WHAT IS YOUR DIAGNOSIS?

Figure 1. Image credit: Emily Y. Chu, MD, PhD, Department of Dermatology, University of Pennsylvania

Editorial note: Welcome to the Journal of Investigative Dermatology (JID) SnapShotDx 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 Halse et al. (https://doi.org/10.1016/j.jid.2019.07.725).

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

QUIZ QUESTIONS

1. What is your diagnosis?
   a. Pigmented basal cell carcinoma
   b. Pigmented squamous cell carcinoma in situ
   c. Melanoma in situ, lentigo maligna type
   d. Tinea nigra
   e. Stasis dermatitis

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2. Which of the following is TRUE regarding the findings from the study by Halse et al. (2019)?
   a. Lentigo maligna (LM) pretreatment biopsies showed a statistically significant difference in immune cell subset densities between the responders and non-responders to imiquimod treatment.
   b. In pretreatment biopsies, the area of the dermis occupied by PD-L1 positive cells was significantly increased in responders to imiquimod as compared with non-responders.
   c. Posttreatment biopsies from responders and nonresponders had the same expression of genes involved in innate immunity.
   d. The most predictive baseline genes for response to imiquimod were CD70 and PRAME.
   e. Within responders to imiquimod therapy, posttreatment biopsies showed upregulation in the signaling pathways affecting leukocyte adhesion.

3. After treatment with imiquimod, which of the following was detected in those who responded to treatment?
   a. Increased production of IFN-1 by plasmacytoid dendritic cells
   b. Increased expression of BCL-2 anti-apoptotic protein
   c. Increased expression of CD28 T-cell receptor
   d. Decreased expression in CTLA-4 costimulatory protein
   e. Decreased expression of IFN-inducible protein 27 (IFI27)

See following pages for detailed answers.
DETAILED ANSWERS

1. What is your diagnosis?

CORRECT ANSWER: c. Melanoma in situ, lentigo maligna type.

Lentigo maligna (LM) is a type of in situ melanoma that usually arises in elderly patients in the setting of chronic sun damage. It typically presents as an ill-defined pigmented macule or patch, usually on the sun-damaged skin on the face, but can also be present in other anatomic sites with chronic sun damage. Dermoscopy can provide some clues to help with the accurate diagnosis. These features include asymmetric pigmentation and dots around the follicles, further evolving to rhomboidal structures and then forming homogeneous pigmented areas and obliteration of the follicular openings (Stolz et al., 2002). The diagnosis of melanoma in situ, LM type is confirmed with histopathology characterized by the proliferation of atypical melanocytes in the basal layer of the epidermis of photo-damaged skin, often with low level pagetoid spread and an effaced rete ridge pattern (Massi and LeBoit, 2014).

Discussion of incorrect answers:

a. Pigmented basal cell carcinoma: Basal cell carcinoma (BCC) is a nonmelanocytic type of skin cancer that is also present on the photo-damaged skin and may be pigmented. However, BCC usually has a pearly surface along with a characteristic rolled border and may ulcerate. Dermoscopy can be helpful in diagnosing pigmented BCC with features showing arborizing vessels, shiny white structures, large blue-gray ovoid nests, and erosions (Reiter et al., 2019).

b. Pigmented squamous cell carcinoma in situ: Squamous cell carcinoma in situ (SCCis) presents as a scaly hyperkeratotic papule or thin plaque on sun-damaged skin. Although SCCis may be pigmented, the lesion shown in Figure 1 is not scaly and hyperkeratotic.

c. Tinea nigra: Tinea nigra is a superficial infection caused by Hortaea werneckii, a common saprophytic fungus. Clinically, patients typically present with well-circumscribed brown—black patches on the palms and soles as opposed to the ill-defined brown patch observed on the shin in Figure 1. At times, it can be confused with acral lentiginous melanoma (Eksomtramage and Aiempanakit, 2019). Potassium hydroxide test will be positive for pigmented short hyphae.

e. Stasis dermatitis: Stasis dermatitis is a common inflammatory skin condition in the elderly population that develops secondary to chronic venous insufficiency and edema. Early symptoms include local erythema and scaling, whereas later symptoms may include skin discoloration, worsening edema, and skin ulceration (Beebe-Dimmer et al., 2005). Although brown pigmentation in the setting of stasis dermatitis is common, it is typically more diffuse on the lower legs than the discrete lesion observed in Figure 1.

2. Which of the following is TRUE regarding the findings from the study by Halse et al. (2019)?

CORRECT ANSWER: b. In pretreatment biopsies, the relative area of the dermis occupied by PD-L1 positive cells was significantly increased in responders to imiquimod compared with non-responders.

According to the study by Halse et al., PD-L1 positive staining was present in the areas of inflammation near the dermal—epidermal junction in LM pretreatment lesions. The study found that responders to treatment had a significantly increased area of PD-L1+ staining cells in the dermis as compared with nonresponders before the initiation of treatment.

Discussion of incorrect answers:

a. LM pretreatment biopsies showed a statistically significant difference in immune cell subset densities between the responders and non-responders to imiquimod treatment: The study found that LM pretreatment biopsies did not show a statistically significant difference in immune cell subset densities between responders and nonresponders to imiquimod treatment, by using collated multiplex immunohistochemistry data.

c. Posttreatment biopsies from responders and non-responders had the same expression of genes involved in innate immunity: Authors in this study looked at the expression of genes in LM lesions after treatment with imiquimod. They found that responders posttreatment had an upregulated expression of genes that are involved in the function of plasmacytoid dendritic cells producing IFN-1 in response to Toll like receptor 7 activation (TLR7). Therefore, the responders did not have the same expression of genes involved in innate immunity.
d. **The most predictive baseline genes for response to imiquimod were CD70 and PRAME:** The authors generated a volcano plot looking at the significantly differentially regulated genes between responders and nonresponders to imiquimod. They found that the most predictive baseline genes were XCR1 and IFN-inducible protein 27 (IFI27), not CD70 and PRAME.

e. **Within responders to imiquimod therapy, post-treatment biopsies showed upregulation in the signaling pathways affecting leukocyte adhesion:** The authors found that signaling pathways unique to responders included T-cell activation, IFN-1 signaling pathway, antigen cross-presentation, regulation of tolerance induction, and regulatory T-cell induction, but not leukocyte adhesion.

3. **After treatment with imiquimod, which of the following was detected in those who responded to treatment?**

**CORRECT ANSWER:** a. Increased production of IFN-1 by plasmacytoid dendritic cells.

The authors of the study found that pre- and post-imiquimod immune gene expression profiles were distinct. Among responders, they found that signaling pathways related to the activation of plasmacytoid dendritic cells and production of IFN-1 were upregulated. In their discussion, they explained that plasmacytoid dendritic cells (BDCA2+ CD123+) are potent producers of IFN-1 in response to TLR7 ligation by imiquimod. Imiquimod mimics the pathogen signals provided by single-stranded RNA viruses, thus binding to TLR7 resulting in endosome formation and upregulation of innate viral sensors and activation of RIG-1. This then results in the production of IFN-1, which are also released in response to infection.

**Discussion of incorrect answers:**

b. **Increased expression of BCL-2 anti-apoptotic protein:**
The authors did not find an increase in the expression of BCL-2 in the imiquimod responder group.

c. **Increased expression of CD28 T-cell receptor:**
CD28 expression was found to be upregulated in nonresponders, not responders, of imiquimod.

d. **Decreased expression in CTLA-4 costimulatory protein:**
Increased, rather than decreased, expression of CTLA-4 was observed in the imiquimod responder group.

e. **Decreased expression of IFI27:**
Increased, rather than decreased, expression of IFI27 was observed in the imiquimod responder group.

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**REFERENCES**


