JOURNAL OF DRUGS IN DERMATOLOGY
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DRUGS • DEVICES • METHODS

Board Review

In partnership with Derm In-Review

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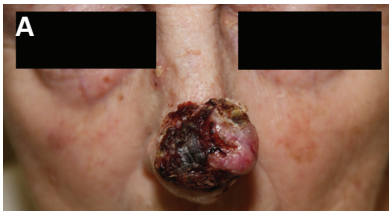
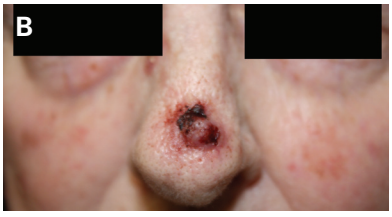
Kathleen Sikora Viscusi, MD

1)





An 86-year-old Caucasian female with no significant past medical history presents with a 5-centimeter exophytic ulcerated nodule, as shown in Image A. Biopsy is performed and shows peripheral palisading, retraction artifact, fibromyxoid stroma, and strands of basophilic staining cells. After thorough discussion of treatment options, the patient is started on vismodegib 150 mg once daily. She returns for follow-up 45 days later, as shown in Image B. All of the following are true regarding the treatment medication ***except***:

A. Vismodegib targets a 7-transmembrane G-protein-coupled receptor.

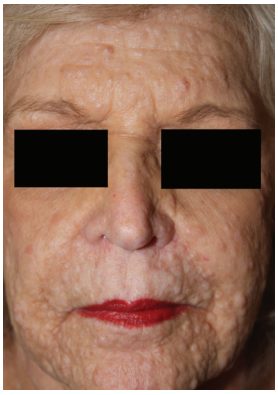
B. GLI1 expression is upregulated during treatment with vismodegib.

C. In plasma, vismodegib is heavily bound to proteins, including high affinity binding with alpha 1-acid glycoprotein.

D. Vismodegib has an estimated half-life of 12 days after single dose administration and four days after continuous once daily administration.

E. Vismodegib is an oral small-molecule inhibitor of the hedgehog pathway (Hh).

2)



A 65 year-old Caucasian female complains of a lifelong history of progressive "cysts" on her face and body, as per the clinical image. She has not sought treatment for these in the past. History is significant for an unknown type of leukemia as a child treated successfully with a bone marrow transplant as well as similar "cysts" affecting her mother and maternal grandfather. Clinical exam reveals innumerable dermal and subcutaneous soft, mobile nodules and multiple (>10) evenly bordered tan/brown patches on the trunk and extremities, ranging from 2-4 cm in size. Based on the history and clinical presentation, which of the following tumors was most likely also present when the patient was a child?

A. Angiofibromas

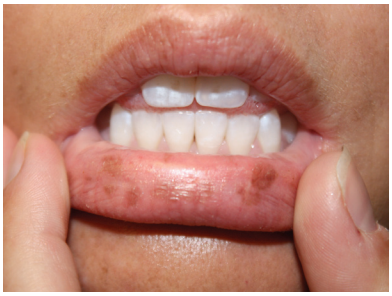
B. Pilomatricomas

C. Juvenile xanthogranulomas

D. Basal cell carcinomas

E. Trichoepitheliomas

3)



A 45-year-old female patient presents with cosmetic concern regarding asymptomatic freckling on the lower lip of approximately 5 years duration. She reports gradual increase in pigmentation and number of lesions in the first 3 years, with lesions more or less stable in size and number during the most recent 2 years. She is otherwise healthy and denies any other somatic complaints. Personal and family history is negative for melanoma or other types of skin cancer, pigmentary abnormalities, colon polyps or cancer, cardiac disease and arrhythmias, or endocrine disorders. Complete physical exam is unremarkable other than ill-defined hyperpigmentation on the upper and lower vermilion of the lips and multiple brown macules on the lower lip, as shown, as well as a 2 mm wide longitudinal pigmented band on the right 3rd fingernail. Biopsy of a representative lesion on the lower lip reveals increased epithelial basal layer pigmentation and normal number and appearance of melanocytes. Based on clinical and histologic correlation, the patient is diagnosed with Laugier-Hunziker syndrome. What the most appropriate next step in managing this patient?

A. Upper and lower endoscopy

B. Reassurance as the pigmentation will fade naturally with time

C. ACTH stimulation text

D. Cardiac evaluation

E. Q-switched alexandrite laser

Images courtesy of Dr. William Hanke of the Laser and Skin Surgery Center of Indiana

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Board Review Answers

1) B. GLI1 expression is upregulated during treatment with vismodegib.

Explanation/Literature Review

The patient above presented with a locally advanced basal cell carcinoma and was treated with vismodegib, an oral small-molecule inhibitor of the Hh pathway that was approved by the Food and Drug Administration (FDA) in 2012 for the treatment of locally advanced and metastatic basal cell carcinoma. Vismodegib targets and inhibits smoothened (SMO), a 7-transmembrane G-protein coupled receptor. Under normal conditions, signaling by SMO results in activation of GLI transcription factors and subsequent induction of Hh target genes, including GLI1 and PTCH1. Thus, there is a strong relationship between activated Hh signal and GLI1 expression. In the phase 1 study, repeat skin biopsies from patients treated with vismodegib demonstrated a greater-than 2-fold downregulation, not upregulation, of GLI1 expression in 76.9% of patients, compared with pretreatment biopsies. Further, studies have shown that vismodegib has an unusual and non-linear pharmacokinetic (PK) profile, including an elimination half-life of 12 days after a single dose but only four days after continuous once daily administration. The unusual PK profile is in part due high-affinity binding to alpha-1-acid glycoprotein (AAG), and plasma concentrations of total vismodegib are strongly correlated with AAG levels.

2) C. Juvenile xanthogranulomas

Explanation/Literature Review

From the information provided by the question stem and accompanying image, the patient meets criteria for a diagnosis of neurofibromatosis (NF), including an affected first degree relative, two or more dermal neurofibromas, and 6 or more café au lait macules measuring >1.5 cm in an adult. Per the literature, it is estimated that children with NF and juvenile xanthograunuloma (JXG) have a 20–32-fold greater risk for juvenile chronic myel¬ogenous leukemia (JCML), aka juvenile myelomonocytic leukemia (JMML), than patients with NF who do not have JXG. However, it is important to note that the vast majority of patients with multiple JXGs do not develop JCML/JMML, even with concomitant NF.

Multiple facial angiofibromas are frequently seen in patients with tuberous sclerosis. Pilomatricomas are usually not hereditary but have been associated with myotonic dystrophy, Gardner syndrome, Rubinstein–Taybi syndrome, and trisomy 9. When a basal cell carcinoma is diagnosed in childhood, one must consider an associated condition, such as basal cell nevus syndrome, xeroderma pigmentosum, Bazex syndrome, Rombo syndrome, albinism, or an underlying nevus sebaceous. Patients with basal cell nevus syndrome are often predisposed to other malignancies, particularly childhood medulloblastoma. Trichoepitheliomas may occur sporadically or be inherited in an autosomal dominant fashion, such as the multiple trichoepitheliomas, cylindromas, and spiradenomas seen in Brooke-Spiegler syndrome.

3) E. Q-switched alexandrite laser

Explanation/Literature Review

Laugier–Hunziker syndrome (LHS) is a benign acquired pigmentary condition affecting the lips (particularly the lower lip), oral mucosa, and acral surfaces and is frequently associated with longitudinal melanonychia. As in the patient above, the pigmented macules in LHS most often appear in adulthood in the absence of other somatic abnormalities. Affected patients do not have malignant predisposition or underlying systemic abnormalities associated with LHS. The hyperpigmented macules in LHS are benign and reassurance and observation is also appropriate; however, the pigmentary changes in patients with LHS do not disappear naturally. The patient above expressed cosmetic concern, and thus treatment options per the literature include cryosurgery, Q-switched Nd:YAG laser, and Q-switched alexandrite laser therapy. Sun protection is also important to prevent recurrence.

Upper and lower endoscopy is indicated in patients with Peutz-Jeghers syndrome (PJS). Although the presentation in this case would be very unusual for PJS, ie, late onset of pigmentation, absence of family history consistent with PJS, and absence of GI signs/symptoms (bowel obstruction, diarrhea, abdominal pain, melena, etc.), endoscopy may still be prudent if the question stem did not explicitly provide the patient's benign diagnosis. Other disorders to consider in the differential diagnosis of pigmented mucocutaneous macules include Addison's disease (ACTH stimulation test), LEOPARD or LAMB syndromes (cardiac evaluation), and drug-induced pigmentation.

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