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MINIREVIEWS

Endoscopic diagnosis of sessile serrated adenoma/polyp with and without dysplasia/carcinoma

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Abstract

Sessile serrated adenoma/polyps (SSA/Ps) are early precursor lesions in the serrated neoplasia pathway, which results in colorectal carcinomas with *BRAF* mutations, methylation for DNA repair genes, a CpG island methylator phenotype, and high levels of microsatellite instability. Some of these lesions can rapidly become dysplastic or invasive carcinomas that exhibit high lymphatic invasion and lymph node metastasis potentials. Detecting serrated lesions, including SSA/Ps with and without dysplasia/carcinoma, is critical, but SSA/Ps can be difficult to detect, are inconsistently identified by endoscopists and pathologists, and are often incompletely resected. Therefore, SSA/Ps are considered to be major contributors to "interval cancers". If colonoscopists can identify the specific endoscopic characteristics of SSA/Ps, their detection and the effectiveness of colonoscopy may improve. Here, the endoscopic features of SSA/Ps with and without dysplasia/carcinoma, including the characteristics determined using magnifying endoscopy, are reviewed in the context of previous reports. Endoscopically, these subtle polyps are like hyperplastic polyps, because they are slightly elevated and pale. Unlike hyperplastic polyps, SSA/Ps are usually larger than 5 mm, frequently covered by a thin layer called the "mucus cap", and are more commonly located in the proximal colon. Magnifying narrow-band imaging findings, which include dark spots inside the crypts and varicose microvascular vessels, in addition to the type II-open pit patterns detected using magnifying chromoendoscopy, effectively differentiate SSA/Ps from hyperplastic polyps. The lesions' endoscopic characteristics, which include their (semi)pedunculated morphologies, double elevations, central depressions, and reddishness, and the use of magnifying endoscopy, might help to detect dysplasia/carcinoma within SSA/Ps. Greater awareness may promote further research into improving the detection, identification, and complete

resection rates of SSA/Ps with and without dysplasia/carcinoma and reduce the interval cancer rates.

Key words: Sessile serrated adenoma/polyp; Invasive carcinoma arising from sessile serrated adenoma/polyp; Serrated neoplasia pathway; Endoscopic diagnosis; Sessile serrated adenoma/polyp with cytological dysplasia

Core tip: The endoscopic features of sessile serrated adenoma/polyps (SSA/Ps) with and without dysplasia/carcinoma are reviewed. Conventional endoscopic characteristics, including a proximal location, a slightly elevated morphology, a pale color, and a mucus cap, are useful for diagnosing SSA/Ps. Magnifying narrow-band imaging, which detects dark spots inside the crypts and varicose microvascular vessels, and magnifying chromoendoscopy, which identifies the type II-open pit pattern, are also effective for differentiating between SSA/Ps and hyperplastic polyps. Furthermore, the lesions' endoscopic characteristics, which include their (semi)pedunculated morphologies, double elevations, central depressions, and reddishness, and the use of magnifying endoscopy, might help to detect dysplasia/carcinoma within SSA/Ps.

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INTRODUCTION

Colorectal serrated lesions were called "hyperplastic polyps", and they were not considered to be malignant[1,2]. Torlakovic *et al*[3] described abnormal proliferations in colorectal serrated polyps that resembled hyperplastic polyps superficially, but could be distinguished histologically based on their abnormal architectural features, and they introduced the term "sessile serrated adenoma". Currently, these polyps are categorized as sessile serrated adenoma/polyp (SSA/P) in accordance with the World Health Organization's recommendations[4]. The typical histology of an SSA/P in a representative case is shown in Figure 1.

SSA/Ps are early precursor lesions in the serrated neoplasia pathway, which results in colorectal carcinomas with high levels of microsatellite instability[5-7]. Recent studies have shown associations between SSA/Ps with and without dysplasia or carcinoma and the methylation or loss of protein expression for DNA repair genes, including *MLH1*[3,6,8-12], a CpG island methylator phenotype[5,6,8,10], *BRAF* mutations[5,6,8-17], and a lack of genetic alterations in *CTNNB1*, which is the gene that codes for β-catenin protein[17]. This pathway is thought to be distinct from the conventional adenoma-carcinoma pathway in which adenomas progress to invasive colorectal carcinomas as a result of a series of genetic alterations, including adenomatous polyposis coli (*APC*) and *KRAS* mutations[6,8,13,14,18,19].

Figure 1 Typical histology of a sessile serrated adenoma/polyp. Crypts with a serrated architecture include those that are irregularly dilated, branch irregularly, and are horizontally arranged (basal).

Some researchers[20-22] have suggested that some serrated lesions might progress rapidly to dysplasia or invasive carcinomas. Furthermore, we reported that the submucosal invasive carcinomas that arose in SSA/Ps exhibited higher potentials for lymphatic invasion and lymph node metastasis than their conventional counterparts that arose from tubular adenomas[23]. Therefore, the detection of serrated lesions, including SSA/Ps with and without dysplasia, is critical. However, SSA/Ps can be difficult to detect, are inconsistently identified by endoscopists and pathologists, and are often incompletely resected[24-27]. Therefore, SSA/Ps are major contributors to the failure of colonoscopy to prevent proximal colonic cancer[28-30], and they account for 5%-7% of the colorectal cancers that occur in the interval between a complete colonoscopy and surveillance, that is, "interval cancer"[31-33]. The identification of the specific endoscopic characteristics of SSA/Ps by colonoscopists may improve their detection and, eventually, may enhance the effectiveness of colonoscopy. Some studies have investigated the endoscopic features of SSA/Ps without dysplasia[34-38], and we clarified the endoscopic characteristics of SSA/Ps that had advanced histology[39].

Here, the endoscopic features of SSA/Ps with and without dysplasia or carcinoma are reviewed in the context of previous reports, including the features detected using magnifying endoscopy.

DIAGNOSIS OF SSA/P USING CONVENTIONAL WHITE-LIGHT ENDOSCOPY

Generally, hyperplastic polyps are traditionally considered non-neoplastic, but SSA/Ps have malignant potential to progress to invasive carcinomas. Therefore,

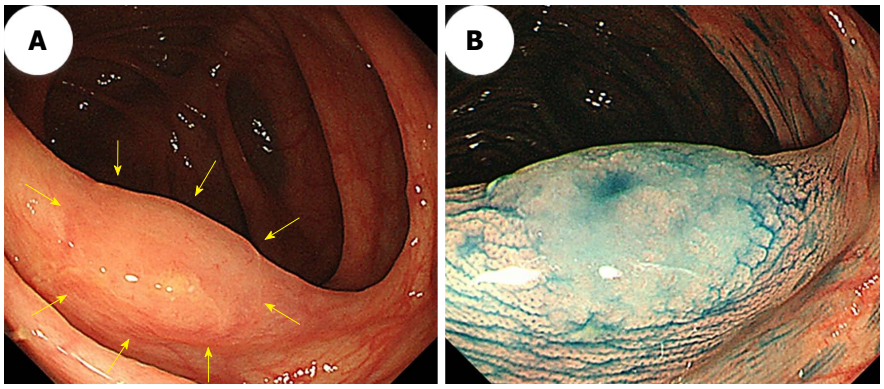

Figure 2 A sessile serrated adenoma/polyp in the transverse colon that measured 13 mm. A: An image from conventional colonoscopy showing the lesion's location (arrows); B: An image from chromoendoscopy following indigo carmine dye spraying.

differentiating an SSA/P from a hyperplastic polyp is clinically important to determine the necessity of an endoscopic resection or to provide support for a recommendation of a surveillance interval[40,41]. Typical hyperplastic polyps are highly prevalent, diminutive sessile polyps that are most commonly located in the sigmoid colon and rectum, and identifying them endoscopically is not particularly difficult[42]. SSA/Ps are subtle polyps, and their endoscopic findings are similar to those associated with hyperplastic polyps, which include a slightly elevated morphology and a pale color. However, in contrast to hyperplastic polyps, SSA/Ps are usually larger than 5 mm, frequently covered by a thin layer called a "mucus cap"[4,34,43,44], and are more commonly located in the proximal colon[14,45]. Conversely, although SSA/Ps are difficult to detect because of their slightly elevated morphology, adhesion of mucus in the proximal colon can be one of the most useful clues for SSA/P detection. Additionally, using white-light endoscopy, Hazewinkel *et al*[37] described the presence of indistinct borders and a cloud-like surface, and showed that these were independently predictive endoscopic characteristics that were associated with the histology of SSA/Ps. Figure 2 shows representative endoscopic images of SSA/Ps.

ENDOSCOPIC DIAGNOSIS OF SSA/P USING NARROW-BAND IMAGING

Difficulties distinguishing between an SSA/P and a hyperplastic polyp are commonly encountered. Many authors have used image-enhanced endoscopy to characterize polyps[46], which involves the use of innovative optical technologies, such as narrow-band imaging (NBI)[47-50]. Bile appears as a bright red fluid using NBI. When a tenacious mucus cap covers SSA/Ps, the mucus cap is clearly viewed using NBI. Therefore, NBI enhances the visibility of SSA/Ps that have mucus caps, which are usually an intense red color[34] (Figure 3A and B).

Furthermore, NBI often reveals small dark dots inside the openings to the crypts of SSA/Ps[37]; these are thought to indicate crypt dilations, which are a key histological feature of SSA/Ps. The presence of these dark spots inside the crypts might help endoscopists to differentiate between premalignant SSA/Ps and hyperplastic polyps during colonoscopy[37,38] (Figure 3C and D). Hazewinkel *et al*[37] have reported that in white-light endoscopy, indistinctive borders and cloud-like surface are two independent predictive characteristics of SSA/P, while in NBI, it is possible to discern an irregular shape and dark spots inside the crypts. The sensitivities, specificities, and overall accuracies determined using white-light endoscopy were 75%, 79%, and 77%, respectively, and those determined using NBI were 89%, 96%, and 93%, respectively[37].

Magnifying NBI can enhance the visibility of the microvessels on a lesion's surface. Yamada *et al*[51] conducted a multivariate analysis, demonstrated that dilated and branching vessels, defined as thickened capillary vessels with branching that is observed on the surface, had a 2.3-fold odds ratio among SSA/Ps compared with hyperplastic polyps. They stated that when dilated and branching vessels, a proximal location, and a tumor size of ≥ 10 mm were combined, the positive predictive value exceeded 90%. Additionally, Uraoka *et al*[52] reported that the presence of varicose microvascular vessels, which were found using magnifying NBI, was useful for differentiating between SSA/Ps and hyperplastic polyps. Unlike the blood vessels around the glands of the superficial mucosal layer such as dilated and branching vessels, varicose microvascular vessels are characterized by the observation of blood vessels running throughout the deep mucosal layer. The presence of varicose microvascular vessels had a significantly higher specificity (88%) for predicting a diagnosis of SSA/P (Figure 3E and F).

DIAGNOSIS OF SSA/P USING MAGNIFYING CHROMOENDOSCOPY

Magnifying chromoendoscopy, which uses indigo carmine or crystal violet staining, follows careful conventional endoscopic examinations. Kudo *et al*[53,54] proposed a classification of colorectal lesions' pit patterns that is associated with the lesions' histologic characteristics.

Table 1 Distinct endoscopic characteristics between sessile serrated adenoma/polyps and hyperplastic polyps

	SSA/Ps	Hyperplastic polyps
Conventional endoscopic features		
Location	Proximal	Distal
Size of tumor	> 5 mm	≤ 5 mm
Color	Pale	Pale
Morphology	Flat elevated	Flat elevated
Mucus cap	Yes	No
Endoscopic features by using NBI	Irregular shape	-
	Small dark dots	
	Dilated and branching vessels	
	Varicose microvascular vessels	
Magnifying chromoendoscopic features	Type II-open pit pattern	Type II pit pattern

SSA/P: Sessile serrated adenoma/polyp; NBI: Narrow-band imaging.

As previously explained[54-56], magnifying colonoscopy is useful for differentiating between neoplastic and nonneoplastic lesions, and for assessing early colorectal cancers' depths of invasion. Both hyperplastic polyps and SSA/Ps have type II pit patterns. Recently, the type II-open pit pattern has been described as a hallmark of SSA/Ps (sensitivity: 66%; specificity: 97%)[35]. Like the small dark dots detected using NBI, a type II-open pit pattern detected using magnifying chromoendoscopy is thought to indicate crypt dilation, which is one of the major histological features of SSA/Ps (Figure 4).

Distinct endoscopic characteristics between SSA/Ps and hyperplastic polyps are summarized in Table 1.

ENDOSCOPIC DETECTION OF SSA/P

The detection of SSA/Ps requires careful colonoscopy. As stated above, because most SSA/Ps are slightly flat-elevated and have subtle mucosal features, SSA/Ps are difficult to detect with endoscopy, and could easily be missed. Therefore, bowel preparation must be excellent. Potential SSA/Ps are initially considered at long view and investigated at close-up view. At long view, the presence of SSA/P is suspected when there is a patch that appears nodular, reddish, covered with mucus, and/or circled by fine debris. Then such a lesion must be approached and the mucosa washed. Finally, at close-up view, using white light and under NBI, the surface pattern and vessels are examined.

Recently, some studies[57,58] have shown that image-enhanced endoscopy such as NBI might increase the detection of serrated lesions in the proximal colon, although the results did not reach significance. Therefore, image-enhanced endoscopy currently cannot be recommended as a detection tool for SSA/P. Additional studies assessing SSA/P detection rates with image-enhanced endoscopy are needed.

ENDOSCOPIC DIAGNOSIS OF SSA/P WITH DYSPLASIA/CARCINOMA

SSA/Ps with advanced histology, including cytologic dysplasia or minimally invasive carcinomas, are rare. Indeed, a previous study's findings showed that the frequencies of cytologic dysplasia and invasive carcinomas among SSA/P lesions were 14% and 1.0%, respectively[59]. The findings from another study showed that three (0.7%) high-grade dysplasias and one (0.2%) submucosal invasive carcinoma were detected among 430 SSA/Ps[60]. Therefore, only a few studies have investigated the endoscopic characteristics of SSA/Ps with dysplasia or carcinoma in detail[39,61,62]. We demonstrated that SSA/Ps without dysplasia (354 of 414; 86%) and SSA/Ps with dysplasia or carcinomas (40 of 48; 83%) were frequently located in the proximal colon[39]. Furthermore, we showed a stepwise increase in the median size of the SSA/Ps that accompanied their dysplastic progression, specifically, from a 10-mm SSA/P that did not have dysplasia to a 12-mm SSA/P with cytologic dysplasia and a 19-mm SSA/P with an invasive carcinoma, but 19 of 48 (39.6%) SSA/Ps with dysplasia or carcinomas measured ≤ 10 mm[39]. The findings from a study by Goldstein[20] showed that the median size of eight SSA/Ps with focal invasive adenocarcinomas or high-grade dysplasia was 8.5 mm (range: 6-12 mm). Another study's findings[63] showed that among eight SSA/Ps with intramucosal carcinomas, submucosal carcinomas, or advanced carcinomas, the largest diameter was ≤ 10 mm. Therefore, SSA/P with dysplasia/carcinoma must be attended to even if the lesion measures 10 mm or less.

Macroscopically, a mucus cap was found in almost all of the SSA/P lesions, including the SSA/Ps with and without dysplasia or carcinoma, in our study[39], suggesting that a mucus cap may be one of the strongest markers of an SSA/P. Additionally, (semi)pedunculated morphologies, double elevations, central depressions, and reddishness were found more frequently in SSA/Ps with dysplasia (17.1%, 63.4%, 9.8%, and 39.0%, respectively) or carcinoma (28.6%, 57.1%, 28.6%, and reddishness 85.7%, respectively) than the frequencies at which these features were found in SSA/Ps without dysplasia (4.6%, 4.6%, 3.9%, and 3.4%, respectively). The presence of at least one of these four markers had a high sensitivity (91.7%) for the identification of dysplasia or a carcinoma within an SSA/P; the specificity was

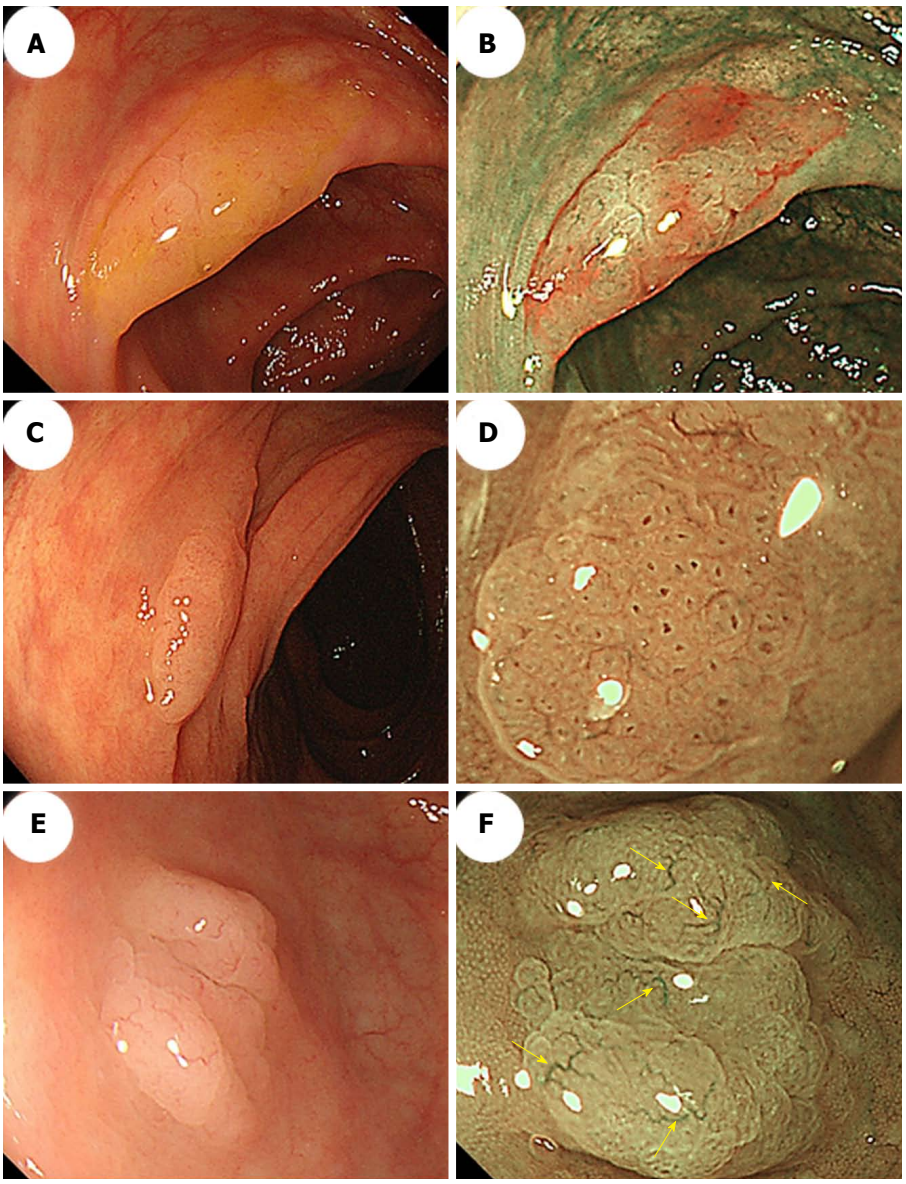

Figure 3 Morphologic characteristics of sessile serrated adenoma/polyps. A: Conventional endoscopy revealed a flat-elevated lesion with a 20-mm diameter that was covered with a mucus cap in the transverse colon. B: Narrow-band imaging (NBI) showed that the SSA/P in (A) was covered with a mucus cap that appeared intensely red. C: Conventional endoscopy showed a flat-elevated lesion with a 14-mm diameter in the ascending colon. D: Magnifying NBI of the SSA/P in (C) revealed dark spots inside the crypts in part of the lesion. E: A conventional endoscopic image shows a flat-elevated pale colored lesion with a 10-mm diameter in the cecum. F: Magnifying NBI of the SSA/P in (E) revealed varicose microvascular vessels (arrows) in part of the lesion. SSA/P: Sessile serrated adenoma/polyp.

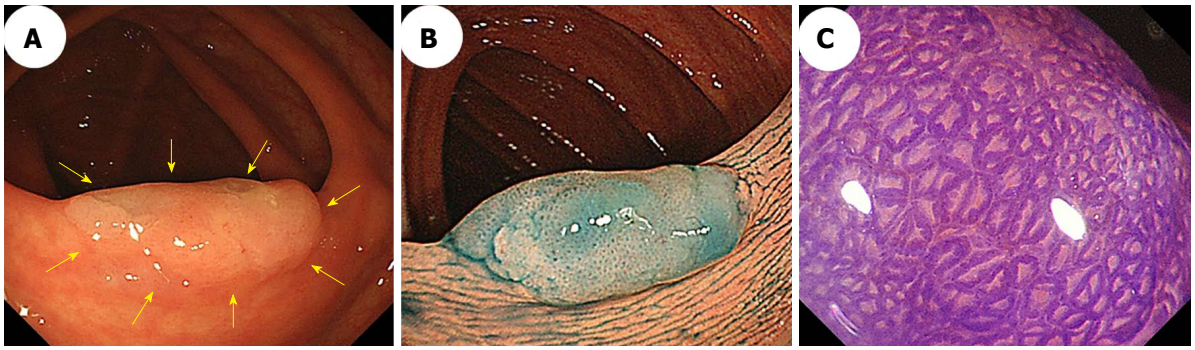

Figure 4 Conventional colonoscopic image (A) and a chromoendoscopic image (B) following indigo carmine dye spraying show an 18-mm sessile serrated adenoma/polyp with a mucus cap that was in the transverse colon (arrows). C: Magnifying chromoendoscopy using crystal violet staining identified a type II-open pit pattern in the lesion.

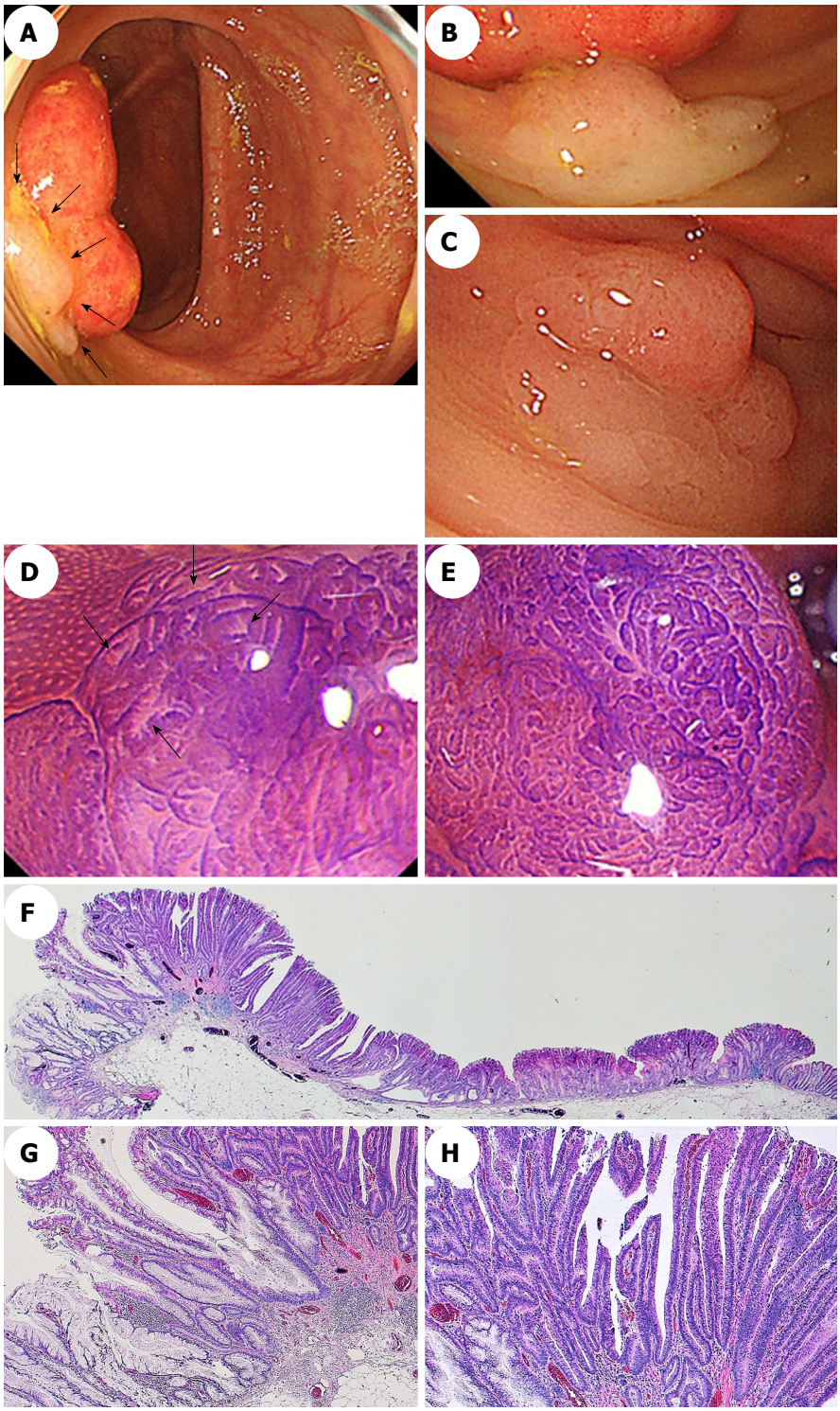

Figure 5 Endoscopic images of a sessile serrated adenoma/polyp with high-grade cytologic dysplasia in a representative case. A-C: A conventional endoscopic view using white-light imaging. A: An endoscopic image shows a pale-color, flat-elevated lesion covered with mucus at the ascending colon (arrows). B: The lesion is covered with mucus cap. C: After washing the target lesion to sufficiently remove mucus, a flat-elevated lesion that had a 13-mm diameter and a dome-shaped double elevation can be clearly seen. The dome-shaped area is slightly red-colored. D and E: Magnifying chromoendoscopic views using crystal violet staining. D: A type II-open pit pattern is partly evident in the edge of the lesion (arrows). E: Type VI-mild pit pattern consisting of areas with irregular pits can be observed at the dome-shaped area. We endoscopically diagnosed the lesion as an SSA/P with cytologic dysplasia, and achieved an en bloc resection by performing an endoscopic mucosal resection. F-H: Histopathologic findings with hematoxylin-eosin staining of the resected specimen. G: Crypts with a serrated architecture exhibit irregularly dilated crypts, irregularly branching crypts, and horizontally arranged basal crypts, corresponding to SSA/P. H: A high-power view shows conventional adenomatous high-grade dysplasia with cytological atypia and architectural dysplasia in the dome-shaped area. The lesion was pathologically consistent with an SSA/P with high-grade cytologic dysplasia. SSA/P: Sessile serrated adenoma/polyp.

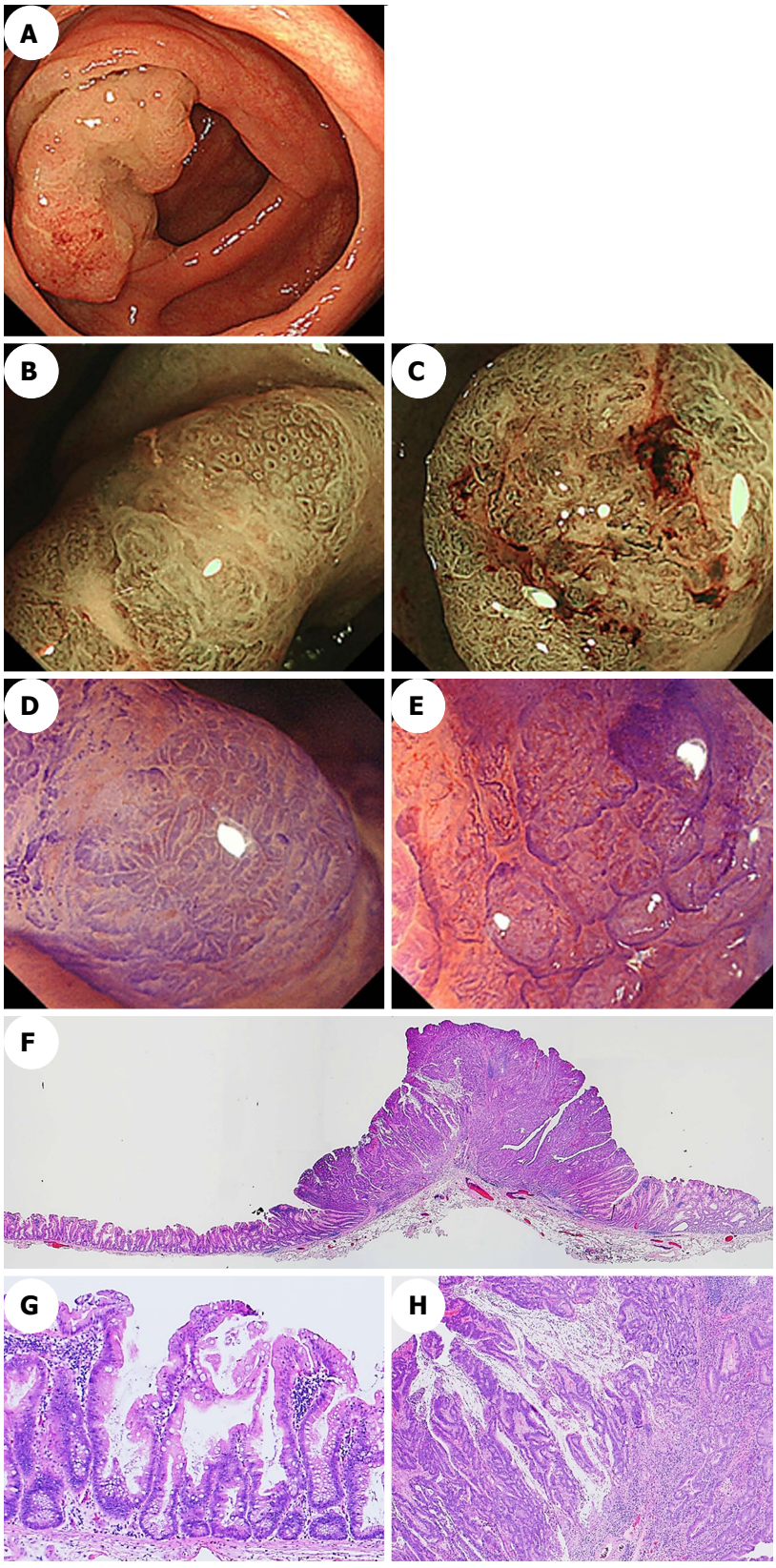

Figure 6 Endoscopic images of a sessile serrated adenoma/polyp with an invasive carcinoma in a representative case. A: A conventional endoscopic image captured using white-light imaging shows a red 55-mm semipedunculated lesion in the ascending colon. B and C: Magnifying narrow-band imaging revealed dark spots inside the crypts on an edge of the lesion and irregular vessel patterns over a large part of the lesion, respectively. D and E: Magnifying chromoendoscopy using crystal violet staining; D: A high-powered view of the marginal zone, the dilated openings of the crypts have a type II-open pit pattern; E: A high-powered view of the middle region in which a type VI-severe pit pattern is evident. We endoscopically diagnosed the lesion as a carcinoma associated with an SSA/P, and achieved an en bloc resection by performing an endoscopic submucosal dissection. F-H: Histopathologic findings with hematoxylin-eosin staining of the resected specimen; G: Crypts with a serrated architecture exhibiting irregularly dilated crypts and irregularly branching crypts, corresponding to SSA/P; H: Well to moderately differentiated adenocarcinomas invade the submucosa with extracellular mucin production. The lesion was pathologically consistent with an invasive submucosal adenocarcinoma associated with an SSA/P. SSA/P: Sessile serrated adenoma/polyp.

85.3%. These findings suggested that the endoscopic characteristics, including a (semi)pedunculated morphology, a double elevation, a central depression, and reddishness, may be useful for accurately diagnosing the presence of advanced histology within an SSA/P.

Magnifying chromoendoscopy is also useful for detecting components associated with dysplasia or a carcinoma within an SSA/P. We found that a type II-open pit pattern was present in SSA/Ps without dysplasia and in SSA/Ps with dysplasia or carcinomas, which indicates that a type II-open pit pattern may be strongly suggestive of the presence of SSA/P components[39]. Furthermore, the type II pit pattern only was detected in all of the cases who had SSA/Ps without dysplasia, whereas type II and other pit patterns, including mixtures of III_L, IV, V_I, or V_N, were found in most of the SSA/Ps with dysplasia or carcinoma. Moreover, all of the cases who had SSA/Ps with invasive carcinomas had the V_I or V_N pit patterns (invasive patterns), which were consistent with the depths of invasion. Accordingly, determining the pit patterns using magnifying endoscopy can effectively assess the depth of invasion of early colorectal cancers that arise from SSA/Ps. Figures 5 and 6 show representative endoscopic images of SSA/Ps with dysplasia or carcinoma.

Finally, there is one important point that must be kept in mind when observing SSA/Ps using colonoscopy. Most SSA/Ps were covered with rich mucus, and subtle endoscopic findings were difficult to detect when sticky mucus was present. After washing the target lesion to sufficiently remove mucus, endoscopic findings such as (semi)pedunculated morphology, double elevation, central depression, and reddishness should be assessed, and pit pattern analysis must be performed.

CONCLUSION

Conventional endoscopic characteristics, including a proximal location, a slightly elevated morphology, a pale color, and a mucus cap, are useful for diagnosing SSA/Ps. Magnifying endoscopy with NBI, which detects dark spots inside the crypts and varicose microvascular vessels, and magnifying chromoendoscopy, which identifies the type II-open pit pattern, are also effective for differentiating between SSA/Ps and hyperplastic polyps. Furthermore, a lesion's endoscopic characteristics, for example, a (semi)pedunculated morphology, a double elevation, a central depression, and reddishness, in addition to the use of magnifying endoscopy, might be useful for identifying dysplasia or a carcinoma within an SSA/P. Greater awareness may promote further research into improving the detection, recognition, and complete resection rates of SSA/Ps with and without dysplasia or carcinoma and reduce the interval cancer rates.

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