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Mycosis Fungoides in Children and Adolescents
A Systematic Review

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IMPORTANCE Comprehensive data on childhood mycosis fungoides (MF) is scarce.

OBJECTIVE To describe clinical features, immunophenotypes, various treatment options, and prognosis of MF in children and adolescents.

EVIDENCE REVIEW This systematic review searched MEDLINE via PubMed, Embase, Cochrane, and Scopus databases in October 2019. The search terms included *mycosis fungoides*, *infant*, *children*, and *adolescent*. No filter for the publication period was used, but studies written in a language other than English were excluded. Reference lists of the relevant articles were also searched manually. Case series and case reports were included if data on childhood MF were extractable. The Asan Medical Center database for cases of childhood MF was also searched. Patients were treated from January 1, 1990, to July 31, 2019, and were younger than 20 years at the time of diagnosis. The methodologic quality of the included studies was assessed with items from the Newcastle-Ottawa scale. Data were analyzed from December 9, 2019, to September 4, 2020.

FINDINGS A total of 571 unique patients were included. The mean (SD) age at diagnosis was 12.2 (4.2) years; at onset, 8.6 (4.2) years. The female-to-male ratio was 1:1.6 (350 male patients [61.3%]). Among 522 patients with data available at diagnosis, stage 1 disease constituted 478 cases (91.6%), followed by stage 2 (39 [7.5%]) and stage 4 (5 [1.0%]). Among the 567 patients with data available, the most common variant of MF was the hypopigmented form (309 [54.5%]), followed by classic MF (187 [33.0%]). The MF lesions were predominantly the $CD4^+$ and $CD8^+$ immunophenotype in 99 (49.5%) and 79 (39.5%) of 200 patients, respectively. Among the treatments, narrowband UV-B was the most frequently used (150 of 426 [35.2%]). Most patients were alive with the disease (185 of 279 [66.3%]); 83 of 279 (29.8%) were in complete remission; and 11 of 279 (3.9%) had died by the last follow-up. A longer time from onset to diagnosis (hazard ratio [HR], 1.24; 95% CI, 1.06-1.45), granulomatous slack skin (HR, 12.25; 95% CI, 1.99-75.26), granulomatous MF (HR, 14.59; 95% CI, 1.31-162.00), a history of organ transplant (HR, 10.15; 95% CI, 0.98-105.37), and stage 2 disease at the time of diagnosis (HR, 10.22; 95% CI, 2.94-35.50) were associated with worse outcomes.

CONCLUSIONS AND RELEVANCE The findings of this review suggest that there is often a significant delay until the establishment of a correct diagnosis of childhood MF, which may be detrimental to the prognosis.

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Supplemental content

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Mycosis fungoides (MF) is the most common form of cutaneous T-cell lymphoma, and it typically affects elderly patients.[1] Childhood MF reportedly constitutes 0.5% to 7.0% of MF cases.[2-5] However, dozens of atypical variants of MF have been described.[6] The proportion of patients who present with atypical variants appears to be higher in children than in adults.[7-9] The clinical behavior and prognosis of each phenotypic variant also seems different[10]; however, data on this subject are not available for childhood MF.

It was previously believed that MF occurring at a young age shows an aggressive behavior.[11] However, more recent series reported a favorable overall prognosis of childhood MF.[8,12,13] The diagnosis of MF can often be delayed in children because it can mimic a wide range of common skin disorders.[14] However, the effect of this delay in the diagnosis of childhood MF on prognosis has not been evaluated.

Overall, comprehensive data on childhood MF are scarce so far. Therefore, by conducting a systematic review, we aimed to describe MF in children and adolescents in terms of its clinical features, immunophenotypes, various treatment options, and prognosis.

Key Points

Question What are the clinical features of childhood mycosis fungoides (MF)?

Findings In this systematic review of 571 children and adolescents with MF, the most common subtype was the hypopigmented form, followed by classic MF. Most patients with MF presented with early-stage disease, and the prognosis of MF seems to be more favorable than in the general population, although a significant delay before the establishment of a correct diagnosis of MF in childhood was associated with a poor prognosis.

Meaning These findings suggest that although the prognosis of childhood MF is not unfavorable, delayed diagnosis may have an adverse effect.

Methods

Medical Records Review

This systematic review was approved by the institutional review board of the University of Ulsan College of Medicine with a waiver of informed consent for the use of retrospective data. We searched the Asan Medical Center database for cases of childhood MF treated from January 1, 1990, to July 31, 2019. The eligible participants were required to be younger than 20 years at the time of diagnosis of MF. The inclusion criteria for classic and variants of MF are shown in eTable 1 in the Supplement.[15,16]

Systematic Review

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[17] an electronic search of 4 databases (MEDLINE via PubMed, Embase, Cochrane, and Scopus) was performed in October 2019. The study protocol was registered on PROSPERO.[18] The search strategy is described in eTable 2 in the Supplement. The search terms included *mycosis fungoides*, *infant*, *children*, and *adolescent*. We used no filter for the publication period but excluded studies written in a language other than English. Reference lists of the relevant articles were also searched manually. Titles, abstracts, and full texts of the retrieved reports were reviewed by 2 independent reviewers (J.M.J. and D.J.L.) for eligibility assessment. Any discrepancy was settled by a third reviewer (W.J.L.). The inclusion criteria were as follows: participants younger than 20 years at the time of diagnosis of MF, case reports and case series with extractable data, and cases that fulfilled the clinical and histopathological inclusion criteria shown in eTable 1 in the Supplement. We used these inclusion criteria for individual cases applicable. For studies in which individual data were not available, we only included studies using diagnostic criteria compatible with ours after reviewing the full text. We excluded any cases in which aggressive cutaneous T-cell lymphomas that may show epidermotropism could not be ruled out.

Data Extraction

Data were extracted by 2 independent reviewers (J.M.J. and D.J.L.) and checked by a third reviewer (W.J.L.). The extracted data included the first author's last name, publication year, country of origin, baseline demographic data (eg, age at diagnosis, age at onset, sex, and race/ethnicity), medical history, information regarding the morphology and distribution of the MF lesions, symptoms, variant, initial clinical diagnosis, stage, results of immunohistochemical studies and T-cell receptor (TCR) gene analysis of the MF lesions, treatment, treatment-related adverse event(s), follow-up duration, any progression during the follow-up period, and final outcome. Overall survival was calculated from the date of the initial diagnosis to the date of death from any cause or the last follow-up. Disease-specific survival was defined as survival free from a death event as a result of MF.

Methodologic Quality

We used the modified Newcastle-Ottawa scale for case reports and case series as previously described.[19] We regarded the quality of the report as good when all 5 criteria were fulfilled, moderate when 4 were fulfilled, and poor when 3 or fewer were fulfilled.

Statistical Analysis

Data were analyzed from December 9, 2019, to September 4, 2020. Descriptive statistics were used for the evaluation of the clinical and immunohistochemical data and the treatment. Continuous data are presented as mean (SD). The risk factors for disease progression, large cell transformation of MF, and the development of secondary lymphoma were assessed by a mixed-effects Cox proportional hazards regression model. Survival analysis was performed using the Kaplan-Meier method, and the significance was tested using the log-rank test. Parameters affecting survival outcomes were assessed by a mixed-effects Cox proportional hazards regression model (eTable 3 in the Supplement). Results are presented as hazard ratios (HRs) with 95% CIs. All statistical analyses were performed using R software, version 3.5.3 (R Foundation). Two-sided $P < .05$ was considered statistically significant.

Results

Literature Search and Methodologic Quality

Initially, 1937 records were retrieved. After removing the duplicates and excluded studies, 128 articles (564 patients) were finally

Table 1. Patient Characteristics

Characteristic	Data[a]
Age, mean (SD), y	
At diagnosis (n = 566)	12.2 (4.2)
At onset (n = 420)	8.6 (4.2)
Sex	
Female	221/571 (38.7)
Male	350/571 (61.3)
Race/ethnicity	
Asian	97/306 (31.7)
Black	45/306 (14.7)
White	82/306 (26.8)
Hispanic	25/306 (8.2)
Middle Eastern	57/306 (18.6)
Stage	
1A	208/522 (39.8)
1B	234/522 (44.8)
1A or 1B[b]	36/522 (6.9)
2A	29/522 (5.6)
2B	10/522 (1.9)
3	0/522
4	5/522 (1.0)
Lymph node involvement	5/522 (1.0)
History of organ transplant	4/571 (0.7)
Associated with lymphomatoid papulosis	11/571 (1.9)

[a] Unless otherwise indicated, data are expressed as number/total number (percentage) of patients.

[b] Indicates patients who did not have a definite diagnosis of either 1A or 1B.

included (eFigure in the Supplement) with 7 of our own patients for a total of 571 patients with a diagnosis of MF. The results of methodologic quality assessment for included studies are shown in eTable 4 in the Supplement.

Patient Characteristics

The demographics of the included patients are shown in **Table 1**. The median time from symptom onset to diagnosis was 3.0 (range, 0-17) years. Three hundred fifty patients (61.3%) were male and 221 (38.7%) were female, for a female-to-male ratio of 1:1.6. Among the 522 patients with data available at diagnosis, most patients had stage 1 disease (478 [91.6%]). Stage 2 disease was noted in 39 patients (7.5%), and only 5 (1.0%) had stage 4 disease. Five hundred seven patients (97.1%) presented with early-stage MF (1A-2A). Most patients presented with patches (362 of 488 [74.2%]), followed by plaques (116 of 488 [23.8%]), tumor (9 of 488 [1.8%]), and erythroderma with significant blood involvement (1 of 488 [0.2%]).

Initial Diagnoses, Symptoms, Variants, and Distribution of the MF Lesions

Eczema and atopic dermatitis (44 of 182 [24.2%]) were the most common initial impressions, followed by MF (33 of 182 [18.1%]), pityriasis alba (25 of 182 [13.7%]), pityriasis lichenoides (14 of 182 [7.7%]), postinflammatory hypopigmentation (12 of 182 [6.6%]), fungal infection (10 of 182 [5.5%]), psoriasis (10 of 182 [5.5%]), and vitiligo (9 of 182 [5.0%]). Pruritus was the most commonly reported symptom of MF (25 of 397 [6.3%]), followed by tenderness (2 of 397 [0.5%]). One patient who presented with erythrodermic MF had systemic symptoms, such as fever, chills, and weight loss.

An atypical variant of MF or a classic MF lesion combined with an atypical variant of MF was shown in 434 of 567 patients (76.5%). The most commonly reported variant of MF in children and adolescents was hypopigmented MF (309 of 567 [54.5%]), followed by classic (187 of 567 [33.0%]) and folliculotropic (36 of 567 [6.4%]) MF. Mean time from symptom onset to diagnosis was the longest in hyperpigmented MF (7.1 [4.8] years), followed by granulomatous slack skin (GSS) (5.2 [2.9] years) (**Table 2**). Hypopigmented MF was seen in 125 of 182 of non-White patients (68.7%). The MF lesions were predominantly found on the lower extremities (187 of 227 [82.4%]), followed by the trunk (164 of 227 [72.2%]) (Table 2).

Immunophenotype and TCR Gene Rearrangement Analysis

Table 2 represents immunophenotypes and TCR gene rearrangement analysis of MF lesions. The patients with predominantly $CD8^+$ MF phenotype (79 of 200 [39.5%]) were significantly younger (mean age at onset, 7.9 [4.1] years) than the patients with the $CD4^+$ phenotype (79 of 200 [39.5%]) (mean age at onset, 9.8 [[4.3] years) ($P = .008$). None of the patients with $CD20^+$ or $CD56^+$ phenotypes experienced disease progression or death. The proportion of cases with predominantly $CD8^+$ phenotype was significantly higher in patients with hypopigmented MF (53 of 101 [52.5%]) than in the other patients with MF (20 of 87 [23.0%]) ($P < .001$). In addition, cases of diminished or loss of CD7 were significantly more frequent in patients with hypopigmented MF (45 of 57 [79.0%]) than in the other patients with MF (22 of 57 [38.6%]) ($P < .001$). However, the frequency of clonality on TCR gene rearrangement analysis (overall, 187 of 262 [71.4%]) was not significantly different between hypopigmented (62 of 83 [74.7%]) and other (95 of 114 [83.3%]) types of MF ($P = .19$).

Treatment

Herein, we identified 32 different treatments for childhood MF (**Table 3**). Among them, narrowband UV-B was the most commonly prescribed (150 of 426 [35.2%]), followed by topical corticosteroids (131 of 426 [30.8%]) and psoralen plus UV-A (PUVA) (126 of 426 [29.6%]). Treatment options for each variant are summarized in eTables 5 to 7 in the Supplement. Detailed information on patients who received systemic chemotherapy or stem cell transplant is shown in eTable 8 in the Supplement. Treatment-related adverse events were rarely reported; these included onycholysis related to PUVA therapy (n = 1), vitiligolike leukoderma after PUVA therapy (n = 1), nausea after psoralen intake (n = 1), skin erythema and itching induced by local radiotherapy (n = 1), topical nitrogen mustard-related skin irritation (n = 1), and fever and flulike symptoms of headache, muscle aches, and lethargy following interferon therapy (n = 2).

Disease Progression, Large Cell Transformation, and Secondary Lymphoma

The mean follow-up duration for the available patients was 59.4 (78.8) months (n = 279). Twenty-one of 279 patients (7.5%) experienced at least 1 episode of disease progression during the follow-up period. None of them experienced progression to include significant blood involvement. The mean interval from diagnosis to the first episode of disease progression was 73.6 (97.5) months.

Table 2. Clinical Variants, Distribution, Immunophenotypes, and TCR Gene Rearrangement Analysis of MF Lesions

Variable	No./total No. (%) of patients	Time from onset to diagnosis, mean (SD), y	Distribution of MF stage (No. [%])
Variant			
Hypopigmented	309/567 (54.5)	3.6 (3.0)	1 (169/173 [97.7]), 2A (3/173 [1.7]), 4 (1/173 [0.6])
Classic	187/567 (33.0)	4.0 (3.4)	1 (102/129 [79.1]), 2A (17/129 [13.2]), 2B (7/129 [5.4]), 4 (3/129 [2.3])
Folliculotropic	36/567 (6.4)	2.2 (2.3)	1 (15/17 [88.2]), 2A (2/17 [11.8])
Unilesional	23/567 (4.1)	3.5 (3.9)	1 (14/17 [82.4]), 2A (2/17 [11.8])
Hyperpigmented	16/567 (2.8)	7.1 (4.8)	1 (13/13 [100])
Poikilodermatous	16/567 (2.8)	4.2 (3.3)	1 (14/14 [100])
Pityriasis lichenoideslike	15/567 (2.6)	1.8 (1.5)	1 (13/13 [100])
Papular	12/567 (2.1)	2.3 (1.7)	1 (7/9 [77.8]), 2A (1/9 [11.1]), 2B (1/9 [11.1])
Pagetoid reticulosis	11/567 (1.9)	4.3 (4.2)	1 (2/2 [100])
Purpuric	11/567 (1.9)	2.1 (1.8)	1 (8/8 [100])
GSS	7/567 (1.2)	5.2 (2.9)	1 (4/5 [80.0]), 2A (1/5 [20.0])
Granulomatous	4/567 (0.7)	3.2 (1.3)	1 (1/2 [50.0]), 2A (1/2 [50.0])
MF palmaris et plantaris	4/567 (0.7)	3.2 (1.7)	1 (3/4 [75.0]), 4 (1/4 [25.0])
Distribution			
Lower extremities	187/227 (82.4)	NA	NA
Trunk	164/227 (72.2)	NA	NA
Upper extremities	152/227 (67.0)	NA	NA
Head or neck	82/227 (36.1)	NA	NA
Immunophenotype			
$CD4^+>CD8^+$	99/200 (49.5)	NA	NA
$CD8^+>CD4^+$	79/200 (39.5)	NA	NA
$CD4^-$ and $CD8^-$	7/276 (2.5)	NA	NA
$CD20^+$	5/50 (10.0)	NA	NA
$CD56^+$	7/41 (17.1)	NA	NA
TIA	16/33 (48.5)	NA	NA
Diminished CD7 expression or $CD7^-$	110/162 (67.9)	NA	NA
Clonal TCR rearrangement (skin lesion)	187/262 (71.4)	NA	NA

Abbreviations: GSS, granulomatous slack skin; MF, mycosis fungoides; NA, not applicable; TCR, T-cell receptor; TIA, T-cell intracytoplasmic antigen.

Progression of MF beyond stage 2A occurred in 13 patients, and the identified risk factors are shown in **Table 4**.

Large cell transformation of MF occurred in 7 of 279 of the patients with MF (2.5%). The mean time interval from the diagnosis to large cell transformation was 19.9 (32.7) months. Presentation with a GSS variant was the only identified risk factor for large cell transformation of MF (Table 4).

Secondary lymphoma other than lymphomatoid papulosis occurred in 5 of 279 patients (1.8%). The mean time interval from the diagnosis of MF to the diagnosis of secondary lymphoma other than lymphomatoid papulosis was 62.9 (73.2) months. The types of secondary lymphoma were as follows: gamma-delta T-cell lymphoma with Epstein-Barr virus–positive B-cell posttransplant lymphoproliferative disorder on the lung (n = 1), orbital precursor B-cell lymphoblastic lymphoma (n = 1), nodal anaplastic large cell lymphoma (n = 1), and Hodgkin disease (n = 2). A history of organ transplant was the only identified risk factor for the development of secondary lymphoma (Table 4). Folliculotropic MF was not a risk factor for MF progression, large cell transformation, or the development of secondary lymphoma.

Outcomes

Most patients were alive with the disease (185 of 279 [66.3%]); 83 of 279 (29.8%) were in complete remission; and 11 of 279 (3.9%) had died by the last follow-up. Patients who were alive with the disease were followed up for a mean of 64.6 (85.9) months. Ongoing phototherapy was performed in 123 of 177 patients (69.5%); topical corticosteroid therapy, in 63 of 177 (35.6%). Specific causes of death were as follows: disease (n = 5), treatment-related complications (development of pneumonia after allogenic stem cell transplant [n = 1], cytomegalovirus pneumonitis development after systemic chemotherapy [n = 1], and unspecified complications of systemic chemotherapy [n = 1]), secondary lymphoma (n = 1), Merkel cell carcinoma (n = 1), and unknown (n = 1).

The 10-year overall and disease-specific survival rates were 87.2% and 94.8%, respectively (n = 279). A longer time from onset to diagnosis (HR, 1.24; 95% CI, 1.06-1.45), GSS (HR, 12.25; 95% CI, 1.99-75.26), granulomatous MF (HR, 14.59; 95% CI, 1.31-162.00), a history of organ transplant (HR, 10.15; 95% CI, 0.98-105.37), and stage 2 disease at the time of diagnosis (HR, 10.22; 95% CI, 2.94-35.50) were associated with poor overall survival outcomes (Table 4).

Table 3. Treatment Modalities

Treatment	No. (%) of patients (n = 426)
Narrowband UV-B	150 (35.2)
Topical corticosteroid	131 (30.8)
PUVA	126 (29.6)
UV-B	49 (11.5)
Topical nitrogen mustard	29 (6.8)
Local radiotherapy	27 (6.3)
Heliotherapy	21 (4.9)
Interferon	17 (4.0)
UV-A	14 (3.3)
Topical carmustine	14 (3.3)
Topical bexarotene	14 (3.3)
Systemic corticosteroid	13 (3.1)
Systemic chemotherapy	13 (3.1)
Oral methotrexate	12 (2.8)
Total skin electron beam therapy	11 (2.6)
Oral acitretin	9 (2.1)
Excision	8 (1.9)
Oral antibiotics	6 (1.4)
Topical tazarotene	5 (1.2)
Topical tacrolimus	5 (1.2)
Stem cell transplant	4 (0.9)
Topical calcipotriol	4 (0.9)
No treatment	4 (0.9)
Other[a]	17 (4.0)

Abbreviation: PUVA, psoralen plus UV-A.

[a] Includes oral isotretinoin, thymopentin, topical tar, extracorporeal photopheresis, topical pimecrolimus, oral tacrolimus, topical anthralin, photodynamic therapy, and topical imiquimod.

On comparing the 10-year overall survival rate of patients whose interval from the onset of lesions to the time of diagnosis was longer than 5 years vs 5 years or less, the 10-year overall survival rate of the former group was significantly worse (HR, 4.40; 95% CI, 1.34-14.44; $P = .008$) (**Figure**). Ten-year overall survival rates of patients with GSS (HR, 10.83; 95% CI, 2.32-50.51; $P < .001$) and granulomatous (HR, 30.25; 95% CI, 3.08-296.80; $P < .001$) MF and the patients with a history of organ transplant (HR, 19.36; 95% CI, 2.13-175.80; $P < .001$) were significantly worse than those of the other patients. The 10-year overall survival of patients with hypopigmented MF was better than that of the others; however, the difference was not statistically significant (HR, 0.21; 95% CI, 0.03-1.71; $P = .10$). The 10-year overall survival of patients with folliculotropic MF was not significantly different from that of the others (0 of 13 vs 11 of 262; $P = .50$).

Discussion

Herein, we found a significant delay until the establishment of a diagnosis of childhood MF in accordance with previously reported diagnostic delay in MF of all ages (median, 4.2 years).[20] In this study, female patients accounted for 38.7% of the cases, which is in agreement with the previously reported range of 37.0% to 40.2% in large cohort studies of MF in the general population.[20-23] Most patients with childhood MF (97.1%) presented with early-stage disease (1A-2A) in this study. This outcome is in contrast to patients with MF in the general population, where 65.8% to 82.2% of patients present with early-stage MF.[20,21,23-29]

Unlike in adults, the classic presentation of MF was noted in only 33.0% of patients with childhood MF in this study.[29] The hypopigmented form can be considered a typical form of childhood MF, particularly among children and adolescents with a dark skin tone. The previously reported proportion of the hypopigmented variant of MF in the general population was 0.4% to 22.0%,[21,23,24,29,30] which was much lower than that in our study. Poikilodermatous MF has often been reported to have an earlier onset compared with classic MF.[6,31] However, the proportion of poikilodermatous variants revealed in this study is within the previously reported range of the proportions of the poikilodermatous variant in MF cohorts of all ages, from 1.1% to 11.2%.[21,23,24,29] The frequency of the purpuric variant of MF shown in our study was also in agreement with a previous large study wherein purpuralike lesions were found in 2% of a cohort of all ages.[30]

Atypical cells of predominantly $CD8^+$ are rare in adults with MF.[32,33] However, a significant proportion (39.5%) of childhood MF cases were predominantly of the $CD8^+$ phenotype in this study. This may be attributable to the hypopigmented form of MF, a major phenotype in our cohort, which showed the $CD8^+$ phenotype significantly more often than other forms of MF did. This finding is also consistent with previous studies reporting that hypopigmented MF often showed a cytotoxic phenotype[34] and that patients with $CD8^+$ MF were younger than patients with general MF at diagnosis.[35] In the present study, the patients with predominantly $CD8^+$ MF were significantly younger than patients with the $CD4^+$ phenotype, suggesting that the $CD8^+$ phenotype is a clue for the diagnosis of MF at a young age. The loss of CD7 is a sensitive and specific finding for MF.[36] This feature can be particularly useful when diagnosing hypopigmented MF in children because diminished or loss of CD7 was found more frequently in patients with hypopigmented MF than in other patients in this study. In this study, more than 10% of patients had $CD20^+$ or $CD56^+$ phenotypes. It is difficult to draw a conclusion regarding whether these relatively higher proportions are representative of MF in children and adolescents in general[37,38] because the numbers of assessable cases were limited. In this study, patients with childhood MF showed TCR gene clonality in 71.4%, which is very similar to the rate in patch/plaque stage MF in the general population (52%-75%).[36,39-41]

Psoralen plus UV-A is commonly suggested as first-line treatment for adults with MF.[42,43] However, narrowband UV-B was used most frequently for patients with childhood MF in this study, possibly because of its better safety profile compared with PUVA. In this study, phototherapy and/or topical immunomodulators were the mainstay treatment for most variants of childhood MF except for localized forms and GSS. Localized therapies, such as surgery and radiotherapy, were frequently performed for unilesional MF and pagetoid reticulosis, with an excellent response rate.

The use of several treatment modalities for adults with MF, such as topical mechlorethamine hydrochloride,[44] oral bexarotene,[45] oral lenalidomide,[46,47] and intravenous denileukin diftitox,[48] could not be found in patients with childhood MF in this study. Their unestablished safety profile in pediatric patients or high levels of toxicity may have prevented their use.

Table 4. Risk Factors for Progression Beyond Stage 2A, Large Cell Transformation, and the Development of Secondary Lymphoma and Parameters Affecting 10-Year Overall Survival

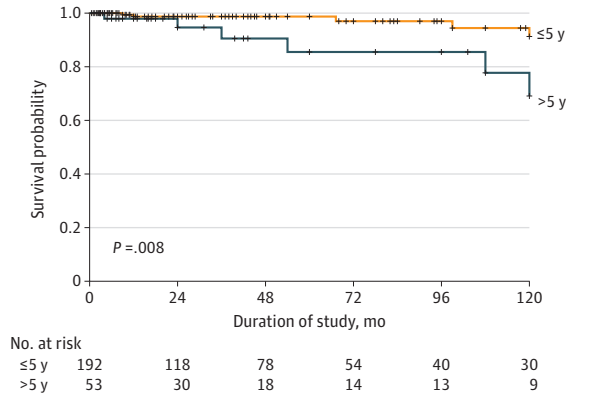
Risk factor/parameter	No. of events/total No. of patients		Univariable analysis		Multivariable analysis[a]	
	With risk factor or parameter	Without risk factor or parameter	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Progression beyond stage 2A						
Age at onset in years	12/244	NA	1.20 (1.04-1.38)	.01	1.21 (1.05-1.40)	.008
Granulomatous MF	1/3	12/271	38.76 (3.20-469.16)	.004	50.57 (4.02-636.10)	.002
Purpuric variant	1/7	12/267	13.36 (1.40-127.86)	.02	21.11 (2.03-219.62)	.01
Large cell transformation						
GSS	2/6	5/268	9.27 (1.55-55.58)	.02	NA	NA
Development of secondary lymphoma other than lymphomatoid papulosis						
History of organ transplant	1/4	4/274	24.69 (1.44-424.67)	.03	NA	NA
Parameters affecting 10-y overall survival						
Time from onset to diagnosis in years	11/245	NA	1.24 (1.06-1.45)	.006	1.21 (1.03-1.43)	.02
GSS	2/6	9/269	12.25 (1.99-75.26)	.007	41.05 (6.01-280.47)	<.001
Granulomatous MF[b]	1/3	10/272	14.59 (1.31-162.00)	.03	NA	NA
History of organ transplant	1/4	10/275	10.15 (0.98-105.37)	.052	172.31 (10.69-2776.26)	<.001
Stage 2 (vs stage 1)	5/24	5/234	10.22 (2.94-35.50)	<.001	12.81 (2.85-57.5)	<.001
Stage 4 (vs stage 1)	0/4	5/234	NA	NA	NA	NA

Abbreviations: GSS, granulomatous slack skin; HR, hazard ratio; MF, mycosis fungoides; NA, not available.

[a] Performed using all of the significant variables in the univariable analysis.

[b] Multivariable analysis could not be performed for this variable because of missing values.

Figure. Survival Outcomes in Childhood Mycosis Fungoides



Survival was compared between patients whose time to diagnosis was longer than 5 years vs 5 years or less after symptom onset.

Herein, 9 patients with early-stage MF received acitretin, and no patient showed disease progression. Extracorporeal photopheresis was conducted for 2 patients, who showed long-term survival. However, both acitretin and extracorporeal photopheresis are not fully evidenced treatments for MF in children as well as in adults.[49,50] The burden of systemic chemotherapy can be much higher and thus should carefully be considered in children based on the observation that half of the mortality cases in patients who received systemic chemotherapy were attributable to the complications associated with the treatment in this study.

Solid organ transplant recipients tend to have an increased risk of developing lymphoma.[51] Consistently, organ transplant was associated with a markedly elevated risk of secondary lymphoma in this study. Considering that the 5-year overall survival for stage 1B MF in the general population was 85.8% in a recent systematic review,[52] the prognosis of childhood MF revealed in this study seems more favorable than that of MF in the general population.

Although both granulomatous MF and GSS are suggested risk factors for the development of secondary lymphoma, granulomatous MF is associated with a poor outcome, whereas GSS usually shows an indolent course.[15,53,54] In this study, however, among the 6 patients with GSS whose follow-up data were available, 2 patients died within 24 months of the diagnosis of MF.[55,56] The risk of large cell transformation was also significantly increased in patients with childhood GSS, with 2 patients experiencing large cell transformation of their MF.[56,57] Whether this suggested aggressiveness is from the intrinsic nature of childhood GSS or other reasons, such as reporting bias, should be elucidated in future studies. Folliculotropic MF has been proposed to adversely affect the survival outcome,[21,58] and the prognosis of hypopigmented MF has been suggested to be more favorable than that of classic MF.[59-62] However, in our study, these subtypes did not show significant differences in prognosis compared with others in children.

Limitations

The limitations of this study include its susceptibility to reporting bias. Second, the efficacy and safety of various treatment options could not be readily compared because the included studies were retrospective cases in which treatment protocols were not standardized. Third, the number of patients in certain variants, such as GSS and granulomatous MF, is very limited.

Conclusions

This systematic review found a significant delay until the establishment of a correct diagnosis of MF in this young age group, which may worsen their prognosis. Hypopigmented MF, which is the most common type of MF in children and adolescents, had a comparable prognosis with other childhood MF types. However, GSS and granulomatous MF can show more aggressive behavior, suggesting that close observation and more active treatment are required. Organ transplant was associated with an increased risk of developing secondary lymphoma and a poor outcome of childhood MF.

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