Dermatology Practical & Conceptual

Distant Metastasis of Merkel Cell Carcinoma: A Descriptive Study

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ABSTRACT

Introduction: There are few studies on the pattern of distant spread of Merkel cell carcinoma (MCC).

Objectives: To analyse the most frequent locations of distant metastases from MCC and their possible relationship with the location of the primary tumour.

Methods: Patients diagnosed with cutaneous MCC between 1988 and 2022 were included in the study. The locations of the first metastases detected were recorded, both at tumour diagnosis and during follow-up after initial treatment.

Results: One hundred patients were diagnosed with MCC. Distant metastases were detected in 31 patients (seven at diagnosis and 24 during follow-up), with a total of 52 locations: 17 non-regional

lymph node metastases, 10 bone, seven liver, six lung, four non-regional cutaneous/subcutaneous, three pancreatic, two adrenal, two pharyngeal, and one mammary. No patient developed metastasis to the central nervous system. Recurrences occurred in 84% of patients before two years of follow-up. Although differences were not significant, MCCs located in the extremities tended to metastasize to extra-regional lymph nodes and those in the head and neck to bone, liver, and lung.

Conclusions: MCC produces metastases mainly in non-regional lymph nodes, bone, liver, and lung. Given its high frequency (1/3 of patients), we consider performing scheduled imaging tests during the first two years of follow-up advisable. Specific imaging tests for central nervous system could be reserved for patients with neurological symptoms.

Introduction

Merkel cell carcinoma (MCC) is a skin tumour with neuroendocrine differentiation first reported by Toker in 1972[1].The risk factors for developing MCC are age over 50 years, exposure to ultraviolet radiation, Caucasian ethnicity, and immunosuppression [2]. In approximately 80% of cases, the presence of MCC-associated polyomavirus is detected [3,4]. MCC is a particularly aggressive tumour that spreads to distant organs in approximately one-third of patients[5]. However, there are few studies on the pattern of MCC dissemination [5-9].

Objectives

The purpose of the present study was to retrospectively analyse the location of distant metastasis from MCC and its relationship with the location of the primary tumour.

Material and Methods

All patients treated for MCC in our hospital between 1988 and 2022 were included in the study. Ours is a university hospital that provides tertiary healthcare to a population of approximately 1 million people.

MCCs were excised with a 2 cm margin whenever possible. Since 2000, sentinel lymph node biopsy has been recommended for all MCC patients when the tumor is not disseminated. Regional lymphadenectomy was performed in positive sentinel lymph node biopsy cases as well as in patients with regional lymphadenopathy detected clinically or by imaging tests. Whenever possible, adjuvant radiotherapy was administered to the primary tumor bed after excision and to the lymph node area after lymphadenectomy. Patients were followed up clinically in the Dermatology and Medical Oncology Departments. Patients who received radiation therapy were also followed up by the Radiation Therapy Department. Patients were evaluated every 3–4 months for the first five years after diagnosis and every six months thereafter up to 10 years. LDH levels were assessed at each visit during the first two years. Regarding imaging tests, until 2008, chest x-rays and abdominal ultrasound were performed alternately during the first two years. After 2008, follow-up was performed using PET CT alternating with TAP CT and cranial CT or brain MRI. Additional complementary examinations were performed according to the clinical and analytical findings.

Clinical data were obtained retrospectively from the patients' medical records and were entered into an electronic database to which only the authors of the article had access. Data collected include the patients' sex, age at diagnosis, date of diagnosis, location of the primary tumor, location in photoexposed or non-photoexposed regions, association with immunosuppression (solid organ transplant, bone marrow graft, hematological malignancy, acquired immunodeficiency syndrome, or immunosuppressive therapy), clinical stage at diagnosis (AJCC 8th edition, 2017), treatment performed, date of recurrence, and type of recurrence (regional or distant). Distant metastases were defined as tumor implants beyond the regional lymphatic basin. The patterns of distant dissemination were defined according to the first organs where MCC dissemination was detected beyond the regional lymph node area, both at diagnosis of the primary tumor and during clinical follow-up (one or several locations in each patient).

Statistical Analysis

Quantitative variables were compared using Student's t test when normality of the distribution was confirmed. Otherwise, Mann-Whitney test was applied. Qualitative variables were compared using the chi-squared test or Fisher's exact test. Due to the limited number of cases, most statistical tests were not applicable, and we were only able to estimate the existence of correlations. The statistical package used was SPSS 17.0 for Windows. A p-value less than 0.05 was considered statistically significant.

Results

One hundred patients with MCC were included in the study. There were 43 females and 57 males aged between 34 and

92 years, median 76.50 years, interquartile range (IQR) 14. Sixteen of the 100 patients (16%) were immunosuppressed. MCC was located in the head and neck region in 39 cases (39%), in the trunk in five cases (5%), and in the extremities in 56 (56%) (24% upper, 32% lower). In 63% of the patients the lesions were located in photoexposed skin. Tumor diameter at diagnosis ranged between 0.5 cm and 17 cm, with a median of 2.45 cm, IQR 3.28. At the time of diagnosis, 33 patients were in stage I, 19 in stage II, 41 in stage III, and 7 in stage IV. Sentinel lymph node biopsy was performed in 57 patients, with a positive result in 33 of them. Regional lymphadenectomy was performed in 43 patients. Radiotherapy was administered to the primary tumor bed in 35 cases, and in 16 of these also to the regional lymph node area. Follow-up time ranged from 0 to 209 months, with a median of 23.50 months (IQR 45).

Distant metastases were detected in 31 patients (seven at diagnosis of the tumor and 26 during the follow-up), in some of them in more than one organ simultaneously. These 31 patients were 16 females and 15 males, aged between 52 and 91 years (median 77, IQR 11). Among patients who developed distant metastases, four were in stage I at the time of MCC diagnosis (4/33, 12%), seven in stage II (7/19, 37%), 13 in stage III (13 /41, 32%), and seven in stage IV (7/7, 100%). Treatment of primary tumor in patients who subsequently developed distant metastases included surgical excision (nine cases), surgical excision with sentinel node biopsy (21 cases), regional lymphadenectomy (19 cases), and adjuvant radiation therapy (13 cases, including primary tumor bed, lymph node area, or both). The organs affected by the first detected distant spread were non-regional lymph nodes (17 cases), bone (10 cases), liver (seven cases), lung (six cases), non-regional skin and/or subcutaneous tissue (four cases), pancreas (three cases), pharynx (two cases), and breast (one case). We did not detect brain metastases in any patient. Time between primary tumor diagnosis and the detection of distant metastases ranged between 0 and 53 months, median 8 months, IQR 3.

Table 1 shows the clinical features of patients according to metastatic site. We did not detect differences in distant metastasis location by sex or immunosuppression. Although differences in distant dissemination pattern by primary tumor location were also not significant, tumors located in the extremities tended to spread to non-regional lymph nodes, while those located in the head and neck region more frequently metastasized to bone, liver, or lung. In 26 of 31 patients (84%) distant metastases were detected in the first two years of follow-up. All pancreatic metastases (3/3) were detected in the first six months.

Discussion

It is well known that some types of cancer tend to metastasize to certain organs. Visceral metastases from cutaneous melanoma are usually located in the lung, central nervous system, and liver [11,12], while uveal melanoma presents a pattern of spread almost exclusively to the liver [13,14]. In cutaneous melanoma, it has been suggested that the development of metastasis to specific organs is influenced by the expression of chemokines. The chemokines CCR7 and CXCR3 have been related to dissemination to the lymph nodes [15],CCR9 to dissemination to the small intestine [16], CCR10 to skin metastases [17,18],and CCR4 to brain metastases [18,19].In the case of uveal melanoma, tropism liver disease is attributed to interactions between hepatocyte growth factor and insulin-like growth factor 1 produced in the liver with its receptors expressed by tumor cells [14,20]. Perhaps due to its low incidence, the patterns of distant metastasis of MCC have not been adequately evaluated. We found few studies on the subject, some with contradictory results [5-10].One of them concluded that MCC does not have a predilection for any specific organ [7] However, in the rest of the surveys the most common locations of distant metastases from MCC were non-regional lymph nodes, liver, bone tissue/bone marrow, and lung (Table 2) [5-10], a pattern clearly different from that of cutaneous melanoma and uveal melanoma [8,11-13].

In accordance with the previously mentioned data, the first distant metastases detected in our patients were most frequently located in non-regional lymph nodes (17), bone (10), liver (seven), and lung (six). It is noteworthy that in our study we did not detect brain metastases in any patient and that in the rest of the published studies they have been only rarely detected (Table 2). Also of note is the occasional dissemination of MCC to organs not usually affected by other cancers, such as the pancreas or pharynx.

Several studies suggest that primary MCC location may influence the organs affected by metastases. Head and neck MCC preferentially spreads to liver [8-10], and trunk MCC to bone [9]. Because of the small number of patients, we were unable to detect any significant association between MCC location and preferential dissemination to certain organs. However, in our study the most frequent locations of distant metastasis were bone and liver for head and neck tumors and non-regional lymph nodes for MCC of the extremities.

According to the literature, 80% of distant metastases appear before two years after the initial diagnosis of the tumor [8]. In our series, 84% of distant metastases were detected before two years, confirming the precocity of MCC in developing metastasis and therefore its high aggressiveness. Since immunotherapy is most effective when the tumor burden is small, early detection of metastases could increase treatment response rates and survival [8]. A better understanding of MCC dissemination patterns will help to define follow-up strategies in the effort to detect metastases earlier [5]. The optimal follow-up of MCC with imaging tests has

Table 1. Clinical Features of Patients with MCC according to the Location of the First Distant Metastasis Detected.

	Non-regional lymph nodes	Bone	Liver	Lung	Skin/ subcutaneous non-regional	Pancreas	Adrenal	Pharynx	Breast
	17/31	10/31	7/31	6/31	4/31	3/31	2/31	2/31	1/31
Sex									
Female 16/31 (51.61%)	8/17 (47.06%)	5/10 (50%)	5/7 (71.43%)	5/6 (83.33%)	3/4 (75%)	2/3 (66.67%)	1/2 (50%)	1/2 (50%)	1(100%)
Male 15/31 (48.31%)	9/17 (52.94%)	5/10 (50%)	2/7 (28.57%)	1/6 (16.67%)	1/4 (25%)	1/3 (33.33%)	1/2 (50%)	1/2 (50%)	0 (0%)
Age (years)									
median 77. IQR 11	76. IQR 14	82. IQR 14	82. IQR 12	81. IQR 8	76.50 IQR 18	72	82.50	53.50	52
Immunosuppression									
7/31 (22.58%)	2/17 (11.76%)	4/10 (40%)	2/7 (28.57%)	0/6 (0%)	1/4 (25%)	1/3 (33.33%)	0/2 (0%)	0/2 (0%)	0/1 (0%)
Photoexposed									
19/31 (61.29%)	10/17 (58.82%)	7/10 (70%)	5/7 (71.43%)	5/6 (83.33%)	4/4 (100%)	1/3 (33.3%)	2/2 (100%)	0/2 (0%)	0/1 (0%)
Site									
Head/neck 11/31 (35.48%)	4/17 (23.53%)	6/10 (60%)	5/7 (71.43%)	4/6 (66.67%)	3/4 (75%)	1/3 (33.3%)	1/2 (50%)	0/2 (0%)	0/1 (0%)
Trunk 3/31 (9.68%)	2/17 (11.76%)	1/10 (10%)	0/7 (0 %)	0/6 (0%)	0/4 (0%)	1/3 (33.3%)	0/2 (0%)	0/2 (0%)	0/1 (0%)
Extremities 17/31 (54.84%)	11/17 (64.71%)	3/10 (30%)	2/7 (28.57%)	2/6 (33.33%)	1/4 (25%)	1/3 (33.3%)	1/2 (50%)	2/2 (100%)	1/1 (100%)
Distant metastasis free time (months)	5, IQR 13	5, IQR 12	8, IQR 15	10, IQR 19	15, IQR 22	2	29	26	40
	17 metastasis	10 met.	7 met.	6 met.	4 met.	3 met.	2 met.	2 met.	1 met.
median 8. IQR 3									
31 patients									
0 m- 7 patients	0- 5	0- 2	0- 2	0- 1	0- 0	0- 1	0- 0	0- 0	0- 0
6 m- 8 patients	6- 5	6- 4	6- 1	6- 2	6- 0	6- 2	6- 0	6- 0	6- 0
12 m- 6 patients	12- 3	12- 2	12- 2	12- 0	12- 1	12- 0	12- 1	12- 1	12- 0
18 m- 4 patients	18- 1	18- 0	18- 2	18- 2	18- 2	18- 0	18- 0	18- 0	18- 0
24 m- 1 patients	24- 0	24- 1	24- 0	24- 0	24- 0	24- 0	24- 0	24- 0	24- 0
30 m- 0 patients	30- 1	30- 0	30- 0	30- 0	30- 0	30- 0	30- 0	30- 0	30- 0
36 m- 2 patients	36- 0	36- 1	36- 0	36- 1	36- 1	36- 0	36- 0	36- 0	36- 0
42 m- 1 patients	42- 0	42- 0	42- 0	42- 0	42- 0	42- 0	42- 0	42- 1	42- 1
48 m- 1 patients	48- 1	48- 0	48- 0	48- 0	48- 0	48- 0	48- 1	48- 0	48- 0
53 m- 1 patients	53- 1	53- 0	53- 0	53- 0	53- 0	53- 0	53- 0	53- 0	53- 0

Table 2. Summary of Reported Series.

	Non-regional lymph nodes	Bone	Liver	Lung	Adrenal	Skin/ subcutaneous non-regional	Pancreas	CNS	Pharynx	Breast	Other
Hawryluk 2013 51 locations	37% (19/51)	20% (10/51)	12% (6/51)	10% (5/51)	6% (3/51)	4% (2/51)	4% (2/51)				8% (4/51)
Kouzmina 2017 30 patients	60 % (18/30)	23% (7/30)	30% (9/30)	30% (9/30)	10% (3/30)	27% (8/30)	20% (6/30)	13% (4/30)			
Lewis 2019 215 patients	41% (88/215)	21% (45/215)	23% (49/215)	7% (15/215)	2% (5/215)	25% (54/215)	8% (18/215)	5% (11/215)			
Song 2020 37 patients	46% (17/37)	27% (10/37)	51% (abd.) (19/37)			19% (7/37)		3% (1/37)			
Maloney 2021 331 patients		21% (68/331)	27% (89/331)	15% (51/331)				2% (6/331)			
Kim 2024 151 patients	62% 94/151	27% 40/151	23% 34/151	6% 9/151	4% 6/151	27% 40/151	5% 8/151	3% 5/151			7% 10/151
Present series 31 patients	**55% (17/31)**	**32% (10/31)**	**23% (7/31)**	**19% (6/31)**	**6% (2/31)**	**13% (4/31)**	**10% (3/31)**		**6% (2/31)**	**3% (1/31)**	

Abbreviation: CNS: central nervous system.

not been established. The National Comprehensive Cancer Network (NCCN) guideline recommends imaging tests only when clinically indicated and also recommends that routine follow-up with imaging tests be considered only in patients with stage IIIB or higher[21].In our study we detected distant metastases in the follow-up of patients diagnosed in all stages, and in seven patients (23% of those with distant metastases), these were present at diagnosis of MCC. These results suggest that imaging tests should be performed both for the initial staging of patients and for clinical follow-up, at least during the first two years. Distant lymph node, bone, and liver metastases must be ruled out. Given the rarity of brain metastases, PET CT follow-up may be appropriate for patients with MCC follow-up, while specific scans to detect brain metastases should be performed only if neurological symptoms appear [5,9].

The limitations of our study are that its retrospective design introduces potential biases in data collection and limits the possibility of establishing causal relationships. Because the sample size is limited, many of the analyzed correlations do not reach statistical significance. Moreover, the lack of uniformity in patient treatment may influence the results. Finally, the low median follow-up, mainly due to the old age of patients, may be insufficient to fully assess the long-term risk of distant metastasis.

In summary, our study confirms the elevated risk of distant metastasis in MCC (1/3 of patients) that usually appears before two years of follow-up (84% of our patients). The most common locations are non-regional lymph nodes, bone, liver, and lung, while the central nervous system is rarely involved. Because immunotherapy may currently improve survival, we consider it advisable to include routine imaging tests in the follow-up of all MCC patients to detect metastasis early on. Specific imaging tests to detect brain metastasis should be reserved for patients with neurological symptoms. Multicenter prospective studies with larger samples of cases that integrate molecular data to identify patients at higher risk of metastasis are needed to confirm these results and to define optimal follow-up protocols.

Ethics Committee: Approval of the study by the Research Ethics Committee of the Bellvitge University Hospital: reference PR318/23.

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