Photoreactions and Testing

7

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7.1 Definition and Types of Reactions

Photosensitivity represents an abnormal cutaneous reaction to light, usually ultraviolet (UV) light. Photosensitive reactions can occur in individuals who lack the usual UV-defense mechanisms, e.g., vitiligo or xeroderma pigmentosum, who have increased endogenous chromophores in their skin, e.g., porphyrias, or who are exposed to exogenous chemicals that are activated in the skin by UV light, e.g., plants, drugs, and UV filters.

These exogenous chemicals activated by UV light can induce skin inflammation by different mechanisms – phototoxicity, photoallergy, or both. Photoactivation of the exogenous chemical can transfer energy to neighboring molecules and induce aggression of the epidermal cells (lesions on DNA bases, oxidation of lipids of cell membranes, or modification of proteins) or generate reactive oxygen species causing a nonspecific inflammatory reaction – phototoxicity. Also, upon receiving UV

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energy, exogenous chromophores can be modified into stable photoproducts or can bind skin proteins forming antigens that are presented to the immune system and induce a lifelong sensitization dependent on specific memory and effector T cells. A further exposure to the chemical and UV light will cause a delayed hypersensitivity reaction – acute photoallergy – and continuous exposure to the photosensitizer may be associated with chronic photosensitivity. Some few chemicals induce exclusively photoallergy, but many have some phototoxic potential and also induce sensitization in a limited number of individuals [1, 2].

Upon UV exposure, cutaneous photoreactions develop when a significant level of the photoactive chemical reaches the skin after oral/parenteral route (systemic photosensitivity) or when the chemical is applied on the skin (contact photosensitivity). The latter is usually divided into photoallergic contact dermatitis (PhACD) and contact phototoxicity.

7.2 Clinical Aspects and Differential Diagnosis

Cutaneous photoreactions are almost exclusively localized to sun-exposed areas, usually the area where there was concomitant exposure to UV and the chemical applied on the skin. In systemic photosensitivity, they usually involve the face, V of the neck, dorsum of the hands and forearms, and spare shaded areas as the submandibular region, retroauricular folds, upper eyelids and upper lip, deep wrinkles, and areas covered by natural hair or clothing (Figs. 7.1 and 7.2). This pattern needs distinction from airborne contact dermatitis that develops also on exposed areas but needs no sun exposure. Shaded areas are also involved in airborne dermatitis, and body folds can even be preferentially involved. PhACD involving the face can also be difficult to distinguish from contact dermatitis from a facial cosmetic, as the relation with sun exposure is not always very evident due to the delay of 1–2 days for lesion expression. PhACD from products used in the mouth can occur only on the lips and chin [3, 4].

Phototoxicity is more frequent, can occur on first exposure as it needs no previous sensitization, and presents typically as exaggerated sunburn that develops within 24–48 h as erythema, eventually with bullae, usually with sharp limits, and tends to regress with brown hyperpigmentation.

Photoallergy is less frequent than phototoxicity and occurs in a limited number of exposed individuals. Except in a few individuals who are already allergic to a cross-reactive molecule, lesions develop after a longer exposure to the photosensitizer (latency period required for sensitization). Once sensitized, the reaction develops within 24–48 h of exposure and, particularly in PhACD, presents as acute or subacute eczema that begins at the area of application but may extend beyond its limits and, eventually, generalize.

Histopathology shows sunburn cells (apoptotic keratinocytes) and nonspecific inflammation in phototoxicity, whereas in PhACD, an acute eczema with spongiosis and T-cell exocytosis is usually observed, but there is no definite histopathologic distinction between these two patterns (Table 7.1).

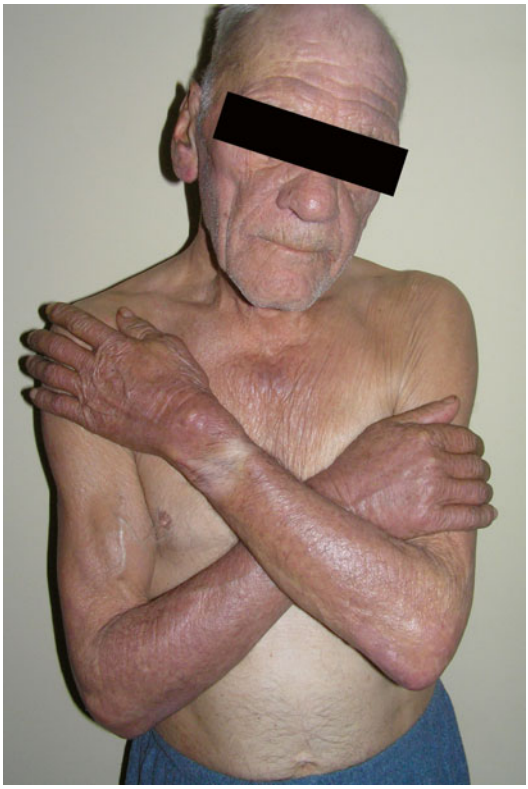

Fig. 7.1 Systemic chronic drug photosensitivity, with symmetrical lesions involving the face and V of the neck and forearms, with protection of the area covered by the wrist watch

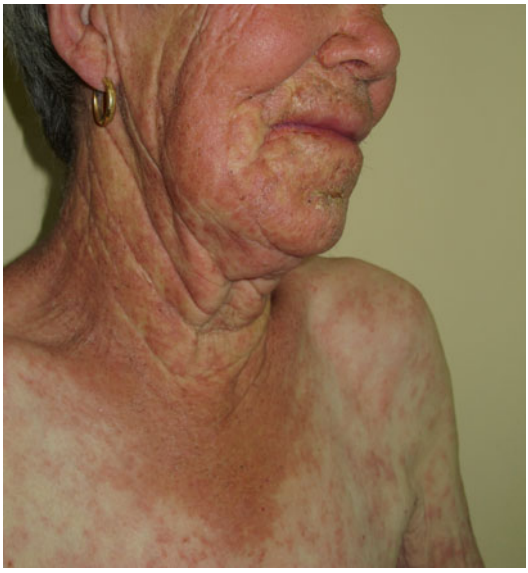

Fig. 7.2 Photoreaction from ingestion of *Hypericum perforatum* infusion with main lesions on photoexposed areas but eczematous and erythema multiforme-like lesions outside the exposed area, suggesting a concomitant photoallergy

Table 7.1 Clinical aspects of photoreactions

Predominant in phototoxicity	Predominant in photoallergy or immune-mediated reactions
Frequent, can occur first exposure	Rare, needs previous sensitization
Lesions with sharp limits	Lesions may extend to covered areas
Exaggerated "sunburn"	Acute vesicular, papular eczema
Pseudoporphyria	Subacute/chronic eczematous lesions
Photoonycholysis	Erythema multiforme-like
Hyperpigmentation	Lichenoid reactions
Hypopigmentation	Cheilitis
Telangiectasia	Urticaria on sun-exposed area
Purpura	Pellagra-like reactions
Histology – sunburn cells	Histology – spongiosis, lymphocyte exocytosis
Quick regression	Possible persistence/recurrence and cross-reactions
Increase in actinic keratosis and nonmelanoma skin cancer in the long term	Possible subacute or chronic cutaneous lupus erythematosus

7.3 Main Causes of Photoreactions

A phototoxic dermatitis occurs frequently after contact with plants rich in furocoumarins (Moracea, e.g., *Ficus carica*, or Rutacea, e.g., *Ruta graveolens*, and citrus fruit peels, particularly lime, *Citrus aurantifolia*). It presents as linear lesions with non-pruritic erythema and bullae, in the acute stage, followed by long-lasting brown hyperpigmentation streaks (Fig. 7.3). Ingestion of infusions of these plants, like *Hypericum perforatum* used as folk medicine to treat depression (Fig. 7.2), can also cause systemic photoreactions [5].

Drugs are the main cause of systemic photosensitivity, mostly dependent on phototoxicity, even though other mechanisms (increased porphyrins levels, as with vemurafenib) [6, 7] and photoallergy also have to be considered (as in photoallergy to the nonsteroidal anti-inflammatory drug (NSAID) piroxicam). Cutaneous lesions in systemic drug photosensitivity involve photoexposed areas mostly in a symmetric distribution and present mainly as eczematous lesions or exaggerated sunburn, or also as pseudoporphyria, simulating porphyria cutanea tarda (naproxen, voriconazole, celecoxib), photoonycholysis (tetracyclines), hyperpigmentation (amiodarone), vitiligo-like lesions (flutamide), telangiectasia (ciprofloxacin), or subacute cutaneous lupus erythematosus (terbinafine, thiazides). Accelerated skin photoaging and an increase in precancerous skin lesions and skin cancers, mostly nonmelanoma skin cancer, are being described as delayed manifestations of exposure to photoactive drugs (voriconazole, fluoroquinolones) [7–11].

Many classic topical photosensitizers have been removed from the European market and now seldom cause PhACD – halogenated salicylanilides used in disinfectant soaps, musk ambrette and bergamot oil used as perfumes, olaquindox an

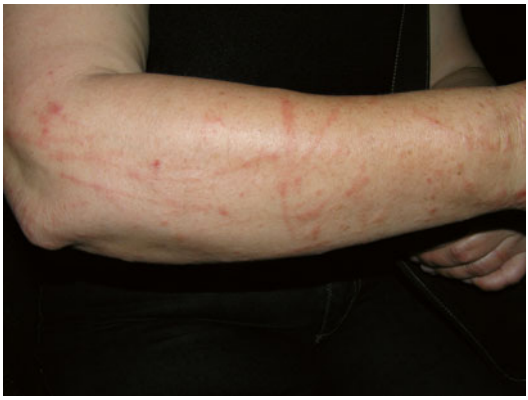

Fig. 7.3 Linear inflammatory and pigmented lesions from phytophotodermatitis from *Ruta graveolens*

antibiotic used as a pig feeder, and PABA (para-aminobenzoic acid) and isopropyl-dibenzoylmethane used in sunscreens. At present, main causes of PhACD are the UV filters and topical NSAID, with predominance for the latter in Southern European countries [12–16]. UV filters are frequently used for individual photoprotection but also to prevent degradation of the products and increase their shelf life. Therefore, apart from sunscreens, where they are present in higher concentrations and number, UV filters are also present in moisturizing, anti-wrinkle, and facial creams and other make-up (e.g., lipstick), nail varnish, shampoos and other cleansing products, and hair products [17]. At present, the main chemicals responsible for PhACD or photoaggravated ACD are oxybenzone or benzophenone 3, octocrylene, butylmethoxydibenzoylmethane, and cinnamates [13, 14, 16, 18]. Newer UV filters, like Mexoryl SX® (terephthalylidene dicamphor sulfonic acid), Tinosorb M® (methylene bis-benzotriazolyl tetramethylbutylphenol or bisoctrizole), and Tinosorb S® (bis-ethylhexyloxyphenol methoxyphenyl triazine), seldom cause PhACD. They are mostly photostable molecules used in mixtures of sunscreens that also photostabilize older photo labile UV filters, like the dibenzoylmethanes. This may explain why, although the use of products containing UV filters is certainly growing, there is no parallel increase in PhACD from these chemicals. Some of them can also cause ACD, particularly Tinosorb M®, due to the surfactant decylglucoside that is used to solubilize the active molecule of bisoctrizole [19, 20].

In most recent studies on photopatch testing, NSAIDs are the main cause of positive photopatch tests, with ketoprofen and related drugs (piketoprofen and dexketoprofen) or cross-reactive substances as the main responsible [16]. Ketoprofen used in gel, and more recently also in transdermal patches, often induces severe forms of PhACD (acute eczema, erysipela-like reactions, erythema multiforme) (Fig. 7.4) that occur very soon after initiating treatment and may persist or recur on sun exposure with no apparent further contact with the drug. This may be explained because, after topical exposure, the drug persists in the epidermis for more than 2 weeks [21]. Also, there are cases of ectopic (at sites distant from the original application), connubial, or "by proxy" contact dermatitis due to contact with the skin/hands

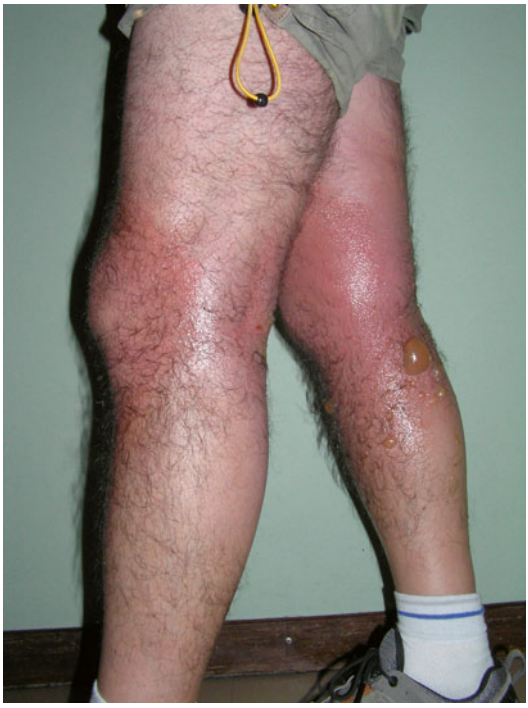

Fig. 7.4 Severe PhACD from a topical NSAID, sparing the thighs under the clothing

contaminated by ketoprofen gel or by contact with contaminated objects, namely, from clothes that retain ketoprofen even after being washed [22–27].

PhACD to ketoprofen is associated with frequent cross-reactive photopatch test reactions to other arylpropionic NSAIDs (tiaprofenic acid and suprofen); benzophenone UV filters, mainly oxybenzone, and the systemic hypolipemic agent, fenofibrate, that induces systemic photosensitivity. Positive photopatch tests to the UV filter octocrylene and patch tests to fragrance mix I and to its constituent cinnamic alcohol are also associated with PhACD to ketoprofen [13, 28–33].

Piroxicam is another NSAID that causes both topical and systemic photoallergy, mostly after previous contact sensitization to thiomersal and its moiety thiosalicylic acid, as photoproducts of piroxicam are chemically similar to these contact allergens [13, 34].

Benzydamine, a topical NSAID used mainly in mouth washes or genital soaps, can cause PhACD, that in the first case presents as cheilitis and chin dermatitis and in the latter involves the dorsum of the hands [3, 35].

Phenothiazine derivatives used in some few European countries as topical antihistamines (promethazine, isothipendyl chlorhydrate) or muscle relaxants (chlorproéthazine) or chlorpromazine whose pills are smashed by caregivers to give disabled patients cause frequent PhACD in countries where they still are available [13, 36–39] (Table 7.2).

Table 7.2 Main exogenous agents causing photoreactions

1. **UV filters**
Benzophenones: oxybenzone, sulizobenzone, mexenone
Dibenzoylmethanes: butyl methoxydibenzoylmethane
Cinnamates: isoamyl-p-methoxycinnamate, ethylhexyl methoxycinnamate, octocrylene, drometrizole trisiloxane
4-methylbenzylidene camphor, phenylbenzimidazole sulfonic acid
2. **Plants** (**main families in Europe**)
Umbelliferae: *Ammi majus*; *Apium graveolens* (celery)
Pastinaca sativa (parsnip); *Petroselinum crispum* (parsley)
Heracleum mantegazzianum (giant hogweed)
Rutacea: Citrus spp., *Citrus aurantica v. bergamia* (bergamot)
Citrus aurantifolia (lime); *Citrus limon* (lemon)
Ruta graveolens (common rue); *Dictamus albus* (burning bush)
Moracea: *Ficus carica* (fig)
3. **Drugs**
a. **Antimicrobials**
Doxycycline, minocycline, sulfamethoxazole
Fluoroquinolones (lomefloxacin[b], ciprofloxacin[b])
Voriconazole, griseofulvin, efavirenz
b. **Nonsteroidal anti-inflammatory drugs** (**NSAIDs**)
Ketoprofen[a], tiaprofenic acid[b], suprofen, carprofen
Piroxicam[c], benzydamine[b], etofenamate[b]
c. **Other drugs**
Chlorpromazine, promethazine[b], chlorproethazine
Amiodarone, furosemide, and thiazide diuretics
Paclitaxel, 5-fluorouracil, dacarbazine, vemurafenib
Fenofibrate, flutamide, sulfonylureas
4. "**Historical**" **photosensitizers**[d]
Perfumes: musk ambrette and bergamot oil
Halogenated salicylanilides
Sunscreens: isopropyl-dibenzoylmethane, PABA
Antibiotics: Olaquindox

Adapted from Gonçalo [2]
[a]Although phototoxic, can induce photoallergic reactions
[b]Induces photoallergic and allergic contact dermatitis
[c]Induces mainly systemic photoallergy
[d]Although "historical" some still induce photoallergic contact dermatitis

7.4 Whom, When, and How to Test Patients

Photopatch testing is indicated to study PhACD and, in selected cases, can be helpful in systemic drug photosensitivity [34, 40), but it is not recommended in typical phototoxic reactions. Therefore, photopatch testing should be performed in all individuals, including children, with dermatitis on photoexposed areas, dermatitis aggravated by UV exposure, sunscreen intolerance, or exposure to NSAID [16, 18]. In patients with chronic photosensitivity (chronic actinic dermatitis, polymorphic

light eruption, cutaneous lupus erythematosus), photopatch testing may be important to exclude a concomitant PhACD, e.g., to a UV filter. In these individuals with a lowered threshold of UV sensitivity, phototesting is usually performed along with photopatch testing, in order to program the adequate UV doses for patch test irradiation [16, 41].

Photopatch testing should be performed, whenever possible, when there are no active lesions or, at least, when the back is clear and when the patient has withdrawn immunosuppressive drugs. If not possible (solid-organ-transplanted patients), interpretation must be cautious, as false-negative results may occur. Photopatch testing should be postponed after sunburn or significant sun exposure on the back, after local use of corticosteroids, and in patients on potential photoactive drugs.

7.5 Photopatch Testing: Technique and Requirements

For performing photopatch testing, apart from material common to contact allergy clinics (allergens and tests chambers), a UV source is necessary. Any broadband UVA source (320–400 nm) with a photometer to quantify UV light delivered to the skin, e.g., a cabin with UVA lamps for PUVA therapy, can be used for UV irradiation.

Recently, ESCD (European Society of Contact Dermatitis and Cutaneous Allergy) and ESP (European Society of Photodermatology) agreed on a recommended European baseline photopatch test series and an extended series including mostly UV filters, NSAIDs, and topical drugs (Table 7.3) to test along with patients' own products (cosmetics, sunscreens, topical drugs). It is recommended whenever possible to perform concomitantly patch testing with the ESCD baseline series of contact allergens and, particularly, with cinnamic alcohol and decyl glucoside that are related, respectively, with PhACD to ketoprofen and ACD to Tinosorb M® [42].

The allergens prepared on the most convenient vehicle are applied in fixed amounts on the chambers as for patch testing (40 mg/cm^2 if in petrolatum) [39, 40]. For photopatch testing, two equal sets of allergens are prepared and applied on symmetrical areas of the back. After a 1 or 2 days occlusion (with no significant variation in test results with these two occlusion times [43]), one set is removed and the skin is irradiated with 5 J/cm^2 of UVA, while the skin under the other set of allergens is shield from light with a UV opaque material [41].

In exceptional cases, UVB irradiation may be necessary to prove photosensitivity, but there is not enough data to recommend regular photopatch testing with this wavelength [44].

When testing a UVA photosensitive patient, e.g., a chronic actinic dermatitis patient, the UVA irradiation dose should be 50–75 % of the MED (minimal erythema dose), preferably calculated on phototests performed concomitantly with photopatch testing [41].

Table 7.3 European photopatch test baseline and extended series, recommended by the ESCD (European Society of Contact Dermatitis and Cutaneous Allergy) and ESP (European Society of Photodermatology)

Series	Type of agent	Name of agent (INCI name for UV absorbers)	Concentration vehicle
Baseline	Classical UV filters	Butyl methoxydibenzoylmethane	10 % pet
		Benzophenone-3	10 % pet
		Benzophenone-4	2 % pet
		Octocrylene	10 % pet
		4-Methylbenzylidene camphor	10 % pet
		Ethylhexyl methoxycinnamate	10 % pet
		Isoamyl-*p*-methoxycinnamate	10 % pet
		PABA	10 % pet
	Newer UV absorbers	Methylene *bis*-benzotriazolyl tetramethylbutylphenol	10 % pet
		Bis-ethylhexyloxyphenol methoxyphenyl triazine	10 % pet
		Drometrizole trisiloxane	10 % pet
		Terephthalylidene dicamphor sulfonic acid	10 % water
		Diethylamino hydroxybenzoyl hexyl benzoate	10 % pet
		Ethylhexyl triazone	10 % pet
		Diethylhexyl butamido triazone	10 % pet
	Topical drugs	Ketoprofen	1 % pet
		Etofenamate	2 % pet
		Piroxicam	1 % pet
		Benzydamine	2 % pet
		Promethazine	0.1 % pet
Extended	UV absorbers	Benzophenone-10	10 % pet
		Phenylbenzimidazole sulfonic acid	10 % pet
		Homosalate	10 % pet
		Ethylhexyl salicylate	10 % pet
		Polysilicone-15	10 % pet
		Disodium phenyl dibenzimidazole tetrasulfonate	10 % pet
	Topical drugs	Dexketoprofen	1 % pet
		Piketoprofen	1%pet
		Ibuprofen	5 % pet
		Diclofenac	5 % pet
	Systemic drugs	Fenofibrate	10 % pet
	Others	Chlorpromazine	0.1 % pet
		Olaquindox	1 % pet
		Triclosan	2 % pet

7.6 Photopatch Testing: Reading and Interpretation of Results

Reactions should be scored according to the guidelines of the International Contact Dermatitis Research Group (ICDRG), as "–" (negative), "+?" (doubtful, only with faint erythema), "+" to "+++" (faint to strongly positive reactions, namely, with erythema, infiltration, and possibly papules for 1+; erythema, infiltration, papules, and vesicles for 2+; and erythema, infiltration, and coalescent vesicles or bulla for 3+), "IR" (irritant), and NT (not tested).

Readings should be performed before and 30–60 min after UV irradiation (D1 or preferably D2) to record reactions present before irradiation (contact allergy) and those that appear immediately thereafter, as in photocontact urticaria. Transient macular erythema that regresses within 24 h, sometimes with residual hyperpigmentation, may occur mostly with phototoxic chemicals, e.g., benoxaprofen, tiaprofenic acid, promethazine, and some UV filters, but this does not represent a positive photopatch test reaction.

For evaluating delayed photoallergic reactions, the most important and obligatory reading should be performed 2 or 3 days after irradiation (D3–D5), the interval necessary for the clinical expression of most T-cell-mediated reactions to the new photoproduct formed during UV irradiation. In this reading, it is important to compare reactions in the irradiated versus the nonirradiated panel of allergens to distinguish a positive patch test reaction or contact allergy (positive reactions in both sets that very often are already present before irradiation) from a positive photopatch test reaction in photoallergy (positive only in the irradiated set) (Fig. 7.5).

A positive patch test in both areas but with a much higher intensity in the irradiated area, usually called a photo-augmented patch test reaction, can occur with contact allergens with some photoactive potential, e.g., etofenamate, ketoprofen, and UV filters [45], and represent the association of allergic and photoallergic contact dermatitis or a photo-augmentation of contact allergy [46].

After patch test reading, evaluation of the relevance of the reactions is mandatory, by going back in detail to the history of recent and past exposure and their possible relation to the site and evolution of the dermatitis. Positive reactions may explain the present dermatitis (current relevance) and can be due to a past exposure, with or without lesions (past relevance or, simply, previous exposure), or be an expression of cross-reactivity [41],

7.7 Advising Patients with Photoreactions

In patients with photoreactions, apart from treating the acute reaction, sun avoidance or use of photoprotective clothing/devices is recommended, as some chemicals can persist in the skin for some days and further UV exposure can aggravate the dermatitis. As UV filters are one of the main causes of photoallergy, a sunscreen

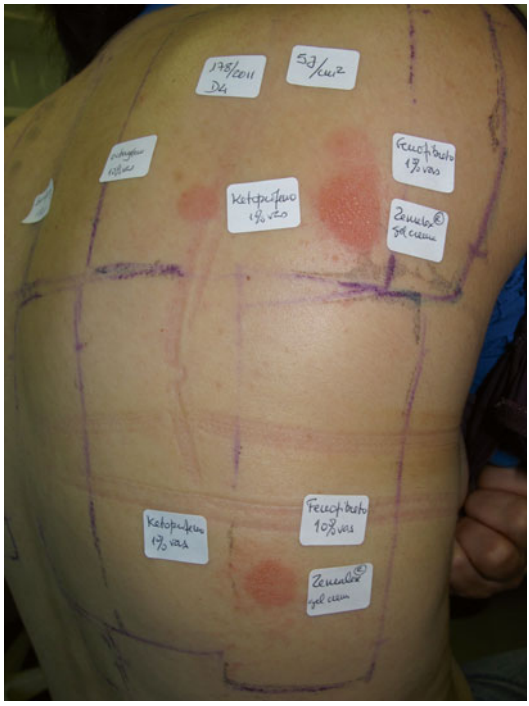

Fig. 7.5 Photopatch test results at D4 (2 days after UVA irradiation with 5 J/cm^2 only in the upper part of the dorsum) with a positive contact allergy to Zemalex cream containing piketoprofen (reactions both in the irradiated and nonirradiated sites) and a positive photopatch test to ketoprofen and fenofibrate (positive only in the irradiated site)

would not be an adequate protective option, unless it is exclusively composed of physical filters (titanium dioxide and zinc oxide), as these have not been reported to induced PhACD or contact dermatitis.

Once a relevant photoallergen is identified during photopatch testing, it has to be further avoided, along with all cross-reactive substances. The list of cross-reactive chemicals is particularly long in patients with PhACD to the benzophenone ring, which includes ketoprofen and some of the other arylpropionic derivatives, UV filters as oxybenzone and octocrylene and oral fenofibrate. Moreover, as patients with reactivity to UV filters often react to more than one chemical [47], particular care should be taken on the choice of future sunscreens, cosmetics, and other products that may contain UV filters [17].

As a preventive measure, it is important to avoid UV exposure or used adequate photoprotection during treatments with known and frequent photosensitizing drugs, as vemurafenib, voriconazole, tetacyclines, amiodarone, or phenothiazines. In some cases, photosensitivity may be so severe as to prevent continuation of a beneficial treatment (vemurafenib) or induce persistent pigmentation of exposed areas with significant cosmetic impairment (minocycline, amiodarone). Moreover, as there is increasing evidence of the relation between photosensitivity and photocarcinogenesis, photoprotection/photo-eviction should be mandatory when exposure to the photosensitizer cannot be avoided.

7.8 Core Message

- Photoreactions due to concomitant skin exposure to an exogenous chromophore and UV light occur due to phototoxicity, photoallergy (T-cell-mediated reaction to a photoproduct), or both.
- Clinical manifestations are polymorphic and occur mainly as exaggerated sunburn with sharp limits that progress to hyperpigmentation (phototoxicity) or eczema on photoexposed areas that may extend beyond.
- Main systemic photosensitizers are drugs, e.g., tetracyclines, fluoroquinolones, voriconazole, NSAID, phenothiazines.
- Main causes of topical photoreactions are plants, UV filters (mainly oxybenzone, octocrylene, butylmethoxydibenzoylmethane), and drugs (ketoprofen, etofenamate).
- Photopatch testing is indicated in all ages in suspected PhACD and dermatitis involving photoexposed areas, namely, to exclude reactivity to a UV filter.
- Use the recommended European baseline photopatch test series, eventually the extended series and patient's own products to diagnose the cause of the photoreations.
- Once identified, the relevant photoallergen and cross-reactive chemicals should be further avoided.
- Careful and adequate photoprotection should follow a diagnosis of a photosensitive reaction.

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