Actinic prurigo
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Summary
Actinic Prurigo (AP), an uncommon idiopathic photodermatosis, presents a distinct clinical picture and can be severely debilitating. The clinical features, investigation and treatment of AP are reviewed. We report the experience of an Australian photobiology unit with this condition.

Pathogenesis
AP is caused by electromagnetic radiation, particularly in the ultraviolet (UV) A, and to a lesser extent UVB, range. The inducing chromophores are not known. It has been suggested that AP is a form of autoimmune disease associated with the putative antigen, an epidermal protein transformed by UV exposure (1). Langerhans’ cells, which normally decrease in number in the skin upon UV exposure, persist in patients with AP and are proposed to present the UV-induced antigen in a more persistent manner or in larger amounts, inducing or augmenting the inflammatory response (2). AP is considered to be a familial dermatosis and has a genetic basis with a preponderance in native populations in North, Central and South America, as well as mestizo (mixed native and Caucasian) groups. Case series of AP have also been reported in Caucasian and Asian populations (3–6). There is a strong association with HLA subtypes. HLA DRB1*0407 is most prevalent, and is found in at least 60–70% of patients, but only a small percentage of controls (4–8% of DR4 positive people) (4, 7). HLA DRB1*0401 is the next most prevalent subtype, present in up to 20% of patients afflicted with this condition (3, 4, 8). There are many polymorphisms in this gene. There has been an overproduction of tumour necrosis factor (TNF)-α by keratinocytes, from patients with AP, exposed to UV radiation, which may explain the good response to thalidomide (9). The TNF gene is located on chromosome 6, close to the major histocompatibility antigen (HLA) locus.

Clinical features
AP affects more females than males in a ratio of 2–4 : 1.4 (4, 10). This has been consistent with the authors’ experience (81% of 21 cases were female). The onset is usually in childhood, with a mean age of onset in a mainly Caucasian group being under 10 years (7). The mean was 14 years in the authors’ patient population (4), with a range of 2–43 years. In native Amerindian populations it may occur earlier, at 4–5 years of age (10). A less common adult-onset form has been reported, and in Asian populations males may be more commonly affected than females (5, 6). Pruritus is intense and chronic. It causes a variety of lesions including erythematous papules and nodules, singly or in groups, lichenified plaques, excoriated lesions (Fig. 1) and may lead to dyspigmentation and scarring. Vesicles are not seen unless there is secondary infection. Lesions are typically found on
sun-exposed sites, particularly the face (Fig. 2) (nose – especially distal third, cheeks, chin, earlobes and forehead), neck, extensor forearms (Fig. 3), dorsal hands and chest. However, covered sites including the back and buttocks may also be affected. Cheilitis is reported to be common, but was only found in 24% of Australian patients (4). Oedema, scaling, crusting and fissuring of the lips are seen. Conjunctivitis is another distinguishing feature of AP, although it is infrequent in Caucasian patients. Conjunctival hyperaemia, oedema, pigmentation and pseudopterygium may accompany the symptoms of pruritus, photophobia and lacrimation (11).

Lesions occur predominantly in the spring and summer months. In temperate climates, AP may improve in winter but may not necessarily disappear completely. In hotter climates, the tendency is for lesions to remain constant all year round (10).

In ethnic populations, where AP is relatively common, it is more prevalent at altitudes over 1000 m than at sea level (10).

Spontaneous remission may occur in adolescence particularly in patients with onset in childhood, but persistence is common (12–14). A significant proportion, but not all, of the children in the authors’ experience have tended to improve as they grew older and mature into adulthood. Those with adult onset disease tend to be more persistent.

Investigations

Phototesting is useful to confirm the diagnosis of AP and determine the action spectrum. Provocation testing is positive in approximately two-thirds of patients with AP, with induction of typical AP lesions (15). It is easier to elicit AP with provocation testing than polymorphous light eruption (PLE). Monochromator testing is often positive, with most patients having reduced minimal erythema doses (MED) in the UVA or combined UVA/UVB range (4). In the authors’ case series, phototesting has shown lowered MEDs in approximately 60% of cases, with abnormal results in the UVA spectrum in all cases with positive phototests (Fig. 4). The results of phototesting can assist in educating the patient regarding preventing exposure as well as in planning treatment with phototherapy.

Histology of skin lesions is not usually helpful as findings are relatively non-specific and considered not diagnostic. Hyperkeratosis, parakeratosis, acanthosis and a predominantly superficial, perivascular lymphocytic infiltrate are commonly seen (16). There may also be spongiosis, epidermal ulceration, dermal oedema, telangiectasia of superficial dermal vessels and the presence of eosinophils. However, lymphoid follicle formation is commonly seen in biopsies of mucosal lesions and may be a useful distinguishing feature (12, 16). It may be necessary to perform a biopsy to exclude other differentials including eczema and lymphomatoid papulosis. HLA typing should be performed. Investigation for antinuclear antibodies (ANA) and extractable nuclear antigens (ENA) and a porphyrin screen should be carried out where appropriate to exclude other photosensitive disorders, and before phototherapy.

Differential diagnosis

There has long been a debate as to whether AP is a chronic variant of PLE. Some similarities do exist – the predominantly young female patient group and the photodistributed, polymorphic nature of the lesions. Onset before puberty, persistence of lesions for more than 4 weeks, involvement of covered sites and mucosal surfaces and scarring are suggestive of AP (7). In PLE, the age of onset is usually between 17 and 30 years. Polymorphous light eruption tends to have a much more obvious temporal association with sun exposure, and may be vesicular. Scarring is
not usually seen in PLE. However, there is a subgroup of patients who have overlapping features, where a definitive diagnosis is difficult based on clinical grounds alone. These patients often describe lesions lasting weeks to months, and may have scarring. Histology and phototesting may not be discriminatory. In these patients, HLA typing may help to distinguish the two conditions, because there is no HLA association in PLE. Patients who do not have HLA DR4 may be best labelled as having ‘persistent PLE’. There also seems to be a subset of patients in whom PLE and AP coexist, or those who give a history of one condition evolving or changing into the other with time (7). In a study of 119 patients with features of PLE or AP, a confident clinical diagnosis could be reached in 87% of patients. Of those with a diagnosis of AP, 90% were positive for the DR4 allele on HLA typing, with 60% of these having the rare DRB1*0407 subtype (7). The association with DRB1*0407 has also been found in other populations (3, 4, 8, 17). The next most commonly reported HLA subtype is DRB1*0401, with approximately 20% of patients testing positive (3).

Photoaggravated atopic dermatitis may be difficult to distinguish from AP. A past personal and family history of atopy, and eczema in the flexures are helpful, as well as a prompt response to standard treatment for eczema.

Other idiopathic photodermatoses such as chronic actinic dermatitis, solar urticaria and hydroa vacciniforme are usually distinct. Less likely differential diagnoses that may be considered include sunscreen allergy or photoallergy, erythropoietic protoporphyria, Jessner’s lymphocytic infiltrate, lupus erythematosus and prurigo nodularis.

Treatment

Sun avoidance is the most important factor in treatment of AP. Patients should be told to wear protective clothing with a dense weave, broad-brimmed hat and sunglasses. Window tinting and gloves are useful for car travel. High sun-protection factor, broad-spectrum sunscreens and lip balm are recommended to be worn at all times, although most patients find them ineffective.

Topical corticosteroids, emollients and oral antihistamines may be helpful for pruritus. Short courses of oral corticosteroids can be used for acute exacerbations, and can have good effect (4). Most patients do not respond to antimalarials such as chloroquine and hydroxychloroquine. Other reported but largely ineffective treatments include β-carotene, vitamin E, cimetidine, pentoxifylline and oral antibiotics (except for treating secondary infection).

Phototherapy, both narrowband UVB (NBUVB) and psoralen plus UVA (PUVA) can be efficacious in clearing and preventing new lesions in some patients. A typical treatment regimen for NBUVB would be irradiation three times per week for 5 weeks (18). However, the effect is usually only temporary, and repeated courses may be necessary to maintain benefit. PUVA phototherapy is not advisable in children.

Thalidomide is to date the most effective treatment in the majority of patients with AP. It usually results in rapid clearing of active lesions and reduction in number and severity of new lesions (4). Its effectiveness may also help confirm the diagnosis of AP (11). Thalidomide was first reported to be of use in 1973, where 32 of 34 patients with AP improved significantly while taking the drug (19). Mean time for improvement was 50 days. Doses of 50–100 mg in children and 100–200 mg in adults are used initially, with maintenance achievable with doses as low as
50 mg per week (20). Some patients are able to stop the drug without a need for ongoing therapy (20). Treatment with thalidomide is limited by peripheral neuropathy, which occurs in 20–50% of patients (21). This is predominantly a painful sensory neuropathy, which may resolve or improve in 50% of patients upon cessation of the drug, and remains unchanged in the remainder. Risk factors for neuropathy are controversial. Cumulative dose may be important (9, 21); however, a prospective study showed that the highest incidence was in the first year of treatment, with daily dose being the most important factor (9). The incidence of neuropathy is higher in females and in older patients, with rare occurrence in children. In Australia, prescription of thalidomide requires a permit and registration with the pharmaceutical company that imports the drug. Pharmion. Patients are required to have regular nerve conduction studies. Reduction of sensory nerve action potentials by greater than 40% should result in cessation of the drug. Teratogenicity is the most feared complication of thalidomide therapy. A single dose of 100 mg in the first 35–50 days of pregnancy is sufficient to cause deformities (9). Patients must be on adequate contraception, including males who must use barrier contraception and not donate sperm. Blood donation is also forbidden while on thalidomide. Common, less important side effects include drowsiness, headaches, constipation and weight gain (9). Thromboembolic events have been seen in patients taking thalidomide for malignancy and lupus erythematosus, where there may be an underlying hypercoagulable state, but this has not been reported in AP (9). Newer thalidomide derivatives such as lenalidomide are less neurotoxic, but anecdotally appear to be less effective than thalidomide in the treatment of AP.

In our experience, photoprotection with sunscreen, appropriate clothing and sun avoidance are helpful, but almost as disabling in some as their condition. Topical corticosteroids or calcineurin inhibitors are moderately helpful in encouraging resolution of lesions once they develop. Antimalarials (hydroxychloroquine predominantly) and immunosuppressive therapy (methotrexate) have only ever been partially effective with a mild reduction in the development of new lesions at best. Our observations on the value of thalidomide concur with the literature. We find thalidomide to be the most effective therapy, but the use is limited by toxicity, and most patients experience disease recurrence upon cessation. NB UVB phototherapy has effectively induced hardening, allowing patients to spend time out of doors, but is only seasonal, with a loss of benefit over winter.

Conclusion

Although an uncommon disorder, AP is an idiopathic photodermatosis, which presents a distinct clinical picture. It can be a severely debilitating condition, with significant adverse impact on quality of life because of restriction of outdoor activity, pruritus and the cosmetic appearance of the rash. It is hoped and expected that as a better understanding of the pathogenesis is gained, more directed and less toxic therapies will enable successful management of this genetically determined condition.

References

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