Merkel Cell Carcinoma Metastatic to the Head of the Pancreas

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ABSTRACT

Context Merkel cell carcinoma is an aggressive cutaneous tumor without clearly defined treatment and high propensity for metastasis.

Case report This case describes a sixty four year old presenting with obstructive jaundice approximately two years after having a Merkel cell carcinoma resected from his finger. He underwent a successful pancreaticoduodenectomy with pathology confirming metastatic Merkel cell carcinoma. This report reviews the history, presentation, and current treatment recommendations for Merkel cell carcinoma.

Conclusions We propose that resection of metastases from Merkel cell carcinoma may confer a survival advantage and should be strongly considered, particularly if isolated.

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare cutaneous malignant tumor of neuroendocrine cells that typically affects Caucasian patients over the age of 65 years. It commonly appears as a red to violaceous, indurated dome-shaped nodule or plaque on sun-exposed areas of the head and neck. MCC is an aggressive tumor with a high incidence of local recurrence, regional lymph node, and distant metastases. The following describes a unique presentation of MCC metastasis as a solid mass in the head of the pancreas causing obstructive jaundice.

CASE REPORT

We present the case of a sixty-four year old Caucasian male presenting with a two-week history of jaundice. An abdominal CT showed a large mass in the head of the pancreas causing compression of the duodenum and gastric dilation without evidence of other peritoneal disease (Figure 1). Although the mass was large, measuring approximately 6 cm, there was no evidence of vascular involvement and by all criteria was resectable. The patient's history was significant for a MCC removed from the fifth digit of the right hand 4 years prior (Figure 2). He subsequently developed a right epitrochlear lymph node metastases while on VP-16 and

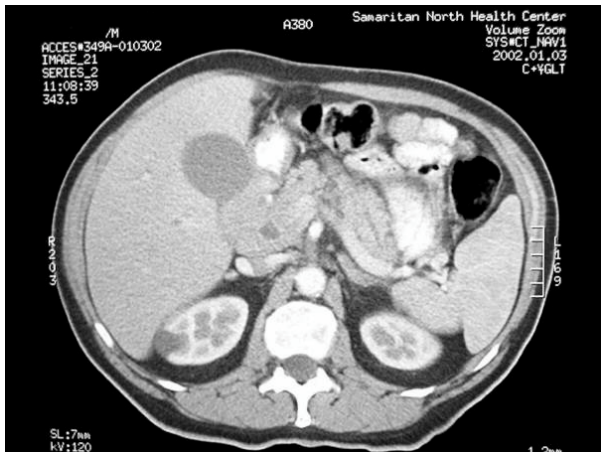

Figure 1. CT scan of mass showing duodenal compression with biliary obstruction.

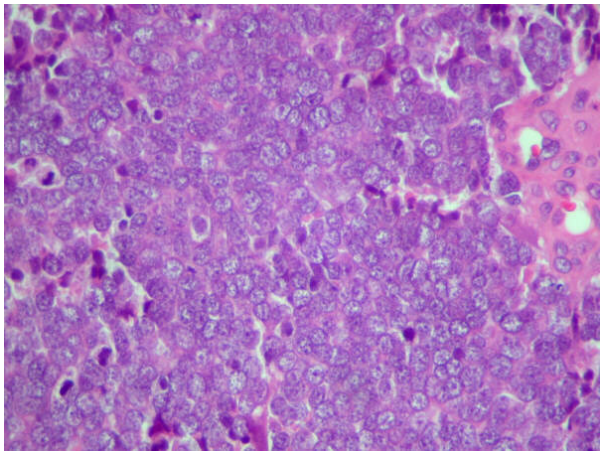

Figure 2. Initial pathologic lesion of finger resected two years prior to presentation.

carboplatin, less than a year from the initial resection. At that time, treatment was changed to taxol and carboplatin in combination with protracted VP-16 with concurrent radiation. Upon completion of radiation and chemotherapy, there was still a small mass present. Subsequent removal and histologic examination demonstrated complete response to treatment.

The current presentation was four years following completion of treatment for MCC. Although the diagnosis was not confirmed by pancreatic biopsy, with the presence of biliary and gastric outlet obstruction in the face of a resectable solid tumor of the pancreatic head, surgery was recommended. There was no evidence of peritoneal disease and a pancreaticoduodenectomy was performed. Pathology revealed a 7 cm solid mass of small cells in the head of the pancreas compressing the common bile duct and the duodenal wall (Figure 3). Immunoperoxidase stains confirmed neuro-endocrine origin and identical histology to the previously resected MCC of the hand. Fifteen nodes were identified and negative for tumor. Post-operative adjuvant external beam radiation therapy of 54 Gy was given to the pancreatic bed in 25 fractions over 40 days.

One year after pancreatic resection, widespread metastatic disease in the abdomen and a large temporal brain lesion were identified. Salvage chemotherapy was initiated but the patient succumbed 7 months later. He survived approximately six years from his initial diagnosis.

DISCUSSION

MCC is a rare malignant neoplasm first described by Toker in 1972 [1] as a "trabecular cell carcinoma of the skin" initially thought to be of primitive sweat gland origin [2, 3, 4, 5, 6]. However, using electron microscopy, dense secretory granules typical of Merkel cells were visualized within the cytoplasm of the tumor cells suggesting that the origin was likely from Merkel cells rather than the primitive sweat gland [3, 4]. The actual function of Merkel cells is not fully known, but several theories have emerged. Friedrich Sigmund Merkel, the German anatomist and histopathologist who first discovered the Merkel cells in the late nineteenth century [7], proposed that the cells played a role in the sense of touch [3, 4]. Today, it is believed that the cells function as slowly adapting type I mechanoreceptors [3].

To date, greater than 2000 cases have been reported in patients, ranging from 7 to 104 years of age [3]. MCC is found predominantly in Caucasians although cases have been identified in other racial groups [3, 4].

MCC appears on the head and neck in approximately 50% of cases. The next most common site is the extremities (40%), followed by the trunk and genitals (less than 10%). Lesions are usually less than 2 cm, but

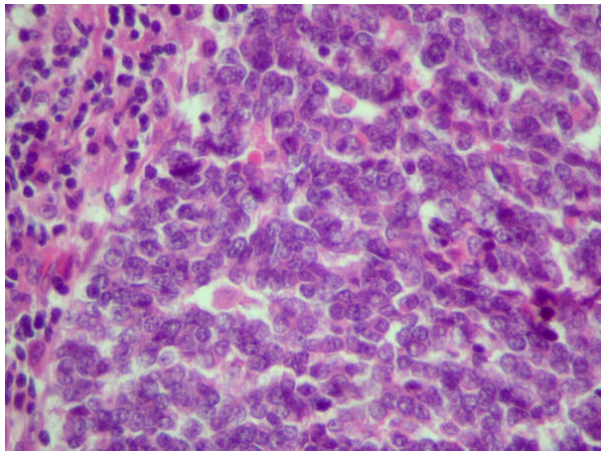

Figure 3. Pathology of pancreatic lesion showing similar characteristics to finger lesion.

have been reported as large as 12 to 15 cm [2, 3, 4]. The tumor may be flesh-colored, red, violaceous, or deep purple and can have a shiny surface with overlying telengiectasias [3, 4]. It can rapidly grow in size and may even ulcerate. Patient symptoms are usually local or secondary to tumor growth or lymph node involvement. Most patients with MCC have localized disease at initial presentation (70-80%). Up to 30% of patients can have lymph node involvement and few (1 to 4%) have distant metastases at the time of diagnosis [3].

The nonspecific appearance of MCC may lead to delay in diagnosis. Other diagnoses to consider include squamous cell carcinoma, basal cell carcinoma, Ewing sarcoma, neuroblastoma, characinoid, retinoblastoma, pyogenic granuloma, amelanotic and melanotic malignant melanoma, or cutaneous metastases of oat cell carcinoma [4, 5, 6]. Immunochemistry and electron microscopy help to confirm the diagnosis. Histologically it is difficult to distinguish MCC from other poorly differentiated small-cell tumors [3, 4]. A MCC diagnosis can be confirmed by positive multinuclear labeling of tumor cells with low molecular weight cytokeratins, marked cytoplasm reactivity for neuron-specific enolase, and negative staining for S-100 protein and leukocyte common antigen [3, 4, 6]. There are 3 histologic patterns of MCC: a trabecular type, intermediate cell type, and a small cell type. The intermediate cell type is the most common and consists of large solid nests of cells of intermediate size, with a trabecular pattern peripherally.

MCC was initially thought to have a good prognosis when described by Toker [1] since of the five cases he reported, only one of the patients died from the cancer itself [3]. However, further reports have documented that the tumor is aggressive and has a poor prognosis, with an increased incidence of local recurrence and systemic spread [4, 8]. Currently, there are no uniformly accepted prognostic factors but some have been identified in small studies. A tumor size greater than 2 cm, location in the head and neck, metastasis at diagnosis (lymph node or distant), evidence of vascular and lymphatic involvement, presence of small-cell histology, and mitotic index greater than 10 mitoses per high-power fields (HPF) all represent unfavorable prognostic factors [2, 3, 4]. Female gender has been proposed as a good prognostic factor [3, 8].

Local recurrence tends to occur within one year of initial excision in approximately one third of patients [9]. Regional lymph node metastases occur in one half to two thirds of patients; most at the time of initial presentation [10]. Hematogenous or distant metastatic disease will ultimately occur in more than one third of patients, even though uncommonly identified at presentation. The most common sites involve the liver, bone, brain, lung and skin. However, metastases to nearly every organ have been reported. Survival in MCC at one, two, and three years is reported as 88%, 72%, and 55% respectively [10]. No five-year survival data has been reported.

This is the first report of a MCC metastasis to the pancreatic head that was resected.

Currently, there are no ongoing prospective clinical trials available to assess the best treatment regimen for MCC. Historical data suggests that for localized disease, surgery consisting of wide-local excision with 2 to 3 cm wide and 2 cm deep margins is the treatment of choice. Adjuvant external beam radiation therapy is strongly suggested if microscopic disease remains or if there is any histologic evidence of angiolymphatic involvement [3, 4]. The unfavorable prognostic factors may also warrant prophylactic or elective lymph node dissection [4]. Lymph node dissection is recommended because of the high rate of early occult spread to regional lymph nodes [3]. The usefulness of sentinel lymph node biopsy has also been questioned to assess occult disease. Although sentinel lymph node biopsy may assist with staging of MCC, there is little evidence to suggest that it has any role in preventing regional recurrence of disease [3]. In one study from Hill *et al*. in 1999 at Memorial Sloan-Kettering, they identified eighteen patients with MCC who underwent

successful sentinel node mapping with only three positive sentinel node patients identified. These patients went on to have complete node dissections and no loco-regional recurrences with a median follow-up of 6.5 months. With such short follow-up, there is not enough evidence to assess a survival advantage [11].

The benefit of elective lymph node dissection is also in question because little evidence exists in the published literature. Shaw and Rumball compared wide-local excision alone to wide local excision and elective lymph node dissection, radiation, or both in patients with Stage I disease. They found an improvement in local control and regional failure rates using additional treatment [9]. Similar findings from Kokaska *et al*. and colleagues show 2 year survival of 100% for patients treated with the addition of an elective lymph node dissection versus 35% for wide local excision alone [12]. However, patient selection remains difficult.

Because MCC treatment has been compared to melanoma, other novel approaches have been explored including isolated limb perfusion with Mmelphalan. Gupta *et al*. were able to show resolution of in-transit metastases in an isolated case report [6]. Unfortunately, most recommendations for therapy of MCC are based on anecdotal reports.

Treatment of metastatic disease from MCC with surgical resection has been for palliation of symptoms. No evidence exists for a survival advantage at this time. Metastases have been reported to lymph nodes, kidney, small bowel, pancreatic body, adrenal glands, abdominal wall, bone marrow, meninges, and parathyroid glands [13]. Although we were unaware of the diagnosis of MCC metastatic to the pancreatic head until after surgery in our patient, he was by all other objective criteria a surgical candidate. The fact that there was no additional evidence of disease at the time of surgery also raises the question of whether resection of isolated metastases provides any survival advantage. Given the small numbers of patients with isolated metastatic MCC, it will be difficult to prove whether aggressive surgical management such as pancreaticoduodenectomy in limited situations is warranted.

Radiation therapy (XRT) may also be used in the adjuvant setting for local recurrence or margin positive resections. Currently, there is no standard radiation regimen. A survival advantage has been suggested by few retrospective analyses. Specifically, Ott *et al*. [8] used XRT in non-specified doses (less or greater than 45 Gy) and showed a survival advantage for those receiving 45 Gy or more to the primary site or regional lymph nodes after resection.

The role of chemotherapy in treating MCC may be the least well studied aspect of adjuvant therapy. Since MCC was initially thought to be resistent to chemotherapy, this modality is mainly reserved for metastatic disease. The typical approach uses regimens similar to those for small cell lung cancer and neuroendocrine tumors in other locations [2, 3, 6]. Some common regimens include cisplatin with etoposide, cytoxan with adriamycin and vincristine, cisplatin with adriamycin, and streptazocin with 5-fluorouracil [4, 8]. The results of therapy are far from promising with significant morbidity reported from the regimens themselves including bone marrow suppression and tumor lysis syndrome [3, 14]. Death from chemotherapeutic toxicities is also common [14].

CONCLUSION

MCC is an aggressive small cell neoplasm that requires wide local excision (2-3 cm margins) and attention to the lymph node basin. The optimal mechanism for lymph node evaluation and management has not been clearly delineated, but sentinel node technology shows promise for identifying selected patients for lymph node dissection. Local recurrence, nodal disease and distant metastases are common with MCC and warrant aggressive local-regional treatment. Radiation therapy may decrease local recurrence and nodal disease. Chemotherapy is of questionable use and has significant

toxicity associated with it. Resection of isolated metastatic disease is appropriate for palliation. However, further investigation is required to evaluate its ability to prolong survival.

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Abbreviations HPF: high-power fields; MCC: Merkel cell carcinoma; XRT: radiation therapy

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