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MAIN ARTICLE

Merkel cell carcinoma of the head and neck: poorer prognosis than non-head and neck sites

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Abstract

Background: Merkel cell carcinoma is a rare, aggressive neurocutaneous malignancy. This study investigated whether patients with Merkel cell carcinoma in the head and neck had poorer outcomes than patients with Merkel cell carcinoma located elsewhere.

Methods: A retrospective study was performed of patients with Merkel cell carcinoma treated at the Jewish General Hospital in Montréal, Canada, from 1993 to 2013. Associations between clinicopathological characteristics and disease-free and disease-specific survival rates were examined according to the Kaplan–Meier method.

Results: Twenty-seven patients were identified. Although basic clinicopathological characteristics and treatments were similar between head and neck and non-head and neck Merkel cell carcinoma groups, disease-free and disease-specific survival rates were significantly lower in the head and neck Merkel cell carcinoma group (log-rank test; $p = 0.043$ and $p = 0.001$, respectively). Mortality was mainly due to distant metastasis.

Conclusion: Patients with head and neck Merkel cell carcinoma had poorer survival rates than patients with non-head and neck Merkel cell carcinoma in our study. The tendency to obtain close margins, a less predictable metastatic pattern, and/or intrinsic tumour factors related to the head and neck may explain this discrepancy.

Key words: Merkel Cell Carcinoma; Head And Neck Neoplasms; Survival Analysis; Skin Neoplasms; Radiotherapy

Introduction

Merkel cell carcinoma is an aggressive neurocutaneous malignancy, first described by C Toker in 1972.[1] This disease typically manifests in sun-exposed areas of the skin, and it tends to grow quickly and metastasise at an early stage.[2] Merkel cell carcinoma occurs more frequently in elderly, light-skinned and immunosuppressed patients.

Recognition of this predilection for immunosuppressed patients led to the discovery of an infectious agent implicated in the pathogenesis of Merkel cell carcinoma, namely the Merkel cell polyomavirus.[3] This virus is thought to play a major role in the oncogenic pathogenesis of Merkel cell carcinoma[3–5] and gives rise to a characteristic tumour (T) antigen molecular signature.[6,7] Histologically, Merkel cell carcinoma stains positively for cytokeratin 20 (CK20), which enables differentiation from other neuroendocrine tumours.[8]

The current recommended treatment for Merkel cell carcinoma depends on clinical stage, but therapeutic options include: wide surgical excision of the primary lesion, sentinel lymph node biopsy, lymph node dissection and radiation therapy.[9–12] The five-year relative survival rates for Merkel cell carcinoma patients with local disease, and regional and distant metastases are 75 per cent, 50 per cent and 20 per cent, respectively.[13]

Approximately 50 per cent of cases of Merkel cell carcinoma arise in the head and neck.[14] The management of head and neck Merkel cell carcinoma presents unique challenges for diagnosis and treatment. Head and neck anatomy makes the oncological treatment of choice more difficult.

A few studies have compared the prognostic and predictive features of head and neck Merkel cell carcinoma with those of Merkel cell carcinoma arising from other anatomical sites. The results of the studies are inconsistent.[2,13,15,16] A retrospective analysis of a 20-year period was conducted at our institution, in which the behaviour of head and neck Merkel cell carcinoma was compared to that of non-head and neck Merkel cell carcinoma.

Materials and methods

Study population

This retrospective study was approved by the Research Ethics Committee of the Sir Mortimer B Davis Jewish General Hospital of Montréal, Québec, Canada. Ethical

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guidelines were followed. Samples and clinicopathological data were handled in a coded fashion. Eligibility criteria included previously untreated patients, without a second primary tumour, treated at the Jewish General Hospital.

The medical records of all patients between 1993 and 2013 were examined to obtain detailed data on the following: demographics (age, gender, race and immune status), clinical stage, primary and adjuvant treatment, disease-free survival, disease-specific survival, and follow up. Disease-free survival was measured from the date of treatment to the date when local, regional or distant failure was diagnosed. Disease-specific survival was defined from the date of treatment to death due to the disease. Patients were staged according to the American Joint Committee on Cancer classification system.[17]

Statistical analysis

For continuous variables, mean and standard error values were determined. Associations between binary variables were examined in contingency tables using the two-sided Fisher's exact test. Relative risk and 95 per cent confidence intervals (CIs) were calculated using two-by-two tables, according to the Mantel–Haenszel method. For the comparison of continuous variables, the Mann–Whitney U test was used. Survival probabilities were estimated according to the Kaplan–Meier method. The log-rank test was applied to assess the significance of differences among actuarial survival curves with a 95 per cent CI. Statistical analyses were performed using SPSS software, version 21.0.0 (IBM, Armonk, New York, USA). A p value lower than 0.05 was considered to indicate statistical significance.

Results

Baseline characteristics

The study population consisted of 27 patients, with a mean age of 72.3 years. All patients were of Caucasian origin. Ten patients were female and 17 were male. Nineteen patients had early stage disease (T_1 or T_2) and five patients had advanced local disease (T_3 or T_4) at presentation. The remaining three patients had a metastatic carcinoma of unknown primary. Ten patients presented initially with regional metastasis, while distant metastasis was present at diagnosis in one patient.

Ten patients had Merkel cell carcinoma arising from the head and neck, while 17 patients had a primary tumour located elsewhere. Importantly, the baseline characteristics did not differ significantly between the head and neck Merkel cell carcinoma group and the non-head and neck Merkel cell carcinoma group ($p > 0.05$). The distributions and relative percentages for each study group are shown in Table I.

Immunohistochemical staining for CK20 (Figure 1) was positive in 21 out of 22 of the reported cases, and did not differ between the head and neck Merkel cell carcinoma group and the non-head and neck Merkel cell carcinoma group ($p > 0.05$).

Therapeutic management

Twenty-four patients underwent wide local excision of the primary tumour. Three cases were inoperable and the patients received primary radiation. In the surgical group, clear margins were obtained in 12 of the 21 documented cases. Patients with head and neck Merkel cell carcinoma were more likely to have positive margins than those with non-head and neck Merkel cell carcinoma, although this did not reach statistical significance (relative risk = 2.0, 95 per cent CI = 0.8–4.98, $p = 0.13$). Adjuvant radiotherapy was given in 92.3 per cent of the documented surgical cases, with a mean dose of 45 Gy. The proportion of patients receiving adjuvant radiotherapy did not differ between the head and neck Merkel cell carcinoma group and the non-head and neck Merkel cell carcinoma group ($p > 0.05$).

Recurrence

Eight patients suffered locoregional recurrence, at a mean time of 8.7 months. Of those, one patient suffered

TABLE I
CLINICOPATHOLOGICAL CHARACTERISTICS OF MERKEL CELL CARCINOMA PATIENTS

Characteristic	HN MCC*	Non-HN MCC†	All patients‡	p value (HN MCC *vs* non-HN MCC)**
Gender (n (%))				
– Female	6 (60)	5 (29.4)	10 (37.0)	0.22
– Male	4 (40)	12 (70.6)	17 (63.0)	
Age (mean (SEM); years)	77.2 (2.6)	69.5 (3.3)	72.3 (2.2)	0.20
Immunosuppressed? (n (%))				
– Yes	5 (50.0)	5 (29.4)	10 (37.0)	0.41
– No	5 (50.0)	12 (70.6)	17 (63.0)	
Clinical stage (n (%))				
– Early (I–II)	7 (70.0)	9 (52.9)	16 (59.3)	0.45
– Advanced (III–IV)	3 (30.0)	8 (47.1)	11 (40.7)	
Pathological lymph node findings? (n (%))				
– Yes	3 (30.0)	10 (58.8)	13 (48.1)	0.24
– No	7 (70.0)	7 (41.2)	14 (51.9)	

*$n = 10$; †$n = 17$; ‡$n = 27$. **Two-sided Fisher's exact test for binary variables, Mann–Whitney U test for continuous variables. HN MCC = head and neck Merkel cell carcinoma; SEM = standard error of the mean

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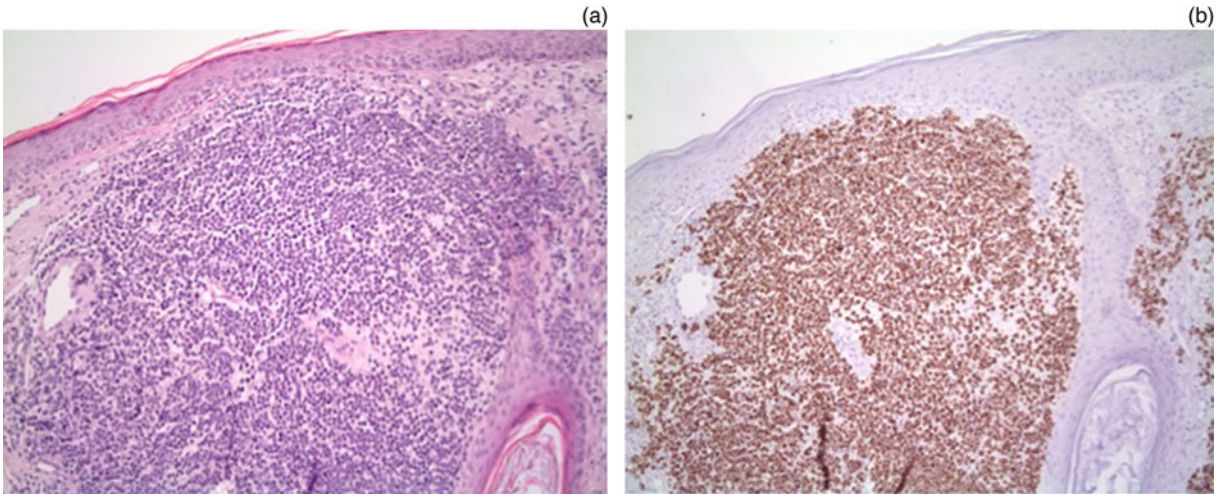

FIG. 1

Immunohistochemical staining of: (a) a typical round blue cell tumour invading the dermis (H&E; ×100), and (b) the same tumour showing typical positivity for cytokeratin 20 (×100).

local recurrence, five patients had regional recurrence, while two patients had recurrence both locally and regionally. Patients with head and neck Merkel cell carcinoma had a poorer disease-free survival rate than those with non-head and neck Merkel cell carcinoma ($p = 0.043$, Figure 2a). Gender, age, race, clinical stage at diagnosis, tumour size and presence of lymph node metastasis were not predictors of recurrence ($p > 0.05$, data not shown).

Survival analysis

The mean follow-up duration of the cohort was 36.9 months. At the end of the follow-up period, 19 patients were alive and 8 were dead. Of the eight deaths, seven were due to distant metastatic disease. A significantly lower disease-specific survival rate was observed in head and neck Merkel cell carcinoma patients compared to non-head and neck Merkel cell carcinoma patients ($p = 0.001$, Figure 2b). Patients older than 75 years had poorer survival probability ($p = 0.038$, data not shown). Immunosuppression, gender, race, clinical stage at diagnosis and presence of lymph node metastasis were not predictors of disease-specific survival ($p > 0.05$, data not shown).

Discussion

Merkel cell carcinoma is an aggressive cancer, with a high tendency for locoregional recurrence and distant spread. This retrospective study analysed the experience of a single institution in Canada. Although this study has several limitations associated with its retrospective nature and limited sample size, we believe

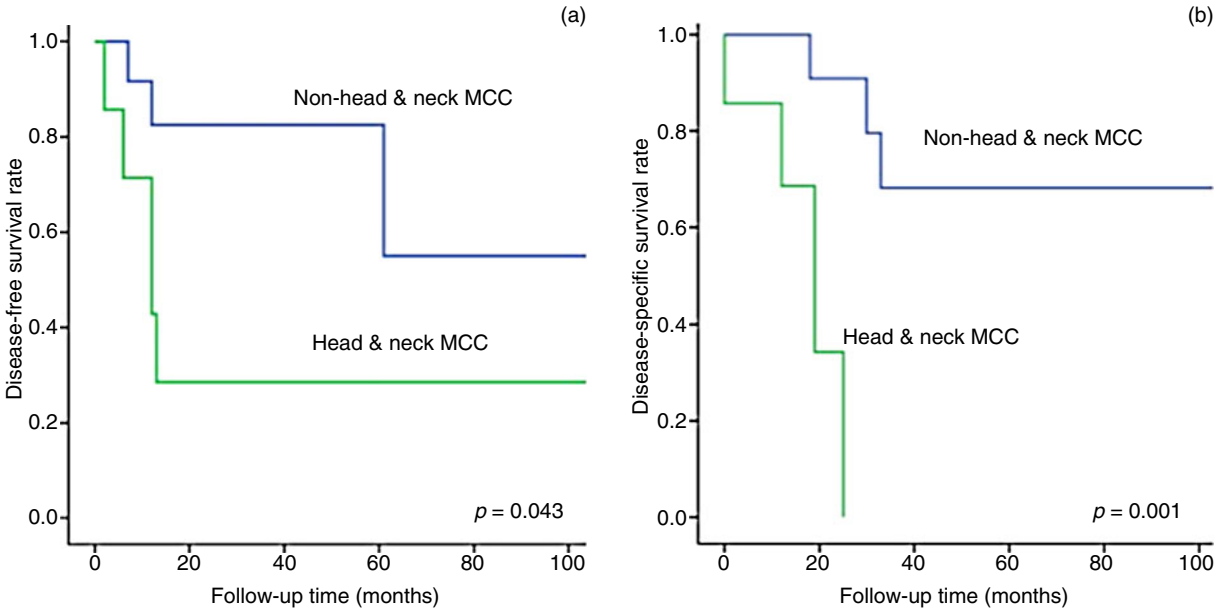

FIG. 2

(a) Disease-free and (b) disease-specific survival rates according to anatomical tumour origin. MCC = Merkel cell carcinoma

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that some lessons can be learned from the findings. We showed that patients with Merkel cell carcinoma arising from the head and neck had poorer disease-free and disease-specific survival rates than their non-head and neck Merkel cell carcinoma counterparts (both groups had similar baseline characteristics).

The prognostic relevance of Merkel cell carcinoma in the head and neck is inconsistent in the literature.[2,13,15,16] A study analysing the Surveillance, Epidemiology and End Results ('SEER') database showed distinct overall survival rates of Merkel cell carcinoma patients according to localisation of the primary tumour. The best prognosis was associated with localisation in the upper limb (60.7 per cent 10-year survival rate); this was followed by the head and neck, the lower limb, and the trunk (rates of 57.1 per cent, 56.7 per cent and 53.7 per cent, respectively).[2] In another population-based study from the Netherlands, a primary in the head and neck tended to predict poorer survival.[13] Further single-institution studies comparing the prognostic features of Merkel cell carcinoma showed higher locoregional recurrence rates[15] and poorer disease-specific survival rates for head and neck Merkel cell carcinoma compared to non-head and neck Merkel cell carcinoma.[16]

The poor prognosis associated with head and neck Merkel cell carcinoma in our study and in other reports in the literature could be explained by several factors. Historically, head and neck surgeons have been limited in terms of surgical margins by anatomical, functional and cosmetic factors specific to the head and neck. The excision of Merkel cell carcinoma primary tumours in the head and neck is often complex and limited by critical structures. This can lead to incomplete excision, with positive pathological margins and increased locoregional recurrence rates.[18–20] Several studies have shown that positive surgical margins are a common event for head and neck Merkel cell carcinoma.[11,19] In this setting, post-operative radiotherapy is essential to enhance locoregional control.[9]

- **Merkel cell carcinoma is a rare, aggressive neurocutaneous malignancy, commonly arising from the head and neck**
- **Tumour localisation may be an important independent prognostic factor**
- **This single-institution study compared head and neck versus non-head and neck Merkel cell carcinoma outcomes**
- **Baseline characteristics were comparable; however, head and neck Merkel cell carcinoma patients had a poorer prognosis**
- **This poor prognosis may result from close surgical margins, a less predictable metastatic pattern and/or intrinsic tumour factors related to the head and neck**

A second factor leading to the poor prognosis of head and neck Merkel cell carcinoma patients may be a less predictable and somewhat erratic metastatic pattern seen in tumours arising from the head and neck. Two independent studies have shown a lack of predictive value of sentinel lymph node status in the head and neck, while there was prognostic significance for primaries located elsewhere.[21,22] Similarly, a recent systematic review of melanoma reported lower accuracy of sentinel node biopsy when performed in the head and neck.[23]

Intrinsic tumour factors may further explain the poorer prognosis for head and neck primaries. A recent experimental study has demonstrated that solar irradiation can stimulate Merkel cell polyomavirus transcriptional activity in a dose- and time-dependent manner.[24] This led to increased amounts of small T antigen, which promoted oncogenesis in *in vitro* and *in vivo* experiments.[24] Primary tumours located in the head and neck are obviously more likely to 'benefit' from such a stimulus. Moreover, a recent study has shown that the oncogene TP53, whose overexpression is associated with poorer survival in cases of Merkel cell carcinoma and many other cancers,[25,26] was mutated in some Merkel cell carcinoma cases. The type of mutation (C to T substitution) seen in those mutated Merkel cell carcinoma cases was suggestive of ultraviolet B exposure, and may result in aberrant protein p53 activation.[27] Although the authors of the study did not specify the origin of the analysed tumours, one can expect this mutation to occur more frequently in head and neck Merkel cell carcinoma.

Conclusion

In our study, patients with Merkel cell carcinoma arising from the head and neck had a poorer survival rate than those with primary tumours located elsewhere. The tendency to obtain close margins, a less predictable metastatic pattern and/or intrinsic tumour factors related to the head and neck may explain this discrepancy. Future studies should investigate the respective roles of anatomy and tumour biology in Merkel cell carcinoma of the head and neck.

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References

1 Toker C. Trabecular carcinoma of the skin. *Arch Dermatol* 1972; **105**:107–10
2 Albores-Saavedra J, Batich K, Chable-Montero F, Sagy N, Schwartz AM, Henson DE. Merkel cell carcinoma demographics, morphology, and survival based on 3870 cases: a population based study. *J Cutan Pathol* 2010;**37**:20–7

https://doi.org/10.1017/S0022215116000153 Published online by Cambridge University Press

3 Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science* 2008; **319**:1096–100
4 Houben R, Grimm J, Willmes C, Weinkam R, Becker JC, Schrama D. Merkel cell carcinoma and Merkel cell polyomavirus: evidence for hit-and-run oncogenesis. *J Invest Dermatol* 2012;**132**:254–6
5 Sastre-Garau X, Peter M, Avril MF, Laude H, Couturier J, Rozenberg F *et al*. Merkel cell carcinoma of the skin: pathological and molecular evidence for a causative role of MCV in oncogenesis. *J Pathol* 2009;**218**:48–56
6 Shuda M, Feng H, Kwun HJ, Rosen ST, Gjoerup O, Moore PS *et al*. T antigen mutations are a human tumor-specific signature for Merkel cell polyomavirus. *Proc Natl Acad Sci U S A* 2008; **105**:16272–7
7 Becker JC, Houben R, Ugurel S, Trefzer U, Pfohler C, Schrama D. MC polyomavirus is frequently present in Merkel cell carcinoma of European patients. *J Invest Dermatol* 2009;**129**:248–50
8 Bobos M, Hytiroglou P, Kostopoulos I, Karkavelas G, Papadimitriou CS. Immunohistochemical distinction between Merkel cell carcinoma and small cell carcinoma of the lung. *Am J Dermatopathol* 2006;**28**:99–104
9 Lewis KG, Weinstock MA, Weaver AL, Otley CC. Adjuvant local irradiation for Merkel cell carcinoma. *Arch Dermatol* 2006;**142**:693–700
10 Jouary T, Leyral C, Dreno B, Doussau A, Sassolas B, Beylot-Barry M *et al*. Adjuvant prophylactic regional radiotherapy versus observation in stage I Merkel cell carcinoma: a multicentric prospective randomized study. *Ann Oncol* 2012;**23**: 1074–80
11 Morand G, Vital D, Pezier T, Holzmann D, Roessle M, Cozzio A *et al*. Merkel cell carcinoma of the head and neck: a single institutional experience. *J Skin Cancer* 2013;**2013**:325086
12 Huber GF. Modern management of Merkel cell carcinoma. *Curr Opin Otolaryngol Head Neck Surg* 2014;**22**:109–15
13 Reichgelt BA, Visser O. Epidemiology and survival of Merkel cell carcinoma in the Netherlands. *A population-based study of 808 cases in 1993–2007.* Eur J Cancer 2011;**47**:579–85
14 Smith VA, Camp ER, Lentsch EJ. Merkel cell carcinoma: identification of prognostic factors unique to tumors located in the head and neck based on analysis of SEER data. *Laryngoscope* 2012;**122**:1283–90
15 Kokoska ER, Kokoska MS, Collins BT, Stapleton DR, Wade TP. Early aggressive treatment for Merkel cell carcinoma improves outcome. *Am J Surg* 1997;**174**:688–93
16 Allen PJ, Bowne WB, Jaques DP, Brennan MF, Busam K, Coit DG. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. *J Clin Oncol* 2005;**23**:2300–9
17 Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. *AJCC Cancer Staging Manual*, 7th edn. New York: Springer-Verlag, 2010
18 Sullivan SR, Scott JR, Cole JK, Chi Y, Anaya DA, Byrd DR *et al*. Head and neck malignant melanoma: margin status and immediate reconstruction. *Ann Plast Surg* 2009;**62**:144–8
19 Kukko H, Bohling T, Koljonen V, Tukiainen E, Haglund C, Pokhrel A *et al*. Merkel cell carcinoma - a population-based epidemiological study in Finland with a clinical series of 181 cases. *Eur J Cancer* 2012;**48**:737–42
20 Haerle SK, Shiau C, Goldstein DP, Qiu X, Erovic BM, Ghazarian D *et al*. Merkel cell carcinoma of the head and neck: potential histopathologic predictors. *Laryngoscope* 2013; **123**:3043–8
21 Fields RC, Busam KJ, Chou JF, Panageas KS, Pulitzer MP, Kraus DH *et al*. Recurrence and survival in patients undergoing sentinel lymph node biopsy for Merkel cell carcinoma: analysis of 153 patients from a single institution. *Ann Surg Oncol* 2011; **18**:2529–37
22 Fritsch VA, Camp ER, Lentsch EJ. Sentinel lymph node status in Merkel cell carcinoma of the head and neck: not a predictor of survival. *Head Neck* 2014;**36**:571–9
23 de Rosa N, Lyman GH, Silbermins D, Valsecchi ME, Pruitt SK, Tyler DM *et al*. Sentinel node biopsy for head and neck melanoma: a systematic review. *Otolaryngol Head Neck Surg* 2011; **145**:375–82
24 Mogha A, Fautrel A, Mouchet N, Guo N, Corre S, Adamski H *et al*. Merkel cell polyomavirus small T antigen mRNA level is increased following in vivo UV-radiation. *PloS One* 2010;**5**: e11423
25 Waltari M, Sihto H, Kukko H, Koljonen V, Sankila R, Bohling T *et al*. Association of Merkel cell polyomavirus infection with tumor p53, KIT, stem cell factor, PDGFR-alpha and survival in Merkel cell carcinoma. *Int J Cancer* 2011;**129**:619–28
26 Milner J, Medcalf EA. Cotranslation of activated mutant p53 with wild type drives the wild-type p53 protein into the mutant conformation. *Cell* 1991;**65**:765–74
27 Van Gele M, Kaghad M, Leonard JH, Van Roy N, Naeyaert JM, Geerts ML *et al*. Mutation analysis of P73 and TP53 in Merkel cell carcinoma. *Br J Cancer* 2000;**82**:823–6

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