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Nodal Merkel Cell Carcinoma in Head and Neck Lesions with an Unknown Primary: A Case Report in Light of the Literature

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ABSTRACT

Merkel cell carcinoma (MCC) is a rare but aggressive neuroendocrine skin cancer. To diagnose nodal MCC with an unknown primary disease is challenging, and it has to be separated from other nodal metastatic neoplasms. We report a unique case of nodal MCC in head and neck lesions with an unknown primary. A 70-year-old woman was admitted to our department with a right submandibular mass. Fine needle aspiration biopsy was performed and indicated malignancy. F-18-fluorodeoxyglucose positron emission tomography (PET) demonstrated abnormal accumulation in the right submandibular lymph node, right palatine tonsil, and right thyroid gland. For diagnostics and treatment, bilateral selective neck lymph node dissection, right tonsillectomy, and right thyroidectomy were performed. Histopathological examination revealed that most parts of the submandibular lymph node were occupied by diffuse sheets of tumor cells. Contrary to our expectation, malignant cells were not detected in the right palatine tonsil and right thyroid. Immunohistochemistry demonstrated a marked positive reaction for AE1/AE3, chromogranin A, synaptophysin, cytokeratin 20 (CK20) and CD56 and a negative reaction for vimentin, leucocyte common antigen (LCA), thyroid transcription factor-1 (TTF1) and cytokeratin 7 (CK7) in the tumor cells. Immunostaining of Merkel cell polyomavirus-large T antigen (MCPyV-LT) showed a positive reaction and MCPyV-positive MCCs were assessed by PCR analysis, demonstrating that viral copy number was 12.8 copies per cell. These histological findings confirmed the diagnosis of Merkel cell carcinoma of the lymph node. In cases of tumors in the lymph node with a neuroendocrine appearance in head and neck lesions, it is necessary to eliminate the possibility of metastasis from MCC.

Key words head and neck; lymph node; Merkel cell carcinoma; neck lymph node dissection; neuroendocrine tumor

Merkel cell carcinoma (MCC) is a rare but aggressive neuroendocrine skin cancer.[1–3] Although Merkel cells are believed to be the source of MCC, the cells of origin in MCC remain a controversial issue. Uncommonly, cases of high-grade neuroendocrine tumors have been encountered in lymph nodes with unknown extra-nodal primary disease, and these tumors are usually described as 'nodal MCC with unknown primary'.[4–7] However, it has been unclear whether nodal MCC is a primary tumor of the lymph node itself or if it represents a metastasis from an occult or regressed extra-nodal lesion. Here, we present a unique case of nodal MCC in a head and neck lesion with an unknown primary.

PATIENT REPORT

A 70-year-old woman was admitted to our department with a right, 3 cm round and immobile submandibular mass. Computed tomography revealed that 3 cm and 2cm mass were observed in the right submandibular. Endoscopic examination did not reveal any primary lesion in head and neck regions. Fine-needle aspiration biopsy (FNA) of submandibular mass was performed and revealed that the gathered individual cells had a nucleus with irregular contour and fine chromatin, with a high nucleo-cytoplasmic and thin perinuclear edges. These findings were not in accordance with typical squamous cell carcinoma (SCC) and malignant lymphoma and metastasis of neuroendocrine tumor was firstly considered (Fig. 1). For detection of primary lesion and staging, F-18-fluorodeoxyglucose positron emission tomography

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Abbreviations: CBDCA, carboplatin; CD, cluster differentiation; CK20, cytokeratin 20; CPT-11, irinotecan; CT, computed tomography; FNA, fine-needle aspiration biopsy; LCA, leucocyte common antigen; MCC, Merkel cell carcinoma; MCPyV-LT, Merkel cell polyomavirus-large T antigen; MRI, magnetic resonance imaging; PET, F-18-fluorodeoxyglucose positron emission tomography; SCC, squamous cell carcinoma; TTF1, thyroid transcription factor-1; VP-16, etoposide

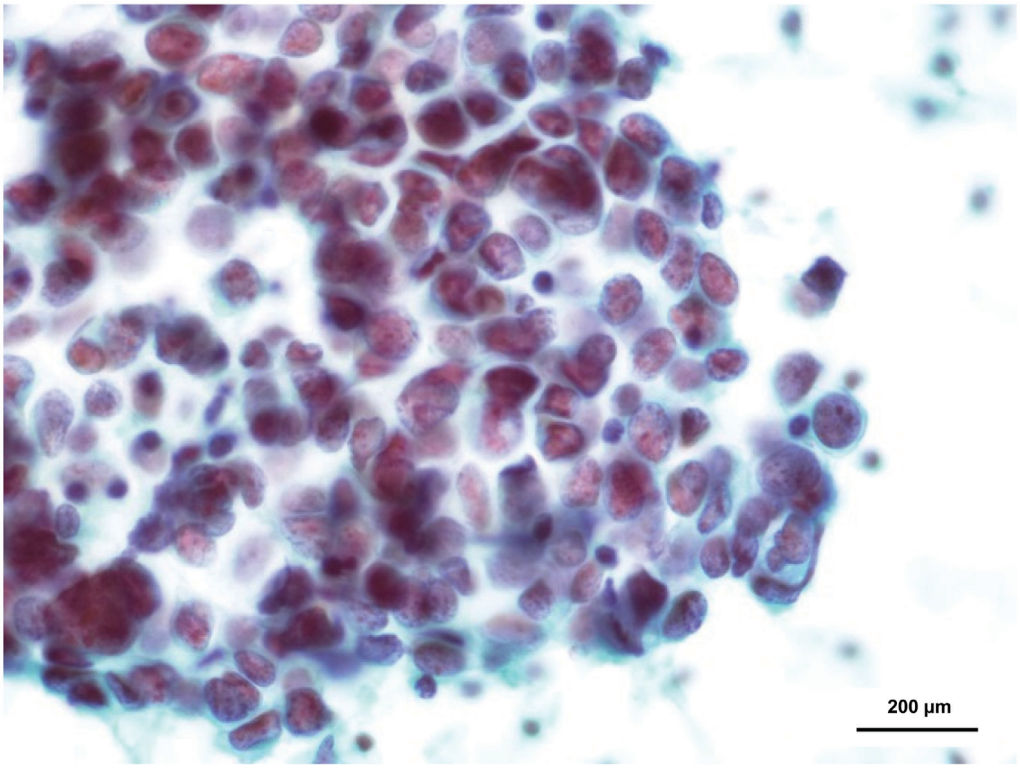

Fig. 1. Fine-needle aspiration biopsy (FNA) revealed that the individual cells had a nucleus with irregular contours and showed fine chromatin.

(PET) was conducted. PET demonstrated abnormal accumulation in the right submandibular lymph node, right palatine tonsil, and right thyroid gland (Fig. 2). The serological data showed serum ProGRP 155.8 pg/mL (baseline: 0–81), NSE13.7 ng/mL (baseline: 0–16.3). For diagnostics and treatment, bilateral selective neck lymph node dissection (I–V), right tonsillectomy and right thyroidectomy were performed. Histopathological examination revealed that most parts of the lymph node were occupied by diffuse sheets of tumor cells. Moreover, the tumor cells were uniformly small rounded cells with scanty cytoplasm and had a round to oval nucleus with dispersed chromatin, and inconspicuous nucleoli in right IB, IIA and IIB lymph nodes (Fig. 3). Contrary to our expectation, malignant cells were not detected in the right palatine tonsil and right thyroid gland. Immunohistochemistry demonstrated a marked positive reaction for AE1/AE3, chromogranin A, synaptophysin, cytokeratin 20 (CK20) and CD56 and a negative reaction for vimentin, leucocyte common antigen (LCA), thyroid transcription factor-1 (TTF1) and CK7 in the tumor cells (Fig. 4). The Ki-67 staining index ranged from 50 to 60%. Immunostaining of Merkel cell polyomavirus-large T antigen (MCPyV-LT) showed a positive reaction and MCPyV-positive MCCs were assessed by PCR analysis, demonstrating that the viral copy number was 12.8 copies per cell (Fig. 5). These histological findings confirmed the diagnosis of nodal MCC in head and neck lesions with primary unknown (stage IIIA). The patient underwent treatment with carboplatin (CBDCA) and irinotecan (CPT-11) chemotherapy. Right superior deep lateral cervical lymph node swelling was observed eight months after the initial treatment. Resection of the lymph node was performed and histological findings confirmed the same results as the initial surgery. She has since undergone treatment with CBDCA and etoposide (VP-16) chemotherapy and radiation therapy (60Gy/25 fractions). Two years later, the patient was in good clinical conditions without recurrence.

DISCUSSION

Nodal MCC with unknown primary is defined as neuroendocrine carcinoma in lymph nodes with microscopic, immunohistochemical, and genetic features similar to those of cutaneous MCC.[8–10] In our case, we initially could not diagnose MCC based on morphological features. However, FNA was very useful as a diagnostic tool in differential diagnosis from SCC and malignant lymphoma. It is generally difficult to diagnose MCC

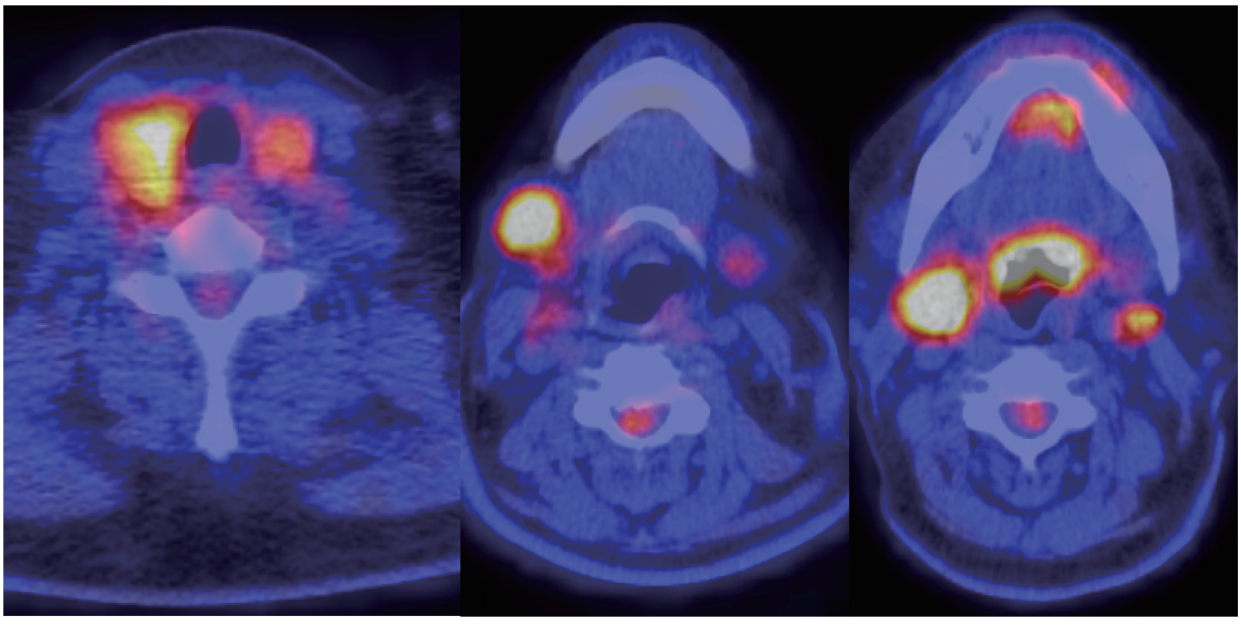

Fig. 2. F-18-fluorodeoxyglucose positron emission tomography (PET) confirmed the presence of abnormal accumulation in the right submandibular lymph node, right palatine tonsil, and right thyroid gland.

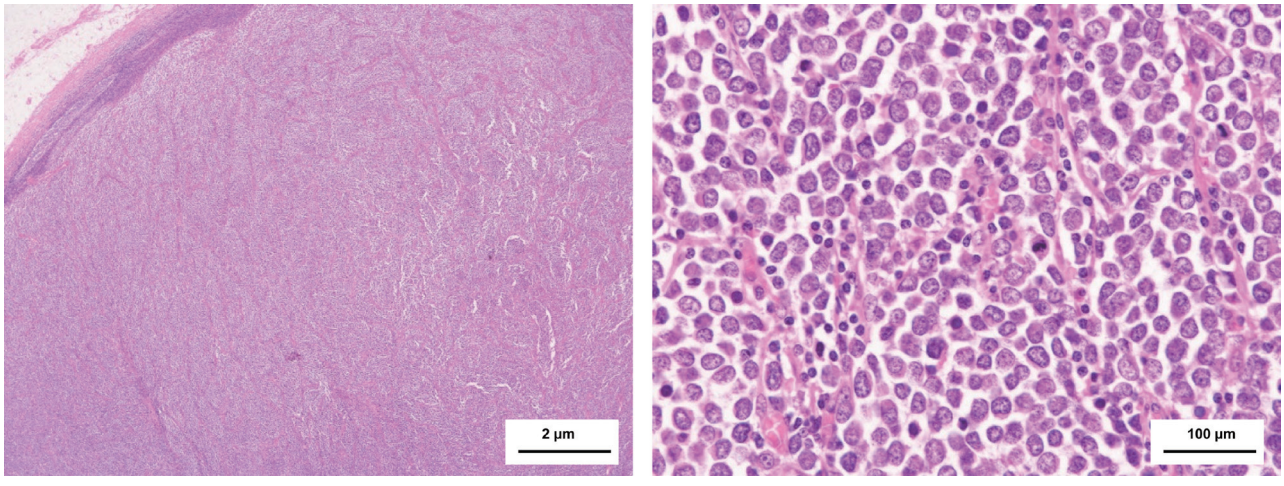

Fig. 3. Histology showed most parts of the lymph node were occupied by tumor, nodules and diffuse sheets of eosinophilic cells with imperceptible cytoplasm, a round nuclei and dispersed chromatin (hematoxylin and eosin stain).

solely by morphologic characteristics. Therefore, several metastatic tumors should be considered in the differential diagnosis such as metastatic neuroendocrine carcinoma including small cell carcinoma from the lung or genitourinary tract, malignant melanoma, B-cell lymphoblastic lymphoma, and mature B-cell lymphoma. Immunohistochemistry is also a key tool to identify the diagnosis of MCC. MCC is positive for neuroendocrine markers such as synaptophysin, chromogranin A and CD56. However, the specificity of these markers is low. In our case, the cells were positive for synaptophysin and chromogranin A, but negative for CD56. CK20 and TTF-1 are useful in distinguishing MCC from metastatic small cell carcinoma. CK20 is a low molecular weight cytokeratin that is only expressed in normal gastrointestinal epithelia, urothelia, and Merkel cells. MCC almost always stains with CK20 in contrast to metastatic SCC.[11] TTF-1 is described as a nuclear transcription factor expressed in epithelial cells of the thyroid and lung. It is expressed in a high proportion of SCC and is not expressed by MCC.[12] Most cases of MCC are CK7-negative, but a significant

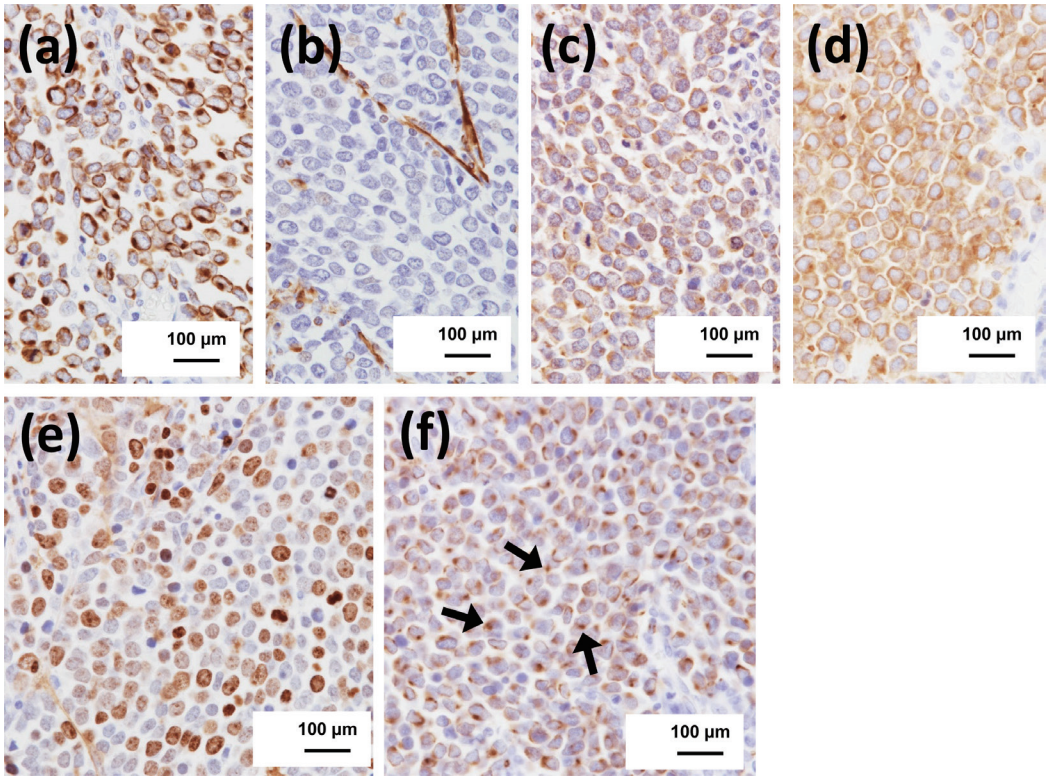

Fig. 4. Immunohistochemistry of AE1/AE3 (**a**), vimentin (**b**), chromogranin A (**c**), synaptophysin (**d**), Ki67 (**e**) and CK20 (arrows: positive cells) (**f**).

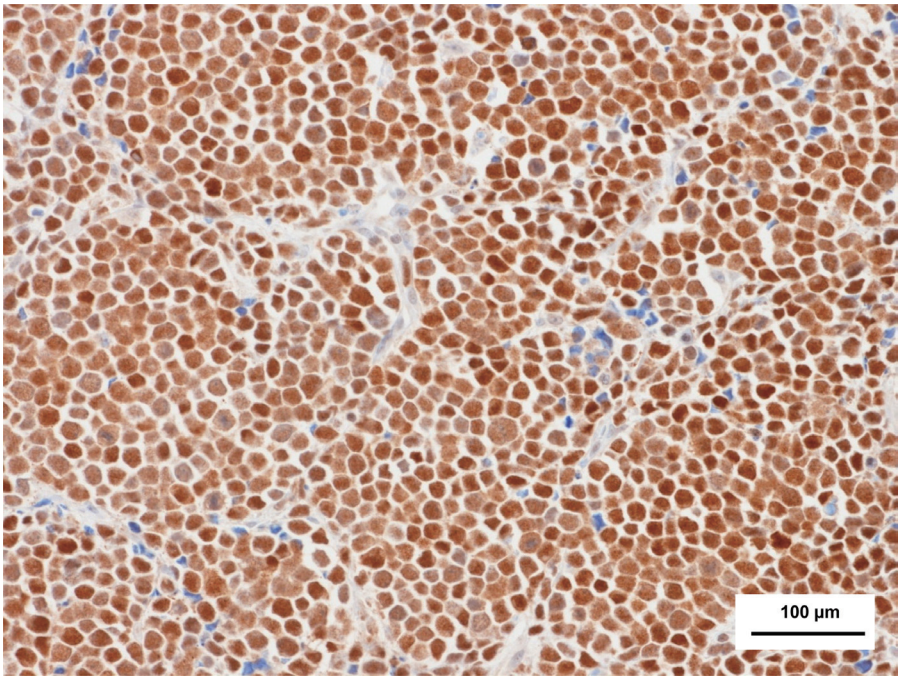

Fig. 5. Immunohistochemistry of MCPyV-LT (Merkel cell polyomavirus-large T antigen).

minority exhibit partial CK7 positivity. CK-7 was negative in our case. MCPyV is a non-enveloped double-stranded DNA virus associated with the pathogenesis of MCC.[13, 14] It is suggested that clonal integration of a polyomavirus might be involved in pathogenesis of MCC.[13] MCPyV-LT is highly specific for MCC and the overexpression of MCPyV was also detected in our case. Detection of MCPyV-LT is clinically important and might help physicians in the diagnosis of MCC. These findings may allow us to speculate that MCPyV might contribute to the pathogenesis of MCC and MCPyV-LT might be used as an additional indicator of MCC. Patients with nodal MCC have a better prognosis than those with metastatic nodal MCC and a concurrent primary tumor.[15–19] Surgical excision of the primary lesion and additional chemotherapy remain central in the treatment of nodal MCC with primary unknown. In recurrent cases, chemotherapy and radiotherapy have been standard treatment modalities.[18, 19] A different regimen from initial treatment was selected from consideration of drug sensitivity in our case. However, recent reports demonstrated that PD-1 and PD-L1 inhibitors have been shown to be superior to other systemic treatments for MCC in advanced stages.[1, 2] The use of these therapies are thus first-line treatment in advanced stages, especially because the side effects of these substances are generally easily controlled.[2]

The authors declare no conflict of interest.

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