Differential Diagnosis of Appendiceal Serrated Lesions and Polyps and Low-Grade Appendiceal Mucinous Neoplasm: Analysis Of 88 Cases

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Abstract

Purpose: To identify clinicopathological features for the differential diagnosis of appendiceal serrated lesions and polyps (SPs) and low-grade appendiceal mucinous neoplasm (LAMN) for the purpose of avoiding over-diagnosis.

Methods: Clinical data and pathological features of 66 patients with SPs diagnosed at the Aerospace Center Hospital between January 2013 and January 2021 were collected and compared to 22 cases of LAMN.

Results: SPs, compared with LAMN, are likely to be associated with acute inflammation (SPs 53.0% vs. LAMN 18.2%), and may be located in the appendix partly, although with smaller diameter (average 9.6 vs. 27.2 mm); epithelial structures of serrated (100% vs. 22.7%) and filiform villous (47.0% vs. 18.2%) were often found in SPs. SPs occasionally show attenuated or flattened morphology (16.7% vs. 100%) and undulating or scalloped (7.6% vs. 40.9%) structures, and can also be accompanied by diverticulum (18.2% vs. 18.2%) and acellular mucin in the appendiceal wall (16.7% vs. 54.5%), which causes confusion with LAMN. The key point of the differential diagnosis is to observe whether the muscularis mucosa exists (loss, 0% vs. 100%) and fibrosis of the appendiceal wall (0% vs. 100%). SMA immunohistochemistry can assist in the diagnosis. Calcification is also indicative of LAMN.

Conclusions: The epithelial structure of SPs can appear flattened and focally scalloped, and can be accompanied by mucin in the appendiceal wall, which may appear as complex lesions, easily over-diagnosed as LAMN. Key differential diagnostic features are identifying the structure of lamina propria, determining whether the muscularis mucosa exists, and whether the appendiceal wall is fibrotic.

Abbreviations

Serrated lesion without dysplasia: SL

Serrated lesion with dysplasia: SLD

appendiceal serrated lesions and polyps:SPs

low-grade appendiceal mucinous neoplasm: LAMN

peritoneal pseudomyxoma: PMP

Declarations

Funding The foundation of Aerospace Center Hospital (20190301-YN-16) . **Competing interests** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. **Availability of data and material** The datasets used and/or analyzed during the current study are available from the corresponding author on

reasonable request. Authors' contribution Study concepts: YL, MJ; Study design: YL, MJ; Data acquisition: YL, HX, CQ; Quality control of data and algorithms: YL, MJ; Data analysis and interpretation: YL, CQ, MJ; Statistic analysis: YL, CQ; Manuscript preparation: YL, CQ, HX, MJ; Manuscript editing: YL, CQ, HX, MJ; Manuscript review: YL, MJ. Ethics approval This study had been approved by the Aerospace Center Hospital Institutional Review Board (Approval No: 20190301-YN-16). Consent for publication No conflict of interest exists in the submission of this manuscript, and manuscript is approved by all authors for publication. The work described was original research that has not been published previously, and not under consideration for publication elsewhere, in whole or in part. Acknowledgements We thank Charlesworth Author Services (www.cwauthors.com) for its linguistic assistance during the preparation of this manuscript.

1. Introduction

Serrated lesions and polyps (SPs) may also occur in the appendix and exhibit a spectrum of morphologic features similar to serrated colorectal polyps, but they have been rarely investigated systematically [1]. When the appendix is dilated, or when the epithelial tissue is flattened, or accompanied by acute inflammation or diverticulum, the lesions of SPs will become complex, and may very easily be over-diagnosed as low-grade appendiceal mucinous neoplasm (LAMN). The aim of this study was to describe the clinical, morphological features of SPs in the appendix and to compare them with a control group of LAMN, to identify the main features for their differential diagnosis.

2. Materials And Methods

2.1 Study group

A total of 2604 patients who underwent appendectomy for any reason between January 2013 and January 2021 at the Aerospace Center Hospital were reviewed. Among them, 516 cases underwent appendectomy after April 2019. The pathology records were searched for the terms "epithelial hyperplasia," "diverticulum," "mucous cyst," "mucinous cystadenoma," "sessile serrated adenoma/Polyp (SSA/P)," "sessile serrated lesion (SSL)" or "LAMN." Cases of LAMN complicated with peritoneal pseudomyxoma (PMP) were excluded. The need for consent for participation was waived given the retrospective nature of the study. This study had been approved by the Aerospace Center Hospital Institutional Review Board (Approval No: 20190301-YN-16).

2.2 Methods

Traditional sampling methods of the appendix include a longitudinal section of the appendiceal tip and two additional cross-sections (middle portion and from the proximal margin of resection). After April 2019, appendix samples *in toto* were submitted for pathology evaluation, which included two longitudinal sections of tip and all the remaining tissues from the excision. edge to the tip).

The specimens were fixed in 10% formalin solution. Tissues were sliced at a thickness of 4 µm and hematoxylin-eosin (HE) stained. Smooth muscle actin (SMA) immunohistochemical staining was used in some cases, which led to possibility of determining whether the muscularis mucosae had disappeared, using the standard avidin-biotin complex technique. A positive result for SMA was defined as cytoplasmic staining.

2.3 Pathology evaluation

SPs and LAMN were re-evaluated microscopically by two pathologists according to the new 2019 World Health Organization classification of non-neuroendocrine epithelial tumors of the appendix (2019WHO). The classification criteria for SPs were as follows (Fig.1): hyperplastic polyp (HP) with straight crypts featuring serration limited to the luminal aspect of the crypt and absence of cytological dysplasia. Serrated lesions (SL) without dysplasia showed distorted crypts with serration and crypt dilatation extending to crypt bases and absent cytological dysplasia. SL with dysplasia (SLD) had the same crypts as SL, but presented cytological dysplasia. The dysplasia could take the form of conventional adenoma-like dysplasia, serrated dysplasia, or traditional serrated adenoma (TSA)-like dysplasia, and multiple morphological patterns of dysplasia may be present within a single polyp [1]. The cytological atypicality was based on nuclear enlargement and hyperchromasia, nucleolar enlargement, apoptotic debris, and mitoses diffusely present in the surface epithelium [1-4].

LAMN diagnostic criteria used included those for mucinous neoplasm. Low-grade cytologic atypia replacement of normal appendiceal mucosa by filiform villous mucinous epithelial proliferation. Lesions may show an undulating or scalloped appearance, with columnar epithelial cells with nuclear pseudostratification growing on fibrotic submucosal tissue. Some cases may be characterized by an attenuated or flattened monolayer of mucinous epithelium. The lymphoid tissue of the appendix is usually absent. The wall may have varying degrees of fibrosis, hyalinization, and calcification. The mucin can dissect through the structures of the appendix and extend to the peritoneal surface or cause rupture of the appendix. Intramural glandular epithelium may protrude into or through the appendiceal wall and exhibit a rounded, pushing pattern of invasion. Serosal involvement may consist of mucin at the surface, or it may consist of replacement of a portion of the appendix with an hyalinizing reaction with strips of low-grade mucinous epithelial cells associated with extracellular mucin [4,5]. Epithelium presenting unequivocal high-grade features or infiltrative patterns was considered unsuitable for the diagnosis of LAMN.

Individuals not meeting the diagnostic criteria and for whom the pathological data were incomplete were excluded from the study. Among the 66 cases of SPs, there were 2 cases of HP, 32 cases of SL, and 32 cases of SLD. Twenty-two cases of LAMN that were confined to the appendix, without PMP were finally included in the study. Among the 66 cases of SP, there were 32 cases (1 case of HP, 16 cases of SL, 15 cases of SLD) diagnosed after April 2019.

The following demographic and clinical parameters were collected for this study: age (years), sex (male, female), surgery type (appendectomy alone, appendectomy combined with other tumors), and clinical

symptoms (appendicitis, appendix cyst) of the patients with appendectomy alone.

The following pathologic features were recorded for each lesion: width of appendix (mm), location in the appendix (partial, entire), epithelial structural (serration, filiform villous, attenuated or flattened, undulating, or scalloped), and the presence of acute appendicitis, diverticulum, mucin extravasation, loss of muscularis mucosae, submucosal fibrosis, and calcification.

2.4 Statistical analyses

Statistical analyses were performed using SPSS v22.0 (IBM Corp., Armonk, NY, USA). Comparisons for categorical variables were performed using Pearson's chi-squared test or Fisher's exact test where appropriate. A two-tailed p -value was used for all analyses and $P<0.05$ was considered statistically significant.

3. Results

3.1 Clinicopathological feature of SPs and LAMN

The incidence rate of SPs was 1.6% (34/2088) with partial sampling of the appendix and when the appendix was sampled *in toto* (after April 2019), the incidence rate increased to 6.2% (32/516) (Table 1). SPs and LAMN occurred more frequently in elderly women, but the sex and age differences were not statistically significant between them, or between SL and SLD ($P>0.05$). LAMN were more likely to be found as appendix cysts pre-operatively, while SPs were more likely to be found during appendectomy combined with other tumors ($P<0.05$).

3.2 Pathological features

Gross pathological observation revealed 28 SPs cases (28/66, 42.4%) with an appendix diameter ≥ 10 mm (mean 9.6 mm, range 4–50), 10 SL cases (10/32, 31.3%) with an appendix diameter ≥ 10 mm (mean 8.1 mm, range 5–15), and 17 SLD cases (17/32, 53.1%) with an appendix diameter ≥ 10 mm (mean 11.4 mm, range 4–50). In LAMN, 19 cases (19/22, 86.4%) had an appendix diameter ≥ 10 mm (mean 27.2 mm, range 6–60). The diameter of the appendix in LAMNs was significantly larger than that in SPs ($P<0.01$); Although in SLD the diameter of the appendix was larger than SL, the differences were not statistically significant.

Pathomorphological characteristics indicated in SPs cases, 11 cases (11/66, 16.7%) involved the entire appendix, while in LAMN there were 18 cases (18/22, 81.8%) ($P<0.01$). Differences in location for SL and SLD were not statistically significant ($P=0.74$). Compared with LAMN, SPs were significantly more likely to be associated with acute inflammation (4/22, 18.2% vs 35/66, 53.0%; $P=0.009$). Although there were more cases of acute inflammation in SLD than in SL, the difference was not statistically significant. Serrated structure should be distinguished from mimicked serrated changes as a response to inflammation (Fig.2). Epithelial structural changes (Fig.3) indicated a similar proportion of epithelial morphology in SL and SLD. Compared with SL, the epithelium of SLD more likely appeared attenuated or

flattened (8/32,25%); although, the presence of diverticulum (8/32, 25%) and acellular mucin division in the appendiceal wall (8/32, 25%) (Fig.4) were more common, there was no significant difference between SL and SLD.

Compared with SPs, the epithelial structural changes involving attenuated or flattened (12/22, 54.5%) and undulating or scalloped changes (9/22, 40.9%) were more common in LAMN. All cases presented completed or focal disappearance of muscularis mucosa (22/22, 100%). Immunohistochemical staining of SMA could identify this alteration (Fig.5). Fibrosis of the appendiceal wall was common in LAMN (22/22, 100%) and 10 cases (10/22, 45.5%) presented calcification, while epithelial structural changes such as serrated (5/22, 22.7%) and filiform villous epithelium (4/22, 18.2%) were rare in LAMN compared to SPs ($P<0.01$ and $P=0.017$, respectively). Twelve cases (12/22, 54.5%) of LAMN presented acellular mucin infiltrating the appendiceal wall; this difference was statistically significant ($P<0.05$) in comparison with SPs. In LAMN, 4 cases (4/22, 18.2%) presented diverticulum and a similar proportion was observed in SPs (12/66, 18.2%).

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4. Discussion

According to the 2019WHO, colorectal SPs may be classified as HP, sessil serrated lesions (SSL), sessil serrated lesions with dysplasia (SSLD), TSA, and serrated adenoma, unclassified polyps [2]. SSL and HP account for about 10% and 30% of all colorectal polyps [6]. Approximately 30% of all colorectal carcinomas arise via the serrated neoplasia pathway [7]. However, the appendix is the terminal organ of the cecum, it is inaccessible by endoscopy. Thus, there is currently minimal information regarding the biologic potential and evolution of mucosal alterations in the appendix [8]. Pathologists have traditionally chosen to apply terms used in pathological diagnosis of the colon to similar lesions found in the appendix. Investigators of appendiceal pathology have mainly focused on how these lesions differ from similar colonic neoplasms. Pai et al. [9] and Choi et al. [10] described differences in these lesions; they reported that appendiceal lesions harbor KRAS codon 12 and 13 mutations in over half of the cases with only a small subset harboring the BRAF V600E mutation. The frequent KRAS mutations seem to be more likely in LAMN [11], suggesting that colorectal diagnostic terminology may not apply to appendiceal serrated lesions. Until 2019, the WHO divided the appendix SPs into HP, SL, and SLD. In the appendix, HP and SL lesions are similar to HP and SSL lesions in colonic neoplasms, although in appendiceal SLD, dysplasia can take the form of conventional adenoma-like dysplasia, serrated dysplasia, or TSA-like dysplasia [1].

The mucosal epithelium of the SPs in the appendix can become flattened and undulating or scalloped focal, and can be accompanied by diverticulum and acute inflammation. Acellular mucin infiltrating the appendiceal wall can also be found in SPs. These conditions make the pathomorphological evaluation more complex and easily confused with LAMN. LAMN has a potential risk of peritoneal dissemination. It is important to distinguish SPs and LAMN.

Appendiceal SPs have also been described. However, except for rare case reports and a few case series [4,12,13], the true incidence is unknown. Yuyucu Karabulut et al. [14] described 960 appendix specimens, 71 cases (7.39%) were diagnosed as SPs, including 36 (50.7%) HP, 33 (46.48%) SSA/PS (now called SL), and 2 (2.81%) TSAs (now called SLD). Most guidelines recommend including a longitudinal section or cross-section of the appendiceal tip and 2 additional cross-sections. Few institutions routinely sample the entire resected appendix, except when neoplasms are detected on examination of the initial sections[8]. Renshaw et al. [15] compared the incidence of SSA/PS in 100 *in toto* appendix resections submitted for histological examination and 100 routinely submitted appendices (partial sampling), and found that among the appendices sampled *in toto*, 11 cases of SSA/PS were identified, compared with 1 case in the

routinely sampled group. In our study, the total incidence rate of SPs was 2.5% (66/2603). As one of China's single-center research centers for PMP, our institution began routinely sampling the entire appendix after April 2019. Since then, 516 appendices have been submitted. The incidence rate of SPs was 6.2% (32/516), which is higher than obtained in the traditionally sampled group (1.6%, 34/2088), which indicates that partial sampling may cause missed diagnosis. Sampling the entire appendix may provide more comprehensive data, which also challenges traditional diagnostic approaches.

As the most common element of the SP family in colorectal neoplasm, HP, comprises 80%–90% of all serrated polyps [16-17]. In our study sample, there were only 2 cases of HP among the SPs. Even in the *in toto* sampling group, the incidence rate was 1/66. This may be related to the fact that patients with HP present no overt clinical symptoms, besides the focal hyperplasia of the mucosa on histological observation. HPs were similar in appearance to the normal mucosa, and tended to be smaller than SL (previously called SSA/P lesions), and the latter were often circumferential [18]. In our study, none of HPs presented attractive diverticulum and mucin extravasation, which may be another reason for missed diagnosis.

The diameters of LAMN (mean 27.2 mm) were significantly larger than that of SPs (mean 9.6 mm) ($P<0.01$), and in some cases these could reach up to 60 mm. Imaging studies can identify such expanded structures and allow a diagnosis of appendix tumors or cysts, and prompt the patient to undergo appendectomy. In our sample population, 13 (59.1%) cases in the LAMN group underwent appendectomy owing to the presence of appendix tumors or cysts. Instead, all cases of SPs could be attributed to appendicitis.

SPs were often associated with acute appendicitis (35/66, 53.0%). It has previously been suggested that the intestinal mucosa can develop hyperplastic and architectural changes mimicking serrated polyps as a response to inflammatory stimuli [19]. Serrated epithelial lesions have also been described for inflammatory bowel disease (IBD) as a reactive response to inflammatory stimuli [20]. Similarly, in the acute appendicitis, the appendiceal mucosa may present with hyperplastic serrated lesions [15]. We also identified 5 additional cases of reactive serrated lesions in our review. In fact, reactive serrated lesions are not real SPs. The key differences were reactive serrated changes that were mostly limited to the surface of the mucosa, while the inflammatory and reactive serrated lesions alterations were always mixed. In real SPs, we can distinctly separate the surrounding inflamed mucosa from serrated lesions, and can observe branching, basal dilation, inverted T-shaped or L-shaped crypts in the background. We also found that SLD (20/32, 62.5%) were more likely to be associated with acute inflammation than SL (13/32, 40.6%). It can also be said that acute inflammation may more likely to lead to mucosal atypia. When SLD are not accompanied by acute inflammation, it may resemble a conventional adenoma with pseudostratified elongated hyperchromatic nuclei or display enlarged, vesicular nuclei with prominent nucleoli, that can easily be identified. Nevertheless, when accompanied with acute inflammation, the discrete distinction and categorization of dysplasia from reparative changes were challenged, which was the most noteworthy diagnostic puzzle we encountered in the review. Conversely, LAMN was less likely to

be associated with acute inflammation (4/22,18.2%), although, there was no statistical significance between SPs and LAMN ($P=0.009$).

The mucosal epithelial structures of SL and SLD were complex, showing serrated, filiform, flattened, or scalloped changes. There were no differences in the proportion of epithelial structural changes between the groups. All SL and SLD cases had typical crypt architectural features, including serration, dilatation, horizontal orientation, L-shape or inverted T-forms. This morphology should be distinguished from crypt changes caused by lymphatic follicles. In the normal appendix, the extensive follicular architecture distorts the crypts in many regions and leads to variable crypt lengths, distribution, and architecture [8]. In the normal appendix, these changes were confined to the clearly identifiable follicular area, and no additional serrated structures were found in the surrounding mucosa.

Serrated and filiform structures were more likely to appear in SPs, while flat and clustered structures were present in LAMN. In the background of flattened or clustered lesions, only 4 cases of LAMN presented focal filiform villous structures, which was not consistent with the literature [1,5]. We speculated that LAMN with an extensive filiform villous structure is more likely to be associated with PMP, but these cases were excluded from the study. Whether this is the result of a selection bias requires further observation.

SPs can also present a flattened mucosa and acellular mucin in the appendiceal wall, which are more likely to be confused with LAMN, and which make the diagnosis more challenging. To improve the differential diagnosis, it is important to sample the entire appendix. In cases with the presence of acellular mucin in the wall, we should focus on whether there is concomitant diverticulum. Diverticula of the appendix can be either acquired or congenital. Congenital diverticula are rarer, and generally consist of the mucosa, submucosa, serosa, and muscular layers, while acquired diverticula disease (ADD) are usually “false” and lack the muscular layers [21]. Increased intraluminal pressure is most commonly due to obstruction (benign or malignant) or inflammation and may predispose to ADD formation in weak areas of the appendiceal vascular walls [22-23]. In our SPs group, 12 cases were accompanied by ADD. Among these, there were 11 cases with mucin accumulation in the appendiceal wall, and all were characterized as acellular mucin. Diverticulum or inflammation leads to increased pressure in the appendix cavity, and then causes mucosal atrophy and flattened mucosa, the lamina propria becomes thinner or even disappears, which can easily be mistaken it for the occurrence of push infiltration and diagnosed as LAMN. In our group, 11 cases of appendiceal SPs appeared with atrophied and flattened mucosa. The lamina propria was notably thinned, but a small amount of residue could still be detected after careful observation. In retrospect, 8 cases of SPs were mis-diagnosed as LAMN, of which 4 cases presented flattened mucosa with diverticula and intramural mucin, 2 cases presented flat mucosa, and the 2 remaining cases presented intramural mucin. Fortunately, no additional surgical procedures were required for these patients. Thus, in such cases, the effective diagnostic points to consider include: observing the existence of muscularis mucosa and the presence of fibrosis in the appendiceal wall. SMA immunohistochemistry can be used to assist in more dubious cases. In the LAMN group, focal/complete disappearance of muscularis mucosa and fibrosis in the appendiceal wall were identified; in 9 cases,

these were limited to submucosa fibrosis and 13 cases there was evidence of full thickness fibrosis. Among these, 4 cases exhibited local fibrosis with a background of SPs. We tend to classify such cases as LAMN, which indicates the potential risk of PMP. Calcification (10/22, 45.5%) was also a good indicator of LAMN diagnosis. It can be recognized by imaging studies prior to surgical procedures.

It is clear that LAMN presents the potential risk of peritoneal dissemination [15]. The pathomorphology of SPs and LAMN are partly overlapped., it is a challenge to distinguish them. And molecular biological differences between LAMN and SPs are required to further our understanding of this disease.

References

1. Yantiss RK, Panczykowski A, Misdraji J et al (2007) A Comprehensive study of nondysplastic and dysplastic serrated polyps of the vermiform appendix. *Am J Surg Pathol* 31:1742–1753. <https://doi.org/10.1097/PAS.0b013e31806bee6d>
2. Misdraji J, Carr NJ, Pai RK. Appendiceal serrated lesions and polyps. Appendiceal mucinous neoplasm. In: WHO classification of tumours editorial board. *Digestive System Tumours*. 5th edition. Lyon, France: IARC Press, 2019, pp.141–146
3. Goldman H, Ming S, Hickock DF (1970) Nature and significance of hyperplastic polyps of the human colon. *Arch Pathol* 89:349–354
4. Longacre TA, Fenoglio-Preiser CM (1990) Mixed hyperplastic adenomatous polyps/serrated adenomas. A distinct form of colorectal neoplasia. *Am J Surg Pathol* 14:524–537. <https://doi.org/10.1097/00000478-199006000-00003>
5. Carr NJ, Cecil TD, Mohamed F et al (2016) 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* 40:14–26. <https://doi.org/10.1097/PAS.0000000000000535>
6. Davenport JR, Su T, Zhao Z et al (2018) Modifiable lifestyle factors associated with risk of serrated polyps, conventional adenomas and hyperplastic polyps. *Gut* 67:456–465. <https://doi.org/10.1136/gutjnl-2016-312893>
7. O'Brien MJ, Zhao Q, Yang S et al (2015) Colorectal serrated pathway cancers and precursors. *Histopathology* 66:49–65. <https://doi.org/10.1111/his.12564>
8. Melissa P (2010) Looking Through a keyhole serrated neoplasia in the vermiform appendix. *Am J Clin Pathol* 13:529–532. <https://doi.org/10.1309/AJCPUPMRP1RTDSU2>
9. Pai RK, Hartman DJ, Gonzalo DH et al. Serrated lesions of the appendix frequently harbor KRAS mutations and not BRAF mutations indicating a distinctly different serrated neoplastic pathway in the appendix, *Hum. Pathol.* 45:227–235. <https://doi.org/10.1016/j.humpath.2013.10.021>
10. Choi EK, Kim D, Divatia M et al (2015) Molecular alterations of appendiceal serrated lesions. *Hum Pathol* 46:1062–1066. <https://doi.org/10.1016/j.humpath.2015.02.017>

11. Zauber P, Berman R, Marolta S et al. Ki-RAS gene mutations are invariably present in low-grade mucinous tumors of vermiform appendix, *Scand J Gastroenterol*. 2011; 46:869–874. <https://doi.org/10.3109/00365521.2011.565070>
12. Williams GT, Du Boulay CE, Roche WR (1992) Benign epithelial neoplasms of the appendix: Classification and clinical associations. *Histopathology* 21:447–451. <https://doi.org/10.1111/j.1365-2559.1992.tb00429.x>
13. Carr NJ, McCarthy WF, Sobin LH. Epithelial noncarcinoid tumors and tumor-like lesions of the appendix. A clinicopathologic study of 184 patients with a multivariate analysis of prognostic factors, *Cancer*. 1995; 75: 757–768. [https://doi.org/10.1002/1097-0142\(19950201\)75:3<757::AID-CNCR2820750303>3.0.CO;2-F](https://doi.org/10.1002/1097-0142(19950201)75:3<757::AID-CNCR2820750303>3.0.CO;2-F).
14. Yuyucu Karabulut Y, Savaş B, Kurşun N et al (2014) Serrated lesions of the appendix: Do they differ from their colorectal counterparts. *Turk J Gastroenterol* 25:29–34. <https://doi.org/10.5152/tjg.2014.4056>
15. Renshaw AA, Kish R, Gould EW (2006) Sessile serrated adenoma is associated with appendicitis in patients 30 years or older. *Am J Clin Pathol* 126:875–877. <https://doi.org/10.1309/BF5KLH7J547AXAA0>
16. Jass JR, Young J, Leggett BA. Hyperplastic polyps and DNA microsatellite unstable cancers of the colorectum, *Histopathology*. 37 (2000) 295–301. <https://doi.org/10.1046/j.1365-2559.2000.01028.x>
17. Jass JR (2007) Classification of colorectal cancer based on correlation of clinical, morphological, and molecular features. *Histopathology* 50:113–130. <https://doi.org/10.1111/j.1365-2559.2006.02549.x>
18. Bellizzi A, Rock J, Marsh W et al (2010) Serrated lesions of the appendix: A morphologic and immunohistochemical appraisal. *Am J Clin Pathol* 133:623–632. <https://doi.org/10.1309/AJCP1UJXP6UURLCH>
19. Higuchi T, Sugihara K, Jass JR (2005) Demographic and pathological characteristics of serrated polyps of colorectum. *Histopathology* 47:32–40. <https://doi.org/10.1111/j.1365-2559.2005.02180.x>
20. Ball CG, Dupre MP, Falck V, Hui S et al (2005) Sessile serrated polyp mimicry in patients with solitary rectal ulcer syndrome: is there evidence of a preneoplastic change. *Arch Pathol Lab Med* 129:1037–1040. <https://doi.org/10.5858/2005-129-1037-SSPMIP>
21. Yucel A, Pergel A, Kocakusak A et al (2011) Multiple caeco-appendiceal fistulas and diverticulosis: a newly defined congenital anomaly of the appendix-report of the first case. *J Gastrointest Surg* 15:2111–2113. <https://doi.org/10.1007/s11605-011-1487-9>
22. Altieri ML, Piozzi GN, Salvatori P, Mirra M et al (2017) Appendiceal diverticulitis, a rare relevant pathology: presentation of a case report and review of the literature. *Int J Surg Case Rep* 33:31–34. <https://doi.org/10.1016/j.ijscr.2017.02.027>
23. Al-Brahim N, Al-Kandari I, Munahai M et al. Clinicopathological study of 25 cases of diverticular disease of the appendix: experience from Farwaniya Hospital, *Pathol Res Int* 404308 (2013). <https://doi.org/10.1155/2013/404308>

Tables

Due to technical limitations, Table 1 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Histomorphology of Appendiceal SPs. (A) HP: Serrated structure partially observed in the appendix (40x). (B) HP: Serration limited to the luminal aspects of the crypt, with a normal crypt and complete muscularis mucosa (100x). (C) SL: circumferential serrated structures are shown. The epithelium showed a filiform villous structure (40x). (D) SL: Distorted crypts with serration and crypt dilatation extending to crypt bases. Reduced or absent lamina propria, and the presence of muscularis mucosa (100x). (E) SLD:

Serrated structures are circumferential. Epithelium showing filiform villous growth and complex structure (40x). (F) SLD: The cytologic atypicality with nuclear enlargement and hyperchromasia, nucleolar enlargement, apoptotic debris, and mitoses (black arrow) diffusely present in the surface epithelium (800x).

Figure 2

Serrated changed accompanied by acute inflammation. (A) The reactive serrated lesions in response to the inflammatory stimuli: Serrated changes limited to the surface of the mucosa (40x). (B) Shown in the normal crypt and complete muscularis mucosa (100x). (C) SL with acute appendicitis: circumferential serrated lesions (40x). (D) SL: The serrated and dilation extending to the crypt bases with abnormal shapes of crypt (100x). (E) SLD with acute appendicitis: Circumferential serrated lesions shown with abnormal crypt shapes (40x). (F) SLD: Atypical cytologic changes with nuclear enlargement, nucleolar enlargement (red arrow), and mitoses (black arrow) (800x) .

Figure 3

Epithelial structural changes in SPs. (A) Serration and filiform villous structures (40x). (B) Serration identified on a flattened and scalloped background (100x)

Figure 4

Diverticulum of SPs. (A) Epithelium and lamina propria diverticula protruding from the wall, accompanied by rupture and the disappearance of the muscular layer (10x). (B) Immunohistochemical staining of the SMA in the diverticula: Shown is the complete muscularis mucosa and rupture of the muscular layer (40x). (C) Acellular mucin division of the appendiceal wall (10x).

Figure 5

LAMN: Local fibrosis in the muscularis mucosae with a background of SPs. (A) The complete muscular layer is visible. However, the muscularis mucosae is replaced by fibrosis and hyalinization (40x). (B) The muscularis mucosae adhered intimately to the muscular layer (200x). (C) Immunohistochemical staining of SMA: The complete muscular layer (40x) and (D) fibrosis of muscularis mucosae (200x) are shown.

Supplementary Files

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- [Table1.ClinicopathologicalfeatureofSPsandLAMN.docx](#)