Cells to Surgery Quiz: February 2020

Frances M. Walocko¹, Divya Srivastava¹ and Rajiv I. Nijhawan¹


WHAT IS YOUR DIAGNOSIS?

![Image](https://example.com/image.png)

**Figure 1.** Image courtesy of Alison Black, MD.

Editorial note: Welcome to the Journal of Investigative Dermatology (JID) Cells to Surgery Quiz. In this monthly online-only quiz, the first question (“What is your diagnosis?”) relates to the clinical image shown, while additional questions concern the findings reported in the JID article by Fan et al. (2019) (https://doi.org/10.1016/j.jid.2019.06.135).

Detailed answers and a list of relevant references are available following the Quiz Questions below.

**QUIZ QUESTIONS**

1. What is your diagnosis?
   a. Amelanotic melanoma
   b. Merkel cell carcinoma
   c. Basal cell carcinoma
   d. Primary cutaneous B-cell lymphoma
   e. Epidermal cyst

¹Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, Texas, USA

Correspondence: Rajiv I. Nijhawan, Department of Dermatology, University of Texas Southwestern Medical Center, 5939 Harry Hines Boulevard, Suite 400, Dallas, Texas 75390, USA. E-mail: Rajiv.Nijhawan@utsouthwestern.edu

© 2019 The Authors. Published by Elsevier, Inc. on behalf of the Society for Investigative Dermatology.
2. As described by Fan et al. (2019), ATOH1 expression has what effect on Merkel cell carcinoma (MCC) cell lines?
   a. ATOH1 expression leads to increased MCC cell viability.
   b. ATOH1 expression leads to increased proliferation of MCC cells.
   c. ATOH1 expression causes induction of a neuroendocrine growth pattern of cells.
   d. ATOH1 expression causes induction of an adherent growth pattern of cells.
   e. ATOH1 expression leads to decreased levels of microRNA-375.

3. How is ATOH1 expression affected by Merkel cell polyomavirus (MCPyV) according to Fan et al. (2019)?
   a. ATOH1 expression only occurs in MCPyV-positive cell lines.
   b. ATOH1 expression only occurs in MCPyV-negative cell lines.
   c. Small tumor antigen MCPyV-positive cell lines show increased ATOH1 expression.
   d. Large tumor antigen MCPyV-positive cell lines show increased ATOH1 expression.
   e. Methylation of ATOH1 by large tumor antigen of MCPyV leads to increased ATOH1 expression.

See following pages for detailed answers.
Merkel cell carcinoma (MCC) is a rare, aggressive form of skin cancer with an annual incidence of approximately 0.7 per 100,000 persons in the United States (Paulson et al., 2018). From 2006–2015, there were an average of 1,972 cases of MCC per year in the United States (Freeman et al., 2019). MCC is a neuroendocrine tumor that shares morphologic, immunohistologic, and ultrastructural features with Merkel cells (Fan et al., 2019). This skin cancer has a high risk of metastases and a lower 5-year survival rate for localized stage than melanoma (72.5% for MCC compared with 97.1% for melanoma) (Freeman et al., 2019).

MCC typically presents as a firm, painless nodule that is red or pink in color, but it can also appear blue, violaceous, or skin-colored. This clinical presentation can lead to it being initially misdiagnosed as a cyst or nonmelanoma skin cancer before biopsy. A majority of lesions undergo rapid growth in three months or less (Heath et al., 2008). This skin cancer is more common in immunosuppressed patients (Heath et al., 2008). Malignant transformation of the tumor has been linked to Merkel cell polyomavirus (approximately 80% of cases) in addition to UVR (Bichakjian et al., 2007; Kassem et al., 2008). The most common clinical features are described in the AEIOU acronym developed by Heath et al. (2008): Asymptomatic/lack of tenderness, Expanding rapidly, Immune suppression, Older than age 50, and UV-exposed site.

The picture presented demonstrates a large, shiny, erythematous nodule on the face in an elderly patient with evidence of actinic damage. The patient had experienced rapid growth of the nodule, and review of systems was significant for weight loss. Biopsy confirmed a diagnosis of MCC.

Discussion of incorrect answers:

a. Amelanotic melanoma: Amelanotic melanoma is a rare form of skin cancer that represents 2–8% of all melanomas (McClain et al., 2012). This type of melanoma lacks melanin and clinically appears as pink, red, or skin-colored nodules. This lack of pigment can lead to misdiagnosis as a benign entity such as eczema, pyogenic granuloma, dermatofibroma, or an intraepidermal nevus. The clinical appearance can also resemble MCC. Similar to MCC, biopsy is essential for diagnosis. Histologically, these tumors are more likely to have greater Breslow thickness and mitotic rate than pigmented melanomas (McClain et al., 2012; Thomas et al., 2014). Amelanotic melanoma is typically of a higher American Joint Committee on Cancer tumor stage than pigmented melanoma, which partially could be due to the difficulty in diagnosis (Thomas et al., 2014). Absence of back nevi, presence of many freckles, and prior amelanotic melanoma are clinical features that should increase suspicion for amelanotic melanoma in fair-skinned individuals (Vernali et al., 2017). The lesion in the provided figure could be confused for an amelanotic melanoma given the appearance, history of sun exposure, and location. Biopsy is essential for appropriate diagnosis and subsequent treatment.

b. Merkel cell carcinoma

Cancer before biopsy. A majority of lesions undergo rapid growth, Immune suppression, Older than age 50, and UV-related (2008): Asymptomatic/lack of tenderness, Expanding rapidly, Immune suppression, Older than age 50, and UV-exposed site.

The most common anatomic sites include the head and neck, followed by the lower limb, upper limb, and trunk, respectively (Heath et al., 2008). This skin cancer is more common in immunosuppressed patients (Heath et al., 2008). Malignant transformation of the tumor has been linked to Merkel cell polyomavirus (approximately 80% of cases) in addition to UVR (Bichakjian et al., 2007; Kassem et al., 2008). The most common clinical features are described in the AEIOU acronym developed by Heath et al. (2008): Asymptomatic/lack of tenderness, Expanding rapidly, Immune suppression, Older than age 50, and UV-exposed site.

The picture presented demonstrates a large, shiny, erythematous nodule on the face in an elderly patient with evidence of actinic damage. The patient had experienced rapid growth of the nodule, and review of systems was significant for weight loss. Biopsy confirmed a diagnosis of MCC.

c. Basal cell carcinoma: Basal cell carcinoma (BCC) is the most common cutaneous malignancy worldwide (Rigel et al., 1996; Cameron et al., 2019). Lifetime risk of developing a BCC is greater than 20% in the United States (Rigel et al., 1996). Male sex, Caucasian race, increased age, and UVR are independent risk factors (Cameron et al., 2019). Clinically, BCCs present as enlarging, nonhealing lesions that may be painful and bleed. They are typically slow-growing lesions with a low rate of metastasis. If not properly treated, BCCs can become locally advanced or metastatic (Cameron et al., 2019). A classic clinical presentation for a nodular BCC is a pearly papule with rolled borders. Dermoscopy can enhance clinical diagnosis of BCCs. Dermatoscopic features include arborizing vessels, blue-gray ovoid nests, comma vessels, corkscrew vessels, and red/white globules (Altamura et al., 2010). Lack of telangiectasias, rolled borders, and central ulceration in the lesion shown make this diagnosis less likely than MCC or amelanotic melanoma.

d. B-cell lymphoma: Primary cutaneous B-cell lymphomas represent 20–25% of all cutaneous lymphomas (Burg et al., 2005). This type of lymphoma originates in the skin and initially presents without extracutaneous disease. Extracutaneous disease can develop in 5–10% of patients (Bradford et al., 2009). The three main types of primary cutaneous B-cell lymphomas include marginal zone lymphoma, follicle center lymphoma, and large B-cell
Cells to Surgery Quiz

ATOH1 is increased in advanced MCCs and can lead to neuroendocrine differentiation, such as MCC and certain lung cancers (Abraham et al., 2016; Nishikawa et al., 2011).

Discussion of incorrect answers:

a. ATOH1 expression leads to increased MCC cell viability: ATOH1 is not required for MCC cell viability per studies completed by Fan et al. (2019). Small interfering RNA was designed against ATOH1 and transfected into cell lines (Fan et al., 2019). MCC cell viability was determined by cell counts every two days in addition to stains to detect catalytically active cells (Fan et al., 2019). Cell viability was not affected by knockdown of ATOH.

b. ATOH1 expression leads to proliferation of MCC cells: ATOH1 is not required for MCC cell proliferation per studies completed by Fan et al. (2019). Small interfering RNA was designed against ATOH1 and transfected into cell lines (Fan et al., 2019). MCC cell proliferation was assessed by cell counts every two days (Fan et al., 2019). Cell proliferation was not affected by knockdown of ATOH1.

c. ATOH1 expression causes induction of an adherent growth pattern of cells: ATOH1 expression is seen in classical MCC cell lines that demonstrate a neuroendocrine growth pattern (spheroid or suspension cell growth patterns) (Fan et al., 2019). MCC cell lines that show an adherent growth pattern of cells represent a variant subgroup of MCC (Leonard et al., 1995). Cells with this growth pattern demonstrate loss of neuroendocrine markers (Leonard et al., 1995). When MCC cell lines that were negative for ATOH1 were transfected to overexpress ATOH, 75% of cells changed their growth pattern from adherent to suspension.

d. ATOH1 expression leads to decreased levels of microRNA-375: Fan et al. (2019) demonstrate that ATOH1 expression correlates with microRNA-375 (miR-375) expression in MCC cells (r = 0.88, P < 0.0001). In addition, in ATOH1-negative cell lines in which ATOH1 was then overexpressed, miR-375 was found to be significantly upregulated (Fan et al., 2019). Aberrant expression of miR-375 is characteristic of cancers with neuroendocrine differentiation, such as MCC and certain lung cancers (Abraham et al., 2016; Nishikawa et al., 2011).
3. How is ATOH1 expression affected by Merkel cell polyomavirus (MCPyV) according to Fan et al. (2019)?

CORRECT ANSWER: d. Large tumor antigen MCPyV-positive cell lines show increased ATOH1 expression.

The two major proteins from the MCPyV genome involved in MCPyV tumorigenesis are the large tumor and small tumor antigens (Wendzicki et al., 2015). Large tumor antigen is important in replication of the virus, whereas small tumor antigen is important in continued cell proliferation (Wendzicki et al., 2015). In experiments completed by Fan et al. (2019), expression of MCPyV large tumor antigen induced endogenous ATOH1 and microRNA-375 expression. Cells also started to grow in a suspension cell (neuroendocrine) growth pattern that expressed ATOH1 (Fan et al., 2019). In comparison, small tumor antigen did not significantly induce ATOH1 expression or change the pattern of cell growth (Fan et al., 2019).

Discussion of incorrect answers:

a. ATOH1 expression only occurs in MCPyV-positive cell lines: Per studies performed by Fan et al. (2019), ATOH1 expression occurs in both MCPyV-positive and -negative MCC cell lines.

b. ATOH1 expression only occurs in MCPyV-negative cell lines: Per studies performed by Fan et al. (2019), ATOH1 expression occurs in both MCPyV-positive and -negative MCC cell lines.

c. Small tumor antigen MCPyV-positive cell lines show increased ATOH1 expression: Expression of MCPyV small tumor antigens did not significantly induce ATOH1 expression or change the cell morphology and growth pattern (Fan et al., 2019).

e. Methylation of ATOH1 by large tumor antigen of MCPyV leads to increased ATOH1 expression: ATOH1 methylation level negatively correlates with ATOH1 mRNA expression in MCC cell lines (r = −0.86, P = 0.003) (Fan et al., 2019). Fan et al. (2019) also note that methylation was increased in variant MCC cell lines, which do not express ATOH1, whereas methylation was decreased in classical MCC cell lines, which do express ATOH1.

ORCID
Rajiv I. Nijhawan: https://orcid.org/0000-0002-2099-9726

REFERENCES


