Twelve cases of Ki-1 positive anaplastic large cell lymphoma of skin

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Abstract

In seven of 12 cases of Ber-H2 (Ki-1) positive anaplastic large cell non-Hodgkin's lymphoma (Ki-1 ALCL) disease remained localised to skin, and in five there was extracutaneous spread. Four patients had histological evidence of pre-existing or coexisting mycosis fungoides, and three patients had a long standing history of eczema or ichthyosis. In two cases the presence of a T phenotype was shown in frozen sections, and in a further six cases a T phenotype was firmly established in paraffin wax sections. Four patients died less than one year after presentation (two with disseminated lymphoma; two from other causes); one died at five years with widespread lymphoma and the remaining seven cases were alive one to 14½ years after presentation. Three of the four patients with associated mycosis fungoides had prolonged survival, contrary to the findings of previous reports which suggest secondary Ki-1 ALCL behaves aggressively.

The recognition of these tumours is important because of their relatively good prognosis. The diagnosis can be readily substantiated immunohistochemically, using a simple panel of antibodies.

The Ki-1 antigen was originally described in Hodgkin and Reed-Sternberg cells and in a small population of cells in normal lymph nodes.^{1,2} It has subsequently been shown in activated T and B cells and in an uncommon form of non-Hodgkin's lymphoma described as "Ki-1 positive anaplastic large cell lymphoma (Ki-1 ALCL)," which has been of T, B, or null cell type.³⁻¹⁰ These lymphomas have mostly been based in nodes but some have originated elsewhere.^{3,7-18} Studies of these lymphomas have recently been facilitated by the introduction of the antibody Ber-H2 (CD 30), which shows the presence of Ki-1 antigen in paraffin wax sections.^{19,20}

Despite a growing number of published findings on Ki-1 ALCL it is still often misdiagnosed, and in this paper we present 12 cases which emphasise that this tumour frequently presents in the skin; the differential diagnosis, immunophenotypic features, and the relation to lymphomatoid papulosis²¹⁻²³ and regressing atypical histiocytosis (RAH)²⁴⁻²⁶ are discussed. Long term follow up was available on most of the cases and

indicates that a high proportion of cutaneous Ki-1 ALCL pursue a non-aggressive course.

Methods

Excised skin tumours were received from all cases. In cases 1, 2, 3, 4, 6, 9, and 10 more than one skin biopsy was performed. Lymph nodes were received from cases 4 through to 8. Case 4 also developed a small intestinal tumour which was resected. In all cases formalin fixed specimens were processed conventionally into paraffin wax and 5 µm sections were stained with haematoxylin and eosin, Giemsa, methyl green pyronin and reticulin stains. Immunohistochemical studies were done on paraffin wax sections using the avidin-biotin-peroxidase technique. The antibodies used are listed in table 1. The tests were done with appropriate positive and negative controls.

Fresh tissue was available from the lymph nodes in cases 4 and 7 and this was subjected to frozen section immunoperoxidase studies for detailed phenotyping. The following antibodies were used: Anti IgD, IgM, anti-κ and λ light chains, T-lineage markers CD2, CD3, CD5, CD4 (T helper/inducer cells), CD8 (T cytotoxic/suppressor cells) and B-lineage markers CD19, CD20, and CD22. The CD20 was supplied by Becton-Dickinson, CD3 by Unipath, and the rest were obtained from Dakopatts.

CLINICAL FINDINGS

The clinical findings are summarised in table 2. Eleven of the 12 patients were men with an age range from 27 to 73 years. They presented with plaque-like, nodular, or ulcerated skin lesions. Case 5 presented with an inflamed chest wall nodule initially thought to be an abscess; this was not biopsied but was clinically identical with the lymphomatous deposit confirmed by biopsy which subsequently developed in his axillary skin. Similarly, case 10 presented with a red and tender swelling of the scrotum which was clinically diagnosed as an inflammatory lesion. In most cases lesions had been present for several months and a tendency for earlier lesions to regress spontaneously was noted by two patients (cases 1 and 3).

A history of pre-existing or coexisting skin disease was obtained in seven cases. Two patients (cases 1 and 6) had had eczematous dermatitis since childhood and a skin biopsy specimen taken from case 6 showed features of chronic dermatitis. Case 7 had a dry ichthyotic skin. Four patients (cases 2, 3, 4, and 10)

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Accepted for publication
27 September 1990

Table 1 Antibodies used for paraffin wax section immunohistochemistry

Antibody (CD Number)	Major specificity	Source
*Ber-H2 (CD30) ¹⁹	Reed-Sternberg cells, activated T and B cells	Dakopatts
Leu-M1 (CD15) ²⁷	Reed-Sternberg cells, granulocytes	Becton Dickinson
LCA (CD45) ²⁸	Leucocytes	Dakopatts
UCHL1 (CD45 RO) ²⁹	T cells, myeloid cells	Dakopatts
MT1 (CD43) ³⁰	T cells, myeloid cells, macrophages, B cell subset	Clonab
CD3 ³¹	T cells	Dakopatts
L26 ³²	B cells	Dakopatts
MB2 ³³	B cells, T cell subset	Clonab
EMA	Epithelial cells, plasma cells, etc.	Dakopatts
*CAM 5-2	Cytokeratin (8, 18, and 19)	Becton Dickinson
*CK1	Cytokeratin (6 and 18)	Dakopatts
* α 1 antichymotrypsin (α 1 ACT)	Macrophages, granulocytes, and a variety of other cells	Dakopatts
*Mac 387 ³⁴	Macrophages, myeloid cells	Dakopatts
KP1 (CD68) ³⁵	Macrophages, myeloid cells	Dakopatts
Vimentin	Mesenchymal cells, some epithelial cells, lymphoid cells, etc	Dakopatts
*S100 protein	Langerhans' cells, Schwann cells, melanocytes, etc	Dakopatts
†HMB 45 ³⁶	Activated and malignant melanocytes	Enzobiochem
‡Anti- κ and λ	B cells	Dakopatts

*Sections were treated with trypsin.

†Done only on cases 3 and 6 where a suggestion of melanoma was initially made.

‡Done in case 6 which showed only MB2 positivity.

α 1 ACT, EMA, and S100 protein were polyclonal and the rest were monoclonal antibodies.

Table 2 Clinical findings

Case No	Age/sex	Presentation	Pre- or co-existing skin disease	Initial pathological diagnosis	Treatment	Course	Current state	Survival (months)*	Extra-cutaneous disease at referral	Bone marrow disease	Constitutional symptoms
1	36 M	Multiple skin nodules on trunk and limbs	Longstanding eczema	Undifferentiated tumour	Radiotherapy and chemotherapy	Skin recurrences $\times$ 4	Alive	60	None	None	None
2	50 M	Multiple skin nodules on left leg	Mycosis fungoides	?Hodgkin's disease ?reactive process	Radiotherapy	Skin recurrences $\times$ 3	Alive	87	None	None	None
3	65 M	Single ulcerated lesion on right leg	Mycosis fungoides	Malignant melanoma	Surgical excision and radiotherapy	Skin recurrence after 12 years	Alive	174	None	N/D	None
4	70 F	Recurrent scalp nodules	Mycosis fungoides	Anaplastic malignant tumour	Radiotherapy	Skin, nodal, and small intestinal recurrences	Dead†	60	None	N/D	None
5	27 M	Abscess-like lesion of chest-wall; axillary lymph nodes	None	Anaplastic (Ki-1 positive) non-Hodgkin's lymphoma (lymph node biopsy)	Chemotherapy	Rapid recurrence of cellulitis-like skin lesion	Dead†	7	Lymph node; ?lung	None	Weight loss
6	31 M	Nodules on temple and chin; neck nodes	Long standing eczema	?Large cell lymphoma (?histiocytic) ?malignant melanoma	Radiotherapy and chemotherapy	Nodal and hepatic recurrence (ultra-sound and computed tomographic scan)	Dead†	9	Lymph node; ?liver	None	None
7	69 M	Single skin nodule on arm; axillary lymph node	Dry, ichthyotic skin	Undifferentiated tumour	Chemotherapy	No recurrences, terminal fungal infection	Dead	2	Lymph node	None	None
8	33 M	Single skin nodule on back; axillary lymph nodes	None	?Hodgkin's disease	Radiotherapy	No recurrences	Alive	66	Lymph node	None	None
9	48 M	Multiple skin nodules on lip, nose, right arm and right leg	None	?Malignant histiocytosis ?T cell lymphoma	Surgical excision and chemotherapy	Skin recurrence—nose and left arm after 9 years	Alive	110	None	None	None
10	73 M	Hard and tender swelling of left scrotum with focal gangrenous change	Mycosis fungoides	Pleomorphic malignant fibrous histiocytoma	Surgery and radiotherapy	No recurrence	Dead	6	None	N/D	None
11	62 M	Thickening and induration of skin right elbow	None	Non-Hodgkin's lymphoma	Radiotherapy	No recurrence	Alive	16	None	N/D	None
12	36 M	Plaque-like skin lesion right neck	None	Inflammatory lesion	Surgical excision	Skin recurrence 1.5 cm above the previous lesion after 10 months	Alive	12	None	None	None

N/D = Not done.

*After development of Ki-1 ALCL.

†Death directly attributable to lymphoma.

Figure 1 Case 3: mycosis fungoides showing numerous small and intermediate sized lymphocytes containing convoluted nuclei which invade the dermis and acanthotic epidermis.

had mycosis fungoides confirmed at biopsy (fig 1). In cases 3 and 4 the mycotic skin lesions had been present for about 12 years, while in case 10 a generalised psoriasiform skin rash had been present for several years; a biopsy specimen taken three months before the development of the scrotal lesion showed features consistent with mycosis fungoides. In case 2 histological features of mycosis fungoides

Figure 2 Case 3: low power view of the cutaneous infiltrate of Ki-1 ALCL. The epidermis (*) is spared and the deeper dermis is occupied by a polymorphic infiltrate.

oides were found in a long standing rash biopsied concurrently with the recently developed nodules of Ki-1 ALCL. In case 8, the skin lesion developed at the site of a jelly fish sting and was present for four years, enlarging slowly, before biopsy.

Treatment varied depending on the initial clinicopathological diagnosis and extent of disease, but in seven patients the disease remained localised to the skin. Seven patients are still alive between 12 and 174 months after the development of Ki-1 ALCL. Five patients (cases 1, 2, 3, 8, and 9) were followed up for more than five years, two of whom had mycosis fungoides. One patient (case 4) died five years after her mycosis fungoides transformed into Ki-1 ALCL and during this period she had nodal and small intestinal disease. The shortest survival times of seven, nine, two, and six months occurred in cases 5, 6, 7, and 10, respectively. Case 10 had severe chronic obstructive airways disease and died of respiratory failure. In case 7 necropsy showed death to have been due to fungal infection of the gastrointestinal tract, with no viable tumour present. Only in cases 4, 5, and 6, therefore, was death directly attributable to the dissemination of lymphoma.

Results

HISTOLOGICAL FINDINGS

The neoplastic component of the cutaneous infiltrate was morphologically similar in all cases, being composed of large cells with abundant eosinophilic, basophilic, or clear cytoplasm and central or eccentric, indented, convoluted or multilobulated nuclei with one or more prominent nucleoli (figs 2 and 3). Multinucleated cells were also present, and nuclei in some of these cells were arranged in a wreath-like fashion. Mitotic figures were conspicuous. There was a variable accompanying infiltrate of lymphocytes, eosinophils, plasma cells and histiocytes. Occasional Hodgkin and Reed-Sternberg-like cells were seen in a few cases.

The infiltrate tended to be cohesive, dense, and diffuse, being centred on the dermis and showing variable extension into the subcutaneous fat. Extension up to the dermoepidermal junction was present in two cases but there was no epidermotropism. Epidermal ulceration was present in biopsy specimens from three cases. In case 10 there was a vigorous fibroblastic proliferation within the lesion which produced a sarcomatoid appearance in places. Focal myxoid change was noted in two cases.

The small intestinal deposit in case 4 (fig 4) and the nodal deposits in cases 4-8 were morphologically similar to the skin infiltrate. There was paracortical or diffuse disease in the lymph nodes and full thickness infiltration of the small bowel wall in case 4. The intestinal mucosa overlying the tumour was ulcerated but the rest of the mucosa was normal and showed no evidence of villous atrophy.

We attempted to subclassify the cases into types I and II as proposed by Chan *et al*⁸; using their criteria, we found a clear distinction difficult to achieve but felt that all cases probably fell into the type II category.

Figure 3 Case 3: high power view of the neoplastic cells. Mononuclear, binucleate, and multinucleate cells with abundant cytoplasm are seen. Many cells have eccentrically placed nuclei.

Figure 5 Case 1: Ber-H2 positive neoplastic cells. Note the strong membrane and paranuclear positivity (arrow); * = epidermis.

Figure 4 Case 4: small intestinal disease as a result of Ki-1 ALCL.

IMMUNOHISTOCHEMICAL FINDINGS
The immunohistochemical findings are summarised in table 3; the results for recurrent skin lesions and for nodal and small intestinal deposits are combined unless otherwise indicated. In all cases most or all of the neoplastic cells were strongly positive with Ber-H2 (CD30), which shows the presence of the Ki-1 antigen. Staining was present both on the cell membrane and within the cytoplasm, and in some cases was particularly concentrated in a paranuclear location (fig 5).
Leucocyte common antigen (LCA) was present in skin lesions from nine of the 12 cases but was absent from nodal and small intestinal recurrences in cases 4, 6, and 7 and could not be shown in the initial or recurrent cutaneous lesions in cases 3, 8, and 10.

Table 3 Immunohistochemical results

Case No	Ber-H2 (CD30)	Leu-M1 ^a (CD15)	LCA ^b (CD45)	UCHL1 (CD45 RO)	MT1 (CD43)	CD3	L26	MB2 ^c	EMA	CAM 5-2	CK 1	α1 ACT ^d	Mac 387	KP 1 (CD68)	Vimentin	S100 protein	HMB 45
1	+	—	+	+	+	—	—	—	—	—	—	—	—	—	+	—	ND
2	+	—	+	—	+	—	—	—	+	—	—	—	—	—	+	—	ND
3	+	—	—	+	+	Weak	—	—	—	—	—	—	—	—	+	—	—
4*	+	—	+	—	—	Weak	—	—	—	—	—	—	—	—	+	—	ND
5	+	—	+	+	+	—	—	—	+	—	—	—	—	—	—	—	ND
6	+	—	+	—	—	—	—	+	—	—	—	+	—	—	+	—	ND
7*	+	—	+	—	+	—	—	+	—	—	—	—	—	—	+	—	ND
8	+	—	Focal	—	—	ND	—	—	—	—	—	—	—	—	+	—	ND
9	+	—	+	+	+	Weak	—	—	—	—	—	—	—	—	+	—	ND
10	+	—	—	—	Focal	Weak	—	—	—	—	—	+	—	—	—	—	ND
11	+	—	+	+	Focal	Weak	—	—	—	—	—	—	—	—	+	—	ND
12	+	—	+	+	+	ND	—	—	—	—	—	—	—	—	+	—	ND

^aPositive in recurrent skin lesions in case 3 and small intestinal disease in case 4.
^bNegative in nodal and intestinal disease in case 4, nodal recurrence in case 6 and node in case 7.
^cPositive in nodal and intestinal disease in case 4; node negative in case 7.
^dNegative in nodal recurrence in case 6.
*In cases 4 and 7 T cell markers were shown in frozen sections.
+ Positive; — negative; ND—not done.

Figure 6 Case 4: strong paranuclear Leu-M1 positivity in the intestinal recurrence.

Leu-M1 staining was absent from the initial skin lesions in all cases. In case 3 focal cytoplasmic positivity was noted in a recurrent skin deposit, but not in the initial biopsy specimen. Strong staining of the paranuclear cytoplasm was present in most of the neoplastic cells in the small intestinal recurrence of case 4 (fig 6).

Staining for T cell markers on paraffin wax sections showed both UCHL1 and MT1 positivity in six cases, three of which were also weakly positive for CD3. Case 4 was also CD3 positive. Three cases showed only MT1 positivity. Staining was absent in paraffin wax-embedded tissue from cases 6 and 8. Immunostains done on fresh frozen material from case 4 were consistent with T cell lymphoma of helper subtype (CD2, CD3, and CD4 positive). In case 7 frozen sections were CD3 negative, but positive for CD2 and CD4.

The pan-B marker L26 could not be detected in any biopsy specimen. MB2, a pan-B marker, which may stain a proportion of T cell lymphomas, was present in cases 6 and 7 and in nodal and gut recurrences in case 4. As indicated above in cases 4 and 7 the frozen section immunostains established a T lineage. In case 6 the neoplastic cells were negative for T cell markers and also for the light chains.

A further notable feature was strong paranuclear positivity for vimentin in 10 cases. Electron microscopical examination of one of the cases confirmed the presence of abundant intermediate filaments in this location.

$\alpha 1$ ACT was shown in two cases but the histiocyte markers Mac 387 and KPI were negative in all specimens. Only two cases were positive for epithelial membrane antigen (EMA).

Discussion

Most reported Ki-1 ALCL have been cases which presented with nodal disease, but skin

disease is not uncommon and figures culled from the major published series on Ki-1 ALCL show that associated skin disease occurs in about 15% of cases.^{3-7,18} It is this aspect which we emphasise in this report. It is not our purpose to review the subject of Ki-1 ALCL in general as this is well covered by other publications.^{3-6,10,13} It is worth noting that the wide age range of our patients (27–73 years) is similar to that reported by Kaudewitz *et al*,¹⁴ although others have emphasised a high incidence in children.^{7,11} As in other studies,^{7,8,10,13} our patients are predominantly male.

The anaplastic histological appearance of these lymphomas led to a wide range of initial pathological diagnoses, including Hodgkin's disease, metastatic carcinoma, malignant melanoma, malignant fibrous histiocytoma and an "unusual reactive process." This has also been the experience of others who also include lymphomatoid papulosis, RAH, and malignant histiocytosis among the diagnoses encountered.^{7,8}

Once they become familiar, the histological appearances of Ki-1 ALCL are rather characteristic but they require immunohistochemical confirmation. This can be achieved by using commercially available antibodies on formalin fixed, paraffin wax embedded tissue. The strong membrane and paranuclear Ber-H2 positivity in most of the neoplastic cells is the most important diagnostic feature. The presence of LCA positivity in most of our cases excludes the possibility of a metastatic carcinoma or malignant melanoma, although a proportion of Ki-1 ALCL may be LCA negative.^{6,8,9,13,20} Absence of cytokeratins is further evidence against a diagnosis of metastatic carcinoma. In this context it is worth noting that embryonal carcinomas and some pancreatic carcinomas show strong Ber-H2 staining,^{4,37} but these would probably be positive for cytokeratins. Many Ki-1 ALCL express EMA which may be another source of confusion.^{6-9,20} In our series only two cases exhibited EMA positivity.

S100 protein, the presence of which can usually be shown in malignant melanomas, was absent in all our cases. Cases 3 and 6, in which the possibility of melanoma was initially suggested, were stained for a melanoma specific marker HMB 45³⁶ but both yielded negative results. The failure to show S100 protein also precludes a diagnosis of Langerhans' cell histiocytosis which may conceivably be confused with Ki-1 ALCL on morphological grounds.

Reed-Sternberg and Hodgkin cells are also Ber-H2 positive but skin disease is exceedingly rare in Hodgkin's disease, particularly as a presenting clinical feature.^{22,38} Histological features which are useful for differentiating Ki-1 ALCL from Hodgkin's disease are dense concentration of neoplastic cells, their cohesive nature, and sparsity of typical Hodgkin or Reed-Sternberg cells in the former condition. Moreover, Reed-Sternberg cells are rarely LCA positive.^{20,28}

True histiocytic lymphomas, which may affect skin, can occasionally be Ki-1 positive,

but are also positive for histiocyte markers KP1 (CD68) and Mac 387 which are not found in Ki-1 ALCL.^{39,40}

Most reported cases of Ki-1 ALCL are of T lineage^{3,5-18}; this is substantiated in the present series and provides useful additional diagnostic information. The specific T cell marker CD3 may be absent or only weakly expressed, however, as in this and other series,^{9,14} and should not be relied on for evidence of T lineage in these tumours.

Both lymphomatoid papulosis and RAH²¹⁻²⁶ present with cutaneous nodules which regress and recur. Although they were originally regarded as benign it is now recognised that they can progress to frank lymphoma. They show morphological similarities to Ki-1 ALCL^{7,8,14} and have been shown to be of T lineage and to be monoclonal.^{26,41,42} Lymphomatoid papulosis is also Ki-1 positive.⁴¹

Our cases 1, 2, 3, 8, 9, 11, and 12, with their apparently benign course, might be regarded as examples of lymphomatoid papulosis or RAH, but we could find no morphological or phenotypic differences between them and the cases which spread systemically. We share the view of Chan *et al*⁸ and Kaudewitz *et al*¹⁴ that RAH, lymphomatoid papulosis, and cutaneous Ki-1 ALCL are the same disease under different names.

Seven of our patients gave a history of pre- or coexisting chronic skin disease. In three this was described as eczema or ichthyosis, only one of them was biopsied and the histology was of chronic dermatitis. In the other four patients the diagnosis of mycosis fungoides was confirmed by biopsy; staining for Ki-1 antigen with Ber-H2 was negative in all these biopsy specimens. The clinical importance of the association with eczema or ichthyosis is uncertain, but the relation of Ki-1 ALCL with mycosis fungoides has been previously recorded^{6,14,43} and has been referred to as secondary Ki-1 lymphoma.¹⁴ It has been suggested that such transformed cases behave aggressively with rapid systemic progression,^{14,43} but our experience is different; two of our four cases were alive without dissemination at 87 and 174 months, respectively, one dying at 60 months with disseminated disease and one dying of unrelated disease six months after presentation.

It is also worth noting that there is a reported association between lymphomatoid papulosis and mycosis fungoides,^{22,23} lending some support to the view expressed above that lymphomatoid papulosis and Ki-1 ALCL are the same disease.

Despite their alarming histological appearances cutaneous Ki-1 ALCL usually have a relatively good prognosis.^{8,14,15,18} Of our 12 cases, seven remained localised to the skin, one showed prolonged survival despite spread to lymph nodes and intestine, and seven were alive from 12 to 174 months after diagnosis confirmed by biopsy. In only three patients was death directly attributable to the neoplastic process, and in one of these (case 5) appropriate treatment was delayed because the skin lesion was clinically misdiagnosed as inflammatory.

In the series of Chan *et al* all five cutaneous cases were alive at one to three years after presentation.⁸ These authors suggested that Ki-1 ALCL could be divided into two histological subtypes and that type I was more aggressive than type II. We have found this subtyping difficult to achieve but tentatively regard all our cases as type II.

In conclusion, we emphasise that the accurate recognition of these tumours is important because of their relatively good prognosis and that the diagnosis can be substantiated immunohistochemically using a simple panel of antibodies reactive in formalin fixed, paraffin wax embedded tissues.

We thank Mrs L Garstang for typing the manuscript. We are grateful to Dr H Ali of Huddersfield Royal Infirmary, Dr S Banik of Blackburn Royal Infirmary, and Dr L J McWilliam of Withington Hospital, Manchester, for providing clinical information and pathological material in three of our cases.

We also thank Mr D Edmondson and Mr K J Elsam for technical assistance.

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