Cells to Surgery Quiz: October 2021

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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. Image published with patient’s consent.

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 Villani et al., 2021 (https://doi.org/10.1016/j.jid.2021.02.760).

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

**QUIZ QUESTIONS**

1. A female aged 67 years with a history of chronic hepatitis C, hypertension, and congenital renal cysts presented with a lesion on her right superior medial chest that has been scabbing and bleeding for a year now. What is your diagnosis?
   a. Squamous cell carcinoma
   b. Cutaneous angiosarcoma
   c. Burn scar
   d. Basal cell carcinoma (BCC)
   e. Dermatofibrosarcoma protuberans

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

   a. The authors identified a somatic mutation signature characteristic of the infiltrative subtype of BCC.
   b. *POSTN* and *WISP-1* are independently crucial to the development of BCC.
   c. The development of infiltrative BCC may be due to a progression from other subtypes through Wnt and integrin signaling, skewing extracellular interactions and enabling an infiltrative subtype to develop.
   d. Wnt signaling is downregulated during BCC development.
   e. Nodular and superficial BCCs are associated with a high risk of local recurrence, whereas infiltrative subtypes are not.

3. **Why did the authors suggest that *POSTN* and *WISP-1* were associated with the infiltrative subtype of BCC?**

   a. The *WISP1* gene product reduces Wnt-1 signaling, which is a crucial tumor-suppressor gene. Loss of this tumor-suppressor function leads to classification as an infiltrative subtype of BCC.
   b. *POSTN* signaling mediates Wnt ligand retention in the extracellular matrix, whereas increased *WISP-1* expression interacts with p53 responses and links Wnt signaling to promote the extracellular environment for the progression to an infiltrative BCC subtype.
   c. *POSTN* signaling is associated with Wnt downregulation, promoting invasion and cancer stem cell proliferation.
   d. *POSTN* and *WISP-1* were not associated with the infiltrative subtype of BCC.
   e. *POSTN* and *WISP-1* are only expressed when the infiltrative subtype is dominant.

See following pages for detailed answers
DETAILED ANSWERS

1. A female aged 67 years with a history of chronic hepatitis C, hypertension, and congenital renal cysts presented with a lesion on her right superior medial chest that has been scabbing and bleeding for a year now. What is your diagnosis?

CORRECT ANSWER: d. Basal cell carcinoma (BCC).

BCCs are the most frequent malignancy in humans and represent a major cost to our healthcare system (Fransen et al., 2012). In populations exposed to high levels of UVR, incidence rates of BCC are extremely high, reaching 2,448 per 100,000 in 2011, far ahead of the rates in many other malignancies (Apalla et al., 2017).

Superficial BCCs are predominantly located on the trunk and present as slightly scaly, nonfirm macules, patches, or thin plaques that are light red to pink in color. The center of the lesion may exhibit an atrophic appearance and may be rimmed with translucent papules (Marzuka and Book, 2015). Nodular BCCs typically present as a pink or pearly papule, often with a telangiectatic vessel frequently seen within it (Marzuka and Book, 2015). The infiltrative subtype typically appears as an ill-defined, smooth, flesh-colored/light pink papule or plaque that is frequently atrophic and can also be indurated. These lesions are notorious for their subtlety (Marzuka and Book, 2015). Of note, many BCCs have mixed histology (Sexton et al., 1990).

In this case, the lesion proved to be a nodular and infiltrative BCC that required two stages of Mohs surgery. The atrophic central aspect and ill-defined borders of the lesion are characteristic of the infiltrative subtype of BCC.

Discussion of incorrect answers:

a. Squamous cell carcinoma: Cutaneous squamous cell carcinoma (SCC) usually presents as an eryhematous papule, nodule, or plaque with scale, crust, or ulceration that is common on the head or neck (Howell and Ramsey, 2021). Cutaneous SCC is the second most common nonmelanoma skin cancer (NMSC) and the most common skin cancer in immunosuppressed patients (Bottomley et al., 2019). BCC and SCC are the two most common types of NMSC, and both can ulcerate and crust as this patient had reported. A biopsy is necessary to confirm the diagnosis.

b. Cutaneous Angiosarcoma: Cutaneous angiosarcoma is a rare mesenchymal malignancy that accounts for <1% of all sarcomas (Conic et al., 2020). The majority of instances occur spontaneously in areas of sun exposure, past radiation therapy, or lymphedema (Conic et al., 2020). It is most commonly found on the head or neck of elderly males and traditionally manifests as an enlarging red, blue, or purple plaque, patch, or nodule on the face or scalp, which may have ulceration and nondistinct margins (Conic et al., 2020). In this patient’s case, the lesion was not as vascular appearing as one would see in angiosarcoma.

c. Burn scar: Cutaneous scarring remains the pathognomonic feature after burns to the skin (Finnerty et al., 2016). The most common form of scar after a burn is the hypertrophic scar, the prevalence of which has been reported as high as 70% (Bombaro et al., 2003). After cutaneous injury, deposition of excess collagen results in a pathologic scar that is thick, nonpliable, itchy, and painful (Tredget et al., 2014). Scars can also appear atrophic, and burn scars also risk the development of skin cancer within them (Wallingford et al., 2011). This patient denied any known trauma or burn to the area.

d. Dermatofibrosarcoma Protuberans: Dermatofibrosarcoma protuberans (DFSP) is a low-grade, slow-growing cutaneous mesenchymal tumor with irregular borders and finger-like extensions into surrounding and deep tissues (Verma et al., 2020). DFSP often presents as an indurated plaque or nodule with minimal symptoms (Asilian et al., 2020). This tumor, as the most prevalent cutaneous sarcoma, accounts for 2% of all sarcomas, with an incidence of 0.8–4.2 cases per million persons annually (Lemm et al., 2003). After cutaneous injury, deposition of excess collagen results in a pathologic scar that is thick, nonpliable, itchy, and painful (Tredget et al., 2014). Scars can also appear atrophic, and burn scars also risk the development of skin cancer within them (Wallingford et al., 2011). This patient denied any known trauma or burn to the area.

e. Squamous cell carcinoma: Cutaneous squamous cell carcinoma (SCC) usually presents as an eryhematous papule, nodule, or plaque with scale, crust, or ulceration that is common on the head or neck (Howell and Ramsey, 2021). Cutaneous SCC is the second most common nonmelanoma skin cancer (NMSC) and the most common skin cancer in immunosuppressed patients (Bottomley et al., 2019). BCC and SCC are the two most common types of NMSC, and both can ulcerate and crust as this patient had reported. A biopsy is necessary to confirm the diagnosis.

2. On the basis of the article by Villani et al., 2021, which of the following is true?

CORRECT ANSWER: c. The development of infiltrative BCC may be due to a progression from other subtypes through Wnt and integrin signaling, skewing extracellular interactions and enabling an infiltrative subtype to develop.

Immunostaining for POSTN and WISP-1 clearly distinguished infiltrative BCCs from other subtypes. BCCs with mixed morphology displayed increased WISP-1 expression in infiltrative areas, whereas nodular areas did not, supporting a continuum between subtypes (Villani et al., 2021). Villani et al., 2021 showed through RNA sequencing that POSTN and WISP-1 help in the development of infiltrative BCC by creating a Wnt signal–active, tumor-supportive extracellular environment (Villani et al., 2021). Gradual changes in
**POSTN** and **WISP-1** expression from nodular to infiltrative BCC suggest that the tumor environment encourages a progression from other subtypes through Wnt and integrin signaling to the infiltrative phenotype. Therefore, **POSTN** and **WISP-1** may be indicative biomarkers to identify this progression (Villani et al., 2021).

**Discussion of incorrect answers:**

a. The authors identified a somatic mutation signature characteristic of the infiltrative subtype of BCC: There are commonly reported somatic mutations present in BCC. However, using whole-exome sequencing of 36 BCC samples combined with previously reported exome data, Villani et al., 2021 determined that infiltrative BCCs do not contain a distinct somatic variant profile. Infiltrative BCCs instead carry nonspecific UV-induced mutational signatures (Bonilla et al., 2016; Villani et al., 2021).

b. **POSTN** and **WISP-1** are independently crucial to the development of BCC: Although **POSTN** and **WISP-1** are both synergistic in the development of infiltrative BCC, they do not work independently to produce BCC. **POSTN** and **WISP-1** create an extracellular environment that promotes the progression toward a specific phenotype of BCC. Of note, infiltrative areas of mixed BCCs expressed **WISP-1**, whereas nodular areas did not, further supporting the idea that **WISP-1** is not independently crucial to the development of BCC (Villani et al., 2021).

d. Wnt signaling is downregulated during BCC development: Wnt signaling pathway plays a critical role in patterning and cell proliferation of embryonic and adult tissues. Activation of the Wnt pathway has been observed in BCCs as shown by overexpression of Wnt proteins in human BCC tumors (Noubissi et al., 2018). Wnt–β-catenin signaling is known to promote cell growth, morphogenesis, and stem cell maintenance. Therefore, BCC would develop as a result of the upregulation of Wnt signaling, not downregulation (Noubissi et al., 2018).

e. Nodular and superficial BCCs are associated with a high risk of local recurrence, whereas infiltrative subtypes are not. Nodular and superficial BCCs are associated with a low risk of local recurrence, whereas infiltrative subtypes have a higher risk for local recurrence (Armstrong et al., 2017; Saldanha et al., 2003).

3. Why did the authors suggest that **POSTN** and **WISP-1** were associated with the infiltrative subtype of BCC?

**CORRECT ANSWER:** b. **POSTN** signaling mediates Wnt ligand retention in the extracellular matrix, whereas increased WISP-1 expression interacts with p53 responses and links Wnt signaling to promote the extracellular environment for the progression to an infiltrative BCC subtype.

**POSTN** is considered a biomarker of poor prognosis in multiple tumor types (González-González and Alonso, 2018). **POSTN** signaling is known to support infiltrative tumor development by mediating Wnt ligand retention in the extracellular matrix (ECM), thereby promoting invasion and cancer stem cell proliferation (Malanchi et al., 2011; Villani et al., 2021). Increased **WISP-1** expression has been shown to link Wnt signaling to ECM promotion of tumor severity in breast cancer and colon cancer (Chiang et al., 2015; Wu et al., 2016). **WISP-1** is also linked to the p53 response to the extracellular environment interactions (Procopio et al., 2015; Sun et al., 2004). Immunostaining for **POSTN** and **WISP-1** clearly distinguished infiltrative BCCs from other subtypes. BCCs with mixed morphology displayed increased **WISP-1** expression in infiltrative areas (Villani et al., 2021).

**Discussion of incorrect answers:**

a. The **WISP1** gene product reduces Wnt-1 signaling, which is a crucial tumor suppressor. Loss of this tumor-suppressor function leads to classification as an infiltrative subtype of BCC. **WISP-1** is implicated in very similar processes to **POSTN**, with increased expression linking Wnt signaling to ECM promotion of tumor severity in breast cancer and colon cancer (Chiang et al., 2015; Wu et al., 2016). In addition, aberrant Wnt signaling is associated with oncogenic properties, thereby promoting tumor development when activated. Deactivation of Wnt signaling would lead to decreased growth (Zhan et al., 2017).

c. **POSTN** signaling is associated with Wnt downregulation, promoting invasion and cancer stem cell proliferation: **POSTN** is a well-known stromal mediator of malignancy and is considered a biomarker of poor prognosis in multiple tumor types (González-González and Alonso, 2018). **POSTN** signaling is known to mediate infiltrative tumor development by mediating Wnt ligand retention and thus promotion of signaling in the ECM, thereby promoting invasion and cancer stem cell proliferation (Malanchi et al., 2011).

d. **POSTN** and **WISP-1** were not associated with the infiltrative subtype of BCC: Immunostaining for **POSTN** and **WISP-1** clearly distinguished infiltrative BCCs from other subtypes. BCCs with mixed morphology displayed increased **WISP-1** expression in infiltrative areas (Villani et al., 2021). **POSTN** and **WISP-1** create a Wnt signal–active, tumor-supportive extracellular environment that promotes the progression toward an infiltrative BCC phenotype (Villani et al., 2021).
e. **POSTN and WISP-1 are only expressed when the infiltrative subtype is dominant**: The study by Villani et al., 2021 suggests that the mechanism of infiltrative BCC subspecification may not be due to a specific underlying causal mutation but instead may be due to a progression from other subtypes through Wnt and integrin signaling, skewing extracellular interactions and enabling an infiltrative phenotype to develop. POSTN and WISP-1 may be indicative biomarkers to identify such progression even in samples when the infiltrative subtype is not dominant (Villani et al., 2021).

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**REFERENCES**

Apalla Z, Lallas A, Sotiriou E, Lazaridou E, Ioannides D. Epidemiological trends in skin cancer. Dermatol Pract Concept 2017;7:1–6.

Armstrong LTD, Magnusson MR, Guppy MPB. Risk factors for recurrence of facial basal cell carcinoma after surgical excision: a follow-up analysis. J Plast Reconstr Aesthet Surg 2017;70:1738–45.

Asilian A, Honarjou N, Faghihi G, Saber M, Mousafarpoor S, Haiezi H. An experience of slow-Moehls micrographic surgery for the treatment of dermatofibrosarcoma protuberans: a long-term cohort study. J Cosmet Dermatol 2020;19:2701–5.

Bombaro KM, Engrav LH, Carrougher GJ, Wiechman SA, Faucher L, Costa BA, et al. What is the prevalence of hypertrophic scarring following burns? Burns 2003;29:299–302.

Bonilla X, Bezrukov F, Kaya G, Zoete V, et al. Genomic analysis identifies new drivers and progression pathways in skin basal cell carcinoma. Nat Genet 2016;48:398–406.

Bottomley MJ, Thomson J, Harwood C, Leigh I. The role of the immune system in cutaneous squamous cell carcinoma. Int J Mol Sci 2019;20:2009.

Chiang KC, Yeh CN, Chung LC, Feng TH, Sun CC, Chen MF, et al. WNT-1 inducible signaling protein-1 enhances growth and tumorigenesis in human breast cancer. Sci Rep 2015;5:8686.

Conic RRZ, Damiani G, Frigerio A, Tsai S, Bragazzi NL, Chu TW, et al. Incidence and outcomes of cutaneous angiosarcoma: a SEER population-based study. J Am Acad Dermatol 2020;83:809–16.

Finney CC, Jeschke MG, Branski LK, Barret JP, Dziewalski P, Herndon DN. Hypertrophic scarring: the greatest unmet challenge after burn injury. Lancet 2016;386:1427–36.

Fransen M, Karahalios A, Sharma N, English DR, Giles GG, Sinclair RD. Nonmelanoma skin cancer in Australia. Med J Aust 2012;197:565–8.

González-González L, Alonso J. Peristin: a matricellular protein with multiple functions in cancer development and progression. Front Oncol 2018;8:225.

Howell JY, Ramsey ML. Squamous cell skin cancer. In: StatPearls [internet]. Treasure Island, FL: StatPearls Publishing; 2021.

Lemm D, Mügge LO, Mentzel T, Hölken K. Current treatment options in dermatofibrosarcoma protuberans. J Cancer Res Clin Oncol 2009;135:653–65.

Malanchi I, Santamaria-Martínez A, Susanto E, Peng H, Lehr HA, Delaloye JF, et al. Interactions between cancer stem cells and their niche govern metastatic colonization. Nature 2011;481:85–9.

Marzuka AG, Book SE. Basal cell carcinoma: pathogenesis, epidemiology, clinical features, diagnosis, histopathology, and management. Yale J Biol Med 2015;88:167–79.

Noubissi FK, Yedjou CG, Spiegelman VS, Tchounwou PB. Cross-talk between Wnt and Hh signaling pathways in the pathology of basal cell carcinoma. Int J Environ Res Public Health 2018;15:1442.

Procopio MG, Laszlo C, Al Labban D, Kim DE, Bordignon P, Jo SH, et al. Combined CSL and p53 downregulation promotes cancer-associated fibroblast activation [published correction appears in Nat Cell Biol 2015;17:1070]. Nat Cell Biol 2015;17:1193–204.

Saldanha G, Fletcher A, Slater DN. Basal cell carcinoma: a dermatological and molecular biological update. Br J Dermatol 2003;148:195–202.

Sexton M, Jones DB, Maloney ME. Histologic pattern analysis of basal cell carcinoma. Study of a series of 1039 consecutive neoplasms. J Am Acad Dermatol 1990;23:1118–26.

Sun Y, Zeng XR, Wengler L, Firestein GS, Cheung HS. P53 down-regulates matrix metalloproteinase-1 by targeting the communications between AP-1 and the basal transcription complex. J Cell Biochem 2004;92:258–69.

Tredget EE, Levi B, Donelan MB. Biology and principles of scar management and burn reconstruction. Surg Clin North Am 2014;94:793–815.

Verma H, Sehgal K, Panchal KB, Chakraborty S, Biswas B, Mukherjee G, et al. Presentation and management of dermatofibrosarcoma protuberans: a single center protocol. Indian J Surg Oncol 2020;11:35–40.

Villani R, Murigneux V, Alexis J, Sim SL, Wagels M, Saunders N, et al. Subtype-specific analyses reveal infiltrative basal cell carcinomas are highly interactive with their environment [e-pub ahead of print]. J Invest Dermatol 2021. https://doi.org/10.1016/j.jid.2021.02.2760 (accessed July 7, 2021).

Wallington SC, Olsen CM, Plasmeijer E, Green AC. Skin cancer arising in scars: a systematic review. Dermatol Surg 2011;37:1239–44.

Wu J, Long Z, Cai H, Du C, Liu X, Yu S, et al. High expression of WISP1 in colon cancer is associated with apoptosis, invasion and poor prognosis. Oncotarget 2016;7:49834–47.

Zhan T, Rindtorff N, Boutros M. Wnt signaling in cancer. Oncogene 2017;36:1461–73.