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A Unique Case of Merkel Cell Carcinoma with Ovarian Metastasis

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Background: Merkel cell carcinoma (MCC) is a rare cutaneous/mucosal malignancy with very aggressive biology and increasing incidence. Ovarian metastasis is an exceptionally rare site for MCC, and only two cases have been reported in the literature.

Case Report: We report MCC with ovarian metastasis. A 34 year-old female with previously excised MCC from preauricular skin presented with a pelvic mass 15 months after first diagnosis. Anti-cytokeratin (CK) 20 positivity, LCA (leucocyte common antigen), and TTF-1 (Thyroid transcription factor-1) negativity confirmed metastatic ovarian MCC. There was no evidence of recurrence or metastasis at 12 months after salpingo-oopherectomy.

Conclusion: MCC should be considered in the differential diagnosis of primary and metastatic undifferentiated small round cell tumors of the ovary.

Key Words: Carcinoma, Merkel cell, metastasis ovarian, neoplasms

Merkel cell carcinoma (MCC) is a rare, aggressive cutaneous and mucosal malignancy that was first described by Toker in 1972 as "trabecular carcinoma" (1). It has shown an increasing incidence from 0.15 to 0.44 cases per 100,000 between 1986 and 2001 in the United States (2). Mortality has been reported to be 30% at 2 years and 50% at 5 years after diagnosis (3). Patients frequently present with recurrence, regional lymph node metastasis, and distant metastasis. Common metastatic sites are the liver, lungs, bones, and brain. Rarely, metastasis to the gastrointestinal system (4), heart (5), tonsil (6), spinal cord (7), testis (8), and orbita (9) have been reported as case reports.

Ovaries are common sites for metastatic malignancies, mostly from colon, stomach, appendix, breast and the genitourinary tract. Previously, two cases with MCC metastasis to ovary has been reported in years 1985 and 1993 (10, 11). We present this unique case with clinical and pathologic features.

CASE PRESENTATION

A 34 year-old woman was admitted to Ear-Nose-Throat department of our institute with a painless nodular mass in the right lower auricular region. She had a 0.7 cm subcutaneous firm, reddish nodule at a defined location. Microscopic evaluation of excisional biopsy revealed dermal infiltration of a homogeneous, poorly differentiated solid tumor (Figure 1). The tumor cells had scant cytoplasm and nuclei with coarse chromatin and micronucleoli. A "salt and pepper" pattern was seen in some nuclei (Figure 2). The epidermis was preserved with no epidermotropism. Immunohistochemically, antibodies against cytokeratin, CD56 (Novocastra, CD564, Newcastle upon Tyne, England), neuron-specific enolase (NSE; Dako, BBS/NC/VI-H14, Glostrup, Denmark), chromogranin (BioSB, clone N/A, Santa Barbara, USA), and cytokeratin 20 (CK20; Novocastra, Ks20.8, Newcastle upon Tyne, England; paranuclear dot-like) were positive in the tumor cells (Figure 3). Immunohistochemical staining with CD99 (Biogenex, HO36.1.1, The Hague, Netherlands), LCA (leucocyte common antigen; Dako, 2B11+PD7/26, Glostrup, Denmark), Tdt (Novocastra, SEN28, Newcastle upon Tyne, England), and TTF-1 (Thyroid transcription factor-1; Novacastra, SPT24, Newcastle upon Tyne, England) were performed for differential diagnosis from primitive neuroectodermal tumor (PNET), malignant lymphoma, leukemia, and small cell carcinoma of the lung, and they were found to

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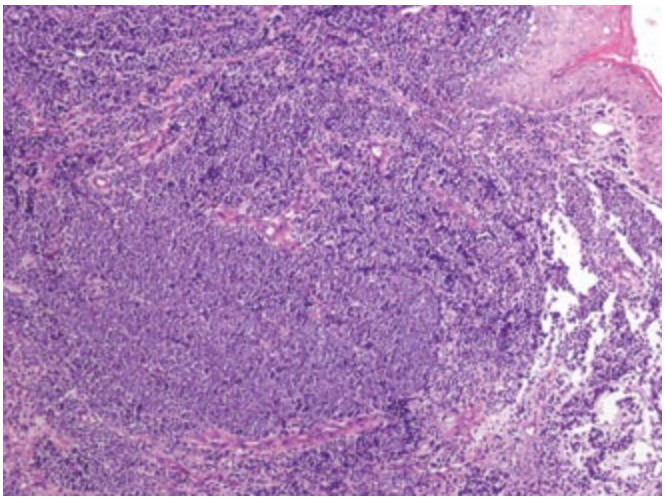

FIG. 1. Merkel cell carcinoma consisting of discohesive, undifferentiated, small, round cells infiltrating dermis. The epidermis is preserved (HE, X40)

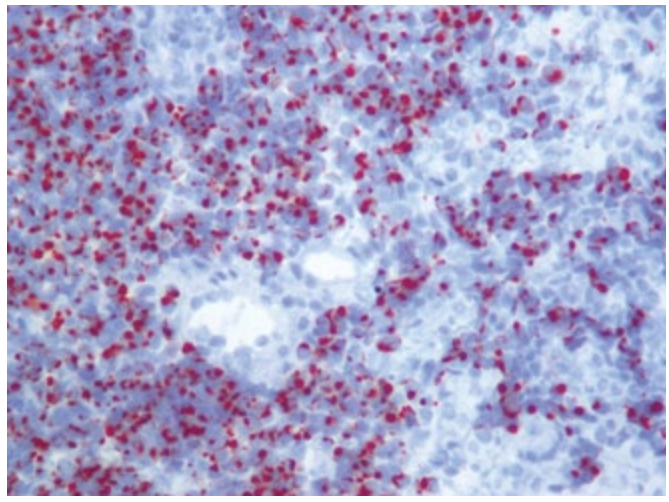

FIG. 3. Characteristic paranuclear dot-like staining by CK20 in tumor cells (Immunohistochemistry, X400)

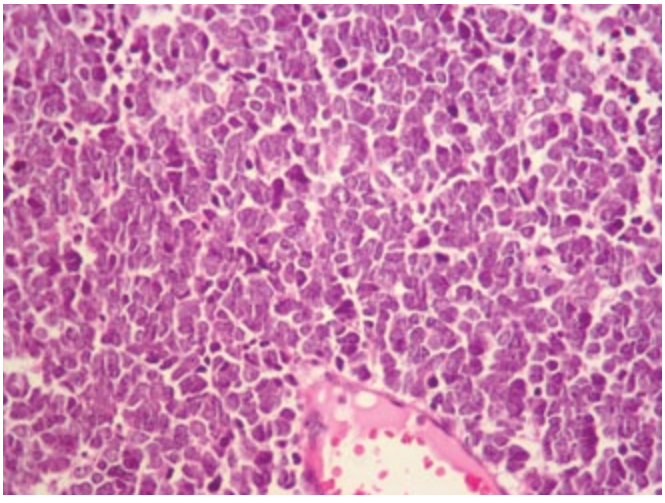

FIG. 2. Tumor cells have scant cytoplasm and round nuclei with coarse chromatin. Increased apoptosis and mitotic figures are present (HE, X400)

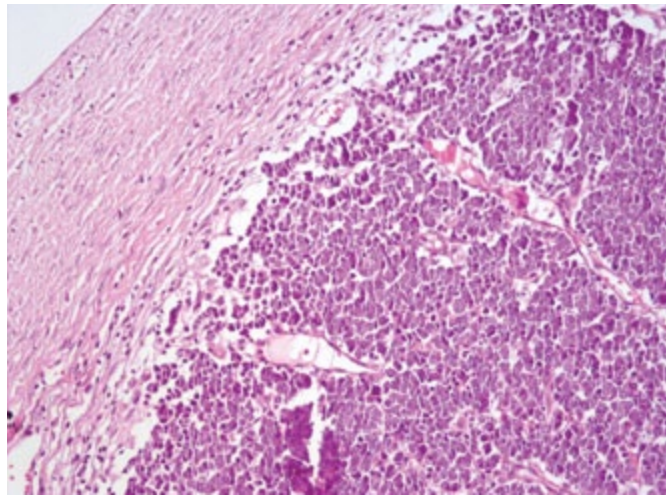

FIG. 4. The ovarian cortex is infiltrated by undifferentiated, small, round cell tumors (HE, X100)

be negative. Immunohistochemical staining was performed using an automated immunohistochemistry staining instrument (Ventana, Benchmark XT, USA).

The patient underwent lower airucular resection and right cervical lymph node dissection, and no metastatic lymph node was detected. After surgery, she received total 4500 cGy (25 fr x180 cGy) radiotherapy (RT). One month after RT, she received four cycles (once in three weeks) adjuvant chemotherapy consisting of 80 mg/m^2 cisplatin (day 1) plus 80 mg/m^2 etoposide (days 1-3).

Fifteen months after the initial diagnosis, she presented with pelvic pain. Radiologically, a 10x9x8 cm solid mass that was superior to the bladder and suggestive of a mesenchymal tumor or metastasis was observed. She underwent surgery at the department of gynecologic-oncology. Written informed consent was obtained from the patient before operation. Intra-operatively, a 12x8 cm solid mass in the left ovary was observed. The right ovary and uterus were normal. A frozen section was reported as a metastatic tumor and a left salpingo-oopherectomy was performed. Paraffin section diagnosis was MCC metastasis to the left ovary. Microscopically, the ovarian stroma was replaced by an undifferentiated small round cell tumor with narrow cytoplasm and coarse chromatin, and inconspicuous nucleolus (Figure 4). Immunohistochemically, CK20 was paranuclear positive, while TTF-1 and LCA were negative. Any other component regarding an associated ovarian teratoma or other primary ovarian tumor was not detected.

After operation, she received six cycles of chemotherapy (once in three weeks) consisting of 1 g/m^2 cyclophosphamide

TABLE 1. Differential diagnosis of ovarian small round cell tumors by immunohistochemistry

	Cytokeratin	Vimentin	LCA	MPO	HMB45	TTF1	CD99
Primary tumors							
SCC, hypercalcemic type	+	+	-	-	-	-	-
SCC, pulmonary type	+	-	-	-	-	+/-	-
Secondary tumors							
Lymphoma	-	-	+	-	-	-	-
Granulocytic sarcoma	-	-	+	+	-	-	-
SCC of the lung	+	-	-	-	-	+	-
PNET	-	+	-	-	-	-	+
Melanoma	-	-	-	-	+	-	-

SCC: small cell carcinoma; LCA: leucocyte common antigen; MPO: myeloperoxidase; TTF-1: thyroid transcription factor-1; PNET: primitive neuroectodermal tumor

+: positive for the antibody; -: negative for the antibody

plus 1.4 mg/m^2 vincristine plus 40 mg/m^2 doxorubicine. She is doing well with no recurrence or metastasis at 12 months after salpingo-oopherectomy.

DISCUSSION

Merkel cell carcinoma usually occurs in elderly patients, predominantly on sun-exposed areas of the head and neck (47-30%), followed by extremities (40%) and the trunk (5-10%) (12). Chronic immunosuppression, such as that caused by HIV infection, organ transplantation, malignant lymphoma, or chemotherapy for solid tumors, has increased the risk of MCC. Our case did not have any of these risk factors. Recently described Merkel cell polyomavirus (MCPyV) was identified in most cases with MCC. We did not investigate the presence of the virus in the present case.

The origin of MCC is still not clear. Immunohistochemical and ultrastructural findings have verified the neural crest origin of the Merkel cells (MCs), which have potential for both neuro-endocrine and epithelial differentiation. Recently, it was suggested that MCs arise from epidermal progenitors during embryonic development. In adults, they mature and then are replaced from an epidermal stem cell source, rather than from the proliferation of differentiated MCs (2). Positivity for CD56, chromogranin, and NSE is supportive for neuroendocrine differentiation of the tumor cells in both primary and metastatic sites.

Skin presentation of MCC is clinically nonspecific and indistinguishable from other non-melanocytic benign and malignant skin tumors. Histopathologic and immunohistopathologic evaluation is always required for an exact diagnosis. Considering the high metastatic potential of this tumor (34-75%), MCC should be kept in mind in differential diagnosis of metastatic tumors with unknown primary. Metastasis of MCC to various parts of the body has been reported. Although ovaries are common sites for metastasis of particular tumors, such as gastrointestinal, genitourinary, and breast carcinomas, metastasis of MCC has been previously published in only two cases (10, 11). Primary sites of both cases were inguinal skin. In the first case, a 62 year-old female showed frequent recurrences and she was operated on for a right iliac mass involving the right ovary one year after first being diagnosed (10). In the second case, a 34 year-old female had metastasis to the left ovary one month after first diagnose (11). Different from these two reported cases with local metastasis, our case showed distant metastasis from preauricular skin 15 months after first diagnose.

Grossly, multinodularity and bilaterality of the ovarian tumor may be a suggestive, but not a diagnostic feature, for a metastatic tumor. This feature is not always valid, as was not in present case which had unilateral metastatic mass.

Histopathologically, MCC is a small, blue, round cell tumor. Therefore, microscopically, differential diagnosis includes identification of metastatic small cell carcinoma of the lung, which is TTF-1 positive, small cell lymphomas, which are LCA positive, primitive neuroectodermal tumor (PNET), which is CD99 positive, malignant melanoma, which is HMB-45 positive, neuroblastoma, which is neuroblastoma marker positive, and rhabdomyosarcoma, which is desmin-positive (Table 1).

Over all, differential diagnosis of the primary small cell carcinoma of the ovary was a challenge in our case. This tumor is a unilateral undifferentiated carcinoma of the ovary in females under the age of 40 years. Microscopically, tumor cells are closely packed and have scanty cytoplasm with small nuclei that contain micronucleoli similar to MCC cells. With adequate sampling, observing the distinctive follicle-like structures with luminal eosinophilic fluid and epithelial nature of the cells is generally helpful for the differential diagnosis. In the present case, a previous MCC history led us to study anti-CK20, which is characteristically paranuclear dot-like that is positive in MCC. CK20 is also positive in mature MCs, but the staining pattern is diffusely cytoplasmic, and this staining pattern is dif-

ferent from MCC cells. A recently described CM2B4 antibody, which recognises the large T (LT) antigen of the MCPyV, has been demonstrated in most of the cases with MCC (12).

In conclusion, distant metastasis of MCC to ovary is extremely rare. The evidence for exact and immediate diagnosis of MCC is to include this rare, but highly aggressive, tumor in the differential diagnosis of small, blue, round cell tumors, especially those that are metastatic.

Ethics Committee Approval: N/A.

Informed Consent: Written informed consent was obtained from the patients for the publication of this case report and any accompanying images.

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