

Clinical behavior of appendiceal mucinous neoplasia: 9 years of experience

Abstract

Appendiceal mucocele is known a mucinous neoplasia of the appendix. It's etiology is not clear. For last 30 years it's incidence has increased to 2,8 cases/million person from 0,6 cases per million. Even if different classification has been made over the years, WHO and AJCC classifications are frequently used.

Objective: The aim of this study was to find the pathologically performing the discrimination between LAMN and HAMN in the extracted specimen and how much the scattering mucin influenced the surgery and patients' follow-up.

Material and Methods:

Patients and Centers: In two different hospitals between 2012-2020, the patients admitted to the emergency department and diagnosed as acute abdomen were evaluated retrospectively. All patients were accepted in the emergency clinic and operated then followed in the general surgical clinic. The appendiceal mucocele diagnosis was based on perioperative observation of mucinous distention or mucin dissemination. After obtaining specimens, the type of the mucinous neoplasm of appendix diagnosis and assessment was made by histopathological investigation.

Results: Appendix mucocele was detected in 19 of 2974 patients included in the study. Two additional patients had advanced pseudomyxoma peritonei (PMP) after previous appendectomy. 11 of the patients (52.4%) were female. The mean age was 63.8 years. The appendix was evaluated preoperatively as enlarged in fourteen patients. In 1 patient, this condition was belonging to the ovary. Adeno cancer in one patient and PMP in 2 patients were clinically detected. Histopathologically, the appendix size was 37.1x71.9 mm. Sixteen of the patients were reported as LAMN, 2 as HAMN, 1 as adenocarcinoma and 2 as PMP. The leukocyte, carcinoembryonic antigen (CEA) and CA 19-9 levels of the patients were found to be significantly higher than normal. The patients were followed up for an average of 30.2 months. Early postoperative complications were seen in 5 patients. Complications evaluated late were seen in 8 patients. Recurrence was detected in one of the patients during the follow-up. The average survival rate was 36.7 months, although it was slightly higher in women. While the effect of leukocytosis, CEA, CA 19-9 on mortality was not significant, but tumor size was ($p < 0.05$). This study has a few limitations. These are the small number of patients, the retrospective evaluation of the patients, and the relatively short follow-up time.

Conclusion: In this study, we found mucocele more frequently than seen in the literature. Histopathologically, low grade mucinous neoplasia (LAMN) was often encountered. Mucocele with acellular mucin scattering were also seen in approximately 20% of the patients. After simple appendectomy, no recurrence was observed during the follow-up. The leukocyte count, tumor markers, and tumor size were evaluated in terms of their effects on postoperative morbidity and mortality. The tumor size had a negative effect on survival only. Finally, the simple appendectomy operation was considered suitable for the treatment.

Keywords: appendiceal mucinous tumors, pseudomyxoma peritonei, mucocele of appendix

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Introduction

Appendiceal mucocele is known a mucinous neoplasia (enlargement) of the appendix, regardless of etiology. It was first described as a pathological entity by Karl Freiherr von Rokitsansky in 1842.¹ The incidence of appendiceal mucocele ranges from 0.2% to 0.3% of appendectomies^{2,3} and occurs more frequently in women (female/male: 3:1), and patients have been reported to have an average age of 55-60 years.^{3,4} The disease is painless and rarely metastases out of the peritoneal cavity.⁵ It's incidence has increased to 2,8 cases/million person from 0,6 cases per million since 1973.⁶ Tumor often represents an acute appendicitis-like presentation with pain slipped to right lower side secondary to distention of the appendix by mucin in early period. In advanced stage of that tumor, large quantity and long-

lasting mucin spillage returns to all abdominal widespread gelatinous structure (ascite).

The staging of the appendiceal tumors was done by Ronnet and Bradley. That used are earlier classification system. The most important limitation of the system is that the stage was only limited to disease involving the peritoneal cavity.⁷ Instead of the 2-tier classification by WHO, 3-tier classification was recently reported in the 8th version of American Joint Committee on Cancer (AJCC) (reported as G; G1, G2, G3 as well, moderate and poorly differentiated) G1 tumor is low grade, but G2 and G3 tumors are defined as high grade. In the same classification appendiceal mucinous neoplasm (AMN) includes serrated polyp with or without dysplasia, low-grade appendiceal mucinous neoplasm (LAMN),

high grade appendiceal mucinous neoplasm (HAMN) and mucinous adenocarcinoma.⁴ LAMN is accepted G1-well differentiated. LAMN also has the presence of epithelium outside the appendix and associates with peritoneal mucin implants. AMN is placed in appendix but also can advanced to peritoneal and pelvic cavity, which causes pseudomyxoma peritonei (PMP).⁸ The clinical manifestation of LAMN is not distinctive. Patients frequently present with signs of acute appendicitis or abdominal pain and indistinguishable mass.^{9,10} Non-epithelial process is often originated from inflammatory or obstructive process of appendix. But it is not common.^{11,12} Today, it is accepted that histological findings and tumor stage at the time of diagnosis are the primary factors affecting treatment; however, due to the rarity of AMN and the existence of various classification systems, there is no universally-accepted approach to their management.⁴

The aim of this study was to be able to make a distinction between LAMN and HAMN as histo-pathologically in the specimen removed by appendectomy and to investigate how peritoneal mucin scattering affects surgical planning and patients' follow-up.

Material and methods

Study population and data collection

Data for this study were obtained from patients with appendiceal mucocele revealed among all appendicitis cases that underwent surgery performed between January 2012 and January 2020 at the General Surgery Departments of TOBB ETU Hospital and Gulhane Training and Research Hospital (formerly known as Gulhane Military Medical Academy) in Ankara, Turkey. The former one is a foundation university hospital but accepts all emergency patients without imposing fees for emergency-related services due to national mandates put forth by the Ministry of Health. The latter has been functioning as a normal training and research hospital since the second half of 2016; before this date, it was a military research and training hospital that was partially open to the public. The patients were selected among the patients who applied when Gulhane was a military hospital. Others are those who applied to the first institution.

All patients with appendicitis who had undergone surgery during the study period were retrospectively evaluated for inclusion into the study by reviewing patient medical files. Any individual aged between 18–80 years applying to the emergency department of either hospital with signs of appendicitis or acute abdominal pain has been admitted and managed accordingly. Of note, the number of young male patients was relatively higher in the Gulhane Training and Research Hospital database because the hospital had primarily served military personnel before the second half of 2016. Patients who underwent appendectomy and were diagnosed with an appendiceal mucocele caused by AMN were included in the study.

Patients' complaints, and comorbidities, imaging studies (if employed, magnetic resonance imaging-MRI; computerized tomography-CT; ultrasonography-USG), appendiceal characteristics, surgical and, histopathological results, white blood cell count (WBC), carcinoembryonic antigen (CEA) and CA19-9 blood levels, complications, survival, and recurrence were taken from patients' files.

Surgical approach and diagnosis

Although surgery for appendicitis is often a training case for residents, such specific cases were performed by a specialist as the mentor in both hospitals. The designated surgeon was invited to the operating room when a mucocele of appendix was occurred. Surgeries

had been performed with (laparoscopic and) open approaches; however, in cases where mucocele-like enlargement of the appendix was observed, procedure was converted from laparoscopic to open.

The surgical procedure was to remove the visible appendiceal mass with its mesentery en-bloc. Visible mucin deposits in the surrounding area were also completely removed and sent for frozen exam. In such cases, thorough washing was performed, and initial samples obtained during the wash were sent for cytologic analysis too.

The patients with appendiceal perforation in the surgery, malignant condition with positive margin, and free mucin pools with/without epithelial cells outside of the appendix which were reported, underwent right colectomy, omentectomy and/or CRS within a week followed by the first surgery. Hyperthermic intraperitoneal chemotherapy (HIPEC) procedure was only employed in two cases with PMP after CRS in this series. Serum levels of CEA, CA19-9, together with leucocyte measurement, were measured preoperatively and continued intermittently after surgery.

Pathologic examination

The staging and grading of AMN is difficult to decide and often confusing. The evaluation was to reveal LAMN cases related to appendix and peri-appendicular tissues according to AJCC (8th Edition-staging of mucinous neoplasm).⁴ Cellular grading classification according to the AJCC 8th Ed. was made as well, moderate and poor differentiation and was expressed with G1, G2, and G3. That was classified as disseminated peritoneal adenomucinosis by Ronnet.¹³ Grading of appendiceal tumors is important for prognosis. The classification made by WHO (2010) was two-tier and it was found as low and high grade mucinous neoplasia. Whereas, in the classification of the AJCC (8th Ed.), which was introduced recently, there have been 3-tier as well, moderate and poorly differentiated.^{7,14,15} The low-grade classification (LAMN) corresponds to the well-differentiated (G1) tumor in the classification of AJCC. G2 and G3 are reported as high-grade mucinous neoplasia. Although low-grade appendiceal neoplasia (LAMN) may be present, the risk of spreading to the peritoneum is frequently found in this type of tumor.^{15,16} Signet ring cells appendix tumor represents a more aggressive tumoral structure as a separate entity. G3 tumors do not always carry signet ring cells.¹⁷ Mucin pool (scattered) is a separate pathological entity. Those do not contain epithelial cells are called the acellular mucin. It was reported in some publications that their presence on the peritoneal surface can be the cause of recurrence in a long follow-up period.^{17,18} Cytologic atypia (rare mitotic activity, cell necrosis and nuclear stratification etc.) presence of mucinous epithelium or local deposition of mucin and/or epithelial tissue outside of appendix were investigated, although these findings or peritoneal involvement were not seen in imaging studies. Simple appendicitis and carcinoma patients were identified in the pathological examination after the appendix removed. Those reported as LAMN were a sort of appendix neoplasia accompanied by low-grade atypia in the mucinous epithelium and localized mucin accumulation around the appendix. Those deposits could not be detected by radiological imaging methods. LAMN was distinguished in two different pathological formations. The presence of mucin in the lumen of the first type neoplasia without an unexpanded appendix was evaluated for dysplastic developments in the mucinous epithelium. The presence or absence of fibrosis on the appendix wall was also evaluated. The other has gathered with high grade dysplasia. In the presence of the most common adverse histologic features like destructive invasion in the appendix wall, high cytologic grade, tumor cellularity, and high grade appendiceal neoplasia is mentioned (G2-G3).

Survival

For patients who develop a malignant condition the period of follow-up after surgery and the time of death due to this disease were recorded. Patients with LAMN were also followed for recurrence or return to PMP disease during the follow-up period. At the same time, the effects of some parameters (leukocytosis, CEA, CA 19-9 and tumor size) on survival were also evaluated. Unfortunately, some patients were lost during the follow-up.

Statistical analysis

Statistical analysis was performed using SPSS v.15. Frequency and descriptive statistics were applied for the parameters. Non-parametric tests were used for ordinal-value data. Chi-square test was used to evaluate the effect of disease-related parameters on mortality. The survival analysis was evaluated using the Kaplan-Meier methods. Cox variation analysis was used to evaluate the effects of variables like leukocytosis, CEA, CA 19-9 and tumor size on patients' survival. The analysis of sample size and numerical values were done using parametric tests. $P < 0.005$ was accepted as statistically significant.

Results

Out of the 2974 cases of appendectomy reviewed during the 9-year study period, 19 (0.63 %) been diagnosed as mucocele and/or related tumor types (LAMN or AMN-H, etc.) of appendix, which were evaluated retrospectively. Two cases, who had appendectomy in

the past were admitted with the clinical diagnosis of mechanic bowel obstruction (ileus) due to advanced highly expanded hypoechoic abdominal mass (the gelatinous acid) which eventually led to diagnosis of PMP. Thus 21 patients formed the study group. In most cases appendix was observed to be enlarged preoperatively at imaging studies. In 13 patients, the enlarged appendix representing mucocele was diagnosed with imaging methods, but true diagnose were based on the pathology report. In one patient, the mass was experienced that originated from the ovary during surgery. All patients underwent complete removal of appendix. When mucin and/or epithelial cells outside of appendix, and malignant condition was assessed, patients underwent right hemicolectomy and/or organ specific oncologic surgery. Mucin scattered around the appendix was detected in five patients. One of them had mucinous adenocarcinoma detected in the enlarged appendix. Those patients were operated with extended margins (Table 2). PMP was identified for those two patients who underwent HIPEC procedure after CRS. There was further treatment, chemotherapy after surgery. The usual follow-up procedure was employed like a cancer patient. Eleven of the patients were females (52.4%) and 10 males (47,5%), with an overall mean age of 63,8 (31 to 73) years (SD 10,6). Table 1 shows the demographic findings, patients characteristics and measured serum inflammatory and oncologic markers' outcomes. That table also shows the complaints of patients at the time of admission. Table 2 shows the intraoperative characteristics, pathology results, morbidity, and mortality results after the surgical treatment. Table 2 also demonstrates the follow-up period for the patients, and the status of morbidity and mortality.

Table 1 Preoperative characteristics of patients with mucocele of the appendix

No	Sex	Age	Co-morbidity	Previous surgery	Main symptoms	WBC (uL)	CEA (ng/ml)	Ca 19-9 (U/ml)	Imaging method	Preoperative Diagnosis
1	F	73	HT	Myomectomy	RLAP, fever, nausea, vomiting	15800	-	-	US	Mucocele of appendix
2	F	57	DM		RLAP, nausea, subfebrile fever	13500	-	-	CT	Appendicitis (with pelvic collection?)
3	F	63	HT	H-BSO	RLAP, nausea, diarrhea	17000	1,3	13	US, CT	Appendicitis Tortioned ovarian cyst and/or Mucocele of Appendix
4	F	71	Hemoragic cystitis, HT, DM	Left hemicolectomy	RLAP, painful urinating	13880	1.2	-	US, CT	Mucocele of Appendix
5	M	41			Abd. pain, nausea	16300	2.2	14.2	CT	Acute abdomen (OMT recurred or Appendicitis)
6	F	63	OMT	H-BSO + Lap. cholecystectomy	Abd. pain, nausea	9800	1.2	21.7	US,CT	Acute abdomen, Appendicitis
7	M	59	DM	Thyroidectomy	RLAP, Abdominal painful mass.	9500	1.7		CT	Acute abdomen, Appendicitis
8	M	31			Abd. pain, fever	12500	-	27,6	US	Appendicitis, or Mucocele of appendix
9	F	73	HT	Laparoscopic Cholesystectomy	RLAP, Intestinal swelling	8550	-	-	CT	Mucocele of Appendix
10	F	69	DM		RLAP, fever, nausea	17300	3,5	11,4	CT	

Table Continued...

No	Sex	Age	Co-morbidity	Previous surgery	Main symptoms	WBC (uL)	CEA (ng/ml)	Ca 19-9 (U/ml)	Imaging method	Preoperative Diagnosis
11	F	75	HT		RLAP, nausea	13200	13.1	37.4	US, CT	Mucocele of appendix
12	F	71	HT, DM, PBS	H-BSO, Variceal sclerotherapy	Abdominal pain, pruritis	5600	4	-	US, CT, MRI	Mucocele of Appendix
13	F	68		Appendectomy	Abd. pain, intestinal swelling sub-ileus, weight loss, vomiting	14600	12,5	-	CT	MBO, abdominal contrast enhanced modules (PC).
14	M	63	HT		RLAP, abdominal discomfort	13700	8.2	14,2	CT	Mucocele of Appendix
15	M	71	HT	Appendectomy	Abd. pain, intestinal bloating, vomiting, ileus	13200	13,1	-	CT, US	MBO, Abd. mass, PC
16	M	67	HT, DM		Abdominal pain, nausea, vomiting	16700	7.3	17.4	US	Mucocele of appendix (or ceecal tumor?)
17	M	59	HT	Laparoscopic Cholecystectomy	RLAP, nausea, vomiting, bloating	21000	2,4	21	US	Mucocele of Appendix, periappendicular abscess
18	M	64		Laparoscopic Cholecystectomy	RLAP, nausea, sub-ileus	12300	2.9	13.6	CT	Mucocele of Appendix
19	F	68	DM	Debridement for diabetic foot	Abd. pain, nausea	17600	2	5,4	US	Mucocele of Appendix
20	M	70			RLAP, vomiting, fever	15300	3.6	2.5	US	Mucocele of appendicitis
21	M	63	HT		Abd. pain, fever	13200	1,3	7.6	CT, MR	Acute appendicitis (Acute abdomen)

HT, hypertension; DM, diabetes mellitus; H-BSO, hysterectomy-bilateral salpingo-oophorectomy; RLAP, rightside lower abdominal pain; US, ultrasound scan; Abd, abdominal; CT, computerized tomography; MRI, magnetic resonance imaging; CEA, carcinoembryonic antigen; OMT, ovarian mucinous tumor; MBO, mechanic bowel obstruction; PBS, primary biliary cirrhosis; PC, peritoneal carcinomatosis

Table 2 Postoperative characteristics of patients with mucocele of the appendix

No	Surgery	Tumor Size (mm)	Mucin Scutter (intraop.)	Peritoneal Involvement	Result of Frozen sect.	Pathology AJCC (WHO and other class.)	Morbidity	Mortality	Cause of death	Followup (month)
1	Appendectomy İleocecal res, local peritonectomy	35X65	Peri-appendicular	Localized at pelvic inlet	Non cellular mucin	Mucocele (LGD-WHO) Appendicitis	Inta-abdominal abscess	Exitus	Senile and frailty	75
2	Appendectomy İleocecal res	45X120	Peri-appendicular	A few smal area at pelvic inlet	Non cellular mucin	Mucocele (LGD)		Alive		71
3	Appendectomy	10x47				LAMN (LGD)	SBMO-early	Alive		68
4	Appendectomy	31x55				LAMN (LGD)		Exitus	MI	27
5	Appendectomy	62x70				LAMN (LGD)		Unkown		
6	Appendectomy Right colectomy PPS	35x70	Peri-appendicular + Small areas on sigmoid colon and sacrum	Peritoneal layer of sigmoid colon (localized)	Non-cellular Mucin	LAMN (LGMN)	Inta-abdominal abscess	Exitus	PMP (gelatinous ascite)	18
7	Appendectomy	20x80				LAMN (LGD)		Alive		50
8	Appendectomy	35x65				LAMN (LGMN9)		Unkown		
9	Appendectomy H-BSO	28x70				AMN-H (musinous cystadenoma-left ovary)		Alive		40
10	Appendectomy	40x65				LAMN (LGMN)		Alive		35

Table Continued...

No	Surgery	Tumor Size (mm)	Mucin Scutter (intraop.)	Peritoneal Involvement	Result of Frozen sect.	Pathology AJCC (WHO and other class.)	Morbidity	Mortality	Cause of death	Followup (month)
11	Appendectomy (laparoscopic to open)	70x120				LAMN (LGD)	Pelvic fluid collection	Alive		33
12	Appendectomy Partial cecectomy	35x60				LAMN (IGMN)		Alive		24
13	CRS+HIPEC	-	Gelatinous ascite	Extended abdominal involvement		Mucinous neoplasm	UTI, Pnomonia, ARDS, MODS	Exitus	ARDS, MODS	1.5
14	Appendectomy	40x65				LAMN (LGMN)		Unkown		
15	CRS+HIPEC	-	Gelatinous ascite	Extended abdominal involvement		Mucinous neoplasm	Athelectasis UTI	Exitus	SBMO (gelatinous ascite)	15
16	Appendectomy	25X70				LAMN (LGMN)		Alive		20
17	Appendectomy Cecectomy	30x65	Peri-appendicular + around the ceaceum	Peritoneal layer of ceaceum	Acelular mucin	LAMN		Alive		19
18	Appendectomy	48x65				LAMN	Athelectasis	Alive		14
19	Appendectomy	30x65				AMN-H		Alive		12
20	Appendectomy	40X65				LAMN		Alive		11
21	Appendectomy + Right colectomy + PPS	55X80	Appendix stuck to the peritoneum at ileocecal fossa	None	Metastatic epithelial cells on the peritoneum resected	Mucinous adenocarcinoma (Colonic type)	Athelectasis UTI	Alive		9

Res, resection; LAMN, low-grade appendiceal mucinous neoplasm; LGD, low grade dysplasia; LGMN, low grade mucinous neoplasia; AMN-H, appendiceal mucinous neoplasm-high grade; BSO+H, bilateral salpingooferectomy+ hysterectomy; PPS, Pelvic peritoneal stripping; CRS+HIPEC, cytoreductive surgery+ hypertermic intraperitoneal chemotherapy; SBMO, small bowel mechanic obstruction; UTI, urinary tract infection; ARDS, acute respiratory distress syndrome; MODS, multiple organ dysfunction syndrome

The most common clinical finding was abdominal pain lateralized to right lower part of abdomen. Two of all had operated on for appendicitis a few years ago. Later they presented with ileus due to the PMP. In terms of comorbidities, few of them had been displayed in this retrospective cohort (Table 1). In patients with progression to PMP, abdominal pain, vomiting frequently, clinical and radiological manifestations of intestinal obstruction had been encountered. Carcino-embryogenic Antigen (CEA) (4,7 ng/ml-SD.4,3), CA19-9 level in blood (14,9 U/ml-SD.8,4) and, leucocyte count (WBC) (13834,7 U/L-SD.3497,9) values did demonstrate notable higher results. However, a direct effect of these high values on mortality (CEA; p:0.844; X²:0.039; CA19-9; p=0,223 x²:1,485; WBC; p=0,805, x²:0,061 results of Chi-Square test respectively) could not be demonstrated.

The mean appendix diameters, (relative tumor size) was 37,1 (ranging between, 10x65) mm, and size was 71,9 (between 47x120) mm. Histopathological findings showed low-grade appendiceal mucinous neoplasm (LAMN) in sixteen cases (76,2%), appendiceal Mucinous Neoplasm-High Grade in 2 cases (9,5%), mucinous adenocarcinoma in one case (4,8%), and PMP in two cases (9,5%).

The total follow-up duration 30, 2 (SD: 22,5) (1 to 75) months. In total, five patients developed relatively early morbidities, such as atelectasis, lung infection, pneumonia, and anastomotic leakage. On the other hand, intraabdominal abscess, urinary tract infection, multiple organ failure syndrome (MODS), and sepsis had been observed as relatively late morbidities at 8 (%36,4) patients in total. A total of 8 patients were excluded from follow-up 5 of whom died (Mortality-23.8%) and 3 patients whose information was not known

(Table 2). Two of the 5 dead patients were who represented with bowel obstruction due to the PMP. One of them died due to sepsis developing in early postoperative period. The other was lost about 1,5 years later, with the same disease occurred. Of the 2 patients with a pathological diagnosis of LAMN, one died of myocardial infarction (MI) and the other died due to the progression of the disease to PMP and its complications. The patient was the only one with a pathological diagnosis of LAMN who developed PMP during follow-up (5,3%).

In this cohort mean survival time was 36,7 (SE: 5.9) months. The survival time was higher in female (46,2 (SE: 7,5) months) than that was in male (21,8 (SE:6,4) months) (Figure 1).

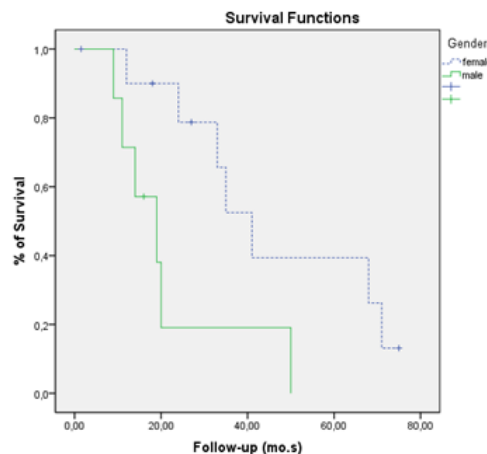


Figure 1 Survival time separated both genders in that cohort was displayed.

In the study, the effect of some parameters obtained from the blood analysis of the patients (leukocytosis, CEA, CA19-9 and tumor size), which may be related to the severity of the disease, on mortality was also investigated. Those were related to disease severity but did not have a significant effect on mortality except tumor size ($p=0,048$) (Table 3).

Table 3 The effects of different variables on mortality are observed in patients

Effects of variables on mortality			
	Mean	P	Exp(B)
Leucocyte	15340,0	,780	1,000
CEA	3,9	,257	,659
CA199	15,8	,241	,889
Tumorsize (cm)	71,7	,048	1,157

Discussion

The disease (AMN) had wide spectrum of diagnosis from adenoma to mucinous adenocarcinoma. The incidence of appendiceal tumor is between 0,5%-2%. However, appendiceal mucinous neoplasms account for 0,4%-1% off all gastrointestinal tumors.^{4,6,19} The clinical manifestation of the disease is atypical, often asymptomatic. The most common findings were right lower quadrant pain (27%) and a palpable mass in the same region (16%). As mentioned above the disease is often discovered by chance, it is seen between the ages 60-75 and little more in females.^{7,11,19} In our study, the incidence was 0.63% with that is slightly higher than reported in the literature. Most of patient in our study were women (52.4%) but the female-to-male ratio (1.1/1) was not consistent with literature with a ratio of 3/1.^{2,4} It could be consisted with the lack of sample size. All the patients in the study applied with findings suggestive of appendicitis. Right lower quadrant (RLQ) pain, nausea and vomiting with leukocytosis were common. Intestinal obstruction or palpable abdominal mass had been detected in a small number of patients (table 1).

Pathological diagnosis of the disease was made with the classification of AJCC (8th Edition), recently. In this study, pathology reports of the patients were not always performed using the same classification. During the retrospective scanning of the patients' records, all reports were re-reviewed and adjusted to AJCC characteristics. LAMN is classified a special T (depth) category. It corresponds to Tis (in-situ). It also indicates LAMN. Histologically, it is seen that the tumor pushes tissue layers forward but does not invade the appendix wall. Thus, there is no correlation between T sub-classification and recurrence. Consequently, T1 and T2 has not been separated each other. LAMN pT3 shows subserosa involvement and LAMN pT4 shows serosa involvement as in other carcinomas.^{19,20} The presence of acellular mucin inside the wall is other important considerations of LAMN. The signet ring cells (SRC) in mucin pools is a poor histopathological finding and has a poor effect on patient survival.¹⁷ In the study all expanded appendices were reported as LAMN. According to AJCC (8th edition),²¹ in the above-mentioned patients, the tumor depth is T4a because LAMN expanded regional serosal surface with acellular mucin, the lymph node evaluation is N0 because none of them have tumor deposits and there is no involvement in the removed lymph nodes, and acellular mucin in the peritoneum is also taken into account. Metastasis evaluation was made as M1a. By pathology department, it was reported that no invasion was observed in the appendix wall in all patients underwent appendectomy in this series. But appendiceal wall was thicker than that was normal (not reported here). The size of appendix was found to be approximately 3,7 cm (>2 cm) wide and 7 cm long. The appendix size in the pathology report corresponded to a considerably larger size than normal as such ($p=0,048$). The scattered mucin was seen in only

4 patients (19%) around appendix. Those were all acellular mucin scatter. Ascites was detected in the abdomen due to PMP in 2 patients (9,5%), adenocarcinoma with spreads locally were detected in one patient. In 4 patients with mucin scattered, simple appendectomy and removal of the peritoneum adjacent to the detected mucin splashes were performed. Mucin was reported as acellular in the pathology report of these patients. For that reason, no additional surgery was applied. No recurrence was observed in the patients with LAMN histopathology during the follow-up.

Tumor markers such as Carcinoembryonic antigen (CEA), CA 19-9 increases in mucinous neoplasm. Elevation during postoperative follow-up also indicates neoplastic recurrence. Elevated CEA levels have been reported in the literature, even in mucinous cystadenoma.²² In our study both CEA and Ca19-9 levels of patients were found to be higher than that was normal in general (CEA: 3,9 ng/ml, CA19-9:15,8 U/ml). But they were not significant in terms of follow-up, prognosis, and survival ($p:0.844$; and $p=0,223$, respectively). Leukocytosis, which is an important parameter in the diagnosis of appendicitis in our patients was not found to be effective on the severity of the disease or morbidity ($p=0,805$).

Surgical treatment for AMN depends on the factors such as tumor size, clear surgical margin, involvement of the cecum and/ or peri-appendiceal area, histo-pathologic grade and lymph nodes involvement. For well differentiated localized mucinous appendiceal tumors (like LAMN), the incidence of nodal spread is very low (less than 2%). Therefore, appendectomy is an appropriate treatment approach only for such tumors with local spread. Right hemicolectomy should be performed in tumors involving the peri-appendicular area, tumors larger than 2 cm in tumor size and high-grade histology, or in tumors where the muscularis propria is involved. Right hemicolectomy is also proper approach for patients who cannot obtain a tumor-free surgical margin after appendectomy.²³ If low-grade AMNs have also had a peritoneal mucin splashes, it is controversial to decide on surgical treatment. In the literature, it is reported that the appearance of acellular and cellular mucin is different from each other.^{7,18,24} However, it has been reported that even if peritoneal mucin splashes are acellular, relapse of the disease may occur even within a long follow-up period, depending on the grade of LAMN from which it originates. For that reason there are who those recommend CRS+HIPEC treatment for such a disease that will be become fatal by covering the entire abdomen, although it is treated with appendectomy or right hemicolectomy in future.^{7,15,24,25} In our study, peritoneal mucin spillage was detected in 4 and PMP was detected in 2 patients. We performed 11 simple appendectomies; two appendectomies with cecectomy, and two with ileocecal resection, 2 right colectomies with pelvic peritonectomy, two underwent to CRS+HIPEC. For the patients undergoing surgery the mucin scattering was removed with their surroundings and send it to "frozen section" then decided the form of surgery. We applied CRS+HIPEC to the patients when cellular mucin dispersed into pelvic peritoneum or surrounding organ was observed or even minimal gelatinous acid was present. Of the 21 patients 2 had been mechanical bowel obstruction due to extended gelatinous acid. Those patients underwent appendectomy many years ago. It is believed that LAMN patients with positive margin, appendiceal rupture/perforation, or mucin, cell or both outside appendix might develop a malignant condition. Eleven patients that underwent a single appendectomy did not experience recurrence. We cannot conclude that single appendectomy can reduce the risk of relapse, but this procedure is probably sufficient when treating patients with a tumor of appendix exhibiting only local disease. No additional treatment is required for patients without PMP if the correct surgical method is selected.

In this study, there are some withdrawals. The limited number LAMN patients from two center were retrospectively included. About thirty months follow-ups could not be enough to decide in sharp about the recurrence. More studies are needed to obtain a better understanding of the pathophysiology of LAMN.

Conclusion

Although it is not possible to reach a clear decision in a series of 21 individuals with such a limited number of patients, we found that mucocele, which is clinically manifested by the enlargement of the appendix, was encountered more frequently than that was in the literature. Most of the patients were diagnosed as LAMN histopathologically. We found that 19% (4/21) of those patients were accompanied by acellular mucin splashes around. When we evaluate that rate with mucocele sizes, we can accept it as low. We observed that none of the patient developed recurrence during follow-up, after simple appendectomy and mucin removal surgery. We detected elevated leucocyte count and measured tumor markers at the time of admission. We could not detect the adverse effects of these deviated values on patient survival. Only had the size of mucocele (tumor). According to above-mentioned findings, it is usual to have a mucocele of appendix in a patient presenting with acute abdomen, and the simple appendectomy operation was considered advisable for the treatment.

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Conflicts of interest

Authors declare that there is no conflict of interest.

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