Topical nitrogen mustard: An effective treatment for cutaneous Langerhans cell histiocytosis

Mary P. Sheehan, MRCPI, D. J. Atherton, FRCP, Valerie Broadbent, FRCP, and J. Pritchard, FRCP

From the Departments of Dermatology and Haematology/Oncology, Hospital for Sick Children, Great Ormond Street, London, United Kingdom

In 16 children with multisystem Langerhans cell histiocytosis (mean age 22 months, range 5 to 36 months) severe symptomatic skin involvement was treated with topical nitrogen mustard (mechlorethamine hydrochloride). In each case, rapid clinical improvement occurred within 10 days; subsequent complete healing was observed in 14 children, and partial healing in 2 others in whom treatment was a component of palliative care. Mean duration of treatment was 3.5 months (range 2 to 6 months). Systemic treatment was averted in 11 patients because response to topical therapy was so favorable, but bone marrow or respiratory failure led to a fatal outcome in 5 other patients. Adverse effects were minimal. One patient developed contact allergy to topical nitrogen mustard after 2 years of intermittent therapy, but was successfully desensitized and was then able to continue treatment. We conclude that the topical application of nitrogen mustard is an effective treatment for cutaneous Langerhans cell histiocytosis. Although adverse effects were minimal in the short term, there remains concern about the possibility of long-term cutaneous carcinogenicity. (J PEDIATR 1991;119:317-21)

In Langerhans cell histiocytosis (histiocytosis X) large numbers of abnormal Langerhans cells occur at sites other than their normal location in the epidermis, causing a variety of harmful effects. The disorder may be confined to one organ system, usually bone, or may affect several. There is now convincing evidence that LCH is a benign reactive process, not a malignant disease.[1]

Single-system disease has an excellent prognosis; it may regress spontaneously, or may require local treatment such as curettage or intralesional steroid injections. Multisystem disease also has a relatively favorable prognosis unless it is associated with vital organ dysfunction, when, before the age of 2 years, there is 30% to 50%, mortality.[2] In many centers, children with multisystem disease receive multiple-agent systemic chemotherapy, but there is no convincing evidence that more intensive therapy improves the long-term prognosis.[3-5] Local treatments that provide symptomatic relief therefore have an important role in the treatment of LCH. We favor a conservative and expectant therapeutic approach.[6]

See related article, p. 274.

LCH	Langerhans cell histiocytosis

Skin involvement is a relatively common component of multisystem disease in younger children.[7] In many patients whose disease is otherwise under control, the skin may be the sole source of troublesome symptoms, which may include pruritus, painful ulceration, purulent exudation,

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Reprint requests: M. P. Sheehan, Department of Dermatology, Hospital for Sick Children, Great Ormond Street, London WC1N 3JH, United Kingdom.

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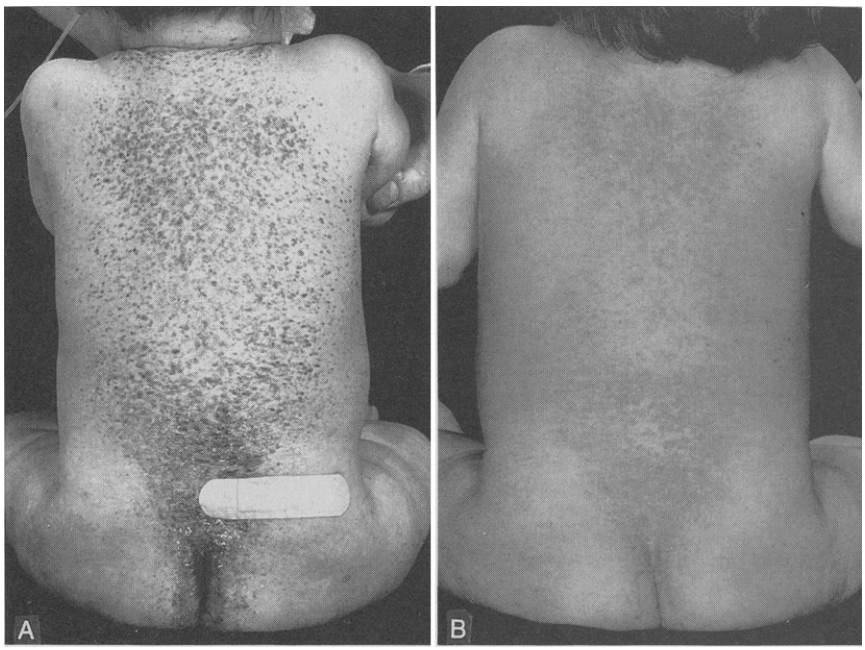

Fig. 1. A, Before treatment. Note extensive papular erythematous truncal rash extending into the natal cleft, with crusting. **B,** After treatment. Note resolution of papules with residual hyperpigmentation, seen best in natal cleft.

discharge from the ears, odor, dysuria, and painful defecation in the case of anogenital disease. In our experience, conventional topical treatment with corticosteroids, emollients, and keratolytics is of limited value when the disease is mild, and virtually without effect when it is severe. Nitrogen mustard has been used successfully in the topical treatment of cutaneous T cell lymphoma.[8-11] Previous reports of its use in cutaneous LCH mostly relate to its use in adults.[12-18] In this paper we describe our experience with the use of topical nitrogen mustard in the treatment of cutaneous LCH in children.

METHODS

Patients. A histopathologic diagnosis of LCH[19] was made in 61 patients between January 1981 and January 1989. Fourteen of the 61 had single-system disease, all in bone, and 47 had multisystem disease. The frequency of individual organ involvement was bone 46 (75%), skin 43 (71%), middle ear 26 (42%), lymph nodes 19 (31%), spleen 14 (23%), mouth 14 (23%), liver 13 (21%), bone marrow 13 (21%), posterior pituitary gland 12 (20%), and eyes 12 (19%).

Of the 43 children with skin involvement, 16 (13 boys) received nitrogen mustard treatment. Their mean age was 13 months (range 6 weeks to 27 months) at the time of diagnosis, and at the start of treatment was 22 months (range 5 months to 3 years). All 16 had previously received courses of oral prednisolone, with resolution of disease in some locations but with persistent symptomatic skin involvement. Four had also received etoposide. In these 16 children, 15 had involvement of the scalp, flexures, and genital region; skin involvement in the remaining patient was restricted to the scalp and proximal flexures. Ulceration was frequent in the groin, axillae, and neck. Purpura was present in 8 patients, generally the more severely affected, including all 5 patients who died. The decision to treat LCH with topical nitrogen mustard was based on the intensity of cutaneous symptoms and the lack of response to oral prednisolone therapy.

Treatment. Treatment techniques were explained to parents in the clinic, and were reinforced by provision of written instructions. Nitrogen mustard was applied topically by the parents at home; 10 mg sealed multiple-use vials of nitrogen mustard powder (Boots Co., Nottingham, U.K.) were provided. An aqueous solution was prepared by injecting 10 ml tap water through the rubber seal of the vial. For each treatment, 2.5 ml of this solution was extracted by syringe, and further diluted with 10 ml tap water, providing a final dilution of 20 mg/dl. This solution was applied to the skin with watercolor brushes of appropriate size. Initially, treatment was undertaken once daily. Thus one 10 mg vial provided treatment for 5 days. Parents were instructed to bathe the child to remove excess nitrogen mustard 10 minutes after application was completed. Parents were instructed to apply solution only to visibly affected areas, and to discontinue application at any particular site

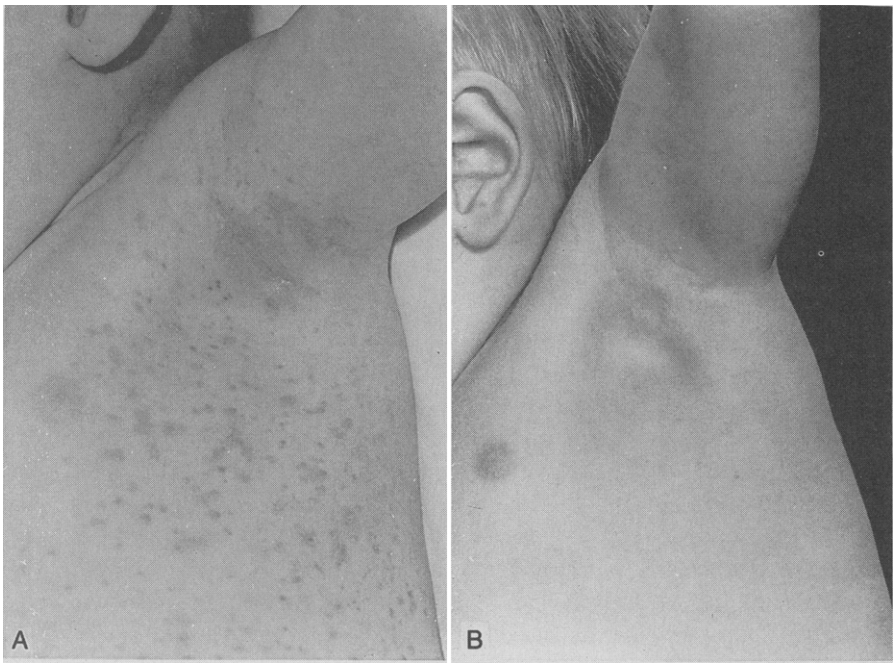

Fig. 2. A, Before treatment. Note discrete crusted erythematous papules affecting the left lateral chest, lateral neck, and inner arm in association with LCH intertriginous rash (left axilla). **B,** After treatment. Note total clearance of rash from left axilla, left lateral chest, neck, and arm regions. There is no evidence of hyperpigmentation in this child.

as soon as lesions had clinically cleared. As the skin disease regressed, treatment frequency was reduced to every second or third day.

Parents were instructed to wear disposable polyethythene gloves while preparing and applying solutions, to avoid applying solution to unaffected skin, and to dilute and thoroughly dispose of any unused solution. Strict attention was paid to the avoidance of skin or eye contact. After bathing the child, parents were instructed to cleanse the bathtub thoroughly.

RESULTS

A single treatment course resulted in complete healing in 14 of the 16 patients (Figs. 1 and 2). Clinical improvement was apparent within 2 to 18 days (means 10 days) in every case, and tended to be seen most rapidly in the scalp. Mean duration of treatment was 2.9 months (range 1.5 to 10 months). Of these 14 patients, 8 have had no recurrence in the skin to date (mean follow-up 4.9 years, range 2 to 9 years). As in the case of initial treatment, retreatment was recommended only if skin involvement was causing distressing symptoms. Six patients required a second treatment course on this basis, after a treatment-free interval of at least 6 months; 4 of these have remained free of skin disease until the present time (mean follow-up 2.8 yeras, range 2 to 5 years); the other 2 required a third course, and subsequently had complete clearance of variable duration. Ten of the 16 patients were receiving oral prednisolone for their skin disease at the commencement of topical nitrogen mustard therapy; all were able to discontinue it during nitrogen mustard therapy.

In the other 2 of the 16 patients, topical nitrogen mustard treatment was initiated for relief of severe cutaneous symptoms during the terminal stages of multisystem disease. Daily treatment led to regression of skin lesions and substantial symptomatic benefit in both children.

Very few adverse effects were seen. A 7-year-old boy who had received treatment intermittently for more than 2 years developed contact dermatitis to nitrogen mustard, confirmed by epicutaneous skin testing; he was desensitized by a modification of the regimen described by Constantine et al.[20] and was subsequently able to continue treatment. Local irritation was not reported despite application of the solution to ulcerated areas of skin and mucosa. Slight hyperpigmentation was seen at the beginning of treatment in 10 patients; this generally faded within a few weeks. We did not observe urticarial reactions, as have been reported previously.[12] Late effects such as skin tumors have been sought, but none have appeared to date (mean follow-up 4.9 years, range 2 to 9 years).

DISCUSSION

We have found that topical application of a dilute aqueous solution of nitrogen mustard is an extremely effective

treatment for cutaneous LCH in children. Clinical response is rapid. We observed no short-term adverse effects, nor any medium-term adverse effects other than the development of contact sensitivity in one child. We prefer an aqueous solution to a cream or ointment formulation, for several reasons. First, an aqueous solution is much more practical for treatment of areas such as the scalp and the external auditory canals, which are predilection sites for LCH. Second, creams and ointments rapidly disseminate from the treated sites in children to normal areas of skin and to eyes and mouth, and to other persons. Conversely, a solution can be applied with great accuracy using watercolor brushes, to minimize application to normal skin. We favor a precise exposure time, and achieve this by washing off excess nitrogen mustard after 10 minutes. This has the additional benefit of minimizing contamination of untreated sites and other persons.

In our center, LCH initially is treated with oral prednisolone unless there is evidence of vital organ dysfunction requiring systemic cytotoxic therapy. In our experience, prednisolone alone fails to provide adequate symptomatic relief of skin disease in about a third of patients. For these children, we currently prefer topical nitrogen mustard to systemic cytotoxic agents, in view of the latters' substantial short- and medium-term toxicity.

There are two principal areas of concern in relation to the use of topical nitrogen mustard. First, there is the possible development of cutaneous malignancy after prolonged therapy, as has been reported in mycosis fungoides, the commonest variety of cutaneous T cell lymphoma.[22-25] The great majority of patients with this condition are older than 45 years. Treatment is applied to the entire body surface, and because of the high recurrence rate, is generally continued for periods of several years. The cutaneous tumors that have occurred in patients with mycosis fungoides treated with topical nitrogen mustard were mostly squamous carcinomas, and most occurred on sun-exposed sites. On the other hand, the occurrence of some of these tumors at sites not exposed to the sun suggests an etiologic role for chemical carcinogens.[24] However, many of these patients had previously been exposed to other treatments known to be carcinogenic, including arsenic, electron beam therapy, and cytotoxic chemotherapeutic agents. Some patients had had previous skin tumors. In the most comprehensive study to date, there was a ninefold increased incidence of squamous carcinoma and a twofold increased incidence of basal cell carcinoma appearing after nitrogen mustard treatment of mycosis fungoides.[9] These tumors were almost invariably simple to treat. More serious cutaneous malignancies, such as malignant melanoma, have not occurred more frequently in these patients.[9] In view of the differences between patients with mycosis fungoides and LCH, including the older age of the patients with mycosis fungoides, their frequent previous exposure to other carcinogenic therapies, and the prolonged treatment periods, it is difficult to make comparisons.

A study in hairless mice demonstrated an increased incidence of skin tumors during topical treatment with nitrogen mustard. It is difficult to relate the findings to the use of this agent in our patients, particularly because fivefold higher concentrations were used, in an alcohol solution.[26] However, the authors noted that three times weekly ultraviolet B radiation was much more carcinogenic than nitrogen mustard alone. In a previous study, the same author had reported that weekly application of an identical concentration of nitrogen mustard for 1 year did not result in an increased rate of tumor production.[27] The demonstration of enhancement of ultraviolet B–induced carcinogenesis by topical nitrogen mustard indicates that patients must be protected from sun exposure during treatment.[26]

No skin tumors have been detected to date in our patients, but they have not yet been observed for a sufficient period for us to draw any conclusions regarding secondary malignancies, and longer term follow-up will be undertaken.

The second area of concern relates to possible harmful effects if nitrogen mustard is systemically absorbed. In view of the intense protein binding of nitrogen mustard,[28] it may be difficult for unbound drug to reach the systemic circulation after topical application. It is encouraging in this respect that no increase in lymphocyte sister chromatid exchanges could be detected after topical nitrogen mustard therapy of mycosis fungoides.[29] However, this issue requires further study, and we are currently evaluating the urinary excretion of nitrogen mustard and its metabolites by mass spectrometry.

These risks must be balanced against the risks associated with systemic cytotoxic therapy for LCH, which has been shown to be followed by a secondary malignancy rate of 14%.[30] We use topical nitrogen mustard only in patients who have failed to respond to prednisolone and who have no other current indication for treatment other than their skin disease. Furthermore, we use topical nitrogen mustard only for skin disease that is provoking substantial distress.

We conclude that topical nitrogen mustard (1) is an effective agent for the symptomatic treatment of cutaneous LCH, (2) can be administered easily and reliably by parents in the home, (3) is free from short-term adverse effects, and only occasionally results in medium-term contact sensitization, and (4) is best used in discrete courses. More than one course may be required, but gratifying and prolonged remissions of skin disease can be achieved in the majority of patients.

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