Phytophotodermatitis: Case Report and Review of the Literature

Paul H. Janda, DO; Sanjay Bhambri, DO; James Q. Del Rosso, DO; Narciss Mobini, MD

Phytophotodermatitis is a common phototoxic dermal reaction caused by the interaction between certain plants, sunlight, and human skin. The causal agents in plants have been identified as furocoumarins, which are photoactive compounds. Although the plants causing phytophotodermatitis vary, in the United States phytophotodermatitis most commonly occurs following exposure to plants belonging to the Rutaceae and Umbelliferae families.

Phytophotodermatitis is a common phototoxic dermal reaction caused by the interaction between certain plants, sunlight, and human skin. Klaber[1] was the first to coin the term in 1942. The causal agents in plants have been identified as furocoumarins, which are photoactive compounds.[2] Although the plants causing phytophotodermatitis vary, in the United States phytophotodermatitis most commonly occurs following exposure to plants belonging to the Rutaceae and Umbelliferae families.[3] Phytophotodermatitis is a phototoxic reaction, occurring in skin exposed to UV radiation after contact with plants containing furocoumarins.[4,5] The clinical changes most commonly include erythema, followed by vesiculation with development of bullae in the skin 24 to 72 hours later and then followed by hyperpigmentation.[3] Phytophotodermatitis is associated with minimal symptomatology and morbidity, although persistent hyperpigmentation may be bothersome or worrisome to some patients, especially when it occurs at commonly exposed locations (ie, face and hands).[4] Accurately recognizing the symptoms of phytophotodermatitis is important in avoiding misdiagnosis and preventing repeated episodes of exposure; phytophotodermatitis has been misdiagnosed as a cutaneous sign of child abuse.[6-8]

Dr. Janda is an intern and Dr. Bhambri is Chief Resident, Dermatology, Valley Hospital Medical Center, Las Vegas, Nevada. Dr. Del Rosso is Clinical Associate Professor, Dermatology, University of Nevada School of Medicine, Las Vegas; Clinical Associate Professor, Dermatology, Touro University College of Osteopathic Medicine, Henderson, Nevada; and Dermatology Residency Director, Valley Hospital Medical Center, Las Vegas. Dr. Mobini is Clinical Assistant Professor, Department of Pathology and Internal Medicine (Dermatology), University of Nevada School of Medicine, Las Vegas.

The authors report no conflicts of interest in relation to this article.

CASE REPORT

A 9-year-old white female, accompanied by her mother, presented with a 4-week history of perioral hyperpigmentation. Macular hyperpigmentation, characterized by a homogenous light brown color, was noted without perivermilion sparing. The eruption was asymptomatic. Both the patient and her mother did not recall any previous eruption or irritation such as redness or a rash around the mouth area. The remainder of the cutaneous examination, including oral and ocular mucosae, was negative for any significant findings.

Past medical and family histories were unremarkable, including dermatologic disorders. Medication history was also unremarkable. There was no history of allergies, including any to medications.

The main diagnostic considerations were postinflammatory hyperpigmentation developing after contact

dermatitis. Photodermatitis, including phytophotodermatitis, was also considered. Initial questioning did not uncover any contactant or photocontactant.

The attending dermatologist was highly suspicious of phytophotodermatitis, despite denial by the patient and her mother of repeated exposure to limes or lemons. Questioning regarding recent travel revealed a 2-week vacation in Fort Lauderdale, Florida. Repeated querying led to the patient finally admitting that she loved eating limes and lemons, especially lemons; in fact, she admitted to eating slices of both limes and lemons every day while on vacation. The patient also admitted being concerned that she would need to stop. The attending dermatologist discussed phytophotodermatitis with the patient and her mother, mentioning that limes and lemons combined with UV (sunlight) exposure are common causes of this type of skin discoloration.

DISCUSSION

Historical Aspects

Phytophotodermatitis has a long, interesting history that dates back to 1000 to 1500 BC. Patients with vitiligo in China, Egypt, and India had certain plant extracts applied to the affected areas and were then instructed to lie in the sun.[9] In 1834, Kalbrunner isolated bergapten (5-methoxypsoralen) from *Citrus bergamia*.[10] Later, in 1916, Freund described hyperpigmented skin lesions resulting from exposure to bergamot oil in perfume and the sun, a condition currently known as berloque dermatitis.[10] Oppenheim, in 1934, coined the term *dermatitis bullosa striata pratensis* to describe an erythematous, bullous eruption in a bizarre configuration appearing on sunbathers who had been lying in grass.[10,11] It was in 1942 that Klaber introduced the term *phytophotodermatitis* to elucidate the role of plants (*phyto*) and light (*photo*) in the manifestation of dermatitis.[10] The work of Kuske established the relationship between the chemical components of certain plant tissues and the development of phytophotodermatitis.[1] Furthermore, Kuske and associates presented evidence that the photosensitizing substances responsible for phytophotodermatitis were of the furocoumarin group. Jensen and Hansen[12] determined the wavelengths that produce the typical lesions of phytophotodermatitis: 320 to 400 nm.[11,13,14]

Photochemistry

Phytophotodermatitis is classified as a phototoxic reaction.[1,3,15,16] The skin contains a compound that absorbs UV radiation and is excited to a reactive state to yield direct toxic effects.[15,17] Furocoumarins are the chemical compounds implicated in phytophotodermatitis.[1,3,4,10,11,18-20]

Plants Commonly Associated With Phytophotodermatitis

Family	Botanical Name	Common Name
Rutaceae	*Citrus acida*	Lime
	Citrus aurantifolia	Persian lime
	Citrus bergamia	Bergamot
	Citrus limon	Lemon
	Citrus paradisi	Grapefruit
	Citrus sinensis	Sweet orange
	Pelea anisata	Mokihana
Umbelliferae	*Anethum graveolens*	Dill
	Apium graveolens	Celery
	Daucus carota	Wild carrot
	Daucus sativus	Garden carrot
	Foeniculum vulgare	Sweet fennel
	Pastinaca sativa	Parsnip
	Petroselinum crispum	Parsley
Moraceae	*Ficus carica*	Fig

They are tricyclic hydrocarbons composed of a furan ring condensed on benzopyrone. Linear furocoumarins (psoralens) are more phototoxic than angular furocoumarins (angelicin).[18] These substances are found in a number of plant families, including Rutaceae (common lime and bergamot) and Umbelliferae (celery, garden and wild carrots, parsley, sweet fennel, dill, and parsnip).[13] The Table provides a more comprehensive list.

The UV spectrum is traditionally divided into 3 subdivisions: UVC (200–290 nm), UVB (290–320 nm), and UVA (320–400 nm). UVA is further divided into UVA_2 (320–340 nm) and UVA_1 (340–400 nm). UVA is associated with aging effects, whereas UVB causes sunburn.

Furocoumarins cause phytophotodermatitis by forming phototoxic compounds on exposure to UVA radiation.[4,10,11,13,15,16,18] On exposure to UVA radiation, furocoumarins absorb photons to form highly reactive, energy-rich triplets. Two distinct reactions occur. The direct photochemical (type I) reaction occurs independently of oxygen and involves furocoumarins and DNA. Covalent bonding of the activated furocoumarins to the pyrimidine bases on opposite strands of epidermal-cell DNA occurs, causing interstrand cross-linking, cell injury, and inhibition of DNA synthesis.[14] It is this collective phenomenon that plays a major role in the cutaneous damage of phytophotodermatitis.[14] The photodynamic (type II) reaction is dependent on oxygen and yields the formation of superoxide anions, hydroxy radicals, and singlet oxygen species. These interact to damage epidermal, dermal, and endothelial cell membranes in addition to intracellular enzymes, ribonucleic acid, and DNA.[10,18] Keratinocytes, melanocytes, Langerhans cells, fibroblasts, and mononuclear and endothelial cells are all targeted by these reactions.[10,13] Phototoxic damage manifests as edema, erythema, vasodilation, and bulla formation. Hyperpigmentation may result from melanocyte stimulation via the type I reaction or from melanocyte injury.[4]

Cutaneous Reaction of Phytophotodermatitis

Phytophotodermatitis and other phototoxic skin reactions are nonimmunologic and do not require previous sensitization.[21] They may arise in any individual, provided that a sufficient amount of a phototoxic compound is present and that it is activated by a threshold radiation dose of the appropriate spectrum.[10,13,18,22] When applied locally, furocoumarins penetrate the skin rapidly and are measurable in the urine after 4 hours.[10,23] Furthermore, phototoxic reactions have been shown to occur within 15 minutes of local application, with UVA sensitivity peaking 30 minutes to 2 hours later.[10,24]

Important Contributory Factors

Despite the common pathogenesis of phytophotodermatitis, reports exhibit marked variation in the severity of reaction.[4,16,25] For instance, there are reports of decreased severity of reaction on areas of skin that have a thicker stratum corneum. Pigmentation from previous sun exposure also plays a protective role.[4,26] Hispanics and African Americans, who have naturally higher amounts of melanin in their skin, are less affected.[4,27] Intactness of the stratum corneum, number of hair follicles, and degree of skin hydration all contribute to the absorption of the phototoxic compounds.[4,19] The ability of a photosensitizer to be absorbed through the skin is another important variable and depends on the vehicle by which the photosensitizer is applied.[20,28] Other contributory factors have been demonstrated, such as sweating, heat, friction, and longer duration of sun exposure, all of which exacerbate phototoxic effects.[4,29] Lastly, furocoumarin concentration has been shown to vary in certain plants, and differing reactions may indicate this variability.[1,2]

Clinical Features

Phytophotodermatitis is the manifestation of a photosensitizing compound combined with exposure to UV radiation. Cutaneous signs of inflammation appear after a latent period of approximately 24 hours and localize only to the areas of skin on which plant phototoxic compounds were deposited, followed by exposure to UVA radiation.[1,3-5,10,11,16-19,28] These signs include erythema, edema, and bullae in unusual configurations, often in the form of "finger marks" or streaks, corresponding to sites of contact on sun-exposed skin.[17] This process culminates at 72 hours. Hyperpigmentation appears after 1 to 2 weeks and lasts for several months.[13,30] Pruritus does not seem to be common, which may help differentiate phytophotodermatitis from toxicodendron dermatitis.[18]

In the absence of erythema and bullae, as was noted in this case, a history of citrus fruit or other plant exposure may aid in diagnosing phytophotodermatitis.[19] The area of skin involved may also aid in diagnosis. For example, a perioral reaction may develop in individuals who return from a trip to Mexico, where they enjoyed margaritas or tequila shots, which involve sucking on a lime after consuming the drink.[1] There are also instances of patients developing phytophotodermatitis on their hands after making fresh lemonade.[18,25] In Europe, phytophotodermatitis is most commonly caused by applying rue to the skin as an insect repellant.[9,11,18] Furthermore, the tradition of wearing leis of *Pelea anisata* in Hawaii has been linked to phytophotodermatitis along the neck.[18,31]

Cases of phytophotodermatitis reported in medical literature are associated with minimal morbidity.[4] As a corollary, it is significant to note the potentially serious

social consequences arising from the misdiagnosis of these lesions as signs of child abuse. Several reports have documented that phytophotodermatitis can be mistaken for the cutaneous signs of child abuse.[7-9,17,32,33]

Histology

Epidermal changes include dyskeratotic cells, mild spongiosis, and intracellular edema at 24 hours, increasing up to 72 hours and still present for 1 week, when hyperkeratosis, parakeratosis, and acanthosis are also evident.[10,11] Dermal changes include endothelial swelling, nuclear dust, and extravasated erythrocytes at 48 hours, culminating at 72 hours, when a mononuclear infiltrate and papillary edema appear.[4,10]

The hyperpigmentation associated with phytophotodermatitis is caused by increased melanin granules in the epidermis, both in the stratum Malpighi and in the hyperkeratotic stratum corneum. After 72 hours, there is increased mitotic activity of the melanocytes from the type I reaction; also, there are increased functional melanocytes, with increased production of melanosomes and upregulated tyrosinase activity.[4,10]

Treatment

Therapy of phytophotodermatitis is primarily symptomatic.[17] During the acute phase, when erythema, bullae, and sometimes pain are present, topical corticosteroid therapy and cold compresses may help alleviate symptoms.[11,17,18] Monitoring for secondary infection is recommended, as is educating the patient on how to avoid future episodes.[17]

There are only 3 globally approved active ingredients in sunscreens that are capable of attenuating long-wavelength UVA radiation: avobenzone, titanium dioxide, and zinc oxide.[1] Sunscreens containing the UVA blocker ecamsule are important in impeding UVA radiation. In addition, sunscreens providing UVA filtering contain physical blocks (titanium dioxide or zinc oxide) or the chemical block avobenzone. It is UVA radiation that is implicated in phytophototodermatitis.[4,10,11,15,16] Ecamsule, a novel UVA filter, provides efficient UVA coverage, better photostability, and enhanced water resistance. Sunscreens containing ecamsule are widely used in Europe and Canada. It was not until 2006 that the US Food and Drug Administration approved the compound.[34] It can be concluded that sunscreens deficient in these ingredients yield insufficient protection against phytophotodermatitis.

For individuals at risk of phytophotodermatitis from occupational exposure, the use of protective gloves for avoiding skin contact with plants is recommended.[11] Although topical hydroquinones applied daily for 6 to 12 weeks may aid in resolving hyperpigmentation, they are generally an unnecessary measure, as these lesions resolve spontaneously.[3,17] Sunscreens are warranted for the affected area, as it may be hypersensitive for several months after the initial insult.[11,18] Since long-wavelength UV radiation is implicated in phytophotodermatitis, chemical sunscreens containing paraaminobenzoic acid or esters of paraaminobenzoic acid are not believed to be optimal; opaque sunscreens containing titanium dioxide and zinc oxide are generally preferred.[11]

REFERENCES

1. Klaber R. Phyto-photo-dermatitis. *Br J Dermatol.* 1942;54: 117-118.
2. Wilkinson JD, Rycroft RJG. Contact dermatitis. In: Rook A, Wilkinson DS, Ebling FJG, et al, eds. *Textbook of Dermatology*. 5th ed. Oxford, United Kingdom: Blackwell Scientific Publication; 1992:611-715.
3. Mitchell JC, Fisher AA. Dermatitis due to plants and spices. In: Fisher AA, ed. *Contact Dermatitis.* 3rd ed. Philadelphia, PA: Lea & Febinger; 1986:418-453.
4. Wagner AM, Wu JJ, Hansen RC, et al. Bullous phytophotodermatitis associated with high natural concentrations of furanocoumarins in limes. *Am J Contact Dermat.* 2002;13:10-14.
5. Mantle D, Gok MA, Lennard TW. Adverse and beneficial effects of plant extracts on skin and skin disorders. *Adverse Drug React Toxicol Rev.* 2001;20:89-103.
6. Barradell R, Addo A, McDonagh AJ, et al. Phytophotodermatitis mimicking child abuse. *Eur J Pediatr.* 1993;152:291-292.
7. Klaber M. Phytophotodermatitis mimicking child abuse. *J R Soc Med.* 1998;91:58.
8. Coffman K, Boyce WT, Hansen RC. Phytophotodermatitis simulating child abuse. *Am J Dis Child.* 1985;139:239-240.
9. Lovell CR. *Plants and the Skin.* Cambridge, MA: Blackwell Scientific, 1993:86-95.
10. Kavli G, Volden G. Phytophotodermatitis. *Photodermatol.* 1984;1:65-75.
11. Pathak MA. Phytophotodermatitis. *Clin Dermatol.* 1986;4: 102-121.
12. Jensen T, Hansen KG. Active spectral range for phytogenic photodermatosis produced by Pastinaca sativa. *Arch Dermatol Syphilol.* 1930;40:566.
13. Finkelstein E, Afek U, Gross E, et al. An outbreak of phytophotodermatitis due to celery. *Int J Dermatol.* 1994;33:116-118.
14. Musajo L, Rodighiero G. Studies on the photo-C4-cycloaddition reactions between skin-photosensitizing furocoumarins and nucleic acids. *Photochem Photobiol.* 1970;11:27-35.
15. Musajo L, Rodighiero G, Dall'Acqua F. Evidences of a photoreaction of the photosensitizing furocoumarins with DNA and with pyrimidine nucleosides and nucleotides. *Experientia.* 1965;21: 24-26.
16. Harber LC, Bickers DR. Phytophotodermatitis. In: *Photosensitivity Diseases: Principles of Diagnosis and Treatment*. 2nd ed. Philadelphia, PA: Saunders; 1989:11-26.
17. Solis RR, Dotson DA, Trizna Z. Phytophotodermatitis: a sometimes difficult diagnosis. *Arch Fam Med.* 2000;9:1195-1196.
18. Bowers AG. Phytophotodermatitis. *Am J Contact Dermat.* 1999;10:89-93.
19. Berkley SF, Hightower AW, Beier RC, et al. Dermatitis in grocery workers associated with high natural concentrations of furanocoumarins in celery. *Ann Intern Med.* 1986;105:331-355.
20. Held JL. Phytophotodermatitis. *Am Fam Physician.* 1989;39: 143-146.
21. Stoner JG, Rasmussen JE. Plant dermatitis. *J Am Acad Dermatol.* 1983;9:1-15.

22. Epstein JH. Phototoxicity and photoallergy in man. *J Am Acad Dermatol.* 1983;8:141-147.
23. Kammerau B, Klebe U, Zesch A, et al. Penetration, permeation and resorption of 8-methoxypsoralen: comparative in vitro and in vivo studies after topical application of four standard preparations. *Arch Dermatol Res.* 1976;255:31-42.
24. Suhonen R. Phytophotodermatitis: an experimental study using the chamber method. *Contact Dermatitis.* 1977;3:127-132.
25. Nigg HN, Nordby HE, Beier RC, et al. Phytotoxic coumarins in limes. *Food Chem Toxicol.* 1993;31:331-335.
26. Sams WM. Photodynamic action of lime oil (*Citrus aurantifolia*). *Arch Derm Syphilol.* 1941;44:571-587.
27. Crow KD, Alexander E, Buck WH. Photosensitivity due to pitch. *Br J Dermatol.* 1961;73:220-232.
28. Kaidbey KH, Kligman AM. Topical photosensitizers: influence of vehicles on penetration. *Arch Dermatol.* 1974;110:868-870.
29. Yoke Marchant Y, Turjman M, Flynn T, et al. Identification of psoralen, 8-methoxypsoralen, isopimpinellin, and 5,7-dimethoxycoumarin in *Pelea anisata*. *Contact Dermatitis.* 1985;12:196-199.
30. Darby-Stewart AL, Edwards FD, Perry KJ. Hyperpigmentation and vesicles after beach vacation: phytophotodermatitis. *J Fam Pract.* 2006;55:1050-1053.
31. Elpern DJ, Mitchell JC. Phytophotodermatitis from mokihana fruits (*Pelea anisata* H. Mann, fam. Rutaceae) in Hawaiian lei. *Contact Dermatitis.* 1984;10:224-226.
32. Hill PF, Pickford M, Parkhouse N. Phytophotodermatitis mimicking child abuse. *J R Soc Med.* 1997;90:560-561.
33. Mehta AJ, Statham BN. Phytophotodermatitis mimicking non-accidental injury or self harm. *Eur J Pediatr.* 2007;166:751-752.
34. D'Souza G, Evans GR. Mexoryl: a review of an ultraviolet filter. *Plast Reconst Surg.* 2007;120:1071-1075.