Prognostic factors of patients with mycosis fungoides

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Abstract
Introduction: Mycosis fungoides (MF) is the most common type of primary cutaneous T-cell lymphoma. Prognostic factors may help to evaluate the course of the disease and may also be useful in selecting appropriate treatment plans for patients.

Aim: To investigate the potential prognostic factors of MF and their correlations with MF stage.

Material and methods: We evaluated the records of patients with MF who were followed in our lymphoma clinic between 1998 and 2015. Age, sex, disease stage, peripheral blood eosinophilia, eosinophil cationic protein, serum total IgE, lactate dehydrogenase (LDH), and β2-microglobulin levels were investigated and recorded at the time of diagnosis.

Results: There was a statistically significant positive correlation between high β2-microglobulin levels and the advanced stage of disease (p < 0.001). The older group of patients had statistically significantly higher levels of β2-microglobulin compared to the younger group (p = 0.001). We found strong, significantly positive correlations between disease stage and β2-microglobulin, LDH, and total IgE levels (p < 0.001, rho = 0.335; p = 0.001, r = 0.302; p = 0.001, r = 0.311, respectively). Additionally, there were significantly positive correlations between LDH levels and β2-microglobulin, total IgE levels (p < 0.001, rho = 0.484; p = 0.001, r = 0.212, respectively). Study limitations: A limited number of patients and the retrospective nature of the study.

Conclusions: We found that β2-microglobulin was a significant prognostic factor in our study population of MF patients. Also, elevated LDH, β2-microglobulin, and total IgE levels were correlated with advanced disease. Thus, these parameters can be used together to identify patients who have progressed to the later stages of the disease and who require more aggressive treatment.

Key words: mycosis fungoides, prognosis, stage.

Introduction
Primary cutaneous T-cell lymphomas are a heterogeneous group of extranodal non-Hodgkin’s lymphomas that present in the skin. Mycosis fungoides (MF) is the most common type of primary cutaneous T-cell lymphoma. It is characterized by skin infiltration of neoplastic T-lymphocytes. The progression of MF is chronic and slow, and the median age at diagnosis is 55–58 years. MF may remain stable or may progress to an advanced stage or a leukemic variant. Prognostic factors may help to evaluate the course of the disease and may also be useful in selecting appropriate treatment plans for patients. In addition to the stage, other potential prognostic markers, such as sex, age, increased levels of serum lactate dehydrogenase (LDH), increased β2-microglobulin, peripheral blood eosinophilia, histological features of folliculotropism (FT), and large-cell transformation have been identified in MF [1–4].

Aim
The aim of this retrospective study was to investigate the potential prognostic factors of MF and their correlations with MF stage.

Material and methods
This study’s design was a single-centre, retrospective cohort analysis. We evaluated the records of patients with MF who were regularly followed in our lymphoma clinic between 1998 and 2015. Patients with missing re-
cords were excluded from the study, while 119 patients with MF were included. There was no serious systemic disease which leads to an increase in the level of β2-microglobulin and LDH in our patients group. The patients were staged according to the TNMB criteria of the National Cancer Institute. Age, sex, disease stage, peripheral blood eosinophilia, eosinophil cationic protein (ECP), serum total IgE count, LDH, and β2-microglobulin levels were investigated and recorded at the time of diagnosis. We also assessed the significance of these parameters as prognostic factors for the disease process.

Statistical analysis

Categorical variables were compared by using χ2 tests. Normality tests were used for continuous variables, and continuous variables were compared with the Mann-Whitney U test and the Student’s t-test. The Shapiro Wilk test was used to evaluate the normality. All statistical analyses were performed using the SPSS version 15.0 statistical software program (SPSS, Chicago, IL). Spearman and Pearson correlation analyses were used to find out the correlations between variables according to the normality tests. The results were considered to be statistically significant when the p-value was less than 0.05.

Results

The study included a total of 119 patients, including 64 (53.8%) men and 55 (46.2%) women, for a male-to-female ratio of 1.16. The mean age of the patients was 52 ±16.3 years (range: 8–86 years). The stage of disease for all patients at the time of initial diagnosis is shown in Table 1.

The relationships between variables are shown in Table 2. β2-microglobulin levels increased as the disease stage increased (rho = 0.335, p < 0.001). At the time of diagnosis, 98 patients were < 60 years old and 21 patients were > 60 years old. The older group of patients had statistically significantly higher levels of β2-microglobulin compared to the younger group (p = 0.001). Also, the mean value and standard deviation was revised as minimum, maximum levels and median level for β2-microglobulin. The median level of β2-microglobulin was 2.15, minimum level of β2-microglobulin was 1.10 and maximum level of β2-microglobulin was 15.30.

Of the 119 MF patients, 10 had the folliculotropic variant. The mean level of β2-microglobulin was 2.6 ±1.8 for classical MF and 2.3 ±1.1 for the folliculotropic variant. This difference was not statistically significant (p = 0.520). β2-microglobulin levels were elevated in 46 (38.6%) patients, LDH levels were elevated in 16 (13.4%) patients, and total IgE levels were elevated in 27 (22.6%) patients.

We found strong, significantly positive correlations between the disease stage and β2-microglobulin, LDH, and total IgE levels (p < 0.001, rho = 0.335; p = 0.001, r = 0.302; p = 0.001, r = 0.311, respectively). Additionally, there were significantly positive correlations between LDH levels and β2-microglobulin, total IgE levels (p < 0.001, rho = 0.484; p = 0.001, r = 0.212, respectively).

Discussion

The literature contains many studies that investigated the prognostic factors for MF. Different parameters were evaluated in single or multiple-centre studies in different countries. However, well-defined prognostic parameters for individual risk assessments are rare [1, 2, 5–8]. Large-cell transformation, erythrocyte sedimentation rate, serum interleukin-2 receptor, eosinophilia, clinical response to therapy, histological variables, serum LDH, and β2-microglobulin have been considered as potential prognostic factors. Some studies reported that these factors were strongly associated with the prognosis of MF, while others reported a limited relationship. Some studies that investigated the superiority of each of these parameters revealed different results [7, 9–11].

In our study, the mean age at the time of diagnosis was younger than that in the literature. Older age has been identified as a prognostic factor in MF. Talpur et al. reported that an age of 66 years or older was an important negative predictive factor. Diamandidou et al. found that an age of 60 years or older was an independent prognostic parameter, similar to our study [1, 10, 11].

In our study there was a correlation between older

Table 1. The stage of disease for all patients at the time of initial diagnosis

| Stage | Patients number, n (%) |
|-------|-----------------------|
| 1a    | 56 (47.1)             |
| 1b    | 21 (17.6)             |
| 2a    | 21 (17.6)             |
| 2b    | 10 (8.4)              |
| 3a    | 3 (2.5)               |
| 3b    | 3 (2.5)               |
| 4a    | 4 (3.4)               |
| 4b    | 1 (0.8)               |

Table 2. The relationship between the stage of disease and LDH, total IgE, eosinophil, ECP, β2-microglobulin (β2M)

| Stage – β2M | p < 0.001; rho = 0.335 |
|-------------|-----------------------|
| Stage – LDH | p = 0.001; r = 0.302  |
| Stage – total IgE | p = 0.001; r = 0.311    |
| Stage – eosinophil | p = 0.446; rho = −0.070 |
| Stage – ECP   | p = 0.201; rho = 0.118 |

*p < 0.05.
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found a significant correlation between elevated IgE, ECP, and eosinophil count and advanced stages of MF. We did not evaluate β₂-microglobulin in patients with MF as previously demonstrated in the literature. Talpur et al. evaluated a total of 1,263 patients with MF and Sézary syndrome over a period of 27 years. They suggested that elevated β₂-microglobulin levels were risk factors associated with progression of disease [1]. Diamandidou et al. reported that β₂-microglobulin was a significant prognostic factor and was correlated with a poorer survival. However, they believed that β₂-microglobulin was not an independent prognostic factor because this result was not supported by multivariate analyses [11]. In our study, we found that β₂-microglobulin alone was a significant negative prognostic factor that correlated with the disease stage. It is known that the folliculotrophic variant of MF has a worse prognosis than classical MF [14, 15]. In our study, β₂-microglobulin was not evaluated as a prognostic parameter between these forms.

LDH is a non-specific marker of tumour burden and several studies have reported that elevated LDH levels are associated with a poor prognosis and that it is a significant prognostic factor for MF [1, 2, 6, 8, 10, 11]. Alberti-Violetti et al. studied advanced-stage MF patients and determined that only LDH and advanced age were associated with a poor prognosis [4]. Vonderheid et al. identified soluble IL-2 receptor as a prognostic marker with possibly better specificity than LDH [16]. Tancrède-Bohin et al. investigated the prognostic values of blood eosinophilia and LDH in 2004, and reported that blood eosinophilia was a stronger prognostic factor than LDH [17]. The results of our study suggest that elevated β₂-microglobulin is a more significant parameter than LDH, particularly for advanced stages of disease.

In our previous study, which included 78 patients, we found a significant correlation between elevated IGE, ECP, and eosinophil count and advanced stages of MF. We did not evaluate β₂-microglobulin or LDH levels or their associations with the disease [18]. However, in the current study, we investigated all of these and determined that ECP levels and eosinophilia were not related to the disease stage.

Conclusions

We found that β₂-microglobulin was a significant prognostic factor in our study population of MF patients. In addition, the results suggested that β₂-microglobulin was a more significant negative predictive marker than LDH. Also, elevated LDH, β₂-microglobulin, and total IgE levels were correlated with advanced disease. Thus, these parameters can be used together to identify patients who have progressed to the later stages of the disease and who require more aggressive treatment. The prognostic parameters have not previously been clearly defined. This may be due to researchers investigating different parameters during different disease stages, and evaluating different populations. The significance of β₂-microglobulin in MF is supported by many studies. However, further prospective studies are needed to evaluate these prognostic factors.

Conflict of interest

The authors declare no conflict of interest.

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