MERKEL CELL CARCINOMA

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Summary

Merkel cell carcinoma (MCC) is a rare but highly aggressive primary cutaneous carcinoma of the skin with neuroendocrine origin. It occurs mostly in elderly and is often associated with Polyoma virus infection. It grows rapidly and metastasizes quickly and is highly resistant to treatment, while its monomorphous nodular, non-pigmented appearance predisposes to misdiagnosis and late treatment. The clinician should be advised of the characteristics of this tumor, in order to ensure early detection and a better prognosis.

We present the case of a 79 year old woman with rapidly growing nodular Merkel cell carcinoma and briefly review the challenges in diagnosis and the updates in the management of this deadly tumor.

***Key words**: Merkel cell carcinoma, neuroendocrine, Polyoma virus infection, radiotherapy.*

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Introduction

Merkel cell carcinoma (MCC) of the skin is a rare, but aggressive tumor. A variety of other terms have been used to describe this tumor, including neuroendocrine or primary small cell carcinoma of the skin, trabecular cell carcinoma, APUDoma of the skin and anaplastic cancer of the skin.

Merkel cells are part of the mechanoreceptors implicated in the fine touch, but many theories about the MCC's origin are cited in the literature, including neuro-endocrine, pluripotent stem cells or even lymphoid cells.

Its incidence is not precisely known, but is estimated to be vary between ~0.13-0.4/100 000 persons/year in Europe, representing less than 1% of all cutaneous malignancies.[1-2]

It predominantly affects older adults with fair skin types and has a high propensity for local recurrence and regional lymph node metastases.

Its mortality is high, as treatment in advanced stages remains elusive and the 10-years survival rate is under 50% (46%). [1-2]

Early detection and prompt surgical treatment are key factors for improving prognosis, so knowing the diagnostic characteristics of this tumor and recognizing it promptly are important for the clinical practice.

Case presentation

We report the case of a 79 year old woman who presented to dermatologic consultation for pruritus and oozing on left cubital area, onset several days after applying various self-

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administered topicals. She was diagnosed with allergic contact dermatitis, but was also referred to our Department for the diagnosis of an underlying cutaneous nodule.

Her past medical history included inactive HCV Hepatitis, tuberculosis in childhood, mild age-related cognitive regression, mild arterial hypertension. She had Fitzpatrick phototype II, had worked indoors and had no history of extensive sun exposure, nor significant skin sun damage.

The clinical examination revealed an asymptomatic smooth, slightly erythematous nodule on the internal side of the left forearm, reportedly developed on normal skin over several months. (Fig. 1) Dermoscopy was unspecific, with pink homogeneous areas and some scattered polymorphous vessels.

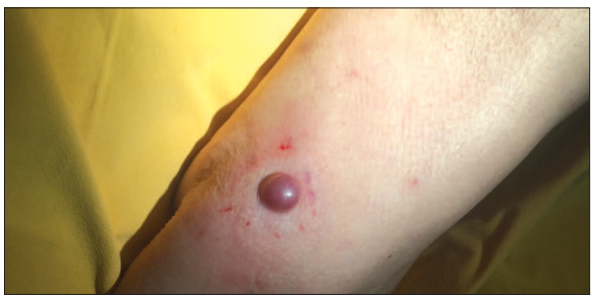

Fig. 1. Clinical: pink / red nodule with smooth surface on the inner side of the left arm

The clinical differential diagnosis included nodular melanoma, cutaneous lymphoma, cutaneous metastases but also a benign tumor.

The tumor was completely excised for pathologic examination which revealed a nodular proliferation of round blue cells of medium size, with basophilic, vesicular nuclei and reduced cytoplasm, extending to superficial hypodermis, over a diameter of 1cm. Lymphovascular invasion was present, along 43 mitoses/mm^2.

Immunohistochemistry revealed CK20 diffuse positive staining, with "nuclear dot" aspect and staining was negative for S100, neurophilament and TTF1. Therefore the diagnosis of Merkel cell carcinoma with nodular growth, intermediate type, with high mitosis activity and lymphovascular invasion was settled. (Fig. 2-5)

The imaging investigations, including thorax-abdomen-pelvis computed tomography and lymph nodes ultrasound were unremarkable, as was the laboratory work. The patient refused the sentinel lymphnode biopsy (SLNB).

The patient was subsequently treated by wide re-excision of the primary tumor site with 2 cm oncological margins, followed by adjuvant radiotherapy of the tumor site.

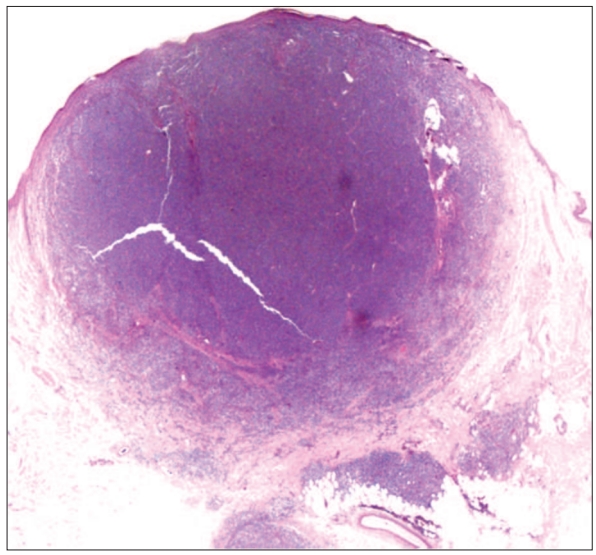

Fig. 2. HE, magnification 20x: Merkel cell carcinoma with nodular, diffuse growth; Without microsatellite, without regression

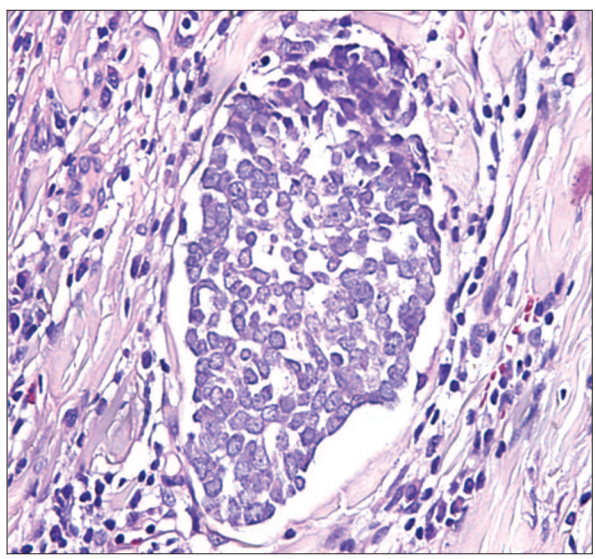

Fig. 3. HE, magnification 400x: Lymphovascular invasion

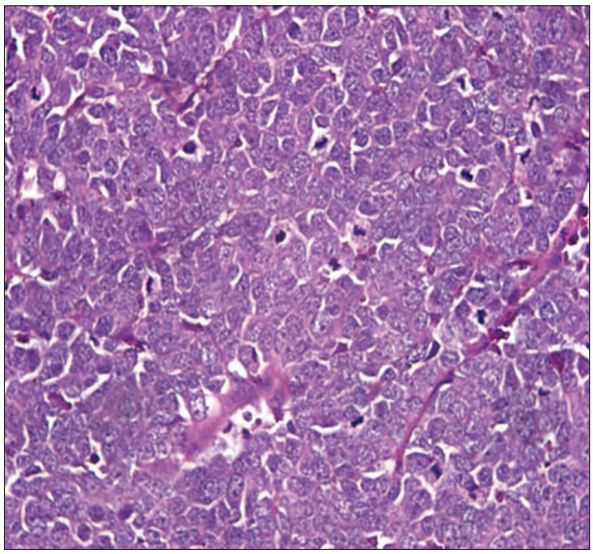

Fig. 4. HE, magnification 400x: Medium cells with basophilic nuclei, vesiculos, monomorphs and reduced cytoplasm; With signs of apoptosis and typical and atypical mitosis

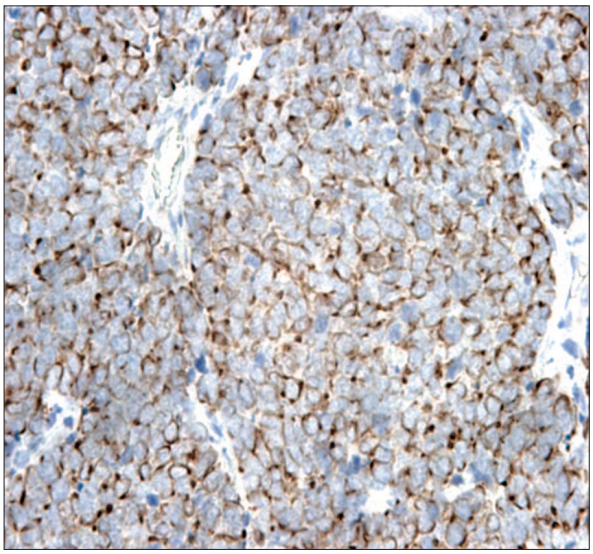

Fig. 5. CK 20, magnification 400x: Paranuclear intense positive proliferation in CK20

Table 1. Merkel Cell Carcinoma Management (adapted after [1])

Management	
Primary tumor	Excision 1-2 cm
Lymph node metastases	Node Dissection: if SLNB + (no proven prognostic benefit) / if macrometastases are targeted
Adjuvant therapies	• Radiotherapy: - Local after primary tumor excision: Increases survival (OS); - Loco-regional: benefits for local control, do not influence survival; recommended if there is extracapsular invasion or disease progression • Chemotherapy: does not affect survival • Immunotherapy: clinical trials • When primary / lymph node surgery is contraindicated: local and regional radiotherapy
Remote metastases	• Chemotherapy: Short-term response does not affect survival • Immunotherapy: Avelumab anti-PD-L1 antibody-approved on 3/23/2017; clinical trials

The evolution was favorable, with no new lesions at 6 months follow-up.

Discussion

Merkel cell carcinoma is an increasingly detected tumor, twice as lethal as melanoma (33-46% fatality rate).[3] It affects primarily elder patients, predominantly males (>60%). While 80% of cases can be associated with a Polyoma virus infection [4], immunosuppression and UV exposure have been showed to play a role in its pathogenesis, with exposed regions of the head and neck area being the most frequent sites. Interestingly, our female patient showed no signs of cutaneous sun damage, and developed the tumor on the photo-protected inner side of the forearm.

The main characteristics of Merkel cell carcinoma respect the *AEIOU* mnemonic (Asymptomatic, Expanding rapidly, Immune suppression, Older than 50 years, and

Ultraviolet-exposed site on a person with fair skin). Three of four criteria have been showed to be present in ~85% of cases [5], and our patient was in the same situation.

The typical clinical presentation is the one seen in our patient, of an asymptomatic, rapidly growing pink/red, smooth nodule. [6]

The main prognostic factors for Merkel cell carcinoma are: the primary tumor size and the distant spread. Thus nodal involvement occurrs in about 14% of tumors smaller than 0.5 cm diameter, in 25% of those smaller than 1.7 cm, and in about 36% of tumors larger than 6 cm. The survival rate at 5 years is 76% for localized tumor without nodal involvement, 50% for 1 involved lymph node and drops to 24% for over 6 metastatic nodes. [1] [7] [10]

Additional markers of unfavorable prognosis are: male sex immunosuppression, older age and head and neck location. The prognostic role of lymphovascular invasion, tumor growth pattern, the presence of mitotic features, G2+ tumour nuclei and vitamin D deficiency are still debated.

The tumor staging occurs according to the American Joint Commission on Cancer (AJCC) TNM classification of year 2010. [1] [7]

Our patient did not present most of the markers of unfavorable prognosis, and her tumor was detected relatively early, at under 2 cm diameter. However, lymphovascular invasion was present in the primary tumor along with high mitotic activity. Since the patient refused SLNB, close monitoring of the nodal status through ultrasound is necessary.

The primary treatment of choice is wide excision and local adjuvant radiotherapy [1]. Adjuvant radiotherapy of regional lymph-nodes does not seem to bring any significant benefit.

Sentinel lymph node biopsy is recommended in patients with clinically normal lymphnodes. [1]

For long time metastatic Merkel carcinoma was considered resistant to classic antineoplastic medicines, with no established therapy for this stage. Very recently (2017) Food and Drug Administration (FDA) approved Avelumab an antibody against PD-L1 for this stage in US.[8]

Moreover, a recent clinical trial of PD1-inhibiting monoclonal antibody Pembrolizumab in therapy-naive metastatic Merkel cell carcinoma patients, showed good results with 56% overall response rate, independent of Polyoma virus infection status, out of which 86% durable responses at 33 weeks. Based on this data, Pembrolizumab was recently listed as a treatment option for patients with metastatic MCC in the 2017 version of USNational Comprehensive Cancer Network (NCCN) guidelines. [9]

Enrolment in clinical trials should be encouraged as potential innovative therapies emerge, such as immunotherapy including anti CTLA4, a pan tyrosine kinase inhibitors and somatostatin analogues. (Tabel 1) [1]

Conclusion

We present a case of Merkel carcinoma, blending typical clinical and atypical features and illustrative for the challenges of diagnostic and treatment of this tumor. Its rapid asymptomatic evolution to large size, being ignored by the patient, its unspecific clinical aspect prone to misdiagnosis and poor prognosis. The suspicion of Merkel cell carcinoma should be raised in any non-pigmented cutaneous nodule, rapidly enlarging, in elderly patients, especially but not exclusively on photo-exposed areas.

Histopathology and immunohistochemistry are mandatory for diagnosis, and in the wait for established new systemic therapies, the early wide excision is the main method to improve prognosis.

Bibliography

1. Lebbe C. et al., Diagnosis and treatment of Merkel Cell Carcinoma. European consensus-based interdisciplinary guideline, Eur J Cancer (2015).
2. Dirk Schadendorf, Céleste Lebbé, Axel zur Hausen, Marie-Françoise Avril, Subramanian Hariharan, Murtuza Bharmal, Jürgen C. Becker, Merkel cell carcinoma: Epidemiology, prognosis, therapy and unmet medical needs, Eur J Cancer January 2017, Volume 71, Pages 53-69, DOI:
3. Houben R, Schrama D, Becker JC., Molecular pathogenesis of Merkel cell carcinoma. Exp Dermatol. 2009 Mar;18(3):193-8. doi: 10.1111/j.1600-0625.2009.00853.x.
4. Liu W, MacDonald M, You J, Merkel cell polyomavirus infection and Merkel cell carcinoma. Curr Opin Virol. 2016 Oct;20:20-27. doi: 10.1016/j.coviro.2016.07.011. Epub 2016 Aug 10.
5. Heath M, Jaimes N, Lemos B, Mostaghimi A, Wang LC, Peñas PF, Nghiem P, Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features, 2008 Mar; 58(3): 375-81. doi: 10.1016/j.jaad.2007.11.020.
6. Klaus Wolff, Lowell A. Goldsmith, Stephen I. Katz, et al.- Fitzpatrick's Dermatology in general medicine. Seventh Edition. McGraw-Hill Medical; section 21 (120): 1088-1094.
7. Merkel Cell Carcinoma. In: AJCC Staging Manual, Springer, New York 2010. p.315.
8. FDA D.I.S.C.O.: Avelumab in Merkel Cell Carcinoma Transcript.
9. Paul T. Nghiem, M.D. et al,PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma, N Engl J Med 2016; 374: 2542-2552 June 30, 2016, DOI: 10.1056/NEJMoa1603702.
10. Jayasri G. Iyer, MD,a Barry E. Storer, et al, Relationships among primary tumor size, number of involved nodes, and survival for 8044 cases of Merkel cell carcinoma April 2014. Volume 70, Issue 4, Pages 637–643.

Conflict of interest
NONE DECLARED

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