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Leaders

Recognising photosensitivity

Photosensitivity is adverse cutaneous responsivity to ultraviolet or visible radiation exposure; such a response may develop minutes, hours or days after exposure and last up to weeks. There are no exact estimates of the prevalence of photosensitivity. However, one of the most common disorders, polymorphic light eruption, is estimated to occur in 10–21% of specific groups.^{1,2} Furthermore, approximately 17%^{3–5} of black patients with systemic lupus erythematosus (SLE) are photosensitive, compared with 32–71% of white patients with the condition. For subacute cutaneous lupus erythematosus the incidence of photosensitivity increases to 52–87%,^{6–8} while for chronic cutaneous lupus erythematosus it is 50–70%.^{3,9,10} Thus the need to recognise photosensitivity is apparent.

The most important clinical feature common to all of the photosensitivity disorders that a rheumatologist might evaluate is the distribution of the skin lesions. The various eruptions predominantly affect sun exposed skin (face, ears, neck, upper central chest, extensor forearms, dorsal hands), generally sparing shaded sites (hair-covered areas of scalp, upper eyelids, periorbital skin, retroauricular triangle, nasolabial folds, underside of nose, underside of lower lip, areas covered by jewellery and thick clothing). There may be a sharp cut off at clothing margins or at sites of jewellery. Although the distribution is often limited to sun exposed areas it may not involve all such areas, perhaps as a result of protection induced by chronic exposure to ultraviolet radiation through consequent tanning, or immunological tolerance. Conversely, non-exposed areas may sometimes be affected because clothing is not always completely protective or the degree of photosensitivity may be sufficiently severe for the disease process to extend beyond the exposed skin and in some cases to erythroderma. Patients with such extensive disease usually initially develop their eruption only on exposed areas.

The morphological changes encountered with photosensitivity are very varied. The rheumatologist is most likely to encounter combinations of erythema, papules, plaques, vesicles, urticaria, bullae, eczema, and altered pigmentation. Infrequently, petechiae, purpura, erythroderma, and scarring may be seen. The most easily recognised photosensitive individuals are those who seek medical advice because sun exposure is temporally related to their intermittent skin eruption, as may happen with some lupus patients. Others may complain of an apparent allergic reaction to sunscreens, but instead are frequently suffering from other photosensitivity for which their sun-

screens are not providing adequate protection, for example that caused by exposure to ultraviolet A (315–400 nm), against which many currently available sunscreens are not fully effective. Other photosensitive individuals, such as some patients taking thiazide diuretics, might present with a chronic persistent rash on exposed sites, although they may not recognise it as light-induced. Finally, much less common are those who present with generalised erythroderma, such as might rarely happen with a light-sensitive psoriasis patient after exposure to ultraviolet radiation.

Investigation of the photosensitive patient commences with a careful history and physical examination. The age of onset of the eruption is important because certain types of photosensitivity typically begin in childhood. It is also essential to ascertain the time course of the eruption, as the various reactions occur minutes, hours or days after exposure and last from an hour up to several weeks. Symptoms such as pain, burning or itching should also be noted. A rash that also occurs near an oven or open fire suggests that heat rather than ultraviolet radiation may be a trigger factor or at least an exacerbating agent.

Other factors of importance in the history are exposure to systemic drugs (table 1) such as certain antibiotics and anti-psychotics,¹¹ or topical agents such as sunscreens and cosmetics. A careful drug history should include attention both to current medications and to drugs to which the patient was exposed at the time the photosensitivity started, as photosensitivity to some degree may occasionally persist for a few weeks after discontinuation of an offending agent. Also important is whether occupational or recreational exposure to ultraviolet radiation has occurred. For example, a patient with lupus who works as a welder or sits in an office under strip lighting may be chronically exposed to ultraviolet radiation if protection is not used. As exposure to plant allergens may worsen some forms of photosensitivity, questions about hobbies, particularly gardening, should also be asked. Finally, a

Table 1 Drugs commonly associated with photosensitivity

Non-steroidal anti-inflammatory drugs (especially benoxaprofen, piroxicam, azapropazone, fenbufen, diclofenac)
Diuretics (thiazides, frusemide)
Antibiotics (tetracyclines, 4-quinolones, sulphonamides, amoxycillin)
Antiarrhythmics/antihypertensives (amiodarone, angiotensin converting enzyme inhibitors, β -blockers, nifedipine)
Histamine antagonists (ranitidine, cimetidine, terfenadine, astemizole)
Antidepressants (amitriptyline, fluoxetine)
Others (carbamazepine, griseofulvin, isotretinoin)

review of systems should include careful attention towards connective tissue disease symptoms and the neurological signs occasionally associated with some of the porphyrias.

Primary laboratory investigations for all photosensitive patients generally include a routine assessment of full blood count, liver function, renal function, serum anti-nuclear antibody and extractable nuclear antigen titres, and possibly skin histology. Such histology is often non-diagnostic but may be used to try to confirm a suspected diagnosis or to classify a clinically atypical eruption. Usually, biopsies are from lesional skin, whether sun exposed or not. However, if SLE is suspected, lesional biopsies from both sun exposed and sun protected skin are helpful, together with a non-lesional biopsy from a sun protected area, for direct immunofluorescence studies.

Secondary investigations may be available only in specialised centres. In patients with a history or signs suggestive of porphyria, or in doubtful cases, assessment of blood, urine, and stool porphyrin concentrations is necessary. Less often useful for the rheumatologist is cutaneous phototesting, which becomes important only if photosensitivity is suspected and the diagnosis is not yet clear; monochromatic wavelengths or broad spectrum wavebands may be used for testing—the former to define (not always easily) the abnormal inducing wavelengths, the latter to reproduce the eruption for diagnosis on clinical and histological grounds (also sometimes difficult). Patch and photopatch testing may also be indicated if contact factors are suspected of promoting the eruption.

Possible diagnoses in patients with photosensitivity are listed in table 2. The rheumatologist is particularly likely to encounter drug-induced photosensitivity. This drug or chemical-induced group includes disorders produced through phototoxic or photoallergic mechanisms, the former presumably via non-immunological inflammatory mechanisms and the latter very possibly through immunological delayed type hypersensitivity. These responses result from the exposure of skin containing agents topically, orally, or parenterally administered, to sufficient and appropriate wavelengths of ultraviolet or visible radiation. Substances associated with such photosensitivity are usually resonating compounds with gram molecular weight <500.¹² Each photosensitiser absorbs only a specific waveband of light which, depending on its cellular location, may be discharged with resulting damage to the nucleus, cytoplasm, or cell membranes. Drug and chemical photosensitivity have been relatively well studied because, in contrast to the situation with the other groups of photosensitivity disorders, the absorbing molecule is usually well defined. For example, the mechanism of photosensitivity has been relatively clearly determined for the porphyrin disorders—conditions in which the photosensitiser is endogenously produced.^{13 14} When light of the

so-called Soret band (400–410 nm) is absorbed by excess cutaneous porphyrin, the absorbed energy raises the electrons of the porphyrin molecule into a more energetic but unstable (“triplet”) state. Energy released on the return of each electron to its stable original state is then transferred to neighbouring molecules, leading to electron-unbalanced free radicals including singlet oxygen, which then damage molecules, cells, and tissues as they transfer their unbalanced electrons back to nearby structures. Unsaturated lipids are particular molecular targets for such activated oxygen species, leading to the induction of protein crosslinks and the destruction of sulphhydryl groups; resultant structural damage appears to be largely from the associated plasma membrane injury. Beta-carotene, a known quencher of free radicals and singlet oxygen, interestingly appears sometimes to have a photoprotective effect in porphyria.

The photoaggravated diseases, dermatoses not caused but worsened by exposure to ultraviolet radiation, also include a number of disorders of special interest to rheumatologists, such as SLE, less often dermatomyositis and occasionally psoriasis. This group also includes all the other diseases with skin manifestations potentially exacerbated by sunlight. Probably radiation-induced modulation of pre-existing inflammatory or immune processes is responsible in these latter disorders, but in general, absorbing molecules and exact mechanisms are poorly understood.

Much more is known, however, about photosensitivity in lupus, there being substantial evidence concerning the tendency of sun exposure to exacerbate cutaneous or systemic manifestations of the disease. Photosensitivity is listed as one of the 1982 revised American Rheumatism Association criteria used to define SLE, and the action spectrum includes both ultraviolet A and ultraviolet B (280–315 nm). Several mechanisms have been proposed and studied experimentally in an attempt to explain this.^{15–17} Ultraviolet radiation has been shown to increase the immunogenicity of DNA, and to induce the expression of extractable antigens such as Ro(SS-A), RNP, and Sm on the keratinocyte cell membrane. Expression of these latter antigens seems to involve active protein synthesis, rather than passive antigen leakage through defective cell membranes. It has been proposed that release of any of these antigenic proteins from their intracellular milieu could then lead to antigen-antibody complex deposition at the dermal-epidermal junction, with possible subsequent systemic release of immune complexes; immune complex deposition could then lead to tissue injury via attachment of effector cells to the antibody Fc fragments. Such tissue injury is known as antibody-mediated cellular cytotoxicity. In support of this hypothesis, lupus patients have been found to have antibodies against ultraviolet radiation-damaged DNA (UV-DNA), thymine dimers being the probable antigenic component. Anti-UV-DNA titres, however, do not necessarily correlate with photosensitivity in lupus patients and other irradiation photoproducts may therefore also play a role.

In addition, a mechanism has been postulated by which ultraviolet irradiation may induce keratinocytes to express and release the chemotactic cytokines interleukin-1 and interleukin-6, thus recruiting lymphoid effector cells to sun exposed areas.^{18 19} These effector cells could then bind to ultraviolet-irradiated keratinocytes by adhesion molecule-ligand interactions such as intercellular adhesion molecule-1—lymphocyte function associated antigen-1. Once there, they could cause cytotoxic damage. It is thus likely that photosensitivity in lupus is a multifactorial process and further studies are required in order to clarify this possibility.

Table 2 Classification of photosensitivity disorders

<i>Drug or chemical-induced disorders</i>	
Phototoxicity	Photoallergy
<i>Photoaggravated disorders</i>	
Systemic lupus erythematosus	Rosacea
Dermatomyositis	Pemphigus foliaceus/vulgaris
Psoriasis	Darier-White disease
Herpes simplex	Seborrhoeic dermatitis
Atopic eczema	Pityriasis rubra pilaris
Grover's disease	Bullous pemphigoid
Lichen planus	Reticular erythematous mucinosis
Acne vulgaris	
<i>DNA repair defective disorders</i>	
Xeroderma pigmentosum	Trichothiodystrophy
Cockayne's syndrome	Bloom's syndrome
<i>Idiopathic disorders</i>	
Solar urticaria	Actinic prurigo
Hydroa vacciniforme	Chronic actinic dermatitis
Polymorphic light eruption	

Much less information is available concerning either the incidence or mechanism of photosensitivity in dermatomyositis. A recent study, however, suggests that photosensitivity is indeed common in the condition, probably occurring in about 50% of patients, through either aggravation or induction of lesions.²⁰

The DNA repair defective photosensitivity diseases are rare and begin in infancy or childhood; however, they are unlikely to present primarily to rheumatologists. The photosensitiser in these disorders is again known and is endogenous cutaneous DNA, as in normal subjects, while the defect is impaired repair of the resultant DNA damage, sometimes also associated with immunological deficiencies.

In the final so-called idiopathic group, which rheumatologists may incidentally encounter from time to time simply because the disorders are relatively common, the precise absorbing molecules producing the various diseases upon absorption have not been identified. This group, by far the largest, includes all the photodermatoses not encompassed within the other categories; as yet they are definitely not united by firm criteria, but it is becoming increasingly likely that some or all have an immunological basis of either immediate or delayed hypersensitivity. The group includes, in particular, polymorphic light eruption, the most common of all the photosensitivity disorders—an itchy, papular rash occurring within hours of exposure to strong sunlight.

General treatment principles for all photosensitive patients require removal of any offending agent, such as a causative drug in the case of a patient with drug photosensitivity, and instruction concerning careful sun protection between the hours of 11 am and 3 pm, use of high sun protection factor sunscreens, and wearing of appropriate protective clothing with a hat. Patients with ultraviolet A sensitivity alone or in addition to ultraviolet B sensitivity, such as might be seen in lupus, need to be aware that many sunblocks until recently have provided only minimal protection in the ultraviolet A range and there is thus an important requirement to seek a suitable modern preparation. Therapy for the eruptions themselves is generally similar to that for other inflammatory dermatoses and involves soothing wet dressings, moisturisers and topical steroids in mild cases, and also intermittent short or medium course systemic steroids, or occasionally immunosuppressive therapy, in more severe cases.

In summary, recognition of photosensitivity requires an initial awareness of the problem by the clinician, followed by a thorough history and physical examination along with appropriate laboratory investigations, particularly assessment of serum antinuclear antibody and extractable nuclear antigen titres, and where necessary, skin histology, immunofluorescence, phototests, and patch and photopatch tests. With the proliferation of drug therapies, outdoor leisure exposure and use of sunbeds, and the apparent

decrease in thickness of the atmospheric ozone layer, the rheumatologist seems likely to encounter more photosensitivity in its various forms. Some drug companies, however, are now wisely beginning to obtain routine photosensitivity data before marketing new drugs. As better understanding of the mechanisms behind photosensitivity develops, it also seems certain that new preventive and therapeutic approaches will evolve, whether as new tolerance-inducing low dose ultraviolet irradiation techniques, novel drugs or improved sunscreens, and the problem of photosensitivity may well be gradually removed from the list of physicians' concerns.

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