



Published in final edited form as:

Int J Dermatol. 2012 September ; 51(9): 1054–1059. doi:10.1111/j.1365-4632.2011.05251.x.

The Clinical Profile of Merkel Cell Carcinoma in Mainland China

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Abstract

Background—Merkel cell carcinoma (MCC) is an aggressive cutaneous malignancy, but little is known about the presence or characteristics of MCC in mainland China. A retrospective chart review was conducted to describe the clinical profile of Merkel cell carcinoma in China.

Methods—At 18 cancer or dermatology hospitals in metropolitan centers from the six geographical regions of mainland China, approximately 3,100,000 pathology database and medical records were searched for cases that had a pathological diagnosis of MCC between 1970 and 2009. A case series was compiled from retrospective chart reviews of identified MCC patients.

Results—Eight out of 18 participating hospitals reported at least one record of a patient with a pathological diagnosis of MCC, and a total of 22 cases were identified. The median age of patients was 65.5, and 59% were female. The median time from the appearance of a lesion to the time of biopsy was 6 months, and the most common location of lesions was the head and neck. The most common treatment used was surgery alone.

Conclusions—MCC appears to be uncommon in mainland China. Patients in this series are elderly, often had lesions on the head/neck region, and most commonly received surgery alone as treatment. In contrast with MCC in Western countries, the current series' patients were all of Asian ethnicity, had larger lesions at presentation, and none were documented as having HIV or other forms of immunosuppression.

Keywords

Merkel cell carcinoma; China; skin cancer; case-series

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Financial Disclosure: None reported.

Introduction

Merkel cell carcinoma (MCC) is a cutaneous malignancy thought to arise from the Merkel cell mechanoreceptors located in the epidermis, and it has a clinical mortality (33%) about twice that of melanoma (15%).¹ Reports from the United States have described a tripling in the incidence of MCC from 1986 to 2001,^{2,3} with a current estimated incidence of 1,500 cases/year.⁴ In 2008, the Merkel cell polyomavirus (MCPyV) was found to be associated with MCC tumors,⁵ and evidence is growing that links the MCPyV with oncogenesis of MCC.^{6,7} The epidemiology and clinical characteristics of MCC have been studied in Europe, Australia, and North America,⁸⁻¹⁰ but have not yet been examined in China aside from a few case reports.^{11,12}

Little is known about the presence or characteristics of MCC in China, and there is no existing cancer registry or similar resource which has collected information on MCC. While MCC is a rare cutaneous malignancy which predominantly affects elderly Caucasians, it is a challenging and aggressive disease with high mortality (as high as 1 in 3) and is associated with immunosuppression.^{1,13} In order to evaluate the presence and characteristics of MCC in China, we conducted a national medical chart-review to describe the clinical profile and manifestations of MCC in mainland China.

Methods

A national retrospective chart review was conducted at 18 participating hospitals representing each of the six main geographical regions of mainland China (East, Mid-South, North, Northeast, Northwest, and Southwest (Figure 1)). Physicians at the pathology departments at the central “tumor” or cancer hospitals in the main provinces and municipalities of these regions were contacted, in addition to dedicated dermatological hospitals if available. As this study focused on mainland China, institutions in Hong Kong, Macao, and Taiwan were not included.

Participating physicians consulted their existing hospital electronic medical records and pathology records for cases of Merkel cell carcinoma (ICD-10 ID C44, pathology morphology code 8247/3)¹⁴ identified from 1970 to 2009. A total of approximately 3,100,000 medical records was searched for cases with a pathological diagnosis of MCC, including both primary diagnoses and referrals. A Chinese-language questionnaire was used to collect clinical information based on previous literature regarding salient features of MCC,^{1,13,15} including patient demographics and clinico-pathological information regarding the characteristics of the skin lesion, pathological findings, concurrent diseases, and treatment. If cases existed, the corresponding charts were reviewed and the questionnaires were returned to the research group at the Cancer Institute, Chinese Academy of Medical Sciences for analysis. No contact with human subjects or analyses of stored biological specimens was conducted. This study was approved by the Public Health-Nursing institutional review board at the University of North Carolina, Chapel Hill, and by a central institutional review board at the Cancer Institute, Chinese Academy of Medical Sciences.

Results

Eight out of 18 participating institutions reported at least one case of MCC, and a total of 22 cases were identified (Table 1). One case was diagnosed in 1996, while the remaining 21 cases were diagnosed in 2001 or after. Participating institutions covered all 6 geographical regions of mainland China, including 14 cities in 13 provinces or metropolitan regions. The institution with the highest number of cases (n=8) was the Cancer Institute, Chinese Academy of Medical Sciences in Beijing.

Of the 22 MCC cases identified, nine (41%) were male, while 13 (59%) were female (Table 2). The median age of the patients was 65.5 years old (range 21–79, average 59). Twenty-one of 22 patients (95%) were of the Han Chinese ethnic majority, while one was of Hui minority background.

The median time from the appearance of a lesion to the time a biopsy was taken was 6 months (range 1–39, average 8.5). The most common location of lesions was the head and neck (9 cases, 41%), followed by the lower limb (5 cases, 23%), lymph nodes (3 cases, 14%), upper limb (2 cases, 19%) groin/buttock (2 cases, 19%), and torso (1 case, 5%). The maximum diameter at time of presentation of most lesions, whether cutaneous or lymph nodal, was greater than 2cm (15 cases, 71%), followed by lesions between 1 and 2cm (4 cases, 19%) and lesions smaller than 1cm (2 cases, 10%). Data on the color of lesions was available for 17 cases, and the most common colors were pink (5 cases, 30%), skin or flesh-color (5 cases, 30%), followed by white/gray (3), yellow/white (2), bluish-purple (1), and pinkish-red (1).

Six patients (27%) presented with lymphadenopathy at the time of diagnosis, two (9%) with metastatic disease, and two (9%) with both lymphadenopathy and metastatic disease. No patients were recorded as being HIV sero-positive, having chronic lymphocytic leukemia, or taking immunosuppressive medications for a pre-existing condition. The most common clinical diagnosis before pathology results was skin cancer (15 cases, 71%), followed by a cyst (4 cases, 19%). Two cases (10%) were thought to be MCC, while infections (2 cases), other cancers (3 cases), and acne (1 case) were also considered.

CK20 staining on immunohistochemistry was reported in 13 patients (59%); nine of these patients (69%) had a positive result while four (31%) had a negative result. The most common treatment used was surgery alone (10 cases, 45%), followed by surgery and radiation (5 cases, 23%), surgery and chemotherapy (4 cases, 18%), and surgery, radiation, and chemotherapy (3 cases, 14%).

Follow-up information on the status of patients following initial diagnosis or hospital admission was available for 13 patients. Of these, six (46%) had recurrent disease detected at a median of 6 months; five (38%) were alive with no record of recurrence at a median of 3 months; and two (15%) were dead after a median of 28 months.

Comment

This study presents a basic clinical profile of 22 patients with MCC identified in the medical records of 18 cancer or dermatology hospitals in mainland China. This series provides an initial step towards describing MCC in China and ascertaining whether MCC in China has similar clinical characteristics to Western MCC cases. Based on our reports from pathology laboratories across China, MCC appears to be uncommon but still occurs in diverse regions of China. This infrequency is not surprising, given that MCC in Western countries typically occurs in Caucasian patients at low incidence rates of 0.44 cases per 100,000.^{2, 3} In our series, most cases were diagnosed in 2001 or later, likely due to the fact that while an electronic search of existing records was conducted, some of the participating institutions did not yet have complete digitalized records extending to the 1990's or earlier.

All of the patients in our series were of Asian descent (all were Han Chinese, while one was of the Hui ethnic minority), while published series on MCC have largely reported on Caucasians.^{10, 13, 16, 17} In a recent study on 3,870 MCC cases from the United States, only 4.1% of cases were among Asians (but also including American Indians and Asian Pacific Islanders).¹⁰

Given that sun exposure is a known risk factor for MCC,¹ increased sun exposure may also be a risk factor for these Asian patients. At least 12 of the 22 patients in this Chinese series had their primary lesions located on highly or moderately sun-exposed areas such as the head and neck or the hand. While these results are not conclusive, MCC appears to be more common on sun-exposed anatomical areas as in Caucasian populations.^{1, 10}

While MCC is typically more common in men,^{2, 3, 10} this series had a majority of women (59%). This may be due to the relatively small sample size of MCC cases ascertained, or the possibility that women were more likely than men to seek dermatological consultation in China. The age at diagnosis in our series (median 65.5) is in agreement with findings that MCC is associated with older age above 65 years old among Caucasian populations.^{2, 3, 10, 17}

The median and mean duration from appearance of a lesions to the time of biopsy in this study (6 and 8.5 months, respectively) are relatively longer than those previously reported in a study of 195 patients from the United States (3 and 5.3 months, respectively).¹³ This longer duration before clinical presentation may be one of the reasons why most MCC lesions in this series were larger (71% were >2 cm in diameter) than the lesions encountered in the U.S., where most lesions are between 1–2 cm at presentation.^{13, 15} The most common colors of lesions in this series were pink or red, and flesh/skin-colored. Compared with a previous study of 195 MCC patients from the U.S., there was a lower frequency of blue/purple lesions but a larger frequency of lesions with a white color (either white/gray or white/yellow).¹³ While additional data are needed, we speculate that these differences may have to do with the appearance of these lesions on Asian skin versus Caucasian skin.

Approximately half (45%) of the patients had either lymphadenopathy, metastatic disease, or both at presentation, being similar with previous studies which found that ~ 30–43% of patients presented with metastatic or nodal disease.^{13, 15} While a U.S. study found that initial clinical diagnoses of primary MCC lesions at the time of biopsy were predominantly non-melanoma skin cancer (19%) or cyst/acneiform lesions (32%),¹³ skin cancer was more often considered as the initial diagnosis (71%) in our series, along with a few alternative diagnoses considered such as sporotrichosis or cysts.

All patients in this series from China received surgical treatment, while approximately a third received additional radiation or chemotherapy, and 3 (14%) received all three treatment modalities. In contrast, a study of 251 patients in the U.S. reported that almost all patients received surgery for primary lesions, while 17% received radiation, and 12% received chemotherapy depending on the extent of disease.¹⁵ Despite the rarity of MCC and the lack of national guidelines for treating MCC, surgery is the main treatment modality employed thus far in China. There did not appear to be an association between the mode of treatments and the presence of nodal or metastatic disease at presentation in this Chinese series.

Follow-up survival data, while only available in 13 cases, suggest a similarly aggressive disease course in China as in other countries, with 39% of patients alive with no record of recurrence at latest follow-up and 61% experiencing recurrent disease or death. This relapse rate of 61% appears to be high compared to rates in other series of MCC cases from the United States of 43%.¹⁵ Although our sample size of cases with recurrence is small, possible reasons for these observed differences in relapse rates include the larger primary tumor sizes at presentation, longer latency times between appearance of the lesion to the time of clinical presentation, and the high rates of lymphadenopathy or metastasis at time of diagnosis among MCC cases in our series. Additionally, the general absence of standardized clinical treatment guidelines and low rates of adjuvant radio- or chemotherapy in China may have contributed to the relatively higher relapse rate. Patients in our series who were alive only

had a median of 3 months of follow-up, and other studies have found that most recurrences occur within 2 years and most deaths within 3 years.¹⁵ One limitation of our study is that complete follow-up data were unavailable for some MCC patients, as no system for active follow-up is yet available in China for this rare disease. Thus, some of the patients who did not have follow-up may have died after their latest clinical encounter. In China, this may be due to a lack of clinical experience with a rare condition like MCC, or due to limited healthcare resources or access.

This case series has several other important limitations. Although included MCC cases were from diverse geographical areas, the participating institutions were urban tertiary care centers which do not necessarily constitute a representative sample of the Chinese population. Further, not all MCC cases in this chart review had complete clinical data, and the study did not include a secondary review of pathology slides to confirm MCC diagnoses, or radiographic and laboratory exclusion of small-cell lung cancer. The rarity of MCC and the lack of uniform use of techniques such as CK-20 immunohistochemistry staining may have led to either over- or under-diagnosis at these centers.¹⁸ However, the inclusion of several hospitals from each of the main six regions of China provided a somewhat broad geographical sample, and the use of large tertiary cancer institutions in this series allowed us to obtain reliable chart review data.

To date, very little has been reported about the presence or characteristics of MCC in mainland China. We speculate that even though MCC most commonly occurs among Caucasians, China's extremely large population may have many other undiagnosed or untreated cases of MCC affecting people from rural and remote regions, or in local community hospitals. There may also be interesting treatment-seeking behaviors or treatment options, including traditional Chinese medicine, that are being used to treat MCC or other cutaneous malignancies. Currently, China's National Cancer Registry does not collect data on MCC, and there are no national guidelines for MCC diagnosis and treatment. Thus, further studies are needed to investigate the epidemiology, diagnosis, and treatment of MCC in China.

This case series has findings consistent with the published literature on MCC, such as the elderly age of patients, the common location of lesions on the head/neck region, and the use of surgery as the primary treatment method. There are, however, several interesting differences in this case series from China, such as that these patients are all of Asian ethnicity, while most previous studies on MCC report on Caucasian patients in Western countries. MCC in East Asia has been reported in single-hospital based case series on 7 patients from South Korea¹⁹ and 16 MCC patients from Japan,²⁰ both of which similarly found that MCC predominates on the head/neck region in the elderly, and is treated primarily with surgery. None of the patients in our series were documented as having HIV, chronic lymphocytic leukemia, or taking immunosuppressive medications. It is still possible, however, that these conditions may play a role in MCC in China as in the West.¹ Further studies are warranted to investigate the role of immunosuppression, as well as the role of the Merkel cell polyomavirus, in the development of MCC in Chinese patients.

Acknowledgments

We are indebted to the following individuals for their invaluable assistance in reviewing charts at their respective institutions: Xiaofen Gu, Yutong He, Sulaiya Husaiyin, Haixin Li, Guangdong Liao, Qing Liu, Li Ma, Jianji Shi, Anrong Wang, Chunyan Wang, Xiaohui Wang, Shuxiang Yao, Lian Zhang, Yan Zhang, Yongzhen Zhang, and Shanshan Zhou.

Funding/Support: P. Song was supported in part by the Fogarty International Clinical Research Scholars Program: Fogarty International Center, National Institutes of Health Office of the Director, through the International Clinical Research Fellows Program at Vanderbilt (R24 TW007988).

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Figure 1. Map showing the six geographical regions of mainland China. Blue stars indicate the location of participating hospitals.

Table 1

Profiles of 22 Patients with Merkel Cell Carcinoma in Mainland China

Patient No./Sex/Age (years)	Time from appearance of lesion to date of diagnosis (months)	Lesion location	Size (cm) and color of lesion	Conditions present at time of diagnosis	Clinician's first impression before pathology diagnosis	CK20 staining on immunohistochemistry	Treatment(s) received	Status at last follow-up (months after diagnosis)
1/F/66	8	Lymph node	>2, skin	LAD	Cyst, skin cancer	Pos	S, C, R	Dead (27)
2/M/60	1	Head/neck	>2, skin		Cyst	Pos	S	
3/M/57	39	Lower limb	>2, NA	LAD	Cyst		S	
4/F/60	4	Groin	>2, NA		Cyst	Pos	S	
5/M/68	6	Head/neck (eyelid)	<1, pink/red		Skin cancer	Neg	S	
6/F/21	7	Rt foot	>2, yellow/white	Metastatic disease	Skin cancer, soft tissue tumor	Pos	S	
7/M/25	24	Lt hand	>2, pink with black spots		Skin cancer		S	
8/M/76	2	Head/neck	>2, blue/purple	LAD	Squamous cell carcinoma	Pos	S	Alive (24)
9/F/66	2	Head/neck	1-2, skin		Skin cancer, sporotrichosis	Pos	S	Recurrence (5)
10/F/65*	2	Head/neck (Lt cheek)	>2, gray/white		Skin cancer, infection		S, C	Alive (100)
11/F/63	12	Trunk/ torso	>2, gray/white	Metastatic disease	Skin cancer	Neg	S, C	Dead (29)
12/F/67	14	Head/neck (Rt cheek)	1-2, gray/white		Metastatic cancer		S	
13/F/55	6	Head/neck (Rt nose)	>2, pink			Pos	S, C, R	Recurrence (7)
14/M/79	4	Lower limb	>2, NA		Aene		S, R	Alive (3)
15/F/42	1	Upper limb			Skin cancer		S, R	Alive (1)
16/M/63	5	Buttock	>2, pink		Skin cancer		S, R	Recurrence (13)
17/F/70	2	Head/neck (Rt cheek)	<1, pink		MCC		S, R	Recurrence (38)
18/M/70	18	Rt inguinal LAD	>2, NA	LAD, metastatic disease	Skin cancer, MCC		S, C, R	Recurrence (4)
19/F/66	6	Head/neck	1-2, skin		Skin cancer	Neg	S, R	Alive (4)
20/F/66	8	Lower limb/buttock	>2, pink	LAD, metastatic disease	Skin cancer	Pos	S, C	Recurrence (3)
21/F/24	12	Lower limb (Lt knee, inguinal lymph nodes)	1-2, skin	LAD	Skin cancer	Neg	S	
22/M/70	3	Rt armpit	>2, yellow/white		Skin cancer, metastatic cancer	Pos	S, C	

C, chemotherapy; LAD, lymphadenopathy; Lt, left; MCC, Merkel cell carcinoma; NA, information not available; R, radiation therapy; Rt, right; S, surgery.

* Patient was of Hui ethnic minority (all other patients were Han Chinese)

Table 2

Summary of Selected Clinical Characteristics of Patients with Merkel Cell Carcinoma in Mainland China

	Number	Percent, other
Sex (n=22)		
Male	9	41
Female	13	59
Age (years) (n=22)		Median 65.5, mean 59, range 21–79
Time from appearance of lesion to biopsy (months)		Median 6, mean 8.5, range 1–39
Lesion Location at Presentation (n=22)		
Head/neck	9	41
Lower limb	5	23
Upper limb	2	19
Lymph nodes	3	14
Groin/Buttock	2	9
Torso	1	5
Size of Lesion (n=20)		
<1cm	2	10
1–2cm	4	19
>2cm	15	71
Color of Lesion (n=17)		
Pink	5	30
Skin/flesh-colored	5	30
White/Gray	3	18
Yellow/White	2	12
Pink/red	1	10
Bluish/purple	1	6
Conditions present at diagnosis (n=8, 45% of total)		
Lymphadenopathy (LAD)	6	27
Metastatic disease	2	9
LAD and metastatic disease	2	9
Treatment Received (n=22)		
Surgery	10	45
Surgery, Radiation	5	23
Surgery, Chemotherapy	4	18
Surgery, Radiation, Chemotherapy	3	14