Case Report / Olgu Sunumu

Primary Nodal Merkel Cell Carcinoma: Rare Presentation

Primer Nodal Merkel Hücreli Karsinom: Nadir Prezentasyon

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Abstract: Merkel cell carcinoma (MCC) is a very rare high-grade neuroendocrine carcinoma that is frequently located in the skin. Although most cases are associated with Merkel cell polyomavirus, there are also cases in which the virus cannot be detected. The purpose of presenting the case of MCC with primary nodal involvement is due to its rare presentation. A 59-year-old male patient presented to the hospital with painless mass in the neck. Imaging analyses revealed necrotic lymphadenopathies on the neck, measuring up to 4.5 cm in size. After an explorative surgery with preliminary diagnoses of lymphoma and squamous cell carcinoma , samples taken from the excised mass showed high-grade neuroendocrine carcinoma morphology. In addition to neuroendocrine markers, CK7 and CK20 positivity were observed in the immunohistochemical tests performed. The patient was diagnosed with primary nodal MCC due to the negativity of the markers performed to exclude other malignancies and the absence of a different focus on PET imaging analysis outside the lymph node. The differential diagnosis of MCC should be kept broad due to the histopathological morphology of small round cell malignant tumors. In high-grade neuroendocrine carcinomas, the possibility of MCC should be ruled out especially if CK20 positivity is present. Although is has been reported that primary nodal MCC cases have a better clinical course compared to nodal metastatic cases with a known primary, there are limited case series studies on this topic. A multisystem approach is recommended for proper clinical management.
Anahtar Kelimeler: Merkel cell carcinoma, Unknown primary, Neuroendocrine carcinoma

Özet: Merkel hücreli karsinom (MHK) sıklıkla deri yerleşimli oldukça nadir görülen yüksek dereceli nöroendokrin karsinomdur. Olguların çoğu Merkel cell polyomavirus ile ilişkilendirilmekle birlikte virusun saptanamadığı olgular da mevcuttur. Bu yazıda oldukça nadir bir prezentasyon olması nedeni ile primeri bulunamayan nodal MHK tanılı olgunun sunulması amaçlandı. 59 yaşında erkek hasta boynunda ağrısız ele gelen kitle varlığı nedeni ile hastaneye başvurdu. Görüntüleme analizlerinde boyunda 4,5 cm'e ulaşan lenfadenopati ile uyumlu nekrotik kitleler saptandı. Lenfoma ve skuamöz hücreli karsinom ön tanıları ile yapılan eksploratif cerrahi sonucunda gönderilen kitleden alınan örnekler yüksek dereceli nöroendokrin karsinom morfolojisinde idi. Yapılan immunhistokimyasal tetkiklerde nöroendokrin belirteçlerin yanısıra CK7 ve CK20 pozitifliği eşlik etmekte idi. Diğer maligniteleri dışlamak amacıyla yapılan belirteçlerin negatifliği ve PET görüntüleme analizinde lenf nodu dışında farklı bir odak saptanmaması nedeni ile olgu primer nodal MHK tanısı aldı. MHK'un histopatolojik olarak küçük yuvarlak hücreli malign tümör morfolojisi nedeni ile ayırıcı tanısı oldukça geniş tutulmalıdır. Yüksek dereceli nöroendokrin karsinomlarda CK20 pozitifliği durumunda MHK olasılığı mutlaka ekarte edilmelidir. Primer nodal MHK olgularının, primeri bilinen nodal metastatik olgulara göre daha iyi klinik seyir gösterdiği bildirilse de bu konuda küçük olgu serili çalışmalar mevcuttur. Doğru klinik yönetim için multisistemik bir yaklaşım önerilmektedir.
Keywords: Merkel hücreli karsinom, Primeri bilinmeyen, Nöroendokrin karsinom

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1. Introduction

Merkel cell carcinoma (MCC) was initially identified as trabecular carcinoma of the skin by Cyril Toker in 1972. Subsequently, it was associated with Merkel cells located in the epidermis, leading to its current nomenclature, MCC (1, 2). However, the precise cellular origin of MCC remains a subject of ongoing debate, with suggestions that it may arise from pre/pro B cells, dermal fibroblasts, or even pluripotent dermal stem cells (3). MCC is highly infrequent cancer, with an incedence of less than one new case per 100.000 individuals per year in the United States and Europe. While MCC most commonly presents as a skin lesion, cases of metastatic MCC without a primary skin lesion have also been sporadically reported (4). Furthermore, it is exceptionally rare for MCC to manifest solely in superficial lymph nodes without accompanying skin lesions or distant metastases (5).

MCC is classified as a neuroendocrine carcinoma based on its cytopathological and immunohistochemical features (6). Mercel cell polyomavirus (MCPyV), first identified in 2008, has been directly linked to MCC and is detected in approximately 80% of cases. As a result, two distinct subtypes of MCC have emerged: virus-positive and virus-negative, which exhibit differing clinical prognoses (7). In accordance with the American Joint Committee on Cancer (AJCC) TNM 8th edition, clinically evident nodal MCC with “no evidence of primary tumor” (T0) and “no distant metastasis” (M0) can be defined as a clinical stage III (anyT cN1-3 M0) or pathological stage IIIA (pT0 N1b or higher M0) (8). We herein report a case of primary nodal MCC of unknown primary (MCC-UP), which represents an exceedingly uncommon manifestation of this already rare neoplasm.

2. Case Report

A 59-year-old male pateint was admitted to the hospital with a complaint of palpable neck swelling persisting for approximately 7-8 months. There was no history of rapid growth of the swelling or pain, and the patient had no prior medical conditions except for diabetes mellitus and hypertension. The patient did not report a history of smoking and alcohol use. Physical examination revealed a semi-mobile, painless mass in the upper cervical triangle on the right side of the neck. On endoscopic examination, the nasopharynx and larynx appeared normal. In imaging analyzes revealed conglomerated necrotic lymphadenopathies measuring 4.5 cm in the right level 2 and 2.7 cm in the left 2 level. Other neck structures were found to be within normal limits. An excisional biopsy and right tonsillectomy were performed on the lesion located on the right side with the preliminary diagnoses of squamous cell carcinoma and lymphoma. The tissues submitted for pathological examination exhibited fragmented necrotic gray-white solid features. Microscopic analysis revealed diffuse necrosis, as well as tumoral infiltration with a conglomerate appearance extending to the surrounding adipose tissue. The neoplasm was characterized by mitosis-active cells with narrow cytoplasm consisting of medium-to-large nuclei with salt-pepper chromatin (Figure 1). For differential diagnosis of high-grade neuroendocrine carcinoma, small cell carcinoma, malignant melanoma, lymphoma and sarcoma, Pancytokeratin (PANCK) was cytoplasmic granular positive, BEREP4, Synaptophysin and CD56 were severely positive, and Chromogranin A was weakly positive, Vimentin, CD45, and Melan A were negative. Following staining consistent with neuroendocrine carcinoma, immunohistochemical markers spesific to the primary organ were applied in a second panel. Immunohistochemical markers including CK7, TTF1 for the lungs, CK20, CDX2 for the colon, PAX8 for the genitourinary system, and p40 for squamous cell carcinoma with neuroendocrine differentiation, which are common localizations, were done. The neoplastic cells were found to be positive CK7 and CK20, whereas TTF1, CDX2, PAX8, and p40 were negative. The Positiviy for CK20 raised the suspicion of MCC in the differential diagnosis, prompting further investigations to support the diagnosis. Focal paranuclear dot-like and diffuse cytoplasmic granular positivity were detected in cells with CK20. Subsequent supportive investigation

demonstrated widespread positivity for SATB2 and positive staining for Neurofilament with a dot-like pattern in the golgi zone, which has specificity for MCC. Some immunhistochemical features are showed in Figure 2 and Figure 3. During the pathological examination, the clinician was contacted, and the patient's clinical history and physical examination were thoroughly reviewed for possible primary skin lesions; however, no lesion was detected. Finally, the pathology report indicated that the findings were consistent with MCC infiltration, but it was recommended that systemic screening to rule out the presence of other neuroendocrine carcinomas and to identify a potential primary site. Ga-68 DOTATATE PET/CT revealed increased activity uptake in lymph nodes in both axillary and inguinal regions, with no involvement detected in other areas. The MCPyV stain applied in an external center to the tumor sent for consultation resulted positive, and the case was classified as nodal MCC-UP based on all the findings. Given the widespread involvement, systemic chemotherapy was initiated.

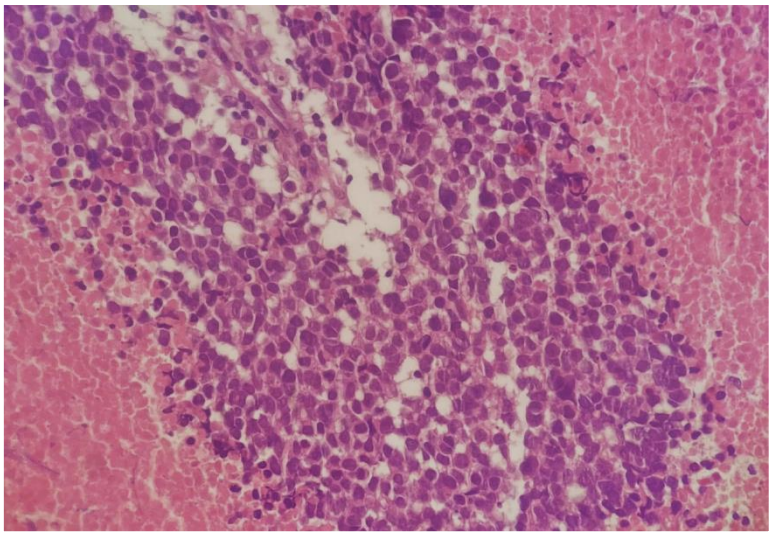

Figure 1. Malignant tumoral cells with salt-pepper chromatin, hyperchromatic nuclei, narrow cytoplasm, abundant mitosis and apoptosis, and surrounding tumor necrosis, H&E staining, X200

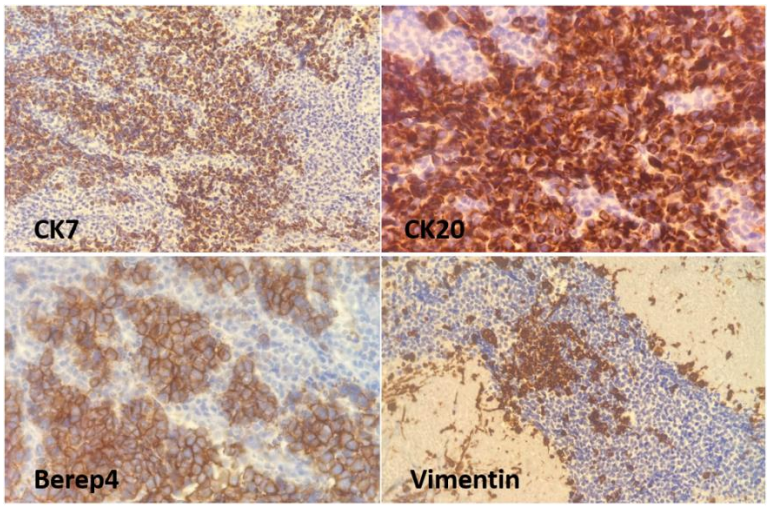

Figure 2. CK7, CK20, Berep4 cytoplasmic granular positive, Vimentin negative in neoplastic cells, Immunohistochemical staining

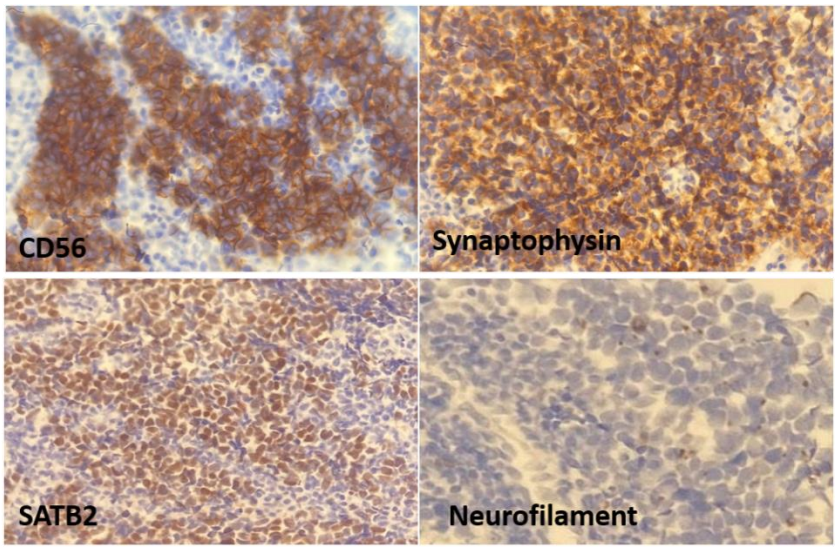

Figure 3. CD56 and Synaptophysin positivity showed neuroendocrine nature of the tumor, and SATB2 and dot-like Neurofilament positivity supported MCC diagnosis, Immunohistochemical staining

3. Discussion

MCC is an extremely rare neuroendocrine carcinoma with high metastatis potential, often localized in the skin (9). Most of the cases with merkel cell polyomavirus, and UV-related damage is blamed in the etiology in up to 20% of cases (10, 11). Nodal MCC-UP accounts for approximately 4% of all MCC cases (12). In a study conducted among nodal MCC-UP cases, 78.2% of the tumors were located in the inguinal region, 16.4% in the axilla, and 5.5% in the head and neck. 65.5% of the patients were male and 89% were over 50 years old (13). Predisposing factors are known as advanced age (eg, >75) and immunosuppression (transplantation, neoplastic infiltration, etc.) (14). But there is evidence in studies that primarily nodal MCCs are not associated with immune suppression. More MCPyV oncoprotein autoantibody titer and more mutations are detected in these tumors than in cases with known primary (15). There are also studies reporting that virus-positive MCC cases have a better prognosis than negative ones (16).

The diagnosis of MCC is quite challenging, especially in nodal presentation. Since it is histopathologically in the morphology of a small round cell malignant tumor, many entities are included in the differential diagnosis such as small cell neuroendocrine carcinoma, primitive neuroectodermal tumor, malignant melanoma, lymphoma, sarcoma, even malignant epithelial tumor with neuroendocrine differentiation. In a tumor with high grade neuroendocrine carcinoma morphology, the CK7 and CK20 staining pattern should be questioned. The expected profile is mostly CK20+/CK7-, but CK20+/CK7+, CK20-/CK7+, CK20-/CK7- cases are also reported in the literature (17-19). The reported incidence of CK7 positivity in MCC is 23-31% (20, 21) In addition, SATB2 and neurofilament positivity in a dot-like pattern are supportive markers with high specificity for MCC (22).

In conclusion, primary nodal MCC-UP is a challenging entity both in histopathological diagnosis and clinical management. In cases with nodal presentation, detailed dermatological physical examination of the case is essential in terms of possible primary skin lesion. The clinical approach recommended in the guidelines is adjuvant radiotherapy with radical surgery in local disease, and conventional chemotherapy in extensive disease. Because it is an extremely rare entity, a multidisciplinary approach is required in its clinical management, and more studies are needed to understand the nature of the disease.

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Ethics

Informed Consent: The authors declared that informed consent form was signed by the patient.

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