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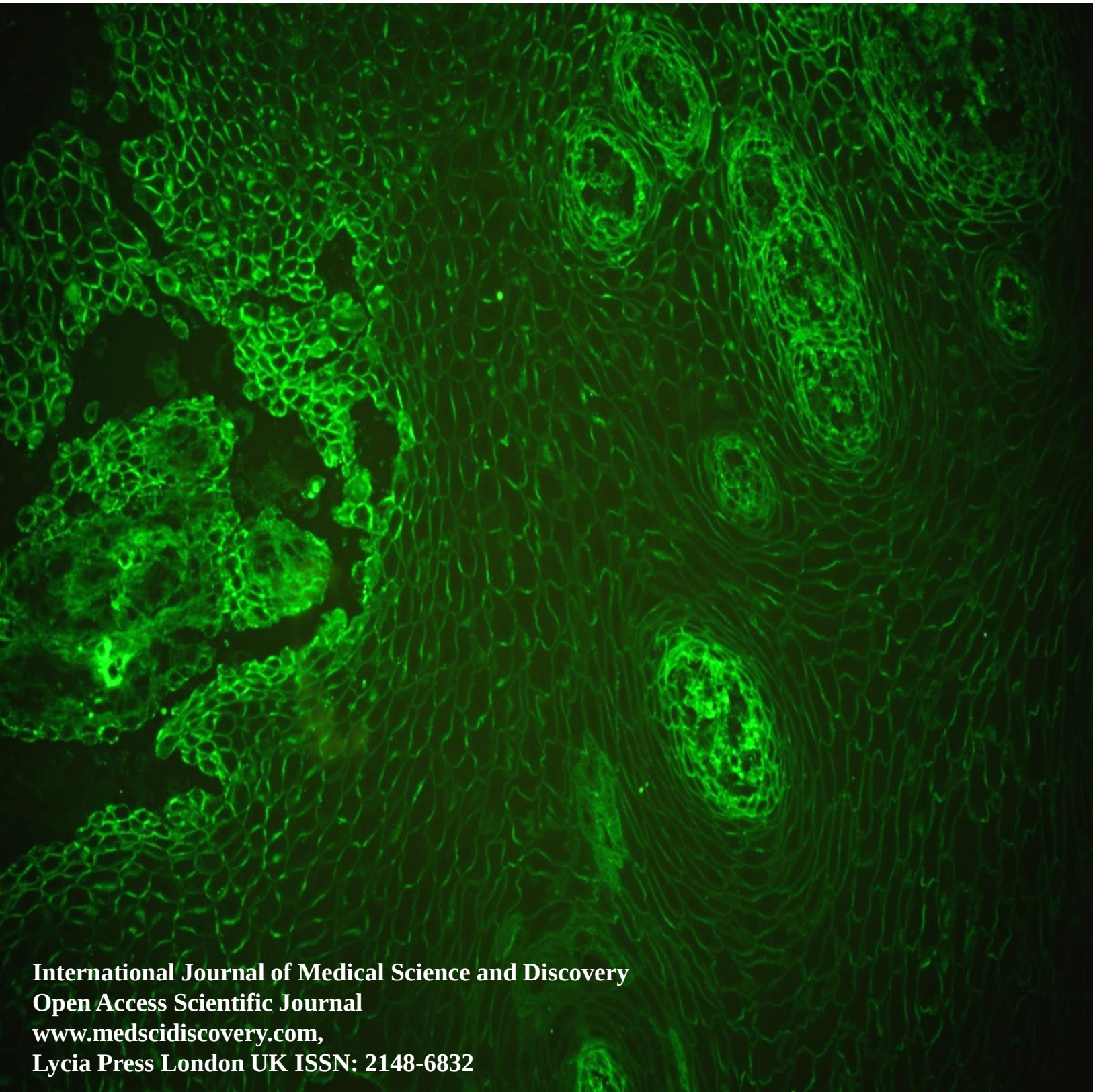

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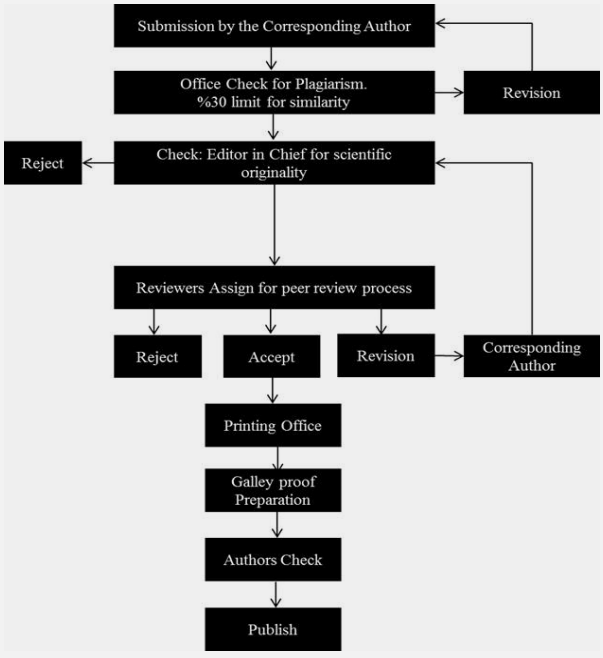

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Medical Science and Discovery, January 2020, Vol.7, No.1

Contents

Research Article

SettingsInflammatory prognostic markers in endometrial carcinoma: Systemic immune-inflammation index and prognostic nutritional index/351-359
Cem Mirili, Mehmet Bilici

Retrospective analysis of clinical, pathological characteristics and prognosis of the patients with endometrial stromal sarcomas/360-363
Hacı Öztürk Şahin, Mehmet Bayrak

SettingsThe Significance of inflammation markers in complete blood count in patients with fibromyalgia/364-367
Gülşah Karataş, Ramazan Gündüz

Peripapillary Microvasculature in Branch Retinal Vein Occlusion (BRVO) Treated With Anti-VEGF: An OCTA Study/368-372
Emine Çiloğlu

Protective effects of dehydroepiandrosterone (DHEA) vs caffeic acid phenethyl ester (CAPE) against ischemia-reperfusion injury in rat ovary/373-378
Ali Doğukan Angın, Önder Sakin, Muzaffer Seyhan Çıkman, İsmet Gün, Ramazan Denizli, Kayhan Basak, Asuman Orçun Kaptanağası, Yasemin Alan, Murat Alan

Case Reports

SettingsPeriodontal and Systemic Treatment Approach on Pemphigus Vulgaris: A Case Report/379-382
Ömer Birkan Ağralı, Gamze Kavuncu, Filiz Pekiner, Cuyan Demirkesen, Leyla Kuru

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Inflammatory prognostic markers in endometrial carcinoma: systemic immune-inflammation index and prognostic nutritional index

Cem Mirili[1]*, Mehmet Bilici[1]

Abstract

Objective: Systemic inflammatory response markers have prognostic significance in many cancer types. Although the prognostic values of neutrophil/lymphocyte (NLR), and platelet/lymphocyte ratios (PLR) have been shown in patients with Endometrial Cancer (EC) there is no information in the literature about systemic immune-inflammation index (SII) and prognostic nutritional index (PNI). In our study, we aimed to reveal the prognostic role of SII and PNI in EC.

Material and Methods: Medical data for 101 patients with EC were reviewed retrospectively. NLR, PLR, SII and PNI values were dichotomized based on receiver operating characteristic (ROC) curve analysis (cut-off values: 3.3; 177; 1035.9, and 38, respectively). At the time of diagnosis concentrations of these four serum inflammatory markers were analyzed to determine their potential association with clinicopathologic characteristics and to assess their prognostic values via the Kaplan-Meier method and multivariate Cox regression analysis.

Results: Patients with higher NLR, PLR, SII, and lower PNI values had shorter progression-free survival (PFS) and overall survival (OS) times. Higher NLR, SII, and lower PNI, were associated with FIGO stages, lymph node involvement, lymphovascular invasion, and cervical stromal invasion while additionally NLR and PNI were associated with worse ECOG performance scores (2-3) and myometrial invasion. In univariate analyses, all these four variables were prognostic for both OS and PFS, whereas in multivariate analyzes only NLR, SII and PNI were found to be independent factors for OS and PFS.

Conclusion: For the first time in the literature SII and PNI were determined to be independent prognostic factors for both OS and PFS in EC.

Key words: Endometrial Neoplasms, Inflammation, Biomarkers, prognostic nutritional index.

Introduction

Endometrial cancer (EC) is the most common gynecological cancer in developed countries and according to 2018 data, it is the 6th most frequently seen cancer in women after breast, colorectal, lung, cervical and thyroid cancers worldwide (1). Although curative surgical treatments can be applied in the early stages of EC (stage 1-2), due to manifestations of irregular or postmenopausal bleeding, the mortality rate of EC has increased by 100% within the last 20 years (2). This circumstance is thought to be related to the increase in the incidence of high-risk histological subtypes (serous, mucinous, mixed and carcinosarcoma), prolongation of life span, increased incidence of obesity, and diagnosis of patients at advanced ages and stages (3). Five-year survival rates in advanced stages (stages 3-4) and in recurrent EC are between 15-17% due to the inability to apply curative treatment options (4). Although the patients have been tried to be classified according to the classical prognostic significance of factors including age, high-risk histopathologic subtype, stage, grade, cervical stromal invasion (CSI), lymphovascular invasion (LVSI), myometrial invasion (MM), and lymph node involvement (LNI), the prognosis of the EC cannot be accurately predicted (5). Therefore it is very important to identify new predictive biomarkers to detect high-risk patients at the time of diagnosis.

The systemic immune response (SIR) to cancer has a key role in the stages of initiation, invasion, progression, and metastasis of carcinogenesis (6). For this reason, inflammatory parameters have an importance in cancer prognosis. Not only albumin, C-reactive protein (CRP), neutrophil, lymphocytes, platelets but also neutrophil/lymphocyte (NLR), and platelet/lymphocyte ratios (PLR) derived from these peripheral blood units are practical, inexpensive, measurable indicators of SIR and their prognostic significance in many solid cancer types including gynecological cancers have been determined (7-8).

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However, in recent years the prognostic significance of the systemic immune-inflammation index (SII) has been increasingly emphasized in cancer patients which are calculated based on the combination of neutrophil, lymphocyte and platelet counts (9-10). Prognostic nutritional index (PNI) which reflects both nutritional and inflammatory status is another inflammatory parameter estimated based on lymphocyte counts and albumin values. PNI was initially used to predict morbidity before gastroenterological surgery, but its prognostic significance has recently been demonstrated in hepatocellular carcinoma (HCC), esophageal, gastric, colon, and lung cancers (11). The increasing amount of evidence is available on the importance of inflammatory markers used for a long time such as NLR and PLR in EC, while any study on the status of SII and PNI has not been performed yet. In this study, we aimed to determine the prognostic significance of these inflammatory markers in EC whose importance has been revealed in different types of cancer.

Material and Methods

This retrospective study was performed on 101 patients (101/ 140) with complete medical records, and without hematologic, autoimmune disease, and secondary malignancies who had been diagnosed as EC and followed up for at least 3 months between April 2001 and 2019 at Erzurum Ataturk University Medical Oncology Department. Following retrieval of clinicopathological data including age, sex, performance status, pathological features, treatment agents used and laboratory data were taken from patient archives and the hospital information operating system. The patients were re-staged according to the 2018 EC staging system criteria of the International Federation of Gynecology and Obstetrics (FIGO). Leucocyte, neutrophil, lymphocyte, hemoglobin, platelet, and albumin values at the diagnosis were recorded. The ratios between neutrophil (N) and lymphocyte (L) (NLR), also between platelet (P) and lymphocyte (L) (PLR) counts were calculated. SII and PNI were calculated based on the following formulas: SII: P x N/L and PNI: 10 x Albumin (g/L) + (0.005 x L)

Ethics committee approval was obtained from the ethics committee of Erzurum Ataturk University. All the procedures were performed according to the 1964 Helsinki declaration.

Statistical Analyzes

Overall survival (OS) was calculated from diagnosis to death and progression-free survival (PFS) was calculated from diagnosis to recurrence or death. Associations between clinicopathologic characteristics with survival times were analyzed by Kaplan-Meier curves and compared by the log-rank test. NLR, PLR, SII, and PNI were determined on the basis of receiver operating characteristic (ROC) analysis for OS. Cut off points for NLR, PLR, SII, and PNI were 3,3, 177, 1035,9, and 38, respectively. Area under the curve (AUC) was over 0.80 for all parameters. The association between NLR, PLR, SII, PNI and clinicopathological parameters was analyzed by chi-square test. Univariate and multivariate Cox-regression analyses were performed to determine effects of probable prognostic factors for OS and PFS, including ECOG performance status, FIGO stage, histological grade, cervical stromal invasion (CSI), lymphovascular invasion (LVSI), myometrial invasion (MM), and lymph node involvement (LNI) status. The number of events of all variables involved in multivariate analysis was more than 10. NLR, PLR and SII were not added to multivariate analyzes at the same time due to high correlation between them by Pearson correlation test.

Two separate multivariate analysis models were used to eliminate this multicollinearity problem: aThe variables (ECOG status, FIGO Stage, grade, lymphovascular space invasion, perineural invasion, SII, and PNI) were tested in a multivariate analysis. bThe variables (ECOG status, FIGO Stage, grade, lymphovascular space invasion, NLR and PLR) were tested in a multivariate analysis. Hazard ratios (HRs) estimated from the Cox analysis were reported as relative risks with corresponding 95 % confidence intervals (CIs). All analyses were performed using the SPSS statistical software package (SPSS statistics 21.0). $P < 0.05$ was considered as statistically significant

Results

The clinicopathological data of 101 study patients including 14 (13.9%) premenopausal and 87 (86.1%) postmenopausal women with a median age of 62 (36-80) years are presented in Table 1. The patients had ECOG performance status scores of 0 (n=8), 1 (n=58), and 2-3 (n=35). According to histologic subtypes, the patients had endometrial adenocarcinoma (n=75), carcinosarcoma (n=12), serous carcinoma (n=7), mucinous carcinoma (n=3), mixed carcinoma (n=1), and According to FIGO staging system, the patients were in disease stages of 1A (n=14), 1B (n=23), 2 (n=8), 3A (n=7), 3D (n=1), 3C (n=24), 4A (n=5), and 4B (n=19). MM (n=86: 85.1%), CSI (n=39: 38.6%), LVSI (n=55: 54.5%), perineural invasion (n=17: 16.8%), and LNI (47:% 46.5) were also detected in respective number of patients. As treatment modalities the patients received brachytherapy (n=5), external radiotherapy (n=37 (36.6%), and chemotherapy (n=73: 72.3%) [as adjuvant (n=54), and palliative (n=19) therapy]. At the end of the median follow-up period of 20 months (3-141 months), disease had progressed in 59 (58.4%) patients while 53 (52.5%) patients died. Median, and average OS and PFS times were 33 vs 55.9 and 26 vs 49.5 months, respectively.

At the time of diagnosis, mean, and median (range) NLR, PLR, SII, PNI values were 3.82 ± 1.86 vs 3.55 (1.02-9.31), 214.2 ± 117.5 vs 184 (55.1-655.8), 1269.6 ± 828.4 vs 1069.6 (176.5-4617.6), and 1269.6 ± 828.4 vs 37.1 (19-38), respectively. Regarding OS, NLR cut-off value of 3.3 had AUC of 0.921 with 90.6% sensitivity and 87.5% specificity (95% CI: 0.867–0.975, p<0.000). While PLR cut-off value of 177 with AUC of 0.801 had 79.2% sensitivity, and 72.9% specificity (95% CI: 0.713–0.889, p<0.000), the SII cut-off value was 1035.9 (AUC=0.856, sensitivity; 81.1%, specificity; 75%, 95% CI: 0.782–0.930, p<0.000), the PNI cut-off value was 38 (AUC=0.854, sensitivity; 81.1%, specificity; 79.2%, 95% CI: 0.070–0.222, p<0.000) (Figure 1). Table 2 shows the relationship between the clinicopathological parameters and the NLR, PLR, SII, and

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PNI. Higher NLR (>3.3) and lower PNI (<38), were associated with worse ECOG performance scores (2-3) (p: 0.027, p: 0.026), FIGO stage (p: 0.005, p: 0,000), MM (p: 0.024, p: 0.045), CSI (p: 0.035, p: 0.003), LVSI (p: 0.002, p: 0.001), and LNI (p: 0.006, p: 0.001), while higher PLR (>177) values were correlated with FIGO stage (p: 0,000), MM (p: 0,005), LVSI (p: 0,043) and LNI (p: 0,001). Higher SII (>1035.9) values were associated with FIGO stages (p: 0,000), CSI (p: 0.006) LVSI (p: 0.043) and LNI (p: 0.000).

Patients with higher NLR, PLR, SII, and lower PNI had both shorter PFS (p: 0.000, p: 0.000, p: 0.000, p: 0.000, respectively) and OS (p: 0.000, p: 0.000, p: 0.000, p: 0.000, respectively) than those with lower NLR, PLR, SII and higher PNI values as demonstrated by Kaplan-Meier curves (Figure 2). The average PFS and OS times of patients with high NLR values were 18.6, and 25.1 months and those with lower NLR were 107.8 and 120 months, respectively.

The median OS times of the patients with higher, and lower PLR values were 18, and 105 months, respectively. Median PFS times for patients with higher, and lower PLR values were 11, and 67 months, respectively. Similarly, median PFS and OS times in patients with higher, and lower SII values were 11 vs 18, and 67 vs 105 months, respectively. In contrast to other inflammatory markers, those with higher PNI values have longer PFS and OS times. (PNI ⩾ 38: PFS: 95, and OS: 95 months, and PNI <38: PFS: 9 and, OS: 18 months).

The prognostic significance of clinicopathological data for OS and PFS by univariate and multivariate analysis is shown in Table 3; According to univariate analysis, ECOG performance status, FIGO stage, grade, MM, CSI, LVSI, LNI, NLR, PLR, SII, and PNI have prognostic significance for both OS and PFS. It was found that NLR, PLR, SII, and PNI were highly correlated with OS and PFS. However, in multivariate analysis of two separate models, NLR, SII, and PNI were independent prognostic factors for both OS and PFS.

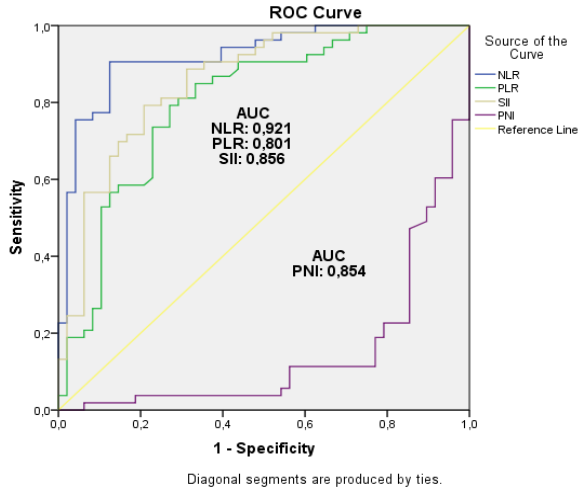

Figure 1: ROC analysis and AUC for sensitivity and specificity of inflammatory parameters: NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio, SII: systemic immune-inflammation index, PNI: prognostic nutritional index

Table 1: Patient Demographics and Clinical Characteristics (n: 101)

	N (%)
Age	
<50	13 (12,9)
≥50	88 (87,1)
Menopausal status	
Premenopause	14 (13,9)
Postmenopause	87 (86,1)
ECOG performance status	
0	8 (7,9)
1	58 (57,4)
2-3	35 (34,7)
Histologic Subtype	
Endometrial adenocarcinoma	75 (74,3)
Mucinous carcinoma	3 (3)
Serous carcinoma	7 (6,9)
Mix carcinoma	4 (4)
Carcinocarcinoma	12 (11,9)
FIGO stage	
1A	14 (13,9)
1B	23 (22,8)
2	8 (7,9)
3A	7 (6,9)
3B	1 (1)
3C	24 (23,8)
4A	5 (5)
4B	19 (18,8)
Grade	
I	8 (7,9)
II	55 (54,5)
III	38 (37,6)
Myometrial invasion	
Yes	86 (85,1)
No	15 (14,9)
Cervical stromal invasion	
Yes	39 (38,6)
No	62 (61,4)
Lymphovascular space invasion	
Yes	55 (54,5)
No	46 (45,5)
Perineural invasion	
Yes	17 (16,8)
No	84 (83,2)
Lymph node involvement	
Yes	47 (46,5)
No	54 (53,5)
Brachytherapy	
Yes	5 (5)
No	96 (95)
External radiotherapy	
Yes	37 (36,6)
No	64 (63,4)
Chemotherapy	
Yes	73 (72,3)
No	28 (27,7)
Progression	
Yes	59 (58,4)
No	42 (41,6)
Status	
Alive	48 (47,5)
Death	53 (52,5)
Age (Mean±SD)	61,53±9,83
NLR (Mean±SD)	3,82±1,86
PLR (Mean±SD)	214,2±117,5
SII (Mean±SD)	1269,6±828,4
PNI (Mean±SD)	36,2±6,8

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Table 2: The association between pretreatment NLR, PLR, SII, PNI and clinicopathological parameters (n:101)

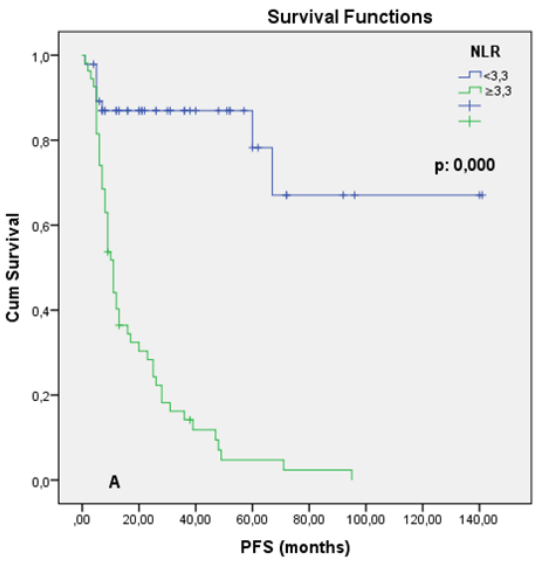
		NLR			PLR			SII			PNI		
	n	<3.3	≥ 3.3	*p*	<177	≥177	*p*	< 1036	≥ 1036	*P*	<38	≥ *38*	*P*
Age				0,134			0,583			0,962			0,353
<50	13	9	4		5	8		6	7		5	8	
≥50	88	38	50		41	47		40	48		46	42	
Menopausal status				0,151			0,426			0,828			0,538
Premenopause	14	9	5		5	9		6	8		6	8	
Postmenopause	87	38	39		41	46		40	47		45	42	
ECOG status				**0,027**			0,098			0,415			**0,026**
0-1	66	36	30		34	32		32	34		28	38	
2-3	35	11	24		12	23		14	21		23	12	
Histologic Subtype				0,616			0,942			0,701			0,078
Endometrial adenocarcinoma	75	36	39		34	41		35	40		34	41	
Others	26	11	15		12	14		11	15		17	9	
FIGO stage				**0,005**			**0,000**			**0,000**			**0,000**
1	37	24	13		26	11		27	10		8	29	
2	8	5	3		5	3		5	3		4	4	
3	32	13	19		9	23		10	22		20	12	
4	24	5	19		6	18		4	20		19	5	
Grade				0,151			0,089			0,115			0,056
1	8	4	4		4	4		2	6		3	5	
2	55	30	25		30	25		30	25		23	32	
3	38	13	25		12	26		14	24		25	13	
Myometrial invasion				**0.024**			**0,005**			0,075			**0,045**
Yes	86	36	50		34	52		36	50		47	39	
No	15	11	4		12	3		10	5		4	11	
Servical stromal invasion				**0,035**			0,051			**0,006**			**0,003**
Yes	39	13	26		13	26		11	28		27	12	
No	62	34	28		33	29		35	27		24	38	
Lymphovascular space invasion				**0,002**			**0,043**			**0,043**			**0,001**
Yes	55	18	37		20	35		20	35		36	19	
No	46	29	17		26	20		26	20		15	31	
Perineural invasion				0,308			0,143			0,143			**0,007**
Yes	17	6	11		5	12		5	12		14	3	
No	84	41	43		41	43		41	43		37	47	
Lymph node involvement				**0,006**			**0,001**			**0,000**			**0,001**
Yes	47	15	32		13	34		11	36		32	15	
No	54	32	22		33	21		35	19		19	35	
Progression				**0,000**			**0,000**			**0,000**			**0,000**
Yes	59	8	51		14	45		13	46		46	13	
No	42	39	3		32	10		33	9		5	37	
Status				**0,000**			**0,000**			**0,000**			**0,000**
Alive	48	42	6		35	13		36	12		10	38	
Death	53	5	48		11	42		10	43		41	12	

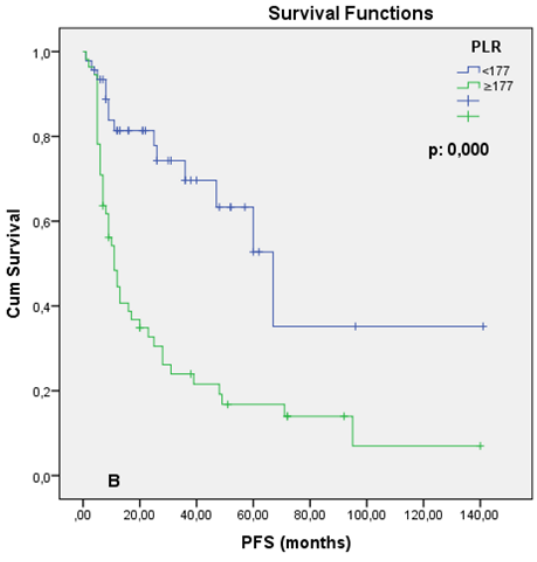
NLR: neutrophil-lymhocyte ratio, PLR: platelet-lymphocyte ratio, SII: systemic immune-inflammation index, PNI: prognostic nutritional index. Statistically signifcant p-values (<0.05). Results were determined by Pearson x2. Fisher's Exact test was used if expected cell count is less than 5.

Table 3. Univariate and Multivariate Analysis of Potential Prognostic Factors for OS and PFS

OS	Univariate HR (%95 CI)	P	Multivariate HR (%95 CI)	P
Age (<50 vs ≥50)	1,934 (0,697-5,368)	0,205	-	-
Menopausal status (premanapuse vs postmenopause)	1,613 (0,641-4,057)	0,310	-	-
ECOG status (0-1 vs 2-3)	3,437 (1,923-6,143)	**0,000**	2,135 (1,078-4,227)	**0,030**[a]
Histologic Subtype (adenocarcinoma vs other)	0,549 (0,295-1,022)	0,059	-	-
FIGO stage (1-2 vs 3 and 4)	1,741 (1,252-2,423)	**0,001**	-	0,383[a]
			0,630 (0,261-1,523)	0,305[a]
			0,497 (0,183-1,348)	0,170[a]
Grade (1-2 vs 3)	2,246 (1,388-3,633)	**0,001**	1,760 (0,872-3,551)	0,115[a]
Lymphovascular space invasion (negative vs positive)	2,675 (1,459-4,903)	**0,001**	1,409 (0,656-3,024)	0,379[a]
Perineural invasion (negative vs positive)	1,962 (1,037-3,713)	**0,038**	0,880 (0,387-2,003)	0,761[a]
NLR (<3.3 vs ≥3.3)	15,472 (5,523-43,34)	**0,000**	11,300 (3,633-35,14)	**<0,000**[b]
PLR (<177 vs ≥177)	3,987 (2,046-7,773)	**0,000**	1,445 (0,675-3,092)	0,343[b]
SII (<1036 vs ≥1036)	4,993 (2,498-9,981)	**0,000**	4,561 (1,914-10,870)	**0,001**[a]
PNI (38 vs ≥38)	5,189 (2,670-10,085)	**0,000**	3,320 (1,518-7,262)	**0,003**[a]
PFS	Univariate		Multivariate	
	HR (%95 CI)	P	HR (%95 CI)	P
Age (<50 vs ≥50)	2,193 (0,793-6,063)	0,130	-	-
Menopausal status (premanapuse vs postmenopause)	1,859 (0,743-4,654)	0,185	-	-
ECOG status (0-1 vs 2-3)	2,830 (1,633-4,906)	**0,000**	1,493 (0,772-2,888)	0,234[a]
Histologic Subtype (adenocarcinoma vs other)	0,576 (0,323-1,026)	0,061	-	-
FIGO stage (1-2 vs 3 and 4)	1,650 (1,304-2,087)	**0,000**		0,241[a]
			0,674 (0,291-1,560)	0,357[a]
			1,260 (0,507-3,129)	0,619[a]
Grade (1-2 vs 3)	2,167 (1,385-3,390)	**0,001**	1,762 (0,913-3,401)	0,091[a]
Lymphovascular space invasion (negative vs positive)	2,364 (1,363-4,098)	**0,002**	1,339 (0,673-2,665)	0,406[a]
Perineural invasion (negative vs positive)	1,826 (1,002-3,400)	**0,049**	0,483 (0,213-1,092)	0,080[a]
NLR (<3.3 vs ≥3.3)	9,441 (4,421-20,362)	**0,000**	7,419 (3,123-17,621)	**<0,000**[b]
PLR (<177 vs ≥177)	3,449 (1,887-6,303)	**0,000**	1,150 (0,584-2,264)	0,686[b]
SII (<1036 vs ≥1036)	4,252 (2,287-7,905)	**0,000**	2,651 (1,206-5,824)	**0,015**[a]
PNI (38 vs ≥38)	6,661 (3,408-13,018)	**0,000**	5,118 (2,349-11,151)	**<0,000**[a]

Statistically signifcant p-values (<0.05). NLR: neutrophil lymhocyte ratio, PLR: platelet lymphocyte ratio, SII: systemic immune-inflammation index, PNI: Prognostic nutritional index. aThe variables (ECOG status, FIGO Stage, grade, lymphovascular space invasion, perineural invasion, SII and PNI) were tested in a multivariate analysis. bThe variables (ECOG status, FIGO Stage, grade, lymphovascular space invasion, NLR and PLR) were tested in a multivariate analysis





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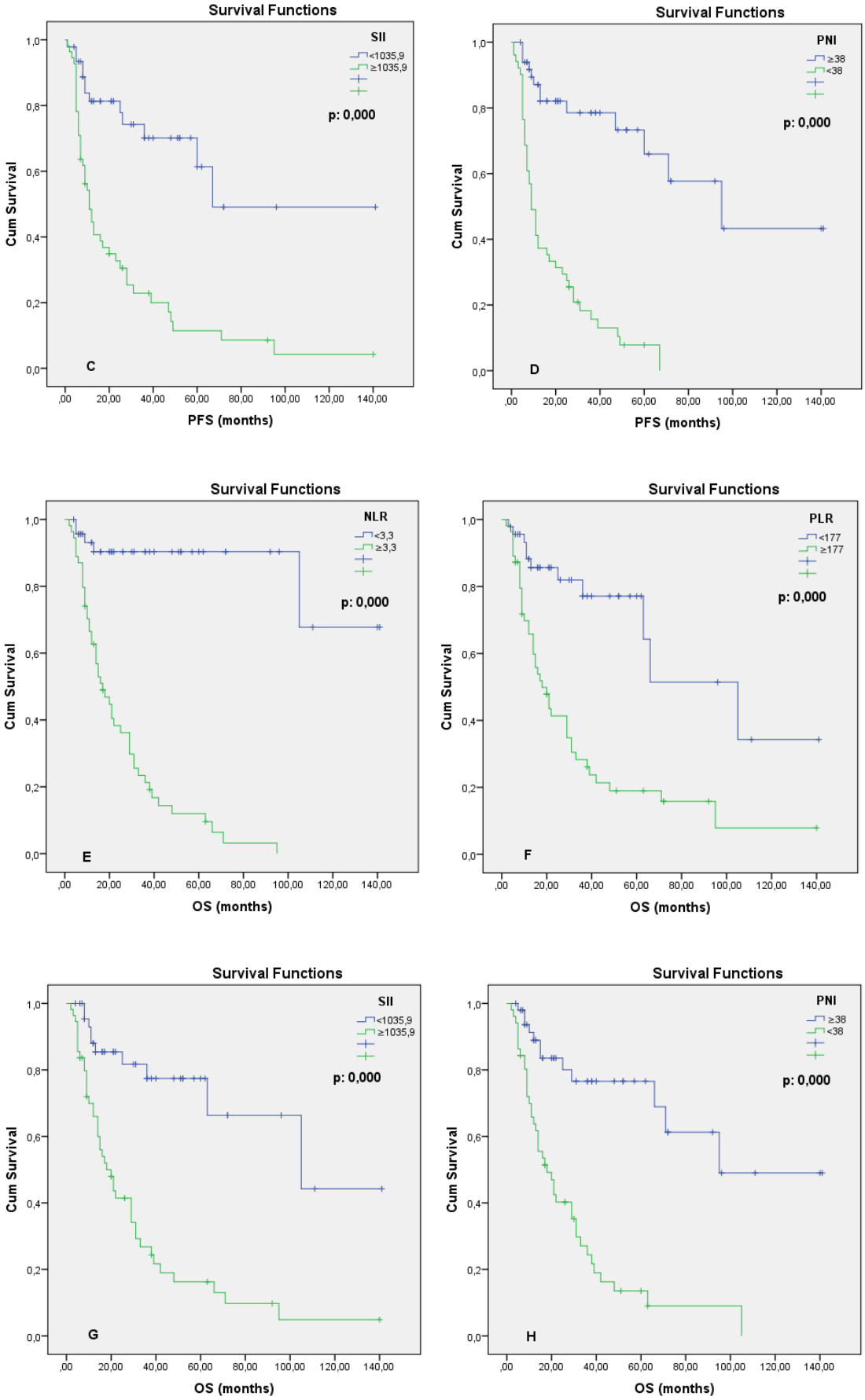

Figure 2: PFS and OS times according to inflammatory markers. NLR (A-E), PLR (B-F), SII (C-G), PNI (D-H). NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio, SII: systemic immune-inflammation index, PNI: prognostic nutritional index

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Discussion

EC is the most frequently seen gynecological malignancy in developed countries and the risk of recurrence and death cannot be clearly defined despite the use of classical prognostic factors. Therefore, new predictive markers are needed. In this study, we aimed to demonstrate the prognostic significance of inflammatory markers such as NLR, PLR, SII, and PNI. For the first time in the literature, we found that higher SII and lower PNI values are related to shorter PFS and OS times in EC. Also, we found that SII and PNI are both independent prognostic factors for OS and PFS.

There are many clinical and pathological factors predicting survival in EC. The most important clinical factors are age and race. However, it is thought that the prognosis is mostly determined by the pathological factors such as FIGO stage and histology (subtype and grade) and it has been identified as an independent factor in many studies.

Especially those with endometrioid type and early FIGO stage lived longer (12). In our study, while age and histologic subtype were not prognostic, FIGO stage groups, histologic grade groups MM, CSI, LVSI, and LNI were prognostic factors for both PFS and OS according to univariate analyses. However, in multivariate analyses, no one is an independent factor for both PFS and OS. In particular, the fact that FIGO stage and subtypes could not be identified as independent factors does not seem to be fully compatible with the literature. When we look at the factors that cause this situation, the first findings that we notice are that the patients are not homogeneously distributed according to these two parameters and the number of patients is low. For example, as shown in Table 1, there are fewer than 10 patients in stage 2, 3A, 3B and 4A groups, while in the other stage groups there are 14 or more patients. However, although some of the classical factors in our study did not reveal prognostic significance independently, we think that age, FIGO stage, histologic subtype, and grade are the most important prognostic factors in EC.

In recent years the prognostic significance of inflammatory markers such as NLR, PLR in many cancer types has been identified due to the increasing number of studies, those aiming to understand the interactive mechanism between cancer types and inflammation. However, although the exact cause of this mechanism is still not clear, it is thought that depending on SIR increased neutrophil, platelet and decreasing lymphocyte counts may contribute to this situation (13). In particular release of inflammatory cytokines (interferon y), interleukins (IL-1a, IL-6, IL-7, IL-8, IL-9, IL-12) and phagocytic mediators (monocyte chemotactic protein 1, macrophage inflammatory protein 1β) increased by neutrophils which leads to induction of DNA damage, and angiogenesis and suppression of apoptosis has been presumed to be the foremost etiological factors. Another possible pathophysiologic mechanism of this condition is that by interacting directly with tumoral cells, the platelets secrete mediators that facilitate the growth and invasion of the cancer cells. Also, platelets inhibit the destruction of tumoral cells by natural killer cells. As opposed to the effects of all these cells, lymphocytes show antitumoral effects through their cell-dependent killing abilities (14). Although there are various hypotheses about the relationship between endometrial cancer and inflammation, the most important mechanism is thought to be increased inflammation-dependent cytokine and growth factors due to unmet estrogen. As a result, NF-κB activity increase and up-regulatıon of COX-2, PGE-2 occur in the endometrial cells. Due to these changes, free oxygen radicals initiate neoplastic tumoral transformation through DNA damage. Therefore, inflammatory markers provided to be prognostic in EC, like other cancers (15).

In two meta-analyses investigating 40,559 and 12,754 patients with many cancer types such as breast, esophagus, stomach, colon, ovary cancers (excl. endometrial cancer) higher NLR and PLR values have been associated with shorter OS (16-17). Either et al. reviewed 26 studies encompassing 10530 patients with only gynecologic malignancies, and detected correlations between higher NLR (>2.95) values with poor event-free survival rates (EFS) ($p < 0.001$) and OS ($p < 0.001$). In one of five EC studies have included in this meta-analysis, higher NLR (>2.4) and PLR (>240), while in another study only NLR was found to be an independent prognostic factor for OS. However in a univariate analysis, Li et al. found that NLR and PLR were related to OS and EFS, but they were not evaluated as prognostic independent factors (18-20). Güleç et al. examined the relationship between inflammatory markers and clinicopathological data in 763 endometrial cancer patients, in this study, they suggested that NLR and PLR are associated with advanced FIGO, MM, CSI, LVSI, and LNI. In addition to that NLR is also associated with histological type and metastasis. In univariate analyses, NLR was identified as a prognostic factor for OS, whereas in multivariate analyses it was suggested that NLR is not an independent prognostic factor (21). Similarly, in our study, patients with high NLR and PLR values had shorter OS and PFS. Besides in univariate analyses, NLR and PLR were prognostic markers for OS/PFS, but multivariate analyses revealed that NLR was also an independent factor for OS and PFS. We detected that NLR and PLR correlated also with advanced FIGO stage MM, LVSI, LNI, while NLR was also associated with ECOG performance status and CSI. Although different cut-off values have been used for the inflammatory markers in the aforementioned studies, as a common finding in all studies, including ours, higher NLR and PLR values have been associated with many adverse clinicopathological features, and in particular, NLR had a prognostic significance in EC. This situation supports the role of inflammation in carcinogenesis of EC.

SII is a brand new developed inflammatory marker which is a combination that allows the simultaneous evaluation of NLR and PLR. Therefore, it is thought that SII better reflects the balance between the inflammatory state and SIR (22). A study showing that SII correlates with the number of circulating tumor cells, which supports this assumption (23). In a meta-analysis, encompassing 7657 patients, but excluding cases with gynecologic malignancies, Yang et al associated high SII values with shorter OS in some cancer types such as urinary system (p

<0.001), HCC (p <0.001), acral melanoma (p <0.001), gastric (p = 0.005), esophageal squamous cell (p = 0.013), small and non-small cell lung cancer (p <0.001, p <0.001) (24). A recent study demonstrated the prognostic role of SII in cervical cancer patients and compared to NLR, PLR, and MLR, only SII was found to be an independent prognostic factor for OS, without any correlation with clinicopathological features (25). Nie et al. associated higher SII (>612) with shorter PFS and OS in 553 epithelial ovarian carcinoma cases and in multivariate analysis they were found to be independent prognostic factors also for both OS and PFS. Besides, they demonstrated that higher SII correlated with lymph node metastasis, advanced FIGO stage, and tumor recurrence (26). However, there is no study showing the relationship of SII with clinicopathological features and its prognostic role in patients with EC. For the first time in literature in our study, the association of SII with clinicopathologic characteristics in patients with EC, and its prognostic role have been demonstrated. Similar to the results of the studies on other types of cancer, higher SII has been associated with shorter OS and PFS and found to be an independent prognostic factor in multivariate analysis. Besides higher SII is associated with advanced FIGO stage, CSI, LVSI, and LNI. However, it was concluded that SII is more predictive for OS and PFS in esophageal, pulmonary cancers, and HCC when compared with other inflammatory markers (27). Contrarily in our study, NLR with the highest AUC value was the most predictive marker for OS followed by SII. We think that this finding may be related to the limited number of patients or the biologic differences between the tumors. To validate the prognostic significance of SII in patients with EC, independent cohort studies should be performed.

According to recent studies, not only the characteristic features of the tumor but also the nutritional and immunological status affects the progression of cancer (28). Although PNI was initially introduced to predict preoperative mortality and morbidity, its prognostic significance has been found in many types of cancer in recent years. It is the most widely used marker for detecting nutritional and immunological status since it is estimated by using lymphocyte counts and albumin values (29). Due to excessive and improper SIR, cytokines such as TNF alpha and IL-6 cause proteolysis in muscle cells leading to cancer cachexia. This pathophysiological process results in decreased albumin levels, and weight loss (30). For the same reason, lymphocytes, which are the main cells of cellular immunity, decrease in number and host cell's ability to kill tumor cells weakens. In light of all this information, a decrease in lymphocyte and/or albumin levels suggests the development of excessive inflammatory reaction and poor prognosis of the cancer patient. This situation explains the relationship between lower PNI values with shorter survival times and poor prognosis. In a meta-analysis of 3414 patients with mostly gastrointestinal cancers, Sun et al. showed that PNI was a prognostic factor in 6 cancer types for OS (pooled OR 2.29, 95% CI 1.42-,3.71) including HCC (pooled OR 1.55, 95% CI: 1.06 -2.26), and gastric (pooled OR 2.26, 95% CI: 1.63 -3.13), esophageal (pooled OR 1.80, 95% CI:1.16 -2.80), pancreatic (pooled OR 1.57, 95% CI:1.20- 2.05), colorectal (pooled OR 1.78, 95% CI:1.45-2.19) (31). Therefore, our study is the first study investigating the role of PNI in EC. According to the results of the only study that investigated the role of albumin in EC, an association between albumin deficiency and advanced FIGO stage, histological grade, and age was identified, and albumin was found to be an independent prognostic factor for PFS in multivariate analyses (32). Our study also confirmed the results of these studies. As an independent prognostic factor for both OS and PFS, PNI is strongly correlated with many worse clinicopathologic characteristics including poor ECOG performance score, advanced FIGO stage, MM, CSI, LVSI, and LNI. We also found that the inflammatory marker most associated with clinicopathologic characteristics is PNI. These results show that the combination of nutritional and inflammatory conditions has a prognostic significance in EC and indicate the necessity of confirmation of these results.

Although our study revealed new data, it has some limitations, including its retrospective design, relatively low number of patients and shorter median follow-up period. Because of these further large, prospective, and randomized controlled multicenter studies will be important to validate our findings.

Conclusion

SIR is also a predictive factor for survival in EC as in other types of cancer. In our study, it is shown that as newly developed inflammatory markers SII and PNI, which are thought to be novel indicators of SIR had prognostic significance as well as well-known markers (NLR, PLR). SII and PNI are independent prognostic factors for both OS and PFS and associated with many clinicopathological features.

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Conceptualization: Cem Mirili, Methodology: Mehmet Bilici; Formal analysis and investigation: Cem Mirili; Writing - original draft preparation: Cem Mirili; Writing - review and editing: Mehmet Bilici; Supervision: Mehmet Bilici.

Ethical issues: Author declare, originality and ethical approval of research. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

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Retrospective analysis of clinical, pathological characteristics and prognosis of the patients with endometrial stromal sarcomas (ESS); the comparison of Low Grade-ESS and High Grade-ESS

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Abstract

Objective: Endometrial stromal sarcoma (ESS) is a rare mesenchymal tumor of the uterus.Literature has limited data about the ESS. The aim of the present study was to contribute to literature by reporting the histo-pathological findings, clinical characteristics of ESS patients and the data about the accuracy of preoperative diagnosis and prognosis.

Material and Methods: A total of 33 patients who were diagnosed and followed up with ESS at Department of Gynecology and Obstetrics of Bursa Uludağ University between 2007 and 2017 were retrospectively analyzed with regard to clinical and pathologic characteristics, surgical procedures they underwent and survival.

Results: Mean age of the patients was 49.5 years and 60.2 years for low grade ESS (LG-ESS) and high grade ESS (HG-ESS) (p=0,01). Post-menopausal hemorrhage was the most common complaint on admission. Correct histological diagnosis was made in only 72.7% of the patients from whom pre-operative endometrial biopsy was obtained. Twelve out of 16 cases (75%) were in Stage 1. While all patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH+BSO), 14 underwent pelvic and para-aortic lymphadenectomy for surgical staging. Lymph node involvement was detected in no patients who underwent lymphadenectomy. The patients with LG-ESS were found to have a good prognosis however the ones with HG-ESS had a high mortality rate even in the early stages (mean survival of 10 months).

Conclusion: High grade ESS cases show different clinical characteristics and prognosis than LG-HSS. Diagnostic accuracy of endometrial sampling is much lower when compared to epithelial uterine malignancies. Metastasis of pelvic-paraaortic lymph nodes of which removal is reported which not to contribute to survival is rare.

Key words: Endometrial stromal sarcoma, diagnosis, lymph node dissection, prognosis

Introduction

Endometrial stromal sarcomas (ESS) constitute <1% of uterine malignancies and <10% of uterine sarcomas (1) and the second most common uterine mesenchymal neoplasia following leiomyosarcoma (2-4). Endometrial stromal sarcomas were revised and classified again by World Health Organization (WHO) in the 2014. While vascular and myometrial invasion of LG- ESS is typically composed of uniform stromal cells and shows mild nuclear atypia and few mitotic features, HG-ESS shows higher nuclear atypia, pleomorphism, mitosis and widespread invasion (5).

While LG-HSSs usually have a good prognosis, HG-ESSs have bad progress and shows recurrence and results in death (1,5,6,7,8,9). Although 80% of ESSs is limited in the uterus during surgery, Stage 1 HG-ESSs show an aggressive course. High grade ESSs frequently recur before completing one year (10).

Adjuvant radiotherapy or chemotherapy was not shown to have a benefit on survival in HG-ESSs (11).

Although elevated serum lactate dehydrogenase (LDH) and CA-125 values can be used for pre-operative diagnosis, their value in preoperative diagnosis is controversial (12).

It is important to perform additional radiologic examinations for distant metastases and thereby avoiding from useless aggressive primary surgery for uterine sarcomas which tend to hematogenous spread besides making an accurate pre-operative diagnosis, intra-operative staging and more careful evaluation of extra-uterine tissues.

While ESSs show a heterogenous mass image on ultra-sonography, low resistance index values on color Doppler examination, they yield an image with high signal density

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on T1-weighted magnetic resonance images due to intra-tumoral hemorrhage and coagulation necrosis (13,14). While pathological examination of endometrial aspiration or dilation-curettage material has a high accuracy rate in uterine malignancies, it is not such efficient in sarcomatous histology (15,16,17).

Limited literature data about endometrial stromal sarcomas makes developing an optimal treatment method difficult. Unnecessary or insufficient treatments could be prevented with accumulating data about these tumors and the most appropriate approach algorithms could be created. In the present study, we retrospectively analyzed the cases with endometrial stromal sarcoma in our hospital and investigated clinical-pathological findings, surgical methods and survival and aimed to contribute to literature.

Method

Clinical-pathological findings, previous surgical procedures and survival of the patients who were diagnosed with ESS according to pathological examination at Department of Gynecology and Obstetrics between 2007 and 2017 were retrospectively analyzed. Data of 22 patients with LG-ESS and 11 patients with HG-ESS who underwent operation in our hospital could be reached.

Surgical staging was done based on FIGO/TNM 2017 guideline. All patients had undergone TAH+BSO. The addition of the procedures like intra-abdominal wash, infra-colic omentectomy, pelvic and para-aortic lymphadenectomy was defined as surgical staging.

Statistical Analysis

Data distribution was evaluated with Kolmogorov-Smirnov test. Inter-group comparisons were done by using Mann-Whitney U test and independent samples t test. Analyses were done with SPSS 22.0 program and a p level of <0.05 was accepted as statistically significant.

Results

Age range of the patients was 33 and 85 years. While mean age of the patients with LG-ESS was 49.5 years, it was 60.2 for HG-ESS (p=0.01). Post-menopausal hemorrhage was the most common complaint (36.8%) followed by the presence of an incidental mass lesion detected with radiologic or pelvic examination (26.3%) and pelvic pain (21%). Pathological examination was reported as benign endometrial pathology in 4 out of 22 patients who underwent pre-operative endometrial sampling, high grade malignant tumor in 2 however the main histological type was not reported. Ratio of pre-operative diagnostic accuracy was found to be 72.7% in our study.

Serum LDH values were known pre-operatively in 12 patients and mean values were 175.4 U/L and 200.3 U/L for LG-ESS and HG-ESS, respectively (p=0.078). CA-125 values were found to be elevated in only 2 out of 15 patients whose values could be reached. While estrogen receptor (ER) was found to be positive in 11 and progesterone receptor (PR) was found to be positive in 9 out of 12 LG-ESS cases whose ER, PR status could be known, estrogen and progesterone receptors were positive in only 2 patients out of 5 with HG-ESS whose receptor status was known. While only TAH+BSO was applied in only 17 out of 33 cases, complete surgical staging was done in 16 (48.4%). Of them, 14 had undergone lymphadenectomy and pelvic or para-aortic lymph node involvement was detected in none of them. Omental involvement was detected in 3 patients who were accepted to be in Stage 3 (Table 1). Post-operative follow-up records could be reached in 11 patients (4 with HG-ESS and 7 with LG-ESS). Three out of 4 patients with HG-ESS had died and mean survival was 10 months. Omental involvement (Stage 3A) was present in 1 of 7 LG-ESS cases and this patient was lost due to bone marrow metastasis at 30th month of follow up. Remaining patients were surviving healthily (36-140 months) (Table 2).

Table 1. Distribution of endometrial sarcomas according to the stages

	Stage 1	Stage 2	Stage 3*	Stage 4
L-ESS	6	-	2	-
H-ESS	6	1	1	-

*:Omental involvement. L-ESS: Low grade endometrial stromal sarcoma, H-ESS: High grade endometrial stromal sarcoma.

Table 2. Clinical data and survival data of the patients whose records could be reached

	Age	Ess	Surgical staging	Stage	Recurrence (months)	Location of recurrence	Survival
1	80	H-ess	+	1b	-	-	44 months healthy
2	62	H-ess	+	1b	+(3. month)	Pelvis	Ex(4.month)
3	66	H-ess	-	-	+(2. month)	Abdomen	Ex(5. Month)
4	61	H-ess	+	1b	+(9. month)	Liver	Ex(22. Month)
5	51	L-ess	-	-	-	-	36. Month healthy
6	56	L-ess	-	-	-	-	40. Month healthy
7	70	L-ess	-	-	-	-	76. Month healthy
8	48	L-ess	-	-	-	-	127. Month healthy
9	45	L-ess	-	-	-	-	123. Month healthy
10	33	L-ess	+	3a	+(28. month)	Bone Marrow	Ex(30. Month)
11	45	L-ess	-	-	-	-	140. Month surviving

L-ESS: Low grade endometrial stromal sarcoma, H-ESS: High grade endometrial stromal sarcoma

Discussion

Endometrial stromal sarcomas are rare uterine malignancies and therefore sufficient literature data and a universal treatment plan are not available.

While Abeler and Nagai reported that the mean age for ESSs was 50.7 and 60.3 years, respectively, it was found to be 53.1 years in our study (3,18). Mean age of LG-ESSs and HG-ESSs was found to be statistically significant, as in our study.

Endometrial stromal sarcomas may be misdiagnosed as leiomyoma or benign uterine pathology pre-operatively (19). Atypical vaginal hemorrhage, metrorrhagia, palpable masses or uterine enlargement are the most common complaints. Guintoli reported abnormal vaginal hemorrhage as the most common complaint on admission (56%) (20). Post-menopausal hemorrhage was the most common (36.8%) complaint also in our study. However these symptoms are non-specific and not lead to differential diagnosis.

Serum CA-125 and LDH values were reported to be the markers which could be used for pre-operative diagnosis of sarcomas (12, 21). While Ning Li detected elevated CA-125 values in 53.8% of the patients (22), CA-125 elevation (>35 U/L) was detected in only 2 patients (13.3%) in our study. Not serum CA-125 values but LDH values were reported to be able to be used for discriminating sarcoma and benign lesions (18).

Lymph node positivity was reported as 10.3% and 18% in LG-ESS and HG-ESS, respectively (1, 8). However Seagle reported that survival was similar between the patients who did not undergo lymphadenectomy and the ones who were detected to have lymph node positivity (23). Today, Gynecologic Cancer Inter-Group does not recommend lymphadenectomy for ESS (10, 23). Lymph node involvement was detected in no patients who underwent lymphadenectomy in our study, supporting the literature.

While ratio of accurate histological diagnosis was reported as 64% for pre-operative endometrial sampling by Bansal, this ratio was 72.7% in our study (17).

Gynecologic Cancer Group trial showed that adjuvant radiotherapy does not prolong overall survival and disease-free survival in Stage 1-2 HG-ESS (24, 25). However hormone receptor positive patients with HG-ESS could be suggested to benefit from hormone therapy (26).

Conclusion

High grade ESSs show different clinical features and prognosis from LG-HSS. Our study showed that HG-ESSs are seen in older ages, progress more aggressively and lead to a poorer survival. Detecting involvement in none of the patients who were performed lymph node dissection leads to suspicion about performing lymphadenectomy in these cases. Serum markers like LDH and CA-125 were seen not to be helpful for discriminating LG-ESS and HG-ESS. Although the rate of an accurate pre-operative histopathological diagnosis is low when compared to epithelial endometrial carcinomas, the accuracy rate of 72.2% found in our study indicates that pre-operative endometrial biopsy has an important place also in endometrial sarcomas. The most appropriate treatment methods could be developed through a more comprehensive perspective together with the accumulating data regarding endometrial sarcomas and thereby unnecessary or insufficient treatments could be avoided and maximum comfort could be provided.

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Significance of inflammation markers in complete blood count in patients with fibromyalgia

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Abstract

Objective: Fibromyalgia is a chronic pain disorder mostly seen in women, it mainly characterized by diffuse body pain accompanied by chronic fatigue and depression-like mood disorders. Its etiology still remains unknown but in some studies, fibromyalgia has been reported to be an inflammatory disease several cytokines shown to be responsible for the possible inflammatory basis of the disease. No laboratory marker is currently available to diagnose the disease. We aimed to investigate the diagnostic significance of inflammation markers in fibromyalgia, including platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte (MLR) ratio, and mean platelet volume (MPV).

Material and Methods: This retrospective and case-control study included 188 patients who were followed up and treated for fibromyalgia in physical therapy and rehabilitation outpatient clinic from 2017 through 2019 and 64 age-matched healthy controls. The PLR, NLR, MLR, MPV and vitamin D were calculated from the results of complete blood count test. The differences between the two groups were examined.

Results: The mean age, hemoglobin levels, and erythrocyte sedimentation rates were not different between the groups. In fibromyalgia group, the values of PLR ($p = 0.031$), NLR ($p = 0.044$), MLR ($p = 0.023$), and MPV ($p = 0.013$) were higher than those in control group, whereas vitamin D levels were significantly lower ($p = 0.021$). In multivariate regression analysis, PLR, NLR and MLR were not found to be independent predictors ($p > 0.05$).

Conclusion: The findings of this study reveal that NLR, MLR, PLR, and MPV are not independent markers for the diagnosis of fibromyalgia, suggesting that fibromyalgia does not appear to be an inflammatory disease.

Keywords: fibromyalgia, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, monocyte to lymphocyte ratio, inflammation marker.

Introduction

Fibromyalgia is a chronic pain condition characterized by a constellation of symptoms, including pain, tenderness, fatigue, anxiety, sleep dysfunction, cognitive impairment, and mood disturbances. Although the etiology of fibromyalgia remains unclear, changes in sleep stages, hormonal and biochemical alterations, mood disorders, and central nervous system dysfunction have been suggested to have a role in the etiologic process (1,2) .

In some studies, fibromyalgia has been reported to be an inflammatory disease, with several cytokines shown to be responsible for the possible inflammatory basis of the disease, such as IL-8 and tumor necrosis factor (TNF) (3-5). Mean platelet volume (MPV), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) are the markers that can be simply detected by complete blood count (CBC) and are reported to increase in the presence of inflammation.

There are studies indicating that PLR and MPV are higher in rheumatoid arthritis patients compared to healthy subjects and their levels are directly proportional to disease activity. Similar findings are also available for other inflammatory diseases (6-9). We aimed to investigate the PLR, NLR, MLR, and MPV levels in fibromyalgia patients in order to determine whether inflammation plays a role in fibromyalgia

Material and Method

Study population: From 2017 through 2019, a total of 188 patients who were admitted to physical therapy and rehabilitation outpatient clinic and diagnosed with fibromyalgia based on the American School of Rheumatology (ACR) 2010 criteria and 64 age-matched healthy subjects were included in the study. Patients with follow-up fibromyalgia and newly diagnosed fibromyalgia were included.

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People without any known disease was included to control group. Exclusion criteria were defined as follows; pregnancy, any cancer history, the presence of leukocytosis and active infection.

Data collection: The patient demographic and laboratory characteristics including age, gender, CBC parameters, erythrocyte sedimentation rate (ESR), and serum 25OH vitamin-D levels were recorded after a retrospective scan of the written archive files or hospital digital automation recording system. The values of the patients at the time of admission to the physical therapy and rehabilitation outpatient clinic were recorded. The PLR, NLR, and MLR were calculated by dividing the platelet count, the neutrophil count, and the monocyte count by the lymphocyte count, respectively. The values (PLR, NLR, MLR, MPV, Vitamin D) were compared between the two groups in order to examine whether to have a significant relationship. The study was conducted in accordance with the Declaration of Helsinki.

Statistical analysis: All statistical analyses were performed using SPSS Statistics version 22.0. Shapiro-Wilk test was used to determine whether or not the data were normally distributed. Student-t test was used for normally distributed data and Mann-Whitney-U test was used for non-normally distributed data. Pearson and Spearman tests were used for correlation analysis. Logistic regression analysis was used to determine the independent predictors. $p < 0.05$ was considered as statistically significant.

Results

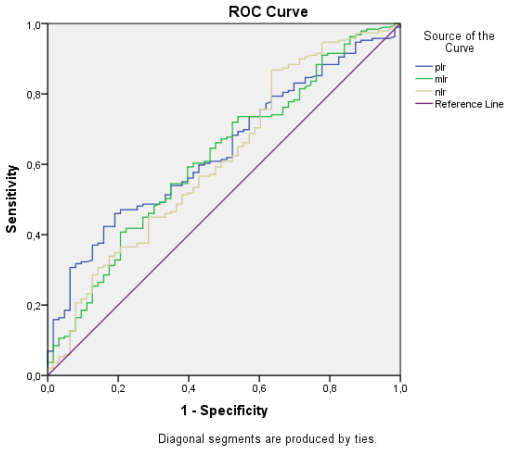
A total of 252 subjects, including 188 patients with fibromyalgia and 64 age-matched healthy controls, were analyzed. The mean age was 48.4 ± 9.3 years for patients and 45.8 ± 10.9 years for the control group, with no significant difference between the groups ($p = 0.066$). In the fibromyalgia group, MPV values were higher ($p = 0.013$) and vitamin D levels were significantly lower than those in the control group ($p = 0.021$). PLR, MLR, and NLR were significantly higher in fibromyalgia group compared to healthy subjects. Hemoglobin and ESR levels were similar between the two groups ($p = 0.352$ and $p = 0.124$, respectively).

The comparisons between the groups are shown in Table 1. When ROC analysis was performed for PLR, MLR, and NLR, the area under the curve was 0.642, 0.614, and 0.623, respectively. According to ROC analysis, the threshold values were 120.3 for PLR, 0.16 for MLR, and 1.76 for NLR (Graphic 1). Multivariate logistic regression analysis including 'age' and levels of 'hemoglobin' (Hb<12 gr/dl - Hb⩾12 gr/dl),, 'vitamin D' (<30 IU - ⩾30IU),, and 'ESR' (<20 mm Hg - ⩾ 20 mm Hg) which might affect CBC results revealed that, PLR, MLR, and NLR were not independent markers for the diagnosis of fibromyalgia ($p = 0.074$, $p = 0.091$, and $p = 0.234$, respectively).

Table 1. Comparison of Hb, MPV, ESR, platelet counts, vitamin-D levels, PLR, NLR, and MLR between fibromyalgia patients versus healthy controls (N=252).

Variables	Fibromyalgia group (n=188)	Control group (n=64)	P
Hb, (gr/dL) mean ± SS	12.76 ± 1.27	12.93 ± 1.28	0.352*
MPV, mean ± SS	10.51 ± 1.30	10.09 ± 1.14	**0.013***
Platelet (x10^3/µL), mean ± SS	287.79 ± 67.53	276.16 ± 58.88	0.224*
ESR, (mm Hg) mean ± SS	20.21 ± 10.24	17.41 ± 7.59	0.124*
Vitamin D (IU), mean ± SS	13.95 ± 9.08	20.14 ± 10.34	**0.021***
PLR, median (range)	133.01 (86 - 354.23)	117.61 (55.92 - 218.95)	**0.031¶**
MLR, median, (range)	0.19 (0.02 - 0.95)	0.16 (0.01 - 0.49)	**0.023¶**
NLR, median, (range)	1.86 (0.13 - 19.83)	1.27 (0.59 - 6.11)	**0.044¶**

PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; ESR, erythrocyte sedimentation rate; Hb, Hemoglobin; MPV, mean platelet volume. ¶Data reported as median (min-max),*Data reported as mean ± standart deviation



Graphic 1. ROC curve for PLR, NLR, and MLR (the values of area under the curve; PLR: 0.642, NLR: 0.614, MLR: 0.623)

Discussion

According to the results of this study, although the values of NLR, PLR, MLR, and MPV were significantly higher in fibromyalgia patients than those in healthy controls, regression analysis revealed that these parameters were not independent biomarkers for predicting the diagnosis of fibromyalgia.

These above-mentioned markers can be easily detected by simple CBC test and are used to determine the inflammation (10, 11). In addition, they are very helpful in determining both activity and prognosis of most rheumatic and proliferative diseases; however, such relation was not found in our study. In fact, the role of inflammation in fibromyalgia is highly controversial and the findings of our study therefore support the absence of inflammatory pattern in fibromyalgia (12). In another study including smaller number of patients and controls than those in our study, no significant differences were shown between the groups in terms of PLR, NLR, and MPV levels (13). In a study analyzing the MPV levels, it was shown that MPV did not have an independent predictive significance for the diagnosis of fibromyalgia (14). In another study with a similar hypothesis, PLR was found to be significantly higher in fibromyalgia patients compared to healthy subjects, but no significant difference was found between the two groups in terms of NLR, showing different results from our findings; however, the authors included smaller sample size than that in our study and did not perform a regression analysis (15). In another study examining the NLR and MPV levels in fibromyalgia, these values were found to be significantly higher in patients with fibromyalgia than those in healthy subjects; however, whether they were independent markers for the diagnosis of fibromyalgia were not examined by a regression analysis (16). By contrast, in another study, which found NLR, but not PLR and MLR, to be significantly higher in fibromyalgia patients than healthy subjects, reported that MLR, NLR, and MLR were the independent determinants for the diagnosis of fibromyalgia in regression analysis performed for fibromyalgia impact questionnaire, suggesting these markers as predictive in determining the severity of the disease. However, these factors (i.e., age, hemoglobin, vitamin D, ESR) that could affect inflammation markers were not differentiated by regression analysis (17). Moreover, it is also possible that the increase in inflammation makers by pain severity may be associated with another inflammatory event that may increase the pain at that time.

Because of the retrospective nature of our study, the fibromyalgia impact questionnaire and its relation with inflammation markers could not be evaluated, but the above-mentioned factors such as age, hemoglobin, vitamin D, and ESR that could affect inflammation markers were analyzed in cox regression analysis.

In patients with rheumatoid arthritis, which is an inflammatory disease, these values were found to be significantly higher than those in the control group, while the results in patients with osteoarthritis are conflicting (18-21). According to the findings of some studies we can say that Chronic low-grade systemic inflammation may also underlie the pathophysiology in chronic generalized pain conditions, such as fibromyalgia (22, 23). Aside from its retrospective nature, not recording the data regarding comorbidities and drug use were the other limitations in our study. Especially vitamin D treatment may affect the blood parameters but unfourtunately vitamin D supplementation was not recorded. By adding these missing data, it will be useful to conduct further prospective studies with larger study groups.

Conclusion

In conclusion, the presence or absence of inflammation in the etiopathogenesis of fibromyalgia still remains controversial and unclear. In our study, although the indirect inflammation parameters in CBC were found to be higher in fibromyalgia patients, none of them could be shown to have an independent association with fibromyalgia

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Ethical issues: Author declare, originality and ethical approval of research. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

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Peripapillary Microvasculature in Branch Retinal Vein Occlusion (BRVO) Treated With Anti-VEGF: An OCTA Study

Emine Çiloğlu[1]*

Abstract

Objective: Aim of this study is to evaluate the changes in peripapillary vessel density (VD) and peripapillary nerve fiber layer thickness (PPRNFL) after intravitreal anti-VEGF injections in patients with Branch Retinal Vein Occlusion (BRVO) with macular edema.

Material and Methods: Sixty eyes of 30 patients with unilateral macular edema due to BRVO who underwent 3 dose loading anti-VEGF treatments were included in the study. The peripapillary capillary vessel density (RPCVD) and PPRNFL were evaluated with optical coherence tomography angiography (OCTA). The measurements were done before and at least one month after a loading dose of anti-VEGF. The measurements of BRVO eyes before treatment were compared with the healthy fellow eyes and the values measured after treatment.

Results: There was a statistical difference between the pre-injection and post-injection periods at the inside disc and peripapillary VD parameters ($p<0.001$, $p=0.01$, respectively). Compared with the fellow eyes of the patients, the vessel density in the eyes with BRVO was significantly lower in the whole image, inside the disc, and peripapillary area. ($p=0.015$, $p=0.020$, $p=0.027$, respectively). There was no significant change in PPRNFL values before and after injections. When eyes with BRVO were compared with healthy eyes, eyes with BRVO showed reduced PPRNFL values initially but that was not statistically significant.

Conclusion: Inside disc and peripapillary VD values were increased after injection. Even though anti-VEGF agents may contribute to neurodegeneration, we think that this increase in perfusion prevents possible neurodegeneration.

Key Words: branch retinal vein occlusion, optical coherence tomography angiography, peripapillary retinal nerve fiber layer, peripapillary capillary vessel density

Introduction

Branch retinal vein occlusion (BRVO) is a relatively common retinal vascular occlusive disease that can cause loss of vision in elderly individuals. The most common cause of visual impairment in eyes with BRVO is macular edema. Laser photocoagulation, intravitreal vascular endothelial growth factor inhibitors (anti-VEGF) or steroid injections are used to treat macular edema. Repeated anti-VEGF injections could be required due to recurrent macular edema.

Recently, optical coherence tomography angiography (OCTA) has begun to be used as a new and noninvasive method for high-resolution visualization of the microvascular structure of the retina and choroid. It allows the quantitative evaluation of perfusion in the optic nerve head, peripapillary, and macular areas. (1)

In studies with OCTA, changes in microcirculation have been shown to be associated with the development of macular edema, and it was shown that parafoveal vessel density in both superficial and deep capillary plexus had been reduced. Also, it was shown that retinal nonperfused areas were decreased with anti-VEGF treatment and retinal blood flow, especially in deep plexus was increased. (2-4)

Peripapillary vessel density (VD) is an in-depth study of glaucoma and diabetic retinopathy. (5) Numerous studies have shown a decrease in vessel density quantitatively after glaucomatous damage. (6,7)

This study aimed to evaluate the changes in peripapillary VD and PPRNFL thickness after intravitreal anti-VEGF injections in patients with BRVO with macular edema.

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Material and Method

Our study is a retrospective study, and records of patients who had received three loading doses of anti-VEGF therapy in three months for macular edema due to BRVO were evaluated. Ethics committee approval was obtained for the study and all procedures were performed in accordance with the Helsinki Declaration.

All patients underwent a complete ophthalmologic examination. The best corrected visual acuity (Snellen), intraocular pressure measurement with Goldmann applanation, anterior segment and fundus evaluation by biomicroscopic examination and OCTA were performed. The inclusion criteria of the patients were; the presence of macular edema due to BRVO, over 40 years of age, no previous injection or laser application. Exclusion criteria were; the presence of diabetes mellitus, age-related macular degeneration, vitreous hemorrhage, high myopia (>-6 diopters), glaucoma, uveitis, ocular trauma, poor quality of OCTA measurements, significant media opacities and lack of control examination.

OCTA (Optovue RTVue XR Avanti; Optovue Inc., Fremont, California) was used for assessment of macular retinal vascularization. AngioVue uses the split-spectrum amplitude-decorrelation angiography (SS-ADA) algorithm to detect erythrocyte movements. Advantage of this software, it makes it possible to visualize the vascularization of choroid and retina noninvasively via motion contrast.

The 4.5 x 4.5-mm scanning area of peripapillary images were centered on the optic disc. Activation of the eye-tracking function was done. Motion correction to minimize motion artifacts arising from micro saccades and fixation changes was applied. The peripapillary capillary vessel density (RPCVD) was measured at a 1.00-mm-wide elliptical annulus extending outward from the optic disc boundary in the radial peripapillary capillary (RPC) zone. The RPC layer extends from the internal limiting membrane to the nerve fiber layer (NFL).

The capillary VD percentages were automatically calculated as the proportion of the area with flowing blood vessels, defined by pixels with decorrelation values above the SS-ADA threshold level. The software version we used provides separate information on peripapillary capillary VD (only information arriving from the RPC layer capillaries is analyzed). For analyses, VD is automatically calculated for the whole image, inside-disc area, and the peripapillary area, respectively.

The PPRNFL thickness was also measured using the AngioVue (Optovue, Inc.). The PPRNFL thickness was assessed at a 3.45-mm-diameter circle around the optic disc in the ONH mode.(Figure 1). Image quality was assessed for all OCTA scans. Poor quality images were defined as scans with quality index <6 or images with residual motion artifacts, segmentation errors were excluded from the analysis. Poor-quality OCTA images were characterized by doubling of vessel images and artifact lines in the target area.

The treatment regimen started with three monthly injections. After this loading phase, the injections were continued in the presence of macular edema. The measurements were done before and at least one month after a loading dose of anti-VEGF. The measurements of BRVO eyes before treatment were compared with the healthy fellow eyes and the values measured after treatment. Statistical analysis of the study was performed using the SPSS 20.0 (IBM Inc., Chicago, IL, USA) program. The Kolmogorov-Smirnov test was used to assess the appropriateness of calculations to normal distribution. In parametric comparisons, the Student t-test was used for two independent groups. Mann-Whitney U test was used for variables with no normal distribution. A 5% level of significance was adopted; therefore, results with a p-value <0.05 were considered significant.

Results

Sixty eyes of 30 patients with unilateral macular edema due to BRVO who underwent 3 dose loading anti-VEGF treatments were included in the study. The mean age of the patients was 58.12 ± 11.05 years. Mean visual acuity (Snellen) was 0.2 at baseline, 0.5 after first injection, and 0.7 after 3 doses of anti-VEGF treatment. (P <0.001)

In the whole image analysis, RPCVD (%) did not differ before and after injection. There was a statistical difference between the pre-injection and post-injection periods at the inside disc and peripapillary VD parameters (p<0.001, p=0.01, respectively). Compared with the fellow eyes of the patients, the vessel density in the eyes with BRVO was significantly lower in the whole image image, inside disc, and peripapillary area. (p=0.015, p=0.020, p=0.027, respectively)

There was no significant change in PPRNFL values before and after injections. When eyes with BRVO were compared with healthy eyes, eyes with BRVO showed reduced PPRNFL values initially but that was not statistically significant.

Table 1: Comparison of OCTA parameters between the BRVO eyes and the fellow eyes

	BRVO	Fellow eyes	P value
RPCVD (%)			
Whole image	48.8±3.15	54.8±2.39	0.015*
Inside disc	47.3±2.24	54.9±3.54	0.020*
Peripapillary	49.2±2.14	53.8±2.58	0.027*
PPRNFL (µm)			
Mean	108.54±8.11	114.36±7.80	0.056
Superior	109.55±9.41	114.72±8.38	0.060
Inferior	107.75±9.22	113.53±8.24	0.055

RPCVD: radial peripapillary capillary vessel density, PPRNFL: Peripapillary retinal nerve fiber layer

Table 2: The OCTA parameters in patients with BRVO after treatment

BRVO	Before treatment	After Treatment	P value
RPCVD (%)			
Whole image	48.8±3.15	49.5±2.82	0.082
Inside disc	47.3±2.24	50.4±2.43	<0.001*
Peripapillary	49.2±2.14	52.8±2.26	0.01*
PPRNFL (µm)			
Mean	108.54±8.11	107.15±8.12	0.850
Superior	109.55±9.41	109.24±8.21	0.650
Inferior	107.75±9.22	106.45±7.86	0.760

RPCVD: radial peripapillary capillary vessel density, PPRNFL: Peripapillary retinal nerve fiber layer

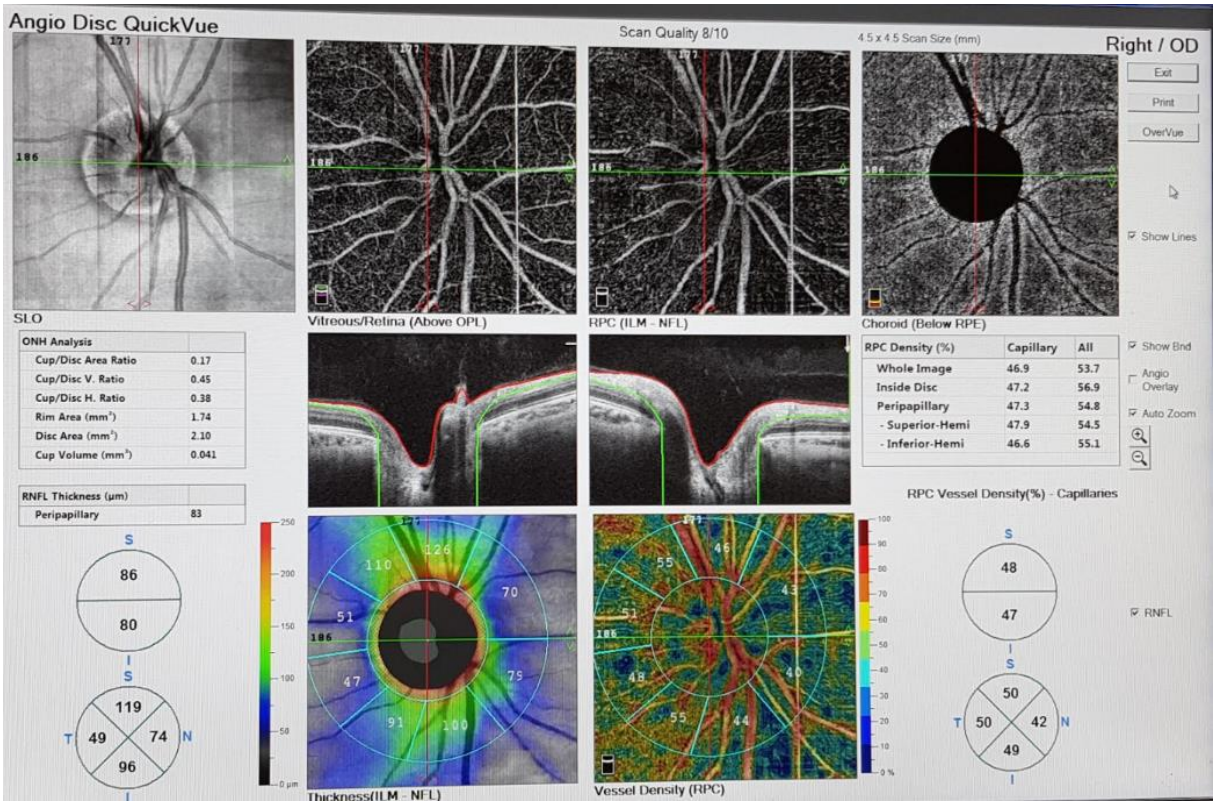

Figure 1: The OCTA image. At the left side peripapillary nerve fiber layer thickness analysis, at the right side the peripapillar capillary vessel density analysis.

Discussion

In this study, we studied peripapillary microvascular changes in patients with BRVO who undergone intravitreal anti-VEGF injections due to macular edema.

There are several studies evaluating OCTA features in RVO. (8,9) FAZ enlargement, capillary dropouts, reduction of VD in the superficial (SCP) and deep capillary plexus (DCP) have been reported. Samara et al. investigated the vascular density of the SCP and DCP in the eyes with BRVO and reported a decrease in vascular densities both in the SCP and DCP with the correlation between FAZ, VD and visual acuity. (10) OCTA may be useful for evaluating microvascular changes before an occlusive event, Adhi et al. showed how the eyes of RVO patients present decreased vascular perfusion of DCP compared to healthy controls. (11)

In this study, when compared with the unaffected eyes of the patients before treatment, it was found that the PPRNFL thickness was significantly thinner, and the whole image, inside the disc and peripapillary VD was decreased in BRVO eyes than the other fellow eyes.

Macular edema is the most common cause of decreased visual acuity in patients with BRVO. Macular edema results from the release of substances that enhance vascular permeability, such as VEGF produced in the retina, due to the disruption of the tight junctions between endothelial cells and adhesions between the vitreous and retina and the disruption of the blood-retinal barrier. (12) Recently, anti-VEGF drugs have been used frequently in the treatment of macular edema due to BRVO.

It was demonstrated that a slight decrease in average macular vessel density, despite the resolution of macular edema, in patients with RVO with macular edema treated with intravitreal anti-VEGF or dexamethasone injections. (13,14) In this study, we evaluated the vessel density of inside disc and peripapillary region in BRVO patients. We found a significant difference in the vessel density of inside disc and peripapillary region before and after treatment in BRVO eyes.

Campochiaro et al. showed that an aggressive blocking of VEGF might reduce but not prevent the progression of retinal nonperfusion(4). Monthly anti-VEGF injections may potentially improve outcomes due to a secondary reduction in the progression of ischemia demonstrated by Mir et al (15).

It is clear that VEGF has not only angiogenic effects but also direct effects on neuronal cells as neuroprotective. Reduced VEGF levels are thought to play a role in neurodegenerative diseases (16).

Many studies have evaluated RNFL thickness after intravitreal ranibizumab injections. Some of these studies reported a decrease in RNFL thickness, while others showed no detectable changes (17-19).

Shin et al. evaluated changes in peripapillary microvascular parameters in the other eyes of patients with unilateral BRVO and reported that peripapillary VD and perfusion density were decreased compared to the control group and RNFL thinning were significant in the average, inferior and temporal quadrants. (20) In our study, peripapillary RNFL was thinner in BRVO eyes than fellow healthy eyes. There was no significant difference in the RNFL values between before and after intravitreal injections. Intravitreal injections of ranibizumab, bevacizumab, or aflibercept reduce only one VEGF subtype, and the other VEGF isoforms may protect the RNFL. Furthermore, the effect of the anti-VEGF monoclonal antibodies is transient, requiring monthly re-injections.

Moghimi et al. reported that the VD of macular and optic nerve head using OCTA is associated with the rate of RNFL loss and should be considered when evaluating the risk for glaucoma progression. (21) Blood flow to the RNFL is supplied by the microcirculation from the retinal RPCs. RPCs are difficult to observe with conventional FFA. OCTA helps to evaluate optic nerve head perfusion.

Conclusion

In BRVO patients, when we compared peripapillary RNFL with the unaffected eye, in BRVO eyes the RNFL were thinner. We did not find any difference between RNFL values before and after intravitreal injection. Inside disc and peripapillary VD values were increased after injection. Even though anti-VEGF agents may contribute to neurodegeneration, we think that this increase in perfusion prevents possible neurodegeneration.

Conflict of Interest: No potential conflict of interest was reported by the author.

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Author's contiributions: EÇ; Design of research, data collection and Patient examinations, **EÇ;** preparation of article and revisions

Ethical issues: Author declare, originality and ethical approval of research. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

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Protective effects of Dehydroepiandrosterone (DHEA) vs Caffeic Acid Phenethyl Ester (CAPE) against Ischemia-Reperfusion injury in Rat Ovaries

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Abstract

Objective: In this study, the effectiveness of caffeic acid phenethyl ester (CAPE) and Dehydroepiandrosterone (DHEA) in preventing ischemia reperfusion injury associated with ovarian torsion have been investigated.

Materials and Methods: Twenty four adult female Wistar Albino rats were randomly divided into four groups. Ovaries were not twisted, and only healthy ovarian tissues were removed from the rats in the first group, while ovaries were twisted for 3 hours in the other groups. The second group did not receive any medications before the ovaries were untwisted, while 20 micromole/kg of CAPE was applied on peritoneal surface to the third group, and 60 mg/kg of DHEA was administered intraperitoneally to the fourth group.

Results: The level of primordial follicles was higher in the third group compared to the second group after the torsion of the ovary ($p=0.017$). The mean level of primary follicles was higher in the first group compared to the number of follicles in the third and fourth groups after the torsion of the ovary ($p<0.001$). The median hemorrhage level was higher in the second group following ovarian torsion compared to that in the first group ($p=0.005$).

Conclusion: Agents that have been considered to reduce injury resulting from ischemia-reperfusion proved ineffective during the early stages in terms of the number of follicles in the ovaries; however, we believe that long-term studies may be more beneficial.

Keywords: Caffeic Acid Phenethyl Ester, Dehydroepiandrosterone, Ischemia-Reperfusion, Ovary, Rat

Introduction

Early detection and treatment is of paramount importance for the preservation of ovarian functions and the prevention of serious morbidities in ovarian torsion (1). There are reports indicating that this condition is more likely to occur in the pediatric population compared to adult women (2), which demonstrates how important the preservation of fertility is. Oxidative processes leading to injury in ovarian torsion and significant increases in oxidative markers in twisted ovaries have been demonstrated in various studies (3-5). To date, a number of antioxidant agents have been used to reduce oxidative injury and cell loss. However, none of these agents has been introduced into routine clinical practice.

Caffeic acid phenethyl ester (CAPE) is one of the most active compounds of honey bee product propolis and has proven beneficits in oxidative injury in various tissues. The effects of CAPE on the brain, kidney, testis, genital organs, ovary and various tissues have been investigated (6-11). Dehydroepiandrosterone (DHEA) has been widely used to increase ovarian reserves in infertile women. Previous studies reported encouraging outcomes with DHEA in terms of improved oocyte and embryo yields and live birth rates in women with diminished ovarian reserves (12-15). In this study, we aimed to analyze the effectiveness of CAPE and DHEA in preventing ovarian injury associated with ischemia-reperfusion and their protective effects on ovarian reserves and against follicle loss.

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Materials and methods

Ethics committee approval for this study was obtained from the animal testing laboratory (Protocol code: 103.2018.mar).

Animals used in the research: Female Wistar albino rats of the Norvegicus species were used in our study. The rats used in the study weighed from 200 to 250 grams. They aged between 10-12 weeks. 4-5 rats were placed in each cage. The rats received light for twelve hours. Rats were provided access to standard rodent pellet foods and tap water at an average room temperature of 21-23 degrees Celsius. Humidity was kept between 40 and 50 percent.

Groups: Group 1 (normal ovary group – Group N): no chemical agents were applied to this group. Decapitation was applied first, and laparotomy was performed afterwards. During laparotomy, the ovaries were removed and fixed in 10% formaldehyde.

Group 2 (the twisted ovary group – Group T): The first laparotomy was performed after anesthesia. Ovarian tissue was found, and a 720-degree torsion procedure was performed. A hypoxia of 3 hours was achieved. The second laparotomy was done, and ovarian tissue detorsion was performed. A 6-hour reperfusion was achieved after detorsion. Decapitation was performed at the end of the second 6 hours. Ovarian tissues were excised by laparotomy.

Group 3 (CAPE group– Group C): The first laparotomy was performed after anesthesia. The left ovary was found, and torsion was performed with 720-degree rotation. Then, it was fixed to the lower abdominal wall. After fixation, the abdomen was closed and exposed to ischemia for 3 hours. At the end of this period, the abdomen was opened again, and detorsion was performed. After detorsion, 20 micromole/kg of CAPE (Sigma-Aldrich Chemie GmbH®, Saint Louis, USA) was applied to the ovarian surface (2). Then, the abdomen was closed again. Reperfusion was achieved for 6 hours, and decapitation was performed at the end of this period. Laparotomy was performed, and both ovaries were excised.

Group 4 (PRP group– Group P): The first laparotomy was performed after anesthesia. The left ovary was found, and torsion was performed with 720-degree rotation. Then, it was fixed to the lower abdominal wall. After fixation, the abdomen was closed and exposed to ischemia for 3 hours. At the end of this period, the abdomen was opened again, and detorsion was performed. The surgical wound was closed following the application of DHEA to the peritoneal surface at a dose of 60 mg/kg diluted in 0.1 ml of sesame oil. Reperfusion was achieved for 6 hours, and decapitation was performed at the end of this period. Laparotomy was performed, and both ovaries were excised.

Operations: In all procedures, latex powder-free gloves were used. Ketamine hydrochloride (10%) 80 mg / kg (Ketalar; Eczacıbaşı Warner Lambert, Istanbul, Turkey) and xylazine hydrochloride (2%) 15 mg / kg (Rompun, Bayer Health Care LCC, Kansas City, KS), were used for anesthesia. Surgical site cleaning was performed with 10% Povidone-iodine solution (Batticon's; Adeka Laboratories, Istanbul, Turkey). 5 cm median incision was used for laparotomy. The left ovary was twisted with blood vessels to achieve a torsion of 720 degrees (Figure 1). The sprained ovarian tissue was sutured to the abdomen with 5/0 silk sutures. After bleeding control, abdominal wall was closed with 2/0 polyglactin 910 sutures. Surgical procedures were completed before 15 minutes to prevent the drying effect of room air.

Histopathological examinations: All examinations were performed by the same pathologist blindly. Removed ovaries were put into 10% formalin. Paraffin blocks were prepared within 24 hours after treatment. Five micrometer tissue sections were taken, and follicle examinations were made in each ovarian tissue by taking 5 different sections. Tissues were stained with hematoxylin eosin and examined by light microscope (Olympus Clinical Microscope, Tokyo, Japan). Paraffin blocks were sectioned using a microtome blade (Leica, Nussloch, Germany).

Histopathological injury scores were evaluated as described by Celik et al. (2). Cellular degeneration, vascular congestion, edema, hemorrhage and inflammation were examined (Figure 1). The evaluations were graded from 0 to 4. Grade 0: normal findings were observed; no abnormal findings were detected. Grade 1: mild vascular congestion, mild edema, absence of hemorrhage or leukocyte infiltration. Grade 2: moderate vascular congestion, moderate edema, absence of hemorrhage or leukocyte infiltration. Grade 3: severe vascular occlusion, severe edema, minimal leukocyte infiltration and minimal hemorrhage. Grade 4: severe vascular occlusion, severe edema, leukocyte infiltration and hemorrhage.

To evaluate ovarian reserves, all follicles were examined as described by Parlakgumus et al. (16) Primordial, primary, secondary (pre-antral), tertiary (antral) and atretic follicles were counted. Primordial follicle is defined as an oocyte with epithelial cell layer in only one layer. Primary follicle is defined as a follicle surrounded by one or more layers of cuboidal granulosa cells. The secondary (pre-antral) follicle is defined as a follicle consisting of antrum follicles and zona pellucida surrounded by two or more cell layers. Tertiary follicles are defined as follicles with layers of antrum, stratum granulosum and surrounding cumulus oophorus. In atretic follicles, the basement that separates the oocyte from granulosa cells often thickens to become the glassy membrane. Fibrous material replaces the granulosa cells, and loss of cohesion may occur in granulosa cells (Figures 2-4).

Statistical analysis:

SSPS Version 15.0 was used for statistical analysis. Kolmogorov-Smirnov test and histogram examinations were used to evaluate the normality of distribution of variables. Mean ± standard deviation or median (interquartile range) values are used to present descriptive analyses. One-way ANOVA test was used to analyze numerical data showing normal distribution. Kruskal-Wallis test was used to analyze numerical data showing non-normal distribution. P value <0.05 was accepted as the statistical significance limit.

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Results

The mean level of primordial follicles in Group C was higher than that in Group T before the torsion of the ovary (p=0.002). The mean level of primary follicles in Group N before the torsion of the ovary was higher than those in groups C, D and T (p=0.002). The mean level of inflammatory cell infiltration in Group N was higher than those in groups C, D and T before the torsion of the ovary (p=0.003) (Table 1).

The mean level of primordial follicles in Group C was higher than that in Group T after the torsion of the ovary (p=0.002). The mean level of primary follicles in Group N was higher than those in groups C and D after the torsion of the ovary (p<0.001). The mean level of hemorrhage in Group T after the ovarian torsion was higher than that in Group N after the torsion of the ovary (p=0.005). The mean level of vascular congestion in Group N was lower than those in Groups T and C after the torsion of the ovary (p=0.007). The mean level of edema in Group N was lower than those in groups C, D and T after the torsion of the ovary (p=0.02) (Table 2). The histopathological appearances of follicles are seen in figures 2-4.

Table 1. Comparison of normal ovary examinations according to groups

		Groups				p
		C	D	T	N	
Primordial Follicle	**Mean**	20,3	11,5	5,7	14,2	0,002[a]
	SD	±5,6	±7,8	±3,9	±4,2	
	Minimum	14,0	4,0	1,0	8,0	
	Maximum	28,0	22,0	11,0	18,0	
Primary Follicle	**Mean**	6,5	8,7	7,5	15,2	0,002 [a]
	SD	±3,3	±2,8	±2,5	±5,0	
	Minimum	3,0	5,0	4,0	7,0	
	Maximum	12,0	12,0	10,0	21,0	
Secondary Follicle	**Mean**	7,7	10,8	7,7	7,2	0,248 [a]
	SD	±2,5	±4,9	±2,1	±3,4	
	Minimum	5,0	4,0	5,0	4,0	
	Maximum	12,0	18,0	10,0	12,0	
Tertiary Follicle	**Mean**	3,5	4,8	4,0	3,8	0,756 [a]
	SD	±1,5	±2,9	±2,7	±1,3	
	Minimum	2,0	1,0	1,0	2,0	
	Maximum	6,0	9,0	7,0	5,0	
Hemorrhage	**Median**	0,0	0,0	0,0	0,0	0,553 [b]
	Percentiles -25	0,0	0,0	0,0	0,0	
	Percentiles -75	0,0	0,0	0,0	0,0	
Vascular Congestion	**Median**	1,0	1,0	1,0	1,0	0,716 [b]
	Percentiles -25	1,0	1,0	1,0	1,0	
	Percentiles -75	2,0	2,0	2,0	1,0	
Cellular degeneration	**Median**	0,5	0,0	1,0	0,5	0,638 [b]
	Percentiles -25	0,0	0,0	0,0	0,0	
	Percentiles -75	1,0	0,0	1,0	1,0	
Inflammatory cell infiltration	**Median**	0,0	0,0	0,0	1,0	0,003 [b]
	Percentiles -25	0,0	0,0	0,0	0,0	
	Percentiles -75	0,0	0,0	0,0	1,0	
Edema	**Median**	0,0	1,0	0,0	0,0	0,282 [b]
	Percentiles -25	0,0	0,0	0,0	0,0	
	Percentiles -75	0,0	1,0	1,0	1,0	

SD: standard deviation, [a]One-way ANOVA test, [b]Kruskal-Wallis test

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Table 2. Comparison of ovarian examinations after torsion according to groups

		Groups				p
		C	D	T	N	
Primordial Follicle	Mean	15,5	8,0	5,5	14,2	0,017[a]
	SD	±7,3	±6,5	±4,0	±4,2	
	Minimum	5,0	1,0	2,0	8,0	
	Maximum	24,0	18,0	12,0	18,0	
Primary Follicle	Mean	4,7	5,7	9,3	15,2	<0,001 [a]
	SD	±1,4	±4,4	±3,3	±5,0	
	Minimum	3,0	1,0	6,0	7,0	
	Maximum	7,0	13,0	14,0	21,0	
Secondary Follicle	Mean	7,7	7,3	9,2	7,2	0,736 [a]
	SD	±4,2	±3,0	±2,9	±3,4	
	Minimum	4,0	4,0	5,0	4,0	
	Maximum	15,0	11,0	13,0	12,0	
Tertiary Follicle	Mean	3,5	2,5	4,7	3,8	0,318 [a]
	SD	±2,8	±1,0	±2,2	±1,3	
	Minimum	0,0	1,0	2,0	2,0	
	Maximum	8,0	4,0	8,0	5,0	
Hemorrhage	Median	2,0	2,0	2,5	0,0	0,005 [b]
	Percentiles -25	1,0	1,0	2,0	0,0	
	Percentiles -75	3,0	2,0	3,0	0,0	
Vascular Congestion	Median	3,0	2,0	2,5	1,0	0,007 [b]
	Percentiles -25	2,0	2,0	2,0	1,0	
	Percentiles -75	3,0	3,0	3,0	1,0	
Cellular degeneration	Median	1,0	1,5	1,0	0,5	0,455 [b]
	Percentiles -25	1,0	1,0	1,0	0,0	
	Percentiles -75	1,0	2,0	2,0	1,0	
Inflammatory cell infiltration	Median	1,0	0,5	1,0	1,0	0,382 [b]
	Percentiles -25	1,0	0,0	1,0	0,0	
	Percentiles -75	2,0	1,0	1,0	1,0	
Edema	Median	2,0	1,5	1,5	0,0	0,027 [b]
	Percentiles -25	1,0	1,0	1,0	0,0	
	Percentiles -75	3,0	2,0	3,0	1,0	

SD: standard deviation, [a]One-way ANOVA test, [b]Kruskal-Wallis test

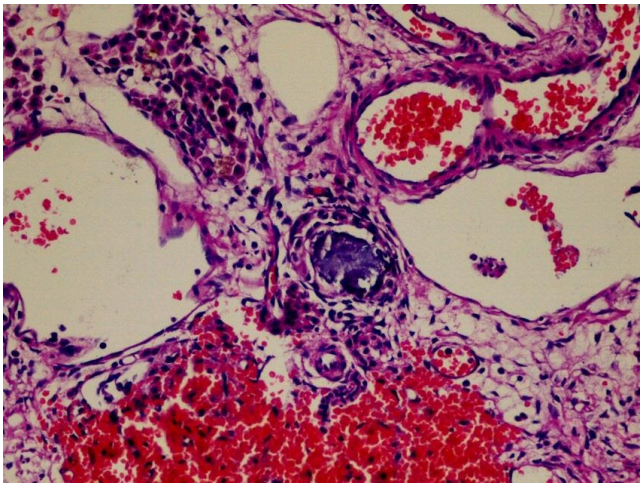

Figure 1: Bleeding in ovarian stroma, congested vessels and secondary follicle x400 hematoxylin eosin

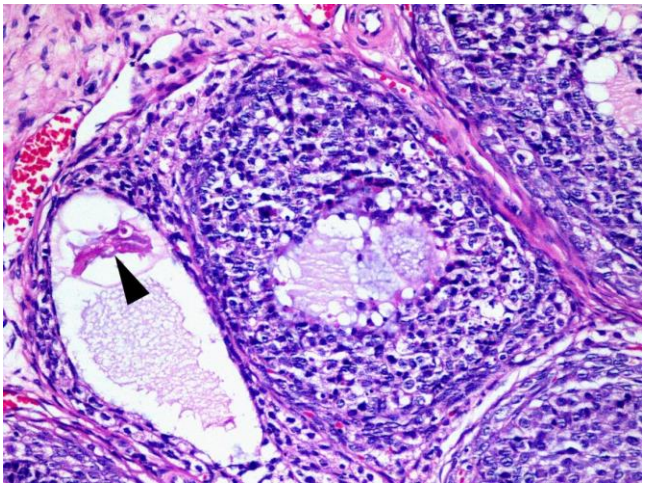

Figure 2: Degenerate follicle in fragmented oocyte x400 hematoxylin eosin

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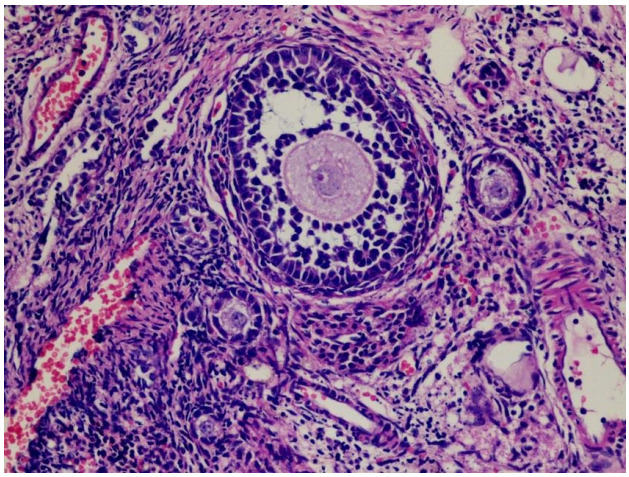

Figure 3: Antral follicles and primary follicles x400 hematoxylin eosin

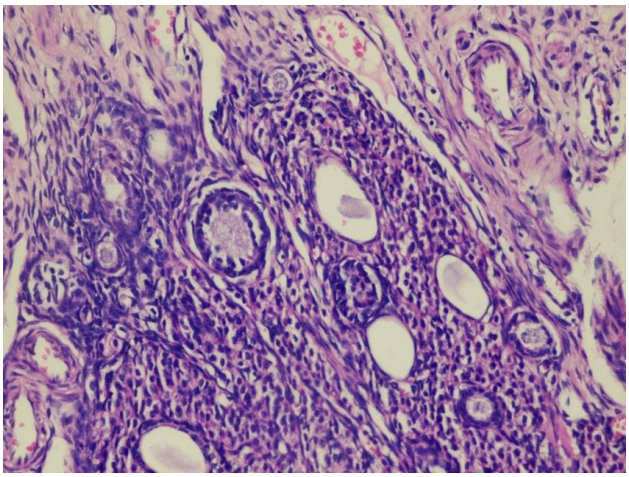

Figure 4: Primordial and primary follicles x400 hematoxylin eosin

Discussion

The examination of normal ovaries revealed statistically significant variations in the numbers of primordial follicles and primary follicles before the torsion of the ovary. These variations appear to be associated with inborn characteristics of these rats. In the examinations after the torsion of the ovary, these significant variations in the numbers of primordial follicles and primary follicles did not change.

However, the level of hemorrhage in the CAPE and DHEA groups after the torsion of the ovary was significantly lower than the group of rats that did not receive medications ($p<0.005$). Vascular congestion and edema was lower in the normal ovary group than the other groups ($p=0.007$ and $p=0.027$, respectively).

In a previous study, Kart et al. investigated factors indicating oxidative damage in ischemia reperfusion (I/R) such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px). However, follicle counts were not investigated in this study. The authors concluded that although CAPE had no significantly superior effects, it might have protective effects against I/R injury (5).

In another study, Celik et al. investigated xanthine oxidase activity, malondialdehyde levels and reduced glutathione levels. The effectiveness of CAPE in preventing I/R injury was also investigated, but follicle counts were not assessed. In this study, the effectiveness of CAPE remained indefinite, and the authors concluded that CAPE might only be effective in reducing I/R injury (2).

In another study investigating the effects of CAPE in I/R injury, Ozler et al. reported torsion-related decreases in the numbers of preantral and small antral follicles (8). The investigator did not use any therapeutic agents. This study investigated the effects of an ovarian torsion of 360 degrees with a reperfusion time of 3 hours. We believe that the differences between the results of this study and our study might be related to the differences in surgical techniques and duration of reperfusion.

Favorable effects of DHEA on ovaries have been established (3). However, the effects of DHEA on follicles in I/R injury were not investigated in any previous studies. In our study, no significant effect of DHEA was observed on follicle counts during the early stages after I/R. However, it would be meaningful if these results were assessed along with long-term outcomes.

In this study, CAPE and DHEA – which are believed to reduce I/R injury as indicated by biochemical and/or histopathological studies demonstrating oxidative injury – made no differences in follicle counts during the early stages following I/R. Based on these results, one may conclude that follicle loss associated with I/R injury may not occur during the early stages after I/R. It may be rational to search for an answer to whether a significant long-term effect would be observed.

Furthermore, we believe that in clinical practice, preventing complete or partial loss of follicles is rather important than seemingly protecting follicles against cellular damage at molecular level. Surely, whether the quantitative presence of these follicles indicates their functionality in terms of fertility is an important matter needing further investigation for an accurate answer.

Conclusion

Agents that have been considered to reduce injury resulting from ischemia-reperfusion proved ineffective in terms of the number of follicles in the ovary during the early stages; however, we believe that long-term studies may be more beneficial.

What is known about this topic

- Ovarian torsion is more common in young women
- Ischemia reperfusion injury is preventable with antioxidant agents, and CAPE is a potent antioxidant agent
- The number of ovarian follicles collected in the treatment of infertility can be increased by DHEA, and DHEA is

one of the most commonly used medical agents by infertility specialists worldwide.

What this study adds

- Ovarian torsion both causes histopathological damage to ovarian tissue and causes follicle loss
- The antioxidant properties of CAPE cannot prevent the damage in ovarian torsion
- The follicle-enhancing effect of DHEA does not provide protective effects on ovarian torsion.

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Ethical issues: Author declare, originality and ethical approval of research. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

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Periodontal and Systemic Treatment Approach on Pemphigus Vulgaris: A Case Report

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Abstract

Objective: In this case report, both the diagnosis of pemphigus vulgaris and the periodontal treatment approach including the use of local/systemic medications are presented.

Case Presentation: 36-year-old female patient applied to the periodontology clinic with complaints of burning mouth and pain. Physical examination revealed cutaneous blisters on nose, hand and fingers while intra-oral examination showed widespread desquamation and ulcers depending on PV and severe gingival inflammation due to the lack of oral hygiene and oral PV. Initial periodontal treatment (IPT) was implemented to the patient along with local and systemic medications. Periodontal parameters including plaque Index (PI), gingival Index (GI), probing depth (PD) and clinical attachment level (CAL) were recorded before and six weeks after IPT. Periodontal treatment procedures did not cause any negative effect on the lesions. Six weeks following IPT and the use systemic medications, all clinical parameters improved significantly. Furthermore, lesions including mucosal blisters and desquamations partially recovered, the patient started to perform oral hygiene more effectively.

It was concluded that atraumatic and non-invasive periodontal treatment supported by the use of local/systemic corticosteroid and immunosuppressive medications was efficient on controlling of widespread desquamations and gingival inflammation of PV patients.

Key Words: Corticosteroids, immunosuppressive, nonsurgical periodontal debridement, pemphigus vulgaris.

Introduction

Pemphigus, originated from Greek word ‘pemphix’ (bubble or swelling), is the name of a potentially life threating autoimmune mucocutaneous disease. The incidence of the disease was reported as 0.1-0.5/100.000 per year in world population.(1) Pemphigus vulgaris (PV) manifests particularly during middle age with an age peak between 4th and 6th decade of life (1). Higher prevalence is reported in Jewish population and Mediterranean countries, particularly (1). The classification of pemphigus is based on the anatomic features of lesions, associated antibody and target antigens (Table 1) (2, 3). The pathogenesis of PV involves immunoglobulin G (IgG) antibodies against desmosome proteins such as desmoglein 3, separating keratinocytes from the basal layer of epidermis (2). PV most commonly affects stratified squamous epithelium (4). Clinically, patients with PV have blister formation and vesiculobullous disintegration of involved areas of skin and mucous membrane (5). In most of the cases oral lesions precede skin lesions. Most frequently affected sites in oral mucosa are reported as labial and buccal mucosa, gingiva and lips (5). Pressing or rubbing on normal looking mucosa can trigger bullae formation or erosion which is called Nikolsky phenomenon. Nikolsky sign is important in differential clinical diagnosis between PV and other immunopathogenic blistering diseases (5). Diagnosis of PV is based on characteristic clinical symptoms confirmed by histopathological and/or direct immunofluorescence microscopic analysis (6). Mostly, oral lesions heal slowly thus patients with PV have discomfort with eating, drinking swallowing and speaking (6). In treatment of patients with PV, moderate to higher dose of systemic corticosteroids play a crucial role. In some circumstances, immunosuppressive agents such as azathioprine, mycophenolate mofetil, cyclophosphamide and methotrexate as well as cyclosporine and chlorambucil can be added to the treatment (6). Moreover, topical and intra-lesional glucocorticoid applications may be useful for resistant mouth lesions (6). In this case report, periodontal treatment approach including local and systemic medications on histopathologically and immunohistochemically diagnosed PV patient was presented.

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Case Presentation

36-year-old female patient was applied to our clinic with intraoral burning and pain complaints. In addition to cutaneous blisters on nose, finger and hand (Figure 1a) intraoral examination revealed severe gingival inflammation, widespread desquamation and ulcers (Figure 1b). PV diagnosis was made according to the histopathological and immunofluorescence evaluation conducted on the biopsy samples taken from the cutaneous and oral lesions. Histological examination with hematoxylin-eosin dye revealed suprabasal acantholysis, neutrophil infiltration in basal membrane and intraepithelial bullae (Figure 1c). Direct immunofluorescence microscopy revealed a fraction of C3 accumulation in basal membrane cell and IgG deposits on epithelial cell surface (Figure 1d).

Patient received IPT including oral hygiene instructions together with mechanical removal of all deposits. During the IPT sessions, local corticosteroid (Nasonex® Aqueous Nasal Spray, Merck Sharp and Dohme, USA) was prescribed for desquamative lesions 4 times per day. She was also prescribed systemic corticosteroid (Prednol®, Mustafa Nevzat, Istanbul) and immunosuppressive (Imuran®, Glaxo Smith Kline, England) by her dermatologist. Before and 6 weeks after IPT, all periodontal parameters; plaque index (PI), gingival index (GI), probing depth (PD), clinical attachment level (CAL) were assessed (Table 2).

Periodontal procedures did not have any negative effect on the lesions. Six weeks after the treatment, all periodontal parameters were improved. Enhancement of the quality of life and patient comfort was provided (Figure 2).

Table 1. Classification of Pemphigus (2, 3).

Type	Anatomic Features	Associated Antibody	Target Antigens
Pemfigus Vulgaris (PV)	Persistent, painful oral lesions; skinfolds are effected; vegetans-like; fetid, reddish plaques		
Mucosal PV		IgG	Desmoglein 3
Cutaneous-mucosal PV		IgG	Desmoglein 1 and 3
Pemphigus vegetans		IgG	Desmoglein 1 and 3
Superficial pemphigus	Characterized by mainly cutaneous lesion		
Pemphigus foliaceus		IgG	Desmoglein 1
Pemphigus erythematosus		IgG	Desmoglein 1
Endemic pemphigus			
Brazil		IgG	Desmoglein1, desmocollin 1
Tunisia		IgG	Desmogleins 1 and 3
Colombia		IgG	Desmoglein 1
Paraneoplastic pemphigus	Characterized by proliferation of various types of tumors, particularly lymphoid hemopathies	IgG	Desmoplakin I/II, Desmoglein 1 and 3, Envoplakin, periplakin, Antigen 170 and 230 kilodalton
Ig A pemphigus	Exudative lesions with vesicopustules	IgA	Desmocollin 1 and another unidentified antigen
Herpetiform pemphigus	Rosette-like lesions	IgG	Desmoglein 1 and 3
Drug-induced pemphigus	Mainly cutaneous lesions	IgG	Heterogeneous

Table 2. Changes in periodontal parameters before and after IPT.

	Before IPT	After IPT	Changes
Plaque Index (PI)	2.78 ± 0.41	1.25±0.51	-1.52±0.57
Gingival Index (GI)	2.64±0.48	0.45±0.42	-2.18±0.67
Probing Depth (mm)	2.21±0.27	1.84±0.18	-0.36±0.24
Clinical Attachment Level (CAL) (mm)	2.89±0.66	2.68±0.82	+0.20±0.35

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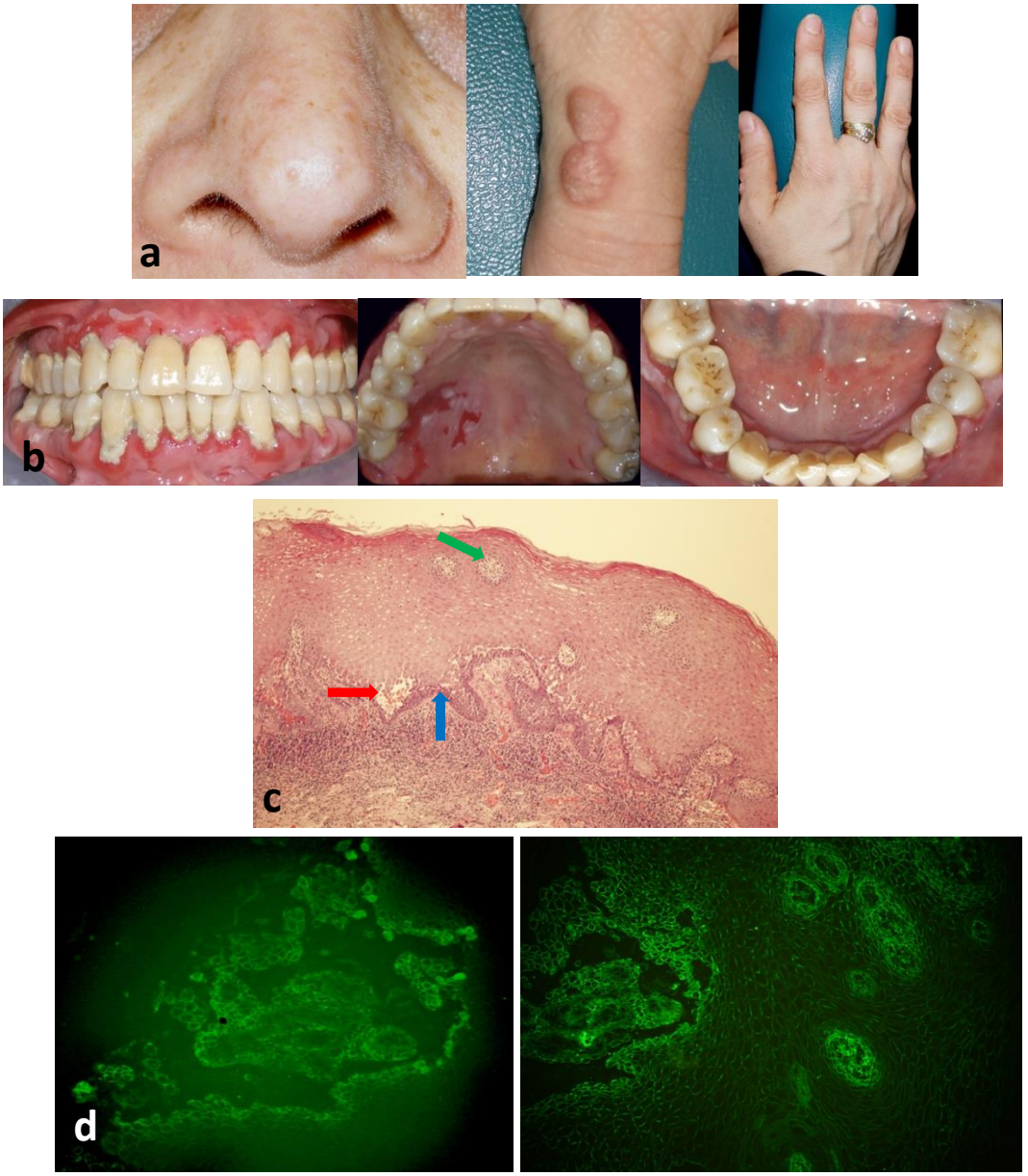

Figure 1: a. Cutaneous blisters on nose, finger and hand **b.** Intraoral clinical view shows lack of oral hygiene because of pain related to desquamative lesions. **c.** Histological examination; → Suprabasal acantholysis → Neutrophil infiltration in basal membrane →Intraepithelial bullae (Hematoxylin-eosin stainX100) **d.** Direct immunofluorescence showed fraction of C3 in basal membrane cells and IgG deposits on epithelial cell surface (X 200 magnification).

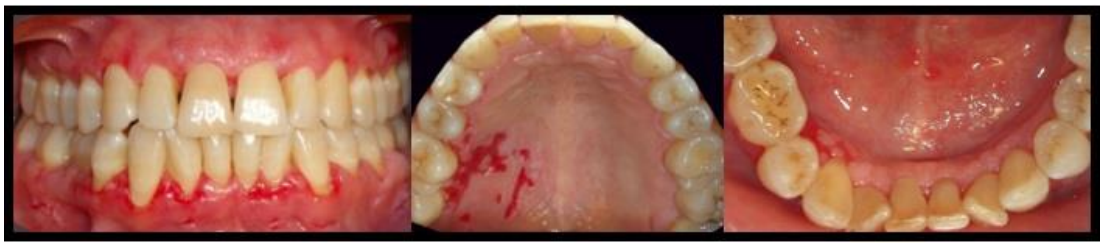

Figure 2: At 6th week follow up intraoral clinical view presents reduced gingival inflammation and healing of PV desquamative lesions

Discussion

In this case report, successfully periodontal treatment of a PV patient was presented. Certain diagnosis of the PV was based on the histopathological and immunofluorescence evaluation in accordance with the literature (1, 7).

The relationship between periodontitis and oral PV is challenged by conflicting results. The lack of correlation between severity of oral lesions and periodontal parameters were reported in studies (8). Thorat et al. showed that in PV patients periodontal parameters such as plaque score, PD and CAL where higher than control group (9). The study by Akman et al. using Community Periodontal Index of Treatment Needs also revealed impaired oral health in PV patients (10). In our case, periodontal status was evaluated before and after the treatment. Initially, the patient was unable to provide adequate oral hygiene due to the painful oral lesions. The severity of the lesions was decreased together with the enhanced clinical parameters.

In the treatment of PV, glucocorticoids have been cornerstone since 1950's (1). Due to the side effects of steroids, some other steroid sparing agents (azathioprine and cyclophosphamide) and intravenous human Ig applications were successfully used for this purpose (6). In our case, in addition to IPT, patient was prescribed for local steroid application to the oral lesions 4 times per day together with systemic corticosteroid and immunosuppressive medication. The improvement in periodontal inflammation revealed by the IPT led to a decrease in the doses of systemically used drugs.

Consequently, successful results can be achieved by reducing inflammation with performing IPT in an atraumatic manner which is supported by corticosteroid or immunosuppressive agents regarding the severity of PV lesions.

Authors' contributions: ÖBA, GK, FP, CD, LK: Patient examination, Project development, Data Collection, Manuscript writing, literature review, Manuscript writing **ÖBA:** Revisions,

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Ethical issues: Author declare, originality and ethical approval of research. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

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