

## CLINICAL CASE CHALLENGES

# Metastatic Merkel Cell Carcinoma Resulting in Complete Heart Block



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**M**erkel cell carcinoma (MCC) is an aggressive, rare cutaneous neuroendocrine carcinoma that can metastasize to the heart in exceedingly rare cases. The incidence of MCC in the United States is 0.7 per 100,000 person-years with a median age of 75 to 80 years at diagnosis and a male predominance (1,2). MCC is seen in older, fair-skinned individuals with immunocompromise, particularly those with leukemia, lymphoma (especially B-cell malignancies), and HIV. Merkel cells are found in the stratum basale of the epidermis and are associated with mechanoreceptors. Merkel cell polyoma virus is a double-stranded deoxyribonucleic acid virus causally linked to MCC. Carcinogenesis in the absence of Merkel cell polyoma virus is related to ultraviolet light exposure. Tumors grow rapidly as firm, painless, fleshy, or bluish-red nodules within the skin, usually on the head or neck in 40% to 50% of cases. Regional metastases and local recurrence are more common than distant metastases. When distant metastases occur, they tend to be found in skin, lymph nodes, adrenal glands, lung, liver, brain, and bone (1). Cardiac metastases of MCC are extraordinarily rare, with only about a dozen cases reported in the literature (3-6). We herein present a unique case of MCC with complete heart block related to an aortic root mass with diagnostic uncertainty given this patient's history of both MCC and lymphoma.

## CASE REPORT

A 73-year-old woman with a history of marginal zone (B-cell) lymphoma of the spleen, hypertension, and hypothyroidism presented for evaluation of left axillary mass. Her lymphoma was diagnosed 6 years prior and was initially treated with splenectomy and rituximab. She had a recurrence 5 years after her initial lymphoma diagnosis and was treated with rituximab, which controlled her disease. The new left axillary mass relevant to her current presentation was mildly painful with a burning sensation down her left arm. She had no fever, chills, night sweats, or weight loss. There were no other new skin lesions. Her vital signs and cardiopulmonary examination were normal. The left axillary mass was 6 cm with mild pain on palpation but no erythema or fluctuance, and there was no other cervical, axillary, or inguinal adenopathy.

Chest computed tomography (CT) imaging revealed a 6-cm left axillary mass involving the cephalic vein and brachial plexus, concerning for lymphoma. She underwent incisional biopsy, the results of which were indeterminate. Excisional biopsy was then pursued for definitive diagnosis. Immunohistochemical staining revealed MCC, and the specimen tested positive for Merkel cell polyomavirus. She did not have a primary culprit cutaneous lesion. The mass was deemed surgically unresectable given the neurovascular involvement. Pembrolizumab with concomitant radiation therapy (60 Gy/6,000 rad in 30 fractions) was initiated. Surveillance imaging at 3 months after 4 cycles of radiation and 4 doses of pembrolizumab showed a marked interval treatment response of the axillary mass without residual mass or nodularity. A positron emission tomography (PET)-CT scan did not show any further fluorodeoxyglucose (FDG) uptake. Pembrolizumab was stopped, and she was followed up expectantly.

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## ABBREVIATIONS AND ACRONYMS

**CT** = computed tomography

**FDG** = fluorodeoxyglucose

**MCC** = Merkel cell carcinoma

**CMR** = cardiac magnetic  
resonance imaging

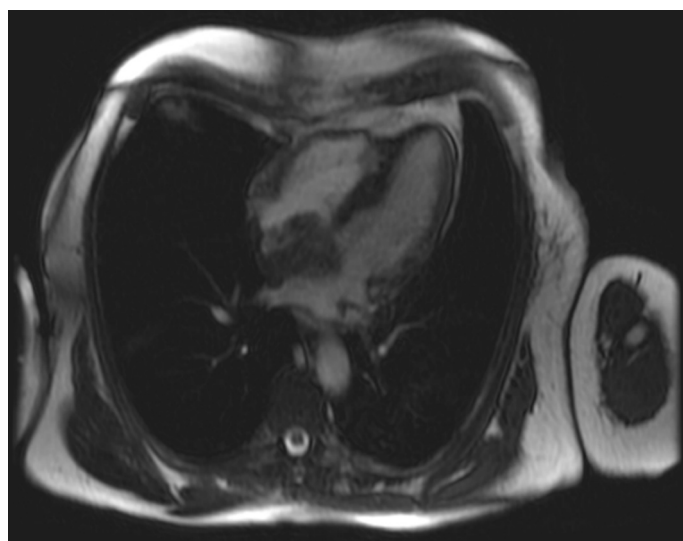
**PET** = positron emission  
tomography

**SUV** = standardized uptake  
value

Eighteen months later, the patient presented with weakness. An electrocardiogram revealed Mobitz type II with a ventricular rate of 69 beats/min. Transthoracic echocardiogram revealed a circumferential aortic root mass. CT angiography demonstrated involvement of the aortic root, aortic valve annulus, tricuspid valve annulus, and the proximal right coronary artery, as well as narrowing of the right ventricular inflow tract. A surgical approach was thus not a treatment option. Cardiac magnetic resonance imaging (CMR) was subsequently obtained for better characterization of the mass. CMR revealed an ill-defined infiltrative mass involving the interatrial septum with expansion across the aortic root (Figure 1). Double inversion recovery sequences revealed infiltration of the mass into the atrial septum with lobulations protruding into the right atrium and tricuspid valve. Diffusion-weighted imaging showed increased signaling, while myocardial delayed enhancement revealed gradual low-level enhancement of the mass. A repeat fludeoxyglucose F 18 PET-CT (14.91 mCi; standard fasting protocol before the examination; CT fusion imaging performed) demonstrated moderate FDG avidity throughout the aortic root mass (7.2 maximum standardized uptake value) (Figure 2). The area of uptake was concerning for transformed lymphoma versus MCC metastasis. There were no pleural effusions or other sites suspicious for malignancy, including the left axillary region. Of note, C-reactive protein levels were within normal limits, and results of blood cultures were negative. Telemetry revealed intermittent third-degree atrioventricular block.

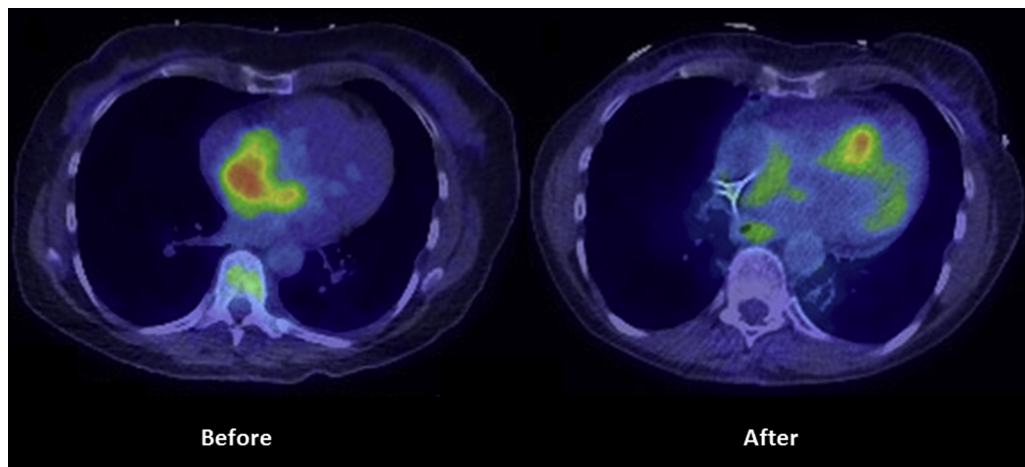
The patient underwent a right atrial endocardial biopsy with concomitant temporary pacemaker insertion, and pathology confirmed metastatic MCC. Immunotherapy with avelumab and radiation (40 Gy/4,000 rad in 5 fractions) were resumed. Repeat PET-CT imaging after these therapies revealed a decrease in right atrial and septal uptake (Figure 2). A single endocardial lead permanent pacemaker was placed to the right ventricle given the symptomatic complete heart block and to provide protection from varying degrees of heart block that could occur with changes to the mass during treatment. A right atrial lead was avoided due to the location of the mass, and the pulse generator was placed in the right chest to avoid the irradiated left chest further complicated by recurrent seroma. There was 99.8% pacing at the time of implantation. Repeat cardiac CT angiogram after 2 months of avelumab and radiation showed considerable shrinkage of the mass and 1.3% pacing. She initially responded well but had to discontinue subsequent immunotherapy due to severe avelumab-related pneumonitis and esophagitis.

**FIGURE 1** Cardiac Magnetic Resonance Imaging in Patient With Merkel Cell Carcinoma



Cardiac magnetic resonance imaging/fast imaging employing steady-state acquisition image revealed an ill-defined infiltrative mass involving the interatrial septum with expansion across the aortic root. The involvement of the aortic root and the nearby conduction system resulted in the development of complete atrioventricular block.

**FIGURE 2** PET-CT Imaging in a Patient With Merkel Cell Carcinoma



Positron emission tomography/computed tomography (PET-CT) imaging shows moderate (7.2 standardized uptake value) fludeoxyglucose F 18 tracer uptake throughout the aortic root mass before (left) and after (right) avelumab and radiation therapies directed against the metastatic Merkel cell lesion.

## DISCUSSION

This case shows that: 1) MCC can metastasize to the heart and cause complete heart block; 2) multiple imaging modalities helped in management but did not ultimately negate the need for tissue diagnosis; and 3) immune checkpoint inhibitor therapy was effective in controlling the MCC.

We present a patient with advanced (stage IV) MCC with aortic root cardiac metastasis disrupting the conduction system and leading to third-degree atrioventricular block. The patient's history of marginal zone lymphoma predisposed her to MCC and also provided another possible etiology for the intracardiac mass, obfuscating the diagnosis. Multiple imaging modalities were used to guide the diagnostic process. The initial echocardiogram was grossly abnormal with an apparent mass infiltrating the atrial septum and the aortic root. The mass's lack of respect for tissue planes on the initial echocardiographic study increased the likelihood of malignancy. The additional imaging modalities further characterized the tissue and supported the suspicion for malignant infiltration. PET-CT imaging (Figure 2) showed the FDG avidity of the mass, which provided additional evidence for the malignant nature of this tumor. CMR with double inversion recovery sequence revealed infiltration of the mass into the atrial septum, with lobulations protruding into the right atrium and tricuspid valve. Repeat CT angiogram after 2 months of avelumab treatment revealed a substantial response to therapy. Despite having excellent characterization of the lesion, however, tissue biopsy was ultimately pursued given the rarity of cardiac MCC, the possibility of lymphoma as an alternative etiology, and the need for a definitive tissue diagnosis to guide disease-directed therapy.

Immune checkpoint inhibitor therapy should be considered for stage IV MCC involving the myocardium, and placement of a permanent pacemaker may be necessary when patients have heart block or lesions threatening the conduction system. It is important to note that heart block, among other cardiac toxicities, resulting from immune checkpoint inhibitors has been reported and should be considered when patients taking these agents present with this condition (7). However, this patient had been off of pembrolizumab for 18 months before developing heart block, and the intracardiac lesion was positioned to cause disruption of the conduction system. Another possible cause for the atrioventricular block is radiation fibrosis of the myocardium following radiation to the left axillary mass. Although these were all considered, the aortic root lesion affecting the conduction system is the most likely cause of her complete heart block. The percent pacing dramatically decreased from nearly 100% to 1.3% with decrease in tumor size while being treated with avelumab, suggesting that MCC was the culprit.

Cardiac masses can be benign or malignant and primary or metastatic. The differential for cardiac masses also includes thrombus, vegetations, and/or foreign bodies. These masses can present with symptoms related to heart failure (especially if the mass is obstructive), arrhythmias, atrioventricular block, embolization, and pericardial effusions [particularly if the mass is malignant]). Primary cardiac tumors are rare, with a frequency of 0.02%, and three-quarters are benign (8). The most common cardiac neoplasms are benign myxomas, with most located in the left atrium. Other benign tumors include fibromas, lipomas, and hamartomas. Primary malignant cardiac tumors are exceedingly rare; the most common is angiosarcoma. Secondary cardiac tumors originating from a distant primary are much more common and ~100 times more common than a primary cardiac neoplasm. Melanoma is the most likely cancer to cause cardiac metastases. However, cardiac metastases from other more prevalent cancers, such as lung, breast, esophageal, leukemia, and lymphoma, are also frequently encountered.

In the detection and evaluation of cardiac masses, symptoms and signs may be present on history and physical examination. An electrocardiogram may reveal nonspecific changes or other findings such as electrical alternans in the event of an associated pericardial effusion. Echocardiography has become the gold standard for initial detection of masses and effusions. CT, CMR, and PET imaging modalities are also used to assess tissue characteristics that favor certain pathologies. Furthermore, advanced cross-sectional imaging provides accurate measurements in different imaging planes and can identify structures affected by the mass. Advanced imaging can guide surgical candidacy and planning as well as assess for response to therapies (9). FDG uptake on PET-CT imaging has been used more frequently in recent years to help differentiate benign and malignant tumors. Malignant tumors generally have high FDG uptake in the 8.0 to 10.8 standardized uptake value range, whereas benign tumors have only slight FDG uptake (mean standardized uptake value for benign tumors  $2.8 \pm 0.6$ ). However, there are reports of benign myxomas exhibiting high FDG uptake; thus, although PET is helpful, it cannot conclusively predict whether a tumor is malignant (10). Ultimately, in cases in which the diagnosis is unclear, endomyocardial biopsy may be used to obtain tissue diagnosis. Exploratory thoracotomy may be necessary in some cases depending on the location of the tumor (8). Management of MCC includes wide local excision of the primary tumor with consideration of adjuvant radiation and immune checkpoint inhibitors; chemotherapy has limited evidence and has not been shown to be particularly effective.

Given the aging population and the close association of MCC with age, the incidence of MCC is expected to rise in the coming years (2). Survival depends largely on staging; 5-year survival for stage IV is 13.5% (1). Our unique case of metastatic MCC with myocardial infiltration around the aortic root resulting in complete heart block supports the use of multimodality imaging combined with tissue biopsy to establish the correct diagnosis and guide management strategy.

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**KEY WORDS** cardiac metastases, complete heart block, Merkel cell carcinoma, pacemaker