**SnapshotDx Quiz: September 2019**

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**WHAT IS YOUR DIAGNOSIS?**

![Image](image-url)  
*Figure 1.* Image courtesy of Milan J. Anadkat, Washington University School of Medicine.

*Editorial note: Welcome to the Journal of Investigative Dermatology (JID) Snapshot Dx 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 Murer et al (2019) ([https://doi.org/10.1016/j.jid.2018.11.028](https://doi.org/10.1016/j.jid.2018.11.028)).

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

**QUIZ QUESTIONS**

1. What is your diagnosis?
   a. Seborrheic keratosis
   b. Pigmented basal cell carcinoma
   c. Pigmented actinic keratosis
   d. Melanoma
   e. Melanocytic nevus

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2. According to the article by Murer et al. (2019) which of the following is FALSE?
   a. Cell membrane gp75 antigen is selectively expressed in melanocytes in both humans and mice and can be an ideal target for antibody-based antitumor therapy
   b. Antibody-dependent cell-mediated cytotoxicity can be significantly boosted with combined cytokine delivery
   c. Recombinant murine TA99 IgG2a antibody directed against a melanoma antigen has significant activity against growth of B16 metastases
   d. TA99 antibody has strong antitumor activity for established neoplastic masses

3. Which of the following is TRUE according to the article by Murer et al. (2019)?
   a. TA99-mTNF fusion antibody displays marked activity against B16 melanoma metastases
   b. TA99-mTNF enhances the recruitment of adaptive immune B and T cells into B16 melanoma tumors
   c. TA99-mTNF leads to incomplete tumor necrosis, leaving a vital tumor rim that regrows over time
   d. Co-administration of fusion antibody with decarbazine, a commonly used melanoma chemotherapeutic agent, inhibits the tumor rim outgrowth

See following pages for detailed answers.
DETAILED ANSWERS

1. What is your diagnosis?

CORRECT ANSWER: d. Melanoma

Melanoma is the fifth most prevalent cancer, and third most common skin cancer (Siegel et al., 2019). The incidence of malignant melanoma has doubled over the last few decades and varies by skin color, ranging from 1.1 to 27.2 per 100,000 individuals in blacks and whites, respectively (Cormier et al., 2006; Guy et al., 2015). Clinical recognition of melanoma requires integration of risk factors, gross morphologic features, and dermoscopic traits. Risk factors include genetic predisposition, white race, increased UV exposure with suntanning or tanning bed use, presence of a large number of nevi or atypical nevi, or immunosuppression. Personal history of melanoma is also considered a significant risk factor. Gross clinical morphologic features that suggest high probability of melanoma include asymmetry of pigment patterns, irregular borders, variegated color, diameter greater than 6 mm, and a history of evolving or changing.

Melanomas can be subtyped into superficial spreading, nodular, lentigo maligna, acral, amelanotic, spitzoid, and desmoplastic melanomas. The most common subtype is superficial spreading and accounts for 70% of all melanomas (Markovic et al., 2007). It typically presents as a variably pigmented macule or thin plaque with an irregular border. Nodular melanomas account for 15–30% and can be pigmented or pink, polypoid papules or nodules that often have small, regular borders, making early detection difficult. Lentigo maligna usually begins as a tan or brown macule in chronically sun-damaged areas and gradually enlarges to a lesion with varied pigmentation, color, and raised areas.

Definitive diagnosis of melanoma requires biopsy. The most important histologic finding, owing to its prognostic implications is the Breslow depth: the thickness of the tumor from the granular cell layer in the epidermis to the deepest malignant cell. This depth, along with regional tissue or nodal involvement and distant metastases are then used to stage the tumor, which determines prognosis and treatment. Most melanomas are diagnosed at an early stage, where surgical excision is curative. For patients with metastatic or advanced disease, treatment includes surgical excision, immunotherapy with checkpoint blockade, targeted therapy against mutant tumor driver molecules, radiation, or cytotoxic chemotherapy.

Discussion of incorrect answers:

a. Seborrheic keratosis: have a typical waxy “stuck-on,” hyperkeratotic appearance, are usually symmetric, and often occur in multiples.

b. Pigmented basal cell carcinomas: tend to have a pearly appearance with less pigmentation and abundant telangiectasias compared with a typical melanoma.

c. Pigmented actinic keratosis: tend to only occur in sun-exposed areas and are generally smaller, less pigmented, erythematous, and hyperkeratotic (“sandpaper roughness”).

e. Melanocytic nevi: compared with melanoma, are generally symmetric, lack irregular borders or color variegation, are smaller with diameters less than 6 mm, do not change over time, and do not ulcerate or bleed.

2. According to the article by Murer et al. (2019) which of the following is FALSE?

CORRECT ANSWER: d. TA99 antibody has strong antitumor activity for established neoplastic masses

In this study, the authors found that co-injection of B16 melanoma cells and TA99 antibody prevented lung metastasis. However, when TA99 is administered alone to mice with established small tumors, there was very minimal tumor destruction, despite the confirmed biologic activity of the antibody. This led the authors to investigate cytokine-fused TA99 antibodies to potentiate activity against established tumors.

Discussion of incorrect answers:

a, b, c are all true statements.

a. Cell membrane gp75 antigen is selectively expressed in melanocytes in both humans and mice and can be an ideal target for antibody-based antitumor therapy: the ideal candidate for antibody-mediated therapy would be a target antigen that is specifically expressed only on tumor cells and not on healthy tissue. An antibody against such an antigen can then recruit immune cells for antitumor cytotoxic activity. Thus, gp75 can be an ideal antigen target.
b. Antibody-dependent cell-mediated cytotoxicity can be significantly boosted with combined cytokine delivery: cytokines, such as IL-2 or tumor necrosis factor, can be fused to the target-specific antibody and significantly enhance antitumor activity. This phenomenon has been demonstrated in lymphoma and leukemia (Börschel et al., 2015; Gutbrodt et al., 2013). Proposed mechanisms include direct anti-cancer cell activity (van Horssen et al., 2006), increased uptake of antibodies into solid tumor mass (Folli et al., 1993), recruitment of innate cells facilitating cell-mediated cytotoxicity into tumor mass (van Horssen et al., 2006), and others.

c. Recombinant murine TA99 IgG2a antibody directed against a melanoma antigen has significant activity against growth of B16 metastases: simultaneous administration of B16 melanoma cells and the gp75-specific TA99 antibody in mice can prevent formation of lung metastasis (Nimmerjahn and Ravetch, 2005).

3. Which of the following is TRUE according to the article by Murer et al. (2019)?

CORRECT ANSWER: c. TA99-mTNF leads to incomplete tumor necrosis, leaving a vital tumor rim that regrows over time

In this study, the authors engineered a recombinant murine homotrimeric TNF-fused TA99 antibody. They experimented with different dosages and combinations of antibody, and observed that simultaneous injection of both TA99 and TNF-TA99 was most potent at inhibiting tumor progression. However, this combination only slowed tumor growth, and after 16–18 days, neoplastic masses eventually overgrew from vital areas surrounding the endothelium at the edges of the tumor lesions.

Discussion of incorrect answers:

a. TA99-mTNF fusion antibody displays marked activity against B16 melanoma metastases: although the TA99 antibody alone can prevent melanoma metastasis, the TNF-TA99 fusion antibody did not prevent melanoma lesions from metastasizing. Interestingly, TNF-TA99 did inhibit tumor growth in mice with established solid melanoma tumors.

b. TA99-mTNF enhances the recruitment of adaptive immune B and T cells into B16 melanoma tumors: the fusion antibody significantly increased infiltration with innate (NOT adaptive) immune cells, such as natural killer and macrophages, which are crucial for antibody-dependent cell-mediated cytotoxicity. Selective depletion of natural killer cells before treatment led to significant loss of therapeutic activity. Thus authors propose that this infiltration of innate immune cells inhibits tumor growth by inducing hemorrhagic necrosis.

d. Co-administration of fusion antibody with decarbazine, a commonly used melanoma chemotherapeutic agent, inhibits the tumor rim outgrowth: to kill the surviving tumor rim that allowed tumor outgrowth, the authors added decarbazine for triple therapy with TA99 and TNF-TA99. Decarbazine is commonly used in treatment of patients with metastatic melanoma. However, this combination therapy did not inhibit tumor rim outgrowth.

REFERENCES


