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ORIGINAL ARTICLE

Primary cutaneous lymphomas: single center experience of dermatology and hematology clinics

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Summary

Purpose: *To present the clinical characteristics, treatments performed, response to treatment, and follow up of 40 patients diagnosed with primary cutaneous lymphoma.*

Methods: *In this retrospective study included were 23 males and 17 females from our center with confirmed diagnosis of primary cutaneous lymphoma over an 8-year period. Data were retrieved from the patient medical records.*

Results: *The median patient age at diagnosis was 59.5 years (range 33-86). Skin biopsies showed that 31 patients (77.5%) had mycosis fungoides (MF), 2 (5%) had anaplastic large cell lymphoma, 3 (7.5%) had diffuse large B cell lymphoma, 3 (7.5%) had poikilodermic mycosis fungoides, and 1 (2.5%) had non-classified non-Hodgkin lymphoma (NHL). In patients with T cell lymphoma clinical stage IA prevailed (42.5%). The 3 patients with B cell lymphoma had stage IE and 2 of them had B symptoms. Sezary cells were detectable in the peripheral blood of 3 patients. Twenty-three patients (57.5%) used only topical corticosteroids, 2 (5%) were treated with PUVA (psoralen ultraviolet A), 1 (2.5%) was treated with PUVA and chemotherapy, 8 (20%) received combination chemotherapy, 1 patient (2.5%) received PUVA+interferon+topical nitrogen mustard, and 1 (2.5%) received chemotherapy+topical nitrogen mustard+interferon. Among 16 patients whith evaluable response to treatment 5 (33%) showed complete remission (CR) and 9 (60%) partial remission (PR). The median follow up time for all patients was 1.5 months (range 1-135). While mean overall survival (OS) time was 123 months (95% CI 100.6-145.3), the estimated median OS was not reached.*

Conclusion: *Early diagnosis of MF is rather favorable in terms of high and long-term response rates to topical treatments.*

Key words: *mycosis fungoides, primary cutaneous lymphoma, primary cutaneous lymphoma, Sezary cells*

Introduction

Primary cutaneous lymphomas are considered a heterogeneous group consisting of T and B cell types which demonstrate clinical, histological, immunophenotypic and prognostic differences. Their incidence is estimated as 0.5-1/100,000 [1]. Extranodal involvement is observed in approximately 27% of NHL. Primary cutaneous lymphoma, following gastrointestinal system lymphomas, is the second most commonly seen extranodal NHL (18%) [2]. Primary T-cell cutaneous lymphomas (PTCL) are defined as clonal proliferation of natural killer cells and malignant T lymphocytes originating from skin, and compose 75-80% of all primary cutaneous lymphomas [3]. Most common subtypes of PTCL (95%) include mycosis fungoides (MF), Sezary syndrome (SS), primary cutaneous anaplastic large-cell lymphoma (PCALL) and lymphomatoid papulosis (LP). MF is the most common type of PTCL among these all (50%). Its incidence is estimated as 0.4/100,000 [4-6]. It is most frequently seen in adult males older than 50 years of age (M/F:1.6-2/1).

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MF may sometimes show a slow progression over decades and it may be seen as patchy lesion initially, and plaque followed by tumor over time. Involvement of lymph nodes and inner organs may be seen at late stages of the disease in some patients. Neoplastic cells in MF are in CD3+, CD4+, CD45R0+, CD8- "memory" T cell phenotype. CD4-, CD8+ mature T cell phenotype can also be seen [7,8]. Prognosis in MF depends on the stage of disease, in other words on the type and prevalence of cutaneous lesions as well as extra-cutaneous involvement. Patients with limited patch/plaque stage MF have similar life expectancy with similar control population in terms of age, gender, and race group. Ten-year disease-specific survival in limited patch/plaque stage (occupying less than 10% of the skin surface) was 97%, while it was 83% in disseminated patch/plaque stage (occupying more than 10% of skin surface), 42% in tumor stage and approximately 20% in histological lymph node involvement [9-11]. Lymph node,inner organ involvement or transformation into large T-cell lymphoma are accompanied with an agressive clinical course .

SS is a disease which is rare in adults. It is diagnosed histologically with disseminated pruritus along with erythrodermia, exfoliation, edema, lichenification, alopecia, onychodystrophy, palmoplantar hyperkeratosis, lymphadenopathy and presence of neoplastic T cells (Sezary cells) over the skin or in lymph nodes or peripheral blood. Diagnosis requires Sezary cells >1000/mm^3 in the peripheral blood (Sezary cells>5% of lymphocyte count). An increase in CD4+ T cell population (CD4/CD8>10), as well as CD3+, CD4+, CD8- phenotypes in neoplastic T cells is in question.

MF and SS are defined immunophenotypically as parts of the same disease spectrum with similar pathogenesis [12-16]. MF treatment includes local or systemic corticosteroids, topical nitrogen mustards (NH2, BCNU),UV-A irradiation + PUVA, interferon alpha2-a/b, retinoids, single agent or combination chemotherapy or combinations of them. Extracorporeal photopheresis can be used in the erythrodermic cases.

Primary B cell cutaneous lymphomas (PBCL) manifest with no evidence of disease outside the skin. The incidence of PBCL is 0.7/100,000 per year [17]. Among all primary cutaneous lymphomas the incidence rates of PBCL varies considerably between European (20-25%) and North American data (3.2-7.7%) [1,18,19]. The most common PBCL subtypes are follicular center cell lymphoma and marginal zone B cell lymphoma according to a classification performed by EORTC.

Table 1. Patient characteristics and skin biopsies

Characteristics	*N*	*%*
Median age, years (range)	59.5 (33-86)	
Gender		
Male	23	57.5
Female	17	42.5
Site of biopsy		
Upper extremity	3	17.5
Back-loin-gluteus	11	27.5
Lower extremity	7	17.5
Chest-abdomen	3	7.5
Nose-face	1	2.5
Face-gluteus-leg	3	7.5
Unspecified	12	30.0
Enlarged lymph nodes (>1.5 cm)		
None	28	70.0
Available	11	27.5
No involvement in biopsy	1	2.5

In this article we present the treatments administered to patients with primary cutaneous lymphoma followed-up in our institute, as well as their clinical features, response to treatment and outcomes.

Methods

Patients

A total of 40 patients with primary cutaneous lymphoma were included in this retrospective study. Twenty-three were male (M/F:1.25/1). Their median age was 59.5 years (range 33-86). All patients visited the dermatology and hematology outpatient clinics of our institute between January 2000 and August 2008. One patient had been diagnosed with primary cutaneous lymphoma in 1997. Biopsy samples of the patients taken from skin lesions were assessed immunohistochemically by a pathologist specialized in this field and were classified according to WHO/EORTC classification of cutaneous lymphomas [1]. Hematologic and biochemical tests as well as serum LDH and CRP measurements were performed in the hematology outpatient clinic following completion of patient systemic physical examination. For disease staging, thoracic and abdominal CT scans were performed, along with bone marrow biopsies. Data regarding patient demographic features and sites of involvement plus enlarged lymph nodes (>1.5 cm) close to these sites are shown in Table 1. Appropiate therapies were administered after a consensus between hematology and dermatology departments in patients whose staging had been completed. For patients receiving systemic treatment, their condition, treatment response and side effects were assessed before each course. For the remaining, assessments were carried out every 3-6 months.

Table 2. Histopathological classification

Classification	*N*	*%*
T cell cutaneous MF	31	77.5
Anaplastic large cell	2	5.0
Poikilodermatous MF	3	7.5
B cell cutaneous lymphoma		
Diffuse large B cell (CD20 +)	3	7.5
Other unspecified	1	2.5

MF: mycosis fungoides

Table 3. Main laboratory and bone marrow results

	N	*%*
Anemia (Hb<11.5g/dL)	4/ 40	10.0
Increased LDH	11/22	50.0
Decreased albumin	3/37	8.0
Increased CRP	5/19	26.0
Increased uric acid	4/32	12.5
Positive bone marrow biopsy	3/27	11.0
Sezary cells in peripheral blood	3/35	8. 6

Hb:hemoglobin, LDH:lactate dehydrogenase, CRP:c-reactive protein

Table 4. Clinical lymphoma staging of patients with respect to T and B cell types

Stage	*N*	*%*
T cell cutaneous lymphoma		
IA (T1N0M0)	17	42.5
IB (T2N0M0)	7	17.5
IIA (T1-2N1M0)	3	7.5
IIB (T3N0-1M0)	2	5.0
III (T4N0M0)	3	7.5
IVA (T1-4N2-3M0)	5	12.5
B cell cutaneous lymphoma T1 B	3	7.5

T1:Limited plaque (< 10% body surface), T2:Disseminated plaque (> 10% body surface), T3:Tumor, T4:Disseminated erythrodermia, N0:No clinically abnormal lymph nodes, N1:Clinically abnormal lymph nodes, N2:Clinically abnormal lymph nodes with biopsy-proven T cell cutaneous lymphoma, M0:No inner organ involvement , M1:Inner organ involvement, T1 B:solitary skin involvement (lesion >5cm)

Statistics

Statistical analyses of the data were performed using the SPSS/PC statistical software package (SPSS, Chicago, IL). Age was presented as median and range. Gender, anatomical regions of skin biopsy, histopathological types of biopsy samples, disease stages, anemia, hyperuricemia, hypoalbuminemia, increased serum LDH and CRP levels, and treatment modalities were presented as percentages. Response to treatment was defined as follows: complete remission (CR) as resolution of all lesions; partial remission (PR) as at least 50% reduction of lesion area; stable disease (SD) as less than 25% decrease in lesions for at least 4 weeks; progression (PD) was defined as 25% increase in lesions or appearance of new lesion(s). Responses to initial therapy, patients with relapsed disease, and second line therapies in relapsed patients were described in percentages. Disease free survival (DFS) was defined as the period between CR to therapy and time of relapse. OS was defined as the period from the time of diagnosis to death from any cause. DFS and OS evaluation were performed by using the Kaplan-Meier method with log-rank test.

Table 5. Treatments administered

Treatment	*N*	*%*
Topical corticosteroids	23	57.5
Radiotherapy	2	5.0
Chemotherapy	8	20.0
PUVA therapy	2	5.0
PUVA therapy, chemotherapy	1	2.5
Chemotherapy, topical nitrogen mustard, interferon	3	7.5
PUVA, topical nitrogen mustard, interferon	1	2.5

PUVA therapy: psoralen ultraviolet A therapy

Results

Histopathologic diagnosis with respect to skin biopsy is shown in Table 2. PTCL was the most common among all lymphomas (90%), while MF was the most common among T cell lymphomas (77.5%).

Among patients having laboratory data, 6 (55%) patients with high serum LDH level (upper limit of normal: 243 IU/L) had advanced-stage PTCL (stage IVA: 2 patients, stage III: 3 patients, stage IIB: 1 patient), hypoalbuminemia (<3.5g/dL) was present in 8%, anemia (hemoglobin<11.5 g/dl) in 10% and increased CRP level (> 8 mg/L) in 26% (Table 3). Cerebriform lymphocytes (>1000/mm^3 in peripheral blood) referred to as Sezary cells were found in both bone marrow and peripheral blood of 3 of 27 patients whose data were available. These 3 patients were diagnosed with SS. The laboratory findings are shown in Table 3. More than half of the patients had stage I disease (primary T cell lymphoma: 42% stage IA, 17% IB; Table 4).

Topical corticosteroids were administered in 57.6% of the patients, and 20% were treated with chemotherapy (cyclophosphamide, methotrexate, vincristine, bleomycin, chlorambucil either alone or in combination). Treatment protocols are shown in Table 5. In assessable patients response

Table 6. Assessment of treatment outcomes

	N	%	*CR N%*	*PR N%*	*Stable N%*	*Progression N%*	*Lost to follow-up N%*
Patients with assessed response	16/40	40	5/31	9/56	1/6	1/6	
Patients with relapse	9/15	60					
Patients receiving treatment for relapse	7/ 9*	78	-	4/57	1/14	-	1/14
Last status	40		2/5	5/12. 5	2/5	-	31/ 77.5

*One patient was not included into the assessment due to ongoing therapy

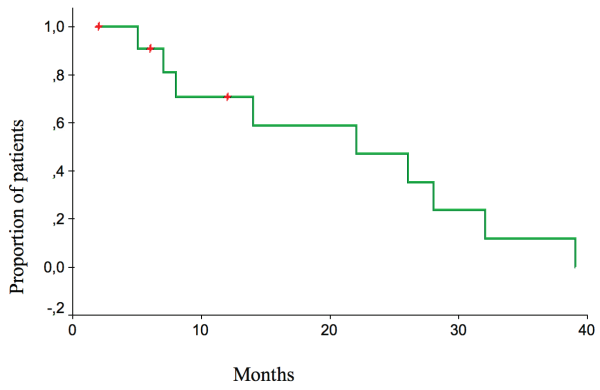

Figure 1. Kaplan-Meier analysis of progression free survival in 14 patients responding to treatment.

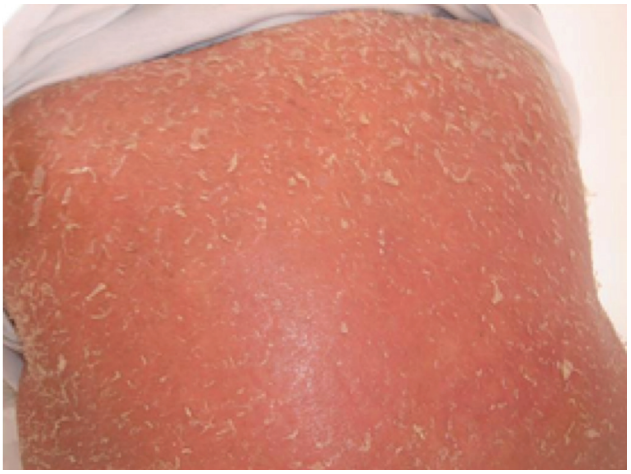

Figure 2. Edema, erythrodermia and exfoliation on the back of a 66-year-old male patient with MF/SS.

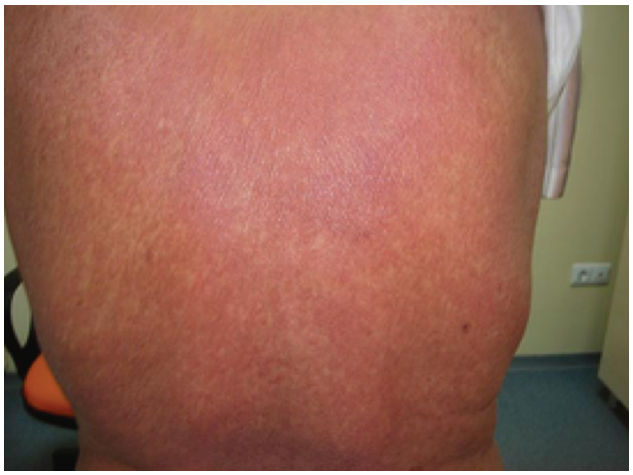

Figure 3. The same patient with MF/SS that regressed after chemotherapy.

was achieved in 14 of 16 (87.5%) (Table 6), with median response time 10 months (range 2-39) and estimated median DFS 22 months (95% CI 5.4-38.5; Figure 1). In addition to the 14 patients with CR or PR, there was one (6%) patient with stable disease. Nine of these 15 patients relapsed during follow-up. Of these 9 patients, 7 were administered new treatment for relapse. Among them 2 had stage III, 2 stage IV A, 2 stage IA and 1 stage II B disease. Two of the relapsed patients who did not receive new treatment had stage IA and stage IB. Three patients received topical corticosteroids, whereas 2 were treated with chemotherapy+topical NH2+interferon alpha2-a/b and 2 had chemotherapy alone. The post-chemotherapy improvement of the skin lesions of 2 male patients with MF/SS, both 66 years old, are shown in Figures 2-5. The Sezary cells in the peripheral blood smears of another 72-year-old male patient with a diagnosis of SS are shown in Figure 6.

The median follow-up time of 40 patients was 1.5 months (range 1-135). Thirty-one of these patients were lost to follow-up, while 2 (5%) are still being followed-up with CR, 5 (12.5%) with PR and 2 (5%) with SD. One patient diagnosed with MF/SS died of his primary disease. While the mean OS time of our patients was 123 months (95%CI,100.6-145.3), the estimated median OS time was not reached.

Discussion

Among our patients with primary cutaneous lymphoma, PTCL was by far the most common type (90%) and among T cell lymphomas, MF patients were the dominating group (77.5%). In a primary cutaneous lymphoma series from Europe including 555 patients, the lymphoma subtypes were as follows: PTCL 74%, MF 51% and primary PBCL 26% [19]. The M/F ratio was 1.45/1 and median age was 59 in the same series. Distribution of

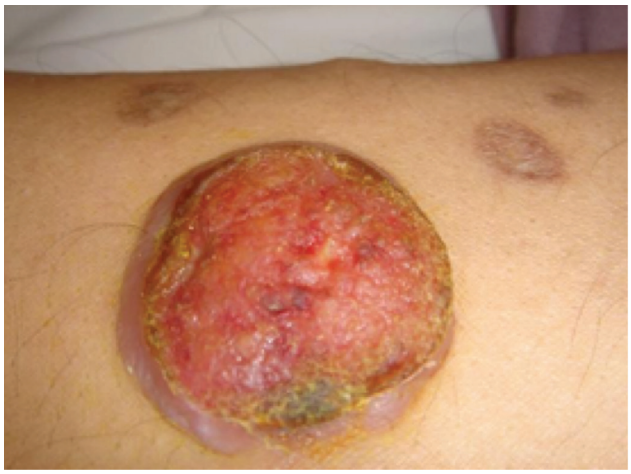

Figure 4. A tumor of the skin at the outer surface of the distal end of the right upper leg in a 66-year-old male patient with MF/SS (prior to chemotherapy).

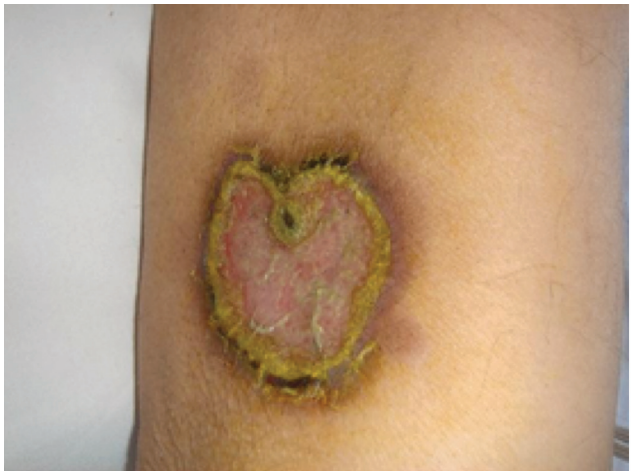

Figure 5. The same patient with MF/SS that regressed after chemotherapy.

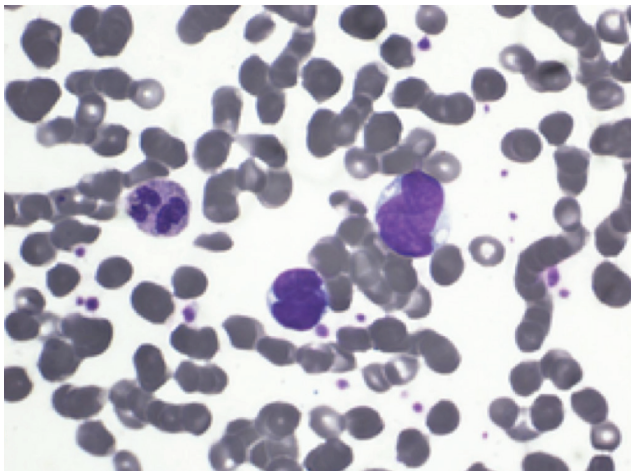

Figure 6. Two cerebriform T lymphocytes in the peripheral blood of a 72-year-old male patient with MF/SS (Wright stain×100).

gender and median age in our trial was similar to this series with a higher rate of MF patients. The findings reported regarding skin in a different series were as follows: limited plaque (T1) 20-50%, disseminated plaque (T2) 25-35%, tumor (T3) 15-25%, erythrodermia (T4) 10-20% [4]. Our findings also coincided with these data (Table 4). Since the rate of those with stage IA T cell lymphoma was the highest, topical corticosteroids were, in turn, the most frequent treatment modality used. Complete remission rates with topical corticosteroids were 63% and 25% in stage T1 (IA) and T2 (IB) disease, respectively [6]. Among 5 patients having T1 disease and whose treatment data were available, complete and partial remission were achieved in 1 and 4 patients, respectively. Treatment data were available in only 2 of 7 patients with T2 disease who achieved complete remission with topical corticosteroids. We believe that the rates of response to treatment will increase if treatment compliance is supervised and follow-up period is prolonged. A median survival of more than 12 years is reported for patients with T1 disease [4,20]. Two-year survival rates were significantly lower in patients with stage IIB-IV disease when compared to those with stage IIA disease (23 vs 86%, respectively; $p<0.005$) [2]. However, despite they made up the majority with 67.5%, the median duration of follow-up of our patients with stage I-IIA disease was only 1 month (range 1-60).

We could not analyse the annual survival since 67% of the aforementioned patients were lost to follow-up after 1 month and 82% after 1-4 months and also because patients died of their primary disease or of other causes. We think that if the response of patients with stage IA disease to topical therapy along with T1 skin lesions be kept in the form of limited plaque, this will lower the need of patient follow-up.

Poor prognostic criteria include older age (>60 years), stage IIB-IV disease, high LDH levels, high beta-2 microglobulin levels, type of skin lesion, involvement of peripheral blood or bone marrow, involvement of inner organs and transformation into large cell lymphoma [5,20]. It has been reported that being older than 60 years of age as well as having high LDH and high-stage disease shortens survival when compared to those not having these criteria (2.5-3 years vs 13 years, respectively) [5]. Fifty percent of our patients were ≥ 60 years of age. The median and 12-24 months DFS of patients with evaluable treatment outcomes was 22 months (range 2-39) and 45-67%, respectively, and DFS in stage IA was 56 and 30% in 5 and 10 years, while it was 74 and 50% in stage IB/IIA [6]. Concerning our study, we could not comment on poor prognostic factors or DFS of our patients because of the limited patient num-

ber whose treatment responses were assessed and the evaluation of T and B cell lymphomas were performed together. The rate of our patients with PBCL was 7.5%, which is similar to that of North America studies [18]. However, although it is not the most frequent type, all were diagnosed with diffuse large B cell cutaneous lymphoma. Also, no patient with B cell lymphoma - leg type - which is too agressive was found in our study. Of the patients with PBCL receiving corticosteroids+chemotherapy, 2 showed complete and 2 partial remission. One patient achieved complete remission with radiotherapy. As a rule, PBCL responds well to radiotherapy. Although 5-year survival rate of PBCL with poor clinical course was 95% and local cutaneous relapse 25%, the 5-year survival rate of aggressive cutaneous PBCL of leg-type, which is seen less frequently, was 60% [2]. Of the 3 PBCL patients responding to treatment 2 are being followed 3 for 2 months and 1 for 6 months, all relapse-free.

Conclusion

Primary cutaneous lymphoma is the second most common type of all extranodal non-Hodgkin lymphomas. Despite its rarity, it is crucial that skin lymphomas should be diagnosed correctly, especially in early-stage patients, and mutual assessments by dermatology & hematology clinics are required in differential diagnosis. Early diagnosis of MF - which is the most frequent one - is rather favorable in terms of high and long-term response rates to topical treatments. In the present study patients with T and B cell primary cutaneous lymphomas were assessed together. However, considering their different clinical course, treatment and prognosis we advocate that these two different lymphoma types be handled as two distinct entities. This distinction, combined with more frequent and longer follow-up, will allow better assessment of treatment responses and survival analyses.

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