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Case Report

Unmasking hidden Merkel cell carcinoma recurrences: Three illustrative cases of patients with rising viral oncoprotein antibody levels and challenge of requiring multi-modal imaging to detect clinical disease ☆,☆☆

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ABSTRACT

Merkel cell carcinoma (MCC) is a neuroendocrine skin cancer with a high risk of recurrence and metastasis. Regular surveillance through physical exams and imaging studies is crucial for the timely detection of recurrences. MCC patients who produce antibodies to the Merkel cell polyomavirus oncoprotein may benefit from antibody testing in addition to routine imaging surveillance for the early detection of disease recurrence. The clinically available Anti MERKel cell panel (AMERK) is a sensitive tumor marker for Merkel cell polyomavirus positive MCC.

Although AMERK is highly sensitive, imaging remains necessary to confirm the location of disease recurrence. MCC exhibits characteristic imaging features, making appropriate imaging modalities, and interpretation important for detection.

List of abbreviations: MCC, Merkel cell carcinoma; MCPyV, Merkel cell polyomavirus; AMERK, Anti MERKel cell panel; RT, Radiation therapy; STU, Standard titer units; CT, Computed tomography; ^{18}F-FDG, 2-deoxy-2-[^{18}F] fluoro-D-glucose; PET-CT, Positron emission tomography-computed tomography; MRI, Magnetic resonance imaging; SUV, Standardized uptake value; ^{68}Ga-DOTATATE, [^{68}Ga]-DOTA-Tyr(3)-Thr(8)-octreotate; DWI, Diffusion-weighted imaging.

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[^{68}Ga]-DOTA-Tyr(3)-Thr(8)-octreotate (^{68}Ga-DOTATATE)

We present 3 representative patient cases that highlight effective utilization of the AMERK test in addition to imaging for the early detection of MCC recurrence. The rise in the AMERK titer may occur before the disease reaches detectable size on computed tomography scans. Positron emission tomography (PET)-CT can serve as an alternative modality for the early detection of disease. Even subtle abnormalities in ^{18}F-FDG uptake may be significant if accompanied by an increased AMERK titer. Alternative imaging modalities, such as ^{68}Ga-DOTATATE PET-CT and magnetic resonance imaging, can be useful in revealing clinically occult disease in MCC patients.

In summary, the AMERK antibody test, alongside imaging, enhances sensitivity in detecting recurrence. By combining these strategies of blood test and imaging, healthcare professionals can identify early signs of MCC recurrence, leading to prompt interventions and improved patient outcomes.

Introduction

Merkel cell carcinoma (MCC) is an aggressive neuroendocrine skin cancer with a current incidence of approximately 3000 cases a year in the United States [1]. MCC has a high propensity to metastasize, and greater than 40% of patients will experience a disease recurrence after completing initial treatment [2]. As such, in most guidelines, regular surveillance is recommended to fit the risk of recurrence.

In addition to standard surveillance modalities, including radiologic scans and physical exams, MCC patients may have additional surveillance benefit through routine serologic evaluation for production of antibody against the Merkel cell polyomavirus (MCPyV) T-antigen oncoprotein [3,4]. The majority of MCC cases caused by MCPyV (the causal agent for 80% of MCC in the United States) can be differentiated at baseline from those caused by the ultraviolet light induction pathway via detection of oncoprotein antibody production [5]. Several groups have reported that in patients who produce antibodies to the MCPyV oncoprotein, the antibody titer levels closely model a patient's tumor burden [3,4,6]. In the United States, this serology test is clinically available as the Anti MERKel cell panel (AMERK) test.

Typically, successful MCC treatment will cause the patient's AMERK titer to decrease significantly compared to their baseline antibody level until the titer is either negative (<74 standard titer units; STU) or has plateaued. Then, if a patient's AMERK titer subsequently increases, a recurrence is highly suspected. A recent report stated that increasing AMERK titers correlate with recurrent MCC with a high positive predictive value (99%) [7]. Therefore, if a patient is seropositive for antibodies to the MCPyV-oncoprotein at baseline, continued AMERK antibody testing every 3-4 months alongside routine cross-sectional imaging is recommended to monitor for potential disease recurrence.

Cross-sectional imaging for MCC, usually with computed tomography (CT) with or without contrast or 2-deoxy-2-[^{18}F] fluoro-D-glucose (^{18}F-FDG) positron emission tomography-computed tomography (PET-CT) is essential for confirming the disease recurrence location, guiding confirmatory biopsy, and informing treatment decisions when necessary [8]. However, the results of imaging studies do not always agree with AMERK titer predictions as standard imaging surveillance does not always locate sites of clinical recurrences in the setting of increasing AMERK titer. To better understand cases in which negative imaging results were discordant with suspected recurrence based on rising AMERK titer, we present 3 representative patients whose cases illustrate important imaging pearls and insights to AMERK for the early detection of MCC recurrence.

Case presentations

Case 1

Patient 1, a 63-year-old male, was diagnosed with MCC on the left arm with microscopic involvement of the left axillary lymph nodes in sentinel lymph node biopsy. Adjuvant radiation therapy (RT) was administered to the primary tumor site and axillary lymph nodes. During this time, the patient had a positive baseline AMERK titer of 381 STU, which decreased to the negative range (<74 STU) 3 months after completing RT. Regular AMERK and imaging every 3-4 months over the next 38 months did not reveal any clinically detectable recurrence.

Four years after the initial diagnosis, the patient's AMERK titer significantly increased to 2250 STU (Fig. 1A). Despite undergoing ^{18}F-FDG PET-CT scans, no signs of disease recurrence were found. However, the patient experienced nonspecific abdominal symptoms, fatigue, and weight loss. Repeat ^{18}F-FDG PET-CT and CT of chest, abdomen, and pelvis scans without contrast, performed 4 and 5 months after the initial increase in AMERK titer, also showed no evidence of recurrence (Fig. 1B). Nonetheless, due to the persistently elevated AMERK titer at 7 months, contrast CT of the abdomen was performed, revealing metastatic disease in the liver. Further imaging, including magnetic resonance imaging (MRI) of the abdomen, chest, pelvis, and brain, confirmed widespread metastatic disease in the liver and bones (Fig. 1B).

Upon review of all available imaging studies by a multidisciplinary team, subtle areas of abnormal uptake in the liver and diffuse low-level marrow uptake were identified on the ^{18}F-FDG PET-CT performed 4 months after the initial increase in AMERK titer. The diffuse low-level marrow uptake was

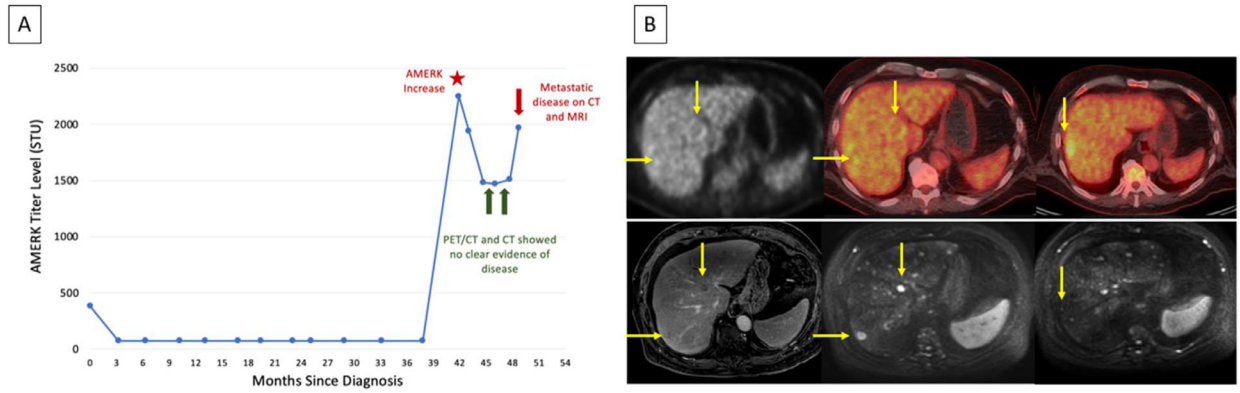

Fig. 1 – (A) AMERK titer over disease course. Note the marked increase in AMERK titer 42 months after the initial diagnosis, which eventually led to the detection of metastatic disease in subsequent imaging studies. (B, top row) ^{18}F-FDG PET-CT, axial view, 5 months after AMERK increase shows subtle uptake in the right hepatic lobe and diffuse marrow uptake. (B, bottom row) MRI, axial view with post-contrast and DWI images, 7 months after AMERK increase, revealing numerous liver lesions.

considered a nonspecific finding that required the assistance of MRI for interpretation. The subtle uptake in the liver was challenging to detect without the presence of MRI images to aid in the evaluation of the ^{18}F-FDG PET images. It remains uncertain whether the combination of contrast CT and ^{18}F-FDG PET images at that time would have led to the identification of these subtle findings on ^{18}F-FDG PET.

Case 2

Patient 2, a 62-year-old male, was diagnosed with MCC in the left arm, with involvement of the left arm lymph nodes. The patient underwent excision of the primary site, in-transit disease removal, left axillary lymph node dissection, and received adjuvant RT. At baseline, the patient's AMERK titer was 18,800 STU, which decreased to 1550 STU 6 months after completing radiation.

Nine months after the initial diagnosis, the patient's AMERK titer increased 6-fold (9480 STU) and continued to fluctuate rapidly thereafter (Fig. 2A). ^{18}F-FDG PET-CT imaging at nine and 11 months after the initial increase in AMERK titer revealed increased activity in the nasopharynx (maximum standard uptake value, SUV of 8.67 and 9.2, respectively), without a corresponding abnormality on CT scans (Fig. 2B). A subsequent biopsy confirmed metastatic MCC in the nasopharynx, with the patient's AMERK titer elevated to 13,700 STU. Surgical resection of the disease site was performed, followed by pembrolizumab treatment for 5 months until it was discontinued due to Guillain-Barré syndrome. Following immunotherapy completion, the patient's AMERK titer initially decreased but later showed a notable increase 8 months after stopping immunotherapy.

Repeat ^{18}F-FDG PET-CT scans were negative for recurrence. However, a [^{68}Ga]-DOTA-Tyr(3)-Thr(8)-octreotate (^{68}Ga-DOTATATE) PET-CT performed 3 months after the second increase in AMERK titer revealed uptake in the sacrum and a small area of subtle fat stranding at the base of the umbilicus, which was confirmed as MCC metastasis through biopsy (Fig. 2C). Upon multidisciplinary team review of prior ^{18}F-FDG PET-CT studies from 1 and 2 months after the second increase in titer, increasing uptake and subtle fat stranding at the base of the umbilicus were noted as new findings compared to previous imaging studies from 1 year ago. Although considered nonspecific due to the potential for evolving fat necrosis to produce a similar appearance, considering the rising AMERK titer, these findings could have been flagged as possible abnormalities to evaluate for recurrence.

Case 3

Patient 3 is a 63-year-old female who was initially diagnosed with MCC on the left cheek, measuring 5 mm. The patient underwent excision of the primary site and sentinel lymph node biopsy, which revealed no microscopic involvement in the parotid gland. However, after 5 months of surveillance, the patient's AMERK titer showed an increase from baseline 89 to 1210 STU, prompting multiple contrast CT scans to investigate for possible disease recurrence (Fig. 3A). Despite these scans, no clear evidence of disease was found and AMERK continuously increased.

Two years later, while still monitoring the increasing AMERK titer, a ^{18}F-FDG PET-CT scan finally revealed MCC recurrence in the left parotid, with a lesion measuring 7 mm (SUV 11.4; Fig. 3B). The patient subsequently underwent definitive radiation therapy targeting the left parotid and neck. Following completion of radiation therapy, the patient remains free of disease for 5+ years.

Discussion

MCC is a highly metastatic cancer that necessitates regular surveillance through physical exams and imaging for effective management. Seropositive MCC patients, who produce antibodies to the MCPyV oncoprotein, may benefit from AMERK tumor marker testing in addition to imaging surveillance for early detection of recurrence.

Imaging features of MCC include intense ^{18}F-FDG PET-CT uptake, soft tissue nodules with or without skin thickening,

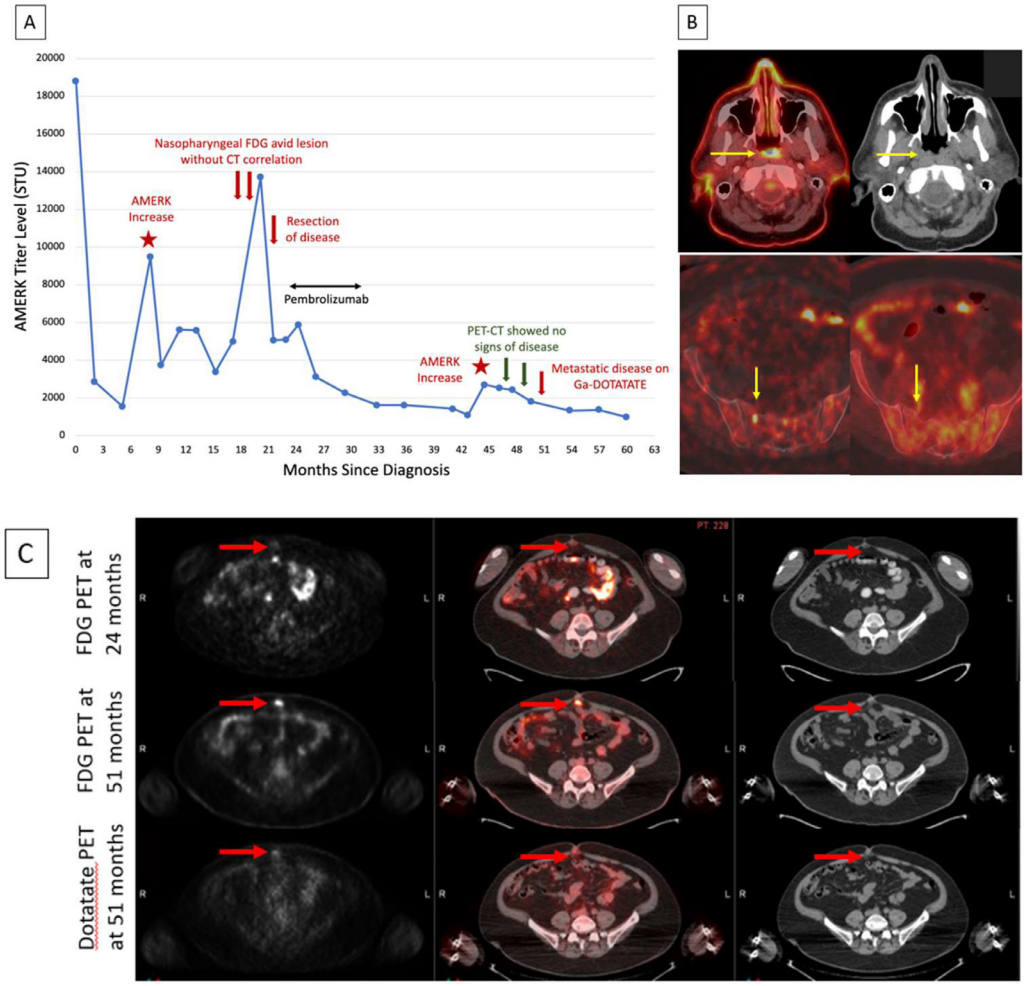

Fig. 2 – (A) AMERK titer over disease course. Note the marked increase in the titer nine months after the initial diagnosis and 8 months after the discontinuation of immunotherapy (44 months after the initial diagnosis). This increased titer eventually led to the detection of metastatic disease in subsequent imaging studies. (B, top row) ^{18}F-FDG PET-CT revealing nasopharyngeal disease (patient's first recurrence). Bottom left: ^{68}Ga-DOTATATE reveals S2 bone marrow involvement of the second recurrence. Bottom right: ^{18}F-FDG PET-CT performed around the same time showed only subtle involvement of the bone marrow. (C, top row) Retrospective review of the ^{18}F-FDG PET-CT scan obtained at the time of nasopharyngeal recurrence showed minimal uptake in fat stranding near the umbilicus (red arrows), middle row: that increased in intensity on ^{18}F-FDG PET-CT obtained shortly before the ^{68}Ga-DOTATATE imaging. Bottom row: ^{68}Ga-DOTATATE that was also showed mildly increased uptake at this site, identifying this as a site of MCC recurrence. Notably, the CT appearance of subtle fat stranding, atypical for recurrences that more typically look like solid nodules, did not change over this time period.

necrosis, fat stranding suggestive of lymphatic invasion, and contrast enhancement and diffusion restriction on MRI in visceral lesions [9]. However, conventional imaging features may not always be evident, as highlighted in this case series.

In most cases, a patient experiencing a significant elevation in their AMERK titer would be expected to show evidence of disease recurrence on CT or PET-CT. ^{18}F-FDG PET-CT is in general more sensitive as illustrated in **case 3**, as the vast majority of MCCs are highly ^{18}F-FDG avid [10,11]. However, both **cases 1 and 2** illustrate that not all MCCs are highly ^{18}F-FDG avid, and therefore even subtle abnormalities in ^{18}F-FDG uptake may be worth noting in the setting of an increased AMERK titer. **Case 1** also suggests that PET-MRI may be another modality to consider when evaluating sites of MCC recurrence [12]. Furthermore, **case 2** illustrates that CT correlates for areas of high ^{18}F-FDG avidity in the context of a detected rise in titer may be subtle and challenging to see.

Due to the high positive predictive value of rising AMERK titers for the presence of MCC recurrence, multimodality imaging workup is necessary when no disease is found on initial imaging. The cases described in this report support the utility of multiple imaging modalities for MCC patients. In addition to CT, MRI, and ^{18}F-FDG PET, ^{68}Ga-DOTATATE PET-CT may also be useful to reveal otherwise occult disease since MCC tumors often express the somatostatin receptor [13], as illustrated by **case 2**.

In summary, despite MCC's aggressive nature, early detection can be advantageous for patients. Multidisciplinary dis-

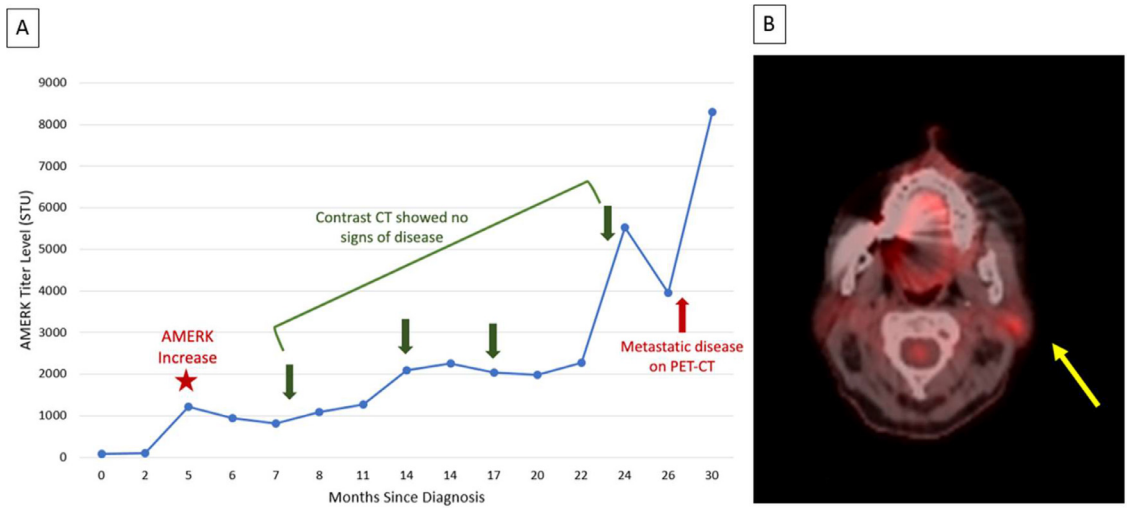

Fig. 3 – (A) AMERK titer over disease course. Note the marked increase in the titer five months after initial diagnosis and thereafter, which eventually led to the detection of metastatic disease in subsequent imaging study. (B) ^{18}F-FDG PET-CT reveals metastatic disease in the left parotid gland.

cussions and comprehensive imaging are key in identifying subtle indicators like those highlighted in this report, facilitating early determination of disease spread. Integrating AMERK titers with imaging evaluations can significantly boost the early detection of MCC recurrence, potentially enhancing patient prognosis.

Authors' Contribution

NAA, SYP, and DLC authored the primary draft of the manuscript. compiled and analyzed key information and data. PN, DLC, and SYP provided senior oversight and helped prepare the manuscript. All authors have read and approved of the manuscript.

Ethical approval

IRB: All studies were performed in accordance with the Helsinki principles and were approved by the Institutional Review Board at the Fred Hutchinson Cancer Research Center (IRB #6585).

Patient consent

All patients included in this study provided written consent for their clinical data to be analyzed for research purposes.

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