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CRP Levels as a Prognostic Factor in Mycosis Fungoides

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ABSTRACT Mycosis Fungoides (MF) and Sézary syndrome (SS) are the most common forms of cutaneous T-cell lymphomas. Few validated prognostic factors have been reported in MF/SS, especially when compared with non-cutaneous lymphomas. Increased C-reactive protein (CRP) levels have recently been associated with poor clinical outcome in various malignancies. The aim of this study was to evaluate the prognostic significance of serum CRP levels at diagnosis in patients with MF/SS. This retrospective study included 76 patients with MF/SS. Stage was assigned according to the ISCL/EORTC guidelines. The follow-up period was 24 months or more. Disease course and response to treatment were determined using quantitative scales. Wilcoxon's rank test and multivariate regression analysis were used to analyze the data. Increased CRP levels correlated significantly with advanced stages (Wilcoxon's test, P>0.0001). Furthermore, increased CRP levels were associated with a lower treatment response rate (Wilcoxon's test, P=0.0012). Multivariate regression analysis showed that CRP is an independent predictor of advanced clinical stage at diagnosis.The present data suggest that elevated CRP levels could serve as a useful prognostic factor in MF/SS and may assist in guiding treatment choices.

KEY WORDS: mycosis fungoides, Sézary syndrome, C-reactive protein (CRP), prognostic factor

INTRODUCTION

Mycosis Fungoides (MF) and Sézary syndrome (SS) are the most common primary lymphomas involving the skin (1). MF is clinically divided into patch, plaque, and tumor stages. The course and outcome of MF are variable, ranging from an indolent course with slow progression over decades to widespread lymph node and visceral involvement. Patients may present at any stage of disease, however most present with early-stage disease characterized by long-standing erythematous patches or plaques involving body areas infrequently exposed to sunlight. *SS is* the leukemic counterpart of MF and features circulating Sézary cells, erythroderma, hyperkeratosis of the palms and soles, and lymphadenopathy (2).

In 1970s, the Mycosis Fungoides Cooperative Group (MFCG) published a classification and staging system for cutaneous T-cell lymphomas, which was based on the TNM (Tumor-Node-Metastasis) classification (3). This system was widely used for decades, until it was revised and updated by the World health Organization (WHO) and European Organization for Research and Treatment of Cancer (EORTC) in 2005 (4), and later further revised by the International Society of Cutaneous Lymphoma (ISCL) in 2007 (5) to include developments related to diagnostic methods as well as introduce blood staging (B).

Several studies have validated the ISCL/EORTC revision for prognosis; a comprehensive study by

Table 1. Clinical stage at diagnosis

ISCL/EORTC staging	Number (% of total patients)
IA	33 (43%)
IB	24 (31%)
IIA	6 (8%)
IIB	3 (4%)
IIIA	4 (5%)
IIIB	1 (1.3%)
IVA	4 (5%)
IVB	1 (1.3%)
Total	76 (100%)

Agar *et al.* (6) validated this system on a large patient cohort of 1502 patients in a single UK center, and another study by Quaglino *et al.* (7) followed 1422 Italian patients.

Usually, the prognosis of patients with MF/SS correlates with clinical stage (8): early disease is characterized by a favorable prognosis (7); however, advanced disease with tumors or erythroderma is associated with decreased survival. Although it is generally accepted that MF evolves from patches to plaques, nodules, erythroderma, and eventually visceral involvement, clinical experience suggests that only a proportion of patients with MF presenting exclusively with skin lesions will develop extracutaneous manifestations (8). The predictive value of different clinical, laboratory, and pathological factors including age, sex, body surface area, lactate dehydrogenase (LDH) (6,8-9) and β_2-microglobulin (10) levels, or folliculotropic histology (11), have not been retained by the ISCL/EORTC classification guidelines. Thus, due to the lack of validated predictive factors, it is currently impossible to provide patients with reliable prognostic information.

An acute phase protein is a protein in which plasma concentration changes from baseline by at least 25% as a response to acute pathological conditions such as bacterial infections, trauma, and myocardial infarction, and also in response to chronic states like chronic inflammatory diseases and cancer (12). Elevated erythrocyte sedimentation rate (ESR) is an indirect screen for elevated concentrations of acute

Table 2. Outcome and response scale based on response type and duration

Complete Response (CR) and no relapse:	
1	Did not progress to a more advanced stage, reached CR within 3 months, no relapse
2	Did not progress to a more advanced stage, reached CR within 3-12 months, no relapse
3	Did not progress to a more advanced stage, reached CR within more than 12 months, no relapse
Complete Response (CR), with relapse after more than 12 months:	
4	Did not progress to a more advanced stage, reached CR within 3 months, relapse after more than 12 months
5	Did not progress to a more advanced stage, reached CR within 3-12 months, relapse after more than 12 months
6	Did not progress to a more advanced stage, reached CR within more than 12 months, relapse after more than 12 months
Complete Response (CR), with relapse after 3-12 months:	
7	Did not progress to a more advanced stage, reached CR within 3 months, relapse after 3-12 months.
8	Did not progress to a more advanced stage, reached CR within 3-12 months, relapse after 3-12 months.
9	Did not progress to a more advanced stage, reached CR within more than 12 months, relapse after 3-12 months.
Complete Response (CR), with relapse after less than 3 months:	
10	Did not progress to a more advanced stage, reached CR within 3 months, with relapse after less than 3 months.
11	Did not progress to a more advanced stage, reached CR within 3-12 months, with relapse after less than 3 months.
12	Did not progress to a more advanced stage, reached CR within more than 12 months, with relapse after less than 3 months.
Did not reach CR:	
13	Did not progress to a more advanced stage, reached PR only.
14	Progressed to a more advanced stage (PD), but not to large cell transformation or to Sézary Syndrome.
15	Progressed to a more advanced stage, to Sézary Syndrome or to large cell transformation.
16	Sézary Syndrome was the initial diagnosis.
17	Died from MF/SS, or from related complications.

Abbreviations: CR: complete response; PR: partial response; PD: progressive disease

phase proteins, and it has been the most widely used marker of inflammation for almost a century. In a study by Marti *et al.* in 1991 (13), elevated erythrocyte sedimentation rate (ESR), an acute phase reactant, did not prove to have prognostic significance in MF. However, in a study by Hallermann *et al.* (14), ESR was identified as a prognostic factor independent of clinical stage. C-reactive protein (CRP) is a classic acute-phase protein which rises during malignancy and inflammation. Circulating levels of CRP have been associated with poor clinical outcome in solid (15) and hematological (16) malignancies. Due to its role as a marker and a prognostic factor in various malignancies, we decided to ascertain the prognostic significance of serum CRP levels at diagnosis in patients with MF/SS.

PATIENTS AND METHODS

Patients

A retrospective review of clinical data was conducted in a cohort of 76 patients with MF/SS followed at the cutaneous lymphomas clinic at the Tel Aviv Sourasky Medical Center in 2006-2014. The study was approved by the Tel Aviv Sourasky Medical Center Institutional Review Board (Helsinki Committee). Demographic data and full medical history were retrieved from the patient charts. All patients underwent a complete workup, as suggested by the ISCL/EORTC revised guidelines (5). Data retrieved for each patient were: gender, age at diagnosis, clinical stage according to ISCL/EORTC classification, and lactate dehydrogenase (LDH) and CRP levels. CRP and LDH levels were determined by standard laboratory techniques. CRP levels above 5 mg/L and LDH levels above 378 U/L were considered as elevated.

Inclusion and exclusion criteria

Only patients with a follow-up period of at least 24 months and with complete follow-up data were included. Patients who were lost to follow-up or did not complete their evaluation were excluded. LDH and CRP measurements were performed during the diagnostic process.

We did not include laboratory data that was gathered during an acute illness or from patients who were simultaneously suffering from another chronic inflammatory or malignant disease.

Clinical Outcome Scale

While many studies focused on survival as a main outcome, this was not suitable for a cohort in which 83% of the patients were diagnosed with early-stage MF (stages IA-IIA) (Table 1). In our study, we focused on disease course and response to treatment. As recommended in the Consensus Statement by the ISCL, USCLC, and EORTC (17), response assessment was performed by the same investigator, to eliminate intra-observer variability. Most patients were diagnosed between 2006-2014. As a result, we were able to avoid problems encountered in studies with a longer follow-up period, such as patients being treated according to outdated treatment protocols. All the patients in this study were treated according to the same contemporary management schemes (18).

We used the response types formulated by Olsen *et al.* in the above-mentioned statement (17) as a reference point for the assessment of response and remission. The responses were classified as complete, partial, disease progression, or relapse after remission. We considered a response only when it lasted at least 4 weeks.

Table 3. Distribution of patients according to clinical outcome

Response type	Number (percentage)
Complete Response – (responses 1-3*)	30 (39%)
Among patients first diagnosed with early disease	30
Among patients first diagnosed with advanced disease	0
Partial Response (response 13*)	14 (18%)
Among patients first diagnosed with early disease	11
Among patients first diagnosed with advanced disease	3
Progressive Disease (responses 14-15, 17*)	8 (11%)
Among patients first diagnosed with early disease	1
Among patients first diagnosed with advanced disease	7
Relapse after Complete Response (responses 4-12*)	23 (31%)
Among patients first diagnosed with early disease	21
Among patients first diagnosed with advanced disease	2
Disease presented with SS (response 16*)	1 (~1%)

*in the ordinal scale presented in Table 2.

Table 4. Percentage of patients with elevated CRP levels in the early MF stages (IA-IIA) and in the advanced stages (IIB-IVB)

	No (%)	Normal CRP levels	Elevated CRP levels
Early MF	63 (83%)	52 (83%)	11 (17%)
Advanced MF/SS	13 (17%)	1 (8%)	12 (92%)
Total	76 (100%)	53 (70%)	23 (30%)

The assessment scale is presented in Table 2.

Statistical Analysis

We stratified clinical stages into 2 severity categories, corresponding to the difference in prognosis and management, similarly to the approach described by Prince *et al.* (18) and Jawed *et al.* (19):

Early MF – stages IA-IIA

Advanced MF/SS – stages IIB-IVB.

Each patient was assigned a clinical outcome score, according to Table 2.

Wilcoxon's rank test was used to analyze the association between increased LDH levels, increased CRP levels, stage at diagnosis, and response to treatment.

Multivariate logistic regression models were used to assess the association between disease progression and response to treatment and CRP levels adjusted for different clinical and patient covariates (age, gender, stage, LDH levels). A two-tailed P value less than 0.05 was considered significant in all tests. Statistical analysis was performed using SAS for Windows 9.2.

RESULTS

Patient Characteristics

Our population included 76 patients, aged 6-91, who presented with MF at a median age (mean) of 59 (55) years, similar to previous studies (7, 20). 38 patients were women and 38 (50%) were men. This ratio was not consistent with other large series (7, 8, 20), which consisted predominantly of male patients. Two patients (3%) died from disease-related causes.

Stage distribution at diagnosis is presented in Table 1. As shown in Table 1, 83% of the patients were diagnosed with early MF. This proportion of patients with early disease is slightly larger than reported in other studies (20, 6). Distribution of patients according to clinical outcome is presented in Table 3. As expected, most patients with early disease at diagnosis achieved complete remission, while most patients who presented with advanced disease progressed to more advanced disease stages (Table 3).

Influence of CRP levels on disease course

Among patients diagnosed with early MF, only 17% had elevated CRP levels. Conversely, in patients with advanced disease, 92% had elevated CRP levels (Table 4). Increased CRP levels correlated significantly with worse disease stage (Wilcoxon's test, P>0.0001).

CRP levels also correlated with a worse response to treatment, measured by our outcome and response scale (Wilcoxon's test, P=0.0012).

Most of the patients in the group with disease that had progressed to a more advanced clinical stage had elevated CRP levels (5 out of a total of 6 patients, 83%) (Table 5).

Most of the patients who reached sustained complete remission had normal CRP levels (responses 1-3, 25 out of 30 patients, 83%), as did most of the patients who had a relapse after a complete remission (responses 4-12, 19 out of 23 patients had normal CRP levels, 83%). Results were not conclusive in the group that only reached partial remission – only 8 out of 14 patients (57%) had normal CRP levels.

Table 5 presents an interesting finding: when looking at the group that had a relapse after a complete remission (responses 4-12), one can see that the

Table 5. Distribution of patients according to clinical outcome, subdivided by CRP levels

Response type	Number (% of total)	Elevated CRP (%)	Normal CRP (%)
Complete remission – (responses 1-3*)	30 (39%)	5 (17%)	25 (83%)
Partial remission (response 13*)	14 (18%)	6 (43%)	8 (57%)
CR, then relapse after 1 year or more (responses 4-6*)	10 (13%)	3(30%)	7 (70%)
CR, then relapse after less than 1 year (responses 7-12*)	13 (17%)	1 (8%)	12 (92%)
Progressive disease (responses 14-15*)	6 (8%)	5 (83%)	1 (17%)
Disease presented with SS (response 16 *)	1(1%)	1(100%)	0
Disease-related death (response 17*)	2(3%)	2(100%)	0

*in the ordinal scale presented in Table 3
Abbreviations: CR: complete response

group which relapsed after more than a year (responses 4-6) had a higher percentage (30%) of patients with elevated CRP levels, when compared with the patients who had a shorter time to relapse (responses 7-12, only 8% of the patients who relapsed within less than a year had elevated CRP); both groups included a similar number of patients (10 and 13).

Multivariate regression analysis showed that CRP is a predictor of worse clinical stage at diagnosis independently of age, although increased age was associated with more advanced stages. The same logistic regression showed that gender was not associated with either increased stage at diagnosis or a worse response to treatment.

Increased LDH levels correlated with a worse stage at diagnosis (Wilcoxon's test, P=0.0026), but LDH did not correlate significantly with response to treatment (P=0.11).

DISCUSSION

CRP is an acute phase reactant, and its level is known to rise during infection, inflammatory diseases, trauma, and surgery. Recent evidence indicates that the host inflammatory response has an important role in the tumor progression. Increased levels of CRP have been linked to advanced disease and worse outcomes in several malignancies (15).

In the present study, we demonstrated an association between elevated CRP levels and a more progressed stage MF at diagnosis (OR=33), poor response to treatment, relapse, or progression to a more advanced clinical stage (P=0.0012).

This association, previously found for several malignancies and now for MF/SS, could be due to[15]:

Causality: elevated CRP levels cause or promote cancer;

Reverse causality: cancer, by stimulating cytokines and chemokines release, induces CRP production by the liver;

Confounding: a third factor, e.g. inflammation, increases both CRP levels and the risk of cancer (progression).

In order to elucidate this association, a review by Allin *et al.* (15) showed that cases with genetic variants that specifically increase circulating levels of CRP were not associated with increased cancer risk, and thus the first hypothesis (causality) was concluded to be unlikely.

The second hypothesis cannot be excluded.

As for the third hypothesis, chronic inflammation in the microenvironment of tumors produces a pro-neoplastic environment. Examples of predispositions to particular cancer diseases due to infections and chronic inflammation include susceptibility to colon cancer due to chronic inflammatory bowel disease and gastric cancer due to bacterial infection with Helicobacter pylori. On the other hand, tumor development and progression can also induce inflammation (21).

However, the immune system can also recognize malignant cells and cause tumor destruction, and thus inflammation (and CRP as an inflammatory marker) has an anti-neoplastic effect as well. However, even if they is a marker of an anti-tumor reaction, elevated CRP levels have been associated with poor prognosis in several types of cancers.

Apart from CRP, which was our main object of investigation, other variables found to have statistically significant prognostic influence were well-established prognostic factors, including stage and age at diagnosis.

Serum LDH was shown to be associated with a survival and progression risk in large studies (6); in our study, increased LDH levels were correlated to a worse stage at diagnosis but did not correlate significantly with response to treatment.

The fact that the group which relapsed after more than a year was characterized by more elevated CRP levels when compared with the patients who had a shorter time to relapse is puzzling and warrants confirmation in a larger patient group. This observation may perhaps be due to the fact that the two groups of patients were characterized by different stages at initial diagnosis. While the group that relapsed after more than 1 year was composed of 8 patients with early disease (IA/IB) and 2 patients in stages IIB and IIIA, the group that relapsed after less than a year was composed of 13 patients with early disease. We have already shown that advanced disease was accompanied by elevated CRP levels. Thus, the elevated CRP among the patients with a slower relapse might be due to the fact they had more advanced disease.

The differences in response among patients diagnosed with the same clinical stage reflect the well-known heterogeneity of MF, although the risk for progression clearly increases over time (6-8, 20).

CONCLUSION

We suggest that routinely measuring CRP levels in MF patients may enable better risk stratification and influence therapeutic decision making. It could also be included in future versions of a multivariate, prognostic index for MF/SS (22).

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