INTERNAL MEDICINE

□ CASE REPORT □

Potential Activity of Amrubicin as a Salvage Therapy for Merkel Cell Carcinoma

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Abstract

Merkel cell carcinoma (MCC) is a rare neuroendocrine carcinoma of the skin with an aggressive clinical course. Although anthracycline- and platinum-based regimens are empirically used as first-line treatments for metastatic or unresectable cases, no salvage therapy has been established. A 73-year-old man with platinum-refractory recurrent MCC was treated with amrubicin. The symptoms improved soon, and a partial response was achieved. A total of nine cycles of amrubicin were administered in nine months with manageable adverse events until disease progression was finally observed. The present findings suggest the potential of amrubicin monotherapy as a second-line therapy for patients with advanced/recurrent MCC.

Key words: Merkel cell carcinoma, amrubicin, platinum agent, neuroendocrine carcinoma

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Introduction

Merkel cell carcinoma (MCC) is a rare neuroendocrine carcinoma of the skin that preferentially occurs in sun-exposed areas in elderly patients. The age-adjusted incidence of this disease increased from 0.15 per 100,000 persons in 1986 to 0.44 per 100,000 persons in 2001 based on data from the U.S. Surveillance, Epidemiology, and End Results (SEER) Program (1). A strain of polyomavirus, Merkel cell polyomavirus, is known to be involved in the carcinogenesis of MCC in some cases (2). MCC has an aggressive natural history, with the majority of patients developing locoregional recurrence and distant metastases within two years from curative-intent surgical resection (1). The role of chemotherapy for MCC remains controversial, as the rare nature of MCC has made it difficult to perform prospective randomized controlled trials in patients with MCC. Anthracycline-based and platinum-based chemotherapies have been used empirically because these agents are effective against another neuroendocrine carcinoma, small cell lung cancer. The overall response rate of a combination of cyclophosphamide, doxorubicin, and vincristine in patients with advanced MCC was 76%, and that of cisplatin and etoposide was 60% (3). However, no data on second-line or salvage chemotherapy have been reported. Despite the high response rates of the first-line chemotherapy, the median overall survival period was 9 months, with a 2-year survival rate as low as 20% (4-6), urging the establishment of second-line chemotherapy.

We herein report a patient with platinum-refractory MCC who was successful treated with amrubicin.

Case Report

A 73-year-old man was referred to our institution because of back pain, fatigue, and a weight loss of 11 kg over the previous 3 months. He was a lifetime non-smoker and had a history of iodine hypersensitivity. Ten years prior to presentation, he underwent surgical treatment for stage IB (pT1N0M0) MCC in his left forearm at another hospital. One year after the surgery, the MCC relapsed to the left neck lymph nodes. He received chemotherapy with carboplatin at a fixed dose of 300 mg with irregular intervals,

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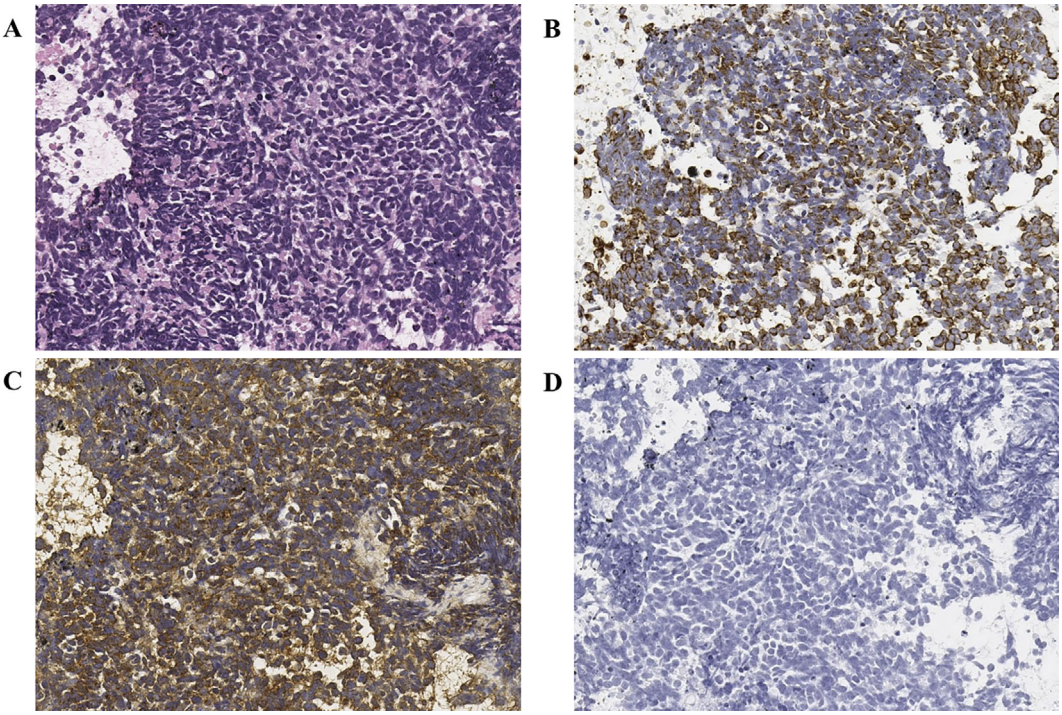

Figure 1. Fine-needle aspiration biopsy of the abdominal mass revealed tumor nests consisting of small round tumor cells with scanty cytoplasm, round-to-oval nuclei, finely dispersed chromatin, and inconspicuous nucleoli (A: Hematoxylin and Eosin staining, original magnification, ×20). An immunohistochemical evaluation showed the small round tumor cells to exhibit membranous and paranuclear dot-like staining with cytokeratin 20 (B: ×20) as well as neuroendocrine markers consisting of chromogranin A (C: ×20), CD56, and synptophysin (data not shown) and negative staining for thyroid transcription factor 1 (D: ×20), indicating a neuroendocrine carcinoma.

for a total of 10 cycles in 5 years, which led to the complete remission of the disease. He remained in remission for four years until three months prior to the presently reported admission.

On admission, his abdomen was soft and flat, and no tenderness was noted on a physical examination. There were no signs of metastatic lesions in the skin except for a scar on the left forearm. Laboratory examinations revealed normal findings except for a decreased hemoglobin concentration of 8.3 g/dL and an elevated neuron-specific enolase (NSE) level of 212 ng/mL, with normal carcinoembryonic antigen (CEA) and CA 19-9 values. No antibodies to human immunodeficiency virus were detected. A computed tomography (CT) scan revealed a conglomerated lesion at the abdominal lymph nodes that was 120 mm in size and located adjacent to the pancreatic tail, with smaller masses in the abdomen and retroperitoneal space.

An [^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET) scan showed enhanced uptake in all the lesions and the absence of metastases in other organs. Endoscopic ultrasound-guided fine-needle aspiration biopsy was performed for a histological examination, showing tumor nests of small round cells with scanty cytoplasm, round-to-oval nuclei, finely dispersed chromatin, and inconspicuous nucleoli (Fig. 1A). Several mitoses and areas of necrosis were observed. The tumor cells were diffusely positive for cytokeratin 20 (CK 20) in a dot-like paranuclear pattern (Fig. 1B), in addition to being positive for neuroendocrine markers, including the cluster of differentiation (CD) 56 (neural cell adhesion molecule), NSE, and chromogranin A (Fig. 1C). In contrast, the tumor cells were negative for thyroid transcription factor 1 (TTF-1) (Fig. 1D) and leukocyte common antigen (LCA). The patient tested negative for polyomavirus in an immunohistochemistry study (data not shown). Based on these findings, a diagnosis of recurrent MCC was established.

The patient received one cycle of carboplatin (at a dose targeting an area under the curve of 5, which was calculated by the Calvert formula (7), on Day 1) plus etoposide (100 mg/m^2 on Days 1-3). Shortly after the chemotherapy, however, the patient complained of worsened back and abdominal pain. A second CT scan obtained at this time showed further enlargement of the abdominal lesion to a size of 144 mm (Fig. 2A). As the registered regimen in our hospital allowed the use of amrubicin for advanced neuroendocrine carcinoma in general in the second-line setting, the patient, who had provided his written informed consent to undergo this therapy, was treated with salvage chemotherapy consisting of amrubicin at a dose of 40 mg/m^2 on Days 1-3 every 3 to 4 weeks, depending on the adverse events.

The patient's symptoms improved soon after starting the chemotherapy. The serum NSE levels returned to normal,

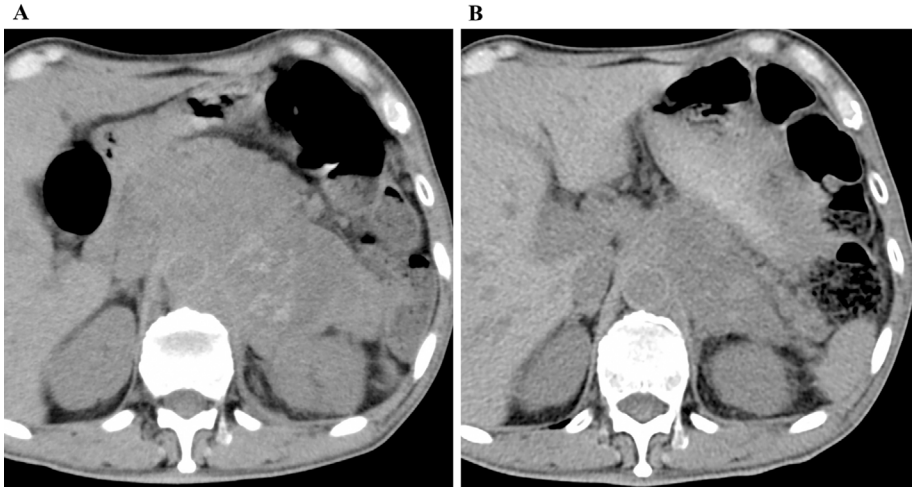

Figure 2. **CT scans of the abdomen just before the start of amrubicin administration (A) and at the completion of two cycles of amrubicin treatment (B) showing tumor shrinkage from a maximum diameter of 144 down to 92 mm. The tumor remained progression-free for 9 months.**

and a partial response was achieved after two cycles had been administered (Fig. 2B). A total of nine cycles of amrubicin were administered over nine months until the tumor progressed. The adverse events were all manageable and included grade 3 neutropenia, grade 3 thrombocytopenia, grade 4 anemia, grade 1 nausea and anorexia, and grade 2 alopecia throughout all of the treatment cycles. He died of the disease 2 months thereafter, which was 11 months after the initiation of amrubicin and 11 years after the resection of the primary site. The autopsy showed multiple metastases to the liver, gall bladder, left adrenal gland, pancreas, paraaortic lymph nodes, peritoneum, and retroperitoneal spaces, but no involvement was observed in the lung or gastrointestinal tract. The histological evaluation confirmed metastatic MCC.

Discussion

The recurrence of MCC in the present patient was confirmed histologically using immunohistochemical evaluations. The absence of a lesion in the thoracic cavity was demonstrated by CT, PET/CT, and autopsy, excluding a newly developed small cell lung cancer lesion. In addition to 10 cycles of first-line carboplatin treatment over 5 years, the re-administration of carboplatin together with etoposide just before the start of amrubicin treatment did not prevent disease progression, confirming the platinum-refractory nature of the patient's disease.

Amrubicin is a synthesized anthracycline derivative that has greater antitumor activity than doxorubicin in human tumor xenograft models (8). A phase II trial of amrubicin in previously untreated patients with extensive small cell lung cancer showed an overall response rate of 76% and a median survival time of 11.7 months (9). In second-line settings, amrubicin yielded response rates of 44-53% and median survival times of 9.3-11.6 months in patients with sensitive relapse of small cell lung cancer, and response rates of 17-50% and median survival times of 5.3-10.3 months in patients with the refractory relapse of small cell lung cancer (10-12). Given that both MCC and small cell lung cancer are neuroendocrine carcinomas, we considered that amrubicin might be useful as a second-line chemotherapy, even for patients with advanced MCC, as well as for those with small cell lung cancer. Consequently, amrubicin yielded a rapid and durable tumor response with remarkable symptom relief.

To our knowledge, this is the first report to show the potential effectiveness of amrubicin as a salvage chemotherapy for platinum-refractory advanced MCC. Although it might be difficult to perform large-scale clinical trials because of the rarity of this disease, amrubicin might be worthy of prospective evaluations in patients with advanced MCC.

The authors state that they have no Conflict of Interest (COI).

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