An Eyelid Mass

Marta E. Couce
UH Cleveland Medical Center, Cleveland, OH

Case report

87 yo man with history of coronary artery disease (s/p CABG); colon adenocarcinoma, s/p resection (1990); prostate carcinoma, GI 4+4 (2010); T1N2M0 lung adenocarcinoma s/p LLL lobectomy (2002 and 2018) and s/p resection of Merkel cell carcinoma of right cheek, 1.5 cm with clear margins (2017), s/p XRT 60 Gy. Presents with right upper eyelid mass with extension to orbit. A right radical resection of upper eyelid with orbital exenteration is performed. Dx: Merkel cell carcinoma.

Introduction

Freidrich Sigmund Merkel, a German histopathologist, first described the Merkel cell (MC) in 1875. Merkel postulated that these cells acted as mechanoreceptors. They were referred to as "Tastzellen" or "touch cells."

MCs have been investigated for over a century, but their distribution, function and origin is still unclear. These cells are found in the basal layer of the epidermis and grouped in touch-sensitive locations in glabrous and hairy skin and in some mucosal locations. Their density varies among each anatomical site. They are concentrated in the palms and soles. They are also present in the lips, hard palate, gingiva esophagus and human eyelid.

MCs are in close contact with nerve fiber endings to form a synapse-like contact zone. They have spike-like cytoplasmic projections which interdigitate with adjacent keratinocytes. Ultrastructurally, they have dense-core secretory granules in the cytoplasm near the nerve fiber connection and are considered to be cells of APUD system. According some scientists they may play role in the proliferation and differentiation of the keratinocytes. Antibodies against anti CK type 20 provide the highest degree of specificity and give an easy identification of MCs at the light microscopic level. They also immunoreact with antibody against synaptophysin. .

Cyril Toker first described Merkel cell carcinoma (MCC) in 1972, on the basis of the histologic characteristics of the tumor; he named it trabecular cell carcinoma of the skin. Subsequent studies involving immunohistochemistry and electron microscopy revealed that these tumors originate from the Merkel cell.

Merkel Cell carcinoma (MCC) is a rare and aggressive neuroendocrine malignancy of the skin with approximately 1,500 new cases diagnosed each year

These neoplasms typically develop in elderly individuals on sun exposed areas in the head, neck, and upper extremities. Diagnosis most commonly occurs in the elderly with a slightly higher prevalence in men. Caucasians have the highest incidence of MCC. These tumors have a high recurrence rate after excision. The incidence of MCC is rising steadily and more than one-third of patients die of MCC, making it twice as lethal as malignant melanoma.

Etiology of MCC is linked to the presence of clonally integrated Merkel cell polyomavirus (MCPyV) and/or mutagenesis from ultraviolet light exposure.

Merkel cell polyomavirus is a member of the polyomavirus family comprised of non-enveloped, double-stranded circular DNA viruses. MCPyV-specific antibodies have been detected in 9% of children under 4 years of age, 35% of teenagers, and 80% of individuals 50 years or older, suggesting that it may be part of the cutaneous microbiome. Interestingly, despite this high prevalence, MCPyV has not been shown to cause any disease other than MCC
MCPyV-related oncogenesis requires integration of the viral genome into the host-genome and mutation of the large T (LT) antigen that is required for viral DNA replication. MCPyV isolated from MCCs, in contrast with MCPyV from non-tumor sources, present mutations that are responsible for the premature truncation of the MCV LT helicase. These mutations do not affect the Rb binding domain, but eliminate the capacity of the viral DNA to replicate. In this way, the virus loses its capability to replicate.

MCPyV DNA integrates into the host genome of approximately up to 80% of MCCs in the northern hemisphere, whereas its presence is much lower in other geographic regions such as Australia.

Metastasis most commonly involved regional lymph nodes, followed by distant lung, skin, CNS, liver and bone.

Immunocompromised patients with T-cell dysfunction are more likely to be affected by MCC. Patients with AIDS have an incidence rate 11-13 times greater than the general population. There are case reports of tumor regression after improvement in immune function.

46%–48% of all Merkel cell carcinomas appear in the head and neck region. Of the tumors presenting in the head and neck, the eyelids are common primary sites with incidence between 5% and 20% of all cases of head and neck MCC. Compared with MCCs occurring in other locations, MCCs of the eyelid appear to be associated with a better prognosis, which may be related to earlier detection.

Clinically, MCC is more commonly identified in the upper eyelid and usually arises near the eyelid margin, often causing partial or complete eyelash loss. The tumor appears as a rapidly growing purple-red "violaceous" vascularized painless

cutaneous nodule, which can be ulcerated. MCC in the eyelid area is commonly misdiagnosed initially as cysts, chalazia, or basal cell carcinomas. Histologically, MCC can be misdiagnosed as lymphoma, melanoma, or metastatic small cell carcinoma of the lung (SCCL).

The clinical behavior and epidemiologic features of eyelid MCC are similar to MCC in other anatomic sites.

The clinical differential diagnosis of Merkel cell carcinoma includes chalazion, sebaceous carcinoma, squamous cell carcinoma, and basal cell carcinoma.

Histopathology

Histologically, the tumor commonly involves the full thickness of the dermis and frequently extends into the subcutaneous fat and adjacent skeletal muscle with a proliferation of monotonous round tumor cells with scant eosinophilic cytoplasmic rim, round and vesicular nuclei with finely granular and dusty chromatin and multiple nucleoli. Apoptotic nuclei and frequent mitotic figures are often seen. A trabecular growth pattern may be present but most often tumor cells are dispersed as sheets lacking a distinct architectural arrangement. Most MCCs are entirely dermal or subcutaneous but some have intraepidermal component. Some are found in association with other non-neuroendocrine carcinomas

Because Merkel cell carcinoma can be confused with sebaceous carcinoma, additional immunohistochemistry and (some times) electron microscopy can be of great value in differentiation. Merkel cell carcinoma expresses cytokeratin polypeptides 8, 18, and 19, which are characteristic of epithelia. It also exhibits a distinct marker profile with dot-like expression of with cytokeratin 20. It stains Positively for neuron-specific enolase and synaptophysin. Electron microscopy demonstrates dense-core cytoplasmic granules.

CAP protocol Merkel Cell Carcinoma

A. Tumor Thickness

Tumor thickness (measured in millimeters from the stratum granulosum to the deepest infiltrating tumor cells) as a prognostic indicator for outcome is more predictive of outcome than maximum tumor diameter (a previous staging parameter).

B. Mitotic Rate

The presence of >10 mitotic figures/high-power field (HPF) has been shown to correlate with large tumor size as well as a poor prognosis. Ki-67 proliferation index of greater than 50% is associated with a significantly worse prognosis.

C. Tumor-Infiltrating Lymphocytes

Tumor-infiltrating lymphocytes (TILs) are defined as lymphocytes present at the interface of the tumor and the stroma. Some authors have suggested that the presence of TILs has been shown to portend a poor prognosis, especially when considered in concurrence with a tumor depth of >5 mm.

D. Tumor Growth Pattern

In a series of 156 patients with MCC, nodular tumor growth pattern (as opposed to infiltrative growth) was found on both uni- and multivariate analysis to correlate with better survival.

Clinical examination.

A complete physical examination should be performed, including a comprehensive ophthalmic exam to assess the extent of the disease. Palpation of the preauricular and cervical lymph nodes is important to assess for possible lymphatic spread. If there is any evidence of lymphadenopathy or if the eyelid appears to be diffusely involved, additional imaging is required to evaluate for systemic spread of the disease.

Treatment

Wide surgical excision with clear margins and pathologic nodal staging. Mohs micrographic surgery or frozen sections are used for histopathologic confirmation of disease-free margins of 5 mm around the eyelids.

Adjuvant radiation therapy, chemotherapy and combination treatments have been reported to be successful in limited cases for palliative purposes or inoperable disease. The role of adjuvant radiotherapy remains controversial, as there is inconclusive evidence for improvement in disease-specific mortality.

Although both MCPyV- positive and -negative tumor cells express PD-L1, the expression levels of PD-L1 in virus-positive tumors seem to be higher than those in virus-negative tumors. No randomized trials are available to compare chemotherapy with immunotherapy. However, data from treatment with immune checkpoint inhibitors are promising with responses both in MCPyV-positive and -negative MCC. Several clinical trials of immune checkpoint inhibitors (anti-PD-1,

PD-L1, and CTLA-4 Abs) administered as monotherapy or in combination with other agents or modalities are ongoing and may provide further treatment options for patients with advanced MCC.

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