

Mycosis Fungoides and Its Relationship to Atopy, Serum Total IgE, and Eosinophil Counts

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Abstract

It has been controversial whether mycosis fungoides is more prevalent in individuals with atopy. In the present study of 728 patients, 29.1% had a history of ≥ 1 common atopic disorders. The patients with atopy had higher total serum IgE levels and eosinophil counts compared with those without atopy. Higher levels were associated with advanced disease but did not otherwise have significant effects on overall survival.

Introduction: A recent serologic study and reports of increased serum total IgE (IgE-t) and eosinophil counts have suggested that the prevalence of atopy is more common in patients with mycosis fungoides (MF) than previously recognized. **Patients and Methods:** Patients with clinicopathologic features that were diagnostic and/or consistent with MF and/or the presence or absence of an atopic disorder (eg, allergic rhinitis, asthma, eczematous dermatitis), which was determined by patient history, eosinophil counts, and serum IgE-t obtained at evaluation, were selected from a patient registry. The MF population was divided into those with atypical and typical clinical presentations. We performed matching of controls using age, sex, and race from the 2005 to 2006 National Health Education Survey.

Results: A history of allergic rhinitis was recorded for 186 of 728 patients (25.5%) with typical MF and 71 of 229 patients (31%) with atypical MF. However, the prevalence of asthma and eczema was low. The IgE-t and eosinophil counts were higher for patients with typical MF than for controls and for patients with atopic diathesis than for patients without atopy. The IgE-t and eosinophil counts were higher for the patients with advanced-stage MF compared with those for the patients with less-advanced disease for both atopic and nonatopic cohorts. In the Cox model with age and clinical stage as covariates, a history of atopy, increased IgE-t, and blood eosinophilia (> 500 cells/mm³) did not correlate with overall survival. **Conclusion:** The findings from the present study did not reveal a significant association of atopy in patients with MF. However, atopy is a factor in the increased IgE-t and eosinophil counts observed in MF. Another factor is related to the disease stage, including possibly the influence of cytokines secreted by T-helper type 2-polarized neoplastic cells.

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Introduction

Mycosis fungoides (MF) is the most common expression of cutaneous T-cell lymphoma (CTCL).¹ The classic progression of MF is from minimally infiltrated cutaneous patch lesions to more infiltrated plaques and, eventually, nodules or tumors. Less common

clinical presentations of MF include erythrodermic and tumor d'emblée variants; however, these were not included in the present study. Advanced MF is characterized by tumors, involvement of lymph nodes and extranodal sites. Disease progression can be accompanied by a histopathologic transition from small-to-intermediate-size neoplastic cells to a large cell lymphoma phenotype (large cell transformation).²

Atopic diathesis (atopy) refers to the tendency of individuals to develop excessive IgE-mediated responses to environmental allergens. Common clinical manifestations include allergic rhinitis/conjunctivitis (hay fever), asthma, and eczematous dermatitis (eczema), including childhood-onset eczema (atopic dermatitis).³ For most epidemiologic studies, the demonstration of atopy has required positive results from prick skin tests to allergens or the detection of allergen-specific IgE (>0.35 kUA/L) to common food or airborne allergens in the blood.

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MF and Atopy, IgE-t, and Eosinophil Count

Serum total IgE (IgE-t) comprises a cognate fraction composed of allergen-specific IgEs and a noncognate fraction that includes nonallergen-specific IgEs.⁴ Patients with clinically active atopic disorders, especially asthma, have an expanded cognate fraction of IgE-t and increased IgE-t levels. IgE-t values > 100 IU/mL has been used to define patients with “probable atopy.” In contrast, IgE-t values < 20 IU/mL have been considered to indicate that atopy is unlikely to be present.^{3,5} However, a proportion of individuals with IgE-t values > 100 IU/mL have been considered to be non-atopic, with symptoms apparently unrelated to atopy. The IgE-t is a nonspecific discriminator for atopic status owing to the wide overlap of nonatopic and atopic individuals at the cutpoint of 100 kU/L.⁶

Several studies have shown increased IgE-t levels in patients with MF compared with controls.⁷⁻⁹ Kural et al⁹ observed a greater frequency of allergen-specific IgEs (ie, serologic evidence of atopy) in Turkish patients with MF compared with controls. Their results implied that atopy is common in patients with MF. In contrast, our group detected IgEs specific for aeroallergens in 3 of 20 patients (15%) with plaque-phase MF, a difference that was not statistically significant compared with the control group.¹⁰

Because eczematous or psoriasiform dermatitis can precede or accompany the diagnosis of MF, it has been proposed that persistent cutaneous inflammation might play a role in the pathogenesis of MF.¹¹ This raises the question regarding whether individuals with an atopic diathesis, in general, and atopic eczema/dermatitis, in particular, might be at increased risk of developing MF.

Whittemore et al¹² observed a greater prevalence of asthma and eczema, but not hay fever, in 174 patients with MF compared with 47 controls. In addition, the results from skin allergy tests were more likely to be positive in those with MF. The multinational Interlymph (International Lymphoma Epidemiology Consortium) study, which combined MF and Sézary syndrome, indicated that patients with pre-existing eczema had a 2.38 relative risk of developing MF or Sézary syndrome compared with controls, with no increased risk of hay fever or asthma.¹³

In contrast, 2 controlled studies from Europe showed no association between the presence of atopic disorders and MF.^{14,15} Moreover, a large uncontrolled study from the Mayo Clinic found that 12 of 102 patients (11.8%) with MF had self-reported an atopic disorder and only 2 patients (2%) reported history of atopic dermatitis.¹⁶ Data from the multi-institutional Mycosis Fungoides Cooperative Group indicated that the frequency of childhood eczema was 5.7% (12 of 211 patients with MF; including erythrodermic MF).¹⁷ The frequency of hay fever and asthma was 10% and 4.3%, respectively, and the prevalence of drug reactions was 21.8%. The differing results from these studies can be explained by the definition of eczema (classic childhood-onset atopic dermatitis vs. variants of atopic eczema in adults or endogenous eczema that might not be atopic), patients' inability to recall childhood eczema or other atopic manifestations, the inclusion of erythrodermic MF with more typical expressions of MF, and the use of increased IgE-t levels as a criterion of atopy.

Patients and Methods

The patients included in the present study were evaluated from 1980 to 2005. The clinical, pathologic, and laboratory data of the patients with a diagnosis of MF were retrieved from a patient

registry. The institutional review board of the Johns Hopkins University approved the present study (approval no. NA_00004267). Patients were classified as having patch, plaque, or tumor-phase MF according to the degree of infiltration (thickness) of the most prominent lesion at the initial evaluation. Patients with erythrodermic MF were excluded. The skin T rating (T1a, T1b, T2a, T2b, and T3) and clinical stage (IA, IB, IIA, IIB, IVA1, IVA2, and IVB) were determined in accordance with the International Society for Cutaneous Lymphomas—European Organization of Research and Treatment of Cancer recommendations¹⁸ ([Supplemental Appendix](#), Comment 1; available in the online version).

Atopy was considered present if the patient had a personal history of asthma, allergic rhinitis or hay fever (with nonseasonal sinusitis excluded), or longstanding eczema thought to result from atopy. This includes eczema with an onset in childhood (atopic dermatitis) but also adult-onset atopic dermatitis, chronic hand or foot eczema, and persistent nummular dermatitis, conditions often associated with a history of allergic asthma or rhinitis/hay fever.^{19,20} Food allergies and type 1 hypersensitivity reactions to hymenoptera stings or drugs were additional possible atopic factors. However, because this information was not routinely obtained, it was not used to determine the prevalence of atopy in the study patients. Patients without documentation of the presence or absence of an atopic condition were excluded from the present study.

Patients were also excluded if they did not have measurements of serum IgE-t available or whose disease was in remission at evaluation. Also, to minimize the influence of previous treatments on IgE-t levels, the patients who had received systemic corticosteroids during or just before evaluation or previous chemotherapy other than methotrexate or immunosuppressive drugs were excluded.

Histopathologic Classification of Cases

All patients selected for the present study had histopathologic findings that were either diagnostic for, or consistent with the diagnosis of, MF, a designation often rendered by dermatopathologists for specimens that lack the major diagnostic criteria of MF such as Pautrier collections or diffuse infiltration of the epidermis with atypical lymphocytes. Equivalent interpretations included probable MF, atypical epidermotropic infiltrate, and band-like/lichenoid infiltrates containing atypical cells. In almost all cases, skin specimens obtained elsewhere before referral were reviewed.

A diagnosis of MF was deemed to be confirmed if (1) ≥ 1 skin specimens were interpreted as diagnostic for MF or as malignant lymphoma compatible with MF, usually from patients with advanced disease (659 patients) or (2) the specimen findings plus the results from an ancillary test with high diagnostic specificity were compatible with MF (14 patients). Specifically, these confirmatory tests demonstrated a T-cell clone using the Southern blot technique²¹ ([Supplemental Appendix](#), Comment 2; available in the online version) and/or loss of a pan T antigen (CD2, CD3, CD5), < 10% CD7⁺ cells in the dermal infiltrate by immunohistochemistry,²² or evidence of aneuploid cells using touch imprint cytophotometry.²³

The other 55 patients with specimens interpreted as consistent with MF had had ≥ 1 less specific ancillary study performed ([Supplemental Table 1](#) available in the online version). Of these 55

specimens, 16 (29%) had evidence of a T-cell clone using polymerase chain reaction (PCR; subgroup 2A), 27 (49%) had CD7⁺ cells expression of 10% to 30% in the dermal infiltrate using immunohistochemistry (subgroup 2B), and 12 (22%) were positive for both ancillary tests (subgroup 2C).

Clinical Classification of MF

Atypical Presentations. Because MF can present with a variety of clinical and histopathologic findings,²⁴ patients with an “atypical” clinical presentation were separated from those with a more “typical” presentation. The atypical MF presentations included the following:

1. Hypopigmented MF (44 patients)²⁵
2. Patients with MF coexisting with cutaneous CD30⁺ lymphoproliferative disease (CD30LPD), which encompasses lymphomatoid papulosis (LyP) and cutaneous CD30⁺ anaplastic large cell lymphoma (ALCL), and were classified in the present study as MF/CD30LPD (41 patients)^{26,27}
3. Unilesional or solitary MF (59 patients)²⁸
4. MF palmoplantaris (23 patients)²⁹
5. MF with a purpuric component, including lesions resembling pigmented purpura, classified as purpuric MF (19 patients)³⁰ and digitate MF (43 patients³¹; [Supplemental Appendix](#), Comment 3; available in the online version)

The remaining atypical MF cases included papular MF (10 patients), interstitial MF (10 patients), MF tumor d’emblée (6 patients), lupus erythematosus-like MF (3 patients), and other rare or difficult to classify presentations. These patients were not included in further analyses.

Typical Presentations. The remaining 728 patients were classified as having typical MF. Nevertheless, distinctive clinical and histopathologic variants were recorded for some patients, and these patients were separated from the main group for analysis. These 195 patients had the following:

1. Evidence of early poikiloderma or parakeratosis variegata, classified as poikilodermic MF (73 patients)³²
2. Lesions with a psoriasiform appearance, classified in our study psoriasiform MF (16 patients)³³
3. Lesions with an eczematous component, including 1 patient with coexisting active atopic dermatitis, classified as eczematous MF (38 patients)
4. Lesions with histopathologic evidence of follicular mucinosis or folliculotropic infiltrates, classified as follicular MF (38 patients^{34,35}; [Supplemental Appendix](#), Comment 4; available in the online version)
5. Lesions of patch or thin plaque MF with atypical CD8⁺ epidermotropic T cells, classified as CD8⁺ MF (30 patients)³⁶

The remaining 533 patients had clinically typical MF but without a description of any of the listed variants. These patients were considered to have MF, not otherwise classified.

Before 2002, serum IgE-t was quantified by various commercial reference laboratories, with the results expressed as IU/mL. After

2002, IgE-t was measured in the Johns Hopkins Dermatology Allergy and Clinical Immunology Reference Laboratory using the Immuno CAP method (Thermo Fisher Scientific, Uppsala, Sweden) and expressed as IU/mL. The absolute eosinophil counts were calculated from the total and differential leucocyte counts. The IgE-t and absolute eosinophil measurements are presented as the median and interquartile range. Because the IgE-t values were skewed, they were normalized by log transformation, and the geometric mean (ie, anti-log of the mean log₁₀ IgE-t value) and its standard error are also presented. Blood eosinophilia was defined as an absolute eosinophil count of > 500 cells/mm³.³⁷

The IgE-t and absolute eosinophil counts of patients with typical MF were compared against an age-, race-, and sex-matched control population selected from the 2005 to 2006 National Health and Nutrition Examination Survey (NHANES). NHANES provides an assessment of the total and allergen-specific IgE antibodies in the U.S. population (available at: <http://www.cdc.gov/nchs/nhanes.htm>).³⁸ The selection of controls from each age-, race-, sex-matched category was performed using the random selection option in SPS, version 13.0, for Windows (IBM Corp, Armonk, NY). Because the NHANES used fill values for IgE-t values less than the lower limit of detection (ie, 2 IU/mL divided by the square root of 2 equals 1.41 IU/mL) and the upper limit of detection was 50,000 IU/mL, our data were modified to reflect these limits. Thus, the samples from 20 patients with MF were assigned an IgE-t value of 1.41 IU/mL, and a potential outlier value of 60,825 IU/mL was changed to 50,000 IU/mL. In the NHANES population, serologic atopy was defined as ≥ 1 aeroallergen-specific IgE of ≥ 0.35 kU/L reactive against allergens from trees (oak, birch), grass (rye, Bermuda), weeds (ragweed, Russian thistle), cat or dog dander, dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), or molds (*Alternaria*, *Aspergillus fumigatus*). IgEs specific for allergens from various foods, cockroaches, and rodents were not included.

Statistical Analysis

The Fisher exact test and Pearson χ^2 test were used to test categorical data in 2×2 and R by C tables, respectively. When the sample size was too large, the Monte Carlo option was used to determine the exact significance levels. The Mann-Whitney U (MW) and Kruskal-Wallis tests were used to compare the median values among 2 and ≥ 3 independent samples, respectively. The parametric *t* test with equal variances not assumed (*t* test) and the 1-way analysis of variance test were also used to confirm statistical significance using normalized log transformed IgE-t values. When 1-way analysis of variance showed significant differences among groups, the Games-Howell post hoc test was used to determine which values were significantly different statistically.

The Cox proportional hazards model and Kaplan-Meier method were used for survival analyses. Because details about the cause of death were not available for many patients, all-cause death was used as the endpoint. The log-rank test of Mantel was used to determine the differences in the survival curves. SYSTAT10 and SPSS, version 13.0, for Windows (IBM Corp) and StatXact-3 (Cytel, Inc, Cambridge, MA) were used for statistical analysis in the present study.

MF and Atopy, IgE-t, and Eosinophil Count

Table 1 Demographics and Clinical Stage Stratified by Mycosis Fungoides Presentation^a

Cohort	Patients (n)	Age (y)	Sex (M; F)	Race (W; B; H; A; O)	T Rating (1a; 1b; 2a; 2b; 3)	Clinical Stage (IA; IB; IIA; IIB; IV)
Typical MF	728	59 (47-70)	438; 290	622; 91; 8; 5; 2	275; 120; 119; 140; 74	387; 216; 40; 54; 31
Poikilodermic MF	73	57 (49-66)	37; 36	67; 5; 1; 0; 0	23; 7; 30; 12; 1	28; 33; 10; 1; 1 ^b
Psoriasiform MF	16	74 (66-78)	8; 8	13; 3; 0; 0; 0	0; 6; 1; 7; 2	5; 3; 5; 2; 1 ^b
Eczematous MF	38	65 (54-74)	19; 19	29; 8; 1; 0; 0	8; 6; 12; 9; 3	14; 19; 2; 3; 0
Follicular MF	38	56 (45-68)	28; 10	36; 1; 0; 1; 0	7; 15; 2; 8; 6	21; 10; 1; 5; 1 ^c
CD8 ⁺ MF	29	57 (42-65)	18; 11	27; 0; 2; 0; 0	16; 4; 4; 3; 2	20; 7; 2; 0; 0
MF, NOC	534	59 (46-70)	328; 206	450; 74; 4; 4; 2	221; 82; 70; 101; 60	299; 144; 22; 41; 28 ^d
Atypical MF	229	55 (42-65)	133; 96	176; 49; 2; 1; 1	127; 38; 52; 10; 2	160; 61; 4; 3; 1
Hypopigmented MF	44	45 (34-52)	14; 30	7; 36; 1; 0; 0	17; 1; 23; 3; 0	19; 25; 0; 0; 0
MF/CD30LPD	41	55 (42-66)	22; 19	35; 5; 0; 0; 1	18; 3; 12; 6; 2	20; 16; 1; 3; 1 ^b
Unilesional MF	59	57 (43-67)	33; 29	55; 4; 0; 0; 0	42; 17; 0; 0; 0	59; 0; 0; 0; 0
Palmoplantar MF	23	55 (43-62)	12; 11	19; 4; 0; 0; 0	9; 13; 1; 0; 0 ^e	21; 1; 1; 0; 0
Purpuric MF	19	57 (38-73)	11; 8	18; 0; 0; 1; 0	14; 1; 4; 0; 0	13; 5; 1; 0; 0
Digitate MF	43	60 (56-68)	41; 2	42; 0; 1; 0; 0	27; 3; 13; 0; 0	28; 14; 1; 0

Data presented as number of patients or median (interquartile range).

Abbreviations: A = Asian; B = black; F = female; M = male; MF = mycosis fungoides; NOC = not otherwise classified; O = other; W = white.

^aComparison of all typical versus all atypical MF categories using the Fisher exact test or χ^2 test: sex, $P = .052$; race, $P = .025$; T rating, $P < .001$; stage, $P < .001$; comparison of 5 typical MF variants, excluding MF, NOC, using χ^2 test: sex, $P = .143$; race, $P = .028$; T rating, $P \leq .001$; stage, $P = .003$; comparison of 6 atypical MF variants using χ^2 test: sex, $P < .001$; race, $P < .001$; T rating, $P < .001$; stage, $P < .001$.

^bStage IV included 1 patient with stage IV2A.

^cStage IV included 1 patient with stage IVB.

^dStage IV included 7 patients with stage IVA1, 19 with stage IVA2, and 2 with stage IVB.

^eThe clinical distinction between patch and plaque lesions on palms or soles is somewhat arbitrary.

Results

The demographics and clinical stage of the typical and atypical MF categories are presented in Table 1. Of the 728 patients with a diagnosis of typical MF, 85.4% were white, significantly greater than the 78.9% for the patients with atypical MF ($P = .006$). The difference might have resulted from the high proportion of black patients with hypopigmented MF (36 of 44 patients).

A difference in racial distribution and clinical stage was also observed among the 5 cohorts with different expressions of typical MF. The difference in racial distribution occurred because only 1 black patient had follicular MF and no black patient had CD8⁺ MF. In terms of clinical stage, the proportion of patients with early-stage MF (clinical stage IA/IB) ranged from 50% for those with psoriasiform MF to 93% for those with CD8⁺ MF. Compared with the 83% for those with typical MF, not otherwise classified, the only difference that was statistically significant was psoriasiform MF ($P = .003$).

Prevalence of Atopy According to Personal Patient History

Of the 728 patients classified as having typical MF, 212 (29.1%) had a personal history of ≥ 1 of the 3 common atopic disorders, including single cases of allergic rhinitis/hay fever (150 patients), asthma (17 patients), and eczema (8 patients). Of the 34 patients with 2 atopic disorders, 18 had had rhinitis and asthma, 15 rhinitis and eczema, and 1 patient asthma and eczema. Three patients had a history of all 3 atopic conditions. Six patients had evidence of active

atopic dermatitis coexisting with MF and were included in the eczematoid MF group.

Influence of Atopic Diathesis on Drug Hypersensitivity

A history of a hypersensitivity reaction to a drug, tetanus toxoid, or contrast media was reported for 136 of 613 evaluable patients (22.2%). Allergic contact dermatitis, including topically applied nitrogen mustard, was excluded. Of these, a reaction to penicillin or its derivatives or sulfonamide-type antibiotics had occurred in 76 (55.9%) and 17 (12.5%) patients, respectively (Supplemental Table 2 available in the online version).

No significant difference in the frequency or type of penicillin or sulfonamide drug reaction was observed between the patients with and without an atopic diathesis. A type 1 hypersensitivity (eg, urticaria, angioedema, anaphylaxis) to penicillin occurred more often in patients without a history of an atopic disorder (34 of 54 patients [63%]) than in patients with such a history (8 of 22 patients [36%]; $P = .044$). No statistically significant difference was noted for sulfonamide-type drugs ($P = 1.00$).

Prevalence of Atopic Conditions Related to Cutaneous Manifestations of MF

In terms of the clinical status of the skin (Supplemental Table 3 available in the online version), the frequency of an atopic disorder determined from patient history differed significantly among patients considered to have typical patch, plaque, or tumor phase MF

Table 2 Influence of Mycosis Fungoides Status on Serum Total IgE Stratified by Patient History of Atopic Disorder

Atopy	Patients (n)	Serum Total IgE ^a (IU/mL)	KW P Value	GM ± SE	ANOVA P Value
Variant					
No			.001		<.001
MFPT	263	36 (12-98)		36 ± 1.1	
MFPQ	201	65 (17-65)		63 ± 1.1	
MFT	52	67 (25-377)		89 ± 1.4	
Yes			<.001		<.001
MFPT	129	45 (15-153)		46 ± 1.2	
MFPQ	61	66 (23-270)		85 ± 1.3	
MFT	22	418 (64-2181)		362 ± 1.5	
Stage					
No			<.001		<.001
T1a	175	29 (10-87)		29 ± 1.1	
T1b	84	51 (11-123)		39 ± 1.2	
T2a	89	53 (18-141)		53 ± 1.2	
T2b	107	89 (27-295)		94 ± 1.2	
T3	37	68 (26-368)		87 ± 1.4	
All stage IV	24	66 (13-249)		68 ± 1.5	
Yes			<.001		<.001
T1a	100	45.5 (13-155)		44 ± 1.2	
T1b	34	74 (28-274)		82 ± 1.3	
T2a	30	34 (20-151)		55 ± 1.4	
T2b	24	58.5 (21-631)		105 ± 1.5	
T3	17	283 (49-1855)		296 ± 1.6	
All stage IV	7	435 (23-2955)		255 ± 2.3	

Abbreviations: ANOVA = analysis of variance; GM = geometric mean; MFPT = mycosis fungoides patch; MFPQ = mycosis fungoides plaque; MFT = mycosis fungoides tumor phase; SE = standard error.

^aData presented as median (interquartile range).

($P = .029$) and when grouped according to the skin T rating ($P = .004$). The prevalence of atopy was greater for patients with clinically early MF (patch-phase MF or T1a skin rating) and then decreased until the tumor phase. In addition, 45% of patients with MF and an eczematous component had had a history of an atopic disorder compared with 29% of patients with a more typical expression of MF. However, this difference did not quite reach statistical significance ($P = .066$).

The prevalence of atopic disorders in those with atypical MF is provided in [Supplemental Table 4](#) (available in the online version). Similar to more typical expressions of MF, approximately one third of patients had a history of atopy, mainly resulting from the 31% prevalence of allergic rhinitis. The prevalence of asthma and eczema was 7.4% and 5.2%, respectively. The difference in these prevalence rates compared with those reported for typical MF was not statistically significant.

Comparison of IgE-t Levels for Nonatopic and Atopic Patients Stratified by Typical MF Status

The influence of the clinical status of typical MF on the IgE-t levels was evaluated in patients with and without a personal history of atopy ([Table 2](#)). Overall, the IgE-t levels were lowest for patients with patch-phase MF and highest for those with

tumor-phase MF for both nonatopic and atopic groups. In addition, the IgE-t levels were higher for each diagnostic category in atopic patients compared with nonatopic patients.

Table 3 Relationship Between Blood Eosinophil Count and Skin T Ratings for Mycosis Fungoides Limited to Skin and Extracutaneous Involvement

Stage	Patients (n)	Patients With Eosinophil Count > 500/ mm ³ (n; %)	Eosinophil Count (Cells/ mm ³) ^a
All T1	386	6 (1.6)	119 (62-204)
T1a	271	3 (1.1)	118 (63-204)
T1b	115	3 (2.6)	120 (59-210)
All T2	246	9 (3.7)	120 (50-233)
T2a	118	1 (0.8)	106 (40-216)
T2b	128	8 (6.3)	143 (64-250)
T3	52	6 (12)	95 (4-222)
All IV	31	3 (10)	100 (48-264)

^aData presented as median (interquartile range).

Table 4 Comparison of IgE-t and Absolute Eosinophil Counts of Typical MF with Matched Patients From 2005 to 2006 NHANES^a

Cohort	IgE-t						Eosinophil Count			
	All Patients (n)	Patients With IgE-t > 100 IU/mL (n; %)	Median (IU/mL; IQR)	MW <i>P</i> Value	GM ± SE	<i>t</i> Test <i>P</i> Value	All Patients (n)	Patients With Eosinophil Count > 500/mm ³ (n; %)	Median (Cells/mm ³ ; IQR)	MW <i>P</i> Value
Typical MF ^b	685	232 (33.9)	51 (48-70)	.145	54 ± 1.1	.114	672	23 (3.4)	117 (58-218)	.091
Negative atopy history	488	155 (31.8)	51 (14-151)		50 ± 1.1		478	16 (3.3)	110 (55-213)	
Positive atopy history	197	77 (39.1)	53 (19-200)		64 ± 1.1		194	7 (3.6)	141 (63-220)	
NHANES controls	685	189 (27.6)	38.7 (15-112)	<.001	44 ± 1.1	<.001	683	36 (5.3)	179 (117-275)	.044
Negative serologic atopy	431	53 (12.3)	23 (11-53)		25 ± 1.1		430	19 (4.4)	173 (116-267)	
Positive serologic atopy ^c	254	136 (53.5)	111 (46-282)		117 ± 1.1		253	17 (6.7)	192 (119-288)	

Abbreviations: GM = geometric mean; IgE-t = serum total IgE; IQR = interquartile range; MF = mycosis fungoides; MW = Mann-Whitney *U* test; NHANES = National Health and Nutrition Examination Survey; SE = standard error.

^aIgE-t: *t* test, *P* = .002, MW, *P* = .040; mean age: *t* test, *P* = .963, MW, *P* = .995; patients with IgE-t > 100 IU/mL, *P* = .014.

^bPatients with coexisting dermatoses unrelated to MF were excluded.

^cDefined as ≥ 1 aeroallergen-specific IgE > 0.35 kAU/L.

The IgE-t values stratified by the skin T ratings for the patients with MF limited to the skin are also listed in [Table 2](#). IgE-t was greater for those with T1b compared with T1a and for T2b compared with T2a for both nonatopic and atopic groups. The IgE-t values for T3 were about the same as those for T2b in the nonatopic group but higher in the atopic group. Also, the IgE-t values in the atopic patients were higher than those for the corresponding T rating of the nonatopic patients. Stratification by clinical stage showed similar trends except that the IgE-t values for stage IIA were equal to or greater than for those for stage IIB or stage IV disease for both nonatopic and atopic groups (data not shown). We suspect this was because stage IIA encompasses patients with advanced skin involvement and patients with early (noneffaced) nodal involvement.

The relationship between atopy and IgE-t for the various clinical manifestations of typical MF is shown in [Supplemental Table 5](#) (available in the online version). Overall, IgE-t was significantly higher for patients with an atopic history. Furthermore, for most clinical variants of typical MF, IgE-t tended to be greater, although the difference was not statistically significant, for atopic patients than for nonatopic patients.

Relationship of Eosinophil Counts to Patients' Atopic History

Blood eosinophilia (> 500 cells/mm³) occurred in only 3.3% and 4.0% of patients with typical and atypical expressions of MF, respectively. The median eosinophil count of patients with a history of an atopic disorder was slightly greater than that for patients without an atopic history ($P = .066$). The eosinophil counts stratified by the IgE-t results for different clinical manifestations of typical and atypical MF are shown in [Supplemental Tables 5 and 6](#) (available in the online version), respectively.

Correlation of Eosinophil Counts and T Ratings

It has been reported that the tissue and blood eosinophil counts are highest in tumor-phase MF than in earlier phases of MF.^{9,39,40} These observations suggest that eosinophil production might be influenced by the skin tumor burden. The relationship between eosinophil counts and skin T ratings for patients with typical MF are presented in [Table 3](#). Just as with the IgE-t levels, the eosinophil counts tended to be higher for patients with more advanced disease than for those with early disease. Blood eosinophilia (> 500 /mm³) exceeded 5% only for patients with a skin rating of T2b and T3 and all subgroups of stage IV.

Comparison of IgE-t and Absolute Eosinophil Counts Between Typical MF and Matched Data From NHANES

Comparison of IgE-t and absolute eosinophils counts between patients with typical MF and matched patients from NHANES are shown in [Table 4](#). For comparison with the age-, race-, and sex-matched patients selected from NHANES, 43 of the 728 patients with typical MF were excluded because of coexisting dermatitis to minimize the influence of non-MF-related cutaneous inflammation on IgE-t levels. The mean IgE-t levels were significantly higher for patients with MF than for the controls (MW test, $P = .040$; t test, $P = .028$; [Supplemental Table 5](#) available in the online version). In contrast, the eosinophil

counts were significantly lower in the patients with MF than in the controls (MW test, $P < .001$).

The prevalence of serologic atopy in the NHANES control population was 37.1% (254 of 685), which was significantly greater than the 28.8% prevalence (197 of 685) in the MF patients determined by patient history ($P = .001$).

Atypical MF/CD30LPD Compared With Previously Reported Data of CD30LPD Only

In an earlier study,⁶ we reported that patients with lymphomatoid papulosis (histopathologic types A and C but not B) and primary cutaneous ALCL had high IgE-t values compared with the reference ranges for nonatopic adults from various centers. Therefore, we compared these results with those from patients with MF/CD30LPD ([Supplemental Table 7](#) available in the online version). IgE-t was slightly lower for patients with coexisting MF (geometric mean, 35 IU/mL) than for patients without MF (geometric mean, 44 IU/mL). This difference was also seen for LyP-A, LyP-C, and ALCL. The differences in IgE-t levels for each comparison were not statistically significant.

Prognostic Implications

Several parameters in the typical MF cohort correlated significantly with the prognosis. As expected, the most important variables were uncategorized patient age, skin T rating, and clinical stage ($P < .001$ for all). The stage-related mean survival time and 5- and 10-year survival rates for patients with typical MF are presented in [Supplemental Table 8](#) (available in the online version). The mean survival was much shorter for those with stage IIB and higher stages. Other significant variables were the skin lesion classification ($P < .001$), a history of an atopic condition ($P = .019$), an uncategorized IgE-t level ($P = .001$) or IgE-t level > 100 IU/mL ($P = .016$), an uncategorized absolute eosinophil count or count > 500 /mm³ ($P = .002$) and a histopathologic diagnosis confirming or compatible with MF ($P = .019$). Patient race and sex were not significant.

When analyzed in the Cox model with patient age and clinical stage as covariates, the presence of atopy, IgE-t level, and eosinophil count did not have significant effects on overall survival, suggesting these variables correlate with clinical stage. However, the classification of cases according to the clinical and histopathologic features retained significance. The reason for this was the relatively poor prognosis of patients with psoriasiform or eczematous MF and the relatively favorable prognosis of patients with poikilodermic and CD8⁺ MF ([Supplemental Table 9](#) available in the online version).

The prognostic implications of the histopathologic grade is shown in [Supplemental Table 10](#) (available in the online version). Overall, the overall survival curves for the 5 subgroups were not significantly different ($P = .192$). The mean survival (13.82 ± 0.93 years) of the 69 patients with a diagnosis consistent with MF was ~ 1 year longer than that (12.63 ± 0.46 years) of the 658 patients with a definite diagnosis. The difference in survival curves was statistically significant ($P = .018$). However, the mean survival (15.59 ± 1.82 years) of the small number of patients with the diagnosis confirmed by a highly specific ancillary study (subgroup 1B) was ~ 3 years longer than that of the patients with a histopathologic diagnosis of MF. This finding supports the view that highly specific ancillary studies are particularly useful to establish the

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diagnosis of MF in specimens with inconclusive histopathologic examination findings. For the analysis of atopy prevalence and IgE levels, all the patients were combined into 1 group, irrespective of the histopathologic grade.

Discussion

In the present retrospective study of MF, a history of allergic rhinitis/hay fever, asthma, or eczema was recorded for 79 of 229 patients (34.5%) considered to have atypical MF and 212 of 728 patients (29.1%) with a more typical clinical and histopathologic presentation. The high prevalence of atopy resulted primarily from the high prevalence of allergic rhinitis/hay fever in the atypical and typical cohort (31% and 25.5%, respectively). In contrast, the overall prevalence of asthma (5.9%) and eczema (4.1%) was relatively low.

The high prevalence of allergic rhinitis/hay fever in our patients with MF should be compared with the prevalence reported by other studies. According to the 2005 to 2006 NHANES, the self-reported frequency of hay fever in the U.S. population is ~13% and slightly greater in women (14.5%) than in men (12.4%).^{41,42} Furthermore, several uncontrolled studies have indicated a prevalence of allergic rhinitis in no more than 10% of patients with MF.^{16,17} The reason for the much greater prevalence of allergic rhinitis in the present study compared with that reported in the study from the Mayo Clinic (6.9%) is unclear. It is possible that the aero-allergen exposures for patients referred to the Mayo Clinic (Rochester, MN) differed from those for patients evaluated in Philadelphia, Pennsylvania.

However, 2 other studies reported that the prevalence of allergic rhinitis was ~30% in patients with MF.^{12,13} In addition, the control population had a similar prevalence of allergic rhinitis. Consequently, because our study lacked a control population, it is not clear whether a relevant association exists between allergic rhinitis and MF.

Given that patient self-report of allergic rhinitis and other atopic conditions is not reliable,⁴³ more objective measures of atopy such as positive skin prick test results to allergens or the presence of allergen-specific IgEs (> 0.35 kUA/L) are currently preferred over the less reliable IgE-t > 100 IU/mL criterion. Whittemore et al¹² reported that 55% of MF patients from the West Coast of the United States had positive scratch or needle allergy test results for inhalants or ingestants compared with 83% of controls. In contrast, Kural et al⁹ reported significantly greater positive skin prick test and allergen-specific IgE responses in Turkish patients with CTCL (34 patients with MF, 5 with Sézary syndrome, 1 with lymphomatoid papulosis) compared with controls. The IgE-t values were also increased in the CTCL patients.

Allergic rhinitis/hay fever is mediated by aeroallergens, most often from plants, trees, and/or dust mites. If patients with MF have a high prevalence of allergic rhinitis/hay fever, a high frequency of aeroallergen-specific IgEs might be expected. In the study by Kural et al,⁹ aeroallergen-specific IgEs were detected in 40% of the CTCL patients. In contrast, we found that only 3 of 20 patients (15%) with typical plaque MF had aeroallergen-specific IgEs > 0.35 kUA/L using the Phadiatop multiple allergen screening test.¹⁰ Of the 685 control patients selected from the NHANES study, 254 subjects (37.1%) had a specific IgE antibody > 0.35 kUA/L to ≥ 1 airborne allergen from trees, grass, weeds, cat or dog dander, dust mites, and/or molds.

However, from these observations, it seems unlikely that allergic rhinitis per se is significantly associated with MF.

Whether an atopic diathesis predisposes patients to developing MF might require a long term longitudinal epidemiologic study. This might be feasible if a genetic marker for atopy can be identified and such individuals followed up to determine whether they have an increased risk of developing MF. Two potential genes of interest associated with a susceptibility to atopic conditions are filaggrin⁴⁴ and claudin-1.⁴⁵

It has been widely accepted that atopic individuals have an increased risk of allergic reactions to drugs, including contrast media and tetanus toxoid. In the present review, 22.2% of patients with typical MF reported a positive history of a hypersensitivity reaction, most often to penicillin or its derivatives. This was nearly double the 11.5% rate reported by Albin and Agarwal.⁴⁶ However, the frequency of allergic reactions was not different for patients with or without a history of an atopic disorder and type 1 hypersensitivity was less frequent in the atopic patients. We attributed the high frequency of penicillin-type reactions to the increased administration of penicillin and other antibiotics to patients with MF compared with the general population (ie, greater exposure rate resulting in a greater drug allergy rate). The lower rate of type 1 hypersensitivity to penicillin-type drugs in atopic patients could have resulted from a reluctance of physicians to administer penicillin and other drugs to patients with a history of atopy.

The present retrospective study also showed that patients with typical MF and a personal history of atopy had a significantly greater IgE-t level than patients without a history of atopy. The absolute eosinophil counts also tended to be greater in atopic patients than in nonatopic patients. However, the difference was not statistically significant. The IgE-t and eosinophil counts were also significantly higher in the NHANES control population with evidence of ≥ 1 aero-specific IgE compared with the controls without an aero-specific IgE. Thus, the atopic status of patients is an important factor in controlling IgE-t levels. Patients with typical MF had a significantly higher IgE-t level compared with the age-, race-, and sex-matched controls selected from the 2005 to 2006 NHANES. However, IgE-t values are influenced by many factors other than age, race, sex, and atopic diathesis, such as tobacco use and socioeconomic conditions, which were not addressed.

Another factor pertains to the severity of clinically active MF. The IgE-t levels showed a tendency to increase with more extensive skin involvement for patients without or with a history of atopy (Table 2). Neoplastic T cells of MF are capable of secreting T-helper type 2 (Th2) cytokines, including interleukin (IL)-4 and IL-13, which are important mediators of IgE production, and IL-5, which influences eosinophil production.⁴⁷⁻⁴⁹ Therefore, it is possible that cytokine secretion by neoplastic cells increases IgE-t levels if the cytokine production by neoplastic cells or the biomass of neoplastic cells in the skin becomes sufficiently high in advanced disease. Cytokines from non-neoplastic cells in the inflammatory infiltrate can also contribute to noncognate IgE-t production.

Another disease-related factor not addressed in the present study pertains to the possible role that secondary colonization of skin lesions by *Staphylococcus* species capable of secreting superantigens might play in enhanced IgE-t production. The study by Talpur et al⁵⁰ indicated that the colonization rate of MF lesions was ~26%

compared with 10% for the general population. We detected IgE reactive against the Staphylococcal superantigens SSA and SSB in 20% of patients with plaque-phase MF.¹⁰

Our observations suggest that the frequent increase of IgE-t in patients with MF is the consequence of an interplay between the patients' atopic diathesis that favors exaggerated IgE responses to allergens (major factor) plus the production of Th2 cytokines by neoplastic and/or inflammatory cells that becomes evident in more advanced disease (factor 2), and, in some patients, the additional IgE-t stimulatory effects of Staphylococcal superantigens from Staphylococcal-colonized lesions (factor 3). However, this pathophysiologic mechanism does not seem to apply for most patients with Sézary syndrome, who have a high Staphylococcal colonization rate of ~ 60%, and IgE that was reactive against Staphylococcal superantigens in 45% of patients in our recent study.¹⁰ Specifically, for 42 patients with Sézary syndrome (T4B2 rating) evaluated by us, the median IgE-t was 46 IU/mL, with above-normal values observed in 15 patients (36%).¹⁰ This was lower than that in the non-Sézary syndrome erythrodermic patients for whom IgE-t levels can be quite high.^{9,10} In a cohort of 55 patients with Sézary syndrome, Scala et al⁵¹ reported a median IgE-t value of 13 IU/mL, lower than that of control patients with contact dermatitis. The reason for the low IgE-t levels for most patients with Sézary syndrome is unclear; however, one possibility is that the neoplastic cells of Sézary syndrome secrete IL-21, an inhibitor of IgE-t production, as a consequence of STAT3 activation and neoplastic plasticity.^{52,53}

Conclusions

The findings from our retrospective study have not demonstrated that patients with either typical or atypical expressions of MF have an increased prevalence of atopy. However, patients with a history of atopy had increased IgE-t levels and higher eosinophil counts compared with their nonatopic counterparts. Furthermore, the IgE-t and eosinophil counts were higher in patients with advanced MF compared with patients with less-advanced disease. The simplest, but not the only possible, explanation for this observation is the influence of cytokines (eg, IL-4, IL-13, IL-5) produced by Th2-polarized neoplastic T cells on the production of IgE-t and eosinophils.

Clinical Practice Points

- Based on patient history, the prevalence of atopy is not increased in those with MF.
- An atopic diathesis was a major factor for the increases in serum IgE-t and eosinophil counts often observed in patients with MF.
- An additional factor that influences the IgE-t and eosinophil counts is the magnitude of disease involvement (T rating, clinical stage), possibly mediated by cytokines produced by neoplastic T cells.

Disclosure

M.E. Kadin received grant support from the Drs. Martin and Dorothy Spatz Cutaneous Lymphoma Research Foundation. All other authors state that they have no conflicts of interest.

Supplemental Data

Supplemental tables and appendix accompanying this article can be found in the online version at <https://doi.org/10.1016/j.clml.2020.11.007>.

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Supplemental Appendix

Comment 1: Because some patients received treatment before referral, it was possible that the skin manifestations of mycosis fungoides (MF) were less severe and, perforce, the skin T rating and clinical stage assigned at the initial evaluation would differ from those assigned at the initial diagnosis. Some patients had undergone radiotherapy with improvement but were referred when their disease had relapsed. However, details about the T rating and stage at the diagnosis were not available for these patients.

Comment 2: For specimens interpreted to be “consistent with MF,” confirmatory ancillary tests with high diagnostic specificity were chosen to minimize the occurrence of false-positive results. Thus, polymerase chain reaction (PCR) evidence of a T-cell clone was not used to confirm the diagnosis of MF because the PCR methods used to study whole skin specimens at the time could occasionally detect T-cell clones in inflammatory mimics of MF, T-cell dyscrasias, and clonal dermatitis. In contrast, the now

infrequently used Southern blot method has greater diagnostic specificity (lower false-positive rate) compared with PCR methods.

Comment 3: The issue of whether patients with finger-like patches or thin plaques arrayed on the trunk and inner extremities have a variant of parapsoriasis en plaques or early cutaneous T-cell lymphoma/MF was debated by 2 eminent groups in the mid-1990s.^{1,2} In that present review, the term “digitate MF” was applied if the histopathologic features had met the criteria for MF, often supported by evidence of T-cell clonality. However, in our experience, and that of others,³ patients with “digitate MF” rarely had progressive disease, albeit the natural history might have been altered by skin-directed therapy used to treat early MF. The term “digitate T-cell dyscrasia” might be preferable to the term “digitate MF.”⁴

Comment 4: Folliculotropic or pilotropic MF is a distinctive clinicopathologic expression of cutaneous T-cell lymphoma.⁵ However, in the present retrospective review, such cases were not recognized before the late 1990s.⁶

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Supplemental Table 1 Histopathologic Diagnosis Including Ancillary Studies

Diagnostic Group	Patients (n)	Histopathologic Classification ± Ancillary Study Results (n)				
		Group 1A	Group 1B	Group 2A	Group 2B	Group 2C
Typical MF ^a	728	659	14	16	27	12
Atypical MF ^b	229	199	9	8	12	1
Hypopigmented MF	44	38	2	1	3	0
MF/CD30LPD	41	38	1	2	0	0
Unilesional MF	59	49	2	5	3	0
Palmoplantar MF	23	20	1	0	2	0
Purpuric MF	19	17	0	0	1	1
Digitate MF	43	37	3	0	3	0

Abbreviations: 1A = histopathologic findings diagnostic of MF on any concurrent or previous specimen; 1B = histopathologic findings compatible with MF plus T-cell clone demonstrated by Southern blot techniques, fewer CD7⁺ cells in the dermal infiltrate by immunohistochemistry, or aneuploidy by touch imprint cytophotometry; 2A = T-cell clone demonstrated by polymerase chain reaction; 2B = 10%-30% of CD7⁺ cells in the dermal infiltrate; 2C = T-cell clone demonstrated by polymerase chain reaction and 10%-30% of CD7⁺ cells in the dermal infiltrate; CD30LPD = CD30⁺ lymphoproliferative disease; MF = mycosis fungoides.

^aComparison of typical and atypical MF using χ^2 test ($P = .120$).

^bComparison of 6 atypical MF cohorts using χ^2 test ($P = .222$).

Supplemental Table 2 Hypersensitivity to Penicillin and Sulfonamide-type Antibiotics Stratified by Atopic History^a

Atopic History	All Patients	Type 1	Rash	Other	NS
Penicillin reaction	76	42 (55)	20 (26)	1	13
No	54	34 (63)	11 (20)	1	8
Yes	22	8 (36)	9 (41)	0	5
Sulfonamide reaction	17	5 (29)	10 (59)	1	1
No	12	4 (33)	8 (67)	0	0
Yes	5	1 (20)	2 (40)	1	1

Data presented as n or n (%).

Abbreviation: NS = not stated.

^aComparison of frequencies using χ^2 test: penicillin vs. sulfonamide hypersensitivity, $P = .047$; penicillin reaction in nonatopic vs. atopic patients, $P = .127$; sulfonamide reaction for nonatopic vs. atopic patients, $P = .184$.

Supplemental Table 3 Prevalence of Atopic Disorders Stratified by Appearance and T Rating of Skin Involvement for Typical Mycosis Fungoides^a

Cohort	All Patients	Atopy	Eczema	Asthma	Rhinitis
MFPT	392	129 (32.9)	14 (3.6)	19 (4.8)	118 (30.1)
MFPQ	262	61 (23.3)	10 (3.8)	14 (5.3)	52 (19.8)
MFT	74	22 (30)	3 (4)	6 (8)	16 (22)
Poikilodermic MF	73	17 (23.3)	2 (3)	0 (0)	16 (22)
Psoriasiform MF	16	3 (19)	1 (6)	0 (0)	3 (19)
Eczematous MF ^b	38	17 (45)	5 (13)	6 (16)	12 (32)
Follicular MF	38	10 (26)	0 (0)	3 (8)	9 (24)
CD8 ⁺ MF	29	8 (28)	0 (0)	3 (10)	5 (17)
MF, NOC	534	157 (29.4)	19 (3.6)	27 (5.1)	141 (26.4)
T1a	275	100 (36.4)	12 (4.4)	14 (5.1)	92 (33.5)
T1b	120	34 (28.3)	4 (3.3)	8 (6.7)	32 (26.7)
T2a	119	30 (25.2)	2 (1.7)	5 (4.2)	27 (22.7)
T2b	140	26 (18.6)	6 (4.3)	6 (4.3)	19 (13.6)
Transformation					
Absent	135	26 (19.3)	6 (4.4)	6 (4.4)	19 (14.1)
Present	5	0 (0)	0 (0)	0 (0)	0 (0)
T3	74	22 (30)	3 (4)	6 (8)	16 (22)
Transformation					
Absent	50	13 (26)	1 (2)	5 (10)	8 (16)
Present	24	9 (38)	2 (8)	1 (4)	8 (33)
All typical MF	728	212 (29.1)	27 (3.7)	39 (5.4)	186 (25.5)

Data presented as n or n (%).

Abbreviations: MF = mycosis fungoides; MFPT = mycosis fungoides patch; MFPQ = mycosis fungoides plaque; MFT = mycosis fungoides tumor phase; NOC = not otherwise classified.

^aDifference in atopic frequency tested using Pearson's χ^2 or Fisher's exact test: clinical phase of MF, $P = .029$; skin T rating, $P = .004$; race, $P = .262$; sex, $P = 1.0$; MF variants, $P = .242$; 5 cohorts with variants of MF, $P = .150$; eczematous MF vs. remaining 4 variants, $P = .027$; eczematous MF vs. all other patients, $P = .042$.

^bOne patient had had clinical evidence of active atopic dermatitis coexisting with MF; another patient had had atopic dermatitis in childhood that clinically inactive during the study period.

Supplemental Table 4 Prevalence of Atopic Disorders in Patients With Atypical Expression of Mycosis Fungoides^a

Cohort	Sex (M/F)	All Patients	Atopy	Eczema	Asthma	Rhinitis
Hypopigmented MF	14/30	44	14 (32)	2 (5)	5 (11)	13 (29)
MF/CD30LPD	22/19	41	14 (34)	1 (2)	0 (0)	13 (32)
Unilesional MF	55/4	59	24 (41)	5 (8)	5 (8)	22 (37)
Palmoplantar MF	12/11	23	7 (30)	2 (9)	3 (13)	5 (22)
Purpuric MF	11/8	19	5 (26)	1 (5)	0 (0)	4 (21)
Digitate MF	41/2	43	15 (35)	1 (2)	4 (9)	14 (33)
All atypical MF	133/96	229	79 (34.5)	12 (5.2)	17 (7.4)	71 (31.0)

Data presented as n or n (%).

Abbreviations: CD30LPD = CD30⁺ lymphoproliferative disease; F = female; M = male; MF = mycosis fungoides.

^aDifference in atopic frequency among 6 groups tested using χ^2 exact test, $P = .871$.

Supplemental Table 5 Influence of Atopic History on IgE-t and Absolute Eosinophil Counts for Clinical Variants of Typical Mycosis Fungoides^a

Atopic History	IgE-t						Eosinophil Count			
	All Patients	Patients With IgE-t > 100 IU/mL (n; %)	Median (IU/mL; IQR)	MW <i>P</i> Value	GM ± SE	<i>t</i> Test <i>P</i> Value	All Patients (n)	Patients With Eosinophil Count > 500/mm ³ (n; %)	Median (Cells/mm ³ ; IQR)	MW <i>P</i> Value
Psoriasiform MF				.737		.653				.093
No	13	6 (46)	87 (26-1565)		129 ± 2.0		13	2 (15)	210 (107-412)	
Yes	3	1 (33)	39		76 ± 2.4		3	0 (0)	4	
Eczematous MF				.154		.169				.394
No	21	9 (43)	77 (39-403)		114 ± 1.5		21	3 (14)	174 (5-319)	
Yes	17	12 (71)	752 (30-2258)		308 ± 1.8		17	4 (24)	225 (95-579)	
Follicular MF				.540		.491				.141
No	28	11 (39)	63.5 (21-272)		66 ± 1.4		27	2 (7)	166 (64-245)	
Yes	10	5 (50)	82.5 (34-446)		102 ± 1.7		10	1 (10)	246 (129-375)	
CD8 ⁺ MF				.081		.067				.803
No	21	4 (19)	23 (12-99)		30 ± 1.4		21	0 (0)	110 (37-185)	
Yes	9	5 (56)	152 (37-568)		114 ± 1.8		9	1 (11)	90 (50-253)	
MF, NOC				.292		.326				.225
No	377	116 (30.8)	43 (12-137)		45 ± 1.1		369	8 (2.2)	109 (55-211)	
Yes	157	57 (36.3)	48 (16-186)		55 ± 1.2		155	3 (1.9)	126 (62-212)	
All typical				.034		.026				.066
No	516	160 (30.0)	49 (14-146)		49 ± 1.1		506	15 (3.0)	110 (55-211)	
Yes	212	86 (40.6)	58 (19-215)		68 ± 1.1		209	9 (4.3)	140 (64-223)	

Abbreviations: GM = geometric mean; IgE-t = serum total IgE; IQR = interquartile range; MF = mycosis fungoides; MW = Mann-Whitney *U* test; NOC = not otherwise classified; SE = standard error.^aDifferences in IgE-t values and eosinophil counts for patients with and without a history of an atopic disorder tested using the Mann-Whitney *U* or *t* test.

Supplemental Table 6 Influence of Atopic History on IgE-t and Eosinophil Counts for Atypical Variants of Mycosis Fungoides^a

Atopic History	IgE-t						Eosinophil Count			
	All Patients	Patients With IgE-t > 100 IU/mL (n; %)	Median (IU/mL; IQR)	MW <i>P</i> Value	GM ± SE	<i>t</i> Test <i>P</i> Value	All Patients (n)	Patients With Eosinophil Count > 500/mm ³ (n; %)	Median (Cells/mm ³ ; IQR)	MW <i>P</i> Value
Hypopigmented	44	13 (30)	54 (11-123)	.154	40 ± 1.3	.157	44	0 (0)	88 (53-123)	.980
No	30	8 (27)	46 (10-108)		31 ± 1.3		30	0 (0)	82 (52-170)	
Yes	14	5 (36)	84 (16-317)		66 ± 1.5		14	0 (0)	90 (51-131)	
MF/CD30LPD	40	11 (28)	27 (11-121)	.103	35 ± 1.3	.072	41	5 (13)	113 (55-310)	.596
No	26	6 (23)	22 (8-94)		25 ± 1.4		27	3 (12)	120 (61-320)	
Yes	14	5 (36)	51 (22-177)		64 ± 1.5		14	2 (14)	98 (3-308)	
Unilesional MF	58	17 (29)	45 (17-128)	.956	45 ± 1.3	.999	58	1 (2)	150 (77-217)	.127
No	35	11 (31)	34 (17-127)		45 ± 1.3		35	1 (3)	144 (57-187)	
Yes	23	6 (26)	53 (7-131)		45 ± 1.4		23	0 (0)	168 (101-256)	
MF palmoplantar	23	10 (43)	64 (11-312)	.841	63 ± 1.6	.203	23	0 (0)	133 (66-224)	.664
No	16	8 (50)	103 (12-339)		57 ± 1.8	.756	16	0 (0)	128 (73-240)	
Yes	7	2 (29)	56 (8-180)		80 ± 2.4		7	0 (0)	138 (53-153)	
Purpuric MF	19	5 (26)	53 (16-120)	.404	62 ± 1.4	.251	17	1 (5)	132 (77-226)	.821
No	14	4 (29)	63 (15-182)		75 ± 1.6		13	1 (7)	132 (77-189)	
Yes	5	1 (20)	39 (17-87)		36 ± 1.5		4	0 (0)	169 (74-344)	
Digitate MF	43	20 (47)	94 (27-256)	.083	86 ± 1.3	.067	43	2 (5)	138 (67-236)	.628
No	28	10 (36)	60 (10-179)		63 ± 1.4		28	1 (4)	134 (70-214)	
Yes	15	10 (67)	140 (72-745)		154 ± 1.4		15	1 (7)	144 (61-244)	
All atypical MF ^b	227	76 (33.5)	53 (15-150)	.092	51 ± 1.1	.057	226	9 (4.0)	120 (65-221)	.545
No	149	47 (31.5)	48 (14-143)		43 ± 1.2		149	6 (4.0)	120 (63-210)	
Yes	78	29 (37)	65 (24-167)		68 ± 1.2		77	3 (4)	120 (67-240)	

Abbreviations: CD30LPD = CD30⁺ lymphoproliferative disease; GM = geometric mean; IgE-t = serum total IgE; IQR = interquartile range; MF = mycosis fungoides; MW = Mann-Whitney *U* test; NOC = not otherwise classified; SE = standard error.

^aDifferences in IgE-t values and eosinophil counts for patients with and without a history of an atopic disorder tested using the Mann-Whitney *U* or *t* test.

^bIgE-t result not available for 1 patient with unilesional MF and 1 patient with MF/CD30LPD.

MF and Atopy, IgE-t, and Eosinophil Count

Supplemental Table 7 Comparison of Serum Total IgE Values for Patients With Cutaneous CD30LPD With or Without Coexisting MF

Cohort	IgE-t			
	Patients (n)	Patients With > 100 IU/mL (n; %)	Median (IU/mL; IQR)	GM $\pm$ SE
MF/CD30LPD	40	11 (28)	27 (11-121)	35 $\pm$ 1.3
CD30LPD ^a	130	39 (30)	39 (13-156)	43 $\pm$ 1.7
MF/LyP-A	23	7 (30)	27 (10-226)	41 $\pm$ 1.4
LyP-A ^a	84	25 (30)	39 (14-185)	42 $\pm$ 1.2
MF/LyP-C	3	1 (33)	24 (2-204)	21 $\pm$ 3.8
LyP-C ^a	26	9 (35)	41 (11-228)	51 $\pm$ 1.4
MF/All LyP	33	9 (27)	27 (12-180)	36 $\pm$ 1.3
All LyP ^a	116	34 (29)	39 (13-140)	42 $\pm$ 1.2
MF/ALCL	7	2 (29)	50 (6-105)	29 $\pm$ 1.7
pcALCL ^a	14	5 (36)	40 (18-239)	58 $\pm$ 1.5

Abbreviations: ALCL = anaplastic large cell lymphoma; CD30LPD = CD30⁺ lymphoproliferative disease; GM = geometric mean; IgE-t = serum total IgE; IQR = interquartile range; LyP-A = lymphomatoid papulosis type A; LyP-C = lymphomatoid papulosis type C; MF = mycosis fungoides; pcALCL = primary cutaneous anaplastic large cell lymphoma; SE = standard error.

^aData from Vonderheid et al.⁶

Supplemental Table 8 Mean Survival and 5- and 10-year Survival Rates (All-cause Death) for Patients With Typical Mycosis Fungoides

Stage	Patients (n)	Survival		
		Mean $\pm$ SE (y)	5-y (%)	10-y (%)
IA	387	15.5 $\pm$ 0.7	85	69
IB	216	12.5 $\pm$ 0.8	80	51
IIA	40	11.8 $\pm$ 1.3	73	56
IIB	54	5.3 $\pm$ 0.7	42	11
IVA1	7	4.7 $\pm$ 1.1	57	0
IVA2	21	2.6 $\pm$ 0.6	24	0
IVB	3	1.7 $\pm$ 1.4	0	0
Total	728	12.9 $\pm$ 0.5	76	55

Abbreviation: SE = standard error.

^aComparison of survival curves among stage categories was significantly different (log-rank test, $P < .001$).

Supplemental Table 9 Mean Survival and 5- and 10-year Survival Rates (All-cause Death) for Patients With Clinicohistopathologic Variations of Typical Mycosis Fungoides^a

MF Cohort	Patients (n)	Survival		
		Mean $\pm$ SE (y)	5-y (%)	10-y (%)
Poikilodermic	73	16.2 $\pm$ 1.0	90	79
Psoriasiform	16	7.1 $\pm$ 1.5	53	33
Ecematous	38	8.9 $\pm$ 1.5	60	35
Follicular	38	10.8 $\pm$ 1.3	68	56
CD8 ⁺	29	19.0 $\pm$ 2.2	87	83
NOC	534	12.7 $\pm$ 0.6	76	52
Total	728	12.9 $\pm$ 0.5	76	55

Abbreviations: MF = mycosis fungoides; NOC = not otherwise classified; SE = standard error.

^aComparison of survival curves among clinical variants was significantly different (log-rank test, $P < .001$).

Supplemental Table 10 Influence of Histopathologic Criteria on Overall Survival for Patients With Typical Clinical Expression of Mycosis Fungoides^a

Histopathologic Group	Patients (n)	Survival		
		Mean $\pm$ SE (y)	5-y (%)	10-y (%)
1A	659	12.6 $\pm$ 0.5	75	53
1B	14	15.6 $\pm$ 1.8	85	85
2A	16	13.7 $\pm$ 1.9	86	70
2B	27	10.6 $\pm$ 0.9	91	62
2C	12	11.6 $\pm$ 1.3	81	81
Total	728	12.9 $\pm$ 0.5	76	55

Abbreviation: SE = standard error.

^aComparison of survival curves for histopathologic groups was not significantly different (log-rank test, $P = .192$).

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