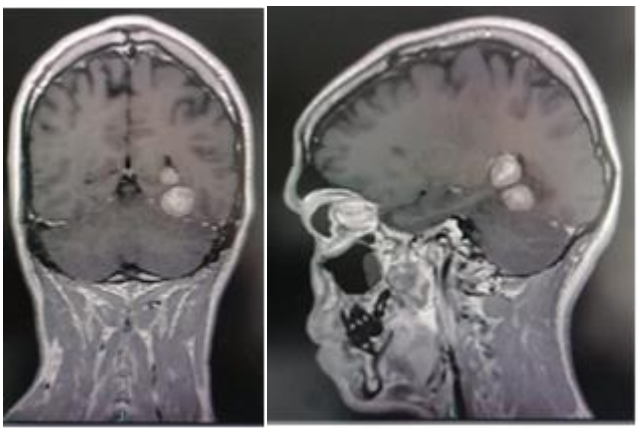
The presence of metastasis in the central nervous system (CNS) is associated with a poor prognosis. Dissemination from uveal melanoma is characterized by being rapid and progressive, in a high percentage is detected at the time of diagnosis of choroidal melanoma. In 20-50% of cases, it is considered the direct cause of death of patients. According to the literature, the average overall survival after detection of tumor activity at the CNS level is 5-7 months and only 8% achieve a survival of 2 years. Multiple trials have described that metastatic activity in the CNS has a lower

rate of therapeutic response compared to other affected organs. (7,8)

The therapeutic options for metastatic melanoma are scarce, and to date it remains a challenge in the field of medical oncology. The systemic management of metastatic uveal melanoma disease consists of extrapolation of the therapy of cutaneous melanoma. The most widely used chemotherapeutics are dacarbizine, fotemustine and temozolomide. Unlike the response to cutaneous melanoma, uveal melanoma is considered chemo-resistant due to the low rate of progression-free period. In addition, metastatic disease to the liver at the time of diagnosis is also associated with a low response to chemotherapy and a worse prognosis. (4,7)

In cases of metastatic cutaneous melanoma, immunotherapy and targeted therapy have shown a higher survival rate. The results in uveal melanoma have not been fully established, since it is considered a less immunogenic neoplasia. In recent years, immunological studies have shown a higher survival rate with the combination of immunotherapy regimens such as Ipilimumab + Nivolumab or Pembrolizumab, resulting in an overall survival of up to 19.1 and 18.4 months, this therapeutic strategy being one of the most promising. (7) Due to the previously mentioned evidence, this is the option that has been implemented in the patient's case, currently being managed with the combination of Ipilimumab and Nivolumab, since it is the one that has shown a greater range of survival and long-term prognosis.

Tumor size is the most important prognostic factor. Other histopathological factors related to poor prognosis are tumor diameter, presence of epithelial cells, mitotic index and extraocular spread. It is stated that the factors related to mortality due to metastatic activity are loss of chromosome 3, tumor diameter and epithelial cells. In cases of liver metastasis, the average survival at 1 and 2 years is 15-20% and 10%, regardless of management. (1,2)



Magnetic resonance imaging of the skull

CONCLUSION

Choroidal melanoma is a rare, highly lethal tumor. Early detection is essential, since management, prognosis and survival depend on it. The noninvasive diagnostic strategy that can be routinely implemented is indirect ophthalmoscopy. An appropriate technique can detect up to 90% of cases.

In the last 30 years, the survival rate has not improved despite new therapeutic strategies. Choroidal melanoma has a high rate of metastasis, leading to a deterioration in overall survival. On the other hand, tumor activity at the level of the central nervous system is considered a poor prognostic factor, increasing the risk of death in the next 10 years, despite adequate management and follow-up.

The management of disseminated disease is a challenge in the medical field. To date, immunotherapy has shown promising results. However, clinical trials are required that focus on researching and designing new therapeutic strategies directed at the molecular and immunological level that favor the survival of this population.

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