Original Article

CD30 and PD-1 in Mycosis Fungoides

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Abstract

Introduction: Mycosis fungoides (MF) is the most common cutaneous lymphoma, accounting for 50% of all cutaneous lymphomas. Programmed death-1 (PD-1; CD279) is a marker of follicular helper T cells and is expressed by the neoplastic T cells of some types of malignant lymphoma, including MF. About 30% of primary cutaneous T-cell lymphomas are CD30 positive and have a broad spectrum from lymphomatoid papulosis to primary cutaneous anaplastic large cell lymphoma. CD30 expression in MF is important for diagnostic purposes, prognostic value, and a therapeutic perspective. In this study, PD-1 and CD30 expression in early MF lesions has been examined, and its relationship between prognosis and survival has been questioned. The byproducts could be unorthodox treatment options. **Methods:** We prospectively applied immunohistochemically CD30 and PD-1 antibodies to the biopsies at our institution. We statistically evaluated the relationship between the expression rates of CD30 and PD-1 in atypical lymphocytes, with recurrence and survival. **Results:** This research with 119 patients was able to show a statistically significant relationship between CD30 and recurrence with PD-1 and poor survival. **Conclusions:** When evaluated together with treatment options, CD30 and PD-1 are markers that may guide the clinical follow-up of aggressive MF cases.

Keywords: CD30 ligand, mycosis fungoides (MF), programmed cell death-1 receptor (PD-1)

Introduction

Mycosis fungoides (MF) is the most common cutaneous lymphoma, accounting for 50% of all cutaneous lymphomas.[1] It has been also shown that MF patients have an increased risk of developing other malignancies, such as lymphomatoid papulosis (LYP), primary cutaneous anaplastic large cell lymphoma (PCALCL), Hodgkin's lymphomas, or nonlymphoid neoplasia.[2]

The neoplastic lymphocytes of MF usually show a T-helper phenotype. Immunohistochemical studies are robust and helpful in demonstrating this. CD3, CD4, and CD8 could be the antibodies to start with. The CD4/CD8 ratio should be evaluated at the level of the epidermis and dermis. The normal ratio of CD4/CD8 is usually between 2:1 and 4:1, and a ratio of more than 10:1 is considered abnormal. The CD4/CD8 ratio should always be evaluated with CD3 because the background of Langerhans cells and macrophages can cause CD4 overexpression.[3] Rarely in early MF, an aberrant CD4+/CD8+ or CD4−/CD8− phenotype can be seen.[4,5] Double-negative cases can be positive with programmed death-1 (PD-1).[6] The earlier algorithms proposed a loss of more than 90% for CD7 and more than 50% for CD2, CD3, or CD5, to be considered abnormal. The detection of a high CD4/CD8 ratio and a low (generally <25%) CD8/CD3 ratio is critical in an appropriate clinicopathological setting for MF.[7] We have investigated the effectiveness of CD3, CD4, and CD8 ratios in the diagnosis of early stages of MF, by applying to naïve and early lesion biopsies. This way strengthening the database of the study was also aimed.

PD-1 (CD279), a membrane molecule, one of the B7 family receptors, is expressed from germinal center-related T cells in normal or reactive lymphoid tissues.[8] Its role as an inhibitory factor makes us consider it creates an immune-free environment and encourages

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the progression of the neoplastic cells.[9] Although the reported results of PD-1 in MF are conflicting, studies have accelerated with the widespread use of anti-PD-1 agents (nivolumab, pembrolizumab, etc.) in other malignancies.[8,10-12]

CD30 is a type 1 transmembrane glycoprotein molecule and is a member of the tissue necrosis factor superfamily. About 30% of primary cutaneous T-cell lymphomas are CD30+ and have a broad spectrum from LYP to PCALCL.[6] CD30 expression in MF is important for three main reasons: diagnostic purposes, prognostic value, and a therapeutic perspective. The percentage of CD30+ cells rarely reaches the 75% cutoff value necessary for the diagnosis of anaplastic large cell lymphoma.[7] Negativity for CD30 has been related to a poor prognosis in transformed MF. Brentuximab vedotin (BV), an anti-CD30 monoclonal antibody, has been a treatment alternative in recent years.[13-15] In an international, open-label, randomized, phase 3, multicenter trial by the ALCANZA study group and others is one of the major trials for anti-CD30 treatment in PCTCL. In the MF group, more than 50% of the patients have an objective response.[16]

In this study, PD-1 and CD30 expression in early MF lesions has been examined, and its relationship between prognosis and survival has been questioned. Prognostic markers for MF are still not well established, and these markers could be important for prognostication. The byproducts could be unorthodox treatment options.

Materials and Methods

Patient selection and clinical parameters

Retrospectively, the pathology archive was searched between 2008 and 2014, and prospectively, the dermatology clinic added the patients to the study in 2015. The first biopsies of the patients were included as naïve biopsies in the study as the diseases of these patients may progress over the years and could be affected by their treatments. Patients that did not have follow-up biopsies were excluded from the study. The clinical characteristics of the patients were obtained from the hospital management system. Informed consent was obtained from patients routinely before their biopsies. Local ethics committee approval of the institution has been obtained in 2015 for the research.

Morphological parameters

Histopathological evaluation was made from archive hematoxylin and eosin slides by two pathologists. On morphological base, biopsies that were characterized by basilar or disproportionate epidermotropism, epidermal cerebriform cells, Pautrier's microabscesses, epidermal lymphocytes larger than dermal lymphocytes, and dermal lichenoid or band-like lymphocytic infiltration were selected. Archive slides were also reevaluated for CD3, CD4, and CD8 expressions.

Immunohistochemical study

CD30 (mouse monoclonal, clone: Ber-H2, 1:40, DAKO, Glostrup, Denmark), PD-1 (Rabbit monoclonal, clone: SP269, 1:100, Spring Bioscience, Pleasanton, California, USA), CD3 (Rabbit monoclonal, clone: 2GV6, ready to use, Ventana, Arizona, USA), CD4 (Rabbit monoclonal, clone: SP35, ready to use, Ventana), and CD8 (Rabbit monoclonal, clone: SP57, ready to use, Ventana) staining were performed on deparaffinized, rehydrated tissue sections obtained from formalin-fixed and paraffin-embedded tissue blocks, using an automated slide stainer (Ventana-XT, Arizona, USA). Antigen retrieval was performed in a citrate buffer. Tonsil tissue was used as a positive control for the markers.

The expression of the atypical cell population was noted for all markers by percentage. If the expression was less than 10%, it was considered negative.

Statistical analysis

Statistical analysis was performed using SPSS 15.0 software (SPSS Inc., Chicago, Illinois). Categorical variables were presented as frequencies and percentages and were compared using Fisher's exact test. Results were considered significant at the $P < 0.05$ level.

Results

Clinical data

Among 1228 biopsies of 185 patients with the criteria of having paraffin blocks belonging to the first biopsies of the patients in the archive, having multiple biopsies of the patients, and having MF diagnosis in at least a biopsy, 119 patients were chosen. All the biopsies were from patch lesions. The total number of biopsies of these 119 patients between 2008 and 2016 was 824 [Figure 1]. The average number of biopsies was 7 (range: 2–18). A total of 75 (63%) were male and 44 (37%) were female. The mean age of the patients was 53 (range: 21–81). The average follow-up period of the patients was 4 years (range: 0–9). The patient with the shortest follow-up died 3 months after diagnosis.

Histopathologically, eight (7%) cases were diagnosed as folliculotropic MF, two (2%) had large cell transformation on their initial, and three (2.5%) had large cell transformation on follow-up. Three (2.5%) had pigmented purpuric dermatosis-like MF. A total of 42 (35%) patients were nonrecurrent, whereas 77 (65%) had a recurrence. Four (3%) died from MF and three (3%) from non-MF or unknown causes.

It was found that 38 (31.9%) patients received narrowband ultraviolet B, 10 (8%) phototherapy, and 1 (1%)

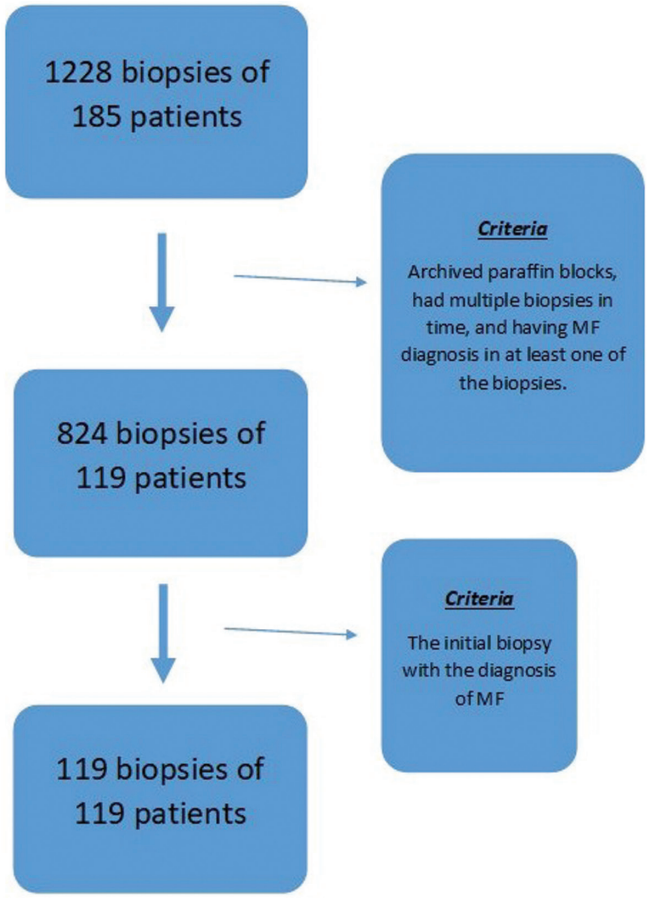

Figure 1: Flow chart of samples selected for the research

radiotherapy. Treatment of 70 (59%) patients was not available from the hospital management system [Table 1].

Immunohistochemical findings

In all cases, CD3, CD4, and CD8 expressions were evaluated in the epidermis and dermis separately. Diffuse CD3 expression was observed in intraepidermal and dermal infiltration in all biopsies. Both epidermal and dermal expression ratios of CD4/CD8 were increased (mean 4/1) in 99 (83%) biopsies [Figure 2], whereas CD4 and CD8 expression rates were similar in 20 (17%) cases. There was recurrence in 66 (55%) in the group with high CD4/CD8 expression rates, and 11 (9%) in the similar CD4/CD8 group. There were no statistically significant differences between the two groups in terms of recurrence (P = 0.32) [Table 2]. In the CD4/CD8 similar group, two (2%) were CD30+, three (3%) were PD-1+, and only one (1%) was both CD30+ and PD-1+.

CD30 expression was observed in 27 (22.6%), and 92 (77.4%) were negative [Figure 3]. Within the CD30+ group, recurrence was observed in 22 (19%), whereas nonrecurrent was 5 (4%). The expression rates of the recurrent group were 10%–50% [Figure 4]. However, the expression rates of the nonrecurrent group were 10%–20%. Within the CD30− patients, recurrence was observed in 55 (46%), whereas nonrecurrent was 37 (31%). There was a statistically significant relationship between CD30 expression and recurrence (P = 0.041) [Table 3]. Among the CD30+ patients, it was striking that the patient with 40% expression had large cell transformation in follow-up biopsies, but the patient with 50% did not.

PD-1 expression was observed in 22 (19%), and 97 (81%) were negative [Figures 4 and 5]. Among PD-1+ patients, recurrence was observed in 16 (14%), whereas nonrecurrent was 6 (5%). Within the PD-1− patients, recurrence was observed in 61 (51%), whereas nonrecurrent was 36 (30%). The expression rates of the recurrent and nonrecurrent groups were between 10% and 90%. There was no statistically significant relationship between PD-1 expression and recurrence (P = 0.46) [Table 3].

Table 1: Demographic data, histologic significant information, and immunohistochemistry results

Demographic data		Results (%)
Number of biopsies from each patient	Min.	2
	Max.	18
	Ave.	7
Sex	Male	75 (63%)
	Female	44 (37%)
Age	Min.	21
	Max.	81
	Ave.	53
Biopsy site	Abdomen	49 (41%)
	Back	21 (18%)
	Leg	15 (13%)
	Thigh	11 (9%)
	Arm	7 (6%)
	Gluteal	5 (4%)
	Unknown and other	11 (9%)
Follow-up period	Min.	3 months
	Max.	9 years
	Ave.	4 years
Therapy	Narrowband ultraviolet B	38 (32%)
	Phototherapy	10 (8%)
	Radiotherapy	1 (>1%)
	Unknown	70 (59%)
Histology and immunohistochemistry		Results (%)
Diagnosis	Classic MF	103 (86%)
	Folliculotropic MF	8 (7%)
	Large cell transformation	5 (4,5%)
	Pigmented purpuric dermatoses-like MF	3 (2,5%)
CD4/CD8 ratio	Min.	1/1
	Max.	25/1
	Ave.	4/1
CD30 expression	Positive	27 (23%)
	Negative	92 (77%)
PD-1 expression	Positive	22 (18%)
	Negative	97 (82%)

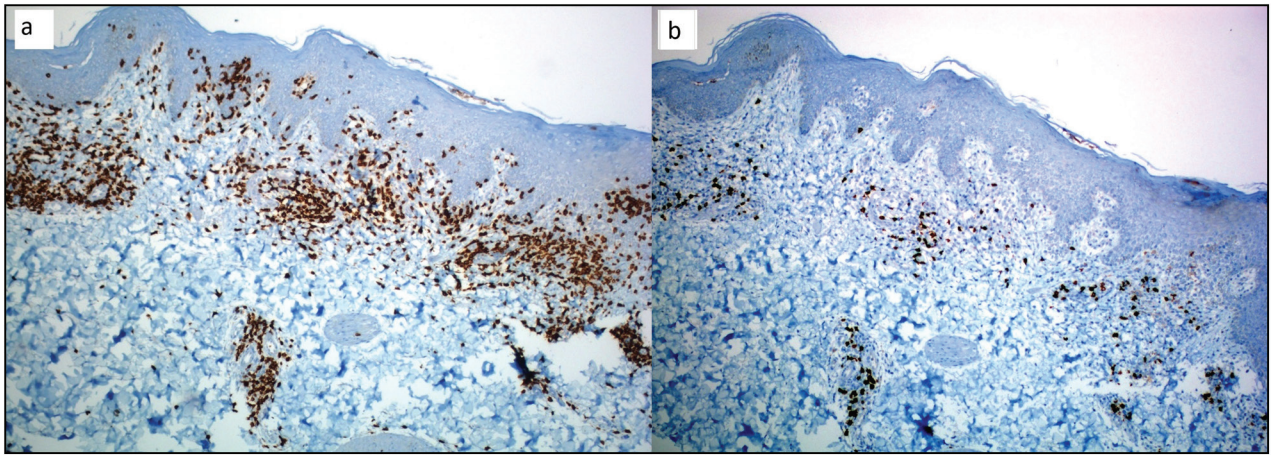

Figure 2: CD4 and CD8 immunohistochemistry staining (magnification, ×100). The high percentage of CD4 expression in atypical lymphocytes of mycosis fungoides (a) compared with CD8 (b) in the same areas of interest

Table 2: Relationship of CD4/CD8 ratio and recurrence

	CD4/CD8 ratio high	CD4/CD8 ratio similar	*P* value
Recurrent	66 (55%)	11 (9%)	0.32
Nonrecurrent	33 (28%)	9 (8%)	
Total	99	20	

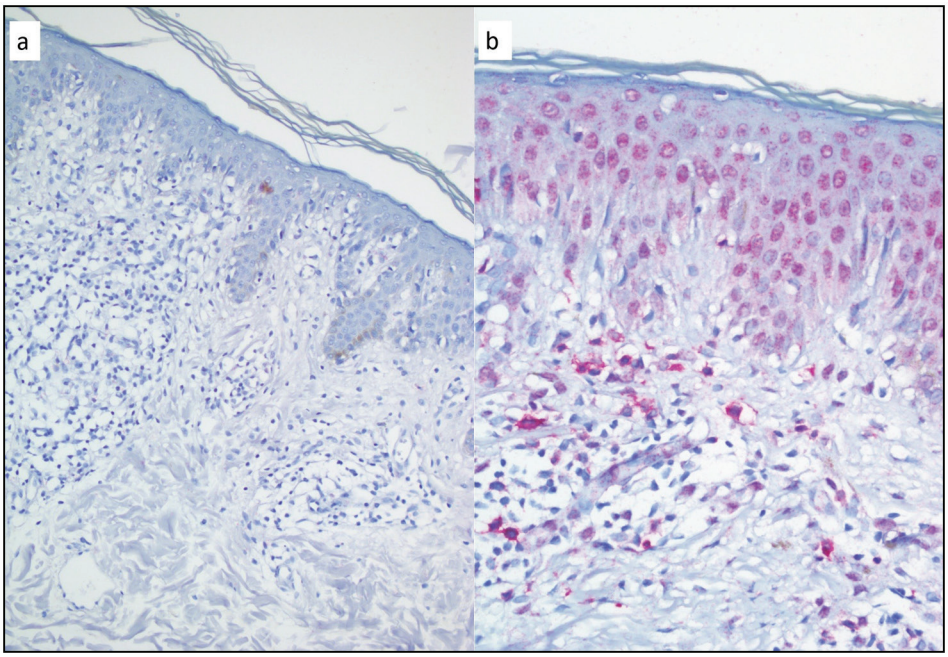

Figure 3: CD30 immunohistochemistry staining (magnification, ×200). (a) Negative. (b) Positive

Only five (4%) of the patients were both CD30+ and PD-1+. A total of 75 (63%) were CD30−/PD-1−. Among CD30+/PD-1+ patients, recurrence was observed in four (3%), whereas nonrecurrent was one (1%). Within the CD30−/PD-1− patients, recurrence was observed in 43 (36%), whereas nonrecurrent was 32 (27%). Among CD30− or PD-1− patients, recurrence was observed in 73 (61%), whereas nonrecurrent was 41 (35%). Within the CD30−/PD-1− patients, recurrence was observed in 43 (36%), whereas nonrecurrent was 32 (27%). There was no statistically significant relationship between dual CD30/PD-1 positivity and recurrence in both (P = 0.66 and P = 0.40) [Table 3].

All MF-caused ex-patient biopsies were PD-1+. The expression rates were 30%–90%. Their ages were between 58 and 81 years old. The follow-up period of these patients

was 1–7 years [Table 4]. One ex-patient developed Sezary syndrome (SS) on follow-up. A statistically significant difference was found between PD-1 expression and survival ($P = 0.001$) [Table 5].

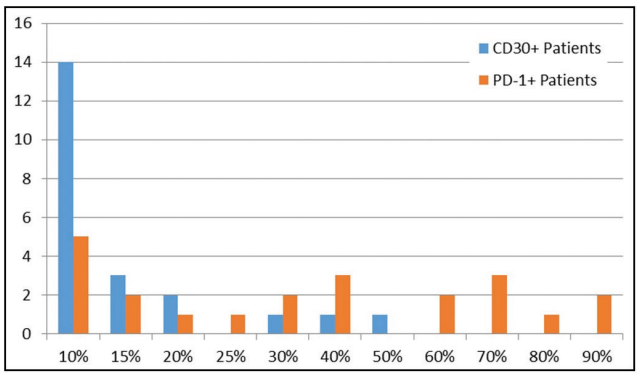

Figure 4: CD30 and PD-1 positivity percentages of patients

CD30 expression was observed in 27 (22.6%) cases and was not observed in 92 (77.4%). PD-1 expression was observed in 22 (18%) of the case, and was not observed in 97 (82%). These are the percentages of the expression within positive biopsies

Discussion

MF is a cutaneous T-cell lymphoma with a generally silent and protracted course. In many cases, a definitive diagnosis can be made only after a careful clinicopathological correlation. The similarity with inflammatory dermatoses has been confusing for dermatologists and pathologists. It has been important to identify clinical and pathological parameters that will facilitate differential diagnosis between early stages of MF and dermatoses and predict the prognosis of early-stage MF. For this purpose, there is a need for safer and more effective biomarkers.[17]

Immunohistochemistry-guided immunophenotyping is not only important for diagnosis but also important to identify the baseline profile. Most of the cases display T-helper CD3+, CD4+, CD8−, and TCR β+ phenotype characteristics of mature memory cells of the Th2 subtype. A high CD4/CD8 ratio in the lymphocytic infiltrates of clinically suspicious lesions is considered highly suggestive for the histopathologic diagnosis of MF and very helpful in clinically suspicious cases. However, CD4/CD8 dual positivity and CD4/CD8 dual

Table 3: Relationship between CD30 and PD-1 with recurrence

	CD30 positive	CD30 negative	*P* value	PD-1 positive	PD-1 negative	*P* value	CD30/ PD-1 dual positive	CD30 or PD-1 negative	*P* value
Recurrent	22 (19%)	55 (46%)	0.041	16 (14%)	61 (51%)	0.46	4 (3%)	73 (61%)	0.66
Nonrecurrent	5 (4%)	37 (31%)		6 (5%)	36 (30%)		1 (1%)	41 (35%)	
Total	27	92		22	97		5	114	

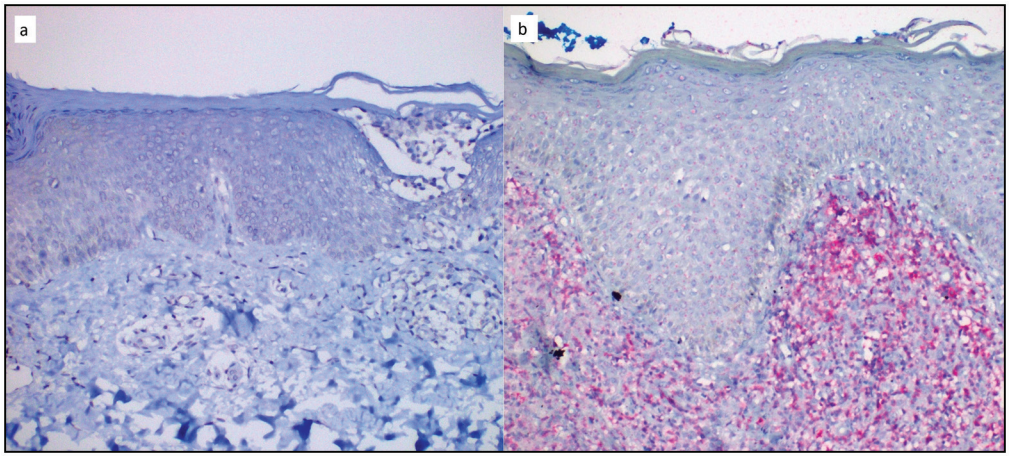

Figure 5: PD-1 immunohistochemistry staining (magnification, ×200). (a) Negative. (b) Positive

Table 4: Summary of clinicopathologic features of ex-patients with mycosis fungoides caused death

	Sex	Age	Epidermal CD4/ CD8 ratio	CD30 expression	PD-1 expression percentage	Number of biopsies through follow-up	Follow-up period (year)
Patient 1	Male	72	8	Negative	60	17	3
Patient 2	Female	66	5	Negative	30	5	7
Patient 3	Male	58	1	Negative	90	2	1
Patient 4	Male	81	5	Negative	30	4	1

Table 5: PD1 expression and survival summary

Survival	PD-1 +	PD-1 –	Total
Ex	4	0	4
Alive	18	94	112
Total	22	94	116

The Fisher exact test $P = 0.001$

negativity are rarely seen variants.[4] Expression of PD-1 has been reported in a double-negative case, suggesting a possible follicular T-helper origin.[5] The expressions of CD3, CD4, and CD8 in this study is compatible with the literature. The CD4/CD8 ratio was increased in 113 cases. Six were CD4/CD8 dual positive, and there was no dual negativity.

CD30 is one of the important markers that is sometimes used in the immunohistochemical evaluation of MF. Although large cell transformation is primarily a morphologic concept, CD30 expression has been linked to it. But it is important to remember that CD30 expression does not define large cell transformation. Only 30%–40% of transformed MF cases show more than 40% CD30 expression. CD30+ cells are rarely found in the epidermis in the patch stage.[18]

Scarisbrick *et al.*[19] found no significant difference in survival between CD30+ and CD30− cases in their series of 1275 advanced-stage MF and SS patients. Again, in Scarisbrick *et al.*'s[19] series of 100 early-stage MF lesions, there was no significant difference between survival rates and CD30 expression. This finding is inconsistent with the results of this study of 119 patients. CD30 expression was observed in 27 (23%) cases in our study, and there is a statistically significant relationship between CD30 expression and recurrence ($P = 0.041$). Additionally, some studies have shown that CD30 expression is a better prognostic marker for both transformed and nontransformed MF.[20,21] In the study by Benner *et al.*[22] consisting of 130 transformed MF patients, CD30 negativity was reported to reduce survival. Talpur *et al.*,[23] in their study of 187 MF-transformed cases, found that CD30 expression of over 10% indicates a good prognosis, even though it shows transformation. In our study, statistically significant results could not be obtained due to the small number of transformed lesions. It is thought that more effective results about the relationship between CD30 expression and recurrence can be obtained in studies involving numerous transformed MF patients.

In our study, a CD30+ case had LYP diagnoses in continuing biopsies. This situation led us to question the place of MF in the classification of CD30 (+) lymphoproliferative diseases.

The other important issue regarding CD30 is BV, which received Food and Drug Administration approval in 2017 as an anti-CD30 antibody-drug conjugate for use in primary cutaneous large cell lymphoma and MF showing CD30 expression. In the phase II study of 32 patients by Kim *et al.*,[24] patients with CD30 expression of more than 5% in the tissue showed a significantly higher response to the drug than those with CD30 expression of less than 5%. Therefore, the demonstration of CD30 in an aggressive MF patient can be important to provide treatment opportunities.

In a study of 26 cases by Kantekure *et al.*,[25] PD-1 was expressed in all lesions in the early patch and plaque stage, whereas expression decreased in MF cases that transited to the tumor phase. In their case reports, Ogunrinade *et al.*[26] emphasized that a case with a high PD-1 expression showed a poor prognosis. Here, CD30 negativity and transformation were also observed and were associated with poor prognosis. Cetinozman *et al.*,[10] in their study that included 60 MF and 27 SS patients, PD-1 expression was observed in 89% of SS patients, whereas PD-1 expression was observed in only 13% of MF patients. In this study, over 50% of the PD-1 expression rate was accepted as positive, and no information was given about the prognosis of the patients.[10] The diversity of PD-1 at varying rates in our study and the literature shows that a cutoff value of this marker has not yet been established and that the mean values should be determined by studying more patients.

In our study, PD-1 expression was observed in 22% of the cases, and it was noted that survival was significantly reduced in these cases. Although a significant relationship between PD-1 expression and recurrence could not be demonstrated, it suggests that patients with PD-1 expression should be followed closely in terms of poor prognosis.

In conclusion, we applied CD30 and PD-1 antibodies to the first biopsies of follow-up MF patients. We statistically evaluated the relationship between the expression rates of atypical lymphocytes with CD30 and PD-1, and recurrence and survival. We have shown that CD30 expression is a statistically significant dependent marker for recurrence, and a statistically significant relationship has been shown between PD-1 expression and poor survival. When evaluated together with treatment options, CD30 and PD-1 are markers that may guide the clinical follow-up of aggressive MF cases.

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Conflicts of interest

There are no conflicts of interest.

Ethical approval

Local ethics committee approval of our institution has been obtained on 2015 for the research with the number of 16.

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