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Cutaneous T cell lymphoma: immunocytochemical study on activation/proliferation and differentiation associated antigens in lymph nodes, skin, and peripheral blood*

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Summary. The expression of activation/proliferation antigens (CD 25, CD 30, Ki 67, transferrin receptor) in lymph nodes and skin were compared in nine patients with mycosis fungoides (MF) with patients with erythroderma not related to MF, and patients with reactive lymphofollicular hyperplasias (a total of 14 patients). A panel of differentiation antigens was analyzed in addition. Reactivities were revealed by the APAAP technique. Activation/proliferation antigen scores in lymph nodes were related to the clinical stages of MF in most instances (low scores in cases of MF stage I/II, high scores in 3/4 cases of MF stage III/IV). They differed markedly in cases of non-MF-erythrodermia with the exception of one patient, and in all cases of reactive lymphofollicular hyperplasia. Expression of activation/proliferation antigens in lymph nodes were different in most cases from those in skin and peripheral blood. For diagnostic use, the activation/proliferation antigen scores were superior to the cell differentiation antigen profiles. Among cellular differentiation antigens, only the extent of CD1 + cells provided some diagnostic information, since the number of these cells were markedly increased in all cases of dermatopathic lymphadenitis with/without MF when compared with reactive lymphofollicular hyperplasia. In the diagnosis of MF, immunohistochemistry of activation/proliferation or differentiation antigens cannot replace routine paraffin histology, but may provide supplement any data in equivocal cases.

Key words: Cutaneous T cell lymphoma – Dermatopathic lymphadenitis – Activation/proliferation antigens – Skin – Lymph nodes

* Dedicated to Professor Dr. Theodor Nasemann on the occasion of his 65th birthday

Offprint requests to: Th. Löning

Introduction

In mycosis fungoides (MF) and the Sézary syndrome (SS), the significant primary cutaneous T cell lymphomas, immunohistochemical studies of cutaneous infiltrates have consistently demonstrated the presence and predominance of the CD 4 subset (helper-inducer) of T lymphocytes (Haynes et al. 1981; Kung et al. 1981; Schmitt et al. 1981; 1982; Haynes et al. 1982; McMillan et al. 1982; Van der Putte et al. 1982; Thomas et al. 1982; Holden et al. 1983; Willemze et al. 1983; Van der Valk et al. 1986). The functional state of the lymphoid cell populations, however, have been soon recognized to be far more complex: A variable loss of T cell antigens (Holden et al. 1982; Nasu et al. 1985; Picker et al. 1987) and in contrast, expression of activation antigens (CD 25 – interleukin II receptor: Klareskog et al. 1986; Strauchen and Breakstone 1987; Sheibani et al. 1987; CD 30/Ki 1: Ralfkiaer et al. 1987b; OKT 9 – transferrin receptor: McMillan et al. 1983; HLA-Dr: Tjernlund 1978; Haynes et al. 1982; Thomas et al. 1982; Willemze et al. 1983), proliferation antigens (Ki 67: Turbitt and MacKie 1986; Weiss et al. 1987) and other antigenic determinants (CD 15/LeuM1: Wieczorek et al. 1985) have been described. These studies have mostly been carried out on skin specimens.

Recently, genotypic analysis revealed clonality in all cases of SS, and in the skin, blood and lymph nodes of patients with stage III/IV MF (Weiss et al. 1985a; O'Connor et al. 1985; Knowles et al. 1986; Ralfkiaer et al. 1987a; Slater 1987). In the early stages of MF (MF I/II), however, immunohistochemical phenotyping and/or gene rearrangement analysis will often not provide differential diagnostic criteria, since antigen profiles are highly variable (Slater 1987), and germ line DNA configu-

rations are constantly found in early MF stage I/II (Ralfkiaer et al. 1987a; O'Connor 1987).

Our immunocytochemical studies on skin and lymph node specimens and peripheral blood lymphocytes of patients with MF have been focussed on activation/proliferation antigens (CD 25, CD 30, transferrin receptor, Ki 67) in order to get further insights into the following questions: Are these antigens expressed or lost with a constant relationship to the stage of MF? Are the profiles of activation/proliferation antigens in skin, lymph nodes and peripheral blood related to each other? Are there antigen patterns diagnostic of dermatopathic lymphadenitis with and without MF?

Materials and methods

Patients with MF (see Table 1) were staged according to Bunn and Lambert (1979). Staging procedures included clinical examination, routine laboratory investigation with complete white blood count and differential white blood count, chest x-ray, computed tomography of the abdomen, bone marrow aspiration biopsy, and immunocytological typing of peripheral blood lymphocytes (PBL) and bone marrow lymphocytes. In the MF group, five female and four male individuals were investigated, the median age being 64, 4 years at the moment of biopsy. In addition, four patients with non-MF-erythrodermia (Table 1), and ten patients with reactive lymphofollicular hyperplasia not related to MF were included in this study.

Skin and lymph nodes obtained from these patients were divided for paraffin embedding and routine histology (H & E, PAS, Giemsa) and for immunohistochemistry. The latter material was snap-frozen in liquid nitrogen and stored at −70° C until use.

Peripheral blood lymphocytes were separated by Lymphoprep (Nyregaard, Norway) density gradient centrifugation and washed three times in RPMI 1640 (Gibco). The cell suspensions were incubated in petri dishes at 37° C for 1 h and again washed three times in RPMI 1640. Viability was assessed by trypan blue exclusion and was always higher than 95%. 1×10^6/ml cells were incubated with appropriate dilutions of primary monoclonal antibodies (1:100, Table 2) for 30 min at 4° C, and washed three times in RPMI 1640. Consecutively, cells were incubated with FITC-labelled goat anti-mouse IgG antibodies (Meloy, USA) for further 30 min at 4° C. After thorough washes in RPMI 1640 a minimum of 200 cells were counted using an interference line filter of 485 nm for excitation. Controls included always incubations with the FITC-labelled antibodies alone.

For cytochemistry cryocut sections of 4–6 μ in thickness were prepared, air-dried overnight, and fixed in acetone/chloroform prior to use (for 30 min). Sections were incubated consecutively with mouse monoclonal antibodies (see Table 2), bridging anti-mouse antibodies (Dakopatts, Hamburg, FRG), and alkaline phosphatase-anti alkaline phosphatase (APAAP) from the mouse (Dakopatts, Hamburg, FRG) for 1–2 h each. Primary mouse monoclonal antibodies were diluted at 1:100 with bovine serum albumin (1%) in RPMI medium (Seromed, Berlin, FRG), pH 7.4–7.6. Bridging mouse antibodies were diluted at 1:20 with complement-inactivated human serum (1:7 dilution of human serum in RPMI medium). The APAAP complex was used at a dilution of 1:50 in RPMI medium, adjusted to a pH of 7.4–7.6. Alkaline phosphatase activity was revealed with naphthol-AS-biphosphate and new-fuchsin at a pH of 8.75. Sections were mounted in Eukitt. Staining was controlled at the tissue level (including positive and negative cases of lymphomas) and antibodies replacing specific primary antibodies by normal sera.

Labelling was semiquantitatively evaluated and graded as follows: 0 = negative; + = less than 10% positive cells; + + = 10–50% positive cells; + + + = more than 50% positive cells. In addition, expression of activation/proliferation antigens (CD 25, CD 30, Ki 67) was scored together building up a range from zero to nine points (each + counted as one point).

Table 1. Patients

Patient	Sex	Age	Clinical diagnosis and stage
Patients with Mycosis fungoides			
1	m	47 Y	Mf I A
2	m	83 Y	Mf I B
3	f	63 Y	Mf IV B
4	f	65 Y	Mf III
5	m	74 Y	Mf II B
6	f	66 Y	Mf IV A
7	f	72 Y	Mf IV a
8	m	37 Y	Mf II B
9	f	73 Y	Mf Ia
Non-Mf-erythrodermia			
10	f	76 Y	erythrodermia (psoriasis vulgaris)
11	m	82 Y	erythrodermia (contact dermatitis)
12	m	62 Y	erythrodermia (contact dermatitis)
13	f	45 Y	erythrodermia (psoriasis vulgaris)

Table 2. Antibodies used

Cluster of Diff. (CD)	antibody	Cells identified
CD 1	OKT6	cortical thymocytes, Langerhans-cells,
CD 2	OKT11	thymocytes, peripheral T-cells, some NK cells
CD 4	Leu-3a+b	T-cell subset (inducer-helper)
CD 5	IOT-1a	T-cells
CD 8	Leu 2a	T-cell subset (cytotoxic-suppressor)
CD 22	BMA 131	B-Cells
CD 25	Il-2-R	TAC antigen expressing cells
CD 30	Ki-1	Hodgkin-cells, SR-cells, activated lymphocytes (T-or B-Cell-type)
Tf-R	Tf-R	activated/proliferating cells (e.g. lymphocytes)
Ki-67	Ki-67	proliferating cells in malignant lymphomas and solid tumors
Ki-M 4b	Ki-M4b	follicular dendritic cells
Ki-M 7	Ki-M7	macrophages

Results

All nine patients with MF (see Table 1) were admitted with characteristic skin lesions. Skin and lymph nodes were routinely evaluated by two

Table 3. Grading and activation/proliferation score of lymph nodes in patients with MF

Case-No	Histology	Grading	Score
1	"Normal"	LN 0	0
2	Dermatopathic lymphadenitis	LN 1	6
3	Lymphonodal manifestation of Mf	LN 3	0
4	Suspicious of early MF	LN 2	6
5	Suspicious of early Mf	LN 2	1
6	Advanced manifestation of Mf	LN 4	7
7	Advanced manifestation of Mf	LN 4	4
8	Dermatopathic lymphadenitis	LN 1	0
9	"Normal"	LN 0	1

histopathologists independently. Case No 3 followed a rapidly fatal course and died 13 months after initial diagnosis. Histological examination of case No 6 revealed a peculiar granulomatous form of MF. Initially, case No 9 showed pathological changes which were only suspicious for MF; 4 months later, MF was confirmed on a subsequent biopsy. Lymph nodes were graded histologically according to Sausville (Sausville et al. 1985, see Table 3). Whereas cutaneous histopathology was usually diagnostic of MF (except for the initial biopsy in case No 9), lymph node pathology was inconclusive in most cases except for cases 3, 6, and 7, which showed advanced destructions of lymph node architecture and polymorphous lymphoid infiltrates.

In the group of non-MF-erythrodermia, two patients suffered from contact dermatitis and two from psoriasis vulgaris (see Table 1). Patients with reactive lymphofollicular hyperplasia were usually not followed up further clinically.

At the time of biopsy, white blood cell counts were not elevated in the patients of the MF- or non-MF-erythrodermia group. Sézary cells did not constitute more than 2% of cells in the peripheral blood, and were absent in the bone marrow in all cases. Lymphocytes (PBL) showed pathological values only in 2/9 patients with MF and in 1/4 patients with non-MF-erythrodermia. Seven cases of MF were investigated for the activation of PBL (CD 25, transferrin receptor), and displayed mild to moderate expressions of activation antigens. Case No 13 of the non-MF-erythrodermia group showed also a slight increase in activated PBL.

Lymph nodes of patients with MF were subdivided into two groups on the basis of the immunohistochemical findings. One series of lymph nodes displayed strong expression of CD 25, Ki 67 and in part CD 30 antigens also (cases No 2, 4, 6, 7; Figs. 1–3). In contrast, the other group (cases No 1, 3, 5, 8, 9) showed only subtle or no expression of these marker molecules (see Table 4). When correlating clinical stages, differentiation and activation antigens of PBL, histopathological lymph node grading (Table 3), and expression of activation/proliferation antigens in tissues (lymph nodes: Table 4; skin: Table 6), interesting relationships and discrepancies were disclosed. In the group of patients with high lymphonodal activation/proliferation scores (cases No 2, 4, 6, 7), three cases with clinically advanced disease were noticed (MF stage III/IV in cases No 4, 6, 7). Routine lymph node histology provided clear evidence of neoplasia (graded as LN4) in two cases only (cases No 6, 7). Case No 4 was classified as LN2 (suspicious of MF, see Table 3). Case No 2 differed greatly from these cases in that clinical stage (MF IB) and lymph node histology (dermatopathic lymphadenitis: LN1) were opposed to the striking expression of CD 25/CD 30/Ki 67 in lymph nodes and CD 25 in PBL.

Increased expression of activation/proliferation antigens in lymph nodes did not mirror the situation in skin infiltrates in any of these cases. Expression of CD 25 was clearly diminished in skin biopsies compared with lymph nodes. All four cases were negative for CD 30 in the skin, although three of them (cases No 2, 4, 6) were positive in lymph nodes. Ki 67 was found only weakly in one skin biopsy (case No 2), but was always seen in lymph nodes in this group. However, expression of transferrin receptor was always observed in skin biopsies in contrast with lymph nodes.

The other group of MF cases with low/absent lymphonodal activation/proliferation scores included patients with MF in early stages (cases No 1, 5, 8, 9), the exception was one patient (case No 3, MF stage IVB, see Table 1, Fig. 4), who died of widespread disease three years later. In cases No 1, 5, 8, 9, peripheral CD4+ lymphocytes were not elevated, and lymph node pathology was not suspicious except for case No 5 (graded as LN 2, see Table 3). Only this case and case No 9 showed a slight increase in the lymphonodal expression of activation/proliferation antigens (CD 30: case No 9; Ki 67: case No 5). The comparison of antigen patterns in skin and lymph nodes revealed CD 25 (case No 1, 5, Fig. 6) and CD 30 (Fig. 5, case No 1) to be expressed strongly in skin infiltrates, while being mostly negative in lymph nodes. In contrast with these cases of low score antigen expression, one patient (case No 3) showed clear evidence of lymph node involvement histopathologically (graded as LN 3). However, our studies

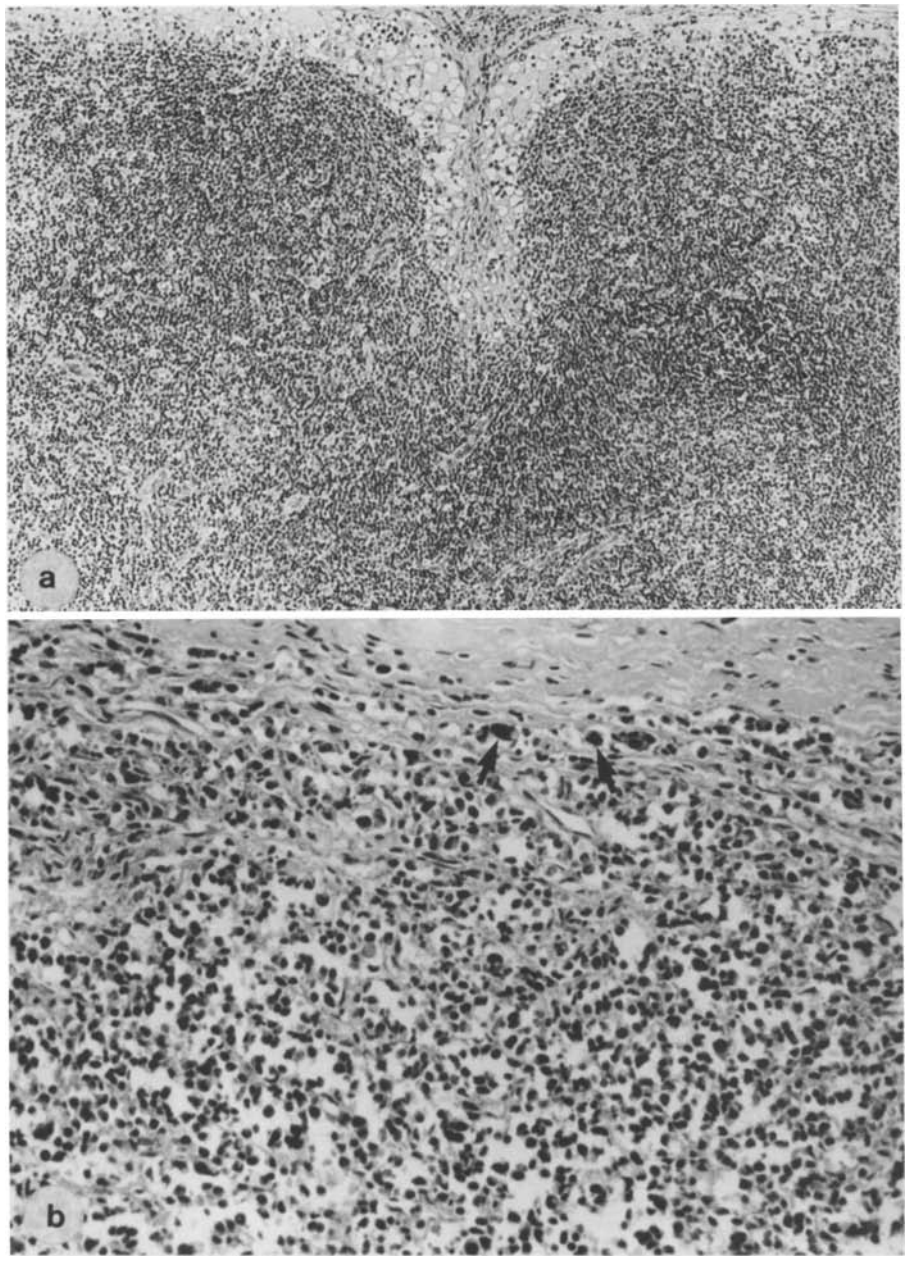

Fig. 1a. Lymph node suspicious of early MF (LN 2). Sinusoidal structure is preserved. Expanded paracortical zones contain numerous large cells (lymphocytes, dendritic cells) in addition to eosinophilic granulocytes. Giemsa Mag. × 80. **(b)** Higher magnification showing polymorphous lymphoid infiltrates. Arrows point to cells with indented hyperchromatic nuclei. Giemsa × 500

on PBL and tissues failed to indicate proliferative activity of the disease with the exception of a very pronounced transferrin receptor expression in skin infiltrates (see Tables 4, 6).

In patients with non-MF-erythrodermia, lymphocyte populations of lymph nodes were especially activated in case No 10 (see Table 5). This case showed extremely high activation/proliferation scores in lymph nodes in the range of the MF cases 2, 4, or 6. The immunocytochemical profile, however, could not be assigned to structural abnormalities or cellular polymorphism in routine histopathology. In this regard, this non-MF case was reminiscent of the MF case No 2.

Skin biopsies were examined for activation/proliferation antigens in cases No 10 and 13 only. In contrast with most of the MF cases, these findings (expression of CD 25 and transferrin receptor in case No 10, and of additional Ki 67 reactivity in case No 13) were related to the observations in blood (case No 13) and lymph nodes (case No 10) (Tables 5, 6). Ten cases of lymph nodes with reactive lymphofollicular hyperplasia were studied. All lymph nodes revealed activation/proliferation

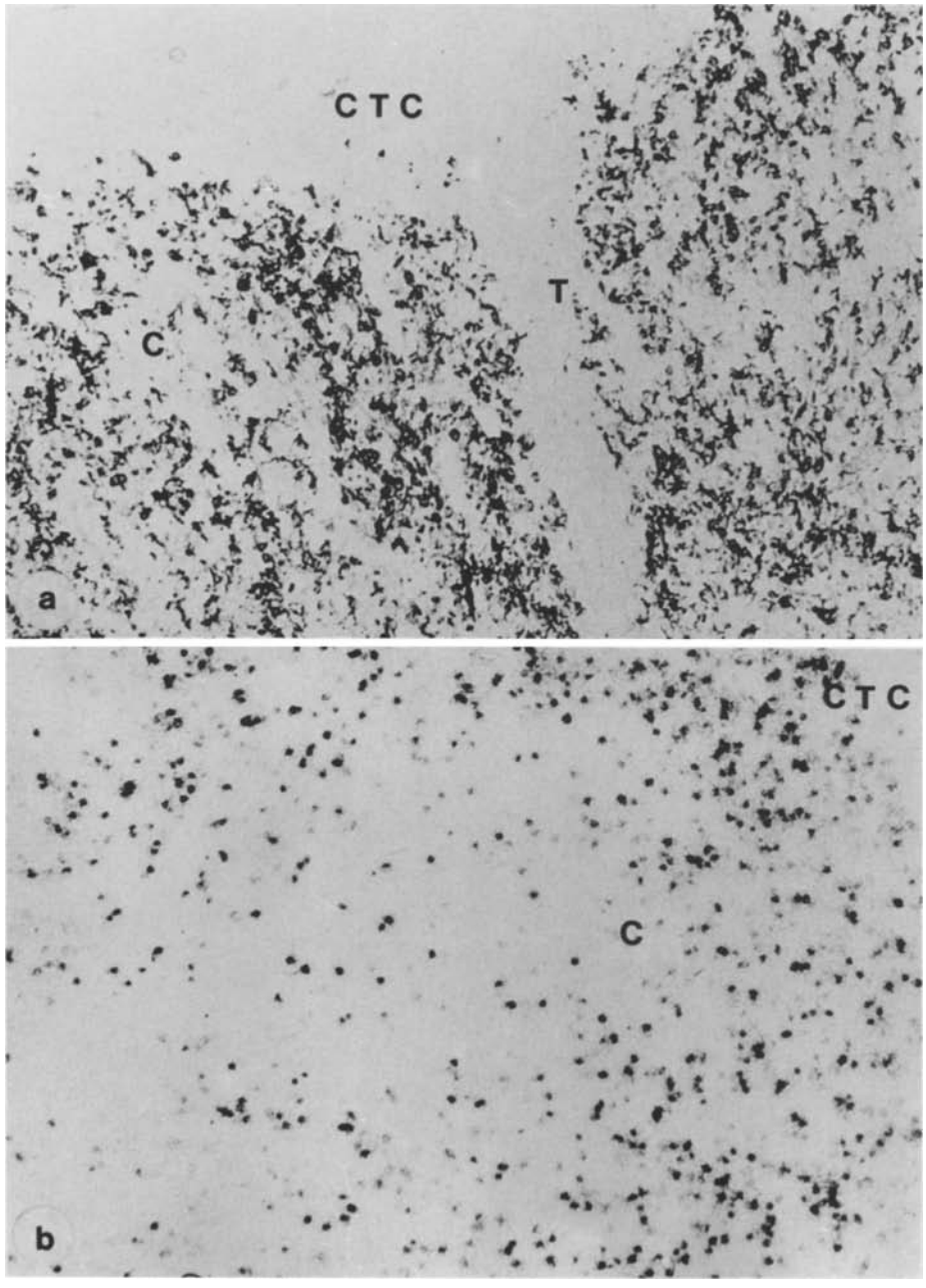

Fig. 2a. Same case. High numbers of CD1+ cells obscure the nodal architecture (CTC=cortical capsule). Effacement of follicles (T=trabeculae). APAAP. No counterstaining. ×80. **(b)** Parallel section. Lymph node cortex (C) harbours numerous Ki 67 positive cells (CTC= cortical capsule). APAAP. No counterstaining. ×80

scores lower than 3 (see Table 5). Among the activation/proliferation marker molecules examined, CD 25 and transferrin receptor were present more frequently (7/10 cases each) than Ki 67 (2/10 cases) and CD 30 (1/10 cases).

In the group with high activation/proliferation scores (cases No 2, 4, 6, 7), we observed a predominance of CD4+ lymphocytes in cutaneous infiltrates. Only case No 2 showed almost balanced numbers of CD4+ and CD8+ cells. CD1+ Langerhans cells constituted a minor part (usually less than 10%) of skin infiltrates. In contrast with the skin, lymph nodes harboured a very variable (very low in cases No 4, 7) number of CD4+ lymphocytes. In lymph nodes of this group, however, high numbers (more than 10%) of CD1+ cells were always present (Fig. 2) and led to a striking effacement of the lymphonodal architecture. In the MF group with low/absent activation/proliferation scores (cases No 1, 3, 5, 8, 9), predominance of CD4+ cells was seen in lymph nodes except for case No 9 (MF stage Ia). Discrepancies in numbers of CD1+ cells were again apparent between cutaneous and lymphonodal infiltrates (more than

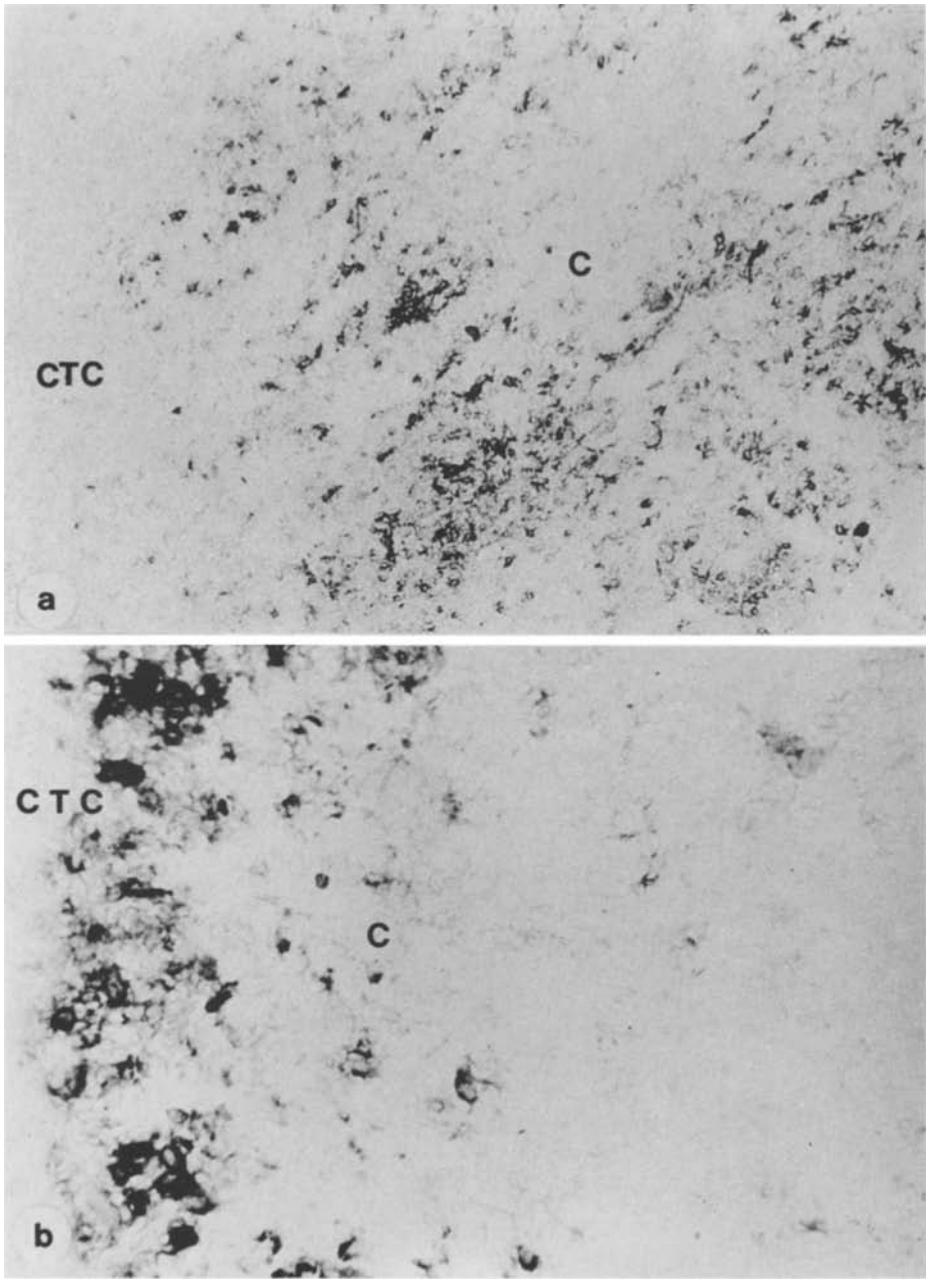

Fig. 3a. Lymph node suspicious of early MF (LN 2) Cortical zone (C) contains numerous CD 25 positive lymphocytes (CTC = cortical capsule). APAAP. No counterstaining. × 80. **(b)** Parallel section. Focal accumulation of CD 30 positive lymphocytes. APAAP. No counterstaining. × 320

10%), although the differences were less pronounced than in the first group of MF patients. Structural changes were not evident except for case No 3. The lymphonodal architecture of the other cases (cases No 1, 5, 8, 9) was preserved. In the non-MF-erythrodermia group, CD4+ T lymphocytes were preponderant in the tissues in most cases, although the amounts changed markedly between cases and within individual cases between skin and lymph nodes. CD1+ cells were again more frequent in lymph nodes (more than 10%) than in dermal infiltrates (less than 10%). Architectural changes were not observed.

In contrast with the MF- and non-MF-erythrodermia groups, lymph nodes with reactive lymphofollicular hyperplasia showed a predominance of CD8+ cells in 80% of cases. An even more striking difference appeared from the analysis of CD1+ cells, which were considerably lower in numbers than in the aforementioned groups, and

Table 4. Immunohistochemical analysis of lymphonodal infiltrates in patients with Mf

case No	1	2	3	4	5	6	7	8	9
Score	(0)	(6)	(0)	(6)	(1)	(7)	(4)	(0)	(1)
Mab									
CD 25	−	+++	−	++	−	+++	++	−	−
CD 30	−	+	−	+	−	+	−	−	+
Ki-67	−	++	−	+++	+	+++	++	−	−
Tf-R	+	−	−	−	−	−	−	−	−
Ki M 4b	++	+++	−	−	++	+++	−	+++	+
Ki M 7	+++	+++	+++	+++	+	+++	+++	++	+++
CD 22	+++	+++	+++	+++	++	++	++	++	+++
CD 5	++	+++	−	++	−	+++	++	+	+++
CD 2	++	+++	++	+	++	+++	++	+	+++
CD 1	++	+++	++	+++	++	+++	++	++	+++
CD 8	+	+	−	++	+	+	−	−	++
CD 4	+++	++	++	+	+++	+++	+	+	+

() activation/proliferation score
Mab = Monoclonal antibodies

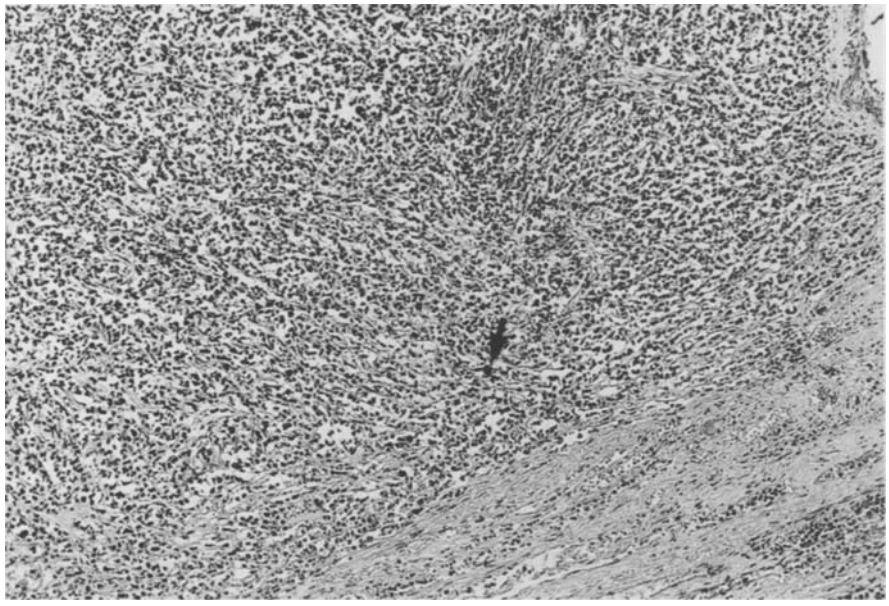

Fig. 4. Lymph node manifestation of MF (LN 3) Destruction of lymph node architecture. Infiltration and scarring of the cortical capsule and perinodal tissue (lower part of the figure). Scattered lymphocytes with nuclei of striking size and chromatin density (arrow). Giemsa × 80

constituted less than 10% of cells in 90% of cases. Lymph node architecture was always preserved.

Discussion

Most cases of MF and SS have been now determined as being clonal expansions of CD4+ T lymphocytes (Kung et al. 1981; Haynes et al. 1981; O'Connor et al. 1985, 1987; Ralfkiaer et al. 1987a). CD4+ T lymphocytes constitute the major cell type in Pautrier microabscesses and in dermal infiltrates (Holden et al. 1983; Chu et al. 1984). Our semiquantitative evaluations of cutaneous infiltrates were in good agreement with previous reports (Thomas and Janossy 1982; Chu et al. 1984; Buechner et al. 1984; Sterry 1985), CD4+ cells representing more than 50%, CD8+ and CD1+cells approximately 20% of the cell population. Simple phenotyping, however, is rarely helpful for differential diagnosis of MF/SS and benign inflammatory dermatoses (for review: Slater 1987), as is shown in our small series. In addition, antigen shift and sometimes a loss of antigen expression may occur to a variable extent (Haynes 1983; Nasu et al. 1985), thus also provoking

Fig. 5. Early skin disease (MF Ia). Some Ki-1-positive cells within Pautrier abscesses (arrows) and in the adjacent dermal infiltrate (arrowheads). APAAP. ×80

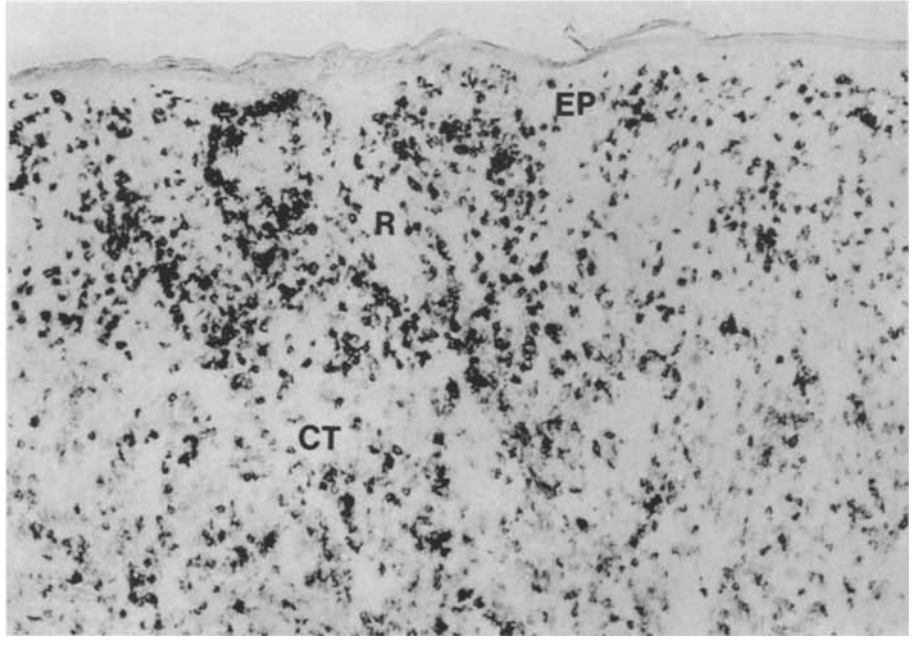

Fig. 6. Early skin disease (MF Ia). Epithelium (*E*) and connective tissue (*CT*) contain numerous CD 25 positive lymphocytes. Aspect of interface dermatitis with intensive infiltration of the dermo-epidermal zone (R = rete pegs). APAAP. No counterstaining. ×80

Table 5. Activation/proliferation antigen profiles of lymph nodes in patients with erythrodermia and reactive lymphofollicular hyperplasias

Case No	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Score	(6)	(0)	(3)	(0)	(2)	(2)	(1)	(2)	(0)	(0)	(1)	(1)	(1)	(1)
Mab														
CD 25	+++	−	++	−	+	++	+	+	−	−	+	+	+	−
CD 30	+	−	−	−	−	−	−	−	−	−	−	−	−	+
Ki-67	++	−	+	−	+	−	−	+	−	−	−	−	−	−

() activation/proliferation score

Mab = Monoclonal antibodies

Table 6. Immunohistochemical analysis of cutaneous infiltrates in patients with Mf and non-MF-erythrodermia

Case No	Mab							
	CD 5	CD 1	CD 4	CD 8	CD 25	CD 30	Ki-67	Tf-R
1	+++	+	+++	+	++	+	−	+
2	+++	+	++	++	+	−	+	+
3	+++	+	+++	+	−	−	+	+++
4	+++	+	+++	+	+	−	−	+
5	++	++	+	+	++	−	−	++
6	++	++	+++	+	+	−	−	++
7	++	+	+++	+	+	−	−	+
8	nd	nd	nd	nd	nd	nd	nd	nd
9	nd	nd	nd	nd	nd	nd	nd	nd
10	++	++	+++	++	+	−	−	+
11	nd	+	+	++	nd	nd	nd	nd
12	++	+	+++	++	nd	nd	nd	nd
13	+++	++	+++	++	+	−	+	+

nd: not done

Mab = Monoclonal antibodies

doubts about the value of T cell markers for this particular diagnosis (especially CD 3 and CD 4 antigens).

The poor diagnostic accuracy of differentiation marker molecules in this diagnostic field prompted us to examine activation/proliferation antigens (transferrin receptor, CD 25, CD 30, Ki 67) in skin biopsies of a large number of MF cases (Meissner et al. 1987). From these studies it became clear that only the combined assessment of activation/proliferation markers provide a supplement in the differential diagnosis of MF stages I–III and non-MF inflammatory dermatoses. Interestingly, the expression of CD 30 (Ki 1) declined in cutaneous infiltrates in advanced stages (MF III/IV) in contrast with the findings in lymph nodes (see below).

An equally challenging field to histopathologists represents the evaluation of lymphonodal spread in MF. In the past, lymph node involvement was assessed by histopathologists by means of different, although closely related grading systems (Scheffer et al. 1980; Willemze et al. 1985; Sausville et al. 1985). Correlations are usually acceptable when focussed on "normal" lymph nodes (LN 0) or unequivocal lymph node manifestations (LN 3 and LN 4 categories; Sausville et al. 1985). Our series of MF consisted of two lymph nodes graded as LN 0, and three cases with clear evidence of lymph node involvement (LN 3/LN 4). The other four cases, however, provided examples of the frequently encountered borderline zone (LN 1/LN 2).

For immunohistochemical monitoring of lymphocyte activation/proliferation, we examined the expression of CD 25 (interleukin II receptor), CD 30 (Ki 1), and Ki 67, a triplet of markers, each of them offered advantages for their known (co−) distribution in this and other lymphomas/leukaemias (Stein et al. 1987; Gerdes et al. 1987; Ralfkiaer et al. 1987b). Our results obtained with this marker triplet were built in a semiquantitative scoring system, which appeared to be valuable for the dissection of cases within the MF group itself, and for dissection of a group of MF cases from non-MF-erythrodermias, and reactive lymphfollicular hyperplasias. Three out of four cases of MF with positive activation/proliferation scores (more than 3′) appeared in the clinical stage III/IV. Cautious interpretation, however, is demanded taking into consideration the positive activation/proliferation score in one patient of the non-MF-erythrodermia group.

Interestingly, activation/proliferation scores of cutaneous infiltrates did not increase parallel to lymphonodal scores, and were even low in the skin in stage III/IV disease. Expression of CD 30 was only observed in case No 1 (MF stage Ia).

Results on differentiation antigen profiles and lymph nodes related to MF are highly variable (Weiss et al. 1985b; Willemze et al. 1985; Slater et al. 1985; Burke et al. 1986). Our own observations were almost in line with the reported heterogeneity of cellular infiltrates. Our series of lymph nodes showed CD4+ and CD1+ cells to be preponderant. These observations, however, revealed no relationship with the clinical stages. Concentrations of CD1+ cells seemed to prevail in cases with high activation/proliferation scores. It appeared as

general rule, that dermatopathic lymph nodes -whether removed from patients with or without MF- contained more CD1+ cells (more than 10% of the total cell population) than lymph nodes with reactive lymphofollicular hyperplasia. While in accordance with other reports (Weiss et al. 1985b; Willemze et al. 1985; Slater et al. 1985), these findings do not support the assumption that CD1+/S 100+ parafollicular cells are an indication of MF related lymph node transformation (Herrera 1987).

The majority of our cases revealed normal CD4/CD8 values and only slight expressions of activation/proliferation antigens in the peripheral blood. Interestingly, in two patients with MF, examination of PBL showed a marked inversion of CD4/CD8 ratios, and at least in case No 2, this observation was associated with high counts of CD 25+ PBL. While lymph nodes in these cases were graded as LN 1/LN 2 (no definitive neoplastic transformation), immunohistochemistry yielded high activation/proliferation scores. Increase in circulating Sézary-like cells and activated CD4+ lymphocytes have been reported in SS/MF, but also to a minor extent in other benign dermatoses (Miller et al. 1980; Schmitt et al. 1982; Fiorini et al. 1983; Fletcher et al. 1984). Hence, this observation provides only circumstantial evidence of the progress of the disease.

The challenge to histopathologists will be to define better the group of lymph nodes with dermatopathic lymphadenitis which can not be subdivided by conventional means. In contrast with simple phenotyping of lymph nodes, analysis of activation/proliferation marker provides help. Of course, case No 10 of our non-MF-erythrodermia group makes it clear that in the individual case even the activation/proliferation marker profiles may lead to considerable pitfalls unless taken together with the clinical and histopathological findings.

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