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Seminars in Cutaneous Medicine and Surgery

Update on Photodermatoses

Frank A. Santoro, MD, and Henry W. Lim, MD

Interactions with ultraviolet radiation (UVR) and chromophores in the skin happen on a daily basis. Photodermatoses, which are abnormal responses to UV exposure, can be classified into subgroups based on pathogenesis. This review will discuss the clinical features, pathogenesis, photobiologic evaluation, prognosis and therapies of the most common photodermatoses.

KEYWORDS photodermatoses, polymorphous light eruption, chronic actinic dermatitis, solar urticaria, erythropoietic protoporphyria, porphyria cutanea tarda, phototoxicity, photoallergy

Photodermatoses is a broad term referring to skin diseases provoked by exposure to ultraviolet (UV) radiation. It can be classified into 4 groups: immunologically mediated photodermatoses, chemical- and drug-induced photosensitivity, photoaggravated dermatoses, and inherited disorders with defective DNA repair or with chromosomal instability (Table 1).[1] In this review we will discuss the clinical features, pathogenesis, photobiologic evaluation, prognosis, and therapies of the more commonly encountered photodermatoses: polymorphous light eruption, chronic actinic dermatitis, solar urticarial, phototoxicity, photoallergy, porphyria cutanea tarda, and erythropoietic protoporphyria. (Table 2)[2-5] lists the characteristics of less commonly seen immunologically mediated photodermatoses.

Approach to Patient with Suspected Photodermatoses

A detailed history, including the relationship between eruption and sun exposure, duration of lesions, effect of window glass-filtered sunlight, exposure to photosensitizing agents, family history, age of onset, seasonal variation, and systemic symptoms are important elements to consider. A skin examination in which one focuses on the morphology and distribution, specifically involvement of the head, face, neck, arms, legs, and torso, and absence underneath the chin, underneath the lips, nasolabial folds, and postauricular area can provide further diagnostic clues. Further investigations, such as antinuclear antibody titers, skin biopsies, phototesting, photopatch testing, and porphyrin levels, might support diagnoses.

Phototesting and Photopatch Testing

Phototesting and occasionally photopatch testing are important parts of evaluation. Phototesting involves exposing a patient's skin to increasing doses of UVA, UVB, and visible light. An immediate assessment to evaluate for solar urticaria and a delayed assessment at 24 hours are performed. The minimal erythema dose (MED) for UVA (MED-A) and UVB (MED-B), defined as the lowest dose of radiation that produces perceptible erythema covering the entire irradiated area, is determined. Phototest responses in common photodermatoses are shown in Table 3.

Up to 10% of patients with photosensitivity will have a positive photopatch test.[6] Photopatch testing involves the application of 2 sets of identical photoallergens. After 24 hours, one set will be irradiated with UVA (10 J/cm^2, or 50% of MED-A if the MED-A is decreased), whereas the other set serves as a control and remains unexposed. A reading is performed at 24 hours and 7 days after irradiation. A photocontact allergic reaction is characterized by a reaction only on the irradiated site. Positive reactions on both irradiated and unir-

Department of Dermatology, Henry Ford Hospital, Detroit, MI.
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Address reprint requests to Henry W. Lim, MD, Department of Dermatology, Henry Ford Med Center – New Center One, 3031 West Grand Boulevard, Suite 800, Detroit, MI 48202. E-mail addresses: fsantor1@hfhs.org (Dr Santoro); and hlim1@hfhs.org (Dr Lim)

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Table 1 Classification of Photodermatoses*

Immunologically mediated
Actinic prurigo
Chronic actinic dermatitis
Hydroa vacciniforme
Polymorphous light eruption
Solar urticaria
Chemical- and drug-induced photosensitivity
Caused by exogenous agents
Photoallergy (topical and systemic)
Phototoxicity (topical and systemic)
Caused by endogenous agents
Cutaneous porphyrias
Pellagra
Photoaggravated dermatoses
Acne vulgaris
Atopic dermatitis
Bullous pemphigoid
Carcinoid syndrome
Cutaneous T-cell lymphoma
Darier's disease
Dermatomyostitis
Disseminated superficial actinic porokeratosis
Erythema multiforme
Grover's disease
Lichen planus
Lupus erythematosus
Pemphigus
Pityriasis rubra pilaris
Psoriasis
Reticular erythematous mucinosis
Rosacea
Seborrheic dermatitis
Viral infections
Inherited disorders with defective DNA repair or with chromosomal instability
Ataxia-telangiectasia
Bloom syndrome
Cockayne syndrome
Hailey–Hailey disease
Hartnup disease
Kindler syndrome
Rothmund–Thomson syndrome
Trichothiodystrophy
Xeroderma pigmentosum

*Modified from Lim et al.[1]

radiated sites *with equal intensity* indicate a contact allergy to the test substance. Positive reactions on both sites with *greater intensity* at the irradiated site indicate both contact and photocontact allergy.

Immunologically Mediated Photodermatoses

Polymorphous Light Eruption

Clinical Features

Polymorphous light eruption (PMLE) is an immunologically mediated photodermatosis that manifests as nonscarring erythematous, pruritic papules, vesicles, pinpoint papules, papulovesicles, plaques, and nodules that erupt usually within a few hours of sun exposure (Fig. 1). Commonly involved sites include the dorsum of the hands, V-area of the neck, and sometimes, malar area of the face. Patients may complain of mild pruritus, whereas some also present with tenderness of the skin. Systemic symptoms, including chills, headache, fever, and nausea, can be observed in some patients. For an individual patient, the same morphology usually is present with each eruption. Pinpoint papules are more commonly seen in patients with darker skin.[7] In temperate climates, the eruption worsens in early spring and improves as the sunny season progresses; this is known as "hardening."

Prevalence ranges from 10% to 20%, varying by geographic location.[8] PMLE is mostly seen in temperate latitudes with initial eruptions observed in the spring. In a cohort of 138 patients,[9] females represented 61.6% of the patients. Sixty-six percent of patients developed PMLE before 30 years old, and 11% after 50 years of age.

Pathogenesis

There is increasing evidence to indicate that delayed-type hypersensitivity immune reactions to ultraviolet radiation (UVR)-induced neoantigens of the skin plays a role in the pathogenesis of PMLE.[10] It is recognized that UVR induces neoantigens in the skin, although their nature is poorly characterized. UVR also has an immunosuppressive effect in the skin. In patients with PMLE, it has been demonstrated that they do not have the same degree of immunosuppression after exposure to UV, and hence are more likely to react to these neoantigens, resulting in the development of skin lesions.[11] Proinflammatory markers, such as E-selectin, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1 and cytokines (interluekin-1, interleukin-18, and tumor necrosis factor-alpha) have also been shown to be increased in the skin of patients with PMLE.[12]

Phototesting

Although many patients with PMLE have normal MEDs (Table 2), repeated exposure to UVA or UVB (ie, provocation phototesting) can elicit lesions of PMLE in more than 60% of patients.[13] Testing with UVA (320-400 nm) has been more effective than UVB (280-320 nm) and combined UVA/UVB at provoking disease; the ease of PMLE provocation does not correlate with clinical morphology or disease severity.

Prognosis

In a patient self-reported survey of 113 individuals on the natural course of PMLE,[9] 39% declared sun sensitivity remained the same; 40%, increased, and 14%, decreased sun sensitivity. A minority of patients had intervals without eruptions, however, the vast majority of them developed PMLE lesions during the follow-up period.

When PMLE involves the malar area, cutaneous lupus erythematosus (LE) needs to be ruled out by appropriate serologic testing (antinuclear antibody, anti SSA/Ro antibodies). However, studies following patients with positive antinuclear antibodies (titer $>$ 1:80) and PMLE have shown that PMLE does not progress into LE.[14]

Table 2 Less Commonly Encountered Immunologically Mediated Photodermatoses

Photodermatosis	Clinical Findings	Treatment
Actinic prurigo	• Age of presentation: childhood • Symptoms/timing: pruritic sensation a couple of hours after sun exposure. Might have chronic pruritus. The disease improves in the winter in temperate climates and shows no variation in tropical climates. • Mucosal involvement is common with involvement of the lip in 30%-60% of patients. Acute chelitis has exudative, yellow-crusted lesions whereas dry and scaling lips are characteristic of chronic chelitis.[2] Conjunctivitis and photophobia are present in 30% of patients.[3] • Morphology: excoriated, papules, or nodules that resolve with scarring. Chronic pruritus might result in lichenified plaques. • Distribution: face, ears, forearms, hands, legs and feet. Involvement of photo-protected areas has been reported, especially in patients reported from the United Kingdom.	• Photoprotection • Symptomatic relief: topical and systemic corticosteroids, antihistamines • Beta-carotene, antimalarials -low doses of PUVA and NB–UVB with patient-reported similar efficacy[4] • Thalidomide (50-100 mg/d): most consistently effective treatment • With the exception of thalidomide, it is often resistant to treatment.[5]
Hydroa vacciniforme	• Age of presentation: childhood • Symptoms/timing: pruritic and stinging sensation followed by the appearance of an erythematous eruption within a few hours after sun exposure. Worsens in spring/summer. • Morphology: the initial lesions are symmetric erythematous macules progressing into papules that undergo vesiculation and crusting, leaving deep, hypopigmented varioliform scars • Distribution: malar area, bridge of nose, lips, ears, and dorsal hands and forearms	• Photoprotection • Beta carotene, omega 3 polyunsaturated fatty acids • NB–UVB phototherapy or PUVA • Antimalarials • Immunosuppressive medications: cyclosporine, thalidomide, and azathioprine

NB-UVB, narrowband UVB; PUVA, psoralen UV.

Treatment

First-line treatment includes hardening of the skin with narrowband UVB (NB–UVB) in the early spring. The mechanism of UV hardening is most likely attributable to the induction of immunosuppression in these patients, who are less likely to be immunosuppressed by exposure to sunlight during daily activity.[15] In a cohort of 281 patients treated with NB–UVB,[16] 63% had no PMLE lesions after treatment, 26% had mild PMLE, and 11% did not respond. Treatment protocol consists of exposure to NB–UVB 3 times a week for 15 sessions, starting at 70% MED and increased as tolerated by 10%-20% each session. In patients who are exquisitely sensitive, a lower starting dose and less aggressive dose increase should be used. In some, oral prednisone (0.6-0.8 mg/kg/d) for the

Table 3 Commonly Seen Results of Phototesting in Selected Photodermatoses*

Photodermatosis	MED-A	MED-B	Visible Light	Comments
Polymorphous light eruption	nl (↓ in 30%)	nl (↓ in 30%)	nl	
Chronic actinic dermatitis	↓ or nl	↓ or nl	↓ or nl	
Solar urticaria	nl	nl	nl	It has an immediate urticarial response that clears in 24 hours
Hydroa vacciniforme	↓	↓ or nl	nl	
Actinic prurigo	↓ or nl	↓ or nl	nl	
Photoallergy, topical	nl	nl	nl	
Photoallergy, systemic	↓	nl	nl	
Phototoxicity, topical	nl	nl	nl	
Phototoxicity, systemic	↓	nl	nl	

MED, minimal erythema dose; nl, normal.
*Modified from Lim et al.[1]

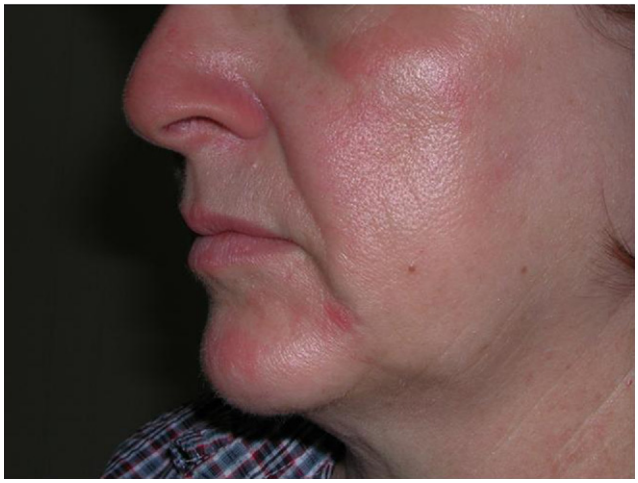

Figure 1 Polymorphous light eruption. Erythematous patches and plaque on sun-exposed sites.

first 7-10 days of hardening therapy may need to be administered. Patients are advised to continue the hardening process at home with intermittent sun exposure (20-30 min of mid-day summer sun exposure, without sunscreen); otherwise, the effect will be lost in 4-6 weeks.[16] NB–UVB is comparable with psoralen UV; it has gained favor over psoralen UV because it has fewer side effects.[16]

Other treatment modalities, such as antimalarials, beta carotene, nicotinamide, omega-3 polyunsaturated fatty acids, *Escherichia coli* filtrate (colibiogen), and *Polypodium leucotomos* extract have been reported to be helpful, but large trials have not been performed to determine their efficacy.[13] Oral and topical corticosteroids treat an acute flare, but they do not prevent future flares; the former can be used (0.6-0.8 mg/kg/d) for 5-10 days in otherwise-healthy patients who wish to have a brief visit to sunny locales during the winter.

Chronic Actinic Dermatitis (CAD)

Clinical

This is an immunologically mediated photodermatosis with a contact dermatitis-like reaction against sunlight-induced endogenous cutaneous antigens. Patients present with pruritic, lichenified eruptions involving photo-exposed skin, particularly on the face, back of the neck, and forearms and dorsal hands, often with a sharp demarcation from non-photoexposed areas (Fig. 2). It spares the upper eyelids, fingerwebs, and postauricular area. Clinical variants range from acute eruption of erythematous patches, papules and plaques to the more characteristic chronic lesions, which are lichenified, excoriated plaques.

CAD has been reported in Europe, the United States, and Asia. It mostly affects older men. In a study of 178 patients,[17] the age distribution was 6% in patients younger than 40 years of age, 43% between 40 and 59 years; and 51% older than 60 years of age.

Hawk and Magnus[18] coined the term CAD, unifying observed presentations of the same condition: persistent light reactivity, actinic reticuloid, photosensitive eczema, photosensitivity dermatitis and actinic reticuloid syndrome. Three diagnostic criteria for CAD are (i) persistent, mostly photodistributed, eczematous eruption, which might be associated with infiltrated papules and plaques; (ii) histologic findings consistent with chronic eczema with or without cutaneous lymphoma-like changes; (iii) abnormal results on phototesting to UVA and/or to UVB and/or to visible light.[19] In a report from the United Kingdom, patients often had allergic contact dermatitis to common or airborne allergens, especially plant antigens (such as Compositae plants), fragrances, and topical medications. In addition, CAD has been described in association with human immunodeficiency virus (HIV)[20] and atopic dermatitis.[21]

Pathogenesis

The pathogenesis of CAD is not completely understood. The presence of $CD8^+$ T-cell infiltrates in affected skin suggests a delayed-type hypersensitivity immune reaction, likely to photo-induced cutaneous autoantigen(s).[22] The autoantigen might be an altered carrier protein, nuclear material (RNA or DNA), or a native skin antigen (such as histidine) altered by UV radiation. Immunologic response to contact allergens, such as sesquiterpene lactone, colophony and fragrances is another potential mechanism.[22] In a British study researchers compared patch and photopatch testing in their patients from 1987 to 1992 and 2000 to 2005; they found a decrease in sesquiterpene lactone reactions and an increase in nonfragrance consumer allergens, such as para-phenylenediamine and preservatives.[23]

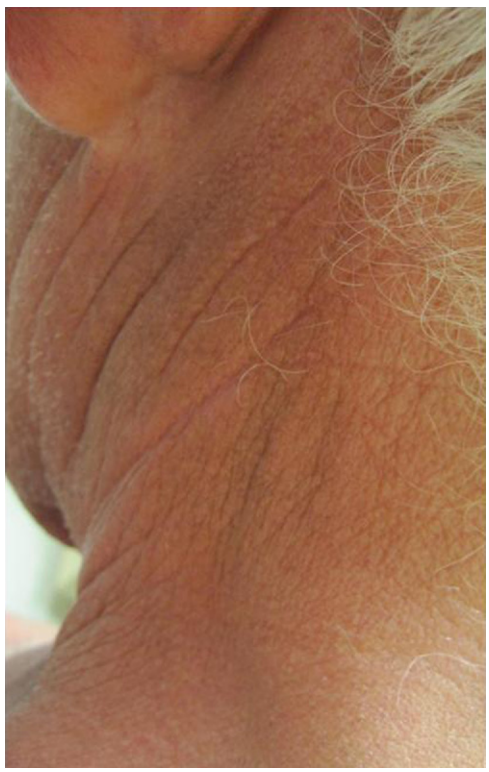

Figure 2 Chronic actinic dermatitis. Erythema and lichenification on sun-exposed site; note the relative sparing of postauricular area.

Phototesting

In a study of 51 patients, the most common abnormal phototesting results were decreased MEDs to both UVA and UVB (65% of patients), followed by decreased MED to UVA alone (14%).[24] In patients who have history of exposure to known photoallergens, photopatch testing is helpful. In contrast to patients in the United Kingdom, studies of patients seen in the United States and Japan did not suggest an increase in incidence of positive photopatch tests.[25]

Prognosis

In a study of 178 patients, 10% of patients had resolution in 5 years, 20% in 10 years, and 50% in 15 years.[26] If photosensitivity resolves, any accompanied contact allergy usually persists. Two predictors of poor prognosis are severe UVB photosensitivity and the presence of 2 or greater contact allergens.

Treatment

Given the marked photosensitivity and wide action spectrum, CAD proves difficult to treat. Photoprotection with broad-spectrum UVA and UVB sunscreens is imperative, although it rarely provides complete clearance. In addition, clear museum film can be fitted to car windows to minimize UV penetration.[17] Some patients might respond to hardening with NB–UVB phototherapy, however; because many are highly sensitive to UVB, oral and topical corticosteroids should be given to the patient before hardening.[17]

Systemic treatments include azathioprine (50-200 mg/d), hydroxychloroquine (200 mg daily or BID), mycophenolate mofetil, 25-40 mg/kg[17] and for resistant cases, cyclosporine (4-5 mg/kg).[24] Of all the options, azathioprine is the only one that has been studied in a double-blind, placebo-controlled manner, while the others have been anecdotal cases or a small case series.

Solar Urticaria

Clinical Features

Solar urticaria (SU) is an uncommon photodermatosis characterized by the appearance of erythema and wheals after sun exposure. The wheals usually appear within 30 minutes of sun exposure with spontaneous resolution within 24 hours. Common locations of eruptions include the V of the neck and arms. Pruritus, and in some, burning, are the primary symptoms.

SU only accounts for 0.4% cases of urticaria.[27] Because it occurs rarely, only case series have been reported. In one Scottish study, investigators estimated prevalence in their population of 3.1 per 100,000.[27] Although most patients have strictly symptoms of SU, there have been reports of SU in conjunction with PMLE and CAD. Associations with medications, porphyria, lupus erythematosus, or topical tar application have been reported.[27]

Pathogenesis

SU is thought to be mediated through a type I hypersensitivity mechanism. A skin chromophore likely absorbs UV photons and produces a photoallergen, which subsequently becomes recognized by specific IgE. The IgE in turn binds to mast cells, causing the release of histamine and other inflammatory mediators.[27]

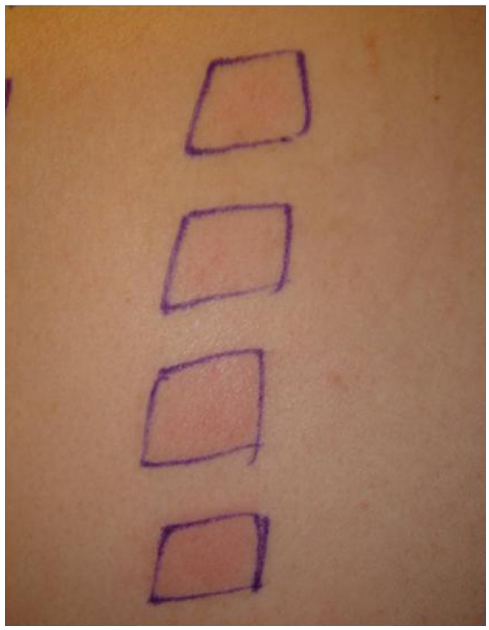

Figure 3 Solar urticaria. Urticaria 10 min after completion of exposure to increasing doses of UVB.

Phototesting

Given the transient nature of the disease, phototesting for disease provocation is an important diagnostic tool; evaluation should be done within 30 minutes of UV or visible light exposure (Fig. 3). Reports of sensitivity to UV and visible light have been variable. In a group of 40 patients in Japan, Uetsu et al[28] reported 60% of their patients were sensitive to only visible light. In contrast, in a cohort of 84 patients studied in Scotland, 6% were sensitive to UVA alone; 1.2% to UVB alone; 31% to visible light alone; 42% to UVA and visible light; and 20% to UVA, UVB and visible light.[27]

Prognosis

Reports of natural history vary. One study reported clinical resolution in 57.5% of patients after 5 years, and 82.5% after 6 years.[29] Another study showed less dramatic resolution with only 15% resolution in 5 years increasing to 24% and 46% at 10 and 15 years, respectively.[27]

Treatment

Oral antihistamines, topical corticosteroids, and cool compresses can provide symptomatic relief of acute eruption. For long-term management, oral antihistamines and broad spectrum sunscreens can be used; however, the latter would not be very effective for patients with action spectrum extending to the visible light range. For patients with visible light photosensitivity, photoprotection needs to be achieved with sun avoidance, clothing, and opaque sunscreens. Systemic agents, such as antimalarials and beta carotene are of little value. Although oral corticosteroids could suppress the eruption, their known side effects preclude their chronic use. Mycophenolate mofetil and cyclosporine can be effective for

recalcitrant disease. Because the pathogenesis likely involves a circulating antibody, both intravenous immunoglobulin and plasmapheresis have been used with some success.[30]

"Hardening" through phototherapy to UVA, UVB, or visible light can be initiated,[31,32] with UVA hardening being the most commonly used therapy. This consists of graduated exposure to increasing doses of UVA. Because the effects of hardening dissipate over a couple of days, patients are encouraged to expose themselves to sunlight, or to continue with maintenance phototherapy throughout the sunny season.

Chemical- and Drug-Induced Photosensitivity

Exposure to UV or visible light can alter topical and systemic agents into potent photosensitizers. Through mechanisms detailed in the sections to follow, photosensitizing agents cause an irritant (phototoxic) or allergic (photoallergic) reaction. Table 4[33] lists common agents that cause these reactions.

Phototoxicity

A phototoxic reaction begins when an agent absorbs photons of energy, usually in the UVA *spectrum*, and causes excitation of the molecule. When these excited state molecules return to their ground state, they transfer energy to surrounding oxygen, thereby inducing the generation of reactive oxygen species (ROS). The ROS cause cellular damage through the oxidation of lipids, nucleic acids and proteins.[34]

Clinically, a phototoxic reaction resembles a sunburn. Painful erythema and occasional bilstering develop minutes to hours in sun-exposed skin. Less common manifestations, such as pseudoporphyria, photo-onycholysis, slate-gray hyperpigmentation, and lichenoid eruptions have been reported. Removal of the offending agent results in resolution.

Voriconazole, a systemic, broad-spectrum antifungal, has been associated with photosensitivity, photoaging, pseudoporphyria, chelitis, and xerosis. Voriconazole does not absorb UVA or UVB. However, its main metabolite, voriconazole N-oxide absorbs UVA and UVB and may be the chromophore for phototoxicity.[35] In patients with voriconazole-induced photosensitivity who were treated for over a year, an association between aggressive squamous cell carcinoma[35] and melanoma[36] has been observed in photo-exposed sites. The association with skin cancer warrants close evaluation and follow-up of patients on voriconazole treatment of >1 year.

Photoallergy

Photoallergic reaction requires sensitization of the immune system through a delayed-type hypersensitivity mechanism. UV radiation induces the chemical or drug to conjugate with a carrier product. This conjugation forms an antigen that elicits an immune response.[34] Upon reexposure to both the agent and the action spectrum, a delayed hypersensitivity response occurs. Photoallergy can be induced by small

Table 4 Common Phototoxic and Photoallergic Medications*

Phototoxic Medications (Systemic)	Photoallergic Medications
Antianxiety drugs	Antimalarial
Alprazolam	Quinidine
Chlordiazepoxide	Antimicrobials
Antiarrhythmics	Topical
Amiodarone	Bithionol
Quinidine	Chlorhexidine
Antidepressants	Dibromosalicylanilide
Desipramine, imipramine	Tetrachlorosalicylanilide
Antifungals	Tribromosalicylanilide
Griseofulvin	Fentichlor
Voriconazole	Hexachlorophene
Antimalarials	Triclosan
Chloroquine	Systemic
Quinine	Quinolones
Antimicrobials	Sulfonamides
Quinolones: ciprofloxacin, enoxacin, oflaxacin	Fragrances
Sulfonamides	6-methylcoumarin
Tetracyclines: tetracycline, demeclocycline, doxycycline, minocycline	Musk ambrette
Trimethoprim	Sandalwood oil
Antineoplastics	Nonsteroidal anti-inflammatory drugs
Fluorouracil	Ketoprofen
Dacarbazine	Piroxicam
Methotrexate	Phenothiazines
Vinblastine	Chlorpromazine, promethazine
Diuretics	Sunscreen ingredients
Furosemide	Benzophenoine-3, 4
Thiazides	Padimate-O, A
Food additives	Homosalate
Sulfites	Menthyl anthranilate
Furocoumarins	para-aminobenzoic acid (PABA)
Psoralens	Avobenzone
Hypoglycemics	
Sulfonylureas	
Tolbutamide, tolazamide	
Glyburide	
Acetohexamide	
Hypolipidemics	
Fibrates: bezafibrate, clofibrate,	
Fenofibrate	
Nonsteroidal inflammatory drugs	
Celecoxib	
Ibuprofen, ketoprofen	
Naproxen	
Piroxicam	

*Adapted from Lim et al.[33]

Table 5 Characteristics of the Porphyrias*

	Clinical Features	Enzyme Deficiency	Elevated Porphyrins or Porphyrin Precursors
Acute porphyrias			
AIP	• Acute neurological attacks • Absence of photosensitivity and cutaneous signs and symptoms	Porphobilinogen deaminase	Urine: ALA, PBG
VP	• Cutaneous findings clinically similar to PCT • Acute attacks similar to AIP	Protoporphyrinogen oxidase	Urine: ALA, PBG Feces: protoporphyrin > coproporphyrin
Hereditary coproporphyria	• Rare • Acute attacks clinically similar to AIP • Erythema and blistering	Coproporphyrinogen oxidase	Urine: ALA, PBG Feces: coproporphyrin III > protoporphyrin
Delta-aminolevulinic acid dehydratase (ALA-D) deficiency porphyria	• Extremely rare • Acute attacks clinically similar to AIP • No photosensitivity or cutaneous signs and symptoms	Delta-aminolevulinic acid dehydratase	Urine: ALA
Nonacute porphyrias			
PCT	• Most common porphyria • Clinically similar to VP • Moderate to severe photosensitivity • Skin fragility, vesicles, bullae, skin fragility, erosions, milia, scarring, hypertrichosis	Uroporphyrinogen decarboxylase	• Urine: isomer III of uroporphyrin, heptacarboxylporphyrins, coproporphyrin • Feces: isocoproporphyrin
Erythropoietic protoporphyria (EPP)	• Age of onset: childhood • Erythema, edema, purpura, skin thickening, waxy scars • Can have liver disease	Ferrochelatase	• Urine: normal • RBC: protoporphyrin • Feces: protoporphyrin
CEP (Günther disease)	• Rare • Age: infancy • Severe clinical course with vesicles, bullae, erosions, ulcers, scarring, hyperpigmentation, hypertrichosis, mutilation • Hemolytic anemia, hepatosplenomegaly • Porphyrins deposit in teeth and bones	Uroporphyrinogen III synthase	• Urine: uroporphyrin I, coproporphyrin I • Feces: coproporphyrin I
Hepatoerythropoietic porphyria	• Rare; considered homozygote form of PCT • Age: infancy • Most patients have severe photosensitivity • Vesicles, bullae, skin fragility, erosions, crusts, milia, scarring, hypertrichosis	Uroporphyrinogen decarboxylase	Identical to PCT, except for elevated RBC protoporphyrin

AIP, acute intermittent porphyria; ALA, delta-aminolevulinic acid; CEP, congenital erythropoietic porphyria; PBG, porphobilinogen; PCT, porphyria cutanea tarda porphyria; RBC, red blood cells; VP, variegate porphyria.

*Adapted from Sassa.[37]

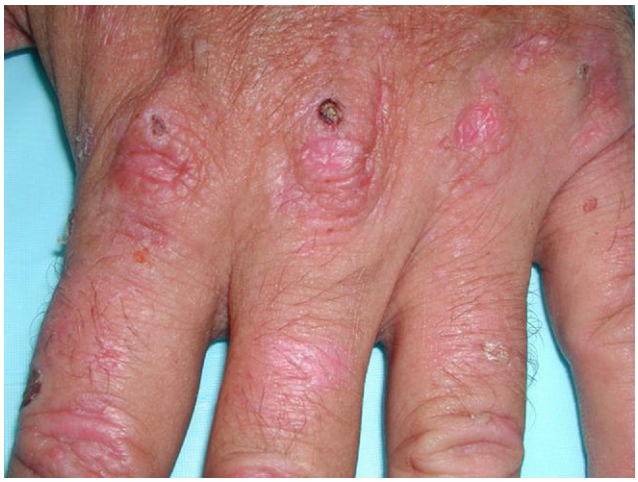

Figure 4 Porphyria cutanea tarda. Skin fragility, manifested as erosions and crusting on traumatized areas.

amounts of the photoallergen. Currently, because of the wide-spread use, sunscreen actives are the most common photoallergen worldwide.

Clinically, a photoallergic reaction resembles contact dermatitis. Pruritic, eczematous eruptions confined to photo-exposed areas erupt in 1-2 days after repeat exposure. Histologic examination reveals spongiotic dermatitis. Removal of the offending agent causes resolution of the dermatitis. Topical and occasionally oral corticosteroids can hasten the resolution.

Porphyrias

The porphyrias are uncommon metabolic conditions caused by deficiencies in the activities of enzymes in the heme biosynthetic pathway. Although most of porphyrias are inherited, some are acquired. In addition to a genetic predisposition, environmental factors influence their clinical development. Table 5[37] lists the clinical features of the acute and nonacute porphyrias, their enzyme deficiencies and notable biochemical findings. The 2 most common types of cutaneous porphyrias will be reviewed: porphyria cutanea tarda (PCT) and erythropoietic protoporphyria (EPP).

PCT

Clinical

PCT commonly presents in the fourth to fifth decade of life with skin fragility and tense, blisters on photo-exposed skin (Table 5). The vesicles and bullae break easily and leave behind denuded areas which crust and heal slowly (Fig. 4). Periorbital hypertrichosis and hyperpigmentation are common, whereas sclerodermoid skin changes (which can occur in nonsun exposed sites) are rare. Risk factors include infection with hepatitis C virus and HIV, alcohol abuse, HFE gene mutation (causes hereditary hemochromatosis), and estrogen intake. The accumulation of porphyrins in the liver, in addition to disease risk factors, leads to low-grade hepatocellular damage. In some patients, without treatment, PCT can progress to liver failure and potentially hepatocellular carcinoma.[38]

Patients with PCT tend to develop glucose metabolism alterations years into their disease course. Associated risk factors with PCT, combined with intrinsic features of PCT (porphyrin accumulation, chronic liver damage and iron overload) likely contribute to the development of diabetes mellitus in patients with PCT.[39]

Pathogenesis

PCT has 3 subtypes, all associated with decreased hepatic uroporphyrinogen decarboxylase (UROD) activity: type I occurs sporadically with normal erythrocyte UROD activity; type II is familial with decreased erythrocyte UROD activity; and type III is also familial but has normal red blood cell UROD activity. The accumulated porphyrins in the skin are photoactivated by electromagnetic radiation in the Soret band region (400-410). This interaction produces ROS that cause cellular damage and lead to characteristic cutaneous findings.[37,38] The enzyme deficiency alone is insufficient to produce the clinical symptoms of PCT, therefore, highlighting the importance of the aforementioned environmental and other risk factors in the production of clinically evident disease.[40]

Treatment

Avoidance of precipitating factors (alcohol, estrogens) and photoprotection are the first-line treatments. It should be noted that because the action spectrum is in the visible light range, only opaque sunscreens are effective. Notably, treatment of hepatitis C virus does not always improve PCT. Periodic phlebotomy decreases outbreaks because iron is a known porphyrinogenic agent. If phlebotomy is ineffective or if the patient has contraindications to phlebotomy, low dose hydroxychloroquine (200 mg twice weekly) can be effective. Antimalarials most likely chelates porphyrins and makes them more soluble, thereby promoting renal excretion.[37] Deferoxamine, a chelating agent, has also provided benefit.[41]

Erythropoietic Protoporphyria

Clinical

Immediately after sun exposure, patients with erythropoietic protoporphyria (EPP) usually have symptoms of burning and stinging. Because most children develop symptoms before they reach 2 years of age, they cry upon minimal sun exposure. Clinical findings include erythema, edema, and petechiae in photo-exposed areas. Typically there is an absence of skin fragility, and blisters are rare. Chronic lesions manifest as lichenification and scarring on chronically exposed areas, such as knuckles of fingers and dorsum of the nose (Fig. 5). Ten percent of patients will develop hepatic injury,[42] and 5% will develop liver failure. Currently, no markers exist to predict individuals at risk of hepatic involvement.

Pathogenesis

EPP has a partial deficiency of ferrochelatase activity leading to accumulation of protoporphyrin. The mechanism of EPP is similar to PCT with activation of the accumulated porphyrins

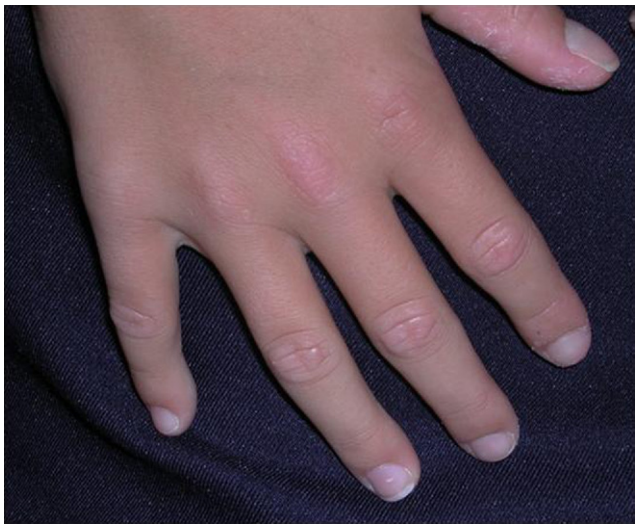

Figure 5 Erythropoietic protoporphyria. Waxing thickening of the knuckles secondary to repeated phototoxic injury.

causing cellular damage. Because protoporphyrin is a lipophilic 2-carboxyl porphyrin, a prominent target for phototoxic injury is the endothelial cell. Thickening and hyalinization of the capillary basement membrane are observed on histologic examination. In addition, accumulation of protoporphyrin in the liver can cause direct hepatocyte toxicity and cholestasis.[43]

Treatment

In addition to photoprotection and sunlight avoidance, beta-carotene has been reported with varying success as a treatment of EPP. Afamelanotide, an alpha melanocyte-stimulating hormone analogue that induces melanin formation, has been shown to improve tolerance to sunlight and less painful episodes in a small cohort of patients with EPP.[44]

Two medical treatments for hepatic disease include cholestyramine (encourages fecal excretion of protophyrin) and inducing iron overload (enhances the conversion of protoporphyrin to heme). In severe cases, bone marrow transplant might have a role in preventing end-stage liver disease.[45] If the patient progresses to end-stage liver disease, liver transplant might be indicated, but because it is not curative of the underlying enzyme deficiency, EPP can cause fibrosis of the transplant.[45]

Conclusions

The diagnosis of photodermatoses requires a detailed history and physical examination. Phototesting, bloodwork, and skin biopsies often confirm clinical suspicion. Improvements in treatment modalities require understanding the mechanisms of diseases and conducting double-blind randomized, multicenter controlled trials. With more objective data, physicians will better serve their patients in controlling the activity of their disease.

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