Nomenclature of appendiceal mucinous lesions according to the 2019 WHO Classification of Tumors of the Digestive System

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ABSTRACT

Background/Aims: To analysis the appendiceal mucinous lesions according to the World Health Organization (WHO) 2019 classification of tumors of the digestive system (non-neuroendocrine tumors of the appendix vermiformis)

Materials and Methods: Clinical and histopathological data of 37 patients with histopathologically proven appendiceal mucinous lesion from January 2010 to May 2019 were evaluated retrospectively. Pathology slides were re-evaluated by two pathologists according to the WHO 2019 classification of tumors of the digestive system.

Results: Totally 37 patients (male:19 female: 18) aged 23 to 93 years were analyzed. Majority of the patients (75.7 %) had underwent appendectomy due to preliminary diagnosis of acute appendicitis (n=22) or periappendiceal tumoral lesions (n=9), the others (n=9) underwent incidental appendectomy. Whereas acute appendicitis was histopathologically diagnosed in 16 (43.2%) patients, perforation was diagnosed in 12 (32.4%) patients (perforation without appendicitis=3, perforation with appendicitis=6). According to the initial, pathology reports were prepared as follows: mucocele (n=10), mucinous cystadenoma (n=9), low-grade mucinous neoplasm (n=6), mucinous adenocarcinoma (n=5), mucosal hyperplasia (n=5), hyperplastic polyp (n=1), adenomatous polyp (n=1). On the basis of the WHO 2019 classification, pathology reports were prepared as follows: low-grade mucinous neoplasm (n=17), simple retention cysts (n=6), hyperplastic polyp (n=6), mucinous adenocarcinoma (n=5), ruptured appendiceal diverticula (n=2), sessile serrated lesion (n=1).

Conclusion: The term of appendiceal mucinous lesion, which is recently introduced into medical literature is suitable to distinguish between lesions with and without malignancy potential. The WHO 2019 classification system has been an important step in simplifying the classification of non- neuroendocrine tumors of the appendix vermiformis.

Keywords: Appendectomy, mucocele, mucinous cystadenoma, mucinous lesions

INTRODUCTION

Appendectomy is the most frequently performed emergency surgical procedure in the world and can be classified as emergency appendectomy, elective appendectomy, prophylactic appendectomy, and incidental appendectomy, in terms of timing and indications of surgery (1). Acute appendicitis (AAp) cases account for a vast majority of appendectomies. Pathological specimens of patients who underwent emergency appendectomy mostly reveal inflammatory cell infiltration secondary to lymphoid hyperplasia and fecaloid. However, parasites, bacteria, fungi, foreign bodies, endometriosis, and benign (mucinous cystadenoma, mucocele, polyps) or malignant (neuroendocrine tumor, adenocarcinoma, mucinous cystadenocarcinoma) appendiceal tumors are less frequently diagnosed besides AAp findings (1). Incidental appendectomy is a term developed to describe appendectomies performed mostly during another abdominopelvic surgical procedure. Indications for incidental appendectomy include the formation of a conglomerate tumoral structure of the appendix vermiformis with abdominoplevic tumors or the detection of isolated appendiceal tumoral lesions. Some cases end up with appendectomy owing to the surgical course of hemicolectomy or ileocolic resection. Whereas the rate of appendiceal tumoral lesions among patients who underwent appendectomy for AAp varies from 0.2% to 0.87%, the rate of tumoral lesions among patients who underwent incidental appendectomy varies from 0.6% to 4.2% (1). Sufficiency of simple appendectomy for appendiceal mucinous lesions , which form the majority of appendiceal tumors, is determined owing to histopathological features of the lesions. Although a variety of classifications for appendiceal mucinous tumors exist, the classification suggested and periodically revised

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by the World Health Organization (WHO) and the peritoneal surface oncology group international (PSOGI) are the two most accepted classifications (2). This study aimed to evaluate appendiceal mucinous lesions of 37 patients treated in our clinic according to the WHO 2019 classifications of non-neuroendocrine epithelial tumors of the appendix vermiformis, as well as sharing clinical course.

MATERIALS AND METHODS

From May 2010 to May 2020, demographic, clinical, and histopathological data of 37 patients who underwent emergency or incidental appendectomy for any reason at Department of Surgery, Inonu University Faculty of Medicine and histopathological findings that were compatible with appendiceal mucinous lesions were obtained from patient information management system (HBYS-ENLIL) and were analyzed retrospectively. This retrospective study was approved by the Inonu University Institutional Review Board for Non-interventional Studies (Approval No: 2020/516).

Both pathology reports and slides of patients diagnosed with benign mucinous neoplasm of appendix (mucocele, mucinous cystadenoma, low-grade mucinous neoplasm [LAMN], etc.) or malign mucinous neoplasm (mucinous adenocarcinoma and others) were re-evaluated by two pathologists experienced in gastrointestinal system pathology, and the definitive diagnosis of appendiceal mucinous lesions were confirmed. The first aim of this study was to compare appendectomy specimens according to the WHO 2019 classification of non-neuroendocrine epithelial tumors of the appendix vermiformis. The second aim was to share results of 37 patients diagnosed with appendiceal mucinous lesions in primary or incidental appendectomy specimens. The WHO 2010 and 2019 classifications of non-neuroendocrine epithelial tumors of the appendix vermiformis have been summarized in Table 1.

MAIN POINTS

- *Primary appendiceal epithelial tumors are basically divided into four group as follows: mucinous, non-mucinous, neuroendocrine, and mixed glandular-endocrine (composite) tumors*
- *Non-neuroendocrine appendiceal epithelial tumors can also be divided into two subgroups as follows: serrated polyp, low-grade mucinous neoplasm , high-grade mucinous neoplasm, mucinous adenocarcinoma , poorly-differentiated mucinous adenocarcinoma with signet ring cells (≤50% signet ring cells), mucinous signet cell adenocarcinoma (>50% signet ring cells), non-mucinous adenocarcinoma, and goblet cell adenocarcinoma*
- *The WHO 2019 classification of tumors of the digestive system has been an important step in simplifying the classification of non- neuroendocrine tumors of the appendix vermiformis.*
- *The term "appendiceal mucinous lesions", which was recently introduced into medical literature, is suitable to distinguish between lesions with and without malignancy potential.*

Clinical Assessment

Patients undergoing surgical treatment with an indication of AAp were evaluated according to the preoperative protocol defined previously (laboratory tests, urine analysis, Alvarado Score calculation, abdominal ultrasonographic examination, gynecological examination for female patients, abdominal computerized tomography when required). Patients underwent emergency appendectomy with either open or laparoscopic procedure performed depending on the clinical status of patients and surgical experience of the team. Patients with an indication of gastrointestinal perforation or incarcerated hernia also underwent an emergency surgical procedure in which pathological condition of appendix vermiformis (tumor, appendicitis, etc.) was diagnosed incidentally during abdominal exploration. One patient underwent re-laparotomy owing to a complication of liver transplantation, and incidental appendectomy was performed during this surgery session. One patient was diagnosed with pseudomyxoma peritonei (PMP) preoperatively and underwent a semi-elective surgical exploration because of mild intestinal obstruction findings. Remaining patients underwent surgical treatment indicated because of other elective conditions, and appendectomy was performed either adjacently to the surgical procedure or separately because of a pathological finding of appendix vermiformis.

Study Parameters

The following demographic and clinical parameters were used for the design of this study: age (years), sex (male, female), preoperative diagnosis, presence of AAp, presence of appendiceal perforation, indication for appendectomy (primary, incidental), surgical approach (open, laparoscopic), length of appendix (mm), width of appendix (mm), surgery type (appendectomy alone or combined with other surgery), follow-up (days), outcome (alive, dead), and histopathological definition with the WHO 2019 classification of non-neuroendocrine epithelial tumors of the appendix vermiformis

Histopathological Examination

The appendectomy specimens were fixed in %10 formalin solution. On macroscopic examination, the appendix length, appendix diameter, surgical border, presence of perforation, luminal dilatation and intraluminal mucin were evaluated. After macroscopic sampling, routinely processed formalin fixed paraffin-embedded tissues were sliced at a

Table 1. WHO classifications of non-neuroendocrine epithelial tumors of the appendix vermiformis. (Bosman FT, Carneiro F, Hruban R H, Theise N. WHO classification of tumours of the digestive system, fourth edition. France: IARC; 2010) (WHO Classification of tumors Editorial Board. Digestive system tumors. Lyon(France):International Agency for Research on cancer; 2019)

WHO 2010	WHO 2019
Epithelial tumors	
Premalign lesions	Hyperplastic polyp
Adenoma	Sessile serrated lesion without dysplasia
Tubular	Serrated dysplasia, Low grade
Villous	Serrated dysplasia, High grade
Tubulovillous	Low-grade appendiceal mucinous neoplasm
Dysplasia (intraepithelial neoplasia)- Low grade	High-grade appendiceal mucinous neoplasm
Dysplasia (intraepithelial neoplasia)- High grade	Adenocarcinoma NOS
Serrated Lesions	Mucinous adenocarcinoma
Hyperplastic polyp	Signet ring cel carcinoma
Sessile serrated adenoma/polyp	Carcinoma, Undifferentiated, NOS
Traditional serrated adenoma	Goblet cell adenocarcinoma
Carcinoma	
Adenocarcinoma	
Mucinous adenocarcinoma	
Low-grade appendiceal mucinous neoplasm	
Signet ring cel carcinoma	
Undifferentiated carcinoma	

thickness of 4 μm and the hematoxylin–eosin (HE) stained slides were examined under a light microscope. Presence of structural and epithelial atypia, status of submucosa and muscularis mucosa, presence of submucosal hyalinization, fibrosis, pushing tumor margin, stromal desmoplasia, single cell infiltration, mucin extravasation were reevaluated by two pathologists on microscopic examination according to the new WHO classification of non-neuroendocrine epithelial tumors of the appendix (The 2019 WHO classification of tumors of the digestive system). In addition, histopathological findings of appendicitis around the lesions were also examined. Mucosa usually markedly thinned or denuded, without atypia and hyperplasia, with luminal dilatation was diagnosed as simple retention cyst. Hyperplastic polyps have similar to their colonic counterparts. Elongated crypts with increased numbers of goblet cells were diagnosed as hyperplastic polyp. Because mucosal hyperplasia is not recommended in the new classification, these lesions turned out to be hyperplastic polyps. Serrated lesion is a localized serrated epithelial lesion with dilatation extending into basal crypts, with or without atypia and retention of the muscularis mucosae. Diagnostic criteria for LAMN was villous pseudostratified mucinous epithelium or monolayered mucinous cells with a broad pushing margin, fibrosis, hyalinization and calcification of the appendiceal wall, various degrees of mucin dissection and the absence of muscularis mucosa. If an infiltrative pattern, stromal desmoplasia and mucin pools with atypical cells, extracellular mucin >%50 of the lesion were observed, then it was called mucinous adenocarcinoma. Ruptured diverticulitis was characterized by hyperplastic changes of the mucosa, maintained crypts, lymphoid follicles in lamina propria, mucin extravasation to the appendix surface, and often a mucosal neuroma.

Statistical Analysis

The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) v25.0 (IBM Corp.; Armonk, NY, USA). The quantitative variables were expressed as median, minimum–maximum (min–max), and interquartile range (IQR). The qualitative variables were reported as number and percentage (%).

RESULTS

This study includes a total of 37 patients, of whom 19 are (51.3%) male and 18 (48.7%) are female with a median age of 64 years (min–max= 23–93, IQR= 33). Median age of the males was 64 years (min–max= 23–93, IQR=36) and that

of the females was 63 years (min–max= 23–87, IQR= 26). Majority of the patients ((75.7%) underwent surgery due to preliminary diagnosis of AAp (n=22) or tumoral lesions of periappendicular space (n=6), whereas the remaining patients (n=9) underwent surgery owing to other conditions, and incidental appendectomy was performed. Perforation was diagnosed in appendectomy specimens in 12 (32.4 %) of the patients (tumor perforation=3, perforation due to AAp=9). Inflammatory histopathological changes resembling AAp was diagnosed in 16 (43.2%) of the patients, among whom three had additional eosinophilic cell infiltration. Diameter of appendix vermiformis varied from 5 mm to 65 mm (median=15, IQR=14), whereas the length varied from 35 mm to 160 mm (median=65, IQR=41). All along the median of 1,291 days (min–max=10–3,538, IQR=1,864) of follow-up, 8 (21.6%), patients died because of conditions not related to the surgical procedure, with a median age of 70 years (min–max= 28–86, IQR= 31). Surviving patients had a median age of 62 years (min–max=23–93, IQR=31).Mortality in half of the non-surviving patients was related to additional conditions. There was no statistically significant difference between the age of surviving and non-surviving patients (p=0.275). Two of the patients diagnosed with mucinous adenocarcinoma in the appendectomy specimens did not consent for a second surgical session for hemicolectomy as well as chemotherapy giving old age as an excuse.

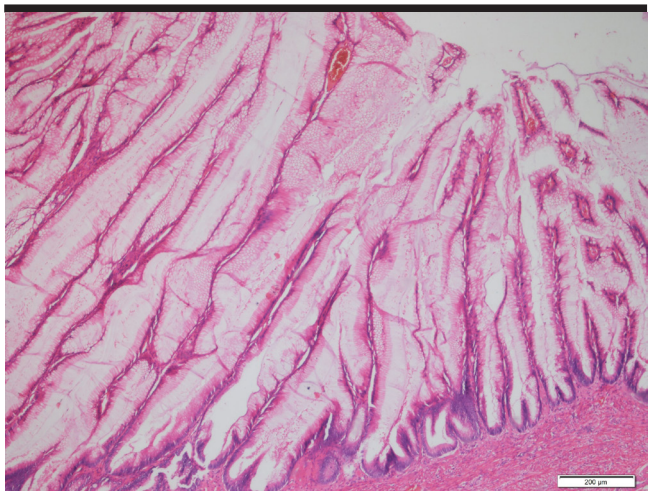

Figure 1. The classic pattern of villous proliferation of cells with apical mucin and mild nuclear atypia in low-grade appendiceal mucinous neoplasm formerly known as mucinous cystadenoma (hematoxylin–eosin, 40×).

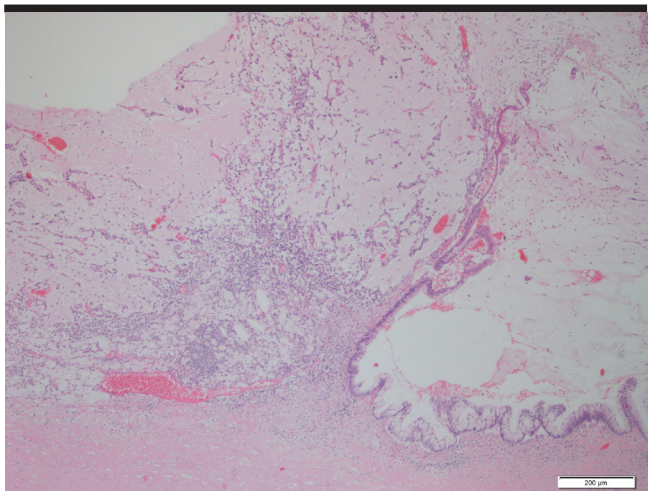

Figure 2. Epithelial denudation and mucin extravasation in a low-grade appendiceal mucinous neoplasm (hematoxylin–eosin, 40×).

According to the initial pathology reports were written as follows: mucocele (n=10), mucinous cystadenoma (n=9), LAMN (n=6), mucinous adenocarcinoma (n=5), mucosal hyperplasia (n=5), hyperplastic polyp (n=1), adenomatous polyp (n=1). On the basis of the WHO 2019 classification, pathology reports were prepared as follows: low grade mucinous neoplasm (n=17), simple retention cysts (n=6), hyperplastic polyp (n=6), mucinous adenocarcinoma (n=5), ruptured appendiceal diverticula (n=2), sessile serrated lesion (n=1). Three of the five patients diagnosed with mucinous adenocarcinoma underwent definitive surgical procedure. The remaining two patients did not consent for right hemicolectomy. Demographic and clinical features of the patients are given in Table 2 and Table 3. The histopathological features of some appendiceal mucinous lesions are shown in Figure 1–6.

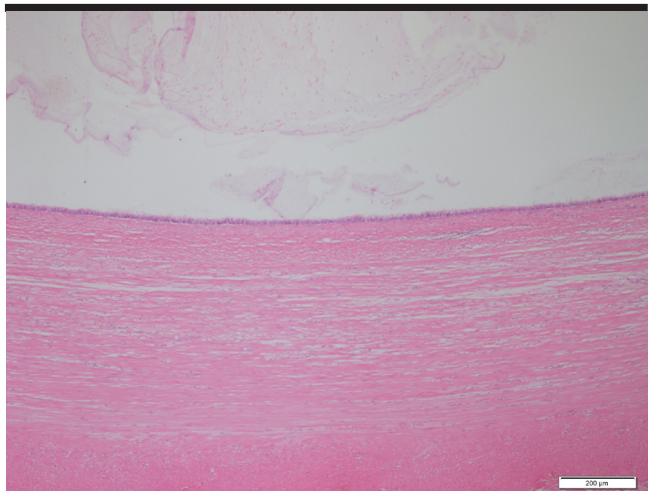

Figure 3. Flattened monolayer of mucinous epithelium, submucosal fibrosis, and absence of lamina propria in low-grade appendiceal mucinous neoplasm (hematoxylin–eosin, 40×).

DISCUSSION

Primary appendiceal tumors are classified into three main groups considering the cell types they origin: epithelial tumors, mesenchymal tumors and lymphomas (2). Primary appendiceal epithelial tumors are sub-grouped as mucinous, non-mucinous, neuroendocrine, and mixed glandular-endocrine (composite) tumors. Appendiceal tumors are detected in 0.2–4.2% (~1%) of appendectomy specimens obtained from patients who underwent appendectomy for any reason, and appendiceal tumors constitute

Table 2. Demographic and clinical features of 37 patients with appendiceal mucinous lesions.

Age	Sex	Preop Diagnosis	AAp (Yes/ No)	Perfor (Yes/No)	Primer/ Incidental	Surgry Type	Width (mm)	Length (mm)	Follow-up (days)	Outcome
72	M	Volvulus	No	No	Incidental	Open	9	75	26	Exitus
62	F	Liver Donor	No	No	Incidental	Open	5	90	3538	Alive
31	F	Liver Donor	No	No	Incidental	Open	13	48	3435	Alive
28	M	Rectum Ca	Yes	No	Incidental	Open	15	50	1631	Exitus
79	M	Gastric perforation	No	No	Incidental	Open	15	40	1063	Exitus
76	F	Pelvic Mass	No	No	Incidental	Open	40	100	2072	Alive
66	M	Explorative Laparatomy	No	No	Incidental	Open	6	65	10	Exitus
57	F	Pelvic Mass	No	Yes	Incidental	Open	20	50	1291	Alive
50	M	Duodenal tumor	Yes (Eos)	Yes	Incidental	Open	15	45	587	Alive
84	M	Aap	Yes	No	Primary	Open	25	60	3384	Alive
64	M	AAp	Yes	No	Primary	Open	10	65	3294	Alive
23	F	AAp	No	No	Primary	Open	15	40	3201	Alive
64	F	AAp (Perforated)	Yes	Yes	Primary	Open	10	90	3163	Alive
36	M	AAp	No	No	Primary	Open	8	70	2628	Alive
23	M	AAp	No	No	Primary	Open	8	80	2595	Alive
87	F	AAp	No	No	Primary	Lap	5	35	2394	Alive
28	F	AAp	No	No	Primary	Open	5	45	2148	Alive
62	F	AAp	No	No	Primary	Open	8	40	1998	Alive
77	F	AAp	Yes	No	Primary	Open	10	80	83	Exitus
46	F	Cecal tumor	No	No	Primary	Lap	40	95	1930	Alive
68	F	AAp (Perforated)	Yes	Yes	Primary	Open	30	60	1716	Alive
34	M	Mesenteric Mass	No	No	Primary	Lap	15	45	1641	Alive
86	F	AAp	Yes	No	Primary	Open	30	90	989	Exitus
41	M	Appendiceal Mass	No	No	Primary	Lap	20	80	1025	Alive
77	M	AAp	Yes	No	Primary	Open	10	60	812	Alive
61	M	Appendiceal Mass	No	No	Primary	Open	20	90	782	Alive
54	F	AAp	Yes	Yes	Primary	Open	40	80	760	Alive
67	M	Appendiceal Mass	No	No	Primary	Lap	65	140	475	Alive
66	F	AAp	Yes	No	Primary	Open	10	60	223	Alive
37	M	AAp (Perforated)	Yes (Eos)	Yes	Primary	Open	20	65	2714	Alive
72	F	AAp	Yes	Yes	Primary	Open	40	160	2092	Alive
28	M	PMP	No	Yes	Primary	Open	24	100	285	Exitus
71	M	AAp (Perforated)	Yes	Yes	Primary	Open	18	65	882	Alive
93	M	AAp	No	Yes	Primary	Open	12	40	769	Alive
69	M	AAp	Yes	Yes	Primary	Open	20	90	673	Alive
68	F	AAp (Perforated)	No	No	Primary	Open	25	102	104	Exitus
43	F	AAp (Perforated)	Yes (Eos)	Yes	Primary	Lap	14	55	203	Alive

0.5% of all gastrointestinal tumors (1, 3). Neuroendocrine tumors and adenocarcinomas (mucinous, signet ring, or non-mucinous) are the two most common primary appendiceal tumors with a rate of 65% and 20%, respectively (3). Mucinous tumors account for 8% of the appendiceal tumors (4). In other words, appendiceal mucinous tumors are detected in 0.2–0.3% of appendectomy specimens (3).

When we evaluate the PSOGI (2012), PSOGI modified Delphi process (2016), and WHO (2019) classification

Table 3. Definition of patients with appendiceal mucinous lesions.

Surgical Approaches	Histopathological Diagnosis (First)	Histopathological Diagnois (Last)
Appendectomy+Hartmann's	Mucosal hyperplasia	Hyperplastic polyp
Appendecotmy+ Donor Hepatectomy	Mucosal hyperplasia	LAMN
Appendecotmy+ Donor Hepatectomy	Mucinous Cystadenoma	LAMN
Appendectomy+ Miles	Mucocele	Simple retention cysts
Appendectomy	LAMN	LAMN
Appendectomy+ TAH+BSO	Mucocele	LAMN
Appendectomy+ Posttransplant exploration	Mucocele	Simple retention cysts
Appendectomy+ TAH+BSO+Lymphadenectomy	Adenoca (Mucinous)	Adenoca (Mucinous)
Appendectomy+ Duodenal resection	Mucocele	Appendiceal diverticula (Ruptured)
Appendectomy	Mucosal hyperplasia	Hyperplastic polyp
Appendectomy	Mucinous Cystadenoma	LAMN
Appendectomy	Mucinous Cystadenoma	LAMN
Appendectomy+ Right Hemicolectomy	LAMN	LAMN
Appendectomy	Mucocele	Simple retention cysts
Appendectomy	Mucocele	Simple retention cysts
Appendectomy	Mucocele	Simple retention cysts
Appendectomy	Mucocele	Simple retention cysts
Appendectomy	Mucinous Cystadenoma	LAMN
Appendectomy	Mucosal hyperplasia	Hyperplastic polyp
Appendectomy	Mucinous Cystadenoma	LAMN
Appendectomy (Refused)	Adenoca (Mucinous)	Adenoca (Mucinous)
Appendectomy	Mucinous Cystadenoma	LAMN
Appendectomy	Mucocele	Sessile serrated lesion
Appendectomy	LAMN	LAMN
Appendectomy	Mucosal hyperplasia	Hyperplastic polyp
Appendectomy	Mucinous Cystadenoma	LAMN
Appendectomy	LAMN	LAMN
Appendectomy	Mucinous Cystadenoma	LAMN
Appendectomy	Hyperplastic polyp	Hyperplastic polyp
Appendectomy	Mucocele	Appendiceal diverticula (Ruptured)
Appendectomy	Mucinous Cystadenoma	LAMN
Appendectomy+ Omentectomy+ Lymphadenectomy	Adenoca (Mucinous)	Adenoca (Mucinous)
Appendectomy	LAMN	LAMN
Appendectomy (Refused)	Adenoca (Mucinous)	Adenoca (Mucinous)
Appendectomy	Adenomatous polyp	Hyperplastic polyp
Appendectomy+ Ileocecal resection	Adenoca (Mucinous)	Adenoca (Mucinous)
Appendectomy	LAMN	LAMN

systems together, we can basically collect appendiceal non-neuroendocrine epithelial tumors in the following sub-groups: serrated polyp with or without dysplasia (low or high grade), LAMN (atypia is low grade), high-grade appendiceal mucinous neoplasm (HAMN; atypia is high grade), mucinous adenocarcinoma (well-, moderately-, poorly-differentiated; >50% mucin), poorly-differentiated adenocarcinoma (mucinous) with signet ring cells (≤50% signet ring cells), mucinous signet cell adenocarcinoma (>50% signet ring cells), non-mucinous adenocarcinoma (well-, moderately-, poorly-differentiated; resembling usual colorectal type), and goblet cell adenocarcinoma (2, 5–7).

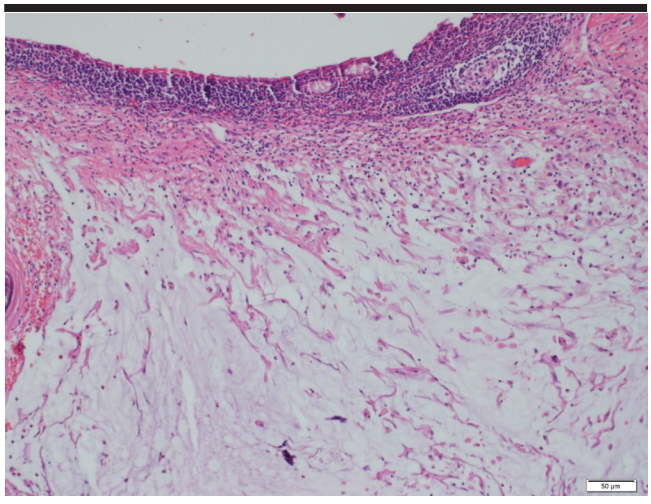

Figure 4. Acellular mucin extravasation into the submucosa in a simple retention cyst (hematoxylin–eosin, 40×).

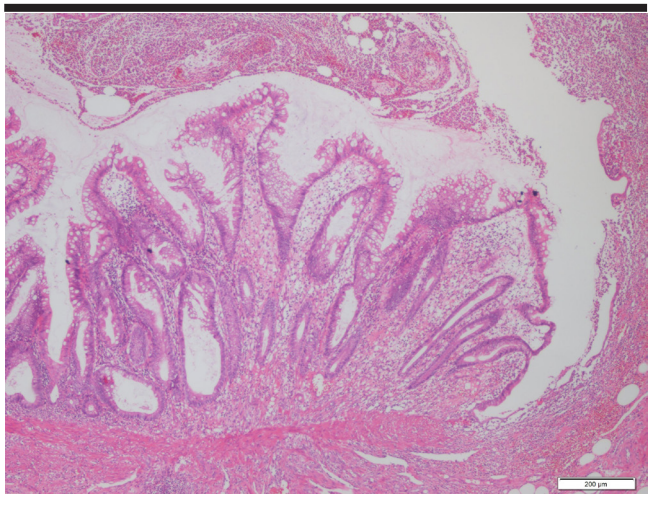

Figure 5. Elongated crypts displaying prominent goblet cells in hyperplastic polyp (left) and acute appendicitis findings (right) (hematoxylin–eosin, 40×).

There is a lack of consensus for classifying appendiceal mucinous tumors and treatment algorithm since Rokitansky first described the appendiceal mucocele in 1842. Mucocele is being used to define a pathological condition over years, although it is a radiological and clinical entity referring to obstructed appendiceal lumen with mucinous secretion. The PSOGI and WHO classifications have the most common consent to standardize appendiceal mucinous tumors terminologically and histopathologically among classifications of similar intent (2, 5). Per our knowledge, there is no published study except up-to-date database using terms such as appendiceal mucinous lesions in the nomenclature. Our opinion reserves collect all these lesions under the same title with neoplastic lesions despite their histopathologically malign or premalign features.

Appendiceal mucinous lesions are classified into two major groups of non-neoplastic lesions (mucocele) and neoplastic lesions (serrated polyps, hyperplastic polyps, LAMN, HAMN, and mucinous adenocarcinomas).

Mucocele is characterized by mucinous secretion collection in distal part of the appendiceal lumen because of chronic obstruction without epithelial hyperplasia or neoplasia resulting in epithelial degeneration. Since simple mucocele/simple retention cyst/ inflammatory mucocele, or obstructive mucocele do not refer to a neoplastic lesion, it does not exist in WHO classification of tumors of the digestive system 2019. Because mucocele is a clinical terminology, simple retention cyst was used instead of

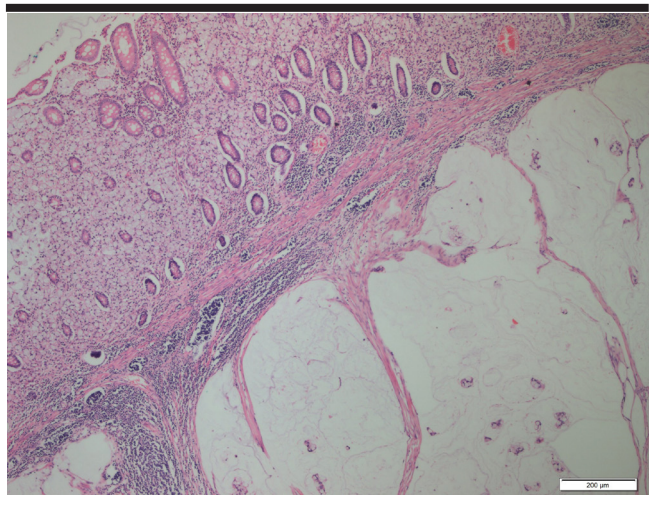

Figure 6. Mucin pool and tumor cells with signet ring cell morphology in an appendiceal mucinous adenocarcinoma (hematoxylin–eosin, 40×).

this term in this study. According to this, re-evaluation of pathological diagnosis of 10 patients reported as mucocele revealed simple retention cyst in six, ruptured appendiceal diverticula in two, sessile serrated lesion without dysplasia in one, and LAMN in the remaining one patient.

Mucinous cystadenoma terminology is eventually being clarified. Appendiceal lesions, previously known to present as mucocele, are classified into four: simple retention cysts, mucosal hyperplasia, mucinous cystadenoma, and mucinous cystadenocarcinomas. Recently, simple mucocele term was replaced by simple retention cyst, whereas mucosal hyperplasia term was replaced by hyperplastic polyps and serrated polyps with or without dysplasia. Carr et al. (5,6) used mucinous cystadenoma term, which did not exist in their subsequent modified Delphi classification (2, 5, 6). It is known that the WHO 2019 classification does not contain mucinous cystadenoma. However, there are studies in the literature suggesting that mucinous cystadenoma malignantly change, rupture, and thus cause PMP clinic, and there are studies suggesting that mucinous cystadenoma have no PMP risk and therefore are not related to real LAMNs (2, 8, 9). However, we support the view that mucinous cystadenomas show a low dysplastic change and therefore should be included in the LAMN classification according to the WHO 2019 classification system. Hence, nine of the patients in this study who were diagnosed with mucinous cystadenoma according to the initial pathology report were confirmed to be LAMN following re-evaluation in accordance with the WHO 2019 classification system.

Serrated polyps with or without dysplasia have similarities with serrated polyps of colon in an absolutely different molecular structure. Focally located polyps in appendiceal epithelium without dysplasia are defined as hyperplastic polyp, whereas flat or diffusely located polyps without dysplasia are defined as mucosal hyperplasia. Serrated polyps, whose biological attitudes are yet to be known, are defined as polyp, regardless of containing dysplasia, and previously these lesions were defined as adenomas, reminding of a benign disease. In this study, in accordance with the initial pathology report, five patients were diagnosed with mucosal hyperplasia and one patient was diagnosed with hyperplastic polyp. Re-evaluation in terms of the WHO 2019 classification system revealed hyperplastic polyp in five patients and LAMN in one patient. That is, hyperplastic polyp terminology is still being used in the WHO 2019 classification system.

Appendiceal adenomas known to be similar to colonic adenomas resulted from APC tumor suppression are rare entities. Hence, WHO 2019 classification does not consist these adenomatous polyps. One patient of this study was diagnosed with adenomatous polyp, which was re-evaluated and diagnosed as hyperplastic polyp in accordance with the WHO 2019 classification system.

LAMN are neoplastic lesions producing mucin, limited in muscularis propria and rarely invading appendiceal epithelium. According to the American Joint Committee on Cancer (AJCC), LAMNs without muscularis propria invasion are classified as in situ tumor (Tis). Mucinous neoplasms with T1 and T2 invasion are not classified in accordance with LAMN. However, LAMNs with subserosal or serosal acellular mucin foci are named as T3 and T4a subsequently. In this study, seven pathological specimens were diagnosed with LAMN in accordance with the WHOinitial pathology report and re-evaluation as per the WHO 2019 classification system confirmed this diagnosis in all of the cases. However, this re-evaluation revealed new 11 LAMN cases, which were previously diagnosed for other conditions according to the initial pathology report.

HAMN are discriminated from LAMNs on the basis of high-grade dysplastic changes of appendiceal epithelium. HAMN have similar low invasion potential and are more aggressive in course compared with LAMN. HAMNs are staged as invasive adenocarcinomas as a consequence of high recurrence risk. None of the patients of this study were diagnosed for HAMN in accordance with the WHO 2010 classification system or the WHO 2019 classification system, which restricts us to comment on recurrence rate of HAMN.

Appendiceal mucinous adenocarcinomas are characterized by invasive glands containing high-grade cytologic atypia and extracellular mucin in >50% of the tumor volume in histopathological examination, which are classified as well-, moderately-, or poorly-differentiated mucinous adenocarcinomas. The latter type is significant in its signet ring cells. The WHO 2019 classification does not alter any definition for mucinous adenocarcinoma. For this reason, diagnosis of five patients in this study remained same.

Appendiceal mucinous lesions are diagnosed incidentally during endoscopic or radiologic examinations for any indication. On the other hand, diagnosis accounts for a vast majority that are obtained from histopathological examination of appendectomy specimens. Retention cysts or serrated polyps have minor risk of rupture that rarely results in recurrence and simulate clinical features of acute

appendicitis or right lower quadrant pain. On the contrary, rupture of LAMN, HAMN, or mucinous adenocarcinomas results in the accumulation of mucinous ascites in abdominal cavity and related complications, which is defined as PMP.

Decision for the treatment of appendiceal mucinous lesions should be made on the basis of the histopathological features of the lesions. Even with a rupture, simple mucocele has hardly ever risk of recurrence, and standard appendectomy is the optimal treatment, which does not require long-term follow-up. Treatment strategies for serrated polyps with or without dysplasia are similar with the one for simple mucocele. A standard appendectomy is sufficient for LAMN and HAMN lesions that are not ruptured and are limited in appendix vermiformis, which does not require long-term follow-up. Although some studies suggest complementary right hemicolectomy for LAMN cases with a positive surgical margin, opposing studies advocate sufficiency of appendectomy as the risk for recurrence is obscure to prognosticate even in cases with neoplastic epithelium or acellular mucin on surgical margin (10–12). We suggest taking operative findings into account. Including a portion of cecal wall into appendectomy specimen, which is easily performed with a surgical stapler, would provide to avoid a positive surgical margin in cases with a lesion extending to the appendiceal basis or cecum. Ileocecal resection or partial cecal resection are applicable for tumors invading the wall of the cecum. For advanced stage or ruptured tumors completion right hemicolectomy with lymphadenectomy or cytoreductive surgery with heated intraperitoneal chemotherapy are options for treatment. In this study, malign lesion was not diagnosed in 32 patients without recurrence during follow-up. Although adenocarcinoma was diagnosed in five patients, two of them did not consent for a complementary hemicolectomy. Remaining three patients were treated in accordance with the principles of oncological surgery.

As a result, the term ''appendiceal mucinous lesions'', which was recently introduced into medical literature, is suitable to distinguish between lesions with and without malignancy potential. For most of the non-rupture appendiceal mucinous lesions, standard appendectomy is an adequate option. Ruptured lesions and adenocarcinoma are candidates for advanced, radical surgical treatment.

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REFERENCES

1. Akbulut S, Koc C, Sarıcı B, Ozcan M, Samdanci E, Yılmaz S. Histopathological features of incidental appendectomy specimens obtained from living liver donors. Turk J Gastroenterol 2020; 31: 257-63. [Crossref]

2. Gundogar O, Kımıloglu E, Komut N, et al. Evaluation of appendiceal mucinous neoplasms with a new classification system and literature review. Turk J Gastroenterol 2018; 29: 533-42. [Crossref]

3. Shaib WL, Assi R, Shamseddine A, et al. Appendiceal Mucinous Neoplasms: Diagnosis and Management. Oncologist 2017; 22: 1107-16. [Crossref]

4. Nutu OA, Marcacuzco Quinto AA, Manrique Municio A, et al. Mucinous appendiceal neoplasms: Incidence, diagnosis and surgical treatment. Cir Esp 2017; 95: 321-7. [Crossref]

5. Carr NJ, Bibeau F, Bradley RF, et al. The histopathological classification, diagnosis and differential diagnosis of mucinous appendiceal neoplasms, appendiceal adenocarcinomas and pseudomyxoma peritonei. Histopathology 2017; 71: 847-58. [Crossref]

6. Carr NJ, Cecil TD, Mohamed F, et al. A Consensus for Classification and Pathologic Reporting of Pseudomyxoma Peritonei and Associated Appendiceal Neoplasia: The Results of the Peritoneal Surface Oncology Group International (PSOGI) Modified Delphi Process. Am J Surg Pathol 2016; 40: 14-26. [Crossref]

7. Xiao J, Li, Liu W. Analysis of Clinical Characteristics of Low-Grade Appendiceal Mucinous Neoplasm (LAMN): A Retrospective Cohort Study of 51 LAMN Patients. J Invest Surg 2020: 1-7. [Crossref]

8. Kilic MO, Inan A, Bozer M. Four mucinous cystadenoma of the appendix treated by different approaches. Ulus Cerrahi Derg 2014; 30: 97-9. [Crossref]

9. Kehagias I, Zygomalas A, Markopoulos G, Papandreou T, Kraniotis P. Diagnosis and Treatment of Mucinous Appendiceal Neoplasm Presented as Acute Appendicitis. Case Rep Oncol Med 2016; 2016: 2161952. [Crossref]

10. Choudry HA, Pai RK. Management of Mucinous Appendiceal Tumors. Ann Surg Oncol 2018; 25: 2135-44. [Crossref]

11. Glasgow SC, Gaertner W, Stewart D, et al. The American Society of Colon and Rectal Surgeons, Clinical Practice Guidelines for the Management of Appendiceal Neoplasms. Dis Colon Rectum 2019; 62: 1425-38. [Crossref]

12. Arnason T, Kamionek M, Yang M, Yantiss RK, Misdraji J. Significance of proximal margin involvement in low-grade appendiceal mucinous neoplasms. Arch Pathol Lab Med 2015; 139: 518-21. [Crossref]