

Metastatic Merkel Cell Carcinoma of the Abdominal Wall

Abstract

Merkel-cell carcinoma (MCC) is a rare skin malignancy seen in elderly males. It is a highly aggressive tumor with a poor prognosis. Surgery is the mainstay of treatment for localized disease with adjuvant radiation depending on the locoregional extent, while chemotherapy has a role in metastatic disease. Emerging data from treatment with immune checkpoint inhibitors look promising. We report a case of MCC in an elderly male diagnosed and treated with chemotherapy and radiation, with a review of the literature of this rare malignancy.

Keywords: *Merkel cell carcinoma, neuroendocrine tumor, skin cancer*

Introduction

Merkel cell carcinoma (MCC) is a primary cutaneous neuroendocrine carcinoma, commonly seen in elderly males. It is highly aggressive, rare malignant tumor of the skin with threefold increase in incidence as per the Western literature.^[1] It is the second leading cause of nonmelanoma skin cancer death with 30% mortality.^[2]

The common features for diagnosing MCC go with acronym: AEIOU (asymptomatic/painless, rapidly expanding (<3 months), immunosuppression, older than 50, and location on an ultraviolet (UV)-exposed site), wherein three or more criteria are seen in 89% of cases.^[3] Regional nodal involvement has high propensity for local recurrence and distant metastases involving the skin, liver, lung, bone, and brain in one-third patients. The treatment of MCC includes surgery, radiotherapy, and chemotherapy/immunotherapy depending on the presence or absence of metastases.

We report a case of metastatic MCC of the abdominal wall in a 56-year-old male.

Case Report

A 56-year-old gentleman presented with painless progressive swelling on the left side of the abdomen for 6 months, associated with skin ulceration and discharge without any constitutional symptoms. Contrast-enhanced computed

tomography (CECT) of the abdomen showed 166 mm × 123 mm × 45 mm heterogeneously enhancing anterior abdominal mass in the left lumbar region, with loss of fat plane between the mass and underlying muscle. The lesion was extending up to the skin with focal areas of ulceration, without intraperitoneal or retroperitoneal extension. CECT of the chest revealed well-defined heterogeneously enhancing lesions in the left lower lobe suggestive of metastases. Biopsy from the primary lesion showed medium-sized neoplastic cells arranged in sheets [Figure 1] with scanty cytoplasm [Figure 2] and round-to-oval nuclei with inconspicuous nucleoli consistent with poorly differentiated malignancy. Immunohistochemistry (IHC) showed leukocyte common antigen-negative, Melan A-negative, pancytokeratin dot-like positive [Figure 3], CD34-negative, cytokeratin 20 (CK20) dot-like positivity [Figure 4], CD 56-positive, CD 117-negative, and chromogranin-negative. Morphology with IHC correlation was suggestive of MCC. Brain and bone scans were normal.

Two cycles of cisplatin/etoposide-based chemotherapy showed a marginal response hence planned to integrate radiation. Concurrent chemoradiation up to 55 Gy in 20 fractions with weekly cisplatin was administered. A good clinical response with 75% tumor regression and improvement in performance status was observed at the end of 10 weeks [Pictures 1 and 2]. Systemic chemotherapy was continued after radiation.

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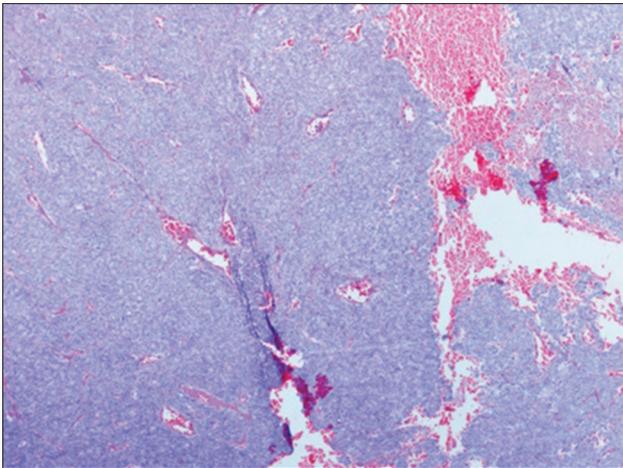


Figure 1: Cellular lesion arranged predominantly in sheets, (H and E, ×40)

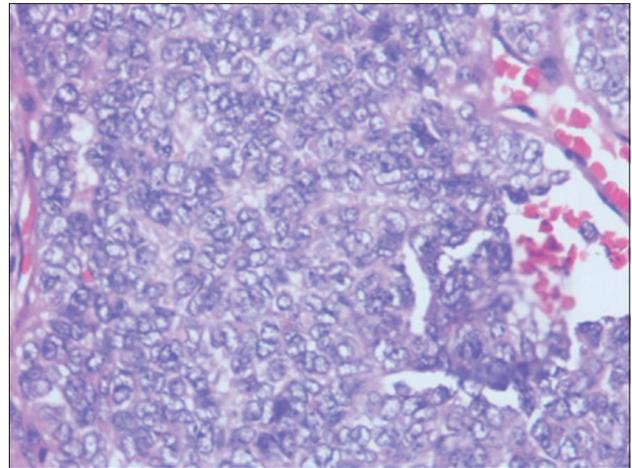


Figure 2: Monotonous population of cells having scanty cytoplasm, round vesicular nucleus with finely granular chromatin with margined nucleoli, (H and E × 400)

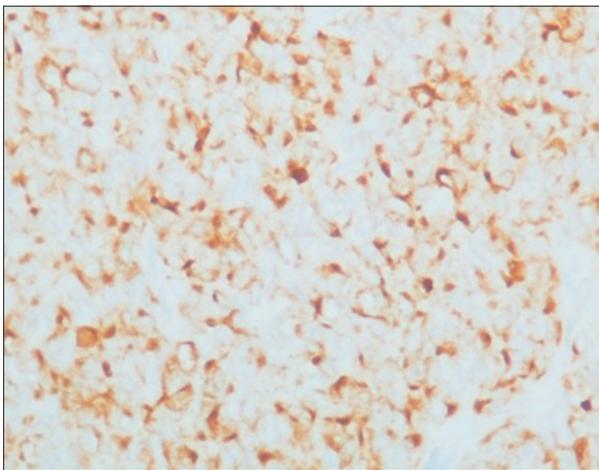


Figure 3: Pancytokeratin immunostaining showing cytoplasmic positivity and focal dot like positivity

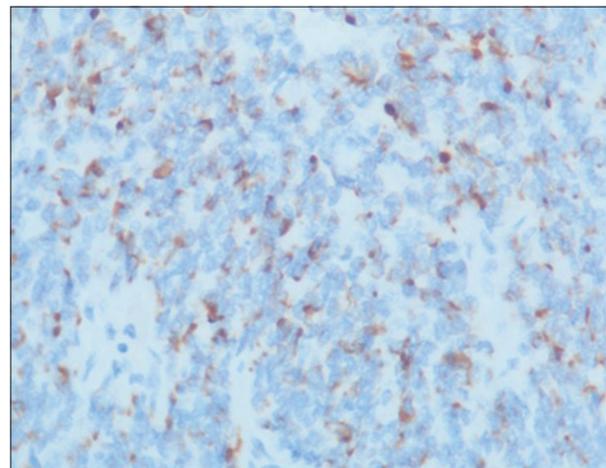


Figure 4: CK20 immunostaining shows characteristic perinuclear dot-like positivity

Discussion

MCC is a rare aggressive tumor of the dermis first reported by Toker in 1972 as trabecular carcinoma of the skin. Tang and Toker (1978) found dense core granules in the cytoplasm of the tumor cells by electron microscopy which led to the hypothesis that this tumor arises from Merkel cells.^[4] The name MCC was coined by De Wolff-Peeters *et al.* in 1980.^[5]

Danish registry reports a 5.4 times increase in the incidence of MCC over 18 years.^[6]

MCC is commonly seen in elderly Caucasians with a mean age of 70 years without sex predilection. The skin of the head and neck is affected in 50% cases, extremities in 40%, and trunk and mucosa in 10%.^[7] Risk factors include sunlight exposure and immunosuppression. Merkel cell polyomavirus (MCPyV) sequences were detected in 80% of MCC tumors when compared 16% in control skin tissues and suggesting the possibility of viral infection as a contributing factor in pathogenesis that could have triggered clonal expansion of the tumor cells.^[8]

Although the initial infection may occur in childhood, virus-positive MCC typically does not occur until age 70 years. Virus-positive MCC has a specific integration pattern and it expresses a large T-cell antigen in tumor cells which inactivates p53 and Rb. They have extremely low mutational burdens, in contrast to UV-induced MCPyV-negative MCCs, which are characterized by a mutational load that is 100 times higher. Viral antigens are foreign and thus potentially strong immune stimulants, and many virus-associated tumors are characterized by robust immune infiltrates and PD-L1 expression.^[9]

MCC typically develops as a painless, nontender rapidly growing nodule or plaque, seen on sun-exposed areas of the body. Nodules are solitary, firm, fleshy to reddish-blue, having a smooth shiny surface.

Histologically, the tumor is composed of strands or nests of monotonously uniform round blue cells containing large basophilic nuclei, inconspicuous nucleoli, and



Picture 1: Clinical image of the swelling at diagnosis



Picture 2: Clinical image of the swelling after treatment

Table 1: Merkel-cell carcinoma staging system (American Joint Committee on Cancer, eighth edition)

Stage	TNM	OS 2 years (%)	OS 5 years (%)
Stage I	Primary <2 cm (T1)	67	81
Stage II	Primary 2 cm or more (T2)	59	67
Stage III	Nodal disease (N1)	49	52
Stage IV	Systemic metastases (M1)	23	11

OS – Overall survival; TNM – Tumor, node, metastasis

minimal cytoplasm. Intermediate type, small cell type, and trabecular type are the three main histological patterns.

IHC of MCC demonstrates epithelial and neuroendocrine markers. The loosely arranged intermediate filaments stain for CKs. Paranuclear dot-like pattern of CK20 expression due to clumping of intermediate filaments is highly specific of MCC. MCC also stains neuroendocrine markers CD56, chromogranin, neuron-specific enolase, and synaptophysin. S100 and other melanoma markers are negative. Thyroid transcription factor-1 differentiates it from metastatic small cell carcinoma of the lung. Strong diffuse positivity of p63 has negative prognostic implication.^[10]

Squamous or sarcomatoid differentiation may be seen occasionally.

The staging of MCC according to American Joint Committee on Cancer (AJCC) eighth edition is shown in Table 1.^[11] Radiological classification based on local and distant metastasis has been proposed (Stage 1: cutaneous involvement, Stage 2: regional nodal invasion, and Stage 3: systemic metastases).^[12] Sentinel node mapping for the regional extent and positron-emission tomography (PET) computed tomography scan for the evaluation of distant metastasis is recommended. The rationale for the implementation of somatostatin receptor scintigraphy (SRS)

in patients with MCC is based on the neuroendocrine characteristics of the malignancy.

Limitations of SRS include nontargeted uptake in various organs, such as the liver, adrenal glands, pancreas, thyroid gland, and spleen, making it difficult to detect metastases. Additional limitations are the inability to detect small lesions due to suboptimal spatial resolution, relatively high cost, longer image acquisition protocol, and the diagnostic dilemma of determining whether a negative 18F-fluorodeoxyglucose PET scan represents the absence of a tumor or a well-differentiated tumor that has a high possibility of expressing somatostatin receptors. To circumvent this, a novel imaging technique using positron-emitting somatostatin analogs (68Ga-DOTATATE) has emerged.^[13]

Poor prognostic factors include male sex, size of the primary tumor >2 cm, and metastatic disease.

The treatment of MCC includes surgery, radiotherapy, and chemotherapy depending on the presence or absence of metastatic disease. For localized disease, wide local excision and sentinel node dissection are the standard of care. Mohs micrographic surgery has been recommended for localized lesions with excellent cosmetic results.

Adjuvant radiotherapy (40–60 Gy) to the primary site and regional nodes reduces the risk of local recurrence and increases median survival.^[14] Adjuvant chemoradiotherapy has been reported to result in improved overall survival when compared to adjuvant radiotherapy in patients with positive margins, tumor size at least 3 cm, and male sex.^[15] Palliative radiation therapy (RT) can be considered for inoperable tumors.

Chemotherapy is recommended for inoperable and metastatic disease. In view of the neuroendocrine features, chemotherapy with platinum/etoposide shows better response. Chemotherapeutic agents such as cyclophosphamide, doxorubicin, vincristine, methotrexate,

and 5-fluorouracil have been tried. In Trans-Tasman Radiation Oncology Group study, concurrent carboplatin/etoposide with radiation showed good locoregional control and survival.^[16] However, in general, there is an initial regression followed by recurrence within 4–15 months.

Biologic agents such as interferons, tumor necrosis factor, and hyperthermia were used in advanced disease. Coexpression of c-KIT in a high percentage of MCC led to the use of tyrosine kinase inhibitors such as imatinib with promising results.^[17,18] Somatostatin analogs showed objective responses with moderate doses and minimal side effects with survivals over 10 months.^[19]

Peptide receptor radionuclide therapy as a new tool in the management of inoperable or metastatic patients with 111 indium-, 90 yttrium- or 177 lutetium-labeled somatostatin analogs has been highlighted in several case reports. 90Y-DOTATOC and 177 Lu-DOTATATE are the most promising, providing long-lasting responses and good survival rates.^[20]

There are several ongoing clinical trials of immune checkpoint inhibitors (anti-PD-1, anti-PD-L1, and CTLA-4 abs) administered as monotherapy or in combination in metastatic and adjuvant^[21] settings. Studies have shown that around 50% of MCCs express PD-1 on tumor-infiltrating lymphocytes and PDL1 on tumor cells. Pembrolizumab therapy in advanced MCC is associated with a 56% objective response rate, including a 16% complete response (CR) rate; virus-associated tumors had an overall response rate (ORR) of 62% compared to 44% with virus-negative tumors.^[22] Similarly, avelumab (PDL1) has shown ORR of 62%, 2 years' progression-free survival (PFS) of 26%, and OS of 36% in a phase 2 trial.^[23] In patients who had received at least one line of chemotherapy, avelumab (anti-PDL1 antibody) has shown an ORR of 33%, with a CR rate of 11% and has been Food and Drug Administration approved. However, it is too early to determine the long-term outcomes of these patients, and there are subsets of patients either refractory to immune checkpoint inhibitors or develop acquired resistance over time. Finally, the combination of conventional cytotoxic chemotherapy and RT in conjunction with immunotherapy remains to be determined.

Our case with a rare site of the presentation was a diagnostic and a therapeutic challenge.

Learning points

1. MCC is a primary neuroendocrine tumor that arises in the skin. It may occur at non sun-exposed sites as well
2. CK20 expression and paranuclear dot-like pattern of intermediate filament staining are highly suggestive of MCC
3. Surgery is the mainstay of treatment for localized disease, and it is usually followed by adjuvant radiation
4. Our case demonstrated a good clinical response, and PFS (more than 10 months and which is ongoing at

the time of writing) can be achieved with cytotoxic chemotherapy and radiation

5. Immune checkpoint inhibitors offer new hope and should be used for durable clinical response.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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