CLINICAL VIGNETTE

Merkel Cell Carcinoma Presenting as a Large Axillary Mass

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Case Report

A 40-year-old female patient presented to the Oncology with recently diagnosed Merkel cell carcinoma. She has a complex medical history, including fragile X pre-mutation, intellectual disability, autism, seizure disorder, and IgA deficiency. The patient's brother, her primary caretaker, noted a lump in her left axilla approximately three months prior to presentation. Subsequent diagnostic imaging, including bilateral diagnostic mammogram and breast ultrasound, revealed at least five masses with cystic components in the left breast, measuring up to 17 mm. Additionally, two large oval masses were identified in the left axilla, measuring 81 x 58 x 72 mm and 39 x 22 x 37 mm. Ultrasound-guided core needle biopsies were performed on the largest left breast mass and one of the left axillary masses. Histopathological examination of the left breast mass revealed benign breast tissue with patchy fibrosis and apocrine metaplasia. However, the left axillary mass biopsy revealed high-grade neuroendocrine carcinoma, consistent with Merkel cell carcinoma. Immunohistochemical analysis of the left axillary mass showed positive stain for cytokeratin 20 (CK20) and insulinoma-associated protein 1 (INSM1), negative staining for cytokeratin 7 (CK7), and thyroid transcription factor-1 (TTF-1), and a KI-67 proliferation index of 80%. At the initial consultation, the patient was asymptomatic and denied any pain. However, obtaining a detailed review of systems was difficult. Physical examination revealed a large hard mass in the left anterior axilla, measuring 16 x 12 cm. No palpable breast masses were detected, and a thorough skin examination did not reveal any suspicious lesions or nodules.

Surgical Oncology evaluation did not advise immediate surgical intervention and proposed initial neoadjuvant therapy followed by reassessment for resectability. Staging studies were performed. PET/CT scan demonstrated intensely FDG-avid left axillary and left subpectoral nodal metastases and an intensely FDG avid right iliac lesion. Brain MRI was negative for brain metastasis. CT-guided biopsy of the right iliac lesion confirmed metastatic Merkel cell carcinoma. Laboratory studies, including complete blood count with differential and comprehensive metabolic panel, were within normal limits. Serological testing revealed positive Merkel polyomavirus VP1 Capsid antibody and an elevated Merkel oncoprotein Ab titer of 220 STU (reference interval: 0-74).

Discussion

Merkel cell carcinoma (MCC), also known as neuroendocrine carcinoma of the skin, is a rare and highly aggressive non-melanoma skin cancer. It most frequently presents in the head and neck region of older adults as a rapidly growing, painless, firm, red or purple nodule on sun-exposed areas of the skin.[1,2] While the head and neck are the most frequent sites of occurrence, MCC also develops on the extremities and trunk. MCC may initially present with lymphadenopathy or distant metastases without an identifiable primary lesion. MCC's characteristic rapid growth often prompts clinical evaluation.

Epidemiological data indicate a rising incidence of MCC, with approximately 3,000 new cases diagnosed annually in the United States.[2,3] Several risk factors have been identified for MCC development, including ultraviolet (UV) exposure, advanced age, immunosuppression, light skin color, and male gender.[4]

MCC was previously thought to arise from Merkel cells, found right below the epidermis and close to the nerve endings that receive the touch sensation. However, another hypothesis is that MCC originates from skin stem cells that acquire neuroendocrine features during malignant transformation. MCCs have heterogeneity in differentiation patterns, which suggests that stem or early progenitor cells are more likely the cells of origin, as these cells are capable of differentiating.[5] The definitive cell of origin of MCC remains unknown.

Merkel cell polyomavirus (MCPyV) is believed to be essential in MCC pathogenesis. Up to 80% of MCCs are associated with MCPyV infection. MCPyV is a ubiquitous, nonenveloped, double-stranded DNA virus that can integrate into the host cell genome. The integrated MCPyV genome then undergoes tumor-specific mutation, leading to persistent expression of two main oncoproteins, the large tumor (LT) antigen and small tumor (sT) antigen. Subsequent mutation of LT allows it to bind and inactivate the retinoblastoma (RB) tumor suppressor protein, resulting in ongoing tumor growth. sT is another oncoprotein that can promote MCC by activating PI3K/AKT/mTOR pathways and inactivating tumor suppressors.[6,7] Ultraviolet (UV) radiation exposure is another important pathogenic factor. MCC has a predilection for sun-exposed skin areas, and MCC has been reported in patients treated with psoralen plus ultraviolet A (PUVA) photochemotherapy.[8,9] It is believed that UV radiation damages the DNA in skin cells, causing mutations

that lead to tumorigenesis. UV exposure is a significant risk factor for virus-negative MCC tumors.

Diagnosis of MCC requires histopathology review. The tumor contains nests of uniform, round, blue cells containing vesicular nuclei with prominent nucleoli and scant cytoplasm.[1] Numerous mitotic figures, lymphovascular invasion, and perineural invasion are commonly seen. Immunochemistry is needed for diagnosis. A typical panel includes positive CD20, positive epithelial markers AE1/AE3, and positive neuroendocrine markers, which may consist of synaptophysin, chromogranin A, INSM1, and/or CD56. MCC cells are negative for TTF-1 and S-100, which can help distinguish MCC from small cell lung cancer and melanoma.[1,9]

After the diagnosis of MCC, complete skin and lymph node examination and imaging for staging is recommended. Occult metastasis resulting in upstaging has been detected in up to 20% of patients presenting without suspicious findings.[10] Given the prevalence of MCPyV in MCC patients, quantitation of serum MCPyV oncoprotein antibodies may be considered as part of the initial evaluation. In seropositive patients, the titer may be followed during surveillance after initial treatment, and a rising titer may be an early indicator of disease recurrence.

MCC management involves a comprehensive multidisciplinary approach, integrating various treatment modalities to optimize outcomes. For localized disease, surgical intervention remains the cornerstone of treatment, serving as the primary therapeutic strategy. Radiation therapy also plays a key role in adjuvant, non-surgical, and palliative settings, with characteristically high MCC radiosensitivity. Systemic treatment is utilized in both neoadjuvant and metastatic settings. In the neoadjuvant context, systemic therapies are typically employed with the aim of achieving resectability. For metastatic disease, systemic therapies offer a critical avenue for managing widespread MCC, aiming to control disease progression and alleviate symptoms.

For clinically node-negative (N0) disease, the standard of care involves excision with 1-2 cm margins and sentinel lymph node biopsy (SLNB). Post-surgical observation is recommended when clear margins are achieved, with no adverse risk factors present, such as tumor size exceeding 1 cm, lymphovascular invasion, chronic lymphocytic leukemia (CLL), HIV infection, or history of organ transplantation. In cases of positive margins or identified adverse risk factors, adjuvant radiation therapy is indicated following surgery. Positive sentinel lymph node findings warrant either radiation therapy to the nodal basin or further nodal dissection. Observational studies have demonstrated that adjuvant radiotherapy can significantly reduce the locoregional recurrence rate and improve overall survival (OS).[11] If curative surgery is not initially feasible, neoadjuvant systemic therapy can be considered. For patients who are deemed poor surgical candidates, definitive radiation therapy is an appropriate alternative treatment option.[12]

Most patients with metastatic disease are treated with systemic therapy. Conventional chemotherapy regimens, including platinum-based combinations, have demonstrated limited durability in their therapeutic response.[13] Immune checkpoint inhibitors (ICIs) have emerged as an effective treatment for MCC. ICIs demonstrate better overall response rates and tend to have more durable responses than chemotherapy treatment.[14] The enhanced efficacy of ICIs in MCC can be attributed to their unique mechanism of action. By blocking immune checkpoints, these drugs effectively unleash the body's immune system, particularly T cells, against cancer cells. This approach is especially potent in MCC due to the inherently immunogenic nature of these tumors, which often arise after viral infections or UV-induced mutations.[14,15]

In a multicenter, phase 2, noncontrolled study, 50 patients with advanced MCC without prior systemic therapy were given pembrolizumab (anti-PD-1) at 2 mg/kg of body weight every 3 weeks. The primary endpoint was the objective response rate. The overall response rate to treatment was 58% (complete response 30% and partial response 28%; 95% CI 43.2 to 71.8). Among the responders, median progression-free survival (PFS) was 16.8 months, and the 3-year PFS was 39.1%. The 3-year OS was 59.4% for all patients and 89.5% for responders.[16,17] Currently, three immune checkpoint inhibitors have received FDA approval for treating metastatic MCC: pembrolizumab, avelumab and retifanlimab. For patients who progress on single-agent immunotherapy, nivolumab plus ipilimumab or chemotherapy are options for subsequent therapy.[18]

Clinical Case Follow-up

Following the diagnosis of metastatic Merkel cell carcinoma, the patient was started on checkpoint inhibitor therapy with pembrolizumab. After two doses, the patient developed new onset pancytopenia (WBC 1.5 x $10^3/\mu L$, Hgb 9.3 g/dL, PLT 111 x $10^3/\mu L$). Subsequent bone marrow biopsy revealed 5-10% Merkel cell carcinoma involvement and increased dysmegakaryopoietic features of unclear etiology. FISH studies for myelodysplastic syndrome (MDS) were negative. The pancytopenia was attributed to MCC infiltration of the bone marrow and was less likely caused by pembrolizumab. Her left axillary mass was stable, so treatment was continued for three additional cycles with stable blood counts.

Unfortunately, after five cycles of pembrolizumab, her left axillary mass started growing again. A restaging PET/CT confirmed disease progression, demonstrating increased size of the left axillary and subpectoral nodal metastases, as well as new cervical lymphadenopathy. The axillary mass began to produce serous discharge and became painful.

In response to disease progression, the patient's systemic therapy was changed to a combination of nivolumab and ipilimumab. She was also given palliative radiation therapy to the large left axillary mass. Despite two cycles of the new systemic therapy regimen and a course of radiation, her clinical condition continued to deteriorate. She also developed a

secondary infection of the skin wound and was hospitalized with sepsis. Following multiple goals of care discussions she was transitioned to home hospice care.

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