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Clinical and Laboratory Investigations

A simple clinical scoring system to improve the sensitivity and standardization of the diagnosis of mycosis fungoides type cutaneous T-cell lymphoma: logistic regression of clinical and laboratory data

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Summary

Background The diagnosis of mycosis fungoides (MF) is notoriously difficult to establish because in the early stages, histological features may be nonspecific or merely suggestive.
Objectives To standardize the diagnosis of MF.
Methods We studied 138 patients with suspected MF referred over a 7-year period to a university department of a dermatology-based cutaneous lymphoma clinic. Six diagnostic criteria were evaluated: clinical morphology, clinical distribution, skin biopsy T-cell receptor gene rearrangement (TCR-GR), skin biopsy pan T-cell marker loss ≥ 2, skin biopsy CD4/CD8 ratio ≥ 6, and skin biopsy diffuse epidermal HLA-DR expression. These six clinical and laboratory criteria were compared by logistic regression analysis in patients with histologically diagnosed MF and those with benign disease.
Results Of the 138 patients, 74 had histology of MF, 47 of benign dermatoses and 17 were indeterminate. Close associations were found between a histological diagnosis of MF and TCR-GR (odds ratio 14·4), classical morphology (7·5), classical distribution (2·5) and diffuse epidermal HLA-DR expression (2·8). Logistic regression models were developed depending on the availability of data (either TCR-GR or HLA-DR). Probabilities for correctly diagnosing MF compared with histology as the 'gold standard' were derived from these logistic regression models. A scoring system assigning point values based on these probabilities was then created in order to assist the clinician in making the diagnosis. If using TCR-GR data, a positive TCR-GR = 2·5 points, the presence of classical morphology = 2·0 points, and the presence of classical distribution = 1·5 points. A total score of ≥ 3·5 points assigns a high probability (> 85%) of having MF. If using HLA-DR expression, then the presence of classical morphology = 2·5 points, a positive diffuse epidermal HLA-DR expression = 2·0 points, and the presence of classical distribution = 1·5 points. In this case, a total score of ≥ 4·0 points assigns a high probability (> 85%) of MF.
Conclusions The logistic regression models and scoring systems integrate clinical and laboratory assessments, allow rapid probability estimation, and provide a threshold for the diagnosis of MF in an objective, standardized manner.

Key words: diagnosis, mycosis fungoides

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Mycosis fungoides (MF) is typically an indolent lymphoproliferative disorder of neoplastic T cells which initially presents in the skin. The lesions can vary morphologically. Classical lesions often begin as well-demarcated scaling patches; with time, lesions may become more indurated, forming plaques and tumours. Patients' lesions may also display a characteristic distribution over 'doubly clothed' areas.

The diagnosis of MF is notoriously difficult to establish because in the early stages, histological features may be nonspecific. Although light microscopic findings have remained the 'gold standard' for diagnosis, most studies show both inter- and intrarater variability in the early histological diagnosis to be high, even among highly experienced dermatopathologists.[1–4]

To improve the reproducibility and sensitivity of the diagnosis of MF, key histological features have been identified[5–8] and several adjunctive tests developed through the years. To define the malignant infiltrate, various tests have been employed: abnormal nuclear DNA content and chromosome complement,[9–12] abnormal nuclear contour and shape,[13–17] loss of pan T-cell markers,[18,19] elevated CD4/CD8 ratio (≥ 6),[20] diffuse epidermal HLA-DR expression,[21] and the presence of a clonal T-cell population as measured by T-cell receptor gene rearrangement (TCR-GR) studies.[22–25] None of these tests alone firmly establishes the diagnosis of MF.

In other complex diseases, such as systemic lupus erythematosus and atopic dermatitis, important clinical and laboratory criteria have been identified to make standardized scoring systems[26–28] to aid in making the diagnosis. We propose a method to standardize the early diagnosis of MF integrating both clinical features and adjunctive laboratory tests. Two logistic regression models were developed based on the statistically significant associations of certain diagnostic criteria compared with the 'gold standard' of histological diagnosis. The models assign a probability that the diagnosis of MF is correct. From these probabilities, a scoring system to simplify patient assessment is proposed with relative weights given to each diagnostic criterion; scores above a defined threshold equate with a high probability (> 85%) of having MF in cases where histology is equivocal.

Materials and methods

Patients

Over a 7-year period, 138 patients with documented or suspected MF who were referred to a Cutaneous Lymphoma Program received a standardized evaluation. Clinical assessment consisted of documenting the morphology and distribution of all lesions as either classical, consistent or atypical for MF. Classical morphology was defined as scaling poikilodermatous patches with fine epidermal wrinkling (poikiloderma atrophicans vasculare), leonine facies, well-demarcated, indurated, scaling plaques, or tumours (Fig. 1a–c). Consistent morphology was defined as scaling dermatitis, erythroderma or alopecia mucinosa. Atypical morphology was defined as nonscaling lesions, with

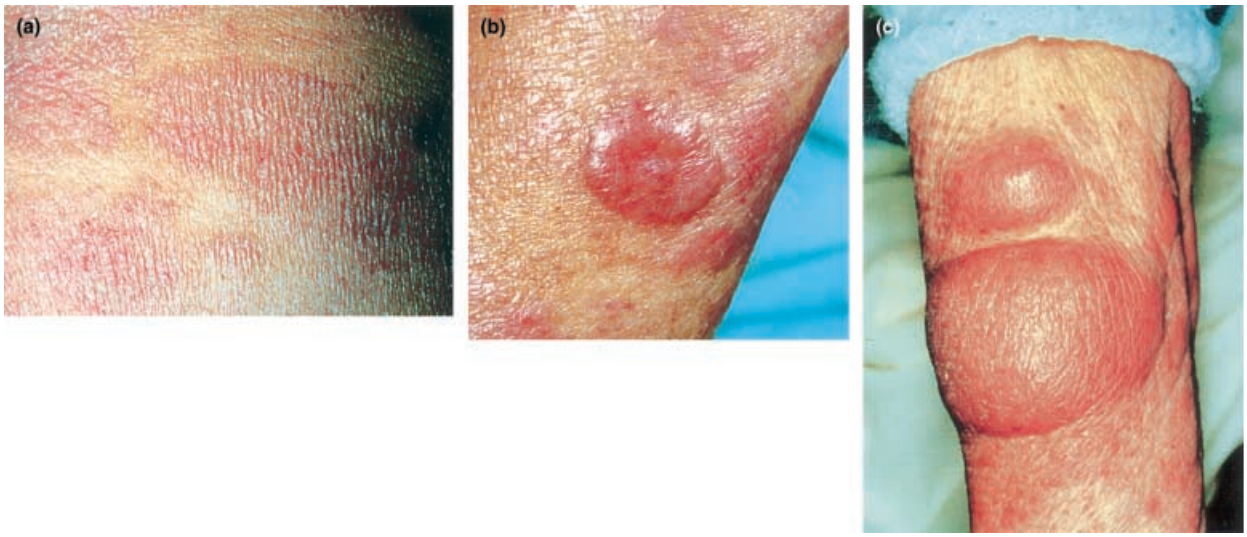

Figure 1. Classical morphology of mycosis fungoides. (a) Scaling patches with epidermal wrinkling; (b) indurated erythematous plaques; (c) indurated erythematous tumours.

none of the above specific features. Patients such as in Figure 1(c) with obvious MF were excluded from consideration, but patients with tumours that were legitimately considered to represent possible prurigo nodules were included. A classical distribution included involvement primarily of the buttocks, lower trunk, upper thighs, upper inner arms, and the periaxillary and inframammary areas (Fig. 2a,b). Consistent distribution was defined as involvement primarily of the extremities, head or upper trunk in addition to the classical distribution. Atypical distribution was defined as distribution not fitting into the above categories. Skin biopsy specimens were taken from the most clinically infiltrative and advanced lesions in all patients and analysed by a staff dermatopathologist.

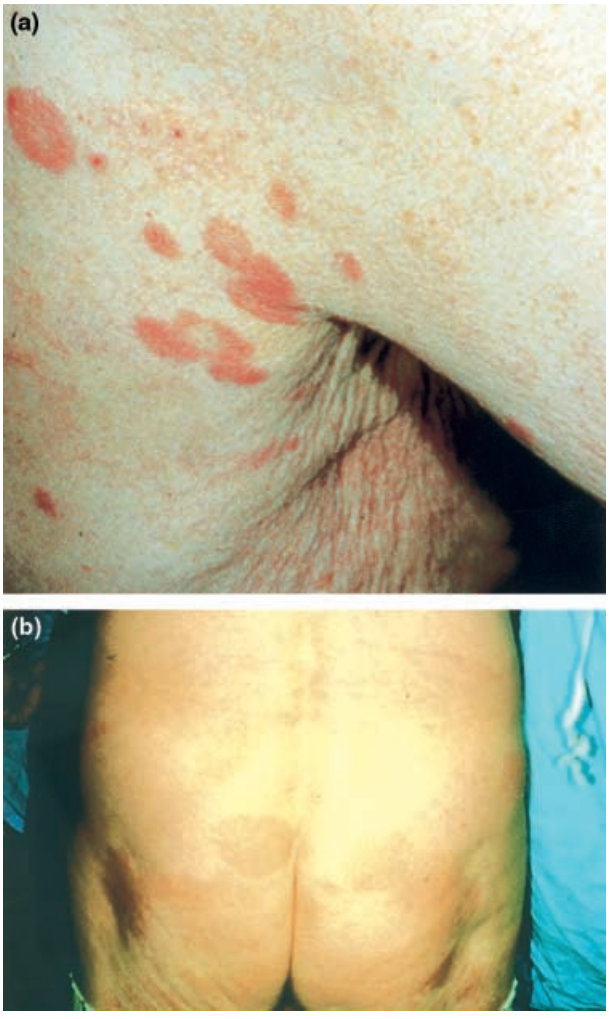

Figure 2. Classical distribution of mycosis fungoides. (a) Involvement of posterior axillary fold; (b) involvement of buttocks. Involvement of upper thighs and upper inner arms is not shown.

Histological evaluation

Biopsies were obtained from patients after at least 1 month off any medications except bland emollients. The major histological criterion used was the degree of lymphocyte atypia (based on nuclear size, density and convolution); other criteria included published morphological features and patterns such as epidermotropism, and the presence of a band-like upper dermal lymphocytic infiltrate in which cells are apposed to basal cells singly and in a linear arrangement (Fig. 3a–c).[6] The overall degree of certainty of the pathologist was expressed using the following terms: (i) not MF; (ii) suggestive of MF; (iii) consistent with MF; and (iv) diagnostic of MF. Patients were classified as having benign disease if repeated biopsies showed no evidence of MF or if features were only suggestive of MF, and as having MF if histological features were consistent with or diagnostic of MF.

Immunophenotyping

Immunophenotyping by immunohistochemical staining of frozen skin biopsy specimens was carried out using an avidin–biotin–peroxidase technique.[29] Sections were stained with a panel of monoclonal antibodies (Becton-Dickinson, San Jose, CA, U.S.A.), including anti-HLA-DR, CD2 (Leu 5b), CD3 (Leu 4), CD4 (Leu 3a), CD5 (Leu 1), CD7 (Leu 9) and CD8 (Leu 2a). We recorded the CD4/CD8 ratio, number of pan T-cell markers lost (CD2, CD3, CD5, CD7) and presence of expression of HLA-DR by epidermal keratinocytes, as stated in the pathologist's report.

T-cell receptor gene rearrangement

For TCR-GR studies, DNA was extracted from frozen tissue according to standard protocols.[30] Ten micrograms of DNA were digested with the restriction enzymes *Bam*HI, *Eco*RI and *Hin*dIII. Restriction fragments were size-fractionated by agarose gel electrophoresis. Southern blots were hybridized with ^{32}P-radiolabelled probes (Oncor, Gaithersburg, MD, U.S.A.) for the constant region (^{C}T Beta) and/or for the joining regions (J Beta 1/11) of the T-cell receptor β chain gene (TCR-GR). The diagnosis of a monoclonal rearrangement required that nongermline bands were seen with two of the three enzymes, or that two nongermline bands were seen with one single enzyme digest.[31]

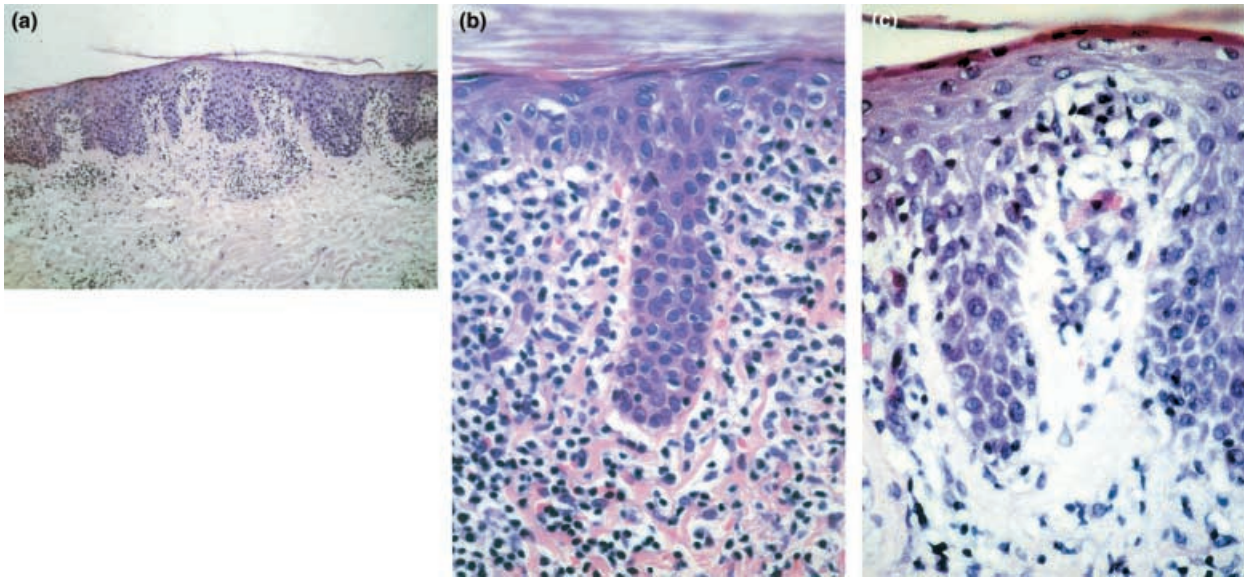

Figure 3. Histology diagnostic of mycosis fungoides. (a) Low-power view showing lymphocytic infiltration of the epidermis (epidermotropism); (b) high-power view showing band-like lymphocytic infiltration of the dermis; (c) high-power view showing lymphocyte atypia (haematoxylin and eosin).

Statistical analysis

Clinical and histological features and adjunctive test data were entered prospectively into a dBase IV database (Microsoft, Seattle, WA, U.S.A.). Statistical analysis was performed using the statistical analysis package STATA (release 3·1, College Station, TX, U.S.A.). In total, six clinical or adjunctive test features were examined. These candidate diagnostic criteria included the following: classical morphology, classical distribution, pan T-cell marker loss ≥ 2, presence of a TCR-GR, CD4/CD8 ratio ≥ 6, and diffuse epidermal HLA-DR expression. The statistical significance of the association of each diagnostic criterion with histology, the gold standard for diagnosis of MF, was assessed using Fisher's exact test in a univariate analysis. These tests were performed on all patients with available data. Data were missing for some patients due to the lack of availability of TCR-GR techniques early in the study period, inadequate DNA yield from biopsy specimens, and variations in the assessment by evaluating physicians.

Logistic regression models were used to assess the independent associations of each diagnostic criterion with a histological diagnosis of MF. Statistical significance was assessed using the Wald test in the multivariate analysis. Two situations were explored, one in which TCR-GR information was used and one in which it was not. In each situation the most predictive model for a diagnosis of MF was determined through a step-up procedure based on maximizing the log likelihood function. Models were based on cases with complete data available for all the criteria included in the model. Diagnostic criteria were entered if they were significant at the 10% level by the likelihood ratio test. The model-predicted probability of a diagnosis of MF was calculated using the formula:

$$\text{Predicted probability} = \exp[XB]/(1 + \exp[XB]),$$

where XB is the linear predictor.

Two scoring systems were developed based on the best models, one in which TCR-GR data were used, and one in which they were not. Firstly, the model coefficients (log odds ratio) were standardized by dividing by their standard errors. Next, the relative weights (points) were determined based on a maximum score of 6·0 by dividing each standardized coefficient by the sum of the standardized coefficients in the model and multiplying by 6·0.

Results

Statistically significant univariate associations were found between the histological diagnosis of mycosis fungoides and positive T-cell receptor gene rearrangement, classical morphology, classical distribution and diffuse epidermal HLA-DR expression, but not CD4/CD8 ratio ≥ 6 or pan T-cell marker loss ≥ 2

Of 138 total patients based on histological classification, 47 patients were assigned to the benign dermatoses group. These included the following diagnoses:

spongiotic dermatitis, interface dermatitis, psoriasiform dermatitis, delayed-type hypersensitivity reaction, benign lymphocytic infiltrate, pityriasis lichenoides et varioliformis acuta (PLEVA) and pseudolymphoma. Histological classification assigned 74 patients to the MF group; 17 were indeterminate. Using the two patient populations (benign dermatoses and MF + indeterminate), univariate associations between the six clinical and adjunctive test data (diagnostic criteria) and the histological diagnosis of MF were determined (Table 1). All but one patient had morphology and distribution recorded, but other variables were not available for some patients; thus, the number of observations (n) varies by parameter. To quantify the strength of association between each criterion and a histological diagnosis of MF, an odds ratio was generated. Statistically significant associations, as expressed by $P \leq 0{\cdot}1$, were found with positive TCR-GR (odds ratio 14·4), classical morphology (7·5), classical distribution (2·5) and diffuse epidermal HLA-DR expression (2·8) (Table 1). CD4/CD8 ratio ≥ 6 showed a weak association (odds ratio 2·2, $P = 0{\cdot}12$), but pan T-cell marker loss ≥ 2 appeared to be unrelated to the histological diagnosis of MF ($P > 0{\cdot}999$).

Development of logistic regression models for diagnosis of mycosis fungoides by multivariate analysis

T-cell receptor gene rearrangement data used. A logistic regression model was built using the diagnostic criteria in a step-up procedure. Odds ratios were generated and significant independent associations expressed as $P \leq 0{\cdot}1$ (Wald test). The most predictive model incorporates the criteria that have the most statistically significant associations with a diagnosis of MF: TCR-GR, morphology and distribution (Table 2). Although diffuse epidermal HLA-DR expression was a statistically significant variable based on the univariate analysis, it did not contribute to the overall diagnostic utility of the final model when TCR-GR data were available. The sensitivity and specificity of this model was determined using our two histologically defined patient groups. A positive predictive value of 82% with a sensitivity of 85% and a specificity of 58% was derived (Table 3).

Once created, the most predictive logistic regression model assigned a probability of having MF to each patient based on clinical features and TCR-GR data. The frequency distribution of patients at each probability level revealed distinct groupings which allowed patients to be divided crudely into low ($P \leq 0{\cdot}40$), intermediate ($0{\cdot}60 \leq P \leq 0{\cdot}85$) or high ($P > 0{\cdot}85$) risk categories (Fig. 4a). In the MF group, 31 of 74 (42%) patients had a high probability, 32 of 74 (43%) had an intermediate probability and 11 of 74 (15%) had a low probability of having MF. In the benign dermatoses group, two of 33 (6%) patients had a high probability, 12 of 33 (36%) had an intermediate probability and 19 of 33 (58%) had a low probability of having MF. The two patients in the benign dermatoses group with a high probability of MF had

Table 1. Statistically significant univariate associations of histological diagnosis of mycosis fungoides (MF) with T-cell receptor gene rearrangement (TCR-GR), morphology, distribution and epidermal HLA-DR expression

Diagnostic criteria	Benign dermatoses[a]	MF[a]	Odds ratio[b]	P-value[c]
TCR-GR	2 (34)	35 (74)	14·36	≤ 0·0001
Morphology	4 (46)	38 (91)	7·5	0·0001
Distribution	12 (46)	43 (91)	2·54	0·026
HLA-DR expression	10 (28)	38 (62)	2·85	0·039
CD4/CD8 ratio	7 (33)	27 (73)	2·18	0·121
Pan T-cell marker loss	5 (32)	13 (74)	1·15	≥ 0·999

[a]Entries are the number with positive criteria out of (n) with available data. Positivity is defined as presence of TCR-GR, classical lesional morphology, classical lesional distribution, diffuse epidermal HLA-DR expression, CD4/CD8 ratio ≥ 6 and pan T-cell marker loss ≥ 2. [b]Odds ratios express the strength of association between the individual diagnostic criterion and a diagnosis of MF. [c]Statistical significance of associations is expressed as $P \leq 0{\cdot}1$ using Fisher's exact test.

Table 2. Establishment and performance of logistic regression model for diagnosis of mycosis fungoides (MF) when T-cell receptor gene rearrangement (TCR-GR) data are used: most predictive logistic regression model[a]

Diagnostic criteria[a]	Estimated odds ratio	Standard error	P-value[b]
TCR-GR	13·10	10·38	0·001
Morphology	4·70	2·93	0·013
Distribution	2·53	1·29	0·068

[a]Model is based on 107 patients with complete data for all the criteria used. [b]Statistical significance of associations is expressed as $P \leq 0{\cdot}1$, using the Wald test.

		Classified by model		
		Benign dermatoses	MF	Total
Classified by histology	Benign dermatoses	19	14	33
	MF	11	63	74
	Total	30	77	107

Model sensitivity, 85%; model specificity, 58%; false positive rate, 18%; false negative rate, 37%; positive predictive value, 82%; negative predictive value, 63%. [a]The sensitivity and specificity of the logistic regression model is based on application of the model to the histologically defined benign dermatoses and MF groups.

Table 3. Establishment and performance of logistic regression model for diagnosis of mycosis fungoides (MF) when T-cell receptor gene rearrangement (TCR-GR) data are used: logistic regression model sensitivity and specificity[a]

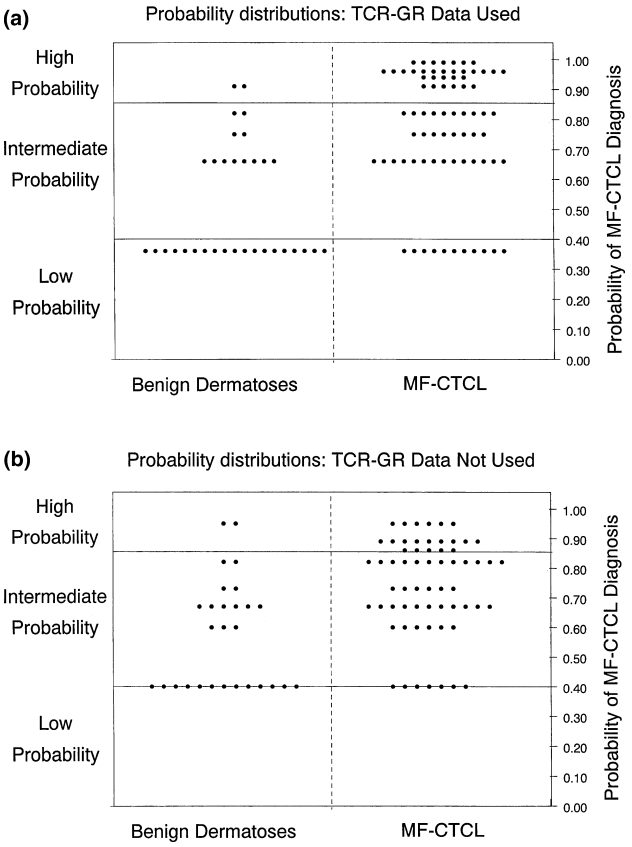

Figure 4. Comparison of mycosis fungoides (MF) probability distributions between histologically defined benign dermatoses and MF type cutaneous T-cell lymphoma (CTCL). Most patients with benign disease are in the low probability group, while most MF patients are in the intermediate-high probability group. (a) Based on the logistic regression model developed from clinical and immunogenotyping data including T-cell receptor gene rearrangement (TCR-GR) data. (b) Based on the logistic regression model developed from clinical and HLA-DR expression data (TCR-GR data not used).

been classified histologically with a diagnosis of spongiotic dermatitis and PLEVA, respectively. Unfortunately, these patients have been lost to follow-up, so it is unclear whether they eventually developed histologically confirmed MF.

Table 4. Establishment and performance of logistic regression model for diagnosis of mycosis fungoides (MF) when T-cell receptor gene rearrangement (TCR-GR) data are not used: logistic regression model utilizing HLA-DR expression instead of TCR-GR data[a]

Diagnostic criteria[a]	Estimated odds ratio	Standard error	*P*-value[b]
Morphology	4·43	2·75	0·016
HLA-DR expression	2·71	1·36	0·047
Distribution	2·43	1·30	0·097

[a]Model is based on 90 patients with complete data for all the criteria used. [b]Statistical significance of associations is expressed as $P \leq 0{\cdot}1$, using the Wald test.

T-cell receptor gene rearrangement data not used. Epidermal HLA-DR expression was a statistically significant variable when univariate analysis was performed (Table 1), but in the presence of TCR-GR data its usefulness in making the diagnosis of MF was not appreciated. A second logistic regression model was developed which incorporated clinical and HLA-DR expression data (Table 4). The sensitivity and specificity of this model (89% and 46%, respectively, Table 5) were similar to those obtained for the most predictive model in which TCR-GR data were utilized. The positive predictive value of this second model was estimated at 79%.

Based on this second model, patients were divided into low ($P \leq 0{\cdot}40$), intermediate ($0{\cdot}60 \leq P \leq 0{\cdot}85$) and high ($P > 0{\cdot}85$) risk categories for having MF (Fig. 4b). The division between these categories was based on that established in the first model. In the MF group, 20 of 62 (32%) patients had a high probability, 35 of 62 (56%) had an intermediate probability and seven of 62 (11%) had a low probability of having MF. In the benign dermatoses group, two of 28 (7%) patients had a high probability, 13 of 28 (46%) had an intermediate probability and 13 of 28 (46%) had a low probability of having MF.

Table 5. Establishment and performance of logistic regression model for diagnosis of mycosis fungoides (MF) when T-cell receptor gene rearrangement (TCR-GR) data are not used: logistic regression model sensitivity and specificity[a]

		Classified by model		
		Benign dermatoses	MF	Total
Classified by histology	Benign dermatoses	13	15	28
	MF	7	55	62
	Total	20	70	90

Model sensitivity, 89%; model specificity, 46%; false positive rate, 21%; false negative rate, 35%; positive predictive value, 79%; negative predictive value, 65%. [a]The sensitivity and specificity of the logistic regression model is based on application of the model to the histologically defined benign dermatoses and MF groups.

Practical scoring system to establish a diagnosis of mycosis fungoides

A clinically useful scoring system was developed from each of the logistic regression models presented in Tables 2–5. A numerical value was given to each criterion based on its strength of association with the diagnosis of MF based on the relative magnitude of the estimated log odds ratio (Tables 6 and 7). For both systems, as a score increased, the corresponding probability of a diagnosis of MF increased until probabilities approached 1·0 (Fig. 5). In patients with a score of 0, the probability of having MF was ≤ 0·40. This probability value was not 0 because a small number of cases diagnosed histologically as MF were classified as benign by the model. Therefore, patients with this score had a finite, but small, chance of having malignant disease. This was appropriate because these patients were judged clinically to have disease suspicious for MF. Scores of 1·5–2·5 in patients with TCR-GR data available, and scores of 1·5–3·5 in patients without TCR-GR data were associated with an intermediate probability (0·60–0·85) of having MF. Scores ≥ 3·5 in patients with TCR-GR data available, and scores ≥ 4·0 in patients without TCR-GR data were associated with a high probability (> 0·85) of having MF.

Table 6. Scoring system to estimate probability of diagnosis of mycosis fungoides (MF). Steps in patient evaluation: (1) clinical evaluation (differential diagnosis includes MF; lesional morphology and distribution are assessed); (2) biopsy (histology is at least suggestive of diagnosis of MF); (3) adjunctive tests [T-cell receptor gene rearrangement (TCR-GR) studies or epidermal HLA-DR expression]; (4) score (add points based on clinical and laboratory results and statistical models)

Diagnostic criterion	Point value (TCR-GR available)	Point value (TCR-GR unavailable)
Positive lesional TCR-GR	2·5	–
Classical morphology	2·0	2·5
Classical distribution	1·5	1·5
HLA-DR expression	–	2·0
Maximum score	6·0	6·0

Discussion

The diagnosis of MF has traditionally been based on the correlation of clinical and histological features, leading to inconsistent and often incorrect diagnoses. Numerous studies show low accuracy and reliability of histological and cytological interpretation of skin biopsy specimens, which led us to search for an improved method of diagnosis.[1–4] The diagnostic value of clinical assessment has not previously been

Table 7. Scores and corresponding probability of diagnosis of mycosis fungoides (MF)

Variables present[a]	Patients MF/benign[b]	Score[c]	TCR-GR available[d]	Variables present[a]	Patients MF/benign[b]	Score[c]	TCR-GR not available[d]	Risk of MF[e]
None	11/19	0	0·36	None	7/13	0	0·40	Low
D	14/8	1·5	0·66	D	6/3	1·5	0·60	Intermediate
M	8/2	2·0	0·75	HLA	11/6	2·0	0·67	Intermediate
				M	6/2	2·5	0·73	Intermediate
GR	10/2	2·5	0·82					Intermediate
				HLA/D	12/2	3·5	0·82	Intermediate
M/D	6/2	3·5	0·91					High
GR/D	5/0	4·0	0·94	M/D	5/0	4·0	0·86	High
GR/M	13/0	4·5	0·96	HLA/M	9/0	4·5	0·89	High
GR/M/D	7/0	6·0	0·99	HLA/M/D	6/2	6·0	0·95	High

[a]'Variables' relates to presence of classical morphology (M), distribution (D), diffuse epidermal HLA-DR expression (HLA) and T-cell receptor (TCR) gene rearrangement (GR). [b]'Patients' relates to numbers in histologically defined benign and MF groups. [c]Score is derived from clinical and laboratory evaluation from Table 6 depending on statistical model used. [d]Predicted probability of a diagnosis of MF based on models in Tables 2–5, depending on TCR-GR data availability. [e]Risk categories of MF: low risk, $P \leq 0{\cdot}40$; intermediate risk, $0{\cdot}60 \leq P \leq 0{\cdot}85$; high risk, $P > 0{\cdot}85$.

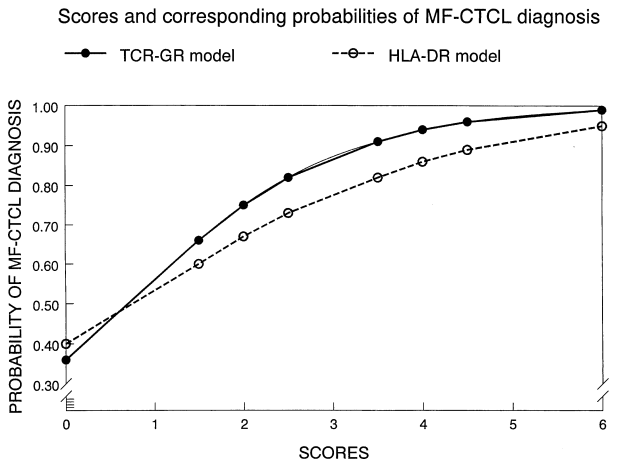

Figure 5. Scores tabulated based on the two scoring systems are correlated with the corresponding model-assigned probabilities of diagnosis of mycosis fungoides type cutaneous T-cell lymphoma (MF-CTCL). As scores increase, the probability of a diagnosis increases proportionately. TCR-GR, T-cell receptor gene rearrangement.

quantified. Confirmation of strong clinical suspicion in individual patients by histopathology is sought, but is frequently not obtained. This need to improve diagnostic ability has led to the application of adjunctive tests to cases of suspected MF. In our study, no single parameter yielded sufficiently discerning results to be considered 'the diagnostic test'. However, the combination of such tests along with the patient's clinical picture provides stronger evidence.

This integration of parameters to diagnose early MF has not been explored until now. We show the relative contribution of classic morphology and distribution to MF diagnostics. We have shown that there is a significant association between the presence of a TCR-GR, classical morphology, classical distribution and diffuse epidermal HLA-DR expression with a histological diagnosis of MF. Logistic regression models were developed to integrate these clinical and laboratory data, assigning a probability (low, intermediate, high) of having MF with a high predictive value (82% or 79%, for models using TCR-GR or HLA-DR data, respectively).

Of all the parameters in our study, the presence of a TCR-GR was the most discriminating criterion. Thirty-five of 74 (47%) specimens from patients with MF demonstrated a positive TCR-GR in contrast to two of 34 (6%) specimens from patients with benign dermatoses (Table 1). These latter two cases were patients with PLEVA and nonspecific spongiotic dermatitis, respectively. Of the 57 patients with early stage MF (stages IA, IB), 23 (40%) had a clonal TCR-GR in the skin. Of the 17 patients with later stage disease (stages II–IV), 12 (71%) had a clonal TCR-GR in the skin. According to our most predictive logistic regression model, a positive TCR-GR without other criteria resulted in a 0·82 probability of having MF. This underscores the point that TCR-GR cannot serve as the one deciding test in diagnosing MF. Although T-cell clonality is characteristic of neoplasia, it is not conclusive evidence of malignancy.[32–34] For this reason, in our models the presence of a TCR-GR alone without classical morphology or distribution assigns only an intermediate risk of a diagnosis of MF.

To best simulate the conditions in which our skin scoring system would be applied, we chose to include only those cases that could be confused with a lesion of MF. Therefore, the odds ratios generated for each individual diagnostic criterion may have been higher if classical cases of benign dermatoses such as psoriasis, atopic dermatitis or allergic contact dermatitis had been included. However, we felt their inclusion would not reflect the 'real life' odds ratio given by our criteria. Additionally, the low proportion of specimens from patients in the MF group with a positive TCR-GR may reflect the relative insensitivity of this technique when carried out by Southern blot methods as compared with the techniques utilizing polymerase chain reaction technology, particularly in early cases of MF.[22]

Our logistic regression models highlight the judgement of an experienced clinician by assigning the clinical picture a high predictive value in the diagnosis of MF. The combined presence of classical morphology and distribution enables the diagnosis of MF to be made with a probability of $> 0{\cdot}85$ in both models (Table 7). In the presence of a histologically consistent or diagnostic biopsy reading, the diagnosis of MF is made. However, in those patients with questionable or histologically equivocal disease, even classical morphology and distribution, although assigned a $> 0{\cdot}85$ probability of a diagnosis of MF, may be insufficient, and additional evaluation and application of the logistic regression models and scoring systems may add further evidence to help the clinician to make the correct diagnosis.

In cases with only classical morphology or classical distribution, adjunctive tests are particularly useful. While morphology or distribution alone equate to a probability of $\leq 0{\cdot}75$, an intermediate risk of MF in both models, the addition of positive TCR-GR data increases the probability to exceed the chosen threshold of $> 0{\cdot}85$ for a diagnosis of MF. Interestingly, if adding only positive HLA-DR data, the threshold of $> 0{\cdot}85$ will

only be met with classical morphology, not classical distribution, which suggests an advantage of TCR-GR over HLA-DR data.

Once a probability and score are determined for a given patient, treatment and follow-up decisions can be made. Those with a high probability of having MF (score $\geq 3{\cdot}5$ if TCR-GR data available or $\geq 4{\cdot}0$ without TCR-GR data available, $P > 0{\cdot}85$) will undergo MF-specific treatment, while those with a low probability of disease (score $= 0$, $P \leq 0{\cdot}40$) will not. Discussions with patients and their families can incorporate these probabilities. Patients in the intermediate category require close follow-up for repeated clinical assessment and skin biopsy as indicated, with the decision to treat based upon the individual situation. It should be understood that the division between intermediate and high probability groups is arbitrary and should be interpreted as such. For some physicians and patients a probability $> 0{\cdot}85$ for the diagnosis of MF will be necessary, thus prompting additional adjunctive tests until individual thresholds are reached.

Several limitations were encountered in the development of the current model. Statistical analysis was complicated by missing data (Table 1). As a result, the models were based on fewer numbers of patients (107 for the model with TCR-GR data available and 90 for the model with HLA-DR data available). However, results were similar when the statistical analyses were carried out using indicator variables (data not shown).

Because patients were referred to our specialty clinic, we realize that our population is skewed. These patients either had MF or had features suspicious for the disease. Given this, it is likely that utilizing a population of patients with a more varied cross-section of benign dermatological diseases for the benign dermatoses group would improve the sensitivity and specificity of our results. However, the true goal of our model is to differentiate early cases of MF from benign disease simulating this malignancy. Our patient groups accomplish this.

We have assessed the association between clinical and laboratory data with histological diagnosis of MF vs. benign dermatoses in our patient population, and have integrated significant associations into logistic regression models which assign a probability of diagnosis of MF. The model-derived probabilities of diagnosis of MF were divided into low, intermediate and high risk, with a threshold probability for the diagnosis of MF chosen at $> 0{\cdot}85$. A simple scoring system for patient assessment was developed to reflect these probabilities. These models help to standardize the diagnosis of MF as well as to provide more concrete information to discuss with patients and their families. This study demonstrates the high value of clinical judgement and is the first approach to diagnosis of MF that integrates clinical, histological and adjunctive laboratory data. These models are likely to evolve over time as new tests are developed.

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