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The Development of a Ki-1-positive Large Cell Non-Hodgkin's Lymphoma in Pagetoid Reticulosis

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A case of the disseminated variant of pagetoid reticulosis is described which progressed after many years of disease to a large cell anaplastic (Ki-1) lymphoma of T-cell type. The lymphoma cells showed abnormal cellular DNA and a high proliferative rate, as revealed by immunophenotypic examination and single-cell DNA measurements. The cells were positive for activation associated antigens and expressed a T-helper/inducer phenotype. A similar phenotype was expressed by the neoplastic cells in the co-existing lesions of pagetoid reticulosis. These findings support the view that pagetoid reticulosis is a variant of the cutaneous T-cell lymphomas which originates from activated lymphoid cells and which may on occasion progress to a potentionally more aggressive lymphoid malignancy. ***Key words: Cutaneous lymphoma; Immunohistology.***

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Pagetoid reticulosis was first described in 1939 (1) and is characterized by prominent epidermal infiltrates of cerebriform mononuclear cells. These cells closely resemble the neoplastic cells seen in mycosis fungoides (MF) in terms of their light microscopic and ultrastructural features (2), they express T-cell associated antigens (3, 4), and they may show clonal rearrangement of T-cell receptor genes (5). These findings have provided firm evidence that pagetoid reticulosis is a variant of the cutaneous T-cell lymphomas (CTCL) rather than a histiocytic condition, as suggested in earlier reports (6).

Two clinical subtypes may be distinguished, i.e. a localized, relatively indolent variant (known as the Woringer-Kolopp subtype) and a more severe condition with multiple skin lesions—the so-called Ketron-Goodman type (7).

In this study, a case of the disseminated variant is described which progressed after many years of disease to a Ki-1-positive, large cell non-Hodgkin's lymphoma of T-cell type.

MATERIALS AND METHODS

Biopsy specimens and blood mononuclear cells were obtained fresh and processed for immunohistological staining and DNA flow cytometry as described in detail elsewhere (8, 9). Samples of lesional skin and involved lymph node tissue were also routinely processed for formalin fixation and paraffin embedding.

Case report

The patient was a 62-year-old Caucasian male who presented in 1969 with disseminated, pruritic, eczema-like plaques on the trunk and extremities. Face, hands and feet were not involved. The initial histological examination was considered suggestive of pemphigus vulgaris. However, in 1976 this diagnosis was revised. At that time, light microscopic and ultrastructural examination revealed epidermotropic infiltrates of lymphoid cells with cerebriform nuclei, and the diagnosis of pagetoid reticulosis was established. There was no evidence of extracutaneous disease, and the patient was treated with topical mechloretamine, supplemented with PUVA (UVA and 8-methoxypsoralen), dithranol and topical corticosteroids.

This treatment resulted in a resolution of all skin lesions, and the patient remained in remission until 1986 when a relapse occurred with disseminated, eczema-like lesions and two lobulated skin tumours, measuring 2 and 4 cm in diameter, on the right knee and calf. Enlarged lymph nodes, measuring 2 and 4 cm in diameter, were present in the right inguinal region. There was no other evidence of extracutaneous disease, and lymphangiography, blood and bone marrow examination, and chest X-ray were normal.

The patient was treated with re-PUVA (i.e. etretinate (Tigason) 75 mg daily in combination with PUVA four times a week) and local electron beam. This resulted in a resolution of both the skin and the lymph node lesions. However, after 3 months, another relapse occurred with three new skin tumours on the right leg. These tumours disappeared after repeated electron beam, and at present only the eczema-like lesions (Fig. 1) persist.

RESULTS

Histopathological studies

The eczema-like lesions of pagetoid reticulosis showed prominent epidermotropic infiltrates of cere-

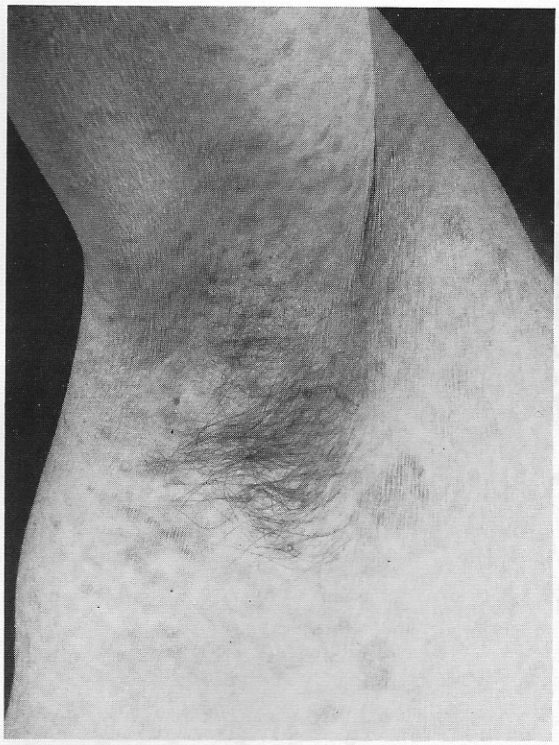


Fig. 1. Eczema-like lesions of pagetoid reticulosis.

briform lymphocytes. Both single-cell exocytosis and Pautrier microabscesses were present (Fig. 2). Very few lymphoid cells were seen in the dermis. Furthermore, these cells had regular nuclei and lacked the atypia of the cells observed in the epidermis.

The skin tumours showed dense, diffuse infiltrates of markedly pleomorphic, large lymphoid cells with highly irregular nuclei and numerous mitotic figures (Fig. 3 *a*). Occasional cells showed a Hodgkin-like morphology and contained lobated nuclei with prominent nucleoli. Classical Hodgkin's cells were, however, not observed, and the morphological features were considered consistent with a diagnosis of a large-cell anaplastic non-Hodgkin's lymphoma. In the epidermis above the dermal infiltrate, single-cell exocytosis was present, but Pautrier microabscesses were not identified.

The enlarged lymph node from the right inguinal region showed diffuse infiltrates of large lymphoid cells similar to those seen in the skin tumours.

Immunophenotypic studies

The neoplastic lymphocytes in the skin tumours and the involved lymph node tissue showed a similar phenotype and were positive for T-cell antigens (Fig. 3 *b*), including CD2, CD3, CD4, CD5, CD7, CD27 and the T-cell antigen receptor, recognized by staining with antibody F101.01 (10). Many cells were positive for activation-associated markers, including HLA-DR, interleukin-2 receptor (CD25) and the Ki-1 antigen (CD30) (Fig. 3 *c*). A substantial number of the cells also expressed proliferation associated antigens, i.e. transferrin receptor and the Ki-67 nuclear antigen (11) (Fig. 3 *d*). Staining for B-cell antigens (CD19, CD22), T-suppressor cell associated antigen (CD8), and macrophage and Langerhans' cell associated markers (CD1, CD11c, CD14) was confined to scattered reactive cells.

The neoplastic cells in the co-existing lesions of pagetoid reticulosis expressed a similar phenotype with the exception that only a minority of these cells were CD30-positive.

Immunocytochemical examination of blood mononuclear cells showed normal ratios of B-cells, macrophages and T-helper and T-suppressor cells. CD30-positive cells were not identified in the blood specimens.

DNA flow cytometry

Normal DNA histograms were seen in the dermal specimens from the eczema-like lesions of pagetoid reticulosis. In contrast, in the specimens form the skin tumours, a discrete aneuploid peak in the hyperdiploid region was identified. This peak accounted for 28% of the cells and was clearly separated from the normal G0/G1 cells (Fig. 4).

DISCUSSION

In this study, a case of the disseminated variant of pagetoid reticulosis is described which progressed after many years of disease to a large-cell anaplastic (Ki-1) lymphoma. The lymphoma cells were positive for pan-T-cell antigens and expressed a T-helper/inducer phenotype. A similar phenotype was expressed by the neoplastic cells in the co-existing lesions of pagetoid reticulosis. This is in keeping with other recent studies which have shown that the neoplastic cells in pagetoid reticulosis are not homogeneous with respect to their T-cell phenotype, but many express either T-helper (4), T-suppressor (3, 12), or aberrant T-cell phenotypes (5). Similar findings have been reported in MF (13), and this supports the view that pagetoid reticulosis is more likely to be a variant of MF (12) than a separate entity (3).

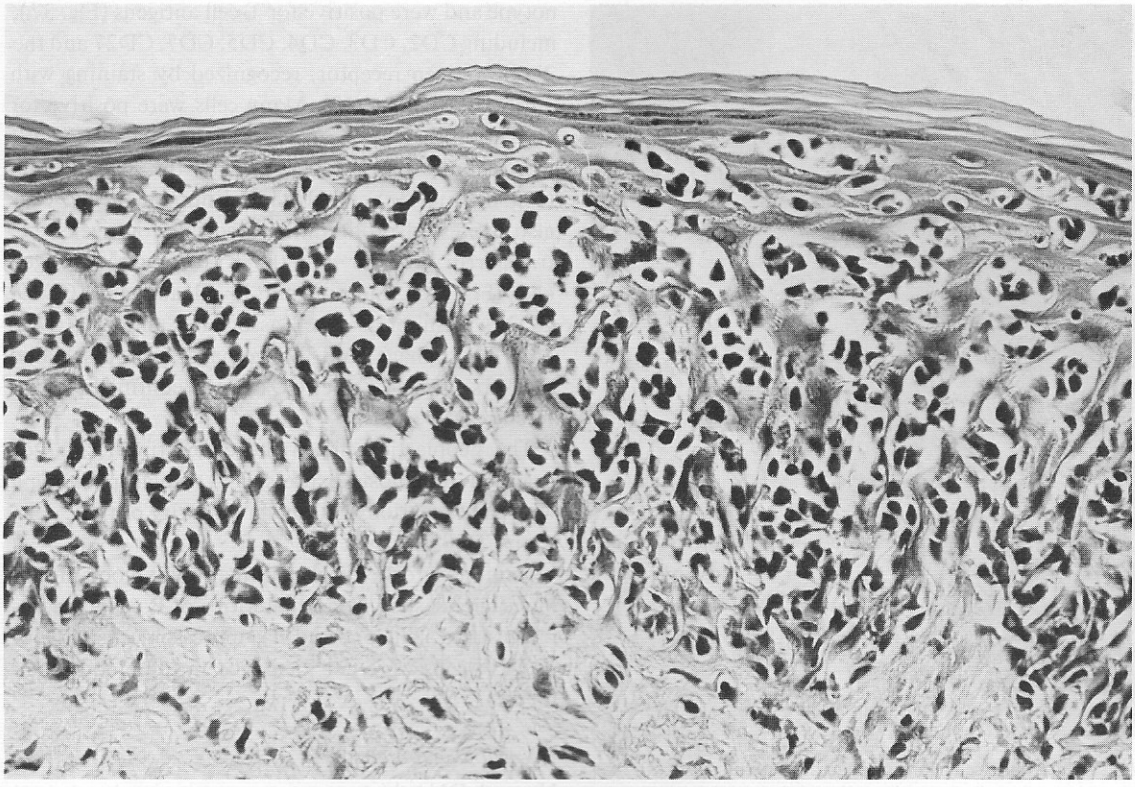
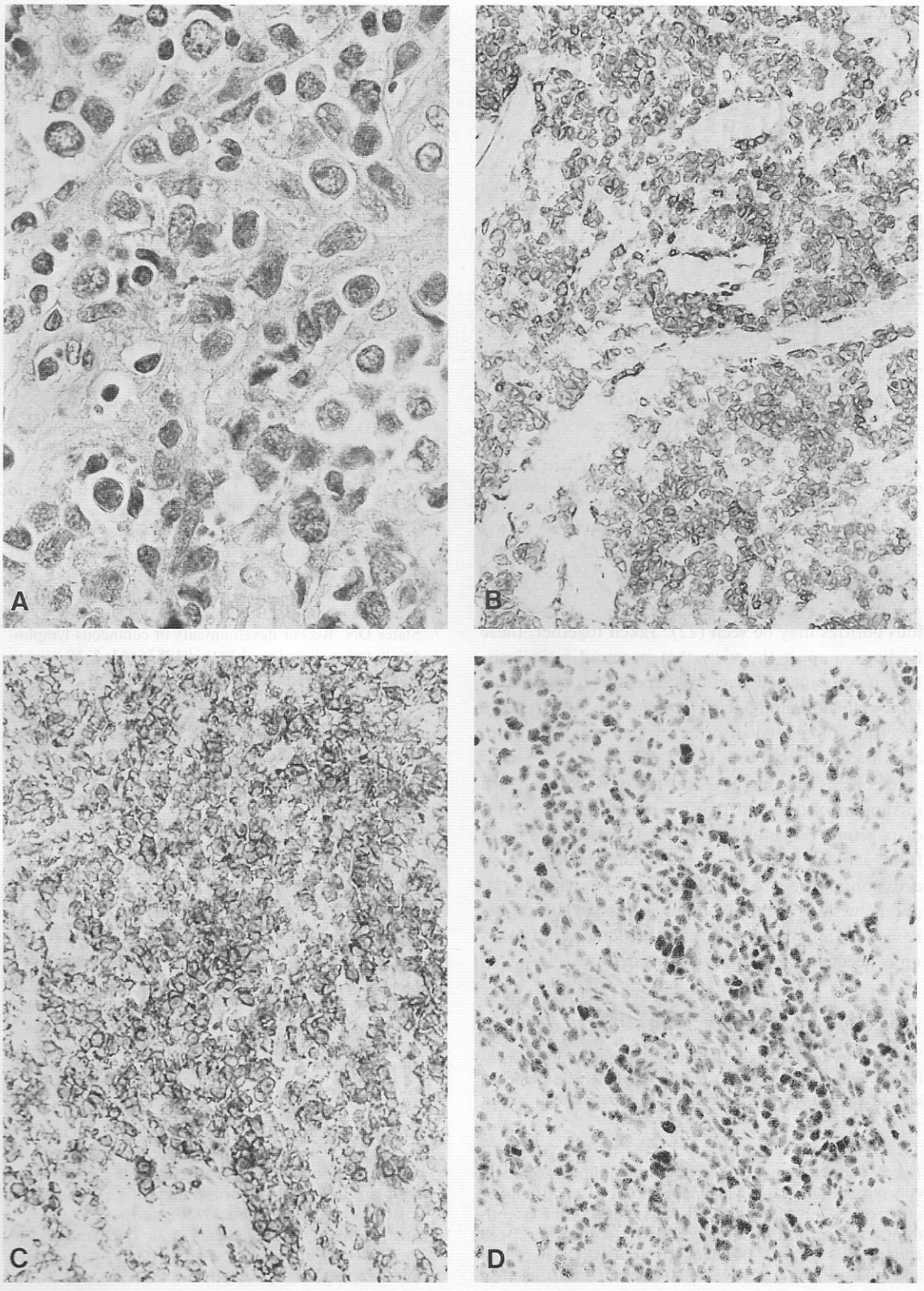


Fig. 2. Prominent epidermal infiltrates of cerebriform mononuclear cells in the eczema-like lesions of pagetoid reticulosis (HE, ×670).

The Ki-1-positive large cell non-Hodgkin's lymphomas were first described by Stein et al. (14) who showed that the Ki-1 antigen (CD30) is not Hodgkin cell specific, as initially suggested (15), but is an activation associated, inducible marker which is also expressed by the neoplastic cells in certain non-Hodgkin's lymphomas, including large-cell anaplastic and pleomorphic lymphomas and also (although more rarely) other entities (8, 14). Subsequent investigations have suggested that the large-cell anaplastic lymphomas are not uncommon in the skin (8, 16) and that cutaneous conditions referred to previously as "regressing atypical histiocytosis" (17) belong to this category of lymphoma (16, 18). There are some indications that these lymphomas may show a relatively indolent course, especially in cases with limited disease (8). This is supported by the present case which has so far shown a protracted clinical course (in spite of the marked atypia and high proliferative rate of the cellular infiltrate).

Although it is well known that large-cell non-Hodgkin's lymphoma may on occasion develop in patients who initially present with other cutaneous conditions, including either MF or lymphomatoid papulosis (19, 20), few such cases have been subjected to a detailed immunophenotypic analysis. Nevertheless, it is conceivable that some such lymphomas may be similar to the large-cell Ki-1 lymphoma seen in the present patient. Indeed, there are several lines of evidence that pagetoid reticulosis, MF, lymphomatoid papulosis and the Ki-1-positive large-cell non-Hodgkin's lymphomas may be related entities. Firstly, the cellular infiltrate seen in these conditions shows many morphological similarities and consists of either MF-like or Hodgkin-like cells (or a mixture of the two). Secondly, the cells frequently express activation associated markers, including not only the Ki-1 antigen (CD30), but also HLA-DR and/or interleukin-2 receptor, as shown in this and other studies of pagetoid reticulosis, lymphomatoid papulosis, and cutaneous and nodal Ki-1 lymphomas (5, 8, 14, 21); and thirdly, in individual patients transitions between these var-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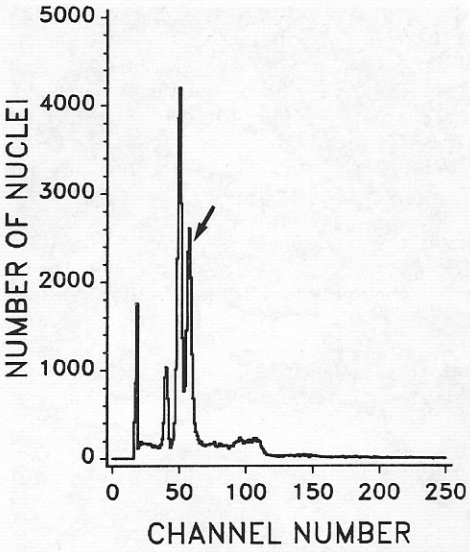

Fig. 4. DNA histogram from dermal specimens from the skin tumours. The first peaks indicate the internal reference standards, i.e., hen and trout erythrocytes. The patient sample showed a discrete aneuploid peak (*arrow*) which was clearly separated from the normal G0/G1 cells.

ious entities may be seen (22). Taken together, these findings support the view that pagetoid reticulosis, MF, lymphomatoid papulosis and the Ki-1-positive large-cell non-Hodgkin's lymphomas constitute a spectrum of related disorders which originate from activated lymphoid cells (8, 14, 22).

In conclusion, the present study provides evidence in support of the view that the disseminated variant of pagetoid reticulosis is a CTCL which originates from activated lymphoid cells and which may on occasion progress to a large-cell non-Hodgkin's lymphoma with a potentially more aggressive clinical behaviour. This strongly suggests that long-term follow-up is needed in patients with this disease.

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Fig. 3. The skin tumours showed diffuse infiltrates of markedly pleomorphic, large lymphoid cells (A, HE, ×810) many of which resembled dedifferentiated variants of the cerebriform cells seen in Fig. 2. The cells were positive for T-cell antigens (B, CD2, ×324) and for activation (C, CD30, ×324) and proliferation (D, Ki-67, ×324) associated markers.

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