Cells to Surgery Quiz: December 2018


**WHAT IS YOUR DIAGNOSIS?**

![Image credit: Reprinted from www.pcds.org.uk, 2018 with permission from The Primary Care Dermatology Society.](image)

**Figure 1.** Image credit: Reprinted from www.pcds.org.uk, 2018 with permission from The Primary Care Dermatology Society.

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 above, while additional questions concern the findings reported in a JID article by Kuonen et al (https://doi.org/10.1016/j.jid.2018.01.040).

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

**QUIZ QUESTIONS**

1. What is your diagnosis?
   a. Dermatitis
   b. Desmoplastic trichoepithelioma
   c. Morpheaform Basal Cell Carcinoma (BCC)
   d. Lichenoid benign keratosis
   e. Cutaneous T-cell lymphoma (mycosis fungoides)

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2. **Which of the following statements is false regarding the staging or treatment of cutaneous BCC?**
   a. Perineural involvement in BCC is associated with basosquamous, infiltrating and morpheaform subtypes.
   b. Patients who have received organ transplants are more likely to have the morpheaform histologic subtype of BCC.
   c. Vismodegib, a first-in-class Hedgehog pathway inhibitor, is another option for treating advanced BCC.
   d. Mohs micrographic surgery (MMS) is the most effective treatment for high-risk BCC.
   e. Risk features for BCC staging are based on size, anatomic location, depth, perineural invasion, and histological differentiation.

3. **Kuonen et al. investigated the role of TGFβ-induced fibronectin in promoting tumor cell motility through integrin α5β1-mediated FAK phosphorylation in in-vivo models of infiltrative BCC.** All of the following are consistent with their findings, except:
   a. TGFβ is associated with peritumoral fibronectin deposition and the transition from the nodular to infiltrative phenotype in human BCC.
   b. Integrin α5β1 mediates increased BCC adhesion and migration on fibronectin.
   c. FAK mediates fibronectin-induced migration in vitro model of BCC.
   d. Phospho-FAK inhibitor prevents fibronectin-induced migration in vitro.
   e. Fibronectin adhesion to integrin α5β1 induces FAK dephosphorylation.

See following pages for detailed answers.
Basal cell carcinoma (BCC) is the most common cutaneous malignancy. Although both the likelihood and rate of metastasis are low, the associated morbidity and recurrence rates of BCC are high (Mackiewicz-Wysocka M. et al., 2013). The main clinical subtypes of BCC include nodular, superficial, and morpheaform. (Rajabi-Estarabadi et al., 2017) Morpheaform or morpheioid, BCC accounts for around 5-10% of all BCC cases (Marzuka and Book, 2015). It typically presents as an indented, scariform skin-colored plaque, and is sometimes confused for scar tissue. The lesion can be identified as a morpheaform BCC due to its smooth and waxy, yellow-white appearance with ill-defined borders (Cunliffe, 2011). It also appears slightly depressed, and is located on the central face (specifically the cheek), which is a characteristic location for morpheaform BCC (Cunliffe, 2011, Mackiewicz-Wysocka M. et al., 2013). Dermoscopic features of morpheaform BCC include irregular vascular patterns, such as arborizing vessels or telangiectasias, translucency, and blue-gray ovoid nests (Emiroglu et al., 2015). Histopathologically, morpheaform BCC is characterized by “narrow strands and nests of basaloid cells with dense sclerotic stroma” (East et al., 2016). (third choice)

Discussion of incorrect answers:

a. Contact Dermatitis (CD) is a common inflammatory cutaneous reaction cause by an irritant or allergen (Rashid and Shim, 2016, Tan et al., 2014). Classic clinical features of contact dermatitis in the acute phase include pruritus, erythema, dryness, and scaling, along with the development of vesicles and bullae, while chronic disease can present with lichenification and fissuring (Tan et al., 2014). Histological findings often reveal cellular necrosis and recruitment of a polymorph inflammatory infiltrate. Clinical identification is usually straightforward as it often relies on patient history and exposure to offending agents. Lesions are usually clearly demarcated and localized to the area of contact, most commonly in the hands and face where exposure to irritants are likely (Tan et al., 2014). The morphologic characteristics of the patches pictured above make the diagnosis of dermatitis unlikely.

b. Desmoplastic trichoepithelioma (DT) is a rare benign adnexal tumor characterized by asymptomatic, solitary, annular, indurated, and centrally depressed papules or plaques with raised borders (Wang et al., 2015). It most commonly occurs in the young to middle aged adult population on the face with a female predominance (Kunz et al., 2018). On dermoscopy, DT presents with well-defined borders and an ivory-white color background, as well as prominent arborizing telangiectasias (Khelifa et al., 2013). There is a lack of lack of blue-gray ovoid nests and leaf-like structures, which helps to differentiate it from basal cell carcinoma (Kunz et al., 2018). Histological features of DT include basaloid cells arranged in small cords and infundibulocystic structures that contain keratin with surrounding fibrotic collagen (Kunz et al., 2018). The pictured lesion is inconsistent with the aforementioned features of DT in that it is flat with a lack of raised borders and there is no central depression. The age of the patient is also inconsistent with DT’s young age of onset, making a diagnosis of DT unlikely.

d. Benign lichenoid keratosis (BLK) is an evolving, solitary papule or plaque that develops from an immunologic response to a variety of precursor lesions in elderly patients. These lesions are typically found on the trunk or extremities, and can vary in color from pink to purple to red-brown (Prieto et al., 1993). The dermoscopic features of BLK reflect the level of regression, usually consisting of various amounts of blue and white structures with localized or diffuse granular patterns (Bugatti and Filosa, 2007). The classic histologic appearance of BLK consists of hyperkeratosis and epidermal acanthosis with a lymphocyte-predominant inflammatory infiltrate, as well as “flanking epidermal foci of lentigo”(Morgan et al., 2005). Although regressing superficial BCCs can be misdiagnosed as BLK, classic morpheaform BCCs (such as the photographed lesion) do not share many of the same features as BLK (Kulberg and Weyers, 2016, Maor et al., 2017).

e. Cutaneous T-cell lymphomas represent a group of malignancies of skin-residing T-cells, with mycosis fungoides (MF) making up almost 50% of all cases. MF typically occurs in older adults, with a predilection for the buttocks and other sun-protected areas (Willemze et al., 2005). MF can have a variety of clinical presentations, from erythematous patches to plaques, and eventually tumors. Characteristic features of MF include a “cigarette paper” wrinkly scale and a round to oval appearance, with later tumor stages demonstrating less scale and a shiny induration (Pulitzer, 2017). Although epidermotropism is pathognomonic for MF, the most common histologic pattern of MF consists of “band-like” or patchy lichenoid infiltrates mixed with coarse bundles of collagen in the superficial dermis (Massone et al., 2005). Other morphologic features include Pautrier microabsesses and atypical lymphocytes with
cerebriform nuclei in a “string of pearls” arrangement (Ahn et al., 2014). Dermoscopy has also proven useful for the diagnosis of MF, especially in early-stage lesions, which tend to demonstrate short linear vessels, yellow-orange patchy areas, and characteristic vascular structures resembling spermatozoa (Lallas et al., 2013).

2. Which of the following statements is false regarding the staging or treatment of cutaneous BCC?

CORRECT ANSWER: b. Patients who had received organ transplants are more likely to have the morpheaform subtype of BCC

The organ transplant recipients (OTRs) who develop BCC most commonly present with the superficial subtype of BCC (Kanitakis et al., 2003). This is in contradistinction to the general population, where the nodular subtype is the most prevalent (Mackiewicz-Wysocka Malgorzata, 2013) and the superficial subtype is the second most common (Marzuka and Book, 2015). Morpheaform is a relatively rare variant of BCC, accounting for an estimated 5 to 10 percent of cases of BCC and does not have an association with OTRs (Scrivener et al., 2002). Basal cell carcinoma has a higher incidence in the general population than squamous cell carcinoma (SCC). Although immunosuppressed organ transplant recipients have an increased risk for BCC, the risk for squamous cell carcinoma increases substantially more than that of BCC. This reverses the typical BCC/SCC ratio in the general population in favor of SCC predominance in the OTR (Kanitakis et al., 2003).

Discussion of incorrect answers:

a. Perineural involvement (PNI) in BCC describes the spread of tumor growth around a nerve. PNI in BCC is relatively rare, with an incidence of <1%, although true rates may be higher. When present, PNI is associated with larger and more aggressive tumors. (Brown et al., 2018). Perineural invasion has recently been identified as a third route of basal cell carcinoma metastasis, along with lymphatic and hematologic spread. BCC with PNI is most commonly found on the nose, forehead, cheek, and maxilla. The most common histologic subtypes in patients with basal cell carcinoma with PNI are infiltrating, morphea, and basosquamous subtypes (Leibovitch et al., 2005).

c. Although surgical excision remains the current gold standard of treatment for any BCC, patients with metastatic or locally aggressive BCC may benefit from Vismodegib. The Hedgehog pathway has been implicated in the development of BCC. Vismodegib, an oral small molecule, acts by inhibiting Smoothened, an important activator of the Hedgehog pathway (Mittal and Colegio, 2017). The hedgehog ligand first binds to its receptor, Patched 1, which allows for release of Smoothened (SMO) prote oncopolypeptide (Nikanjam et al., 2018). Vismodegib was approved by the FDA in 2012 as the first in its class for patients with advanced or metastatic BCC.

d. MMS is currently indicated for the treatment of high-risk BCCs such as those that are larger than 2cm, are recurrent, are in high risk areas, or appear locally aggressive on histology (Rajabi-Estarabadi et al., 2018) (Leibovitch et al., 2005). MMS has the highest cure rate for BCC and is an excellent choice for tumors in areas requiring tissue preservation such as the face (Marzuka and Book, 2015). Additionally, the long term recurrence for BCC in one study of patients receiving MMS is 3.4% for primary BCC and 4.9% for recurrent BCC, similar to other reported rates in the literature (Veronese et al., 2012). Despite difficulty in determining the recurrence rate for BCC due to lack of reporting, one study demonstrated a 3.5% recurrence rate after surgical excision and 2.1% after MMS (Chren et al., 2013).

e. Although a formal staging system for risk stratification specific to patients with BCC is not available due to the exceedingly low incidence of regional and distant metastasis, the most clinically relevant risk stratification utilized in the management of patients with BCC is the differentiation between localized tumors at low risk versus high risk for recurrence. The most clinically relevant stratification of BCC is provided by the National Comprehensive Cancer Network (NCCN) Guidelines (Bichakjian et al., 2017), which takes both clinical and pathologic factors into account. Risk features include age, sex, anatomic location, recurrent lesion, lesion size, immunosuppression, history (radiation, burn, organ transplant), histologic subtype, invasion beyond the reticular dermis, and perineural involvement (Kim et al., 2018).

3. Kuonen et al. investigated the role of TGFβ-induced fibronectin in promoting tumor cell motility through integrin α5β1 -mediated FAK phosphorylation in in-vivo models of infiltrative BCC. All of the following are consistent with their findings, except:

CORRECT ANSWER: e. Fibronectin adhesion to integrin α5β1 induces FAK dephosphorylation

Integrin binding to extracellular matrix (ECM) typically activates FAK through autophosphorylation at tyrosine 397 (Y397), providing a binding site for downstream activating molecules implicated in proliferation, survival, and motility (Tilghman and Parsons, 2008). Kuonen, et al. suspected that
this mechanism could also be at play in BCC, and checked the phosphorylation status of FAK at Y397 in BCC cell lines, on adhesion to fibronectin. They observed high levels of phospho-FAK at the cell membrane of BCC growing on fibronectin but not on those growing on poly-L-lysine. Consistently, the integrin α5β1 inhibitors K34C (pharmacologic inhibitor) and P1D6 (blocking antibody) reduced cell adhesion and migration of BCC cells on FN and efficiently prevented FAK phosphorylation, bringing proof that this event is mediated by α5β1 integrin. They also observed preferential phospho-FAK in infiltrative-like areas of BCC tumors in mice injected with TGFβ.

Discussion of incorrect answers:

a. Kuonen, et al., by using two different BCC allografts, showed higher levels of fibronectin and higher density of S100A4 fibroblasts at the periphery of infiltrative compared with nodular BCC. Human samples were tested by quantitative real-time PCR for various secreted cytokines reported to promote fibronectin deposition. Among the various cytokines tested, TGFβ was found to be significantly higher in infiltrative compared with nodular BCC, both at the mRNA and protein levels. These results suggest that TGFβ may be a key regulator of fibronectin induction and tumor infiltration in BCC.

b. Using an adhesion assay, Kuonen, et al. found that both the human UW_BCC_T2 and murine ASZ_001 BCC cell lines are able to adhere very efficiently to fibronectin when compared with control (uncoated) or collagen I. They showed that long-term cultures on fibronectin revealed phenotypic modifications such as reduced cell-to-cell contacts and longer cytoplasmic extensions, indicating greater cell motility. For both UW_BCC_T2 and ASZ_001 cell lines, fibronectin coating promoted cell migration. Integrin α5β1 is a main fibronectin receptor, binding to its arginine-glycine-aspartic acid domain. They observed a significant expression of integrin α5β1 at the mRNA level and more importantly at the protein level in both UW_BCC_T2 and ASZ_001 cell lines. This showed that fibronectin promotes efficiently the migration of BCC cells through a mechanism implicating integrin α5β1 binding.

c. Kuonen and et al. also silenced FAK expression in tumor cells through lentiviral-mediated expression of FAK-targeting short hairpin RNA to test the functional role of FAK in fibronectin-induced migration. A significant reduction in the FAK level was observed at both the mRNA and protein levels in both UW_BCC_T2 and ASZ_001 cell lines and FAK silencing efficiently prevented fibronectin-induced migration in vitro (Third choice).

d. The previous findings suggested that phospho-FAK targeting may prevent BCC infiltration in human. They evaluated the effect of PF-562271, an enzymatic phospho-FAK inhibitor in vitro and observed that it could efficiently prevent fibronectin-induced migration of BCC cells. Similar to FAK silencing, PF-562271 also significantly reduced tumor cell growth on fibronectin in vitro.

REFERENCES


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