Mycosis fungoides (MF) is a primary cutaneous T-cell lymphoma with slow disease progression. There is a lack of descriptive data from Sweden concerning patients with this diagnosis. This study extracted data on patients admitted to the dermatology department at Lund University Hospital, Sweden from 1996 to 2010. Forty-four patients with clinically and histopathologically verified MF were identified during the period, with a mean follow-up time of 5.6 years. Median age at initial diagnosis was 64 years. In several cases other skin diseases preceded MF onset, such as non-specific dermatitis (32%) and parapsoriasis (30%). The majority of patients (86%, \( n = 38 \)) had limited-stage (IA–IB) disease at the time of diagnosis. Overall response rate to psoralen plus ultraviolet A (PUVA) treatment was 81%. In adnexal MF, a trend to higher rate of progression to an advanced stage was observed when compared with non-adnexal disease (40% and 21%, respectively). Increased levels of soluble interleukin-2 (IL-2) receptor correlated with disease stage, being elevated in advanced stages or adnexal disease, but almost never elevated in early non-adnexal limited-stage disease. Overall mortality was 25%, but only 11% could be verified as caused by MF. Key words: mycosis fungoides; cutaneous T-cell lymphoma; sIL-2r.

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Mycosis fungoides (MF) is a cutaneous T-cell lymphoma (CTCL) with a worldwide incidence of approximately 0.36–0.64/100,000 and a median age range at diagnosis of 55–58 years. Of all primary CTCL, MF comprises 44–62% (1–4). At present, MF is an incurable disease, and the most common treatments for achieving remission or avoidance of progression include psoralen plus ultraviolet A (PUVA), ultraviolet B (UVB), topical mustine (not available in Sweden), topical corticosteroids, photodynamic therapy (PDT), oral retinoids and chemotherapy in addition to radiotherapy. Newer agents include histone deacetylase inhibitors, such as vorinostat and romidepsin, and further denileukin diftitox, a recombinant fusion protein (5–8). Due to the indolent disease course, there is a divergence between incidence and prevalence of MF. MF patients display a chronic disease, lasting from years to decades, and many patients die from age and intercurrent diseases unrelated to the lymphoma. Published registry data on lymphoma indicate that approximately 25% of patients with MF die of their disease (9). However, retrospective studies indicate less than 10% disease-specific mortality (4).

In MF, routine blood analyses are of limited value. Lactate dehydrogenase (LDH) is a non-specific marker of tumour burden associated with poor prognosis (9, 10). There is less data available on T-cell-specific soluble IL-2 receptor (sIL-2r), but it may serve as a potential marker for disease activity and prognosis in CTCL, similar to LDH (11). As sIL-2r has been routinely evaluated at our department, it enabled us to study this factor’s relationship with MF and the severity of disease.

The aim of this retrospective study was to investigate the demographics, the dermatological diagnoses preceding MF, time from onset of symptoms until diagnosis of MF, choice of therapy, and the time to progress to a more advanced stage (stages II–IV) and the overall survival of the study population. A further aim was to determine whether sIL-2r could be used to evaluate the severity of the disease.

MATERIALS AND METHODS

From the patient record system at the Department of Dermatology, Lund, Sweden, we identified all patients who had been registered from January 1996 to December 2010 with an initial diagnosis of CTCL. Data collection was approved by the regional ethics committee (number 2013/212). Patient records with International Classification of Diseases 10th revision (ICD-10) diagnosis, starting with C84 (CTCL) and specifically C84.0 (MF), were examined. A total of 73 patients were registered as having CTCL and MF. Twenty-nine patients were excluded due to other histology, questionable clinical picture or having a CTCL-diagnosis other than MF. Since Sezary’s syndrome (SS) is a diagnosis of its own, patients with SS (\( n = 5 \)) were also excluded from the study. A final total of 44 patients with clinically and histologically verified MF were included in the study.

Staging of the disease was made according to the European Organization of Research and Treatment of Cancer (EORTC), latest revision 2007 (12), using descriptions of the efflorescence (patch, plaque, tumour, erythroderma) and of the extent of the disease. This, together with patient photographs, yielded an estimate of the percentage of skin area engaged when registering according the tumour-node-metastasis-blood (TNMB) classification and staging.
A histopathology re-assessment was included to ensure the correct diagnosis and was also analysed for identifying progression into tumour stage or large-cell transformation. Analysis of T-cell receptor clonality was performed from 2002 onwards using multiplex polymerase chain reaction (PCR) (13). Furthermore, results from magnetic resonance imaging (MRI) or computed tomography (CT) investigation for nodal/systemic spread were taken into account. In cases with nodal involvement, fine-needle aspiration cytology examination was performed, and considered in the initial staging as well as at progression. Assessment of treatment response was limited to phototherapy plus radiation and could only be described in terms of overall or no response. Systemic therapy could only be evaluated in general terms, such as clinical benefit, stable disease or disease progression. As part of the routine laboratory analyses, levels of sIL-2r were determined in blood samples from most patients at the time of diagnosis of CTCL.

The data was statistically handled in Excel 2013 as descriptive table charts (Microsoft) and in SPSS 17.0 for Windows as box-plots (SPSS, Chicago, IL, USA). Mann–Whitney test was used for comparing the sIL-2r patient groups. The significance limit was set to $p < 0.05$.

RESULTS

A total of 44 patients with clinically and histopathologically verified MF were identified. The histopathological pattern comprised immunohistochemically confirmed CD3$^+$/CD4$^+$ positive cells, with visual atypia and epidermotropism. True Pautrier’s abscesses were seen in 32% ($n = 14$) of cases. Not uncommonly, despite cells and histology typical of MF, CD30$^+$ cells and eosinophils were often present to a minor degree.

In all, 29 patients underwent analysis of T-cell receptor gene rearrangement with multiplex PCR and, of these, 28 were positive. Five patients had β-receptor clonality, 7 had γ-receptor clonality, 12 had both γ- and β- and δ-receptor gene rearrangement, and 4 had δ-receptor clonality with a combination of either γ- or β-receptor gene rearrangement.

The median age at diagnosis was 64 years, age range 30–85 years. The median time from onset of symptoms until established diagnosis was 4 years ($n = 39$, mean 7.6 years). The male to female ratio was 1.6:1.

Preceding MF, 14 patients were diagnosed with dermatitis (histopathologically classified as non-specific) and 13 with parapsoriasis. Of those with parapsoriasis, 10 patients were registered as large plaque variant, confirmed with biopsy, and the remaining 3 were not specified. The diagnosis of large plaque parapsoriasis was made based on the typical clinical presentation of irregular or oval scaly patches in combination with a histopathological pattern of superficial lymphoid dermal infiltrate, some degree of lymphocytes in epidermis but absence of atypical T cells. Two patients with MF had a history of lymphomatoid papulosis, and, in both cases, were clinically and histopathologically typical for the disease (Fig. 1).

At the time of diagnosis, 86% ($n = 38$) had limited stage of MF. Fifty percent were in stage IA and 36% had stage IB with a cutaneous involvement of >10%. Among these patients with limited stage MF, 32% ($n = 12$) presented with patches and 68% ($n = 26$) with patches/plaque.

Fourteen percent ($n = 6$) had an advanced stage IIA–III. No patient had stage IV at initial diagnosis (Fig. 2).

Progression and survival

The mean follow-up time was 67 months (5.6 years). Disease progression from early stages of MF (IA–IB) to advanced stages with at least nodal involvement (II–IV) was seen in 25% including all subtypes of MF, with a median time to progression of 41 months (mean time 50 months). Among stage IB patients with cutaneous involvement of more than 10% of body surface, progression to advanced stage was more common than in stage IA patients; 44% vs. 18% (Fig. 2). Three patients progressed to stage IVB with lung and liver involvement ($n = 1$), meningeal infiltration ($n = 1$) and involvement of lymphoma in parotid gland ($n = 1$). The latter had parotid infiltration combined with positive cell clonality in enlarged lymph nodes and more than 50% atypical CD$^+$4 cells in blood.

Overall mortality was 25% ($n = 11$) with an age range of 65–82 years, median age 75 years. In 5 patients, death was caused by lymphoma (11% of MF cohort), while in 6 patients the cause of death was of unclear aetiology or due to other diseases (Fig. S1$^\dagger$).
Adnexal mycosis fungoides

Eleven patients had an adnexal subtype of MF: 8 patients had a folliculotropic subtype, 2 patients had a syringotrophic variant and 1 had both folliculotropic and syringotrophic lesions with a histological pattern of atypical CD4+ cells infiltrating the adnexal structure. This adnexal MF group (n = 11) was compared with non-adnexal MF patients (n = 33). The groups were not large enough to allow for any statistical comparisons; however, the following was noted: there was a higher male:female ratio of 2:7:1 (n = 8/3). Those with adnexal MF stage IA–IB (n = 10) had a higher likelihood of progression to advanced stages (4/10, 40%) than did patients with similar stages in the non-adnexal MF group (6/28, 21%). Three patients developed large-cell transformation, while in the group with non-adnexal MF, only one patient experienced large-cell transformation. The majority of those with adnexal disease had increased levels of sIL-2r at initial diagnosis; 67%, compared with 15% of non-adnexal MF patients. Almost half of the patients with adnexal MF died within the study period (45%, n = 5) (Fig. S11).

Topical treatments

All patients were treated with topical corticosteroids, usually clobetasol 0.05% and an emollient, mostly in combination with phototherapy. Five patients received additional treatment with topical tacrolimus. One patient received adapalene for follicular changes in the face and chest area with almost complete remission of all lesions.

UV, PDT and radiation therapy

Twenty-six patients (59%) were treated with PUVA and 5 (11%) with narrowband UVB (nbUVB) as first-line therapy. PUVA was administered twice a week to a total of 24–30 times. The majority (85%, n = 22) receiving PUVA therapy showed a response to treatment. UVB was given as narrowband UVB 3 times weekly with a similar number of treatments as PUVA. Patients treated with nbUVB had stage IA–IB, mainly with patches, and all responded to treatment.

Photodynamic treatment was used for localized recalcitrant plaques in 4 patients, with a response in all of them. Twelve patients received radiation therapy for either localized tumourous MF (n = 10) or refractory plaques (n = 2) with subtotal or total clearance. Two patients (stage IIA and IIB) were treated with total skin electron beam radiation (TSEB) with only a short period of remission and with considerable side-effects.

Systemic treatment and chemotherapy

In total, 41% (n = 18) of the patients received systemic therapy and/or chemotherapy (Tables SI and SII). The most common systemic treatment comprised retinoids, such as acitretin, isotretinoin and bexarotene (n = 11; 25%). The majority of the patients with retinoid treatment would eventually need chemotherapy (7/11). Only 2 patients received interferon alpha treatment and this was given in conjunction with PUVA.

Five patients were treated with acitretin combined with PUVA and all except one continued with systemic treatment of acitretin after phototherapy since they appeared to have a clinical benefit, keeping the disease in a steady state and, in risk-patients, to prevent development of squamous cell carcinoma after several treatment cycles of PUVA.

Six patients were treated with isotretinoin; this was given to patients with side-effects due to acitretin, or if they had adnexal involvement. Isotretinoin appeared to keep the disease stable in the majority of these patients for a mean of 12 months.

Bexarotene was given to 3 patients in dosages slightly below the target dosage of 300 mg/m² per day, resulting in stable disease in 1 of the patients.

Thirty-two percent of the MF patients (n = 14) received one or more chemotherapy agent. Methotrexate was the most common first-line chemotherapy (n = 10/14). Three patients did not respond at all, while stable disease was seen in 7 patients (n = 7/10). Chlorambucil combined with tapering dosages of prednisolone or prednisone was administrated to 4 MF patients. No treatment response was seen in any of these patients; however, 2 patients stopped treatment after only 3–4 weeks due to infections (Table SII). Five patients received one or more of the following chemotherapeutic agents: CHOP standard regimen (cy clophosphamide, doxorubicin, vincristine, prednisone), gemcitabine and pegylated doxorubicin (Tables SI and SII). All of the patients had either lack of effect or showed signs of progressive disease during therapy or within 4 months of treatment. Finally, the monoclonal antibody alemtuzumab was given to 4 patients. One patient showed stable disease during therapy, but had an immediate relapse after cessation of treatment, while 3 patients had no response, possibly owing to shortened treatment due to adverse effects (infections).

Out of all 14 patients treated with chemotherapy, 7 died (disease-specific death n = 5) and of the remaining surviving patients the majority (n = 5) had disease progression by the end of the study period and were planned for subsequent systemic treatment.

sIL-2r analysis

Out of the 44 patients with MF, 28 were analysed for their serum levels of sIL-2r at initial diagnosis (6/28 had
adnexal disease). Nine had an increased sIL-2r (>700 kU/l) and, of these, 4 had adnexal disease, 2 had erythroderma, 2 had lymphadenopathy and 1 had widespread plaque disease that advanced to tumorous stage within 6 months. Thus, all patients with increased sIL-2r value had either adnexal disease or advanced stage of MF (Fig. 3).

Out of the remaining 19 patients with normal sIL-2r levels, 16 (85%) had limited non-adnexal disease stage IA–IB. Only 3 patients with normal sIL-2r levels had advanced stage MF or adnexal disease: 2 patients with adnexal MF (IA–IB) (518–695 kU/l) and 1 patient with MF in tumorous stage (571 kU/l). Interestingly, these patients had no further disease progression during the study period.

DISCUSSION

The median age at initial diagnosis in this study was 64 years, which is higher than previously reported median ages in the range 54–59 years (1, 3, 14), probably reflecting the population-based catchment area of our academic centre, at which almost all patients with CTCL are admitted from other clinics. Coherent with earlier studies time from onset of symptoms to established diagnosis of MF was considerable (median 4 years). Similarities with international data were also seen in the case of sex proportions, with MF being more common in men (1.6:1) and especially in adnexal MF (2.7:1) (15, 16).

The most common dermatological diagnoses preceding MF were non-specified dermatitis and parapsoriasis. It is possible that the dermatitis diagnosis was related to the existence of pre-MF, even though no atypical T cells were seen in the biopsies from the patients. However, chronic eczema cannot be ruled out, since some reports have suggested an association between chronic inflammation in the skin and subsequent development of CTCLs (17, 18). In cases of preceding parapsoriasis, it is plausible that these patients, both clinically and histopathologically, had this diagnosis per se and not an early variant of MF. It is known from other data that 7.5–35% of patients with parapsoriasis will be diagnosed with MF over time (19, 20). In many cases, the development of MF is preceded by other dermatoses without evident histopathological atypia. However, clonal T-cell receptor rearrangement might be detected before atypical lymphocytes can be identified by histopathology, at least in the case of parapsoriasis (21). This supports hypotheses on the pathogenesis of MF, that constantly activated T-lymphocytes might eventually give rise to an atypical T-cell clone (22). Some researchers have noticed a possible connection with microbial colonization/infection and MF (23–25). Interestingly, in at least 4 patients in our study, we observed a temporary clinical improvement in the current MF disease stage when bacterial infections were treated.

Lymphomatoid papulosis has been seen to proceed to MF in a few percent of the cases, and similar figures were found in our, albeit small, clinical cohort. Lymphomatoid papulosis has been described to proceed to MF in 4–25% of cases (26–28).

MF is considered an indolent disease and most studies show that patients with stage IA have a normal life expectancy (29). Even though the majority of patients in the study had MF confined to the skin at initial diagnosis, we noticed that 25% progressed to more advanced stages. Poor prognostic factors among MF stage IA–IB patients were widespread disease (IB) and adnexal disease. In agreement, reports on the latter subtype being more aggressive and having a worse outcome, have been published during the last 10 years (16, 30). Since a quarter of the patients with MF stage IA–IB in the current study progressed to stage IIA–IVB, this portion could be considered to have a poorer outcome considering survival data of advanced stages from other studies (28). This is consistent with cohort data indicating approximately 25% disease-specific mortality (9, 31). However, those figures are derived from lymphoma registry studies. Other follow-up studies indicate a disease-specific mortality of less than 10%, which is quite similar to our present data (4). This discrepancy indicates the difficulty of assessing the exact influence of MF on mortality, and thus whether the patient dies of MF or other diseases.

PUVA with topical steroid treatment was the most frequently used first-line therapy (59%). The response

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Fig. 3. Levels (kU/l) of soluble interleukin-2 receptor (sIL-2r) among patients with mycosis fungoides at initial diagnosis with limited disease stages (IA–IB) (n = 17/28), (median = 495, mean = 511 kU/l *= 1,158) vs patients with advanced stages (II–IV) and adnexal disease (n = 56/28), (median = 1,009, mean = 1,313 kU/l *= 3,507). There is a significant difference in levels of sIL-2r between the 2 groups; p = 0.001.
rate was satisfactory, but, as shown by others, recurrence almost always occurs, with a mean time to relapse of 17–20 months (32). UVB is an alternative treatment of MF, but with less effect on infiltrated lesions, such as plaques, and with shorter remission duration than for PUVA treatment (32).

Soluble IL-2r is not specific for CTCL and can therefore not be used for diagnostic purposes. However, earlier data from Vonderheid et al. (33) point to the possibility of using sIL-2r as a prognostic marker of possibly better specificity than LDH. Our study indicates that sIL-2r may be a clinically useful marker of disease severity. Notably, in the majority of patients with increased levels at the time of MF diagnosis, advanced-stage disease or adnexal MF histology was seen. Therefore, it is possible that strategies using evaluation of this marker at the time of diagnosis and then continuously during follow-up to evaluate disease progression, may be beneficial.

It is important to point out that this is a retrospective study from a single centre. The number of included patients is limited and a potential selection bias regarding the included patients cannot be ruled out. In addition, several choices of treatments, such as systemic treatment and chemotherapy, could not be satisfactorily evaluated in this retrospective analysis. New prospective studies are mandated incorporating clinical status and new possible markers in relation to given treatments. However, the strength of this study is the thoroughly descriptive data from patient records, including photographs and histopathological assessment, together with evaluation of sIL-2r at initial diagnosis in the majority of patients.

In conclusion, this is the first retrospective study reported from Sweden on demographic data and overall outcome of patients with MF. The majority had early stage IA–IB disease at diagnosis. More than a quarter progressed to an advanced stage within a time-period of 5.6 years. Twenty-five percent of all patients with MF died during the study period, but less than half of the deaths could be attributed to the lymphoma. Adnexal subtype of MF showed a trend to a poorer outcome, and increased levels of s-IL2r at initial diagnosis indicated a more advanced stage or adnexal disease.

The authors declare no conflicts of interest.

REFERENCES


