Merkel cell carcinoma. A review

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Background. Merkel cell carcinoma (MCC) is a rare potentially fatal skin tumour affecting older mainly white people and younger immunosuppressed individuals. While uncommon, the incidence is increasing relative to melanoma and with twice the lethality. The benign appearance of the tumour usually on exposed skin parts, contrasting with its extensive microscopic invasion, can delay timely diagnosis. Recurrent MCC is currently attributed to the recently discovered Merkel cell polyomavirus. This brief review of MCC covers the history, epidemiology, etiology, clinical and histological features, treatment and prognosis.

Methods. Literature search using PubMed and search words Merkel cell carcinoma (MCC), etiology, treatment for the years 1972 to 2010.

Results and conclusion. Merkel cell carcinoma is a rare malignancy with uncertain prognosis. Due to the uncommon occurrence and dearth of randomized studies, there is no agreement on optimal treatment. The tumor has only recently been included in the international classification of tumors (NCCN). The treatment approaches found to be best are radical surgery of primary tumor, drainage of lymph node extension and possibly adjuvant loco-regional radiotherapy. The basis of successful treatment however, remains prevention regular dermatological examination in immunosuppressed patients and early initiation of combination therapy, based on radical surgery supplemented by radiotherapy and palliative chemotherapy in the last resort.

Key words: merkel cell carcinoma (MCC), etiology, treatment

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INTRODUCTION

Merkel cell carcinoma (MCC) is a malignant neuro-endocrine tumor first described by Toker in 1972 as a "trabecular carcinoma of the skin" from its characteristic microscopic structure¹. The term "Merkel cell carcinoma" was used prior to the 1980s but the tumor had been known under various synonyms before this. Merkel cells, located in the basal layer of the epidermis and hair follicle form a picture of large light cells, synaptically connected to the sensory nerve endings¹. In vertebrates, Merkel cell nerve endings are cutaneous mechanoreceptors but the origin of Merkel cells is unclear. They may originate in the epidermal epithelial cells or neural crest from where they later migrate into the epidermis. Their differentiation from the main pluripotent cells is dependent on the essential transcription factor Atoh1 (factor atonal homolog 1) (ref. ²)

Epidemiology, etiology

Merkel cell carcinoma is rare, with an incidence of around 5 cases per 1 million population and extremely rare in children^{3,4}. Though the trend is increasing, it is many times rarer than malignant melanoma⁵ occurs mainly in people older than 65, more in men and those

with immune dysfunction due to cancer, HIV infection or transplantation. The high incidence of post transplant malignancies is closely related to the length and type of immunosuppressive therapy used as a number of studies have shown that the intensity of the immunosuppression is directly related to the incidence of post transplant tumours^{6,10}. Immunosuppression has been shown to lead to DNA damage⁷. Some post-transplantation malignancies are related to oncogenic viruses (eg EBV, HPV and MCPyV) (ref.⁸) and in transplantation patients there is increased metastatic potential via blood, lymphatic and perineural invasion^{9,10}.

For MCC, described is also the simultaneous occurrence of other tumors such as breast and ovarian cancer, blood malignancies and anaplastic meningiomas. One likely trigger is UV radiation¹¹.

In the etiology of MCC, several chromosomal abnormalities have been described, the most common being chromosomes 1, 6, 11 and 16 but the best known are trisomy of chromosomes 1 and 6. DNA alterations have been reported primarily in advanced tumors with a three-fold risk of metastasis over tumors without involvement of DNA. Recurrent malignant Merkel cell tumours have recently been connected to infection with the "Merkel cell polyomavirus" (MCPyV) (ref.⁸)

Clinical and histological features

Merkel cell carcinoma occurs mainly on the face and neck (40-60%), followed by the trunk (33%) and rarely on the extremities (10-20%) (ref.¹²). On the face the main sites are the cheeks and eyelids but it also occurs on the lips, forehead and nose. The literature also describes the gluteal area where it may mimic a cyst and cause late diagnosis¹³. Clinically it manifests as a solid, painless tumor exophytic in character, skin colored, sometimes reddish, with a very aggressive growth^{14,15}. The flat form may also occur. The differential diagnosis must involve distinction from basocellular and squamous cell carcinoma which are common skin malignancies in parallel or skin metastasis from another primary site. Other possibilities are malignant lymphoma, keratoakanthoma, amelanoblastic melanoma and deeply located parts of a cyst¹³. A tumor that has been removed very often recurs locally and metastasizes early to lymph and blood vessels. The incidence of malignancies of any duplicate (see above) significantly worsens the prognosis and mortality increases several times. The macroscopically seemingly enclosed form of the cancer contrasts with its tendency to microscopic

spread to distant sites. Most of the nodules are localized tumors in the dermis: only 10% of Merkel cell tumors are intraepithelial. The cytological picture is characterized by dull, monotonous medium size nuclei with numerous mitoses. Histologically there are three types of tumor. The trabecular type, described as a typical Toker trabeculae construction involving adnexa such as hair follicles¹. This is the least frequent. The intermediate type and variant based on small cells occur more frequently and are much more malignant^{16,17}. Exceptionally, there is no transitional form of the cancer.

Immunohistochemically, the tumor can be marked with the help of epithelial and neuroendocrine markers. Epithelial markers include low molecular weight cytokeratins (8, 18, 19, 20) of which for diagnosis, the major one is cytokeratin 20 (CK - 20) (ref.^{18,19}). CK - 20 is formed in the epithelial cells of the gastrointestinal and urinary system and Merkel cells. However, in 5% - 25% of MCC, CK-20 positivity is not found. Another epithelial marker which controls the determination and differentiation of cells is thyroid transcription factor 1 (TTF - 1), consisting of epithelial cells of the thyroid gland, lung and

Table 1. Use of immunohistochemical markers in the diagnosis of Merkel cell carcinoma (source: Koljonen, Merkel cell carcinoma, World Journal of Surgical Oncology 2006,4:7).

	CK-20	TTF-I	NSE	S-100	GrA	SYP	NFP	CD56	MAP-2	LCA
MCC	+	-	+	-	+/-	+/-	+	+	+	-
SCLC	-	+	+/-	-	-/+	+	-/+	+	+	-
MM	-	-	-	+	-		-		+	-
LGNEC	+		+		+	+	-/+			
Malignant lymphoma	-	-	-	-	-		-/+			+

+ positive, + / - Mostly positive, + / - Mostly Negative - Negative. CK20 - cytokeratin 20, TTF I - thyroid transcription factor I, NSE -neuron-specific enolase, GRA - chromogranin A NFP -neurofilament proteins, CD56 - neural adhesion molecule, MAP-2 microtubule associated protein, LCA - leukocyte common antigen, SCLC -small cell lung carcinoma, MM - malignant melanoma, LGNEC - low-grade neuroendocrine carcinomas.

Table 2. The prognosis.

	T	N	M	5 year survival
Stadium 0	Carcinoma in situ	Regional metastasis absent	Distant metastasis absent	
Stadium I	> 2 cm	Regional metastasis absent	Distant metastasis absent	81%
Stadium II	< 2 cm	Regional metastasis absent	Distant metastasis absent	67%
Stadium III	Regardless of tumour size	Regional metastasis present	Distant metastasis absent	52%
Stadium IV	Regardless of tumour size	Regional metastasis present	Distant metastasis present	11%

brain²⁰. It is mainly used in the differential diagnosis of MCC and small-cell lung cancer where the TTF is positive and CK - 20 negative²¹.

One standard marker used in the diagnosis of neuroendocrine tumors is neuron-specific enolase (NSE) (ref.^{22,23}). More recently, markers used in the diagnosis of MCC are CD56 and NCAM (neural cell adhesion molecule) (ref.^{24,26}). Likewise, chromogranin A (CrA) is another representative marker in the diagnosis of endocrine tumors²⁶. MCC is demonstrated by positive immunoreaction to CrA. Recently discovered neuroendocrine markers are microtubule-associated proteins (MAPS) which form part of the microtubule cytoskeleton of proteins in the peripheral and central nervous system^{27,28}. Most often used is the MAPS - 2 marker which has high sensitivity and specificity. Liu et al.²⁶ found a positive MAPS - 2 in all patients with MMC while the marker CK - 20 was not in all cases conclusive. In general, we can say that MCC shows itself as a neuroendocrine tumour. The immunohistochemical distinction between Merkel cell carcinoma and other malignancies is shown in Table 2.

In microscopic images, it is necessary to distinguish between undifferentiated carcinoma, metastasis of lung carcinoma, small cell lymphoma, Ewing sarcoma, rhabdomyosarcoma, neuroblastoma, osteosarcoma and chondrosarcoma²⁹⁻³¹.

Treatment and prognosis

To determine the stage of disease, the recommendation, as in the case of malignant melanoma is PET investigation, to exclude locoregional and distant metastases. For a large microscopic tumor progression in the surrounding areas, the first choice is radical surgery. The radicality of the excision is similar to malignant melanoma, that is, wide enough with a safety margin of 2-5 cm. For very rare tumors and difficult preoperative clinical diagnosis, after histopathological verification, reoperation is usually required. The radicality of the treatment is proportional to the stage of the disease (Table 1) (ref.³²). In the first and second stages without nodal or distant metastasis, radical excision is performed, accompanied in patients at risk by radiotherapy. In the third stage, where locoregional metastases have occurred, expanding output using draining lymph node removal followed by radiotherapy is done. The total radiation dose is usually 45 – 65Gy (ref.^{33,34}). In the fourth stage, or presence of distant organ metastases, the treatment is palliative involving chemotherapy, supplemented by radiotherapy. The tumor frequently metastasizes to the lungs, liver and bones. The chemotherapeutic agents most commonly used are etoposide and carboplatin³⁵. The most recent treatment for MCC is biological (cetoximab) (ref.³⁶). Another potential therapeutic option is use of the anti-tumor apoptotic and interferon alfa³⁷. After treatment, vital is follow up at regular monthly intervals in the first year, then at quarter year intervals. The total length of the follow-up should be at least five years.

The prognosis is not good but depends on the stage of disease at the time of initiation of treatment. Five-year

survival of I. - II. stage is suggested to be up to 75%, III. stage in 59% and presence of distant metastases, or IV. stage, only 25% (ref.³⁸).

DISCUSSION

As mentioned above, MCC is presumed to be based on the Merkel cell (MC), whose origin is not entirely clear². Second, among Merkel tumor cells there are morphological and biological differences. The frequent presence of neuroendocrine granules, and positivity for cytokeratin 20 (CK - 20) in the case MCC provide evidence that the tumor is based on the MC (ref.³⁹). However, the MC and MCC differ in the characteristic of neurofilaments which are only visible in MCC. Another argument supporting the distinction between MC and MCC, is the characteristic picture of mitosis which is not apparent in the Merkel cell⁴⁰. There are also differences in the localization of tumor and Merkel cells. While the tumor is located practically only in the dermis, Merkel cells are present exclusively in epidermal structures. The question in the debate also remains the cause of the malignant change. One subject of study is the cause of alteration in growth factors, such as α -PDGF (platelet-derived growth factor- α , which has a major role in angiogenesis). Swicka et al.⁴¹ showed a mutation of PDGF receptor- α . In contrast, activating mutations eliminate the c-kit (CD117 syn.) cytokin receptor on the surface of hematopoietic cells, strongly associated with SCF (stem cell factor) important for the assessment of cell differentiation. The tumor tissue also demonstrates high expression of VEGF receptors (vascular endothelial growth factor), specifically, VEGF-A (91%), VEGF-C (75%) and VEGF-R2 (88%) (ref.⁴²). Essential for tumor formation is the failure of cell cycle regulation. In general, important regulators of the cell cycle, preventing uncontrolled cell division, are retinoblastoma protein (RB), factors that inhibit proliferation and tumor suppressor protein p53 as a suppressor gene product inhibits cell proliferation and induces apoptosis⁴³. Both factors are considered crucial tumor suppressor mechanisms and their failure is essential for the emergence of a tumor. Mutations of p53 in MCC have been detected only sporadically which contrasts with p53 mutations in other tumors where they may be up to 50% (ref.^{44,45}). Mutations in p63, a relative of the p53 "family" in MCC significantly correlate with tumor aggressiveness⁴⁶. As mentioned, MCC can form in patients with weakened immune systems. The Merkel Cell Polyomavirus (MCPyV) was described for the first time in January 2008 as one of seven known human viruses that play a role in malignant disease⁸. After the integration of viral DNA into the cellular genome occurs and the expressed small and large T antigen are multifunctional proteins. Large T antigen binds to the cell cycle regulator and tumor suppressor proteins p53 and RB, thereby inactivating which results in stimulation of the cell cycle and the start of oncogenesis. It has become clear however that the virus MCPyV seroprevalence among the general

population is high. Any direct effect of the virus on cancer therefore remain controversial. From a prognostic point of view, positive MCPyV in MCC is unclear and opinions differ.

In the treatment of MCC, prevention plays a crucial role and early excision of the tumor extension. The excision of the tumor using Mohs micrographic surgery was first described by Frederick Mohs in 1930s⁴⁷. The principle of tumor excision is a sharp curette, and other progressive verification of positivity of edges under the microscope. Samples of tissue are taken from the dermis, where the tumor is located until the resection margins are negative and the defect can be reconstructed. Mohs micrographic technique has been recommended especially in areas with high demands on aesthetics, such as localized tumors of head and neck. Brisset et al.⁴⁸ however, point to the lower survival of patients treated with Mohs technique compared to patients with extensive radical excision supplemented by cervical block dissection.

Even though the general nature of the tumor is rapid growth and early metastases, there are published data on spontaneous regression⁴⁹. Mori et al.⁵⁰ observed high apoptotic tumor activity in 8 cases of patients treated for MCC. Inoue et al.⁵¹ studied the mechanism of spontaneous regression in 7 patients (4 patients with spontaneous regression, 3 without spontaneous regression). The study looked at a number of parameters (TUNEL index, labeling index of proliferating cell nuclear antigen (PCNA) labeling index of bcl-2 protein expression of p53 in tumour cells) and extent of lymphocytic infiltration around the tumor. The number of T lymphocytes in the infiltrate was higher in patients with spontaneous regression than in patients where no regression occurred. The frequency of T-lymphocytes in the infiltrate around the tumor is therefore considered one of the main causes of spontaneous regression.

CONCLUSION

Merkel cell carcinoma is a rare malignancy with an uncertain prognosis. Due to the rare occurrence and dearth of randomized studies, optimal treatments are generally not known. The tumor has only recently been included in the international classification of tumors (NCCN). The basis of successful treatment remains prevention, consisting of regular dermatological examination in immunosuppressed patients and early initiation of combination therapy, based on radical surgery supplemented by radiotherapy and chemotherapy in the last resort.

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