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REVIEW ARTICLE

Post-transplant Merkel Cell Carcinoma

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Malignant tumours are the foremost complications of immunosuppressive treatment. They are a major challenge for organ transplant recipients and their treating physicians. This paper reviews the aetiology and current treatment of an unusual neuroendocrine skin cancer, Merkel cell carcinoma (MCC), caused by a Merkel cell polyomavirus infection. MCC occurs more frequently than expected in immunosuppressed subjects, especially in organ transplant recipients. The current literature comprises reports of 79 organ transplant recipients with MCC. The risk of MCC in organ transplant recipients is increased up to 66–182-fold compared with the general population. In addition to the increased risk of developing MCC, immunosuppressed individuals have poorer MCC-specific survival. The aim of this review article is to familiarize organ transplant doctors with this unique and clinically challenging skin cancer, and to provide recent data on the diagnosis and current treatment recommendations for an immunosuppressed population. ***Key words: neuroendocrine carcinoma; skin; malignancy; outcome.***

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The eponym Merkel cell carcinoma (MCC) refers to a rare, poorly-differentiated, aggressive primary neuroendocrine skin cancer with Merkel cell polyomavirus (MCV) association.

In this review we sought to outline and summarize the data for this rare type of skin cancer, focusing especially on post-transplant cases. Furthermore, we sought to introduce the principles of managing this clinically challenging skin tumour, and to illustrate the effects that post-transplantation states have on the behaviour of MCC and how they reflect its line of treatment and prognosis.

OVERVIEW OF MERKEL CELL CARCINOMA

The histological entity of MCC was first founded when Toker described 5 original cases in 1972 (1). Later, dense neurosecretory granules in the cytoplasm of the tumour cells identified the tumour as a neuroendocrine carcinoma.

Histologically, the tumour is a dermal-based lesion with repeated extensions to underlying subcutaneous tissue. The tumour is composed of monotonous small round blue cells with sparse cytoplasm and abundant mitoses (2). Diagnosis is based on typical histology representation on haematoxylin-eosin-stained slides together with the results of immunohistochemistry (3), positivity for cytokeratin 20 (CK-20) and negative staining for thyroid transcription factor 1 (TTF-1). Furthermore, the tumour expresses both epithelial and neuroendocrine markers, and thus exhibits both epithelial and neuroendocrine differentiation (4). As the histology bears resemblance to small round-cell tumours, differential diagnosis can be difficult. MCC can be classified into 3 distinct subtypes; intermediate subtype, which is the most frequent histological subtype, followed by trabecular and small-cell types. However, the clinical significance of subtyping is minimal.

Clinically MCC usually presents with a non-tender, rapidly growing red/pink or blue skin lesion. In the early stages it is usually mistaken for a benign lesion, however, larger lesions have an unmistakably malignant appearance (Fig. 1). The tumour may grow to a considerable size in just a few months and be locally invasive with high metastatic potential. The tumours are staged according the American Joint Committee on Cancer (AJCC) staging system, which takes into consideration the microscopic examination of sentinel node biopsies (SLNB).

Although generally considered as an aggressive tumour, with a high mortality rate (5), MCCs can have a variable clinical course. Outcome data stratified by tumour size, nodal status and distant metastasis show the majority of MCC patients have a relatively good 5-year outcome; approximately 60% of patients with negative sentinel lymph nodes are alive after 5 years, and for those with positive nodal status, the 5-year survival is over 40% (6). Some clinical and pathological prognostic markers are associated with a poor prognosis, comprising male sex, older age (7), increased tumour size (8) and an immunocompromised state. However, the most important prognostic marker is the presence or absence of metastatic dissemination to the local lymph basin (8).

Apart from in the Nordic countries, the overall incidence rates of MCC in men are higher than for

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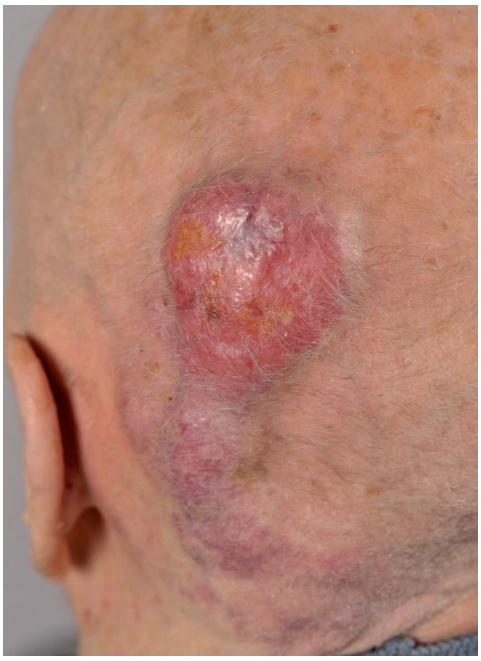

Fig. 1. Typical Merkel cell carcinoma presentation on the head. The tumour presents as solitary nodule with a red-to-purple erythematous colour.

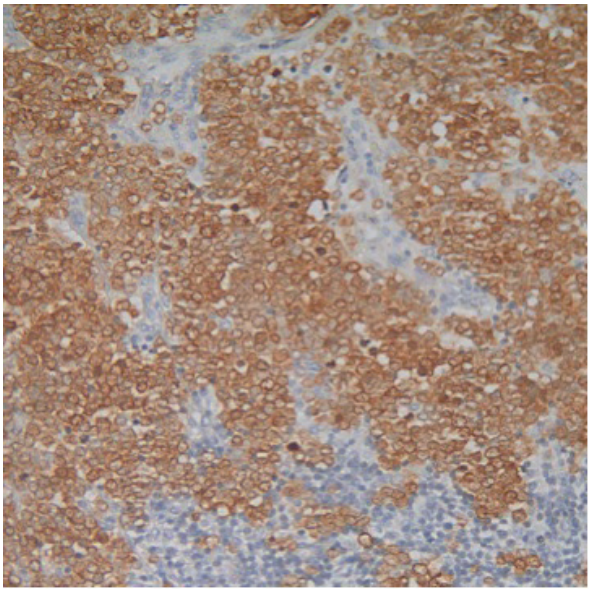

Fig. 2. Example of Merkel cell polyomavirus detection by immunohistochemistry. The Merkel cell polyomavirus is expressed by nearly 100% of the tumours cells. Negative staining consists of stromal cells, lymphocytes and endothelial cells. Original magnification ×200.

women (9). Although MCC is rare, with an incidence of approximately 0.6 cases per 100,000 person-years (9), markedly increasing incidences have been reported globally. Over a relatively short period, of decades, the age-adjusted incidence increased 8% in the USA (10). Advances in diagnostics and the increase in elderly age-groups and sun exposure underlie this phenomenon.

Primary risk factors for MCC include immunosenescence of advancing age, white race, various immunocompromised states and cancer-related immune deficiency. MCC is principally a disease of fair-skinned elderly individuals, with a mean age at diagnosis of approximately 75 years (5). The tumours usually occur on sun-damaged skin of the head and neck and the extremities, offering indirect evidence for UV exposure as an aetiological factor. The specific immunodeficiency-related risk factors include UV-induced immunosuppression, organ transplantation, HIV/AIDS, and autoimmune diseases. Usually an immunocompromising state precedes MCC if it occurs before the age of 50 years (11). Another well-recognized feature is the tendency of MCC to occur in association with other primary tumours, mostly skin and lymphohaematopoietic cancers and, in particular, B-lymphoproliferative disorders (12).

As recently as 2008, a new polyomavirus with double-stranded DNA, named Merkel cell polyomavirus (MCV) was discovered (13) (Fig. 2). MCV is a common, if not ubiquitous, human infection (14). Accumulated data indicate that MCV does not secondarily infect tumour cells. Firstly, the virus is integrated clonally into the genomes of MCC primary tumours and their metastases (13). Secondly, the large T (LT) antigen, an early gene encoded by MCV, is truncated by MCC-specific mutations and expressed continuously. Truncation enables the LT antigen to inhibit the retinoblastoma tumour suppressor protein to prevent lytic viral replication that would otherwise damage the cancer cells (15). Without the crucial truncating mutations, the traces of MCV in various non-cancerous and cancerous tissues represent a passenger virus without carcinogenic properties. International Agency for research on Cancer (IARC) released a consensus statement in 2013 declaring the direct causal nature of MCV (16).

The late genes of MCV encode proteins that form the viral capsid required for the initial MCV infection. They are not expressed in MCC tumours, and thus have no role in tumour maintenance. The small T antigen, also a late gene of the MCV genome, is expressed in MCC tumours and acts downstream in the mammalian target of rapamycin (mTOR), a member of the phosphatidylinositol 3-kinase (PI3K) cell survival pathway, signalling pathway implicated in the regulation of cell growth and proliferation (17–19). The PI3K pathway is, in fact, up-regulated in MCV-positive MCCs, which can potentially lead to suppression of p53 protein expression (18). Mutations that activate the *PI3KCA* gene are found in 10% of MCC tumours, most often in MCV-negative ones. Although it is debatable whether expression of ST viral oncoproteins is required for MCC tumour progression as crucially as LT expression, the mTOR pathway seems to plays a fundamental role in the pathogenesis of MCC (20, 21).

MERKEL CELL CARCINOMA AFTER ORGAN TRANSPLANT

Merkel cell carcinoma and immune surveillance

MCC is sensitive to boosts in immune function and surveillance. Case reports describe the spontaneous regression of MCC tumours after biopsy or cessation of immunosuppression, constituting 1.4% of all reported MCC cases (22). Administration of immunosuppressive medication has, in some cases, led to swift development of MCC tumour in previously immunocompetent hosts. It was thought that the duration of immunosuppressive therapy is an important co-factor for MCC development, but the MCC development succeeding immunosuppression can be rapid in a favourable host (23).

MCV-specific T-cell responses detected in the peripheral blood of MCC patients are characterized by $CD4^+$ helper cells, which react to a broad range of peptides derived from viral capsid and oncoproteins (24). IgG antibodies against ST and LT are also relatively specific to MCC: they are found in 40.5% of MCC patients, but in only 0.9% of healthy controls (25). The levels of LT and ST antibodies correlate to tumour mass, and increase in the event of spread or metastasis of MCC (25). However, surveillance for MCV infection is not mediated only by humoral immunity and $CD4^+$ Th1-cells, but also by cell-mediated immunity. MCV-specific $CD8^+$ T-lymphocytes are found in the peripheral blood in over half of MCV-positive MCC patients, increasing with disease progression and decreasing with successful MCC treatment (26). In addition, MCV-positive tumours contain significantly increased numbers of tumour-infiltrating $CD8^+$ ad $CD3^+$ lymphocytes, NK-cells, macrophages and Tregs ($FoxP3^+$) compared with virus negative tumours (27, 28). The number of $CD8^+$ lymphocytes correlates with a favourable prognosis of MCC (27, 29).

MCC tumour cells employ certain mechanisms to evade the tumour surveillance by tumour-infiltrating lymphocytes (TILs). The loss of vascular E-selectin expression, an important factor in T-cell entry to the skin, correlates with poor intra-tumoural $CD8^+$ infiltration and prognosis in MCC tumour cells (30). Decreased activity of TILs in MCC is seen as decreased expression of co-stimulatory signal molecules, as well as expression of certain T-cell exhaustion markers (31). These findings suggest that the restriction of T-cell entry into the tumour and reductions in T-cell function might be considerable and even targetable forms of immunoevasion in MCC.

Post-transplant Merkel cell carcinoma

In 1999 Penn & First (32) observed a connection between therapeutic immunosuppression and MCC. They reported 41 MCC cases in the Cincinnati Transplant Tumor Registry. Few epidemiological studies address the incidence of post-transplant MCC (Table I). Recently, epidemiological knowledge increased markedly, when Clarke et al. (33) published the so-far largest number of MCCs in a defined cohort of organ transplant recipients (OTRs). They showed that the overall risk of MCC was increased 23.8-fold and adjusted risks are highest among older recipients with increased time since transplantation, and varies by organ type. The earlier reports show that post-transplant incidence of MCC is significantly increased and varies broadly according to the research institute and the transplanted organ. Solid-organ transplantation carries a general 4.95-fold increase for MCC (34) and MCC accounts for $<5\%$ of all skin cancers in OTRs (35). Among renal-transplant recipients, the standardized incidence ration (SIR) of MCC varies from 52 to 66 (36, 37), in liver transplant recipients it is 182 (37), among heart

Table I. *The main findings of epidemiological cohort studies on Merkel cell carcinoma in organ transplant recipients (OTRs) patients. The standardized incidence ratios (SIRs) are obtained by dividing the number of cases in the study population with the expected number of cases in the reference population*

Reference	Study population	Cases, *n*	Reference population	SIR (95% CI)	Mean age, years
Clarke et al. (33)	Scientific Registry of US Transplant Recipients				
	Kidney OTRs ($n=111,775$)	70		13.8	n/a
	Liver OTRs ($n=40,238$)	15		8.4 (0.3–1.1)	n/a
	Heart/OTRs ($n=17,693$)	20		20.8 (0.9–2.4)	n/a
	All other OTR ($n=19,792$)	5		6.7 (0.2–1.2)	n/a
Krynitz et al. (37)	Swedish transplant registry 1970–2008		Swedish population		
	Kidney OTRs ($n=7,952$)	6		52 (19–113)	n/a
	Liver OTRs ($n=1,221$)	2		182 (22–656)	n/a
	Heart/lung OTRs ($n=1,012$)	2		121 (3.1–671)	n/a
Na et al. (38)	Australian transplant registry 1987–2006		Australian population		
	Heart/lung OTRs ($n=2,718$)	n/a		103 (60–166)	n/a
Koljonen et al. (36)	Finnish transplant registry 1967–2005		Finnish population		
	Kidney OTRs ($n=4,200$)	3		66 (14–194)	59
Penn & First (32)	Cincinnati Transplant Tumor Registry 1968–1998				
	All OTRs ($n=10,955$)	41	n/a	n/a	53

n/a: not available.

transplant recipients 103 (38), and among heart/lung recipients 121 (37). In this respect, MCC represents a serious complication among immunocompromised patients, as the risk of MCC increases 15-fold over that of the general population (39).

The initial 41 OTR MCC patients reviewed by Penn & First (32) were young, mean age 53 years and the course of the disease was more aggressive compared with the general MCC population. Since then, this notion has been confirmed repeatedly. Paulson et al. (40) demonstrated in a heterogeneous cohort of 41 individuals with multiple forms of systemic immunosuppression including 12 OTRs, that immunosuppression leads to an increased chance of developing MCC and poorer MCC-specific survival. Later on, Arron et al. (41) showed, with a cohort of 1 liver, 3 lung, and 4 kidney transplant recipients, that besides being younger than average, the OTR-MCC patients had an increased risk of tumour progression, all-cause mortality and MCC-specific death.

The existing literature contains more case reports than epidemiological studies; the majority of the case report patients are male and their mean age at diagnosis is 57 years (age range 25–72 years) with a mean latency of 6 years (range 2–27 years) (Table SI and SII[1]).

To the best of our knowledge, only one study has addressed the occurrence of MCV in the MCC tumours of OTRs, and the occurrence is low (36). MCV is expressed with a higher frequency in basal cell carcinoma and squamous cell carcinoma samples of the OTRs (42). In renal OTRs, 7% of the saliva samples and 21% of the oral biopsies carried MCV DNA (43). MCV viruria was evident in 30% of renal OTRs (44, 45). In transbronchial biopsies from lung transplant recipients MCV was found in 34%, with a relatively high virus copy number, but not differing from native lungs (46).

Prevention and treatment

Treatment of MCC is multi- and interdisciplinary. In 2015, a new European consensus guideline for diagnosis and treatment of MCC was published (2).

The management of skin cancer in OTR requires a multidisciplinary approach, especially for high-risk MCC patients. Each case should be discussed in the multidisciplinary tumour board. The involvement of transplant team, plastic and ENT surgeons, pathologists, medical oncologist and radiation oncologist cover all aspects of diagnosis and care of MCC patient.

Lifestyle modifications after organ transplant, sun protection and sunscreen use, suggested to all OTRs against skin malignancies, are also advisable in the prevention of MCC (47). Regular total body skin examinations for new skin lesions and increasing the skin cancer awareness reduces skin cancer mortality and may improve the quality of life (48).

There are no guidelines for the treatment of post-transplant MCC, due to its rarity. However, the general treatment guidelines for MCC are applicable to both non-OTR and OTR MCC patients. The guidelines for MCC adhere to the guidelines for high-risk post-transplant non-melanoma skin cancers (49).

Surgery is the foundation of the treatment. Localized disease is treated with excision with pathologically clear margins. Current recommendations are based on the clinical size of the primary tumour: excision with 1-cm margins for tumours ≥ 2 cm, and excision with 2-cm margins for tumours > 2 cm (50). Although there is no solid conclusion on the width of the surgical margins, the excision of the fast-grown tumour may result in a large defect, resulting in a functional and aesthetic defect, especially if the tumour occurs in the face. However, the anatomical location of the tumour or the large size should not restrict adequate excision, due to multiple reconstructive options available (51).

Sentinel lymph node biopsy (SLNB) is recommended for all MCC patients, if the disease is not systemic at diagnosis (52). SLNB improves diagnostics and prognostic precision; approximately 30% of MCC cases that are estimated to be local are clinically present with microscopic nodal metastases detected in histological examination. SLNB is reliable and repeatable technique in MCC. However, what is SLNBs predictive value, remains deciphered as it seems that SLNB status do not predict either recurrence or survival (53), nor it is an independent predictor of survival in head and neck MCC (54). Currently other ways of staging MCC are under investigation. The most promising seems to be the FDG–PET (55, 56).

When tumour spread to local lymph nodes is clinically and pathologically verified, a completion lymph node dissection should be considered. However, recent studies have shown that radiation therapy alone can provide regional control rate comparable to completion lymph node dissection for both microscopic and palpable lymph node disease (57). Treating the primary tumour in inoperable patients with radiotherapy alone leads to acceptable results (58), and when the completion lymph node dissection is too risky for the patient, radiotherapy of the lymph node basin can be considered (59). Administration of adjuvant radiotherapy diminishes recurrences, but does not increase the overall survival (60). Controversial findings in a Surveillance Epidemiology and End Results (SEER)-based population suggest that the increase in survival seen with adjuvant radiation therapy is not disease-specific and might be a result of selection bias.

Treatment of systemic MCC is palliative. Postoperative chemotherapy has not been proven effective despite trials with various chemical compounds. The most

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frequently administered chemotherapeutic agents are those used in other neuroendocrine carcinomas, most commonly polychemotherapy with cisplatin, etoposide and/or doxorubicin (61, 62).

Reduction in immunosuppression to the lowest level while maintaining good graft function should be considered in all OTR MCC patients, as it is for transplant recipients with aggressive squamous cell carcinoma or melanoma (63). Conversion from calcineurin inhibitors to a regimen based on mTOR inhibitors that exert an anti-angiogenic and antitumor effect may be recommended. Case reports have reported transient remission of metastatic MCC after cessation of cyclosporine (64). Inhibition of the mTOR pathway in human MCC cell lines induces autophagy and cell death (65). Recently it has been shown that some 10% of the MCC tumours have mutations in the *PIK3CA* gene and the cell lines with this mutation are particularly sensitive to inhibition of the PI3K/mTOR pathway (66). A few clinical cases have reported the use of rapamycin in the treatment of MCC in OTR, although the switch to rapamycin did not offer survival advantage (67), probably due to the fact that the switch was made after systemic dissemination. Rapamycin therapy is associated with significant wound-healing problems, thus a switch to rapamycin should be scheduled after the necessary operations.

Capecitabine, is a prodrug of 5-fluoruracil and was first approved for the treatment of metastatic breast and colorectal cancers. Later it was noted that patients on capecitabine medication for metastatic breast and colon cancers presented with irritation and inflammation of actinic keratoses that led to the resolution of these precancerous lesions (68). Succeeding trials have shown that oral capecitabine may lead to remission of squamous cell carcinoma of the skin (69). Currently only sporadic papers have reported the use of capecitabine in MCC (56, 70, 71). The numbers are too small to draw conclusions on the effect on MCC.

FUTURE TREATMENTS

Perhaps, the improvement most likely to occur in the near future is the paradigm shift from mutilative surgical treatment to non-surgical treatment of MCC. MCC is a radio-sensitive tumour, and recent studies have succeeded in treating both primary and regionally metastatic MCCs (59, 72). How this will translate to the OTR MCC patients, remains to be determined.

MCC tumour cells contain activating mutations of c-KIT that mark susceptibility for the tyrosine kinase inhibitor imatinib mesylate in other neuroendocrine carcinomas (73). MCC cell growth has been impaired *in vitro* with the administration of imatinib methylate, but clinical trials have not replicated the effect (69). Other mechanism-based treatment options currently tested in clinical trials include the tyrosine kinase receptor inhibitors pazopanib and cabozantinib, the somatostatin analogue ocreotide, and the surviving inhibitor YM-155 (74).

High levels of antibodies against viral capsid proteins improve the prognosis of MCC (75). Thus, the use of MCV capsid protein particles as vaccine against MCC has been suggested (14). Vaccinations for at-risk groups are not feasible, as the viral infection occurs at an early age, and even though strong humoral responses are associated with better survival, the cancer progression is not inhibited. No studies have been conducted regarding the chemoprevention of MCC with retinoids in OTR patients. Treatment protocols remain to be established for other non-melanoma cancers as well, acitretin being the most favourable retinoid in OTR cases according to the current view (76). Retinoids have been reported to directly activate the PI3K/Akt/mTOR pathway in different cell types. Considering the PI3K-activating mutations detected in MCC, the effects of retinoids in terms of MCC prevention are difficult to predict.

Several immunological treatment options have recently been found effective in curbing MCC cell proliferation *in vitro*. Interferon-α and -β subtypes restrict tumour cell proliferation and decrease lymphotoxin alpha expression, but *in vivo* treatments have led to unfortunate adverse effects (77). Intralesional interferon-β treatment is the most promising of possible interferon therapies (74). Administering interleukin-2 and interleukin-15 increases cytokine production, activates T-cells, increases T-regulatory cell count and diminishes tumour cell count (31).

Advances in the treatment of melanoma are also serving as ground breakers in managing metastatic MCC. Current clinical trials include treatments with an anti-PD-L1 molecule and the autologous transfer of MCV-specific $CD8^+$ lymphocytes, both of which have shown promising results in melanoma. In another recruiting clinical trial, MCC patients are treated with ipilimumab, which is already approved for melanoma by the US Food and Drug Administration (FDA).

CONCLUSION

In conclusion, although the occurrence of MCC in individual OTR is very rare, the morbidity and mortality brought on by MCC warrants active screening. When a rapidly growing nodule arises on a skin of an immunosuppressed person, a tissue biopsy is called for. Even younger patients (< 50 years) should be inspected for skin lesions with MCC in mind. No preventive measures against MCV infection or MCC are in use for OTR patients. In the case of MCC, transplant units are advised to work as a part of the multidisciplinary team, and the doses of immunosuppressive medication should be re-evaluated and possibly lowered. In the future, MCV-specific biologic cancer therapies might benefit MCC OTR patients in particular.

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