Article Title:

Hyperpigmentation From Chronic Kratom Use: a Case Report and Review of the Literature

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Abstract

Introduction

Kratom is a psychoactive substance extracted from the leaves of the Mitragyna speciosa tree that is often used as an inexpensive opioid substitute in the form of powder or tea leaves. Kratom formulations include the alkaloid compounds mitragynine and 7-hydroxymitragynine, which are thought to primarily act as partial agonists at μ-opioid receptors while also activating dopaminergic receptors.[1] Kratom has recently become more commonly used in the U.S with data collected between 2018-2021 suggesting a yearly prevalence of 2 million active users and 3 million lifetime users.[2] A rare cutaneous side effect that has recently been implicated with kratom is hyperpigmentation. We report another rare case of hyperpigmentation associated with chronic kratom use and review what is currently known about this adverse effect of the substance.

Case Report

A 34-year-old female presented with a 6-year history of brown to gray patches in a photodistributed pattern involving her face, chest, arms and hands with knuckle sparing. The patient had been consuming kratom tea for over 12 years. The patient had been taking 6-8 teaspoons of kratom daily in a paste formulation. Pathology report from a shave biopsy of the patient's right forearm showed numerous superficial dermal deposits of clustered brick brown, nonpolarizable pigments, ranging in size from 1-2 μm. In addition, several isolated linear clumps of pigments were found parallel to the dermal collagen fibers. Epidermal architecture was maintained with preserved normal distribution of junctional melanocytes. Prussian blue iron stain was negative for hemosiderin; however, the pigments were positive for Fontana-Masson stain, a melanin marker.

Conclusion

With Kratom use on the rise, it should be important for dermatologists and primary care providers to be able to recognize signs of kratom toxicity in the form of hyperpigmentation.

1. Introduction

Kratom is a psychoactive substance extracted from the leaves of the Mitragyna speciosa tree that is often used as an inexpensive opioid substitute in the form of powder or tea leaves. Kratom formulations include the alkaloid compounds mitragynine and 7-hydroxymitragynine (7-OHMG), which are thought to primarily act as partial agonists at μ-opioid receptors while also activating dopaminergic receptors.[1] Kratom has recently become more commonly used in the U.S with data collected between 2018-2021 suggesting a yearly prevalence of 2 million active users and 3 million lifetime users.[2] The commonly reported adverse effects of kratom are hepatotoxicity, neurologic symptoms and physical withdrawal symptoms.[3]

A rare cutaneous side effect that has recently been associated with kratom is hyperpigmentation. Early survey reports published in East Asian countries exploring the side effects of chronic kratom use incidentally noted darkening of complexions (Table 1). However, a definitive connection between kratom use and hyperpigmentation remained speculative until recently. A recently published case report describing hyperpigmentation in a photo-distributed pattern in a chronic kratom user has helped illuminate this potential adverse effect. [4] We present another rare case of hyperpigmentation associated with chronic kratom use and review additional literature on the topic.

2. Case Presentation

A 34-year-old Caucasian female presented to the dermatology clinic for diffuse hyperpigmentation. The patient presented with a worsening presentation of the same complaint she had reported at the clinic two years ago, which had started six years prior. At the initial visit, the physical examination revealed brown-to-gray patches in a photodistributed pattern involving her face, chest, arms, and hands with knuckle sparing. There was also a similar pigmentary change around the edges of an old scar on her left shin (Figure 1H). The patient denied pruritus, erythema, fevers, chills, or nausea at both the initial and current visits. The patient's review of systems was negative except for the presence of the pigmentation.

At the present visit, the patient exhibited a similar but darkened pigmentation pattern (Figure 1A-G). The patient's vitals were 98.6°F, 14 breaths per minute, and 130/76 mmHg blood pressure. No osteopathic findings were recorded at this visit. The patient's medical history was significant for levetiracetam use for seizure management, untreated Hepatitis C, and multiple periods of off-brand opioid use, with the last use reported in 2016. The patient reported no surgical history or known diagnosed allergies. The patient also denied using any other medications. At the last visit, bloodwork ruled out hemochromatosis, HIV, heavy metal consumption, and Addison's disease. Drug-induced hyperpigmentation was considered, but the patient had denied a history of commonly implicated medications such as minocycline and amiodarone. A shave biopsy of her right forearm was performed, and the biopsy result was suggestive of drug-induced hyperpigmentation. Levetiracetam was suspected to be the cause of the drug-induced hyperpigmentation due to supporting literature indicating it as a possibility.[5] The drug was subsequently discontinued. Despite discontinuation, the hyperpigmentation continued to worsen by the next visit this year.

Upon further questioning, the patient mentioned that she was a frequent drinker of kratom tea as an opioid substitute and had been using it for over 12 years. The patient had been taking 6-8 teaspoons of kratom daily in a paste formulation. The patient reported depression, fatigue, and body aches as withdrawal symptoms when not taking the tea. The biopsy from the initial visit, where histological sections from the patient's upper forearm were taken, was re-examined with further histochemical stains. The sections showed numerous superficial dermal deposits of clustered brick-brown, nonpolarizable pigments, ranging in size from 1-2 μm (Figure 2A). In addition, several isolated linear clumps of pigments were found parallel to the dermal collagen fibers. Epidermal architecture was maintained with preserved normal distribution of junctional melanocytes (Figure 2B). There was no background inflammation or other morphological features suggesting inflammatory dermatosis. CD117 immunostaining did not reveal an increased number of mast cells in the superficial dermis. Prussian blue iron stain was negative for hemosiderin; however, the pigments were positive for Fontana-Masson stain, a melanin marker (Figure 2C).

As kratom is now considered the likely etiology of the hyperpigmentation, the patient was advised to taper off kratom and to reevaluate the hyperpigmentation at a future visit. The patient was also referred to an addiction medicine clinic to assist with weaning off the tea if needed however, the patient expressed that they are not ready to make the transition at this time.

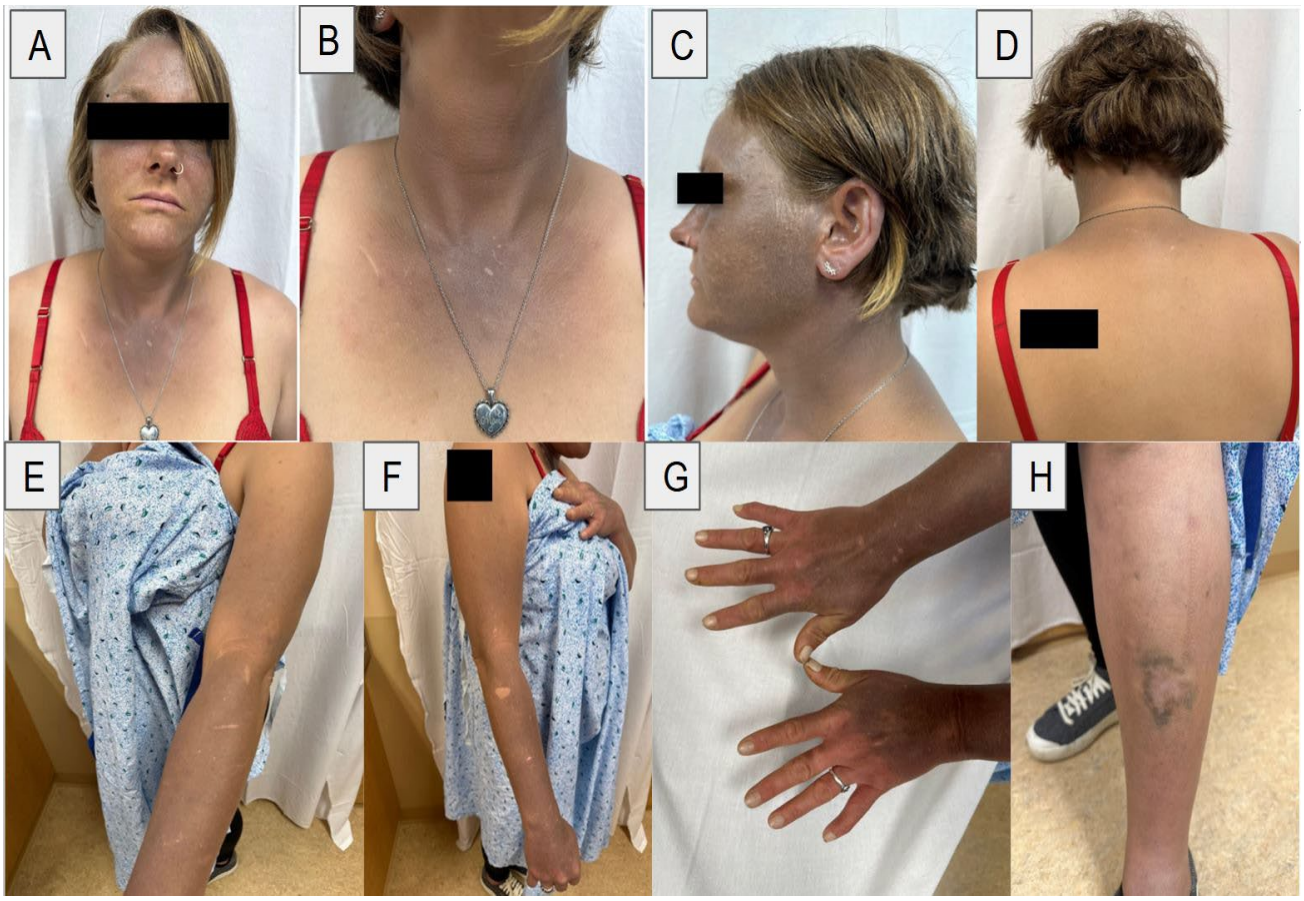

Figure 1: Kratom induced hyperpigmentation at clinic visit. A: Frontal view depicting hyperpigmentation of the face, neck and chest, B: Frontal view depicting hyperpigmentation of the neck and chest. C: Left side profile view depicting hyperpigmentation on the patient's face and neck, D: Dorsal view depicting hyperpigmentation of the patient's neck, E: Left side view depicting hyperpigmentation of the patient's arm and forearm, F: Right side view depicting hyperpigmentation of the patient's arm and forearm with sparing of old scarring, G: Top view of the hyperpigmentation of both of the patient's hands depicting knuckle sparing, H: Side view of the patient's left shin depicting hyperpigmentation around an old scar.

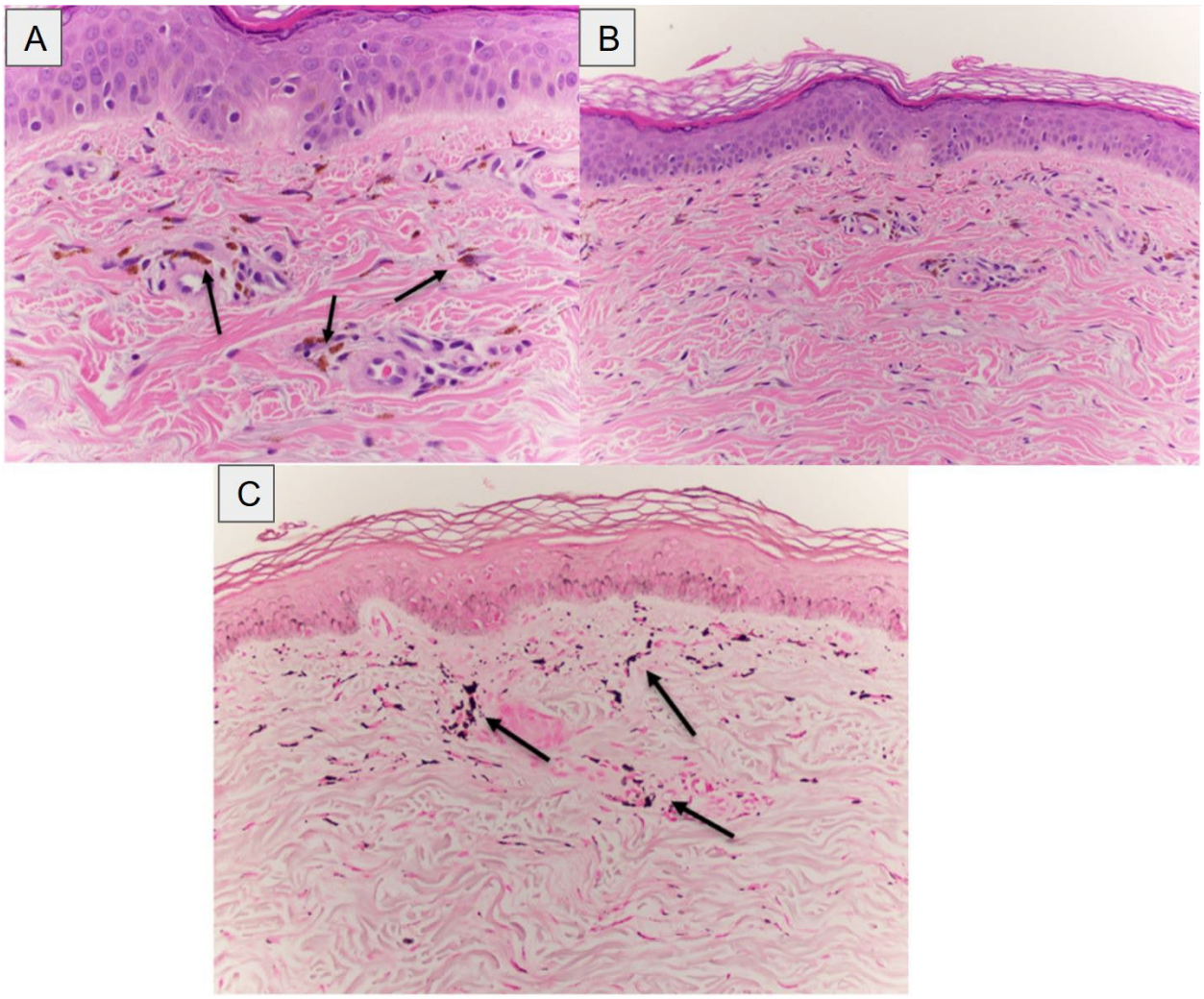

Figure 2: Kratom induced hyperpigmentation skin biopsy. A: hematoxylin and eosin stain was used to identify the possible distribution of pigment at the skin biopsy sites. The biopsy depicts evidence of melanin incontinence as evidenced by the arrows with the superficial dermis showing deposits of pigment, B: A hematoxylin and eosin stain was used to identify the architecture of the dermis and epidermis at the skin biopsy sites. This biopsy depicts unchanged epidermal architecture, C: A Fontanna-mason stain was used to identify pigment incomitance at the site of the skin biopsy as indicated by the arrows

3. Discussion

Previously published literature has implicated kratom use as a cause of the development of different types of hyperpigmentation and thus, it is our favored causative agent over levetiracetam (Table 1).[4-15] The combined morphological findings in our biopsy results together with clinical history were suggestive of kratom-induced hyperpigmentation. Differential diagnosis could include another variant of drug-induced hyperpigmentation or argyria; however, due to clinical history and distinct morphological features of the pigment deposits, diagnosis of kratom-induced pigmentation was made.

In the earliest of the referenced studies, Suwanlert *et. al*. describes the observation that chronic kratom users with substance abuse disorders can present with a muddy gray complexion akin to those seen in cirrhotic patients. This general finding of skin hyperpigmentation amongst long and short-term kratom users was also referenced in several survey studies in eastern countries summarized in table 1. In the referenced case reports, the studies describe patients that presented with a photo distributed pattern of pigmentation following kratom use akin to our patient's presentation.[4,7, 11-14] The patient that is presented in this report has a darker and more diffuse photo-distributed pattern of hyperpigmentation similar to the patient in Tunsuriyawong *et. al's* study. This highlights the possible progressive nature of this adverse effect. This patient also featured knuckle sparring similar to the patient in Suleman *et. al.,* indicating a possible recurring clinical pattern with this adverse effect. A unique pigmentation pattern seen in this study is pigmentation surrounding old scarring. This has not been seen in the referenced literature.

In Tunsuriyawong *et. al.,* the earliest published case report, a biopsy revealed epidermal hyperpigmentation and numerous melanophages in the papillary dermis. In Powell *et. al.*, hand and elbow biopsy sections revealed a normal distribution of junctional melanocytes, scattered deposits of nonpolarizable intrahistiocytic, perivascular, and interstitial red-brown pigment and a positive Fontana-Masson stain. The biopsy results were also able to rule out the presence of inflammation, hemosiderin, fungal or bacterial infection and pigmented purpuric dermatosis. Our study had similar findings regarding the distribution of junctional melanocytes, lack of evidence for inflammation and hemosiderin, however the deposits of pigments in our study had a smaller distribution of sizes with some deposits appearing parallel to collagen fibers. The positive Fontana-Masson stain in both biopsy results and the absence of minocycline or amiodarone in either patient gives credence to the notion that kratom may be involved in inducing melanin production. In Johnson *et. al.*, a neck biopsy results showed pigment-laden histiocytes with a negative result on Fontana-Masson and Prussian Blue stains. In Suleman *et. al.*, a biopsy revealed deposits of refractile, perivascular intrahistiocytic brown pigment. The pigment deposition stained positive with Fontana-Masson stain and negative for Periodic Acid Schiff and Prussian Blue stains. This study also supports our and Powell *et. al*.'s, conclusions given it's positive Fontana-Masson stain. Together, these findings suggest biopsy and histochemical staining are reliable diagnostic tools for evaluating kratom-induced hyperpigmentation.

To this point, the mechanism behind kratom's ability to cause hyperpigmentation is largely unclear. It has been postulated that mitragynine can cause activation of melanocytes-stimulating substance via modulation of D_2 receptors.[15] This in turn may be linked to activation of the melanocyte-stimulating substances.

From an osteopathic perspective, this patient was unfortunately not evaluated by an osteopathic physician; however, there are some osteopathic findings that may have been relevant if the patient had been evaluated, and these are pertinent to the current discussion. Patients with substance abuse struggles may present with withdrawal symptoms associated with somatic dysfunction indicative of autonomic imbalances.[16] For example, a patient experiencing acute kratom withdrawal symptoms may present with tachycardia, anxiety, and diarrhea, at which point the patient may benefit from autonomic-balancing indirect treatments targeted at cervical or thoracic segments. An osteopathic encounter may have also guided the final treatment plan with a Five Models of Care discussion on how to combat what is described in the literature as a disruption in dopamine homeostasis."[17] The ensuing discussion would likely include a behavioral focus centered around using resources available to the patient to manage the dependence. This approach would ensure that the physician is using a holistic method to manage the patient's substance abuse rather than fixating on the unique side effect of the tea. It is unclear if this would have changed the patient's mind about an intervention however a good discussion could have been had.

From a dermatologist's perspective, this case highlights the need to consider kratom toxicity when evaluating patients with diffuse hyperpigmentation after ruling out the more likely etiologies. The publication of recent case reports on this topic, combined with our findings, also sheds light on the use of histological stains as a diagnostic strategy for this unlikely effect of long-term kratom use.

From an osteopathic perspective, this case emphasizes the need for a whole-person approach to treating patients struggling with dependence. The patient presented in this case will require a biopsychosocial model of care to address her condition, including equipping her with tools to manage withdrawal symptoms that may arise during the tapering off of kratom. Osteopathic treatment can play a crucial role in alleviating these symptoms and supporting the patient during this process.

Table 1: A Summary of Kratom Associated Hyperpigmentation in the Literature

Study Authors (Publication Year)	**Age (yrs), Sex, Race of patient(s)**	**Kratom ROA, Dose, Regimen**	**Length of Kratom use**	**Location and Description of Pigmentation**	**Final Outcome**
Suwanlert et. al. (1975)	30 Thai participants with one described: 55 years, male, Thai	Chewing leaf or consumption of grinded leaf with hot fluids. Participants in study consumed 10-30 leaves a day	1-35 years; patient described had been using kratom for 35 years	Darkening complexion on face cheeks bilaterally	NR[a]; only one participant open to discontinuing kratom
Tunsuriyawong et. al. (2002)	66 years, male, Thai	Chewing leaf, patient chewed 25	30 years with pigmentation	Darkening of skin on trunk, back and extremities with	NR

		kratom leaves a day	beginning in last 5-6 years	buttock and skin crease sparing	
Vicknasingam et. al. (2010)	132 Malaysian participants, 3 Chinese participants and 1 "Indian/Other" participant	Fluid preparation, participants consumed 3.2 glasses of kratom daily on average (apx[a] 250 ml per glass)	72 participants had been using for 2 years or less while 64 patients had been using for over 2 years	Hyperpigmentation of cheeks was reported in 42 short term users and 21 long term users	NR; 78% of participants reported being unable to cease use of kratom
Saingam et. al. (2013)	34 male Thai participants	Chewing leaf, Chronic users had consumed 10–80 leaves per day on average while sporadic users had consumed 1 to 20 leaves per day on average	Chronic users had been using kratom for 3-50 years continuously while sporadic users had been using for 1-6 years	Study reports that "regular users" in the study had "dark skin"	NR; 18 users unsuccessfully tried to quit kratom use while 3 users quit successfully. No mention of change in pigmentation
Eaimchaloay et. al. (2019)	106 Thai participants with an average age of 32.6 years	45 users chewed kratom leaves, 60 users boiled kratom and 1 user consumed kratom capsules. 21 users reported using kratom less than 3 times a day while 24 users reported using kratom more than 3 times a day	38 kratom users part of the chewing group reported having used kratom for more than a year while 51 kratom users in the boiling group reported having used kratom for over a year	41.9% of total users reported hyperpigmentation as an adverse result of kratom use	NR
Powell et. al. (2022)	54 years, male, Caucasian	Powdered form consumed with orange juice 3-4 times a day	4-5 years	Blue-to-gray hyperpigmentation in patches on arms and face	NR
Johnson et. al. (2023)	56 years, female, NR	4–5 doses (unspecified) per day	7 years	Blue-to-gray hyperpigmented patches on face,	NR

				neck, chest, arms and legs	
Suleman et. al. (2023)	32 years, male, Caucasian	Kratom supplements (unspecified)	4-5 years	Blue-to-gray hyperpigmented patches over hands (sparing knuckles), arms, face and neck	NR
Patel et. al. (2024)	30 years, male, Caucasian	Kratom capsules, 815 grams daily for the 1st year and 3-7 grams daily for the next 4 years	5 years (hyperpigmentation began 4.5 years into use)	Dark gray-blue hyperpigmentation of the cheeks of the face, back of the neck and the backs of the hands and forearms.	Hyperpigmentation has not regressed in the 16 months after discontinuing kratom
Gandhi et. al. (2024)	63 years, male, NR	3 bottles of liquid kratom per day (apx 180 mg of mitragynine and less than 8 mg of [a]7-OHMG.)	5 years (hyperpigmentation began 4 years into use)	Tender and pruritic hyperpigmented patches on the face, neck and forearm	NR
Tassavor et. al. (2024)	34 years, female, Caucasian	6-8 teaspoons of kratom daily in a paste formulation	12 years (hyperpigmentation began 6 years into use)	Brown to gray hyperpigmented patches on the face, chest, arms, hands (with knuckle sparing) and on the left shin	NR

[a] NR not reported, Apx approximately, 7-OHMG 7-hydroxymitragynine

Table 1 A chronological summary of the findings in the relevant literature associating kratom with hyperpigmentation. Study findings were organized by patient demographics, kratom regimen and ROA, length of kratom use, details regarding the distribution of hyperpigmentation and outcome regarding kratom use

4. Disclosures

The authors have no competing interests or relevant financial/non-financial interests to disclose relevant to the content of this article. Consent was obtained from the patient for depiction in this study and publication of the manuscript. Study pathology report was performed by Chae Young Eun and Olga Nikolskaia. Manuscript was prepared by Bryan Tassavor and reviewed and approved by the primary investigator, Ruth Jobarteh-Williams.

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