eases of the vulva, immunofluorescence can be of assistance in diagnosis. The examples of pemphigus vulgaris and bullous pemphigoid all gave their characteristic DIF findings (6).

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Focal Contact Sensitivity to Nitrogen Mustard in Lesions of Cutaneous T-Cell Lymphoma (*Mycosis Fungoides*)

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Abstract. A report is presented on a patient with mycosis fungoides who developed a remarkable focal contact sensitivity to topically applied nitrogen mustard in aqueous solution (1/5000). Although the nitrogen mustard was applied over the entire skin surface, repeated challenge demonstrated that the eczematous contact dermatitis reaction was limited precisely to the areas of clinically identifiable mycosis fungoides. The surrounding normal skin showed no response. The basis for the surprising focal induction and localization of contact dermatitis is not known but might refleet the presence of a clone of malignant T-lymphocytes which became specifically sensitized to the nitrogen mustard.

Key words: Mechlorethamine; Nitrogen mustard; Contact dermatitis; T-cells; Lymphoma; Mycosis fungoides

Application of a powerful contact allergen to the entire skin surface certainly offers a unique opportunity to explore further the nature of contact dermatitis in man. Such an opportunity is provided the physician who uses topical chemotherapy in the treatment of mycosis fungoides. The entire skin is painted daily with a known sensitizing antigen, nitrogen mustard (mechlorethamine HCl). Once sensitization has occurred the response to any further contact with nitrogen mustard is an eczematous contact dermatitis similar to that seen in poison ivy sensitized or DNCB sensitized patients. In keeping with the basic immunologic tenets of allergic contact dermatitis, the entire skin is sensitized.

The present report describes a patient in whom such an allergic contact dermatitis was induced, but in whom the sensitivity was sharply limited to the lesions of his mycosis fungoides. On painting his entire skin with nitrogen mustard, only his plaques of mycosis fungoides developed eczematous contact dermatitis. The uninvolved skin showed no response whatsoever. This finding merits study since it could enlarge our understanding of the immunology of contact dermatitis.

CASE REPORT

This 59-year-old male first noted pruritic inflammatory plaques appearing over his trunk, arms and legs in 1973. Two biopsies in November 1974 failed to reveal changes other than those of dermatitis. The condition persisted and in May 1976 two additional biopsies showed the histologic changes of mycosis fungoides. Steroid creams were applied, affording some relief.

He was hospitalized in June 1976 for staging of his disease. A skin biopsy confirmed the diagnosis of mycosis fungoides. A blood count, urinalysis, automated 12 unit blood chemistry profile, and bone marrow were all normal. Upper and lower gastrointestinal films, as well as a urogram, lymphangiogram and liver–spleen scan were normal. Patch tests to 30 common contact allergens as well as intradermal tests to Candida, Staphylococcus and trichophytin antigens were negative.

A course of ten treatments with topical nitrogen mustard (mechlorethamine HCl 1/5 000 aqueous) was applied to the entire skin surface. This was effective and tolerated

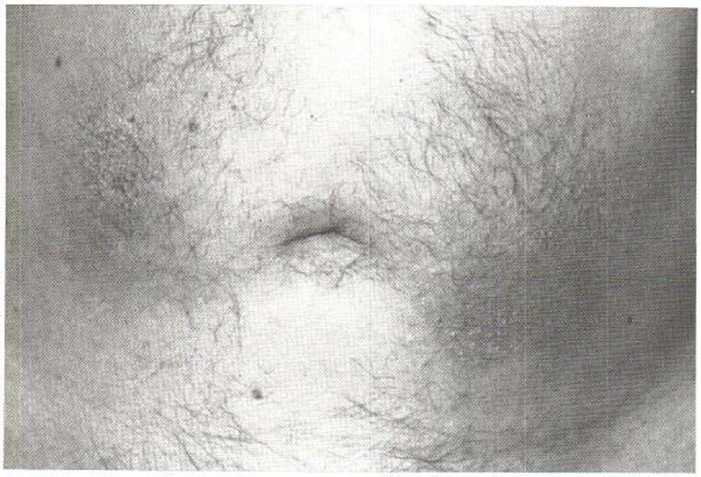

Fig. 1. Abdomen of patient, showing plaques of mycosis fungoides and normal skin. Photograph taken on second day of second course of nitrogen mustard. The skin had shown no change.

well. The mycosis fungoides remained in clinical remission until November 1978 when a tumor of the buttock began to enlarge. A biopsy showed mycosis fungoides.

The patient was rehospitalized in January 1979, at which time he had widespread large pigmented plaques over the trunk, arms and legs (Fig. 1). A repeat of the 1976 battery of tests was negative.

Daily application of nitrogen mustard (1/5000) uniformly over the entire skin surface was made by a nurse. After four treatments the skin of the mycosis fungoides plaques became eczematized, whereas the skin uninvolved in the lymphoma showed no change (Fig. 2). The reaction was so severe that the nitrogen mustard was discontinued. A biopsy showed the pattern of a contact dermatitis reaction superimposed on mycosis fungoides.

Re-application of the nitrogen mustard solution a week later was associated with shaking chills and a temperature elevation to 101.0°F within 6 hours. Again, a sixth nitrogen mustard treatment was followed by the same systemic reaction. Another application a week later was followed in 6 hours by a temperature of 102.5°F, malaise, swelling and marked chills. Four subsequent HN_2 treatments, each preceded by a bolus of oral prednisone, 40 mg, were not associated with any systemic reaction, although the eczematous response in the mycosis fungoides plaques reappeared. This was treated topically with saline compresses and steroid ointments.

Open patch tests with nitrogen mustard (aqueous, 1/5000) on normal skin were negative, whereas on a plaque of mycosis fungoides a 2+ eczematous reaction occurred at 48 hours. Two closed patch tests with a few flakes of powder on normal skin produced sharply circumscribed bullae with no surrounding eczematous change.

Following discharge from the hospital, the patient received nitrogen mustard treatments once a week over a 6-month period, each preceded by a single dose of 40 mg of prednisone. No further systemic reactions occurred, and the eczematous reaction disappeared as the mycosis fungoides lesions faded. Further treatment has not been necessary for the past year and a half.

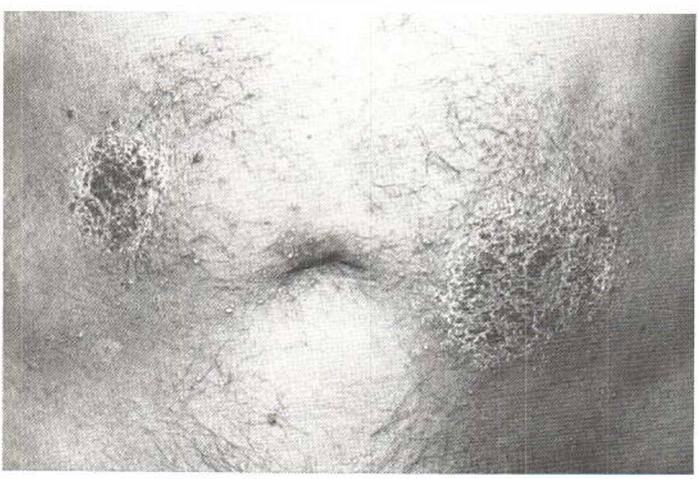

Fig. 2. Abdomen of patient, showing eczematous contact dermatitis which developed on fourth day of painting entire body surface with aqueous 1/5000 nitrogen mustard. No the the sharp localization to plaques of mycosis fungoides, with exemption of normal skin. Biopsy of reaction showed pattern typical of allergic contact dermatitis in mycosis fungoides.

DISCUSSION

This remarkable, previously unreported induction and localization of a contact dermatitis limited to cutaneous T-cell lymphoma lesions deserves comment. It is an especially intriguing finding, since the T-lymphocyte is at once the central cell in the genesis of contact sensitivity (2, 6), and the cell that undergoes malignant change in the lymphoma called mycosis fungoides (1, 7).

This focal dermatitis does not appear to represent a cytotoxic or primary irritant effect as seen regularly with 5-fluorouracil treatment of actinic keratoses. The application of dilute nitrogen mustard to mycosis fungoides lesions in other patients does not regularly produce a dermatitis, as would be expected of an irritant. My patient showed no dermatitis until after the fourth application. Furmatitis until after the fourth application. Furthermore, 3 years prior to this reaction he had tolerated nitrogen mustard with no eczematization.

It would seem likely that the patient had developed a true allergic contract sensitivity to nitrogen mustard which expressed itself not on the compound. His systemic response of chills, malaise and fever after further HN_2, later aborted by prednisone, also suggest a hypersensitivity.

The phenomenon of contact sensitization to nitrogen mustard is common, with as many as a third of all patients showing it (3, 10). In keeping with other examples of contact dermatitis, the entire skin surface is considered to be sensitized and reactive. The anomalous finding in my patient is absence of any reaction to nitrogen mustard in the skin which was free of mycosis fungoides. Nor did patch testing of this normal skin show other than the anticipated primary irritant, vesicant action of the pure compound. The absence of any dermatitis in the areas surrounding the primary irritant bullae speaks strongly against the presence of an allergic type contact sensitivity.

Why did my patient have circumscribed loci of sensitivity? Certainly such a focal response is counter to the rule that, once sensitization has developed, sensitized T-lymphocytes circulate through the entire skin rendering all sites sensitive. However, mycosis fungoides is a cutaneous tumor of immunocytes. One might therefore hypothesize that a malignant clone of T-cells had become specifically sensitized to HN_2, and thus sensitization would be restricted to the tumor sites. One might also envisage the intralesional presence of malignant T-cells of the auxiliary or 'helper' type to be responsible for the selective pattern of sensitization exhibited by my patient.

Another factor which may have been involved in the specific localization of contact sensitivity in the mycosis fungoides plaques is that of the epidermal macrophage, the Langerhans cell. It has been implicated in mycosis fungoides, serving as a central target cell for the inflammatory reaction (4). At the same time it is a key determinant of allergic contact dermatitis (8). In its absence, animals cannot be sensitized to contact allergens. Furthermore, destruction of this cell by PUVA therapy leads to a loss of contact sensitivity (9). The converse possibility remains that in mycosis fungoides this cell is hyper-active in the processing of contact antigens and thus induces focal sensitivity.

Do other patients with mycosis fungoides show this phenomenon of focal contact dermatitis? Although not reported, it is possible that widespread mycosis fungoides may exhibit islands of non-sensitized normal skin which have escaped notice during widespread mustard sensitivity reactions. The answer may come from close observation of the reactivity pattern of sensitized patients and by threshold titre patch testing of normal and lymphomatous skin. Indeed, the phenomenon of focal sensitivity may be more common than our rules would indicate. When drugs such as penicillin are given internally we recognize allergic reactions that are not uniformly generalized but appear in plaques reminiscent of the plaque response seen in this patient. This also occurs when the drug is a contact allergen (5).

In summary, the application of a powerful contact allergen to the entire skin surface offers the clinician an awareness of phenomena never appreciated when exposure to the allergen is spotty and random. Who would dare paint a patient from head to toe with poison ivy antigen? What a remarkable experimental tool we have in topical nitrogen mustard!

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Induction of Tinea Cruris by Topical Nitrogen Mustard and by Systemic Chemotherapy

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Abstract. The present report describes the rapid clinical appearance of superficial fungous infections after the initiation of topical nitrogen mustard treatment in one patient and a short course of systemic cytotoxic drugs in another.

Key words: Tinea cruris; Immunosuppression; Nitrogen mustard; Chemotherapy; Cyclophosphamide; Mycosis fungoides

CASE REPORTS

Patient 1

This 50-year-old white male had had maculo-squamous lesions over his trunk and extremities for 9 months. He also presented with plaques of poikiloderma vasculare atrophicans of the axillae and groin which had been present since childhood. There was no clinical evidence of fungal infection of the hands, feet, nails or elsewhere. Histologic examination of the lesions on the trunk and groin revealed mycosis fungoides.

Topical nitrogen mustard (10 mg in 50 ml of water freshly prepared) was applied over the entire skin ocne daily. By the seventh day the entire groin area was covered with a florid white scaling plaque which showed numerous hyphae on direct K●H examination.

The eruption cleared following 3 weeks of oral griseofulvin (500 mg b.i.d.) therapy, and discontinuation of the nitrogen mustard therapy.

Patient 2

This 54-year-old white male had had a generalized erythroderma and lymphadenopathy for 2 years. All of his toe nails were dystrophic and microscopic examination of the involved plate revealed hyphae. There was no other clinical evidence of fungous infection.

The patient was hospitalized and, on the basis of biopsies and general studies, a diagnosis of lymphoma cutis was made. He was given a course of cyclophosphamide, 9 mg/kg. I.V. daily ×5; vincristine, 2 mg ×1; prednisone, 80 mg/day. Upon completion of this 5-day course, he was discharged from the hospital, much improved. He was advised to take cyclophosphamide orally, 50 mg t.i.d.

Two weeks later, upon his return, he was found to have an exuberant scaling tinea cruris, as revealed by KOH examination. Treatment with griseofulvin (ultramiscrosize dispersion in polyethylene glycol), 250 mg/day, and topical miconazole cream was effective in eradicating both clinical and microscopic evidence of the fungal infection within 3 weeks. The lymphoma persists.

DISCUSSION

Although immunosuppressed patients show a heightened incidence of viral, bacterial, and systemic fungal infections of the skin (5), they do not commonly develop superficial fungal infections (4, 7). Nonetheless, the body does defend itself against dermatophytosis by immunological means (1, 8). Specifically, the defense is a cell-mediated immune one (3, 6). Interference with this immune system may account for the strange "tinea incognito" in patients treated topically with potent steroids (2).

In my patients, it seems likely that the topical nitrogen mustard (patient 1) and, in turn, the systemic cyclophosphamide (patient 2) each depressed the normal cell-mediated immunity to the point where the skin could no longer fend off the growth of dermatophytic fungi.

The present report appears to be the first in which a topical agent, known to impair the cellular immune system, was responsible for the appear-