Cells to Surgery Quiz: April 2022

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WHAT IS YOUR DIAGNOSIS?


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 Boudra et al. (2021) (https://doi.org/10.1016/j.jid.2021.09.026).

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

QUIZ QUESTIONS

1. What is your diagnosis?
   a. Bowen’s disease
   b. Cutaneous horn
   c. Squamous cell carcinoma (SCC)
   d. Basal cell carcinoma
   e. Actinic keratosis

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2. In a patient with biopsy-proven invasive SCC of the head that has recurred and progressed after cisplatin therapy and is currently deemed inoperable, which of the following are Food and Drug Administration–approved systemic therapies?
   a. Surgical excision
   b. Curettage and electrodessication
   c. Nivolumab
   d. Cemiplimab
   e. c and d

3. Boudra et al. (2021) evaluated the levels of 5-hydroxymethylcytosine (5-hmC) and alterations in the ten–eleven translocation (TET) family of enzymes in cutaneous SCC (Rowe et al., 1992). Which of the following is incorrect about their findings?
   a. Levels of 5-hmC are globally reduced in cutaneous SCC.
   b. Genomic alterations in TET1, TET2, and TET3 were found in 8–10% of SCC tumors.
   c. There is no difference in 5-hmC level between low-stage and high-stage tumors.
   d. Loss of both TET2 and TP53 increased spontaneous SCC tumor development compared with TP53 loss alone.
   e. Loss of TET2 resulted in a greater number and more advanced lesions after chemical carcinogenesis.

See following pages for detailed answers
Squamous cell carcinoma (SCC) (Rowe et al., 1992) is the second most common cutaneous malignancy and has a high risk of spreading. On average, there are 1.8 million diagnosed cases of SCC per year in the United States and 15,000 deaths (Miller and Weinstock, 1994). Lifetime risk includes 9–14% for men and 4–9% for women with a range of 200,000–400,000 cases annually. Risk factors for SCC include sun exposure, UVR, cigarettes, and tanning beds. Commonly affected areas include the head, neck, hands, and arms (Day et al., 1982). SCC can appear as a firm, red nodule with scaling crust from an ulcer or scar and evolve into an open sore. Dermoscopy aids in the clinical diagnosis of SCC, showing erythema, keratin masses, red–brown erosions, ulcerations, and linear irregular vessels. Other diagnostic methods include reflectance confocal microscopy, which uses near-infrared laser light with 830 nm to develop 200–300 nm gray, horizontal images (Rishpon et al., 2009). Biopsy uses near-infrared laser light with 830 nm to develop 200–300 nm gray, horizontal images (Rishpon et al., 2009). Biopsy aids the diagnosis of suspicious lesions (Medical Advisory Secretariat, 2010). On histology, SCC can appear as nests of squamous epithelial cells from the epidermis and extend to the dermis with abundant eosinophilic cytoplasm (Clark et al., 2012). SCC is definitively diagnosed with biopsy; dermoscopy and reflectance confocal microscopy may be helpful adjuncts before a biopsy. Biopsy methods include punch, shave, and excisional biopsy. Histologic characteristics to be included in the biopsy report include the degree of differentiation, histologic subtype, depth, perineural invasion, high-risk features, TNM (tumor, nodes, metastases) staging, and margins (Longhitano et al., 2020). Computerized tomography and magnetic resonance imaging may be useful for TNM staging and grading for lesions that have metastasized. The American Joint Committee on Cancer and the Brigham and Women’s Hospital (Boston, MA) outline the criteria for TNM staging (Que et al., 2018).

Treatment of localized SCC includes nonsurgical and surgical treatment options. Nonsurgical options for SCC in situ (SCCIS) may include 5-fluorouracil (5-FU), photodynamic therapy (PDT) (5-aminolevulinic acid [ALA]), and vigorous cryotherapy according to the National Comprehensive Cancer Network (NCCN) guidelines (National Cancer Comprehensive Network, 2021), with the acknowledgment that cure rates may be lower than with surgical treatment. Surgical treatment for localized invasive SCC is the gold standard with Mohs micrographic surgery for SCCs that occur in high-risk areas or those having high-risk features. Sentinel lymph node biopsy may be supported in SCCs meeting certain tumor diameter and thickness characteristics and multiple high-risk factors (National Cancer Comprehensive Network, 2021).

Discussion of incorrect answers:

a. Bowen’s disease: Bowen’s disease (BD) (Ko et al., 2014) is clinically seen as a red, scaly patch, with an incidence of 1.42 per 1,000 in the Caucasian population (Neagu et al., 2017). BD is an in situ SCC that may also present as a pigmented, verrucous, well-demarcated scaling patch with a crusted surface. Unusual presentations can be seen in subungual, periungual, genital, perianal, and palmar sites, and multiple lesions may present at one time (Neubert and Lehmann, 2008). The risk of progression to an invasive carcinoma has been reported between 3 and 5% (Neubert and Lehmann, 2008). Treatment options include cryotherapy, excision, curettage and electrodessication (C&E), 5-FU, radiotherapy, imiquimod, and PDT.

b. Cutaneous horn: A cutaneous horn is also known as cornu cutaneum. These are protrusions of white or yellow material organized into a cone shape that arise from premalignant or malignant skin lesions with or without pain and may develop in benign, premalignant, or malignant lesions. Cutaneous horns are typically seen in populations aged between 60 and 80 years and are equal between males and females. Pathology shows redundant hyperkeratosis with or without orthokeratosis or parakeratosis. Treatment depends on the underlying pathology. A 38.9% rate of malignant or premalignant disease has been reported by Yu et al. (1991). Actinic keratoses were seen in 83.84% of premalignant cases, and SCC was seen in 93.75% of malignant cases (Mantese et al., 2010).

c. Basal cell carcinoma: Basal cell carcinoma (BCC) is responsible for 50% of all cancers in the United States (Marzuka and Book, 2015), and despite having negligible mortality, it can result in notable morbidity (Fania et al., 2020). The clinical subtypes of BCC are nodular, superficial, and morpheaform BCCs. BCCs tend to occur on the face and hair-bearing skin of the head and neck and the upper and lower extremities. Nodular BCC (NBCC) is the most common subtype diagnosed clinically (50–79%), and it appears as a papule or nodule with a pearly, shiny edge with small arborizing telangiectasias. NBCC is characterized histologically by nests of basaloid cells with distinct borders with peripheral palisading (Fania et al., 2020). Superficial BCC is the second most common subtype (up to 15%) and presents as a sharply circumscribed, scaly, pink macule; papule; or thin plaque. Morpheaform BCC, accounting for up to 10% of cases, presents as a shiny, smooth indurated plaque or
depression with poorly defined edges (Marzuka and Book, 2015). The most common treatment for a BCC is C&E, surgery, and Mohs surgery in high-risk areas and in tumors with high-risk features.

e. Actinic keratosis: Actinic keratoses (AKs) are classically known as precancerous lesions and are formed through the proliferation of atypical keratinocytes (KCs), usually on skin-exposed regions of the body (Berman and Cockerell, 2013). In both sexes, AKs occur most commonly on the head and neck and the upper extremities and present as patches or plaques, generally with poorly defined borders, and may be covered with dry scale (Reinehr and Bakos, 2019). Because AKs present with different degrees of hyperkeratosis, palpation can significantly aid in the diagnosis. Although AKs can often be diagnosed clinically, dermoscopy can aid in the diagnosis. Over 60% of AKs remain stable, and some will even involute spontaneously, but AKs can transform to an SCC. Treatment options for AKs are divided into ablative or surgical therapy, such as cryosurgery, and topical therapy such as 5-FU, imiquimod, and diclofenac. Treatment is individualized; many patients will continue to develop new lesions (Reinehr and Bakos, 2019). AKs can be classified into three grades on the basis of the dermoscopic findings: grade I findings include erythematous pseudonetwork and discrete scales, grade II findings include erythematous pseudonetwork and keratotic and enlarged follicular openings, and grade III findings include hyperkeratosis with thick scales or enlarged keratotic follicular openings associated with scales (Zalaudek et al., 2014).

2. In a patient with biopsy-proven invasive SCC of the head that has recurred and progressed after cisplatin therapy and is currently deemed inoperable, which of the following are Food and Drug Administration–approved systemic therapies?

CORRECT ANSWER: e. c and d.

Nivolumab is a fully human IgG4 anti–PD-1 mAb that gained initial approval by the Food and Drug Administration (FDA) in 2014 (Food and Drug Administration, 2014). A randomized, open-label, phase 3 trial of 361 patients with recurrent SCC of the head and neck whose disease showed progression after 6 months of platinum-based therapy was conducted to evaluate the overall survival in comparison with that of standard single-agent chemotherapy (Ferris et al., 2016). Nivolumab was then given to the participants at a dose of 3 mg/kg of body weight every 2 weeks (U.S. National Library of Medicine, 2019a). Standard therapy consisted of either methotrexate, docetaxel, or cetuximab. Results showed that the median overall survival was 7.5 months for the patients receiving nivolumab compared with 5.1 months for the patients in the standard therapy group (U.S. National Library of Medicine, 2019b). As a consequence, nivolumab was then approved in 2016 for patients with recurrent or metastatic SCC of the head and neck with disease progression on or after platinum-based therapy (Ferris et al., 2016). Nivolumab is also currently approved for patients with unresectable or metastatic melanoma as a single agent or in combination with ipilimumab and as adjuvant therapy for patients with melanoma who have lymph node involvement or metastatic disease who have undergone complete resection (Food and Drug Administration, 2014). In general, PD-1 inhibitors are associated with immune-related adverse events, including dermatitis, colitis, hepatitis, uveitis, nephritis, and pneumonitis (Spiers et al., 2019). When nivolumab was assessed in the clinical trial, the five most common adverse events occurring in patients were fatigue (33%), nausea (20%), rash (18%), decreased appetite (17%), and pruritis (17%) (Ferris et al., 2016). Currently, there is no other approved use of nivolumab for cutaneous SCC (cSCC); however, a multicenter, Simon’s two-stage, phase II trial is currently underway, with the goal of evaluating the safety and efficacy of nivolumab on patients who have not received systemic therapy with metastatic or locally advanced cSCC (NCT03834233).

Cemiplimab is a human mAb directed against PD-1 that is currently approved for the treatment of patients with metastatic cSCC or locally advanced SCC who are not candidates for curative surgery or curative radiation (Food and Drug Administration, 2018). An interventional phase 2 study of cemiplimab in patients with advanced cSCC showed that 47% of patients in the metastatic-disease cohort responded to the therapy, with a 6-month duration of response in about 57% of participants (Migden et al., 2018). An expansion cohort of a phase 1 study with patients who have locally advanced or metastatic SCC showed that about 50% of patients responded to cemiplimab therapy with dosing of 3 mg/kg of body weight given every 2 weeks (Migden et al., 2018). The most common adverse effects that were seen included diarrhea (27%), fatigue (24%), nausea (17%), constipation (15%), and rash (15%), with four patients discontinuing therapy in relation to adverse reactions. (Migden et al., 2018). An open-label, phase 2, single-trial arm was carried out on 78 patients with histologically confirmed locally advanced cSCC (Migden et al., 2020). About 13% of patients achieved a complete response, and 31% achieved a partial response (Migden et al., 2020). Currently, cemiplimab is being evaluated in a randomized, placebo-controlled, double-blind study as adjuvant therapy after surgery and radiation in patients with high-risk cSCC (NCT03969004).

Discussion of incorrect answers:

a. Surgical excision: The NCCN recommends standard surgical excision with 4–6 mm margins and
postoperative margin assessment for local, low-risk cSCC (National Cancer Comprehensive Network, 2021). Low-risk SCC is defined as being localized in the trunk or extremities with a size ≤2 cm that is well-defined in a patient who has no history of immunosuppression, radiotherapy, or chronic inflammatory process in the site of the lesion; history of rapid growth; or history of neurologic symptoms. Another acceptable surgical modality for the treatment of low-risk cSCC is Mohs micrographic surgery, especially lesions that may necessitate a tissue-sparing surgical technique owing to specific locations that may affect cosmesis or functionality. A systematic review comparing different surgical modalities for the treatment of cSCC found that 5-year local recurrence for Mohs surgery was 3.1% compared with 8.1% for standard surgical excision (Rowe et al., 1992). Another systematic review found 12 retrospective studies that showed an average local recurrent of 5.4% with margins ranging from 2 to 10 mm (Lansbury et al., 2013).

b. Curettage and electrodesiccation: The NCCN also recommends C&E as an option for treatment of local, low-risk cSCC (National Cancer Comprehensive Network, 2021). There are certain considerations that need to be taken into account before using C&E as a treatment modality. If the lesion is located in terminal hear-bearing areas such as the scalp, pubic, and axillary regions, and beard, other surgical treatment modalities should be used owing to the risk of the tumor extending down the hear follicle. In addition, NCCN guidelines recommend that if the tumors appear to extend beyond the dermis, other surgical modalities should be used (National Cancer Comprehensive Network, 2021). Tumors that are located in embryonic fusion plane areas such as the middle of the nose, medial canthi, nasolabial sulci, and nasolabial folds should be treated with other surgical modalities such as Mohs surgery to ensure that clear margins are achieved given that these areas are considered high risk for further tumor invasion (Dim-Jamora and Perone, 2008; Panje and Celley, 1979).

A less invasive therapeutic option, PDT, has been used in dermatology for the treatment of precancerous and superficial cancerous lesions such as AKs, SCCIS (BD), and BCC (Morton et al., 2013; Ozog et al., 2016). PDT is successful in achieving a cytotoxic effect on malignant cells by creating endogenous ROS through the use of a nontoxic photosensitizer that is irradiated with light at a specific wavelength (Kwiatkowski et al., 2018). A commonly used agent is ALA, which functions as a prodrug that is a precursor to protoporphyrin IX that serves as a photosensitizer in malignant lesions (Kwiatkowski et al., 2018). PDT is advantageous in treating these lesions owing to its accumulation and selectivity for malignant or pathologic cells (Vrouenraets et al., 2003). However, owing to its hydrophilic nature, ALA is limited for use in superficial lesions given that it has to cross the highly lipid-rich matrix found in the stratum corneum to achieve its effect (Champeau et al., 2019). Although PDT may be successful in managing superficial lesions, the use of such therapy in invasive SCC has been shown to recur at a rate of 26.4% (Lansbury et al., 2013). SCC that is not in situ may require more invasive treatment modalities such as traditional surgical excision or Mohs surgery.

c. Nivolumab: Nivolumab is a fully human IgG4 anti–PD-1 mAb that gained initial approval by the FDA in 2014 (Food and Drug Administration, 2014). A randomized, open-label, phase 3 trial of 361 patients with recurrent SCC of the head and neck whose disease showed progression after 6 months of platinum-based therapy was conducted to evaluate the overall survival in comparison with that of standard single-agent chemotherapy (Ferris et al., 2016). Nivolumab was given to the participants at a dose of 3 mg/kg of body weight every 2 weeks. Standard therapy consisted of either methotrexate, docetaxel, or cetuximab. Results showed that the median overall survival was 7.5 months for the patients receiving nivolumab compared with 5.1 months for the patients in the standard therapy group. As a consequence, nivolumab was then approved in 2016 for patients with recurrent or metastatic SCC of the head and neck with disease progression on or after platinum-based therapy (Ferris et al., 2016). Nivolumab is also currently approved for patients with unresectable or metastatic melanoma as a single agent or in combination with ipilimumab and as adjuvant therapy for patients with melanoma who have lymph node involvement or metastatic disease who have undergone complete resection (Food and Drug Administration, 2014). In general, PD-1 inhibitors are associated with immune-related adverse events, including dermatitis, colitis, hepatitis, uveitis, nephritis, and pneumonitis (Spiers et al., 2019). When nivolumab was assessed in the clinical trial, the five most common adverse events occurring in patients were fatigue (33%), nausea (20%), rash (18%), decreased appetite (17%), and pruritis (17%) (Ferris et al., 2016). Currently, there is no other approved use of nivolumab for cSCC; however, a multicenter, Simon’s two–stage, phase 2 trial is currently underway, with the goal of evaluating the safety and efficacy of nivolumab on patients who have not received systemic therapy with metastatic or locally advanced cSCC (NCT03834233).

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treatment of patients with metastatic cSCC or locally advanced SCC who are not candidates for curative surgery or curative radiation (Food and Drug Administration, 2018). An interventional phase 2 study of cemiplimab in patients with advanced cSCC showed that 47% of patients in the metastatic-disease cohort responded to the therapy, with a 6-month duration of response in about 57% of participants (Migden et al., 2018). An expansion cohort of a phase 1 study with patients who have locally advanced or metastatic SCC showed that about 50% of patients responded to cemiplimab therapy, with dosing of 3 mg/kg of body weight given every 2 weeks (Migden et al., 2018). The most common adverse effects that were seen included diarrhea (27%), fatigue (24%), nausea (17%), constipation (15%), and rash (15%), with four patients discontinuing therapy in relation to adverse reactions (Migden et al., 2018). An open-label, phase 2, single-arm trial arm was carried out on 78 patients with histologically confirmed locally advanced cSCC (Migden et al., 2020). About 13% of patients achieved a complete response, and 31% achieved a partial response (Migden et al., 2020). Currently, cemiplimab is being evaluated in a randomized, placebo-controlled, double-blinded study as an adjuvant therapy after surgery and radiation in patients with high-risk cSCC (NCT03969004).

3. Boudra et al. (2021) evaluated the levels of 5-hydroxymethylcytosine (5-hmC) and alterations in the ten–eleven translocation (TET) family of enzymes in cutaneous SCC (Rowe et al., 1992). Which of the following is incorrect about their findings?

CORRECT ANSWER: b. Genomic alterations in TET1, TET2, and TET3 were found in 8–10% of SCC tumors.

Boudra et al. (2021) utilized the cBio cancer genomics portal, an open-access and open-source resource whereby users can explore large-scale cancer genomics datasets, to analyze ten–eleven translocation (TET) enzyme sequence variants in human SCC. They found that genomic alterations were present in TET1, TET2, and TET3 in 3–4% of SCC tumors, not 8–10% of SCC tumors. Interestingly, they also found that some of the samples analyzed had changes in more than one TET gene.

Discussion of incorrect answers:

a. Levels of 5-hmC are globally reduced in cutaneous SCC: Boudra et al. (2021) developed a microarray composed of human cSCC tumors to quantify the levels of 5-hydroxymethylcytosine (5-hmC). They performed immunohistochemistry on the tissue microarray utilizing antibodies against 5-hmC and quantified 5-hmC levels by counting positive tumor cell numbers and scoring for intensity of staining. Compared with those in normal skin, Boudra et al. (2021) found that global 5-hmC levels were reduced in the tissue microarray composed of human cSCC tumors.

c. There is no difference in 5-hmC level between low-stage and high-stage tumors: Boudra et al. (2021)’s human tissue microarray consisted of 98 cutaneous primary SCC samples and 83 adjacent normal skin samples. The 98 cutaneous primary SCC samples were staged according to the Brigham and Women’s Hospital staging system: 10 of the samples were T1, 20 were T2a, and 68 were T2b. Although the levels of 5-hmC were found to be globally reduced in cSCC, Boudra et al. (2021) found no association between tumor stage and reductions in 5-hmC levels (P < 0.001). However, one must also consider that the sample sizes for the T1 (Yip et al., 2009) and T2a (Carassa et al., 2003) stages were limited.

d. Loss of both TET2 and TP53 increased spontaneous SCC tumor development compared with TP53 loss alone: Boudra et al. (2021) utilized a murine K14-CreER mice system, which expresses an inducible Cre recombinase in basal KCs, to investigate TET2’s role in cSCC development. They found that TET2 can function as a tumor suppressor in both carcinogen-induced and spontaneous SCC models. Loss of TP53 alone results in the formation of SCC tumors; however, Boudra et al. (2021) discovered that loss of TP53 in addition to the loss of TET2 resulted in increased tumor penetrance, high spontaneous tumor incidence, and lower tumor-free survival.

e. Loss of TET2 resulted in a greater number and more advanced lesions after chemical carcinogenesis: Boudra et al. (2021) found that loss of TET2 resulted in more advanced lesions and a greater number of lesions after chemical carcinogenesis. They developed multiple mouse genotypes, including the following: Tet2<sup>L/L</sup> (Tet2<sup>L/L</sup> + tamoxifen [100 mg/kg for 5 consecutive days], n = 5; Tet2<sup>L/L</sup> + vehicle, n = 3; K14-CreERTet2<sup>L/L</sup> + vehicle, n = 6); Tet2<sup>L/L</sup>/p53<sup>L/L</sup> (K14-CreERTet2<sup>L/L</sup> + tamoxifen [100 mg/kg for 5 consecutive days], n = 16); Tet2<sup>L/L</sup> + Tet2<sup>L/L</sup>/p53<sup>L/L</sup>, or p53<sup>L/L</sup> (Carassa et al., 2003); K14-CreERTet2<sup>L/L</sup>/p53<sup>L/L</sup>+ (Carassa et al., 2003); K14-CreERTet2<sup>L/L</sup>/p53<sup>L/L</sup> (n = 26); K14-CreERTet2<sup>L/L</sup>/p53<sup>L/L</sup> (Yip et al., 2009); K14-CreERTet2<sup>L/L</sup>/p53<sup>L/L</sup> (n = 22); K14-CreERTet2<sup>L/L</sup>/p53<sup>L/L</sup> (n = 16); K14-CreERTet2<sup>L/L</sup>/p53<sup>L/L</sup> (Yip et al., 2009); K14-CreERTet2<sup>L/L</sup>/p53<sup>L/L</sup> (n = 29); and K14-CreERTet2<sup>L/L</sup>/p53<sup>L/L</sup> (Carassa et al., 2003). Tamoxifen-treated K14-CreERTet2<sup>L/L</sup> (n = 16) and Tet2<sup>L/L</sup> (n = 5) mice as well as vehicle K14-CreERTet2<sup>L/L</sup>
and Tet2−/− (n = 3) mice were given 5-nitroquinolone-N-oxide (5-NQO) in their drinking water. After treatment with 5-NQO, mice developed dysplasia, papillomas, and SCC. Tet2−/− mice developed a significantly higher percentage of oral SCC tumors than Tet2+/+ mice, who primarily developed benign papillomas and dysplasia.

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