Merkel Cell Carcinoma of Unknown Primary Origin

Merkel cell carcinoma (MCC) is a rare and highly aggressive primary cutaneous neuroendocrine carcinoma most often occurring in the elderly. Risk factors include chronic sun exposure and immunosuppression (1). MCC is associated with frequent recurrences and a high metastatic potential and mortality rate (1). It is the second most common cause of skin-cancer-related death after melanoma. At primary diagnosis with an apparent cutaneous tumor, loco-regional metastases are present in up to 30% of patients, and 6-12% have distant metastatic disease (2-3). Up to 5% of cases present with unknown primary origin (4). Five-year overall survival for patients with advanced or metastatic disease is 13-18% (4).

We report two cases of MCC presenting without primary cutaneous involvement; first at an unusual location in the adipose tissue of the right breast, and the second one with only a clinically positive left inguinal lymph node.

In October 2018, a 78-year-old woman presented with a 15-week history of a painless solitary mass in the upper outer quadrant (UOQ) of the right breast with no visible cutaneous involvement. Her medical history included hypertension, dyslipidemia, and plaque psoriasis. She underwent ultrasound guided biopsy, and histopathology confirmed the diagnosis of metastatic MCC (mMCC). Positron emission tomography/computed tomography (PET/CT) scans showed increased standardized uptake values in the mass in the UOQ and an additional mass in the lower inner quadrant (Figure 1A). The patient underwent mastectomy and lymph node dissection of the right axilla. Histopathology confirmed mMCC and negative axillary lymph nodes. Regular follow-up (clinical

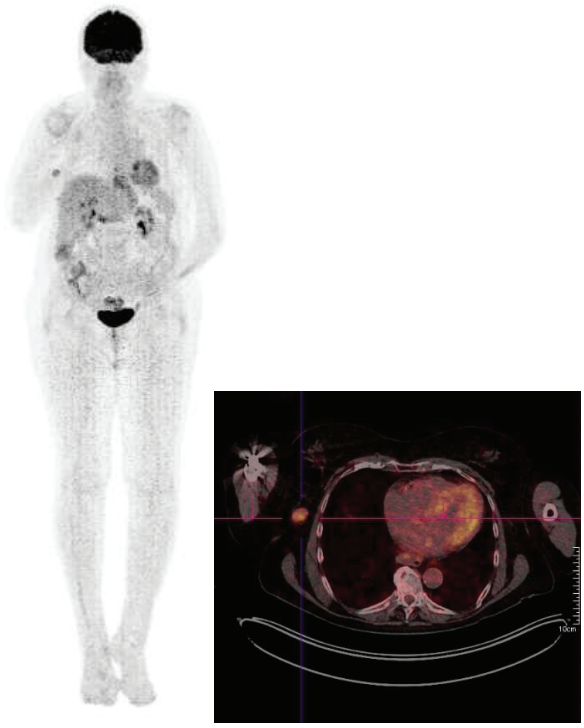

Figure 1A. Intensive FDG uptake in the tumor of the right breast. No primary cutaneous lesion detected.

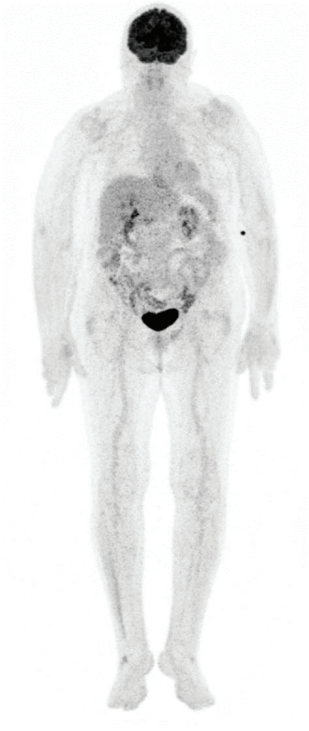

Figure 1B. Follow up F-18 FDG PET/CT after 4 years – no disease recurrence.

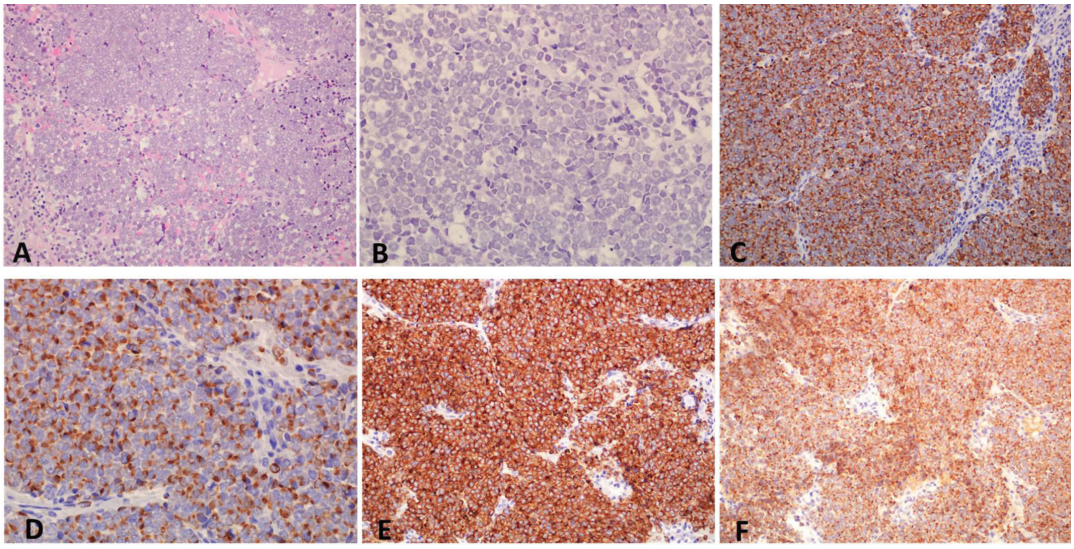

Figure 2. (A, B) Nests of basophilic tumor cells displaying round nuclei, powdery chromatin, scant cytoplasm, and nuclear molding, hematoxylin and eosin magnification ×100 and ×400. (C) Positive membranous CKAE1/AE3 immunostaining, magnification ×100. (D) Positive CK20 perinuclear dot-like immunostaining, magnification ×400. (E) Positive synaptophysin immunostaining, magnification ×100. (F) Positive chromogranin A immunostaining, magnification ×100.

examination, PET/CT scan, ultrasound, mammography) every 6 months revealed no disease recurrence during this 4-year period (Figure 1B).

In September 2021, a 66-year-old man was referred to our Clinic with clinically detectable painful left inguinal lymphadenopathy. Excisional biopsy was performed, and histopathology confirmed the diagnosis of mMCC (Figure 2). After an extensive clinical and imaging evaluation (PET/CT scan), which confirmed disseminated disease (Figure 3A), initial treatment with the programmed cell death ligand 1 inhibitor (anti PD-L1) avelumab was proposed. The first cycle consisting of seven intravenous applications, and was applied in October 2021. After one year

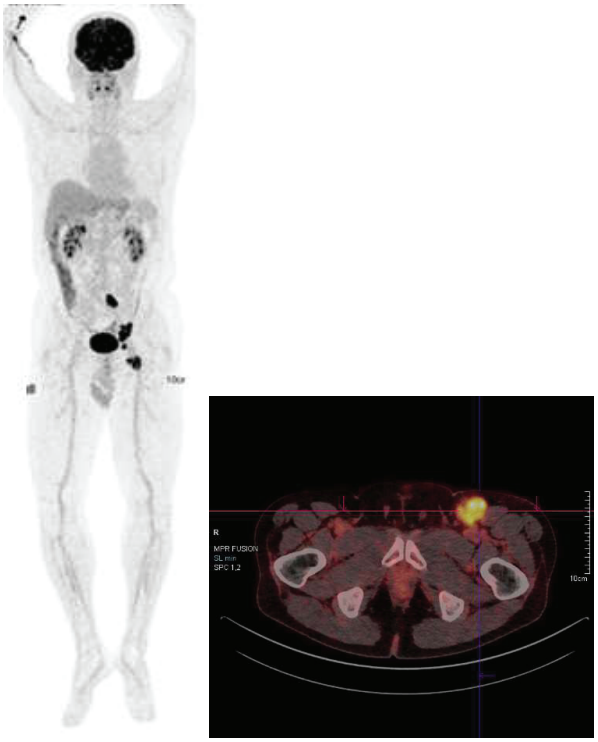

Figure 3A. Intense FDG uptake in the left iliac lymph nodes and left inguinal nodes. No primary cutaneous lesion.

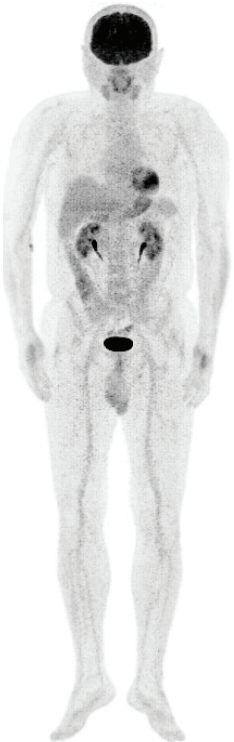

Figure 3B. Follow-up F-18FDG PET/CT after 18 months demonstrates complete response to therapy.

and completion of the third cycle of therapy, imaging assessment (PET-CT scan) detected a solitary lesion in the pancreas. Fine needle aspiration biopsy confirmed a distant metastasis of MCC that was later treated with stereotactic radiosurgery. The fourth cycle of immunotherapy was completed in March 2023. No treatment-related adverse events were noted during these 18 months of follow-up. Recent PET/CT scans demonstrated scaring tissue in the pancreas with no signs of locoregional or distant metastatic disease (Figure 3B).

Management of MCC should be individualized based on the specific pattern of disease presentation. The presence of nodal disease is one of the most powerful predictors of overall survival and risk for developing distant metastatic disease (3-4).

Multidisciplinary tumor board discussions are mandatory for the management of advanced MCC.

New emerging treatment options have once again returned focus to this rare and highly-aggressive entity. Until recent years, mMCC was managed with extensive surgery, radiotherapy, or chemotherapy, but responses were not durable (1). Based on new clinical trials, immunotherapy has now become a rational and promising treatment option and is considered as first-line treatment in patients with advanced MCC (5). The management of patients with MCC of unknown primary origin should adhere to that for patients with an identifiable primary tumour (6).

Although cutaneous manifestations are the hallmark of MCC, only a minority of cases have been reported in the literature without any cutaneous involvement (7-10). Our cases highlight this unusual presentation of MCC that could be misleading and contribute to delayed diagnosis. We therefore emphasize the importance of considering rare forms of malignancies such as MCC even in the absence of a primary cutaneous lesion.

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