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SHORT REPORTS

Delayed Pressure Urticaria Syndrome: A Clinical Expression of Interleukin 1

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Study of a patient with the bullous delayed pressure urticaria syndrome showed remarkable congruence of the extra-cutaneous findings and the known effects of interleukin 1: malaise, fever, myalgia, arthralgia, leukocytosis, increased sedimentation rate, and circulating acute phase reactants. As a result of this "clinical assay" for interleukin 1, we conclude that the delayed pressure urticaria syndrome is the clinical expression of interleukin 1, synthesized in the skin as a result of pressure and released into the circulation. Delayed urticaria, mediated by interleukin 1, is to be contrasted with immediate type urticaria, long known to be histamine mediated. (Received Janaury 7, 1986.)

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Interleukin 1 (IL-1) has now emerged from the tissue culture laboratory to become a major hormone essential for our understanding of a variety of immunologic and inflammatory responses (1, 2). Although interleukin 1 still eludes routine measurement in blood, this polypeptide is the well recognized mediator for fever, leukocytosis, and the elevated sedimentation rate (3). It also has been implicated in rheumatoid arthritis (4), gout (5), scleroderma (6), gingivitis (7), and ultraviolet light reactions (8).

In this report we show that the delayed pressure urticaria syndrome fits the clinical expression of interleukin 1.

CASE REPORT

A forty-year-old white male had had recurrent attacks of large painful hives on his shoulders, hips, arms and knees for the past 6 months. Severe attacks were regularly associated with chills, mild fever (99.5°), fatigue, muscle soreness, stiff joints and vesicles or bullae surmounting the hives (Fig. 1). Mild episodes were limited to swelling of the palms, soles and beltline. At times the tongue was involved and dysphagia was present. New lesions developed almost daily, spontaneously remitting in 4 to 5 days. Flares had been noted after river bank catfishing and mowing the lawn. Control had been achieved only with prednisone 100 mg/day. He had had hypertension since age 16 and was being treated with guanabenz acetate.

A diagnosis of bullous delayed pressure urticaria syndrome was made.

Upon admission to the hospital his temperature was 99.8°F and blood pressure 164/96 mm/Hg. The blood pressure cuff site regularly became swollen four hours after blood pressure measurement, as did the venapuncture sites. Normal laboratory findings included: CBC, twenty channel blood chemistry, urinalysis, EKG, chest X-ray, renogram, stool examination, cultures of urine, stool and vesicular fluid from skin lesions, rheumatoid factor, CEA, anti-DNA, anti-SM, anti-RNP, Raji cell immune complexes, total complement, prothrombin time, serum protein electrophoresis, immunoglobulins (IgG, IgA, IgM), serum cortisol, and serologic studies for syphilis, histoplasmosis, blastomycosis, coccidioidomycosis, and aspergillosis. Abnormal findings were: relative neutrophilic leukocytosis (9 500 white cells/mm^3, 68% neutrophils), sedimentation rate 20 mm/hour, C-reactive protein 1: 256, streptozyme 100 units, antinuclear antibody 1: 256 speckled pattern, C1Q binding immune complexes 25% (normal below 13%), and cryoglobulins 4.5 mg/dl. He also had extensive gingivitis but no apical abscesses.

An intradermal skin test to the house dust mite, *Dermatophagoides farinae* (Hollister-Stier 0.05 ml) produced a strongly positive immediate urticarial reaction. By 6 hours it was a 6 inch diameter elevated tumor-like wheal, which gradually faded over 48 hours. Intradermal skin tests to Candida, Trichophyton,

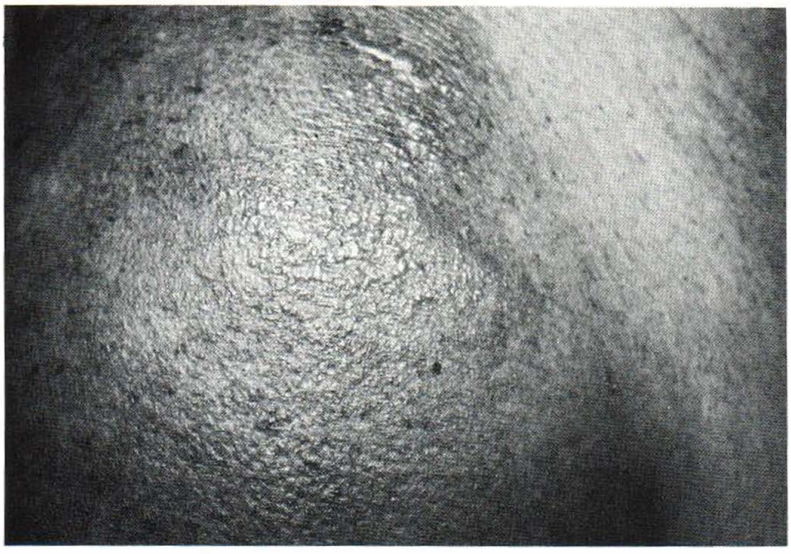

Fig. 1. Erythematous urticarial plaque with central confluent vesiculation appearing 8 hours after pressure on patient's left shoulder. Photograph taken at 24 hours.

bacterial, and flea antigens were negative. Patch tests with twenty-eight contact allergens revealed no delayed sensitivities.

Skin biopsy of a large vesiculobullous urticarial lesion on the shoulder revealed a necrotic epidermis with patchy inflammatory infiltrates throughout the dermis and superficial subcutis. The infiltrate was perivascular and composed of lymphocytes, monocytes, and eosinophils. Some small vessels were filled with neutrophils. There was no vasculitis. Cellular debris and many eosinophils were found in the upper dermis and intraepidermal bulla. Proteinaceous material, including fibrin, was seen in the deeper dermis. Immunofluorescent studies were negative for IgA, IgM, IgG, C_3, C_4, C_{1q}, fibrinogen and albumin.

Lesions could be reproduced by direct firm pressure, such as with the blood pressure cuff, or by the mechanical pull of adhesive tape applied overnight. Discontinuance of the guanabenz acetate and rechallenge had no effect on the lesions. Ketoconazole 200 mg daily was prescribed and the patient was advised to avoid catfishing, lawn mowing and drinking beer. This rapidly led to excellent control. The patient no longer developed lesions, and adhesive tape challenges were negative.

However, six months later a single challenge of river bank catfishing resulted in a two day flare. The ketoconazole was then discontinued and in the ensuing year and a half, attacks have been limited to swelling of the palms and soles following manual labor or prolonged standing. There have been no associated systemic symptoms.

DISCUSSION

To date there has been no explanation for the delay between the pressure stimulus and the appearance of urticaria and systemic signs and symptoms in the delayed urticaria syndrome, despite comprehensive clinical studies of 105 patients (9–13). We propose that synthesis of interleukin 1 (IL-1) in the skin and its subsequent release is the central biochemical event, accounting for both the delay in urtication and the extra-cutaneous findings.

Although at this time we are unable to measure IL-1 directly as is done in the tissue culture laboratory, its presence is evidenced by the findings regularly observed in the delayed pressure urticaria syndrome (Table I).

The therapeutic response of this disease also favors IL-1 as the key mediator for this syndrome. Corticosteroids, known to block the action of IL-1, are effective whereas antihistamines are ineffective (11). Moreover, drugs which commonly exacerbate ordinary urticaria, such as aspirin and other non-steroidal anti-inflammatory agents, also provide relief, apparently by blocking IL-1 induced prostaglandin synthesis. The ameliorative action of

Table I. *"Clinical assay" for presence of interleukin 1 in delayed pressure urticaria syndrome*

	IL-1	Delayed pressure urticaria	Postulated mechanism of IL-1
Fever	+	+	Action on hypothalamus
Myalgia	+	+	Muscle proteolysis
Arthralgia	+	+	Chondrocyte dissolution
Leukocytosis	+	+	Release of neutrophils from bone marrow
Increased sedimentation rate	+	+	Increased fibrinogen synthesis
Acute phase reactants (C-reactive protein)	+	+	Hepatocyte stimulation
Malaise-loss appetite	+	+	Central nervous system effects
Urticaria	Not previously reported	+	Synthesis of IL-1 in macrophage/ monocytes in dermis (inducing arachidonate synthesis of urticariogenic prostaglandins, etc.)
Vesiculation	Not previously reported	+	Synthesis and release of IL-1 from Langerhans' cell and keratinocytes
Stimulus	Antigens, toxins, silica crystals etc.	Pressure/antigens	Acts on macrophages, Langerhans' cells, monocytes, endothelial cells, fibroblasts and keratinocytes
Delay	4–6 hours	4–6 hours	Time for synthesis (not preformed or stored)
Assay	Biological (thymocyte proliferation)	Clinical (signs and symptoms)	

ketoconazole in our patient remains unexplained, although it was given to reduce the yeast antigen load.

Our "clinical assay" reveals IL-1 to be acting on the hypothalamus, liver, muscle and cartilage of these patients. We propose that this IL-1 comes from skin locally impaired by pressure. Macrophages, monocytes, fibroblasts, and endothelial cells all have the potential to synthesize IL-1 in response to a wide variety of injuries, and we wish to add pressure to this list. Pressure dependent trans-capillary release of circulating antigens could explain our patient's heightened sensitivity to pressure whenever exposed to inhalant allergens, such as those encountered while fishing or mowing.

The 4–6 hours required for synthesis and release of threshold amounts of IL-1 appears to explain the puzzling delayed onset of signs and symptoms. This contrasts sharply with histamine-mediated urticaria in which antigens or stroke pressure trigger mast cell degranulation and release of preformed histamine to produce an immediate hive or dermographism. While the histamine-mediated wheal fades in one to two hours, the delayed-onset lesion persists for several days. The continuing lesion seemingly reflects the continuing synthesis of interleukin 1 by the injured cells, and the consequent T cell proliferation.

The presence of vesicles and bullae surmounting the large delayed hives, reported only once before (14), speaks to the intensity of our patient's reaction. They also implicate IL-1, since the Langerhans' cell and the keratinocyte are proven sources of IL-1 in tissue culture (15). The role of this hormone in initiating necrotic changes in the epidermis and oral mucosa as in his gingivitis (7) deserves further study.

Since IL-1 can mobilize neutrophils from the bone marrow, the neutrophil may serve as a marker for IL-1 reactions in the skin. It was present in our patient's lesions and has been

reported as the dominant finding in a newly described disease, neutrophilic urticaria, also construed to represent urticaria induced by physical stimuli (16).

Delayed pressure urticaria provides an expanded awareness of IL-1 mediated disease. Our patient's episodic attacks enabled us to detect IL-1 through its systemic effects and then to trace the source of this "cell-injury hormone" to pressure-injured skin. IL-1 may well be implicated in the pathogenesis of other types of urticaria as well as other types of vesiculobullous disease, such as allergic contact dermatitis.

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Analysis of Increased Urinary Acid Glycosaminoglycans in a Patient with Relapsing Polychondritis

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Tadaki T, Aiba S, Igarashi M, Tagami H. Analysis of increased urinary acid glycosaminoglycans in a patient with relapsing polychondritis. Acta Derm Venereol (Stockh) 1987; 67: 441–445.

We analysed the composition of glycosaminoglycans (GAGs) found in an increased amount in the urine from a patient with relapsing polychondritis (RP) by means of electrophoresis.