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Merkel Cell Carcinoma: Diagnostic and Therapeutic Workup from a Head and Neck Surgeon Perspective

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Mini Review

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Abstract

Merkel cell carcinomas (MCC) are highly aggressive skin malignancies, resulting in death of more than one-third of patients with increasing incidences over the past decades. The carcinogenesis is associated with Merkel cell polyomavirus (MCPyV) infection and/or ultraviolet-induced DNA mutations. Diagnosis is made by histology and specific immunohistochemical stains. Among them, cytokeratin 20 (CK20) expression represents indeed the most important marker. The treatment consists of either wide local excision to achieve clear margins accompanied by nodal dissection or radiation therapy. In advanced stage diseases, survival rates still remain low, but immunotherapy with PD-L1 and PD-1 inhibitors are promising. The increasing incidence, the rapidly and aggressive clinical course as well as some unsolved diagnostic and therapeutic challenges underline the need for a better understanding of MCC. Therefore, the aim of this short review was to present an overview of the current literature regarding diagnosis and treatment of MCC patients.

Keywords: Merkel cell carcinoma; Diagnosis; CK20; Treatment

Introduction

In the early 1970-ties Dr. Toker first identified a trabecular carcinoma with dense core granules that are also present in Merkel cells [1,2]. Dr. Merkel, a German anatomist, described the Merkel cell itself as touch mechanoreceptors of the skin [1,3]. Due to these similarities it was hypothesized that these cells represent the origin of this trabecular carcinoma, which was renamed to MCC from then on. However, recent research suggests that epidermal progenitor cells are the most likely origin of the MCC [4,5]. In 2008, a new human MCPyV was discovered as oncogenic driver in the majority of MCCs. The MCPyV associated MCC pathway is different from the previously known UV-induced mutations. The UV-induced MCC shows mostly a CK20 negative expression pattern whereas MCPyV associated MCC is CK20 positive [6,7]. MCC has shown a dramatically increasing incidence over the last 30 years [8,9]. This rise is explained by improved diagnostic methods and growing age of the population. Particularly, elderly Caucasians within the 6th-7th decade of age and immunosuppression are most at risk [9,10].

Diagnostic Workup

Since MCC initially cause few symptoms, clinicians should bear in mind the AEIOU acronym, standing for asymptomatic, expanding rapidly, immune compromised, older than 50 years, UV-exposed fair skin. MCC lesions appear in 80% as reddish blue colored nodules that occur in not sun-exposed areas [11]. These tumors are MCPyV associated and do express CK20 antigen [12].

In contrast, the second group of approximately 20% of MCCs includes patients with lesions localized in sun-damaged skin areas that are already initially suspicious for non-melanoma skin cancer. These tumors correspond to virus independent UV-induced mutations and are CK20 negative [13]. Finally, the third group represents MCCs of unknown primary with nodal disease without any detectable skin lesions [14].

Diagnosis of MCC is made by histology based on haematoxylin-eosin stains showing small round blue tumor cells with mitoses and finely dispersed chromatin ("salt-and-pepper appearance"). The most important immunohistochemical marker for MCC is CK20 that proofs diagnosis in 85% - 95% [15]. The remaining CK20 negative MCC can be identified by a neurofilament (NF) positivity and thyroid transcription factor 1 (TTF-1) negative expression pattern [16,17].

Initial diagnosis of MCC is often delayed, because of its rarity and unspecific clinical presentation. In clinical routine MCC tumors are often biopsied or inaccurately resected with close margins that is unfortunately linked to a higher incidence for recurrent disease, poorer response to postoperative radiotherapy and a higher mortality [18]. As a consequence, clinical suspicion of MCC should lead to a wide local excision with clear margins as primary diagnostic workup. Further clinical workup includes staging according the AJCC 8th edition [19], whereas defining the nodal involvement is key for further treatment. In particular, the biggest challenge is the presence of occult lymph node metastases that occur in 25% to 30% of cases [20,21]. At our department, we strictly recommend FDG-PET/CT imaging for first radiologic work up. Unfortunately, due to prolonged waiting times caused by restricted capacities, patients can be also accurately staged by ultrasonography, CT and MRI scans [22,23].

Treatment

As already mentioned, MCCs are treated primarily with wide local excision to achieve at least 1-2 cm clear margins. However, if margins are positive after resection, either re-resection or if no further surgical intervention is possible, primary radiation therapy is warranted. Nodal disease should be treated by surgical resection but patients who are not eligible for surgery under general anaesthesia can also be treated with radiotherapy [24,25]. For MCC patients with distant metastatic disease, effective treatment options still remain limited until today (26). However, novel immunotherapies with PD-1 and PD-L1 immune checkpoint inhibitors showed promising data that recently resulted in an updated NCCN guideline [27].

Conclusions

MCC is a highly aggressive skin malignancy with a significantly raising incidence. Carcinogenesis is either associated with the MCPyV infection or UV-induced mutations and the mainstay of histopathologic diagnosis represents the CK20 expression. Clinical suspicion of MCC should lead to wide local excision of the primary tumor with clear margins instead of diagnostic biopsies at the initial presentation. After staging with FDG-PET/CT and/or ultrasonography, CT and MRI imaging, regional lymph node dissection is recommended to confirm lymph node status. The treatment therefore consists of surgery with wide resection with/without neck dissection and adjuvant radiation therapy or primary radiotherapy. Treatment of distant metastatic disease remains limited but new immunotherapies with PD-L1 and PD-1 inhibitors showed promising results.

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