WHAT IS YOUR DIAGNOSIS?

Figure 1. Image courtesy of M. Laurin Council, Washington University School of Medicine, St. Louis, MO.

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 Delyon et al. (2020) (https://doi.org/10.1016/j.jid.2020.06.039).

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

QUIZ QUESTIONS

1. A 50-year-old Caucasian woman presented with a several-year history of an asymptomatic lesion on the left shoulder. In the past 2 months, the lesion was noted to grow and was measured just over 4 cm² at the time of presentation. What is the most likely diagnosis?
   a. Keloid
   b. Dermatofibroma
   c. Dermatofibrosarcoma protuberans (DFSP)
   d. Cutaneous leiomyosarcoma
   e. Dermatomyofibroma
2. Which of the following is true regarding trial design and outcomes in the study by Delyon et al. (2020)?
   a. Partial response was defined as a reduction of the largest diameter of the tumor by \( \geq 50\% \) at 12 months or at surgery, if performed before 12 months.
   b. The majority of patients with surgery eventually had complete resection with free margins.
   c. The most common cutaneous adverse effect was alopecia.
   d. In matched tumor samples at a 6-month status after treatment with pazopanib, VEGF receptor (VEGFR) mRNA VEGFR-2 expression was significantly greater in responders than in nonresponders.
   e. Participants were excluded if they had previously received imatinib or if their DFSP exhibited fibrosarcomatous transformation.

3. What finding was DFSP associated with in the phase II clinical trial Delyon et al. (2020)?
   a. Elevated plasma levels of soluble VEGFR-2
   b. Presence of the \( \text{COL1A1-PDGFB} \) fusion gene
   c. Preserved p16 expression
   d. Overexpression of the transcripts associated with the EGFR pathway
   e. Reduced PDGF receptor signaling

See the following pages for detailed answers
DFSP is a slow-growing, locally aggressive malignancy most commonly found in young to middle-aged adults; it may also be congenital or present during childhood. Approximately 50–60% of lesions are found on the trunk, 20–30% on the proximal extremities, and 10–15% on the head and/or neck; there is a unique predilection for the shoulder and pelvic regions (Li et al., 2017). Clinically, DFSP presents as an asymptomatic plaque, which over several years develops into a group of firm, keloid-like nodules that are deeply rooted in the subcutaneous tissue and may be painful, nonhealing, and/or purulent (Bogucki et al., 2012). Although DFSP is infrequently metastatic, it often requires multiple resections for clearance, and in cases with fibrosarcomatous transformation (as is seen with approximately 5–15% of DFSP), there is an increased relative risk of metastasis and a worsened prognosis (Liang et al., 2014; Rutkowski et al., 2017).

Regarding histopathologic examination, in the classic nodular form of DFSP, monomorphous spindle cells are generally arranged in short fascicles forming a storiform pattern, and they often infiltrate the subcutaneous tissue in a honeycomb pattern (Liang et al., 2014). In the setting of fibrosarcomatous transformation, DFSP may show a herringbone appearance in which long sweeping fascicles of spindle cells intersect at various angles (Liang et al., 2014).

Discussion of incorrect answers:

a. **Keloid**: Keloid scars present as firm, irregular, fibrotic nodules and plaques, which typically form at sites of previous trauma (scar, cut, burn, etc.) and grow beyond the original borders of the wound. Whereas keloids may mimic DFSP clinically, these entities are histologically unique, with keloids classically showing a haphazard array of thick hyalinized collagen bundles in contrast to the monomorphic spindle cells in a storiform pattern typical of DFSP (Betarbet and Blalock, 2020). Furthermore, immunostaining for CD34 is negative in keloids but characteristically positive in DFSP (Li et al., 2017).

b. **Dermatofibroma**: Dermatofibroma (DF) is a common benign tumor that classically presents as a firm papule or nodule with a rim of hyperpigmentation and exhibits dimpling with lateral pressure. They are thought to occur as a reaction to trauma, such as arthropod bites or cuts while shaving. Whereas early DFSP may appear similar to DF, the latter is typically smaller, more regular, and more well-circumscribed. Although DFSP may share some histologic features with a large or highly cellular DF, immunostaining assists in differentiating the two, with DF typically showing factor XIIIa positivity and CD34 negativity in contrast to DFSP. DF is also characterized by epidermal hyperplasia, peripheral collagen trapping, multinucleated giant cells, and hemosiderin deposition (Bogucki et al., 2012).

d. **Cutaneous leiomyosarcoma**: Cutaneous leiomyosarcoma is a rare smooth muscle neoplasm comprising roughly 3% of soft tissue sarcomas. Clinically, cutaneous leiomyosarcoma presents as a solitary, firm, skin-colored to red-brown nodule or plaque that favors the lower extremities of the elderly. Histologically, leiomyosarcoma has a range of features to differentiate it from leiomyoma, including hypercellularity, cytologic atypia, and easily identifiable mitotic figures; it also demonstrates immunohistochemistry positivity for desmin, smooth muscle actin, and h-caldesmon (Zacher et al., 2018).

e. **Dermatomyofibroma**: Dermatomyofibroma is a rare benign cutaneous neoplasm of fibroblasts and myofibroblasts that favors the shoulders in young women (Campagnolo et al., 2017). Histologically, dermatomyofibroma appears as a well-circumscribed plaque composed of long fascicles of spindle-shaped cells running parallel to the skin surface through the reticular dermis (Viglizzo et al., 2008). Unlike DFSP, dermatomyofibroma typically stains negative for CD34.

2. Which of the following is true regarding trial design and outcomes in the study by Delyon et al. (2020)?

CORRECT ANSWER: b. The majority of patients with surgery eventually had complete resection with free margins

DFSP is often difficult to resect with clear margins. Before the advent of targeted therapy with imatinib for unresectable DFSP, further treatment options were limited to radiotherapy. In this phase II clinical trial, 14 of the 18 patients who received pazopanib and then had a surgery achieved complete resections with free margins (61% of the total population). This also included four patients with fibrosarcomatous DFSP who underwent surgery; two (50%) had a complete resection. This degree of efficacy was felt by the authors to be
related to the reduction in tumor size below the threshold of partial response (PR) (reduction of the largest diameter of the tumor by ≥30%) (Delyon et al., 2020).

Discussion of incorrect answers:

a. Partial response was defined as a reduction of the largest diameter of the tumor by ≥50% at 12 months or at surgery, if performed before 12 months: PR was defined as a reduction of the largest diameter of the tumor by ≥30% at 6 months or at surgery, if performed before 6 months. On the basis of the standard Response Evaluation Criteria in Solid Tumors (RECIST) criteria, 2 patients had a PR (9%) and 12 had a stable disease (55%) at 6 months or at surgery (Delyon et al., 2020).

c. The most common cutaneous adverse effect was alopecia: The most common cutaneous adverse effects were hair depigmentation (n = 10, 43%), rash (n = 5, 22%), alopecia (n = 4, 17%), and hand–foot syndrome (n = 3, 13%). Of all the adverse effects, hypertension was the most common, affecting 20 participants (87%) (Delyon et al., 2020).

d. In matched tumor samples at a 6-month status after treatment with pazopanib, VEGF receptor (VEGFR) mRNA VEGFR-2 expression was significantly greater in responders than in nonresponders: Plasma levels of soluble VEGFR-2 have been previously shown to be a biomarker modified during treatment with antiangiogenic therapy (Llovet et al., 2012; Peña et al., 2010), and this study confirmed that pazopanib responders had significantly higher plasma levels of soluble VEGFR-2 at baseline than patients with stable or progressive disease. However, VEGFR mRNA VEGFR-2 expression in tumor specimens (both at baseline and 6 months) was not significantly different between responders and nonresponders. This, the authors concluded, suggested that pazopanib acted on soluble VEGFR-2 rather than on tumor VEGFR-2 (Delyon et al., 2020).

e. Participants were excluded if they had previously received imatinib or if their DFSP exhibited fibrosarcomatous transformation: This phase II clinical trial of pazopanib included patients with histologically proven, unresectable DFSP, which was either primary, locally recurrent, or metastatic and measurable according to the RECIST, version 1.1. Patients with fibrosarcomatous DFSP were included if molecularly confirmed by the detection of the t(17;22) translocation, and patients previously treated with surgery, radiotherapy, or imatinib were included. Although resistance to imatinib was too rare to be retained as an inclusion criterion, the authors concluded that pazopanib may merit further investigation as a therapeutic for unresectable, imatinib-resistant DFSP (Delyon et al., 2020).

3. In their phase II clinical trial, Delyon et al. (2020) showed that pazopanib resistance in DFSP was associated with what finding?

CORRECT ANSWER: d. Overexpression of the transcripts associated with the EGF pathway

To assess for the biomarkers associated with a response to pazopanib, Delyon et al. (2020) classified patients who had both baseline and follow-up DFSP tumor samples available for analysis (n = 16) as responders and nonresponders on the basis of a PR and stable and/or progressive disease, respectively, after pazopanib therapy. Gene Set Enrichment Analysis revealed that the baseline overexpression of transcripts involved in the EGFR pathway was associated with pazopanib resistance (Delyon et al., 2020). Similar to the pazopanib targets VEGF and PDGF receptor (PDGFR), EGFR is a tyrosine kinase receptor. Increased EGFR activation has been reported in DFSP (Ugurel et al., 2014). Furthermore, increased signaling through the EGFR pathway has been associated with DFSP progression and fibrosarcomatous transformation (Osio et al., 2018). These findings suggest that EGFR may be a future candidate for targeted therapy in DFSP.

Discussion of incorrect answers:

a. Elevated plasma levels of soluble VEGFR-2: Delyon et al. (2020) found that patients with DFSP who responded to pazopanib had significantly higher plasma levels of soluble VEGFR-2. Angiogenesis is vital to tumor pathogenesis, and in soft tissue sarcomas, overexpression of VEGF has been associated with worse prognosis (Iyoda et al., 2001). Notably, VEGFR-2 is the main receptor for VEGF and is targeted with high affinity by pazopanib (Sloan and Scheinfeld, 2008).

b. Presence of the COL1A1-PDGF fusion gene: Translocation (17;22) produces the COL1A1-PDGF fusion gene, which is present in most DFSP tumors (Dadone-Montaudié et al., 2018). This fusion gene is typically screened for with FISH (Karanian et al., 2015).

c. Preserved p16 expression: The p16/cyclin D-CDK4 pathway is known to play a role in DFSP pathogenesis (Park et al., 2018). Furthermore, loss of p16 expression is associated with DFSP progression and poor prognosis (Siref et al., 2018). Whereas there was no significant difference in CDKN2A (coding for p16) expression between responders and nonresponders, Delyon et al. (2020) observed loss of p16 expression
on immunohistochemistry in one nonresponder and preserved expression in three responders.

e. **Reduced PDGF receptor signaling:** The COL1A1-PDGFB fusion present in DFSP tumors leads to the upregulation of PDGFR signaling through an autocrine loop (Dadone-Montaudié et al., 2018). Reduced PDGFR signaling would not be characteristic of DFSP and was not identified as a marker for resistance to pazopanib by Delyon et al. (2020).

**REFERENCES**


