Late Diagnosis Merkel Cell Carcinoma with History of Basal Cell Carcinoma

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Abstract: Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine tumor. The etiopathogenetic remains unclear, associated with Merkel cell polyomavirus. MCC presents as an asymptomatic lesion or dome-shaped nodules that clinically benign. Diagnosis is based on histopathology and immunohistochemistry assay. This therapy includes excision, radiotherapy, immunotherapy, and chemotherapy. This case report is aimed to give more understanding of the diagnosis and management of MCC. A 47-year-old man presented with multiple pale-reddish tumors for eight months previously. Initially, the clinical feature was reddish, scaly, and dry patches spread over the extremities. The biopsy two years ago showed BCC. There was no regional lymph node involvement. Physical examination found verrucous tumors, with the largest size of 5 centimeters, erythematous macules, papules, erythematous plaques, crusts, and scales on the right elbow and leg. Excision was followed by split-thickness skin graft and chemotherapy. One month post-surgery, the patient had tetraparesis, and he died due to distant metastases one month later. The diagnosis of MCC was established on history, clinical, histopathological, and immunohistochemistry examinations. Sun exposure, elderly age, and fair-skin type are the major factors that can cause MCC. Patient sustains advanced stage and distant metastatic with a mortality rate between 33%- 46 %. MCC generally occurs on elderly fair-skinned men with high UV exposure and poor prognosis at an advanced stage.

1 INTRODUCTION

Merkel cell carcinoma is a rare and aggressive neuroendocrine tumor (Schadendorf et al, 2017; Harms, 2017), high risk of metastasis, recurrence, and death (Schadendorf et al, 2017; Pulitzer, 2017), known as the second largest cause of death from skin cancer after melanoma (Harms, 2017). Although MCC is rarely found, it is estimated that around 1500 new cases are found every year in the United States with incidence rate tripled than the same cases in the last 20 years (Schadendorf et al, 2017). The aetiopathogenesis of MCC is still unclear, with tumor cells showing similar histological and morphological features with Merkel cell even though Merkel cells are postmitotic cells and mostly located in the area of palms and soles, oral and genital mucosa, and nail plates (not predilection areas of MCC) (Xue et al, 2019). MCC is associated with Merkel cell polyomavirus (MCPyV) infection tumor (Schadendorf et al, 2017; Harms, 2017) which is found in 80% cases of MCC, exposure to ultraviolet light, and immunosuppression condition (Xue et al, 2019; Femia et al, 2018). Several factors that are thought to increase the risk of MCC include sunlight, prolonged exposure to UV light and photochemotherapy, 81% MCC occurs in the sun-exposed area (Tegeder et al, 2017). Human polyomavirus infection is usually asymptomatic, except in immunocompromised individuals, with symptoms of progressive multifocal neuropathy or leukoencephalopathy (Femia et al, 2018). The latest pathogenesis model divided MCC into two groups: positive virus group (80% found in the northern hemisphere) and negative virus groups found most frequently in the southern hemisphere (Schadendorf et al, 2017; Harms, 2017). In the positive virus group, MCPyV will encode the modifying gene (T antigen), so that tumor cell proliferation occurs, whereas in the negative virus group UV light is thought to induce genetic changes and acts as a driver mutation (Xue et al, 2019; Femia et al, 2018). The risk of MCC is influenced by ethnicity, age,

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gender, and history of treatment (Harms, 2017). More than 95% of MCC patients have light skin type, occur in men, age above 50 years (Xue et al, 2019).

MCC is characterized as a soft red or violet nodule, overgrowing, in sun-exposed area (Harms, 2017). Crusting and ulceration are rarely found in the early stages of the disease (Xue et al, 2019). Abbreviations of AEIOU are used to show clinical changes in MCC: **a**symmetrical, **e**xpanding rapidly, **i**mmune system suppression, **o**lder than 50, **U**V-exposed site in light-skin patients (Schadendorf et al, 2017; Harms, 2017), with 89% of patients show 3 or more characteristics of AEIOU (Schadendorf et al, 2017). Based on their histological features, MCC is divided into 3 subtypes: trabecular, intermediate, and small cell. The trabecular type is usually found in mixed tumors, and the standard type is the most common type characterized by a basophilic nucleus with high mitotic activity. While the small cell type is undifferentiated and indistinguishable from small cell carcinoma in other locations. Histopathological features in MCC include the hyperchromatic nucleus and high mitotic activity (Schadendorf et al, 2017; Tegeder et al, 2017). Immunohistochemical examination show positive staining for cytokeratin 20 and neuron-specific enolase and gives negative results for thyroid transcription factor-1 (Schadendorf et al, 2017; Ko et al, 2016; Harms et al, 2016). Staging MCC based on AJCC (American Joint Committee on Cancer) criteria with four significant division stages based on tumor size, lymph node involvement, and presence/absence of metastases (Harms et al, 2016).

Several treatments for MCC include surgery, radiotherapy, chemotherapy, and immunotherapy tumor (Schadendorf et al, 2017; Harms, 2017; Femia et al, 2018; Cassler et al, 2016; Tello et al, 2018). In cases with primary lesions are generally performed wide excision and SLNB (Sentinel Lymph Node Biopsy) with 1-2 cm free margin. In high-risk tumor conditions (location of the head and/or neck, size more than 1 cm, positive excision margin, lymphovascular invasion) or high-risk patient (immunocompromised condition) (Xue et al, 2019; Femia et al, 2018) surgery is followed by 50Gy to 66Gy radiotherapy in the primary lesions and regional lymph nodes as an adjuvant after the wound healing process (Xue et al, 2019; Femia et al, 2018). In small primary tumor lesions (less than 1 cm), no involvement of lymph nodes, lymphovascular invasion, or immunosuppression, postoperative radiotherapy is not recommended (Krispinsky et al, 2018). Radiotherapy can be used as monotherapy in conditions that surgical therapy cannot be performed, either due to unresectable tumors, patient rejection or due to the risk of morbidity in surgery (Femia et al, 2018). Chemotherapy can be useful as palliative therapy in conditions of patients who are not operable or in metastatic conditions. Chemotherapy regimens for MCC based on the protocol for small cell lung cancer by giving carboplatin / cisplatin-etoposide as the first line (Xue et al, 2019; Femia et al, 2018). However, in the case of patients who have received surgical therapy or radiotherapy or both, chemotherapy as an adjuvant is not recommended because it can increase morbidity (associated with neutropenia) and mortality, decreased quality of life, resistance to chemotherapy, and suppressing the immune system (Tegeder et al, 2017). Although chemosensitive, the effectiveness of chemotherapy in MCC cases tend not to be durable (Xue et al, 2019).

The aim of this case report is to give more understanding of the diagnosis and management of Merkel cell carcinoma.

2 CASE

A 47-year-old Chinese male came with complaints of pale-reddish tumor in his right arm and leg eight months ago. Soft rapidly enlarged and quickly bled tumor, in some parts covered with pus and foul-smelling, painful (+). Initially, skin disorders were reddish, scaly, and dry patches spread over the extremities. At his initial disease, he denied having a fever, fatigue, weakness in limbs, unintentional weight loss, and other systemic symptoms. Two years ago, the patient had taken a surgery on the right hand with biopsy result showed basal cell carcinoma. History of sunlight exposure (+) because he was a foreman. History of family members with the malignant disease was denied.

Generalist status: the patient was compos mentis, good nutritional status with 167 cm height, 75 kg body weight, 120/80 mmHg blood pressure, pulse 80 x/minute, respiratory frequency 18 x/minute, and 36^{o}C axillary temperature. From dermatological status, there was a variety size of verrucous tumors, the largest tumor was 5 cm, with crust, papules, erythematous macules, scally, erythematous plaques on the elbow and right leg. There was no involvement of regional lymph nodes. Blood laboratory test showed mild anemia; gamma GT 108 U / L; urea 41 mg / dL; creatinine 1.6 mg / dL; chloride 108 mmol / L; non-reactive anti HIV screening; ASTO qualitative negative, HsCRP 1.28

mg/L; HBsAg negative; anti HCV 0.15. From peripheral blood smear testing, erythrocytes were obtained: mild anisocytosis (normocytic, microcytic), mild poikilocytosis (ovalocyte, pear shape, teardrop), polychromatic +; leukocytes: normal amounts estimation, monocytosis, neutrophilia, atypical lymphocytes +; platelets: estimated quantities are difficult to analyze, clumping ++, were dominated by normal forms, large forms +.

Biopsy specimens showed fragments of tumor tissue coated with a flattened squashed epithelium, keratinized, some of them were ulcerative with swollen and hyperemic connective tissue stroma caused of lymphocytes, leukocytes, histiocytes contained tumor masses in the form of nests of malignant cells with pleomorphic, hyperchromatic round, oval nuclei, provide salt and pepper picture, some vesicular, eosinophilic cytoplasm, arranged molding, uninterrupted, in rows around blood vessels, and also groups of cells with a pseudo rosette structure. Immunohistochemical staining showed the most positive cells for synapthopicin, NSE, CK 7, and CK 20. Differential diagnosis included basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

Excision was followed by split-thickness skin graft and chemotherapy using cisplatin 50 mg and paclitaxel 300 mg/50 cc protocol. One month after surgery, the patient had tetraparesis, and he died due to distant metastases one month later.

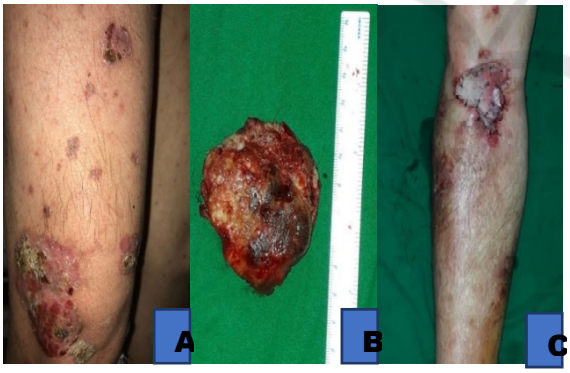

Figure 1. A. The verrucous flesh-red tumor partially is covered by crust, painless in suppression, soft on touch; B. Mass of tumor cells after excision; C. Post split-thickness skin graft surgery

3 DISCUSSION

The incidence of Merkel cell carcinoma correlates with exposure to UV light in light-skin individuals along with age and mostly found at the location of the head, neck, and upper extremities (Schadendorf et al, 2017)About 10% of patients are found younger than 50 years old. (Tegeder et al, 2017) The UV exposure is thought as a cause of cellular mutations which is resulting in uncontrolled proliferation, especially in the virus-negative group.(Kneiling et al,2011) MCC more often attacks men (62%) than women (38%). (Harms et al,2017).

MCC lesions mostly appear as nodules that are red-violet, soft, rapidly enlarged, and painless in suppression. (Schadendorf et al, 2017) In the patient has found 3 characteristics of abbreviation AEIOU (asymptomatic, expanding rapidly, and lesions at the location of the body exposed to UV) show suspicion towards MCC. (Schadendorf et al, 2017). 65% of MCC patients only have limited skin disease, 26% of patients are accompanied by regional lymph node involvement and 8% of patients with distant metastases.(Xue et al,20019; Harms et al,2017). Histopathological features of MCC at low enlargement in the form of large nodules that are infiltrating the dermis or subcutaneous, with stromal changes including mucin, inflammation, and increased vascularity. At high magnification, the tumor consists of small round cells with a few cytoplasms and pale, smooth neuroendocrine chromatin (salt and pepper image), can also be found hyperchromasia, accompanied by epidermal involvement in the form of scattered pagetoid images, also rosette. (Schadendorf et al, 2017; Harms et al,2017). In addition to histopathological examination with hematoxylin-eosin staining, enforcement of the diagnosis of MCC requires immunohistochemical staining including keratin-20 (CK 20), thyroid transcription factor-1 (TTF-1), CD 56, chromogranin A, synaptophysin, and neurofilament protein (NFP). CK 20 is a sensitive marker for MCC, with positive results are found in 89% -100% cases of MCC. (Femia et al, 2018) In addition to CK-20, the presence of at least one marker which is derived from neuroendocrine differentiation (ex synaptopodin) can confirm neuroendocrine tumor origin. (Pulitzer, 2017) MCC and BCC provide similar morphological features caused by mucin in stromal or intratumor, but the presence of CK20 and dotlike keratin expression can distinguish MCC from BCC. (Pulitzer, 2017; Harms,2017). In SCC with strong neuroendocrine differentiation, it is often difficult to distinguish from MCC because of the discovery of CK20 and neuroendocrine granules that are also positive for SCC biopsy. However, SCC always gives negative results for MCV. (Pulitzer, 2017)

Patients were referred to the plastic surgery department for excision and split-thickness skin graft. The choice of therapy in MCC cases is based on several characteristics of the disease, including clinical stage, the involvement of regional lymph nodes, comorbid factors, and general condition of the patient. Surgical excision with 1-3 cm borders at the location of the primary tumor is the foremost step in the treatment of MCC, where patients with high-risk tumors should be followed by radiotherapy as an adjuvant. (Schadendorf et al, 2017; Xue et al, 2019; Femia et al, 2018) Split thickness skin graft is a skin-tight technique to cover the defect of extensive skin and epithelial failure. The donor location is usually chosen from the lateral thighs, with the skin to be draped with holes using No. 11 and sewn to the side of the wound. This technique provides faster healing results (between 4-6 weeks) and a more acceptable appearance.(Kneiling et al,2011;Yi et al,2015) Clinical output in MCC patients with the latest therapy is still weak, with the incidence of disease progression and metastasis occur in the first three years after the diagnosis is established. The size of the primary tumor is the most reliable indication of the occurrence of metastases, where small tumor (less than 1 cm) has a risk of metastases 10-20% (Harms,2017). The most common metastases are lymph node glands, followed by metastases at a distant location of the skin, lungs, nervous system center, bone, and liver. Chemotherapy with carboplatin / cisplatin-etoposide is recommended for stage IV MCC. (Schadendorf et al, 2017; Xue et al, 2019;Harms,2017; Femia et al, 2018) 5-year survival rates are 51% for patients with localized disease, 35 % in diseases with lymph node involvement, and only 14% in distant metastatic disease (Harms,2017).

4 CONCLUSION

A case of Merkel cell carcinoma has been reported in a 47-year-old male Chinese patient, with a dermatological examination in variety size of verrucous tumor, the largest tumor is 5 cm, accompanied by crusting, papules, erythematous macules, squares, erythematous plaques on the elbows and right foot, without the involvement of regional lymph nodes. The results of histopathological and immunohistochemical examination supported the diagnosis of Merkel cell carcinoma. Therapy modalities of this patient are excision surgery and split-thickness skin graft followed by cisplatin-paclitaxel chemotherapy, but the patient died due to distant metastases to the central nervous system.

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