Immunocytochemical characterisation of cutaneous lymphomas other than mycosis fungoides

ELISABETH RALFKIAER,* TA SAATI,† J BOSQ,‡ G DELSOL,† KC GATTER,‡
DY MASON†

*From the *Departments of Pathology and Dermatology, The Finsen Institute, University of Copenhagen, Denmark, †Laboratoire Central d'Anatomie Pathologique, CHU Toulouse Purpan, France, and the ‡Nuffield Department of Pathology, John Radcliffe Hospital, University of Oxford, England*

SUMMARY The immunophenotypic properties of 25 cutaneous non-Hodgkin lymphomas other than mycosis fungoides or Sezary syndrome were investigated and correlated with clinical and histopathological data. The 11 low grade lymphomas were all of B cell origin, whereas the 14 high grade lymphomas comprised B and T cell tumours, true histiocytic proliferations, and one "null" cell lymphoid neoplasm. For the high grade lymphomas correct prediction of the immunological phenotype based on morphological criteria was only possible in three cases. In contrast, all of the low grade lymphomas showed the non-epidermotropic infiltration pattern considered to be characteristic of cutaneous B cell tumours. For these conditions, however, immunophenotypic investigations provided a convenient means of improving discrimination between benign (polyclonal) and malignant (monoclonal) lesions, and also showed similarities with nodal lymphomas in terms of expression of lymphoid subset markers and composition of the non-neoplastic white cell infiltrate. No differences were identified between primary and secondary or concurrent cutaneous and extra-cutaneous lymphomas.

Cutaneous non-Hodgkin lymphomas other than mycosis fungoides or Sezary syndrome constitute a heterogeneous group of neoplasms and most of these disorders are likely to represent cutaneous equivalents of nodal malignancies. Immunophenotypic investigations form a useful supplement to their histogenetic characterisation and may provide a common conceptual basis for their classification.

It is generally accepted that cutaneous non-Hodgkin lymphomas can be divided into two principal distinct categories on clinical, histopathological, and immunophenotypic criteria—that is, mycosis fungoides or Sezary syndrome and other variants of lymphoma.¹⁻⁵

The mycosis fungoides or Sezary syndrome cases are epidermotropic lymphocytic lymphomas, which originate from T cells and present (and possibly arise) in the skin.⁵ In the fully developed cases both conditions usually show characteristic clinical pictures,^{5,6} and they currently form the most well defined entities of the spectrum of disorders known as the cutaneous T cell lymphomas.⁷

Compared with mycosis fungoides or Sezary syndrome other cutaneous lymphomas constitute an ex-

remely heterogeneous group of neoplasms. Even though evidence has accumulated that these tumours presumably represent the cutaneous equivalents of nodal non-Hodgkin lymphomas,^{1,3} uniformly accepted criteria for their histopathological diagnosis and classification have not as yet been established.^{1-4,8}

Immunocytochemical staining techniques have formed a valuable adjunct to the histological diagnosis and classification of nodal lymphoma infiltrates^{9,10} and have provided important insights into T cell subset heterogeneity among cutaneous T cell lymphomas of the mycosis fungoides or Sezary syndrome type.^{11,12} Few comprehensive immunophenotypic studies of other categories of cutaneous lymphoma have been reported. In this study the immunophenotypic characteristics of 25 cases of such disorders were investigated and correlated with clinical and histological data.

Table 1 Monoclonal antibodies

Antibody	Specificity	Source or reference, or both
DAKO-LC	Leucocyte common antigen	Dako ¹⁶
anti-HLA-DR	HLA-DR	BD
B4	Pan B cell (CD19)*	CC
B1	Pan B cell (CD20)	CC
Tol5/4KB128	Pan B cell (CD22)	Dako
anti-IgM	IgM	Dako
anti-IgD	IgD	Dako
anti-lambda	λ	Dako
anti-kappa	κ	BD
anti-Leu-5/Lyt3	Pan T cell (E rosette receptor) (CD2)	BD/NEN
anti-Leu-1/Lyt2	Pan T cell; some normal and malignant B cells (CD5)	BD/NEN ^{17 18}
anti-Leu-4	Pan T cell (CD3)	BD
anti-Leu-3	T helper and inducer cells; macrophages (CD4)	BD ¹⁹
anti-Leu-2	T suppressor and cytotoxic cells (CD8)	BD
anti-Leu-7	Natural killer cells	BD
OKT6	Cortical thymocytes; Langerhans' cells (CD1)	Ortho
R4/23	Follicular dendritic cells	Dako ²⁰
anti-Leu-M3	Macrophages	BD
KB90	Macrophages (p150, 95 molecule)	DY Mason
EBM11	Macrophages	Dako
FMC32	Macrophages	²¹
OKM1	Granulocytes, monocytes, macrophages (C3bi receptor)	Ortho
My9	Myeloid cells; monocytes	²²
My7	Myeloid cells; monocytes (CDw13)	²³
E29	Epithelial membrane antigen	²⁴
KL1	Keratin	²⁵

*CD numbers refer to the antigens defined by the First and Second International Workshops on Human Leucocyte Differentiation Antigens. Dako = Dakopatts; BD = Becton Dickinson; CC = Coulter Clone; NEN = New England Nuclear; Ortho = Ortho Diagnostics.

Material and methods

Twenty five patients with cutaneous non-Hodgkin lymphomas other than mycosis fungoides or Sezary syndrome were investigated. The diagnosis of mycosis fungoides or Sezary syndrome was based on clinical and histopathological criteria, as described previously.⁵

CLINICAL EVALUATION

Clinical evaluation included physical examination, blood count, chest radiograph, lymphangiography, lymph node biopsy, blood and bone marrow examination, and liver biopsy. Based on the outcome of these investigations the patients were graded in accordance with the Ann Arbor system.¹³

HISTOPATHOLOGICAL EVALUATION

Routinely processed paraffin embedded skin biopsy specimens were stained both with haematoxylin and eosin and May-Grunewald Giemsa and then classified in accordance with the Kiel classification¹⁴ and the international working formulation for clinical usage.¹⁵ An attempt was also made to predict the immunological phenotype of the various infiltrates by assessing the histological infiltration patterns (T; B; non-T, non-B) described by Burg *et al.*³

PROCESSING OF FRESH BIOPSY SPECIMENS

Skin biopsy specimens were frozen and stored in

liquid nitrogen. Cryostat sections (6 μ m) were air dried overnight at room temperature, fixed in acetone for 10 minutes¹⁰ and either stained immediately or wrapped in aluminium foil and stored at -20°C until staining, when the sections were allowed to warm to room temperature before unwrapping.

ANTIBODIES AND HISTOCHEMICAL REAGENTS

Table 1 gives details of the monoclonal antibodies used in this study. Rabbit antimyeloperoxidase was a generous gift from Dr I Olsson. Immune complexes of alkaline phosphatase and mouse monoclonal anti-alkaline phosphatase (APAAP complexes) were prepared as described previously.²⁶ Unconjugated rabbit antimouse immunoglobulin, peroxidase conjugated rabbit antimouse immunoglobulin, peroxidase conjugated swine antirabbit immunoglobulin, and rabbit antihorseradish peroxidase were all purchased from Dakopatts, Copenhagen, Denmark. Levamisole, diaminobenzidine-tetrahydrochloride, naphthol AS-MX, and New Fuchsin were obtained from Sigma.

IMMUNOENZYMATIC STAINING PROCEDURES

Cryostat sections were incubated with monoclonal antibody and stained using a three stage immunoperoxidase method¹⁰ or the alkaline phosphatase:antialkaline phosphatase (APAAP) technique.²⁶ The polyclonal antibody was stained by a peroxidase:antiperoxidase (PAP) method.⁹ The presence of peroxidase was shown by using di-

aminobenzidine and hydrogen peroxide,⁹ and alkaline phosphatase by using a naphthol AS-MX-New Fuchsin substrate.²⁶ Endogenous tissue alkaline phosphatase activity was inhibited by adding 1 mM levamisole to the substrate solution.²⁶ Positive controls were performed by staining benign hyperplastic lymph nodes or tonsils; negative controls by omitting the primary monoclonal or polyclonal antibody.

Results

CLINICAL DATA (Table 2)

Cases could be divided into: primary cutaneous tumours showing no evidence of extracutaneous disease (eight cases); concurrent cutaneous and extracutaneous lymphomas in which the clinical or histological staging procedures showed nodal or visceral spread, in addition to the cutaneous lesions (12 cases); and secondary cutaneous neoplasms (five cases) disseminating to the skin from lymph nodes or bone marrow 12 to 108 months (median: 60 months) after diagnosis.

Men slightly predominated in each of these three groups of patients, and the age distribution was essentially similar among them. The median length of follow up was similar among patients with primary and concurrent cutaneous lymphomas (16 and 15 months, respectively). Whereas six of 12 patients with concurrent cutaneous and extracutaneous lesions died from their disease (with a median survival time of eight months) all but one of the eight patients with primary skin lymphomas are still alive at the time of writing. The overall survival for the patients with secondary cutaneous lymphomas ranged from 15 to 109 months (median: 72 months). Prognosis subsequent to the development of cutaneous lesions in these patients, however, was poor (one to 12 months (median: 4.5 months)).

HISTOLOGICAL DATA (Table 2)

Eleven tumours were classified as low grade lymphoid malignancies—that is, lymphocytic, centrocytic, centroblastic and centrocytic lymphomas, or immunocytomas. All of these cases showed a B cell infiltration pattern in the form of a distinctive “grenz” zone between epidermis and the dermal infiltrate (Figs. 1 and 2). Follicular areas were identified in three of the germinal centre cell tumours (cases 2–4), while the remaining low grade tumours showed only diffuse infiltration.

The remaining 14 lymphomas were high grade malignancies—that is, centroblastic, immunoblastic, lymphoblastic, or unclassified large cell lymphomas. All these cases showed diffuse infiltrates, and with the exception of cases 5, 7, and 14, their histological infiltration pattern was of the non-T, non-B type (Fig. 3).

The median length of follow up was 16 months for the high grade tumours and 24 months for the low grade malignancies. Nevertheless, whereas 10 of the 14 patients with high grade tumours died from their disease, all but one of the 11 patients with low grade lymphomas are alive at the time of writing, and four are in complete remission.

PHENOTYPIC DATA (Table 3)

Neoplastic cells In all cases the neoplastic cells reacted with antileucocyte common antibody and were negative for epithelial cell markers (keratin, epithelial membrane antigen), confirming their lymphoid origin. Nineteen tumours showed B cell phenotypic properties, three (cases 6, 7, 20) expressed markers characteristic of T lymphocytes, and two (cases 18 and 24) showed antigenic profiles resembling those found on macrophages. The remaining case (19) was classified as a “null” cell lymphoid malignancy, as the cells were negative not only with antibodies against B cells, T cells, and macrophages, but also with antimyeloid reagents (My9, My7, antimyeloperoxidase) and antibody (anti-Leu-7) against natural killer cells.

All the B cell tumours were positive both for HLA-DR and for the pan B cell CD19, CD20 or CD22 antigens, identified by antibodies B4, B1, and To15/4KB128, respectively (Fig. 1). Expression of the T cell associated CD5 antigen (recognised by anti-Leu-1) was confined to three lymphocytic lymphomas (cases 1, 9, 21; Fig. 1) and two centroblastic and centrocytic tumours (cases 2 and 4). Thirteen of the B cell tumours expressed both heavy and light chains, individual tumours being monotypic for either κ or λ chains (Fig. 2). The remaining six B cell neoplasms (cases 8, 15, 17, 22, 23, 25) either lacked detectable immunoglobulin or expressed heavy chains (Fig. 3) in the absence of light chains.

Among T cell lymphomas, two (cases 6, 20) expressed all three pan T cell CD2, CD5, and CD3 antigens recognised by anti-Leu-5/Lyt3, anti-Leu-1/Lyt2, and anti-Leu-4, respectively. In the remaining case (7) a proportion of the tumour cells did not express the CD5 marker. All three T cell tumours resembled peripheral T-helper/inducer cells, being positive for the CD4 antigen (antibody anti-Leu-3) and negative both for CD8 (antibody anti-Leu-2) and CD1 (antibody OKT6). HLA-DR was expressed by a proportion of the tumour cells in all T cell cases.

Both of the macrophage tumours (18, 24) expressed HLA-DR and the macrophage associated antigens recognised by antibodies KB90 (anti-p150,95), EBM11, FMC32, anti-Leu-M3 and/or OKM1 (against the C3bi receptor). Furthermore, both cases showed the strong cytoplasmic positivity for the CD4 marker (anti-Leu-3) characteristic of macrophages. Other anti T cell antibodies and all anti B cell antibodies were consistently negative, except that case 24

Table 2 Clinical data

Case No	Age	Sex	Histology*	Infiltration pattern§
Primary cutaneous lymphomas				
1	45	M	Malignant lymphocytic (sl)	B
2	61	M	Centroblastic and centrocytic (fm)	B
3	70	M	Centroblastic and centrocytic (fm)	B
4	53	F	Centroblastic and centrocytic (fm)	B
5	54	F	Immunoblastic (IB)	B
6	15	F	Lymphoblastic (LB)	non T, non B
7	43	M	Unclassified large cell (uncl)	T
8	67	M	Unclassified large cell (uncl)	non T, non B
Concurrent cutaneous and extracutaneous lymphomas				
9	60	M	Malignant lymphocytic (sl)	B
10	75	F	Immunocytoma (sl)	B
11	72	F	Immunocytoma (sl)	B
12	62	M	Centrocytic (dsc)	B
13	57	M	Centroblastic and centrocytic (dm)	B
14	61	F	Centroblastic (dlc)	B
15	47	M	Immunoblastic (IB)	non T, non B
16	76	M	Lymphoblastic (LB)	non T, non B
17	60	M	Lymphoblastic (LB)	non T, non B
18	24	F	Unclassified large cell (uncl)	non T, non B
19	40	F	Unclassified large cell (uncl)	non T, non B
20	82	M	Unclassified large cell (uncl)	non T, non B
Secondary cutaneous lymphomas				
21	69	M	Malignant lymphocytic (sl)	B
22	79	F	Centroblastic and centrocytic (dm)	B
23	64	M	Unclassified large cell (uncl)	non T, non B
24	73	F	Unclassified large cell (uncl)	non T, non B
25	59	M	Unclassified large cell (uncl)	non T, non B

*Kiel classification with corresponding working formulation in parentheses. sl = small lymphocytic lymphoma; fm = follicular lymphoma, mixed small and large cell, dsc = diffuse lymphoma, small cleaved cell; dlc = diffuse lymphoma, large cell; dm = diffuse lymphoma, mixed small and large cell; uncl = unclassified large cell lymphoma of diffuse type. IB = immunoblastic; LB = lymphoblastic.

†A+ = alive with active disease; Ao = alive in remission; D+ = dead from lymphoma.

§assessed using criteria described by Burg *et al.*³

Table 3 Phenotype of infiltrating malignant cells in skin biopsy specimens from cutaneous non-Hodgkin lymphomas other than mycosis fungoides and Sezary syndrome.

		Antibodies					
Case No	Histology	Anti-HLA-DR	Anti-pan-B cell (CD19, 20, 22)	Anti-IgM	Anti-IgD	Anti-kappa	Anti-lambda
Primary cutaneous lymphomas							
1	Malignant lymphocytic	++ *	++	++	—	—	++
2	Centroblastic and centrocytic	++	++	++	—	++	—
3	Centroblastic and centrocytic	++	ND	++	—	++	—
4	Centroblastic and centrocytic	++	++	++	+	++	—
5	Immunoblastic	++	++	++	—	++	—
6	Lymphoblastic	++	—	—	—	—	—
7	Unclassified large cell	+	—	ND	ND	ND	ND
8	Unclassified large cell	++	++	—	—	—	—
Concurrent cutaneous and extracutaneous lymphomas							
9	Malignant lymphocytic	++	++	++	++	++	—
10	Immunocytoma	++	++	++	—	++	—
11	Immunocytoma	++	++	++	—	—	++
12	Centrocytic	++	++	++	—	—	++
13	Centroblastic and centrocytic	++	ND	++	++	++	—
14	Centroblastic	++	++	++	—	++	—
15	Immunoblastic	++	++	—	—	—	—
16	Lymphoblastic	++	++	++	—	++	—
17	Lymphoblastic	++	++	+	+	—	—
18	Unclassified large cell	++	—	—	—	—	—
19	Unclassified large cell	++	—	—	—	—	—
20	Unclassified large cell	+	—	ND	ND	—	—
Secondary cutaneous lymphomas							
21	Malignant lymphocytic	++	++	++	++	—	++
22	Centroblastic and centrocytic	++	++	—	+	—	—
23	Unclassified large cell	++	++	—	—	—	—
24	Unclassified large cell	++	—	—	—	—	—
25	Unclassified large cell	++	+	—	—	—	—

†detected using the anti-macrophage reagents anti-Leu-M3, KB90, EBM11, FMC32 and/or OKM1.

‡B = B cell lymphoma expressing the immunoglobulin heavy and light chains indicated in the parentheses (M = IgM; D = IgD; K = kappa; L = lambda; Ig- = immunoglobulin negative); T(H) = T cell lymphoma of helper/inducer type; M = macrophage tumour; "null" = null cell lymphoid malignancy; HX = histiocytosis X like.

*++ = labelling of most (>50%) of the cells; + = labelling of a proportion (20–50%) of the cells; +/- = labelling of a few (5–10%) of the cells; — = negative or only occasional cells positive; ND = not done.

Actual phenotype	Stage	Duration of disease before cutaneous spread (months)	Treatment	Follow up (months)	Present condition†
B cell	Ie		None	14	A +
B cell	Ie		chemotherapy	54	Ao
B cell	Ie		chemotherapy	88	Ao
B cell	Ie		X-ray treatment	2	A +
B cell	Ie		X-ray treatment	36	D +
T cell	Ie		chemotherapy	14	A +
T cell	Ie		X-ray treatment	7	A +
B cell	Ie		chemotherapy	18	Ao
B cell	IV		chemotherapy	24	A +
B cell	IV		chemotherapy	42	Ao
B cell	IV		chemotherapy; X-ray treatment	8	A +
B cell	IV		chemotherapy	16	A +
B cell	IV		chemotherapy	18	Ao
B cell	IV		None	0.5	D +
B cell	III		chemotherapy; X-ray treatment	7	D +
B cell	IV		chemotherapy	21	A +
B cell	IV		chemotherapy	8	D +
Macrophage	IV		chemotherapy	14	D +
Null cell lymphoid neoplasm	IV		chemotherapy	60	D +
T cell	IV		chemotherapy; X-ray treatment	9	D +
B cell	IV	60	chemotherapy	72	D +
B cell	IV	72	X-ray treatment	90	A +
B cell	IV	108	chemotherapy	109	D +
Histiocytosis X like	IV	12	chemotherapy	15	D +
B cell	III	14	chemotherapy	20	D +

Anti-pan-T cell (CD2, 3)	Anti-pan-T cell (CD5)	Anti-T helper (CD4)	Anti-T suppressor (CD8)	OKT6 (anti-CD1)	Anti-macrophage†	Conclusion†
-	++	-	-	-	ND	B (ML)
++	++	-	-	-	-	B (MK)
-	-	-	-	-	-	B (MK)
-	+	-	-	-	-	B (MDK)
-	-	-	-	-	-	B (MK)
++	++	++	-	-	-	T (H)
++	+/-	++	-	-	ND	T (H)
-	-	-	-	-	-	B (Ig-)
-	++	-	-	-	ND	B (MDK)
-	-	-	-	-	-	B (MK)
-	-	-	-	-	-	B (ML)
-	-	-	-	-	-	B (ML)
-	-	-	-	-	-	B (MDK)
-	-	-	-	-	-	B (MK)
-	-	-	-	-	-	B (Ig-)
-	-	-	-	-	-	B (MK)
-	-	++	-	-	-	B (MD)
-	-	++	-	-	++	M
++	++	++	-	-	-	"null"
-	-	-	-	-	-	T (H)
-	++	-	-	-	ND	B (MDL)
-	-	-	-	-	ND	B (D)
-	-	++	-	-	-	B (Ig-)
-	-	-	-	++	++	HX
-	-	-	-	-	-	B (Ig-)

Fig. 1 Lymphocytic lymphoma showing (a) non-epidermotropic B cell infiltration pattern with distinctive "grenz" zone. (Haematoxylin and eosin.) Neoplastic cells are strongly positive for T cell associated CD5 marker (b), in addition to pan B cell CD 22 antigen (c). Staining for pan T cell CD3 antigen is confined to surrounding reactive T lymphocytes (d). All Figs. $\times 400$, except (c) $\times 200$.

Fig. 2 B cell infiltration pattern in cutaneous germinal centre cell tumour (a) (Haematoxylin and eosin) $\times 200$ composed of mixture of centroblasts (cb) and centrocytes (cc) (b) (Haematoxylin and eosin) $\times 600$. Neoplastic cells show clear monotypic expression of κ chains (c) $\times 400$, staining for λ chains being negative (d) $\times 400$. Tumour cells are focally intermingled with follicular dendritic cells shown by staining with antibody R4/23 (e) $\times 400$.

Fig. 3 Non-B, non-T infiltration pattern (a) (Haematoxylin and eosin) $\times 200$ in high grade lymphoma composed of lymphoblasts (b) (Haematoxylin and eosin) $\times 600$. Cells expressed IgM (c) $\times 400$ and more weakly IgD (d) $\times 400$, but lacked detectable light chains. Reactive macrophages (e) (KB90) $\times 400$ and T lymphocytes (f) (anti-Leu-4) $\times 400$ were interspersed among neoplastic cells and also showed clustering around blood vessels.

expressed the CD1 antigen found on cortical thymocytes and Langerhans' cells. This histiocytosis X like tumour did not show any specific clinical features, such as lytic bone lesions.

Non-neoplastic white cell types Follicular dendritic cells (Fig. 2) were confined to the B cell tumours, being found in one of two immunocytomas (case 10) and in all centrocytic (12) and centroblastic and centrocytic tumours (cases 2-4, 13, 22), whereas tissue macrophages (Fig. 3) and Langerhans' cells were present in all the infiltrates.

Reactive T lymphocytes were also present in all lesions and in high grade tumours often clustered close to blood vessels (Fig. 3). Fig. 4 shows the ratio between T helper/inducer and T suppressor/cytotoxic cells in the cutaneous B cell tumours. Most of the germinal centre cell tumours showed a predominance of T helper lymphocytes, whereas the remaining B cell lymphoma subtypes did not show any consistent ratio between T helper and T suppressor cells.

Anti-Leu-7 (reactive with a peripheral white cell population which includes natural killer cells) labelled cells in some of the infiltrates but was usually present in low numbers.

CORRELATION BETWEEN PHENOTYPIC, CLINICAL, AND HISTOLOGICAL DATA (Tables 2 and 3)

The incidence of individual histopathological and immunophenotypic lymphoma subtypes was essentially similar among primary, concurrent, and secondary cutaneous neoplasms. In keeping with their non-epidermotropic histological infiltration patterns, all of the low grade lymphomas were of B cell origin. Accordingly, the high grade tumours accounted for the entire range of immunophenotypic heterogeneity found in the present material. For these lesions pre-

diction of a correct immunological phenotype based on morphological criteria was only possible in three cases (5, 7, 14).

Discussion

The results indicate that cutaneous non-Hodgkin lymphomas other than mycosis fungoides or Sezary syndrome constitute an extremely heterogeneous group of neoplasms in terms of their histopathological characteristics and immunophenotypic properties, and also substantiate that these disorders can be divided into three main categories on clinical criteria: primary, concurrent, and secondary cutaneous neoplasms.⁴

Detailed immunophenotypic data on a comparable series of patients have been provided in only one previous report,⁴ whereas other phenotypic investigations have used different clinical or histopathological selection criteria, less extensive antibody panels, polyclonal reagents, rosetting methods or enzyme cytochemical rather than immunological techniques.^{3 27-29} Nevertheless, some general trends can be deduced, and these agree with the present study. These include the observed predominance of B cell tumours among cutaneous low grade lymphomas other than mycosis fungoides or Sezary syndrome^{3 4} and the quite extensive immunological heterogeneity found among the high grade lymphomas,^{3 4 17} which either resembled B cells, T cells, macrophages, or (more rarely) so called "null" lymphocytes. It is uncertain whether the "null" lymphocyte phenotype reflects neoplastic proliferation of immature precursor cells devoid of the range of lineage associated markers assessed in this study, or whether it results from diminished or changed antigen expression on malignant as opposed to normal lymphoid cells (although there is indirect evidence in favour of the second possibility).^{10 11}

The finding that some of the cutaneous high grade tumours in the present material seemed clearly to be of macrophage rather than of lymphoid origin is also in keeping with a previous study,²⁸ and it has even been proposed that true histiocytic proliferations account for most cutaneous large cell lymphomas.²⁸ Although our data do not substantiate this suggestion, they indicate that macrophage derived tumours may occur more often in the skin than in lymphoid organs. It is also evident, however, that these tumours are not homogeneous as they include both neoplasms that resemble "ordinary" tissue macrophages^{19 21} and also tumours showing an antigenic profile similar to that of Langerhans' cells (positivity both for macrophage associated antigens and for the CD1 marker).³⁰ Although this phenotype is very characteristic of the typical histiocytosis X cases

Fig. 4 Ratio between reactive T cells of helper and inducer and suppressor and cytotoxic type in cutaneous B cell lymphomas.

seen in infants and children,¹⁹⁻³¹ it has also been identified in a limited number of elderly patients with disease confined to nodal or cutaneous areas.³² This suggests that histiocytosis X like proliferations may encompass a broader spectrum of disorders than has been generally accepted in the past.³²

The overall tendency towards a more favourable prognosis among primary as opposed to concurrent and secondary cutaneous lymphomas and among low as opposed to high grade tumours is in keeping with previous reports^{1,2} and supports the concept that the extent of these neoplasms and also their histological subtype are important prognostic variables. Even though it has been proposed that cutaneous tumours of different histogenesis may show differences in clinical behaviour or response to treatment,²⁷⁻²⁸ there is as yet no definite evidence that the tumour phenotype has independent prognostic importance. With the possible exception of the macrophage tumours mentioned above, however, there has not been any indication that cutaneous tumours differ appreciably from those seen in lymph nodes. Accordingly, we assume that immunological heterogeneity is likely to have similar prognostic implications for cutaneous and nodal neoplasms.³³ Immunophenotypic investigations should therefore be used routinely as an adjunct to the histological classification of cutaneous high grade lymphomas, as present and previous studies³⁻⁴ show that the immunological phenotype of most of these lesions cannot be predicted morphologically. Furthermore, these methods form an obvious and very convenient means of improving the controversial histopathological distinction⁸ between benign (polyclonal³⁴) and malignant (monoclonal) cutaneous B cell infiltrates.

In spite of the fact that cutaneous lymphomas in this and previous studies¹⁻⁴ have usually resembled nodal non-Hodgkin lymphomas, none of the currently available classification schemes for nodal lymphomas has been generally adopted for cutaneous infiltrates.³ Another major application for immunophenotypic investigations is therefore to test the hypothesis that cutaneous and nodal lymphomas are essentially identical in origin, thus providing a common conceptual basis for their classification. This applies both to high and low grade lymphomas. In particular, even though the B or T cell lineage of low grade lymphomas can usually be determined by assessment of their histological infiltration patterns,³ heterogeneity among these conditions in terms of expression of lymphoid subset markers can only be shown by immunophenotypic techniques (which also show the nature and origin of associated non-neoplastic white cells). The conceptual importance of these aspects is illustrated by the following two observations, both of which support the view that cutane-

ous and nodal lymphomas are essentially similar. First, the cutaneous B cell tumours positive for the T cell associated CD5 antigen (recognised by antibody anti-Leu-1) showed the same cytological characteristics as anti-Leu-1-positive nodal B cell malignancies.¹⁷⁻¹⁸ Second, the cutaneous germinal centre cell lymphomas contained non-neoplastic white cell types (follicular dendritic cells, T cell subsets similar to those found in corresponding nodal malignancies.²⁰⁻²⁹⁻³⁵

This study indicates that cutaneous non-Hodgkin lymphomas other than mycosis fungoides or Sezary syndrome constitute a heterogeneous group of neoplasms and supports the concept that most of these tumours represent cutaneous equivalents of nodal lymphoma subtypes. Use of immunophenotypic methods forms a valuable supplement to their histogenetic characterisation and may assist in providing uniform criteria for their classification.

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Request for reprints to: Dr Elisabeth Ralfkiaer, Department of Pathology, the Finsen Institute, University of Copenhagen, 49 Strandboulevarden, DK-2100 Copenhagen Ø, Denmark.