ORIGINAL ARTICLE

The role of hematological parameters in distinguishing acute appendicitis from lymphoid hyperplasia

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ABSTRACT

BACKGROUND: One of the most misdiagnosed appendicular pathologies is lymphoid hyperplasia (LH) that can be managed conservatively when identified early and is self-limiting. The aim of this retrospective study was to compare acute appendicitis (AA) with LH in terms of hematological parameters to determine whether there is a hematological predictor to distinguish the two diseases.

METHODS: Complete blood cell counts of patients with AA were compared with those having LH.

RESULTS: One-hundred-ninety-five patients (118 male/77 female) underwent appendectomy. Histopathological examination revealed acute AA in 161 patients (82.6%), and negative appendectomy (NA) in 19 patients (9.7%). Of the NA specimens, 16 were LH (8.2%). Thirteen patients (6.7%) had AA with simultaneous LH. White blood cell count (p=0.030, neutrophil (p=0.009), neutrophil percentage (p=0.009), and neutrophil/lymphocyte ratio (p=0.007) were significantly higher in AA whereas lymphocyte count (p=0.027), lymphocyte percentage (p=0.006) were significantly higher in LH. Multi logistic regression analysis revealed white blood cell count as the only independent predictor in distinguishing AA from LH with a 69.1% sensitivity, 80.0% specificity, 77.5% positive predictive value, and 72.1% negative predictive value. The cut-off value for white blood cell count was 11.3 Ku/L, and every one unit (1000/mm^3) increase in white blood cell count raises the risk of AA by 1.24 times, while values below this value will increase the likelihood of LH.

CONCLUSION: The most predictive complete blood count parameter in distinguishing LH from AA appears to be as white blood cell count.

Keywords: Acute appendicitis; complete blood count; lymphocyte; lymphoid hyperplasia; neutrophil; white blood cell count.

INTRODUCTION

Acute appendicitis (AA) is the most frequent common cause of emergency abdominal surgery with a 7% life time incidence risk of 7%.[1] The diagnosis is based primarily on the combination of clinical evaluation with laboratory tests and imaging methods. Although it has dropped Despite falling from 14.7% to 8.5% in the past last two decades, the rate of negative appendectomy (NA) rate is still remains high.[2] NA rates are higher especially in children and women of childbearing women age. Since Alvarado,[3] a number of scoring systems have been developed and are still being developed under development to improve increase the diagnostic accuracy for of AA.[4–8] On the other hand, some current recent studies are investigating the diagnostic accuracy of inflammatory markers.[9,10] However, despite advances in scoring systems, laboratory biomarkers, and radio-diagnostics, the AA diagnosis of AA did still does not reach to 100%.

One of the most misdiagnosed appendicular pathologies is LH, which is usually confused as AA whether by ultrasound (US) examination or physical exam and even during surgery.

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The true and exact diagnosis of LH can only be confirmed with histopathological examination. On the other hand, LH is a distinct separate phenomenon that can be conservatively managed when it is identified early and is self-limiting.[11]

Lymphoid hyperplasia (LH) is a cell reaction to viral infections anywhere elsewhere of in the lymph nodes in the body, such as tonsils, adenoids, and appendix. The appendix is actually considered a lymphoid organ due to its intense lymphoid tissue content. Appendiceal lymph nodes, which are more intense in childhood, decrease in quantity with aging. While it's found in a much more intense amount in childhood, the number of the appendiceal lymph nodes decreases with during the aging process. Appendix reacts like other lymphoid tissues when exposed to a viral agent. Following infection by a viral infection origin, the inflamed serosa of appendix swells becomes swollen with to a pink to red appearance, referred as called as surgically "pink appendicitis." Besides an isolated entity, LH is much more commonly seen with viral induced mesenteric adenitis/enteritis. In addition to being an isolated disease, LH is mostly seen in viral-derived mesenteric adenitis/enteritis.[12]

Clinical studies are mainly focused on radiological findings to distinguish differentiate AA from LH, but the role played by hematological parameters in predicting and differentiating distinguishing the two entities is has not been discussed in detail.[13,14]

The purpose of this retrospective study is to compare the AA with and LH in terms of hematological parameters to determine whether there is a hematological predictor to for distinguishing the two diseases.

MATERIALS AND METHODS

After approval of the ethical committee, 195 patients who underwent appendectomy between January 2015 and January 2019 were retrospectively analyzed. Patient's age, gender, preoperative complete blood count (CBC) parameters including white blood cell count (WBC), red cell distribution width (RDW), mean corpuscular volume (MCV), mean platelet volume (MPV), neutrophil (NEU), neutrophil percentage (NEU%), lymphocyte (LYM), lymphocyte percentage (LYM%), monocyte (MONO), monocyte percentage (MONO%), and neutrophil/lymphocyte ratio (NLR) and histopathologically diagnosed appendiceal specimens were taken from patient's folder.

Inclusion Criteria

Patients 18 years and older were included in the study. Patients with only histopathologically confirmed AA and LH are compared. Patients who had appendicitis with concurrent LH or other pathologies were included for demographic data but excluded in comparison of AA with LH regarding the CBC parameters.

Statistical Analysis

Data analysis was performed by using IBM SPSS Statistics version 21.0 software (IBM Corporation, Armonk, NY, USA). Whether the distribution of continuous variables was normal or not, it is determined by visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov). Descriptive analyses were presented using means and standard deviations for normally distributed variables (WBC, LYM, MONO%); using medians and interquartile range for the non-normally distributed variables (age, RDW, MCV, MPV, NEU%, NEU, LYM%, MONO, NLR).

If WBC, LYM, MONO% values were normally distributed, the Student's t-test was used to compare these parameters to be having appendicitis or not. Otherwise, Mann Whitney U test was used for comparisons of the not normally distributed data (Age, RDW, MCV, MPV, NEU%, NEU, LYM%, MONO, NLR). Categorical variables were analyzed by Chi-square.

The optimal cut-off points for NLR, LYM, NEU, WBC, and NEU% were evaluated by receiver operating characteristics analyses, calculating the area under the curve to give the maximum sum of sensitivity and specificity.

Determining the best predictor(s) which effect on LH was evaluated by Binary Logistic Regression Analyses. The univariate analyses to identify variables associated with AA were investigated using Chi-square, Student's t-test, Mann Whitney U test, where appropriate. Hosmer Lemeshow goodness of fit statistics was used to assess model fit. $P<0.05$ was considered statistically significant.

RESULTS

Histopathological specimens of 195 patients who were explored for AA are examined. One-hundred-eighteen patients were male (60.5%) and 77 patients were female (39.5%). The median age was 32 (23–44) years. Histopathological examination of the specimens revealed AA in 161 patients (82.6%), AA with concurrent LH in 13 patients (6.7%), and AA with concurrent appendicular neuroendocrine tumor in two patients (1%), respectively. On the other hand, 19 patients (9.7%) had NA. Of these, 16 patients (8.2%) had LH, whereas three patients (1.5%) had reactive changes, (Fig. 1 and Table 1).

The distribution of hematological parameters in patients with AA (161 patients) and LH (16 patients) are summarized in Table 2. The mean WBC levels were significantly higher in AA than in LH (13.77±4.23 vs. 11.32±4.59, p=0.030). The median neutrophil count NEU was significantly higher in AA when compared with LH (10.60 [7.48–14.05] vs. 6.68 [5.01–9.68], p=0.009). The median NEU% neutrophil percentage was significantly higher in AA than in LH (77% [68.28–84.50] vs. 68.4% [56.15–74.43], p=0.009). On the other hand, mean lymphocyte count LYM was significantly less in AA than in

Table 1. Descriptive frequencies

Features	n (%) / Mean±SD / Median (IQR)
Age (n=195)	32 (23–44)
Gender (n=195)	
Male	118 (60.5%)
Female	77 (39.5%)
Histopathological diagnosis (n=195)	
Acute appendicitis	161 (82.6%)
Acute appendicitis with simultaneous lymphoid hyperplasia	13 (6.7%)
Acute appendicitis with appendicular neuroendocrine tumor	2 (1.0%)
Negative appendectomy	19 (9.7%)
Lymphoid hyperplasia	16 (8.2%)
Reactive changes	3 (1.5%)
Hematological parameters (n=177*)	
WBC	13.55±4.31
RDW	15.10 (14.30–15.80)
MCV	88.70 (85.15–91.85)
MPV	7.88 (7.20–8.74)
NEU	10.20 (7.27–13.95)
NEU%	75.90 (66.25–83.00)
LYM	2.15±0.95
LYM%	16.10 (9.71–22.50)
MONO	0.80 (0.58–1.04)
MONO%	6.19±2.43
NLR	4.68 (2.75–8.51)

*Only acute appendicitis and lymphoid hyperplasia patients were included in the analysis. LYM: Lymphocyte (K/uL); LYM%: Percentage of lymphocytes (K/uL); MONO: Monocyte; MONO%: Percentage of monocytes (K/uL); MCV: Mean corpuscular volume (fl); MPV: Mean platelet volume (fl); NLR: Neutrophil / lymphocyte ratio; RDW: Red cell distribution width (%); WBC: White blood cell count (K/uL); SD: Standard deviation.

LH (2.10±0.91 vs. 2.64±1.19, p=0.027). Further, the median LYM %mphlyocyte percentage was significantly less in AA than in LH (15.60 [9.30–21.95] vs. 23.10 [16.40–34.00], p=0.006). The median NLR was significantly higher in AA when compared with LH (4.78 [3.17–9.06] vs. 2.96 [1.57–4.48], p=0.007).

Multi logistic regression analysis including age, gender, WBC, and lymphocyte count in diagnosing AA reveal statistical significance with WBC count (p=0.007; 95% C.I: 1.062–1.459). One-unit increase in WBC value increases the risk of AA by 1.24 times (Table 3).

The possibility of diagnosing AA with WBC was 73.5% (AUC: 0.73, 95% CI 0.61–0.86, p=0.003). The possibility of diagnosing AA with neutrophil count NEU was 74.2%. (AUC: 0.74, 95% CI 0.0.61–0.88, p=0.002). The possibility of diagnosing AA with NEU% was 69.9% (AUC: 0.69, 95% CI 0.55–0.84, p=0.011). The most suitable cutting point was determined according to youden index, (Fig. 2 and Table 4).

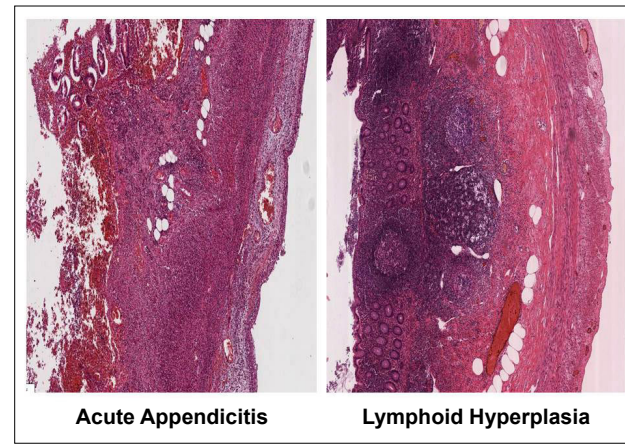

Figure 1. Microscopic image of acute appendicitis and lymphoid hyperplasia (H&E staining ×4 HPF).

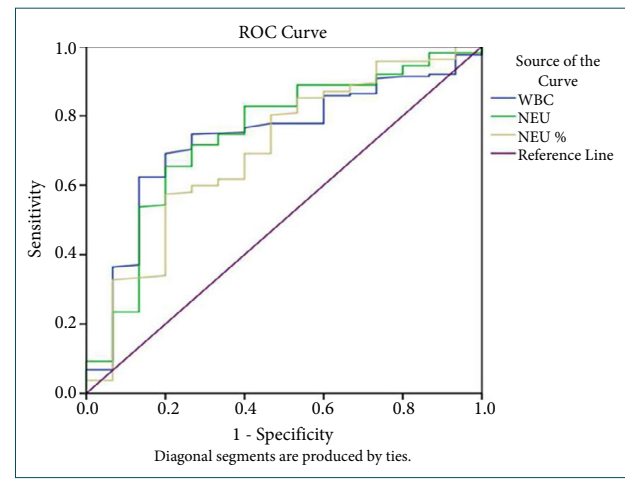

Figure 2. Receiver operating characteristics curves of WBC, NEU and NEU%.

DISCUSSION

The underlying pathophysiology of acute purulent appendicitis AA is the luminal obstruction created caused by a fecalitis, parasite, or foreign body (barium contrast agent). Luminal obstruction leads to bacterial infection following inflammation and mucosal ischemia leads to bacterial infection.[15,16] On the other hand, appendiceal LH is an inflammatory response to a viral agent of the lymphoid follicles located found in the mesentery and lamina propria of the appendix vermiformis. LH is confirmed histopathologically if a cluster of more than 10 lymphoid nodules all of which containing lymphoid follicles ≥2 mm are detected in the wall of the appendix The diagnosis of LH is confirmed histopathologically when a cluster of more than 10 lymphoid nodules, all 2 mm in width, is detected in the wall of the appendix.[13] However, LH itself can may lead

Table 2. Distribution of hematological parameters in patients with acute appendicitis and lymphoid hyperplasia

	Acute appendicitis (n=161)	Lymphoid hyperplasia (n=16)	p
Age	33.00 (23.50–46.00)	27.50 (22.25–34.50)	0.146**
Gender			
Male	100 (92.6)	8 (7.4)	0.343*
Female	61 (88.4)	8 (11.6)	
White blood cell count	13.77±4.23	11.32±4.59	0.030***
Red cell distribution width	15.10 (14.30–15.80)	15.25 (14.43–15.88)	0.682**
Mean corpuscular volume	88.70 (85.25–91.95)	88.20 (83.05–91.28)	0.546**
Mean platelet volume	7.84 (7.18–8.70)	8.12 (7.50–9.10)	0.223**
Neutrophil count	10.60 (7.48–14.05)	6.68 (5.01–9.68)	0.009**
Neutrophil count %	77.00 (68.28–84.50)	68.40 (56.15–74.43)	0.009**
Lymphocyte count	2.10±0.91	2.64±1.19	0.027***
Lymphocyte count %	15.60 (9.30–21.95)	23.10 (16.40–34.00)	0.006**
Monocyte count	0.80 (0.59–1.07)	0.71 (0.49–0.83)	0.138**
Monocyte count %	6.15±2.43	6.53±2.51	0.556***
Neutrophil/lymphocyte ratio	4.78 (3.17–9.06)	2.96 (1.57–4.48)	0.007**

*Chi square test. **Student's t-test. ***Man-Whitney U test.

Table 3. Examination of acute appendicitis by logistic regression analysis according to some features

	B	SE	p	Exp (B)	95% C.I for Exp (B)
WBC	0.219	0.081	0.007	1.245	1.062–1.459
Age	0.050	0.028	0.077	1.051	0.995–1.111
Gender	0.599	0.582	0.303	1.821	0.582–5.695
LYM	-0.476	0.297	0.109	0.621	0.347–1.113
Constant	-1.121	1.454	0.441	0.326	

WBC: White blood cell count; LYM: Lymphocyte count; SE: Standard error; CI: Confidence interval.

Table 4. The validity of diagnosing acute appendicitis with the cut-off values of some hematological parameters

	Cut off value	Sensitivity	Specificity	PPV	NPV
WBC	11.3	69.1	80.0	77.5	72.1
NEU	8.44	65.4	80.0	76.5	69.8
NEU%	74.80	57.4	80.0	74.2	65.2

WBC: White blood cell count; NEU: Neutrophil count; PPV: Positive predictive value; NPV: Negative predictive value.

to AA due to compression and collapse of the lumen by peri-appendicular edema However, LH itself can cause AA as a result of compression and obstruction of the lumen due to perpendicular edema. Therefore, it should be kept in mind that LH may be limited or can progress to AA depending on the severity of inflammation.[17] Further, although these two diseases are accepted as separate entities, they may appear sometimes intertwined. In the present study, 8.2% of NA cases had LH, while 6.7% of patients had AA with simultaneous and LH simultaneously.

Today, the treatment approach for AA is concentrated focused around three on three axes: First, accurate and timely diagnosis; Second, to reduce the NA rate by avoiding unnecessary laparotomy. Third, the selection of patients to be followed up non-operatively without surgery.[18–20]

In addition to physical examination, radiological imaging is often critical in making a diagnosis; -especially in patients whose pain is ambiguous and clinical symptoms are mild. Compared to findings obtained on US, the lumen seen as a central dot or line cannot be visualized on CT. When compared with findings on US, the lumen seen as central dot or line can not to be visualized with CT.[12] On US, collection of peri-appendicular fluid with appendicular intraluminal fluid and existence of an incompressible blunt tubular structure >6 mm are radiological findings supporting the diagnosis of AA. Appendicular intraluminal fluid and peri-appendicular fluid collection on US are radiologic signs supporting the diagnosis of AA in addition to an non-compressible blind-ended tubular structure >6 mm.[21,22] On the other hand, the most indicative radiological finding decisive for LH is thickening of the lamina propria (>0.8 mm) within the appendix wall.[23] Many patients who had LH undergo appendectomy which in turn raises NA rate. Many patients with LH un-

dergo appendectomy, which increases the NA ratio. While LH is sometimes and even often self-limited, patients with mild symptoms and signs and radiologically confirmed by US as having appendix thickness <6 mm, can be considered for 24-h conservative monitoring. While LH is often self-limiting, patients with mild symptoms and signs, and confirmed radiologically to have appendix thickness <6 mm by US may be considered for 24-h conservative follow-up. At the end of the follow-up period, the decision will be made whether discharge or appendectomy will be made according to the regression or progression of the patient's clinical picture. Although Despite its viral origin, antibiotic treatment is recommended during this period for the regression of LH during this period. Because it is believed that suppression of bacterial infection in the early stage of AA may prevent the progression to ischemia and bacterial invasion during the early stage of AA.[17] However, in cases where high-quality images cannot be obtained on US due to abdominal gas or in cases with appendix thickness of 5–6 mm, making a definitive diagnosis can be difficult. However, it may be difficult to make a definitive diagnosis in cases where high-quality images cannot be obtained on US due to abdominal gas or in cases with an appendix thickness of 5–6 mm. In this case, besides clinical and radiological findings, CBC parameters can help to differentiate AA from LH. In this situation, in addition to clinical and radiological findings, CBC parameters can help to differentiate AA from LH. High WBC values (>10500/mm^3) and NEU% (>75%) which are also used in many scoring systems such as the Alvarado score, can provide diagnostic information in favor of suppurative AA. However, we could not find any studies that addressed dealing with CBC singularly alone in distinguishing the differentiation of AA from LH.

After researching the English literature, to our knowledge, this is the first study to compare AA with LH only in the context of CBC alone context. Results of the present study reveal that -although weak- an association exists in distinguishing AA from LH according to WBC values. The results of this study show that there is a weak, albeit weak, relationship in separating AA from LH based on WBC values. Of the CBC parameters, WBC was the most powerful parameter by multi-logistic regression analysis in predicting acute AA with a 69.1% sensitivity, 80.0% specificity, 77.5% PPV, and 72.1% NPV. According to multiple logistic regression analysis, among the CBC parameters, WBC was found to be the most powerful parameter in predicting acute AA with 69.1% sensitivity, 80.0% specificity, 77.5% PPV, and 72.1% NPV. The cut-off value for WBC was 11.3 Ku/L, and every 1 one-unit increase of WBC raises the risk of AA by 1.24 times and decreases the likelihood of LH. In the present study, the cut-off value for WBC is 11.3 Ku /L, and an increase in WBC by one unit increases the risk of AA by 1.24-fold and reduces the likelihood of LH. In other words, values of WBC values above the cut-off level 11.3 Ku/L cut-off level will increase the likelihood of AA probability, while values below this will increase the likelihood of LH.

The study has some limitations. First, it's in retrospective nature. Second, the sample size is small. Third, the histopathological examination was performed by different pathologists rather than by a single pathologist, which has the potential to affect results to a certain extent.

Conclusion

In conclusion, AA and LH are separate entities according to their etiopathogenesis. In fact, these two different pathologies can be seen sometimes intertwined. In the absence of a concurrent AA, LH alone by itself is a distinct phenomenon that can be conservatively managed conservatively when it is identified early and is self-limiting. The most powerful strongest CBC parameter in differentiating to separate LH from AA appears to be as WBC, with a cut-off value of 11.3 Ku/L. Further randomized studies consisting of large patient population are needed to reach a definitive conclusion. More randomized studies with large patient populations are needed to reach a definitive conclusion.

Ethics Committee Approval: This study was approved by the Sakarya University Faculty of Medicine Ethics Committee (Date: 20.05.2020, Decision No: 71522473/050.01.04/267).

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ORİJİNAL ÇALIŞMA - *ÖZ*

Akut apandisiti lenfoid hiperplaziden ayırmada hematolojik parametrelerin rolü

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AMAÇ: Sık karışan apendiküler patolojilerden biri, erken teşhis edildiğinde konservatif olarak tedavi edilebilen ve kendi kendini sınırlayabilen lenfoid hiperplazidir. Bu geriye dönük çalışmanın amacı akut apandisiti lenfoid hiperplaziyle hematolojik parametreler açısından karşılaştırmak ve iki hastalığı ayırt etmede hematolojik bir prediktör olup olmadığını saptamaktır.
GEREÇ VE YÖNTEM: Akut apandisit tanılı hastalar ile lenfoid hiperplazi tanılı hastaların tam kan sayımları kıyaslandı.
BULGULAR: Yüz doksan beş hastaya (118 erkek/77 kadın) apendektomi yapıldı. Histopatolojik incelemede 161 hastada (%82.6) akut apandisit, 19 hastada (%9.7) negatif apendektomi saptandı. Negatif apendektomilerin 16'sı lenfoid hiperplaziydi (%8.2). On üç hastada (%6.7) eş zamanlı lenfoid hiperplazi ile birlikte akut apandisit saptandı. Beyaz küre sayısı (p=0.030, nötrofil sayısı (p=0.009), nötrofil yüzdesi (p=0.009) ve nötrofil/lenfosit oranı (p=0.007) akut apandisitte anlamlı olarak daha yüksek iken lenfosit sayısı (p=0.027), lenfosit yüzdesi (p=0.006) lenfoid hiperplazide anlamlı olarak daha yüksekti. Çoklu lojistik regresyon analizinde, akut apandisiti lenfoid hiperplaziden ayırmada beyaz küre sayısı %69.1 duyarlılık; %80 özgüllük; %77.5 pozitif prediktif değer ve %72.1 negatif prediktif değer ile tek bağımsız prediktör olarak saptandı. Kesit değeri 11.3 Ku/L olan beyaz küre sayısının her 1 birim (1000/mm^3) artışı, akut apandisit riskini 1.24 kat arttırırken, bunun altındaki değerlerde lenfoid hiperplazi olma olasılığı artmaktadır.
TARTIŞMA: Lenfoid hiperplaziyi akut apandisitten ayırmada en güçlü hematolojik parametre beyaz küre olarak gözükmektedir.
Anahtar sözcükler: Akut apandisit; beyaz küre sayısı; lenfoid hiperplazi; lenfosit; nötrofil; tam kan sayımı.

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