ORIGINAL ARTICLE

Uncommon causes of acute appendicitis: Retrospective analysis of 6785 histopathological findings in a tertiary center

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ABSTRACT

BACKGROUND: This study aims to determine the uncommon causes of acute appendicitis in analyzed post appendectomy specimens.

METHODS: Histopathology reports of 6785 removed appendices were analyzed retrospectively in order to confirm the uncommon cause of acute appendicitis in single tertiary institution.

RESULTS: Unusual cause of acute appendicitis was found in 98 (1.44%) samples (40 female and rest 58 male patients). Neuroendocrine tumor of the appendix was the most common pathology, followed by serrated adenoma, low-grade appendicular mucinous neoplasm, hyperplastic polyp and intestinal parasite. In four patients (0.05%), appendicular adenocarcinoma was confirmed with an overall mortality of 75%. Age was significantly higher in uncommon acute appendectomies than in ordinary appendectomies. Survival analysis of unusual appendectomies showed that advanced age is of prognostic importance (Kaplan Meier p<0.0001). There was also a difference in survival between different disease groups in unusual appendectomies, but Cox multifactorial analysis showed that these two factors were not statistically significant.

CONCLUSION: Although rare, unusual causes are the etiological factor responsible for acute appendicitis. These reasons should be kept in mind in the older age group and the diagnosis of appendicitis should be made carefully.

Keywords: Acute appendicitis; etiology; unusual.

INTRODUCTION

Acute appendicitis (AA) is a condition that requires emergency surgical procedure in most of the cases (open or laparoscopic appendectomy).[1] Its incidence varies according to geographic region from 2% to 9%. The most common cause for AA occurrence is luminal obstruction of the appendix vermiformis by appendicolith, lymphoid hyperplasia, stool impaction and appendicular or cecal tumor.[2] Other etiologic factors described to be associated with AA are certain infectious agents, environmental factors and neurogenic mechanisms (neurogenic appendicopathy).[3–5]

The pre-operative diagnosis of AA, although preoperatively established by the clinician, is proven by the pathologist's report. Histopathological analysis of the removed appendix has two major roles: Confirmation of the appendicular inflammation and eventually to reveal its etiology. Retrospective series and case reports of unusual and rare causes of AA are reported. The described "unusual findings" comprehend low-grade appendicular mucinous neoplasm (LAMN), neuroendocrine appendicular tumor (NET), appendicular adenocarcinoma, lymphoma, gastrointestinal stromal tumor

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(GIST), granulomatous inflammation, endometriosis externa, appendicular mucocele, tuberculosis, intraluminal *Enterobius* vermicularis, ascariasis, amebiasis, etc.[6–11]

The purpose of this study was to look into the differences in the occurrence and distribution of morbidity and mortality based on demographic characteristics (age, gender, etc.) of rare pathological findings found in appendectomy specimens of patients who had surgery for AA at a single institution.

MATERIALS AND METHODS

Retrospective review of 6785 histopathology reports of removed appendices in a single tertiary institution was conducted. Cases were collected retrospectively, based on the pathology reports of patients who were operated for AA between May 2006 and March 2022 with the decision of the institutional ethics committee (Number: E-48670771-514.99). Demographic data such as age and gender of the patients were obtained from the population registration system information as well as whether they were alive or not. Concomitant appendectomies performed during another procedure were not included in this study.

Statistical Analysis

SPSS v. 18.0.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Clinical and pathological parameters were analyzed with Chi-square test (for categorical variables), Mann–Whitney U-test (for numerical variables with non-normal distribution), Kruskal–Wallis test (for non-parametric analysis of the independent groups), receiver operating characteristic (ROC) test (for determining age cut off), Kaplan–Meier (for survival analysis) and multivariable Cox regression methods. Statistical significance was set for $p \leq 0.05$.

RESULTS

Out of 6785 analyzed histopathology reports, 98 (1.44%) of them were diagnosed with uncommon causes for AA. Among them, 40 were female and the other 58 were in male patients. The mean age in these patients was 45.7±17.8 years (range: 15–89 years). There was no statistical difference in age between the male and female group ($p=0.435$, Mann–Whitney U-test). Overall, appendicular perforation rate was 7.57% (514 patients) and in the uncommon appendicitis cases, the perforation rate was 7.14% (seven patients). There was no statistical difference between these two groups.

The most frequent pathology happened to be appendicular NET, followed by serrated adenoma, LAMN, hyperplastic polyp and intestinal parasite (Fig. 1). Different types of unusual histopathology findings are presented in Table 1. The overall incidence of appendicular adenocarcinoma occurrence in the analyzed specimens was 0.05% (four patients) in all of the analyzed specimens.

No additional surgical intervention was performed on any of the patients except for the complementary surgeries performed for adenocarcinoma patients. All of the patients underwent right hemicolectomy.

Analysis of the difference in age between the patients with different causes of uncommon AA presented statistically significant ($p<0.001$). All the ages differed from each other (Fig. 2).

The rare appendectomy diagnostic groups had a wide age distribution. Those with similar mean ages were evaluated together. When neuroendocrine tumor, intestinal parasite, mucocele, GIST, neuroma and endometriosis groups were combined, the mean age was (mean: 35.33 years). The mean age of polyps (hyperplastic, serrated and adenomatous polyps) and LAMN groups (mean 64.76 years) was also statistically high (Kruskal–Wallis $p<0.0001$). In the adenocarcinoma group the mean age was 44.5 years.

Mortality was recorded during the follow-up period in part of the patients with uncommon histopathology findings. The statistical analysis showed that gender had no influence on survival ($p=0.503$). However, histopathology results of uncommon AA were found to have a statistically significant effect on survival ($p<0.0001$) (Fig. 3).

Patients diagnosed with appendicular adenocarcinoma had a mean age of 44.5 in the uncommon pathology group and the mortality rate was high (75%). In cases with serrated adenoma (mean age of 62.1), hyperplastic polyp (mean age of 53.6) and tubulovillous adenoma (mean age of 66.6), survival was shorter in comparison with other common appendicitis pathologies.

Perforated appendicitis as a cause of mortality in general group and uncommon group presented without statistical significance. In addition, in the uncommon group, there was no correlation between perforation and mortality ($p>0.05$). NET prevalence was more common but there was no mortality in this group.

Mortality caused by uncommon AA etiology was as follows: 75% (three patients) with appendicular adenocarcinoma, 50% (one patient) with tubulovillous adenoma, 11.1% (two patients) with serrated adenoma and 10% (one patient) with hyperplastic polyp.

Early mortality occurred in three patients (3%) in the postoperative 1st month for reasons such as perforated appendix and ileus due to adhesion among the patients who developed mortality other than adenocarcinoma. The mean age of these three patients with early mortality was 71.1 years.

The ROC test was used to determine the age cut off. The cut off value for age was 55 years (71% sensitivity and 79% specificity, $p=0.008$).

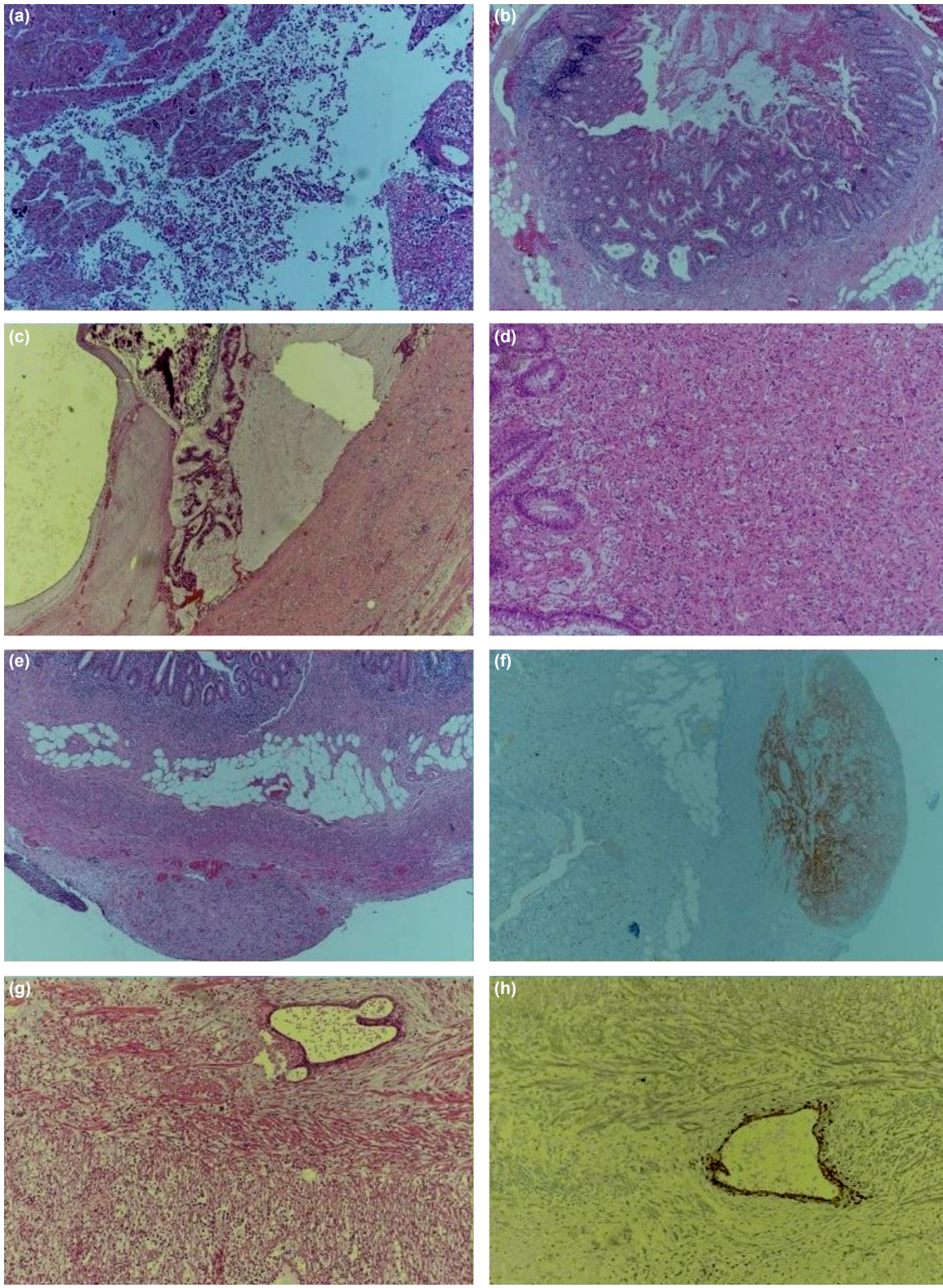

Figure 2. (a) ×100 HE *Enterobius* vermicularis, **(b)** ×40 HE; serrated adenoma, **(c)** ×40 HE low-grade appendicular mucinous neoplasm, **(d)** ×100 HE neuroendocrine appendicular tumor, **(e)** ×40 HE gastrointestinal stromal tumor (GIST), **(f)** ×40 GIST (DOC1+), **(g)** ×10HE endometriosis, and **(h)** ×10 endometriosis (ER+).

In the Cox regression analysis using this cut off value to investigate which is the independent factor for survival, age and pathology of unusual errors come to the fore. It was observed that the probability of an uncommon etiology finding is increased in advanced age, whereas age and diagnosis were not independent of each other (Table 2).

Table 1. Types and features of uncommon pathologies

Cause	Total, n (%)	Gender, n (%)		Mean age (years)	Mortality	Survival (mean months)
		Female	Male			
Neuroendocrine tumor	38 (38.8)	15 (37.5)	23 (39.7)	36.9	0	76.1
Serrated adenoma	18 (18.4)	6 (15)	12 (20.7)	62.1	2	34.9
LAMN	11 (11.2)	5 (12.5)	6 (10.3)	50.4	0	59.7
Hyperplastic polyp	10 (10.2)	5 (12.5)	5 (8.6)	53.6	1	41.8
Intestinal parasite	10 (10.2)	5 (12.5)	5 (8.6)	37.1	0	105.3
Adenocarcinoma	4 (4.1)	1 (2.5)	3 (5.2)	44.5	3	33.4
Intramucosal neuroma	2 (2)	1 (2.5)	1 (1.7)	41.7	0	33.1
Tubulovillous adenoma	2 (2)	1 (2.5)	1 (1.7)	66.6	1	66.7
Mucocele	1 (1)	0	1 (1.7)	28.2	0	151.2
Gastrointestinal stromal tumor	1 (1)	0	1 (1.7)	37.3		67.6
Endometriosis externa	1 (1)	1 (2.5)	0	38.9	0	40.1
Total	98 (100)	40	58	45.7	7	49.6

LAMN: Low-grade appendicular mucinous neoplasm.

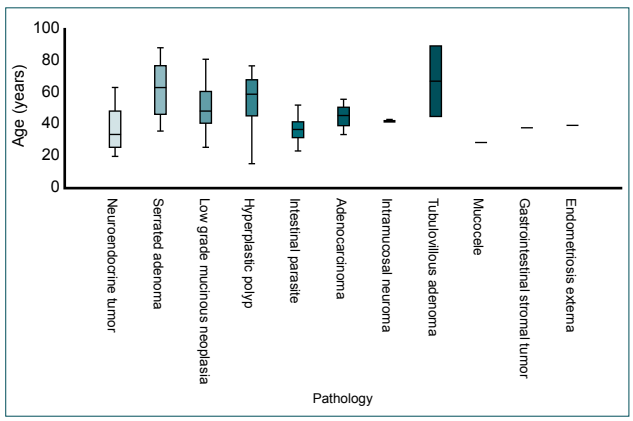

Figure 2. Age distribution according to different pathology.

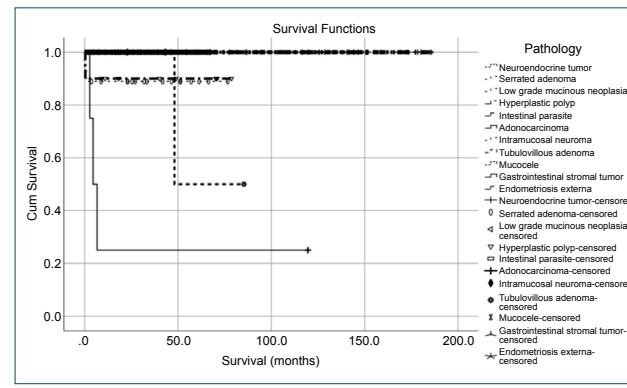

Figure 3. Kaplan–Meier curve for the survival function depended on the histopathology finding.

DISCUSSION

AA is one of the most common manifestations of acute abdominal surgery and appendectomy is one of the most frequently performed surgical procedures worldwide.[12]

Primary pathological event in AA is luminal occlusion, which increases the intraluminal pressure in the appendix and causes subsequent ischemia.[13] The incidence of AA roughly parallels the incidence of lymphoid development, with the highest incidence occurring between the ages of 10 and 30. Although the gender ratio is equal in cases of AA occurring before puberty, the incidence in males begins to increase gradually during adolescence. By the age of 15–25, the gender ratio shifts to 2:1 in favor of males. This bias decreases with age and the relevant incidence re-equalizes. In our series, this rate was 1.5/1 in favor of males. Many common and unusual etiologies can lead to appendicular lumen obstruction.[6] The mean age for appendectomies was reported to be 32 years, but in our unusual series, it was found to be 45.7 years.

Regardless of the etiology, the development of luminal obstruction has been suggested as the most important factor in the etiopathogenesis of AA. Lymphoid hyperplasia is the most common underlying condition of AA in the first 20 years of life, while fecal obstruction in elderly patients. Despite its descriptive name, this occlusive process has been shown to involve predominantly neurogenic proliferation. Therefore, neurogenic appendicopathy and appendicular neuroma have recently been proposed as alternative diagnostic terminology. Regardless of this, the molecular mechanisms underlying this pathogenic process remain unknown. It is believed to develop secondary to hyperplasia of neuroendocrine cells, as appendicular lumen replacement by fibrous tissue and chronic inflammatory cells is often accompanied by markedly increased proliferation of nerve cells and neuroendocrine cells. They

Table 2. Cox Regression test results

Variables in the equation								
	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Year 55	1.703	0.975	3.050	1	0.081	5.493	0.812	37.161
Pathology			9.279	10	0.506			
Pathology (1)	10.222	126.596	0.007	1	0.936	27506.448	0.000	1.579E+112
Pathology (2)	-0.457	254.323	0.000	1	0.999	0.633	0.000	1.912E+216
Pathology (3)	9.911	126.598	0.006	1	0.938	20149.716	0.000	1.161E+112
Pathology (4)	0.154	270.594	0.000	1	1.000	1.167	0.000	2.496E+230
Pathology (5)	13.051	126.594	0.011	1	0.918	465768.844	0.000	2.664E+113
Pathology (6)	0.182	641.329	0.000	1	1.000	1.199	0.000	.
Pathology (7)	11.541	126.598	0.008	1	0.927	102806.317	0.000	5.922E+112
Pathology (8)	0.154	766.798	0.000	1	1.000	1.167	0.000	.
Pathology (9)	0.154	766.798	0.000	1	1.000	1.167	0.000	.
Pathology (10)	0.182	898.098	0.000	1	1.000	1.199	0.000	.

are rarely present, with a reported prevalence of 0.1%. In our series, this rate was found to be 0.044% when neuromas were evaluated together with the case in GIST (3/6785).[14]

The differential diagnosis between appendicular neuroma and AA is difficult and depends on the patient's clinical history, symptoms and laboratory and physical examination findings. Most appendicular neuromas are found incidentally in asymptomatic patients when pathological examination of the appendix reveals fibrous obliteration.[10,15]

NETs, which is considered the most common type of primary tumor of the appendix and accounts for approximately 60% of all appendicular tumors, is found in 0.3–2.3% of patients undergoing appendectomy. The appendix is the site of approximately 12% of NETs and is usually discovered as an incidental histopathological finding following appendectomy.[13] NETs are rarely diagnosed preoperatively.[15]

The incidence of appendicular NETs (0.8%) in this study was in range with other published reports.[16,17]

In 70–95% of cases, NETs are <1 cm in size and located at the tip of the appendix. Most appendicular NETs are benign and metastases are rare. The calculated risk of metastasis from tumors <1 cm is close to zero, enabling treatment with simple appendectomy. However, increased tumor size (≥2 cm) is associated with a significantly increased (up to 85%) risk of metastasis. Tumor size (≥2 cm), histological grade, mesoappendix invasion, lymphovascular invasion are indicated as prognostic indicators of appendiceal NETs. Therefore, these factors can be evaluated and hemicolectomy can be considered.[18] Because none of the NETs detected in our series had pathological features that required additional surgery, no additional surgery was performed for NETs after appendectomy. Despite their aggressiveness, localized NETs have an excellent prognosis with a 10-year survival rate of 90%.[16,17] The mean survival in our series is 76 months, which is consistent with the literature.

Mucosal hyperplasia or mucosal metaplasia was the previous names for the appendix's serrated lesions. After defining and characterization of colorectal serrated polyps and their relationship with KRAS/BRAF mutations, appendiceal serrated polyps of the appendix should only be divided into dysplastic and non-dysplastic polyps. Appendix serrated adenomas have a reported mean age of 71 years.[19] Our patients were 62 years old on average.

The risk of progression and clinical significance of appendix serrated polyps are greater than their counterparts in the rest of the large intestine. The malignant potential of serrated lesions of the appendix is uncertain.[20] No dysplasia was seen in serrated lesions in our series, and the patients needed no additional surgeries.

It can be tricky to histologically distinguish hyperplastic polyps from sessile serrated lesions. Serrated polyps come in a variety of forms, including sessile serrated lesions and hyperplastic polyps, each of which has a unique malignancy risk and requires a distinct level of surveillance.[21]

The layout of the literature generally centers on how these lesions can be distinguished. In comparison to serrated adenomas, hyperplastic polyps were a little more common in the younger age group (53.6 years) in our series. However, in Ka-

plan–Meier survival charts, the survival curves almost overlap at the same level.

Tubulovillous adenoma of the appendix (adenomas) is present in 0.02–0.03% of appendectomy specimens. It is reported in the literature that it was seen in the 5th and 6th decades.[21] In our series, the rate of tubulovillous adenoma was 0.029% and the mean age of the patients was 50 years.

LAMNs are relatively rare, albeit increasing in incidence, tumors of the appendix that are histologically characterized by mucinous epithelium with low-grade cytologic atypia, but the absence of overt aggressive features, such as infiltrative growth pattern or destructive invasion with associated desmoplastic reaction of the stroma. The biological behavior and clinical course of LAMNs is heterogeneous and highly dependent on the extent of disease involvement (i.e., tumor stage) at presentation. Patients with disease confined to the appendix wall appear to have negligible risk of disease recurrence following appendectomy.[22]

In contrast, some patients present with pseudomyxoma peritonei (PMP), a clinical syndrome characterized by intraperitoneal mucinous implants and progressive accumulation of mucinous ascites, most of which are now thought to arise from peritoneal dissemination of LAMNs.[23] Patients with LAMN-associated PMP have slowly progressive, yet incurable disease with a high risk for recurrence, morbidity and eventual mortality, even though reported 5- and 10-year survival rates are 50–86% and 45–68%, respectively.

There is no established LAMN treatment. Controversy exists regarding the extent of surgery and the role of chemotherapy, including early post-operative intraperitoneal chemotherapy and hyperthermic intraperitoneal chemotherapy.[22,23]

The majority of LAMN patients in the literature are reported to have not reached serosa in the early stages. It has been reported that appendectomy is sufficient for LAMNs that have not reached the serosa. All of our patients were found to be in the early stages and required no further surgical intervention.

Adenocarcinoma of the appendix is a very rare tumor, first described in 1882, with <300 cases recorded between 1882 and 2004. Its incidence is reported to be <0.5% of all the gastrointestinal malignancies.[24] In this study, the incidence of appendicular adenocarcinoma is reported to be similar with the previous reports. In the adenocarcinoma group, the mean age (mean 44.5 years) was considerably lower than the appendix adenocarcinomas in the literature (61.3 years).[25]

Early period (first 1 month) mortality in appendectomies has been reported as 1.8%.[26] In our series (unusual appendectomy), this rate was found to be 3%. While the literature reports that colorectal cancer patients who are younger than 50 years old have a higher chance of survival (5-year survival is 65%), in our series, the median length of survival was 33.4 months. We think that the reason for this situation is serosal invasion in three patients with a mortal course (more advanced stage than the patients in the literature).

Various parasites were described in the literature as unusual findings in the appendectomy specimens (*Schistosomes species, Entamoeba* histolytica, pinworms, *Enterobius* vermicularis, Ascaris lumbricoides).[14] The presence of *Enterobius* vermicularis in the specimens is reported to range from 0.2% to 41.8%.[3,6–8] In this study, 10% of the uncommon causes of AA belonged to *Enterobius* vermicularis, but his overall incidence among all analyzed specimens was only 0.15%.

Endometriosis is defined with the presence of ectopic endometrial tissue outside the uterine cavity. Although many women in reproductive age suffer from this condition, the gastrointestinal tract localization is rare. The mean age has been reported as 32 in the literature, our patient's age is close to this data.[27] In most of the cases, intestinal endometriosis occurs in the rectum and the sigmoid colon and rarely in the appendix. Appendicular endometriosis is usually asymptomatic, but can sometimes cause appendicitis, perforation and intussusception. Appendicular endometriosis, which has 2.8% prevalence in patients with endometriosis, has similar symptoms as AA. The histological presence of endometrial tissue in the analyzed sample is the basis for the diagnosis of appendicular endometriosis.[9,27] In this study, the prevalence of the appendicular endometriosis was 2.5%.

First described in 1842, mucocele is an obstructive dilatation of the appendix resulting from an intraluminal accumulation of mucoid material.[28] The incidence of this condition in appendectomy specimens has been reported from 0.2% to 0.7%. Mucoceles are often asymptomatic and are discovered incidentally during appendectomy, laparotomy for another indication, or histological examination of an operated specimen. Standard treatment for mucinous cystadenoma is appendectomy, while the right hemicolectomy is mandatory for cystadenocarcinoma.[6,9] This study presented 1.7% prevalence of appendicular mucocele. The patient in our study who had a mucocele underwent no additional surgery.

Most of the appendicular NET, LAMN, and primary adenocarcinomas are diagnosed incidentally during surgery for AA. Therefore, even if appendectomy specimens show normal macroscopic features, histopathological analysis can provide clinically useful information about the patient's condition and help to improve patient outcome by revealing previously unrecognized disease.

The most common mesenchymal tumor in the gastrointestinal tract is GIST. It is extremely rare in the appendix and accounting for only 0.1% of all GISTs. It can occur in any part of the appendix. They are accompanied by symptoms similar

to appendicitis. The morphology is similar to that of the small and large intestines. Its key differential diagnosis is neural proliferation. Despite the fact that malignancy is documented in gastrointestinal system GISTs, no malignancy has been identified in appendix GISTs in published studies to date. This is due to the tumor's smaller size and early detection rather than its biological nature.[29]

Conclusion

Uncommon causes for AA presented with 1.44% of all operated cases. Some are caused by malignant appendicular tumors and therefore, clinicians should be alert in these patients by performing proper treatment and follow-up.

The most common cause for AA in the uncommon group is NET. Age and the uncommon pathology are the most important factors affecting mortality. Is the advanced age or the uncommon pathology which affects mortality is not clear. Therefore, the literature needs more studies to determine the effect of advanced age or uncommon pathology on mortality.

Ethics Committee Approval: This study was approved by the İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee (Date: 21.03.2022, Decision No: E-48670771-514.99).

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ORİJİNAL ÇALIŞMA - *ÖZ*

Akut apendisitin nadir sebepleri: Üçüncü basamak merkezde 6785 olgunun geriye dönük histopatolojik analizi

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AMAÇ: Bu çalışmanın amacı apendektomi sonrası patolojik incelemesi yapılan spesmenlerde akut apendisitin nadir görülen nedenlerini araştırmaktır.
GEREÇ VE YÖNTEM: Nadir görülen apendisit sebeplerini belirlemek için üçüncü basamak tek merkezde opere edilmiş 6785 olgunun histopatoloji raporları geriye dönük olarak analiz edilmiştir.
BULGULAR: Doksan sekiz (40 kadın, 58 erkek) olguda (%1.44) sıra dışı akut apendisit nedeni bulunmuştur. Apendiksin nöroendokrin tümörleri en sık izlenen patolojidir. Bunu sırasıyla serrated adenom, low grade apendiküler müsinöz neoplasm, hiperplastik polip ve intestinal parazitler izlemiştir. Dört (%0.05) hastada apendiks adenokarsinomu saptanmış olup mortalitesi %75'tir. Nadir görülen apendektomi sebeplerinde yaş, normal apendektomilere göre anlamlı olarak daha yüksektir. Sıra dışı apendektomilerin sağ kalım analizi, ileri yaşın prognostik öneme sahip olduğunu göstermiştir (Kaplan Meier p<0.0001). Sıra dışı apendisitlerde farklı hastalık grupları arasında sağ kalım farkı saptanmıştır. Ancak Cox multifaktöriyel analizi bu iki faktörün istatistiksel olarak anlamlı olmadığını göstermiştir.
TARTIŞMA: Sıra dışı apendisit nedenleri oldukça nadirdir. İleri yaş grubunda bu tanılar akılda tutulmalı ve apendisit tanısı dikkatle verilmelidir.
Anahtar sözcükler: Akut apendisit; etiyoloji; sıra dışı.

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