Kratom as a novel cause of photodistributed hyperpigmentation

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CASE REPORT

A 54-year-old Caucasian man presented with slowly progressive, asymptomatic, hyperpigmented patches that developed on both of his arms over 18 months. On examination, the patient was found to have diffuse hyperpigmented patches on his arms and face in a photodistributed manner, with notable sparing of the knuckles on both hands (see Figs 1 to 4). In the decade preceding his presentation at our clinic, he was on various opiate pain medications for degenerative osteoarthritis. Over the last 4-5 years, to reduce his opioid use, he began weaning himself off of his prescription opiates and replacing them with the plant kratom (*Mitragyna speciosa*). During this period, he consumed an over-the-counter powder form of kratom mixed with orange juice 3-4 times a day. His other medications and supplements included aspirin, a fish oil supplement, and modafinil. He had no other relevant medical history.

Kratom use in the United States has increased dramatically over the past decade. As measured by call reports to the United States National Poison Data System, in 2011, there were 11 reported kratom exposures and in the first 7 months of 2018, there were 357 reported exposures.[1] An anonymous, cross-sectional survey conducted from January 2017 to December 2017 identified 2798 kratom users. According to the survey, 97.7% lived in the United States, 60.7% were female, 89.8% were White, and 40.9% used kratom for opioid withdrawal.[2]

Few reports of kratom-associated hyperpigmentation can be found in the medical literature. One report describes "skin pigmentation on the cheeks, due to the capacity of mitragynine to increase the production of melanocytes-stimulating substance."[3] Online forums such as Reddit have mentions of kratom hyperpigmentation. For example, a female user who took a self-reported 40 g/day of kratom for 3 years reported darkening below her eyes and in the cheek bone area.[4] A 5-year user who tanned regularly reported several "permanent bruise-looking things."[4] Another Reddit user who noticed hyperpigmentation on the forehead in the winter said that it "fades considerably but it takes months. And like I said it comes right back after a relapse, but in more places."[5]

Kratom is a plant of the Rubiaceae family and is found in southeast Asia. Kratom acts as an analgesic and is used similarly to an opioid. The main alkaloid, mitragynine, is metabolized in the liver by CYP3A4 to 7-hydroxymitragynine. Mitragynine acts as an agonist on mu and delta receptors. The half-life of mitragynine is 23.24 ± 16.07 hours.[6] As an agonist, 7-hydroxymitragynine has high affinity for mu receptors and low affinity for kappa receptors. The half-life of 7-hydroxymitragynine is 98.7 minutes in human plasma.[7] Kratom can be purchased over-the-counter and online. It is sold in varying amounts such as ounces, all the way to kilos, and usually comes in a powdered form, but it can also be sold as leaves to make tea. Kratom is used not only to treat pain but also to alleviate anxiety, increase energy, elevate mood, and reduce the symptoms of posttraumatic stress disorder.[8]

The two sites affected by discoloration—the right radial dorsal hand and left lateral elbow—were biopsied. The sections stained with Melan-A showed a normal distribution of junctional melanocytes. Confined to the area of background solar elastosis were scattered deposits of clustered, refractile, nonpolarizable, intrahistiocytic, perivascular, and

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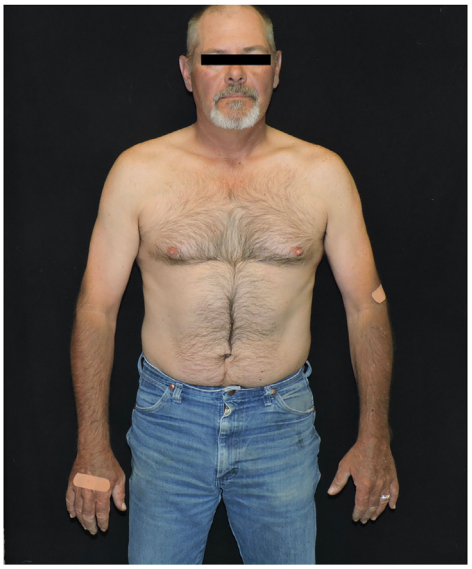

Fig 1. Kratom hyperpigmentation in the upper portion of the body.

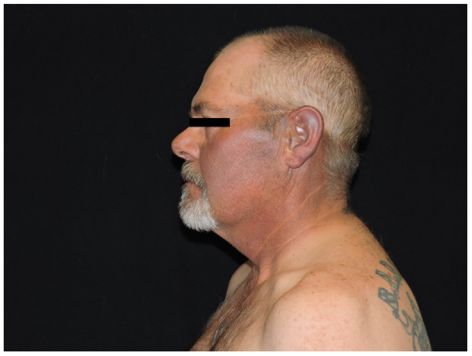

Fig 2. Left profile of the patient showing kratom hyperpigmentation.

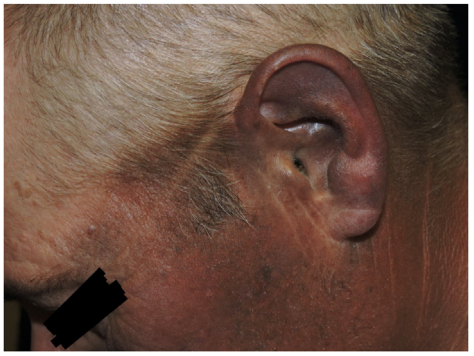

Fig 3. Left profile close-up of the patient showing kratom hyperpigmentation.

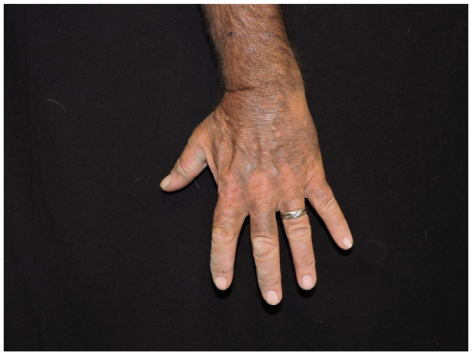

Fig 4. Kratom hyperpigmentation on the left hand.

interstitial red-brown pigment, ranging in size from 1-12 μm (Figs 5 and 6). Besides the presence of pigment-laden histiocytes (Fig 7), no significant inflammation was noted. Scant extravasated erythrocytes were noted; however, a Perls stain was negative for hemosiderin. The pigment was positive for Fontana-Masson stain (Fig 8). Colloidal iron highlighted a normal amount of dermal mucin. Periodic acid–Schiff stain with diastase was negative for fungal organisms. A Gram stain was negative for bacterial infection.

Pigmented purpuric dermatosis was considered in the differential diagnosis; however, in contrast to the golden brown to green, irregular deposits characteristic of hemosiderin, the pigment seen in these biopsies was red-orange, regularly spherical, of overall smaller dimension, and negative for Perls iron stain. Melanin pigment related to postinflammatory pigmentary alteration differs with its fine, dark brown appearance, contrasting with the larger granules seen in this case. Tattoo pigment also differs by its very fine pigment and associated chronic or granulomatous inflammation. Further, although the red-orange color noted in these biopsies could be considered similar in appearance to Monsel solution, this was ruled out because these were not prior procedural sites, and Monsel pigment is irregularly shaped, of variegated coloration, and often positive on Perls stain. Finally, the size and coloration of the granules led to the consideration of drug-induced hyperpigmentation. The lack of staining with Perls Prussian blue, positive in antimalarial and minocycline hyperpigmentation, effectively ruled out these etiologies. However, in both biopsy sites, the particles were diffusely positive for Fontana-Masson (known to be positive in cases of exposure amiodarone, imipramine, minocycline, tricyclic antidepressants, phenothiazine, and antimalarial drugs), indicating a physiologic process leading to induced melanin production and dropout.

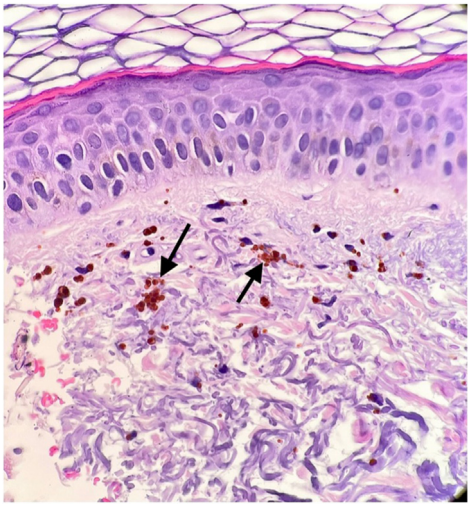

Fig 5. Pigment deposition in upper dermis (*arrows*) (Hematoxylin-eosin stain; original magnification: ×400.)

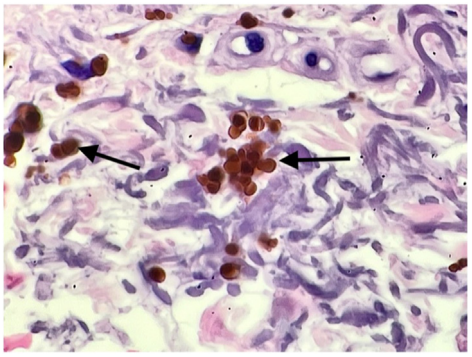

Fig 6. Pigment deposition in upper dermis (*arrows*). (Hematoxylin-eosin stain; original magnification: ×600.)

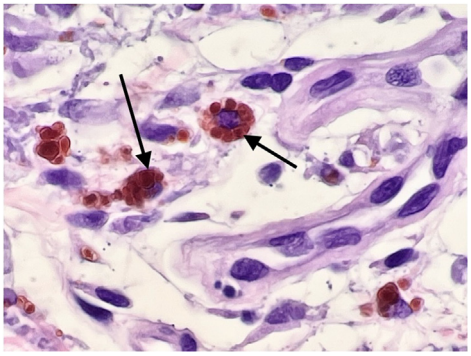

Fig 7. Pigment deposition within macrophages (*arrows*) (Hematoxylin-eosin stain; original magnification: ×600.)

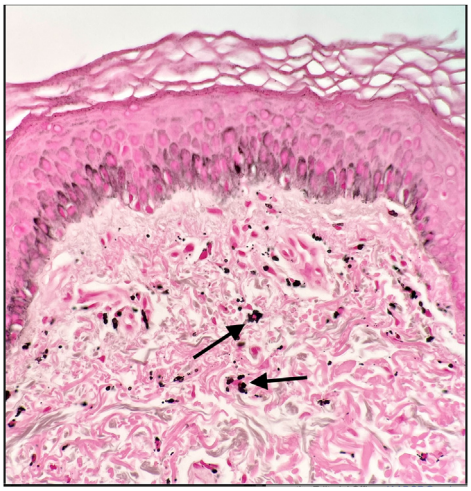

Fig 8. Pigment deposition positive for melanin content (*arrows*) (Fontana-Masson stain; original magnification: ×400.)

DISCUSSION

Individuals who chronically consume kratom at high doses may be susceptible to hyperpigmentation. In our patient, the clinical findings included hyperpigmented skin in sun-exposed areas with blue-gray discoloration. The pigment was deposited around veins and occasionally within macrophages, confirmed by CD68 staining. The key pathologic finding of Fontana-Masson positivity indicates that the pigmented granules contain melanin, a common feature in other drug-related pigmented rashes.[9] The bioactive ingredient of kratom, mitragynine, is known to have dopaminergic, adrenergic, and serotonergic activity, and it is its attenuation of dopamine that is believed to lead to a boost in melanocyte-stimulating peptides. We hypothesize that this process or simple melanin-drug complex deposition may be responsible for hyperpigmentation and skin darkening in kratom users.[10] Mass spectrometry analysis of the pigment granules seen in tissue may be useful in delineating the precise makeup of the pigment deposition.

Kratom-associated hyperpigmentation should be considered in the differential diagnosis when evaluating patients for other drug-associated pigmentary disorders, especially those found in a photodistributed pattern. Our preliminary histological analysis and description serves as a starting point for the further evaluation of the cutaneous side effect of this widely used compound. As kratom use becomes more widespread, this side effect may be seen more often and further understanding and evaluation is needed.

Conflicts of interest

None disclosed.

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