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Original Article

Herniation of crypts in hyperplastic polyp and sessile serrated adenoma: a prospective study

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Abstract: Presence of colonic crypts in submucosa was previously termed as herniation of crypts, pseudoinvasion, epithelial-misplacement, or inverted hyperplastic-polyp. It is considered as an important criterion for diagnosing sessile serrated adenoma (SSA), which links to a higher risk of synchronous and future colorectal cancers compared with hyperplastic polyp (HP). Here, we aimed to study the frequencies, diagnostic specificity and synchronous neoplasms of herniation of crypts in HP and SSA. We prospectively included all HP and SSA cases and 514 randomly-selected colorectal polyps of normal histology diagnosed from 2013 to 2015 at our institution. We calculated the frequencies of herniation of crypts by histology, sex, age, size, race, location, prior polyp-history and synchronous neoplasms (including colorectal cancers and adenomas). Binary and ordinal (ordered) logistic regression analyses were used to identify potential associations. Among the 2,560 colorectal polyps in the subjects with average-risk of colorectal cancer, the frequencies of herniation of crypts were 1.79% (10/559) in SSA, 0.2% (3/1487) in HP and 0% (0/514) in polypoid normal tissue. The specificity of herniation of crypts for diagnosing serrated polyp (HP and SSA versus normal tissue) was 100% (514/514), but its sensitivity was 0.64% (13/2046), while the specificity of herniation of crypts for diagnosing SSA (versus HP and polypoid normal tissue) was 99.85% (1998/2001) and its sensitivity was 1.79% (10/559). Our multivariate analyses identified an independent association between herniation of crypts and diagnosis of SSA (Odds ratio [OR]=9.37, P=0.015 for versus HP and normal tissue, and OR=11.47, P=0.009 for versus HP). We also found that herniation of crypts in SSA and HP did not independently link to race or synchronous neoplasms (including cancers and adenomas). In summary, our data show that, while herniation of crypts is rare, its presence is highly suggestive of SSA.

Keywords: Sessile serrated adenoma, herniation of crypts, diagnostic specificity, hyperplastic polyp, synchronous neoplasm, cancer precursor

Introduction

Serrated colorectal polyps are classified as sessile serrated adenoma (SSA), hyperplastic polyp (HP) and traditional serrated adenoma according to the World Health Organization (WHO) classifications of tumors of the digestive system [1]. SSA is known to link to synchronous and future colorectal cancer, but HP is not [2-4]. Therefore, it is important to histologically distinguish these two entities. However, SSA is often confused with HP-which poses diagnostic challenges [5]. The interobserver agreements on diagnosing SSA (versus HP) are unacceptably low, with the kappa values ranging from 0.14 to 0.55 [5-9]. In addition, when differentiating serrated polyps, the pathology trainees are strongly influenced by the information of the polyp's anatomic location [10]. The low reproducibility of diagnosing serrated polyps, however, might be improved by training or standardization of the diagnostic criteria [8, 11]. Several diagnostic guidelines and a consensus were indeed proposed, including the ones by the WHO working group, the German Society of Pathology, the American Gastroenterological Association, and the pathology committees of the UK Bowel Cancer

Screening Programme and the British Society of Gastroenterology in the U.K. [1, 12-14]. Another approach to improve the diagnostic accuracy for serrated polyps is to identify biomarkers to assist in differentiating SSA and HP, with MUC6 as a specific but less sensitive marker [15, 16]. Additional markers and careful appraisal of the proposed diagnostic criteria are needed.

Colonic crypts may be present in the muscularis mucosae or submucosa in association with serrated polyps, which was previously termed as herniation of crypts [12, 13], pseudo invasion [17-19], epithelial misplacement [20-22], or inverted hyperplastic polyp [22-24]. The German Society of Pathology considered herniation of crypts as one of the four important diagnostic criteria for SSA [14]. The other three important criteria were hyperserration/serration and columnar dilatation in the lower third of the crypt, and inverted T- or L-shaped crypt above the muscularis mucosae. In agreement with the German criteria, the U.K. diagnostic guidelines also included herniation of crypts as one of the seven diagnostic criteria for SSA [12]. Interestingly, the American consensus too mentioned that herniation of crypts was not unusual, but did not include it as part of the differentiating features of serrated polyps [13]. Despite the great interest in and the endorsed use of herniation of crypts for diagnosing SSA, the frequency of herniation of crypts in either HP or SSA to our knowledge has not been reported. It is also not clear whether herniation of crypts is associated with the diagnosis of SSA (versus HP and/or normal tissue) or with synchronous colorectal neoplasm, although SSA was reportedly associated with synchronous neoplasms [3, 4, 25-27]. Therefore, this study on the prospectively-collected 2,560 colorectal polyps was aimed to characterize herniation of crypts in SSA and HP, focusing on its frequency and its potential association with synchronous neoplasms.

Methods

This prospective study was approved by the Institute Review Board (IRB) of the University Medical Center of Princeton, Plainsboro, NJ, USA. The inclusion criteria of the study were: 1, asymptomatic patients (i.e. colonoscopy was performed for screening purpose); 2, no history of inflammatory bowel diseases; 3, slides were available for review; 4, past polyp-history was available for review. We prospectively collected all qualified-for-inclusion HP and SSA cases submitted to our department from 2013 to 2015. As control group, we also randomly-selected 514 colorectal polyps with normal histology, which were endoscopically identified as a colorectal polyp and showed normal histology.

We de-identified and collected the following information: patient age, sex, race, polyp location (left colon/rectum, transverse colon versus right colon), polyp-size measured under microscopy as described before [3, 28], pathologic diagnosis, synchronous neoplasm (defined as an adenoma, HP, SSA or colorectal carcinoma identified in the same colonoscopy procedure) and prior history of colorectal polyp. The advanced adenomas included adenomas with high-grade dysplasia, villous component or a size >1 cm. All cases were reviewed by two of the authors (KH and LZ). When a disagreement occurred, a third pathologist at the department would review the case and resolve the disagreement. The diagnostic criterion for SSA was the presence of "at least one unequivocal architecturally distorted, dilated, and/or horizontally branched crypt", as recommended by the American Gastroenterological Association [13]. A polyp was considered positive for herniation of crypts when it has one or more crypts present below the mucosa (i.e. into or below muscularis mucosae, **Figure 1**). We also searched the relevant follow-up data in our health information system in September 2017. We then collected the information on any follow-up colonoscopy performed on the patients with herniation of crypts at our hospital, or performed at an outside hospital but noted in our medical charts.

The statistical analyses were performed using STATA version 14.0 (Stata Corp, College Station, Texas, USA). The sensitivity and specificity were calculated as described before [29]. Fisher exact test, chi-square test and binary logistic and ordered (ordinal) logistic regression analyses were used. All *P* values were 2-sided. When a *P* was less than 0.05, a statistical significance was considered as being reached. Only when a variable had a *P* of 0.10 or less in the univariate regression analysis, it would be included in the multivariate regression analys-

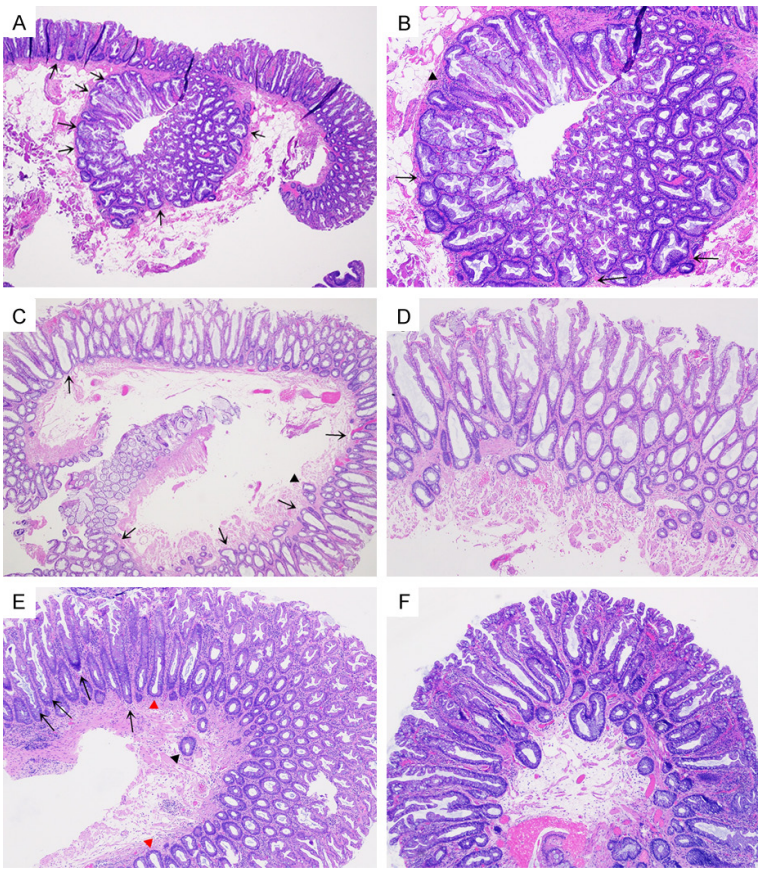

Figure 1. Representative photomicrographs showing herniation of crypts in serrated colorectal polyps. Herniation of crypts in a sessile serrated adenoma shows lobular configuration in the submucosal fat (A), inverted "T" shaped crypts (A, arrows), histology and cytology similar to those of the crypts in the mucosa and loss of muscularis mucosae (B, arrows), as well as minimal lamina propria (B, arrow head). Another sessile serrated adenoma with herniation of crypts showing "L" shaped and dilated crypts (C, arrows) and a crypt herniated into muscularis mucosa (C, arrow head, and D). A hyperplastic polyp has the features of top-heavy "V" shaped crypts and two small foci of herniation of crypts (E). Sometimes, the differentiating between hyperplastic polyp and sessile serrated adenoma could be challenging. For example, a serrated polyp shows many "V" shaped crypts (E, arrows), occasional slightly dilated or straight crypts (F, red arrow heads) and herniated crypts into submucosa (F, black arrow head). Considering the lack of hyperserration or definite columnar dilation in the lower third of the crypts, the location of left colon, small size, and the polypoid configuration (F), a diagnosis of hyperplastic polyp was rendered after a group discussion.

is except herniation of crypts, which was the research focus of this study and included in all multivariate regression analyses.

Results

Baseline characteristics of the study subjects

We prospectively identified 2,560 colorectal polyps, which met the inclusion criteria, and were detected and resected during screening colonoscopy between 2013 and 2015, including 514 (20.1%) randomly-selected subjects with polypoid tissue of normal histology, 1487 (58.1%) with HP and 559 (21.8%) with SSA. The subjects were categorized as 13 (0.5%) with herniation of crypts and 2543 (99.5%) without (**Table 1**). There were 30.8% (4/13) females in the herniation group and 51.4% (1,306/2,543) females in the no-herniation group. The median ages of subjects with herniation and without herniation were 60.6 (standard deviation [SD] 6.8) and 58.8 (SD 10.1) years, respectively. No statistically significant difference was found between the groups in terms of sex and age. The mean size of polyps of with herniation and without herniation were 6.2 mm (SD 0.28) and 3.6 mm (SD 0.25), respectively. Among the subjects with normal histology, none of them (0/514) had herniation of crypts, while 0.2% (3/1,487) of the subjects with HP and 1.72% (10/559) of the subjects with SSA had it ($P<0.001$). Race and location were not found associated with the frequency of herniation of crypts (**Table 1**, $P=0.268$ and $P=0.604$, respectively), while the Non-Hispanic Whites tended to have a higher frequency of SSA than Non-Hispanic Blacks and Asians (**Table 2**, $P=0.08$). The prevalence of synchronous adenoma and carcinoma was 46.2% (6/13) and 42.0% (1,050/2,547) in herniation and no-herniation groups, respectively ($P=0.784$), while those of synchronous advanced adenoma and carcinoma were 15.38% (2/13) and 4.67% (119/2,547) in herniation and no-herniation groups, respectively ($P=0.123$). No significant difference was found between with herniation and no-herniation groups with regard to the lesion location, presence of synchronous neoplasm or prior history of colorectal polyp.

Table 1. Baseline characteristics of the colorectal serrated polyps by presence of herniated crypts

	Without herniated crypts		With herniated crypts			*P*
	N	Mean (SD)	N	Mean (SD)		
Size (cm)	2,476	0.36 (0.25)	11	0.62 (0.28)		0.0007
Age (years)	2,543	58.9 (10.1)	13	60.6 (6.8)		0.533
	N	%	N	%	Total	*P*
Sex						
Female	1,306	99.69	4	0.31	1,310	
Male	1,237	99.28	9	0.72	1,246	
Total	2,543	99.49	13	0.51	2,556	0.167
Diagnosis						
Normal	514	100	0	0	514	
HP	1,484	99.8	3	0.2	1,487	
SSA	549	98.21	10	1.79	559	
Total	2,547	99.49	13	0.51	2,560	<0.001
Location						
Right	676	99.71	2	0.29	678	
Transverse	321	99.69	1	0.31	322	
Left	1,538	99.35	10	0.65	1,548	
Total	2,535	99.49	13	0.51	2,548	0.604
Race						
NH-White	1,533	99.29	11	0.71	1,544	
Hispanic	14	100	0	0	14	
NH-Black	48	97.96	1	2.04	49	
Asian	251	100	0	0	251	
Other	3	100	0	0	3	
Total	1,849	99.26	12	0.64	1861	0.268
Synchronous neoplasm						
None	849	99.53	4	0.47	853	
HP	380	99.22	3	0.78	383	
SSA	243	100	0	0	243	
TA	951	99.58	4	0.42	955	
Advanced Adenoma/CRC	119	98.35	2	1.65	121	
Total	2,542	99.49	13	0.51	2,555	0.247
Prior history						
Normal	1,751	99.49	9	0.51	1,760	
HP	179	99.44	1	0.56	180	
SSA	58	100	0	0	58	
TA	407	99.75	1	0.25	408	
Advanced adenoma and CRC	118	99.16	1	0.84	119	
Total	2,513	99.52	12	0.48	2,525	0.698

Note: NH, non-Hispanic; SSA, sessile serrated adenoma; HP, hyperplastic polyp; TA, tubular adenoma; CRC, colorectal carcinoma.

Factors associated with diagnosis of sessile serrated adenoma

We first examined the factors associated with a diagnosis of SSA compared with HP or normal histology (**Table 3**). Our univariate analysis found that SSA was associated with herniation of crypts, older age (65+ years), size of polyps, left side location and presence of synchronous neoplasm. Among these potential factors, our

Table 2. Association between race and the diagnosis of sessile serrated adenoma and hyperplastic polyp

	Hyperplastic polyp		Sessile serrated adenoma		Total	*P*
	N	%	N	%		
NH-White	941	(73)	345	(27)	1,270	
Hispanic	9	(82)	2	(18)	11	
NH-Black	37	(82)	8	(18)	45	
Asian	149	(82)	32	(18)	180	
Others	2	(67)	1	(33)	3	
Total	1,135	(75)	374	(25)	1,509	0.08

Note: NH, Non-Hispanic.

multivariate analysis revealed that herniation of crypts remained a statistically significant factor (versus HP and normal tissue, Odds ratio [OR]=9.37, 95% CI [confidence intervals]: 1.55-56.59, *P*=0.015). The polyp size and presence of synchronous neoplasm were also the independent factors for SSA. Our multivariate analysis also found that herniation of crypts was associated with SSA (versus HP, OR=11.47, 95% CI: 1.84-71.49, *P*=0.009).

Factors associated with synchronous advanced adenoma

A univariate analysis and a subsequent multivariate analysis were conducted to identify the factors associated with synchronous neoplasms (**Table 4**). Only diagnosis of SSA and age were associated with synchronous advanced adenoma and carcinoma. The diagnosis of SSA, male gender, older age (65+ years), polyp location of the left side and prior history of colorectal polyp were independently associated with synchronous colorectal adenoma and carcinoma. However, the presence of crypt herniation did not link to synchronous neoplasm in either univariate or multivariate analyses, compared with absence of crypt herniation. (**Table 4**, OR=2.71, 95% CI: 0.58-12.67, *P*= 0.207 for synchronous advanced adenoma and carcinoma, and OR=1.60, 95% CI: 0.47-5.44, *P*=0.452 for synchronous adenoma and carcinoma, respectively).

Morphological and clinical features

Morphologically, the herniation of crypts in the muscularis mucosae or submucosa was histologically and cytologically bland and similar to the crypts in the mucosa, showed a lobular configuration and had no associated fibrosis or hemosiderin laden macrophages (**Figure 1**). They always connected with the crypts in the mucosa (above muscularis mucosae) either on the original or deeper sections.

Our calculation showed that the specificity of herniation of crypts for diagnosing serrated polyp (HP and SSA versus polypoid normal tissue) was 100% (514/514), but its sensitivity was 0.64% (13/2046), while the specificity of herniation of crypts for diagnosing SSA (versus HP and polypoid normal tissue) was 99.85% (1998/2001) and its sensitivity was 1.79% (10/559).

Among the 13 patients with serrated colorectal polyps showing herniation of crypts, two (15.4%) had follow-up colonoscopy that was performed at our hospital or documented in our health information system. Both of them were SSA and had a follow-up colonoscopy in 2017 which showed tubular adenoma. One of the patients was diagnosed in 2014 and had synchronous tubulovillous adenoma, tubular adenoma and HP at the time. The other patient was diagnosed in 2015 and had a synchronous HP.

Discussion

In this study on the prospectively-collected 2,560 colorectal polyps in subjects with average-risk of colorectal cancer, the frequencies of herniation of crypts were 1.79% (10/559) in SSA, 0.2% (3/1487) in HP and 0% (0/514) in polypoid tissue with normal histology, suggesting a nearly 9-fold difference between SSA and HP and nearly 100% specificity for diagnosing HP and SSA (versus polypoid normal-tissue). Our multivariate analyses identified a significant, independent association between herniation of crypts and diagnosis of SSA (OR= 11.47 for versus HP, OR=9.37 for versus HP and normal tissue). We also found that herniation of crypts in SSA or HP did not independently link to race, synchronous adenoma and carcinoma, or synchronous advanced adenoma and carcinoma.

Our findings are novel in several aspects. This study of 2,560 colorectal polyps provides the first account of the frequencies of herniation of

Table 3. Multivariate analyses on the factors associated with the diagnosis of serrated colorectal polyp

	SSA vs HP, n=1,985				SSA vs HP vs Normal, n=2,478			
	OR	OR 95% CI		*P*	OR	OR 95% CI		*P*
Herniated crypts (presence vs absence)	11.47	1.84	71.49	0.009	9.37	1.55	56.59	0.015
Age (65+ years vs <65 years)	0.93	0.70	1.23	0.595	1.05	0.87	1.27	0.595
Site (left vs transverse vs right)	0.46	0.40	0.53	<0.001	0.99	0.89	1.09	0.769
Sex (Male vs female)	0.95	0.74	1.23	0.718	0.93	0.79	1.10	0.387
Synchronous neoplasm	1.05	0.95	1.15	0.354	1.14	1.07	1.21	<0.001
Size (cm)	426.23	219.63	827.18	<0.001	650.20	380.16	1112.06	<0.001

Note: OR, odds ratio; CI, confidence intervals; SSA, sessile serrated adenoma; HP, hyperplastic polyp; vs, versus.

Table 4. Multivariate analyses on the factors associated with synchronous neoplasm of serrated colorectal polyp

	Synchronous advanced adenoma and carcinoma, n=2,479				Synchronous adenoma and carcinoma, n=2,452			
	OR	OR 95% CI		*P*	OR	OR 95% CI		*P*
Diagnosis (SSA vs HP vs normal)	1.56	1.17	2.09	0.003	1.22	1.05	1.41	0.01
Herniated crypts (presence vs absence)	2.71	0.58	12.67	0.207	1.60	0.47	5.44	0.452
Age (65+ years vs <65 years)	2.06	1.42	2.99	<0.001	1.40	1.16	1.69	<0.001
Site (left vs transverse vs right)	-				0.82	0.75	0.91	<0.001
Sex (Male vs female)	-				1.77	1.50	2.09	<0.001
Size (cm)	-				0.59	0.39	0.88	0.01
Prior history of detectable polyp	-				1.11	1.05	1.19	0.001

Note: Synchronous advanced adenoma included any adenoma with high-grade dysplasia, villous component or size >1 cm. -, not included due to a P>0.2 in the univariate analysis; OR, odds ratio; CI, confidence intervals; SSA, sessile serrated adenoma; HP, hyperplastic polyp; vs, versus.

crypts in SSA, HP and polypoid normal tissue, while past studies on serrated polyps with herniation of crypts included only HP cases (no sub-classification of HP and SSA at the time) [22-24]. We also demonstrated the nearly 100% specificity of herniation of crypts for diagnosing SSA and HP versus polypoid normal tissue, albeit the very low sensitivity. Moreover, we reported the early evidence that herniation of crypts in SSA and HP was not independently associated with synchronous neoplasms, although SSA itself is found to correlate with synchronous neoplasms in earlier reports and this study [3, 4, 25-27, 30-32]. Further, we found that the presence of herniation of crypts (versus absence) in colorectal polyps seemed not to link to the polyp's location. This finding may be attributable to the low frequency of herniation of the crypts and thus inadequate statistical power. Our finding also disagrees with the reported dominance of herniation of crypts in either left colon or right colon in prior studies [22, 24]. Besides the different patient-populations, this disagreement is likely attributable to the inclusion of control cases in this study, which was not included in prior case-series [22, 24]. In addition, the association between race and the frequency of SSA is controversial [33-37]. In contrast to the reported lower prevalence of SSA in Asians [34, 36, 37] and lower prevalence in Non-Hispanic Black (versus Non-Hispanic Whites) [33, 35], we found borderline statistical-significance in a possibly higher frequency of SSA in Non-Hispanic Whites (versus Non-Hispanic Blacks, Hispanics and Asians, **Table 2**), but no association between race and the frequency of herniation of crypts (**Table 1**). This difference may be due to the small sample size of ours and inclusion of Hispanics in our study. Finally, all cases in this study were included using a prospective study design which minimized recall biases.

SSA has been shown as an important precursor for synchronous and future colorectal cancers [2-4]. Based on the important earlier wo-

rks on the subject [22-24, 33-35, 38], this study seems to expand our understanding of herniation of crypts in SSA and HP, and that of race disparity in serrated colorectal polyps. First, herniation of crypts appears very specific for HP and SSA (versus polypoid normal tissue) and highly specific for SSA (versus HP), supporting the inclusion of it as a diagnostic criterion for SSA in the German and UK guidelines [12, 14]. Herniation of crypts may also occur in tubular/villous adenomas and traditional serrated adenomas [19-21]. However, these adenomas could be easily distinguished from HP and SSA by the presence of low-grade dysplastic epithelium, and thus are unlikely a diagnostic challenge for the cases of HP and SSA. Second, we explored whether herniation of crypts in SSA and HP was associated with race and synchronous neoplasms, and our data do not support herniation of crypts as a prognostic factor for synchronous neoplasms. Finally, our data revealed that the anatomic location of the herniation of crypts did not link to SSA or HP, compared with polypoid normal tissue. This argues against the prevailing theory that it originates from "misplaced epithelium". It is plausible that some of the cases with herniation of crypts well are related to misplacement [17-21, 39, 40]. Indeed, 10 of the 13 (76.9%) serrated polyps with herniation of crypts were located in the left colon. One of our hypotheses, supported by earlier reports on SSA, is that herniation of crypts is resulted in by downward growth of the crypts in SSA, and links to SSA compared with HP as shown in our study [19, 24, 25, 41-43]. Should the misplacement theory be valid in all SSA and HP cases, one would expect a similar frequency of herniation of crypts in SSA and HP. However, our data showed otherwise.

The limitations of our study should be considered while applying our findings to the clinical practice. We had a relatively small-number of the HPs and SSAs with herniation of crypts, which is attributable to the very-low frequency nature of this histology, but may be partially compensated by our large size of the control cases. Moreover, the follow-up time in this study was about 2 years which is relative short. A larger and long-term study is therefore needed to validate our findings and to examine the association between herniation of crypts in SSA and the adenoma detection frequencies in follow-up colonoscopy. Furthermore, our diagnostic criteria for SSA were consistent with that of the American consensus (i.e. at least crypt qualified for SSA), but inconsistent with that of the WHO classification (i.e. 2 or more qualified for SSA) [1, 12, 13]. A validation study using the other criteria may be interesting and supplementary to ours. Finally, we did not include the cases of polypoid mucosal prolapse or colonic mucosubmucosal elongated polyps where submucosal herniation and epithelial hyperplasia can also occur [44, 45]. The mucosal prolapse has characteristic vertically oriented muscle bundles, and colonic mucosubmucosal elongated polyps have characteristic elongated configuration (as the name implies) and dilated blood vessels and lymphatics. Therefore, we feel these two entities are not immediate differential diagnoses for HP or SSA, which may be subject to future studies.

In summary, we characterized the clinicopathological features and synchronous neoplasms of the polypoid normal tissue, HP and SSA with herniation of crypts. Our data support considering herniation of crypts as an additional diagnostic criterion for HP and SSA, which is specific for SSA. Our findings also suggest that the "misplaced epithelium" theory could not explain all cases of herniation of crypts. Future mechanistic studies are warranted to unravel its pathogenesis and its role in colonic carcinogenesis.

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Disclosure of conflict of interest

None.

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