

Chronic urticaria responding to subcutaneous heparin sodium

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SIR, A 43-year-old woman was referred to the dermatology department in 2002 because of a 5-year history of relentless, debilitating urticaria. Her past medical history was unremarkable but there was a family history of hypothyroidism (mother), multiple sclerosis (sister) and coeliac disease (daughter). Blood tests including full blood count, erythrocyte sedimentation rate, C-reactive protein, urea, creatinine, electrolytes, liver function tests, thyroid function tests, antinuclear antibodies, thyroid autoantibodies and C4 were all normal or negative. Autologous serum skin testing was not carried out.

Cetirizine, loratadine, fexofenadine, hydroxyzine, chlorpheniramine, ketotifen, montelukast, cimetidine and doxepin were all tried in standard doses in various combinations. Cetirizine and loratadine were also tried at 20 mg daily with additional sedating antihistamines at night. None of these treatments conferred any significant benefit. Ciclosporin 4 mg kg⁻¹ was given for 6 weeks. This cleared her urticaria but relapse occurred as soon as the dose was reduced below 3 mg kg⁻¹. Ciclosporin was not continued long term as the risks were felt to outweigh the benefits. A course of psoralen plus ultraviolet A (PUVA) was then tried twice weekly. This was effective but only during treatment. Urticaria relapsed within a week of discontinuing PUVA. Methotrexate was tried for 10 weeks, initially at 10 mg weekly, increasing to 15 mg weekly after 4 weeks. It made no difference to her urticaria. Warfarin was also tried in view of two case reports^{1,2} and a double-blind placebo-controlled study in eight patients³ describing its effectiveness. It had no beneficial effect in our patient, as noted in another published study of four patients with chronic urticaria.⁴

In 2003, she was admitted with suspected appendicitis. Prophylactic subcutaneous heparin sodium was given at a dose of 5000 IU twice daily for 3 days during her admission. Her urticaria cleared dramatically and completely, but relapsed immediately when heparin was discontinued. She requested continued treatment with heparin and after a discussion about the risks was recommenced on self-administered subcutaneous heparin sodium 5000 IU twice daily, with the same dramatic effect.

The patient remains completely clear of urticaria after 15 months of treatment. If heparin is discontinued or the dose reduced, the urticaria returns. The activated partial thromboplastin time, as expected, was not prolonged by 5000 IU of heparin administered subcutaneously at 12-h intervals.⁵ She has not so far experienced significant adverse side-effects of heparin such as excessive bleeding tendency, heparin-induced thrombocytopenia, skin necrosis or osteoporosis. Baseline bone densitometry was normal.

Heparin is a naturally occurring glycosaminoglycan in the secretory granules of mast cells and basophils. It is able to

interact with various plasma and cell surface proteins, conferring upon it numerous biological properties.⁵ Heparin has been shown to have a role in the modulation of mast cell mediator release both *in vitro* and *in vivo*. It has a dose-dependent inhibitory effect on the *in vitro* release of histamine from basophils induced by serum as well as plasma from patients with chronic urticaria.⁶

Forty per cent of patients with chronic urticaria have an acute weal and flare response to intradermal injections of autologous serum.⁷ It has been proposed that this is due to IgG autoantibodies against the high-affinity IgE receptor FcεRIα on mast cells.⁸ However, heat decomplexed and IgG-depleted serum has also been observed to elicit a weal and flare response.⁹ Fagiolo *et al.* have demonstrated that mixing heparin with autologous serum immediately prior to intradermal injection diminishes the weal and flare reaction in patients with chronic urticaria. As the action of heparin was immediate, the authors felt it was unlikely to be mediated by second messenger intracellular pathways.¹⁰ Acute cutaneous reactions of sheep to intradermal injection of an allergen but not histamine have been reduced by pretreatment with intravenous heparin, demonstrating the ability of heparin to modulate mast cell mediator release rather than end organ response.¹¹

The exact mechanism of action of heparin in the context of urticaria is therefore still unknown. To our knowledge, there have been no published reports of the effectiveness of heparin as a treatment for chronic urticaria.

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Conflicts of interest: none declared.

Persistent acantholytic dermatosis and extensive lentiginous 'freckling': a new entity?

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SIR, We read with great interest a case report by Cooper et al.¹ recently published in the Journal, of two women with an extensive Grover's-like eruption with lentiginous 'freckling'. The authors argued that the lentiginos were sun-induced. We report two similar cases of persistent acantholytic dermatosis associated with extensive lentiginos.

Patient 1. A 60-year-old man, with skin phototype III, was seen for a generalized papular and pruritic dermatosis of 2 years' duration. A few months earlier, he had developed numerous small brown macules on the trunk and limbs. Physical examination of the skin disclosed scaly brownish-red papules, 2–3 mm in size, and numerous lentiginous macules disseminated over the limbs and the trunk, mostly on the thighs (Fig. 1), the shoulders and the thorax. The nails were normal. He had no family history of skin disease and had never sun-bathed regularly. Five successive biopsies of the papular lesions showed variable patterns of focal acantholytic dyskeratosis, spongiosis and hyperkeratosis, associated with a perivascular dermal lymphohistiocytic infiltrate and a few melanophages. Histology of a lentigine showed elongation of the epidermal ridges and hyperpigmentation of the basal cells with an increased number of melanocytes (Fig. 2). Direct immunofluorescence was negative. Treatment with acitretin 0.5 mg kg⁻¹ daily and topical calcipotriol twice daily was instituted. Six months later, the pruritus was controlled and most of the papular lesions had disappeared, whereas a marked increase in the number of lentiginos was noted.

Patient 2. A 43-year-old woman, with skin phototype III, presented with a 13-year history of pruritic cutaneous eruption. There was no family history of any skin disease, or of excessive sun exposure or sun-bed use. Examination disclosed 'lichen-like', purple squamous papules, associated with profuse lentiginos which were disseminated over the limbs and



Fig 1. Patient 1. Erythematous scaly lesions with freckling on the thigh.

the trunk. Three cutaneous biopsies of the papular lesions showed a variable pattern of focal acantholysis, few dyskeratotic cells and a perivascular lymphocytic infiltrate with melanophages. Biopsy of a pigmented macule on the back showed hyperpigmentation of the basal cells with moderate melanocytic proliferation. Direct immunofluorescence on a papule was negative. Topical calcipotriol was unhelpful.

These two observations are unusual because of the clinical presentation: extensive chronic papular and pruritic eruption compatible with persistent acantholytic dermatosis and profuse lentiginos prevalent over sun-protected sites. The absence of a family history of skin disease, the late age at onset, the distribution of the skin lesions without nail involvement and the focal feature of acantholysis do not support a diagnosis of Darier's disease. In our patients, the prevalence of lentiginos over sites without sun exposure and the absence of medical history of excessive sun exposure clearly seem to rule out