# MERKEL CELL CARCINOMA AS A NEUROENDOCRINE CUTANEOUS TUMOR A SERIES OF SIX CASES AND REVIEW OF LITERATURE

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## Abstract

Merkel cell carcinoma is a very rare disease and a highly aggressive primary cutaneous neuroendocrine carcinoma primarily affecting elderly and immunosuppressed individuals. MCCs are positive for epithelial and neuroendocrine markers, but are negative for lymphoid and melanoma markers. Tumor genesis is still unclear, but recent works have suggested that epidermal stem cells and/or dermal neuroendocrine stem cells might be the MCC source.
Authors present a series of 6 cases diagnosed in our laboratory with Merkel Cell Carcinoma. One is located in ala nasi dexter, one in region genu sinister, and 4 sites of metastatic lymph nodes. The distribution according to gender is 2 male and 4 female. The age is from 55 years old to 74 years old.
A correct differential diagnosis between other similar pathologies is important to proceed with a multidisciplinary approach and treatment.

**Keywords:** Merkel Cell Carcinoma, immunohistochemistry, histology, neuroendocrine tumor.

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## 1. INTRODUCTION

Merkel cell carcinoma is a rare occurrence of a highly aggressive primary cutaneous neuroendocrine carcinoma. It affects mostly elderly and immunosuppressed individuals. It is first described as trabecular carcinoma by Toker in 1972 [1].

Merkel cells are considered a type of neuroendocrine cell of the skin, because they share some features with nerve cells and hormone-making cells. Merkel cells are encountered mainly in the epidermis. In 2008, genomic integration of the Merkel cell Polyomavirus (MCPyV) was identified as the primary oncogenic driver for about 80% of MCCs, while the remaining MCPyV-negative cases were subsequently shown to harbor a high tumor mutation burden with prominent UV-signature [2-6].

Several other candidate cells of origin for MCC have been suggested in the MCPyV-negative cases, including epithelial and non-epithelial progenitors [7-9]. A subset of MCCs arises in association with squamous cell carcinoma in situ (SCCIS).

This has generated the option of investigating the molecular genetic alterations in each component, thus determining any possible etiologic relationship between the two oncological occurrences. Some sources have applied targeted next-generation sequencing to seven paired in situ squamous cell carcinoma (SCCIS) and MCPyV-negative MCC samples, sequencing these components separately [10]. These results strongly suggest a direct clonal association by demonstrating high mutational similarities between the two tumoral components.

There is evidence that MCPyV-negative MCC can arise from a distinctive subset of SCCIS, which harbors specific genetic alterations such as TP53 and RB1 inactivation [11]. Epigenetic dysregulations further contribute to the SCC to MCC transformation.

We will present a series of 6 cases diagnosed in our laboratory with Merkel Cell Carcinoma. One is located in ala nasi dexter, one in region genu sinister, and 4 sites of metastatic lymph nodes. The distribution according to gender is 2 male and 4 female. The age is from 55 years old to 74 years old.

## CASE PRESENTATION

### Case 1.

We present a 64-year-old male presented at the Department of Radiology with an enlargement of the right inguinal lymph node. He had a history of SCC of the right iliac region, which was diagnosed by biopsy 3 years ago. The tumor was surgically removed obtaining negative margins and the histopathologic examination of the H-E sections has shown a SCC compatible morphology.

The radiologist performed a percutaneous tru-cut biopsy of the enlarged lymph node and sent that for histopathologic examination. The sample was sent to the laboratory with the suspicion of metastasis from squamous cell carcinoma. After the Hematoxylin – Eosin examination the histopathologic findings don’t match the diagnosis of squamous cell carcinoma. In the H-E the histopathologic examination presents a small round blue cell tumor with a high N: C ratio, round / oval nuclei, and finely dispersed chromatin. Immunohistochemistry was used to confirm the diagnosis. Immunohistochemistry has shown MCC with characteristic CK20 expression and negative immunohistochemistry for P63. There was no associated SCC or squamous differentiation.

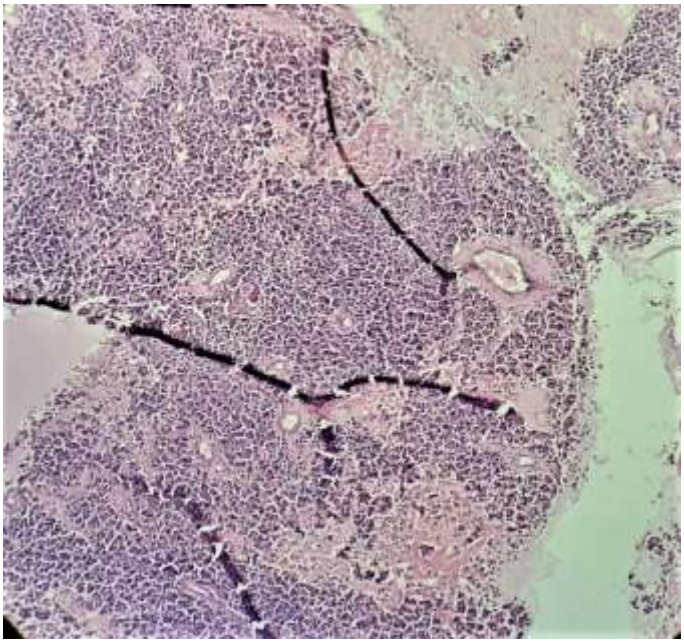

Figure 1. Microscopic appearance of the lesion in H-E sections (x40)

The "small round blue cell" histologic pattern of MCC must be differentiated from several other tumors, such as malignant lymphoma, and small-cell melanoma. Therefore, immunohistochemical staining is required. MCCs are positive for epithelial and neuroendocrine markers but are negative for lymphoid and melanoma markers.
Further, the tumor cells of MCC display additional antigens in varying frequency and intensity; these include, among others, synaptophysin and CD56. The immunohistochemical panel results are: CKAE1/AE3 (+++), S100 (---), MelanA (---), CD56 (++-), CD45 (---), P63 (---), CK5/6 (+--), CK20 (+++), SYN (+++), Chromogranin (+++). After that, the diagnosis of Merkel Cell Carcinoma was reached. The patient was referred for a RM total body for any eventual distant metastasis in other organs or regions. After the examination, the RM shows no evidence of distant metastasis. Despite MCC, the patient is diagnosed also with type 2 diabetes mellitus and with dyslipidemia. The patient underwent locoregional lymph node excision and after that radio and chemotherapy.

**Case 2.**
A 70-year-old male noticed a red lesion with a diameter of 0.5 cm in the ala nasi dexter. The lesion appeared around 4 months ago and has grown in dimension. The patient during these months went to the dermatologist and the diagnosis of hemangioma was suspected. After this, the patient makes a consultation with the plastic surgeon, where it is decided to make an excision of the lesion, and the material is sent for histopathological examination. In the Hematoxylin- Eosin staining the epithelial lining with many flat layers can be observed, under which and in close contact are seen hyperchromic cells, with light to moderate atypism, some of which have an axial appearance, between which there are small capillaries filled with blood with erythrocytes. These findings don't support the diagnosis of capillary hemangioma and in these situations, an immunohistochemical examination is required. In the immunohistochemistry the cells results : CD 45 (+--), CK20 (---), CD31 (+--), CKAE1/AE3 (+++) dot like, Synaptophysine (+++), Cromogramine (+--) dot like, CD56 (+++). The immunohistochemical panel supports the diagnosis of Merkel Cell Carcinoma. The tumor has a diameter of 3 mm and a depth of 1 mm. Resection margins are clear around 3 mm lateral and

the depth border is around 2 mm. The patient was referred to the Department of Oncology for treatment.

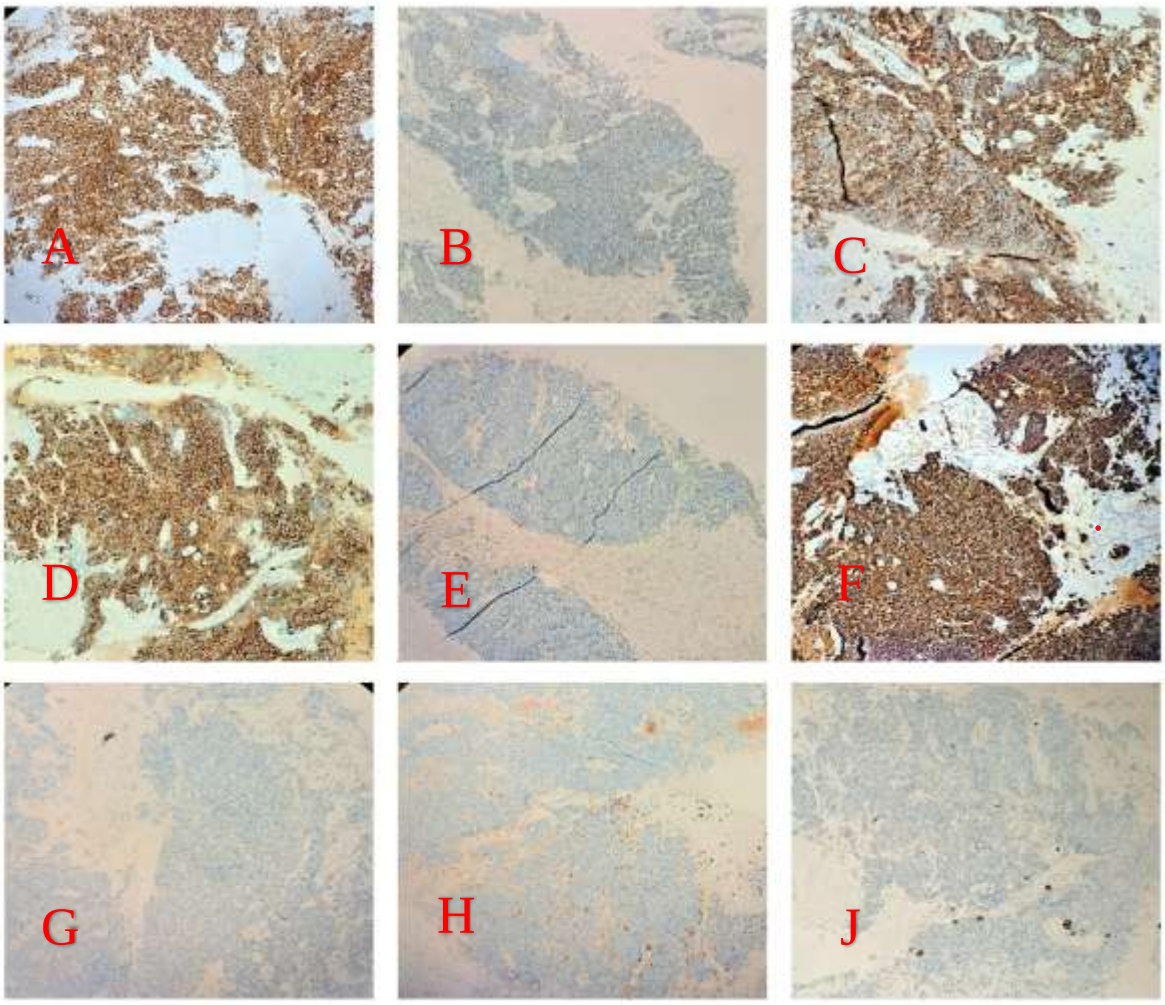


Figure 2. Immunohistochemical examination. A) CK20, B) p63, C) CD56, D) Synaptophysine, E) S100, F) CKAE1/AE3, G) MelanA, H) CD45, J) CD5/6.

**Case 3.**

A 65-year-old female presented with an axillary mass. A tru – cut biopsy of the axillary lymph nodes was performed. The Hematoxylin – Eosin examination was made in another healthcare laboratory and they brought only paraffin blocks for immunohistochemical examinations since the diagnoses weren't established with H-E staining. We don't have information about the clinical history of the patient and the concomitant diseases. In the H – E the lesion presents with small round cells with hyperchromatic nuclei and very few cytoplasm. In immunohistochemistry examination the tumor cells result CKAE1/AE3 (+--) dot like, CD45 (---), S100 (---), CD56 (+++), Ki67 70 %, Synaptophysin (+++), Chromogranin (---), CD99 (---), WT1 (---), TTF1 (---). These results support the diagnosis of metastatic Merkel cell carcinoma in the axillary lymph node.

**Case 4.**

A 74 years old lady complained an inguinal lymph node enlargement. The enlargement was noted by the patient around 6 weeks ago. Before 3 years the patient was

treated for Merkel cell carcinoma of the abdomen. The patient after the consultation with the family doctor is recommended for an ultrasound of the lymph nodes. The radiologist found it appropriate to make a tru -cut biopsy because of the non-symmetric enlargement of the lymph nodes and the irregular appearance. Taking into consideration the history of the patient immediately the immunohistochemical examination is performed and the results are CKAE1/AE3 (+++), CD45 (+--), Ki67 80 %, CD56 (+++), CK7 (---), CK20 (+++) dot-like, P63 (---), Synaptophysin (+++), Chromogranin (+++) dot-like. In this way, the diagnosis of metastatic Merkel cell carcinoma in the inguinal lymph node is established. The patient is referred to a specialized cancer treatment center.

**Case 5.**

A 55-year-old female with an inguinal enlargement from 3 months. At our laboratory of the pathology, the paraffin block was brought for immunohistochemistry. The results are : CD45 (---), CKAE1/AE3 (+++) dot like, Ki67 40 %, Synaptophysin (+++), Chromogranin (+++), CD56 (++-). These results support the diagnosis of metastatic neuroendocrine tumor in the inguinal lymph node.

**Case 6**.

A 75-year-old lady presented with a tumoral mass in the region of genu sinister measuring 4 x 4 cm. The clinical diagnosis suspected is a lipoma. In the macroscopy, the tumor presents as e-beige mas with elastic consistency localized in the subcutis region. The lesion is very near the margins of resection. In the H-E staining the microscopic appearance doesn't support the diagnosis of lipoma. The lesion is composed of small round cells with hyperchromatic nuclei and small cytoplasm. After these findings the diagnosis of a neuroendocrine tumor is suspected and an immunohistochemical examination is required. The results of the immunohistochemistry are as follows: CKAE1/AE3 (+++), Ck7 (---), CK20 (+++), CD45 (---), CD56 (+++), MelanA (---), S100 (---) Ki67 90 %, chromogranin (+++), Synaptophysin (+++). All these findings lead to the diagnosis of Merkel Cell Carcinoma which is less than 1 mm far from the margins.

## 2. DISCUSSION

MCC is much less common than most other types of skin cancer, but it’s one of the most dangerous types. The accurate tumor genesis is still unclear and recent works have suggested also epidermal stem cells and dermal neuroendocrine stem cells as MCC sources. MCC can start anywhere on the body. Merkel cell tumors often look like firm, pink, red, or purple lumps or bumps on the skin. They usually don't hurt, but they're fast-growing and can sometimes open up as ulcers or sores [12]. MCC appears more often as a solitary, rapidly growing cutaneous red to a violet nodule that might be clinically confused with other benign skin lesions, for example, inflammatory lesions or cysts, or with malignant tumors such as skin lymphomas, squamous cell carcinoma or metastasis [13, 14]. MCC incidence has tripled during the last years with an increase of 0.8% per year and it represents worldwide the second death caused by cutaneous tumors after melanoma, with a 5-year mortality of 30% [15].

In our study, 3 cases are lymph node metastases from previous Merkel cell carcinoma and we have one case that arises from a previous squamous cell carcinoma diagnosed 5 years before the metastases. The other 2 cases are diagnosed as primary cutaneous Merkel cell carcinoma.

Diagnosis requires microscopic evaluation as the clinical appearance is nonspecific and can mimic a variety of benign and malignant skin lesions. Therefore, the pathologist plays a crucial role to confirm the tumoral origin of the lesion and to rule out other tumors.
In the cases presented in this study, the neuroendocrine marker Chromogranin is positive in all cases, CD56 also is positive in all cases and Synaptophysin is positive in 4 cases. These findings suggest that chromogranin and CD56 are more sensitive in Merkel cell carcinoma and synaptophysin is less sensitive. All cases are positive for CKAE1/AE3 and negative for CD45.

The treatment of Merkel Cell Carcinoma is a multidisciplinary approach with wide local excision and sentinel lymph node biopsy in clinically node-negative patients with or without adjuvant radiotherapy.

## 3. CONCLUSIONS

Merkel cell carcinoma (MCC) is a rare malignant skin neoplasm with the potential for local recurrence, spreading to regional lymph nodes (LNs) and distant metastases. It has a poor prognosis and it is very important a diagnosis in early stages. Also, a correct differential diagnosis between other similar pathologies is important to proceed with a multidisciplinary approach and treatment.

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