



Association of granulomatous appendicitis and simple laboratory tests. Controlled observational study.

Granülomatöz apandisitinin basit laboratuvar testleriyle ilişkisi. Kontrollü gözlemsel çalışma.

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Abstract

Aim: Granulomatous appendicitis (GA) is evaluated as different clinical situation from specific causes, and very rare. It is defined as the presence of granulomatous inflammation in the appendix. Its etiology can be infectious, or noninfectious. However its differentiation from tumor can be challenging with macroscopic appearance in the operation. In this study, we aimed to present a case series of GA cases, evaluate prediction and association of GA before surgery.

Material and Methods: A descriptive study is designed. All appendectomies between 2007 and 2015 were reviewed. The patients who diagnosed with GA by histopathological evaluation constituted study group. The rest constituted the control group. Demographic data, complete blood count parameters (22 parameters for each) were recorded. Categorical variables were expressed as frequencies and percentages. Baseline characteristics were compared using the t-test and Mann-Whitney U test. Fisher's exact test was used to compare categorical variables. The differences were considered statistically significant if the p value was less than 0.05 at a 95% confidence interval.

Results: During study period, 4570 patients were operated for acute abdomen with the presumptive diagnosis of acute appendicitis. Eight (0.2%) patients constituted study group. For control group sample size was calculated as 527 cases (95% power to show a 50% difference in the rate of the primary outcome, with a 2-sided type I error rate of 5%. Additional 142 to decrease errors). Demographic findings like age and gender didn't show difference between the groups (p=0.499 and p=0.477, respectively). EOS# and EOS% were higher in study group than control group (p<0.0001 and p<0.0001, respectively). Logistic regression analysis showed that EOS% effect was significant with p of <0.0001, odds ratio of 0.522 and Nagelkerke R² of 0.191.

Conclusion: Diagnosis of GA with macroscopic appearance in operation is a challenging for a surgeon. We found that EOS# and EOS% are associated with GA.

Keywords: Acute appendicitis, Granulomatous appendicitis, Prediction

Öz

Amaç: Granülomatöz apandisit (GA), spesifik nedenler ile oluşan farklı klinik durum olarak değerlendirilir ve çok nadirdir. Apendikste granülomatöz inflamasyon varlığı olarak tanımlanmaktadır. Etiyolojisi enfeksiyöz veya enfeksiyon dışı olabilir. Bununla birlikte, operasyondaki makroskopik görünümüyle tümörden ayırmak zor olabilir. Bu çalışmada, GA vaka serisi sunmayı ve cerrahiden önce GA öngörüsünü ve ilişkisini değerlendirmeyi amaçladık.

Araç ve Yöntemler: Tanımlayıcı bir çalışma tasarlandı. 2007 ile 2015 yılları arasındaki tüm apendektomiler gözden geçirildi. Histopatolojik değerlendirme ile GA tanısı alan hastalar çalışma grubunu oluşturdu. Geriye kalanlar kontrol grubu oluşturdu. Demografik veriler, tam kan sayımı parametreleri (her biri için 22 parametre) kaydedildi. Kategorik değişkenler frekanslar ve yüzdeler şeklinde ifade edildi. Temel özellikler, t-testi ve Mann-Whitney U testi kullanılarak karşılaştırıldı. Kategorik değişkenleri karşılaştırmak için Fisher'in kesin testi kullanıldı. P değerinin %95 güven aralığında 0.05'den düşük olması halinde farklar istatistiksel olarak anlamlı kabul edildi.

Bulgular: Çalışma süresi boyunca 4570 hasta akut karın için akut apandisit teşhisi ile ameliyat edildi. Çalışma grubunu sekiz hasta (%0,2) oluşturdu. Kontrol grubu için örneklem büyüklüğü %50 farkı göstermek için, %95 güce sahip olacak şekilde, 2 taraflı %5 tip I hata oranı ile 385 olarak hesaplandı. Hata payını azaltmak için yapılan eklemeler (142) ile son sayı 527 olarak hesaplandı. Yaş ve cinsiyet gibi demografik bulgular gruplar arasında fark göstermedi (sırasıyla p=0,499 ve p=0,477). Çalışma grubunda EOS# ve EOS% kontrol grubuna göre daha yüksekti (sırasıyla p<0,0001 ve p<0,0001). Lojistik regresyon analizi EOS% etkisinin anlamlı olduğunu gösterdi (p<0,0001, odd's oranı: 0,522, Nagelkerke R²:0,191).
Sonuçlar: Operasyonda makroskopik görünümü ile GA'nın teşhisi cerrah için zorlayıcıdır. EOS # ve EOS%'nin GA ile ilişkili olduğunu tespit ettik.

Anahtar kelimeler: Akut apandisit, Granülomatöz apandisit, Ön görmek

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Introduction

Granulomatous appendicitis (GA) is an uncommon cause of acute abdomen and may be presented as appendicular mass. It is defined as the presence of granulomatous inflammation in the appendix. Its etiology can be infectious, i.e., *Mycobacterium tuberculosis*, *Yersinia pseudotuberculosis*, parasites, and fungal infection, or noninfectious, i.e., Crohn's disease, sarcoidosis or in the case of tumors, or idiopathic [1, 2].

GAs are usually presented as acute appendicitis, and usually detected as an incidental finding during operation and pathological evaluation of appendix. Sometimes it can't be predicted with simple laboratory and diagnostic imaging like ultrasound; however its consequence after surgery may differ from acute appendicitis [3, 4]. The confirmatory diagnosis is made by histopathology and is characterized by the presence of non-necrotizing epithelioid granuloma, and mucosal ulcerations [5, 6].

GA can be presented as appendicular mass in diagnostic evaluation or operation. But differentiation of GA from tumor can be challenging with macroscopic appearance in the operation. In this study, we aimed to present a case series of GA cases, evaluate prediction of GA before surgery and discuss the entity under review of literature.

Material and Methods

We designed a descriptive study using retrospective review of prospectively collected data. The local institutional review board approved the study, and the universal principles of the Helsinki Declaration were applied.

All appendectomies between 2007 and 2015 were reviewed. The patients who diagnosed with GA by histopathological evaluation constituted GA group (study group). The patients who diagnosed with acute appendicitis by histopathological evaluation constituted control group. Patients with diagnose of non-appendicitis, e.g., mucocele, or tumor were excluded.

Demographic data, e.g., age and gender, and complete blood count parameters (BASO#: Basophil count, BASO%: Basophil percent, EOS#: Eosinophil count, EOS%: Eosinophil percent, Hct: Hemotocrit, Hgb: Hemoglobin, LY#: Lymphocyte count, LY%: Lymphocyte percent, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, MCV: Mean corpuscular volume, MO#: Monocyte count, MO%: Monocyte percent, MPV: Mean platelet volume, NEU#: Neutrophil count, NEU%: Neutrophil percent, Pct: Platelet concentration, PDW: Platelet distribution width, Plt: Platelet, RBC: Red blood cell count, RDW: Red blood cell distribution width, WBC: White blood cell count) which are taken before operation were recorded. We then performed univariate and multivariate analyses using binary logistic regression to examine the associations.

In study group, preoperative presumptive diagnoses were evaluated, operation notes regarding suspicious intraoperative findings, radiological and histopathological evaluations were recorded. All study cases were followed-up by routine examination and telephone interview.

Statistics

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 22.0 (IBM SPSS, New York, USA) & PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA). Normal distributions of the variables were assessed via Kolmogorov-Smirnov test and

histograms. Normally-distributed continuous variables were expressed as mean ± standard deviation (SD), and median and interquartile range is used for non-normally-distributed continuous variables. Categorical variables were expressed as frequencies and percentages. Baseline characteristics of the study and control groups were compared using the t-test for normally distributed continuous variables and Mann-Whitney U test for continuous variables without normal distribution and ordinal variables. Fisher's exact test was used to compare categorical variables. The statistical results were presented at a 95% confidence interval. The differences were considered statistically significant if the p value was less than 0.05.

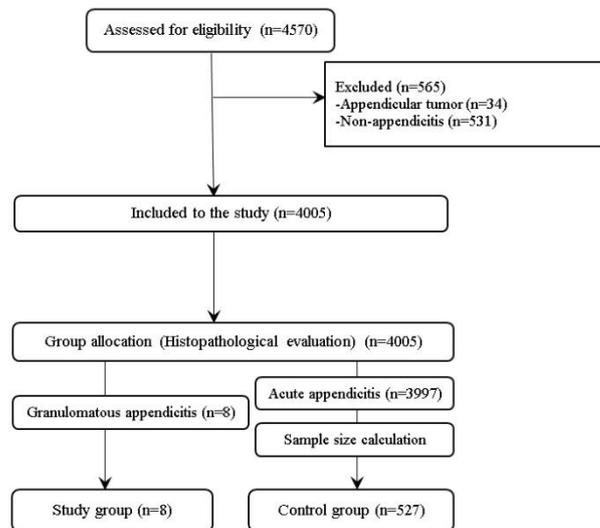
Results

During study period, 4570 patients were operated for acute abdomen with the presumptive diagnosis of acute appendicitis. In eight (0.2%) patients, histopathologic evaluation demonstrated a transmural inflammatory infiltrate in appendix with lymphoid follicles, indicative of granulomatous inflammation of appendix. These patients constituted the study group. After exclusion of 565 patients, 3997 patients constituted control group. We estimated that with a sample size of 385 control group patients, the study would have 95% power to show a 50% difference in the rate of the primary outcome, with a 2-sided type I error rate of 5%.

Also 142 patients added to decrease errors, and at the end, 527 patients constituted the control group. Selection of control group sample from 3997 patients were performed by computer generated numbers as a randomization model.

The diagram of the study is shown in figure 1.

Figure 1: Flowchart diagram



Patients' characteristics are provided in table 1. Demographic findings like age and gender didn't show difference between the groups (p=0.499 and p=0.477, respectively). Evaluation of complete blood count parameters revealed that EOS# and EOS% were higher in study group than control group (p<0.0001 and p<0.0001, respectively). Binary logistic regression analysis showed that EOS% effect was significant with p of <0.0001, odds ratio of 0.522 and Nagelkerke R2 of 0.191 (table 2).

In study group, the mean age was 31.1±10.7 years (20-46). Female to male ratio was 1 (4/4). Abdominal pain was present in all eight patients and nausea in three. Indications for surgery were acute abdomen in eight (100%) patients with presumptive diagnosis of acute appendicitis.

Table 1: Characteristics of groups

	Study group (n=8)	Control group (n=527)	p ^{1,2}
Age (Mean±SD)	31.1±10.7	28.5±10.6	0.499
Gender (M/F)	4/4	335/192	0.473
Complete blood count parameter	Median (IQR)	Median (IQR)	p ³
BASO#	0.02 (0.05)	0.04 (0.06)	0.640
BASO%	0.20 (0.49)	0.24 (0.41)	0.690
EOS#	0.30 (0.17)	0.04 (0.11)	<0.001*
EOS%	2.93 (1.56)	0.27 (0.86)	<0.001*
Hct	35.7 (11.4)	39.5 (6.2)	0.211
Hgb	12.25 (4.2)	13.3 (2.2)	0.387
LY#	1.29 (1.99)	1.88 (1.27)	0.149
LY%	14.4 (13.6)	12.2 (11.55)	0.888
MCH	27.6 (2.6)	28.8 (2.5)	0.232
MCHC	33.5 (1.9)	33.7 (0.9)	0.777
MCV	81.15 (3.7)	85.7 (6.3)	0.064
MO#	0.76 (0.61)	0.86 (0.50)	0.103
MO%	5.9 (2.2)	6.0 (3.0)	0.663
MPV	6.8 (1.2)	7.3 (1.3)	0.100
NEU#	9.07 (8.01)	12.10 (6.2)	0.088
NEU%	74.8 (15.4)	80.7 (13.5)	0.471
Pct	0.21 (0.15)	0.18 (0.06)	0.571
PDW	18.15 (33.3)	17.6 (1.4)	0.127
Plt	291.5 (219)	249.0 (84)	0.425
RBC	4.35 (1.0)	4.68 (0.62)	0.304
RDW	15.3 (4.7)	15.5 (1.4)	0.862
WBC	13.25 (9.4)	14.6 (6.3)	0.121

SD: Standard deviation, M: Male, F: Female, IQR: Interquartile range, ¹ t-test, ² Fisher's exact test, ³ Mann Whitney U test, * p<0.05

Table 2: Binary logistic regression

	S.E.	p	OR	95% CI for OR Lower Upper	Nagelkerke R2
EOS%	0.181	<0.0001	0.522	0.366 0.743	0.191
Constant	0.520	<0.0001	160.420		

Table 3: Characteristics of study group (Granulomatous appendicitis patients)

No	Sex	Age	Size cm	Pre-op diagnosis	US	CT	Operative findings Operation
1	F	20	1.5	AA	AA	AA, AM	Normal Open appendectomy
2	F	22	2	AM	AA	AM	Right hemicolecotomy
3	M	23	1.5	AM	AA, free fluid	AM, perforation, free air	AM, Perforated appendicitis Ileocecal resection
4	M	24	1	AA	AA	AA	AA Open Appendectomy
5	M	29	1	AA	AA		AA Laparoscopic appendectomy
6	M	42	0.5	AA	AA		AA Open Appendectomy
7	F	43	1	AM	AA	AM	AA Open Appendectomy
8	F	46	2	AA	AA		AM Right hemicolecotomy

US: Ultrasound findings, CT: Computed tomography findings, F: Female, M: Male, AA: Acute appendicitis, AM: Appendicular mass

Detailed information about the cases of study group is summarized in table 3. Preoperative imaging were performed in all patients with ultrasound which is showed suspicion of acute appendicitis in all, and in five patients with computed tomography which is suspected of appendicular mass in four patients (figure 2), acute appendicitis in one. In operation, we detected appendicular mass in three of eight patients, and right hemicolecotomy was performed in two (figure 3), ileocecal resection in one with the suspicion of tumor due to macroscopic appearance. Only appendectomy is performed in remaining five patients. In histopathological evaluation, Crohn's disease was suspected in three patients. In follow-up, entero-cutaneous fistula was detected in two patients, Crohn's disease in four. The patients with fistula were treated with conservative approach.

Figure 2: Computed tomography a, b, c: Multiplanar images of one patient showing the appendicular mass (axial, coronal, sagittal), d, e: axial images.

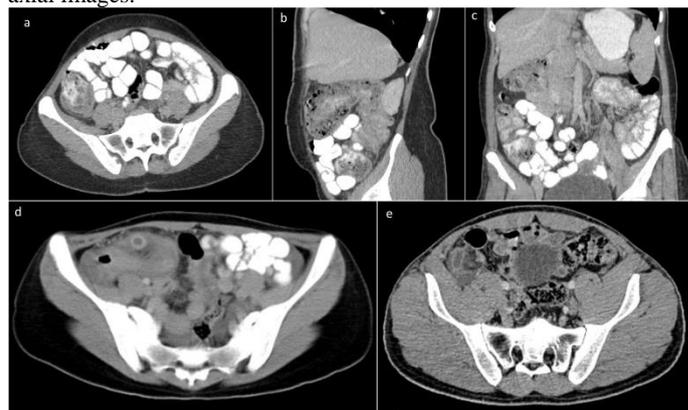
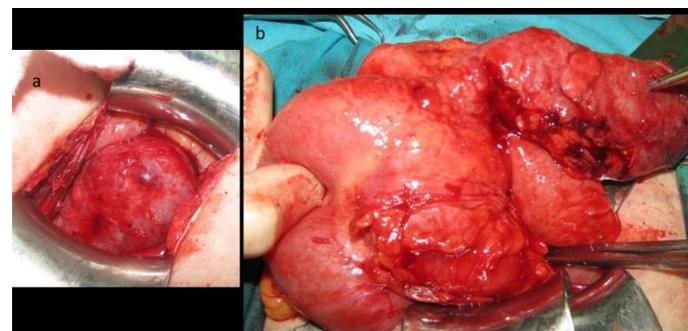


Figure 3: Operative view a: First appearance in surgery, b: Appendicular mass



Discussion

GA is a rare clinical entity and it is reported that GA constitutes less than 2% of all appendectomies in literature [7]. We found that 0.2% of appendectomy cases were GA, and they were all found incidentally. Our analysis for prediction effort was showed that EOS# and EOS% was significantly higher in GA patients.

The presentation of the condition does not differ from acute appendicitis, however they are usually more silent [1, 2]. Laboratory studies may provide little data and especially specific serology helps to diagnose at the onset of symptoms as it turns negative shortly after appendectomy [1]. In our study we found that complete blood count parameters, e.g., EOS#, EOS%, were different in GA patients.

Physical examination can be similar with an acute appendicitis. Imaging modalities like ultrasound cannot show a specific feature. Findings in ultrasound can be similar to that of a normal acute appendicitis. Therefore the patients are usually appendectomized due to presumptive diagnose of an acute

appendicitis, and the definitive diagnose of granulomatous appendicitis is achieved by histopathological examination [8, 9]. Treatment of GA is usually simple appendectomy, however some challenges may be shown in inflammatory bowel diseases, i.e. fistula in Crohn's disease [10]. In our study we performed ultrasound examination in all patients, however all examinations suspected only acute appendicitis. Computed tomography were taken in five patients and suspected appendicular mass in four patients, however it didn't change applied surgical treatment. Two right hemicolectomy and one ileocecal resection were performed in three of eight patients. Only appendectomy was performed in remaining patients. Unfortunately enterocutaneous fistula was developed in two of these patients.

The etiology of GA can be infectious or non-infectious causes. Isolated granulomatous inflammation of the appendix is rare situation, and its etiology is still unknown [7]. Non-infectious causes are responsible for 62% of cases, and diverticulitis, Crohn's disease, foreign-body reactions, tumors and sarcoidosis are main etiologies. Although Crohn's disease cannot be demonstrated with histopathological examination of GA in some patients, it is shown that approximately 5 and 10% of patients with GA will develop Crohn's disease in their lifetimes [3,4,11]. In our study, we detected Crohn's disease in four patients (50% of GA patients).

Infectious causes are responsible for 38% of cases, and constitute *Yersinia*, *Mycobacterium tuberculosis* and other microorganisms, e.g., parasites and fungi [12-14]. *Yersinia* infection accounts for up to 25% of GA [13]. *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* species are most responsible ones. In our study, *Enterobias vermicularis* infestation was found in one patient's appendix specimen at pathological evaluation. Tuberculosis was detected in one patient at follow-up, and treated accordingly. Idiopathic GA was suspected in remaining patients.

Some limitations are available in this study including its retrospective design and lack of advanced imaging technique like CT in some of the patients. New clinical studies with larger series are needed to confirm the aforementioned data of this study and to develop a protocol for detection of this pathology.

In conclusion, definitive diagnosis of GA could not be achieved in some cases with preoperative advanced imaging studies or macroscopic appearance in surgery. Preoperative laboratory studies, e.g., EOS# and EOS%, were found associated with GA. Treatment modality of this entity may be challenging for the surgeon, simple appendectomy or right hemicolectomy can be used accordingly in the operation.

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