



# Unexpected Histopathological Diagnoses in Acute Appendicitis Specimens: A Retrospective Analysis of 2076 Patients

## Akut Apandisit Spesmenlerinde Beklenmeyen Histopatolojik Tanılar: 2076 Hastanın Retrospektif Analizi

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### ABSTRACT

**Aim:** Acute appendicitis is the most common cause of emergency abdominal surgery in the world. Although the etiology of appendicitis is still not fully known, possible causes include lumen obstruction. Fecaloid and lymphoid hyperplasia are the most common causes of lumen obstruction. However, some rare conditions may cause acute appendicitis by causing lumen obstruction. Here, we aimed to present the pathology results of 2076 patients operated due to acute appendicitis in our hospital and the unexpected histopathological findings in the light of the literature.

**Method:** Patients who were emergently operated with diagnosis of appendicitis between January 2016 and February 2020 in Gaziantep Dr. Ersin Arslan Training and Research Hospital were retrospectively screened. Incidental appendectomies were excluded. Data of 2076 patients were reached. Gender, age, and pathology results of the patients were analyzed. Pathology preparations were reassessed by two pathologists. Pathology results were analyzed under two categories as general findings and unexpected findings. Fisher's chi-square test was used for statistical analysis.

**Results:** A total of 2076 patients were included in the study and analyzed. Of the patients, 1368 (66%) were man, 708 (34%) were woman, and the mean age was 33±12.9 years. Acute appendicitis was found in 1309 (63.1%) patients, gangrenous-perforated appendicitis in 305 (14.7%) patients, negative appendectomy in 105 (5.1%) patients, phlegmonous appendicitis in 32 (1.5%) patients, and unexpected pathological findings in 62 (3%) patients. Among the unexpected pathological findings were fibrous obliteration in 31 (50%) patients, mucosal hyperplasia in 8 (13%) patients, appendicular diverticulitis in 7 (11.3%) patients, retention cyst in 5 (8.1%) patients, mucinous cystadenoma in 3 (4.8%) patients, well-differentiated neuroendocrine tumor in 2 (3.2%) patients, eosinophilic infiltration in 2 (3.2%) patients, foreign body reaction in 2 (3.2%) patients, granulomatous appendicitis in 1 (1.6%) patient, and parasitic infestation was detected in 1 (1.6%) patient.

**Conclusion:** Unexpected histopathological findings are rare in appendectomy specimens and these diagnoses help guide the patient's treatment.

**Keywords:** Appendicitis, neuroendocrine neoplasm, mucocele, adenocarcinoma, carcinoid

### ÖZ

**Amaç:** Akut apandisit dünya üzerinde en sık acil karın ameliyatıdır. Apandisit etiyolojisi hala tam olarak bilinmemekle birlikte olası nedenler arasında lümen obstrüksiyonu yer alır. Fekaloit ve lenfoid hiperplazi lümen obstrüksiyonuna neden olan en yaygın nedenlerdir. Ancak bazı nadir durumlar da lümen obstrüksiyonu yaparak akut apandisit neden olabilmektedir. Biz burada hastanemizde akut apandisit tanısıyla opere edilen 2076 hastanın patoloji sonuçlarını ve bunlar arasında beklenmeyen histopatolojik bulguları literatür eşliğinde sunmayı amaçladık.

**Yöntem:** Gaziantep Dr. Ersin Arslan Eğitim ve Araştırma Hastanesi'nde Ocak 2016-Şubat 2020 tarihleri arasında akut apandisit tanısıyla acil opere edilen hastalar retrospektif olarak tarandı. İnsidental apendektomiler çalışma dışı bırakıldı. Toplam 2076 hastanın verisine ulaşıldı. Hastaların cinsiyet, yaş ve patoloji sonuçları analiz edildi. Patoloji preparatları iki patolog tarafından tekrar değerlendirildi. Patoloji sonuçları genel bulgular ve beklenmeyen bulgular olarak iki kategori altında incelendi. İstatistiksel analizde Fisher's ki-kare testi kullanıldı.



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**Bulgular:** Toplam 2076 hasta çalışmaya dahil edilip analiz edildi. Bu hastalar 1368 (%66) erkek olup, toplam yaş ortalaması 33±12,9 idi. Akut apandisit 1309 (%63,1), gangrenöz-perfore apandisit 305 (%14,7), negatif apendektomi 105 (%5,1), flegmanöz apandisit 32 (%1,5), beklenmeyen patolojik bulgular ise 62 (%3) hastada saptandı. Beklenmeyen patolojik bulgular içerisinde, 31 (%50) hastada fibröz obliterasyon 8 (%13) hastada mukozal hiperplazi, 7 (%11,3) hastada apendiküler divertikülit, 5 (%8,1) hastada retansiyon kisti 3 (%4,8) hastada müsinöz kistadenom 2 (%3,2) hastada iyi defansiyenöroendokrin tümör, 2 (%3,2) hastada eozinofilik infiltrasyon, 2 (%3,2) hastada yabancı cisim reaksiyonu, 1 (%1,6) hastada granümatöz apandisit ve 1 (%1,6) hastada parazit enfestasyonu saptandı.

**Sonuç:** Apendektomi spesmenlerinde beklenmedik histopatolojik bulgular nadir olup, bu tanılar hastanın tedavisini yönlendirmeye yardımcı olmaktadır.

**Anahtar Kelimeler:** Apandisit, nöroendokrin neoplazm, mukosel, adenokarsinom, karsinoid

## Introduction

Acute appendicitis remains one of the most common causes of emergency abdominal surgeries in the world. Appendectomy is performed in patients with suspected or definite acute appendicitis. Appendectomy not only removes the appendix but also prevents mortal complications such as perforation, plastron and sepsis.<sup>1</sup> While the risk of development of acute appendicitis is higher in men, women are more exposed to appendectomy. The incidence of acute appendicitis is 8.6% in men and 6.9% in women. The appendectomy rate is 12% in men and 23% in women.<sup>2</sup> Appendicitis can be seen in all age groups but is often seen between 10-20 years of age.<sup>3</sup>

Although the etiology of appendicitis is still unknown, lumen obstruction is one of the possible causes.<sup>4</sup> Lumen obstruction prevents the discharge of mucosal secretions, resulting in increased lumen intra-pressure. As a result of increased pressure, venous and lymphatic drainage deteriorates, causing necrosis and perforation.<sup>5</sup> Fecaloid and lymphoid hyperplasia are the most common causes of lumen obstruction. However, some rare cases can cause an acute appendicitis by causing lumen obstruction. Among these are enterobiasis, ascariasis, tapeworm, actinomycosis, schistosomiasis, amebiasis, carcinoid tumor, adenocarcinoma, endometriosis, granulomatous diseases, gastrointestinal stromal tumors and mucocele.<sup>6</sup>

There are many studies reporting unexpected histopathological findings following examination of appendectomy specimens.<sup>7,8,9</sup> In this way, benign and malignant tumors and infectious diseases can be diagnosed early and treated. In order to emphasize that unexpected histopathological findings are important in appendectomy specimens, we conducted a retrospective analysis of appendectomy specimens in our hospital. We aimed to present the pathology results of 2076 patients with acute appendicitis in our hospital and the unexpected histopathological findings among them with the literature.

## Materials and Methods

Patients who were admitted to the emergency service with the diagnosis of acute appendicitis between January 2016

and February 2020 in Gaziantep Dr. Ersin Arslan Training and Research Hospital were retrospectively screened. Incidental appendectomies were excluded. Data of a total of 2076 patients were accessed. The gender, age and pathology results of the patients were analyzed. Negative appendectomy and unexpected histopathological findings by gender were evaluated separately. The distribution of pathological findings by age was analyzed. Pathology preparations were re-examined by two pathologists (MT, DA). Pathology results were analyzed under two categories as general findings and unexpected findings. Acute, gangrenous-perforated and phlegmatous appendicitis were included in the group of general pathological findings. Appendicular diverticulitis, eosinophilic infiltration, granulomatous appendicitis, fibrous obliteration, mucosal hyperplasia, mucocele, mucinous cystadenoma, mucinous neoplasia, neuroendocrine tumor, parasite infestation and foreign body reaction were included in the group of unexpected pathological findings. In statistical analysis, quantitative variables were expressed as mean ± standard deviation, median, minimum-maximum and range. Qualitative variables were reported as number and percentage (%). Fisher's chi-square test was used to compare qualitative variables. A p value less than 0.05 was considered statistically significant.

## Results

A total of 2076 patients were included in the study and analyzed. Of the patients, 1368 (66%) were man, 708 (34%) were woman, and the mean age was 33±12.9 years. The majority of the patients were between the ages of 21-30 (36%) years and 1.2% of the patients were over 70 years (Table 1). Acute appendicitis was detected in 1309 (63.1%) patients, gangrenous-perforated appendicitis in 305 (14.7%) patients, lymphoid hyperplasia in 263 (12.7%) patients, negative appendectomy in 105 (5.1%) patients, phlegmatous appendicitis in 32 (1.5%) patients, unexpected pathological findings in 62 (3%) patients. Among the unexpected pathological findings, fibrous obliteration was found in 31 (50%) patients, appendicular diverticulitis in 7 (11.3%) patients, retention cyst in 5 (8.1%) patients, mucinous

cystadenoma in 3 (4.8%) patients, well-differentiated neuroendocrine tumor in 2 (3.2%) patients, eosinophilic infiltration in 2 (3.2%) patients, foreign body reaction in 2 (3.2%) patients, granulomatous appendicitis in 1 (1.6%) patient, and parasite infestation in 1 (1.6%) patient (Table 2).

**Table 1.** Demographic characteristics of patients undergoing appendectomy

Features of patients	Result
Number of patients	2076
Gender	
Male	1368
Female	708
Features about age	
All patients	33.01±12.9
Males	31.5±11.8
Females	35.96±14.3
Distribution of patients by age	
15-20	320
21-30	743
31-40	508
41-50	286
51-60	128
61-70	66
>70	25
Distribution of patients with negative appendectomy by age	
All patients	105
Males	66 (4.8%)
Females	39 (5.5%)
15-20	13
21-30	34
31-40	23
41-50	20
51-60	10
61-70	3
>70	2

Acute appendicitis was detected in 890 (65.1%) of male and 419 (59.2%) of female patients. The frequency of acute appendicitis was significantly higher in men ( $p=0.01$ ). Perforated appendicitis was detected in 196 (14.3%) of male and 109 (15.4%) of female patients. Perforated appendicitis was more common in women, but there was no statistical significance between genders ( $p=0.51$ ). Negative appendectomy was detected in 66 (4.8%) of male and 39 (5.5%) of female patients. Negative appendectomy was more common in women, but there was no statistical significance between genders ( $p=0.53$ ) (Table 3). The majority of patients with negative appendectomy was between the ages of 21-30 years.

Unexpected pathological findings were found in 62 (3%) patients, 38 (1.8%) of whom were male and 24 (1.2%) of whom were female. Fibrous obliteration was detected in 31 (1.5%) patients, mucosal hyperplasia in 8 (0.9%) patients, appendicular diverticulitis in 7 (0.3%) patients, retention cyst (mucocele) in 5 (0.2%) patients, mucinous

**Table 2.** Histopathological findings of appendectomy specimens

Histopathological findings	Total
Acute appendicitis	1309 (63.1%)
Gangrenous-perforated appendicitis	305 (14.7%)
Lymphoid hyperplasia	263 (12.7%)
Negative appendectomy	105 (5.1%)
Phlegmatous appendicitis	32 (1.5%)
Unexpected histopathological findings	62 (3%)
Fibrous obliteration	31 (50%)
Mucosal hyperplasia	8 (13%)
Appendicular diverticulitis	7 (11.3%)
Retention cyst	5 (8.1%)
Mucinous cystadenoma	3 (4.8%)
Neuroendocrine tumor, well differentiated	2 (3.2%)
Eosinophilic infiltration	2 (3.2%)
Foreign body reaction	2 (3.2%)
Granulomatous appendicitis	1 (1.6%)
Parasite infestation	1 (1.6%)

**Table 3.** Comparison of histopathological findings by gender

	Male (n=1368)	Female (n=708)	Statistical analysis
Acute appendicitis	890 (65.1%)	419 (59.2%)	$p<0.05$
Perforated appendicitis	196 (14.3%)	109 (15.4%)	
Negative appendectomy	66 (4.8%)	39 (5.5%)	$p>0.05$

cystadenoma in 3 (0.1%) patients, well-differentiated neuroendocrine tumor in 2 (0.1%) patients, eosinophilic infiltration in 2 (0.1%) patients, foreign body reaction in 2 (0.1%) patients, granulomatous appendicitis in 1 (0.05%) patient, and parasite infestation in 1 (0.05%) patient.

## Discussion

The incidence of acute appendicitis is higher in men. The differential diagnosis includes normal menstruation, dysmenorrhea, ovarian torsion, ectopic pregnancy, and pelvic inflammatory disease, which are especially seen in premenopausal women.<sup>10</sup> This explains why women are mostly exposed to negative appendectomy. There are studies reporting the negative appendectomy rate as 6.3-22.8% in the literature.<sup>1,11</sup> In our study, negative appendectomy was found in 5.1% of the patients, and it was found more in women who were operated, but the difference was not statistically significant ( $p=0.53$ ). The lower rates of negative appendectomy compared to the literature was thought to be a result of the widespread use of ultrasound and computed tomography, which have become routine in the preoperative period.

Although rare, different pathologies of the appendix can be encountered in patients who have been operated with a pre-diagnosis of acute appendicitis. These include congenital anomalies such as appendix duplication and appendix vermiformis agenesis.<sup>12,13</sup> No congenital anomalies were found in our clinical series. Unexpected histopathologies can be detected in appendectomy specimens. In a literature review, the rate of unexpected histopathological diagnoses was reported as 1.7%, and the rate of primary and secondary adenocarcinoma and mucinous cystadenocarcinoma of the appendix was reported as 0.03%.<sup>6</sup> In our study, the rate of unexpected histopathological findings was 3% and primary and secondary adenocarcinoma and mucinous cystadenocarcinoma of the appendix were not detected.

Fibrous obliteration is thought to develop as a result of neurogenic proliferation and is also referred as neurogenic appendicopathy and appendiceal neuroma. In addition, the molecular mechanism in its pathogenesis is unknown. It is thought to occur as a result of obstruction of the lumen of the appendix with fibrous tissue secondary to hyperplasia of neuroendocrine cells. Fibrous obliteration is seen in 9.7% of incidental appendectomy specimens.<sup>14</sup> In acute appendicitis series, it is seen at a rate of 0.8-4.5% and constitutes 27.1-65% of unexpected histopathological findings.<sup>15,16</sup> In our study, fibrous obliteration was detected in 31 (1.5%) patients and constituted 50% of unexpected histopathological findings.

Appendicular diverticulum is an extremely rare condition. Its incidence is 0.004-2.1% in appendectomy specimens,

while it is 0.2-0.6% in routine autopsy series.<sup>17</sup> Appendicular diverticulum can be acquired or congenital. Acquired diverticula are mostly seen in patients aged >30 years old. In another series in which appendectomy was performed due to acute appendicitis, appendicular diverticulum was detected at a rate of 0.8%, and diverticulitis was found in 61.5% of them.<sup>18</sup> In the presence of diverticulum, the risk of perforation and mortality is higher than acute appendicitis without diverticulum.<sup>19</sup> In our study, appendicular diverticulum was detected in 7 (0.3%) patients, appendicular diverticulitis was detected in 6 (86%) patients, and no perforation was observed.

Appendiceal mucocele was first described by Rokitansky in 1842<sup>20</sup>. It occurs as a result of obstructive dilatation of the appendix and mucoid material filling the lumen. Appendiceal mucocele is rare, with an incidence of 0.07-0.63% in appendectomy specimens.<sup>21</sup> Histopathologically, there are four subtypes. These are retention cyst, mucosal hyperplasia, mucinous cystadenoma and mucinous cystadenocarcinoma.<sup>22</sup> When total excision is performed without perforation in the benign forms of retention cyst, mucosal hyperplasia and mucinous cyst adenoma, 5-year survival is 100%.<sup>23</sup> In our study, mucosal hyperplasia was detected in 8 (0.4%), retention cyst (mucocele) in 5 (0.2%) and mucinous cystadenoma in 3 (0.1%) patients, and mucinous cystadenocarcinoma was not detected.

Mucosal hyperplasia was first described by MacGillivray<sup>24</sup> in 1972 as mucosal metaplasia associated with colon cancer. Thereupon, in another study, appendices in the specimens of patients who underwent ileocelectomy were examined. Mucosal hyperplasia was found in 30% of adenocarcinomas, 11.8% of adenomatous polyps, and 6.5% of non-neoplastic specimens.<sup>25</sup> In our study, mucosal hyperplasia was detected in 8 (0.4%) patients, and it constituted 13% of unexpected histopathological findings. Colonoscopy was performed in these patients for malignancy screening and to detect accompanying colon pathologies, and no evidence of malignancy was found.

Granulomatous appendicitis is a rare condition in appendectomy specimens. Granulomatous infection of the appendix was first reported in 1953 by Meyerding and Bertram<sup>26</sup> as a finding of Chron's disease. Granulomatous appendicitis is detected at a rate of 0.1-2% in appendectomy materials.<sup>27</sup> In its etiology, not only Chron's disease, but also infectious or non-infectious causes such as *Yersinia* species, sarcoidosis, tuberculosis, foreign body reactions, schistosomiasis, actinomycosis and eosinophilic infiltration.<sup>28,29</sup> In our study, granulomatous appendicitis 1 (0.05%), eosinophilic infiltration 2 (0.1%), foreign body reaction 2 (0.1%) and parasite infestation were observed in 1 (0.05%) patient. However, no granulomatous formation was

detected in eosinophilic infiltration and parasite infestation. Carcinoid tumor (neuroendocrine tumor) is the most common primary malignant lesion of the appendix and constitutes 60% of all appendix tumors.<sup>30</sup> Carcinoid tumor is detected in 0.3-0.9% of appendectomy specimens.<sup>31</sup> It frequently affects young patients and it occurs between ages of 32 and 42.2 years.<sup>32,33</sup> Carcinoid tumors of the appendix are generally small in size, benign in character, and their metastases occur less than 2%, and tumor sizes are smaller than 1 cm in 70-95% of them.<sup>34</sup> In our study, carcinoid tumor (neuroendocrine tumor) was detected in 2 (0.1%) patients, and the ages of the patients were 27 and 32 years. The findings were consistent with the literature. Tumors of both patients were well differentiated. Tumor sizes were 3 and 4 mm and invasion of muscularis propria was detected. Neither of them had lymphovascular and perineural invasion.

## Conclusion

Although acute appendicitis is a disease classified as benign and its surgery is a daily surgery, unexpected histopathological findings can be detected in the examination of appendectomy specimens. The variety of these findings can range from premalignant lesions to malignancies. It should be noted that the histopathological evaluation of appendectomy materials is a guide for the diagnosis and treatment of additional diseases present in the patient.

## Ethics

**Ethics Committee Approval:** Ethics committee approval was not obtained because it was a retrospective study.

**Informed Consent:** Informed consent was obtained from all participants for surgery.

**Peer-review:** Internally peer reviewed.

## Authorship Contributions

Surgical and Medical Practices: U.U., R.G., K.G., Concept: U.U., M.T., Design: R.G., D.A., Data Collection or Processing: M.T., D.A., Analysis or Interpretation: R.G., M.T., D.A., Literature Search: U.U., R.G., K.G., Writing: U.U., R.G.

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