Cells to Surgery Quiz: February 2022
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WHAT IS YOUR DIAGNOSIS?

Figure 1. Image courtesy of Rajiv I. Nijhawan, Department of Dermatology, University of Texas Southwestern Medical Center.

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 Seviiri et al. (2021) (https://doi.org/10.1016/j.jid.2021.03.034).

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

QUIZ QUESTIONS

1. A male aged 72 years has a history of bilateral lung transplantation in the previous 5 years. The patient has a history of voriconazole exposure as well. What is your diagnosis?
   a. Keratoacanthoma
   b. Actinic keratosis
   c. Seborrheic keratosis
   d. Well-differentiated squamous cell carcinoma (SCC)
   e. Verruca vulgaris
2. On the basis of the article by Seviiri et al. (2021), which of the following is true?
   a. Risk stratification using polygenic risk scores (PRSs) from the general population for developing basal cell carcinoma (BCC) or SCC in low UVR environments cannot be generalized to solid organ transplant recipients (SOTRs).
   b. PRSs improve the prediction of BCC and SCC risk in SOTRs in a high UV environment over established skin cancer risk factors.
   c. PRSs did not alter the classification of risk for BCC or SCC (high/medium/low groups) of SOTRs.
   d. SOTRs with a high genetic risk as established by PRS are equally at risk for developing SCC and BCC as SOTRs with low genetic risk.
   e. Risk stratification benefits are only observed in the short term after solid organ transplantation.

3. What findings regarding tumor burden or multiplicity of keratinocyte cancers did the authors suggest?
   a. In areas of low UVR, tumor burden is higher.
   b. Age has no effect on tumor burden.
   c. PRSs improve the predictive accuracy for tumor multiplicity.
   d. Chronic immunosuppression does not contribute to tumor burden.
   e. Predictive risk for tumor multiplicity determined by PRSs does not have clinical utility.

See following pages for detailed answers.
Squamous cell carcinoma (SCC) is the most frequently diagnosed malignancy in patients who have received solid organ transplants (Rashtak et al., 2015). It commonly presents on the head or neck and may present as an erythematous or flesh-toned lesion with scaling or crusting (Howell and Ramsey, 2021). Furthermore, voriconazole use is associated with an increased risk of SCC among lung transplant recipients after controlling for immunosuppression (Hamandi et al., 2018). Voriconazole is an antifungal medication commonly prescribed as prophylaxis to prevent invasive aspergillosis in lung transplant patients. Voriconazole and its metabolites may increase susceptibility to UV-induced DNA damage or disrupt DNA repair mechanisms (Williams et al., 2014), increasing the risk of cutaneous malignancy in lung transplant recipients.

**Discussion of incorrect answers:**

a. **Keratoacanthoma:** Keratoacanthoma typically presents as a dome-shaped 1–2 cm lesion that has a central keratin plug. It has a period of initial rapid growth and then stabilizes or may spontaneously regress (Zito and Scharf, 2021). Etiologies include UV, immunosuppression, carcinogen exposure, genetic mutations, and recent surgery or trauma to the area. To differentiate between keratoacanthoma and SCC, an excisional biopsy can be the best diagnostic test (Zito and Scharf, 2021). Whereas keratoacanthomas can be reactive in nature and even potentially self-resolve, lesions that persist may behave more as an SCC and require surgical intervention (Work Group et al., 2018). Of note, many dermatopathologists do not distinguish between a keratoacanthoma and a well-differentiated SCC histologically despite their distinct clinical appearance, possible reactive nature, and propensity to regress.

b. **Actinic keratosis:** Actinic keratosis is a precursor lesion to SCC that develops in areas of high-sun exposure and may present with pruritus, bleeding with minor trauma, and pain (Marques and Chen, 2021). On examination of the skin, erythematous, scaly papules, or plaques can be seen. Age, male sex, immunosuppression, and chronic sun exposure increase the risk of developing actinic keratoses (Marques and Chen, 2021). On average, there is an 8% risk of actinic keratoses progressing into a malignant process in immunocompetent patients, making early detection and treatment important (Hashim et al., 2019). Treatment includes lesion-directed therapies such as surgery and cryotherapy and field-directed therapy such as topical medications and light-based therapies (Marques and Chen, 2021).

c. **Seborrheic keratosis:** Seborrheic keratosis is a benign and slow-growing epidermal skin tumor that is more commonly observed in older adults (Greco and Bhutta, 2021). They result from a proliferation of immature keratinocytes (KCs) and appear to be well-demarcated papules or plaques that are round or oval in shape, with a characteristic stuck-on appearance. They more commonly present as light to dark brown but may also appear yellow or gray in color (Greco and Bhutta, 2021). Rapid growth or onset of these lesions may indicate internal malignancy and warrant further evaluation. Treatment is not necessary for these benign lesions but includes cryotherapy (Greco and Bhutta, 2021).

e. **Verruca vulgaris:** Verruca vulgaris or the common wart is typically due to human papillomavirus, which infects the epithelial layer of the skin (Luria and Cardoza-Favarato, 2021). Common warts can appear anywhere but are often on the extremities and are generally not painful. They have an irregular appearance, ranging from 1 mm to several centimeters in size (Al Aboud and Nigam, 2021). Treatment of cutaneous warts includes cryotherapy, surgical removal, and immunomodulant medications (Luria and Cardoza-Favarato, 2021).

2. **On the basis of the article by Seviiri et al. (2021), which of the following is true?**

CORRECT ANSWER: b. PRSs improve the prediction of BCC and SCC risk in SOTRs in a high UV environment over established skin cancer risk factors.

The risk of developing SCC or basal cell carcinoma (BCC) is increased in individuals who have received solid organ transplants, particularly in environments with high exposure to UVR (Seviiri et al., 2021a). GWASs have shown the associations between genetic variants or SNPs and the development of KC cancers. These SNPs likely reside in KC response elements (Chahal et al., 2016). To generate polygenic risk scores (PRSs), a large number of genetic markers were obtained from patients with liver, lung, and kidney transplants. Of the high genetic risk population, about half of solid organ transplant recipients (SOTRs) developed BCC and SCC (Seviiri et al., 2021a).
et al., 2021a). The study showed that PRSs improved risk predictions by 2% for BCC and SCC over traditional risk factors such as age, sex, and skin pigmentation. PRSs altered the risk category of 19.03% and 18.10% of SOTRs with BCC and SCC, respectively (Seviiri et al., 2021a). Because PRS can further provide risk stratification, screening and prevention strategies may be modified according to classified risk.

Discussion of incorrect answers:

a. **Risk stratification using polygenic risk scores (PRSs) from the general population for developing basal cell carcinoma (BCC) or SCC in low UVR environments cannot be generalized to solid organ transplant recipients (SOTRs):** In a low UVR environment, PRSs from the general population can effectively stratify the risk for developing KC cancers in organ transplant recipients (Seviiri et al., 2021b). Findings showed that the highest genetic risk group as determined by PRS had an increased risk of BCC compared with the general population (those who have not received an organ transplant). Those in the lowest genetic risk group showed a similar risk of BCC to that shown by the general population (Seviiri et al., 2021b). PRSs, as derived from GWASs for the development of nonmelanoma skin cancer in non-transplant recipients, have shown to predict the risk of these cancers in a group of patients with either heart, lung, or liver transplants (Stapleton et al., 2020).

c. **PRSs did not alter the classification of risk for BCC or SCC (high/medium/low groups) of SOTRs:** PRSs derived from genetic information reclassified the risk of KC carcinoma. Of the SOTRs, 19.03% were stratified into a different group for developing BCC and 18.10% for SCC (Seviiri et al., 2021a). Of SOTRs, 9.67% were reclassified into a higher risk group, whereas 9.37% were reclassified into a lower risk group (Seviiri et al., 2021a). On the basis of the assigned risk group, clinical decision making may change for proper detection, screening, and prevention.

d. **SOTRs with a high genetic risk as established by PRS are equally at risk for developing SCC and BCC as SOTRs with low genetic risk:** Organ transplant recipients with a high genetic risk are at higher risk for developing SCC and BCC than SOTRs with low genetic risk, consistent with other study findings as well (Seviiri et al., 2021b; Stapleton et al., 2019). SOTRs with a high genetic risk had a 3.2-fold increased risk for SCC and a 3.5-fold increased risk for BCC in a high-UVR environment compared with SOTRs with low genetic risk (Seviiri et al., 2021a). About half the SOTRs in the top PRS quintile developed BCC or SCC during the follow-up period (Seviiri et al., 2021a).

e. **Risk stratification benefits are only observed in the short term after solid organ transplantation:** Risk stratification benefits of KC cancers are observed in the long term as well as after organ transplantation and can alter clinical management by developing proper screening and prevention of patients at an increased risk (Seviiri et al., 2021a). The mean duration of follow-up in this study was 9.61 years after solid organ transplantation, so patients had been chronically immunosuppressed. PRSs still provided further risk stratification of SCC and BCC in this time period over other risk factors (Seviiri et al., 2021a).

3. What findings regarding tumor burden or multiplicity of keratinocyte cancers did the authors suggest?

**CORRECT ANSWER: c. PRSs improve the predictive accuracy for tumor multiplicity**

Tumor burden or multiplicity refers to the number of discrete events of skin cancer in an individual that occur during a specific time period (Pandeya et al., 2017). Multiplicity can be influenced by factors such as age, sex, and previous skin cancer history (Pandeya et al., 2017). Multiplicity rates tend to be higher in areas with high UVR. PRSs improve the predictive accuracy for tumor multiplicity of KC cancers compared with traditional risk factors such as age, sex, skin pigmentation, and red hair (BCC R2 = 0.21 vs. 0.19, P = 3.2 × 10^-3; SCC R2 = 0.30 vs. 0.27, P = 4.6 × 10^-4) (Seviiri et al., 2021a). With improved predictive accuracy, preventative interventions can be developed for optimal disease management.

Discussion of incorrect answers:

a. **In areas of low UVR, tumor burden is higher:** As cited in Seviiri et al. (2021), the multiplicity of BCC and SCC is increased in areas of high UVR, such as in Australia, where individuals tend to have fair skin pigmentation as well (Pandeya et al., 2017; Way et al., 2020). The incidence of KC cancers is also increased in this region. Of the patients that had an excision performed for BCC or SCC, 74% had two or more lesions removed (Pandeya et al., 2017).

b. **Age has no effect on tumor burden:** Age is strongly correlated with the multiplicity of KC cancers (Pandeya et al., 2017). In male patients aged >70 years, over half had multiple excisions removed (Pandeya et al., 2017). Increased incidence of SCC and BCC was observed with increasing age, with 80% of the individuals in the study having their first
skin cancer event at age ≥55 years (Pandeya et al., 2017).

d. **Chronic immunosuppression does not contribute to tumor burden:** SOTRs with chronic immunosuppression are at greater risk for developing SCC and BCC, especially in high UVR environments (Seviiri et al., 2021a). Duration of immunosuppression is a risk factor for KC cancer (Mudigonda et al., 2013). It has been shown that 1 year after transplantation in lung transplant recipients, the incidence of multiple discrete skin cancer events is high (Way et al., 2020). Of lung transplant recipients who were taking immunosuppressive drugs for a median of 3.3 years, 23% developed SCC, and 24% developed BCC during the follow-up period of 1.7 years (Way et al., 2020).

e. **Predictive risk for tumor multiplicity determined by PRSs does not have clinical utility:** PRSs improve the predictive accuracy for tumor burden (Seviiri et al., 2021a). By utilizing PRSs for the prediction of tumor burden, clinical guidelines regarding screening, prevention, and intervention of KC cancers can be targeted to reduce the burden of these cancers in the SOTRs with chronic immunosuppression (Seviiri et al., 2021a).

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**REFERENCES**


