Anatomoclinical aspects of conjunctival malignant metastatic melanoma

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Abstract

Conjunctival malignant melanoma is a rare tumor with a high risk of local recurrence, lymph node and systemic metastases. The aim of this study was to correlate tumor thickness, tumor ulceration, high mitotic rate, epithelioid cells with the presence of metastases and death from conjunctival malignant melanoma. We report the case of a 33-year-old patient who presented with a left eyelid ptosis associated with an eyelid prominence, foreign body sensation in the eye, and bloody discharge, symptoms occurring about one month earlier. Ophthalmologic examination revealed in eyelid conjunctiva two vegetant and ulcerative tumors of 8/6 mm and 3/3 mm. The two tumors were surgically removed with safety margins. The diagnosis of amelanotic malignant melanoma of the conjunctiva with brain metastasis was made by routine morphological methods and immunohistochemical reactions (HMB45, vimentin, S100 protein). Systemic metastases (skin, brain, lung, liver, kidney, peritoneal) and peripancreatic lymph node metastases were detected at 1.9 years after the diagnosis of conjunctival malignant melanoma. The patient died three months after the surgical excision of brain metastasis. Early diagnosis is essential to prevent tumor recurrence, ocular invasion, systemic and lymph node metastases, and preserving visual function.

Keywords: conjunctival malignant melanoma, metastases, immunohistochemistry.

Introduction

Malignant melanoma is a relatively common skin tumor arising from the melanocyte cells located in the basal layer of the multilayered Malpighian epithelium. It commonly develops on sun-exposed areas of skin and is often fatal. Although with a much lower frequency, this tumor can also form in other tissues, such as lachrymal sac [1], uvea, mucous membranes, including the vulva, rectum, oral cavity, respiratory tract, and conjunctiva [2]. Although histologically similar to malignant melanomas of the skin, conjunctival melanomas are rare tumors, their incidence in the white population being of 0.2–0.8 cases per million populations [3]. Conjunctival melanomas account for only 1.6% of all non-cutaneous melanomas [2] and 5% of all ocular melanomas [4].

Unlike cutaneous melanomas, there is no clear evidence of an association with UV light exposure, but the study conducted in Sweden by Triay et al. (2009) [5] showed an increase in conjunctival melanomas in sites exposed to sun. Conjunctival melanoma is more common in adults and elderly, the majority of patients being older than 40 years. Invasive conjunctival melanoma can be heavily pigmented, sparsely pigmented, or amelanotic. The tumors may be unifocal or multifocal [6].

The patients with advanced conjunctival melanoma identified clinically and confirmed histologically have a poor prognosis due to the development of lymph node and systemic metastases [7–9]. Conjunctival melanoma invades locally the subepithelial region and metastasizes at distance to the regional lymph nodes and then systemically [6]. These metastases occur because the subepithelial conjunctival stroma contains blood and lymphatic vessels [7].

Patient and Methods

A 33-year-old patient presented in 2012 to the IIrd Ophthalmology Clinic of the “Prof. Dr. Nicolae Oblu” Emergency Hospital, Iassy, Romania, with two tumors located on the left upper palpebral conjunctiva. History revealed that the patient was clinically diagnosed with bulbar conjunctival melanosis. One month before presentation, the patient noticed a left eyelid prominence, foreign body sensation, and bloody discharge. The clinical diagnosis was nodular melanoma of the left upper palpebral conjunctiva and bulbar conjunctival melanosis. The tumors were surgically removed with safety margins and topical 5-Fluorouracil treatment. Tumor excision was followed by plasty using lower lip mucosa. For one year, the patient refused referral to a specialized service. In 2013, the patient was admitted in emergency to the IIIrd Neurosurgery Unit with grade 1 coma, right hemiplegia, aphasia, and jaundice syndrome. CT scan of the brain identified a left parietal tumor, which was surgically excised. Subsequently, while admitted to the Oncology Clinic, multiple cutaneous, lung, liver, peritoneal, renal
metastases and peripancreatic lymph node metastases were detected. The patient died three months after the surgical excision of brain metastasis.

Tumor fragments collected from the conjunctival tumors and brain metastasis were fixed in 4% formalin, embedded in paraffin, and stained with Hematoxylin–Eosin. For immunohistochemical reactions, were used three monoclonal antibodies (anti-HMB45, anti-S100 protein, anti-vimentin).

**Results**

Ophthalmologic examination revealed moderate ptosis, a prominence in the central area of the left upper eyelid, and two vegetant, ulcerative masses located in the palpebral conjunctiva (Figure 1). Slit lamp examination revealed in the left bulbar conjunctiva areas of pigmentation in the external paralimbic sector, suggestive of melanosis. Physical examination did not show periauricular or submandibular adenopathies.

Macroscopically, the tumors were brown, and of 8/6 mm and 3/3 mm in size. Microscopically, the two removed tumors located in the palpebral conjunctiva consisted of tumor cells arranged in sheets, separated by connective tissues septa. Tumor cells were large, presented marked cytological atypia, abundant eosinophilic cytoplasm, and nuclei were irregular with numerous atypical mitoses (three mitoses/medium power field) (Figure 2). The tumor invaded the **substantia propria** for a distance of 8 mm into the subjacent conjunctival epithelium and presented an ulcerated area and intratumoral hemorrhagic foci (Figure 3). The anatomopathological diagnosis was invasive, amelanotic, malignant melanoma of the conjunctiva, epithelioid subtype, developed **de novo**; histological grade G3.

Figure 1 – *Conjunctival malignant melanoma of the left upper eyelid.*

Figure 2 – *Amelanotic, epithelioid conjunctival malignant melanoma. Sheets of epithelioid neoplastic melanocytes with marked atypia and numerous atypical mitoses. The tumor sheets are surrounded by connective-vascular tissues septa (HE staining, ×400).*

Figure 3 – *Amelanotic, epithelioid conjunctival malignant melanoma. Beneath the conjunctival epithelium, the deep tumor proliferation is formed of neoplastic melanocytes with marked atypia and numerous atypical mitoses (HE staining, ×100).*

Figure 4 – *Brain metastasis from amelanotic, epithelioid conjunctival malignant melanoma. The tumor is delimited by nervous tissue showing reactive gliosis. Tumor tissue consists of epithelioid neoplastic melanocytes with marked atypia and numerous atypical mitoses. Intratumoral hemorrhagic foci (HE staining, ×100).*

Macroscopically, brain metastasis was brown and of 25/12 mm in size. Microscopic examination of the brain tumor fragments showed tumor proliferation well delimited by the surrounding tissue that showed reactive gliosis.
nucleated giant neoplastic melanocytes were also identified. Tumor stroma was composed of connective tissue septa with capillary vessels (Figure 5). Immunohistochemical reactions were positive for HMB45, S100 protein, and vimentin in the neoplastic melanocytes of conjunctival malignant melanoma (Figures 6–8) and brain metastasis.

Figure 5 – Brain metastasis from amelanotic, epithelioid conjunctival malignant melanoma. Tumor tissue is composed of multinucleated epithelioid and giant neoplastic melanocytes, with abundant eosinophilic cytoplasm (HE staining, ×200).

Figure 6 – Amelanotic, epithelioid conjunctival malignant melanoma. Cytoplasm of epithelioid neoplastic melanocytes is highly positive for HMB45 (IHC staining, ×100).

Figure 7 – Amelanotic, epithelioid conjunctival malignant melanoma. Cytoplasm of epithelioid neoplastic melanocytes is highly positive for S100 protein (IHC staining, ×200).

Figure 8 – Amelanotic, epithelioid conjunctival malignant melanoma. Cytoplasm of epithelioid neoplastic melanocytes is highly positive for vimentin (IHC staining, ×40).

Discussion

Conjunctival malignant melanomas arise from melanocytes located in the basal layer of conjunctival epithelium, cells derived from the neural crest [10]. In 75% of cases, these melanomas develop from primary acquired melanosis with atypia, in 12% develop de novo, and the remaining melanomas develop from a conjunctival nevus [7]. In our patient an acquired melanosis of palpebral conjunctiva or conjunctival nevus were not identified, the tumor being a conjunctival malignant melanoma developed de novo.

The origin of conjunctival melanoma is of prognostic importance irrespective of tumor size and location. Patients with conjunctival malignant melanoma developed from primary acquired melanosis or nevus have a better survival than those with de novo tumors [11]. Thus, for conjunctival malignant melanoma developed from primary acquired melanosis the 10-year survival rate was 86%, compared to 69% for de novo malignant melanoma [12].

Microscopically, in the structure of conjunctival melanoma one or more types of neoplastic melanocytes are identified: polyhedral, epithelioid, spindle or ballooned [13]. In our patient, both the primary conjunctival tumor and brain metastasis consisted of epithelioid neoplastic melanocytes. In brain metastasis neoplastic melanocytes were larger, more pleomorphic, and sometimes had two or even more nuclei.

Conjunctival melanoma occurs almost exclusively in Caucasians and in only less than 1% African-Americans [14]. In the Caucasian population, the tumor has an annual prevalence 0.2–0.5 cases per million populations without gender predilection [15]. In the U.S., an increased incidence was found in white men over 60 years of age [10, 16].

Conjunctival malignant melanoma has a potential for metastases, high morbidity and mortality rate [11, 17, 18]. Thus, metastasis occurred in 16% of patients at five years, 26% at 10 years, and 32% at 15 years [11]. Numerous studies have demonstrated that in conjunctival melanomas metastasis is initially in the preauricular and submandibular lymph nodes [19, 20]. Conjunctival malignant melanoma metastasizes by contiguity to the nasal cavity [21], eyeball, orbit, and paranasal sinuses [22]. Distant
metastases via the blood flow occur in the lungs [23], liver, digestive tract [24], brain [2], bones [25], parotid gland [26], and skin [20, 23]. Metastases rarely occur in the bladder, upper urinary tract [27], or mammary gland [28]. Median times to regional and systemic metastases are approximately 2.3 and 3.4 years, respectively [29]. Our patient was diagnosed with brain, lung, liver, kidney, peritoneal, subcutaneous, and peripancreatic lymph node metastases at 1.9 years after primary tumor removal. Incomplete tumor excision was demonstrated by many studies as a poor prognostic factor [7, 30].

Histopathological findings associated with poor prognosis include tumor thickness greater than 0.8 mm [7], although other authors claim a value of 1.5–2 mm [6, 17]. In our patient, the thickness of conjunctival malignant melanoma was 8 mm. A group of researchers from the University of Texas “MD Anderson” Cancer Center at Houston presented a study of 44 patients with conjunctival melanoma treated surgically. Their study showed that the histopathological factors of poor prognosis are represented by non-limbal location, tumor thickness (greater than 2 mm), ulceration, mitotic rate (more than one mitosis/mm²), lymphovascular invasion in substantia propria, epithelioid tumor cell, and microsatellitosis [17]. Numerous clinical studies dealt with the prognostic value of clinical and histopathological parameters in malignant conjunctival melanoma [2, 7, 10, 11, 17]. The clinical data show conjunctival malignant melanoma in younger patients has a poor prognosis compared to elderly [31]. In the study by Esmaeili et al. (2012) [17], 23% of the followed up patients were classified into the risk factor group and died 40 months after surgery.

Anastassiou et al. (2002) [30] have analyzed 69 patients with conjunctival malignant melanoma treated surgically over a 28-year period. In their study, the authors reported the following risk factors for relapse: irregular pigmentation of tumor cells (amelanotic or mixed pigmentation), tumor invasion beyond the substantia propria, and the presence of epithelioid tumor cells. As significant risk factors for death from conjunctival melanoma, the authors reported: tumor location in the palpebral conjunctiva, caruncle, fornix, tumor invasion beyond the substantia propria, and nodular or mixed growth pattern.

Paridaens et al. (1994) [32] studied 256 cases of conjunctival malignant melanoma for an average of nine years and identified the unfavorable prognostic factors. These are represented by the location of the tumor in the eyelid fornix, caruncle, and eyelid margin, the presence of multicentric melanoma, tumor thickness greater than 4 mm, presence of epithelioid cell in tumor structure, and lymphatic invasion. These factors are significantly associated with a mortality rate 2–5 times higher than in their absence.

The study of Baderca et al. (2013) [33] was retrospective and included 32 cases of ocular biopsies from 2006 to 2011. The study was composed of both, benign and malignant tumors that were grouped according to their localization (conjunctiva and uvea) and to the histological type of the cells. Between ocular melanomas, the most common were those with uveal localization, 77% of the cases. The most frequent localization of ocular melanomas was choroid (54%), followed by ciliary body (11.5%), iris (4%), and conjunctiva (19%). Most of conjunctival melanomas were constituted of both epithelioid and spindle cells.

Our patient was in the young age group, and the conjunctival melanoma was located in the non-bulbar conjunctiva, was multicentric, with superficial ulcerations, deep tumor invasion (8 mm), was composed of epithelioid tumor cells with numerous mitoses (average 20/10 high-power fields). He was classified as stage pT4b, pN3, pM1 according to AJCC Classification for conjunctival melanoma [34]. In the management of patients with conjunctival malignant melanoma in different clinical stages the following are used various methods of treatment, represented by surgical excision of the tumor with 3–4 mm safety margins, brachytherapy, cryotherapy and orbital exenteration [2, 7, 10, 15].

Conclusions

 Conjunctival melanoma is an extremely rare malignancy that can metastasize and cause patient death. Poor prognostic factors are tumor thickness over 2 mm, tumor ulceration, high mitotic rate, and epithelioid cell type. These prognostic factors correlate with the presence of metastases and patient death. In making the diagnosis, deciding the treatment and management of conjunctival malignant melanoma a multidisciplinary approach involving an ophthalmologist, anatomopathologist, radiologist, surgeon and oncologist is essential.

References

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Received: March 5, 2014
Accepted: August 25, 2014