Annals of Case Reports
Fenning S, et al. Ann Case Rep: 9: 102013
www.doi.org/10.29011/2574-7754.102013
www.gavinpublishers.com

OPEN ACCESS

Case Report

GAVIN PUBLISHERS

First Report of Merkel Cell Carcinoma in Two Brothers

Shlomit Fennig[1], Elena Didkovsky[2], Eyal Fenig[3*]

[1]Institute of Oncology, Kaplan Medical Center, Rehovot, and Faculty of Medicine, Hebrew University, Jeruselem

[2]Pathology Unit, Rabin Medical Center – Beilinson Hospital, Petach Tikva, Israel

[3]Institute of Oncology, Davidoff Center, Rabin Medical Center – Beilinson Hospital, Petach Tikva, and Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

***Corresponding author**: Eyal Fenig, Institute of Oncology, Davidoff Center, Rabin Medical Center – Beilinson Hospital, Petach Tikva, and Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Citation: Fenning S, Didkovsky E, Fenig E (2024) First Report of Merkel Cell Carcinoma in Two Brothers. Ann Case Report. 9: 2013. DOI:10.29011/2574-7754.102013

Received: 08 October 2024, **Accepted:** 14 October 2024, **Published:** 16 October 2024

Abstract

Merkel cell carcinoma (MCC) is a very rare aggressive malignant tumor. Risk factors include older age, exposure to ultraviolet radiation, immunodeficiency status, and infection with Merkel cell polyomavirus (MCPyV). MCC not been considered to run in families, and a review of the medical literature failed to reveal any cases of MCC in first-degree relatives. The aim of this report was to describe for the first time the development of MCC in two brothers. The extremely low likelihood of siblings acquiring the disease, compounded by the similar clinical presentation of the tumor on the skin of the right thigh in both brothers, suggests a possible unknown predisposing factor. Genetic predisposition analysis should be performed in family members of patients with MCC.

Keywords: Merkel cell carcinoma, non-melanoma skin cancer, familial MCC, Merkel cell polyomavirus.

Introduction

Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine malignancy of the skin [1]. The aggressive nature of the disease is manifested by a high risk of recurrence, relatively high rate (40%) of advanced disease(lymph node involvement or distant metastases) at the time of diagnosis, and high specific mortality rate of 26% to 32% [2-4] Numerous risk factors contribute to MCC development, including age over 65 years, fair skin, exposure to ultraviolet (UV) radiation, infection with Merkel cell polyomavirus (MCPyV), and chronic immunosuppression [5].

Although MCC is considered a rare malignancy, new published data indicate a consistent increase in incidence from 0.7 cases per 100,000 persons [6] up to 1.6 cases per 100,000persons in areas with a fair-skinned population and high levels of UV radiation [7]. Older men with fair skin are at highest risk. The reported incidence in males in Israel is 0.28 [8]. MCC is not considered to run in families, and there are no reports of familial MCC in the medical literature.

Herein we describe the first occurrence, to our knowledge, of MCC in siblings.

Case Presentation

A 72-year-old male presented to our tertiary medical center with a mass in the skin of the right thigh that was subsequently diagnosed as MCC. Three years later, his younger brother, aged 74 years, presented with a similar mass and diagnosis.

The brothers were born in Morocco in February 1945 and May 1946 and immigrated to Israel in 1964 with the whole family. They

had an additional 4 brothers and 5 sisters. One sister died of acute myeloid leukemia and another died of pancreatic carcinoma. Two of the remaining sisters and one brother had vitiligo. The older brother with MCC had been diagnosed with Hodgkin's disease 5 months before presentation. The son of the younger brother had Hodgkin's disease at age 20 years.

No genes associated with cancer predisposition were found on genomic analysis [9]. Immunochemistry using CM2B4,a monoclonal antibody against an epitope in exon 2 of the MCPyV T antigen [10], was positive in the older brother and negative in the younger one. Both brothers had fair skin with actinic dermatitis, with basal and squamous cell carcinomas in sun-exposed area on the face and forearms.

The clinical presentation of MCC was extremely similar in the two brothers. In both, the primary tumor originated in the skin of the right thigh with in-transit cutaneous metastases. However, the older brother also had massive regional lymph node involvement of the right groin whereas sentinel lymph node biopsy in the younger brother was negative for malignancy. The pathological stage in both was IIIB (AJCC, 8th edition) [11]. In accordance with our departmental treatment policy, both brothers underwent wide local excision with groin dissection followed by radiation (50 Gy) to the tumor bed and right groin and concomitant delivery of 2 cycles of carboplatin and etoposide.

Several months after completion of treatment, subcutaneous masses were found in the right thigh in both brothers, confirmed by fine needle aspiration. A good response was shown to immunotherapy with avelumab [anti-programmed cell death 1 (PD1)] although the tumor mutation burden and programmed death ligand 1 (PDL1) expression were low. The older brother stopped avelumab after 10 months because of a side effect of severe fatigue. He remained disease-free for 23 months, at which time the tumor recurred in the skin of the right thigh. Avelumab was restarted, but he died after 2 months of pneumonia complicated by septic shock. The younger brother completed 2 years of avelumab and has been in unmaintained remission for 18 months.

Discussion

Our thorough review of the medical literature failed to disclose any reports of familial MCC. To our knowledge, this is the first report of MCC in siblings. Moreover, our additional review of the epidemiological data of all 312 patients with MCC treated at our tertiary medical Center from July1984 to present yielded no similar cases ofMCC in first- and even-second degree relatives.

The rarity of this cancer, the involvement of Hodgkin's disease, and the similarity in the clinical presentation of the two brothers suggest that this is not a purely incidental finding and that a genetic predisposition might play a role. Only the older brother was positive for MCPyV. The main MCC risk factor common to both brothers was exposure to UV radiation.

Mohsin et al. **[12]** reported genetic risk factors for early-onset (age <50 years) MCC in 7 patients. Six were found to have variants in genes associated with hereditary cancer syndromes (2 ATM, 2 BRCA1, 1 BRCA2, and 1 TP53) and 1 had a variant in a gene associated with immunodeficiency and lymphoma (MAGT1). We did not find a genetic predisposition in our cases, and both brothers were older than 70 years.

Conclusion

We describe the development of MCC in 2 brothers. Although very rare, the occurrence of MCC in two first-degree relatives suggests the possibility of a predisposing genetic factor. Further genetic research in family members of patients with MCC is required to resolve this issue.

Acknowledgements: None.

Ethical Guidelines: The study conforms to the standards required by the Declaration of Helsinki and was approved by the Institutional Review Board of Rabin Medical Center (0101-07), which waived the need for informed consent.

Conflict of Interest: The authors declare no conflict of interests.

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