





Article

Evaluation of the International Society for Cutaneous Lymphoma Algorithm for the Diagnosis of Early Mycosis Fungoides

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Abstract: The International Society for Cutaneous Lymphoma (ISCL) proposes a diagnostic algorithm for early mycosis fungoides (MF) that includes clinical, histological, immunophenotypical, and molecular criteria. Here, we analyzed the immunologic markers and features of T-cell clonality in 38 early MF cases and 22 non-MF cases to validate the ISCL algorithm. We found that CD5 and CD7 expression differed significantly between early MF and non-MF cases, with epidermal discordance of CD7 expression more frequently identified in early MF. Notably, increasing the cut-off value for CD7 expression from 10% to 22.5% improved its sensitivity. Furthermore, TCR- γ and β chain rearrangements were more frequently detected in early MF than in non-MF cases. Based on these findings, we propose CD5 and CD7 deficiency as mandatory immunopathologic criteria and PCR-based testing for TCR- γ and β chains as required molecular/biologic criteria to improve the efficiency of early MF diagnosis using the ISCL algorithm.

Keywords: mycosis fungoides; ISCL algorithm; CD5; CD7; TCR- γ ; TCR- β



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1. Introduction

Mycosis fungoides (MF) is the most common type of primary cutaneous T-cell lymphoma and is characterized by the evolution of patches, plaques, and tumors on the skin [1]. Most cases of MFs wax and wane and exhibit indolent clinical courses; however, MF is incurable and can progress to the tumor stage with a poor prognosis [2,3]. Moreover, early MF at the patch stage has diverse clinicopathologic mimickers, from spongiotic or interface dermatoses to other cutaneous hematologic diseases [4], which can lead to misdiagnosis. Therefore, clinicians and pathologists must carefully evaluate clinicopathologic characteristics to accurately diagnose MF in its early stage.

The International Society for Cutaneous Lymphoma (ISCL) proposes an algorithm for the diagnosis of early MF and Sézary syndrome based on clinical, histologic, immunohistochemical (IHC), and molecular features, which are most important for recognizing classic MF at its initial presentation [5,6]. According to the ISCL algorithm, the diagnosis of early MF requires a total of four points for clinicopathologic and ancillary features. Clinical criteria are non-sun-exposed location, size/shape variation, or poikiloderma with persistent and/or progressive patches/thin plaques. Histopathological criteria are epidermotropism without spongiosis or lymphoid atypia with superficial lymphoid infiltrate. The molecular/biologic criterion is the presence of T-cell receptor (TCR) gene rearrangement based on polymerase chain reaction (PCR) testing. Lastly, immunopathologic criteria are CD2, CD3, CD5, and CD7 expression, although these ancillary features are not applicable if no clinical or histopathologic major criteria are fulfilled.

Several previous studies validated the ISCL diagnostic algorithm to demonstrate its effectiveness and accuracy [7,8]. These studies show some limitations of the algorithm, such as low specificity and accuracy of individual parameters, although the algorithm was able to detect significant differences between early MF and other mimickers. Although TCR gene rearrangement as a molecular/biologic criterion is included in the algorithm, details concerning TCR types or loci are not well described [5]. Among immunopathologic criteria, CD2, CD3, and/or CD5 deficiency and epidermal/dermal discordance of CD2, CD3, CD5, and/or CD7 have only ~10% sensitivity, whereas CD7 deficiency has ~40% sensitivity and 80% specificity [9–12]. Because the clinicopathologic features of early MF are often indistinguishable and complex, diagnosis is heavily dependent on ancillary features. Therefore, ascertaining reliable molecular and immunopathologic markers is needed to improve the diagnostic accuracy of the ISCL algorithm for early MF.

In this study, we classified cases into early MF or non-MF groups according to the ISCL diagnostic algorithm. By comparing each parameter of the algorithm between groups, we identified the most reliable biomarkers that can play a determinant role in efficiently diagnosing early MF and established new cut-off values that differentiate early MF from its mimickers.

2. Materials and Methods

2.1. Patients and Samples

We retrospectively obtained specimens from 60 patients who were biopsied with clinical suspicion of MF from 2008 to 2021 at Severance Hospital, Yonsei University College of Medicine, and reviewed their associated clinical presentation, microscopic findings, IHC staining results, and molecular studies. Slides stained with hematoxylin and eosin were reviewed by two pathologists (HJR and SKK). Ancillary studies were performed upon diagnosis. All methods and experimental protocols using human tissue were carried out in accordance with relevant guidelines and regulations as approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System (IRB no. 4-2021-0462). The ISCL algorithm for the selection of eligible cases of early MF is shown in Figure 1. A total of 38 early MF and 22 non-MF specimens were included in this study.

The mimickers were clinically diagnosed as annular erythema, drug eruption, parapsoriasis, chronic eczema, pseudolymphoma, psoriasiform dermatitis, and lupus panniculitis after ICH and molecular work-up, although eight cases were still clinically suspicious for early MF (Supplementary Table S1).

2.2. IHC Staining

IHC staining was performed at diagnosis. Formalin-fixed paraffin-embedded (FFPE) blocks were cut into 4- μ m-thick sections and processed using heat-induced epitope retrieval. IHC staining was performed in an automated immunostainer (Ventana Discovery[®] XT, Ventana Medical System, Inc., Oro Valley, AZ, USA). Antibodies against CD2 (PA0271, Novocastra, 1:100, Buffalo Grove, IL, USA), CD3 (A0452, Dako, 1:100, Santa Clara, CA, USA), CD5 (NCL-CD5-4C7-L-CE, Novocastra, 1:25, Buffalo Grove, IL, USA), and CD7 (NCL-L-CD7-580, Novocastra, 1:100, Buffalo Grove, IL, USA) were utilized. Three pathologists (HJR, SHK, and SKK) blinded to the pathologic information independently evaluated IHC staining.

All immunohistochemical markers were assessed by light microscopy. The percentage of positive cells for immunostaining in the epidermis and dermis was measured, each percentage differed by at least 30%, epidermal discordance was defined [5,12]. If the expression of the markers were less than 30%, the complete loss of expression in the epidermis or the dermis was regarded as discordance.

2.3. DNA Extraction and TCR Gene Rearrangement Analysis

TCR gene rearrangement analysis was performed at diagnosis to evaluate TCR clonality. Genomic DNA was extracted from 10- μ m sections cut from FFPE tissue blocks using the

Maxwell[®] CSC DNA FFPE extraction kit (Promega, Madison, WI, USA) and the Maxwell[®] CSC instrument. Polymerization was performed with identiClone TCR- γ , β , and δ gene clonality assay kits according to the manufacturer's instructions (Invivoscribe, San Diego, CA, US). After purification by electrophoresis and dyeing in 6% polyacrylamide for 2 h, analysis was conducted using the gel imaging system.

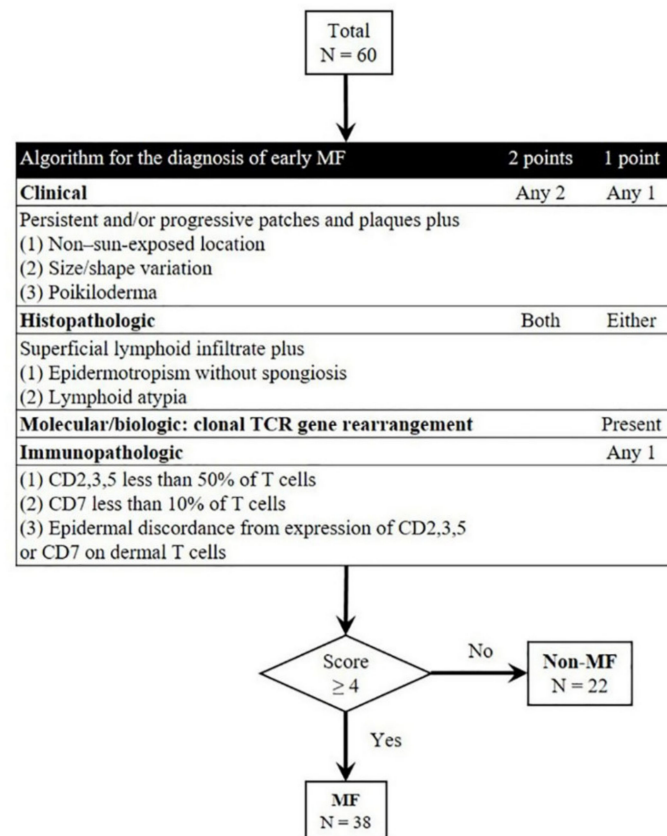


Figure 1. ISCL algorithm for the selection of early MF cases.

2.4. Statistical Analysis

All statistical analyses were performed using SPSS version 26.0 (IBM, Chicago, IL, USA) and GraphPad Prism version 7.04 (GraphPad Prism 7, San Diego, CA, USA). Categorical data are reported as frequencies and percentages, and continuous data are reported as mean and standard deviation (SD) or standard error of the mean (SEM). Differences between groups were compared using χ^2 tests, Fisher's exact tests, or unpaired t-tests. Receiver operator characteristic (ROC) curves were constructed for IHC results, and the area under the ROC curve (AUC) was calculated. To choose optimal cut-off values, Youden's index [13] for each antibody was calculated, and Muller's value was used as a measure of the discriminative ability of the AUC [14]. Two-sided p -values <0.05 were considered statistically significant. P -values are indicated as follows: * $p < 0.05$; ** $p < 0.005$; *** $p < 0.0005$.

3. Results

3.1. Clinicopathologic Features of Early MF

We reviewed 60 cases of pathologically diagnosed early MF (ISCL score ≥ 4 , $n = 38$) and its mimickers (non-MF; ISCL score < 4 , $n = 22$) according to the ISCL algorithm for the diagnosis of early MF and Sézary syndrome (Supplementary Table S1).

There was no significant difference in sex or age at diagnosis between groups. As expected, however, there were significant differences between groups with respect to clinical, histopathologic, molecular/biologic, and immunopathologic parameters (Table 1).

Table 1. Clinicopathologic features of early MF and non-MF.

	Early MF (n = 38)	Non-MF (n = 22)	p-Value
Sex (male:female)	22:16	10:12	0.4254
Age (years, mean ± SD)	43.13 ± 2.858	51.91 ± 3.896	0.0717
Total ISCL score (mean ± SD)	4.868 ± 0.1261	2.0 ± 0.1861	<0.0001
Clinical points			<0.0001
0	1	9	
1	7	8	
2	30	5	
Histopathologic points			0.0500
0	3	5	
1	15	12	
2	20	5	
Molecular/biologic points			<0.0001
0	2	16	
1	34	4	
Immunopathologic points			<0.0001
0	11	20	
1	25	0	

3.2. Determinative Immunopathologic Markers of Early MF

Figure 2 shows representative clinical features of early MF during the patch stage, including the histologic findings of epidermotropism and lymphoid atypia and the immunopathologic features of CD2, CD3, CD5, and CD7 deficiency (Figure 2a).

Next, we compared the expression of each immunopathologic marker between early MF and non-MF groups to identify the most reliable markers and their cut-off values (Table 2 and Figure 2b).

Table 2. Immunopathologic features of early MF and non-MF.

	Early MF (n = 38)	Non-MF (n = 22)	p-Value
IHC (% ± SEM)			
CD2	84.08 ± 3.155	92.27 ± 1.174	0.0590
CD3	91.84 ± 1.722	93.41 ± 0.764	0.5065
CD5	81.18 ± 3.438	92.50 ± 1.175	0.0174
CD7	17.45 ± 2.648	42.95 ± 4.763	<0.0001
Epidermal discordance			
CD2	0	0	>0.9999
CD3	0	0	>0.9999
CD5	2	0	0.5402
CD7	15	0	0.0010

We found that CD5 expression was significantly lower in early MF (81.18 ± 3.438%) than in non-MF (92.50 ± 1.175%, $p = 0.0174$), although there was no significant difference in epidermal discordance in CD5 expression by dermal T-cells. CD7 expression was also significantly lower in early MF (17.45 ± 2.648%) than in non-MF (42.95 ± 4.763, $p < 0.0001$), and epidermal discordance in CD7 expression by dermal T-cells was more frequently identified in early MF (15/38, 39.5%) than in non-MF (0/22, 0%, $p = 0.0010$). There were no significant differences in CD2 and CD3 expression between groups.

Next, we constructed ROC curves and calculated AUCs for immunopathologic markers (Figure 2c and Table 3). Youden's index was calculated for each marker to determine its optimal cut-off value (Supplementary Table S2).

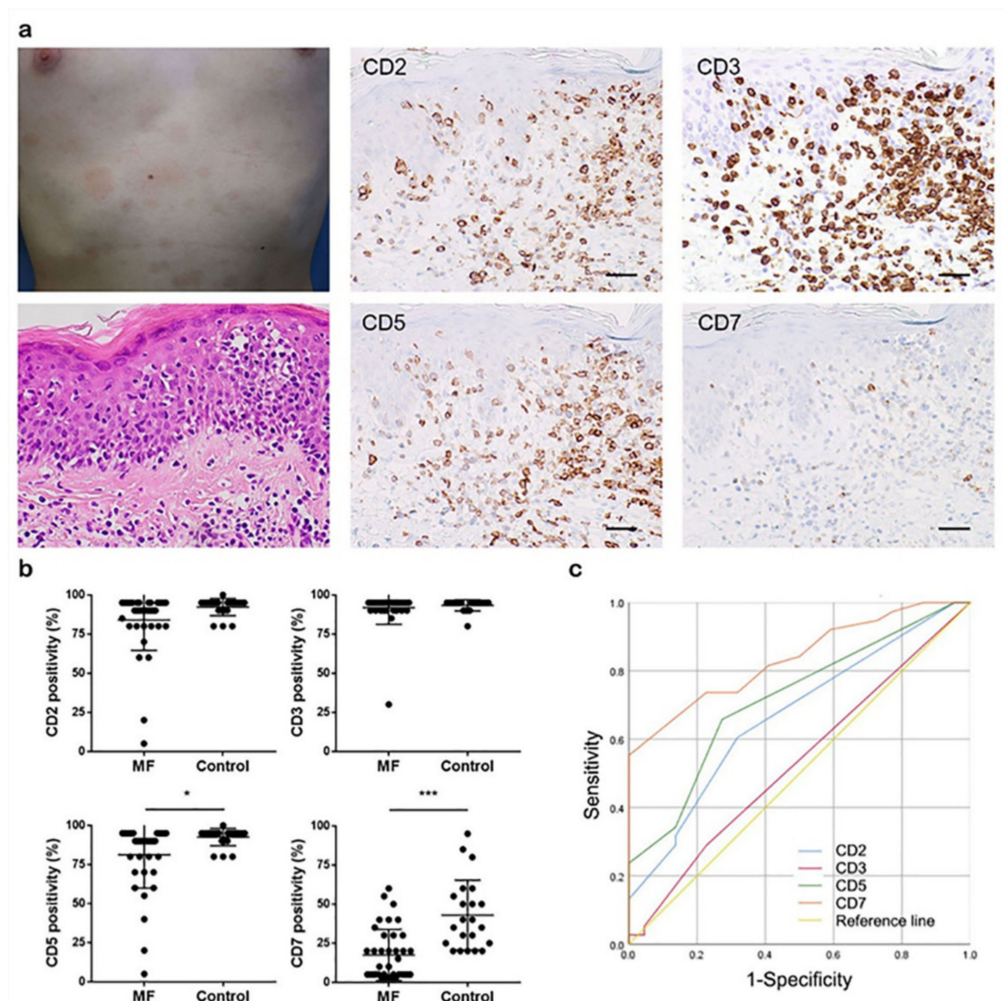


Figure 2. Clinicopathologic features of early MF. (a) Representative clinicopathologic findings during the patch stage of MF. Magnification, 200 \times ; scale bar, 50 μ m. (b) Comparative analyses of CD2, CD3, CD5, and CD7 expression. (c) ROC curves for CD2, CD3, CD5, and CD7 expression. * $p < 0.05$; *** $p < 0.0005$.

Table 3. Data from ROC curves for CD2, CD3, CD5, and CD7 expression in early MF versus non-MF.

IHC	AUC	Muller's Value	SE	95% Confidence Interval		p -Value	Cut-Off (%)	Sensitivity (%)	Specificity (%)
				Lower	Upper				
CD2	0.669	Poor	0.071	0.529	0.808	0.031	92.5	60.5	68.2
CD3	0.531	Fail	0.077	0.379	0.682	0.696	92.5	28.9	77.3
CD5	0.718	Fair	0.067	0.587	0.849	0.005	92.5	65.8	72.7
CD7	0.837	Good	0.050	0.739	0.934	0.000	22.5	73.7	77.3

According to Muller's value, the AUCs of CD2 and CD3 showed poor and failing discriminatory abilities, respectively, at the highest Youden's index. CD2 had a high cut-off value (92.5%) with low sensitivity (60.5%) and specificity (68.2%), although it was statistically significant ($p = 0.031$). CD3 also had a high cut-off value (92.5%) with very low sensitivity (28.9%, $p = 0.696$). CD5 and CD7 showed fair and good discriminatory abilities, respectively. CD5 had a high cut-off value (92.5%) with 65.8% sensitivity and 72.7% specificity ($p = 0.005$). CD7 had a cut-off value of 17.5% at the highest Youden's index with 55.3% sensitivity and 100.0% specificity. However, if we chose 22.5% as the cut-off value for CD7, it had 73.7% sensitivity and 77.3% specificity ($p < 0.001$).

3.3. Molecular Features of Early MF

To specify the features of clonal TCR gene rearrangement in early MF, we performed PCR-based detection of TCR- γ , δ , and β chain genes (Figure 3a). We found that 20 out of 60 cases had oligoclonal TCR rearrangements (33.3%). Whereas 36 out of 38 early MF cases (94.7%) had monoclonal or oligoclonal T-cells, only 3 out of 22 non-MF cases (9.1%) had monoclonal or oligoclonal T-cells ($p < 0.0001$). TCR- γ and β gene rearrangements were more frequently identified in early MF than in non-MF (Table 4 and Figure 3b). TCR- β gene rearrangement was not detected in non-MF cases. There was no difference in TCR- δ gene rearrangement between groups ($p > 0.9999$).

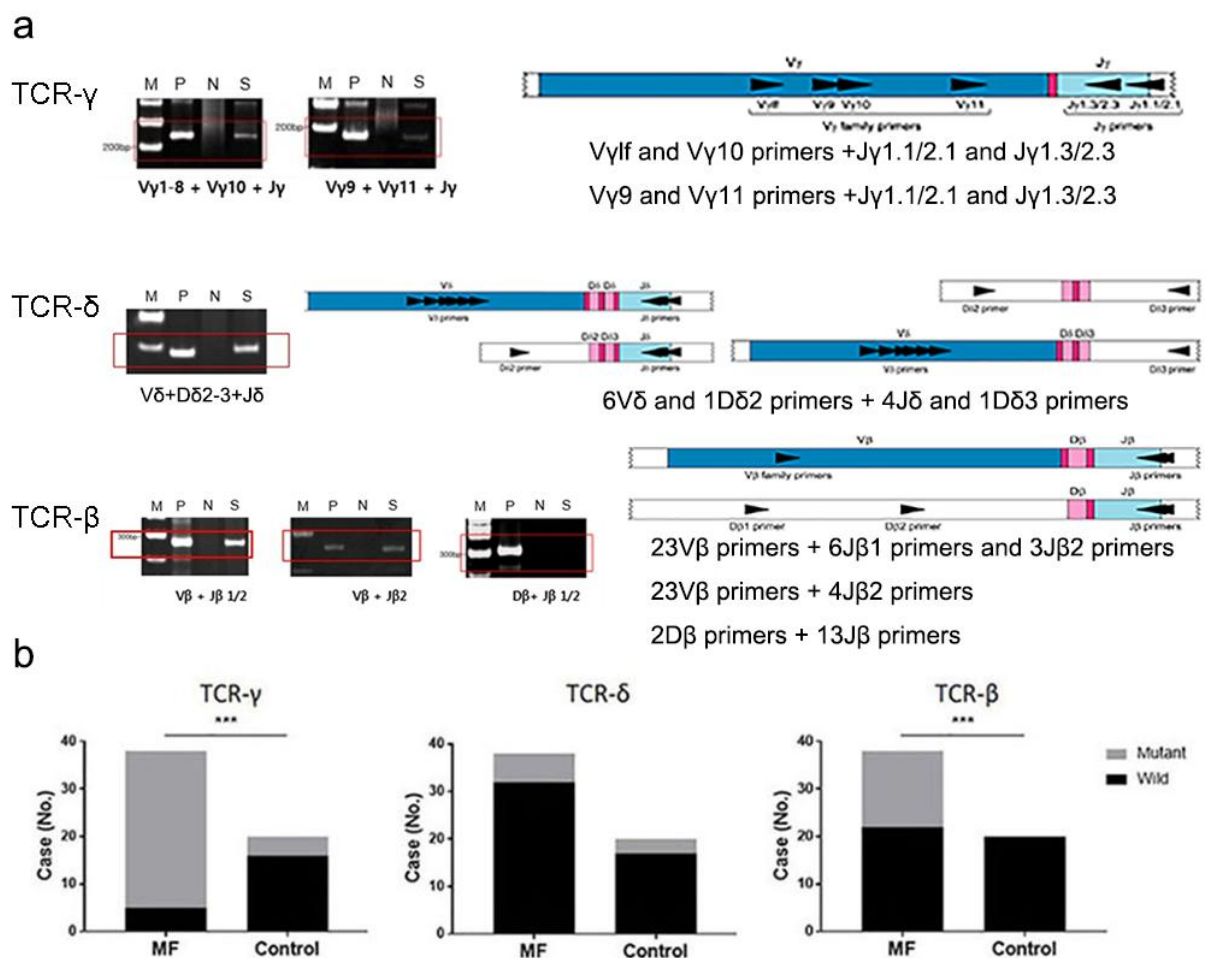


Figure 3. Clonal TCR gene rearrangement in early MF and non-MF. (a) PCR-based testing results. (b) Quantification of TCR gene rearrangement. *** $p < 0.0005$.

Table 4. Molecular profiles of early MF and non-MF.

	Early MF (n = 38)	Non-MF (n = 22)	p-Value
TCR gene rearrangement			<0.0001
TCR- γ	33 (86.8%)	4 (18.2%)	<0.0001
TCR- δ	6 (15.8%)	3 (13.6%)	>0.9999
TCR- β	16 (42.1%)	0 (0.0%)	0.0002

4. Discussion

We classified early MF and non-MF cases according to the ISCL diagnostic algorithm and analyzed each parameter in the algorithm to improve the accuracy and reliability of ancillary findings. We found that total, clinical, pathologic, molecular, and immunopathologic scores differed significantly between groups. Therefore, benign mimickers should easily be able to be excluded according to the ISCL diagnostic algorithm. However, a diagnostic problem still remains because the clinical features of early MF vary greatly across patients [4,15], and the histologic features of MF during the patch stage are subtle, as lymphocytic infiltrates can be scant and lymphocytic atypia can be minimal [16,17]. If clinico-histologic features are similar and the sum of clinical and histologic scores is <4 according to the ISCL algorithm, immunopathologic and molecular/biologic features can play a determinant role in diagnosing early MF.

Although the ISCL algorithm clearly specifies the antibodies that must be stained, their cut-off values are undependable due to their low sensitivities [9–12]. Thus, we calculated the cut-off value of each marker based on its ROC curve to improve the reliability of molecular/biologic criteria. We found that CD2 and CD3 expression were similar between groups and had poor and failing discriminatory abilities, respectively. The optimal cut-off value for CD2, CD3, and CD5 expression was 92.5%, although the ISCL algorithm recommends a cut-off value of <50% for each marker [5,6]. Actually, only three out of 38 early MF cases showed less than 50% expression of CD2, CD3, or CD5 in this study. Furthermore, a 92.5% cut-off value is so high that it is difficult to differentiate the loss of expression from a reactive pattern. CD5 expression differed significantly between groups, but there were only two cases of early MF with CD5 epidermal discordance. Notably, however, CD7 expression and its epidermal discordance not only differed significantly between groups but also had a good discriminatory ability, with 73.7% sensitivity and 77.3% specificity at a 22.5% cut-off value. Although the ISCL diagnostic algorithm recommends a <10% cut-off value for CD7 expression, we found that only 18 out of 38 early MF cases (47.4%) showed <10% CD7 expression. Instead, we identified 22.5% as an optimal cut-off value for CD7 expression, with 28 out of 38 early MF cases (73.7%) showing <22.5% CD7 expression. Therefore, we propose that evaluation of CD5 and CD7 expression should be included in the diagnostic criteria for early MF, but CD2 and CD3 expression are not helpful for diagnosis. When the new cut-off values of CD5 and CD7 expression are applied to this data set, three non-MF cases are re-diagnosed as early MF and then, the specificity of the ISCL diagnostic algorithm could rise from 63.6% to 73.7%.

The ISCL diagnostic algorithm for early MF clearly documents the methodology for PCR-based analysis of TCR gene rearrangement. However, critical clones and features of TCR genes are not included. To evaluate these molecular features, we performed PCR-based testing to detect the monoclonality or oligoclonality of TCR- γ , δ , and β chains. We found that TCR- γ and β chains were frequently mutated in early MF but that there was no difference in TCR- δ mutation between early MF and non-MF groups. Notably, TCR- β clonality was not identified in any non-MF cases, therefore we believe that TCR- β clonality has 100% specificity in early MF. TCR rearrangements were also detected in 4 out of 22 non-MF cases in this study, which are presumed to be persistent cutaneous inflammatory infiltrates of monoclonal or oligoclonal T-cells due to conditions secondary to autoimmune or iatrogenic immune dysregulation and chronic idiopathic dermatoses [18–20].

In this study, after making pathologic diagnoses, dermatologists changed the clinical diagnosis from mycosis fungoides to parapsoriasis in 7 out of 22 non-MF cases. Parapsoriasis describes a group of cutaneous diseases that can be characterized by scaly patches or slightly elevated papules and/or plaques dispersed on the trunk or proximal extremities that have a resemblance to psoriasis [21]. Histologically, it shows cutaneous lymphoproliferations and refers to a heterogeneous group of uncommon dermatoses similar to psoriasis. It is broadly divided into two main types: small plaque parapsoriasis (SPP) and large plaque parapsoriasis (LPP). While SPP is generally considered a chronic benign condition, LPP is regarded as a premalignant dermatosis with a substantial risk of progression to

mycosis fungoides. Actually, 10% to 30% of LPP cases progress to a frank cutaneous T-cell lymphoma [22]. It is known that monoclonal populations of T-cells could be found in 20% or more cases of LPP [23]. Therefore, the major differential diagnosis of parapsoriasis includes early-stage MF and chronic eczema, which usually cannot be distinguished on histologic grounds alone [24]. Thus, we included parapsoriasis as one of the mimickers of mycosis fungoides. However, there is considerable debate on the terminology and relation of parapsoriasis to MF. We believe that there was still a possibility of the evolution of mycosis fungoides in parapsoriasis cases involved in this study, and parapsoriasis could not be entirely defined by the ISCL algorithm.

In conclusion, we propose CD5 and CD7 deficiency as mandatory immunopathologic criteria and PCR-based testing for TCR- γ and β chains as required molecular/biologic criteria to improve the efficiency of diagnosing early MF using the ISCL algorithm. In particular, the cut-off value of CD7 expression should be increased from <10% to <22.5% to improve the discriminatory ability of this criterion.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/cells10102758/s1>, Table S1: Clinicopathologic features and ISCL scores of cases included in the study; Table S2: Curvilinear coordinates of ROC, sensitivity, specificity, and Youden's index for CD2, CD3, CD5, and CD7 expression.

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Informed Consent Statement: Patient consent was waived due to the retrospective nature of the study and minimal risk to the patients.

Data Availability Statement: Data are available from the corresponding author upon request.

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References

1. Cerroni, L.; Sander, C.A.; Smoller, B.R.; Willemze, R. *World Health Organization Classification of Tumours*, 4th ed.; Elder, D.E., Massi, D., Scolyer, R.A., Willemze, R., Eds.; International Agency for Research on Cancer: Lyon, France, 2018.
2. Benner, M.F.; Jansen, P.M.; Vermeer, M.H.; Willemze, R. Prognostic factors in transformed mycosis fungoides: A retrospective analysis of 100 cases. *Blood* **2012**, *119*, 1643–1649. [[CrossRef](#)] [[PubMed](#)]
3. Van Doorn, R.; van Haselen, C.W.; van Voorst Vader, P.C.; Geerts, M.L.; Heule, F.; de Rie, M.; Steijlen, P.M.; Dekker, S.K.; van Vloten, W.A.; Willemze, R. Mycosis fungoides: Disease evolution and prognosis of 309 Dutch patients. *Arch. Dermatol.* **2000**, *136*, 504–510. [[CrossRef](#)] [[PubMed](#)]
4. Gru, A.A.; Schaffer, A. *Hematopathology of the Skin: Clinical & Pathological Approach*, 1st ed.; Wolters Kluwer Health: Philadelphia, PA, USA, 2017.
5. Pimpinelli, N.; Olsen, E.A.; Santucci, M.; Vonderheid, E.; Haeffner, A.C.; Stevens, S.; Burg, G.; Cerroni, L.; Dreno, B.; Glusac, E.; et al. Defining early mycosis fungoides. *J. Am. Acad. Dermatol.* **2005**, *53*, 1053–1063. [[CrossRef](#)] [[PubMed](#)]

6. Olsen, E.; Vonderheid, E.; Pimpinelli, N.; Willemze, R.; Kim, Y.; Knobler, R.; Zackheim, H.; Duvic, M.; Estrach, T.; Lamberg, S.; et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: A proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood* **2007**, *110*, 1713–1722. [[PubMed](#)]
7. Vandergriff, T.; Nezafati, K.A.; Susa, J.; Karai, L.; Sanguinetti, A.; Hynan, L.S.; Ambruzs, J.M.; Oliver, D.H.; Pandya, A.G. Defining early mycosis fungoides: Validation of a diagnostic algorithm proposed by the International Society for Cutaneous Lymphomas. *J. Cutan. Pathol.* **2015**, *42*, 318–328. [[CrossRef](#)] [[PubMed](#)]
8. Amorim, G.M.; Quintella, D.C.; Niemeyer-Corbellini, J.P.; Ferreira, L.C.; Ramos, E.S.M.; Cuzzi, T. Validation of an algorithm based on clinical, histopathological and immunohistochemical data for the diagnosis of early-stage mycosis fungoides. *An. Bras. Dermatol.* **2020**, *95*, 326–331. [[CrossRef](#)] [[PubMed](#)]
9. Lindae, M.L.; Abel, E.A.; Hoppe, R.T.; Wood, G.S. Poikilodermatous mycosis fungoides and atrophic large-plaque parapsoriasis exhibit similar abnormalities of T-cell antigen expression. *Arch. Dermatol.* **1988**, *124*, 366–372. [[CrossRef](#)] [[PubMed](#)]
10. Smoller, B.R.; Santucci, M.; Wood, G.S.; Whittaker, S.J. Histopathology and genetics of cutaneous T-cell lymphoma. *Hematol. Oncol. Clin. N. Am.* **2003**, *17*, 1277–1311. [[CrossRef](#)]
11. Wood, G.S.; Hong, S.R.; Sasaki, D.T.; Abel, E.A.; Hoppe, R.T.; Warnke, R.A.; Morhenn, V.B. Leu-8/CD7 antigen expression by CD3+ T cells: Comparative analysis of skin and blood in mycosis fungoides/Sezary syndrome relative to normal blood values. *J. Am. Acad. Dermatol.* **1990**, *22*, 602–607. [[CrossRef](#)]
12. Michie, S.A.; Abel, E.A.; Hoppe, R.T.; Warnke, R.A.; Wood, G.S. Discordant expression of antigens between intraepidermal and intradermal T cells in mycosis fungoides. *Am. J. Pathol.* **1990**, *137*, 1447–1451. [[PubMed](#)]
13. Youden, W.J. Index for rating diagnostic tests. *Cancer* **1950**, *3*, 32–35. [[CrossRef](#)]
14. Muller, M.P.; Tomlinson, G.; Marrie, T.J.; Tang, P.; McGeer, A.; Low, D.E.; Detsky, A.S.; Gold, W.L. Can routine laboratory tests discriminate between severe acute respiratory syndrome and other causes of community-acquired pneumonia? *Clin. Infect. Dis.* **2005**, *40*, 1079–1086. [[CrossRef](#)] [[PubMed](#)]
15. Stevens, S.R.; Ke, M.S.; Birol, A.; Terhune, M.H.; Parry, E.J.; Ross, C.; Mostow, E.N.; Gilliam, A.C.; Cooper, K.D.; Interdisciplinary Cutaneous Lymphoma Program. 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. *Br. J. Dermatol.* **2003**, *149*, 513–522. [[CrossRef](#)] [[PubMed](#)]
16. Shapiro, P.E.; Pinto, F.J. The histologic spectrum of mycosis fungoides/Sezary syndrome (cutaneous T-cell lymphoma). A review of 222 biopsies, including newly described patterns and the earliest pathologic changes. *Am. J. Surg. Pathol.* **1994**, *18*, 645–667. [[CrossRef](#)]
17. Sanchez, J.L.; Ackerman, A.B. The patch stage of mycosis fungoides. Criteria for histologic diagnosis. *Am. J. Dermatopathol.* **1979**, *1*, 5–26. [[CrossRef](#)]
18. Delfau-Larue, M.H.; Laroche, L.; Wechsler, J.; Lepage, E.; Lahet, C.; Asso-Bonnet, M.; Bagot, M.; Farcet, J.P. Diagnostic value of dominant T-cell clones in peripheral blood in 363 patients presenting consecutively with a clinical suspicion of cutaneous lymphoma. *Blood* **2000**, *96*, 2987–2992. [[CrossRef](#)]
19. Plaza, J.A.; Morrison, C.; Magro, C.M. Assessment of TCR-beta clonality in a diverse group of cutaneous T-Cell infiltrates. *J. Cutan. Pathol.* **2008**, *35*, 358–365. [[CrossRef](#)] [[PubMed](#)]
20. Guitart, J.; Magro, C. Cutaneous T-cell lymphoid dyscrasia: A unifying term for idiopathic chronic dermatoses with persistent T-cell clones. *Arch. Dermatol.* **2007**, *143*, 921–932. [[CrossRef](#)] [[PubMed](#)]
21. Patterson, J.W. *Weedon's Skin Pathology*, 5th ed.; Elsevier: Amsterdam, The Netherlands, 2021; pp. 114–115.
22. Lazar, A.P.; Caro, W.A.; Roenigk, H.H., Jr.; Pinski, K.S. Parapsoriasis and mycosis fungoides: The Northwestern University experience, 1970 to 1985. *J. Am. Acad. Dermatol.* **1989**, *21*, 919–923. [[CrossRef](#)]
23. Kikuchi, A.; Naka, W.; Harada, T.; Sakuraoka, K.; Harada, R.; Nishikawa, T. Parapsoriasis en plaques: Its potential for progression to malignant lymphoma. *J. Am. Acad. Dermatol.* **1993**, *29*, 419–422. [[CrossRef](#)]
24. Kempf, W.; Burg, G.; Massone, C.; Cerroni, L.; Pulitzer, M.; Crowson, A.N.; Magro, C.M. *Barnhill's Dermatopathology*, 4th ed.; Barnhill, R.L., Ed.; Mc Graw Hill: New York, NY, USA, 2020; pp. 1184–1185.