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Incidence of Merkel Cell Carcinoma in Olmsted County, Minnesota: A Population-Based Study

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Abstract

Background—Merkel cell carcinoma (MCC) is a rare, aggressive, often cutaneous malignancy. The incidence has been estimated from national registries in the US and abroad and data indicate variations depending on the region studied. The objective of this study was to determine the incidence of MCC in Olmsted County, MN.

Methods—Using the Rochester Epidemiology Project, which contains health records for all the residents of Olmsted County, MN, we retrospectively reviewed the records for all cases of MCC from 1976 to 2011.

Results—The overall annual age- and sex-adjusted incidence of MCC in Olmsted County during 1976-2011 was 0.35 per 100,000 person-years (95% CI, 0.14-0.57). The incidence tended to be higher among men than women with 0.69 per 100,000 (95% CI, 0.24-1.14) and 0.10 per 100,000 (95% CI, 0-0.24), respectively.

Conclusions—This data is within the range of prior MCC incidence reports and the incidence of MCC in Olmsted County, MN is consistent with rates reported in the remainder of the United States.

Keywords

Merkel Cell Carcinoma; Non-Melanoma Skin cancer; Epidemiology; Incidence; Multidisciplinary Care

Introduction

Merkel Cell Carcinoma (MCC) is a rare, aggressive, often cutaneous, malignancy. Incidence data to date has been gathered primarily from national cancer registries.¹⁻⁷ Though certainly rare, the limited incidence data available ranges by a factor of ten depending on the registry studied.^{3, 6}

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A population based study in Finland found an incidence of MCC from 1989 to 2008 of 0.11 for men and 0.12 for women and suggested a rising incidence until 1993, when the rate stabilized.⁶ A population based study in Western Australia found an incidence of MCC from 1993 to 2007 of 1.0 per 100,000 for men and 0.63 per 100,000 for women.³ Between these extremes, the Surveillance, Epidemiologic and End-Results (SEER) database and Danish Cancer Register and have reported an overall estimated age-adjusted rate ranging from 0.22 cases per 100,000 person-years from 1995 to 2006 to 0.32 per 100,000 person years from 1992 to 2001.^{1, 2, 5} Separate studies suggest increases in incidence per year from 1986 to 2001.^{8, 9}

Given the regional differences and relative scarcity of data, the primary aim of this study was to estimate the incidence of MCC in Olmsted County, Minnesota, a well-studied population owing to the wealth of information available in the Rochester Epidemiology Project.^{10, 11} We also examined the individual patient characteristics and their disease management among different specialties. With this large variation in incidence data available, we hope to add clarity to the incidence data by adding the incidence of MCC among our population.

Materials and Methods

We reviewed cases of MCC diagnosed within the population of Olmsted County, Minnesota from January 1, 1976 to December 31, 2011. Olmsted County is located in the Southeastern region of Minnesota, approximately 90 miles southeast of Minneapolis and St. Paul. Age, sex, and ethnic characteristics of the patients in Olmsted County are similar to those of Minnesota in general.¹² According to census data from 2000, 90.3% of the population of Olmsted County is white, 10.8% is age 65 or older, and 34.7% has a Bachelor's degree or higher.¹²

This study was approved by the Mayo Clinic and the Olmsted Medical Center Institutional Review Boards and access was granted to the resources of the Rochester Epidemiology Project (REP), which were used to conduct this study. The REP is a unique infrastructure that maintains a comprehensive medical records linkage system containing medical diagnoses and surgical procedures for nearly all residents of Olmsted County since the 1960s.¹⁰⁻¹²

Using the REP, 2639 potential cases of MCC from 1976 to 2011 were identified by searching Hospital Adaptation of the International Classification of Diseases (HICDA) and ICD-9 codes. The ICD-9 coding varied across the time period from a non-specific ICD-9 code of 173.x with a description of "other malignant neoplasm of skin" which encompassed cutaneous malignancies ranging from squamous cell carcinomas to MCC, atypical fibroxanthomas, dermatofibrosarcoma protuberans, and Spitz tumors to specific ICD-9 codes for MCC of 209.31-209.36 and 209.75 which became active in October 2009. Of the 2639 patients, 104 patients who did not provide authorization for use of records for research purposes were excluded. Cases with pathologic diagnosis of MCC were identified and data abstracted. In each case, a dermatopathologist or pathologist made or confirmed the diagnosis of MCC based on a permanent section biopsy specimen. In many cases diagnosed

after 1996, immunostains were used for confirmation. Many of these patients were part of a larger study of 240 MCC patients treated at Mayo Clinic during 1981-2008, though as a large tertiary center, the majority of these patients were not residents of Olmsted County, MN and thus not considered in this incidence study.^{13, 14}

The data was collected by one abstractor (MBC). Socio-demographic data including age at diagnosis, gender, Fitzpatrick type, education level, and tobacco use was collected. Diagnosis information abstracted included histopathologic data, recurrences, and metastases. Disease treatment data including specialists visited, type of procedure performed, and imaging were also collected. Finally, date of last relevant clinical follow-up, vital status and date of last follow-up were recorded. The results were summarized using standard descriptive statistics (frequency and percentages for categories variables and mean or median and range for continuous variables). The overall annual incidence of MCC in Olmsted County during 1976-2011 was calculated with the assumption that the entire population of Olmsted County during this time period was at risk.¹⁵ The numerator was the number of persons with MCC diagnosed within this period and the denominator was obtained from the decennial census data for 1976-2011, with linear interpolation between census years. Rates were age- and sex-adjusted to the total population structure of the U.S. in 2010. The 95% confidence intervals (CIs) for the rates were calculated assuming a Poisson error distribution.

Results

Over the 36 year period, 11 patients with a confirmed histopathologic diagnosis of MCC while a resident of Olmsted County were identified. Six of seven stained for CK20 with either a perinuclear dot pattern or dot-like staining pattern. The remaining cases were prior to 1996 and not stained with CK20. Among the 11 patients, 9 (82%) were male and the median age at diagnosis was 77 years (range, 61 - 91 years). Four cases were diagnosed in the 1980's, 2 in the 1990's and the remaining 5 in the 2000's. The overall annual age- and sex-adjusted incidence of MCC in Olmsted County during 1976-2011 was 0.35 per 100,000 person-years (95% CI, 0.14-0.57). The incidence tended to be higher among men than women with 0.69 per 100,000 (95% CI, 0.24-1.14) and 0.10 per 100,000 (95% CI, 0-0.24), respectively.

All patients were Caucasian. Only one patient had a history of a solid organ transplant prior to diagnosis. Seven (64%) were either current or former tobacco users. Three primary MCC were from the scalp, two from the cheek, one from the nose, two from the upper extremities, and three were from the trunk and lower extremities. The demographic and treatment details are listed in Table 1. Table 2 presents the treatment and follow-up details.

Six (55%) cases initially presented to a dermatologist. Eight (73%) saw a dermatologist through the course of their management. Eight total specialties were involved in the care of these patients: dermatology, radiation oncology, medical oncology, ENT, plastic surgery, orthopedics, internal medicine and family medicine, and general surgery. The most number of specialties seen by a single patient for diagnosis and treatment of MCC was four by two patients.

Regarding staging, eight (73%) received CT scans. Three (27%) received PET scans. Four (36%) received sentinel lymph node biopsies. Six (55%) had metastatic disease, either to the lymph nodes, in-transit, or distant. Two (18%) were classified as stage IA disease, three (27%) as stage IB, two (18%) as stage IIIB, and four (36%) as stage IV disease.

Treatment depended on stage of disease. Nine (82%) included some type of surgical treatment, either wide local excision, or Mohs surgery. The two that did not have surgical treatment were diagnosed in 1983 and 1987, and were initially biopsied by excision technique. Adjuvant radiation therapy was included in treatment regimens in three (27%) cases and two of these three also had adjuvant chemotherapy.

The time between diagnosis and treatment ranged from 0 days to 75 days. When a separate specialty from the specialty where the diagnosis was made was involved in treatment, the average time between diagnosis and treatment was 56.8 days. When the same specialty was involved in diagnosis and treatment, the average time was 16.7 days.

At last follow up, eight (73%) had passed away. Three (27%) of these were attributable to their MCC and their pathologic stages were IIIB (2) and IV. The time from diagnosis to death due to MCC was 134, 200, and 769 (2.1 years) days respectively. Of the three remaining stage IV patients, two died of unrelated causes at 2.2 and 3.3 years from diagnosis, and one is alive with no evidence of disease at 22.6 years from diagnosis. Of the five patients with stage IA or IB disease, three died of unrelated causes, and two have survived, now at 4.1 and 7.6 years from diagnosis.

Discussion

This study provides the incidence of MCC in Olmsted County from 1976 to 2011. With an overall age and sex-adjusted incidence of 0.35 per 100,000 person-years, this is within the range of previously reported incidence data.¹⁻⁶ Lower incidence rates, 0.11 and 0.12 per 100,000 person years for men and women respectively, were reported in Finland from 1989 to 2008.⁶ The highest incidence rates were reported in Western Australia, 1.0 and 0.63 per 100,000 person years for men and women respectively from 1993 to 2007, which the authors hypothesized was due to the high levels of solar radiation and fair skinned population.³ The incidence rate in our study was more similar to the results from the Danish Cancer Register of 0.22 cases per 100,000 person-years from 1995 to 2006, and SEER data from the US of 0.32 cases per 100,000 person years from 1992 to 2001.^{1, 2, 4, 5, 9} Our data supports the reported incidence across the United States; however, as seen across the world, certain regions may have significantly higher or lower rates, which would be important to capture.

Our data supports a preponderance of MCC among elderly males with 0.69 cases per 100,000 person-years for males vs. 0.10 cases per 100,000 person-years for females. Interestingly, this is consistent with the Agelli and Clegg data, but is in contrast to the data from the Danish Cancer Register, which found greater incidence among females.^{1, 2, 5} Kaae and colleagues attribute this to the greater number of HIV infected males in the SEER database as compared to the Danish Cancer Register.⁵

Characteristics of the MCC cases are in line with previous descriptions with the majority of cases involving the head and neck (6, 55%) of elderly males (9, 82%).² The aggressive nature of MCC is certainly evident in the follow up of the patients, with three of 11 patients eventually succumbing to their MCC, and six with metastatic disease.

In addition to allowing ascertainment of incidence data, the use of the REP database allows examination of the clinical records of the individuals diagnosed with MCC.^{10, 11} MCC requires multidisciplinary care, which is advocated for by many sources and is certainly available in Olmsted County and Mayo Clinic, where all of the patients diagnosed with MCC were seen for some portion of their care.¹⁶⁻²⁰ Looking at these 11 cases, there has been much heterogeneity in the treatment path followed. Of the eight specialties involved in the treatment of Olmsted County MCC patients, dermatology was involved in 8 and involved in the initial diagnosis in only 6 of the 11 cases. While this represents the majority, it also indicates that a large proportion of these cases are seen by other specialties first.

This subset of patients is too small to make any sort of comparison between specialties. However, a difference of nearly 40 days can be seen when we compare the treatment times when diagnosed and treated within the same specialty (16.7 days) or when those two specialties differed (56.8 days). This is certainly understandable, but with an aggressive malignancy, time to treatment can be paramount, and organized multidisciplinary becomes important.

While there are obvious benefits to an incidence study based on the REP, namely quality healthcare data based on a relatively contained population, there are important limitations to the interpretation of this data. Given the rarity of MCC and the relatively small population of Olmsted County, MN in comparison to the sizes of populations involved in national registry data, only eleven cases make up the incidence among the studied population. Mayo Clinic is a large tertiary center with referrals for treatment of MCC from all over the country, but only a small subset of the patients treated make up the population of Olmsted County.^{13, 14, 21} The REP is a robust database with limited biases that covers a multitude of healthcare delivery options within Olmsted County and can accurately identify and describe the cases of MCC present.¹⁰⁻¹² All cases were pathologically confirmed, though CK-20 staining was not performed on the cases observed prior to 1996 since the introduction of CK-20 staining for confirmation in 1995.^{22, 23} Any error would be one of omission, which would underestimate the incidence. The population of Olmsted County is primarily Caucasian and limited to Southeast Minnesota. As a result, the data reported may not be representative of MCC patients in other parts of the US or abroad. Also, previous studies have made references to a rise in incidence of MCC over time.^{2, 4, 5, 8, 9} While we do see more cases of MCC diagnosed in the most recent decade (2000's) compared to the two previous (1980-2000), it is difficult to make any conclusions with the limited incidence cases due to the rarity of MCC. More cases are needed from separate regions to better clarify the variation in incidence of MCC abroad and perhaps help shed light on particular risk factors.

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Abbreviations

MCC	Merkel Cell Carcinoma
SEER	Surveillance, Epidemiologic and End-Results database
NMSC	Non-Melanoma Skin Cancer
SCC	Squamous Cell Carcinoma

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Table 1

Demographics and Diagnosis

Patient	Gender	Age at Diagnosis (years)	Race	Educ at ion	Tobacco Use	Solid organ transplant	Site	T	N	M	Pathologic Stage	Metastasi s
1	M	78	German, Hungarian	HS Grad	No	No	Chest	T4	N1B	Mx	IIIB	Yes
2	M	61	German	Some College	Yes	No	Cheek	T1	Nx	Mx	IA	No
3	M	77	Caucasian	Some College	Yes	No	Scalp	T1	pN0	M1a	IV	Yes
4	M	66	Caucasian	Post Grad	Yes	Yes	Scalp	T1	N2	M0	IIIB	Yes
5	M	84	Caucasian	HS Grad	Yes	No	Cheek	T1	pN0	M0	IA	No
6	F	91	Caucasian	Post Grad	No	No	Wrist/Hand	T1	cN0	M0	IB	No
7	M	85	Caucasian	College Grad	Yes	No	Arm	T0	N1B	M1a	IV	Yes
8	M	84	Caucasian	8th grade or less	Yes	No	Scalp	T1	Nx	M0	IB	No
9	F	65	Caucasian	Post Grad	No	No	Leg	T1	N1B	M1a	IV	Yes
10	M	65	Caucasian	Post Grad	No	No	Nose	T1	cN0	M0	IB	No
11	M	77	Caucasian	8th grade or less	Yes	No	Buttock	T1	cN1	M1a	IV	Yes

HS, high school; Post Grad, post graduate-level work;

Table 2

Treatment and Follow-Up

Patient	Specialties Seen	Days Between Diagnosis and Treatment	Treatment	SLN Results	Site of mets	Status at last follow-up	Days Between Diagnosis and Last Follow-up or Death
1	Dermatology, Plastic Surgery	49	WLE/SLN, LND, Mohs	Positive	LN	Death, MCC	134
2	Dermatology	--	Nothing Further			Death, other	2754
3	Dermatology, ENT, Radiation Oncology, Medical Oncology	24	WLE/SLN, Parotidectomy, Radiation	Negative	Skin	Death, other	803
4	Dermatology, Radiation Oncology	12	Mohs		Skin	Death, MCC	200
5	Dermatology, ENT, Radiation Oncology	14	WLE/SLN, IFN	Negative		Alive NED	1492
6	Dermatology, Orthopedics	63	WLE			Death, other	1542
7	General Surgery, Medical Oncology, Dermatology	55	WLE/SLN, LND, Chemotherapy, Radiation	Positive	LN	Death, other	1200
8	General Surgery	--	Nothing Further			Death, other	1789
9	Orthopedics, Radiation Oncology, Medical Oncology	0	WLE, SLN, LND	Positive	Skin, LN	Alive NED	8251
10	Family Medicine, Dermatology, ENT	42	Mohs			Alive NED	2775
11	Family Medicine, Medical Oncology, General Surgery, Radiation Oncology	75	WLE, Chemotherapy, Radiation		LN	Death, MCC	769

ENT, ear, nose and throat; WLE, wide local excision; SLN, sentinel lymph node biopsy; LND, lymph node dissection; IFN, Interferon; NED, no evidence of disease.