ORIGINAL ARTICLE

Paraneoplastic syndromes (PNS) associated with Merkel cell carcinoma (MCC): A case series of 8 patients highlighting different clinical manifestations

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Background: Paraneoplastic syndromes (PNS) are commonly associated with neuroendocrine cancers, such as small cell lung cancer.

Objectives: We examined the association of PNS in Merkel cell carcinoma (MCC), a rare neuroendocrine skin cancer.

Methods: We identified PNS associated with MCC based on chart review of a Seattle-based repository and examined the incidence of MCC-associated hyponatremia in an independent cohort within Kaiser Permanente Northern California.

Results: Eight PNS cases were identified from the Seattle repository. Three distinct PNS types were observed: cerebellar degeneration (1 case), Lambert-Eaton myasthenic syndrome (2 cases), and malignancy-associated hyponatremia (5 cases). Moreover, the incidence of severe hyponatremia (serum sodium <125 mmol/L) coincident with MCC was identified among 4.3% (9 of 211) patients with MCC in the Kaiser Permanente Northern California cohort.

Limitations: We did not have access to complete medical records on all patients so it was not possible to determine the prevalence of PNS in MCC.

Conclusions: MCC can be associated with PNS similar to those found in other neuroendocrine cancers. Clinicians should be aware of these presentations as PNS often precede the identification of the underlying malignancy and usually resolve with appropriate treatment of the cancer. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2016.04.040.)

Key words: cerebellar degeneration; Lambert-Eaton myasthenic syndrome; malignancy-associated hyponatremia; Merkel cell carcinoma; neuroendocrine; paraneoplastic syndrome.

A paraneoplastic syndrome is a physiological response to an underlying malignancy caused by ectopic hormone secretion or an autoimmune response to cancer-associated antigens.[1] Paraneoplastic syndromes (PNS) have been reported in association with several cancers, most commonly small cell lung cancer (SCLC) and breast, gynecologic, and hematologic malignancies.[2,3] PNS types and their

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presentations differ based on the underlying malignancy. Neuroendocrine malignancies (bronchial carcinoids, carcinoid tumors, and pancreatic islet cell tumors) are associated with a variety of PNS types including Cushing syndrome, acromegaly, and hypercalcemia.[4]

Although it is estimated that up to 8% of cancers are associated with PNS,[2] the prevalence in patients with SCLC is up to 20%.[1] SCLC is reported to be associated with syndrome of inappropriate antidiuretic hormone (SIADH) and Lambert-Eaton myasthenic syndrome (LEMS).[5,6] SCLC is a neuroendocrine tumor with similar histologic features to Merkel cell carcinoma (MCC), an uncommon but often aggressive cutaneous neuroendocrine cancer. MCC is associated with sun exposure, advanced age, fair skin, immune suppression, and the Merkel cell polyomavirus, identified in 80% to 90% MCC.[7] Given a shared neuroendocrine differentiation with SCLC, it is likely that MCC may demonstrate similar presentations of PNS.

CAPSULE SUMMARY

- Paraneoplastic syndromes in patients with Merkel cell carcinoma have been described in individual case reports.
- We describe 8 patients with paraneoplastic syndromes including endocrine (hyponatremia) and autoimmune etiologies and review 13 published cases.
- This aggregate description of Merkel cell carcinoma–associated paraneoplastic syndromes should enable early recognition and management of this life-threatening but treatable disorder.

The literature regarding PNS in MCC is limited to individual case reports (summarized in Table I). Here we describe 8 new cases of PNS associated with MCC. The incidence of severe MCC-associated hyponatremia is also explored in an independent cohort.

METHODS

Patients

The cases analyzed were from the Repository of Data and Specimens for MCC at the University of Washington in Seattle (n = 452) and Kaiser Permanente Northern California (KPNC) (n = 211), a large, integrated health care delivery system. This study was institutional review board–approved by Fred Hutchinson Cancer Research Center (no. 6585) and KPNC (no. CN-09Masgar-03). Patients were diagnosed with MCC between 1980 and 2014. Analyses for this study were carried out between August 2006 and January 2014.

Identification of PNS cases

Patients in the Seattle-based repository were followed up prospectively for survival and recurrence. Although no formal protocol or screening was used to detect PNS across all patients in the cohort, those with symptoms suggestive of PNS were evaluated in detail for evidence of a PNS based on the previously described characteristics of PNS in MCC and other neuroendocrine carcinomas. Cases were reviewed using established criteria to confirm the diagnosis of LEMS and paraneoplastic cerebellar degeneration.[21,22]

Severe hyponatremia was defined as 1 serum sodium value below 125 mmol/L.[23] Medication history was available for patients in the Seattle repository and was reviewed to ensure that no patient was taking medications known to induce hyponatremia. To classify a patient as having malignancy-associated hyponatremia, there must have been clinically significant MCC at time of severe hyponatremia and resolution of hyponatremia upon successful MCC treatment.

To examine the incidence of severe hyponatremia among an independent cohort of MCC cases, serum sodium values from 211 patients in the KPNC repository were reviewed. The median number of serum sodium samples available per patient was 14 (range 1-106). To be classified as severe hyponatremia, patients needed to have: (1) serum sodium below 125 mmol/L, (2) evidence of MCC at time of hyponatremia, and, (3) no history of hypernatremia or hyponatremia. Five cases were excluded as they did not meet these criteria. In addition, we verified that the patients from KPNC were not receiving chemotherapeutic drugs at the time of their low serum sodium, as chemotherapy can lead to hyponatremia.[24] However, because not all potentially relevant treatment and medication records were accessible at the time of analysis of the KPNC cohort, these cases were identified as severe hyponatremia coincident with MCC but not conclusively determined to be paraneoplastic in nature.

RESULTS

PNS were identified in 8 patients with MCC within the Seattle repository: 1 patient had paraneoplastic cerebellar degeneration with autonomic neuropathy, 2 patients had LEMS, and 5 patients had malignancy-associated hyponatremia. The clinical characteristics of these reported cases are summarized in Table II. Seven patients were male and 1 was female. The median age at diagnosis of MCC was 58 years (range