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ORIGINAL ARTICLE

The relationship between C-reactive protein, carbohydrate antigen 125, and hematological parameters to endometriotic nodule localization in pelvis

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Abstract

Background: Endometriosis is a pelvic inflammatory process, and hormonal, environmental, and genetic factors play a role in its etiopathogenesis; especially, deep pelvic endometriosis exhibits an extensive anatomical distribution. In the present study, we evaluated the contribution of routinely measured hematological parameters to the diagnosis as the number of endometriotic nodule localization increases, when evaluated with C-reactive protein (CRP) and carbohydrate antigen (CA) 125.

Methods: The present study included patients with histopathologically confirmed diagnosis of endometriosis who underwent surgery at our hospital between January 2007 and December 2018. Their medical records were examined retrospectively.

Results: In total, 205 patients were included in the study, of which 129 patients (62.9%) with ovarian endometrioma and 76 patients (37.1%) with deep infiltrative endometriosis were assigned to Group 1 and Group 2, respectively, and the two groups were compared. Endometriotic nodules were observed in several localizations in 71 patients (34.6%) of the 205 patients with endometriosis. Pelvic nodules were grouped as per their four different localizations: uterosacral, recto-vaginal, bladder, and ureteral. Because the anatomical localization of endometriotic nodules increased in the pelvis, the variability in the levels of CA 125 and CRP as well as hematological parameters was examined. There were significant differences in hemoglobin ($p < 0.036$), CA 125 ($p < 0.000$), and CRP ($p < 0.007$) levels between patients with nodules in ≤2 localizations and those with nodules in ≥3 localizations.

Conclusion: Our study included a total of 205 patients. There was a significant difference in the CRP, CA 125, and hemoglobin levels between Group 1 and Group 2, but it was concluded that coexistence of the endometriotic nodule had no effect on the other hematological parameters. For this purpose, prospective studies with a larger number of patients are needed.

Keywords: CA 125; C-reactive protein; Endometriosis; Endometriotic nodule

1. INTRODUCTION

Endometriosis is a gynecological disease characterized by histological stromal and glandular endometriotic tissues localized outside the uterine cavity, with retrograde flow of endometrial cells being held responsible in its etiology.[1] Its main symptoms are dyspareunia, chronic pelvic pain, and infertility. It has been reported that it mostly affects women of reproductive age.[2] Its overall incidence is 5% to 10%.[3] Basically, the three types of lesions that have been reported are as follows: ovarian endometriosis, deep infiltrating endometriosis (DIE), and superficial peritoneal endometriosis.[4] DIE is defined as a subperitoneal invasion by the lesion that is >5 mm in depth; it is most commonly localized in the recto-vaginal septum, uterosacral ligaments, para-rectal space, and uterovesical region. DIE is defined as a subperitoneal invasion that is deeper than 5 mm, although it might be misleading.[5] In fact, it was found that many lesions in the pouch of Douglas as well as in the peritoneum or uterosacral ligaments had infiltrated the tissues deeper than 5 mm; however, it may be inaccurate to categorize them under deep endometriosis.[5] Therefore, some researchers prefer to define deep endometriosis pathologically as external adenomyosis or adenomyosis-like nodules.[1] The coexistence of deep endometriosis with nodules in different anatomical regions of the pelvis and high correlation with ovarian endometriosis raise the question of whether there exist three different diseases with a common or different pathogenesis. It is controversial whether endometriotic nodules localized in different regions within the pelvis are a product of constantly self-repeating tissue healing or repair as a phenotype of a condition such as progressive recurrent menstrual bleeding or caused by genetic changes.

It seems plausible that successful implantation and survival of ectopic endometrial cells on the peritoneal surface can be explained by molecular abnormalities or a failure in the

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immunological system leading to an inability in cleaning up these implants.[6,7]

In our study, we compared preoperative hematological parameters of patients with advanced-stage endometriosis (Stage 3/4) with those of patients with ovarian endometrioma only and evaluated their correlation with carbohydrate antigen (CA) 125 and C-reactive protein (CRP) levels. In addition, we aimed to evaluate the effects of the increasing number of anatomical localizations of extragenital endometriotic nodules on these parameters.

2. METHODS

Our study included 205 patients who underwent surgery owing to endometriosis in our hospital between January 2007 and December 2018 and in whom histopathological examination revealed deep pelvic endometriosis and ovarian endometrioma. Smokers, patients with gynecological or non-gynecological malignancies, those with autoimmune or systemic disease, those who present symptoms of a systemic or chronic inflammatory disease, and those in whom the final pathological examination revealed uterine fibroids, adenomyosis, endometrial polyp, or malignancy were excluded from the study. Patients with recto-vaginal involvement, deep pelvic invasion, and complete or partial obliteration of the pouch of Douglas along with endometriotic cysts observed during surgery were considered to have advanced-stage (Stage 3/4) disease according to the scoring system of American Fertility Association.[8] Patients were divided into two groups: those with advanced-stage endometriosis and those with only ovarian endometriosis. All patients underwent gynecological examination before surgery. Results of the analysis of peripheral venous blood samples collected before surgery were recorded. Blood samples were immediately centrifuged at 3000 rpm for 15 minutes. The upper limit of the normal range for the serum CA 125 level was considered to be 35 IU/mL, and the upper limit of normal range for the CRP level was considered to be 5 mg/L. All CA 125 values were the results on the second day of the men's period before the operation. Leukocyte, neutrophil, lymphocyte, and platelet counts were recorded. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated using these parameters. The mean platelet volume (MPV, fL) and hemoglobin levels (g/dL) were determined. The hematological parameters, including the leukocyte count, platelet count, neutrophil count, lymphocyte count, hemoglobin levels, NLR, and PLR, were calculated and evaluated for their correlation with CA 125 and CRP levels using statistical methods.

2.1. Statistical analysis

The analysis was performed using IBM SPSS 20 statistical software. The data were presented as mean, standard deviation, median, minimum, maximum, percentage, and number. Continuous variables were tested to assess whether they were normally distributed using the Shapiro-Wilk *W* test when the sample size was <50 and using the Kolmogorov-Smirnov test when the sample size was >50. An independent samples *t* test was used when the assumptions for normal distribution were met, and otherwise, a Mann-Whitney *U* test was used in the comparison between two independent groups. A Pearson's correlation coefficient was used to compare two continuous variables if they were normally distributed, and Spearman's rank correlation coefficient was used for variables that were not normally distributed. Logistic regression models were used to identify the risk factors between the groups. A p value of <0.05 was considered to be statistically significant.

3. RESULTS

Our study included a total of 205 patients. The mean age of the patients was 32.73 ± 7.09 years. This included 129 patients (62.9%) with ovarian endometrioma and 76 patients (37.1%) with deep infiltrative endometriosis who were assigned to Group 1 and Group 2, respectively, and the two groups were compared. The mean age of the patients was 31.99 years in Group 1 and 33.97 years in Group 2. Endometriotic nodules were observed in various localizations in a total of 71 (34.6%) of the 205 patients with endometriosis. Pelvic nodules were grouped as per their four different localizations: uterosacral, recto-vaginal, bladder, and ureteral. The distribution of endometriotic nodules is presented in **Table 1**. Of these patients, 87 were multiparous (42.4%), 79 were nulliparous (38.5%), and 37 (18%) were not sexually active. Patients' clinical and demographic characteristics are presented in **Table 1**. The mean values of the laboratory parameters that were evaluated for their variability in the present study are presented in **Table 2**. There was no significant difference between Groups 1 and 2 in terms of the lymphocyte count (p = 0.330), neutrophil count (p = 0.109), platelet count (p = 0.660), MPV (p = 0.686), leukocyte count (p = 0.292), NLR

Table 1

Patients' demographics and clinical characteristics

	n (%)/Mean ± SD (N = 205)	*p*
Age, y	32.73 ± 7.09	
Group 1	31.99 ± 7.23	0.045
Group 2	33.97 ± 6.71	
Patients with recto-vaginal nodule	48 (23.4%)	
Patients with uterosacral nodule	52 (25.4%)	
Patients with ureter nodule	41 (20%)	
Patients with bladder nodule	37 (18.1%)	
No. of nodules		
0	134 (65.4%)	
1	16 (7.8%)	
2	17 (8.3%)	
3	24 (11.7%)	
4	14 (6.8%)	
Multiparous patients	87 (42.4%)	
Nulliparous patients	79 (38.5%)	
Sexually inactive patients	37 (18%)	
Symptoms		
Dysmenorrhea	106 (51.7%)	
Dyspareunia	55 (26.8%)	
Infertility	80 (39%)	

Table 2

Mean laboratory values of patients

	Mean ± SD
C-reactive protein (CRP)	5 ± 6
CA 125 levels, IU/mL	71.7 ± 106.2
Hemoglobin, g/dL	13.15 ± 1.47
Neutrophil count, 10^3/μL	4.8 ± 2.3
Lymphocyte count, 10^3/μL	2.2 ± 1.6
Platelet count, 10^3/μL	281.3 ± 64.9
MPV, fL	9.1 ± 1.5
Leucocyte count, 10^3/μL	7.59 ± 2.41
N/L ratio (NLR)	2.69 ± 3.14
P/L ratio (PLR)	145.98 ± 60.16

CA = carbohydrate antigen; MPV = mean platelet volume; NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio.

Table 3

Comparison quantitative variables between the groups

	Ovarian endometrioma	Deep infiltrating endometriosis	
	Mean ± SD	Mean ± SD	*p*
C-reactive protein (CRP)	4.657 ± 6.48	5.33 ± 4.40	0.007
CA 125 levels, IU/mL	45.82 ± 31.22	115.513 ± 160.94	0.000
Hemoglobin, g/dL	13.31 ± 1.40	12.86 ± 1.54	0.036
Neutrophil count, 10^3/µL	4.83 ± 2.02	4.71 ±.2.72	0.109
Lymphocyte count, 10^3/µL	2.23 ± 1.94	2.16 ± 0.66	0.330
Platelet count, 10^3/µL	280.39 ± 63.43	282.90 ± 67.64	0.660
MPV, fL	9.12 ± 1.54	9.18 ± 1.56	0.686
Leucocyte count, 10^3/µL	7.58 ± 2.14	7.57 ± 2.82	0.292
N/L ratio (NLR)	2.59 ± 1.92	2.85 ± 4.55	0.064
P/L ratio (PLR)	145.17 ± 52.62	147.36 ± 71.65	0.647

CA = carbohydrate antigen; MPV = mean platelet volume; NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio.

Table 4

Comparison of quantitative variables according to the number of localizations of the nodules

	≤2 nodules	≥3 nodules	
	Mean ± SD	Mean ± SD	*p*
C-reactive protein (CRP)	4.38 ± 5.94	7.23 ± 4.52	0.007
CA 125 levels, IU/mL	59.32 ± 87.67	125.86 ± 154.79	0.000
Hemoglobin, g/dL	13.19 ± 1.47	12.94 ± 1.47	0.036
Neutrophil count, 10^3/µL	4.85 ± 2.24	4.53 ± 2.54	0.109
Lymphocyte count, 10^3/µL	2.24 ± 1.74	2.07 ± 0.64	0.330
Platelet count, 10^3/µL	279.92 ± 65.57	287.42 ± 62.08	0.660
MPV, fL	9.16 ± 1.46	9.07 ± 1.91	0.686
Leucocyte count, 10^3/µL	7.65 ± 2.40	7.27 ± 2.47	0.292
N/L ratio (NLR)	2.69 ± 3.21	2.67 ± 2.89	0.064
P/L ratio (PLR)	144.45 ± 59.84	152.53 ± 61.89	0.647

CA = carbohydrate antigen; MPV = mean platelet volume; NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio.

(p = 0.064), and PLR (p = 0.647); however, the mean hemoglobin level was significantly higher in the ovarian endometrioma group (p < 0.036). The hemoglobin levels were significantly higher in Group 1 than in Group 2. There was a significant difference between the CRP and CA 125 levels between the groups (p = 0.007 and p < 0.001). The mean CRP and CA 125 levels were significantly higher in the deep infiltrative endometriosis group. The analysis of the variables is presented in **Table 3**.

The variabilities in the CA 125 and CRP levels and hematological parameters were examined in relation to an increase in the number of anatomical localizations of endometriotic nodules in the pelvis. There were no significant differences in the systemic inflammatory response (SIR) markers, but there were significant differences in the CA 125 (p < 0.000), CRP (p < 0.007), and hemoglobin levels (p < 0.036) levels between patients with nodules in ≤2 localizations and patients with nodules in ≥3 localizations (**Table 4**). As the localization of endometriotic nodules in the pelvis increased in the patients included in our study, the CA 125 and CRP levels showed a moderate positive correlation, CA 125 and CRP levels increased with increasing number of anatomical localizations of endometriotic nodules, showing a moderate positive correlation and the results are presented in **Table 5** (CA 125: r = 0.415, p < 0.000; CRP: r = 0.256, p < 0.000).

In the logistic regression model involving the use of the enter method, only CA 125, among the other risk factors, was found

Table 5

Correlation between the number of nodules and CRP and CA 125

No. of endometriotic nodules	CRP	CA 125
r	0.256	0.415
p	0.000	0.000
N	205	205

CA = carbohydrate antigen; CRP = C-reactive protein.

Table 6

Logistic regression model for the risk factors between groups

					95% CI for Exp(*B*)	
	B	SE	Sig.	Exp(*B*)	Lower	Upper
CRP	–0.042	0.033	0.207	0.959	0.899	1.023
CA 125	0.025	0.005	0.000	1.025	1.016	1.035
Hb	–0.176	0.122	0.148	0.838	0.660	1.065
MPV	0.139	0.117	0.236	1.149	0.913	1.446
WBC	0.004	0.101	0.965	1.004	0.824	1.225
N/L	0.072	0.108	0.508	1.074	0.869	1.328
P/L	–0.004	0.004	0.378	0.996	0.988	1.005
Constant	–0.606	2.256	0.788	0.545	...	...
CA 125	0.022	0.004	0.000	1.022	1.014	1.031
Constant	–1.987	0.312	0.000	0.137	...	...

CA = carbohydrate antigen; CRP = C-reactive protein; Hb = hemoglobin; MPV = mean platelet volume; NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio; WBC = neutrophil count.

to be significant (p < 0.001). In the logistic regression involving the use of the backward LR method, only CA 125 was found to be a significant risk factor between the groups (p < 0.001). According to the results of the model, only CA 125 was found to be a risk factor between the groups (p < 0.001). Constant (B) value was also found to be significant in the model p < 0.001 (**Table 6**).

4. DISCUSSION

Regardless of its localization, the development of ovarian endometrioma or deep pelvic endometriosis seems to be a chronic inflammatory process and a result of progressive endometriosis. There is no consensus on how endometriotic foci develop during the reproductive period. Although many theories have been proposed, the most widely accepted theory suggests the presence of retrograde menstruation and implantation of endometrial tissue that flows backward through the fallopian tubes, especially in peritoneal endometriosis.[2] Zhang et al investigated the roles of activated platelets *in vitro* and concluded that endometriotic lesions have all the molecular mechanisms necessary to induce smooth muscle cell metaplasia and fibrogenesis, and as a conclusion, they pointed out the importance of platelets in the formation of endometriotic lesions and revealed that the lesions are exposed to self-repeating damage and healing processes.[9] As an indicator of platelet activity and platelet count, the MPV has been shown to play an important role in the inflammatory processes, as demonstrated by the studies.[10] The study by Yavuzcan et al found no significant difference in these values between the group with Stage 3/4 endometriosis (deep infiltrative endometriosis) and the group with ovarian endometrioma (OMA). The study by Bodur et al[11] showed that MPV increased significantly in patients with adenomyosis with similar pathophysiological mechanisms as those with endometriosis.

The efforts towards finding a less invasive method to establish the diagnosis of endometriosis have shifted the focus of studies

to the markers of inflammation.[12] PLR and NLR are simple SIR markers that can be assessed from the parameters of the complete blood count.[13] Recent studies have indicated that these markers are of prognostic value in various diseases.[12] The ratio of these two cell types (NLR and PLR) can also occur in malignancies as in many inflammatory diseases and can be used as an indicator of both inflammatory and anticoagulant responses.[10] In recent years, it has been shown that NLR is increased especially in malignancies and that it can be used as an indicator of prognosis.[14] In a study investigating the effect of endometrial pathologies on NLR, NLR was found to be significantly increased in patients with endometrial cancer.[15] An increase in NLR in endometriosis has been investigated based on the assumption that it is caused by similar endometriotic cells. It has been suggested that hyperestrogenism, oxidative stress, and long-term chronic inflammation may play a role in endometriosis-related ovarian cancer.[16] Another study reported significantly higher NLR and PLR in advanced-stage ovarian cancer.[17] A study by Sihyun Cho et al reported a significantly stronger correlation between NLR and the CA 125 level in the endometriosis group than in the healthy control group. The present study found no significant difference between the groups in terms of MPV, NLR, and PLR. This finding of no difference in the markers of systemic inflammation between the groups in the present study was in contrast with that of many other studies showing that chronic inflammation plays a role in the pathophysiology of endometriosis does not suggest that they are of no significance in endometriosis. The markers of systemic inflammation are not indicative of the significance of endometriosis. We believe that it would be more appropriate to conduct a study with a larger group of patients, including those with benign or malignant diseases originating from the endometrial cells.

Serum CRP is widely used as a marker of continuing inflammation in clinical practice and can be measured in most laboratories.[18]

In a study[13] reported elevated CRP levels in women with Stage III and IV endometriosis. However, Lermann et al.[19] found no statistically significant difference in the serum CRP levels between patients with endometriosis and healthy controls. In another study, CRP levels were found to be significantly higher in patients with endometriosis.[12] In addition, the presence of excess iron in the peritoneal cavity suggests that endometriotic lesions cause oxidative damage, ultimately leading to chronic inflammation.[5] A study by Barrier et al[20] reported that these patients have varying amounts of inflammatory cells in the peritoneal fluid. In our study, we found that CRP levels, a component of the inflammatory process, were significantly higher in the advanced-staged endometriosis group because the coexistence of nodules increased.

A definitive diagnosis of endometriosis is established by direct visualization of the lesions and by histopathological confirmation. Although laparoscopy is a minimally invasive procedure, it has disadvantages such as complications intrinsic to the procedure, necessity of general anesthesia, and cost of the procedure. Several models have been developed to create a less invasive diagnostic method that incorporates widely available markers. CA 125 is the most frequently used marker for this purpose.[21] CA 125 seems to be the most important marker in diagnosing endometriosis, but its sensitivity (20%-50%) has limited its clinical use in the diagnosis. Both sensitivity and specificity of CA 125 have been shown to be higher in diagnosing advanced-stage endometriosis (Stage 3/4).[22] However, a meta-analysis of 23 studies evaluating the diagnostic performance of CA 125 has not shown sufficient reliability. In our study, CA 125 levels were found to be significantly higher in the patient group with advanced endometriosis and in that with a higher number of extragenital pelvic endometriotic nodules.

As shown in the present study, the leukocyte count, leukocyte differential count, PLT, MPV, NLR, PLR, CA 125, and CRP are not sufficient alone to detect endometriosis. When evaluated together with CA 125, the use of CRP, which is an easily available and easy-to-study marker, was found to be significantly higher, especially in the presence of endometriotic nodules; the most important advantage of our study is that these markers can be obtained easily from almost all patients through routine complete blood count without additional cost or testing.

In conclusion, the pathophysiology of endometriosis is yet to be identified, and various hypotheses have been proposed. However, neither implantation nor metaplasia nor lymphatic or hematologic spread theories can explain all clinical signs. The key point of all these discussions is whether endometriotic cells are similar to or different from those in the endometrium. For a disease with a highly complex pathophysiology, the paucity of markers and imaging methods lead to a delay in diagnosis and a significant decrease in quality of life of patients with endometriosis. Although CRP and CA 125 provide guidance in patients with advanced-stage disease, invasive procedures are needed to identify patients with early stage disease. Although CRP, CA 125, and blood parameters were found to be significant in our study due to the high rates of false positivity, it seems difficult to be a prospective screening marker.

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