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CLINICAL REPORT

New Insights into Associated Co-morbidities in Patients with Cutaneous T-cell Lymphoma (Mycosis Fungoides)

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Studies of associated cancer in patients with mycosis fungoides (MF) have focused primarily on secondary cancers in North American and European populations. This study investigated the association between MF and malignancies, anxiety and depression in the Israeli population. Data on Israeli patients with MF and age- and gender-matched controls were collected from a database of population- based cohort (683 patients; 1,700 controls) and an institution- based cohort (343 patients; 846 controls) and analysed by univariate and multivariate methods. MF was significantly associated with Hodgkin's lymphoma in both cohorts (multivariate odds ratio (OR) 7.83, univariate OR ∞, respectively); acute leukaemia (multivariate OR 10.1, first cohort) and lung cancer (multivariate OR 10.15, second cohort). MF was significantly associated with anxiety and depression (multivariate OR 1.59, OR 1.51, respectively in first cohort). The current study provides support to the associations between MF and other cancers: Hodgkin's lymphoma, acute leukaemia and lung cancer. The study also emphasizes the association between MF and anxiety and depression. ***Key words: mycosis fungoides; cutaneous T-cell lymphoma; Hodgkin's lymphoma; lung cancer; acute leukaemia; anxiety; depression.***

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Mycosis fungoides (MF), including its leukaemic variant, Sézary syndrome (SS), is the most common type of primary cutaneous T-cell lymphoma. MF is more prevalent among men than women (1) and typically presents in the early stage (patches/plaques without extracutaneous involvement) with variable progression to the late stage (tumours with or without lymph node or visceral involvement). Erythroderma and SS are forms of late-stage MF that usually arise *de novo*.

Previous epidemiological studies of MF/SS-associated co-morbidities have focused mainly on secondary cancers (2–7). The most consistent observation was an increased risk of the development of secondary lymphomas (2–4, 7). Other malignancies that were inconsistently found to be increased in MF included cancers of the lung (4, 7), colon (4), urinary system (3), biliary system (3), vulva (2), melanoma (3), and acute myeloid leukaemia (2). All the studies were limited primarily to either North America (2–5) or Europe (Great Britain and Finland) (6, 7). Given the evidence for a pathogenic role of genetic and environmental factors in cancer, it is important that investigations are conducted in diverse populations in order to properly define the epidemiology of MF-associated malignancies. In addition, only a few studies have shown the impact of MF on patients' health-related quality of life and psychological well-being (8–12). The aim of the present study was to examine the association between MF, other malignancies, anxiety and depression in Israeli patients.

MATERIALS AND METHODS

To evaluate the association between MF and co-morbidities, cross-sectional studies were performed in 2 cohorts.

In the population-based cohort, data were collected from the comprehensive electronic medical database of Clalit Health Services (CHS), the largest public health maintenance organization in Israel, serving a population of approximately 3,900,000, or 54% of the total population of Israel. The CHS database receives continuous real-time input from pharmaceutical, medical and administrative computerized operating systems, which facilitates epidemiological studies. CHS Chronic Diseases Registry is based on information drawn from hospital and primary care physician reports. The validity of registry CHS diagnoses has been found to be high (13). In recent years, we have used the CHS database to study disease associations in patients with psoriasis (14–18), pemphigus (19) and lichen planus (20).

The clinical diagnostic codes for MF/SS were introduced to the database in January 2002; therefore, for the present analysis, we included patients registered from that date to the end of 2008. Age- and gender-matched control subjects were selected randomly from among the other members of CHS without a diagnosis of MF.

For the institution-based cohort, data were collected from the computerized medical files of all patients with biopsy-proven MF who were diagnosed and managed from 1970 to 2009 at the Cutaneous Lymphoma Clinic of the Department of Dermatology, Rabin Medical Center (RMC), a tertiary university-affiliated hospital in central Israel. The following

patient information was recorded: date of birth, age at onset of MF, date of diagnosis of MF, and stage at diagnosis. In order to make use of the CHS database to identify co-morbidities in the institution-based cohort, we included only those patients and controls treated at RMC who were enrolled in CHS. In relevant cases, additional information was extracted from the RMC database, such as the specific histopathological type of associated malignancy and the date of its diagnosis.

Basal cell carcinoma and squamous cell carcinoma were excluded from the study due to coding difficulties in the CHS registry. Furthermore, it was not possible to properly investigate the association between non-Hodgkin's lymphoma (NHL) and MF due to possible misclassifications of MF as NHL in the CHS database.

Patients were divided into different socio-economic groups using data from the CHS database. The CHS database is categorized into 3 levels of socio-economic groups based on the location of the clinic where patients are registered.

Statistical analysis was performed with SPSS software, version 15. A χ^2 test was used to compare distributions of age, socioeconomic status, and sector between patients with and without MF; Student *t*-test was used to compare the sex distribution. The proportion of the study and control groups with co-morbidities was compared with univariate analyses. Statistically significant differences were determined by χ^2 tests. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. For observations with a value of zero, 95% CI were calculated by Cornfield's method using STATA software. Diseases significantly associated with MF on univariate analyses were entered into a multivariate logistic regression model. Significance was set at $p < 0.05$. The study protocol was approved by the institutional review boards of both CHS and RMC.

RESULTS

Cohorts

The institution-based cohort included 343 patients with MF who were diagnosed and treated at the Cutaneous Lymphoma Clinic of RMC (RMC cohort) and 846 age- and gender-matched controls.

A total of 856 patients was identified in the population-base cohort; of these, 173 patients overlapping in both CHS and RMC databases were excluded, leaving 683 patients in the population-based cohort for the study (CHS cohort). Patients in CHS cohort were matched with 1,700 age- and gender-matched controls.

Background characteristics

Table SI (available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1496) demonstrates the distribution of age, sex, socioeconomic status, and ethnicity among patients with MF in each cohort and their respective age- and gender-matched control subjects. Mean age at the time of analysis was significantly higher in patients with MF in the CHS cohort compared with the RMC cohort ($p = 0.002$). The MF group in both cohorts had a similar male predominance (ratio: ~1.8:1, 2:1, respectively, $p = 0.4$).

Within both cohorts, patients with MF had a significantly lower proportion of low socioeconomic status compared with the control group. MF was diagnosed significantly less often among Arabs than Jews. Information about the stage of MF at diagnosis was available only for the RMC cohort. The vast majority of patients had early-stage disease: 157 (48.3%) stage IA (patch and/or plaques covering ≤ 10% of the body surface area without any extracutaneous involvement), 134 (41%) stage IB (patch and/or plaques covering > 10% of the body surface area without any extracutaneous involvement), and 6 (1.7%) stage IIA. Twenty-five patients (8%) were diagnosed with late-stage MF (IIB, III, or IV including SS). In 11 patients, stage was not recorded.

Malignancies associated with mycosis fungoides

In univariate analyses, patients with MF had a significantly higher proportion of Hodgkin's lymphoma (in both cohorts); acute leukaemia (in the CHS cohort) and lung cancer (in the RMC cohort), compared with the control group (Table SII; available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1496). Specifically, Hodgkin's lymphoma was diagnosed in 4 patients with MF from the RMC cohort: in 2 of them, it preceded the diagnosis of MF by 6–7 years (although in one, the onset of MF preceded the diagnosis of Hodgkin's lymphoma by 10 years), and in one it followed the diagnosis of MF; in the fourth patient, the temporal relationship of the 2 diseases could not be determined accurately from the database. Three of the affected patients had early-stage MF and one had late-stage MF.

In multivariate analysis of RMC cohort (Table I), patients with MF had a significantly higher proportion of any cancer than controls (OR 1.77), and specifically, of lung cancer (OR 10.15). Of the 4 patients with lung cancer in the RMC cohort, 2 had squamous cell carcinoma and 2 had adenocarcinoma. Lung cancer was diagnosed 9 years before MF in one patient and several months after MF in 3 patients. All 4 patients had early-stage MF. In multivariate analysis of the CHS cohort, patients with MF did not have a significantly higher frequency of cancer (any type) than the controls. However, on analysis of specific cancers, patients with MF had a significant association with Hodgkin's lymphoma (OR 7.83) and acute leukaemia (OR 10.10), and a near-significantly higher association with thyroid cancer (OR 4.23).

Regarding lung cancer, In the CHS cohort there were 3/6 smokers among patients with MF compared with 5/8 in the control group. In the RMC cohort there were 2/4 smokers among patients with MF compared with 1/1 in the control group.

Mental health conditions

Univariate (Table II) and multivariate (Table I) analyses demonstrated that MF was significantly associated with anxiety and depression in the CHS cohort (multivariate

Table I. *Multivariate analyses of the association between mycosis fungoides (MF) and co-morbidities (Clalit Health Services database: population-based cohort, Rabin Medical Center: institution-based cohort)**

	Population-board cohort ($n=683$)			Institution-based cohort ($n=343$)		
	Odds ratio	95% confidence interval	*p*-value	Odds ratio	95% confidence interval	*p*-value
Cancer						
Any cancer	1.211	0.913–1.605	0.184	1.77	1.211–2.586	0.003
Hodgkin's lymphoma	7.83	1.563–39.221	0.012	Not applicable		
Lung cancer	1.883	0.645–5.496	0.247	10.155	1.126–91.607	0.039
Acute leukaemia	10.1	1.118–91.257	0.039	0.822	0.085–7.926	0.865
Thyroid cancer	4.236	1.001–17.920	0.05	1.373	0.123–15.283	0.797
Depression and anxiety						
Depression	1.514	1.075–2.132	0.018	1.317	0.802–2.162	0.286
Anxiety	1.595	1.072–2.373	0.021	1.416	0.736–2.725	0.18

*Models are adjusted for patients' age, gender and socio-economic status.

OR 1.59, 1.51, respectively). Psychoses, schizophrenia, bipolar disease, alcohol abuse and smoking were not significantly associated with MF in either cohort (Table II).

DISCUSSION

The vast majority of previous epidemiological studies have focused on secondary malignancies following the diagnosis of MF/SS (2–7). These include 4 institution-based series (2, 3, 5, 6) and 3 population-based series (3, 4, 7). Only one study assessed both population-based and institution-based cohorts (3). In almost all the cohorts, patients with MF/SS had an elevated risk of secondary neoplasms (mean RR 1.73, range 1.32–2.4). In 2 investigations of the prevalence of malignancy before the diagnosis of MF, both from the USA, the reported rates were 9.4% in a population-based cohort (21) and 12.2% in a cohort from the MD Anderson Cancer Center (2). The latter study, conducted in 672 patients, noted a significantly higher overall prevalence of all cancers in patients with MF (16.6%) relative to controls. This proportion is close to the 14.9% proportion of malignancy in our institution-based cohort. In our study, patients with MF had a higher proportion of Hodgkin's lymphoma than controls in both population and institution-based cohorts, and of lung cancer and acute leukaemia in institution-based and population based- cohort, respectively. Similarly, among the secondary malignancies reported in the literature following the diagnosis of MF, the most consistent findings were noted for lymphoid neoplasms. Rates of Hodgkin's lymphoma were found to be elevated in 4 cohorts of MF (2, 3, 7), with the standardized incidence ratio (SIR) ranging from 17.14 to 27.27, and rates of NHL were increased in 3 cohorts (2–4), with SIRs ranging from 5.5 to 9.87. Furthermore, in our study, Hodgkin's lymphoma preceded or followed the diagnosis of MF in 4 patients in the RMC group; these data were unavailable for the population-based cohort. Similar bidirectional association was noted for the contemporaneous occurrence of B-cell lymphoma and MF (22, 23).

There are several possible explanations for the co-existence of 2 types of lymphoma, including those of different lineages (B cell and T cell) in the same patient. Treatment of the first neoplasm may contribute to the development of a secondary neoplasm. Alternatively, the immunodeficiency inherent in patients with a neoplasm may create conditions that encourage the development of a secondary neoplasm. In addition, the 2 malignancies may have a common origin (neoplastic stem cells), with genetic events predisposing the individual to the independent development of the different types of lymphoma. Other explanations are exposure to carcinogens or viruses that affect both B- and T-cell precursors, and production of cytokines by the first

Table II. *Univariate analyses: association between mycosis fungoides (MF) and mental and substance abuse disorders (Clalit Health Services database: population-based cohort, Rabin Medical Center: institution-based cohort)*

	Population-based cohort				Institution-based cohort			
	Patients $n=683$ *n* (%)	Controls $n=1,700$ *n* (%)	OR (95% CI)	*p*-value	Patients $n=343$ *n* (%)	Controls $n=846$ *n* (%)	OR (95% CI)	*p*-value
Psychoses	4 (0.6)	24 (1.4)	0.411 (0.142–1.190)	0.101	2 (0.6)	10 (1.2)	0.490 (0.107–2.249)	0.359
Schizophrenia	3 (0.4)	21 (1.2)	0.353 (0.105–1.186)	0.092	3 (0.9)	11 (1.3)	0.670 (0.186–2.416)	0.54
Bipolar disease	1 (0.1)	6 (0.4)	0.414 (0.050–3.445)	0.415	0 (0.0)	1 (0.1)	0	1
Depression	61 (8.9)	98 (5.8)	1.603 (1.149–2.236)	0.005	27 (7.9)	53 (6.3)	1.278 (0.790–2.069)	0.317
Anxiety	3 (6.3)	68 (4)	1.612 (1.089–2.388)	0.017	15 (4.4)	27 (3.2)	1.387 (0.729–2.641)	0.319
Alcohol abuse	3 (0.4)	13 (0.8)	0.573 (0.163–2.015)	0.385	1 (0.3)	5 (0.6)	0.492 (0.057–4.225)	0.518
Smoking	139 (20.4)	392 (23.1)	0.853 (0.686–1.060)	0.151	119 (34.7)	300 (35.5)	0.967 (0.743–1.258)	0.802

CI: confidence interval; OR: odds ratio.

neoplasm that facilitate or stimulate the development of the secondary neoplasm (22).

Our study supports earlier observations that patients with lymphoma are at increased risk of acquiring lung cancer relative to the general population (24, 25). This association has been ascribed mainly to anti-lymphoma therapies, although the precise mechanism has not been elucidated. In 2 population-based studies on MF from the USA and Finland, respectively, Kantor et al. (4) reported a 2.8 relative risk of lung cancer, and Väkevä et al. (7) reported a SIR of 2.7. Iatrogenic cancer risks in these populations were considered. Since studies on large cohorts failed to demonstrate a connection between non-cutaneous cancer and psoralen plus ultraviolet A (PUVA) (26), and given the fact that half of the patients with lung cancer in the latter study were diagnosed with MF before or shortly after PUVA was commenced, it was concluded that PUVA plays no major part in the subsequent cancers observed (7). Regarding other possibly carcinogenic treatments, only 30% of patients with lung cancer had received cytotoxic drugs for the treatment of their MF (7).

In the present study, all 4 patients with MF and lung cancer had the more common non small-cell type, and in 3 of them it was diagnosed within several months after the diagnosis of MF. Since these 3 patients had early-stage MF, it is unlikely that the subsequent primary cancer malignancy was attributable to the skin-targeted therapy they had briefly received.

We also found that MF is significantly associated with acute leukaemia, specifically myeloid type (AML). This finding provides support to an earlier observation (2), but the reason for this association is unclear. Some authors have suggested that anti-lymphoma drugs (27, 28), and especially alkylating agents (29) may exert carcinogenic effects leading to leukaemia. However, these treatments are usually reserved for patients with advanced MF. In addition a few case reports have described the development of AML after PUVA treatment for MF (30, 31). Others have reported the simultaneous development of lymphoma and AML, which was not always iatrogenic (32).

AML may be associated with adult T-cell leukaemia/lymphoma and is of particular interest given the clinical, histopathological and, in some cases, pathogenic resemblance of MF and adult T-cell leukaemia/lymphoma (33). Further epidemiological studies are needed to confirm the association between MF and acute leukaemia.

The different pattern of associated cancers detected in our 2 cohorts might be attributable to 2 main factors: (*i*) referral bias and other non-generalizable properties of the patients in the institution-based cohort, including the use of different types of treatment at different clinics; and (*ii*) possible misclassification of MF in the population-based cohort. Huang et al. (3) also reported a lack of consistency in MF-associated secondary malignancies on comparison of data from the 9 population-based US cancer registries that constitute the Surveillance, Epidemiology, and End Results Program (SEER-9) and a cohort from Stanford University.

Our study identified an important association of MF with anxiety and depression. This is the first cross-sectional study on the prevalence of these mental health conditions in MF. Because the date of diagnosis was unavailable in the medical electronic database, we were unable to determine the temporal relationship. The profound impact of MF on patient functioning and emotional well-being was reported by the Cutaneous Lymphoma Foundation Survey (8). At the same time, emotional distress has been known to induce or exacerbate psoriasis, a prototype of benign T-cell-mediated skin disease (34). Thus, further studies are needed to explore the cause-effect relationship between mental stress and MF. Physicians should be aware that patients with MF may have associated psychological distress, including anxiety and depression. In relevant cases, patients should be treated accordingly. The mental status of the individual patient should be taken into consideration when choosing the treatment option for this chronic malignant disease. It is also important to consider maintenance treatment in order to prolong disease-free intervals, thereby preserving patient quality of life (35).

In summary, in Israeli patients we identified and provides support to the association of MF with other malignancies (Hodgkin's lymphoma, acute leukaemia and lung cancer). We found that anxiety and depression are important co-morbidities in patients with MF, which can significantly impact on patient quality of life and therefore merits further clinical and research attention.

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