Cells to Surgery Quiz: September 2020

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WHAT IS YOUR DIAGNOSIS?

Figure 1. Image courtesy of M. Laurin Council, MD. The patient has provided written consent for her photograph to be used in this capacity.

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 Haug et al. (2020) (https://doi.org/10.1016/j.jid.2020.01.035).

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

QUIZ QUESTIONS

1. A 69-year-old white woman with a history of renal transplantation presents with a 1.5-cm pink plaque with central crust on the left suprabrow. The lesion is painful, and the surrounding skin is paresthetic. On biopsy, extensive perineural invasion is found. What is the most likely diagnosis?
   a. Microcystic adnexal carcinoma
   b. Basal cell carcinoma
   c. Squamous cell carcinoma
   d. Atypical fibroxanthoma
   e. Verruca vulgaris

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2. Haug et al. (2020) found perineural invasion to be most strongly associated with which of the following clinical or histologic findings?
   a. Increased tumor thickness
   b. Desmoplastic growth
   c. Increased tumor horizontal size
   d. Immunosuppression
   e. Grade of tumor differentiation

3. In their prospective study, Haug et al. (2020) examine the prognostic effects of perineural invasion, de-differentiation, and desmoplasia for patients with squamous cell carcinoma. According to their study, which of the following is considered a marker of poor prognosis?
   a. De-differentiation
   b. Tumor horizontal size ≥ 10 mm
   c. Tumor thickness ≥ 8 mm
   d. Desmoplastic growth and perineural invasion
   e. Caliber of involved nerve ≤ 0.1 mm

See following pages for detailed answers.
1. A 69-year-old white woman with a history of renal transplantation presents with a 1.5-cm pink plaque with central crust on the left suprabrow. The lesion is painful, and the surrounding skin is paresthetic. On biopsy, extensive perineural invasion is found. What is the most likely diagnosis?

CORRECT ANSWER: c. Squamous cell carcinoma

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer, and its incidence is increasing yearly in the United States (Que et al., 2018). Risk factors for cSCC include UV exposure, fair skin, age, and immunosuppression. Solid organ transplant recipients (SOTRs) have a 65-fold to 250-fold increased incidence of cSCC over the general population, and tumors in the SOTR population behave more aggressively (Collins et al., 2019). Although skin cancer is less common in patients with skin of color, this population is also at risk (Agbai et al., 2014). cSCC typically presents as an erythematous scaly papule, plaque, or nonhealing ulcer on sun-exposed areas such as the head and neck, dorsal arms, and hands (Gurudutt and Genden, 2011). However, cSCC is also seen in sun-protected areas and sites of chronic inflammation (Agbai et al., 2014).

As in the case shown, perineural invasion (PNI) can be observed in cSCC, with an overall incidence reported between 2% and 14%, and is a known risk factor for disease progression (Haug et al., 2020; Que et al., 2018). Staging systems commonly used to predict the risk of disease progression in cSCC such as local recurrence and metastasis include the American Joint Committee on Cancer, 8th edition (AJCC 8) staging system, the staging system used by Breuninger et al. (2012), and the Brigham and Women’s Hospital staging system (Roscher et al., 2018).

Discussion of incorrect answers:

a. Microcystic adnexal carcinoma: Microcystic adnexal carcinoma (MAC) is a rare cutaneous adnexal neoplasm that typically presents on the head and neck, particularly the centrofacial area including the upper and lower lips, as a slow-growing smooth indurated nodule, plaque, or cyst-like tumor (Gordon et al., 2017). MAC shares histopathologic features of infiltrative basal cell carcinoma (BCC), syringoma, and desmoplastic trichoepithelioma. Notably, misdiagnosis following initial biopsy has been reported in 27% to 69% of cases (Chiller et al., 2000; Snow et al., 2001). MAC has a low risk for metastasis but is a locally aggressive tumor. Although slow growing, MAC invades deep tissue early in its course, and PNI is frequently present (Gordon et al., 2017).

b. Basal cell carcinoma: BCC is the most common skin cancer, with more than 3.3 million cases in the United States annually. Unlike the lesion shown, BCC most commonly presents as a pink pearly papule or plaque with small arborizing telangiectasias. Intermittent bleeding, crusting, and progression to ulceration with a rolled border is often noted (Marzuka and Book, 2015). Although BCC may cause significant local destruction if left untreated, metastasis is rare (Work Group et al., 2018). PNI can be seen in BCC and is a marker for aggressive behavior (Marzuka and Book, 2015).

c. Atypical fibroxanthoma: Atypical fibroxanthoma (AFX) is an uncommon low-grade sarcoma. Similar to the case shown, AFX typically presents on the sun-exposed skin of older adults. These lesions are often rapidly growing red-pink papules with a propensity to ulcerate and bleed. PNI is not typical of AFX and would suggest a diagnosis of pleomorphic dermal sarcoma, which exists along a clinicopathologic spectrum with AFX (Soleymani et al., 2019).

d. Verruca vulgaris: The common wart or verruca vulgaris is a benign epidermal proliferation secondary to human papillomavirus infection that can appear anywhere on the skin and may mimic cSCC (Ockenfels, 2016).

2. Haug et al. (2020) found perineural invasion to be most strongly associated with which of the following clinical or histologic findings?

CORRECT ANSWER: b. Desmoplastic growth

Haug et al. (2020) found that PNI was most frequently observed in patients with desmoplastic squamous cell carcinoma (dSCC). Of the 145 patients with dSCC, 21 (14.5%) exhibited PNI. Although many of the histologic and clinical findings listed in the answers were associated with PNI, the strongest association was observed with desmoplasia. Notably, PNI-positive tumors in that series were also exclusively found on the head and neck (Haug et al., 2020). The association between the grade of tumor differentiation and PNI remains unclear in the literature (Harris et al., 2017; Schmults et al., 2013).

Discussion of incorrect answers:

a. Increased tumor thickness: In their study, Haug et al. (2020) found that mean tumor thickness was significantly larger in PNI-positive dSCCs (8.8 mm,
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In their prospective study, Haug et al. (2020) examine risk factors related to prognosis for cSCC. Their study included 1,399 primary cSCCs diagnosed from 2005 to 2015. Those tumors were analyzed for the presence of PNI. PNI was detected more frequently in patients with in-transit metastases, local recurrence, lymph node—positive disease, and distant disease (Haug et al., 2020). Haug et al. (2020) performed multivariate analyses to study risk factors related to disease progression and identified the following as significant markers of local recurrence and distant disease: (i) tumor horizontal size ≥ 20 mm, (ii) tumor thickness ≥ 6 mm, (iii) desmoplastic growth, (iv) perineural invasion, and (v) immunosuppression (Haug et al., 2020).

**Discussion of incorrect answers:**

a. **De-differentiation:** Haug et al. (2020) note that the relationship between de-differentiation and PNI is poorly elucidated in the literature (Breuninger et al., 2019). In their study, Haug et al. (2020) examined de-differentiation by labeling cases with non-presence of desmoplasia. They found that poor prognosis was not related to de-differentiation, a finding replicated by others (Brantsch et al., 2008; Breuninger et al., 1997).

b. **Tumor horizontal size ≥ 10 mm:** Tumor horizontal size ≥ 20 mm, not ≥ 10 mm, is considered a risk factor for poor prognosis. In their multivariate Cox proportional hazards regression model, Haug et al. (2020) found a significant difference in progression-free survival for tumors ≥ 20 mm (hazard ratio, 1.76; \( P = 0.0053 \)) compared with tumors <20 mm.

c. **Tumor thickness ≥ 8 mm:** In their study, Haug et al. (2020) measured tumor thickness from the uppermost cell (including ulceration) to the deepest level of invasion. Progression-free survival was significantly lower in patients with tumor thickness ≥ 6 mm (68%) than patients with tumor thickness < 6 mm (90%, log-rank \( P < 0.0001 \)) (Haug et al., 2020).

d. **Caliber of involved nerve ≤ 0.1 mm:** In their study, Haug et al. (2020) did not calculate differences in prognosis based on nerve caliber. Their study included 21 dSCCs with PNI. Of those 21 tumors, all nerves were located in the dermis or deeper. In 20 of the 21 tumors, nerves with invasive disease were measured to have calibers > 0.1 mm, with just one nerve measuring <0.1 mm (Haug et al., 2020). Current literature does not associate poor prognosis with tumors demonstrating PNI with nerve caliber <0.1 mm (Karia et al., 2018, 2017; Que et al., 2018; Ruiz et al., 2019).

**REFERENCES**


