Acta Derm Venereol (Stockh) 1993; 73: 255–258

Cutaneous T Cell Lymphoma of Signet Ring Cell Type: A Specific Clinico-pathologic Entity

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We describe a new case of signet ring cell peripheral T cell lymphoma in a 45-year-old man. This lymphoma had a very indolent course, since – without treatment – the clinical staging has shown no evidence of disease progression 11 years after initial symptoms. Immunophenotype indicated pan T antigens (Leu 4 CD3, Leu 1 CD5) and T suppressor cytotoxic antigen (IOT8 CD8) expression. Several T antigens (Leu 5b CD2, Leu 9 CD7, Leu 3a CD4) were not expressed. The proliferation index was less than 5% with Ki 67 monoclonal antibodies. The ultrastructural study showed characteristic cytoplasmic vacuoles containing microvesicles. Five cases of signet ring T cell lymphoma, which were very similar to our case, have been previously described. Their characteristics were primary cutaneous presentation, indolent course, good response to current therapies and a long survival period. The indolent course of these signet ring cell lymphomas may indicate that this type of lymphoma is a low grade malignant lymphoma and not only a morphological pattern. ***Key words: Peripheral T cell lymphoma; Primary cutaneous lymphoma.***

(Accepted February 15, 1993.)

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Signet ring lymphoma is a rare histological variant of non-Hodgkin's lymphoma, first described by Kim et al. in 1978 (1). The tumour cells are characterized by the presence of cytoplasmic vacuoles that give a signet ring appearance. The first examples of signet ring lymphoma were recognized as being of B cell lineage (1, 2). However, 5 cases (3–6) of signet ring cell lymphoma of T cell type were later reported. The prognosis of these 5 T cell signet ring lymphomas was good. We here describe a new case of T cell signet ring lymphoma of the skin which is very similar to the 5 previous cases, the one apparent difference being that it followed an even more indolent course.

CASE HISTORY

A 45-year-old man developed a 2 × 2 cm cutaneous nodule on the right shoulder. The lesion was reddish and indurated. His general health was otherwise good. Biopsy was performed and a diagnosis of a pseudo-lymphoma made. Two years later the nodule had slowly grown and was surrounded by others.

A new skin biopsy revealed malignant lymphoma. The patient was investigated for evidence of systemic disease. The chest x-ray was negative and no abnormalities were detected on computerized tomographic scan (CTS) of the chest and the abdomen; liver and spleen scans were normal. He had a single small right mobile axillary lymph node. Bone marrow and right axillary lymph node biopsies showed no tumoral infiltration. Serum protein levels and peripheral blood count were normal, but there was a slight increase in the number of T cytotoxic suppressor cells in the blood (984 per mm^3). These CD8 lymphocytes had a normal phenotype without phenotypic hole. Anti HTLV1 serology was negative.

Because of the indolent course no treatment was given. During the clinical follow-up there was no tumor regression, and the patient developed 20 other cutaneous nodules, 0.5–2 cm diameter, on the right arm and both shoulders. All the nodules were firm, painless and slow-growing and their color ranged from pale to reddish.

Repeated chest x-rays and CTS of the abdomen over the following 9 years were negative. Eleven years after presentation the patient remained well.

MATERIALS AND METHODS

Light microscopy

Ten biopsies in 8 different sites were performed. Tissue was fixed in Bouin's liquid, processed and embedded in paraffin wax by conventional techniques. Sections were stained by haematoxylin and eosin, periodic acid schiff (PAS), mucicarmine, alcian blue (pH = 2.5) and Giemsa.

Immunostaining

Portions of the skin biopsy were frozen at −150°C in isopentane, quenched in liquid nitrogen and stored at −70°C. A three-step immunoperoxidase procedure was performed using a method described elsewhere (7). Cryostat sections were incubated first with the monoclonal antibodies listed in Table I. Peroxidase activity was revealed as described by Graham & Karnowsky (8). Nuclei were counterstained with haematoxylin.

Electron microscopy

Fresh tissue was cut into millimeter cubes, fixed in glutaraldehyde liquid, post-fixed in 2% osmium tetroxide and embedded in epon. Semi-thin sections were stained with toluidine blue and representative blocks, showing numerous lymphoid cells with atypical reniform nuclei, were selected for ultrastructural examination.

RESULTS

Light microscopy

All the skin biopsy specimens had a similar appearance. They contained lymphoid infiltrate without epidermotropism (Fig. 1a). The areas of lymphoid cells were circumscribed and surrounded by non-invaded dermal connective tissue.

The majority of neoplastic lymphoid cells were monomorphous, medium-sized (9–13 μm) but sometimes larger, with a clear cerebriform nucleus and a prominent central nucleolus. In 30–60% of these cells the nucleus was eccentric with a signet ring appearance (Fig. 1b). These cells contained an abundant amount of vacuolar cytoplasm. The vacuoles did not stain for mucin with PAS, mucicarmine and alcian blue stains. Giemsa stain did not show cytoplasmic azurophilic granulations. Mitotic cells were rare.

Immunostaining

The staining of tumoral cells was positive for pan T antibodies

Table I. *Immunophenotyping of our case*

Monoclonal antibodies	Abnormal cell reactivity
Pan B (To_{15}, CD_{22})	–
IgG	–
IgA	–
IgM	–
Ig_D	–
Kappa	–
Lambda	–
Leu 4 (CD_3)	+
Leu 1 (CD_5)	+
Leu 9 (CD_7)	–
Leu 3a (CD_4)	–
IoT_8 (CD_8)	+
IoT_6 (CD_1)	–
Leu 5b (CD_2)	–
Transferrin receptor	–
Leu 7	–
IoT_{2a} (HLA II DR)	–
IoT_{14} (CD_{25})	–
Ki-1 (CD_{30})	–
EMB 11	–
Ki-67	<5%

Leu 4 CD3 (Fig. 2a), Leu 1 CD5, and for IOT8 CD8 antibody. On the other hand, these cells did not express T helper antigen (Leu 3a CD4), the transferrin receptor or the corticothymocyte antigen recognized by the anti IOT6 CD1 antibody; Leu 9 CD7 and Leu 5b CD2 were also negative. The proliferative index was very low, since less than 5% of the nuclei were labelled with Ki-67 antibody.

Other markers such as activated lymphocytes IOT2a HLADR, IOT14 CD25 and Ki-1 CD3O were negative. Immunoglobulin light and heavy chains, pan B antigen (TO15 CD22, CD20) and Calla (IOT5 CD10) were not expressed by tumoral cells.

Among the few reactive cells, those at the periphery of the tumoral cells were Leu 4 CD3 and Leu 3a CD4 positive cells. The clusters of B cells recognized by the TO15 CD22 antibody were very rare and polyclonal.

Immunophenotyping of our case indicated the presence of a mature T cell lymphoma of CD8 phenotype without "activation state" markers.

Electron microscopy

The neoplastic cells had a large reniform and deeply indented nucleus with marginated heterochromatin and a central, prom-

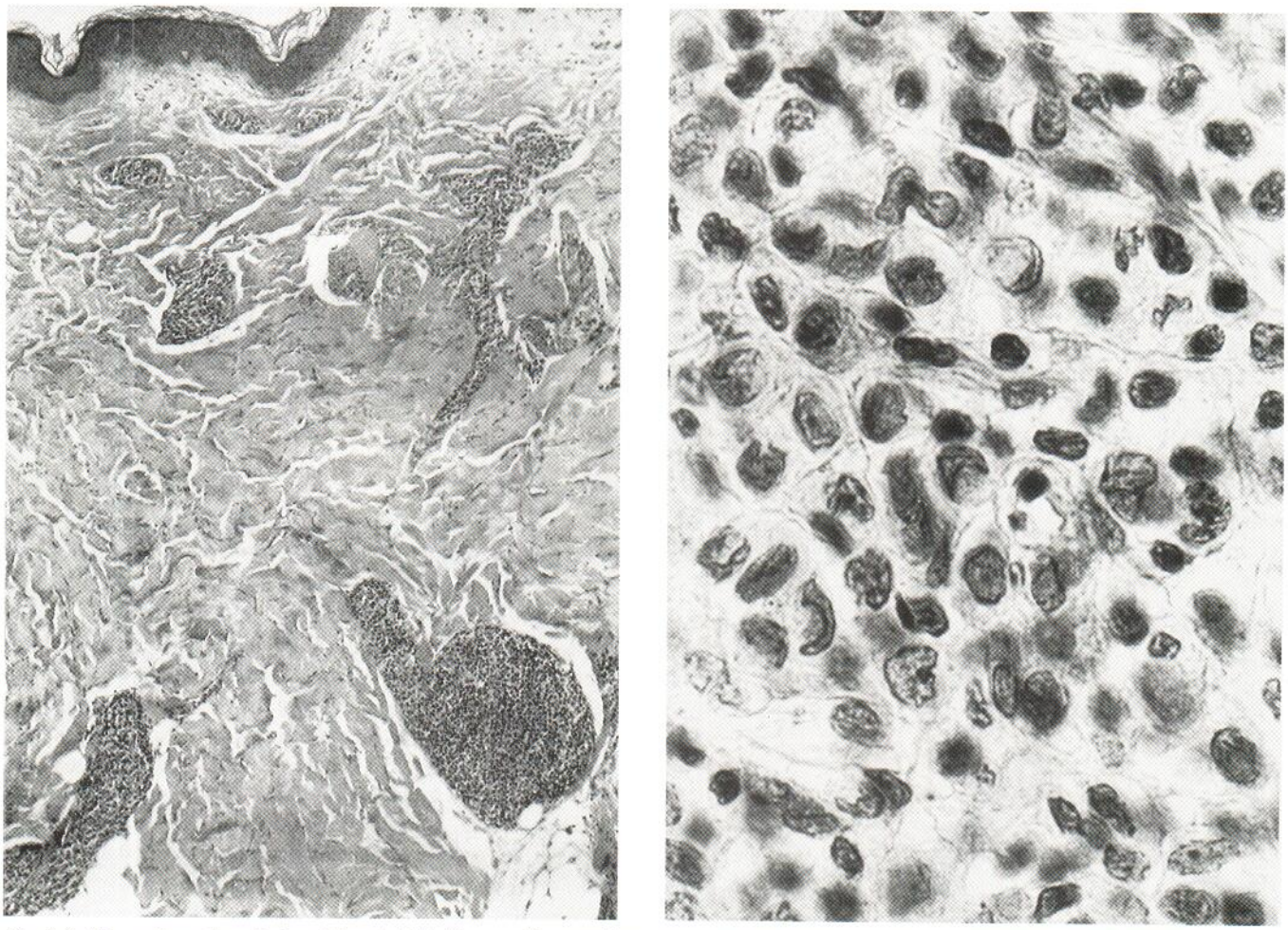

Fig. 1. (*a*) Deep dermal, periadnexal lymphoid infiltrate without epidermotropism. HE (G ×25). (*b*) At higher magnification, intermediate and large lymphoid cells with signet ring appearance. HE (G ×1000).

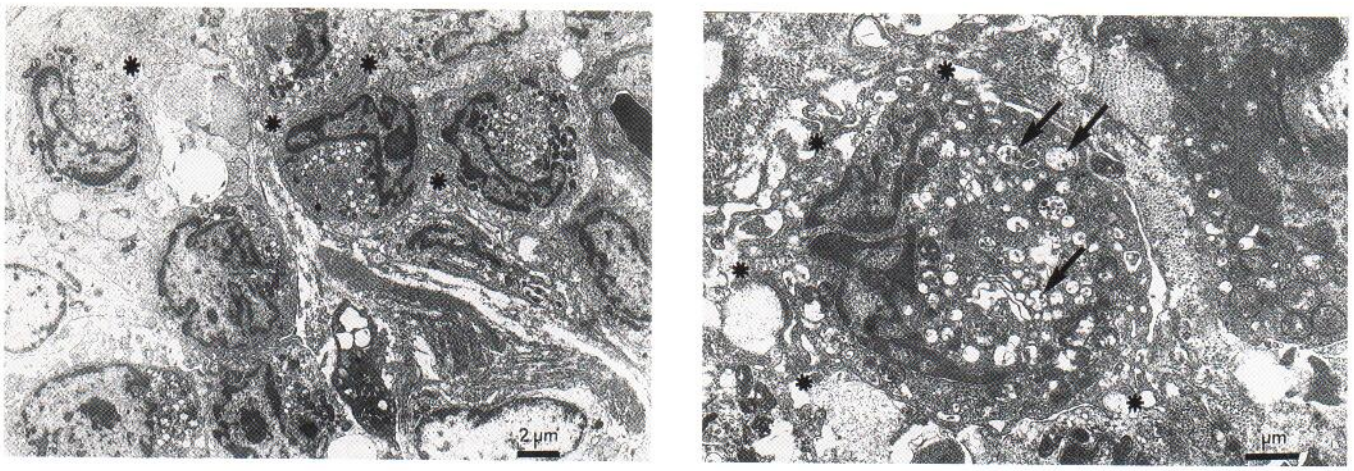

Fig. 2. Electron microscopy. (*a*) Small and numerous cytoplasmic vacuoles. Indented nucleus with a single prominent central nucleolus. Note microvilli, pseudopodal-type processes and cytoplasmic interdigitations (*) at the periphery of the neoplastic lymphoid cells. (*b*) Pseudomyelinic features and large vacuoles (→) containing microvesicles.

inent nucleolus. The concavity of these nuclei contained a prominent golgiosome and, around it, numerous small vacuoles (Fig. 2a) which ranged from 0–2 to 1–6 µm in size. Some of the vacuoles were electrolucent, but most were filled with a variable number of microspherules (Fig. 2b). Some other membrane-bound lucent spaces contained membranous (pseudo-myelinic features) and amorphous material. Many of the vacuoles seemed to be marginated near surface microvilli, interdigitations and pseudopodal type extensions of the membrane, suggesting micropinocytosis.

DISCUSSION

Signet ring T cell lymphoma is considered to be a rare and controversial type of lymphoma (9). Nevertheless, most authorities would accept signet cell lymphoma as a specific lymphoma entity. Two types of signet cell lymphoma are described, the so-called inclusion type and the clear vacuole type. Because our case was not positive for immunoglobulin and did not show PAS positivity, we assume that our case is a signet cell lymphoma of clear vacuole type. The clear vacuole type can show cytoplasmic internalized T antigens from the cell membranes. Signet cell lymphoma exists as a nodal disease and has been described as a cutaneous lymphoma since 1985 (3, 4). Signet cell cutaneous lymphoma can be of B and T cell type (2–6). Our case of primary cutaneous malignant lymphoma was classified as a peripheral non-epidermotropic T cell lymphoma with signet ring appearance. Although genotypic evidence of clonality does not always equate with malignancy, some authors consider that genotyping should be undertaken to establish the diagnosis of malignant lymphoma. In our case, no genotypic studies were performed to assess the malignancy of this lymphoid proliferation but the immunostaining in our case showed the loss of two pan T antigens (Leu 5b CD2 and Leu 9 CD7). This loss of expression of differentiation antigens represents a valuable alternative to genotypic studies for the diagnosis of T cell non-Hodgkin's lymphoma. Because CD8 lymphocytosis was found, the possibility of cutaneous changes representing cutaneous involvement of a chronic T cell lymphocytic leukaemia may be discussed. However, our case is not chronic lymphocytic leukemia because the blood and cutaneous CD8 T cell lymphocytes had a different phenotype, the CD8 lymphocytosis did not increase during the 10 years' follow-up and because of the lack of lymph node involvement. Therefore, in view of its morphological features associated with a T cell phenotype and its very indolent course, our case is very rare. It is noticeable that all but one of the 5 previously reported cases of signet ring T cell lymphoma lost the CD7 pan T antigen (Table I). This particular aberrant T cell phenotype was already reported (10). These authors reported 9 patients with cutaneous T cell epidermotropic lymphoma with CD8 phenotype. Four of these cases did not express CD7 and had a chronic evolution, whereas 5 expressed CD7 and had a rapid disease progression. Nevertheless our case differs from these 4 chronic cases because in our case it was a non-epidermotropic lymphoma and did not express CD2. In Agnarsson's study (10) chronic evolution was associated with $CD2^+$ $CD7^-$ phenotype whereas rapid progression was associated with $CD2^-$ $CD7^+$ phenotype.

Because only 5 cases of T cell signet ring lymphoma have been previously reported, it is not possible to determine whether this type of lymphoma is a new variant of peripheral T cell lymphomas. It may be considered either as a distinct entity or as a morphological variant. Nevertheless, it is remarkable that all these 5 cases and our case had similar clinical and histopathological features (Table I). These similarities are: 1) occurrence in elderly white men, 2) the involvement of the skin, 3) long-standing nodular skin lesions localized in the upper part of the body (head, neck and shoulders), 4) pathologically identified diffuse large cell type lymphoma, 5) T mature immunophenotype, 6) characteristic ultrastructural feature with the signet ring appearance and presence of saccules containing microvesicles, and 7) very indolent course with or without specific treatment.

In our case the course of the disease was very indolent because the patient developed relatively few cutaneous nodules on shoulders and arm without treatment over 11 years. Ki-1

positive anaplastic lymphoma may also show a rather indolent course, but in our case immunophenotyping failed to demonstrate any staining with CD30 markers (Ki-1 and Ber-H2). Despite intermediate and large neoplastic cells of this peripheral T cell lymphoma, our patient received no specific treatment. Signet ring lymphoma seems to have a favorable prognosis. Long survival periods have already been reported as well in B cell signet ring lymphoma (9 years in Moir's case) (11) as in T cell signet ring lymphoma (10 years in the second case of Weiss et al.) (3). All 6 cases of cutaneous signet ring T cell lymphoma had a good prognosis despite nodal and even widespread disease (clinical stage IV in one case), and a signet ring B cell cutaneous lymphoma case survived for 7 years without systemic disease (12).

In addition to the signet ring appearance and the very indolent course, another original feature of our case is the T cytotoxic suppressor immunophenotype. Immunophenotyping of the 5 prior cases of signet ring T cell lymphoma showed 4 to be of helper phenotype, while one initially manifested suppressor phenotype but in a later biopsy expressed helper phenotype. The case presented here was CD8 (suppressor phenotype) positive in 3 different frozen biopsy specimens. Although peripheral T cell cutaneous lymphoma was considered to have a poor prognosis and those of cytotoxic suppressor immunophenotype an acute clinical course (12), our case has shown no evidence of systemic disease progression without treatment 10 years after the first symptoms. It is noticeable that our case has a CD7 negative, CD8 positive phenotype and that its indolent nature supports the findings of Agnarsson et al. (10). Therefore, whatever the type of lymphoma, a signet ring appearance should be sought since it appears to have a favorable prognosis (indolent course and/or good response to radiotherapy or chemotherapy). We need further studies on cutaneous lymphomas with more than 30% of the cells of signet ring appearance to know if signet ring cell lymphoma may be regarded as a morphological variant or a specific entity.

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