Merkel Cell Carcinoma of the Eyelid:
A Clinicopathological Case Report and Review of the Literature

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Abstract

Background: Merkel cell carcinoma (MCC) of the eyelid is a rare and aggressive tumor with neuroendocrine features, which occurs predominantly in elderly individuals and patients with compromised immune status. We report the clinical, histopathologic, and immunohistochemical findings of the tumor.

Case: A 61-year-old woman presented with a progressively enlarging lobulated reddish mass on her left upper eyelid, which had developed over a period of 2 months. The mass was resected, and the eyelid was reconstructed using the Cutler-Beard procedure.

Observations: Histopathologic and immunohistochemical analysis of the eyelid tumor revealed a neuroendocrine carcinoma with features that are typical of MCC. The tumor demonstrated frequent mitotic figures and infiltrative margins.

Conclusion: This case illustrates the typical clinical and histopathologic features of MCC, with histologic changes that are indicative of its highly invasive nature.

Introduction

Merkel cell carcinoma (MCC) is a rare cutaneous malignant disease with neuroendocrine features. First described by Toker1 in 1972, this distinct entity was termed trabecular carcinoma of the skin, based on its histological characteristics. MCC is considered to arise from primary malignant proliferation of Merkel cells. The Merkel cells have an epithelial origin and are located in the basal layer of the epidermis, probably playing a role in the perception of mechanical stimuli and acting as neurosensory transmitters. The tumor most often occurs in subjects who have been exposed to the sun, and in elderly individuals involving the head and neck. The tumor initially presents as a painless nodule for a duration of several months.3 It behaves aggressively, producing early local recurrences and lymphatic and distant metastases. MCC can develop on the eyelids (among other sites), and often histologically mimicks malignant lymphoma, undifferentiated melanoma, sebaceous carcinoma or cutaneous metastases of neuroendocrine carcinoma.3 A definitive diagnosis often depends on immunohistochemical analysis and electron microscopic examination. The present case...
The report describes the clinical, histopathologic, and immunohistochemical features of MCC of the eyelid, and includes a brief review of the literature.

**Case Report**

A 61-year-old woman presented with a progressively enlarging mass on her left upper eyelid, which had developed over a period of two months. She complained of pain and local tenderness. Her medical history revealed hypothyroidism, but no history of ocular trauma, toxin exposure, or smoking. The patient's mother had died from colon cancer and her sister had died from gastric cancer. On examination, a firm, reddish, well-circumscribed and pedunculated mass was seen on the left upper eyelid, and extended from the lateral canthus to the center of left upper eyelid (Fig. 1). The tumor measured 20 mm × 14 mm. A systemic investigation for evidence of a primary tumor located elsewhere produced negative results. A biopsy of the mass disclosed features consistent with MCC. The mass was subsequently resected, and the eyelid was reconstructed using the Cutler-Beard procedure. All surgical margins of the specimen were tumor-free. A systemic evaluation, including a computed tomography (CT) scan of the chest and abdomen, was normal. No evidence of recurrence, regional lymphadenopathy, or distant metastasis was detected within 10 months after surgical excision of the tumor.

**Histological Findings**

The eyelid tumor contained diffuse, infiltrating, monomorphic-like neoplastic cells showing a large nucleus with basophilia and granular nuclear material. The cells also possessed scanty cytoplasm. In some areas, the tumor showed a pattern that suggested an

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**Fig. 1** The Merkel cell carcinoma manifests as a circumscribed erythematous mass in the left upper eyelid.

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**Fig. 2** Histological examination of the mass shows a uniform population of round cells with granular basophilic chromatin and scanty cytoplasm. Multiple abnormal mitotic figures (short arrows) and pyknotic cells (long arrows) are present. Bar = 60 μm.
epithelial origin. However, most of the tumor was composed of undifferentiated sheets of tumor cells. There were numerous mitotic figures and scattered cell fragments with pyknotic nuclei, probably indicating apoptosis (Fig. 2). Mononuclear inflammatory cells were seen in both the superficial and deep dermis, but were sparse.

**Immunohistochemical Findings**

The tumor cells showed diffuse positive cytoplasmic immunoreactivity for NSE (Fig. 3, top left), synapto-

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**Table 1** Comparative Immunohistochemical Findings of Merkel cell carcinoma of the Skin and the Present Tumor

<table>
<thead>
<tr>
<th>Immunohistochemical Marker</th>
<th>Merkel cell carcinoma in the Skin</th>
<th>Present Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuron-specific enolase (NSE)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CK20</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Chromogranin</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Neurofilaments</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ki-67</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>p53</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Pankeratin</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Low molecular weight cytokeratin</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>High molecular weight cytokeratin</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Common leukocyte antigen</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thyroid transcription factor (TTF-1)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table was modified from references 26.
Merkel cell carcinoma, previously known as primary small cell carcinoma or neuroendocrine carcinoma is a rare neoplasm with an incidence of 23/10,000,000. Currently, the term MCC has prevailed as being the most suitable designation. Only 0.8% of MCC involve the eyelid. MCC in the eyelid occurs in older persons with a mean age of 74 years; however, it has occurred in younger patients. The youngest reported patient with this tumor was a 15-year-old girl with ectodermal dysplasia, who had MCC of the eyelid and metastasis to the parotid gland. The tumor is predominantly found in females (female : male, 2 : 1), MCC is frequently associated with other premalignant and malignant skin lesions such as actinic keratoses and squamous cell carcinomas, in which ultra violet has been implicated to be the common etiologic factor. Moreover, several reports have suggested that patients infected by the human immunodeficiency virus, patients who have received immunosuppressive therapy, and individuals with chronic lymphocytic leukemia are at increased risk of developing MCC of the skin.

MCC of the eyelid primarily occurs near the palpebral margin and initially appears as a symptom-free red or brown papule or nodule that suddenly undergoes rapid growth with pain. In some cases, ulceration leads the patient to seek medical attention. Other cases of MCC of the eyelid have features that masquerade as a recurrent chalazion.

Gould et al. recognized three histologic types of MCC: trabecular, intermediate, and small cell which exhibit different clinical features and biologic behaviors. The trabecular type represents the original case of MCC described by Toker. This form has an organoid growth pattern that forms trabeculae, composed of large differentiated basaloid cells with no significant mitotic activity. This type of MCC appears to occur less frequently and has a better prognosis than the other two types. The intermediate variant of MCC is the most common type, and is composed of intermediate-sized cells with a high mitotic index. The present case belongs to this intermediate variant. The small cell type, which is similar to the neuroendocrine carcinoma of the lung and other sites, is characterized by clusters of small undifferentiated cells with hyperchromatic nuclei often separated by abundant stroma. This type frequently shows crushing artifact and necrosis, and has an aggressive clinical course similar to that of the intermediate type.

Ultrastructurally, the most relevant features of MCC are the existence of abundant cytoplasmic intermediate filaments, frequently observed as compact paranuclear aggregates, and dense-core neurosecretory granules preferentially located in the cytoplasmic processes. The granules are more frequently found in the trabecular and intermediate cell types.

Until recently, electron microscopy was the technique of choice for an accurate diagnosis of MCC. However, it has the drawback of being unavailable in most clinical laboratories. In contrast, immunohistochemistry is routinely performed in many laboratories. This method allows a precise diagnosis, since MCC is usually positive for CK20, low molecular weight cytokeratins, neuroendocrine markers (NSE, chromogranin, and synaptophysin) and NF, and are negative for vimentin, S-100 protein, LCA, HMB-45, TTF-1, and high molecular weight cytokeratins. This profile allows the differentiation between MCC and most other malignancies included in the differential diagnosis; mainly lymphoma, metastasis of neuroendocrine carcinoma, and melanoma.

Neuron-specific enolase was used as a nonspecific immunohistologic marker, and CK20 was used as a specific antigen for MCC. CK20 immunoreactivity is usually granular and perinuclear; on electron microscopy it corresponds to distinctive fibrous bodies that are composed of aggregates of intermediate filaments and neurofilaments. It has been reported that CK20 has been reported to be useful for the differentiation of MCC from metastatic neuroendocrine carcinoma, lymphoma, squamous cell carcinoma, basal cell carcinoma, and malignant melanoma. Moreover, Merkel cells contain intermediate filaments in their cytoplasm and express low-molecular-weight simple epithelial-specific cytokeratins (CKs) (nos. 8, 18, and 19), in contrast to keratinocytes that express higher-molecular-weight CKs (nos. 1, 2, 5, 10, 11, and 14). However, unlike previous investigations that have demonstrated expression of low-molecular-weight cytokeratins and pankeratin in the skin, we were unable to show the presence of low molecular weight cytokeratin and pankeratin in this case of MCC of the eyelid. In an attempt to find a discriminatory marker, we found antibodies to specific CKs including CK20 appears to be very useful for the differentiation of MCC.

Chromogranin is a major protein of neurosecretory granules and is expressed at variable intensities in 33% to 80% of MCC. Synaptophysin is another neuroen-
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Small cell size, high mitotic rate, and large tumor size are reportedly associated with an adverse prognosis in MCC of the skin. Moreover, tumors located at the eyelid, recurrent local disease, and metastasis at the time of diagnosis indicate a poorer prognosis. The prognostic significance of proliferation markers in MCC of the eyelid have not yet been investigated. In our case, there was high expression of bcl-2 and MIB-1; two factors that may suggest a poor prognosis. However, an association between proliferation markers and a poor prognosis in MCC of the eyelid has not yet been reported. Further studies are needed to investigate the relationship between proliferation markers and prognostic data.

Acknowledgement

This work was supported in part by NEI core grant EYO3040 and by an unrestricted grant from Research to Prevent Blindness Inc., New York, NY and the clinical photo was provided by Michael A. Burnstine, M.D.

References

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眼瞼メルケル細胞癌 免疫組織学的検索を行った1例報告と文献的考察

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【要旨】61歳女性の左上眼瞼に原発したメルケル細胞癌を経験した。腫瘍を摘出してCutler-Beard法により上眼瞼再建術を施行した。病理組織学的にはメルケル細胞癌と診断された。免疫組織学的にはNeuron-specific enolase (NSE), CK20, synaptophysin, chromogranin, neurofilaments, bcl-2, mib-1, p53, pankeratin, low molecular weight cytokeratinsが陽性であり、high molecular weight cytokeratins, common leukocyte antigen, thyroid transcription factorが陰性であった。以上から、眼瞼メルケル細胞癌と診断した。

〈Key words〉メルケル細胞癌、眼瞼、免疫組織化学、増殖マーカー(p53, MIB-1, bcl-2)