

Morbidity and Causes of Death in Patients with Cutaneous T-cell Lymphoma in Finland

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Cutaneous T-cell lymphomas (CTCL), especially mycosis fungoides, can be considered as a state of longstanding low-grade systemic inflammation. Many studies have focused on secondary cancers with CTCL, but information about comorbidities is limited. A total of 144 patients with CTCL at Helsinki University Central Hospital during 2005 to 2015 were studied to determine associated comorbidities and causes of death in this cohort. Compared with an age-standardized control population, the prevalence of type 2 diabetes mellitus was increased among patients with CTCL with no link to obesity. Patients with CTCL had a lower prevalence of hypertension, myocardial infarction and stroke than the control group. The 3 most common causes of death were CTCL, coronary artery disease and lung cancer. The increased risk of myocardial infarction or stroke reported previously was not detected in this patient group.

Key words: mycosis fungoides; cutaneous T-cell lymphomas; morbidity; diabetes mellitus.

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Cutaneous T-cell lymphomas (CTCL) are a rare group of non-Hodgkin's lymphomas in which neoplastic cells primarily home to the skin. The most common type of CTCL is mycosis fungoides (MF), the clinical course of which is usually very indolent, depending on the stage of the disease. In the early stages the prognosis is favourable, but progression to tumours or nodal involvement predicts a poor prognosis (1). Sézary syndrome (SS) and subcutaneous panniculitis-like T-cell lymphoma (SPTL) are rare forms of CTCL. SS is understood to arise from a different subset of T cells (central memory cells) and is currently not considered to be a leukaemic variant of MF, where the cells arise from skin resident-effector memory T cells (2).

MF is understood to arise through longstanding chronic inflammation, and can be considered as a state of longstanding low-grade systemic inflammation (3). Chronic systemic inflammation has recently been accepted to be an important contributor to metabolic diseases. Inflammatory mediators released in chronic inflamma-

tion can lead to hypertension, type 2 diabetes mellitus (DM2) and atherogenesis (4, 5). Psoriasis is an example of chronic systemic inflammation with an elevated risk of cardiovascular diseases. In addition, patients with atopic dermatitis appear to have increased risk of cardiovascular disease, heart attack and stroke (6, 7). In advanced stages of CTCL the immunoprofile is polarized towards Th2-activated memory cells, similarly to atopic dermatitis.

Most previous studies of comorbidities in CTCL have focussed on cancer. These studies have demonstrated an increased risk of secondary cancers in patients with CTCL (8–11). There are only a few previous studies concerning other comorbidities in CTCL (12–14). In MF the recently reported increased risk of myocardial infarction may be mediated by chronic inflammation (14). Evaluation of cardiovascular risk factors in patients with MF has demonstrated an increased rate of cardiovascular risk related to higher levels of total cholesterol and low-density lipoprotein (LDL) cholesterol than in control patients (12). Interestingly, MF has also been linked to increased risk of anxiety and depression (13).

The prognosis and survival of patients with CTCL is dependent on the stage of the disease (15–17). Patients with non-advanced stages of CTCL seldom die of the disease itself, and reports of causes of death in this patient group are sparse.

The aims of this study were to examine comorbidities in the largest cohort of Finnish patients with CTCL and to assess the most common causes of death in this patient group.

PATIENTS AND METHODS

A total of 144 patients with CTCL, treated in the Skin and Allergy Hospital, Helsinki University Central Hospital (HUCH), Helsinki, Finland, during the period 1 January 2005 to 18 February 2015 were analysed retrospectively.

Patient search was based on a confirmed dermatological and histopathological diagnosis. The majority of patients had a diagnosis of MF ($n=122$). There were 8 patients with SS, 8 with SPTL, and 6 with anaplastic large cell lymphoma. All except one of the patients with SPTL had an $\alpha\beta$ -phenotype. Clinical patient data and comorbidity data was collected from the comprehensive electronic medical patient records of HUCH. Staging of the patients was performed according to current guidelines (15). Systemic treatment information was also collected from patient charts. Demographic and survival data for the 144 CTCL patients is presented in **Table I**.

Table I. Demographic and survival data of the study patients

Patient characteristics	Cutaneous T-cell lymphomas cohort (n = 144)
Female, n	50
Male, n	94
Mean age at diagnosis (years)	66.4
Alive (%)	78
Cutaneous T-cell lymphomas diagnosis	
Mycosis fungoides, n	122
Sézary syndrome, n	8
Panniculitis-like T-cell lymphoma, n	8
Primary cutaneous anaplastic large cell lymphoma, n	6

The prevalence of coronary artery disease, hypertension, stroke, myocardial infarction and DM2 was compared with that of a standardized, representative sample of the Finnish general population. The data for the general population came from the National Health 2000 Examination Survey (n=8,028) representing the Finnish population aged 30 years and over (18). For this analysis individuals within the age range of the patients were selected (n=6,268). This sample of the general population was weighted to reflect the age distribution of the patients. The prevalence of the diseases in the population data is based on confirmed diagnoses, which, in turn, are based either on a medical examination as a part of the survey or on medical records and register data.

The statistical significance of the difference in the prevalence of the diseases between the groups was tested using χ^2 tests (2-sided likelihood ratio test and Fisher's exact test). *p*-values <0.05 were considered statistically significant.

Detailed causes of death were obtained from Statistics Finland.

RESULTS

The study cohort consisted of 144 patients who were followed up for 10 years. The majority (65%) of the patients were men and 35% were female and the majority (n=122) had MF (Table I). The mean age at diagnosis was 66.4 years. Different CTCL subtypes according to age group are presented in Table II. There were 6 patients who had more than 3 malignancies in addition to CTCL. The most common other types of cancer were lung cancer, prostate cancer, colorectal cancer and bladder cancer.

The majority of the patients in this study were stage IA–IIA (70%). Hypercholesterolaemia was detected in 46/144 patients (32%). Only 23 patients (16%) had received retinoid therapy and 9 of them (40%) had hypercholesterolemia. None of these 9 patients died of coronary artery disease or myocardial infarction. Eight

Table II. Cutaneous T-cell lymphomas subtypes by age group

Age	Mycosis fungoides, n	Sézary syndrome, n	SPTL, n	PCALCL, n
20–29 years	1	0	1	0
30–39 years	0	0	3	2
40–49 years	3	1	1	0
50–59 years	14	2	0	0
60–69 years	45	3	2	3
70–79 years	29	2	1	0
>80 years	30	0	0	1

SPTL: subcutaneous panniculitis-like T-cell lymphoma; PCALCL: primary cutaneous anaplastic large cell lymphoma.

Table III. Prevalence of different diseases in patients with cutaneous T-cell lymphomas (CTCL) compared with control patients

Disease	CTCL cohort (n=144) n (%)	Control cohort (n=6,268) n (%)	2-sided significance ^a	2-sided significance ^b
Coronary artery disease	17 (11.8)	1,238 (19.8)	0.012	0.019
Hypertension	71 (49.3)	3,804 (60.7)	0.006	0.007
Myocardial infarction	1 (0.7)	429 (6.9)	<0.001	<0.001
Stroke	5 (3.5)	547 (8.7)	0.013	0.023
Type 2 diabetes mellitus	24 (16.7)	615 (9.8)	0.012	0.011

^aLikelihood ratio test; ^bFisher's exact test.

patients had received doxorubicin, but none of them had myocardial infarction.

Overall prevalence data for coronary artery disease, hypertension, myocardial infarction, stroke, and diabetes mellitus in the patient and controls cohort are shown in Table III. Five of the 144 patients had experienced stroke and one patient had experienced transient ischaemic attack. Only one patient had experienced myocardial infarction. The prevalence of coronary artery disease, hypertension, myocardial infarction and stroke was statistically lower than in the control group.

All cases of diabetes mellitus in the CTCL cohort were of type 2, and the prevalence was statistically higher than in the age-matched control group (Table III). In the patient records, 23 patients (16%) had a mention of obesity and 54 (37.5%) were smokers.

During the follow-up time, 31/144 patients died. The 3 most common causes of death were cutaneous lymphoma (n=12), coronary artery disease (n=5) and lung cancer (n=4). The 12 deceased cutaneous lymphoma patients consisted of 8 MF, 2 SS and 2 primary anaplastic large cell lymphoma subtypes. Four patients died of lung cancer (Table IV).

DISCUSSION

There are only a few studies of comorbidities in patients with CTCL. The risk of myocardial infarction and stroke was found to be increased in patients with CTCL in a

Table IV. Cause of death in cutaneous T-cell lymphomas (CTCL) subtypes

CTCL subtype	Cause of death, n
Mycosis fungoides (n=21)	MF 8 Cancer (colon, prostate) 4 Coronary artery disease 3 Lung cancer 2 Myocardial infarction 1 Intoxication 1 Cerebral stroke 2
Sézary syndrome (n=8)	Sézary syndrome 2 Lung cancer 2 Alcoholic hepatic failure 2 Coronary artery disease 2
PCALCL (n=6)	PCALCL 2 ^a
SPTL (n=6)	Panniculitis-like T-cell lymphoma 0 ^b

^aFour patients are alive. ^bAll patients alive.

PCALCL: primary cutaneous anaplastic large cell lymphoma; SPTL: subcutaneous panniculitis-like T-cell lymphoma.

Danish cohort of 483 patients with MF and 623 with parapsoriasis (14). In this study, the risk was increased within the first 5 years after diagnosis. Our analysis of 144 patients with CTCL did not find any increased risk of coronary artery disease compared with an age-standardized control population. Causes of death were obtained from Statistics Finland using the main cause of death. In our control population it was not possible to detect myocardial infarction, but only coronary artery disease. Coronary artery disease does not always end in myocardial infarction. Our study was retrospective and thus dependent on the recorded events. Some diagnoses may not have been recorded, although, for example, myocardial infarction and stroke usually are the main events in deteriorating health and are usually mentioned in patient charts. Regarding specific causes of death of the patients with CTCL, 1 myocardial infarction and 2 strokes were found.

A previous study evaluating cardiovascular risk factors in patients with MF has reported that patients with MF have increased risk of cardiovascular diseases (12). In particular, levels of total cholesterol and low-density lipoprotein were significantly higher in patients with MF. We could only collect a diagnosis of hypercholesterolaemia from the patient charts (32%), but could not perform any risk analysis with our control material. Patients with CTCL are often treated with retinoids, but hypercholesterolaemia is controlled with concomitant anti-lipid drugs routinely used during treatment. In our patients hypercholesterolaemia was not related to death.

The majority of our patients with CTCL were not in an advanced stage of the disease. Thus, most of the treatments this cohort had were skin directed. Only 8 patients had experienced doxorubicin treatment. Only one patient died of myocardial infarction, but he was not treated with doxorubicin. Thus, we think that the common known cardiotoxic effect of this drug did not have any impact on the results. The patients in this study seldom received anti-neoplastic drugs or poly-chemotherapies because only a small proportion of them were at an advanced stage of the disease.

Our patients had an increased prevalence of DM2 compared with the control group, and obesity was not linked to DM2. There are no previous reports regarding DM2 in patients with CTCL. Fallah et al. (19) reported autoimmune diseases associated with non-Hodgkin's lymphoma (NHL), but no association with DM type I with a higher risk of NHL was found. Obesity has been linked to MF in a previous article (20). In obesity, the chronic low-grade inflammation of fat tissue releases proinflammatory cytokines, which are responsible for regulation of T-cell responses favouring lymphomagenesis (21). The association of obesity and the risk of non-Hodgkin's lymphomas has been reviewed by Larsson & Wolk (22), who found that elevated body mass index (BMI) was associated with increased risk of NHL.

Our control group comprised 6,268 participants in the National Health 2000 Health Examination survey carried out in the period 2000 to 2001. These individuals were in the age range of the patients from the original representative sample of 8,028 of the Finnish general population aged 30 years and over. The data are based on home interviews and medical examination, complemented by medical records and register data.

In our cohort, the most common cause of death was CTCL; it was registered as a primary cause of death in 32% of this group of patients. In a recent Danish study, the comparative percentage was 27% (9). The most common other cancer-related cause of death was lung cancer, which has been reported previously to be increased in patients with MF (3, 5). Although the prognosis of SS is poor and survival is low, only 2 of our 8 patients with SS died of the disease itself. Interestingly, the other causes of death in this subgroup were lung cancer, myocardial infarction and alcoholic hepatic failure in equal proportions.

In conclusion, this study reports comorbidities in Finnish patients with CTCL. An increased prevalence of DM2 was found, but the previous observation of increased risk of myocardial infarction or stroke in this patient group was not verified in this study. The current study is the first to report a link between DM2 and CTCL. This link may be related to chronic inflammation, which is common in DM2 and MF, the most common form of CTCL. Further studies, in larger patient populations, are warranted.

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