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Case report

Metastatic Merkel cell carcinoma with an unknown primary tumor presenting as lymphadenopathy: A case report

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ABSTRACT

Introduction and importance: Merkel cell carcinoma is one of the rare neuroendocrine tumors of the skin. Neuroendocrine nodal MCCUP is a rare and poorly understood malignancy. In this article, we introduce a case of MCCUP with primary manifestation of lymphadenopathy.

Case presentation: A 62-year-old woman presented with lymphadenopathy in the inguinal region, and the diagnosis of metastatic Merkel cell carcinoma was made in the excisional biopsy. The primary source of the tumor was not found in the imaging workup and the patient underwent lymphadenectomy.

Clinical discussion: MCCUP is a rare subtype of MCC, with specific diagnostic criteria. Most MCCs are symptom-free, requiring biopsy for confirmation. NE tumor marker analysis is crucial for distinguishing NE carcinoma, with CK20 and another NE marker sufficient for MCCUP diagnosis. LCA is not found in MCC tumors, and Ki-67 is used for prognosis. Treatment includes surgery, radiotherapy, and sometimes chemotherapy, although its efficacy is debated.

Conclusion: MCCUP is a rare disease affecting primarily elderly, several treatment regimens have been considered for the treatment of this rare tumor. One of the treatments with good results can be extensive surgery and patient follow-up.

1. Introduction

"Trabecular carcinoma of the skin" that was first described by Toker in 1972 has been renamed to Merkel cell carcinoma (MCC) [1]. MCC is an uncommon and aggressive neuroendocrine (NE) tumor of the skin with early and frequent regional lymph nodes metastasis that predominantly affect sun-exposed skin of old immunocompromised light skin patient with mild male predominance [2–4]. This malignancy is known for its tendency to recur frequently and has a significant potential for metastasis, contributing to a high mortality rate [5]. Different malignancies especially hematologic malignancies and being infected by Merkel cell polyomavirus are other associated factors with MCC [6–9]. In fact, MCC ranks as the second leading cause of skin cancer-related deaths, following melanoma. At the time of initial diagnosis, approximately 30 % of patients may have loco-regional metastases, while 6–12 % may present with distant metastatic disease [10,11]. Notably, around 5 % of cases arise with unknown primary origin [12]. The overall Five-year survival rate for individuals diagnosed with advanced or metastatic disease ranges from 13 % to 18 % [12]. In nodal MCC of unknown primary (MCCUP) inguinal lymph node most frequently involved [13]. We report a case of MCC, in line with the SCARE criteria [14], without an apparent primary site presenting as a painless right inguinal lump for 5 months in a 62-year-old woman.

2. Case presentation

A 62-year-old woman presented with firm, immobile, painless, non-tender 4 cm right inguinal mass form 5 months ago. Her past medical history included hypertension, type 2 diabetes mellitus and hyperlipidemia who was treated with Metformin, Losartan and Amlodipine tablets. There was no positive finding in the history and examination of other sites of the body. Abdominopelvic computed tomography (CT) with contrast revealed 35 mm hyper-dense mass at right inguinal region which was found to be an enlarged lymph node hence the patient

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underwent excisional biopsy. Pathology report demonstrated lymphoid tissue diffusely infiltrated by neoplastic small round cells with high nucleus-cytoplasmic ratio, round nuclei, indistinct nuclei and scant cytoplasm and numerous mitotic figures were found. Immunohistochemistry (IHC) staining exhibited positive reactivity for cytokeratin 20 (CK20), synaptophysin and Ki-67 and negative reactivity for leucocyte common antigen (LCA) which confirms the diagnosis of MCC. In clinical evaluation neither primary cutaneous tumor nor regressed primary skin lesion were found. The patient underwent detailed imaging studies that showed no evidence of para-aortic and intra-abdominal lymphadenopathy. After meticulous clinical and radiological investigations detected no primary extra-nodal sites or distant metastases, the diagnosis of MCCUP was made. Then a surgical plan was made for the patient. In the operating room, an incision was made in the right inguinal region, and superficial and deep inguinal lymphadenectomy was performed (Fig. 1). 15 superficial and deep lymph nodes were excised. And the site of the surgical incision was initially repaired. Then the patient was transferred to the surgery department and was discharged from the hospital two days after the surgery. The pathology report after surgery also showed metastatic Merkel cell carcinoma (Fig. 2). Due to no detection of extra-nodal primary site and distant metastasis in investigations, the patients' follow-up was done without adjuvant treatment by performing a PET scan and Sonography at one month, 6 months and one year after the surgery. The patient had no problems in the follow-up.

3. Clinical discussion

MCCUP is an uncommon and scarce subgroup of all MCC patients [15]. Both clinical and immunohistopathological criteria need for definite diagnosis of MCCUP. Most of the MCCs were asymptomatic, indeed biopsy is necessary [16]. Initial immunohistochemical analysis for NE tumor marker (e.g., broad-spectrum keratin (BSK), cytokeratin 20 (CK20), synaptophysin, neuron-specific enolase (NSE), chromogranin A (Cr A)) should be positive to established the tumor as NE carcinoma. Also, negative reactivity to some immunohistochemical staining (e.g., thyroid transcription factor-1 (TTF-1), LCA) require for distinguishing MCCUP from metastatic NE carcinoma of other site of primary. Furthermore, positive CK20 with another NE marker was considered to be adequate for MCCUP diagnosis [17,18]. Based on different literatures immunoreactivity for LCA was not detected in any MCC tumor [19,20]. Immunohistochemical detection of Ki-67 marker used to evaluate

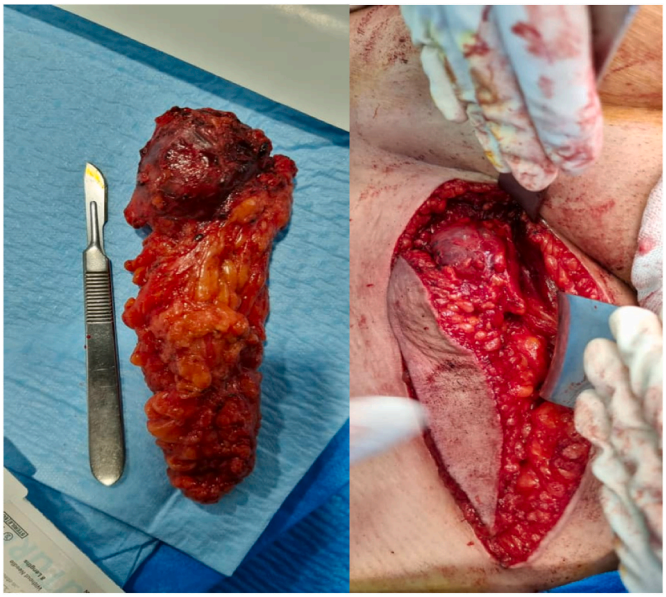

Fig. 1. Intra operative images demonstrated enlarged lymph nodes.

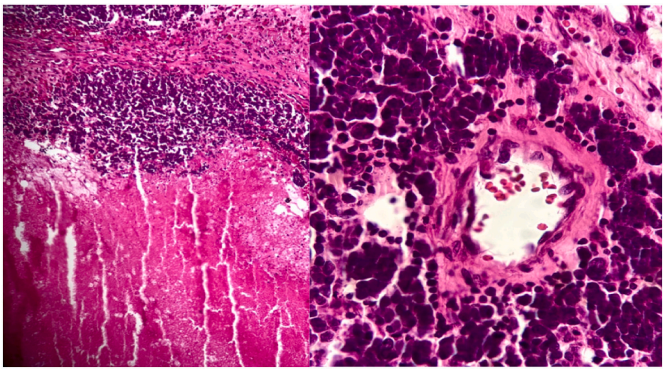

Fig. 2. Microscopic view confirming Merkel cell carcinoma.

prognosis of NE neoplasms of digestive system [21]. Regardless of advantage use of Ki-67 proliferative index for different NE neoplasms, independently influence of these prognostic markers for MCC did not affirm [22]. Our patient underwent detailed radiological imaging that showed no extra-nodal primary site and distant metastases. The result of histopathology coincident with classic morphological feature of MCC. Also, positive reactivity to CK20 and synaptophysin and negative immunoreactivity to LCA were detected. However high mitotic activity and marked positive reaction to Ki-67 can delineated aggressive behavior of these tumor. Furthermore, no evidence of cutaneous primary tumor or regressed skin lesion were detected. Based on clinical, radiological and immunohistopathological features the diagnosis of MCCUP was made. According to highly immunogenicity of MCC spontaneous regression of cutaneous primary site can occur [23,24]. Despite underlying immunity patients with MCC are susceptible to local recurrence, lymphatic dissemination and distant metastasis [25]. Furthermore significantly better prognosis, improvement of overall survival, reduction in the death from any cause, lower risk of recurrence and distant metastasis were revealed in MCCUP in contrast to nodal metastatic MCC with known primary site [15,24,26–30]. By definition of American joint committee on cancer (AJCC) both nodal metastatic MCC of known primary and MCCUP are classified as stage IIIB [15,31]. Consequently, significant difference in initial treatment between MCC with known primary and MCCUP were not detected [24]. Because of the scarcity of the published literatures and lack of clinical experiences in standard treatment modality, initial therapy for MCCUP remain surgery, radiotherapy and/or chemotherapy. Notably there is significant controversy about usage of radiotherapy and/or chemotherapy [17,26,27,30,32,33]. The use of adjuvant or neoadjuvant therapies is not yet standard in clinical settings, but it represents a highly promising area of research. The CM 358 study, which investigated nivolumab in a neoadjuvant context [34], showed encouraging results, highlighting the potential of this treatment strategy. Ongoing trials aim to clarify the benefits of early intervention in Merkel cell carcinoma (MCC). In the CM 358 study, the rates of pathological complete response and major pathological response were recorded at 46.2 % and 15.4 %, respectively. For comparison, neoadjuvant anti-PD-1 trials in non-small cell lung cancer (NSCLC) and melanoma reported pathological complete response rates of 15 % and between 19 % and 25 % [35,36]. Nevertheless, no improvement of overall survival was observed either in adjuvant radiotherapy or chemotherapy [32]. But also, reduction of loco-regional recurrence was demonstrated [27]. Therefore, variable suggestion recommended for treatment. Concerning multimodality treatment of MCCUP, our patient underwent lymph node dissection without adjuvant treatment.

4. Conclusion

MCCUP is a rare disease that mainly affects the elderly. Unlike most

cases of this tumor, which are seen in sun-exposed areas, our case occurred in the inguinal area, which is not usually exposed to the sun. In this case, the diagnosis of MCCUP was determined based on clinical examination, radiological (Abdominopelvic computed tomography (CT) with contrast and Sonography), Sentinel lymph node biopsy and immunohistopathological (Immunohistochemistry (IHC) staining) findings. Due to limited published literature and a lack of clinical experience in standard treatment methods, the primary treatment options for MCCUP are currently surgery, radiotherapy, and/or chemotherapy. In regard to recommendations for treating MCCUP, our patient underwent lymph node dissection without adjuvant treatment due to no detection of extra-nodal primary site and distant metastasis in meticulous clinical and radiological investigation. The pathology report after surgery also showed the same diagnosis (Fig. 2). PET scan and Sonography at first month then at 6 months interval was performed for follow up. There was no problem in the follow-up.

Consent

Written informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Ethical approval

Ethics approval is not required for case reports in our institution (Imam Ali Hospital, Alborz University of Medical Sciences, Karaj, Iran) as they are deemed not to be research.

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Author contribution

Alireza Shirzadi and Mojtaba Ahmadinejad designed the research study. Bahar Bajelan and Fateme Mohammadifard wrote and revised the manuscript; Javad Zebarjadi Bagherpour reviewed and approved the final manuscript.

Guarantor

Javad Zebarjadi Bagherpour.

Research registration number

1. Name of the registry: None. Our report is not ‘First in Man’ study.
2. Unique identifying number or registration ID: None. Our report is not ‘First in Man’ study.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): None. Our report is not ‘First in Man’ study.

Conflict of interest statement

The authors declare that they have no competing interests.

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