Merkel cell carcinoma

J. C. Becker*

Division of General Dermatology, Medical University of Graz, Austria

Merkel cell carcinoma (MCC) is a highly aggressive neuroendocrine carcinoma of the skin. The incidence of this rare tumor is increasing rapidly; the American Cancer Society estimates for 2008 almost 1500 new cases in the USA. Thus, the incidence of MCC will exceed the incidence of cutaneous T-cell lymphoma. Moreover, the mortality rate of MCC at 33% is considerably higher than that of cutaneous melanoma. These clinical observations are especially disturbing as we are only recently beginning to understand the pathogenesis of MCC. For the same reason, the therapeutic approach is often unclear; reliable data are only available for the therapy of locoregional disease.

Key words: carcinogenesis, epidemiology, neuroendocrine carcinoma of the skin, polyomavirus, signal transduction

epidemiology

Merkel cell carcinoma (MCC) is a very aggressive carcinoma of the skin [1]. In 1972 Toker described five patients with unusual skin tumors where histologically anastomosing trabeculae and cell nests in the dermis dominated, so that he used the name ‘trabecular carcinoma of the skin’ [2]. Subsequently, the discovery of electron-dense neurosecretory granules in the tumor cells permitted their classification among the neuroendocrine carcinomas. As Merkel cells, which belong to the amine precursor uptake and decarboxylation system (APUD) system, are the only cutaneous cells that form such granules, it was postulated that these carcinomas derived from these cells. Notably, very recent evidence indicates that Merkel cells derive from pluripotent epidermal stem cells [1]

The American Cancer society predicted for 2008 1500 new cases of MCC in the USA alone; the incidence of MCC would thus exceed that of cutaneous T-cell lymphomas (http://www.cancer.org). Similar data have been reported for Australia [3]. Within a 15-year period from 1986 to 2001 the age-adapted incidence of MCC rose with a statistically significant annual increase of 8% [4]. This rise is more dramatic than the increased incidence of cutaneous melanoma. Even though the incidence of melanoma, which is primarily due to the higher number of melanomas diagnosed early, has risen drastically in past decades, the age-adapted increase rate in incidence in the time period between 1986 and 2001 was only 3% annually. Furthermore, the mortality rate of MCC at ~33% is definitively higher than that of melanoma.

MCC is a carcinoma of the elderly; the mean age of patients at the time of initial diagnosis is ~70 years. MCC patients are often immunosuppressed. For example, MCC occurs much more frequently in patients with organ transplants and HIV infections (12/100 000/year) and at a significantly younger age (~50% <50 years) [5]. Accordingly, there is a high degree of association of MCC with squamous cell carcinoma, basal cell carcinoma, Bowen disease, internal malignancies and hematological neoplasias. The role of UV light in the development of MCC is seen more as an immunosuppressive than as a mutagenic/carcinogenic effect. Pathogenetically, in addition to disturbed antigen presentation, the induction of immunosuppressive cytokines such as interleukin (IL)-10 and tumor necrosis factor α (TNF-α), the isomerization of trans-urocanic acid to cis-urocanic acid and the formation of reactive oxygen species are blamed [6, 7].

clinical features and histology

MCC characteristically develops rapidly over weeks to months on chronically sun-damaged skin as a firm-elastic red to livid hemispherical tumor with a smooth, shiny surface [1, 8]. The typical clinical features of MCC can be explained by the fact that the tumor usually grows in a hemispherical fashion to the outside and in an iceberg-like fashion in depth, so that the intact epidermis is stretched. In addition to the frequent hemispherical or nodular forms, more rarely plaque-like variants occur, especially on the trunk. Even initially MCC grows in an infiltrating manner, but ulcerations are very rare and are observed only in very advanced tumors. Satellite metastases can occur quite early.

Due to the relatively uncharacteristic features of MCC, the diagnosis in most cases is first made on the basis of histopathology [9, 10]. Histologically, MCC appears as an asymmetric dermal tumor with irregular margins composed of tumor cells arranged in strands or nests [10]. The tumor spreads into the reticular dermis and subcutis; the papillary dermis, epidermis and adnexa are usually spared. With hematoxylin–eosin staining the cells are monomorphous and display a typical nuclear chromatin pattern. The tumor cells are characterized by a large, relatively pale nucleus. The cytoplasm is scant and contains argyrophil granules and often
MCC is not yet fully understood, but reports are increasing that contribute to a better understanding [13].

The classical mitogen-activated protein (MAP) kinase signaling pathway plays a key role in many processes such as proliferation, suppression of apoptosis, migration and differentiation. The relevance of the Raf/MEK/ERK cascade for tumorigenesis has been evident for a long time, but was underlined in 2002 with the discovery that B-Raf, one of the three isoforms of Raf, is present in a mutated form in many tumor entities. The B-Raf mutation analysis of MCC samples surprisingly shows no activating B-Raf mutations [14]. Furthermore, immunohistochemical studies showed that despite high proliferation indices and existing expression of ERK, the ERK protein generally occurs in the non-phosphorylated form and is thus inactive.

The inactivity of the MAP kinase pathway together with the report that inhibition of Ras farnesylation by apoptosis induction suppresses the growth of MCC xenografts in the naked mouse model [15] suggest that another Ras-dependent signaling pathway may be of special relevance in MCC. The most important Ras-regulating signal pathway next to the Raf/MEK/ERK cascade involves class 1 phosphoinositide 3 kinase (PI3K) and the Akt kinase.

The antagonist of PI3K that dephosphorylates PIP3 is the phosphatase and tensin homolog deleted in chromosome 10 (PTEN) that is frequently inactivated in human tumors, including MCC. Akt develops its anti-apoptotic and cell cycle-regulating effects via a series of target molecules (>30 have already been described) such as e.g. the pro-apoptotic protein Bad, pro-caspase 9, forkhead transcription factors or the pro-apoptotic protein Bcl-2. Additionally, Akt can directly phosphorylate and activate Bad, pro-caspase 9, forkhead transcription factors or the pro-apoptotic protein Bcl-2. Akt regulatory effects are mediated via a series of target molecules (PTEN) that is frequently inactivated in human tumors, including MCC. Akt regulates the expression of genes involved in the control of the cell cycle, the induction of apoptosis or senescence and DNA repair [19]. p53 mutations are occasionally observed in MCC. In 3 of 15 tumors examined and in 2 of 6 MCC cell lines p53 mutations were present [20, 21]. Moreover, the previously mentioned apoptosis induction associated with p53 depression in MCC xenografts [15] suggests that the regulation of p53 expression or stability may be disturbed in MCC.

Table 1. Immunohistochemistry of Merkel cell carcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Primary tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Diameter &lt; 2 cm</td>
</tr>
<tr>
<td>Ib</td>
<td>Diameter &gt; 2 cm</td>
</tr>
<tr>
<td>II</td>
<td>Locoregional metastases</td>
</tr>
<tr>
<td>III</td>
<td>Distant metastases</td>
</tr>
</tbody>
</table>
The proteins whose expression is induced by p53 include p21. Together with p27 and the proteins of the Ink4 family p21 belongs to the inhibitors of cyclin-dependent kinases (CDKs). These CDK inhibitors, expressed upon various extra- and intracellular stimuli, can prevent the transition from the G1 to the S phase of the cell cycle [22]. By binding to cyclin/CDK complexes these are inactivated and the phosphorylation of Rb1 (product of the retinoblastoma susceptibility gene) does not take place. Rb1 is a key molecule in gene expression promoting the G1/S transition. The Rb1/E2F signaling pathway is of such central significance for the control of cell proliferation that it is assumed that its regulation is disturbed in practically all tumors. Gene loss or inactivating mutations of Rb1, viral Rb1-incativating oncoproteins (e.g. human papilloma virus E7 or polyoma virus large T antigen), overexpression and activating mutations of CDKs, as well as inactivating mutations and loss of expression of p16Ink4a and p15Ink4b have been described. For MCC little data on the regulation of the cell cycle by Rb1 exist and studies on a possible loss of Rb1 are contradictory. Leonard and Hayard [23] found LOH for the marker D13S233 (13q14.3), which is located close to the Rb1 gene, in 18 of 24 MCC samples examined. Furthermore, in all MCC cell lines they analyzed, no Rb1 could be detected by western blot. In contrast, Popp et al. [20] reported no loss of the 13q region in 10 MCCs analyzed by comparative genome hybridization.

Recently Feng and coworkers [24] were able to provide evidence of possible viral oncogenesis. They studied MCC samples using digital transcriptome subtraction (DTS), a method with which the same working group has already identified Kaposi sarcoma-associated herpesvirus type 8. These studies resulted in the discovery of a genome encompassing 5387 bp of a new polyomavirus, the Merkel cell polyomavirus (MCV). Since the discovery of the mouse polyomavirus by Gross in 1953, polyomaviruses have been suspected as possible causes of cancer in humans. Even though polyomaviruses can induce tumors in animal models, there has not yet been any definitive proof that they play a relevant role in human carcinogenesis. These small (40–50 nm in diameter) double-stranded DNA viruses code for several proteins, among them large T(tumor) antigen, in their circular genome [25]. The large T antigen regulates the life cycle of the virus as well as the cell cycle of the host cell. The last occurs via interaction with the tumor suppressor gene p53 and the members of the retinoblastoma (RB) gene family. This viral stimulation of the cell cycle is the main driving force of the oncogenic potential of polyomaviruses. Polyomaviruses often induce latent infections without manifest disease, but can, e.g. in an immunosuppressed host, induce tumors. In animal models tumor development is usually preceded by the integration of the polyomavirus DNA into the host genome. Interestingly, Feng and coworkers [24] report that in six of eight MCV-positive tumors viral DNA was found integrated in the tumor genome. Integration occurs in a fashion that leads to the assumption that MCV infection/integration occurs before the clonal expansion of the tumor cells. Indeed, we could recently demonstrate that expression of the oncogenic T antigens is mandatory for maintenance of MCC cell lines [26].

**staging, prognosis and follow-up**

For initial staging the current guidelines recommend ultrasonography of the draining lymph nodes and the abdomen as well as a chest X-ray [9]. Further imaging should be considered for unclear findings. Due to the high frequency of lymphatic metastases, sentinel lymph node biopsy is generally performed and reveals micrometastatic involvement in ~25% of cases [27, 28]. The presence of micrometastases in the sentinel lymph nodes appears to denote poorer prognosis. When distant metastases are expected the appropriate imaging of the various organs should be performed [29]. Somatostatin receptor scintigraphy does not appear very suited to determining tumor spread. The value of the recently introduced 68gallium-DOTATOC PET is currently being investigated [30].

The stage classification for MCC is not uniformly defined. Usually the stage classification shown in Table 2 is employed [9]. Very likely consideration of the lymph node status will lead to improved appraisal of the prognosis [28].

The 5-year survival rate of MCC patients is 75%, 59% and 25% for primary tumors, lymph node metastases (and/or local recurrences) and distant metastases, respectively. Most recurrences occur within 2 years of diagnosis of the primary tumor [1, 8, 4]. Retrospective studies on >400 patients reported in the literature reveal the following unfavorable prognostic factors: advanced tumor stage (locoregional metastases or distant metastases), male gender, location of the primary tumor in the head-and-neck region or on the trunk and the presence of immunosuppression. Prognostic significance is also assigned to the histological type: the trabecular type is the best differentiated, while the small-cell type is least differentiated; measuring tumor thickness also appears to allow for prognostic classification [10, 31, 32]. Further histological characteristics of prognostic significance are the presence or absence of tumor-infiltrating lymphocytes [33, 34].

To date no scientifically founded studies on follow-up of MCC exist. In most German departments of dermatology in the first year tight control at short intervals of 6 weeks is done.

<table>
<thead>
<tr>
<th>Factor</th>
<th>MCC</th>
<th>B-cell lymphoma</th>
<th>Melanoma</th>
<th>Small-cell lung cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK20</td>
<td>+a</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Vimentin</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Neurofilaments</td>
<td>+b</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Chromogranin A</td>
<td>+/-</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>(CgA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuron-specific enolase (NSE)</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+/-</td>
</tr>
<tr>
<td>S100</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Leukocyte common antigen (LCA)</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Thyroid transcription factor 1 (TTF-1)</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

aPlaques.
bIn the majority of cases.
due to the risk of local recurrences and regional lymph node metastases [1]. After this in the following year follow-up is quarterly and after this at half-year intervals. In the course of follow-up, in addition to clinical examination with lymph node palpation, lymph node sonography especially of the regional lymph node basins is performed. Once-yearly abdominal sonography and a chest X-ray or perhaps other forms of imaging are performed. The role of determining serum markers such as e.g. chromogranin A or NSE in improving evaluation of prognosis or early detection of metastases is unclear [35, 36].

therapy

For primary tumors without indications of the presence of organ metastases complete surgical excision is the basic therapy [37, 38]. Due to the high rate of local metastases, which can be attributed to subclinical satellite metastases, if possible, a safety margin of 3 cm should be observed [9, 39, 40]. In special locations where balancing the entire situation necessitates a smaller safety margin, this should be compensated by a complete histological examination of the excision margins including immunohistology to detect CK20 and perhaps radiation therapy intervention [40, 41]. When micrometastases are found in the sentinel lymph node, this should be followed by complete lymphadenectomy [26].

MCCs are usually radiosensitive [42, 43]. Retrospective analyses show that the high local recurrence rate after R0 surgery of the primary tumor alone can be reduced significantly by combined locoregional adjuvant radiation therapy (surgical scar with 3 cm safety margin as well as regional lymph node basin) [1, 44]. For primary MCCs and local recurrences adjuvant radiation therapy of the tumor region and the regional lymphatic draining basin is recommended [9, 45, 46]. The required total dose is considered to be 50 Gy with a single dose of 2 Gy five times weekly. For MCCs at the stage of distant metastases radiation therapy is employed in a multimodal therapy concept in addition to surgical excision and/or systemic chemotherapy [43, 38]. This approach must be adapted to the individual case and is usually done with a palliative intention. Even though MCC is considered a chemosensitive tumor, an evidence-based standardized chemotherapy does not yet exist. Due to morphological similarities in the past schemes that are established for small-cell lung cancer have often been chosen; these include, among others, anthracyclines, antimebolites, bleomycin, cyclophosphamide, etoposide and platinum derivatives singly or in combination [9, 47–49]. With administration of these in part highly toxic regimens relatively high remission rates of up to 70% are achieved, but due to the generally short duration of remission this does not lead to a significant increase in survival time. It appears that complete healing is not achieved in this stage of the disease. It is further significant that there is obviously no correlation between intensity of therapy and response. Therefore, systemic chemotherapy is indicated as a palliative measure when distant metastases are present, but, especially due to the high degree of toxicity of most chemotherapeutic agents for elderly patients (limited hepatic and renal function as well as hematopoiesis), it must be adapted to the individual case. Well-tolerated monotherapies include etoposide or anthracyclines, e.g. liposomal encapsulated doxorubicin [9].

The description of Merkel cell polyomavirus by Feng et al. [24] by making a viral oncogenesis of MCC possible opens new therapeutic possibilities such as e.g. use of interferons with their antiviral effects or the development of immunotherapeutic strategies. For the latter target antigens include not only viral proteins but also proteins induced by polyomaviruses such as survivin. To date only sporadic case reports exist where immunotherapy agents have been used in MCC. Anecdotal case reports exist on the successful use of TNF-α, interferon-α (IFN-α), anti-CD36 antibodies or vaccines [50].

Imatinib is a tyrosine kinase inhibitor successfully used in the treatment of chronic myelogenous leukemia, gastrointestinal stromal tumors and dermatofibrososarcoma protuberans. The rationale for administering imatinib for MCC is based on the observation that the receptor tyrosine kinase Kit is often expressed in tumor tissue [51, 52], while normal Merkel cells are predominantly Kit negative. Activating Kit mutations have indeed not yet been found in MCC [53]. A recent study to test the clinical efficacy of imatinib therapy in advanced MCC had to be discontinued due to lack of efficacy [54].

The role of treatment with somatostatin analogues (octreotide, pasireotide) has been reported controversially in small case series or case reports [55–57].

conclusions

Our knowledge on the biological behavior of MCC and existing data on optimum treatment of this disease are limited. As for other diseases where no prospective randomized studies exist, an interdisciplinary consensus has established treatment guidelines that are regularly updated [9].

disclosure

Professor Becker has indicated that he is a member of speakers’ bureaux for Cephalon Pharma, BMS and Novartis, and a consultant for BMS and Novartis.

references
