Acta Scientific CANCER BIOLOGY (ISSN: 2582-4473)

Volume 4 Issue 10 October 2020

Case Report

Merkel Cell Carcinoma, a Case Report, Literature Review and Treatment Updates

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Received: August 14, 2020

Published: September 24, 2020

Abstract

Merkel cell carcinoma (MCC) is a primary neuroendocrine malignancy of the skin, presenting as firm, painless, rapidly growing nodule. MCC often presents in elderly, fair-skinned individuals in sun-exposed areas. Diagnosis is often overlooked at time of presentation due to its rarity, but MCC is twice as deadly as malignant melanoma. MCC are Small round blue cell tumor of uncertain origin and an association with the polyomavirus has been seen in > 80% of MCC. This study present a case of MCC which was initially diagnosed as SCC of skin but Immunohistochemistry revealed the diagnosis of MCC, as stains for CD56, CK20, CK7 and synaptophysin were positive. In addition to surgical excision, the patient also received risk adapted adjuvant therapy as described. This case report and literature review elucidates the clinical, histopathologic and management aspects of MCC, which will help in recognizing and treating these tumors.

Keywords: Merkel Cell Carcinoma (MCC); CD56; CK20; CK7; Synaptophysin

Introduction

Merkel cell carcinoma are rare primary neuroendocrine malignancy of skin, with incidence of 0.6 per 100,000 [1]. It occurs mostly in older adults (average age 66 - 76) with fair skin. Male-to-female ratio approximately 2:1. MCCs typically present as firm, painless, rapidly growing, single red or purple cutaneous dome-shaped nodule on sun exposed region of the body with initial indolent growth, however, the course of MCC is aggressive with nodal invasion, distant metastasis and high recurrence rates [2]. 65% present with localized disease [3].

Although, there is no established risk factors for the disease, some of the risk factors are: Light skin, older age, UV exposure, immune suppression, organ transplant (x24 risk) [4], CLL, melanoma and myeloma [5]. Merkel cell polyomavirus (MCPyV) is ubiquitous and can be detected in normal skin flora as well as other tumors, but clonal integration of viral DNA provides evidence of causal relationship [6]. MCPyV is prevalent, with antibodies detected in 80% of individuals over 50 years old, but the only cancer it is associated with is MCC. Remaining viral-negative cases of MCC are mostly associated with UV-related DNA mutations [7].

Normal Merkel cells exist in basal epidermis and around hair follicles and act as mechanoreceptors. Merkel cell carcinoma is most common in sun-exposed areas (42.6% head and neck, 23.6% upper limb, 15.3% lower limb) [6].

MCC are Small round blue cell tumor of uncertain origin. Merkel cell polyomavirus detected in >80% of MCC [8,9]. Theories of origin include sensory cells in skin mechanoreceptors or skin stem cells that undergo malignant differentiation [10,11]. Three subtypes exist (small cell type, trabecular type, and intermediate type) but these are not thought to be prognostic.

We report a case of MCC of left upper eyelid, in a 61 years old female from Mongolia who has a history of left parotid adenoid cystic carcinoma for which he underwent parotidectomy in 2016. We also give overview of treatment updates.

Case Report

A 61 year old female patient native of Mongolia presented with complaints of left upper eyelid red-purple dome shaped papule. The lesion was progressively enlarging in size and painful. She started with oral antibiotics as well as local application. The lesion was still progressive in size. Biopsy from the lesion was done which revealed Merkel cell carcinoma. Subsequently, she underwent wide local excision of the lesion. Two year later she had local recurrence with left upper neck swelling and then she presented to our hospital for further management.

A non-contrast MRI head and neck was done which revealed altered signal intensity in left upper lid possibly involving the conjunctival reflection of the lid, abutting the overlying skin and mild altered intensity thickening along the adjoining lateral aspect of the globe. Remaining bilateral orbit including the bony orbit, globe the retro-orbital fat, extra-ocular muscles, bilateral optic nerve, optic tract and chiasma unremarkable. Bilateral cavernous sinus showed normal flow signals.

In view of recurrent disease and cervical lymphadenopathy a PET CT scan was performed which revealed FDG avid local disease and FDG avid left cervical level II lymph node, No other FDG avid lesion anywhere else in the body.

She underwent wide local excision of primary along with left radical neck dissection. Frozen section from additional supero-medial margin was free of malignant cells.

HPE (S-1110/20): Malignant small round cell tumor. All margins free of tumor, LVSI +VE, PNI -VE. Forty four lymph nodes were dissected out of which eighteen showed evidence of nodal metastasis. Extranodal extension seen.

IHC: Synaptophysin - Diffusely positive, CD56- Diffusely Positive, Chromogranine focal positive, TTF-1 negative, CK-20, CK-7 positive. Finding were consistent with MCC.

Depending upon histopathology report and multidisciplinary discussion patient received adjuvant concurrent chemoradiotherapy with weekly Inj Cisplatin 40 mg/m^2 body weight along with 56 Gy in 30 fractions to ipsilateral lymphatic drainage area over 6 weeks. Since all margins were free from malignant cells the primary tumor site was not irradiated. After 3 weeks of concurrent chemo-radiotherapy she developed sub centimeter nodules on the lateral side of upper lid. Subsequently the primary tumor site was treated with 6 MeV electron prescribed at 8 mm depth.

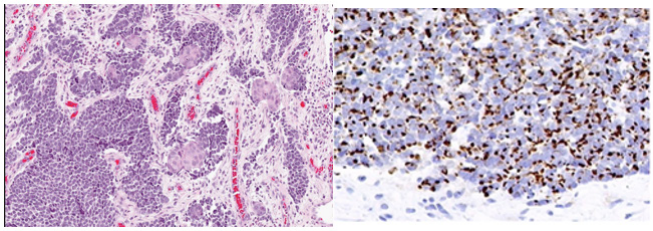

Figure : 1st image shows Merkel cell carcinoma focal squamous differentiation; individual aggregates of tumor cells shows dual squamous and small round blue cell tumor (neuroendocrine) features. 2nd image shows perinuclear dot like cytokeratine (CK-20) staining, characteristic of MCC.

Discussion

The histological presentation of MCC is small, round, blue-cell tumors and need to be distinguished from lymphoma, melanoma, sarcoma, and metastatic skin deposits from other neuroendocrine carcinomas, in particular small cell lung carcinoma. Immunohistochemical study characteristics of neuroendocrine carcinoma of the skin is low-molecular-weight (CAM 5.2) keratin, and more specifically CK20 expression, which is often evident by paranuclear immunostaining [12]. CK7 is characteristically negative in MCC and may be positive in small cell lung carcinoma [12]. Neuroendocrine markers (neurofilament protein, chromogranin, and synaptophysin) are frequently expressed in MCC tumors [13]. The tumor cells are negative for leukocyte common antigen, HMB-45, Melan-A, desmin, and myogenin. Most recently, CD56, a marker for neural cell adhesion molecule [14,15].

Common sites of MCC metastasis include distant lymph nodes (60%), distant skin (30%), lung (23%), central nervous system (60%), and bone (15%) [12]. CT and MRI scans are obtained to evaluate MCC and for treatment planning, but there is no accepted imaging algorithm. Recently, however, some studies have shown that FDG-PET is a highly sensitive modality for MCC evaluation before and after treatment [16].

The standard of care of the primary tumor is surgical. Removal by wide local excision is typical with margins of 1 - 3 cm, with some surgeons also using Mohs micrographic surgery to ensure adequate clear margins at excision with sentinel lymph node biopsy for clinically negative node patients. Local recurrence rates with Mohs micrographic surgery are lower than with wide excision because thorough histologic evaluation of margins is best. For clinically palpable regional disease, lymph node dissection is recommended with consideration of adjuvant radiation therapy. Adjuvant treatment should be initiated early (4 - 6 weeks) as MCC is aggressive tumor and recurrence occur at early. MCC spreads to regional lymph nodes within 2 years in 70% of cases. When lymph nodes are affected, 5-year survival is approximately 50% [17]. If surgery to primary would be disfiguring or otherwise morbid, definitive RT may be appropriate.

Although chemotherapy is highly effective for small cell carcinoma of lung, for MCC, there is no clear role for concurrent or adjuvant chemotherapy for locoregionally confined disease. Given the morphologic and immunohistologic similarities to small cell carcinoma, MCC also is similarly chemosensitive. It is most widely accepted as a last-line effort in stage II disease to prevent progression to distant metastasis and in stage III disease as a palliative effort [16]. The most common regimen used is either cisplatin/etoposide or carboplatin/etoposide. There is no clear data for benefit to concurrent chemo-RT although phase II data does exist with concurrent cisplatin/etoposide [18]. In metastatic setting, phase II data suggests response rates of > 50% to PD-1 (Pembrolizumab) or PD-L1 (avelumab) inhibition [19-21].

New treatment modalities are being explored. Immunotherapy has shown some results for early stage MCC. Interferon alfa 2b and tumor necrosis factor have shown some promise. The antigens mucin 1 and epithelial cell adhesion molecule are expressed in 85% and 70% of MCC cases, respectively [22].

The lack of data on chemotherapy in the elderly population is not unique to MCC; rather, it is a common problem in cancer research. Most cancers occur in patients 65 years and older, yet there is a paucity of data on the effects of chemotherapy because elderly patients are poor candidates for phase 1 and phase 2 trials.

Limited evidence available suggests that RT reduces locoregional recurrence. Risk factors, which some consider indications for PORT after definitive surgery, include LVSI, immune suppression, positive margins if further resection not possible. For small tumors (< 1 cm) without risk factors, observation may be reasonable. Regional nodal RT is indicated for SLNB-positive patients, but if full node dissection is performed and there are no adverse features e.g. multiple nodes positive or ECE, consider observation. After negative SLNB, it is reasonable to observe regional nodes unless patient is at high risk for false-negative SLNB [23].

For margin-negative resection, consider 50-56 Gy/25-28 fx. For microscopically positive margins, consider 56 to 60 Gy. For gross residual disease or for definitive treatment, consider 60 to 66 Gy. For microscopically positive nodal disease (+SLNB or node dissection), consider 50 to 56 Gy to regional nodes. Consider up to 60 Gy to regional nodes for extracapsular extension.

Conclusion

MCC is a rare, aggressive carcinoma that usually arises in sun-exposed regions of the body. Physicians should consider MCC as a differential diagnosis when encountering a rapidly growing, painless lesion. Early diagnosis and treatment may improve patient survival rates. However, due to the rarity of MCC, further studies are needed to develop treatment protocols for metastatic disease.

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