Cells to Surgery Quiz: May 2019

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**Figure 1.** Image credit: Eva A. Hurst, MD

**Editorial note:** Welcome to the Journal of Investigative Dermatology (JID) Cells to Surgery Quiz. In this monthly online-only quiz, the first question relates to the clinical image above, while additional questions concern the findings reported in a JID article by Olsen et al. (https://dx.doi.org/10.1016/j.jid.2018.09.022) that provides new information about that disease entity.

The quiz questions may be found in the menu bar on the right-hand side of this page. A list of references relevant to the quiz follows the image. Question 3 refers to the article by Olsen et al. (2019)

**QUIZ QUESTIONS**

1. A 67-year-old man presents with a 4-month history of an enlarging exophytic tumor on his right arm. Clinical examination did not show any palpable lymphadenopathy. Incisional biopsy shows at least a 10-mm malignant melanoma with ulceration. Results of positron emission tomography-computed tomography (PET-CT) are negative for metastatic disease, and sentinel lymph node biopsy performed during tumor resection is negative. What is the clinical stage of this melanoma?
   a. IB
   b. IIA
   c. IIB
   d. IIC
   e. IV
2. For this question, assume that the sentinel lymph node biopsy result was positive for melanoma and that the PET/CT showed multiple fludeoxyglucose (FDG)-avid pulmonary nodules. Brain magnetic resonance imaging (MRI) results were negative for intracranial metastasis. The result of tumor mutation analysis is negative for BRAF V600E/K mutation. The patient is discussed by a multidisciplinary panel, and his tumor is deemed unresectable. In addition to palliative debulking to remove the primary tumor, and if an appropriate clinical trial is not available, which of the following represents the best treatment option?

   a. Combination dabrafenib and trametinib
   b. Palliative radiation therapy
   c. Ipilimumab plus nivolumab
   d. Ipilimumab plus talimogene laherparepvec (TVEC)
   e. Indoleamine 2,3-dioxygenase (IDO) inhibitor

3. Olsen et al. (2019) estimated the associated risks for melanoma with phenotypic characteristics in a large population-based prospective study. Which of the following is a conclusion of their research?

   a. Multiple keratinocyte cancers are associated with invasive melanoma.
   b. Tendency to burn is strongly associated with development of melanoma.
   c. Invasive melanoma is most strongly associated with nevus density at 21 years, tanning ability, and red hair color.
   d. There is a strong association between high nevus density and the development of melanoma on the head and neck.
   e. Patients with high nevus density and increased tendency to freckle had a significantly higher risk of invasive melanoma compared with patients with just one of these characteristics.

See following pages for detailed answers.
DETAILED ANSWERS

1. A 67-year-old man presents with a 4-month history of an enlarging exophytic tumor on his right arm. Clinical examination did not show any palpable lymphadenopathy. Incisional biopsy shows at least a 10-mm malignant melanoma with ulceration. Results of positron emission tomography-computed tomography (PET-CT) are negative for metastatic disease, and sentinel lymph node biopsy performed during tumor resection is negative. What is the clinical stage of this melanoma?

CORRECT ANSWER: d. IIC

Clinical staging of melanoma is determined with biopsy and histologic depth of penetration from the primary melanoma, along with clinical assessment of the regional lymph nodes. Pathologic staging uses information from the initial biopsy and from wide local excision, surgical assessment of lymph nodes by sentinel or complete lymph node dissection, and full body imaging. The AJCC 8th edition melanoma staging system details the latest guidelines (Gershenwald and Scolyer, 2018; Gershenwald et al., 2017).

The clinical photograph shows a large ulcerated malignant melanoma with a reported Breslow depth of at least 10 mm. The tumor is therefore T4b. Physical examination did not show any palpable lymphadenopathy. Results of full body imaging to assess metastasis were negative, as were results of sentinel lymph node testing.

Therefore, this tumor is best described as malignant melanoma, clinical stage IIC (T4bN0Mo).

Patients with intermediate-thickness melanomas constituted the primary study group in the MSLT-1 trial in which the therapeutic and prognostic evaluation for performance of sentinel lymph node biopsy were evaluated (Morton et al., 2014). Because thick melanomas such as the one pictured have a significant chance of distant metastasis at presentation, their staging imaging studies (including brain magnetic resonance imaging, whole-body fludeoxyglucose (FDG) PET-CT or CT of chest, abdomen, pelvis) may be performed before surgery and sentinel lymph node evaluation. If imaging results for distant metastases are negative, as in this patient, sentinel lymph node biopsy may be performed for both prognostic information and possible inclusion in a clinical trial.

Discussion of incorrect answers:

a. IA: Clinical stage group IA malignant melanoma describes a T1a tumor, which is a nonulcerated tumor with a thickness of less than 0.8 mm. Ulceration describes complete loss of epidermis above the tumor with associated inflammation (Gershenwald et al., 2017). Ulceration is a poor prognostic factor and has been associated with a melanoma-specific survival, similar to that of a nonulcerated primary tumor in the next tumor group (Balch et al., 2009; in ’t Hout et al., 2012; Gershenwald et al., 2017). The patient in the photograph has a tumor with extensive ulceration and a depth of at least 10 mm.

b. IB: A clinical stage IB tumor describes either a primary T1b or a T2a tumor (Gershenwald et al., 2017). For patients with tumors in the T1b category whose tumors range from 0.8 to 1.0 mm in depth, it is critical to consider sentinel lymph node biopsy. Sentinel lymph node metastases occur in fewer than 5% of patients with tumors less than 0.8 mm in thickness. However, for melanomas with depths of 0.8 to 1.0 mm, sentinel lymph node metastases occur in 5%—12% of cases (Andtbacka and Gershenwald, 2009; Cordeiro et al., 2016; Han et al., 2013; Murali et al., 2012). The role of sentinel lymph node biopsy should be considered on a case-to-case basis and pursued after a discussion of risks and benefits (Wong et al., 2018).

c. IIA: Clinical stage IIA melanoma represents a tumor that is either a primary T2b or T3a (Gershenwald et al., 2017). In either case, lymph nodes are clinically negative.

d. IV: Clinical stage IV melanoma describes malignant melanoma that shows distant metastasis. In a patient for whom a sentinel lymph node biopsy is indicated for pathologic staging, this should be performed to evaluate the regional lymph node basin (Crompton et al., 2019). If the result is positive, full body imaging with PET-CT and brain magnetic resonance imaging should be done to determine the presence of metastatic disease. In this patient with a high-risk T4b tumor, baseline staging may be performed before development of a surgical or treatment plan (and sentinel lymph node biopsy).

2. For this question, assume that the sentinel lymph node biopsy result was positive for melanoma and that the PET/CT showed multiple fludeoxyglucose (FDG)-avid pulmonary nodules. Brain magnetic resonance imaging (MRI) results were negative for intracranial metastasis. The result of tumor mutation analysis is negative for BRAF V600E/K mutation. The patient is discussed by a multidisciplinary panel, and his tumor is deemed unresectable. In addition to palliative debulking to remove the primary tumor, and if an appropriate clinical trial is not available, which of the following represents the best treatment option?
CORRECT ANSWER: c. Ipilimumab plus nivolumab

Treatment options for advanced melanoma include IL-2, immune checkpoint inhibitors, and oncolytic intratumoral virus therapies like TVEC (Sullivan et al., 2018). The Society for Immunotherapy of Cancer (SIC) recommends the following: complete diagnostic work-up, including full body imaging, serum lactate dehydrogenase (LDH) levels, genetic mutation analysis, and surgical evaluation (Sullivan et al., 2018). If patient performance status is good and the tumor is deemed unresectable, then most panel members recommend enrollment in a clinical trial, if available, followed by combination ipilimumab plus nivolumab therapy. This recommendation is based on a prospective clinical trial, which showed that despite an increase in adverse effects, there are significantly improved response rates with combination ipilimumab plus nivolumab therapy (Wolchok et al., 2013).

Nivolumab is a PD-1 inhibitor. PD-1 interacts with PD-L to disable T cells. Nivolumab interferes with PD-1 and PD-L interaction to allow T-cell activation (Buchbinder and Desai, 2016). Ipilimumab is an IgG1 monoclonal antibody directed against CTLA-4, a molecule that attaches to T cells and blocks the costimulatory signal required for T-cell activation (Buchbinder and Desai, 2016). By blocking CTLA-4, ipilimumab allows for T-cell activation, permitting host T cells to attack the tumor (Buchbinder and Desai, 2016). In a phase III trial, 945 patients were randomly assigned to receive ipilimumab alone, nivolumab alone, or combination ipilimumab plus nivolumab (Wolchok et al., 2017). Progression-free survivals were reported: 2.6 months for ipilimumab alone, 6.9 months for nivolumab alone, and 11.5 months for the combination of ipilimumab plus nivolumab. The overall survival rates at 3 years were 34%, 52%, and 58% respectively (Wolchok et al., 2017).

Discussion of incorrect answers:

a. Dabrafenib/trametinib: Dabrafenib is a BRAF inhibitor that can be used as a single agent or in combination with a MEK inhibitor like trametinib for the treatment of BRAF mutant metastatic melanoma. BRAF mutations are common in malignant melanoma, occurring in 40%–50% of patients who present with metastatic disease (Kong et al., 2016). BRAF mutations lead to persistent activation of the MAPK pathway, a driver of cell growth and proliferation (Kong et al., 2016). For patients with an activating BRAF V600E/K mutation, there is evidence that combination BRAF and MEK inhibition leads to improved survival (Larkin et al., 2014; Long et al., 2015). The patient is BRAF mutant negative; therefore, he is not a candidate for therapy with BRAF inhibition.

b. Palliative radiation therapy: If the patient were not a candidate for systemic therapy because of medical comorbidities, then radiation therapy to the mass could result in pain relief and some regression of the mass. With a mass of this size, it is unlikely to achieve a complete response. Melanoma is commonly considered a radiation-resistant neoplasm, and it requires high doses per fraction to achieve good response and local control. Systemic therapy is preferred because of the distant metastases and good performance status (Olivier et al., 2007).

c. Ipilimumab plus talimogene laherparepvec (TVEC): Ipilimumab is an IgG1 monoclonal antibody directed against CTLA-4. TVEC is a modified oncolytic herpes simplex 1 virus, which multiplies in human tumor cells and causes cell lysis. When tumor cells lyse, antigens are released and provoke a tumor-specific immune response (Kohlhapp and Kaufman, 2016). The combination of ipilimumab plus TVEC is effective; however, TVEC is generally recommended after a trial of combination immunotherapy, specifically for patients with limited tumor burden or injectable tumor (Luther et al., 2019).

d. Indoleamine 2,3-dioxygenase (IDO) inhibitor: IDO is an enzyme expressed on tumor cells that acts in the rate-limiting step of tryptophan catabolism (van Baren and Van den Eynde, 2015). IDO, when activated, can help tumor cells evade the immune system. IDO inhibitors, like epacadostat, are currently being studied in combination with pembrolizumab (Jochems et al., 2016).

3. Olsen et al. (2019) estimated the associated risks for melanoma with phenotypic characteristics in a large population-based prospective study. Which of the following is a conclusion of their research?

CORRECT ANSWER: c. Invasive melanoma is most strongly associated with nevus density at 21 years, tanning ability, and red hair color.

In a prospective study, Olsen et al. (2019) studied melanoma risk with phenotypic characteristics. Their study followed 38,854 participants over 3.5 years. Within that time, 253 developed invasive melanoma. Participants with red hair had a 3-fold increased risk of invasive melanoma (hazard ratio [HR] = 3.11, 95% confidence interval [CI] = 1.50–6.43). Those with inability to tan also had a 3-fold increased risk of invasive melanoma (HR = 3.39, 95% CI = 1.85–6.20).
Participants with high nevus density at age 21 years were 5 times more likely to develop invasive melanoma (HR = 4.91, 95% CI = 2.81–8.55).

Discussion of incorrect answers:

a. Multiple keratinocyte cancers are associated with significant risk of developing invasive melanoma: Olsen et al. (2019) did not explicitly study the association between keratinocyte cancers and the development of invasive melanoma. Rather, they studied the synergy between a history of two or more keratinocyte cancers and a high nevus density. The reported synergy index was 2.96 (95% CI = 1.54–5.69).

b. Tendency to burn is strongly associated with development of melanoma: Historically, a strong association has been reported between sunburn and development of melanoma (Whiteman and Green, 1994). In the study by Olsen et al. (2019), the inability to tan, rather than the propensity to sunburn, is reported as being more strongly tied to melanoma risk. This result was surprising, and the authors explain that earlier studies often combined patients’ immediate (possibly sunburn) and delayed responses (likely tanning) to sun exposure, endpoints that are now reported separately (Olsen et al., 2019).

c. There is a strong association between high nevus density and the development of melanoma on the head and neck: Olsen et al. (2019) identified a strong association between high nevus density and melanoma of the trunk, not the head and neck. This finding is consistent with several other studies, including the Melanoma Inquiry of Southern Sweden (Nielsen et al., 2012) and the Nurses’ Health Study/Health Professionals Follow-up Study (Cho et al., 2005).

d. Patients with high nevus density and increased tendency to freckle had a significantly higher risk of invasive melanoma compared with patients with just one of these characteristics: Olsen et al. (2019) studied the association between high nevus density and each of the following: (i) decreased ability to tan, (ii) increased tendency to freckle, and (iii) presence of more than 10 actinic keratosis. Patients with high nevus density and one of those additional listed traits did have a higher risk of invasive melanoma. However, after calculating the synergy index, the association was not statistically significant (Olsen et al., 2019).

REFERENCES


