

Marijuana: An Unusual Cause of Fixed Drug Eruption

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Abstract

Fixed drug eruptions (FDE) are a frequently reported mucocutaneous drug eruption. We present a case of multiple mucocutaneous lesions due to marijuana use presenting as FDE. Marijuana use continues to increase worldwide with the growing legalization for both medicinal and recreational use. As a consequence, it is crucial that clinicians be aware of any possible adverse reactions. The most common systemic and cutaneous signs of marijuana use are reviewed here. Dermatologists may be the first provider to encounter such clues, and as such we may be the first to recognize substance abuse and dependence, allowing earlier intervention for treatment.

Introduction

First described by Burns in 1889, subsequently named “eruption erythematopigmentee fixe” by Brocq, the “fixed drug eruption” is one of the most common types of drug eruptions, and its incidence continues to increase over the years relative to other drug eruptions.¹⁻³ The most characteristic findings of FDE are “lesions that recur at the same anatomic sites upon repeated exposure to an offending agent,” according to Pai et al.³ A large number of drugs, including barbiturates, penicillin, sulfonamides, tetracycline, bismuth and iodides, have been linked to FDE.⁴ Marijuana use, however, remains an underreported cause of FDE. As legalization of marijuana in the United

States becomes more widespread, it is important for clinicians to recognize the cutaneous manifestations of marijuana use. Because drug abuse carries a negative stigma, patients are not always immediately forthright in reporting their history of illicit drug use. By both recognizing cutaneous signs and routinely inquiring about illicit drug use, dermatologists can be the first to recognize signs of illicit drug use in patients, resulting in earlier treatment.

Case Presentation

A 32-year-old man presented to the dermatology clinic with complaints of recurring hyperpigmented patches on his face over the past year that were transient. He denied any pain, pruritis or discomfort. He noticed that the lesions would erupt in the same location on his face each time, on a monthly basis, and resolve in six to seven days. He denied any prior medical history and reported no medication use including over-the-counter medications.

Physical examination revealed a well-defined, 2 cm, circular hyperpigmented patch over his right zygoma with mild scaling at the periphery (Figure 1). Additionally, two 0.5 cm hyperpigmented macules bilaterally on the lower lip, and a 1 cm macule in the philtral ridge, were seen on examination (Figure 2).

Shave biopsy of the zygomatic lesion revealed interface vacuolar changes with dermal melanophages and some eosinophils, as well as near-full-thickness epidermal necrosis (Figures 3 and 4). The PAS stain failed to reveal any dermatophytes. However, the PAS did reveal normal thickness of the epidermal basement membrane, consistent with fixed drug eruption.

After the biopsy results returned, a careful review of the patient’s medical history revealed that each episode was produced by the same event -- recreational use of marijuana. A short course of topical corticosteroid therapy resulted in complete resolution of the lesions, and the patient was advised to abstain from marijuana use.

Discussion

Fixed Drug Eruptions

Drug eruptions are one of the most common cutaneous disorders encountered by dermatologists, representing 2% to 3% of all dermatological issues.³ FDE is a form of drug allergy that presents as single or multiple round, sharply demarcated, dusky red lesions several centimeters in diameter that occur at the same sites after each administration of the inciting drug.⁵ Pruritis and burning are often associated symptoms. The average age of onset is approximately 30 years old, and the most commonly implicated medication is trimethoprim-sulfamethoxazole.^{5,6} Between the time when the individual is first exposed to the medication and development of the first lesion, a variable refractory period can exist, ranging from a week to months or even years.⁵ With subsequent exposure, lesions appear within 30 minutes to eight hours. Typically, the lesions heal with residual hyperpigmentation. However, other types of FDE have been reported (Table 1).

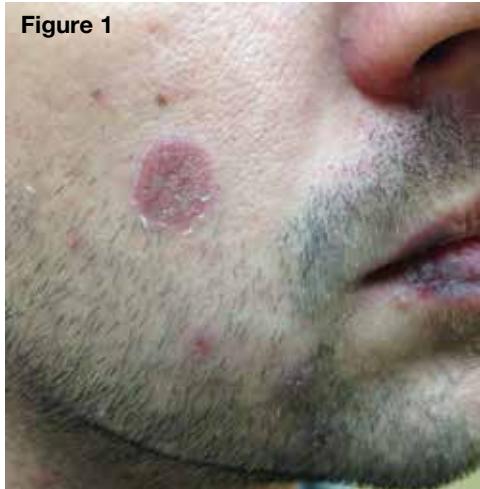


Figure 1



Figure 2

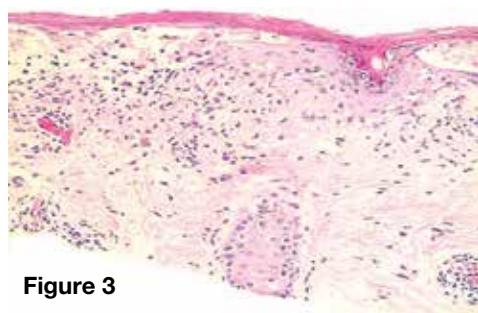


Figure 3

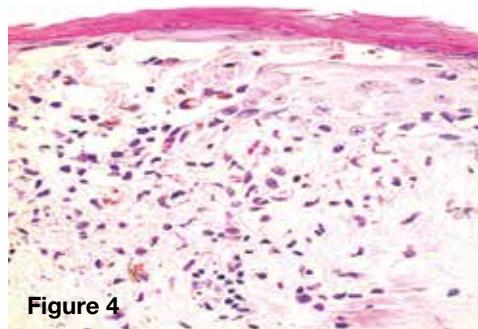


Figure 4

Table 1. Types of Fixed Drug Eruptions (FDE) and Examples of Causes^{3,5}

FDE Type	Presentation	Known Causes
Pigmenting	Lesions that heal with residual hyperpigmentation	Barbiturates, penicillin, NSAIDs sulfonamides, tetracyclines, bismuth, iodides
Erythema multiforme-like	Lesion with three zones: central, dusky purpura; elevated, edematous, pale ring; and surrounding erythema	Mefenamic acid ²⁰
Toxic epidermal necrolysis-like	Widespread, bullous lesions	NSAIDs ²¹
Linear	Multiple lesions that are distributed linearly; may follow Blaschko's lines or nerve-root distribution	Trimethoprim
Wandering	Involved sites that don't flare with each exposure and activity that does not always appear at the same location with each recurrence	Acetaminophen
Nonpigmenting	Lesions that do not leave any residual hyperpigmentation and appear uniformly red	Pseudoephedrine hydrochloride, tetrahydrozoline, contrast media, betahistine, etodolac
Bullous	Subepidermal blisters that heal without scarring	Aminophenazole, antipyrine, barbiturates, cotrimoxazole, trimethoprim, sulfamethoxazole, diazepam, mefenamic acid, acetaminophen, phenylbutazone, piroxicam, sulfadiazine, sulfathiazole

Our patient presented with the classic pigmented FDE, with lesions appearing within six hours of marijuana use.

While generally only a solitary lesion appears on first exposure, repeated administration of the medication can lead to new lesions or an increase in size of the original lesions.⁵ Although they can occur anywhere on the skin, FDE's most

commonly occur on the glans penis, lips, palms, soles and groin area.⁵ Overall, the legs are most commonly affected in women and the genitalia are most commonly affected in men.¹

As explained by Pai et al., the reaction "is believed to be a lymphocyte CD8-mediated reaction, wherein the offending drug may induce local reactivation of memory T cell lymphocytes ...

Table 2: Cutaneous manifestations of illicit drug use^{8,10}

Illicit Drug	Percent of Americans Using (12+ Years Old)	Cutaneous Manifestations
Cannabis	7.5%	Contact urticaria, cannabis arteritis, skin aging
Cocaine/Crack	0.6%	Nasal septal perforation, "snorter warts," madarosis, bullous erythema multiforme, "crack hands," scleroderma, Henoch-Schonlein purpura, vasculitis due to levamisole
Ecstasy	0.4% hallucinogen use (including LSD and ecstasy)	"Ecstasy pimples," guttate psoriasis
Methamphetamine	0.2%	"Meth mites," "meth mouth," xerosis, premature aging
Heroin	0.1%	Track marks, cellulitis, candida folliculitis, transcutaneous botulism, granuloma formation, pruritis, fixed drug eruption, "puffy hand syndrome," tourniquet hyperpigmentation

targeted initially by the viral infection."¹ Histological examination displays two possible scenarios depending on when the biopsy is done. In lesions that are only one to two days old, examination reveals hydropic degeneration of basal keratinocytes with dyskeratotic cells in the epidermis and exocytosis of mononuclear cells.³ Healed hyperpigmented lesions often demonstrate pigmentary incontinence revealing dermal melanophages with little perivascular infiltration of inflammatory cells, as seen in our patient.³ To identify the culprit of the FDE, provocation tests can be done, with the patch test being the most commonly used method. The patch test is effective as long as it is placed over a previously involved site and the patient is not in the refractory period.³ Challenging a patient with an oral provocation test has been associated with generalized bullous lesions in some cases.⁵ In our case, we did not re-challenge the patient with the suspected drug due to legal concerns. Treatment consists of cessation of the suspected drug along with the use of topical steroids and systemic antihistamines.³ Extensive lesions, or those with bullae, may require systemic corticosteroids.³ Post-inflammatory hyperpigmentation can be treated with hydroquinone bleaching creams.⁵

Cutaneous manifestations of illicit drug use

According to the Substance Abuse and Mental Health Administration, in 2013 "an estimated 24.6 million individuals aged 12 or older were current illicit drug users," representing over 9% of the population in the United States.⁸ Dermatologists may be the first to recognize drug abuse in select patients, allowing for earlier intervention and treatment (**Table 2**). As often the vascular and cardiac manifestations are internal, they cannot be readily seen by clinicians outside of dermatology.

Cannabis

Cannabis remains the most commonly used illicit drug, with an estimated 7% of the population in the United States using this substance regularly.⁹ Since the Neolithic times, cannabis, which is the Latin name for hemp, has been widely used, with the first account of marijuana in the Western medical literature reported in 1840 by the British physician O'Shaughnessy.^{9,10} Today, *Cannabis sativa* has a wide variety of uses ranging from recreational use for its psychoactive properties or medicinal properties, to biofuel, insulation, animal litter, paper, cosmetics, rope and fabric manufacturing.¹⁰ The stem provides the fibers, while the resin produced from the flowering tops is often used recreationally. The seeds are commonly used for birdseed or fishing bait.¹¹ There are four subspecies of *Cannabis sativa*, varying in geographic location and in application (**Table 3**). "Hashish" refers to the unadulterated resin that is collected and dried, while marijuana refers to the cut flowers, leaves and stems, which generally possess a fifth of the potency of hashish.⁹

Cannabis can be smoked or consumed in foods, infusions or vapor form. Delta-9-tetrahydrocannabinol (THC), the main

Table 3: Subspecies of Cannabis sativa¹⁰

<i>Cannabis sativa</i> Subspecies	Use	Region
Sativa (cultivated hemp)	Recreational (high tetrahydrocannabinol [THC] content), industrial uses	Worldwide, primarily equatorial regions
Indica (Indian hemp)	Recreational use (high THC content), seldom used for its fiber	Himalayas, Middle East, India
Spontanea (wild hemp)	Industrial use (low THC content, not commonly used for recreation)	Eastern Europe, China, Russia
Kafiristanica (Afghan hemp)	Recreational use (high THC content), unfit for manufacturing of fibers	Afghanistan, Pakistan

psychoactive substance in cannabis, which is found in the plant's resin, is responsible for its perception- and mood-altering properties. The concentration of THC can vary from 0.1 to 12%, depending upon the subspecies and method of preparation.¹² Onset of activity after smoking marijuana is within 10 to 20 minutes, and the effects usually resolve within three hours.⁹ Cutaneous manifestations of marijuana present as conjunctival injection, contact urticaria, and type 1 hypersensitivity, which can include anaphylaxis or cannabis arteritis. Cannabis arteritis, a subtype of thromboangiitis obliterans, is seen mainly in long-term users.¹² Cannabis arteritis is believed to be caused by the vasoconstrictive side effects of THC and contaminants such as arsenic (known to cause thromboangiitis obliterans in cigarette smokers) and is one of the major causes of peripheral arterial disease in patients under the age of 50.^{10,12} Manifestations of this atherogenesis include Raynaud's phenomenon; digital necrosis with small, dry necrotic patches on the extremities; and decreased tibial and pedal pulses. Diagnosis is based upon duplex ultrasound in order to differentiate it from atherosclerosis.¹² Treatment includes cessation of marijuana, aspirin (81 mg to 200 mg daily) or, in severe cases, iloprost.¹² Smoking marijuana is also associated with premature skin aging, resulting in prominent wrinkles.⁷ A case of erythema multiforme-like recurrent drug eruption was also reported with marijuana use.¹³ No reported cases of fixed drug eruption secondary to marijuana use were found in a literature search.

In the 1980s, an epidemic of fixed drug eruptions occurred in Holland due to heroin being smoked, and presented as hyperpigmented lesions of the tongue.¹⁴ Despite denial by our patient, one possibility is that heroin may have been mixed in the marijuana cigarette, and thus the FDE may have been due to adulterants and not the marijuana.

Conclusion

To our knowledge, this is the first case report describing fixed drug eruption elicited by recreational marijuana use. With 19.8 million current users in the United States and the growing rate of use associated with legislature changes, questions regarding a patient's recreational drug use should be included in the patient's history.⁸ By recognizing the cutaneous findings of illicit drug use, dermatologist can stand on the forefront of early recognition.

References

- Pai VV, Bhandari P, Kikkeri NN, Athanikar SB, Sori T. Fixed drug eruption to fluconazole: a case report and mini-review of literature. Indian J Pharmacol. 2012;44(5):643-645.
- Brocq L. Eruption erythema-pigmentee fixe due a l'antipyrine. Ann Dermatol Venereol. 1894;5:308-313.
- Lee AY. Fixed drug eruptions. Incidence, recognition and avoidance. Am J Clin Dermatol. 2000;1(5):277-285.
- Stritzler C, Kopf AW. Fixed drug eruption caused by 8-chlorotheophylline in Dramamine with clinical and histologic studies. J Invest Dermatol. 1960;34:319-330.
- Gendernalik SB, Galeckas KJ. Fixed drug eruptions: a case report and review of literature. Cutis. 2009;84(4):215-219.
- Ozkaya-Bayazit E, Bayazit H, Ozarmagan G. Drug related clinical pattern in fixed drug eruption. Eur J Dermatol. 2000;10(4):288-291.
- Liu SW, Lien MH, Fenske NA. The effects of alcohol and drug abuse on the skin. Clin Dermatol. 2010;28(4):391-399.
- Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. The NSDUH Report: Substance Use and Mental Health Estimates from the 2013 National Survey on Drug Use and Health: Overview of Findings. SAMHSA: Rockville (MD); 2014.
- Lieberman CM, Lieberman BW. Current concepts: marihuana—a medical review. N Engl J Med. 1971;284(2):88-91.
- Tennstedt D, Saint-Remy A. Cannabis and skin diseases. Eur J Dermatol. 2011;21(1):5-11.
- Williams C, Thompstone J, Wilkinson M. Work-related contact urticaria to Cannabis Sativa. Contact Dermatitis. 2008;58(1):62-63.
- Hennings C, Miller J. Illicit drugs: what dermatologists need to know. J Am Acad Dermatol. 2013;69(1):135-142.
- Ozyurt S, Muderrisoglu F, Ermete M, Afsar F. Cannabis-induced erythema multiforme-like recurrent drug eruption. Int J Dermatol. 2014;53(1):e22-23.
- Westerhof W, Wolters EC, Brookbakker JT, Boelen RE, Schipper ME. Pigmented lesions of the tongue in heroin addicts-fixed drug eruption. Br J Dermatol. 1983;109(5):605-610.

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