Merkel Cell Carcinoma: A Rare and Underdiagnosed Entity

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ABSTRACT **Background:** Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine skin tumor with an increasing incidence in Western countries. Predominantly affecting older individuals, MCC represents less than 1% of malignant skin tumors.

Objectives: To characterize the clinical presentation, therapeutic interventions, and follow-up outcomes of MCC patients. To promote heightened clinical awareness regarding the early recognition and diagnosis of MCC.

Methods: We conducted a retrospective cohort study analyzing medical records of MCC patients at the Shaare Zedek Medical Center between 2015–2022. From 19 initially identified patients, 17 met the inclusion criteria. Data collection included demographic, epidemiological, clinical, and pathological characteristics.

Results: The study included 17 patients, predominantly of Jewish origin, with a mean age of 70.06 years; 58.8% female. Medical co-morbidities included 64.7% hypertension and 35.3% diabetes. MCC tumors were predominantly left-sided (58.8%), with varied locations including limbs, trunk, and face. Surgical treatment consisted of excision and primary closure (64.7%) or skin grafting (23.5%). The average tumor diameter was 3.41 cm clinically and 3.83 cm pathologically. Lymph node involvement occurred in 29.4% of cases; 23.5% showed metastatic disease at diagnosis, with metastases diffused in different body areas. Kaplan-Meier survival analysis showed no statistically significant differences across most variables, except for a significantly lower survival rate in patients with ischemic heart disease ($P = 0.009$).

Conclusions: Our study reveals unique characteristics of MCC, predominance of female patients, and a slightly younger average diagnosis age compared to existing literature. The 2-year survival rate in our cohort was 82%. The study underscores the importance of early detection and diagnosis of MCC, thereby enhancing clinical awareness and improving patient outcomes.

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KEY WORDS: Merkel cell carcinoma (MCC), skin cancer, neuroendocrine skin cancer, survival, lesion

Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine skin tumor [1]. MCC accounts for less than 1% of all cutaneous malignancies [2,3]. Due to its rarity, epidemiological data remains ambiguous and are primarily based on case reports and single country reviews [2]. In Europe, the incidence rate between 1995 and 2002 was 0.13 per 100,000 [3]. In the United States, the incidence rate in 2011 was 0.79 per 100,000 [4,5]. A 95% increase in absolute case numbers was reported for the period between 2000 and 2013, with the most recent diagnosis of approximately 2000 new MCC cases annually [5,6].

The rise in cases is partly due to population aging. In 2013, the median diagnosis age in the United States was 75–79 years, with 84% of patients aged 65 years or older. By 2025, when those aged 65 years and older will presumably constitute 20% of the population, an increasing number of people will be at an elevated risk for MCC [7]. The cellular origin of MCC remains controversial. The association between immunosuppression and MCC is linked to high-risk subgroups, including solid organ transplant recipients and patients with hematologic malignancies, who exhibit a markedly increased incidence of MCC [8]. Additional known risk factors include fair skin, advanced age, male sex, and concurrent malignancies [9]. The prevailing hypothesis, based on histological characteristics of tumor cells, suggests derivation from Merkel cells, which are sensory cells located in the epidermis [7]. Several factors contribute to MCC etiology, including ultraviolet (UV) radiation exposure, Merkel cell polyomavirus (MCPyV), and immunosuppression. MCPyV is detected in up to 80% of MCC cases in the European population.

MCC is characterized by local recurrence and distant metastases, which contributes to its particularly aggressive nature. Survival rates vary according to different factors, primarily disease extent at initial presentation and,

particularly, regional lymph node involvement. Five-year survival rates range from 60–87% for patients presenting with localized disease, 39–62% for those with lymphatic involvement, and 11–20% for distant metastases. Clearly, MCC remains highly lethal.

Despite its severity and rising incidence, data on MCC, especially from tertiary centers in Israel, is limited. The treatment of MCC usually includes wide excision with sentinel node biopsy, often followed by radiation. Advanced cases are typically treated with immunotherapy, such as PD-1/PD-L1 inhibitors like avelumab or pembrolizumab. Chemotherapy may be used when immunotherapy is contraindicated, although it offers limited long-term benefits [10].

In this study, we address that gap by analyzing clinical and demographic features of MCC patients treated at a single Israeli tertiary center between 2015–2022, with a mean diagnosis age of 70, which is slightly younger than the commonly cited median of 75–77 years [11,12], with the highest incidence reported in over 85-year-old individuals [13,14]. Our aim was to provide a thorough analysis of MCC, including its epidemiology, clinical characteristics, underlying pathogenesis, and treatment strategies [10]. Co-morbidities likely reflect the more advanced age of our cohort rather than a direct link to MCC. We examined advanced-stage diagnoses and the mean tumor diameter at presentation. By detailing clinical features, sex, co-morbidities, and outcomes, our study results offer insight into MCC in a regional context and underscores the importance of local data in guiding care.

PATIENTS AND METHODS

Our study was based on the collection of existing data from medical records of patients diagnosed with MCC at our institution. Patients were identified through the pathology database from which all reports indicating a diagnosis of MCC were collected. For each patient, demographic, epidemiological, clinical, and pathological data were gathered. Diagnosis of MCC was confirmed by positive immunostaining for CK MNF116, CK20, CD56, synaptophysin, chromogranin, and neurofilament (NF) and negative staining for LCA, TTF-1, GATA3, PAX8, CDX2, and a melanoma cocktail (S-100, HMB-45, Melan-A). We included all consecutive patients diagnosed with MCC and treated at the Shaare Zedek Medical Center, Jerusalem, Israel, between 2015 and 2022. Patients whose ongoing care was provided at another institution or who were lost to follow-up for other reasons were excluded from the study. Nineteen patients were identified with MCC. Of these, 17 met inclusion criteria. Two patients were excluded due to insufficient medical information in medical records. Advanced disease was defined as stage 3–4. The institutional review board approved our retrospective single center observational study.

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA). The collected data were summarized in frequency tables, summary statistics, confidence intervals, and standard *P* values. All statistical tests were conducted at a two-sided significance level of α=0.05, unless stated otherwise. *P*-values were rounded to two decimal places. To characterize the study groups on a basis of demographic and clinical data prior to hospitalization, the distribution of continuous variables with normal distribution was presented as mean ± standard deviation (SD), whereas the distribution of discrete variables was presented in the form of interquartile range ± SD. Categorical variables were presented as frequencies. The Kaplan- Meier model of univariate analysis was used for patient survival rates. We acknowledge that limited sample size may constrain statistical power; hence, the conclusions should be interpreted with appropriate caution.

RESULTS

PATIENT DEMOGRAPHICS

The study included 17 patients with an average age of 70.06 years. The youngest patient was 50 years old and the oldest was 95; 10 patients were female. Most patients treated at the Shaare Zedek Medical Center are either Jewish or Arab. In our study, ethnically, 16/17 patients were Jewish. Regarding co-morbidities, 11 of 17 had hypertension and 6 of 17 had diabetes prior to their MCC diagnosis. While these co-morbidities impact overall survival, they are not specifically correlated with MCC-related outcomes. Most participants (14 of 17; 82.4%) did not have ischemic heart disease and none were active smokers. Four patients (23.5%) had an additional malignancy besides MCC: one with breast cancer, two with squamous cell carcinoma of the skin, and one with chronic lymphocytic leukemia [Table 1].

Table 1. Patient demographics

Variable	n=17
Age, mean ± SD	70.06 ± 13.39
Sex: female, n (%)	10 (58.8%)
Jewish, n (%)	16 (94%)
Arab, n (%)	1 (6%)
Hypertension, n (%)	11 (64.7%)
Diabetes, n (%)	6 (35.3%)
Ischemic heart disease, n (%)	3 (17.6%)
Additional malignancy, n (%)	4 (23.5%)
Pathological diameter, mean ± SD	3.83 ± 1.75 cm
Clinical diameter, mean ± SD	3.41 ± 3.04 cm
Surgical excision and primary closure	13 (64.7%)
Reconstruction type: skin graft	4 (23.5%)
Side: left	11 (64.7%)

SD = standard deviation

TUMOR CHARACTERISTICS

For 10 of 17 patients (58.8%), the MCC tumor appeared on the left side of the body. Four cases appeared in the lower limbs, five in the upper limbs, six on the trunk, and two on the face. MCC was identified in various body locations, with no specific predilection for a particular side or region. The average clinical tumor diameter was 3.41 cm, and the average pathological diameter was 3.83 cm. Lymph node involvement occurred in 29.4% of cases and 23.5% of patients had metastatic disease at diagnosis. Stages 1–2 represented primary disease stage (35.3%), while stages 3–4 were advanced (41.2%).

TREATMENT

In total, 13 (64.7%) patients underwent surgical excision and primary closure and 4 (23.5%) were reconstructed with a spilt thickness skin graft. Clinical diagnosis of MCC is inherently challenging due to the non-specific presentation of its skin lesions. Figure 2 illustrates four distinct types of MCC lesions found in our patients, highlighting the variability in lesion characteristics, including size, color, and morphology, which can closely mimic other skin benign or malignant lesions. Accurate diagnosis typically requires dermoscopy, histopathological evaluation, and immunohistochemical staining to differentiate MCC from other dermatological lesions [15,16]. Early and precise identification is critical to improving outcomes.

SURVIVAL OUTCOMES

Two-year survival data were collected; 3 (17.6%) patients died within 2 years of diagnosis [Table 2], of whom two were the eldest of the study group, aged 87 and 95 years, respectively.

Table 2. Outcomes

Variable	Descriptive
Survival months (2-year survival): median (interquartile range)	24 (20.5–24)
Two-year survival, n (%)	14 (82.4%)

KAPLAN-MEIER SURVIVAL ANALYSIS:

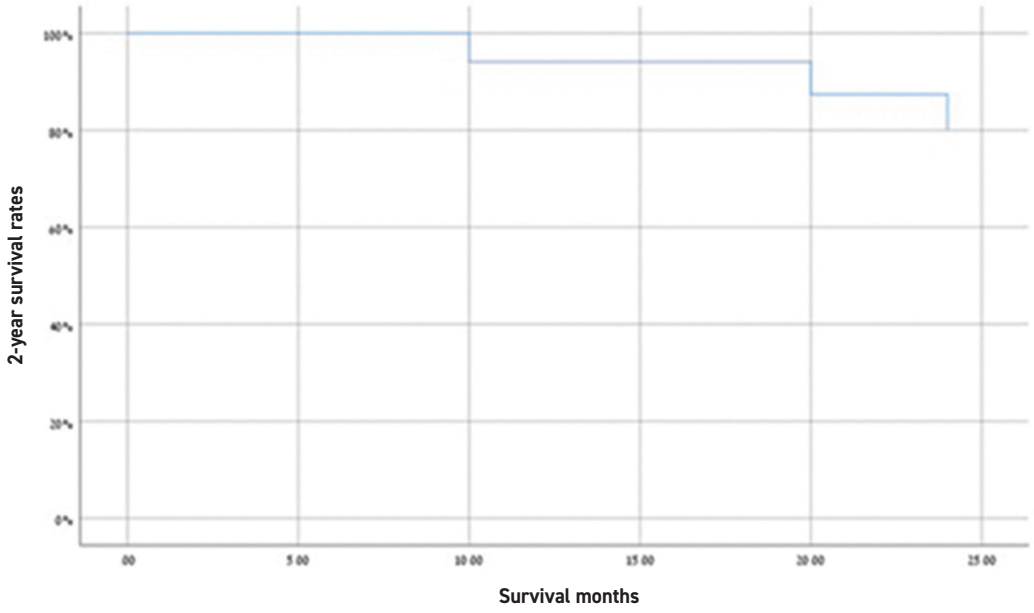
The overall survival rate is presented according to Kaplan-Meier on Figure 1. No statistically significant difference in survival rate was found between men and women ($P = 0.236$). Patients without hypertension showed a higher survival rate, but this rate was not statistically significant ($P = 0.226$). Patients with type 2 diabetes had higher survival, but without statistical significance ($P = 0.733$). Patients with ischemic heart disease had a significantly lower survival rate ($P = 0.009$). Survival rates were similar for patients with other malignancies ($P = 0.544$) or for those who had primary closure. Patients with lymph node involvement had similar survival rates to those without lymph node involvement ($P = 0.354$). The presence of metastatic disease did not decrease survival rates ($P = 0.931$). Patients with advanced-stage disease (3–4) had similar survival rates to those with early-stage disease (1–2; $P = 0.557$). Survival outcomes did not differ significantly among patients with advanced stage disease, in contrast to established literature indicating poorer prognosis with later stage MCC. This discrepancy is likely attributable to the limited cohort size. The association between ischemic heart disease and reduced survival may reflect the underlying morbidity of the condition.

DISCUSSION

Due to the rarity of MCC, the current knowledge about it is relatively limited. The aim of this study was to describe the morbidity status in the Jerusalem area by reviewing patients according to demographic characteristics and co-morbidities, as well as reviewing the disease according to pathology reports, disease stage, treatment, and survival. The median age at diagnosis was 70 years.

Regarding demographics, we found that MCC patients in Israel were diagnosed at a younger age, approximately

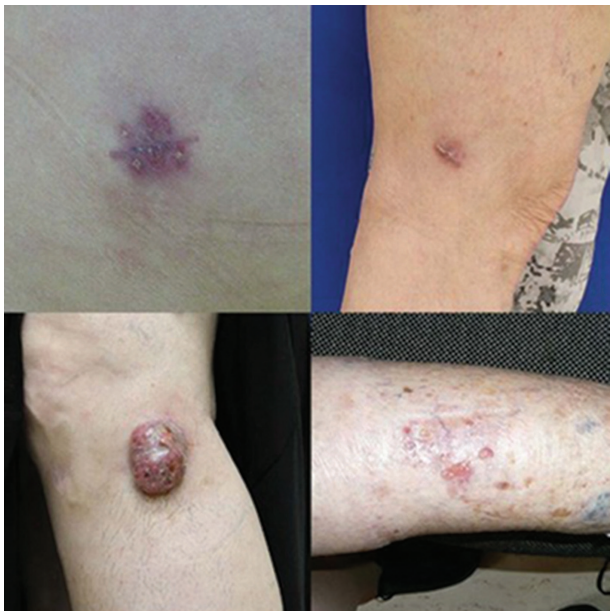
Figure 1. Kaplan Meier 2-year survival rates



5 years earlier than the median age of 75–79 years reported for MCC patients in the United States as of 2013 [6]. In the United States, for all age groups, the percentage of men with MCC is higher than for women [6], whereas in our study group, the majority (59%) of cases were women. Female sex has been reported to be a negative prognostic factor [2], while our study demonstrated a difference that was not statistically significant.

Although the small sample size might be the influencing factor, the female predominance in our sample could influence the overall survival rate due to a possible biological or referral bias. Among our study participants, only one patient was of Arab ethnicity, 94% were Jewish. Our findings are similar to those found in the United States. Camayo and Dane [10] found an overrepresentation of patients of European origin (89.9%) concomitant with an underrepresentation of the remaining ethnic groups relative to the general US population. There is a clear trend of higher incidence among the Jewish population in our study that relates to the precincts of Jerusalem. Of the various co-morbidities we examined (hypertension, type 2 diabetes, and ischemic heart disease), we found that 65% of study participants were diagnosed with hypertension, which may be correlated with the relatively advanced age of the patients rather than directly association with MCC. In addition, 35% had type 2 diabetes, and 17% had ischemic heart disease.

Figure 2. Four types of Merkel cell carcinoma



Our study further demonstrated statistically significant lower survival rates among patients with ischemic heart disease. This finding may not be a negative prognostic factor, but rather a reflection of the natural course of ischemic heart disease. Comparisons of survival rates for other co-morbidities did not show statistical significance. To

the best of our knowledge, the literature does not provide data on the relationship between these co-morbidities and the risk of developing MCC or survival rates. One of the known risk factors for MCC is the presence of additional malignancies, particularly hematological. Hematological cancers and their treatments can cause immunosuppression, which is a risk factor for MCC and a negative prognostic factor [17]. In our study, 23% of patients had other malignancies, including breast cancer, squamous cell carcinoma, and chronic lymphocytic leukemia. Although our study showed lower survival rates for these patients, the result was not statistically significant; however, this trend needs further investigation.

Some 41% of our patients were diagnosed with advanced stage disease. The 2-year survival rate was 82%. The mean clinical tumor diameter at diagnosis was 3.41 cm, and the mean pathological diameter was 3.83 cm; 29% of patients had lymph node involvement at diagnosis, and 23% had metastases. According to the literature, 5-year survival rates range from 60–87% for patients presenting with localized disease, 39–62% for those with lymphatic involvement, and 11–20% for those with distant metastases [9].

In our patients, 59% of MCCs were distributed on the left side and 76% in the upper body region. These areas are more exposed to UV radiation, with the upper body generally less covered than the lower and possibly because the left side faces the car window while driving. These findings are consistent with the understanding that UV radiation is a risk factor for MCC. A study conducted in Germany, the United States, and Finland, where the driver's side is on the left, also showed a predilection for MCC on the left side of the body. These data appear to support the role of UV radiation in the etiology of MCC. However, the study also found that the tumor primarily appeared on the left side of the lower limbs, suggesting there may be additional reasons for preference for this side in MCC [17]. Nevertheless, the location of the tumor in the upper limbs has been identified as a positive prognostic factor [10].

Limitations of this study include its retrospective design, single-center data not documented prospectively for the purposes of this research, and limited sample size. Moreover, since multivariate analysis was not performed due to limited sample size, the strength and generalizability of our conclusions are impacted. Consequently, the quantity and nature of information were not uniform across our records. These factors warrant a multicenter study with a larger sample size.

CONCLUSIONS

In our study population, the majority of MCC tumors appeared on the left side of the patient's body, similar to what we found in the literature. The most affected ethnic group in the United States is of European descent, parallel to our findings that the Jewish population in Jerusalem is more likely to be affected than the other local ethnic group. In contrast to the literature, most MCC patients in this study were women, and the average age at diagnosis was at least 5 years younger. Regarding aspects that cannot be compared to the literature, 94% of patients were of Jewish ethnicity, 65% were diagnosed with hypertension, and the 2-year survival rate was 82%. These findings should be interpreted with caution due to the stated limitations, namely, small sample size, retrospective analysis and lack of multivariable analysis. MCC is a rare and aggressive tumor associated with a high mortality rate. However, its clinical diagnosis remains challenging, highlighting the critical importance of early detection. We hope that our research elicits awareness of this rare and dangerous malignancy while addressing the challenges of its clinical underdiagnosis with the ultimate goal of improved recognition and outcomes.

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Capsule

On adult neurogenesis in humans

Whether adult neurogenesis occurs in the human hippocampus is one of the most debated issues in neuroscience. **Dumitru** and colleagues used a single-cell transcriptomic approach to address this issue in human samples of various ages from birth through adulthood. Machine learning algorithms helped the authors to identify proliferating neural progenitor cells in the adolescent and adult human hippocampus that resembled progenitor cells found in mice and pigs. The results support the idea that adult neurogenesis occurs in the human hippocampus and add valuable insights of scientific and medical interest.

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Eitan Israeli

Capsule

A gatekeeper of type 2 immunity

Tuft cells have key roles in initiating and propagating type 2 immune responses in mucosal tissues, but whether they have regulatory machinery for constraining these responses is unknown. **Wang** et al. found that the transcription factor Spi-B serves as a checkpoint of type 2 immunity by restraining tuft cell activation in the small intestine. Mice lacking Spi-B developed spontaneous type 2 inflammation and increased responses against helminth infection and food allergens. Pharmacological inhibition of downstream signaling pathways reduced the severity of food allergy in mice, suggesting that targeting this pathway therapeutically could help to manage tuft cell-mediated type 2 inflammatory disorders.

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Eitan Israeli

Capsule

Stem cell-derived, fully differentiated islets for type 1 diabetes

Zimislecel is an allogeneic stem cell-derived islet-cell therapy. A total of 14 participants (2 in part A and 12 in parts B and C) completed at least 12 months of follow-up and were included in the analyses by **Reichman** et al. C-peptide was undetectable at baseline in all 14 participants. After zimislecel infusion, all the participants had engraftment and islet function, as evidenced by the detection of C-peptide. Neutropenia was the most common serious adverse event, occurring in three participants. Two deaths occurred, one caused by cryptococcal meningitis and one by severe dementia with agitation owing to the progression of preexisting neurocognitive impairment. All 12 participants in parts B and C were free of severe hypoglycemic events and had a glycated hemoglobin level of less than 7%. These participants spent more than 70% of the time in the target glucose range (70–180 mg per deciliter). Ten of the 12 participants (83%) had insulin independence and were not using exogenous insulin at day 365.

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