

Latest update on the clinical features and management of Merkel Cell Carcinoma

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Abstract

Merkel cell carcinoma (MCC), is a rare, highly malignant skin tumour, with a poor prognosis. Though the aetiology of MCC is not known, but there are several features that it shares with melanoma. These include the natural history, clinical features and behaviour, e.g. an early spread to nodal sites, high local recurrence rate and early metastasis.

Incidence of MCC is seen to be increased in immuno-suppressed transplant patients, in patients with rheumatoid arthritis and in B cell malignancies, with a strong male predominance. Despite the ongoing research and advancement, MCC yet poses a challenge to the clinicians because of its rarity.

The purpose of this paper is to review the most salient and clinically relevant updates of MCC since its first publication in July 2007 in JPMA. In order to expedite an improved understanding of the new diagnostic modalities, treatment and preventive measures, along with the new staging system established in 2009 after an extensive literature review, and an analysis of over 5,000 patients using the National Cancer Database has all been included in our article.

Keywords: Merkel Cell Carcinoma, Skin Cancers, Radiotherapy, Chemotherapy.

Introduction

Merkel cell carcinoma (MCC) is an aggressive dermal tumour of neuro-endocrine origin. It is a rare, highly malignant primary skin tumour, originally called "trabecular carcinoma" of the skin. Approximately 2000 cases of MCC have been reported. The annual age-adjusted incidence per 100 000 is 0.23 for white individuals and 0.01 for black individuals.¹

MCC poses a challenge to the clinician because of its rarity and poor prognosis.² Toker first described it in 1972.³ Toker had observed that the tumour originates from the neuroendocrine cells of the basal epidermis of the skin. Merkel described the cell of the origin as epidermal, non-dendritic, non-keratinocytic cell that he referred to as a tactile cell.⁴ Electron microscopy and immunocytochemical studies are often required for accurate diagnosis.

The recently discovered Merkel cell polyomavirus (MCPyV) harboured in the inflammatory monocytes is said to be implicated in the oncogenesis of Merkel cell carcinoma (MCC).⁵

Clinical Features:

Although this carcinoma is usually found in elderly

individuals, it can occur in young patient as well. Median age at presentation is around 67 years. The vast majority of patients affected by MCC are white. It has strong male predominance. Most MCCs occur on sun exposed areas of the body.⁶

Common sites of the tumour are: Head and neck (47-50%); Extremities (40%) and Trunk (8%).

The aetiology of MCC is not known. Sun exposure is considered as one of the risk factors as ultra violet exposure induced C to T mutation was found in some MMC cell lines.⁷ The occurrence of MCC has also been reported in HIV infected patients together with other malignancies. Recent reports have shown an increased incidence in immuno-suppressed transplant patients, in rheumatoid arthritis and in B cell malignancies.

The natural history of MCC shares many common features with melanoma.

Like melanoma, MCC is also a cutaneous malignancy of same embryonic origin. These two malignancies also show similar clinical features and behaviour, e.g. an early spread to nodal sites, high local recurrence rate and early metastasis.⁸

Yom et al from the department of Radiation Oncology, M.D. Anderson Cancer Centre, Houston suggested that the differential diagnosis of Merkel cell carcinoma should be included in patients presenting with mucosal lesions of head and neck, especially if the tumour is sub-mucosal. MCC can also involve the tongue. Mucosal MCC is aggressive, and there is a high risk for local recurrence and regional and distant metastasis.⁹

Traditionally, Immunohistochemical markers like CK20 +, CK7-and-TTF1 are used in order to distinguish between MCC and other tumours.¹⁰

Diagnostic evaluation:

Histologically, the tumour consists of sheets of small round blue cells, an appearance that is similar to melanoma and metastatic small cell carcinoma. Immunohistochemical stains may be used to determine whether the primary tumour is indeed a primary MCC of the skin or cutaneous metastases from a visceral small cell carcinoma.

MCC has immunohistochemical features of both neuroendocrine and epithelial cells. It is usually positive for cytokeratin, CK20 (unlike melanoma and metastatic squamous cell carcinoma), and is usually negative for S100 and thyroid transcription factor 1 (TTF-1), a newly described nuclear protein that appears to be specific for small cell carcinoma of pulmonary origin.¹

A report published in Anticancer Research in June 2006 has evaluated the role of cell cycle-regulatory proteins (p53/p21/p27) in Merkel Cell Carcinoma's pathogenesis and

prognosis. Twenty-four primary MCC specimens with corresponding clinical data were analysed by immunohistochemistry for p21, p27 and p53 antibodies. The staining was evaluated semi-quantitatively and the results were analysed. p53 was negative in 80% and p21 in 71% of the samples. Positive staining for p27 was evident in 92% of the samples. However, the expression of these antibodies did not correlate with the outcome of the patient.

The proportion of p53- and p21-negative samples seems to indicate that correction processes after DNA damage are not activated during MCC pathogenesis, a supposition that is supported by the aggressive nature of this tumour. It was concluded that, the above mentioned three cell cycle regulators cannot serve as prognostic markers for survival.¹¹

Under the microscope most of the MCC specimens show a clear Grenz zone separating the epidermis from the tumour. The immunohistochemistry of MCC exhibits positive staining to neurofilament, cytokeratin, neuron specific enolase and epithelial membrane antigen.¹²

Staging:

Patient with MCC can be staged according to the American Joint Committee on Cancer (AJCC) staging system for skin cancer. Alternatively, a relatively simple system was proposed by Yiengpruksawan et al¹¹ which can be used for stage grouping:

Stage I: patients with localized disease; those with tumour of less than 2 cm are considered stage 1A, whereas those with tumour of 2 cm or more are considered as stage 1B.

Stage II: with regional lymph node metastasis

Stage III: with distant metastasis.

Yiengpruksawan and colleagues have reported that at the time of first consultation 70% to 80% of patients with MCC have stage I, 10% to 30% have stage II, and 4% to 15% have stage III disease.

A new MCC staging system has been established in 2009, being based on an extensive literature review, and an analysis of over 5,000 patients using the National Cancer Database.

Stages I & II MCC are defined as disease that is localized to the skin at the primary site. Stage I is for primary lesions less than or equal to 2 centimeters, and stage II is for primary lesions greater than 2 cm. Stage III is defined as disease that involves nearby lymph nodes (regional lymph nodes). Stage IV disease is found beyond regional lymph nodes.

In this system, the disease is being divided into stages depending on the severity of disease. The stage at diagnosis is a major determinant of the chance for spread (metastasis),

treatment options and chance for recovery.¹³

Primary Tumour (T)¹⁴

TX: Primary tumour cannot be assessed
 T0: No evidence of primary tumour (e.g., nodal/metastatic presentation without associated primary)
 Tis: In situ primary tumour
 T1: ≤ 2 cm maximum tumour dimension
 T2: >2 cm but ≤ 5 cm maximum tumour dimension
 T3: >5 cm maximum tumour dimension
 T4: Primary tumour invades bone, muscle, fascia, or cartilage.

Regional Lymph Nodes (N)¹⁴

NX: Regional lymph nodes cannot be assessed
 N0: No regional lymph nodes metastasis
 cN0: Nodes negative by clinical exam (no pathologic node exam performed)
 pN0: Nodes negative by pathologic exam
 N1: Metastasis in regional lymph node(s)
 N1a: Micrometastasis
 N1b: Macrometastasis
 N2: In transit metastasis.

The following are the definitions of terms used in AJCC-2010 staging system:

- ◆ Clinical detection of nodal disease done via inspection, palpation, and/or imaging.
- ◆ Micrometastases are diagnosed after sentinel or elective lymphadenectomy.
- ◆ Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or needle biopsy.
- ◆ In transit metastasis: a tumour distinct from the primary lesion and located either (1) between the primary lesion and the draining regional lymph nodes or (2) distal to the primary lesion.

Distant Metastasis (M)¹⁴

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

Patients with primary Merkel cell carcinoma with no evidence of regional or distant metastases (either clinically or pathologically) are divided into two stages: stage I for primary tumours no more than 2 cm in size and stage II for primary tumours larger than 2 cm in size. Stage I and stage II are further divided into A and B substages based on method of nodal evaluation. Patients who have pathologically proven node negative disease (by microscopic evaluation of their draining

lymph nodes) have improved survival (substaged as A) compared with those who are evaluated only clinically (substaged as B). Stage II has an additional substage (IIC) for tumours with extracutaneous invasion (T4) and negative node status regardless of whether the negative node status was established microscopically or clinically. Stage III is also divided into A and B categories for patients with microscopically positive and clinically occult nodes (IIIA) and macroscopic nodes (IIIB). There are no subgroups of stage IV Merkel cell carcinoma.¹⁵

Anatomic Stage/Prognostic Groups¹⁴

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

The Department of Pathology, Memorial Sloan-Kettering Cancer Center (MSKCC), New York, introduced the much favoured "4-tiered" or "four - stage" system,¹⁶ before the advent and publication of the new AJCC consensus staging system. This system was based on the largest number of patients and was the best validated¹⁷ by Andea AA et al.

The stages in the MSKCC system are as follows:

Stage I: local disease <2 cm

Stage II: local disease ≥ 2 cm

Stage III: regional nodal disease

Stage IV: distant metastatic disease.

The prognostic significance of the suggested 12 elements to be described in pathology reports of resected primary lesions, and the nine elements to be described in pathology reports of sentinel lymph nodes, has not been validated prospectively.¹⁸

Although immune suppression and ultraviolet radiation have long been associated with the MCC oncogenesis, recent studies also show involvement of a new polyomavirus and bcl-2.¹⁶ Several tumour classifications have been published in the literature, with the 4-tiered system from Memorial Sloan-Kettering Cancer Center the most widely used.

Management:

MCC is a rare tumour and all information pertaining to its behaviour, therapy and prognosis is based on retrospective reports. The two potentially curative treatment modalities are surgery and radiotherapy. The optimal therapy is individualised in any given patient with the appropriate use of operative resection and radiation therapy. Several authors reported that

postoperative radiotherapy to the primary tumour and regional lymphatic significantly improves local control and disease free survival.¹⁹

MCC has a poor prognosis, with 5-year survival of 30% to 68%.^{13,20-23}

It was only a single study by Allen PJ, et al.,¹³ in which a review of the Memorial Sloan-Kettering Cancer Center's MCC database was performed, having identified 251 patients who had been treated between 1970 and 2002. Patient, tumour, and treatment-related factors were analyzed for their association with recurrence and survival, but no association was found between irradiation and locoregional control.¹³

In a retrospective analysis of tumour registries from the 6 hospitals of the Scripps Health facilities, California, USA,²⁴ twenty-two patients were identified over the last decade, after review of their Hospital and clinic charts along with their pathology specimens. Amongst these, eight patients underwent Mohs' surgery with no subsequent local recurrence; however, out of the six patients who received adjuvant radiation therapy, only one of them developed disease recurrence within the radiation field. Seven patients received systemic chemotherapy, whereas one denied treatment after a punch biopsy.²⁴

Another collaborative retrospective study of 45 MCC patients, from the National Naval Medical Center, Bethesda; Shadyside Hospital, Pittsburgh; and Pittsburgh Cancer Institute,²⁵ is being published in the Journal of American Academy of Dermatology. Patients with stage I disease were found to be histologically and clinically disease free after Mohs' excision. Subsequent radiation was given electively to the primary site in 20 patients, whereas 25 patients did not receive any adjuvant radiation therapy. Consequently, one marginal recurrence (4%) and 3 in-transit metastases were observed in the Mohs' surgery alone group, whereas none were observed in the Mohs' surgery and radiation group.²⁵

In the context of the two above mentioned studies, it was finally concluded that Mohs' surgical technique combined with radiation therapy provided excellent local control. Adjuvant radiation appears unessential to secure local control of primary MCC lesions, completely excised with Mohs' micrographic surgery. Adjuvant radiation is recommended for patients who are unable to have complete excision, or if complete histologic margin control is unavailable, and should be considered for patients with large or recurrent tumours. As such, the role of irradiation after Mohs' surgery is not very clear.^{24,25}

However, recent data suggest an association between the use of radiation and overall survival. Mojica et al²⁶ retrospectively analyzed the Surveillance, Epidemiology, and End Results (SEER) database from the National Cancer

Institute from 1973 to 2002, and found a significant association between the use of radiation and survival.

The mainstay of treatment is wide local excision of tumour with reconstructive surgery.²⁷

Management of primary lesion with clinically localised disease is wide excision with a margin of at least 2 cm whenever possible. The excision should include the skin and subcutaneous tissue. Resection of the underlying fascia is also performed when the tumour is close to it. Excision margins of less than 3cm are associated with high incidence of local failures.²⁸ Due to high incidence of nodal metastasis, prophylactic lymphadenectomy is also suggested in some reports, alternatively sentinel node biopsy can be considered as an appropriate procedure in clinically node negative patient. Approximately 25% of patients found to have metastatic disease in the sentinel node biopsy. Early removal of microscopic disease detected by this diagnostic approach may offer the patient a greater opportunity for cure.²⁹ It is often difficult or impossible to excise MCC of the head and neck or distal extremity with a wide margin. Adjuvant radiotherapy can be considered in these cases. If the primary cancer is to be treated with radiotherapy alone, the regional lymphatic may be electively irradiated. Patient who present with fixed, unresectable nodal metastasis are treated with preoperative radiotherapy followed by salvage surgery of the primary site with a possible nodal dissection.

MCC is a radiosensitive tumour, adjuvant radiotherapy has been advocated in order to control local as well as regional disease.¹⁹ Radiation induced toxicity should be considered and discussed with the patient. Adjuvant radiation to the nodal bed after complete lymphadenectomy in patients with metastatic disease is generally not recommended. Regional recurrence is uncommon after a complete lymphadenectomy is performed in patients who had positive sentinel node biopsy.²⁹ On the other hand in patients with clinically proven regional disease adjuvant radiation treatment improves regional control.

There is no established dose response curve for the MCC. It is quite likely that its response to radiation is similar to that observed in squamous cell carcinoma. Therefore, the dose fractionation schedule for patients with negative surgical margin is of the order of 60 Gray in 30 fractions over 6 weeks or equivalent.³⁰

Systemic chemotherapy is recommended in patients with regional or systemic metastasis as a palliative measure. It gives 50% to 60% palliative response rate which is found to be more evident in patients with regional disease and less for visceral metastases. The use of various chemotherapeutic agents, both single and in combination, are reported in the literature. Agents like cyclophosphamide, doxorubicine, vincristine, etoposide, cisplatin, carboplatin, octreotide and dacarbazine have shown some palliative benefits.³¹ The option

of systemic chemotherapy should be offered to patients who present with nodal or metastatic disease.³²

A meta-analysis was published in Archives of Dermatology, June 2006 issue. Lewis et al² of Veterans Affairs Medical Centre, Providence performed an Ovid Medline search covering published articles from January 1966 to May 2004. The search yielded 242 discrete citations. Reports from all 242 citations were reviewed. Further ,601 citations, abstracts were reviewed to assess the level of relevance for potential inclusion; reports from 63 of these citations were reviewed. An additional 28 secondary references were reviewed, for a total of 333 reports. A total of 1254 patients were included in the analysis. Statistically significant reductions in local (hazard ratio [HR], 0.27; P < .001) and regional (HR, 0.34; P < .001) recurrence were observed among patients treated with combination therapy compared with surgery alone.

Similar rates of distant metastasis were observed between treatment groups (HR, 0.79; P =.31). Overall survival rates were 87% (1 year) and 49% (5 years). Cause-specific survival rates were 90% (1 year) and 62% (5 year). In general, differences in overall (HR, 0.78; P = 0.16) and cause-specific (due to MCC: HR, 0.72; P = .14) survival rates between treatment groups did not reach statistical significance. A subgroup analysis that excluded single-patient case reports and studies of only 1 treatment group revealed a significant overall (HR, 0.63; P =0.02) and cause-specific (HR, 0.62; P = .04) survival advantage after treatment with combination therapy.

It was concluded that surgery plus adjuvant irradiation was associated with significantly lower rates of local and regional recurrence of MCC than surgery alone. Prospective investigation is needed to clarify the presence of a survival benefit from combination therapy.²

Swann and Yoon³³ have done a review of MCC which is published in the Seminars of Oncology in February 2007. They have drawn some pertinent conclusions on the prognosis and management of MCC. The prognosis of MCC is variable. Natural history of localized disease is indolent and these tumours are well controlled with local excision alone. On the other side of the spectrum, majority of tumours behave aggressively and have a tendency for locoregional recurrence and distant metastases. In locally advanced and metastatic disease the option of systemic chemotherapy with regimens similar to those which are used in the treatment of small cell carcinoma of the lung, may be considered in adjuvant setting following surgery.³³

MCC is characterized by a high incidence of local and regional recurrence. Long term survival with low incidence of recurrence is reported in patients with early stage of the tumour. Most recurrences occur in the first 24 months and frequent follow up during this period is recommended. Patients who

develop a local recurrence after primary excision (regardless of site) should undergo re-excision, if possible, and adjuvant radiotherapy should be considered if not previously given. The long survival can be achieved after the treatment of loco regional recurrence. Voog and colleagues have reported that patients with loco-regional relapse and distant metastasis had 2 year survival rate of 35% and 17% respectively, versus 86% and 100% respectively for those who do not have these two forms of recurrences. The median overall survival after starting chemotherapy was 9 months for patients with distant metastasis and 24 months for patient with loco regional disease.³¹ The role of immunotherapy is not fully defined. Immunotherapeutic agents such as alpha- interferon or intralesional application of tumour necrosis factor-alpha were shown to have some effects in some patients.^{34,35}

Sandel HD et al³⁶ from the Department of Head and Neck Surgery, Georgetown University Hospital, Washington DC conducted a retrospective study and literature review in order to compare the clinical and histopathological criteria including tumour size and depth of invasion with clinical outcomes in MCC patients. The state cancer registry provided patients records (n = 46) diagnosed with Merkel cell carcinoma from 1992 to 2002. Pathology slides were reviewed for tumour size, depth of invasion, Clark level, and marginal status. Disease-free survival rates were found to be 52%, 39%, and 9% at 1, 2, and 5 years, respectively. The average disease-free interval was 18.4 months (range, 1-80 months). No correlation was found between tumour size (P =0.49), depth (P = 0.41), or Clark level (P = 0.82) to overall survival. A trend was found comparing tumour size or depth of invasion with local recurrence (P =0.07) but with no correlation to regional recurrence (P =0.93 and P = 0.60) or distant metastasis (P = 0.16 and P = 0.24). Overall recurrence was found in 60.7% of patients with local recurrence occurring in 18.1%, regional recurrence 40.9%, and distant recurrence 47.8%. Comparing patients with positive versus negative margins at initial excision, local recurrence was found in 33.3% versus 9.09% (P = 0.19), regional recurrence 66.6% versus 27.2% (P = 0.08), and distant metastasis 66.6% versus 45.4% (P = 0.36), respectively. No correlation was found between tumour sizes or depth of invasion to patient survival or metastasis. However, there was a trend toward increased local and regional recurrence rates when comparing size and depth and in specimens with positive tumour margins.³⁶

These outcomes are consistent with those reported in recent literature and further characterize the unpredictable nature of this disease. An aggressive approach should be taken, including wide local excision with negative tumour margins and lymph node dissection.

Ortin Perez et al³⁷ have reported eight cases of MCC who underwent sentinel node biopsy. All sentinel nodes were

successfully harvested. Three patients (37.5%) showed metastatic involvement and they were subjected to regional lymphadenectomy. This report published in the European Journal of Surgical Oncology in February 2007 suggested that sentinel node biopsy appears to be a reliable staging technique which can be considered in the surgical management of MCC.³⁷

A retrospective review was published in the Journal of Surgical Oncology in March 2007.³⁸ The review of 38 consecutive patients with surgically treated extremity MCC was presented. Surgical techniques of Wide local excision and Mohs' surgery was compared. No difference in local recurrence was found between the two procedures. A reduced local recurrence rate was observed in patients who were treated by adjuvant radiotherapy with a hazard ratio of 0.29 (95% Confidence Interval [0.10, 0.85]).

It has no impact on overall survival. This retrospective review further supports the rationale of using adjuvant radiation therapy in improving locoregional tumour control in MCC patients.³⁸

The rationale of giving External beam radiation therapy is very well established. Matthew Foote et al.,³⁹ in a clinical investigation, reported a retrospective analysis of 112 MCC patients, diagnosed between January 2000 and December 2005, and treated with curative-intent RT. With a median follow-up of 3.7 years, the 2-year and 5-year overall survival rates were 72% and 53%, respectively, and the 2-year locoregional control rate was 75%. Patients who did not receive elective nodal RT had a much higher rate of nodal relapse compared with those who did (HR = 6.03; 95% CI, 1.34-27.10).

It was therefore concluded that a dose-response existed for subclinical and gross MCC, with doses of ≥ 50 Gy for subclinical disease, and ≥ 55 Gy for gross disease to be considered. The draining nodal basin should also be treated in all patients.³⁹

In the 1st February 2010 issue of the International Journal of Radiation Oncology, Biology and Physics (IJROBP),⁴⁰ a review of 60 cases of MCC of lower limb has been published. The authors have concluded that radiotherapy improves relapse free survival when compared with surgery alone. It is recommended that elective treatment should be given to the inguinal nodes in order to reduce the risk of relapse.⁴⁰

A retrospective analysis of 112 patients of MCC has recently been published in IJROBP, July 2010 issue.³⁹ The authors have tried to quantify the radiation dosage required for the control of subclinical and gross diseases. According to the recommendation, a dose for subclinical MCC of more than or equal to 50 Gy should be considered in order to achieve a

response. For gross disease, 55 Gy or more should be considered. The draining nodal basin should be treated in all patients.³⁹

Conclusion

Merkel cell carcinoma (MCC) is an aggressive dermal tumour of neuro-endocrine origin. It is a rare and highly malignant primary skin tumour. As described in this review article multi modality customised management is planned for an individual patient of MCC. It is advisable to discuss cases in a multi-disciplinary expert panel tumour board before embarking on the first modality of treatment.

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