

Retrospective Analysis of Second Primary Malignancies in Patients with Mycosis Fungoides and Sézary Syndrome in Croatia

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ABSTRACT Introduction: Patients with mycosis fungoides (MF) have a higher risk of developing second primary malignancy. The type of second malignancy varies across the studies, and no established guidelines currently exist for screening MF patients.

Objective: To identify MF and Sézary syndrome (SS) patients at a potentially higher risk of developing a secondary primary malignancy, assess the prevalence of other secondary malignancies, and evaluate whether MF with other primary malignancies leads to a worse prognosis based on MF variants.

Methods: This observational single-center retrospective study followed 84 patients for a minimum of five years.

Results: We identified 16 patients (19%) with second malignancy, of whom eight (50%) had hematological neoplasms. Among other malignancies, breast cancer was the most common (N=5), followed by other malignancies, including lung cancer, prostate cancer, kidney cancer, and so on. The median age at disease onset was 53.0 years, while median age at second malignancy diagnosis was 60.5 years. No sex predominance was observed. Although not statistically significant, seven of sixteen patients (43.75%) who developed second malignancy had MF variant (such as folliculotropic MF) or Sézary syndrome. Disease progression was more common in patients with MF variant.

Conclusion: A higher risk for developing a second primary neoplasm was observed. However, additional cancer screening beyond routine age- and sex-appropriate examinations is not yet included in the current guidelines. Based on our findings, we recommend that MF patients undergo regular preventive screenings for the early detection of other primary malignancies.

Introduction

Primary cutaneous T-cell lymphomas (CTCL) belong to a heterogeneous group of non-Hodgkin lymphomas (NHL), primarily affecting the skin and not having extracutaneous manifestations at the time of diagnosis. NHL primarily appear in the lymph nodes, and in the case of extranodal occurrence, they most often affect the gastrointestinal system, and then the skin elsewhere. MF presents with clinical variants such as folliculotropic (FMF), pagetoid reticulosis, and granulomatous slack skin, and rare variants such as hypopigmented, hyperpigmented, ichthyosiform, palmar and plantar, poikilodermatic form, et cetera [1].

A second primary malignancy (SPM) is a new, unrelated cancer that arises in an individual with a history of cancer, separate from a recurrence or metastasis of the original disease.

Patients with MF and Sézary syndrome (SS) have a higher risk of developing other second primary malignancies, most commonly hematological cancers (non-Hodgkin lymphoma, Hodgkin lymphoma, lymphomatoid papulosis, leukemia, multiple myeloma) and solid tumors such as skin cancer, lung cancer, breast cancer, prostate cancer, kidney cancer, colorectal cancer, and bladder cancer, likely due to chronic immune dysregulation, prolonged inflammation, and prior treatments [2-8].

The objectives of our study were to identify MF and Sézary syndrome (SS) patients at a potentially higher risk of developing a secondary primary malignancy, to assess the prevalence of other secondary malignancies, and to evaluate whether MF with other primary malignancies leads to a worse prognosis based on MF variants.

Patients and Methods

This observational single-center retrospective study included patients diagnosed with CTCL at the Department of Pathology and Cytology and the Department of Dermatology and Venereology at the Clinical Hospital Centre Zagreb and University of Zagreb, a tertiary center with referral center for dermatological oncology. The diagnosis of CTCL was confirmed based on immunohistopathology analysis in conjunction with the clinical findings. All patients diagnosed with CTCL between 1 February 2003 and 31 December 2017 and followed for at least five years, were included in the study.

A total of 84 patients (N=84) met the inclusion criteria and were followed up until 31 December 2022.

The following data were analyzed for MF patients: age at onset of lesions, age at diagnosis, staging at diagnosis, sex, disease progression, high-grade transformation, type of MF and MF variants, development of secondary primary malignancy, age at diagnosis of secondary primary malignancies, and development of non-melanoma skin cancer (NMSC) and melanoma. Staging of the disease was determined according to TNMB classification [9].

Statistical Analysis

The data are presented in tables and graphs. The normality of the distribution of numerical data was assessed using Smirnov-Kolmogorov test, and corresponding non-parametric statistical tests were applied based on the results. Quantitative data are presented as medians with interquartile ranges, while categorical data are reported as absolute frequencies with corresponding proportions or 95% confidence intervals (CIs). Differences in quantitative values were analyzed using the Mann-Whitney U test. Differences in categorical variables were analyzed by Fisher's exact test, or Fisher-Freeman-Halton's exact test in the case of contingency tables that were larger than the 2 x 2 format. The Kaplan-Meier curve with the associated log-rank test was used to analyze survival until disease progression. All p-values less than 0.05 were considered statistically significant. In the analysis and graphic displays, the licensed program support IBM SPSS Statistics for Windows, version 29.0.1, was used.

Results

The study included total of 84 patients: 50 males and 34 females. The majority of patients (N=48, 57.1%) had early-stage disease (IA + IB). Disease progression was observed in 19 patients (22.6%), and 14.3% of the patients had fatal outcome. Among our cohort, 33.3% (28 patients) had some of the variants of MF or SS. The MF variants of MF included nine patients with large cell transformation (eight patients had CD30+ large cell transformation, while one patient had CD30- large cell transformation), two with hypopigmented MF, three with erythroderma, six with folliculotropic MF (FMF), two with syringotropic MF, 1 with

poikilodermatous form, and one with CD4+CD8+ MF. Additionally, five patients had SS. All patient with SS had stage 4A according to TNMB classification. Disease progression was significantly more common in this subgroup ($P<0.001$). A significant association was found between advanced disease stages and the presence of MF or SS variants, with higher stages more prevalent in these patients ($P<0.001$). These patients also had a significantly shorter survival time to disease progression ($P<0.001$) (Table 1).

Within our cohort, 16 patients (19.0%) developed a second primary malignancy, with eight (50.0%) of these with hematological neoplasms. No case of melanoma was diagnosed; however, five patients developed NMSC during follow-up. All patients who developed NMSC had been

previously treated with PUVA therapy. The most common solid organ malignancy was breast cancer (five patients). Other primary malignancies included papillary thyroid cancer, endometrial cancer, prostate cancer (two patients), sublingual squamous cell carcinoma, lung cancer, and kidney cancer, together accounting for 8% (9.52%) of study population (Table 2). Among these 16 patients, four (25%) had two or more other primary malignancies in addition to CTCL. Of these four patients, three were female, and all three had breast cancer as one of the other primary malignancies. One patient had MF, breast cancer, and endometrial cancer. The second patient had SS, breast cancer, and squamous cell sublingual cancer. The third patient had MF, breast cancer, papillary thyroid cancer, and monoclonal gammopathy of

Table 1. Average Survival to Progression according to the Specific Form of MF or SS. Patients with specific form of MF or SS had a significantly shorter survival to progression ($P<0.001$).

Variant of MF or SS	Median survival to progression			
	Time (months)	Standard error	95% CI	
			Lower	Upper
No	47.81	2.25	43.40	52.23
Yes	7.46	1.39	4.74	10.18
Total	34.09	3.89	26.47	41.71

Table 2. Type of Second Primary Malignancy.

Second primary malignancy	N=16 (19%)
Hematologic neoplasms	N=8 (50%)
Chronic lymphatic leukemia (N=2)	
Hodgkin lymphoma	
B-cell large cell NHL	
Tonsillar NHL	
Monoclonal gammopathy	
MGUS (Monoclonal gammopathy of undetermined significance)	
SMM (Smoldering, multiple myeloma)	
Non-hematologic neoplasms	N=8 (50%)
Breast cancer (N=5)	
Prostate cancer (N=2)	
Kidney cancer (N=2)	
Thyroid papillary cancer	
Endometrial cancer	
Sublingual squamous-cell cancer	
Lung cancer	
Non-melanoma skin cancer	N=5 (5.95%)
BCC (N=4)	
SCC	
Melanoma	None

undetermined significance (MGUS). The only male subject in this subgroup, in addition to MF, had chronic lymphocytic leukemia (CLL) and kidney cancer. Of these 16 patients who developed a second primary malignancy, seven (43.75%) had an MF variant. Among these seven patients, five (31.25%) experienced disease progression, although these findings were not statistically significant (Table 3).

In the group of patients who developed second primary malignancy, the distribution by sex was the same: 50% were female (N=8) and 50% were male (N=8). The median age at onset of CTCL was 53.0 years (interquartile range, 40.5–62.8 years), and the median time to diagnosis was 3.0 years (interquartile range, 1.0-10.0 years). The median age at diagnosis of the second malignancy was 60.5 years. In this cohort, CTCL preceded the appearance of the second

primary cancer, with an average time of 7.5 years between the two diagnoses (Table 4).

Discussion

Our study supports the evidence of an increased risk of second primary malignancies in patients with MF. We examined the percentage of patients who developed a second primary malignancy, considering that previous literature has reported an increased incidence of a second primary malignancy in patients with CTCL [2-8,10-13]. In our cohort of 84 patients 19% (N=16) developed another primary malignant disease.

Among these second primary malignancies, hematological neoplasm were the most frequent, occurring in 50% (N=8) of patients, which is in concordance to previous

Table 3. Differences in Categorical Clinical Indicators in relation to the Specificity of the Disease.

		MF variant or SS				p-value
		No		Yes		
		N=55		N=28		
		N	%	N	%	
Sex	Male	34	61.80%	16	55.20%	0.642
	Female	22	38.20%	12	44.80%	
Stage*	IA	18	21.40%	0	0.00%	<0.001
	IB	25	29.8%	5	5.96%	
	IIA	2	2.40%	1	1.19%	
	IIB	6	7.14%	12	14.29%	
	IIIA	0	0.00%	4	14.80%	
	IIIB	0	0.00%	1	1.19%	
	IVA	1	1.19%	5	18.50%	
	IVB	0	0.00%	0	0.00%	
Second primary malignancy	No	47	83.93%	21	75.0%	0.158
	Yes	9	16.07%	7	25.0%	
Hematological neoplasms	No	52	92.86%	24	85.7%	0.118
	Yes	4	7.14%	4	14.3%	
Breast cancer	No	52	94.5%	27	93.1%	1.000
	Yes	3	5.5%	2	6.9%	
Other non-hematological malignancies	No	48	87.3%	28	96.6%	0.253
	Yes	7	12.7%	1	3.4%	
Folliculotropic MF	No	55	100.0%	23	79.3%	0.001
	Yes	0	0.0%	6	20.7%	

Table 4. Descriptive Statistics of Sociodemographic Values.

	N	Min	Max	Centile		
				25.	Median	75.
The median age at the onset of disease	80	8.00	83.00	40.50	53.00	62.75
Median time to diagnosis CTCL	71	1.00	51.00	1.00	3.00	10.00
The median age at the second primary malignancy	16	34.00	82.00	52.25	60.50	70.50

studies [2-4,8,10,12-14]. The most common solid organ cancer was female breast cancer, observed in 31.25% (N=5) of the cases. The types of second primary malignancies varied across studies. According to the meta-analysis and systematic review by Goyal et al. [7] in 2021, which included 12 studies and 11,214 patients with MF and CTCL, 8.5% developed a second primary malignant disease. In that cohort, the most common second primary malignancies were non-Hodgkin lymphoma (NHL) 20%, Hodgkin lymphoma (HL) 17.8%, lung cancer 15.1%, bladder cancer 8.3%, breast cancer 6.5%, melanoma 3.2%, and kidney cancer 2.9% [7]. Contrary to these findings, Brown et al. did not find an increased incidence of lung, colon, urinary tract, melanoma, or biliary system cancer development [4]. The type of second primary malignant disease differed in the studied groups of patients, and some study groups (like ours) report no melanoma case [2,6,8]. In contrast, there are studies that identified melanoma as a frequent secondary malignancy (Goyal et al. excluded melanoma in situ in their study) [3,11,15].

Our study did not find any sex predominance, in contrast to previous studies, which reported a higher incidence in males, with a male-to-female ratio ranging from 1.2:1 to 2.9:1, according to the systematic review and meta-analysis by Goyal et al. [7]. The average age at CTCL diagnosis was between 44.6 and 68.0 years, and the median age at diagnosis of second primary malignancy was 3.29 years after CTCL diagnosis (ranging from 2.1 to 5.4 years). In our study, the interval between CTCL diagnosis and second malignancy was longer. However, unlike some studies, we did not exclude patients whose second malignancy preceded their CTCL diagnosis. The age at onset of CTCL and other primary malignant diseases has differed in the studies published so far. The median age at diagnosis of second primary malignant disease in our cohort was 60.5 years, and the average time from CTCL diagnosis to the development of another primary malignancy was 6 years (median: 54.5 years). Our study found a higher percentage other primary malignancies compared to previously published reports [2-6,8,11-15]. We believe that this may be due to the study design. Some studies excluded patients who developed a second malignancy before or within the first year of CTCL diagnosis, likely to assess potential treatment-related factors [3,4,8]. However, we believe that studies designed in that way may not provide the prevalence of other primary malignant diseases in CTCL patients. Our result of 19.5% of patients with a second primary malignancy is comparable to the 20.2% reported by Macagno et al. [11], a study that similarly did not exclude cases in which the second malignancy preceded CTCL. According to that study, 39.5% of patients had NMSC, and 28.9% had MM. In contrast, in our study, there was no case of melanoma, and five cases of NMSC (5.95%). The patients who developed NMSC in our study were treated with PUVA

therapy. We also considered an MF variant as a potential risk factor for developing second primary malignancies. Although statistical significance was not reached, 43.75% (7/16) patients who developed another malignancy had MF variant or SS. In our study group, patients with FMF more often had disease progression, consistent with the findings of Agar et al. [16]. Their study demonstrated that FMF is associated with an increased risk of disease progression, and multivariate analysis identified advanced skin stage (T), the presence of tumor clone without Sézary cells in peripheral blood (B0), elevated LDH levels, and FMF as independent predictors of poor survival and increased risk of disease progression. Furthermore, large cell transformation and tumor distribution were independent predictors of disease progression [16].

Conclusion

We believe that further research is needed to explore the relationship between primary cutaneous lymphomas and other primary malignancies. Even though the association between CTCL and other primary malignancies was proven more than 40 years ago, possible risk factors for their development have still not been discovered. The hypothesis of a single causative factor for the development of both neoplasms is less likely due to the heterogeneity of the second primary malignancies in relation to CTCL. Several previous studies excluded patients with a second primary malignancy preceding CTCL to determine whether the type of treatment affected the development of a second primary malignancy, but the heterogeneity of other primary cancers makes this unlikely. It is more likely that the cause is a tumorigenic microenvironment and an altered immune response that led to the development of the first neoplasm. In our study, as in most previous studies, a higher risk of developing a second primary neoplasm was demonstrated, but additional tests for early detection of cancer beyond routine age- and sex-appropriate examinations are still not part of the guidelines. Regular check-ups and a multidisciplinary approach are necessary. Based on this study, we conclude that patients with CTCL should regularly undergo preventive examinations for the purpose of early detection of other primary malignant diseases.

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