

Merkel Cell Carcinoma of the Eyelid

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Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine carcinoma. Merkel cells were originally described as clear oval cells in the basal layers of the epidermis, with neuroendocrine features. The incidence of MCC is rising, with an annual increase of 8%. Ultraviolet exposure and immunosuppressive status are the main known risk factors for MCC. In addition, there is a potential role for Merkel cell polyomavirus (MCV) in the pathogenesis of MCC due to its DNA presence in about 80% of MCC tumors [1]. MCC commonly occurs in sun-exposed areas in the head and neck. The diagnosis of MCC is challenging due to its non-typical appearance. It may present as a painless, indurate, solitary dermal nodule with a slightly erythematous to

deeply violaceous color, and rarely, an ulcer. Investigators have used the acronym AEIOU to summarize this tumor entity as Asymptomatic, Expanding rapidly, and more likely to occur in Immunosuppressed patients older than 50 years in Ultraviolet-exposed skin [1]. Surgery, radiotherapy and chemotherapy are applied in variable sequences in a stage-dependent manner. We report two cases of eyelid MCC in elderly patients who were misdiagnosed as having chalazion.

PATIENT DESCRIPTIONS

PATIENT 1

An 87 year old Caucasian woman presented with a painless 1 cm diameter lesion on the left upper eyelid. One month earlier she had been examined by an ophthalmologist and was treated for a chalazion. She was referred to the oculoplastic clinic due to continuous growth of the tumor. The lesion was a red violaceous firm nodule with a smooth shiny surface overlying telangiectatic blood vessels [Figure 1A].

The anterior segment and the fundus were otherwise normal. No lymphadenopathy was noted. An incisional biopsy revealed an extensive tumor surface consisting of small tumor cells with round nuclei, fine chromatin, partly powdery, and bright. One focus of papillary dermis with vascular invasion was noted. Immunohistochemistry staining demonstrated positivity for CK20, NSE and SYN, and negative staining for LCA and TTF1 [Figure 1B]. Computed tomography (CT) of the head, neck, chest and abdomen revealed no evidence of metastatic spread. Preoperative lymphoscintigraphy demonstrated drainage to the left retro-auricular and supraclavicular lymph node. Intraoperative lymphatic mapping was performed, using intradermal injection of 0.3–0.5 ml patent blue V 2.5% dye (Guerbet, Aulnay-sous-Bois, France) and a gamma-detecting probe (Neoprobe 1000 or 2000, Neoprobe Corporation, Dublin, OH, USA).

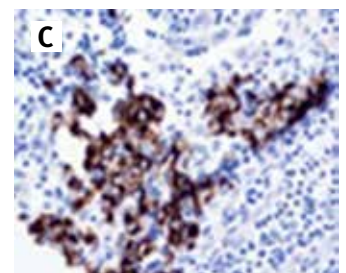
Sentinel node retrieval and wide local excision of the primary lesion with 5 mm margins and immediate reconstruction



[A] Case 1. Right upper eyelid at presentation showing a firm, red-violaceous nodule with a smooth shiny surface overlying a telangiectatic blood vessel



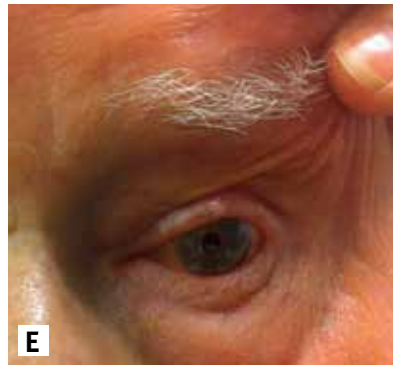
[B] Case 1. Immunohistochemistry study showing positive staining for CK 20 (marked in brown)



[C] Case 1. Right upper eyelid 4 months postoperatively showing a contour with no evidence of tumor recurrence



[D] Case 2. Left upper eyelid showing a well-defined reddish-pink 2 mm mass between the eyelashes. Telangiectatic vessels seen overlying the surface



[E] Case 2. Left upper eyelid 2 months postoperatively showing a normal contour with no evidence of tumor recurrence

completed the surgical procedure. Margins were seen to be clear on frozen sections. The sentinel lymph nodes (SLN) (parotid, supraclavicular and jugulodigastric) revealed no metastatic spread. The patient was classified, according to criteria of the AJCC (American Joint Committee on Cancer), as T1N0M0 (≤ 2 cm, without evidence of regional lymph node involvement based on lymph node biopsy, and no distant metastases). The skin defect, comprising most of the upper lid, was reconstructed by tarsal sliding of the transposition flap from the same eyelid and skin graft from the contralateral eyelid. The patient did not receive adjuvant radiation therapy. At 18 months follow-up, the patient is free of disease, with a satisfactory functional and cosmetic outcome [Figure 1C].

PATIENT 2

A 91 year old Caucasian male presented with a 2 mm diameter lesion on the left upper temporal eyelid, between the eyelashes [Figure 1D]. At presentation the lesion was considered a simple chalazion and was treated with warm compresses and topical steroids, with no improvement. An incisional biopsy was performed and a diagnosis of MCC was determined. The patient underwent CT of the head, chest and abdomen, and ultrasound of the neck, with no evidence of metastases. Preoperative lymphoscintigraphy using technetium (Tc)-99m radiopharmaceuti-

cal with perilesional intradermal injections demonstrated drainage to two left pre-auricular nodes. Intraoperative lymphatic mapping enabled identification and retrieval of an intraparotid and a pre-auricular sentinel node. Wide local excision with 5 mm margins using frozen sections was performed; for eyelid reconstruction we used a local tarsal flap, employing a sliding technique for the posterior lamella and a skin graft from an upper eyelid blepharoplasty for the anterior lamella.

One fragmented sentinel lymph node was deemed metastatic without extracapsular extension. The patient was classified as T1N1a (≤ 2 cm primary tumor with regional lymph node micrometastasis and no distant metastasis). The patient declined radical neck dissection, but he received adjuvant radiation therapy to the tumor bed and pre-auricular region to a total dose of 45 Gy in 25 fractions of 1.8 Gy each, using 6 MeV electron beam with eyelid protection. At 24 months follow-up there was no evidence of tumor recurrence and a satisfactory functional and cosmetic outcome of the upper eyelid was noted [Figure 1E].

COMMENT

A bare 2.5% of MCC growing on eyelids, mostly involving upper eyelids, was reported between 1973 and 2006. The prognosis of MCC of the eyelid is generally poor, considering its aggressive nature and high

local recurrence rate. An average disease-free interval of 7.4 months was reported in one cohort of 18 patients. The reported survival rates (disease-specific) vary from as low as 35% at 3 years to 51% at 5 years [2]. The clinical initial benign appearance may be misleading towards other common diagnoses, namely chalazion, basal cell carcinoma, epidermoid cyst, or even amelanotic melanoma. However, with a high index of suspicion, biopsy should be carried out without delay followed by definitive surgery. The diagnostic evaluation should include a total body evaluation for which CT is acceptable. Merkel cell carcinoma is highly avid for FDG (18 fluorodeoxyglucose) and this imaging modality is therefore efficient. However, since MCC is also somewhat of an “orphan disease,” administrative restrictions limit the usage of PET-CT (positron emission tomography-CT) for this indication. When replaced by CT, we tend to scan the head, chest and abdomen and use ultrasound of the neck to better and more accurately characterize the lymph nodes. Historically, a number of staging systems were used for patients with MCC. These have since been consolidated into the 2010 TNM staging system supported by both the AJCC and the International Union of Cancer Control [3].

Application of the sentinel node technique to MCC has gained popularity since our first publication [4]. This is by far the most accurate staging system available to date and is associated with earlier detection of microscopic disease in the lymph nodes. Given the tendency of MCC to recur locally, wide local excision has been practiced as the standard of care [3]. The recommendation for the optimal minimum width and depth of normal tissue margins that should be excised around the primary tumor elsewhere in the body is 3 cm, which is not applicable to the head and neck region, and specifically for eyelid lesions. Our patients underwent excision with 5 mm margins, and three intraoperative biopsy samples of the lateral, medial and nasal margins were confirmed by frozen section to be free of tumor cells. We used a skin graft from the contralateral

upper eyelid with excellent functional and cosmetic results [Figure 1E].

Pathologic involvement of regional lymph nodes is present in 23%–45% of all patients with MCC of all sites [5]. The rate of sentinel lymph node positivity in MCC is correlated with increasing diameter of the lesion, increasing thickness, increasing mitotic rate, and an infiltrative growth pattern. Pfeiffer et al. [5] found that 68% of patients with MCC larger than 2 cm had positive sentinel lymph nodes. Furthermore, they revealed that 23% of patients with MCCs < 1 cm have positive nodes, which is still a high enough rate of positivity to justify SLN biopsy even for lesions < 1 cm in size [5].

Currently there are two schools of thought regarding the management of regional lymph nodes in a patient with newly diagnosed MCC of eyelid without palpable or detectable lymphadenopathy. One advocates empiric radiation therapy for regional lymph nodes for all patients, while the other favors SLN biopsy and further radiation only for patients with positive SLN. SLN biopsy is a more complicated procedure and mandates general anesthesia in most cases. Contradicting data exist regarding survival and recurrence rates following positive vs. negative SLN biopsy. Pfeiffer et al. [5] recently concluded that

data on MCC of the eyelid are insufficient to determine the effect of SLN status on recurrence rate and prognosis [5]. A recent retrospective case series showed that even tumors with low tumor category are associated with regional nodal and distance metastatic disease. Therefore, it is reasonable to consider SLN biopsy for all MCC of eyelids, regardless of tumor size. On the other hand, in the head and neck region there is a presumed higher incidence of false negative SLN biopsy, due to aberrant lymph node drainage and frequent presence of multiple sentinel node basins. The very high radiation sensitivity of MCC on one hand, and the aggressive nature of the tumor and the high rate of recurrence on the other, led many to add adjuvant radiation therapy to the primary site and nodal basins as a standard of care. This may be particularly relevant in the case of eyelids, where local recurrence may be disastrous.

Radiotherapy for MCC may well substitute for radical surgery, if this type of intervention is declined by the patient or if there are severe co-morbidities. The role of chemotherapy is debatable and there are currently no randomized trials that enable standardization. Recurrences of MCC occur most frequently within 7.5 months (4–10 months) after surgery, and rarely after a 2 year disease-free interval.

The cases presented here demonstrate that suspicious lesions with clinical features of MCC should be investigated as soon as possible. The option of sentinel lymph node biopsy combined with radiotherapy is appealing as it improves staging, may reduce recurrence, and helps in the choosing of adjuvant therapies.

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