

Original

Magnifying Colonoscopy Findings for Differential Diagnosis of Sessile Serrated Adenoma / Polyps and Hyperplastic Polyps

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Abstract : Sessile serrated adenoma / polyps (SSA / Ps) are thought to be precursors of colorectal cancers. However, current endoscopic techniques for differentiating SSA / Ps from conventional hyperplastic polyps (HPs) have low diagnostic accuracy. The aim of the present study was to assess the ability of mucosal crypt patterns to distinguish SSA / Ps from HPs. We examined 140 lesions from 93 patients that had been diagnosed histologically as SSA / Ps or HPs at the Showa University Hospital between June 2010 and May 2012. Three experienced colonoscopists reviewed the endoscopic findings of magnifying colonoscopy. Type II open-shape (Type II-O) pit patterns and varicose microvascular vessels (VMVs) were identified according to previously proposed definitions. Although 140 lesions were initially identified for the study, 27 lesions were excluded from analysis because of insufficient endoscopic findings. Thus, endoscopic findings from a total of 113 lesions (68 SSA / Ps and 45 HPs) were evaluated. Of 113 serrated polyps, 51 lesions (44 SSA / Ps and 7 HPs; $P < 0.01$) had Type II-O pit patterns. The inter- and intra-observer agreement for these patterns among three colonoscopists was $\kappa = 0.61$ (range 0.57–0.65) and $\kappa = 0.68$ (range 0.52–0.94), respectively. The positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity of Type II-O pit patterns for differentiating between SSA / P and HP were 86%, 61%, 65%, and 84%, respectively. In contrast, the PPV, NPV, sensitivity, and specificity of VMVs were 68%, 43%, 37%, and 73%, respectively. The results indicate that Type II-O mucosal crypt patterns may be useful for the differential diagnosis of SSAPs and HPs.

Key words : colorectal neoplasms, magnifying endoscope, sessile serrated adenoma / polyp, Type II open-shape pit pattern, varicose microvascular vessel

Introduction

Serrated polyps (SPs) of the colorectum are currently classified on the basis of World

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Health Organization (WHO) criteria¹⁾ as hyperplastic polyps (HPs), sessile serrated adenoma / polyps (SSA / Ps), or traditional serrated adenomas (TSAs). HPs were traditionally considered as non-neoplastic lesions without malignant potential. However, some HPs show molecular features similar to those of colorectal cancers (CRCs)^{2, 3)}. Recent studies have proposed that the serrated pathway begins with HPs and progresses through SSA / Ps or TSAs to CRCs⁴⁻⁷⁾. Notably, SSA / Ps have recently been described as immediate precursors to CRCs that develop via a serrated pathway with CpG island methylator (CIMP) phenotypes and *BRAF* mutations. The serrated pathway may be involved in approximately 30% of CRCs⁸⁾.

Recent advances in endoscopic equipment have improved the differential diagnosis of colorectal neoplasms. Although TSAs can be easily diagnosed endoscopically by their reddish color and pinecone-like appearance, several studies have reported a low diagnostic accuracy of current endoscopic techniques for differentiating SSA / Ps from conventional HPs^{9, 10)}. Recently, it has been proposed that novel endoscopic features of SSA / Ps could improve their differentiation. For example, Kimura *et al*¹¹⁾ identified a novel mucosal crypt pattern, namely the Type II open-shape (Type II-O) pit pattern, specific to SSA / Ps. This crypt pattern is similar to the hyperplastic crypt patterns (stellar or papillary pits), but the pits are wider and more round in shape, reflecting crypt dilatation. Moreover, Uraoka *et al*¹²⁾ reported that varicose microvascular vessels (VMVs) are effective for predicting a diagnosis of SSA / Ps. VMVs are defined as vessels thicker than meshed capillary vessels that meander as varicose veins, a pattern that differs from the capillary pattern of the mucosal vascular network. Although both studies reported a high specificity for the diagnosis of SSA / Ps and HPs, the sensitivity and negative predictive value (NPV) of the techniques were insufficient.

Thus, the aim of the present retrospective study was to investigate the differences in the clinicopathological features and endoscopic findings between SSA / Ps and HPs.

Methods

Patients and endoscopic image samples

Images were evaluated retrospectively in the present study. Of patients undergoing polypectomy, endoscopic mucosal resection (EMR), or endoscopic submucosal dissection (ESD) at Showa University Hospital between June 2010 and May 2012, information was reviewed for 140 lesions from 93 patients that had been diagnosed histologically as SSA / Ps or HPs. Of these 140 lesions, 21 had no images using optical magnification and 6 lesions could not be evaluated because of poor quality of the endoscopic image. Thus, 113 lesions (68 SSA / Ps and 45 HPs) from 84 patients were included for analysis in the present study. All images for these 113 lesions were obtained during high-definition magnifying colonoscopy (CF-H260AZI or PCF-240ZI ; Olympus Optical, Tokyo, Japan).

Evaluation of endoscopic images

Three experienced colonoscopists (K.K., A.K., and T.M.) independently evaluated images obtained by chromoendoscopy and narrow band imaging (NBI) using magnifying colonoscopy.

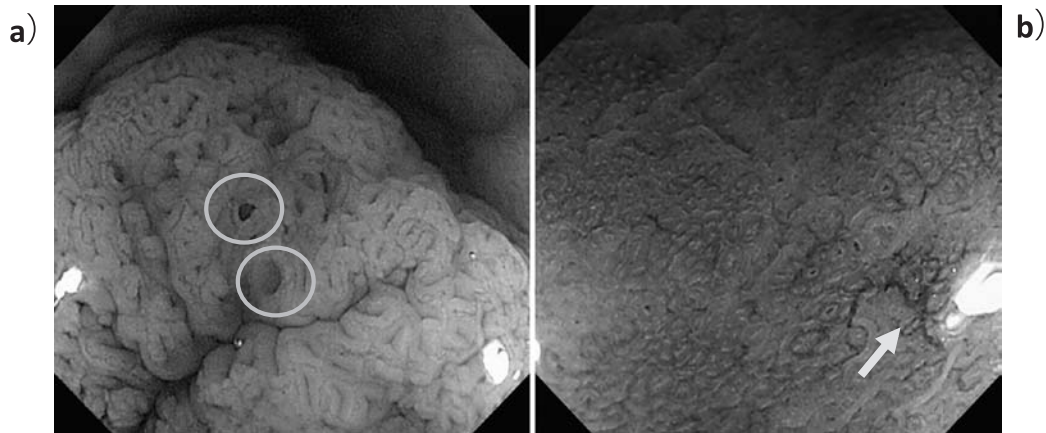


Fig. 1. Appearance of sessile serrated adenoma/polyps (SSA / Ps) on magnifying endoscopy. (a) Chromoendoscopy showing Type II open-shape (Type II-O) pit patterns (circles) and (b) narrow band imaging showing varicose microvascular vessels (VMVs; arrows).

The following endoscopic features were reviewed: (1) pit pattern; (2) the presence of a Type II-O pit pattern; and (3) VMVs. The colonoscopists were blinded to both clinical information and histological diagnoses.

The pit patterns of each lesion were determined using the modified classifications described by Kudo *et al*¹³⁾, whereas Type II-O pit patterns were identified according to the definitions proposed by Kimura *et al*¹¹⁾ (Fig. 1) and VMVs were identified according to the definitions proposed by Uraoka *et al*¹²⁾ (Fig. 1).

The colonoscopists evaluated the endoscopic findings of each lesion twice, in different order, in order to assess intra-observer variability. Endoscopic findings from each colonoscopist were evaluated for interobserver variability. The final endoscopic findings were determined by the majority method.

Histological diagnosis

All resected specimens were reviewed by a senior pathologist (T.Y.), who was blinded to the endoscopic findings. The histological diagnoses of SSA / Ps and HPs were based on WHO criteria¹⁾.

Data analysis and statistics

Median values and ranges were calculated. Continuous variables (age and tumor size) were analyzed using Wilcoxon tests. Categorical variables were compared between tumor groups using χ^2 or Fisher's exact tests when testing small samples. All tests were two-sided, and $P < 0.05$ was considered significant. In addition, the sensitivity, specificity, positive predictive value (PPV), NPV, and accuracy of the Type II-O pit pattern and VMVs for the differential diagnosis of SSA / Ps and HPs were calculated. Inter- and intra-observer agreements were calculated using Fleiss κ measurements. Interpretation of κ values was according to Landis and Koch¹⁴⁾, as

Table 1. Clinicopathological features of SSA / P and HP

| | | SSA / P | HP | P value |
|-----------------------|----------------|------------|------------|----------|
| No. of lesions (pts.) | | 68 (48) | 45 (41) | |
| Gender | Male | 27 (56%) | 25 (61%) | 0.61 |
| | Female | 21 (44%) | 16 (39%) | |
| Age (years) | Median (range) | 60 (36–83) | 56 (29–80) | 0.74 |
| Location | Proximal* | 58 (85%) | 22 (49%) | < 0.01 |
| | Distal* | 10 (15%) | 23 (51%) | |
| Size | Median (range) | 9 (4–25) | 7 (4–22) | < 0.01 |
| | < 5 mm | 2 (2%) | 10 (22%) | < 0.01** |
| | 6–9 mm | 33 (49%) | 27 (60%) | |
| | 10 mm ≤ | 33 (49%) | 8 (18%) | |
| Macroscopic type | Superficial | 61 (90%) | 27 (60%) | < 0.01 |
| | Protruded | 7 (10%) | 18 (40%) | |

SSA / P : sessile serrated adenoma / polyp, HP : hyperplastic polyp

* Proximal : cecum, ascending and transverse colon ; Distal : descending and sigmoid colon, and rectum

** < 10 mm vs. 10 mm ≤

follows : 0, poor agreement ; 0.00–0.20, slight agreement ; 0.21–0.40, fair agreement ; 0.41–0.60, moderate agreement ; 0.61–0.80, substantial agreement ; and 0.80–1.00, almost perfect agreement. All statistical analyses were performed using JMP version 10 (SAS Institute, Cary, NC, USA).

Results

Clinicopathological features of SSA / Ps and HPs

Table 1 lists the clinicopathological features of the 68 SSA / Ps and 45 HPs. Compared with HPs, SSA / Ps were found more frequently in the proximal colon (cecum, ascending and transverse colon) than in the distal colon (descending and sigmoid colon, rectum ; 85% vs. 49% ; $P < 0.01$). Analysis of lesion size revealed that SSA / Ps were significantly larger than HPs (median size 9 vs. 7 mm). The frequency of lesions ≥ 10 mm was significantly higher for SSA / Ps than HPs (49% vs. 18%, respectively ; $P < 0.01$). Macroscopically, superficial lesions were more frequently found in the case of SSA / Ps than HPs. There were no significant differences in patient gender and age between the SSA / P and HP groups.

Comparison of SSA / P and HP endoscopic findings

Type II pit patterns were detected in both SSA / Ps (67 / 68 ; 99%) and HPs (36 / 45 ; 80%). Type II-O pit patterns were found in 44 of 68 SSA / Ps (65%) and in seven of 45 HPs (16%). This difference was statistically significant ($P < 0.01$). However, VMVs were observed in only 25 SSA / Ps (37%) and 12 HPs (27%), a difference that was not statistically significant (Table 2).

Table 2. Comparison of endoscopic findings between SSA / P and HP

| | | SSA/P N = 68 | HP N = 45 | P value |
|---------------|---------------------------------------|-----------------|--------------|-----------|
| Pit pattern* | II | 67 (99%) | 36 (80%) | < 0.01*** |
| | III _L / IV | 1 (1%) | 5 (11%) | |
| | III _H / IV _H ** | 0 (0) | 4 (9%) | |
| Type II-O pit | presence | 44 (65%) | 7 (16%) | < 0.01 |
| | absence | 24 (35%) | 38 (84%) | |
| VMV | presence | 25 (37%) | 12 (27%) | 0.26 |
| | absence | 43 (63%) | 33 (73%) | |

SSA / P: sessile serrated adenoma / polyp, HP: hyperplastic polyp, Type II-O pit: Type II open-shape pit pattern, VMV: varicose microvascular vessel

* Kudo's classification, ** tubular appearance with serration, *** II vs. III_L / IV, III_H / IV_H

Table 3. Differential diagnosis of SSA/Ps with HPs

| | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) |
|---------------------------------------|-----------------|-----------------|---------|---------|--------------|
| Type II-O pit | 65 | 84 | 86 | 61 | 73 |
| VMV | 37 | 73 | 68 | 43 | 51 |
| Combination factors | | | | | |
| ≥ 10 mm* and Proximal** | 46 | 84 | 82 | 51 | 61 |
| Type II-O pit, ≥10 mm* and Proximal** | 32 | 93 | 88 | 48 | 57 |

Type II-O pit: Type II open-shape pit pattern, VMV: varicose microvascular vessel, PPV: positive predictive value, NPV: negative predictive value

* lesion size greater than 10 mm, ** proximal colon (cecum, ascending and transverse colon)

Differential diagnosis of SSA / Ps and HPs

Table 3 lists the differential diagnoses for SSA / Ps and HPs using Type II-O pit patterns, VMVs, clinicopathological factors, and their combination. Type II-O pit patterns showed higher specificity (84%) and PPV (86%) than the other findings. However, their sensitivity and NPV were insufficient. The overall accuracy of Type II-O pit patterns was 73%. In contrast, the diagnostic accuracy of VMVs was lower than that of Type II-O pit patterns. We also examined the accuracy of differential diagnosis using a combination of two clinicopathological factors, namely lesion size (≥ 10 mm) and location (proximal colon). The specificity and PPV of this combination were similar to those of the Type II-O pit pattern, but the sensitivity and NPV were lower. We also examined the performance of differential diagnosis using a combination of the Type II-O pit pattern and the clinical features mentioned above. Although this combination improved the specificity and PPV, the sensitivity and NPV were worse than those of the Type II-O pit pattern alone.

Table 4. Inter- and intra-observer variability of endoscopic findings

| | Inter-observer variability (κ -value) | | | Intra-observer variability (κ -value) | | |
|---|---|---------|---------|---|------|------|
| | K.K–A.K | A.K–T.M | K.K–T.M | K.K | A.K | T.M |
| Pit pattern* (type II vs. non-type II) | 0.55 | 0.43 | 0.79 | 0.85 | 0.74 | 0.92 |
| Type II-O pit | 0.60 | 0.57 | 0.65 | 0.52 | 0.59 | 0.94 |
| VMV | 0.59 | 0.44 | 0.51 | 0.65 | 0.70 | 0.87 |

Type II-O pit : Type II open-shape pit pattern, VMV: varicose microvascular vessel

* Kudo's classification

Inter- and intra-observer variability of endoscopic findings

The inter- and intra-observer variabilities for identification of pit pattern, Type II-O pit pattern, and VMV among the observers are given in Table 4. The mean inter- and intra-observer agreement for the Type II-O pit pattern was $\kappa = 0.61$ (range 0.57–0.65) and $\kappa = 0.68$ (range 0.52–0.94), respectively. The mean inter- and intra-observer agreement for VMW was $\kappa = 0.51$ (range 0.44–0.59) and $\kappa = 0.74$ (range 0.65–0.87), respectively. The overall agreement for final diagnosis indicated fair or moderate agreement.

Discussion

The present study evaluated the clinicopathological and endoscopic features of SSA/Ps and HPs. In this study, SSA/Ps were more often located in the proximal colon and were larger than HPs. These clinicopathological features are consistent with those reported previously^{6, 15–18}. The frequency of Type II-O pit patterns was significantly higher in the case of SSA/Ps than HPs. With regard to the differential diagnosis, the specificity and PPV of the Type II-O pit pattern were sufficient, whereas the sensitivity and NPV were not. These results are similar to those reported previously^{11, 19}. However, in the present study, VMVs had lower diagnostic accuracy than those reported by Uraoka *et al*¹². Therefore, the usefulness of VMVs for the differential diagnosis of SSA/Ps and HPs requires further investigation. In addition, the diagnostic performance of the Type II-O pit pattern was higher than that of a combination of two clinicopathological features, namely lesion size >10 mm and location in the proximal colon. These results suggest that the detection of the Type II-O pit pattern could be useful for the differential diagnosis of SSA/Ps and HPs. However, the lower sensitivity of the Type II-O pit pattern makes the differential diagnosis of SSA/Ps without a Type II-O pit pattern and HPs an important issue. Table 5 lists the clinicopathological features of SSA/Ps and HPs without Type II-O pit patterns. SSA/Ps without Type II-O pit patterns were also more frequently found in the proximal colon and were larger than HPs. SPs without Type II-O pit patterns with these characteristics require particular attention for the differential diagnosis of SSA/Ps from HPs.

Investigation of the inter- and intra-observer variability of the Type II-O pit pattern and VMV revealed acceptable κ values for both. These results demonstrate that the endoscopic diagnosis

Table 5. Clinicopathological features of SSA / Ps and HPs without type II-O pits

| | | SSA/P N = 24 | HP N = 38 | P value |
|------------------|------------------------------------|-----------------|--------------|----------|
| Location | Proximal | 18 (75%) | 15 (39%) | < 0.01 |
| | Distal | 6 (25%) | 23 (61%) | |
| Size | Median (range) | 8.5 (6–25) | 7 (4–18) | < 0.01 |
| | ≤ 5 mm | 0 (0%) | 9 (24%) | < 0.01** |
| | 6–9 mm | 13 (54%) | 24 (63%) | |
| | 10 mm ≤ | 11 (46%) | 5 (13%) | |
| Macroscopic type | Superficial | 24 (100%) | 33 (87%) | < 0.01 |
| | Protruded | 0 (0%) | 5 (13%) | |
| Pit pattern* | II | 23 (96%) | 29 (76%) | 0.07*** |
| | III _L / IV | 1 (4%) | 5 (13%) | |
| | III _H / IV _H | 0 (0%) | 4 (11%) | |

SSA / P : sessile serrated adenoma / polyp, HP : hyperplastic polyp

* Kudo's classification, ** < 10 mm vs. 10 mm ≤, *** II vs. III_L / IV, III_H / IV_H

for both findings did not depend on the observers.

Rex *et al* recommended complete endoscopic removal of all SPs, except for diminutive sigmoid or rectal lesions²⁰⁾. However, in the present study, no SSA / P without Type II-O pit patterns was observed among lesions that were ≤ 5 mm in size. Therefore, we suggest that endoscopists should remove lesions when Type II-O pit patterns are detected in SPs by chromoendoscopy or electronic chromoendoscopy (e.g. NBI). Otherwise, tumor location (proximal location) and size (> 5 mm) should be considered when contemplating SP removal.

In summary, the results of the present study indicate that Type II-O pit patterns may be useful for the differential diagnosis of SSA / Ps and HPs. However, identification of more specific features of SSA / Ps is necessary.

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Conflict of interest disclosure

The authors declare they have no competing interests.

References

- 1) Snover DC, Ahnen DJ, Burt RW, *et al*. Serrated polyps of the colon and rectum and serrated polyposis. In *Boz-man FT, Carneiro F, Hruban RH, et al. eds. WHO classification of tumours of the digestive system. 4th ed.* Lyon: International Agency for Research on Cancer; 2010. pp 160–165.
- 2) Jass JR, Baker K, Zlobec I, *et al*. Advanced colorectal polyps with the molecular and morphological features of

- serrated polyps and adenomas: concept of a 'fusion' pathway to colorectal cancer. *Histopathology*. 2006;**49**:121–131.
- 3) Otori K, Oda Y, Sugiyama K, *et al*. High frequency of K-ras mutations in human colorectal hyperplastic polyps. *Gut*. 1997;**40**:660–663.
 - 4) Konishi K, Yamochi T, Makino R, *et al*. Molecular differences between sporadic serrated and conventional colorectal adenomas. *Clin Cancer Res*. 2004;**10**:3082–3090.
 - 5) Yano Y, Konishi K, Yamochi T, *et al*. Clinicopathological and molecular features of colorectal serrated neoplasias with different mucosal crypt patterns. *Am J Gastroenterol*. 2011;**106**:1351–1358.
 - 6) Shinmura K, Konishi K, Yamochi T, *et al*. Molecular features of colorectal polyps presenting Kudo's type II mucosal crypt pattern: are they based on the same mechanism of tumorigenesis? *Endosc Int Open* (Internet). 2014;**2**:E171–E177. (accessed 2014 Jun 10) Available from: <http://dx.doi.org/10.1055/s-0034-1377518>
 - 7) O'Brien MJ, Zhao Q, Yang S. Colorectal serrated pathway cancers and precursors. *Histopathology*. 2015;**66**:49–65.
 - 8) Bettington M, Walker N, Clouston A, *et al*. The serrated pathway to colorectal carcinoma: current concepts and challenges. *Histopathology*. 2013;**62**:367–386.
 - 9) Boparai KS, van den Broek FJ, van Eeden S, *et al*. Hyperplastic polyposis syndrome: a pilot study for the differentiation of polyps by using high-resolution endoscopy, autofluorescence imaging, and narrow-band imaging. *Gastrointest Endosc*. 2009;**70**:947–955.
 - 10) Hasegawa S, Mitsuyama K, Kawano H, *et al*. Endoscopic discrimination of sessile serrated adenomas from other serrated lesions. *Oncol Lett*. 2011;**2**:785–789.
 - 11) Kimura T, Yamamoto E, Yamano HO, *et al*. A novel pit pattern identifies the precursor of colorectal cancer derived from sessile serrated adenoma. *Am J Gastroenterol*. 2012;**107**:460–469.
 - 12) Uraoka T, Higashi R, Horii J, *et al*. Prospective evaluation of endoscopic criteria characteristic of sessile serrated adenomas / polyps. *J Gastroenterol*. 2015;**50**:555–563.
 - 13) Kudo S, Tamura S, Nakajima T, *et al*. Diagnosis of colorectal tumorous lesions by magnifying endoscopy. *Gastrointest Endosc*. 1996;**44**:8–14.
 - 14) Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;**33**:159–174.
 - 15) Lash RH, Genta RM, Schuler CM. Sessile serrated adenomas: prevalence of dysplasia and carcinoma in 2139 patients. *J Clin Pathol*. 2010;**63**:681–686.
 - 16) Hetzel JT, Huang CS, Coukos JA, *et al*. Variation in the detection of serrated polyps in an average risk colorectal cancer screening cohort. *Am J Gastroenterol*. 2010;**105**:2656–2664.
 - 17) Shida Y, Ichikawa K, Fujimori T, *et al*. Differentiation between sessile serrated adenoma / polyp and non-sessile serrated adenoma / polyp in large hyper plastic polyp: A Japanese collaborative study. *Mol Clin Oncol*. 2013;**1**:53–58.
 - 18) Sano W, Sano Y, Iwatate M, *et al*. Prospective evaluation of the proportion of sessile serrated adenoma / polyps in endoscopically diagnosed colorectal polyps with hyperplastic features. *Endosc Int Open* (Internet). 2015;**3**:E354–E358. (accessed 2015 Mar 2) Available from: <http://dx.doi.org/10.1055/s-0034-1391948>
 - 19) Ishigooka S, Nomoto M, Obinata N, *et al*. Evaluation of magnifying colonoscopy in the diagnosis of serrated polyps. *World J Gastroenterol*. 2012;**18**:4308–4316.
 - 20) Rex DK, Ahnen DJ, Baron JA, *et al*. Serrated lesions of the colorectum: review and recommendations from an expert panel. *Am J Gastroenterol*. 2012;**107**:1315–1329.

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