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Case Report

Identification of a Cervical Merkel Cell Carcinoma Using Intraoperative Near-Infrared Imaging

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Abstract

Merkel Cell Carcinoma is a rare and aggressive skin cancer. Treatment is based on staging and relies on either surgical or radiation therapy. For surgeons, the primary challenge is identifying the extent of disease and clinically relevant lymph nodes for accurate staging. Thus, our group has proposed using near-infrared (NIR) imaging during neck dissections to delineate the tumor borders and draw the attention of the surgeon to suspicious lymph nodes. Here, we present a case report detailing how intraoperative imaging of the neck demonstrated tumor fluorescence in Level 1 and 2 lymph nodes. NIR imaging also located an additional lymph node which showed evidence of microscopic disease. This case demonstrates the use of intraoperative NIR imaging as a useful adjunct to facilitate identification of surgical borders of a Merkel cell tumor in the neck. Enhanced visualization and additional visual information from imaging can provide a significant advantage in the resection of head and neck cancers.

Introduction

Merkel Cell Carcinoma (MCC) is an aggressive skin cancer of the merkel cells. Merkel cells are located along the top skin layer abutting the sensory nerve endings responsible for touch. Although the etiology of the cancer is unknown, it is generally linked to the Merkel Cell Polyomavirus (MCP) [1,2]. The virus is found in 35% of children at age thirteen and up to 85% of people age fifty and older who develop this disease [3]. In a recent review, the incidence of Merkel cell cancer was estimated to be approximately 2.3 cases per million among Caucasians and roughly 0.1 cases per million African Americans annually [4]. The carcinoma is most commonly found in older white patients with either immunodeficiency disorders or prolonged exposure to UV radiation exposure.

The pathological diagnosis for Merkel Cell Carcinoma is based on gross and cytological examination [5]. Grossly, MCC tumors are found in the dermis and they appear as red or violaceous firm nodules, appearing most commonly on the head and neck. The tumor usually has a smooth, shiny surface and develops very rapidly over a few weeks. Most of the tumors are in the dermis,

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generally leaving the epidermis and adnexa unaffected. On electron microscopic examination, MCC cells are known to have several unique features. The cells have a membrane bound, dense core structure inside the cytoplasm very similar to neurosecretory type granules. Additionally, the cells contain fibrous bodies composed from intermediate filaments localized in a perinuclear fashion.

Treatment is based on staging and relies on either surgical or radiation therapy [6,7]. The most common treatment for Merkel Cell Carcinoma patients is the surgical removal of the primary tumor with two to three centimeter margins [8]. For regional nodal staging, patients undergo either sentinel lymph node biopsy for clinically negative nodes or node dissection for clinically palpable nodes. Based on pathological staging, surgical treatment may be followed by radiation therapy. On average, the five-year survival rate is 75% for localized disease but 25% for patients with disseminated disease [9].

For surgeons, the primary challenge is identifying the extent of disease and clinically relevant lymph nodes for accurate staging [10]. Techniques are available to aid in the detection of these tumors, including intraoperative pulmonary ultrasound, radionucleotide imaging, and computed tomography (CT)-guided and spiral wire localization. However, these technologies are accompanied by challenges of their own including technical challenges and poor sensitivity. Thus, our group has proposed using near-infrared imaging during neck dissections to delineate the tumor borders and draw the attention of the surgeon to suspicious lymph nodes.

For Merkel Cell Carcinomas, we proposed utilizing indocyanine green (ICG) for intraoperative molecular imaging. ICG is a non-targeted tracer that works by the Enhanced Permeability and Retention (EPR) effect. Essentially, the high permeability of the blood vessel in the tumor allows the ICG to extravasate and it is retained in the extravascular tumor tissue allowing for intraoperative imaging [11-15]. The EPR effects allows for tumor specificity without receptor targeting leading to our hypothesis that the use of systematic ICG could aid in the identification of the tumor burden in Merkel Cell Carcinoma and ultimately help define resection margins [16,17].

In this report, we present a case of resection of a Merkel Cell Carcinoma utilizing the FDA approved near-infrared fluorescence contrast agent ICG.

Clinical Summary

KA is an 85-year-old Caucasian male who developed a left submandibular mass which was biopsy proven neuroendocrine tumor consistent with Merkel cell with concern of involvement of ipsilateral cervical lymph nodes (Figure 1) [18]. A PET/CT scan two months prior to the operation showed no other sites of disease. The patient was deemed a reasonable surgical candidate and was scheduled for primary tumor resection with a lymph node dissection.

The intraoperative molecular imaging study was performed after informed consent and approval by the Institutional Review Board (IRB) at the University of Pennsylvania were obtained. The patient was enrolled in the trial via IRB approved written consent. The patient was injected with 5.0 mg/kg of ICG dye 24 hours prior to surgery as an outpatient. This period provided time for the optical contrast agent to accumulate in the tumor tissues.

The following day, the patient was brought to the operating room for a standard-of-care neck dissection. A single large lymph node was palpable and suspicious, but the other lymph nodes appeared grossly unremarkable and the margins of the tumor were well-delineated. To determine if the intraoperative imaging could provide additional data, a NIR imaging system was used to scan the neck. Surgical fluorescent imaging was performed with the Iridium imaging system (Visionsense, Philadelphia, PA). The Iridium is an FDA-approved high-definition 3-dimension camera capable of emitting and absorbing light in the NIR spectrum. Intraoperative imaging of the neck demonstrated *in situ* tumor fluorescence in two lymph nodes- the palpable node identified by the surgeon under normal light, and an additional lymph node that was previously considered unremarkable (Figure 2). The neck dissection was then completed in standard fashion and

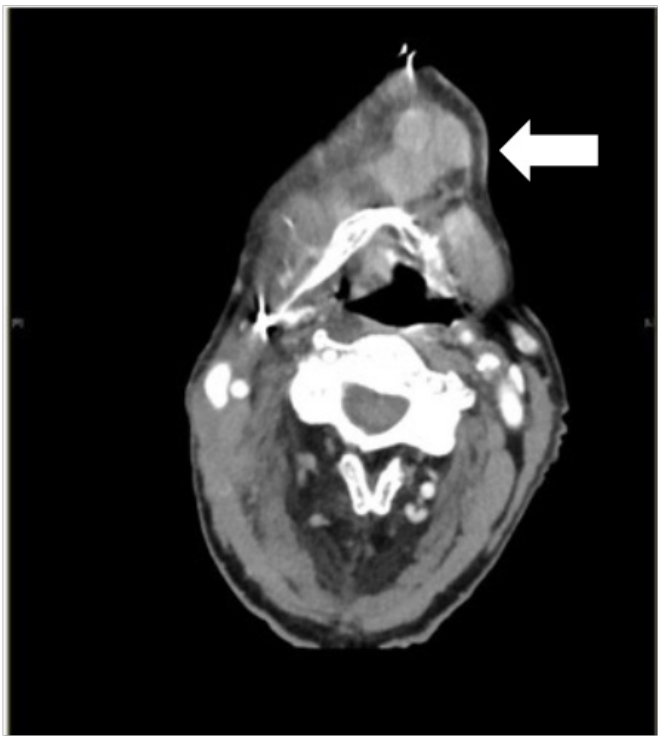

Figure 1: CAT scan demonstrating left submandibular Merkel Cell Carcinoma. Arrow indicates tumor location.

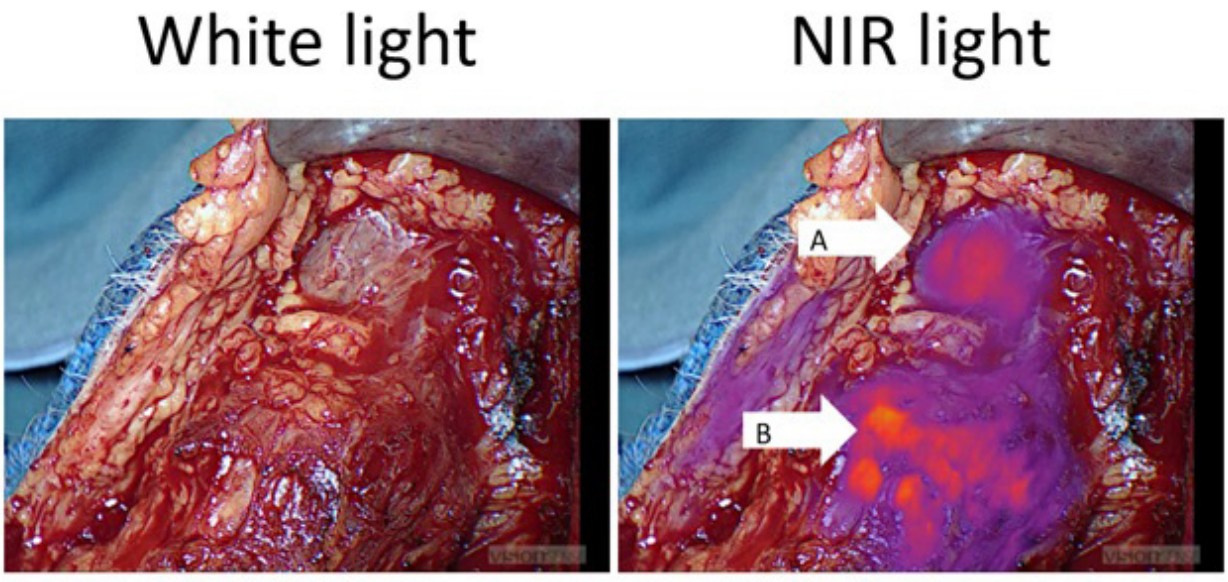

Figure 2: The left image demonstrates the neck after removing the overlying skin. The right image shows the NIR view of the neck with optical contrast highlighting the metastatic lymph nodes (A) and primary tumor (B).

a total of five lymph nodes levels 1 and 2 were removed. After completing the resection, the wound bed was then re-examined using the NIR imaging system. No residual fluorescence was identified.

To quantitate the tissue fluorescence, we used region-of-interest software and the HeatMap plugin within ImageJ (http://rsb.info.nih.gov/ij/; public domain free software developed by National Institutes of Health). Fluorescence was measured in arbitrary units (A.U.) based on the number of photons that reached the camera detector. Tumor fluorescence was based on the entire tumor. These measurements were then used to generate a tumor-to-background ratio (TBR). The TBR of the tumor was 4.8 A.U. and the large and small lymph nodes had a fluorescence of 3.6 and 2.5 A.U., respectively.

On final pathological evaluation, the tumor was described as a metastatic high grade neuroendocrine carcinoma consistent with Merkel Cell Carcinoma present in two of the five lymph nodes. The largest of the two lymph nodes was 6.5 centimeters with an extracapsular extension. This one was suspected by the surgeon and had been completely replaced by the metastatic carcinoma with extranodal extension. The additional lymph node detected by molecular imaging also showed evidence of microscopic disease. The remaining lymph nodes were not fluorescent during surgery and were pathologically negative for cancer. The attached skin, fibroadipose tissue and the skeletal muscle with focal hemorrhage had no visible tumors. All margins were negative for cancer.

The patient did not opt for radiation given the advanced age. Subsequently, the patient presented with a solitary liver metastasis at 9 months and was started on systemic therapy using pembrolizumab (anti-PD1 immunotherapy). The patient is alive at 14 months from the initial operation with no evidence of cervical recurrence.

Discussion

This case demonstrates the use of intraoperative NIR imaging as a useful adjunct to facilitate identification of surgical borders of a Merkel Cell Carcinoma tumor in the neck. In surgical oncology, intraoperative molecular imaging has been increasingly demonstrated to be a useful supplement to the standard surgical approach. Intraoperative molecular imaging may be useful to locate the primary tumor and/or metastasis. Additionally, NIR can be used to identify positive margins and protect uninvolved normal structures. Enhanced visualization and additional visual information from NIR imaging may provide the surgeon an advantage in the safe and efficient removal of tumors adjacent to vital structures, a significant advantage in the resection of head and neck cancers with the goal being to decrease the morbidity associated with traditional aggressive radical neck dissection. Particularly in the head and neck, overzealous dissection can lead to inadvertent injury to normal structures.

Intraoperative optical imaging provides unique advantages that are not available with other intraoperative modalities. First, it does not require ionizing radiation. Thus, this technology is safe for patients and the personnel performing the procedure. Second, although optical probes have limited penetration depths due to tissue scattering and blood absorption, the lesions are surgically exposed and can be easily visualized. Alternative particles that permit deeper tissue visualization require higher excitation energy and risk desiccating tissues. Lastly, optical images are easy to interpret in real time during surgery.

Our group has been interested in using intraoperative molecular imaging for a wide array of head and neck cancers. Moving forward, our group is working towards identifying targets on head and neck cancers and then developing targeted optical contrast agents. These optical contrast agents can be injected prior to surgery to highlight the primary tumor. This approach will likely be more specific than the described case. In addition, it will be more sensitive because targeted delivery of contrast agents will tend to accumulate higher levels of tracers than the enhanced permeability and retention technique.

In summary, we presented a first-in-human use of intraoperative molecular imaging for a case of cervical Merkel Cell Carcinoma.

References

1. Engels EA, Frisch M, Goedert JJ, Biggar RJ, Miller RW (2002) Merkel Cell Carcinoma and HIV infection. Lancet 359: 497-498.
2. Chang Y, Moore PS (2012) Merkel Cell Carcinoma: a virus-induced human cancer. Annu Rev Pathol 7: 123-144.
3. Liu W, MacDonald M, You J (2016) Merkel cell polyomavirus infection and Merkel Cell Carcinoma. Curr Opin Virol 20: 20-27.
4. Agelli M, Clegg LX (2003) Epidemiology of primary Merkel Cell Carcinoma in the United States. J Am Acad Dermatol 49: 832-841.
5. Mauzo SH, Ferrarotto R, Bell D, Torres-Cabala CA, Tetzlaff MT, et al. (2016) Molecular characteristics and potential therapeutic targets in Merkel Cell Carcinoma. J Clin Pathol 69: 382-390.
6. Schrama D, Ugurel S, Becker JC (2012) Merkel Cell Carcinoma: recent insights and new treatment options. Curr Opin Oncol 24: 141-149.
7. Prieto I, Perez de la Fuente T, Medina S, Castelo B, Sobrino B, et al. (2016) Merkel Cell Carcinoma: An algorithm for multidisciplinary management and decision-making. Crit Rev Oncol Hematol 98: 170-179.
8. Cassler NM, Merrill D, Bichakjian CK, Brownell I (2016) Merkel Cell Carcinoma Therapeutic Update. Curr Treat Options Oncol 17: 36.
9. Schadendorf D, Lebbe C, Zur Hausen A, Avril MF, Hariharan S, et al. (2017) Merkel Cell Carcinoma: Epidemiology, prognosis, therapy and unmet medical needs. Eur J Cancer 71: 53-69.
10. Brummer GC, Bowen AR, Bowen GM (2016) Merkel Cell Carcinoma: Current Issues Regarding Diagnosis, Management, and Emerging Treatment Strategies. Am J Clin Dermatol 17: 49-62.
11. Jiang JX, Keating JJ, Jesus EM, Judy RP, Madajewski B, et al. (2015) Optimization of the enhanced permeability and retention effect for near-infrared imaging of solid tumors with indocyanine green. Am J Nucl Med Mol Imaging 5: 390-400.
12. Singhal S, Nie S, Wang MD (2010) Nanotechnology applications in surgical oncology. Annu Rev Med 61: 359-373.
13. Singhal S (2016) The Future of Surgical Oncology: Image-Guided Cancer Surgery. JAMA Surg 151: 184-185.
14. Keating JJ, Okusanya OT, DeJesus E, Judy R, Jiang J, et al. (2016) Intraoperative Molecular Imaging of Lung Adenocarcinoma Can Identify Residual Tumor Cells at the Surgical Margins. Mol Imaging Biol 18: 209-218.
15. Keating J, Newton A, Venegas O, Nims S, Zeh R, et al. (2017) Near-Infrared Intraoperative Molecular Imaging Can Locate Metastases to the Lung. Ann Thorac Surg 103: 390-398.
16. Lee JY, Thawani JP, Pierce J, Zeh R, Martinez-Lage M, et al. (2016) Intraoperative Near- Infrared Optical Imaging Can Localize Gadoinium-Enhancing Gliomas During Surgery. Neurosurgery 79: 856-871.
17. Okusanya OT, Holt D, Heitjan D, Deshpande C, Venegas O, et al. (2014) Intraoperative near-infrared imaging can identify pulmonary nodules. Ann Thorac Surg 98: 1223-1230.
18. Robbins KT, Shaha AR, Medina JE, Califano JA, Wolf GT, et al. (2008) Consensus statement on the classification and terminology of neck dissection. Arch Otolaryngol Head Neck Surg 134: 536-538.