HHS Public Access

Author manuscript

Pathology. Author manuscript; available in PMC 2016 September 29.

Published in final edited form as:

Pathology. 2014 December ; 46(7): 610–616. doi:10.1097/PAT.0000000000000166.

Mycosis fungoides with large cell transformation: clinicopathological features and prognostic factors

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Summary

Large cell transformation of mycosis fungoides (MF-LCT) occurs in 20–50% of advanced MF, and is generally associated with poor prognosis, although some patients have indolent disease. We sought to identify clinicopathological prognostic factors in a large number of patients with MF-LCT. We identified patients with MF-LCT treated between 1991 and 2012 at a referral centre for cutaneous lymphoma. Clinical and pathological records, and histopathological slides were reviewed. Associations of clinicopathological variables with disease-specific survival were analysed. In 51 patients with MF-LCT, factors significantly associated with shorter survival were: age >60 years (25 versus 61 months, $p = 0.01$), stage III/IV (25 versus 44 months, $p = 0.049$), high serum lactate dehydrogenase (LDH; 24 versus 53 months, $p = 0.007$), absent papillary dermal involvement (8 versus 30 months, $p = 0.008$); follicular mucin at transformation (24 versus 42 months, $p = 0.007$); and the absence of fibrosis at transformation (21 versus 42 months, $p = 0.03$). Patients presenting with transformation at diagnosis had better survival than those who started with a small cell phenotype ($p = 0.02$). Age >60 years was independently associated with poorer survival (HR 5.61, 95%CI 1.17–26.8, $p = 0.03$), and the presence of fibrosis at transformation was independently associated with improved survival (HR 0.30, 95%CI 0.09–0.97, $p = 0.045$). In patients with MF-LCT, clinical features (age, stage, serum LDH) are important in assessing prognosis. Additional clinical and pathological features identified in this study may also assist in prognostic stratification. Studies of larger cohorts should be performed to validate the prognostic significance of these features.

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Conflicts of interest and sources of funding: The authors state that there are no conflicts of interest to disclose.

Keywords

Cutaneous T-cell lymphoma; large cell transformation; mycosis fungoides; pathology; prognosis; skin; tumour

Introduction

Large cell transformation (LCT) in mycosis fungoides (MF) is the histopathological transformation of neoplastic small lymphocytes to a clonally identical[1,2] large cell phenotype, which may occur in 20–55% of advanced MF cases.[3,4] Less commonly, patch or plaque stage MF may exhibit large cell morphology *de novo*.[3,5,6] LCT is often a histological marker of poor prognosis, and is associated with mean 5-year survival of less than 20%.[3] However, some patients with well-documented LCT have indolent disease with long-term survival.[7–10] Given the clinical heterogeneity amongst MF patients who exhibit LCT, it is important to seek additional means of accurately identifying patients who will have an aggressive clinical course, in order to optimise therapeutic strategies.

Features that have been previously shown to predict outcome in patients with transformed MF include advanced stage at transformation,[3,5,8–11] increased extent of skin lesions, folliculotropism and CD30 expression.[10,12] In this study, we investigated a large set of clinical, histopathological, immunophenotypical and molecular parameters in an attempt to identify features with prognostic utility in MF patients with LCT.

Materials and Methods

Patient selection

This retrospective study was conducted with the approval of the Institutional Review Board at Memorial Sloan Kettering Cancer Center (MSKCC). Patients with primary cutaneous T-cell lymphoma with LCT diagnosed between 1991 and 2012 were identified from the MSKCC pathology archive. The database was queried using the following Boolean search parameters: free text including ‘large cell transformation’, ‘large cells’, or ‘progression’ were required, with a diagnosis of ‘mycosis fungoides’ or ‘cutaneous T-cell lymphoma’, or the names of clinicians PM or SH, identifying potential cases. Histological review was performed by a dermatopathologist with expertise in cutaneous lymphoma to confirm cutaneous T-cell lymphoma with features of LCT using the criteria of >25% large cells (>4× the size of a small lymphocyte). Cases in which the key slides showing transformation were not available for review were excluded from the study. Cases which met the above criteria were further clinically confirmed as MF, via detailed chart review and clinical reassessment as well as with integration of immunohistochemical and molecular data in consensus with two clinical cutaneous lymphoma experts (in dermatology and haematology). Staging was performed using the criteria proposed by the ISCL (International Society for Cutaneous Lymphoma)/EORTC (European Organization for Research and Treatment of Cancer).[13]

Clinical and pathological data

Patient charts, clinical images, defining histopathology slides, and molecular data were reviewed. All additional biopsies from the selected patients were reviewed when available, and pathological reports were reviewed when slides were no longer accessible.

Clinical features assessed (Table 1) were: patient age; gender; race/ethnicity; dates and clinical stage (per TNMB classification) at first sign, first diagnosis, first presentation at our institution, first tumour, and first histological documentation of LCT; dates of death/last follow up; patient status; number of skin sites biopsied; number of extracutaneous sites biopsied for lymphoma evaluation; sites of extracutaneous disease; serum lactate dehydrogenase (LDH) and absolute eosinophils prior to and at LCT; evidence of clonal T-cell gene rearrangements in blood and/or tissue samples (including comparison of clones in individual patients where multiple results were available); and medication/treatment history specific to cutaneous T-cell lymphoma (CTCL) and response to therapies.

The following pathological features were documented (Table 1): dates and sites of all reviewed biopsies; presence or absence of LCT; % large cells of atypical lymphocytes; density, characterised as mild, moderate or high number of cells per high power field; specific site involvement of infiltrate; presence/absence of fibrosis; ulceration; epidermotropism; spongiosis; epidermal hyperplasia; eosinophils; neutrophils; follicular mucin; folliculotropism; and Langerhans cell hyperplasia. Histopathological stage (tumour versus plaque versus patch) was noted. Mitotic rate and eosinophil number were quantified per 5 high power fields (HPF). Partial immunohistochemical data were available for 47 patients. Immunohistochemical stains assessed included CD3 (40 patients/90 cases); CD4 (41 patients/98 cases); CD7 (29 patients/58 cases); CD8 (40 patients/96 cases); CD4:CD8 ratio (39 patients/87 cases); CD30 (38 patients/105 cases); CD56 (19 patients/26 cases) and Ki-67 (15 patients/26 cases). CD30 localisation (primarily dermis versus epidermis), percent of entire infiltrate, and cell number/5 HPF was assessed in available cases.

Statistical analysis

Analyses were carried out using IBM SPSS Statistics 20 software (IBM Corporation, USA). Associations of clinical and pathological variables with disease-specific survival (DSS) were assessed by the Kaplan–Meier method (differences between survival functions for different strata were assessed with Mantel–Cox log rank tests). DSS was defined as the interval between diagnosis of first LCT and death from CTCL. Patients with no events during follow-up (e.g., no death) were censored. p values of <0.05 were considered to be statistically significant.

Multivariate Cox proportional hazards models including variables that were statistically significant in univariate analyses were explored. Inclusion of some variables (each of which had ≤5 patients in one level) resulted in unstable multivariate models; therefore, they were excluded from the final multivariate model (along with other variables that were closely correlated with one another).

Results

Clinical features

Fifty-one patients (24 females, 27 males) were identified with confirmed LCT (Table 2). The mean age of LCT was 63 (range 25–102) years. LCT occurred prior to cutaneous tumour development ($n = 9$), concurrently with or following cutaneous tumour development ($n = 30$), or extracutaneously without eventual cutaneous tumour development ($n = 12$). At the time of data analysis, 27 patients had died (22 confirmed to have died of disease), and 24 were alive. Most of the patients who died of disease were advanced stage (IIB–IVB) and most (15/27) also had tumours. No patient with early stage disease (IA–IIA) died. Three of the 12 patients without skin tumours at the time of LCT died; they included a 90-year-old woman with lung involvement (stage IVB), a 75-year-old woman with a second (B-cell) nodal lymphoma as well as stage IVA2 (N3) involvement by her cutaneous T-cell lymphoma, and a 56-year-old male with stage IVA2 (N3) MF. Of the remaining nine patients without skin tumours at the time of LCT, seven had patch/plaque disease (one was N1, none of the remaining six had documented nodal disease), and two did not have evidence of skin disease, but had nodal (N2, 1 patient) and blood (IVA1, 1 patient) involvement. The last two patients had had skin disease previously, which was in remission at the time of transformation.

Pathological features

From the patients with confirmed LCT, 317 biopsies were taken, of which 251 had slides available for review. Patients had an average of four documented skin biopsies performed for evaluation of lymphoma (range 1–13), and an average of 1.4 (0–6) non-skin biopsies for lymphoma which included the lymph nodes, bone marrow, parotid gland, lung, tonsil and bladder. The average number of skin biopsies reviewed per patient for the study was 3.6 (0–13).

Thirty-seven patients had biopsies showing both non-transformed and transformed MF within skin and extracutaneous sites. We largely limited our analysis to biopsies showing large cell transformation, and selected the most infiltrated lesions for review. However, certain features, such as follicular involvement or subcutaneous involvement were recorded if present in *any* biopsy showing such findings, under the term ‘ever’ (Table 2).

Most patients had moderate to high density infiltrates of atypical lymphocytes and, in many, the density increased after transformation. All 51 patients had >25% of large lymphocytes within the infiltrates. Of 42 patients who showed transformation in the skin, the percentage of large cells in the infiltrates at LCT varied: 15 of 42 patients had 100% large cells (Fig. 1A), while 27 of 42 patients had 25–75% large cells. Thirty-four of 50 patients in whom this variable was evaluable developed tumours as their thickest pathological stage, and in 24 of 42 patients, LCT occurred within tumour-stage MF. Sixteen patients maintained patch/plaque stage MF. Folliculotropism (Fig. 1B), fibrosis (Fig. 1C), vascular prominence, Pautrier microabscesses, neutrophils, eccrinotropism and epidermotropism were commonly found in at least one of the patients' biopsies, although they were less prevalent in transformation biopsies than in other biopsies (Table 2). Fifty percent of biopsies had >3

mitoses per HPF at transformation, while 50% had fewer than 3 mitoses per HPF at transformation.

Associations of clinicopathological variables with survival

Clinical variables in patients who underwent transformation that showed statistically significant associations with shorter median survival were: age >60 years at transformation (25 versus 61 months, $p = 0.01$; Fig. 2A); stage II or greater at transformation (25 versus 44 months, $p = 0.049$); and elevated serum LDH at transformation (24 versus 53 months, $p = 0.007$; Fig. 2B) (Table 3).

Pathological variables correlating with shorter survival were: absent papillary dermal involvement (8 versus 30 months, $p = 0.008$); presence of subcutaneous involvement at transformation (19 versus 44 months, $p = 0.04$); follicular mucin at transformation (24 versus 42 months, $p = 0.007$; Fig. 2C); the absence of epidermal hyperplasia ever (4 versus 39 months, $p < 0.001$); and the absence of fibrosis at transformation (21 versus 42 months, $p = 0.03$; Fig. 2D). Predominance of CD30 in the epidermis rather than dermis was associated with poorer survival (11 versus 42 months, $p = 0.02$).

In a multivariate model including age, stage, serum LDH and fibrosis at transformation, age >60 was independently associated with poorer survival (HR 5.61, 95%CI 1.17–26.8, $p = 0.03$), and the presence of fibrosis was independently associated with improved survival (HR 0.30, 95%CI 0.09–0.97, $p = 0.0045$).

Discussion

Mycosis fungoides is the most common variant of primary CTCL, defined as an uncontrolled proliferation of mature, skin-homing cutaneous T-lymphocyte antigen (CTLA)-expressing, CD4+, CD45RO+ helper T-cells. While rare overall, with a yearly incidence in the US of approximately 2000, MF comprises more than 70% of all primary cutaneous lymphomas, approximately 2% of all lymphomas, and is thought to affect at least 30,000 people in the US alone, at any given time.[14]

MF usually behaves as an indolent lymphoma, but patients with tumour stage (T3) disease exhibit 5-year survival as low as 45%[15] and median survival of 35 months.[8,9] Prognosis in MF is typically stratified by stage, which is based on extent of body surface area involvement, type of skin lesions, or presence of extracutaneous involvement. In particular, patients with LCT have been noted to have a generally short median survival of 19–36 months.[8,9] In our cohort, the mean age of death was found to be 67.4 years (range 31–90). This represents a loss of 10 years from the average life expectancy for a male in the US in 2009 (average life expectancy 75.5, versus 64.9 years in our cohort), and a loss of 9 years for a woman in the US in 2009 (average life expectancy 80.5 versus 71 years in our cohort).

The idea that LCT signified worsening disease was initially, in part, inferred from similar findings in systemic B-cell lymphoma[16] and was sustained by the idea that the large lymphocytes were the histological expression of a transition to an independent malignant lymphoma.[17] The definition of LCT has evolved over time: at one point, LCT implied a

change in classification of a CTCL to a subtype of large cell lymphoma;[4] subsequently, the term was defined as requiring >50% large cells[18] or a 'predominance' of large cells;[19] the current minimum criteria for LCT include the presence of >25% large cells or the presence of microscopic aggregates of large cells.[3,18]

Recent studies have questioned the assertion that LCT is an independent prognostic variable in patients with MF. No difference in survival was noted in three studies of patients with tumour stage (IIB) LCT.[7,10,19] Furthermore, the overall median survival of patients with LCT was found to be 99–100 months.[7,10] Regardless, it is clear that there is a poorly defined subset of patients with LCT who have adverse outcomes. Our goal in this study was to attempt to identify potential prognostic factors within the group of patients who have LCT.

In our analysis of 51 MF patients with LCT, we found that potential markers of tumour burden, namely, stage at either first sign of disease or at transformation, site of first transformation in lymph nodes (versus skin), and serum LDH>220 were significantly associated with survival. These findings validate previous studies. Salhany *et al.*, Diamandidou *et al.* and Greer *et al.* found significant differences in survival between patients with stage I-IIA versus IIB (T3) disease.[3,5,9] More recently, Benner *et al.* found a significant difference between IIB (T3) versus IV (extracutaneous disease), but not between stages IB versus IIB.[10] While our patients with extracutaneous transformation (particularly in the lymph nodes) had a significantly poorer survival (21 versus 39 months, $p < 0.001$), we also saw a trend ($p = 0.06$) towards poorer survival for patients with stage II versus stage I disease at transformation.

Our finding that follicular mucin at transformation correlated with adverse outcomes (24 versus 42 month survival, $p = 0.007$) is novel. As folliculotropism was previously found to be associated with poorer survival[7,10] and higher risk of disease progression,[7] and non-transformed folliculotropic MF is known to have a poorer survival than non-folliculotropic MF, this finding may warrant further examination. While folliculotropism did not correlate significantly with survival in our group, there was a trend to this effect. Interestingly, we found follicular mucin in five of 36 patients at the time of transformation. In a study of all stage MF, Van Doorn *et al.* found 10.4% of patients to show follicular mucinosis at the time of diagnosis. In this group, follicular mucinosis was independendly associated with MF-related mortality.[20]

The expression of CD30 (Ki-1), a marker of lymphocyte activation, in some cases of MF-LCT suggests a shift to an activating phenotype. We found a statistically significant correlation between poorer survival and predominant CD30 localisation in the epidermis rather than dermis (11 versus 42 months, $p = 0.02$). This seems to align with most previous studies which showed that overall CD30 expression in LCT is associated with a better prognosis.[6,9,10,21] Conversely, one study of non-transformed MF showed that increased dermal CD30 correlated with a shorter survival. However, in that study, stage was not included in the analysis,[12] and CD30 proportion did not correlate with Ki-67, which also related to survival.

Pathological features including lack of papillary dermal involvement, and subcutaneous involvement at LCT as well as lack of epidermal hyperplasia could be surrogates for pathological tumour stage, which although not significant on overall analysis, was significantly associated with survival in our analysis of 'chronic' versus 'dead of disease' cases. Other apparently significant prognostic features such as age at either first sign, diagnosis or transformation may reflect vulnerability due to increasing senescence of the immune system with advancing age.[22,23] Fibrosis at transformation, epidermal hyperplasia, and ulceration could also be related to T-cell subset and cytokine milieu, and may be surrogates for evidence of long-standing disease (fibrosis, hyperplasia) versus rapidly evolving disease (atrophic epidermis, ulceration).

In our patients, differences in mitotic rate (analysed as a continuous variable, or in a binary fashion comparing >3/5 HPF to <3/5 HPF) only trended towards significance; however, this trend is in keeping with a previous report of Ki-67 association with worse outcome in non-transformed MF,[12] although others have shown that in MF, Ki-67 seems to correlate with stage.[24,25] Mitotic rate in Sezary syndrome (CTCL) has been shown to be generally low.[26]

As with previous reports,[10] we did not find a statistically significant association of percent large cells within tumour tissues and outcomes. However, we did notice a trend toward significance of % of large cells with outcomes, when we looked at this as both a continuous or binary variable (25–50% versus 75–100%). It is difficult, in the absence of multivariate analysis, to interpret the significance of this trend, particularly without controlling for stage.

It has been noted that limitations in studies of potential prognostic features of transformed MF in the past have included small size (median sample: 22 patients),[10] and lack of discrimination of Sezary syndrome and stage distinctions, preventing adequate power or capability for multivariate analysis. These are also often performed at large referral centres, which may result in lead-time bias.[10] Furthermore, many such studies[3,4,8,19,27] report large percentages of tumour stage MF, hovering around 50%, which could bias findings. In multivariate analysis, we found that age >60 years and absence of fibrosis at transformation were independently associated with poorer survival. However, these findings must be tempered by the limitations of our multivariate model, namely: (1) small numbers of patients in the arms of some variables which, when included, resulted in unstable multivariate models; and (2) differences in sample type and size of patient biopsies, some of which did not always capture features of interest, resulting in missing datapoints and the prohibitive exclusion of a majority of cases from the multivariate models. Studies of larger datasets with complete datapoints are required to validate our findings.

Overall, our results indicate that there are associations of poorer outcomes with specific histopathological features in transformed MF. One feature not previously shown to be significant in transformed MF is the presence of follicular mucin at transformation. Other features include high tumour cell density, subcutaneous involvement, and CD30 epidermal versus dermal predominance. Longer survival was associated with the presence of epidermal hyperplasia ever, and dermal fibrosis at transformation. We confirm the findings of others, that a clinically advanced stage at transformation, and older age and higher stage at transformation, and a serum LDH >220 U/L appear to correlate with shorter survival.

Further studies involving larger patient cohorts with multivariate analysis should help to better evaluate the prognostic utility of individual features in clinical practice.

Acknowledgments

We are grateful to Drs Klaus Busam and Ahmet Dogan for editorial suggestions and support.

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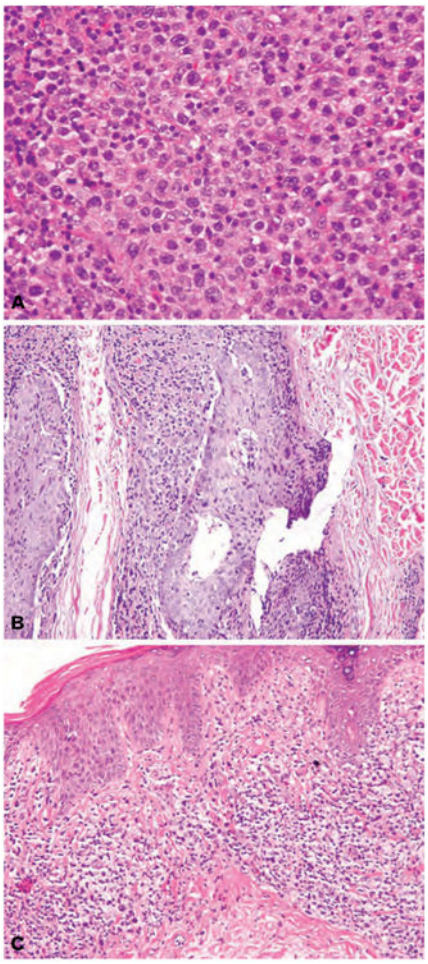

Fig. 1.

(A) H&E stain. Diffuse dermal infiltrate comprised of 100% large cells (>4× the size of a normal lymphocyte). (B) H&E stain. Hair follicles with folliculotropic infiltrate of small and large lymphocytes, at least 25% of which show large cell transformation, associated with intra-epithelial mucin deposition (follicular mucin). (C) H&E stain. Bandlike (lichenoid) infiltrate of small and large atypical lymphocytes associated with fibrotic, eosinophilic collagen bundles characteristic of chronic disease.

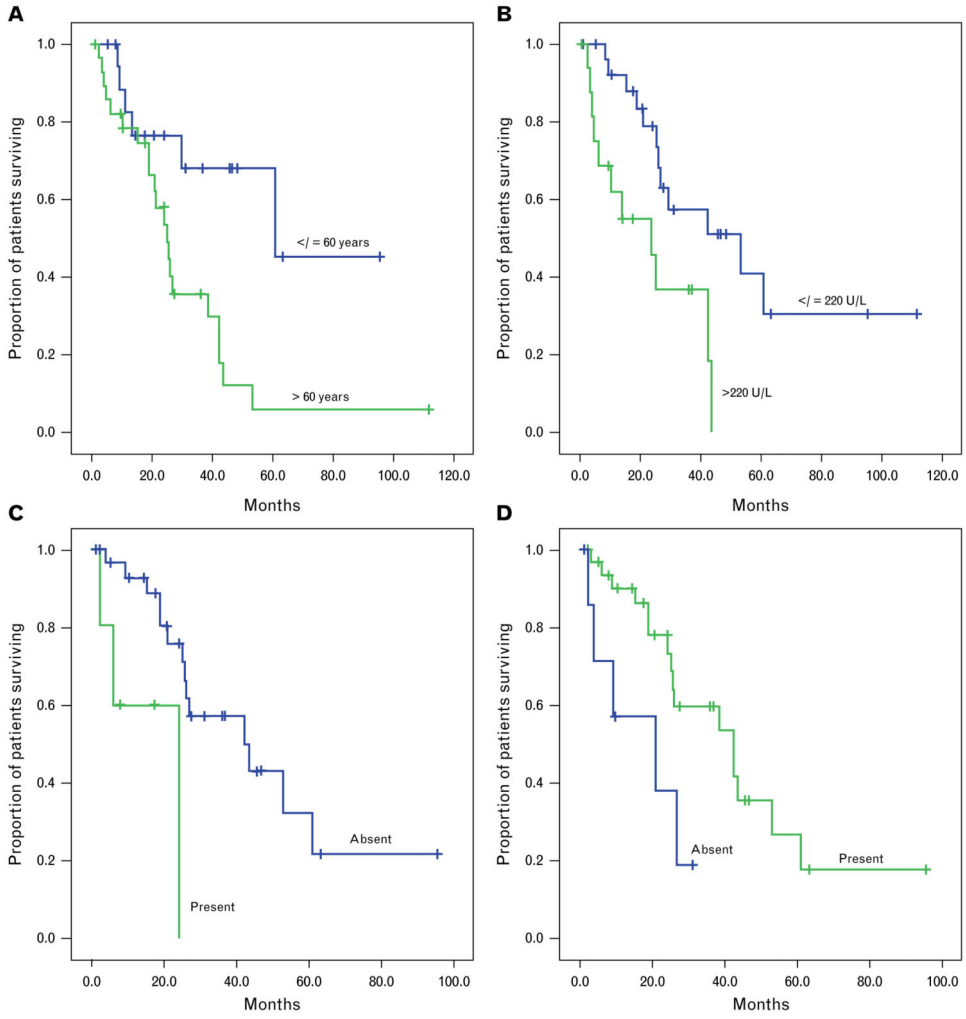

Fig. 2.

Kaplan–Meier curves showing associations of selected clinicopathological variables with disease-specific survival from the date of transformation. (A) Age at transformation (p = 0.01). (B) Serum LDH level at transformation (p = 0.007). (C) Follicular mucin at transformation (p = 0.007). (D) Fibrosis at transformation (p = 0.03).

Table 1
Clinical, histological and immunohistochemical features assessed in patients with LCT

Clinical
Age
Sex
Race/ethnicity
Age/stage at first histological documentation of LCT
Age of death/last follow-up
Number and sites of skin and extracutaneous tissue biopsied for lymphoma
Serum LDH prior to and at LCT
Absolute and percent eosinophils prior to and at LCT
Medication history (no., type, and response to therapy)
Histological
Presence or absence of LCT defined as lymphocytes >4× the size of ‘normal’ lymphocytes comprising ≥25% of the entire atypical infiltrate
% of all atypical lymphocytes showing large cell morphology
Density of infiltrate: estimated number of cells per HPF, assessed as low, moderate, or high
Location of infiltrate: specific involvement of epidermis, papillary dermis, reticular dermis, subcutis, follicular epithelium, or sweat gland epithelium
Presence/absence of fibrosis: defined by thickened or wiry collagen bundles in dermis
Presence/absence of ulceration: defined by full-thickness erosion of epidermis, including basement membrane
Epidermotropism: presence of atypical lymphocytes extending into the epidermis, out of proportion to any visible spongiosis
Pautrier microabscesses: aggregates of at least 3 atypical lymphocytes in the epidermis, sometimes visibly associated with Langerhans cells, in the absence of the vase-like shapes more typically seen in spongiotic dermatitis
Spongiosis: visible intercellular oedema
Epidermal hyperplasia: acanthosis/widening of epidermis beyond that expected for the specified region of the skin
Eosinophils: quantified by light microscopy, per 5 HPF
Neutrophils: present or absent
Langerhans cell hyperplasia: present or absent within the epidermis on H&E stain
Follicular mucin: intercellular mucin in follicular epithelium, seen on H&E stain, with or without ‘lake-like’ collections
Folliculotropism: presence of atypical lymphocytes extending into the follicular epithelium, out of proportion to spongiosis
Histopathological stage: tumour vs plaque vs patch (as previously described)
Mitotic rate: number of atypical lymphocytes observed to be in mitosis per 5 HPF
Immunohistochemical
CD3
CD4
CD8
CD7
CD4:CD8
% CD30 of total infiltrate
Absolute CD30/5 HPF
Dermal vs epidermal predominance of CD30

% Ki-67

HPF, high power field; LCT, large cell transformation; LDH, lactate dehydrogenase.

Table 2
Summary of relevant clinical and pathological features of patients with LCT

Parameter	Mean, years (range)	
Age at onset of symptoms	56 (15–99)	
Age at biopsy-confirmed diagnosis of MF	60 (22–99)	
Age at development of tumour-stage MF	64 (22–102)	
Age at LCT of MF	63 (25–102)	
Parameter	*n*/Total	%
Sex		
Female	24	47
Male	27	53
Race		
Causasian	44	88
Black	3	6
Asian	3	6
Number of patients who developed tumour stage disease in skin	39/51	76
Number of patients DOD	24/51	47
Thickest stage = tumour		
Ever	34/50	68
At LCT	24/42	57
Involvement of subcutis		
Ever	17/47	36
At LCT	11/37	30
Ulceration		
Ever	17/50	34
Folliculotropism		
Ever	35/47	74
At LCT	25/36	69
Follicular mucin	11/47	23
At LCT		
Eccrinotropism		
Ever	15/49	31
At LCT	8/40	20
% large cells in skin at diagnosis of LCT		
100%	15/42	36
25–75%	27/42	64
Fibrosis		
Ever	46/50	92
At LCT	33/41	80
Vascular prominence		
Ever	48/50	96

Parameter	Mean, years (range)	
At LCT	34/41	83
Epidermal hyperplasia		
Ever	47/50	94
Epidermotropism		
Ever	45/50	90
At LCT	34/40	85
Pautrier microabscesses		
Ever	37/50	74
At LCT	27/41	66
Neutrophils		
Ever	19/50	38
At LCT	10/41	24

DOD, dead of disease; Ever, at any time during follow-up period; LCT, large cell transformation; MF, mycosis fungoides.

Table 3

Statistically significant associations of clinical and pathological variables with disease-specific survival from first transformation

		Univariate analysis*		Multivariate analysis†	
Variable/Level	***n***	**Median survival (months)**	***P* value**	**HR (95%CI)**	***p* value**
Age at transformation					
≤60 years	19	61	0.01	1.00 (ref)	
>60 years	32	25		5.61 (1.17–26.8)	0.03
Stage at transformation					
I	11	44	0.049	1.00 (ref)	
II-IV	40	25		2.56 (0.56–11.78)	0.23
Serum LDH at transformation					
Normal (≤220)	27	53	0.007	1.00 (ref)	
Elevated (>220)	17	24		1.96 (0.70–5.50)	0.20
Cell density in skin biopsy at transformation‡					
Low	4	26	0.02		
Moderate	22	42			
High	16	24			
Follicular mucin at transformation‡					
No	31	42	0.007		
Yes	5	24			
Fibrosis at transformation					
No	8	21	0.03	1.00 (ref)	
Yes	33	42		0.30 (0.09–0.97)	0.045
Site of predominant CD30 staining of neoplastic lymphocytes‡					
Epidermal	4	11	0.02		
Dermal	34	42			

Clinicopathological variables that did not show statistically significant associations with survival are not shown.

*Median survival and *p* values (from Mantel–Cox log rank test of survival distributions) estimated using the Kaplan–Meier method.

†Hazard ratio (95% confidence intervals for hazard ratio) and *p* values derived from multivariate Cox proportional hazards models.

‡Inclusion of these variables (each of which had ≤5 patients in one level) resulted in unstable multivariate models. Therefore, they were excluded from the final multivariate model which is shown.