A Case of Cutaneous T Cell Lymphoma Treated with Recombinant Interleukin 2 (rIL-2)

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We report a case of cutaneous T cell lymphoma (CTCL) treated with local injection of recombinant interleukin 2 (rIL-2). The biopsy specimen showed marked infiltration of large convoluted cells admixed with small lymphocytes and histiocytes in the epidermis, dermis and subcutis. After six injections of rIL-2, 4 nodules out of 5 on the left lower leg disappeared and the remaining large nodule was diminished in size. A biopsy specimen from the diminished nodule showed infiltration of small lymphocytes with histiocytes and plasma cells in the dermis. The atypical cells, large hyperconvoluted lymphocytes, had disappeared. A large number (28%) of lysozyme- and α_1-anti-chymotrypsin-positive cells were demonstrated by immunohistochemistry. The patient maintained complete remission for a period of 13 months. He then noticed a small red nodule on the back of the left foot, which was histologically confirmed as a recurrence. Chemotherapy cleared the lesion. (Received March 4, 1988.)

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Recently, lymphokines have been used as therapeutic agents against malignant neoplasms. Interleukin-2 (IL-2), interferon (IFN)-α, β and γ, and tumour necrosis factor (TNF) are included among these agents. However, they do not have sufficient effect to cure patients affected by malignant neoplasms. On the other hand, lymphokine-activated killer (LAK) cells, generated by culture of normal peripheral lymphocytes with IL-2 in vitro, have a strong antitumour activity (1). LAK cells lyse fresh allogeneic or, autologous tumour cells or cultured tumour cell lines, but not normal cells (2). These LAK effector cells are thought to be heterogeneous, in other words, activated natural killer (NK) cells, tumour-specific cytotoxic T cells and macrophages are all thought to have LAK activity (3, 4). In fact, adoptive immunotherapy with LAK cells and recombinant IL-2 (rIL-2) has been shown to have a strong anti-tumour effect in a patient with malignant melanoma (5). If rIL-2 is injected around the tumour, the agent could activate tumour-infiltrating lymphocytes (TIL). Thus it seems that subcutaneous injection of rIL-2 can provide an in vivo model system of LAK cell immunity.

In this report, we present a case of CTCL treated with subcutaneous injection of rIL-2 and discuss the relation between CTCL and rIL-2 treatment. For this purpose, we performed a multiparameter investigation of infiltrating cells within the skin, using a series of monoclonal antibodies and hetero-antisera.

CASE REPORT

A 30-year-old man was referred to our Department in October 1985, because of a one-month history of cutaneous and subcutaneous nodules on his lower left leg. Physical examination showed one ill-demar-

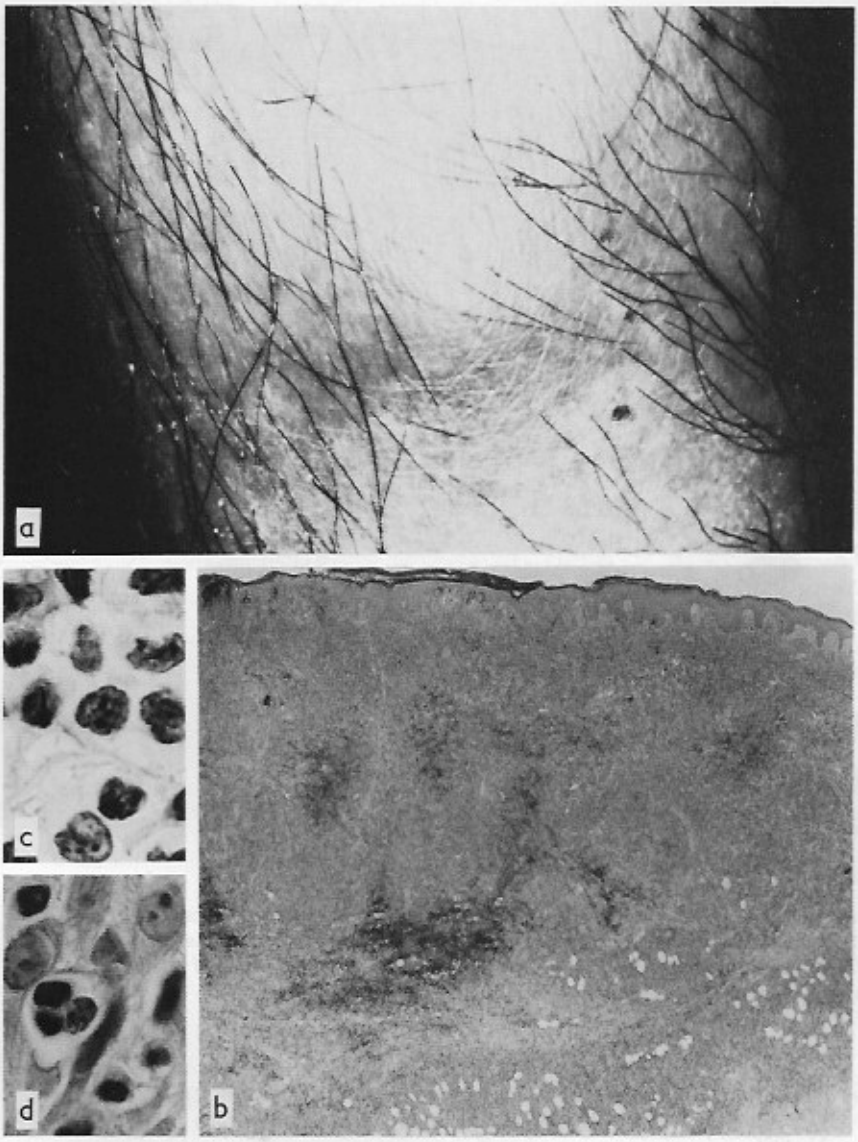

Fig. 1. (*a*) Clinical presentation in October, 1985, showing a 2.5×2 cm subcutaneous nodule with a reddish surface on the left lower leg. (*b*) Biopsy specimen taken in October, 1985, showing marked cellular infiltration in the dermis and subcutis (H-E stain, ×10). (*c*) High-power view showing a dermal infiltrate consisting of medium-sized and large lymphocytes with an irregularly folded nuclear membrane (×500). (*d*) Pautrier's microabscesses are seen (×500).

cated reddish nodule and four subcutaneous nodules with a reddish or normal skin colour on the lower part of the left leg (Fig. 1). No abnormality suggestive of extracutaneous disease was revealed. Determinations of hemoglobin, total and differential white blood cell count, and serum proteins were all within normal limits. However, hepatic dysfunction was evident (GOT 29 mU/ml, GPT 69 mU/ml). No monoclonal integration of HTLV-I proviral DNA into the peripheral blood lymphocytes was detected (data not shown).

The patient was treated by subcutaneous injection of rIL-2 (200 units six times; a generous gift from Takeda Chemical Industries Co.) around the nodules every other day. After 2 weeks of this treatment,

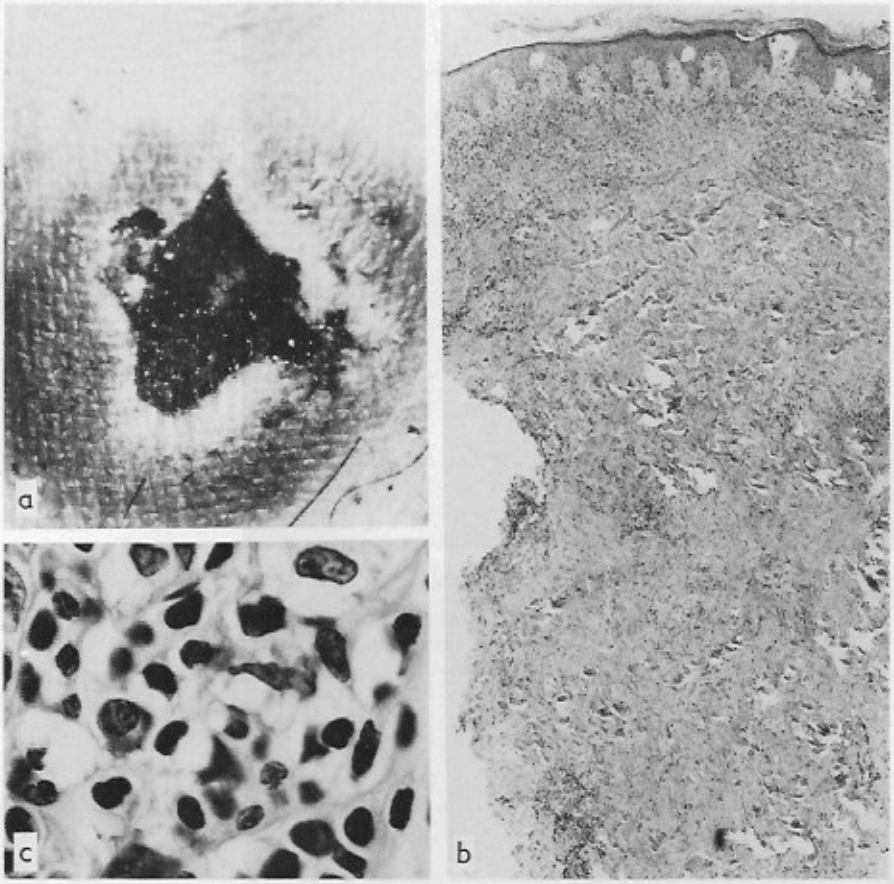

Fig. 2. (*a*) Clinical presentation in November, 1985, showing diminished and ulcerated nodules. (*b*) Biopsy specimen obtained on November 12, 1985, showing cellular infiltration in the upper dermis, and epidermis (H-E stain, ×10). (*c*) Excision sample showing marked cellular infiltration consisting of small and medium-sized lymphocytes, plasma cells and histiocytes in the dermis (×500).

four of the five nodules had disappeared and the other was diminished in size and ulcerated (Fig. 2). The ulcer was surgically excised on November 28, 1985. Intravenous administration of rIL-2 was then given once a week until February 27, 1986.

Laboratory data were not influenced by the rIL-2 treatment. The patient maintained complete remission for about 13 months from December 1985 to December 1986. He then noticed a small reddish nodule on the back of the left foot in January 1987. Thereafter, systemic chemotherapy consisting of VEPMTX (vincristine sulphate, cyclophosphamide, methotrexate and prednisolone) was given from January 1987, resulting in a rapid and good response.

Light microscopic findings

Histologic examination by light microscopy of a biopsy sample from the nodule on the lower portion of the left lower leg obtained on October 22, 1985, revealed marked cellular infiltration in the epidermis, dermis and subcutis (Fig. 1). Pautrier's microabscesses consisting of large lymphoid cells were seen. The large lymphoid cells had hyperchromic, irregularly shaped and hyperconvoluted nuclei (Fig. 1). The dermal infiltrates consisted of a proliferation of large lymphoid cells with irregularly folded nuclei. Occasionally, small lymphocytes, plasma cells and histiocytes were found among the atypical lymphocytes. A sample from the ulcer excised on November 12, 1985, showed marked cellular infiltration composed of small and medium-sized lymphocytes, plasma cells and histiocytes in the dermis (Fig. 2). No atypical large lymphocytes with an irregularly folded nuclear membrane were seen (Fig. 2).

Immunohistochemical findings

Antigens recognized by monoclonal antibodies and heteroantisera were investigated by either the ABC (avidin–biotin peroxidase complex) method on cryostat sections, or by the PAP (peroxidase–anti-peroxidase complex) method on paraffin sections. Details of the immunological properties of the infiltrated cells obtained from biopsied skin are shown in Table I. Before rIL-2 therapy (22 October, 1985), cells staining with anti-lysozyme and anti-α_1-anti-chymotrypsin antisera, which define macrophages, were abundant (28%). The proportion of MT-1-positive T cells was only 60%. After rIL-2 treatment (12 November, 1985), macrophages were still 28%, but T cells were decreased (45%). Two weeks after local rIL-2 therapy (28 November, 1985), macrophages were decreased (6%) and T cells were increased (88%). When the patient had a recurrence on the back of his left foot (January 29, 1987), macrophages were abundant (17%) and T cells formed the major population (83%). The atypical cells were positive for MT-1 (74%), Leu 4 (83%), Leu 3a (61%) Leu 1 (66%) and HLA-DR (66%), indicating that they expressed the phenotype of activated helper T cells, but negative for Ki-1 (0%), Leu 8 (1%) and Leu 9 (0%); Leu 2a positive infiltrating lymphoid cells comprised 12%.

DISCUSSION

CTCL was first described by Lutzner et al. in 1975 (1) and defined as helper T cell lymphoma with marked affinity for the skin. Usually it is a slowly progressing lymphoma, except for certain variants. In our present case, cutaneous and subcutaneous nodules showed progressive enlargement on the lower portion of the lower left leg during a 2-month period. No extracutaneous involvement was evident. Microscopically, atypical lymphocytes with irregularly folded nuclei were predominant in the epidermis, dermis and subcutis. Pautrier's microabscesses, consisting of large lymphoid cells and Langerhans' cells, were detected. Atypical lymphocytes showed CD3, CD4 positivity and CD8 and CD25 negativity, indicating that they bore helper T cell markers on their cell surface.

Photochemotherapy (PUVA), topical steroid therapy, topical irradiation and topical chemotherapy are some of the typical treatments applied in the early stage of CTCL, while in the late stage or aggressive type of CTCL, chemotherapy and radiotherapy are used. However, none of these treatments has been effective for late-stage CTCL, except for some new forms of therapy, e.g., extracorporeal photochemotherapy. IL-2 is a type of lymphokine produced by activated helper T cells and has been used as a therapeutic agent for malignant neoplasms (5). Intravenous administration of IL-2 has not been so effective against skin tumours, but subcutaneous injection around skin tumours has been found useful. In our present case, four out of five nodules disappeared and the remaining one was diminished in size and ulcerated after subcutaneous injection of rIL-2. Subcutaneous injection of rIL-2 around tumours is thought to constitute an in vivo model of LAK cell induction if infiltrates are present.

Before rIL-2 therapy, T cells (MT-1-positive cells) accounted for 60% and macrophages (lysozyme- and α_1-antichymotrypsin-positive cells) for about 30%. After rIL-2 treatment, the

Table I. *Surface markers of infiltrating cells obtained from biopsied skin*

	1985/10/22	1985/11/12	1985/11/28	1987/1/29
Pan T MT-1[a]	60%	45%	88%	74%
S-100[b]	3%	0%	3%	1%
Lysozyme[b]	28%	28%	6%	17%
α_1-antichymotrypsin[b]	32%	25%	3%	nd
κ[b]	12%	0%	5%	4%
λ[b]	3%	1%	3%	3%

[a] Bio-Science products AG, Emmenbreucke, Switzerland.
[b] DAKOPATTS a/s, Glostrup, Denmark.

percentage of T cells was decreased (45%), and atypical lymphocytes had disappeared. Two weeks after rIL-2 therapy, the percentage of macrophages was decreased (6%) and that of T cells was increased (88%). A biopsy specimen from the recurrent nodule on the back of the left foot showed 17% macrophages, 83% T cells and large atypical lymphocytes in the dermis. These facts led us to suspect that macrophages or a macrophage-activated mechanism were related to the tumour immunity, which was enhanced by IL-2.

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