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Applicability and prognostic value of the new TNM classification system in 135 patients with primary cutaneous anaplastic large cell lymphoma

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ABSTRACT

Objectives: To test the applicability and prognostic value of the new TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome in patients with primary cutaneous anaplastic large cell lymphoma (C-ALCL) and to evaluate the prognostic significance of other clinical parameters, in particular the site of presentation.

Design: Retrospective cohort analysis.

Setting: Dutch Cutaneous Lymphoma Group database.

Patients: One hundred thirty-five patients with C-ALCL.

Main Outcome Measures: Clinical variables, including T category and site of presentation.

Results: Eighty patients (59.3%) presented with T1 disease, 37 (27.4%) with T2 disease and 18 (13.3%) with T3 disease. Median follow-up was 56 months (range, 11-288 months). Five-year disease-specific survival (DSS) was 93% for T1 disease, 93% for T2 disease, and 77% for T3 disease (P=.19). Patients with skin lesions on a leg had a reduced 5-year DSS compared with lesion on other sites (82% for leg vs 95% for head and neck, 96% for trunk, and 95% for arm; p=0.23). Patients with leg involvement (n=32) had significantly worse 5-year DSS than did patients without leg involvement (n=103; 76% vs 96%; P=.03 after adjustment for T-category).

Conclusions: The new TNM system can be applied well to patients with C-ALCL and may provide prognostic information, in particular, P when combined with site of presentation. Patients with T2 or T3 disease with skin lesions on the leg may have a reduced survival and require close surveillance during follow-up.

INTRODUCTION

Primary cutaneous anaplastic large cell lymphoma (C-ALCL) is a non-Hodgkin lymphoma of T-cell origin that presents in the skin without evidence of extracutaneous disease at the time of diagnosis. It is characterized by large cells with an anaplastic, pleomorphic or immunoblastic cytomorphology and expression of the CD30 antigen by more than 75% of the tumor cells.[1] Patients with C-ALCL show overlapping clinical, histological and immunophenotypical features with lymphomatoid papulosis (LyP) that together form a spectrum of disease, collectively designed as primary cutaneous CD30-positive lymphoproliferative disorders.[2] Distinction between C-ALCL and LyP is based on a combination of clinical, histological and immunophenotypical criteria.[3] C-ALCL is regarded as an indolent type of cutaneous T-cell lymphoma (CTCL), as illustrated by several large studies[3-5] showing 10-year disease-specific survival (DSS) of approximately 90% and 10-year overall survival (OS) of approximately 75%. Risk factors that predict an unfavorable course, occurring in few patients with C-ALCL, are largely unknown. However, several studies[3,6-8] have suggested that ages older than 60 years, absence of spontaneous remission, and presentation with multifocal skin lesions may correlate with reduced survival. Moreover, extensive single-limb involvement and localization on the head and neck have been associated with a less favorable prognosis.[4,9]

Recently, a new TNM classification system has been developed for primary cutaneous lymphomas other than mycosis fungoides (MF) and Sézary syndrome (SS). This classification system is primarily meant to document extent of disease in a consistent manner, facilitating comparison of studies at different institutes (Table 1).[10] Recent studies[11-13] have started to evaluate the clinical usefulness of this TNM system. Studies of large groups of cutaneous B-cell lymphomas confirmed its applicability and suggested that this system has prognostic significance in primary cutaneous diffuse large B-cell lymphomas, leg type, but not in primary cutaneous follicle centre lymphomas and primary cutaneous marginal zone lymphomas. However, studies in CTCL other than MF and SS, have not been published thus far.

The aim of the present study was to test the applicability and prognostic value of this TNM classification system for C-ALCL. In addition, the prognostic significance of other clinical parameters, in particular the site of presentation, was evaluated.

METHODS

Patients

Between January 1, 1986, and December 31, 2007, 155 patients with C-ALCL had been included in the database of the Dutch Cutaneous Lymphoma Group, and follow-up data were collected yearly for each patient. All of the cases were reviewed by an expert panel of dermatologists and hematopathologists before entry in this database. All of the cases met the criteria of the World Health Organization-European Organization for Research and Treatment of Cancer classification, and none of them had evidence of extracutaneous disease at the time of diagnosis.[1] Patients with a follow-up of less than 12 months, unless they died of their lymphoma (n=17), and patients with human immunodeficiency virus-associated (n=2) or posttransplantation (n=1) ALCL were excluded. Six patients with skin lesions suggesting C-ALCL but who developed

characteristic skin lesions of MF during follow-up were excluded because a diagnosis of transformed MF was considered more likely. The final study group contained 135 patients. Seventy-nine of these 135 patients were included in a previous study[3] that aimed to define guidelines for diagnosis, management and treatment for this group of cutaneous lymphomas. This study was approved by the Medical Ethical Committee of the Leiden University Medical Center, Leiden, the Netherlands.

Assessment of clinical variables (including T category)

In all of the patients, the following clinical parameters were scored retrospectively: sex, age at diagnosis, site of presentation, extent of disease at presentation, spontaneous remission of initial skin lesions, type and result of initial therapy, occurrence and site of relapse, disease-free survival after complete remission (in months), duration of follow-up (in months) and current status. Extent of disease was scored using the proposed TNM classification system for primary cutaneous lymphomas other than MF and SS (Table 1). Because patients with C-ALCL have, by definition, no extracutaneous disease (lymph node or visceral) at the time of diagnosis, only T categories were scored.

Statistical analysis

Statistical analysis was performed using SPSS 16.0 (SPSS Inc, Chicago, Illinois). Rates of DSS and OS were calculated from date of diagnosis until death from lymphoma and death from any

Table 1. Classification and description of the proposed TNM classification system for cutaneous lymphomas other than mycosis fungoides and Sézary syndrome[10]

Classification	Description
T1	Solitary skin involvement. T1a: Solitary lesion ≤ 5 cm in diameter T1b: Solitary lesion > 5 cm in diameter
T2	Regional involvement of skin: multiple lesions limited to 1 body region or 2 contiguous body regions. T2a: All-disease-encompassing in a ≤ 15 cm diameter circular area T2b: All-disease-encompassing in > 15 and ≤ 30 cm diameter circular area T2c: All-disease-encompassing in a > 30 cm diameter circular area
T3	Generalized skin involvement. T3a: Multiple lesions involving two noncontiguous body regions T3b: Multiple lesions involving ≥ 3 body regions
N0	No clinical or pathologic involvement of lymph node
N1	Involvement of one peripheral lymph node region that drains an area of current or prior skin involvement
N2	Involvement of ≥ 2 peripheral lymph node regions or involvement of any lymph node region that does not drain an area of current or prior skin involvement
N3	Involvement of central lymph nodes
M0	No evidence of extracutaneous non-lymph node disease
M1	Extracutaneous non-lymph node disease present

cause, respectively, or last follow-up without an event. Survival curves were estimated using the Kaplan-Meier technique, and comparison between curves was performed using the log-rank test. Prognostic factors were evaluated by means of univariate and multivariate analysis with OS and DSS as end points, and $P<0.05$ were considered significant. Clinical parameters included for univariate analysis were sex, age (≤ 60 vs. > 60 years), extent of disease (T category), site of presentation, and complete spontaneous remission of initial skin lesions. Multivariate analysis was performed using significant univariate variables from the Cox proportional hazards regression analysis.

RESULTS

Clinical characteristics at diagnosis, type of initial treatment and follow-up data are provided in Table 2. The study group included 97 males (71.9%) and 38 females (28.1%), with a median age at diagnosis of 61 years (range, 8-89 years). Using the TNM system, 80 patients initially had a solitary skin lesion (T1), 37 had regional skin lesions (T2), and only 18 had generalized skin lesions (T3). Representative examples are presented in Figure 1.

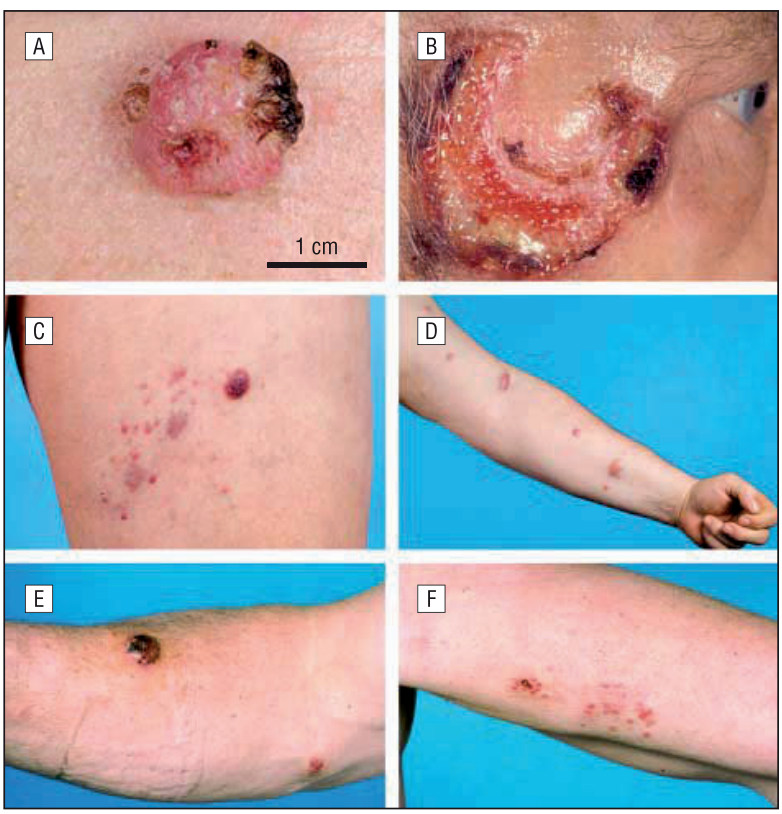

Figure 1. Examples of different T categories in patients with C-ALCL. Examples of different T categories in patients with C-ALCL: A, T1a; B, T1b; C, T2a; D T2b; E and F, T3b (skin lesions on trunk not shown).

Table 2. Clinical characteristics at diagnosis, type of initial treatment and follow-up data of 135 patients with C-ALCL

Variable		Value
Sex*	Male	97 (71.9)
	Female	38 (28.1)
Median age (range)		61 (8-89)
Extent of disease*	T1 (solitary skin lesion)	80 (59.3)
	T2 (regional skin lesions)	37 (27.4)
	T3 (generalized skin lesions)	18 (13.3)
Site of skin involvement*	Head/neck	42 (31.1)
	Trunk (incl. buttock)	32 (23.7)
	Arm	22 (16.3)
	Leg	21 (15.6)
	Generalized skin involvement	18 (13.3)
Spontaneous remission of initial skin lesions*		
	Absent	88 (65.2)
	Partial	23 (17.0)
	Complete	24 (17.8)
Initial therapy*	Radiotherapy	58 (43.0)
	Surgery	39 (28.9)
	None/topical steroids	24 (17.8)
	Multiagent chemotherapy	8 (5.9)
	Methotrexate	3 (2.2)
	PUVA	2 (1.5)
	Topical nitrogen mustard	1 (0.7)
Results initial therapy*	Complete remission	129 (95.5)
	Partial remission	2 (1.5)
	Progressive disease	4 (3.0)
Median disease free survival after initial therapy (range)		21 (1-182)
Occurrence and site of relapses*		
	None	62 (45.9)
	Skin only	53 (39.3)
	Extracutaneous disease	20 (14.8)
Median duration of follow-up (range)		56 (11-288)
Current status*	Alive without disease	95 (70.4)
	Alive with disease	9 (6.6)
	Death from lymphoma	12 (8.9)
	Death from other cause	19 (14.1)
Disease specific survival,%	5 y	91
	10 y	89
Overall survival,%	5 y	80
	10 y	71
Risk for extracutaneous disease,%		
	5 y	13
	10 y	24

PUVA: psoralen-UV-A; *Data are given as number (percentage)

Table 3. Distribution of different T categories in 135 patients with C-ALCL

T category	No. (%)	5-year DSS (%)	5-year OS (%)
T1	80 (59.3)	93	85
T1a	75 (55.6)	96	88
T1b	5 (3.7)	60	40
T2	37 (27.4)	93	81
T2a	24 (17.8)	96	86
T2b	8 (5.9)	100	86
T2c	5 (3.7)	80	60
T3	18 (13.3)	77	63
T3a	7 (5.2)	83	71
T3b	11 (8.1)	71	57

The distribution of the different T categories and the subgroups within these main T categories, and the corresponding 5-year DSS and OS rates are given in Table 3. Solitary or regional skin lesions at presentation (T1 and T2 disease) were localized on the head and neck in 42 patients (31.1%), on the trunk in 32 (23.7%), on a single arm in 22 (16.3%), and a single leg in 21 (15.6%). Eighteen patients had generalized skin lesions (T3 disease).

Initial therapy consisted of radiotherapy or excision in most patients (Table 2). Only 8 of 135 patients had been treated with multiagent systemic chemotherapy initially. Twenty-three of 24 patients with spontaneous remission had not received any treatment other than topical steroids in 6 of them because of complete spontaneous remission of the skin lesions. During follow-up, none of these 24 patients, including 4 cases initially presenting with multifocal skin lesions, showed the waxing and waning of skin lesions typical of LyP, thus confirming a diagnosis of C-ALCL.

During follow-up 53 of 135 patients (39.3%) developed 1 or multiple cutaneous relapses, while 20 of 135 (14.8%) patients developed extracutaneous disease, including 10 patients with involvement of only peripheral lymph nodes draining an area of current or previous skin involvement and 10 with more extensive nodal or visceral disease. The median duration for development of extracutaneous disease was 18 months (range 2 to 125 months). Development of extracutaneous disease in these 20 patients was not associated with progression to a higher T category. After a median follow-up of 56 months (range, 11-288 months), 95 patients were alive without disease, 9 were alive with disease, 12 patients died of lymphoma, and 19 patients died from unrelated causes. Ten-year DSS was 89% and 10-year OS was 71%.

Prognostic parameters

Univariate analysis showed that sex, age (≤ 60 vs. > 60 years), extent of disease (T category), site of presentation, and complete spontaneous remission of initial skin lesions were not significantly related to survival. Multivariate analysis was, therefore, not performed. Regarding extent of disease, 5-year DSS for patients with T1disease was 93%, with T2 disease was 93%, and with T3 disease was 77%, indicating that patients with T3 disease have a reduced, although

statistically nonsignificant, survival rate compared with patients with T1 or T2 (P=.19) (Table 3 and Figure 2). Analysis of survival in different subgroups of T categories showed a significantly reduced 5-year DSS for patients with T1b vs T1a disease (60% vs 96%, P<0.001), but the number of patients (n=5) with T1b disease does not allow firm conclusions to be drawn. Subgroups of T2 or T3 disease showed no significant differences in survival.

Analysis of site showed a trend toward reduced 5-year DSS in patients presenting with skin lesions on a leg (82% for leg vs 95% for head and neck, 96% for trunk, and 95% for arm; P=0.23) (Table 4). Thus, in contrast to previous studies,[9] skin lesions on the head or neck were not associated with a less favorable prognosis.

Further analysis showed that in patients with multifocal skin lesions (category T3), those with involvement of one (n=4) or both legs (n=7) had a 5-year DSS of 67% compared with 100% in

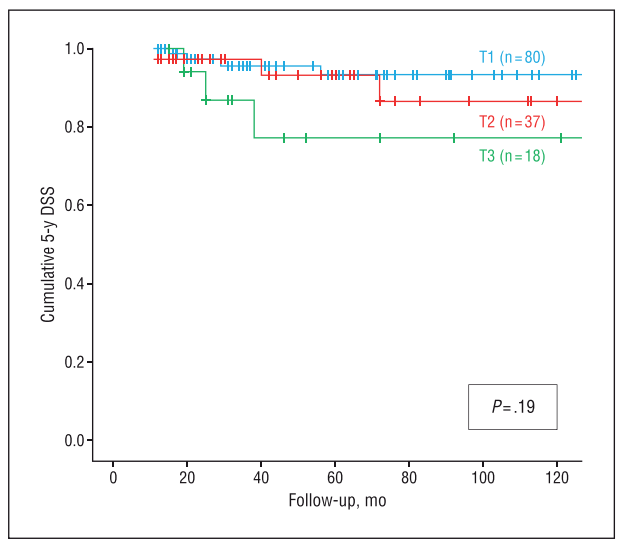

Figure 2. Five-year disease-specific survival (DSS) for the different T categories in patients with cutaneous anaplastic large cell lymphoma

Table 4. Different sites of skin involvement in 135 patients with C-ALCL

Site of skin involvement	No. (%)	5-yr DSS (%)	5-yr OS (%)
Head	42 (31.1)	95	87
Trunk	32 (23.7)	96	85
Arm	22 (16.3)	95	90
Leg	21 (15.6)	82	62
Generalized skin involvement	18 (13.3)	77	63
Legs involved	11 (8.1)	67	53
Legs not involved	7 (5.2)	100	86

patients without leg involvement (P=0.20) (Table 4). Moreover, in the total study group, 5-year DSS of patients with leg involvement (n=32) and patients without leg involvement (n=103) were 76% and 96%, respectively (P=0.007; after adjustment for T category, P=0.03 (Figure 3 and Table 5).

COMMENT

In the present study the clinical usefulness of the new TNM classification system for primary cutaneous lymphomas other than MF and SS was tested on a group of 135 patients with a C-ALCL. Although primarily meant to document extent of disease in a consistent manner, we also evaluated the prognostic value of this classification system for this group of C-ALCL. The results of this study show that this new TNM system can be applied well on this group of CTCL. Five-year DSS in patients with T1 disease was 93%, with T2 disease was 93%, and with T3 disease

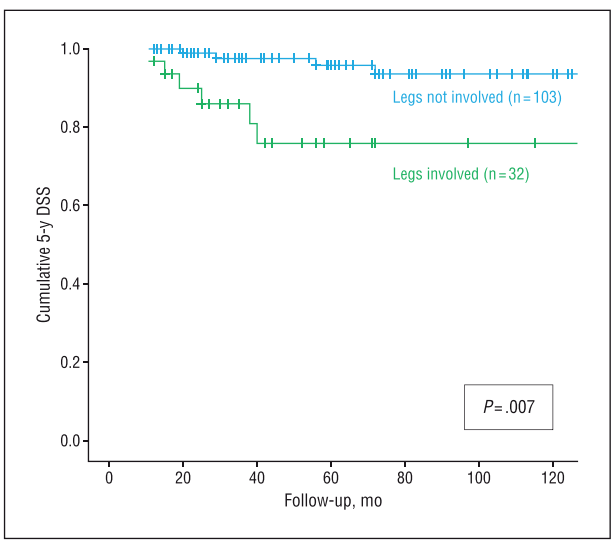

Figure 3. Five-year disease-specific survival (DSS) of patients with cutaneous anaplastic large cell lymphoma with and without leg involvement

Table 5. 5-year DSS in patients with and without leg involvement in different T categories

		Legs not involved (n=103)		Legs involved (n=32)		
T category	**No. (%)**	**D+ (%)**	**5-yr DSS, %**	**D+**	**5-yr DSS, %**	**p-value**
T1	80 (59.3)	4/70 (6)	94	1/10 (10)	90	0.39
T2	37 (27.4)	2/26 (8)	100	2/11 (18)	76	0.13
T3	18 (13.3)	0/7	100	3/11 (27)	67	0.20
Total group	135 (100)	6/103 (6)	96	6/32 (19)	76	0.03*

D+: patients who died from lymphoma/number of patients in each T category; *Adjusted for T category

was 77%, suggesting that patients with generalized skin lesions have a less favorable prognosis than do patients with solitary or localized skin lesions. Previous studies[3,4,6] have also suggested a correlation with reduced survival in patients with multifocal skin lesions. In the group of 18 patients with generalized skin lesions (T3 disease), 3 of 11 with involvement of the legs died of lymphoma (all were patients with involvement of both legs), compared with none of the 7 patients without leg involvement (5-year DSS 67% vs 100%). Also, in the patients with regional skin lesions (T2 disease), leg involvement was associated with reduced 5-year DSS (76% vs 100%4). In the total group of 135 patients, those with leg involvement had significantly worse survival than did those without leg involvement. These observations are in agreement with those of a previous study, which suggested that patients with extensive limb involvement are at risk for a poor prognosis.[4] The fact that in univariate analysis site of presentation was not statistically significantly related to survival can be explained by small sample sizes (Table 4). The same holds true when analyzing the association with survival for leg involvement within the 3 T categories separately (Table 5).

Apart from localization on the leg, presentation on the head and neck has also been associated with a less favorable prognosis.[9] In the retrospective cohort analysis of 157 patients with solitary or localized C-ALCL retrieved from the Surveillance, Epidemiology, and End Results (SEER) database, patients with skin lesions on the head and neck showed a significantly increased risk of death. In contrast, in the present study, patients presenting with skin lesions on the head and neck had a 5-year DSS of 95%. Only one of 42 patients (2.4%) with a solitary skin lesion on the head andneck region died of lymphoma (56 months after diagnosis). These different results are difficult to explain. However, because diagnoses in the SEER database are not verified independently, it cannot be excluded that the SEER cohort contains several patients with folliculotropic MF. Such patients preferentially present at the head and neck region, commonly contain many CD30-positive blast cells, and have a worse prognosis than C-ALCL.[14,15]

In conclusion, these results show that the new TNM system can be applied well to patients with C-ALCL and may provide prognostic information, in particular when combined with site of presentation. Patients with T2 and T3 disease with skin lesions on the leg were found to have a worse prognosis compared with patients without leg involvement. However, we do not believe that there is enough reason to adapt the current guidelines for the initial treatment of C-ALCL in these patients. These guidelines indicate that patients with solitary or localized skin lesions can best be treated with excision or radiotherapy, whereas in patients with multifocal skin lesions low-dose oral methotrexate or, in the case of few scattered skin lesions, radiotherapy is preferred.[3] However, patients with regional of generalized skin lesions that involve the leg should be controlled very closely and may require systemic chemotherapy in an earlier phase of disease progression.

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