SHORT COMMUNICATION

A Challenging Diagnosis of Merkel Cell Carcinoma Occurring in the Lymph Nodes and Skin of a Patient with Mantle Cell Lymphoma: A Case Report

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Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine carcinoma of the skin caused by either Merkel cell polyomavirus (MCPyV) or ultraviolet (UV) damage. It presents as a firm, non-tender, rapidly growing papule or nodule, usually in men over the age of 50 years; other risk factors include immunosuppression and cumulative sun exposure (1). MCC has a disease-specific mortality rate of 33% at 3 years and a high overall recurrence rate at 40%, with a tendency to metastasize rapidly to lymph nodes and distant organs (1–3). This skin cancer thus requires close surveillance with physical examinations and imaging.

Mantle cell lymphoma (MCL) accounts for approximately 2–10% of B-cell lymphoma subtypes. It mainly affects older adults (median age 68–69 years), usually males. It is a moderately aggressive lymphoma of nodal sites with frequent dissemination to extranodal sites, including bone marrow, spleen, gastrointestinal tract, and liver. Patients usually present with advanced (stage III/IV) disease at diagnosis (4). Cutaneous involvement affects approximately 1% of patients with MCL, and usually indicates systemic disease (5). Lesions present as flesh-coloured or erythematous plaques or nodules (5). Diagnosis is made via biopsy, although skin lesions may show increased uptake on positron emission tomography-computed tomography (PET/CT). Most cases are associated with a t(11;14)(q13;q32) translocation resulting in overexpression of cyclin-D1 and oncogenesis (4).

Because both MCL and MCC can present in the skin and lymph nodes, distinguishing the two presents a clinical challenge when coincident in the same patient. We describe here a challenging case of a patient with known MCL in the skin and lymph nodes who developed MCC in a lymph node.

CASE REPORT

A 75-year-old man presented to the dermatologist with an erythematous, tender papule on his left upper back (**Fig. 1**). Punch biopsy demonstrated MCL, which was confirmed by bone marrow biopsy. Cytogenetics revealed the hallmark t(11;14)(q13;q32) translocation. The patient was diagnosed with stage IV MCL and treated with radiotherapy.

Four years later, he developed an enlarged left inguinal lymph node that was initially soft and painful, then became hard and non-tender. Lymph node excision revealed the presence of both MCC and MCL (**Fig. 2**). Histopathological examination demonstrated an effaced lymph node with significant crush artefact entirely replaced by 2 distinct tumour cell populations. One population was composed of cohesive clusters and diffuse sheets of large epithelioid

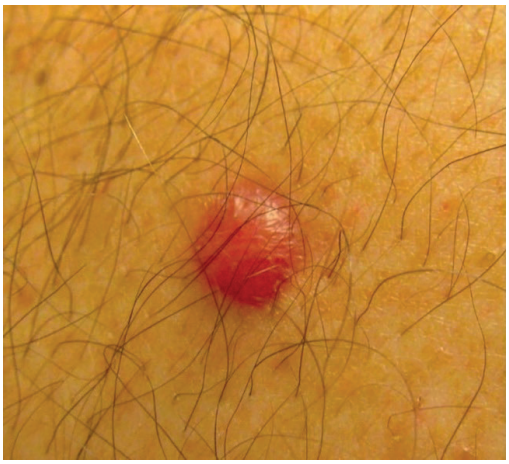

Fig. 1. The patient first presented with a small, erythematous tender 7 mm papule that was biopsied and diagnosed as cutaneous mantle cell lymphoma (MCL).

tumour cells with basophilic nuclei, granular chromatin, indistinct nucleoli, and scant cytoplasm (Fig. 2A–B). Immunohistochemistry showed that these basaloid tumour cells stained positively for CK20 and AE1/AE3 in a perinuclear dot-like pattern and neuroendocrine markers chromogranin A and synaptophysin, consistent with a diagnosis of metastatic MCC (Fig. 2C–D). Admixed was a second population composed of clusters of small to intermediate-sized monomorphic lymphoid cells with irregular nuclear contours, condensed chromatin, distinct nucleoli, and small amounts of cytoplasm (Fig. 2E). Immunohistochemistry confirmed these atypical lymphoid cells were CD20-positive, PAX5-positive B cells that co-expressed CD5 and cyclin D1, consistent with MCL (Fig. 2F–G). Flow cytometry supported the diagnosis, and fluorescence in situ hybridization (FISH) analysis detected a *CCND1::IGH* rearrangement in a subset of cultured cells.

PET/CT revealed lymphomatous involvement above and below the diaphragm (**Fig. 3**). Thorough total-body examination revealed progression of cutaneous MCL, but no primary cutaneous MCC was identified. The patient's MCL specialist planned treatment of the MCL with rituximab and bendamustine; however, the MCC specialists expressed concern that further immunosuppression would exacerbate the patient's MCC. The pathologist clarified that MCC constituted the dominant component in the node, and MCC treatment with the programmed cell death protein 1 (PD-1) immune checkpoint inhibitor pembrolizumab was planned. However, prior to initiation, the patient presented to the emergency department with neck lymphadenopathy, abdominal pain, and left pelvic pain. CT showed bulky lymphadenopathy of the retroperitoneum and left inguinal and pelvic regions. Biopsies of left cervical and inguinal nodes demonstrated MCC and MCL. The patient was restaged from IIIA to stage IV MCC and started on pembrolizumab with rapid improvement.

He had a durable response of 13 months beyond his 1 year of treatment, until biopsy of an enlarged left pelvic node revealed

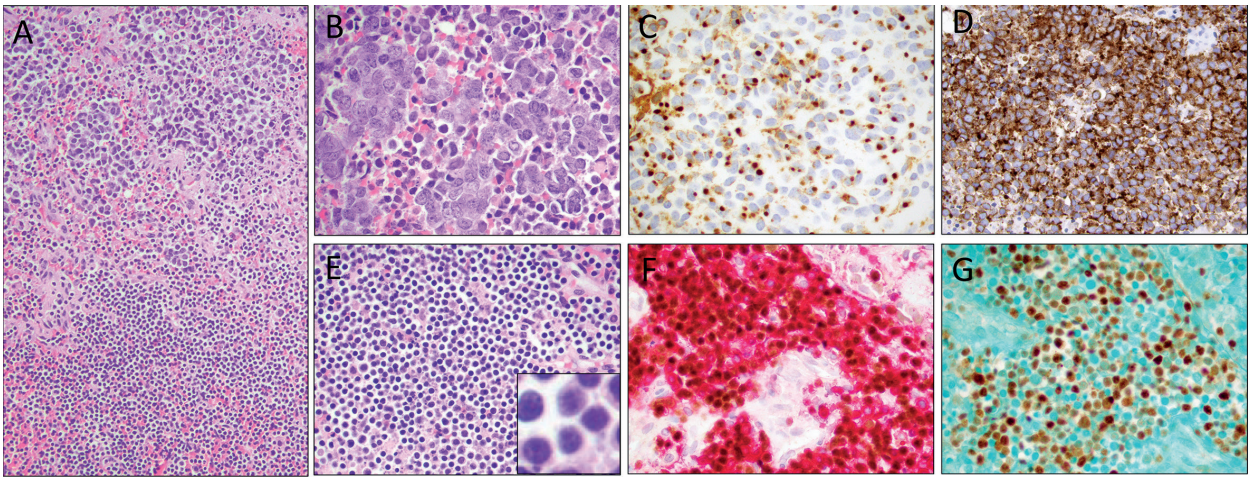

Fig. 2. Histopathological features of metastatic Merkel cell carcinoma (MCC) and mantle cell lymphoma (MCL) coexisting in an inguinal lymph node. (A) The haematoxylin and eosin (H&E)-stained sections show an effaced lymph node with 2 distinct tumour cell populations (H&E, ×200). There are cohesive clusters and diffuse sheets of large epithelioid cells with basophilic nuclei, granular chromatin, indistinct nucleoli, and scant cytoplasm (B; ×600). These basaloid tumor cells stain positively for both CK20 (C; ×600) and AE1/AE3 (not pictured) in a perinuclear dot-like pattern, and neuroendocrine markers chromogranin A (D; ×400) and synaptophysin (not pictured), consistent with MCC. (E) Admixed are large clusters of small to intermediate-sized monomorphic lymphoid cells that exhibit irregular nuclear contours, condensed chromatin, distinct nucleoli, and small amounts of cytoplasm (H&E, ×600; high magnification inset). These atypical lymphoid cells are PAX5-positive (brown chromogen) B cells that co-express CD5 (red chromogen) (F; ×600); cyclin D1 is also positive (G; ×600), consistent with MCL.

MCL and MCC. Pembrolizumab was restarted, resulting in a near complete response, but treatment was discontinued due to new-onset diabetes insipidus. Eight months later, the patient developed exquisitely tender plum-coloured firm indurated papules on the skin of the bilateral mons pubis with significant inguinal lymphadenopathy and scrotal oedema. Biopsy confirmed MCC with a background of MCL. The patient received radiotherapy and etoposide, but his performance status declined significantly as his disease progressed. At a follow-up appointment, he was found to be tachycardic, tachypneic and febrile to 38.3°C, and was subsequently admitted for *Salmonella* bacteremia. He died several weeks later.

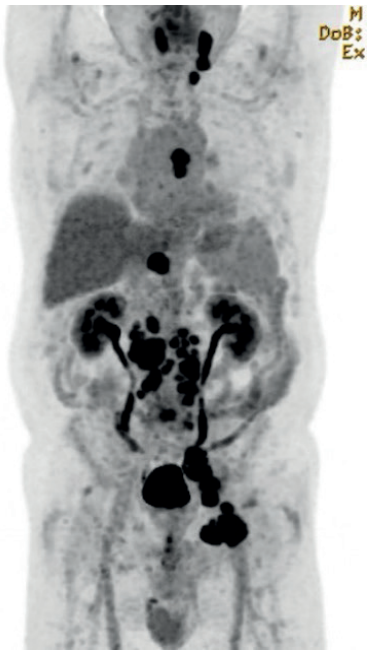

Fig. 3. Staging positron-emission tomography-computed tomography showed fluorodeoxyglucose-avid lymphadenopathy along the cervical chain, above and below the diaphragm, and in the left groin, the largest measuring approximately 4.5 x 4.5 cm.

DISCUSSION

MCL rarely manifests in the skin, while MCC often first presents as a skin or subcutaneous nodule or papule. The higher incidence of MCC in chronically immunosuppressed patients, such as those with organ transplants, HIV, or haematological malignancies, is well established (1, 2). Several studies estimate a 3.4–10.2-fold elevated risk of developing MCC after lymphoproliferative disorders, most commonly non-Hodgkin lymphoma (NHL) (1, 6, 7). One study of patients with MCC identified in the Surveillance, Epidemiology, and End Results (SEER) national database found that 90 (2.5%) out of 3,613 patients with MCC had a history of lymphoma, and those with NHL who subsequently developed MCC had a significantly lower overall survival rate (8).

The unusual presentation of metastatic MCC of uknown primary site co-occurring in a lymph node with MCL may have posed a diagnostic challenge on histology alone. However, the use of immunohistochemistry and ancillary studies, including flow cytometry and cytogenetics, confirmed these concurrent diagnoses. Importantly, MCC tumour cells express epithelial antigens, most characteristically low molecular weight keratins and cytokeratin-20, and neuroendocrine markers, such as chromogranin A and synaptophysin, and do not express most lymphoid markers. Still, several markers, including TdT, PAX5, CD56, CD117, and BCL-2, can be positive in both MCC and various haematological malignancies (9). In fact, recent literature has identified an association between expression of pre-B and B-cell markers such as TdT, PAX5, and CD117 with MCPyV (10). As MCC is rapidly fatal if not diagnosed and treated promptly, the dermatopathologist played a critical role in the clinical course of this patient.

Concurrent MCC and haematological malignancy can also pose a treatment challenge. In the current case we prioritized MCC treatment (with pembrolizumab) given the greater involvement of MCC in the lymph nodes. Furthermore, this recognition helped avoid the usual treatment of rituximab for MCL, which has been associated with rapid growth of MCC (11–14). Skin cancer patients with concurrent haematological malignancies also tend to have lower response rates to anti-PD-1 immunotherapy, which is first-line for unresectable MCC (15). For these patients, other treatment avenues may need to be explored, keeping in mind the importance of avoiding exacerbation of 1 disease while treating the other. MCC in the setting of haematological malignancy can present a diagnostic and clinical challenge. Pathologists and clinicians should be aware that MCC can be co-incident with MCL in order to aid in diagnosis of this aggressive skin cancer.

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The authors have no conflicts of interest to declare.

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