Merkel Cell Carcinoma: A Case of Complete Spontaneous Remission and Review

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Abstract

Merkel Cell Carcinoma (MCC) is a rare and highly malignant primary tumor of the skin seen mostly in elders or those with immune compromise. The incidence of this likely ultraviolet radiation-related tumor has been shown to be rising at a faster rate than melanoma. Though the prognosis is grim for metastatic disease spontaneous remissions have been reported. We report the 16th documented case of MCC with complete spontaneous remission and a review of Merkel Cell Carcinoma.

CASE STUDY

An 86 year-old white male presented with a firm, raised, painless, nodular and erythematous 0.8 centimeter lesion of his left distal index finger enlarging four to five months. An excision was performed and microscopic examination revealed a proliferation of small, round cells within the dermis. Nuclear to cytoplasmic ratios were high and chromatin was salt and pepper in character. Mitoses were numerous and there was tumor necrosis. Immunostains for synaptophysin and chromogranin showed strong cytoplasmic positivity, confirming neuroendocrine differentiation. Cytokeratin AE1/AE3 and cam 5.2 showed cytoplasmic dot positivity, characteristic of neuroendocrine neoplasms. The cells were negative for S100 protein, making melanoma very unlikely.

A diagnosis of Merkel cell carcinoma (MCC) with involved margins was made and the patient underwent chest, abdomen and pelvic CT without primary lesions found. A second excision revealed MCC with clean margins. Further intervention was declined. Eleven months later the patient presented with a 2 cm firm and painless nodule on the dorsum of the left hand noticed three weeks earlier. The lesion was removed and pathological diagnosis of MCC was made involving margins. A second excision revealed only deep margin involvement. Again chest, abdomen and pelvic CT were negative. Wide excision, lymph node dissection and radiation were recommended by oncology and declined by the patient.

Seven months later (23 months after first excision) a painless firm mass proximal to the left medial cubital area of 3 x 5 cm without skin involvement was presumed metastatic MCC. No other axillary lymphadenopathy was palpable. At age 87 the patient refused biopsy, debulking or other intervention. The mass then resolved without intervention over the next several months and no evidence of recurrence of MCC has been found over the subsequent nine years.

REVIEW OF MERKEL CELL CARCINOMA

INTRODUCTION

In 1875 Fredrich Sigmund Merkel described cells of the snouts of pigs he believed to have receptor function. A carcinoma of the skin with similar cells was first documented by Toker in 1972 as Trabecular carcinoma [1]. This rare and very aggressive malignant primary tumor has since been termed Merkel cell carcinoma (MCC). Possible etiologic factors include 1) ultraviolet (UV) radiation as MCC tends to appear on sun-exposed skin, and a regional incidence correlation has been found with UVB [2,3]; and 2) declining immune function with an association with immunosuppressive therapy, viral human immunodeficiency, and 76% occurring in those over 65 [4,5].

EPIDEMIOLOGY

Agelli and Clegg reported on the epidemiology of MCC based upon a prospective study from 1973 to 1999 of the Surveillance, Epidemiology, and End Results Program (SEER). The age-adjusted incidence rates (per 100,000 person-years) were 0.34 in males and 0.17 in females and cases were much more common in whites (94%) and in elders over age 65 (76%) [4]. Further, SEER data

demonstrated an increasing incidence of 0.15 cases per 100,000 person-years in 1986 to 0.44 in 2001 with the incidence in males tripling [6] . This represented an age-adjusted increase of 8% per year compared to a 3% year increase for melanoma [6] .

PATHOLOGY AND DIAGNOSIS

The tumor most often appears on sun-exposed areas of the head and neck (50%) but can also appear on the extremities (40%). Grossly it appears as a painless firm, rapidly growing, shiny, erythematous to blue, solitary nodule usually less than 2 cm in diameter [7] . It can spread by dermal invasion producing satellite lesions [8] and in a series of 1024 MCC patients local lymph node spread occurred in 55% and metastasis to distant lymph nodes (60%), distant skin (30%), lung (23%), central nervous system (18%), and bone (15%) [2] .

MCC appears microscopically as small, basophilic tumor cells with scant cytoplasm and round to oval, hyperchromatic, evenly dispersed nuclei.

Mitotic rate is high, apoptotic bodies may be present and nucleoli may be absent or few in number. The cells are found in the dermis and may extend into the subcutaneous fat [9] . Immunohistochemical stains are needed to differentiate MCC from other skin tumors including small cell carcinoma of the lung, lymphoma, carcinoid, neuroblastoma, retinoblastoma, Ewing's sarcoma, and rhabdomyosarcoma [10]

STAGING AND TREATMENT

Many staging systems have been used for MCC. Recently, however, a four tier system for staging of MCC has been developed as tumor size over 2 cm is an independent predictor of survival (table 1) [11] .

Figure 1

Table 1: Four tier staging system for MCC with size of primary over 2 cm indicating stage II disease

STAGING OF MCC	
Stage I	primary ≤2 cm
Stage II	primary >2 cm
Stage III	regional metastasis
Stage IV	distant metastasis

Seventy percent of patients present with stage I or II disease, 25% at stage III and 5% present with distant metastases (stage IV) [2,12,13]

Surgical wide local excision (WLE) at the primary site with 2-3 cm margins is well accepted as initial treatment with the goal of tumor free margins. A chest X-ray is appropriate at initial diagnosis to rule out small cell lung cancer as the primary tumor. Some recommend CT or MRI to find metastasis, however, a high false-positive rate may provoke unnecessary procedures [14] .

Sentinel lymph node biopsy (SLNB) is considered standard of care for patients with clinically localized disease. Some 20% of SLN may be positive for MCC using CK-20 immunostaining [7,15] .

Radiation treatment to the site of the primary lesion does not improve survival with lesions < 2 cm and tumor free WLE margins [2,12,16] . For larger lesions or if tumor-free margins cannot be obtained local-regional radiation treatment is indicated [7] .

Chemotherapy for metastatic MCC has produced response but patients usually die within weeks to months thus its use is unclear [17] .

PROGNOSIS

Forty to 45% of cases have recurrence [2,12] . Disease prognosis is best defined by lymph node involvement. The strongest factor associated with survival is stage with five year survival rates of 81%, 67%, 52% for stages I, II, and III, respectively reported [7] Stage IV has a poor prognosis with a reported 11% two year survival rate [12] and survival as low as six months [18] . A retrospective study of 1665 cases from the SEER registry to 2002 demonstrated an improvement in the overall median survival from 45 months to 63 months associated with the use of adjuvant radiation therapy. Factors associated with an improved prognosis include size < 2 cm, female gender and local radiation treatment [19] .

As of 2007 fifteen complete spontaneous remissions (CSR) (complete clinical disappearance of the tumor) of MCC have been reported in the literature [16,20,21] Apoptosis and T-cell immune response involvement has been suggested as the mechanism [22] . This represents the sixteenth case of CSR, in an 86 year-old male with tumor-free survival of over nine years.

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