Atypical Skin Bronzing in Response to Belumosudil for Graft-vs-Host Disease

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PRACTICE **POINTS**

- Drug-induced hyperpigmentation is a common cause of acquired hyperpigmentation and should be evaluated after metabolic or endocrine causes are ruled out.
- Belumosudil for chronic graft-vs-host disease can induce rapid-onset diffuse bronzing hyperpigmentation, even in the absence of other systemic or laboratory abnormalities.
- Treatment entails discontinuation of the offending agent and limitation of exacerbating factors such as sun exposure.

To the Editor:

Drug-induced hyperpigmentation is a common cause of an acquired increase in pigmentation. Belumosudil is an oral selective inhibitor of Rho-associated coiled-coil containing protein kinase (ROCK2) that is approved for the treatment of chronic graft-vs-host disease (GVHD). We describe a patient who developed diffuse skin bronzing 3 weeks after initiation of belumosudil treatment.

A 64-year-old fair-skinned woman presented to the dermatology clinic with bronzing of the skin and dystrophic nails 3 weeks after starting belumosudil for treatment of chronic GVHD. Six months prior to presentation, the patient had received a bone marrow transplant for chronic lymphoid leukemia. She presented to dermatology 6 months after the transplant with a new-onset rash that was suspicious for GVHD. Physical examination revealed pruritic pink papules diffusely scattered on the legs and forearms (Figure 1). The patient declined biopsy at that time and later followed up with oncology. The patient's oncologist supported a diagnosis of GVHD, and the patient began treatment with belumosudil 200 mg/d which was intended to be taken until treatment failure due to progression of chronic GVHD.

Three weeks after starting belumosudil, the patient developed diffuse bronzing of the skin and brown, evenly colored patches scattered on the trunk, back, and upper and lower extremities on a background of the presumed GVHD rash (Figure 2). The hyperpigmentation

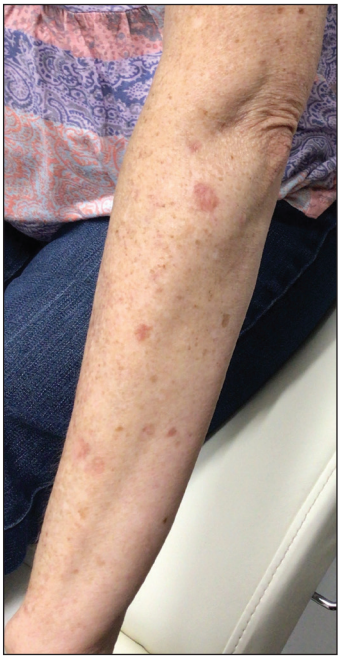

FIGURE 1. Smooth pink papules diffusely scattered on the left forearm that were suspicious for graft-vs-host disease.

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was abrupt, starting on the chest and spreading to the abdomen, extremities, and back (Figure 3).

Again, the patient was offered biopsy for the new-onset pigmentation but declined. During this time, she had no notable sun exposure and primarily stayed indoors despite living in a region with a sunny semi-arid climate. Her medication and supplement list were reviewed and included acalabrutinib, a multivitamin, lutein, biotin, and a fish oil supplement. A compete blood cell count as well as ferritin, transferrin, cortisol, and adrenocorticotropic hormone levels were unremarkable.

The patient continued to take belumosudil for treatment of GVHD. The hyperpigmentation faded slightly by a 2-month follow-up visit but persisted and was stable. She has not tried other treatments for GVHD to manage the hyperpigmentation.

Conditions known to cause diffuse bronzing of the skin include Addison disease, hemochromatosis, Cushing disease, and medication adverse events. Our patient presented with an absence of systemic symptoms, normal laboratory results, and no clinical indicators suggesting alternate causes. Given that the onset of the hyperpigmentation was 3 weeks after she started a new medication, we hypothesized that the bronzing was an adverse effect of the belumosudil—though this correlation cannot be definitively proven by this case.

The most common offending agents for drug-induced skin hyperpigmentation are nonsteroidal anti-inflammatory drugs, antimalarials, amiodarone, cytotoxic drugs, and tetracyclines.[1,2] Our patient's medication list included the cytotoxic agent acalabrutinib, a Bruton tyrosine kinase inhibitor used for the treatment of non-Hodgkin lymphoma. It has been associated with dermatologic findings of ecchymosis, bruising, panniculitis, and cellulitis, but there are no known reports of

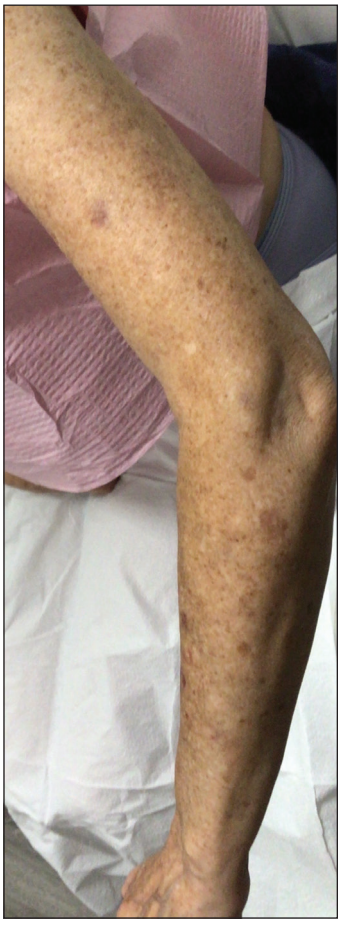

FIGURE 2. Brown, evenly colored patches and diffuse skin bronzing over the left forearm 3 weeks after treatment with belumosudil for graft-vs-host disease.

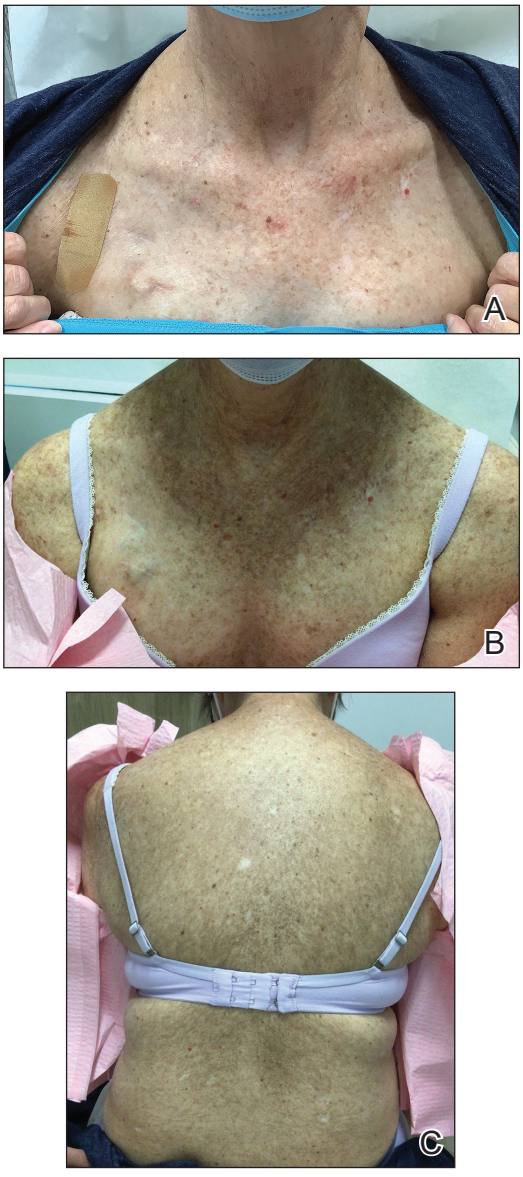

FIGURE 3. A, The patient's chest prior to starting belumosudil treatment. B and C, Diffuse bronzing and hyperpigmentation developed on the patient's chest and back within 3 weeks of initiating treatment with belumosudil.

hyperpigmentation.[3] Our patient had been taking acalabrutinib for 6 months when the GVHD rash developed. At the time, she also was taking a multivitamin and lutein, biotin, and fish oil supplements, none of which have been associated with hyperpigmentation.

Polypharmacy adds a layer of difficulty in identifying the inciting cause of pigmentary change. In our case, symptoms began 3 weeks after the initiation of belumosudil. There were no cutaneous reactions observed in the ROCKstar study of belumosudil; the most common adverse events were upper respiratory tract infection, diarrhea, fatigue, nausea, increased liver enzymes, and dyspnea.[4,5] Patients on belumosudil have developed aggressive cutaneous squamous cell carcinoma.[6] However, a search of PubMed articles indexed for MEDLINE using the search terms *acalabrutinib* or *belumosudil* with *hyperpigmentation* or *cutaneous reaction* returned no reports of these medications causing hyperpigmentation or cutaneous deposits.

Treatment of drug-induced hyperpigmentation is difficult because discontinuation of the offending agent typically confirms diagnosis, but interruption of treatment is not always possible, as in our patient. The skin changes can fade over time, but effects typically are long lasting.

Dermatologists play a key role in the identification of drug-induced skin hyperpigmentation. After endocrine or metabolic causes of skin hyperpigmentation have been ruled out, a thorough review of the patient's medication list should be done to assess for a drug-induced cause. Treatment is limited to sun avoidance, as interruption of treatment may not be possible, and lesions typically do fade over time. These chronic skin changes can have a psychosocial effect on patients and regular follow-up is recommended.

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