Prognostic Significance of a Polymerase Chain Reaction–Detectable Dominant T-Lymphocyte Clone in Cutaneous Lesions of Patients With Mycosis Fungoides

By Marie-Hélène Delfau-Larue, Sophie Dalac, Eric Lepage, Tony Petrella, Janine Wechsler, Jean-Pierre Farcet, and Martine Bagot

Although mycosis fungoides (MF) is considered to be an indolent lymphoma, survival is highly influenced by TNM stage. At diagnosis, most MF patients present with early stage disease and a high probability of long-term survival. Treatment is generally directed towards skin lesions, and achievement and duration of complete responses are variable. A dominant T-cell clone is detectable in the cutaneous lesions of 60% of patients. The aim of this study was to determine whether the presence of a T-cell clonal population influences the clinical course of the disease after topical therapy. Cutaneous biopsies from 68 patients were histologically diagnosed as MF and T-cell clonality was analyzed by in vitro amplification of TCR-γ chain gene rearrangements (polymerase chain reaction γ [PCRγ]). After a median follow-up of 48 months, response to treatment was clinically assessed. Age, sex, duration of symptoms before diagnosis, type of cutaneous lesions (T stage), TNM stage, and PCRγ were evaluated as predictive factors of response to treatment in univariate and multivariate analyses. Univariate analysis demonstrated that T1 cutaneous lesions (*P* = .05) and PCRγ negativity (*P* = .007) were associated with a higher complete remission rate. Using multivariate analysis, T stage (relative risk, 3.13; *P* = .06) and PCRγ (relative risk, 4.4; *P* = .01) remained independent significant predictive parameters of response. In conclusion, T stage and cutaneous PCRγ at diagnosis are the two predictive parameters of treatment response for MF. Therefore, the cutaneous PCRγ findings should be considered in the analysis of future therapeutic trials.

MYCOSIS FUNGOIDES (MF) is the most common subtype within the group of cutaneous T-cell lymphomas (CTCL).[1] The natural history of MF is characterized by an indolent yet orderly progression through four stages: patch, plaque, tumor, and visceral involvement. The characteristic lesions of this disease begin as macular lightly erythematous patches that subsequently evolve into well-demarcated scaling plaques. These plaques may then progress to tumor lesions and subsequently spread to the viscera, but this progression is not necessarily seen in all patients (reviewed in Lorincz[2]).

Among patients with MF, the prognosis is highly variable. MF is classified into clinical stages using the TNM classification and the staging system established at the National Cancer Institute (Bethesda, MD) (Table 1).[3,4] Previous studies of prognostic indicators have shown consistently that the skin (T) stage and the presence or absence of extracutaneous disease are the most important determinants of outcome.[5-7] Patients with limited skin involvement (T1) have a favorable prognosis,[8] whereas patients with erythrodermic MF (T4) or tumor (T3) have an unfavorable prognosis.

Numerous therapeutic strategies have been tried in MF (reviewed in Diamandidou et al[9]). Treatment regimens in early MF are generally directed towards skin lesions, ie, psoralen and ultraviolet A (PUVA), topical chemotherapy (nitrogen mustard), and electron beam therapy. Each approach produces similar response rates, and there are no randomized trials demonstrating the superiority of one regimen over another.

The diagnosis of CTCL relies on histopathological examination of skin biopsies.[10] The T-cell receptor γ chain gene (TCRγ) rearrangement provides a convenient genetic marker for the study of clonality in cutaneous mature T-cell infiltrates (reviewed in Wood et al[11] and Volkenandt et al[12]). Like other investigators, we have reported that the frequency of detection by polymerase chain reaction (PCR) of a dominant T-lymphocyte clone in lesions histologically typical of MF (regardless of stage) is 60%.[13-16] The presence or absence of a detectable dominant T-cell clone is identical in different lesions of the same type (patch/plaque, tumor, erythroderma) from the same patient.[17] In 89% of cases, the PCRγ(+) or PCRγ(−) nature of the cutaneous lesions is maintained during the course of the disease after therapy. When the samples are positive, the clonospecific imprint of the tumoral population also remained stable with time.[17]

To study the influence of a dominant monoclonal T-cell population in cutaneous lesions of MF on the clinical course of the disease after topical therapy, we studied the effect of clonality on the achievement of complete remission in 68 patients.

MATERIALS AND METHODS

Patient selection and staging. From December 1, 1988 until August 31, 1994, a cutaneous biopsy was performed for histological and molecular studies on all patients with a clinical picture suggestive of MF. The criterion for including patients in this study was the existence of lesions histologically typical of MF, ie, band-like subepidermal infiltrates, the presence of Sezary cells, and single-cell epidermotropism and/or clusters of cell-forming Pautrier's microabscesses.[10] Patients were excluded if they had more than 15% circulating Sezary cells or if clinical data were not available. Sixty-eight patients were eligible. Staging at presentation was performed according to the modified TNM classification of cutaneous T-cell lymphomas[3,4] (Table 1). After diagnosis, all patients received topical treatment consisting of either mechlorethamine (33 patients), total skin electron beam irradiation (TSEB; 25 patients), PUVA therapy (5 patients), topical steroids (4 patients), or

From the Service d'Immunologie Biologique, Unité d'Information Médicale, Département de Pathologie, Service de dermatologie du Pr Revuz, Hôpital Henri-Mondor, Créteil, France; the Service de Dermatologie du Pr Lambert, Hôpital du Bocage; and the Département de Pathologie, CHU de Dijon, Dijon, France.

Submitted July 9, 1997; accepted June 21, 1998.

Supported by aid from the Ligue contre le Cancer de l'Yonne.

Address reprint requests to Marie-Hélène Delfau-Larue, MD, Service d'Immunologie Biologique, Hôpital Henri-Mondor, 51 av du marechal Delattre de Tassigny, 94010 Créteil, France.

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0006-4971/98/9209-0052$3.00/0

Table 1. Staging and TNM Classification of MF

Stage	T	N	M
IA	T1: eczematous lesions, plaques: <10% of body surface	N0: no palpable lymph node; histologically no evidence of MF	M0
IB	T2: eczematous lesions, plaques: >10% of body surface	N0	M0
IIA	T1/T2	N1: palpable lymph node; histologically no evidence of MF	M0
IIB	T3: tumors (more than 1)	N0/N1	M0
III	T4: erythroderma	N0/N1	M0
IVA	T1-T4	N2: no palpable lymph node, histological MF N3: palpable lymph nodes, histological MF	M0
IVB	T1-T4	N0-N3	M1: histologically confirmed visceral involvement

local electron beam irradiation (1 patient). The type of treatment administered was not influenced by the PCRγ results.

Evaluation criteria. Patients were classified in two categories according to their clinical status at the time of the last clinical update: complete remission (CR), ie, no clinically detectable lesion; or no CR, ie, presence of lesions with either a stable clinical stage or progression.

TCRγ gene rearrangement analysis by GC clamp multiplex PCR-denaturing gradient gel electrophoresis (DGGE). DNA was extracted from frozen 4-mm punch biopsy samples by standard proteinase K digestion and phenol/chloroform precipitation. Various amounts of DNA (from 250 ng up to 1 μg) were assayed. Two hundred fifty nanograms of DNA was chosen because results were similar to those with 1 μg DNA and it allowed DNA banking. Thus, during patient follow-up, DNA specimens from the diagnostic biopsies could be assessed concurrently with DNA from new biopsies for comparison. TCRγ chain gene rearrangements were studied using a GC clamp multiplex PCR/DGGE procedure, as previously described.[18] Briefly, four oligonucleotides matching the four Vγ segment families and four oligonucleotides matching the Jγ junction segments were used in a single 50 μL PCR reaction (multiplex PCR) in a thermal cycler (Perkin Elmer 480; Perkin Elmer, Norwalk, CT). After 40 cycles, 30 μL of amplified products was run on a 6.5% polyacrylamide gel containing a linearly increasing 10% to 60% denaturing gradient (DGGE). The use of oligonucleotides matching all the Vγ and Jγ functional segments combined with DGGE allows the achievement of a migration profile specific for each T-cell clone.[18]

The sensitivity of the technique depends on the type of Vγ-Jγ rearrangement present in the tumoral population and the intensity of the reactional infiltrate in the pathological skin biopsy. We determined the range of sensitivity of our technique by diluting DNA from the Jurkat T-cell line in DNA extracted from normal skin[15] or from reactive lymph nodes.[18] Jurkat cells possess a rearrangement often used by normal T cells (VIJI) on one allele and a rarer rearrangement on the other allele (VIV-JI). We found the sensitivity to be 0.1% for the rare rearrangements in a poorly cellular infiltrate and 5% for the more frequent rearrangements hidden by dense reactional infiltrates. This means that one or two discrete bands will be visible when a dominant T-cell clone constitutes from 0.1% to 5% or more of the total cell population.[15,18]

Results of PCR were expressed as positive [PCRγ(+)] when a dominant T-cell clone was detectable and negative [PCRγ(−)] when a polyclonal pattern of T-cell infiltration was shown. In the latter case, the presence of a smear on the gel ensured that T-cell DNA was present and amplified.

Statistical methods. Complete response rates according to pretreatment prognostic factors and PCRγ results were compared by χ^2 or Yates χ^2 test. All parameters found to be significant at the 0.1 level in the univariate analysis were included in a logistic regression analysis of response. The study was stopped on February 1, 1998, 41 months after inclusion of the most recent patient. The tests were regarded as significant if the two-sided *P* value was less than .05.

RESULTS

Initial patient features. Table 2 summarizes the clinical characteristics of the 68 patients included in this study and the number of PCRγ(+) patients for each characteristic. Seventy-one percent of patients presented in early stage disease with patch/plaque-type cutaneous lesions (IA, IB, and IIA). Among the 68 patients studied, 62% had cutaneous lesions histologically typical of MF that were PCRγ(+). The PCRγ(+) rate was independent of sex, age at diagnosis of MF, and duration of cutaneous symptoms before diagnosis. There was no correlation between the detection of a dominant T-cell clone and either the cutaneous or extracutaneous extension of the lesions (Table 2). The only direct link between clinical features of the disease and clonality was the absolute relationship between the tumoral lesions and the presence of a dominant T-cell monoclonal population; 100% of tumoral lesions were PCRγ(+).

Patient clinical features at the last clinical update. After a median follow-up of 48 months, 33 of 68 patients (48%) were in clinical CR as assessed by the absence of cutaneous lesions.

Table 2. Patient Characteristics and Presence of a Dominant T-Cell Clone Detected by GC Clamp Multiplex PCR-DGGE in Cutaneous Lesions

Patient Characteristics	No. of Patients	No. of Patients With Cutaneous PCRγ(+)
Total no.	68	42 (62%)
Age at MF diagnosis (yr)		
≤65	43	27 (62%)
>65	25	15 (60%)
Sex		
Male	41	25 (61%)
Female	27	17 (63%)
Duration of symptoms before MF diagnosis (mo)		
<120	54	33 (61%)
≥120	13	9 (69%)
Not determined	1	0
Type of cutaneous lesion		
Patch/plaque (T1/T2)	51	30 (59%)
Tumor	8	8 (100%)
Erythroderma	9	4 (44%)
TNM staging		
IA	19	11 (58%)
IB	13	8 (62%)
IIA	16	9 (56%)
IIB	5	5 (100%)
III	6	3 (50%)
IV	9	6 (67%)

Sixteen patients died during the follow-up period. The initial characteristics of these patients are shown in Table 3. For 10 of them, the cause of death was attributable to MF. All patients who died of their MF had a dominant clonal population in the initial cutaneous lesion. By contrast, no PCRγ(−) patients died of MF during the same follow-up time ($P < .01$).

Nineteen patients were alive but not in CR at the last clinical update. Two had relapsed after an initial complete response, whereas the disease staging remained stable in the others, either without extension of the lesions (15/19) or an increase in the number of cutaneous plaques (2/19).

Factors that influence the CR rate. We studied the influence of the clonality of cutaneous lesions at the time of diagnosis on the CR status after treatment. In univariate analysis, two parameters were associated with a higher CR rate: T1 cutaneous lesions ($P = .05$) and PCRγ(−) lesions ($P = .007$). The age of the patient at time of diagnosis (65 *v* >65 years), the sex, the duration of symptoms before the diagnosis of MF (120 *v* >120 months), and the TNM staging showed no prognostic value (Table 4). A multivariate regression analysis including T stage (T1 *v* T2 to T4) and PCRγ demonstrated that PCRγ negativity was a significant independent predictor of CR after treatment (relative risk, 4.4; $P = .01$; Table 5).

DISCUSSION

The study of factors influencing survival in MF have enabled three groups of patients to be identified.[5] Good-risk patients are those with patch/plaque skin disease, a negative peripheral blood smear, and no evidence of visceral disease or nodal disease (stages IA, IB, and IIA). This subgroup has a median survival of greater than 12 years.[5-8] Poor-risk patients are those with visceral disease or effaced lymph nodes (stage IV), with a median survival of 2.5 years. The intermediate-risk group (stages IIB and III) has a median survival of 5 years. At diagnosis, the majority of patients belong to the good-risk group.[5,6,19] In this group, most of the treatment regimens are directed towards skin lesions (for review, see Diamandidou et al[9]). The relapse rate after treatment and the disease-free interval are very variable from one patient to another and, at present, no predictive criterion of therapeutic efficacy has been demonstrated. To study the influence of a detectable T-cell clone on the treatment response, patients were classified into two groups according to whether or not they were in CR at the last clinical update. Median follow-up was 48 months. A statistical univariate analysis identified a factor influencing the CR rate that was already known to influence survival,[5,19] ie, localized patch/plaque type disease. In addition, this study demonstrated the independent predictive value of dominant T-cell clone detection in the skin lesions. PCRγ(−) patients more frequently

Table 3. Initial Characteristics and Cause of Death of Patients Who Died During the Study

Patient No.	Age at Inclusion (yr)	TNMB	Stage	PCRγ	Survival (mo)	Cause of Death	MF Staging at Time of Death
1	70	T1N0	Ia	(+)	33	MF	IV
2	63	T3N0M0	IIb	(+)	9	MF	IV
3	76	T3N1	IIb	(+)	27	MF	IV
4	43	T3N1	IIb	(+)	48	MF	IV
5	50	T4N1	III	(+)	6	MF	IV
6	94	T4N1	III	(+)	21	MF	IV
7	47	T4N3	IV	(+)	10	MF	IV
8	72	T3N3	IV	(+)	12	MF	IV
9	89	T3N2	IV	(+)	17	MF	IV
10	70	T3N3M1	IV	(+)	2	MF	IV
11	93	T2N0	IIa	(−)	9	UD	IIa
12	79	T1N1	IIa	(−)	30	MI	CR
13	74	T2N1	IIa	(−)	35	HF	IIa
14	62	T2N0	Ib	(+)	29	CVA	Ia
15	59	T2N1	IIa	(+)	18	GIT Ca.	IIa
16	81	T2N1	IIa	(+)	79	CVA	IIa

Abbreviations: UD, undiagnosed; MI, myocardial infarction; HF, heart failure; CVA, cerebrovascular accident; GIT Ca., gastrointestinal cancer.

Table 4. Factors That Influence the CR Rate

Patient Characteristics	No. of Patients	No. of Patients in CR	*P* Value*
Total no.	68	33 (48%)	
Age at MF diagnosis (yr)			
<65	43	22 (51%)	.57
>65	25	11 (44%)	
Sex			
Male	41	18 (44%)	.34
Female	27	15 (56%)	
Duration of symptoms before MF diagnosis (mo)			
<120	54	25 (46%)	
>120	13	8 (62%)	.3
Not determined	1	0	
T stage			
T1	23	15 (65%)	
versus			.05
T2	28	13 (46%)	
T3	8	1 (12.5%)	
T4	9	4 (44%)	
TNM staging			
IA	19	12 (63%)	
IB	13	6 (46%)	
IIA	16	7 (44%)	
versus			.34
IIB	5	1 (20%)	
III	6	2 (33%)	
IV	9	5 (55%)	
PCR			
(−)	26	18 (69%)	
(+)	42	15 (36%)	.007

*χ^2 or Yates corrected tests.

Table 5. Influence of Initial Parameters on Response Rate (by Logistic Regression Analysis)

Variable	No. of Patients	Relative Risk of CR	*P*
T stage			
T1	23	3.13	.06
T2 to T4	45		
PCR			
(−)	26	4.4	.01
(+)	42		

achieved CR than those with a detectable dominant T-cell clone [PCRγ(+)].

The technique used in this study for the analysis of TCRγ gene rearrangements detected the presence of a dominant monoclonal T-cell population in 62% of lesions histologically typical of MF (Theodorou et al[15] and this study). This result contrasts with the 90% positivity reported by Wood et al.[20] When we modified our technique to make it one log more sensitive by studying the various possible VγJγ combinations separately (monoplex PCR), we also found that 90% of MF lesions had a detectable dominant monoclonal or oligoclonal T-cell population. However, 20% of the chronic eczematous lesions studied were also positive (data not shown). We decided to preserve the specificity of our test rather than to increase its sensitivity, and the GC clamp multiplex PCRγ and DGGE methodology was used.

Previously, we have shown that, in the same patient, whether positive or negative, the PCRγ result of different lesions biopsied on the same day or during the course of the disease was homogeneous and remained constant in 90% of cases. When the PCR was positive, the clonospecific imprint of the dominant population was identical in the various cutaneous lesions.[17] Thus, whether positive or negative, the PCRγ result appears to be a patient-dependent feature rather than a lesion-dependent feature. This finding is critical in studying the predictive value of PCRγ.

The relationship between the T-cell clonality in cutaneous lesions and the clinical staging of the MF patients points to the tumoral form as a peculiar form of the disease. The clinical observation that a minor subset of patients progresses to a tumoral stage of the disease, even after several decades, supports this hypothesis. Indeed, a dominant T-cell clone is detected in 100% of tumoral cases, whatever the technique used, including Southern blot, which is less sensitive than PCR (reviewed in Wood[21]). This result may, at first, appear to be discordant with previously published data showing that the PCRγ result is patient-dependent and not lesion-dependent. However, the rarity of tumoral forms (~10% of MF, of which some are tumoral at presentation) and the fact that 38% of early forms of MF are PCRγ(−) mean that the probability of a patch/plaque PCRγ(−) lesion evolving into a tumoral PCRγ(+) lesion is low (3.8% at the most). Moreover, patients who are PCRγ(+) at diagnosis, who less frequently achieve a CR, may progress more often to a tumoral form than patients who are PCRγ(−). This possibility will be studied by the long-term follow-up of patients included at an early stage of disease. In the tumoral form, the prognosis is most often unfavorable not only with respect to treatment response, but also with respect to survival.[2] This finding suggests that, in the initial population of malignant cells, one or more additional genetic events may occur in a single cell leading to a growth advantage for this cell, to a clinical presentation with a tumoral stage, and to a high malignant cell/reactive cell ratio and therefore a positive PCRγ. Previous studies have demonstrated the presence of multiple cytogenetic abnormalities in tumoral lesions.[1,22]

Data reported in the literature suggest that the cytokines produced by the malignant T-cell clone may have a role in the in situ recruitment of an inflammatory infiltrate.[20,21] Furthermore, numerous reactive nonmalignant lymphocytes have been shown to infiltrate patch/plaque-type MF lesions.[21,23] If the ratio of clonal tumoral cells to reactive polyclonal cells is lower than the clonality detection threshold, the PCRγ will be negative. In this context, two elements could explain the association between a PCRγ(−) result and the higher probability of achieving CR. On the one hand, the tumoral mass in PCRγ(−) lesions may be less than that of the PCRγ(+) lesions. On the other hand, the polyclonal reactive cells, which represent the majority of cells in PCRγ(−) lesions, might play a role in the control of tumor growth. This hypothesis is in concordance with the data reported by Hoppe et al,[24] who demonstrated that, in patch/plaque-type lesions (T1/T2), the actuarial survival of patients is correlated with the percentage of $CD8^+$ lymphocytes infiltrating the lesion.

An analysis of the patients who died during the follow-up period of the study showed that the number of patients who died due to their MF in the PCRγ(+) group (10/42) was significantly greater than in the PCRγ(−) group (0/26) ($P < .01$). In our series, 48 patients had an initial clinical presentation with a good prognosis in terms of survival (stages IA, IB, and IIA). Only 1 of these patients died of his/her disease during the study period. Among the 20 patients with a poorer prognosis (stages IIB, III, and IV), 9 have died. Multivariate analysis, including the staging and PCRγ, found that the predominant factor for survival was the staging (data not shown). A recent report has suggested that, in the group of stage IA patients, a lower CR rate might be associated with disease progression.[8] A longer follow-up of our patients could help to clarify the influence of PCRγ on survival in the good prognosis group.

In conclusion, using GC clamp multiplex PCRγ-DGGE, the detection of a dominant monoclonal T-cell population in the cutaneous lesions of a patient with histologically documented MF decreases the probability of achieving a CR after treatment. Thus, PCRγ distinguishes two subsets of patients and should be part of the initial staging of MF patients. It should be included as a predictive criterion in the analysis of therapeutic trials.

ACKNOWLEDGMENT

The authors are indebted to Samir Agrawal for helpful discussion and re-reading of the manuscript. We thank Prof P. Saiag (CHU Ambroise Paré, Paris, France), Dr N. Franck (CHU Cochin Tarnier, Paris, France), and Dr P. Brunet (Hopital Joffre, Corbeil, France) for their help in follow-up data collection.

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