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Merkel cell carcinoma with axillary metastasis; a case report of a rare disease

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ABSTRACT

Merkel cell carcinoma is a rare primer neuroendocrine carcinoma of the skin. It is an extremely aggressive tumor. This rare carcinoma is seen with high local and regional recurrence ratios and distant metastasis. We report that a 64 years old female patient who had undergo an excision in another center because of a mass on 4 cm proximal of her right elbow had been diagnosed with Merkel cell carcinoma with positive surgical margins. She was treated with wide re-excision and axillary dissection at our clinic.

1. Introduction

Merkel cell carcinoma (MCC), is a rare primary cutaneous neuroendocrine tumor originating from the basal layer of the skin which is associated with the terminal axons.[1,2] It is more common in the elderly patients. Although the tumor usually occur in sun exposed areas like head-neck region in 50% of the cases; it could occur in other parts of the body(3). It is seen as a painless, firm, ulcerated skin lesion usually smaller than 2 cm.[4] Having a poor prognosis, this tumor must be treated with wide surgical resection and lymphadenectomy.[2] Radiotherapy has been reported to aid achievement of local control.[5] Our case is a 64 year old female patient with axillary lymph node metastasis.

2. Case report

A 64 year old female patient noticed a 2 cm mass located 4 cm proximal to the elbow and underwent surgical excision in another hospital. The mass was diagnosed as Merkel cell carcinoma. The patient admitted to our clinic. An incision scar was seen on the right arm with lymph nodes fixed to surrounding tissue on the right axilla. Breast examination and other system examinations did not reveal any pathological findings. She had hypertension. No other disease was found in family history. She underwent mammography and ultrasound of the breast and the axilla. No pathological findings were noticed in the breasts in both of these radiological imaging modalities. Pathological lymph node were noticed in the axilla. The patient underwent wider resection encompassing the previous incision and axillary lymph node dissection under general anesthesia. The resection material was examined as frozen section and the surgical margins were found to be clear. The patient was discharged at the 4th postoperative day. Residual tumor progression was not observed in the pathological specimen. 5 out of 26 axillary lymph nodes had diffuse infiltration of pleomorphic cells with middle size, irregular nuclei, narrow cytoplasm, frequent mitosis; considered as metastatic(Fig. 1). Merkel cell carcinoma is a predominantly dermal-based tumor arranged in solid sheets and nests, composed of small, round to oval cells with vesicular nuclei, multiple small nucleoli and scant amphophilic cytoplasm.[17] There are numerous mitotic figures and apoptotic bodies. The histological differential diagnoses include other small, round, blue cell tumors such as metastatic small cell carcinoma of the lung, melanoma, lymphoma, leukemia cutis and basal cell carcinoma. On an IHC study performed by Sur *et al* on 15 MCC cases, the tumor cells were found to be positive for AE1/AE3 (100%), CAM 5.2 (100%), Ki-67 (100%), CK20 (93%), CD56 (100%), Bcl-2 (100%), Neuron specific enolase (NSE) (100%), synaptophysin (87%), chromogranin-A (73%), TdT (53%) and CD117 (53%) and were negative for TTF-1, Leukocyte common antigen (LCA), CD20, CD3 and CD34.[18] The tumor cells are also immunoreactive to neurofilament, Ber-EP4, EMA, Pax-5, and rarely CK7 and CD99.[17,18] CK20 is a sensitive and fairly specific immunomarker for MCC, showing membrane and paranuclear dot

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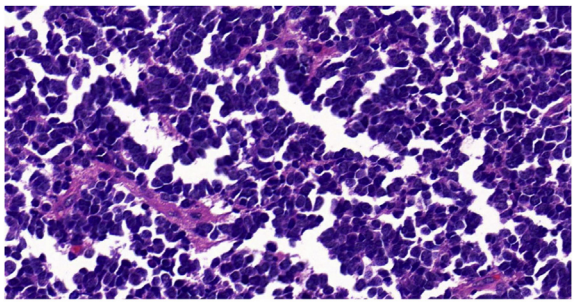

Fig. 1. Diffuse infiltration of pleomorphic cells with middle size, irregular nuclei, narrow cytoplasm, frequent mitosis; considered as metastatic.

positivity in the tumor cells In the immunehistochemical staining; the tumor cells were stained commonly with cytoplasmic synaptophysin and cytoplasmic point like CK20, less commonly with kromogranin-A and not stained by neither TTF-1 nor CK7. Ki67 index in the tumor cells were close to 100%(Fig. 2). This features were reported to be the metastasis of merkel cell carcinoma.

The patient was consulted with the department of medical oncology. The patient underwent PET-CT with 18F-FDG and no other pathological involvement was detected. Systemic chemotherapy was initiated with cisplatin and ethoposide. The patient is still followed by the departments of medical and surgical oncology.

3. Discussion

Merkel cell carcinoma is an aggressive tumor with poor prognosis.[4] It is seen as a painless, firm, solitary, red-purple colored small dermal nodule with a shiny surface and telengiectasias.[2] Mean age at diagnosis is 69. 50% of the cases are located in the head and neck region, 40% are located in the extremities and 10% are located at the trunk. Cases have been reported in the oral mucosa, larynx, esophagus, cervix and vulva.[3] 5 year median survival in patient with MCC is 50–68%.[4,6] Local recurrence (27–60%), lymph node involvement (45–91%) and distant metastasis (18–52%) are common.[4,7] This rare neoplasia originates from round shaped Merkel cells which are a derivative from neural crest cells. These cells are located at the basal layer of the epidermis and they include neurosecretory granules.[6]

Although the etiology of Merkel cell carcinoma is uncertain several risk factors have been identified. Exposure to UV radiation and skin cancers related with exposure to light (squamous cell carcinoma, basal cell carcinoma), exposure to arsenic and AIDS, chronic lymphocytic leukemia, congenital dysplasia syndrome and immune suppression after transplant surgery are among the risk factors(4–8). Our patient did not have any of these risk factors.

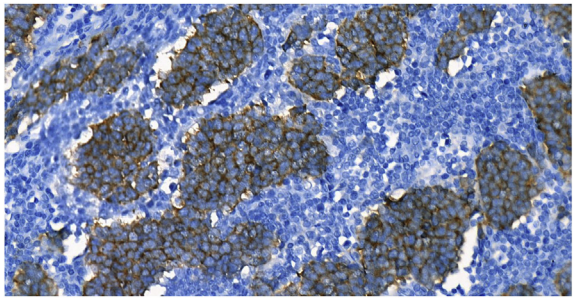

Fig. 2. Tumor cells were stained commonly with cytoplasmic synaptophysin and cytoplasmic point like CK20, less commonly with kromogranin-A.

Recently, Merkel cell polyomavirus has been associated with Merkel cell carcinoma.[9] Feng H. et al.[10] reported in 2008 that genomic integration of polyomavirus DNA was seen in 40–100% of the cases suggesting a role in the etiology of MCC. After this pioneer study, other studies on the relationship with polyomavirus and MCC have been undertaken, placing MCC into the neoplasia triggered by viruses.

There is no consensus on the treatment of Merkel cell carcinoma.[8,11] Treatment options vary according to the stage of the disease. Lymph node involvement is an important prognostic factor.[4,7] In the early stages, it is advised that the tumor is removed with at least 3 cm horizontal and 2 cm vertical margins.[4,7,11] Local recurrence is quite low in tumors smaller than 2 cm and excised with 2.5 cm clear surgical margins.[12] In our case, no tumor cells were observed in the excised tissue because of previous excision. Sentinel or routine lymph node dissection; or the utilization of adjuvant radiotherapy in patients without any lymph node involvement in the radiological studies is still controversial.[4,13] Radiotherapy is advised in patients with lymph node involvement, without clear surgical margins or patients not suitable for radiotherapy.[12] In a meta-analysis comparing surgical excision with surgical excision combined with radiotherapy; it was found that local and regional control increased in the second group.[14] Jabbour et al.[15] performed a study in 1992–2004 with 82 patients. they reported that addition of radiotherapy to the primary tumor zone and area of lymph node involvement increased the disease free survival and overall survival. Thus addition of radiotherapy to all stages of MCC should be considered. Since our patient had lymph node involvement she was consulted with medical oncology and radiation oncology. Her treatment still continues.

Although MCC is sensitive to chemotherapy, the role of chemotherapy in treatment is not clear. According to National Comprehensive Cancer Network treatment guidelines, only stage IV MCC patients should undergo chemotherapy. Disease free survival and general survival increased only in this group. Adjuvant chemotherapy in patients with regional lymph node involvement without distant metastasis should be utilized only on selected cases.[5]

The other poor prognostic factors are, larger than 2 cm tumor size, male gender, immune-suppression and location in lower extremities. The rate of local recurrence is high (39%) even in stage I disease. Distant metastasis usually occurs in 50–60% of the patients 10 months after diagnosis.[16] Survival in patients with widespread disease is approximately 8 months after diagnosis.[7,12] Regional metastasis is quite common. Common sites of distant metastasis are liver, bone, lung and bone.[4,7] Although quite rare, pleural, intestinal and gastric metastasis have been reported.[4,11] In our patient no distant metastasis was observed in the PET-CT.

Although the treatment of MCC is still controversial; early diagnosis and proper surgical resection still constitute the most important factors affecting prognosis. The diagnosis should be made before surgery and appropriate treatment plan should be made. Treatment should be multidisciplinary. Radiotherapy could be utilized in establishing local and regional control in all stages of merkel cell carcinoma. Solitary mass with atypical locations should be evaluated for the presence of malignancy and fine needle biopsy should be utilized to establish diagnosis.

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