Thiazide lichenoid photodermatitis

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Drug-induced lichenoid photodermatitis generally appears as a dermatitis, mainly on sun-exposed sites. Once recognised, photoallergic and phototoxic drug eruptions are managed by stopping the offending drug and implementing sun protection measures. Topical corticosteroids are also used, mainly for photoallergic reactions.

Case presentation

A 78-year-old man presented with a 12-month history of a dermatitis-like rash (Figures 1a to c). It had gradually worsened and was eventually severe, particularly on sun-exposed areas of his face, neck, upper trunk, arms, forearms and dorsal hands and fingers. The rash was quite itchy and he felt it became worse after sun exposure.

The patient had hypertension, which was controlled with medication, and osteoarthritis but was otherwise well. He had started irbesartan two years previously, but adequate blood pressure control was not achieved after six months so hydrochlorothiazide was added to his treatment. He was still using a combined irbesartan and hydrochlorothiazide preparation when he presented with the rash. His arthritis was of moderate severity and he used paracetamol and occasionally ibuprofen for pain relief.

The patient had no personal or family history of atopy and no history of previous allergies of any kind. The rash was not settling with betamethasone valerate cream, which he tried on all sites except the face, where he was using hydrocortisone 1% cream without improvement.

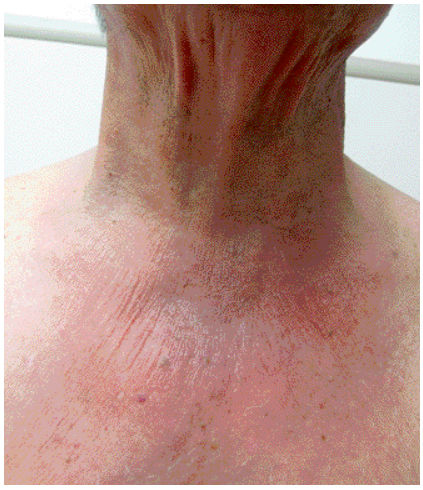
Diagnosis

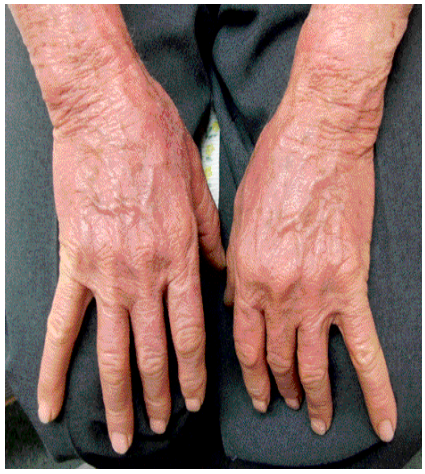
The likely diagnosis was hydrochlorothiazide-induced lichenoid photodermatitis. This was a clinical diagnosis – a skin biopsy was not performed because the rash cleared over three weeks after he stopped taking the combined irbesartan and hydrochlorothiazide tablets (his treatment was switched to a calcium channel blocker) and started using betamethasone dipropionate ointment twice daily to all sites, including the face (application time on the face limited to 10 days). A skin biopsy would have been recommended if the rash had not settled.

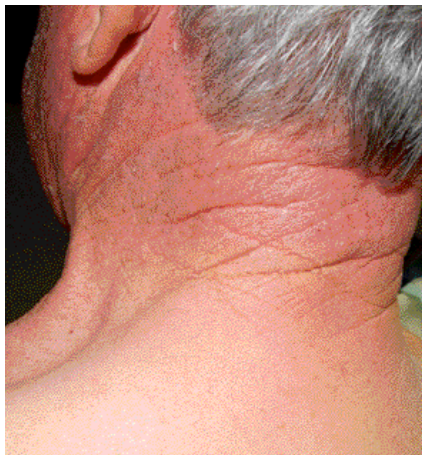
Differential diagnoses

Dermatitis

Various types of dermatitis are possible in this clinical situation. Atopic dermatitis is more common in children, but it can start at any time and not rarely in older age. Generally there is a personal or family history of one or more forms of atopic illness. Photoexacerbated atopic







Figures 1a to c. A 78-year-old man with a dry dermatitis type rash in a photoexposed distribution, shown here on the upper chest (a, top), hands (b, middle) and neck (c, bottom).

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dermatitis is a rare variant. Seborrhoeic dermatitis is usually mild and occurs mainly on the scalp, central face and (sometimes) mid-chest. Occasionally it is more severe and it too can be photoexacerbated. Rarely it becomes very extensive, even erythrodermic.

Allergic contact dermatitis, a delayed type of allergy, occasionally occurs in areas of exposed skin and may be photoallergic or airborne. Photoallergic contact dermatitis requires light, usually ultraviolet light, to change the chemical structure of the (photo)allergen and generate a slightly different chemical that T-cells recognise as an allergen. Chemical sunscreens found in many commercial products are the most common photoallergens, but others include biocides in soap such as trichlorocarbanilide (which is found in Palmolive Gold soap, for example) and some chemicals found in lichens on trees and in perfumes. Airborne contact dermatitis is caused by allergens landing on the skin. These are usually not type I protein allergens that cause hayfever and asthma (pollens, dusts, moulds) but rather specific chemicals in some sawdusts (e.g. colophony from conifer wood) and wind-blown dusts from the large *Asteraceae* plant family (which includes daisies, various weeds and herbs) and chemicals used in industry (e.g. some volatile substances found in epoxy resins).

A severe version of airborne or photoallergic contact dermatitis is chronic actinic dermatitis, which persists even when allergen exposure is avoided or minimised. Patch testing performed over five days at specialised centres is required to identify the allergen(s) in this situation.

Dermatitis in which no clear cause is identified is also quite common, particularly in older people.

Photosensitive connective tissue diseases (CTDs)

Lupus erythematosus (LE, various forms), dermatomyositis and, occasionally, mixed connective tissue disease are the main photosensitive connective tissue diseases (CTDs). Of these, dermatomyositis is the most likely to resemble the case patient's presentation, but the wide variation in clinical presentation of these connective tissue diseases makes any possible.

The main clinical variants of LE are discoid (DLE), subacute cutaneous (SCLE) and systemic (SLE). DLE often affects only the skin; some patients with SLE, which is much less common, have a DLE rash. DLE forms scattered, well demarcated, red, slightly scaly plaques that sometimes damage the skin enough to cause scarring and permanent destruction of hair follicles. The rash most often affects the face, scalp, neck, upper trunk or upper limbs, and about half of patients affected are aware that sun exposure exacerbates it. The ANA is positive in about 20% of cases (often low titre) but extractable nuclear antigens (ENAs) are often normal.

The classic rash of SLE is the butterfly rash over the nose and medial cheeks – more erythema and minimal dryness. It is usually photosensitive. To diagnose SLE other systemic and laboratory features need to be present but patients do not necessarily need to meet the American Rheumatism Association diagnostic criteria (which form more of a guideline).

SCLE tends to be a more extensive rash on the upper trunk and upper limbs and less commonly on the face. It may be like psoriasis or more annular. Some patients also have systemic involvement, but most commonly it only involves the skin. People with SCLE are usually positive for the anti-Ro antibody on testing for ENAs. Thiazides and terbinafine, in particular, but also other drugs, such as calcium channel blockers and ACE inhibitors, can cause SCLE.[1]

Different drugs can cause different forms of LE, including a specific drug-induced form that involves the skin in

only a quarter of cases. It is most often caused by hydralazine, TNF-inhibiting biological therapies, procainamide, minocycline, beta blockers and phenytoin.

Dermatomyositis usually involves both muscle weakness from myositis and a rash. Pulmonary disease and mild arthritis may also occur. The rash may precede the myositis, sometimes for an extended time, or the myositis may never develop (amyopathic dermatomyositis). The rash particularly affects sun-exposed sites, resembling a dermatitis. It often also affects the scalp, and has a slight purplish-tinge to the redness on and near the eyelids (heliotrope rash). On the backs of the hands it concentrates over the knuckles and dorsal interphalangeal joints as red, slightly dry to more psoriasiform papules or thin plaques (Gottron's papules). In adults, there is an increase in risk (approximately three-fold) for malignancy, especially non-Hodgkin's lymphoma and cancers of the ovaries, stomach, colon, pancreas and lungs. Drugs occasionally cause a dermatomyositis-like eruption: 50% of cases are due to hydroxyurea (most often with no myositis) and the rest are caused by a range of drugs, particularly penicillamine and the statins (most often with myositis).[2]

Photosensitive drug eruptions

Photosensitive drug eruptions are a group of drug eruptions that are not commonly seen. These are discussed further below (see Comment section).

Tinea

Tinea is usually easy to identify as an asymmetrical, red, scaly, itchy rash with a more active edge. It slowly expands or spreads to other sites, often starting on the feet and then spreading to the groin. More extensive forms on the body and face can be more difficult to diagnose, particularly if the clinical signs have been masked by use of potent topical corticosteroids.

Most often, tinea of the face or of the body or limbs is caused by the anthropophilic fungus *Trichophyton rubrum*. Occasionally people with this form of tinea notice that it is photoaggravated.

Pemphigus

There are a number of different types of pemphigus, and all are quite uncommon. They are due to circulating autoantibodies that bind to desmogliens (protein components of desmosomes that help bind keratinocytes in the skin and other tissues together). Pemphigus vulgaris is a more severe immunobullous disease affecting skin and mucosae. The particular desmoglien targeted in pemphigus foliaceous is expressed in the skin, not mucus membranes, so it spares the latter site. It particularly affects the face, scalp and upper trunk, and it can be severe. Sunlight is not known to be an aetiological factor in pemphigus foliaceus or vulgaris. Occasionally, pemphigus is drug induced, particularly by drugs containing sulfhydryl groups such as captopril and penicillamine.

Diagnosis of pemphigus requires special biopsies, with specimens sent for direct immunofluorescence to detect pathogenic antibodies in the epidermis. Circulating antibody titres can also be measured.

Comment

Clinically, this patient's rash was highly suggestive of hydrochlorothiazide-induced lichenoid photodermatitis. Photosensitive drug eruptions are broadly divided into phototoxic and photoallergic types (and there are subtypes of each).

Phototoxic drug eruptions are due to photons of particular wavelengths in sunlight acting directly on the drug or its metabolites to produce chemicals (often reactive oxygen species) that are toxic to the skin and thereby cause a rash. They are usually due to ultraviolet A (UVA) light, but some chemicals are also activated by shorter wavelength UVB light. (Thiazide phototoxicity, for example, appears to involve both UVA and UVB light.[3]) UVA light penetrates further into the skin than UVB light; it also passes through window glass and is less efficiently blocked by water and most sunscreens. The reactions are dose dependent, although only a small proportion of treated patients develop them. Drugs most prone to cause these eruptions are:

- tetracyclines (particularly doxycycline)
- NSAIDs (especially propionic acid derivatives like ibuprofen and naproxen)
- fluoroquinolones (like norfloxacin, ciprofloxacin and moxifloxacin)
- amiodarone
- phenothiazines
- hydrochlorothiazide
- sulfonylureas.

Phototoxic drug eruptions may be immediate (starting within 30 minutes of sun exposure [e.g. doxycycline]) or intermediate (starting within eight to 24 hours of sun exposure [e.g. hydrochlorothiazide]).

Pseudoporphyria, a subcategory of a phototoxic drug eruption, is a non-inflammatory blistering rash usually occurring on sun-exposed limbs (usually the legs) of elderly patients. It is rarely seen, but is most often due to naproxen, frusemide or nalidixic acid.

Photoallergic drug eruptions require ultraviolet light (usually UVA light) to change the drug or its metabolites to a chemical that is recognised by the immune system to generate the rash. This is mediated by T-cell activation via the classic type IV delayed type hypersensitivity response involving antigen processing by skin dendritic cells (Langerhans cells). The eruptions are idiosyncratic and not dose dependent, and only a small proportion of patients treated with a particular drug develop this type of rash. Drugs most prone to cause these eruptions are:

- some drugs with a sulfur moiety (thiazide diuretics, sulfonamide antibiotics, sulfonylureas and phenothiazines)

- quinine, quinidine
- griseofulvin
- tricyclic antidepressants
- selective serotonin reuptake inhibitors
- antimalarials
- some NSAIDs.

A patient needs to take the drug for period of time for sensitisation to occur – this might be a week or a more prolonged time (as for the case patient presented here). When a person has already been sensitised to a drug and then starts taking it again, the rash usually occurs within 24 hours if there is also sun exposure. Most often, the rash resembles dermatitis but sometimes it has additional features of lichen planus – there is a clinical overlap between the two – hence the term lichenoid photodermatitis. Only a small proportion of lichenoid drug eruptions are photo-induced, and these also clinically overlap with dermatitis and lichen planus.[4] In addition, some drugs induce other photosensitive rashes – in particular, different forms of LE or dermatomyositis (discussed above). These can be viewed as another form of a photoallergic drug eruption with additional factors needed for the development of LE or dermatomyositis.

Clinically, drug-induced lichenoid photodermatitis appears most often as a dermatitis, as in the presented case. The rash is itchy, red and dry, with a papular quality usually becoming confluent. It occurs on predominantly sun-exposed sites but tends to spread slightly onto less sun-exposed areas, potentially making it more difficult to recognise as being sun-induced. Sun-induced rashes tend to spare relatively nonexposed skin under the chin and behind the ears, but as the rash spreads, these sites may become affected (as in the presented case). At the more lichen planus end of the clinical spectrum, photoallergic drug eruptions tend to be more violaceous red papules and small plaques on and near sun-exposed sites. Unlike lichen planus, they tend to have more dermatitis-like features and less commonly affect mucosae, hair or nails. The clinical distinction of drug-induced dermatitis and lichenoid drug eruptions from the photoallergic forms is the predominantly sun-exposed distribution and, commonly, history of photosensitivity. By distinction, the phototoxic drug eruptions tend to be more strictly localised to sun-exposed sites and present as a sunburn happening more easily than expected and more quickly after sun exposure. Phototoxic drugs can also cause photo-onycholysis (lifting of sun-exposed nails due to damage of the nail bed).

Compared with other drugs, cutaneous side effects from thiazides are uncommon. In the literature, the most commonly reported side effects are photosensitivity and drug induced LE (usually SCLE). Clinician reports to the TGA Office of Medicines Safety Monitoring (formerly ADRAC) are somewhat difficult to interpret. In 443 reports of skin reactions to hydrochlorothiazide, there were 57 cases of photosensitivity (type not specified), none of pseudoporphyria and 18 of dermatitis-like rashes compared with 162 cases of nonspecified rashes (Dr J. Elijah, personal communication, June 2010). Less common cutaneous side effects reported in the literature include lichenoid drug eruption, dermatitis, acute generalised exanthematous pustulosis, angioedema–urticaria, exanthems, erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis, fixed drug eruption and vasculitis. The literature suggests phototoxic reactions are more common than photoallergic reactions as the cause of thiazide photosensitivity, but some of the reported cases do not make this distinction clear. Also, sometimes these reactions are not clearly distinguished from thiazide-induced SCLE. Indeed, the presented case has these limitations, given the lack of histopathology and lupus serology testing, but the clinical pattern makes lichenoid photodermatitis the most likely diagnosis.

Sulfonamide drugs include antibiotics (such as sulfamethoxazole), thiazide diuretics, indapamide and frusemide. Sulfonylurea antidiabetic agents are closely related to sulfonamides. Thiazide diuretics have a nonaromatic sulfhydryl moiety – even though other sulfonamides and sulfonylureas have similar groups, chemical differences mean they rarely immunologically cross react),[5] and reactions to one of the drugs rarely seems to lead to cross reactions to one of the related drugs.

Management

Once recognised, photoallergic and phototoxic drug eruptions are simply managed by stopping the offending drug and implementing sun protection measures. Topical corticosteroids are also used, mainly for photoallergic reactions, which take longer to settle. Phototoxic reactions settle quickly and photoallergic ones usually settle well in two to three weeks. Either may leave considerable postinflammatory pigmentation, particularly in darker skinned individuals, which clears much more slowly. MT

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COMPETING INTERESTS: None.