Case Report

A challenging case of ocular melanoma

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Abstract

Ocular melanoma is a rare malignancy found in clinical practice. In this paper, we present a case of highly aggressive ocular melanoma, which was surgically removed at the Department of Ophthalmology and diagnosed at the Department of Pathology, Emergency University Hospital, Bucharest, Romania, using conventional histopathological techniques. Uveal melanoma, a subset of ocular melanoma, has a distinct behavior in comparison to cutaneous melanoma and has a widely divergent prognosis. Approximately half of patients with ocular melanoma will develop metastatic disease, predominantly with hepatic, pulmonary or cerebral location, over a 10 to 15 years period. No systemic therapy was associated with an evident clinical outcome for patients with advanced disease and overall survival rate remains poor.

Keywords: ocular melanoma, enucleation, metastasis, unfavorable prognosis.

Introduction

Melanoma is a malignant proliferation of cells named melanocytes, responsible for skin, iris and hair color. Ocular presentation of this tumor is rarely seen. However, melanoma is the most frequent primary malignant neoplasm of the eye diagnosed in adults, the second being intraocular lymphoma [1–3]. This aggressive tumor regularly causes irreversible anatomical and functional changes sometimes with great clinical impact [4]. The incidence of intraocular melanoma ranges from 4.3 to six cases per one million people in the U.S., reaching 7.5 cases per one million in Scandinavian countries [5]. In other European countries, epidemiological data imply an incidence between 5.3 and 10.9 cases per one million people [6]. Uveal melanoma interests both genders equally [7].

Although pediatric and congenital cases [8] have been reported, uveal melanoma commonly occurs in older persons [9]. The mean age of patients included in the Collaborative Ocular Melanoma Study (COMS) and suitable for treatment with 125I brachytherapy was 59 years [10]. Roughly, older patients tend to have larger tumors and are likely to die from disseminated melanoma after enucleation [11].

Because there are no lymphatics adjacent to the uveal tract, metastasis occurs through local extension and vascular dissemination. The most frequent site of metastasis for uveal melanoma is the liver counting for almost 80–90% of ocular melanoma patients with metastases [12]. Other common sites of metastasis include the lungs, bones, brain and skin. Up to 50% of patients will develop metastases within 15 years after primary tumor treatment and the liver will be involved in 90% of cases [13, 14]. Therefore, patients should not be considered fully cured even after a 10-year interval of monitoring [15, 16].

We present a rare and challenging case of a massive intraocular melanoma, which developed areas of calcification and bone formation in the tumoral mass. These features found in the tumoral mass are very rare, only seven cases being reported so far [17, 18].

Case report

A 59-year-old underprivileged female patient presented with a massive mass in her right orbit, entirely replacing the eye, with no vision, and with mild diffuse pain. The tumoral mass was initially small but has progressively increased in size over the years. On clinical examination there was a black-brown tumoral mass occupying the entire right orbit with obvious proptosis, roughly measuring 25 mm, firm in consistency and without bleeding on palpation. The normal ocular structures, such as the sclera, pupil, iris, were all replaced by this single tumoral mass.

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The patient had no vision on this side. Both the upper and lower eyelids appeared to be notably stretched, but normal. The opposite eye was normal. With this clinical picture, suspicion of ocular melanoma was raised and the patient was taken up for orbital exenteration under general
anesthesia performed in the Department of Ophthalmology, Emergency University Hospital, Bucharest, Romania. The mass was exenterated en bloc, preserving both eyelids, as they were not involved by the tumoral growth. The right orbital cavity was packed with antiseptic compresses, which were removed after 48 hours. In the postoperative period, there were no relevant complications.

After the surgical enucleation, the affected eyeball and adjacent tissue samples were sent for histopathological examination and final diagnosis to the Department of Pathology of the same Hospital. On gross examination, the eyeball measured 27/26 mm with an evident black-pigmented tumoral mass of approximately 21 mm in the longest diameter, perforating and infiltrating the sclera and with clear signs of invasion in the surrounding tissue (Figure 1).

Figure 1 – Heavily pigmented ocular melanoma with massive extrascleral extension.

Specimen samples were fixed with 10% buffered formalin and were processed by conventional histopathological methods using paraffin embedding, sectioning and Hematoxylin–Eosin (HE) staining. Light microscopy examination revealed a large-sized uveal melanoma mostly consisting of epithelioid type cells (after the revised Callender’s classification). The tumoral cells were heavily pigmented, with clear atypical neoplastic features – irregular shapes and sizes with large nuclei and prominent nucleoli (Figures 2 and 3). Within the tumoral mass, we observed areas of necrosis, hemorrhage, calcification, bone formation and fibrosis (Figures 4–6). The average mitotic index counted 20–23 atypical mitoses/mm² (Figure 7). We also observed multiple tumoral foci infiltrating the sclera (Figure 8), the adjacent fibroadipose tissue, the blood vessels and the proximity of the optic nerve (Figure 9). There was no evidence of extrinsic muscles invasion.

We have also performed immunohistochemical tests. The paraffin blocks acquired by histopathological processing were sliced at microtome resulting sections with 3-μm thickness mounted on slides cover with poly-L-Lysine. After that, the sections were deparaffinized in toluene and alcohol successive baths, one hour (15 minutes by bath), rehydration (three successive alcohol baths with decreased concentration: 96%, 80% and 70% (10 minutes in each bath) and followed by a bath with distilled water, where the sections were hold for 10 minutes. Washing in PBS (phosphate-buffered saline), incubation with normal serum, for 20 minutes, incubation with primary antibody over-night, Dako LSAB kit, washing in carbonate buffer and development in 3,3’-diaminobenzidine hydrochloride/hydrogen peroxide and nuclear counterstain with Mayer’s Hematoxylin. We used the following antibodies from Neo Markers LabVision: Melanoma, clone HMB-45 (Thermo Fisher Scientific Inc., USA, 1:80 dilution), MART-1/ Melan-A, polyclonal (Thermo Fisher Scientific Inc., USA, 1:100 dilution), S100 protein, clone 4C4.9 (Thermo Fisher Scientific Inc., USA, 1:100 dilution), Ki67, clone SP6 (Thermo Fisher Scientific Inc., USA, 1:200 dilution). The immunoreactive cells were semiquantitative evaluate as follow: diffuse positive, >75% positive cells; positive, 25–75% positive cells; focal positive, <25% positive cells and negative cells.

Immunohistochemical tests showed diffuse appearance of positive HMB-45 in tumor cells (Figure 10), diffuse appearance of positive Melan-A in tumor cells (Figure 11), diffuse appearance of positive S100 in tumor cells (Figure 12), and Ki67 express more than 30% nuclear positivity in tumor cells, particularly at the deep edge of the tumoral mass (Figure 13).

Figure 2 – Epithelioid cells with marked nuclear hyperchromatism in ocular melanoma. HE staining, 100×.

Figure 3 – Epithelioid cells with pleomorphic vesicular nuclei containing prominent eosinophilic nucleoli in ocular melanoma. HE staining, 400×.
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Figure 4 – Ocular melanoma with necrosis and ossification. HE staining, 40×.

Figure 5 – Ocular melanoma with well-differentiated bone. HE staining, 100×.

Figure 6 – Ocular melanoma with fibrosis and calcification. HE staining, 100×.

Figure 7 – Epithelioid cells with nuclear pleomorphism; multiple mitoses or abnormal forms in ocular melanoma. HE staining, 200×.

Figure 8 – Melanoma cells infiltrated the sclera. HE staining, 40×.

Figure 9 – Melanoma nodule near the optic nerve. HE staining, 40×.
Discussion

Uveal melanoma arises from ocular stromal melanocytes and represents the most common primary intraocular tumor in adults. Applying the revised Callender’s classification is the key aspect in diagnosis and early management of uveal melanomas. On microscopic examination, uveal melanomas can have four distinct types of cells [19–22]: spindle A cells (cells with slender nuclei lacking visible nucleoli), spindle B cells (cells with larger nuclei and distinct nucleoli), epithelioid cells (larger polygonal cells with one or more prominent nucleoli) and Intermediate cells (similar to but smaller than epithelioid cells).

The most frequent types are mixed-cell uveal melanomas (86% of cases). Our case was largely composed of epithelioid cells, thus being in uveal melanoma after Callender. The 5-year survival rate is different based on the Callender’s classification and we should point out that the presence of even a few cells from the most aggressive category has a deep impact on prognosis. Therefore, the survival rate for pure spindle A type is 90–100%, 66–75% for spindle B, 50% for spindle B type associated with epithelioid cells and only 25–33% for pure epithelioid type [23, 24]. Other prognostic factors are the size of the tumor, the extension into the sclera, cell type, mitotic activity, the presence of necrosis and lymphocytic infiltration and the aspect of the nucleoli (distinct or indistinct). The epithelioid cell-type, the macroscopic infiltration of the sclera, the patchy areas of necrosis and the distinct nucleoli in our case coincide with an ominous prognosis. The large size of the tumor (21 mm in diameter), the high mitotic rate (23 mitoses) and the presence of a small nodule adjacent to the optic nerve imply a high risk of metastases. Recurrent CT investigations confirmed our clinical suspicions and revealed pulmonary and liver metastases, with a grim prognosis [25–27].

An interesting and rare feature of this case is represented by the calcification and the bone formation found in the tumoral mass. Only seven cases of calcification in intraocular melanoma were reported until 2009 [18]. These types of findings occur mostly in retinoblastomas and choroidal osteomas [18]. The first to describe calcifications in a choroidal melanoma were Jensen & Anderson in 1974, in a case with spontaneous regression [18, 28].
Kellner et al. (1993) reported three cases of calcification-like echographic pattern in uveal melanomas treated with brachytherapy postulating that the calcifications occurred in the necrotic residual tumors [28]. Chan et al. also reported a case of intraocular melanoma with calcification in the region of the perforated Bruch’s membrane, but in this instance, there were areas of fibrosis, calcification, bone formation and osteocytes surrounded by the tumoral mass [29]. Kiratli & Bilgiç also described tumoral calcifications in juxtapapillary melanoma after fractional transpupillary thermotherapy and Csákány & Tóth described an area of calcification at the limit of spindle and epithelioid cells in an ocular melanoma [17, 18]. Our case presents calcifications and bone formation adjacent to an area of necrosis. There is no correlation with brachytherapy or other forms of treatment, as only enucleation was done. Contrary to the cases described before, were the tumors were small and presented with signs of regression, this tumor had impressive dimensions and pulmonary and liver metastasis were found.

Bone formation or osseous metaplasia is a rare diagnosis in different pathology as in ocular melanoma or gastrointestinal adenocarcinomas [30] whereas in the skin this feature is frequently present. The mechanism leading to osteogenesis in different types of tumors remains unknown, but theories are postulating the idea of cellular transition from fibrocytes to fibroblasts and typical osteoblasts [30].

A key aspect for an effective treatment of patients diagnosed with uveal melanoma is to assess the prognostic factors related to the type of tumor, the size, the presence of necrosis and invasion and the mitotic rate [31]. The optimal treatment for primary and metastatic melanoma remains controversial and numerous theses are being studied, in order to obtain new and better results. Although enucleation was considered to be appropriate, it is thought that manipulation of the affected eye during this procedure may lead to iatrogenic metastatic spread. Hence, some alternative therapies, such as laser coagulation and radiotherapy are further investigated [32]. Patients with primary uveal melanoma can benefit, depending on the status and tumor type, of either surgery or radiation treatment. A last category includes brachytherapy, teletherapy and transpupillary thermotherapy (TTT) as options [33–35].

Systemic chemotherapy certified in protocols for cutaneous malignant melanoma proved to be inefficient for metastatic uveal melanoma. Therefore, the attention was drawn towards regional therapy (direct treatment, particularly to the liver, the most frequent site of metastasis, as mentioned previously). Such treatments consist of immuno-/chemo-embolization, radio-embolization (SIR-Spheres) or percutaneous hepatic perfusion (PHP) [36]. Recent studies [37] have shown that the inhibition of c-Met (hepatocyte growth factor receptor), a protein with tyrosine kinase activity, may prevent metastases of uveal melanoma, designating Crizotinib as an adjuvant drug for patients with high risk of disseminated disease.

As an extension of our previous studies regarding ocular melanoma [38], we focused on uveal melanoma, another peculiar entity in this field of pathology; therefore, we diagnosed a case of uveal melanoma with interesting and rare features, represented by the calcification and the bone formation found in the tumoral mass (this is mainly found in retinoblastomas and choroidal osteomas). All this strange cases with distinctive aspects found in our continuous research, help us to fully understand the big picture of a specific disease; to understand its complexity, due to its several macroscopic or microscopic aspects, and last but not least, to give us the opportunity to offer the patient a better personalized treatment.

**Conclusions**

No systemic therapy has been associated with an evident clinical outcome for patients with advanced disease. A more comprehensive insight of the combined effect of the multiple genetic, molecular and histopathological alterations in ocular melanoma can lead to an ultimately effective treatment. However, more information or data about drivers of uveal melanoma proliferation, differentiation, metastasis and survival should be gathered from the multiple trials currently underway.

**Conflict of interests**

The authors declare that they have no conflict of interests.

**Author contribution**

Mariana Costache and Daniela Alina Popa-Checheanu have equally contributed to this study.

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