Dermatology Practical & Conceptual

Importance of the C-Reactive Protein to Albumin Ratio in the Diagnosis and Prognosis of Mycosis Fungoides

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ABSTRACT

Introduction: The C-reactive protein to albumin ratio (CAR) lately has demonstrated as a prognostic factor and an indicator of disease activity, severity and prognosis in solid organ malignancies and inflammatory diseases. However, the effects of CAR have not been investigated in mycosis fungoides (MF) patients yet.

Objectives: This study aimed to determine the potential role of CAR as a diagnostic and a prognostic indicator in MF.

Methods: We retrospectively investigated the electronic medical records of 97 patients with MF admitted to the Dermatology Clinic of Health Sciences University, Diskapi Yildirim Beyazit Training and Research Hospital between January 2014 and December 2020. In total, 60 patients with MF were enrolled in the study. CAR was evaluated, patient and control group. Also, the other clinicopathological factors including age, lactate dehydrogenase, stage of disease, beta-2-microglobulin levels, and sedimentation levels were evaluated.

Results: The median value of CAR was 0.85 (0.10-7.51) in the patient group, whereas it was 0.39 (0.0-1.11) in the control group ($P < 0.001$). Patients with disease progression (N = 16, 13M, 3 F) had a median value of CAR 0.84 (0.10-7.51) and the median value of CAR (N = 44) was 0.86 (0.12-4.57) in the group of patients with stable disease. The CAR value had no prognostic significance ($P > 0.05$).

Conclusions: There is no association between the CAR and progression in the stage in MF patients. But the CAR is significantly higher in patients with MF than in the control group. The CAR can be a guide for us in cases where we have difficulty in diagnosing.

Introduction

Primary cutaneous lymphomas are a heterogeneous group of extranodal non-Hodgkin lymphomas. Mycosis fungoides (MF) is the most common type of primary cutaneous T-cell lymphomas (CTCL) caused by malignant proliferation of clonal T lymphocytes in the skin. MF was generally affecting older patients with the median age at diagnosis between 55 and 60 years old and affecting more men than women. The children can also be affected by this lymphoma. The disease usually begins as brownish erythematous patches in sun-protected areas and progresses slowly over the years, and in some patients may remain in the same stage for years without progress. Currently, there is no cure for MF and symptomatic treatment is given especially in early-stage disease. While it is aimed to increase the quality of life in early-stage patients, it is aimed to increase life expectancy in advanced stage patients. The main treatment of early-stage disease is skin-directed treatments (topical corticosteroids and phototherapy). When the disease progresses to advanced stages, systemic therapy including systemic chemotherapy is applied and the disease can be fatal [1-4]. Therefore, to diagnose the disease and anticipating the prognosis is an important need. An indicator that informs the prognosis of the disease and provides information about the severity of the disease can be useful in making treatment decisions in complex cases.

C-reactive protein (CRP) to albumin ratio (CAR) was calculated as the ratio of serum CRP level (mg/L) to serum albumin level (g/dL), which were obtained from the biochemistry profile. CAR is a novel inflammation-based prognostic score and an inflammation biomarker in inflammatory processes. CAR is associated with poor outcomes and severity of inflammation in various diseases, such as psoriasis, cardiovascular diseases, ischemic stroke, sepsis, acute pancreatitis, uveitis, Takayasu arteritis, and cancers. CAR has higher diagnostic accuracy than C-reactive protein alone [5-13]. CAR has been considered as a valuable indicator of inflammatory status and prognosis in cancers, it has not been evaluated in patients with MF.

Objectives

In this investigation, our aim was to assess the applicability of the CAR value, readily and inexpensively derived from blood parameters, in both diagnosing and prognosticating MF disease.

Methods

We reviewed the files of MF patients in the Dermatology Clinic of Health Sciences University, Diskapi Yildirim Beyazit Training and Research Hospital between January 2014 and December 2020. A total of 97 patients were retrieved initially, 37 were excluded from the study due to lack of follow-up and insufficient laboratory values. The study enrolled all patients aged 18 and over who had available data. Inclusion criteria include being diagnosed with MF clinically and histopathologically, and no history of inflammatory disease and malignancy (non-MF). All our patients had not yet received treatment when they were included in the study. Data on age, sex, duration, onset age and stage of disease, serum biochemistry profile, including serum CRP, albumin, lactate dehydrogenase (LDH) and beta2 microglobulin levels and complete blood count, were collected. Blood samples were taken from all patients under the same conditions in our hospital laboratory. TNMB and histopathological staging of the cases were performed in accordance with International Society for Cutaneous Lymphomas/European Organization of Research and Treatment of Cancer (ISCL/EORTC) criteria at the time of peripheral blood sampling, retrospectively.

Healthy volunteers who underwent routine physical examination in our hospital were taken as the control group. The patient and control groups were matched in terms of age and gender. Persons who had other autoimmune diseases, liver or kidney disease, hematologic disease, diabetes, cancer, acute or chronic infections were excluded from the study.

Disease progression was considered as tumor development and transition to advanced stages (stage IIB and above). Because with tumor development, the disease transforms from early stage to advanced stage disease. Tumor stage and above stages are considered advanced stage disease in MF(2). In this study, 3 of our patients were in stage IIA at the time of diagnosis, but subsequently showed tumor formation through their plaques and progressed to stage IIB. At the same time, those who were initially in the advanced stage group but showed improvement and moved to the early-stage group were included in the "good prognosis" group. We have 2 patients with this situation. The tumors of patients who were initially Stage IIB regressed clinically and pathologically and progressed to the plaque stage. One of these patients is directly followed as stage IB because there is no lymph node involvement. The other patient is followed as stage IIA. In our clinic, file records of all our patients are kept meticulously. The disease prognoses of all patients included in the study were examined one by one and recorded. Patients who are at an advanced stage and whose disease does not regress are not included in the "good prognosis" group.

The data obtained were transferred to the computer environment and evaluated with the SPSS (v.15.0) statistics package program. The compliance of the data to normal distribution was evaluated with the Kolmogrov Smirnov test.

This study was approved by the tertiary hospital ethics committee. Written informed consent was obtained from all participants

Table 1. Comparison of the laboratory findings of the patient and control group

	Control Median (min.-max.)	Patient Median (min.-max.)	Statistical analysis z/t; P
CRP	1.80 (0.0-4.78)	3.84 (0.5-26.0)	6.461; <0.001
Sedimentation	3.0 (1.76-23.0)	10.5 (0.0-41.0)	4.266; <0.001
Albumin	4.6 (4.0-5.43)	4.38 (3.38-5.08)	2.930; 0.009
Neutrophil	3715 (1600-8810)	4170 (0.0-15.6)	1.738; 0.082
Eosinophil	130.0 (10.0-800.0)	200.0 (10.0-2610.0)	1.961; 0.05
CAR	0.39 (0.0-1.11)	0.91 (0.12-7.51)	6.629; <0.001
N/L	1.78 (0.81-5.58)	2.02 (0.0-15.6)	1.653; 0.098
Lymphocyte	2045.0 (1110.0-3950.0)	2035.0 (500.0-4860.0)	0.558; 0.578
Platelet	246.0 (143.0-357.0)	256.0 (128.0-418.0)	1.817; 0.072

CAR = CRP to Albumin Ratio; CRP = C Reactive Protein; N/L:Neutrophil to Lymphocyte ratio.

Results

The study group consisted of a total of 120 people, including 60 MF (28 female, 32 male) patients and 60 (28 female, 32 male) control group. Patient age ranged from 20 to 83 years (51.95±13,64). There was no difference in age and gender between control and patient groups in the study (P > 0.05 for each). Based on ISCL/EORTC staging, 9 patients (15 %) were stage IA, 2 (3.3 %) were stage IB, 34 (56.7 %) were stage IIA, 6 (10.0%) were stage IIB, 7 (11.7 %) were stage IIIB, 1 (1.65 %) was stage IVA1 and 1(1.65 %) was stage IVA2.

The median value of CAR was 0.91 (0.12-7.51) in the patient group, whereas it was 0.39 (0.0-1.11) in the control group. There was a statistically significant difference between groups (P < 0.001). There was a statistically significant difference in sedimentation, CRP, albumin and eosinophil levels between patient and control groups (Table 1).

Patients were first evaluated according to stages. In stage I (T1, T2), there are patients with only skin findings without involvement of any other area. Stage I is divided into two: Stage IA and Stage IB. T1 represents patients with patches and/or plaques covering <10% of the body. However, since the tumor burden of patches and plaques is not the same, this stage is divided into two as T1a and T1b in the final classification (14). T1a consists of patches only, while T1b consists of plaques ± patches. These patients are also considered stage IA. T2 represents patients with patches and/or plaques in >10% of the body. T2a consists of patches only, while T2b consists of plaque ± patches. There was not a statistically significant difference between the CAR values of the patients, stages, and those with only skin involvement and those with lymph node and systemic involvement (Table 2).

16 patients had progressive disease (13M, 3 F). Lymphocyte count, sedimentation, LDH and Beta2 microglobulin were found to be associated with poor prognosis in these patients. Patients with disease progression (N = 16) had a median value of CAR 0.94 (0.42-7.51) and the median value of CAR (N:44) was 0.91 (0.12-4.57) in the group of patients without disease progression. The CAR value had no prognostic significance (P > 0.05) (Table 3).

Table 2. Relationship between patients C-reactive protein to albumin ratio values and stage

Stage		N (%)	C-reactive protein to albumin ratio Median (min-max)
IA	T1a	7 (11.7)	0.73 (0.26-1.48)
	T1b	2 (3.3)	0,91 (0.32-1.49)
IB	T2a	2 (3.3)	1.14 (0.78-1.50)
	T2b	0 (0.0)	
IIA		34 (56.7)	0.91 (0.12-4.24)
IIB		6 (10.0)	0.97 (0.44-7.51)
IIIA		0 (0.0)	
IIIB		7 (11.7)	1.37 (0.44-2.30)
IVA		2 (3.3)	1.07 (1.04-1.09)

Conclusions

MF, the most common CTCL, is characterized by the clonal proliferation of skin homing mature T-cells in chronically inflamed skin lesions. Malignant T-cells create a chronic inflammatory environment in which they take control of the inflammatory environment, suppressing cellular immunity and anti-tumor responses, while fostering their own expansion [15]. The median time from onset of symptoms to diagnosis is 3 to 4 years, also it can be decades. Clinicopathological correlation is necessary for the diagnosis of MF. Making the diagnosis is difficult for both the pathologist and the clinician because the findings are non-specific. Classical form of MF presents as persistent, progressive erythematous

Table 3. Distribution of patients in the study group according to variables thought to be related to their prognosis

	Poor prognosis (N = 16) Median (min-max)	Good prognosis (N = 44) Median (min-max)	t-test; P
Beta2 microglobulin	2.40 (1.53-4.09)	1.96 (1.18-3.77)	2.281; 0.023
CRP	3.72 (1.70-26.0)	3.89 (0.50-19.0)	0.478; 0.633
Sedimentation	4.00 (0.0-29.0)	11.0 (2.0-41.0)	2.079; 0.038
Albumin	4.45 (3.38-4.9)	4.5 (3.48-5.08)	0.831; 0.406
Neutrophil	2.87 (0.82-15.60)	1.99 (0.00-4.87)	0.157; 0.878
Eosinophil	200.0 (10.0-1400.0)	200.0 (10.0-2610.0)	0.241; 0.809
CAR	0.94 (0.42-7.51)	0.91 (0.12-4.57)	0.301; 0.763
N/L	2.87 (0.82-15.60)	1.99 (0.0-4.87)	1.639; 0.101
Disease duration	3.0 (1.0-21.0)	4.0 (0.50-35.0)	0.575; 0.565
Lymphocyte	1800.0 (500.0-4000.0)	2100.0 (1000.0-4860.0)	2.124; 0.046
Platelet	230.0 (128.0-418.0)	271.0 (187.0-406.0)	1.298; 0.210
LDH	214.0 (173.0-399.0)	187.0 (145.0-403.0)	2.684; 0.007

CAR = CRP to Albumin Ratio; CRP = C Reactive Protein; LDH = lactate dehydrogenase; N/L:Neutrophil to Lymphocyte ratio.

patches or plaques of variable size and shape, which have a scaly atrophic surface, located on sun-protected areas. MF can appear in many clinical forms, except for the classic patch-plaque-tumor type. Due to the atypical types of MF, the list of diseases in the differential diagnosis of MF is quite extensive. This is why the MF is known as the ''great imitator'' [1,3,16]. In cases where there is no clinical and pathological agreement on the diagnosis of MF, multiple biopsies should be taken from the lesions at regular intervals. The patient should be informed and should not be excluded from follow-up.

The degree of skin involvement and the presence of extracutaneous disease are the most important criteria for long-term life expectancy in MF. Therefore the TNMB (tumor, node, metastasis, blood) staging remains an important prognostic factor in MF. This classification has 9-level and early stage includes stages IA, IB and IIA. Other stages known as advanced or tumor stage. MF may remain stable or may progress to an advanced stage or a Sezary syndrome. Although the disease progresses with a poor prognosis in advanced stages, patients with MF having T1 stage have a similar life expectancy to that of control populations [2,17]. In addition, factors such as male gender, older age, histopathological type (folliculotropic MF, poor prognostic), large cell transformation, high serum beta2-microglobulin and lactate dehydrogenase LDH levels, and peripheral eosinophilia have been shown to be important in prognosis. Recently, the high neutrophil-lymphocyte ratio has been added to this list [2,18,19]. Our study also confirmed previous findings and concluded that the beta2 microglobulin, sedimentation and LDH is associated with a poor prognosis [20]. Anticipating prognosis in patients may be important in terms of close follow-up of patients and therapies to be selected.

CRP is a positive acute-phase reactant secreted by the liver during the inflammatory processes. Multiple studies have demonstrated that elevated serum CRP levels are associated with a poor prognosis for various solid tumors and lymphomas [21-23]. We also found that CRP levels were significantly higher in patients with MF than in the control group. Also, albumin is a negative acute-phase protein synthesized by the liver and reflects the nutrition status of the host. Pretreatment serum albumin level is a known prognostic marker of several solid malignancies and several hematological malignancies [24-26]. Therefore, CAR, a combined model of both CRP and albumin, demonstrated the outcome of the disease in some diseases better than either would show individually [5-11]. In addition the usability of CAR, an inexpensive parameter that can be easily calculated from the biochemistry profile, was evaluated in our study. In this study, we found the median CAR value significantly higher in patients with MF than in the control group. As we mentioned before, it can take years to make a definitive diagnosis of MF. We think that the CAR can be used as an additional indicator to guide us in the direction of MF in patients with suspected MF. We suggest that in patients with suspected MF, those with high CAR should be followed more closely.

Since CAR has been used as an indicator of inflammation, its use in the assessment of severity and activity of diseases involving the skin such as psoriasis and Behcet disease. It has been shown that the CAR value in psoriasis patients decreased significantly after treatment with a biologic agent. Thus, it has been shown that CAR can be a good indicator

of the severity of systemic inflammation in psoriasis [8]. It has been shown that in patients with chronic uveitis such as Behcet disease, CAR may be a marker for acute uveitis. CAR is an important parameter in determining the activation of the uveitis and correlated with the severity of intraocular inflammation in uveitis [12,13].

The prognostic value of CAR and its association with the advanced tumor have been established quite clearly in various solid organ tumors recently. The prognostic importance of CAR value in pancreatic cancer, which is one of the cancers with the poor prognosis, has been investigated many times. It has been shown that the CAR value increases in advanced disease and it has been reported that the CAR value is associated with prognosis. The CAR value is also shown to be useful in monitoring the effectiveness of chemotherapy in pancreatic cancer [7,27-29]. In a study conducted in 200 patients with newly diagnosed non-metastatic breast cancer, it was shown that increased CAR rate is associated with a high risk of recurrence or death in patients with breast cancer. In addition, the cut-off value was found to be lower in studies conducted in breast cancer compared to studies in other malignancies. It was interpreted that the cut-off value increased as more patients with advanced disease were included in the study [30]. In another study, high CAR was significantly associated with short-term survival prognosis of terminal cancer patients [31]. In a study in which 192 patients with acute pancreatitis were evaluated; The CAR was found to be the prognostic score in acute pancreatitis [9]. In our study, there was no association with CAR value and prognosis.

We compared the CRP, albumin, and CAR values with the control group, we found a significant difference in MF. But we did not find any of the CRP, albumin, and CAR values associated with prognosis. It well known that the prognosis of patients with cancer is associated with the clinical stage of cancer. MF is T-cell skin lymphoma. The prognosis is good unless there is systemic involvement. Especially distant metastases and the development of Sezary syndrome (advanced stage disease) are the main reasons that shorten the life span. Only one of our patients had Sezary syndrome, and one had N2 lymph node involvement. Systemic metastasis was not observed in any of the patients. While designing the study, we also considered tumor development and transition to advanced stages as poor prognosis. However, while tumor development detected 15% of our patients, none of these patients progressed to stage 4, which is systemic involvement. Also in a study conducted in patients with pancreatic cancer, it was shown that CAR has prognostic importance only in stage 3-4 (advanced stage) patients [27]. These reasons may have caused that CRP, Albumin, and CAR values were not related to prognosis in MF.

There were several limitations to our study. Possible missing data due to being a retrospective study. The collection of variables from a small group of patients at a single center makes it difficult to generalize these results to the general population. In our study, the number of patients classified as IIA is higher. Most stage I patients can be followed up in external centres with other diagnoses due to diagnostic difficulties. Since the possibility of systemic involvement is low in stage I disease, they can be followed up by physicians in secondary care hospitals. Since our center is a 3rd step treatment center, there are few stage I patients. Stage III disease is a rare stage. Therefore, there are few erythrodermic patients in our study group. Stage IV patients are followed up by hematology because they represent advanced stage and metastatic patient group. However, this does not reduce the reliability of our study. As it is known, only skin involvement occurs in stage I disease. In a disease that is very difficult to diagnose in the early stage, elevated systemic markers are not expected because systemic involvement is not common. Additional prospective studies with larger patient populations and with a predominance of advanced-stage patients, involving multiple centers are required to evaluate the CAR as a prognostic predictor.

Although CAR has been demonstrated to have a prognostic role in various solid malignancies and inflammatory diseases, it seems that there is no association between the CAR and progression in stage in MF patients. But the CAR is significantly higher in patients with MF than in the control group. The CAR can be a guide for us in cases where we have difficulty in diagnosing.

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