Cells to Surgery Quiz: May 2022

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WHAT IS YOUR DIAGNOSIS?

Figure 1. Image courtesy of David Mutch, Washington University School of Medicine in St. Louis

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 Kolitz et al. (2021) (https://doi.org/10.1016/j.jid.2021.10.009).

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

QUIZ QUESTIONS

1. A 76-year-old woman presents with a 2.0 × 1.8 cm friable, exophytic plaque involving her labia minora. The lesion is painful and pruritic. Biopsy reveals deeply infiltrative, keratinizing nests of atypical cells with nuclear pleomorphism and numerous mitoses. Human papillomavirus (HPV) is detected on PCR. What is the most likely diagnosis?

   a. Low-grade squamous intraepithelial lesion
   b. High-grade squamous intraepithelial lesion
   c. Vulvar intraepithelial neoplasia, differentiated type
   d. Vulvar squamous cell carcinoma (VSCC), HPV associated
   e. VSCC, HPV independent

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2. Kolitz et al. (2021) hypothesized that HPV-positive and HPV-negative VSCCs are biologically and behaviorally distinct. In this study, which of the following is associated with worse overall survival for patients with VSCC?
   a. HPV status
   b. p16 expression
   c. PD-L1 expression
   d. Circular RNA with the E7 oncogene expression

3. In this study, PD-L1 expression did inversely correlate with overall survival, highlighting a potential opportunity for targeted therapy. Which of the following immune checkpoint inhibitors targets PD-L1?
   a. Pembrolizumab
   b. Nivolumab
   c. Cemiplimab
   d. Avelumab
   e. Ipilimumab

See following pages for detailed answers
Vulvar cancer is rare, with just over 6,000 new cases diagnosed in the United States in 2021 (National Cancer Institute Surveillance, Epidemiology, and End Result Program, 2021). Although a rare diagnosis, both the incidence and associated mortality of vulvar cancer have increased annually by 0.6% and 1.7%, respectively (National Cancer Institute Surveillance, Epidemiology, and End Result Program, 2021). Importantly, squamous cell carcinoma (SCC) is the most common cancer to affect the vulva, comprising more than 80% of vulvar cancer diagnoses (Michalski et al., 2021; Rogers and Cuello, 2018).

Clinically, vulvar SCC (VSCC) presents as a painful, pruritic plaque or ulcer, most commonly involving the labia. VSCC derives from one of two pathways: human papillomavirus (HPV) associated or HPV independent (Allbritton, 2017). Histologically, HSIL shows moderate cytologic atypia involving more than one third of the epidermis. Because of its premalignant nature, HSIL is treated with surgery, ablative laser, or topical immunomodulatory therapy (Allbritton, 2017).

c. Vulvar intraepithelial neoplasia, differentiated type: Vulvar intraepithelial neoplasia, differentiated type (dVIN) is another precursor to malignant VSCC. Unlike HSIL, dVIN is HPV independent. dVIN affects women aged 60–80 years and usually arises within a background of chronic inflammation, for example, in the setting of lichen sclerosus or lichen planus (Allbritton, 2017). Nearly 35% of dVIN will progress to invasive VSCC (Allbritton, 2017). Because of its high risk for progression to invasive malignancy, dVIN is treated with excision (Preti et al., 2014).

e. VSCC, HPV independent: HPV-independent VSCC, similar to dVIN, is thought to arise from chronic inflammatory conditions (Alkatout et al., 2015; Kolitz et al., 2021). Interestingly, in other HPV-associated malignancies, such as SCC of the head and neck, HPV status helps to stratify outcomes (Blitzer et al., 2014; Li et al., 2017). In this study, Kolitz et al. (2021) studied the effect of HPV status on the clinical and biologic behavior of VSCC.

2. Kolitz et al. (2021) hypothesized that HPV-positive and HPV-negative VSCCs are biologically and behaviorally distinct. In this study, which of the following is associated with worse overall survival for patients with VSCC?

CORRECT ANSWER: c. PD-L1 expression.

Kolitz et al. (2021) conducted a retrospective cohort study that included 36 patients with invasive VSCC. Using RNA in situ hybridization and nested PCR, the authors detected 20 HPV-positive tumors (Kolitz et al., 2021). After HPV status was determined, the authors compared outcomes between patients with HPV-positive tumors and those with HPV-negative tumors. HPV status did affect overall or progression-free survival with any significance (Kolitz et al., 2021). Although PD-L1 expression did not correlate significantly with HPV status, its expression was identified as a predictor of overall survival (Kolitz et al., 2021): patients whose tumors expressed higher PD-L1 showed worse overall survival than those with weaker PD-L1 expression. Although the authors detected circular RNA with the E7 oncogene (circE7) in HPV-positive tumors, its presence did not predictably influence survival (Kolitz et al., 2021).
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Discussion of incorrect answers:

a. **HPV status**: Kolitz et al. (2021) detected the characteristics predictive of lower overall survival in invasive VSCC, including recurrent or nodal disease, treatment with wide local excision over vulvectomy, and absence of nodal dissection. The authors also identified the predictors of progression-free survival, including multifocal disease, performance of wide local excision over vulvectomy, and absence of nodal dissection. HPV status was not associated with decreased overall or progression-free survival.

b. **p16 expression**: p16 is often used as a marker for HPV status. Kolitz et al. (2021) used immunohistochemistry to detect p16 expression and found that p16 expression did correspond with HPV positivity \( (P = 0.0172) \). However, similar to HPV status, p16 expression did not affect overall survival in patients with VSCC.

c. **Circular RNA with the E7 oncogene expression**: In their study, Kolitz et al. (2021) aimed to differentiate HPV-positive from HPV-negative VSCC tumors by identifying the presence of circE7. circE7 was previously identified in head and neck SCC as a predictor of overall survival (Chamseddin et al., 2019). Although the authors detected circE7 in HPV-positive tumors, its expression did not influence survival (Kolitz et al., 2021).

d. **Ipilimumab**: Ipilimumab is an immune checkpoint inhibitor that targets PD-1. It has also been approved for a variety of indications, including but not limited to melanoma, nonsmall cell lung carcinoma, urothelial carcinoma, and Hodgkin lymphoma (U.S. Food and Drug Administration, 2022).

e. **Pembrolizumab**: Pembrolizumab is an immune checkpoint inhibitor that targets PD-1. Although not currently approved by the United States Food and Drug Administration for vulvar carcinoma, it has been approved in combination with chemotherapy, with or without bevacizumab, for persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1. It has also received approval in a variety of other cancers, including but not limited to endometrial cancer, colorectal cancer, nonsmall cell lung cancer, and melanoma (U.S. Food and Drug Administration, 2022).

3. In this study, PD-L1 expression did inversely correlate with overall survival, highlighting a potential opportunity for targeted therapy. Which of the following immune checkpoint inhibitors targets PD-L1?

**CORRECT ANSWER: d. Avelumab.**

Checkpoint inhibitors are a class of drugs that are helpful in a variety of locally advanced and metastatic cancers. Some cancers are able to evade the host's immune system by stimulating immune checkpoint targets. Immunotherapeutic drugs block checkpoint proteins from binding with their targets so that T cells are alerted to and will attack the abnormal cancer cells. Pembrolizumab, nivolumab, cemiplimab, avelumab, and ipilimumab are all immune checkpoint inhibitors, but only avelumab targets PD-L1 (Barrios et al., 2020).

Discussion of incorrect answers:

a. **Pembrolizumab**: Pembrolizumab is an immune checkpoint inhibitor that targets PD-1. Although not currently approved by the United States Food and Drug Administration for vulvar carcinoma, it has been approved in combination with chemotherapy, with or without bevacizumab, for persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1. It has also received approval in a variety of other cancers, including but not limited to endometrial cancer, colorectal cancer, nonsmall cell lung cancer, and melanoma (U.S. Food and Drug Administration, 2022).

b. **Nivolumab**: Nivolumab is an immune checkpoint inhibitor that targets PD-1. It has also been approved for a variety of indications, including but not limited to melanoma, nonsmall cell lung carcinoma, urothelial carcinoma, and Hodgkin lymphoma (U.S. Food and Drug Administration, 2022).

c. **Cemiplimab**: Cemiplimab is an immune checkpoint inhibitor that targets PD-1. At the time of publication, it has been approved for advanced and metastatic cutaneous SCC, locally advanced and metastatic basal cell carcinoma in patients who have either failed or in whom a hedgehog pathway inhibitor is contraindicated, and nonsmall cell lung carcinoma (U.S. Food and Drug Administration, 2022).

e. **Ipilimumab**: Ipilimumab is an immune checkpoint inhibitor that inhibits the protein CTLA-4. It is used in patients with advanced or unresectable melanoma and in combination with nivolumab in patients with mesothelioma, renal cell carcinoma, colorectal carcinoma, hepatocellular carcinoma, and nonsmall cell lung cancer (U.S. Food and Drug Administration, 2022).

**REFERENCES**


