Merkel cell carcinoma

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ABSTRACT

Merkel cell carcinoma (MCC) is a rare cutaneous malignancy, with aggressive behaviour. The discovery of MCC polyomavirus (MCPyV) provided a major insight into pathogenesis of MCC, as MCPyV is present in most MCC tumours. The primary treatment of locoregional MCC is surgery, and sentinel lymph node biopsy should be performed in all cases at clinical stage I-II. Adjuvant radiotherapy decreases disease recurrences in stage I-III of the disease. Chemotherapy is primarily used for palliation and provides overall response rates of approximately 70%; however, the disease often recurs within a few months. All cases of MCC should be managed in an experienced multidisciplinary setting.

KEY WORDS: cutaneous neuroendocrine carcinoma, Merkel cell carcinoma, therapy

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare neuroendocrine cutaneous malignancy with an aggressive behaviour. It was first described by Cyril Toker in 1972 [1].

The incidence rate of MMC is low. It is estimated at 0.23 cases per 100 000 Caucasians. People of European origin are at a significantly higher risk of developing MMC (which may be attributable to insufficient levels of melanin providing protection for the skin) [2–5].

MCC rarely occurs in patients younger than 50 years of age. The rate of incidence is significantly higher among elder patients which may point to an accumulation of oncogenic processes. The average age of patients is 69–75 years. MCC occurs 1.5–2 times more often in male patients than female patients.

The risk of developing MCC is 11 times higher for people with AIDS and other disorders in the cell response of the immune system as well as B-type lymphomas. Another key factor in MCC development is exposure to ultraviolet radiation [1, 2].

In 2008, researchers discovered a polyomavirus which they named *Merkel cell polyomavirus* (MCV). It is responsible for approx. 80% of all MCC cases. The researchers proved that MCV occurs naturally in the majority of human population without causing any symptoms. Similar to the Kaposi's sarcoma caused by the herpes virus, MCV mutates in case of an immunodeficiency [1, 2].

MCC occurs most often on sun-exposed areas of the skin. 50 –60% of cases originate on the head and neck, 30–40% on the extremities, less frequently on the rump and extremely rarely on genitals [1–4, 6–12].

It is difficult to estimate the dynamics of MCC at the beginning. Its course may be relatively slow or very rapid. It may progress locally or metastasize to distant organs [1, 2, 13].

CLINICAL CHARACTERISTICS

In terms of morphology, MCC is a rapidly enlarging nodule or reddish mass with a shiny, smooth surface, with multiple telangiectasias around the primary site [14]. Patients rarely have more than one nodule/mass. MCC usually presents without symptoms and takes the form as a reddish neoplasm which enlarges rapidly in immunosuppressed patients, elderly patients and patients whose skin has been damaged by ultraviolet light. MCC originates in the skin. However, it may infiltrate both underlying structures and the epidermis. Unlike with other neuroendocrine tumours, endocrine symptoms are rarely a part of the clinical presentation of MCC. It spreads through lymph and blood vessels. Small MCC's, below 20 mm in size, are capable of metastasizing through cutaneous lymph vessels, leading to formation of satellite nodules [2, 13, 14].

At the point of diagnosis, in 50% cases MCC has already metastasized to lymph nodes and in 35% cases to distant organs. Metastatic foci beyond lymph nodes are most frequently located in the skin (28%), liver (13%), bones (10%) and brain (6%). They are less frequently found in the bone marrow (1.6%), pleura (1.6%), pancreas (0.8%), testicle (0.8%), bladder (0.8%) and stomach (0.8%) [2, 9–12].

The relevant literature reports on the spontaneous regression of even advanced lesions.

DIAGNOSIS

On presentation of clinical symptoms, diagnosis for MCC is rarely taken into consideration. Primary diagnostic procedures include open biopsy of the primary site or core biopsy in case of larger lesions.

When analysed under the microscope, MCC is a microcellular carcinoma, little diversified, made of small cells (a little larger than lymphocytes) with scant cytoplasm, round nucleus and fine-grained chromatin. Characteristic features include numerous mitotic figures, apoptotic cells and necrotic foci. There are abundant capillaries in the stroma. Preparations stained with haematoxylin and eosin show that intermediate filament clusters change colour and can be observed as spheres near the poles of the nucleus, which is a diagnostic test for this type of tumour.

MCC cells are similar to epithelial and neuroendocrine cells in terms of the ultrastructure and antigen structure. To date, it has not been finally determined whether MCC originates from normal Merkel cells.

Neurosecretion granules are also present in the MCC cells. Under the light microscope, MCC can be hardly distinguished from small-cell lung cancer, lymphomas, Ewing's sarcoma and neuroblastoma. This is why immunohistochemical test must be performed to confirm positive reaction to cytokeratin CK20, thyroid transcription factor 1 (TTF-1), chromogranine A and synaptophysis, and to establish that there is no reaction with S 100 and leukocyte antigen [1, 14].

TNM STAGING SYSTEM

The AJCC developed the new TNM classification of the Merkel cell carcinoma 2010 [15, 16] (Tables 1–4).

TABLE 1.
T – original tumour.

TX	Primary tumour cannot be assessed.
T0	No evidence of primary tumour.
Tis	Carcinoma in situ.
T1	Tumour 2 cm or less in greatest dimension.
T2	Tumour more than 2 cm but 5 cm or less in greatest dimension.
T3	Tumour more than 5 cm in greatest dimension.
T4	Tumour invades tissues such as bones, muscles, fascia and cartilage.

TABLE 2.
N – regional lymph nodes.

NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
cN0	Regional lymph nodes negative by clinical exam[a] (no pathologic node exam performed).
pN0	Regional lymph nodes negative by pathologic exam.
N1	Metastases in regional lymph nodes.
N1a	Micrometastasis[b].
N1b	Macrometastasis[c].
N2	In transit metastasis[d].

[a] Clinical detection of nodal disease may be via inspection, palpation and imaging.
[b] Micrometastasis – metastasis found by pathologic exam but not found by clinical exam. The size of focus under pathologic exam is irrelevant for grading as micro- or macrometastasis.
[c] Macrometastasis – metastasis found in clinically suspicious regional lymph nodes (metastasis is confirmed by BAC or by histological exam of nodes removed by therapeutic lymphadenectomy).
[d] In transit metastasis – a tumour distinct from the primary lesion and located either between the primary lesion and the regional lymph nodes or distal to the primary lesion.

TABLE 3.
M – distant metastasis.

M0	No distant metastasis.
M1	Metastases beyond regional lymph nodes.
M1a	Metastases to skin, subcutaneous tissues, or distant lymph nodes.
M1b	Metastases to lungs.
M1c	Metastases to all other visceral sites.

TABLE 4.
Tumour stage.

Stage	T	N	M
0	Tis	N0	M0
IA	T1	pN0	M0
IB	T1	cN0	M0
IIA	T2/T3	pN0	M0
IIB	T2/T3	cN0	M0
IIC	T4	N0	M0
IIIA	any T	N1a	M0
IIIB	any T	N1b/N2	M0
IV	any T	any N	M1

Comments on the New TNM classification

1. Depending on which method is used to assess regional lymph nodes, stage I and II tumours are classified as subcategory A if there is no regional lymph node metastasis confirmed by histological exam of the excised nodes, or subcategory B – if the absence of lymph node metastasis was established by clinical exam only.
2. In stage II, subcategory C was identified to encompass lesions in which the primary tumour invades issue other than skin (T4) but there are no regional lymph node metastases (irrespective of the method used for lymph node evaluation).
3. In clinical stage III, subcategory A was identified (metastases in regional lymph nodes confirmed by pathological exam but not identified by clinical exam) and subcategory B (metastases in regional lymph nodes identified by clinical exam).

Pathological grading of progression

1. Pathological grading of disease progression consists in evaluation of regional lymph nodes which have been excised during sentinel node biopsy, and therapeutic or completion lymphadenectomy.
2. The natural course of MCC varies depending on the progression stage at diagnosis identified by a pathological exam.
3. A sentinel lymph node biopsy should be performed for MCC patients (metastasis is identified in 30% histological exams of the sentinel lymph node).

Histological grading of malignancy

Histological grading of tumour malignancy is not performed during assessment of clinical stage of Merkel cell carcinoma.

PROGNOSIS

Once the disease has metastasised to distant organs of the body, the prognosis is poor (the median survival period is 6.8–10 months). In other cases prognosis depends on a number of factors [1, 2, 4, 15]. The following factors are considered to be clinically relevant for the prognosis:

1. the depth of tissue infiltration
2. diameter of the tumour base
3. severe immunosuppression (HIV/AIDS, chronic lymphocytic leukaemia and condition after organ transplantation)
4. presence of tumour infiltrating lymphocytes (TIL)
5. manner of primary tumour growth (nodular or infiltrating)
6. size of tumour cell nests in regional lymph nodes
7. condition of regional lymph nodes
8. tumour infiltration beyond lymph node capsule evaluated during histological exam of regional lymph nodes after metastasis has been identified
9. presence of isolated tumour cells in regional lymph nodes.

In stage I, the disease can be controlled better by combining the-rapeutic surgery with irradiation. Treatment is ineffective in 26% cases while a maximum of 22% patients experience a recurrence. The five-year survival rate among stage 1 MCC patients is 64%.

TREATMENT

Merkel cell carcinoma requires aggressive therapy owing to its high recurrence rate (20–75%) and frequent metastasis to regional lymph nodes (31–80%) and distant organs (26–75%). At present, surgical excision of the tumour involving microscopic monitoring of tissue margins is considered to be the preferred procedure for MCC. The tissue margins should be between 1 and 3 cm [2, 17]. In case of lesions located on the head or neck such large margins are unfeasible. This is why most often a surgical margin of 1–2 cm is used, and the surgery is combined with adjuvant radiotherapy at doses of at least 50–55 Gy [18].

In clinical stages I and II of the disease, when there is no evidence of lymph node metastasis in a clinical exam, apart from the wide excision of the lesion a sentinel lymph node biopsy is recommended with a follow-up lymphadenectomy in case the biopsy result is positive [2, 17, 19]. In case lymph node metastases are identified, adjuvant radiotherapy should be provided to the patient, which significantly statistically extends progression-free survival but has no effect on the long-term survival.

When planning radiotherapy, a 3–5 cm margin should be added to the area of the tumour bed to cover local lymph flow. Where the sentinel lymph node has not been biopsied, the regional lymph flow may also be electively irradiated. In case the margins are smaller than 3 mm or positive, the total dose of radiotherapy must be increased or, in some medical facilities, chemotherapy is recommended. Where there is no possibility to perform a radical excision of the tumour, the total dose must also be increased or radiotherapy must be used in combination with interstitial brachytherapy.

Distant metastases are an indication for chemotherapy. Owing to structural and histological similarities, the same chemotherapeutic agents are used as those used for small-cell lung cancer: cyclophosphamide, doxorubicin, vincristine, cisplatin and etoposide [2].

The future of advanced therapies for MCC is linked with development of immunotherapy and further research on MCPyV's role in the pathogenesis of this tumour [1].

SUMMARY

Merkel cell carcinoma is a rare malignancy with an aggressive behaviour [18]. Local excision of the tumour alone, without adjuvant radiotherapy often proves insufficient because 73% patients experience a local recurrence of the disease and 48% patients develop a metastatic disease. Given that MCC spreads easily through skin lymph vessels, a sentinel lymph node biopsy should be performed to improve planning of effective therapy. Currently, the primary treatment method of locoregional MCC is surgery and radiotherapy. The role of chemotherapy in MCC treatment is controversial and it is primarily used for palliation. Systemic treatment is initiated in case of lymph node metastasis, locoregional recurrence (with no option for surgical treatment or radiotherapy) and metastatic disease. All cases of MCC should be managed in a multidisciplinary setting [2, 20].

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