



Serrated lesions of the appendix: Do they differ from their colorectal counterparts?

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ABSTRACT

Background/Aims: The aim of this study is, therefore, to classify appendiceal serrated polyps in a large case series with respect to the recent World Health Organization classification using diagnostic criteria provided for colorectal serrated polyps.

Materials and Methods: A total of 960 appendix specimens diagnosed between 2005 and 2010 were reviewed retrospectively, and cases presenting with a polyp with serrated morphology were classified with reference to the recent World Health Organization criteria. Histologic criteria comprised architectural features of the crypts, including serration, branching, basal dilatation, inverted T- or L-shaped crypts together with cytologic features comprising a mucin pattern, dysplasia, in terms of pseudostratification and nuclear atypia, mitoses in the upper crypts, and cytoplasmic eosinophilia.

Results: A total of 71 cases (7.39%) were diagnosed as serrated polyps, including 36 (50.7%) hyperplastic polyps, 33 (46.48%) sessile serrated adenoma/polyps, and 2 (2.81%) traditional serrated adenomas. There were 32 males and 39 females with an age range of 2 to 82 years. Histology revealed that the majority of both hyperplastic polyps (63.9%) and sessile serrated adenomas/polyps (74.3%) involved the entire appendiceal circumference. Basal dilatation (94.3%), basal serration (94.3%), T-/L-shaped crypts (94.3%), and ectopic crypts (68.6%) were significantly more commonly observed in sessile serrated adenomas/polyps compared to hyperplastic polyps. Dysplasia was observed in 31.4% of sessile serrated adenomas/polyps, while hyperplastic polyps did not show dysplasia.

Conclusion: The results of the present study suggest that appendiceal serrated polyps, despite bearing many similarities with their colorectal counterparts, may have some special features due to the anatomic uniqueness of the organ itself and also the polyps arising from its mucosal lining.

Keywords: Appendix, serrated lesions, sessile serrated adenoma/polyp, hyperplastic polyp

INTRODUCTION

The term "serrated polyp" is used for polyps demonstrating sawtooth-like infolding of the surface and crypt epithelium, likely as a consequence of an increase in the cellular proliferation zone, extending from lower to mid or upper crypts, as well as an inhibition of programmed cellular exfoliation (apoptosis/anoikis) of the surface mucosa. The family of serrated polyps (SPs) is a heterogeneous group of lesions (1) comprising hyper-

plastic polyps (HPs), sessile serrated adenomas/polyps (SSA/PS), and traditional serrated adenomas (TSAs) (1). Though serrated polyps are mostly confined to the colorectum, appendiceal serrated polyps, which may differ from their colorectal counterparts, have also been reported. However, except for rare case reports and a few case series (2-4), their true incidence is unknown. Lesions that are similar to those known as serrated polyps today have previously been reported under a vari-

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ety of names, such as mucosal metaplasias, hyperplasias, and diffuse hyperplasia (5). The review of the literature revealed that only one case of serrated adenoma of the appendix had been published (6) until Rubio's first report on serrated adenomas of the appendix. In his report, Rubio defined serrated adenomas as "adenomas with sawtooth-like dysplastic epithelium found in more than 50% of basal crypts." He also stated that serrated and villous adenomas of the appendix appeared to be highly aggressive lesions, more so than adenomas of the colon and rectum (7). A brief description of HPs and SSPs was given in this report with no mention of dysplasia in SSPs, while a recent paper included a third category of SPs with mixed features of hyperplastic and adenomatous polyps, probably reflecting dysplasia in a serrated polyp (8). The latter study consists of additional information on the immunophenotypic characteristics of HPs and SSAs, which were similar to their colorectal counterparts. The recent WHO classification, on the other hand, did not provide additional criteria for the diagnosis of serrated lesions of the appendix, thereby suggesting a similar approach as in colorectal serrated polyps.

The aim of this study is, therefore, to classify appendiceal serrated polyps in a large case series with respect to the recent WHO classification using diagnostic criteria provided for colorectal serrated polyps.

MATERIALS AND METHODS

A total of 960 appendix specimens diagnosed between 2005 and 2010 were reviewed retrospectively, and cases presenting with a polyp with serrated morphology were classified with reference to the recent WHO criteria (1), regardless of the initial diagnoses. All cases were routinely sampled by three pieces, including the tip and two representative cross-sections of the appendix wall (Figure 1). Serial sections were performed when needed in the re-evaluation process. Histologic criteria comprised architectural features of the crypts, including serration, branching, basal dilatation, inverted T- or L-shaped crypts (Figure 2a) together with cytologic features comprising a mucin pattern (classical goblet cells, microvesicular cells, and gastric foveolar epithelium) (Figure 2b), dysplasia, in terms of pseudostratification (Figure 2c) and nuclear atypia (enlargement, vesiculation, prominent nucleoli) (Figure 2d), mitoses in the upper crypts, and cytoplasmic eosinophilia (Figure 2e). HPs were characterized by superficial epithelial serration with the lesion's configuration tapering down to a preserved proliferative zone (Figure 3). SSA/PPs exhibited an array of characteristic crypt architectural abnormalities, dilatation and branching, transverse-lying crypts, extension of serration toward the crypt base, and the presence of differentiated mucous cells in the form of gastric and goblet cells in the crypt base (Figure 4). The size of the polyps was not provided, since almost all of the cases except for one were incidentally detected on microscopic examination. The localization and orientation with respect to the appendiceal mucosa (focal or circumferential) were noted. Clinical infor-



Figure 1. Two vertical slices together with a horizontal slice of the tip of the appendix forming a "smiling face."

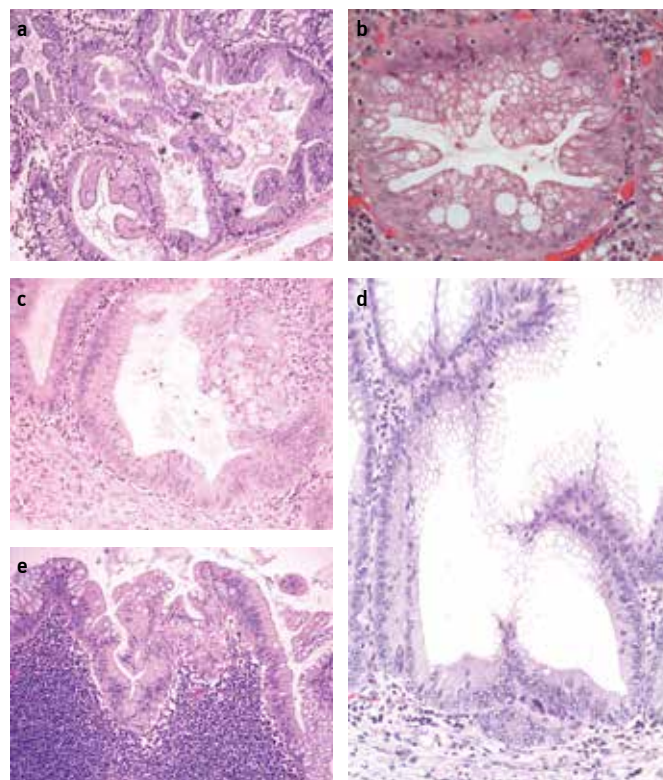


Figure 2. a-e. Characteristic crypt architectural abnormalities, dilatation and branching, transverse-lying crypts, extension of serration toward the crypt base, and the presence of differentiated mucous cells in the form of gastric and goblet cells in the crypt base (H&E; x200) (a). Gastric type of epithelium (H&E; x400) (b). Pseudostratification, cytologic atypia (H&E; x200) (c). Nuclear atypia (enlargement, vesiculation, prominent nucleoli) (H&E; x200) (d). Cytoplasmic eosinophilia (H&E; x200) (e).

mation, including patient's age, gender, and type of specimen (appendectomy and right hemicolectomy), was retrieved from the pathology files.

All morphologic parameters and demographic features were compared using a two-tailed Mann-Whitney U-test and Fisher's exact test, as appropriate, and a p value less than 0.05 was considered as significant.

RESULTS

A total of 71 cases (7.39%) were diagnosed as SPs, including 36 (50.7%) HPs, 33 (46.48%) SSA/PPs, and 2 (2.81%) TSAs. TSAs and

SSA/Ps were grouped together for statistical purposes. There were 32 males (mean age 46.6 years) and 39 females (50.1 years) with an age range of 2 to 82 years. There were 66 appendectomies with a preoperative diagnosis of acute appendicitis, while 5 appendices were dissected from specimens received as right hemicolectomies performed for colorectal carcinoma. The mean diameter of the appendices was 2.69 mm, and the mean length was 5.36 cm. Fifty cases showed acute appendicitis, whereas 6 had accompanying lesions, such as mucocoele (n=4) and solitary diverticulum (n=2). In 47 cases, polypoid lesions were located at the tip of the appendix (n=47), of which 16 were focal, while 31 were covering the mucosa in a circumferential fashion. Among the remaining polypoid lesions located at the proximal end of the appendix (n=24), 6 were focal and 18 were circumferential. All cases were detected as incidental lesions on routine microscopy, except one polypoid lesion detected in gross evaluation.

Patients with a diagnosis of HP (44.7 years) were younger than patients presenting with SSA/P (52.5 years), while the female/male ratio for these 2 groups was detected as 19/17 for HP and 20/15 for SSA/Ps. Acute appendicitis was present in 69.4% of HPs and in 71.4% of SSA/Ps. One (2.8%) HP case had mucocoele, whereas 5 (14.3%) SSA/P cases had accompanying mucocoele (n=3) and solitary diverticulum (n=2) in the appendiceal wall. There were 20 (55.6%) HPs localized at the tip of the appendix, while 16 (44.4%) were localized at the proximal end of the appendix, compared with 27 (71.1%) SSA/Ps localized at the tip and 8 (22.9%) at the proximal end ($p=0.05$). There was no

significant difference for the mean diameter of the appendix between SSA/Ps (2.9 ± 2.5) and HPs (2.4 ± 1.7) or for the mean length of appendix between SSA/Ps (5.7 ± 1.4) and HPs (4.9 ± 1.4). These data are summarized in Table 1.

Histology revealed that the majority of both HPs (63.9%) and SSA/Ps (74.3%) involved the entire appendiceal circumference, hence circumferential, on the cross-section. Basal dilatation (94.3%), basal serration (94.3%), T-/L-shaped crypts (94.3%), and ectopic crypts (68.6%) were significantly ($p<0.01$) more commonly observed in SSA/Ps compared to HPs. All cases had goblet cells and microvesicular cells, whereas 25.7% of SSA/Ps and 8.3% of HPs possessed gastric type of epithelium in the crypt bases ($p=0.05$). Dysplasia was observed in 31.4% of SSA/Ps, while HPs did not show dysplasia ($p<0.05$). Pseudostratification (34.3%) ($p<0.01$), nuclear atypia (31.4%) ($p<0.05$), and cytoplasmic eosinophilia (28.6%) ($p<0.01$) were significantly more commonly observed in SSA/Ps than in HPs. Microscopic features of appendiceal SPs are presented in Table 2.

DISCUSSION

The present study aimed to classify appendiceal serrated polyps with respect to the recent WHO classification. To our knowledge, this is the first study using WHO criteria for the classification of appendiceal serrated polyps and comparing HPs with SSA/P in the appendix. It is difficult to discuss these findings with the few papers focusing on appendiceal serrated polyps, since they lack the current classification and nomenclature (Table 3).

The few publications mentioning the presence of serrated polyps in the appendix goes back to the original report of Longacre and Fenoglio-Preiser on serrated adenomas, in which 12 of 110 cases of mixed hyperplastic adenomatous polyp of the colon and rectum were reported to be localized in the cecum-appendix (2). Unfortunately, the number of lesions localized exclusively to the appendix was not specified. In a subsequent publication by Williams et al. (3) reviewing 42 benign epithelial neoplasms of the appendix, no cases of serrated polyp were reported. Later, Carr et al. (4) classified benign tumors of the appendix into simple mucocoele, hyperplastic polyp, and adenoma, which was further subclassified into tubular, mucinous, or cystadenoma and mixed lesions with both hyperplastic and adenomatous features. Of the 42 adenomas, one was tubular, 16 were villous, and the remaining 25 had an undulating pattern

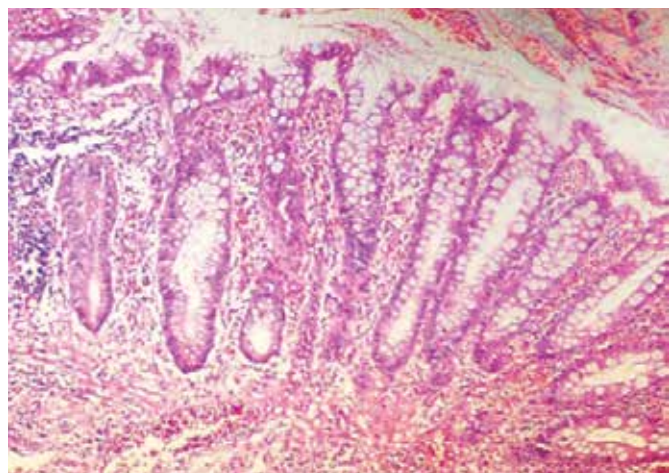


Figure 3. Hyperplastic polyp with dilatation and serration in the upper crypt zone and narrowing in the lower part (H&E; x100).

Table 1. Summary of clinical and macroscopic results of two diagnosis groups

Polyp	Mean age	Sex (F/M)	Diameter (mm)	Ap size (cm)	Localization of lesion (t/p)	Size of lesion (s/f)	Acute Appen.
SSA (35)	52.5	20/15	2.9	5.7	27/8	26/9	25 (71.4%)
HP (36)	44.7	19/17	2.4	4.9	20/16	23/13	25 (69.4%)
p values	>0.005	>0.005	>0.005	>0.005	>0.005	>0.005	>0.005

AP: appendix; t: tip; p: proximal; c: circumferential; f: focal

Table 2. Microscopic findings of serrated polyps of the appendix

Lesion	Basal crypt dilatation	Serration	T/L crypts	Ectopic crypts	Dysplasia	Pseudo- stratification	Cytoplasmic eosinophilia	Mucus type		
								Intestinal	Microvesicular	Gastric
SSA (n:35)	33 (94.3%)	33 (94.3%)	33 (94.3%)	24 (68.6%)	11 (31.4%)	12 (34.3%)	10 (28.6%)	35 (100%)	7 (20%)	9 (25.7%)
HP (n:36)	3 (8.3%)	1 (2.8%)	1 (2.8%)	1 (2.8%)	0 (0%)	0 (0%)	2 (5.6%)	36 (100%)	4 (11.1%)	3 (8.3%)
p values	0.000	0.000	0.000	0.000	0.036	0.000	0.010		0.301	0.050

SSA: sessile serrated adenoma; HP: hyperplastic polyp

Table 3. Review of the literature on appendiceal serrated polyps

MacGillivray JB. (5) 1972	100 appendices 2 mucosal metaplasias
Longacre T, et al. (2) 1990	110 mixed hyperplastic adenomatous polyp of the colorectum 12 localized in cecum-appendix
Williams G, et al. (3) 1992	42 benign epithelial neoplasms of the appendix (no cases of serrated adenoma)
Williams GR, du Boulay CE, et al. (17) 1993	42 benign epithelial lesions of the appendix
Carr N, et al. (4) 1995	42 adenomas of appendix tubular adenoma (n=1) villous adenomas (n=16) undulating growth pattern (n=25)
Rudzki Z, et al. (6) 2002.	Synchronous serrated adenoma of the appendix and high-grade ovarian carcinoma: a case demonstrating different origin of the two neoplasms.
Jass JR, et al. (10) 2003	no case of serrated adenoma of the appendix was presented in that monography
Rubio CA. (7) 2004	38 non-carcinoid non-neoplastic or neoplastic polyps or tumors of the appendix
Bellizzi AM, et al. (8) 2006	100 appendectomy cases. 1 sessile serrated adenoma and 11 adenomas were found, all in patients 30 years or older.
Yantiss RK, et al. (18) 2007	56 serrated polyps, a control group of 17 mucinous cystadenomas, and 4 adenocarcinomas with adjacent serrated polyps of the appendix
Jass JR, et al. (9) 2010	Normal mucosa (n=20) Hyperplastic polyp (n=6) Sessile serrated adenoma (n=12) Mixed serrated adenoma (n=16) Typical mucinous cystadenoma (n=14) Conventional adenoma (n=2)
Present study 2012	960 appendectomy specimen, 36 HPs, 33 SSA/Ps, 2 TSAs

TSAs: traditional serrated adenomas; HPs: hyperplastic polyps; SSA/Ps: sessile serrated adenomas/polyps

of growth, though not named as "serrated adenomas" (4). The first detailed paper on appendiceal serrated polyps came from Rubio, who found 4 HPs, 10 SAs, 6 VAs, and 8 mucinous adenocarcinomas among the 38 epithelial tumors of the appendix (7). A brief description of HPs and SAs was given in this report, with no mention of dysplasia in SAs, while a recent paper included a third category of SPs with mixed features of hyperplastic and adenomatous polyps, probably reflecting dysplasia in a serrated polyp (8). In the latter paper, HPs were classified based on the presence of epithelial serration in the absence of cytologic dysplasia. The distinction of SSPs from HPs mainly depended upon crypt architectural features, though the recent WHO

classification criteria were not employed, unlike the present study. This study provided additional information on the immunophenotypic characteristics of HPs and SSAs, which were similar to their colorectal counterparts (8).

The most common members of the SP family, HPs, comprise 80%-90% of all serrated polyps and are found throughout the colon and rectum yet with distal predominance. Histologically, HPs are characterized by their simple elongated crypt architecture and narrow crypt bases resembling normal mucosa, with proliferative activity confined to the basal third of the crypts (9,10). SSA/Ps, on the other hand, account for 8%-

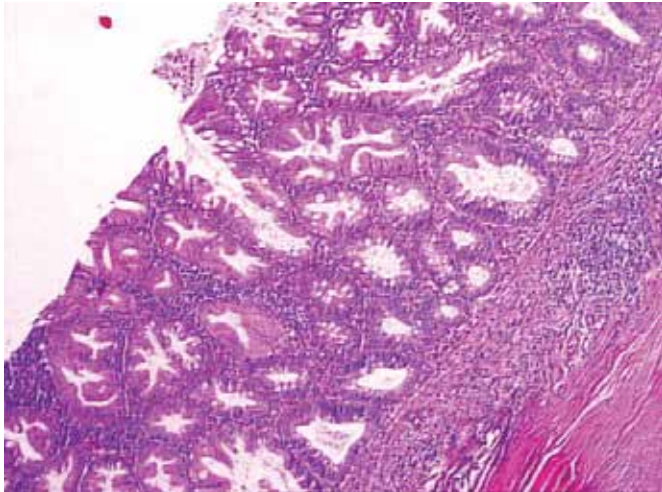


Figure 4. Sessile serrated adenoma/polyp with dilated basal crypts and exaggerated serration (H&E; x100).

20% of serrated polyps, with a predilection for the right colon. Their diagnosis is based mainly on crypt architectural features, including serration, dilatation, horizontal orientation, L-shape or inverted T-form at the base of the crypts (10,11) that show an asymmetrical proliferative zone, and goblet cell or gastric foveolar cell differentiation (12). The rarest type of SPs, TSA, has a protuberant growth pattern with a complex villiform configuration and premature crypt formation, defined as “ectopic crypt” (11,13). Much less is known about the morphologically similar serrated lesions of the appendix, however, despite the increasing number of publications on their colorectal counterparts. Though the recent WHO classification seems to have ended the ongoing discussion on the differential diagnosis of the various types of serrated polyps, no specific criteria have been attributed to the appendiceal SPs. Therefore, we applied the current WHO classification criteria for the SPs in our series. The results of our study showed that morphologic parameters, such as crypt dilatation towards the crypt base, basal serration, T-/L-shaped crypts, and to a lesser extent ectopic crypts, seem to be the most discriminatory criteria in defining SSA/Ps. These correlate with the diagnostic features of SSA/Ps of the colorectum, while pseudostratification and cytoplasmic eosinophilia were observed with an unexpected frequency in the SSA/Ps of the appendix, though they are characteristic features of colorectal TSAs. This could not be attributed to the TSAs that were grouped with SSA/Ps in the study, since they were very few in number. The presence of pseudostratification together with other nuclear features of atypia is suggestive of the adenomatous type of dysplastic change in appendiceal SSA/Ps, which may also show “serrated dysplasia.” Moreover, the presence of ectopic crypts in SSA/Ps of the appendix is also an unusual feature compared to the colorectum, where ectopic crypts are considered to be the defining feature of TSAs (14).

It has previously been suggested that the intestinal mucosa can develop hyperplastic and architectural changes mimicking serrated polyps as a response to the inflammatory stimuli

(14). Serrated epithelial change has also been described in solitary rectal ulcer syndrome and in IBD as a reactive response to the inflammatory stimuli (15). Similarly, it was suggested that appendiceal mucosa may present with hyperplastic serrated changes in the context of acute appendicitis (15). However, in Renshaw's report, sessile serrated adenomas observed in a background of acute appendicitis were distinctly separated from the surrounding inflamed mucosa with hyperplastic change. Moreover, no transition was present between the hyperplastic change seen in the inflamed area and polypoid lesion (16). In the present study, the majority of HPs and SSA/Ps showed acute appendicitis in the background appendiceal wall, and the lesions were distinctly identifiable with their slightly elevated surface compared to the neighboring mucosa. Renshaw et al. (16) discussed whether the adenoma might be a contributing factor in the onset of acute appendicitis—a more likely possibility, since the polypoid growth might cause obstruction of the lumen, leading in bacterial colonization, which results in acute appendicitis. Before drawing conclusions, however, it should be stressed that all these studies, including ours, were undertaken on appendectomy specimens that were surgically taken out for acute appendicitis. Thus, a mere coincidental concurrence of acute appendicitis and serrated polyp might be present.

The effect of sampling on the identification of mucosal serrated lesions was evaluated in a recent paper that showed that the incidence of SSA was significantly higher in the entirely submitted appendices. HPs tended to involve a portion of the appendiceal circumference (i.e., focal), and SSA/Ps tended to involve the entire appendiceal circumference. The authors concluded that sampling was critical for identification of these lesions, and routine sampling with 3-4 pieces seemed insensitive for detecting them (8). In the present study, the serrated polyps of the appendix were detected on microscopic examination in all cases except one case, which was identified macroscopically by the pathology resident. We also observed that both SSA/Ps and HPs tended to involve the entire appendiceal circumference and were mostly localized at the tip. Since this was a retrospective study, the polyps were reviewed microscopically, and instead of their true diameter, the polyp's location with respect to the circumference of the appendix was determined as circumferential or focal. Since these are very small lesions, probably undetectable by the naked eye, extensive sampling, including the tip of the appendix together with an enthusiastic pathologist, seems to be crucial for the identification of appendiceal serrated lesions.

In conclusion, the results of the present study suggest that appendiceal serrated polyps, despite bearing many similarities with their colorectal counterparts, may have some special features due to the anatomic uniqueness of the organ itself and also the polyps arising from its mucosal lining. We, therefore, believe that our findings need to be supported by future studies involving comparative evaluation of serrated polyps of the

appendix and the colorectum on both morphologic and molecular grounds.

Ethics Committee Approval: N/A.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - Y.Y.K., A.E.; Design - Y.Y.K., B.S.; Supervision - A.E.; Resource - Y.Y.K., A.E.; Materials - A.E., Y.Y.K.; Data Collection&/or Processing - Y.Y.K.; Analysis&/or Interpretation - B.S., N.K.; Literature Search - Y.Y.K., A.E.; Writing - Y.Y.K.; Critical Reviews - A.E., B.S.

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