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Retrospective Study

Usefulness of analyzing endoscopic features in identifying the colorectal serrated sessile lesions with and without dysplasia

Wang RG *et al*. Endoscopic features of SSLs

Abstract

BACKGROUND

Sessile serrated lesions (SSLs) are often missed on colonoscopy, and studies have shown this to be an essential cause of interstitial colorectal cancer. The SSLs with dysplasia (SSL-D$^+$), in particular, have a faster rate of carcinogenesis than conventional tubular adenomas. Therefore, there is a clinical need for some endoscopic features with independent diagnostic value for SSL-D$^+$s to assist endoscopists in making immediate diagnoses, thus improving the quality of endoscopic examination and treatment.

AIM

To compare the characteristics of SSLs, including those with and without dysplasia (SSL-D$^+$ and SSL-D$^-$), based on white light and image-enhanced endoscopy, to achieve an immediate differential diagnosis for endoscopists.

METHODS

From January 2017 to February 2023, cases of colorectal SSLs confirmed by colonoscopy and histopathology at the Gastrointestinal Endoscopy Center of Beijing Tsinghua Changgung Hospital were collected. The general, endoscopic, and histopathological data were reviewed and analyzed to determine the diagnostic utility. Univariate analysis was used to find potential diagnostic factors, and then multivariate regression analysis was performed to derive endoscopic features with independent diagnostic values for the SSL-D$^+$.

RESULTS

A total of 228 patients with 253 lesions were collected as a result. There were 225 cases of colorectal SSL-D$^-$s and 28 cases of SSL-D$^+$s. Compared to the colorectal SSL-D$^-$, the SSL-D$^+$ was more common in the right colon (P = 0.027) with complex patterns of depression, nodule, and elevation based on cloud-like surfaces (P = 0.003), reddish (P < 0.001), microvascular varicose (P < 0.001), and mixed type (Pit II, II-O, IIIL, IV) of crypt

opening based on Pit II-O (P < 0.001). Multifactorial logistic regression analysis indicated that lesions had a reddish color [odds ratio (OR) = 18.705, 95% confidence interval (CI): 3.684-94.974], microvascular varicose (OR = 6.768, 95%CI: 1.717-26.677), and mixed pattern of crypt opening (OR = 20.704, 95%CI: 2.955-145.086) as the independent predictors for SSL-D$^+$s.

CONCLUSION

The endoscopic feature that has independent diagnostic value for SSL-D$^+$ is a reddish color, microvascular varicose, and mixed pattern of crypt openings.

Key Words: Sessile serrated lesions; Dysplasia; Endoscopic features

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Core Tip: The colonoscopic features of colorectal sessile serrated lesions (SSLs) make them easy to be overlooked in screening, which is an essential reason for the emergence of interstage colorectal cancer. With the advancement of endoscopic techniques and refinement of the serrated carcinoma pathway, the SSL is gradually being recognized by endoscopists, especially for SSL with dysplasia (SSL-D$^+$), which requires extra attention. In this study, we analyzed the endoscopic features of SSLs with and without dysplasia, and found characteristics that could independently diagnose SSL-D$^+$ by multifactorial analysis, which is informative for immediate diagnosis by endoscopists.

INTRODUCTION

At the end of the 20th century, a group of lesions with characteristics similar to those of hyperplastic polyposis identified by Torlakovic and Snover[1], which showed a broad-based growth pattern endoscopically but lacked heterogeneous hyperplasia and were

dubbed "sessile serrated adenoma (SSA)". According to the 2010 World Health Organization (WHO) Classification of Tumors of the Digestive System, the SSA/polyp (SSA/P) is a subtype of the serrated polyp. However, the 5th edition of the WHO Classification of Gastrointestinal Tumors 2019 renamed SSA/Ps to sessile serrated lesions (SSLs) due to the progression of the serrated pathway of colorectal carcinoma[2]. SSLs have poorly defined borders, pale surfaces, and a mucus-covered cap, which is difficult to differentiate from the surrounding mucosa, resulting in both their neglect during colonoscopic screening and adverse events of incomplete resection during endoscopic treatment[3,4].

The unique endoscopic features of colorectal SSLs make it a significant risk factor for the development of interstitial colorectal cancer. Notably, with the continuous advancement and development of endoscopy techniques, equipment, and accessories, potent tools exist for the precise observation and prompt diagnosis of colorectal SSLs. Based on the pathologic diagnostic criteria, SSLs were categorized as SSLs with and without dysplasia (SSL-D^+ and SSL-D^-). In addition, there have been reports of SSL-D^+s transforming into submucosal invasive carcinomas within a short period[5-7], that is to say, once a diagnosis of SSL-D^+ has been made, the progression to serrated adenocarcinoma can be rapid.

MATERIALS AND METHODS

Research object

From January 2017 to February 2023, colorectal SSLs confirmed by histopathology during colonoscopy at the Gastrointestinal Endoscopy Center of Beijing Tsinghua Changgung Hospital were retrospectively collected. Inclusion criteria: Cases with clear endoscopic images revealing the microstructure of the lesion surface, the images have been retrospectively reviewed; cases with complete clinical and pathological data; cases with a histopathologically confirmed diagnosis of SSL-D^- or SSL-D^+, it is highlighted that the histopathological diagnosis of all cases has been reviewed using WHO Classification of Gastrointestinal Tumors 2019 criteria; and all cases that signed an

informed consent form and underwent endoscopic resection. The exclusion criteria included cases with unclear endoscopic figures and a non-removed mucus cap; cases unable to identify the surface microstructure; cases without a complete resection; and cases combining ulcerative colitis and hereditary polyp syndrome.

Equipment and instruments

The endoscopic systems were colonoscopy series EC-590WM/EC-790ZP (Fuji Film, Japanese) and CF-H290I/CF-HQ290I (Olympus, Japanese), which utilized white light, blue laser imaging (BLI) and narrow band imaging (NBI) to observe and store images of lesions. In addition, an endoscopic procedure was performed using ERBE 200D high-frequency electrosurgery equipment, an Enrico Woodpecker knife (EK-410D), and a Boston Scientific single-use submucosal injection needle and snare device.

Analysis methods

Suspected SSLs were analyzed by colonoscopy in white light and BLI/NBI mode with the following characteristics: Site (left/right colon), size (</≥ 10 mm), surface mucus cap (no/yes, Figure 1A), surface morphology (cloud-like/mixed-like: Depressed, nodular, elevated), lesion color (pale/reddish) (Figures 1B and C), crypt black spots (no/yes, Figure 1D), and microvascular varicose (no/yes, Figure 1E), crypt opening morphology (Pit II-O type/mixed type base on Pit II-O, Figure 1F). Three seasoned endoscopists (with more than ten years of gastrointestinal endoscopy operation) examined all endoscopic figures. The decision was accepted if there was unanimity among the three endoscopists; otherwise, a vote was held.

Pathological diagnostic criteria

After colorectal SSLs were resected, the lesion surface was rinsed of mucus and impurities to expose the lesion morphology and contour, spread with a specimen needle, and fixed in 10% formaldehyde solution. The specimen was collected, embedded, sectioned, stained with hematoxylin-eosin, and observed under the

microscope following the guidelines for gastrointestinal mucosal specimens and pathological examination. The histological diagnosis followed the criteria outlined in the 2019 WHO Classification of Tumors of the Digestive System and the relevant literature[2,8] (Figures 2A and B).

Statistical methods

Data management and statistical analysis were performed using SPSS 20. Case counts were expressed as cases (in %). The χ^2 test and Fisher's precision probability test were used to compare univariate data. Variables with $P < 0.1$ were included in the multivariate logistic regression analysis. $P < 0.05$ indicates a statistically significant difference.

RESULTS

General data

This study collected 228 patients with histopathologically confirmed SSL, of which 119 (52.19%) were male, and 109 (47.81%) were female. The mean age of the SSL-D$^-$ group was 57.25 ± 12.02 years, while the SSL-D$^+$ group was 60.00 ± 11.27 years. In the enrolled cases, a total of 253 lesions were identified (two lesions in 18 patients, three lesions in two patients, and four lesions in one patient), with 225 (88.93%) cases being colorectal SSL-D$^-$s and 28 (11.07%) cases being colorectal SSL-D$^+$s. Three patients were detected with one SSL-D$^-$ and one SSL-D$^+$. Regarding gender and age, there were no statistically significant differences between the SSL-D$^-$ and SSL-D$^+$ groups ($P > 0.05$).

Endoscopic features

Endoscopic features of colorectal SSL-D$^-$s: 146 cases located in the right colon, 186 with diameter ≥ 10 mm, 48 with complex morphology (*e.g.,* depressions, nodules, and elevations based on cloud-like), 119 covered with mucus cap, 9 with a reddish color, 130 with black dots visible on the surface of lesions in BLI/NBI pattern and 15 with visible

submucosal microvascular varicose under BLI/NBI pattern. As for crypt opening, the pattern mixed type (II, II-O, IIIL, IV) based on Pit II-O type had 2 cases.

Endoscopic features of colorectal SSL-D$^+$s: 24 cases located in the right colon, 27 with diameter ≥ 10 mm, 13 with complex morphology (*e.g.,* depressions, nodules, and elevations based on cloud-like), 19 covered with mucus cap, 18 with a reddish color, 16 with black dots visible on the surface of lesions in BLI/NBI pattern, and 15 with visible submucosal microvascular varicose under BLI/NBI pattern. As for crypt opening, the pattern mixed type (II, II-O, IIIL, IV) based on Pit II-O type had 15 cases.

Compared to the SSL-D$^-$, the SSL-D$^+$ occurred more frequently in the right colon, and its surface displayed a complex morphology of depressions, nodules, and elevations on a cloud-like surface with a reddish hue. The crypt opening was predominantly of mixed type (II, II-O, IIIL, IV), and the lesion mucosa displayed microvascular varicose. The above endoscopic features of colorectal SSL-D$^+$s were statistically distinct from those of SSL-D$^-$s ($P < 0.05$). In contrast, the differences were not statistically significant ($P > 0.05$) for the lesion diameter exceeding 10 mm, with or without a mucosal cap, and the presence or absence of black spots in the BLI/NBI pattern. The general and endoscopic features data as shown in Table 1.

Independent diagnostic factors of SSL-D$^+$

The right colon, mixed surface morphology, reddish color, mixed crypt opening pattern, and intramucosal microvascular varicose are potential factors for the independent diagnosis of SSL-D$^+$s, according to the univariate analysis. Multifactorial logistic regression analysis of the above factors revealed that the location features of the right colon ($P = 0.172$) and complex pattern of surface shape (*e.g.,* depressions, nodules, and elevations on a cloud-like basis, $P = 0.817$) were not independent diagnostic factors for SSL-D$^+$s. Meanwhile, lesion of reddish color [odds ratio (OR) = 18.705, 95% confidence interval (CI): 3.684-94.974], the finding of microvascular varicose within the mucosa (OR = 6.768, 95%CI: 1.717-26.677), and crypt opening showing the mixed type

(II, II-O, IIIL, IV) based on Pit II-O (OR = 20.704, 95%CI: 2.955-145.086) were independent diagnostic factors for SSL-D$^+$s (Table 2).

DISCUSSION

In this study, a univariate analysis was used to find endoscopic features of potential value in the diagnosis of colorectal SSL-D+s, upon which a multivariate logistic regression analysis was performed to obtain endoscopic features of independent diagnostic value in predicting SSL-D+s and their diagnostic validity. This finding serves as positive guidelines for colonoscopists' immediate endoscopic diagnosis and provides a basis for the use of appropriate endoscopic therapies.

In a population-based case-control study conducted in Denmark, the risk of colorectal cancer was significantly higher in cases of colorectal SSLs than in cases of conventional adenomas[9]. Studies suggest that it takes 7-15 years for colorectal SSL-D$^-$s to progress to SSL-D$^+$s, and after 5-7 years of follow-up, 3.03%-12.5% of SSL patients develop colorectal cancer[10]. SSL-D$^+$s proliferation progresses to colorectal cancer much earlier, with cases reported previously indicating that SSL-D$^+$s progress to invasive submucosal carcinoma within 1-2 years[11-13]. This finding suggests that ignoring SSLs is likely to increase the risk of colorectal cancer in the intermediate stages. Therefore, early identification and treatment of SSLs (especially SSL-D$^+$s) is crucial. Meanwhile, among colorectal SSLs, SSL-D$^+$s are uncommon, and only 28 cases of SSL-D$^+$s are identified in this study, representing 11.07% (28/253), similar to the structure of previous studies[14].

The size of colorectal SSLs > 10 mm positively correlates with SSL-D$^+$s' emergence, but in a study that included 48 cases of SSL-D$^+$s, over one-third of cases had a diameter ≤ 10 mm[15,16]. Consistent with the present study's findings, the size of colorectal SSLs is not an independent diagnostic factor for SSL-D$^+$s. Mucus cap has been confirmed as the primary distinction between colorectal SSLs and HPs; however, it has no diagnostic value for distinguishing the SSL-D$^-$ and SSL-D$^+$, which is consistent with the results of this study[16,17]. With image enhancement endoscopy (*e.g.,* BLI/NBI), the crypt openings of colorectal SSLs frequently exhibit small brownish-black dots with an enlarged crypt.

Considered a critical histological distinction between SSLs and HPs, but this phenomenon has no diagnostic value for SSL-D$^-$s and SSL-D$^+$s[17,18].

In this study, the location of the lesion in the right colon was confirmed as a potential diagnostic factor for the SSL-D$^+$ (P = 0.027), similar to previous studies[19,20]. However, in a multifactorial regression analysis screening for independent diagnostic factors of SSL-D$^+$s, the location was not found to be an independent factor (P = 0.172). This is likely because previous studies have focused on the sensitivity and specificity of the single factor of right hemicolectomy in predicting SSL-D$^+$s without excluding the possibility that other endoscopic features interfere with its independent diagnostic value[4,15,21,22].

In addition, endoscopic examination of the colorectal SSL-D$^+$ reveals the following predominant morphology: (Semi)pedunculated, double elevations, central depressions, and reddishness[16,22]. In the univariate analysis of this study, SSL-D$^+$s endoscopically demonstrated predominantly complex morphology of depressions, nodules, and elevations based on cloud-like surfaces (P = 0.003), indicating that the mixed morphology of the lesion is a potential diagnostic factor, which is consistent with the result of previous studies. However, in the multifactorial regression analysis, the morphology of colorectal SSL-D$^+$s did not have an independent diagnostic value (P = 0.817), which may be explained by the fact that the morphology of SSLs is particularly susceptible to the influence of the examination environment in the intestine, and when factors such as intestinal peristalsis or the amount of gas in the intestinal lumen change, so does the morphology of the lesion.

In this study, the colorectal SSL-D$^+$ is more likely to exhibit a reddish color under conventional white light endoscopy, and this is an independent diagnostic factor for SSL-D$^+$ according to multifactorial regression analysis (OR = 18.705, 95%CI: 3.684-94.974), similar to previous findings[15,16]. It is not difficult to understand that when SSLs with dysplasia or cancer are diagnosed, there is a corresponding increase in the demand for blood supply.

It has been established that intramucosal microvascular varicose differs from the superficial mucosal glands' surrounding microvasculature. Therefore, at sites of colorectal SSL-D$^+$s, there may be dilated and irregular capillaries, and in serrated adenocarcinomas with submucosal infiltration, their surface microvascularity or structure disappears[19,21,23]. In other words, this endoscopic feature is important for suggesting an immediate diagnosis. As this study found, the rate of microvascular varicose is higher in the SSL-D$^+$ group than in the SSL-D$^-$ group and the differences are statistically significant (P = 0.006).

The use of magnified endoscopy to observe SSLs revealed that the appearance of type III, IV, and V crypt open morphologies based on type II-O is a characteristic of the SSL-D$^+$, which is a high-risk marker for the progression of serrated lesions to colorectal cancer[4,19]. In this study, the SSL-D$^+$ crypt opening exhibited mixed (Pit II, IIIL, and IV) type based on Pit II-O (OR = 20.704, 95%CI: 2.955-145.086), this result is in line with previous studies. This study also found that the mixed crypt opening of SSLs also the greater diagnostic validity than the reddish color and intramucosal microvascular varicose.

The following deficiencies persist in this study. First, there is a retrospective, single-center clinical study, and there may be some bias in the endoscopists' subjective evaluations. Second, all the cases included in this study were precancerous, which may lead to bias in the study results. The reason is that if cases of SSL-D$^-$s, SSL-D$^+$s, and SSL cancerous lesions are included, it would be realized to analyze the consecutive complete endoscopic features of such lesions in different stages, and that design might be more convincing. Third, the cases enrolled in the study were discovered by different endoscopists, which inevitably affects the evaluation's consistency.

CONCLUSION

Observation allows endoscopic features of colorectal SSLs to be effectively identified. SSL-D$^+$s should be strongly suspected when lesions exhibit a reddish hue, Pit III, IV, and V mixed crypt opening patterns based on II-O and microvascular varicosity. In

addition, when performing an endoscopic procedure of the SSL-D$^+$, *en-bloc* and curative resection should be strongly ensured.

ARTICLE HIGHLIGHTS

Research background

Missing diagnosis of sessile serrated lesions (SSLs), especially SSLs with dysplasia (SSL-D$^+$s), is an important cause of interstitial colorectal cancer, and in this study, we hoped to find endoscopic features that have independent diagnostic value for SSL-D$^+$s.

Research motivation

Previous studies on the endoscopic features of SSLs have focused on their differentiation from hyperplastic polyps and tubular adenomas, and comparisons of the endoscopic features of SSLs without dysplasia (SSL-D$^-$s) and SSL-D$^+$s have remained at the level of prediction of the sensitivity and specificity of individual endoscopic features. There have been several reports in the literature that SSL-D$^+$s have a risk of faster progression to adenocarcinoma compared to SSL-D$^-$s and conventional tubular adenomas. Therefore, it is important to look for endoscopic features that have independent predictive value for SSL-D$^+$s and assist the endoscopist in making immediate diagnoses.

Research objectives

This study looks for endoscopic features that have independent diagnostic value for colorectal SSL-D$^+$s. These features may help endoscopists to make immediate diagnoses during colonoscopy.

Research methods

In this study, endoscopic features potentially predictive of SSLs were first analyzed by univariate analysis, and then multivariate logistic regression analysis was performed to

obtain endoscopic features with independent diagnostic value for predicting SSL-D$^+$s and the diagnostic validity of these endoscopic features.

Research results

In univariate analysis, location, size, surface shape, color, microvascular varices, and crypt opening pattern of colorectal SSLs had value in predicting SSL-D$^+$s. In multifactorial regression analysis, color, microvascular varices and crypt opening pattern had independent diagnostic value in predicting SSL-D$^+$s.

Research conclusions

Reddish color, microvascular varicose, and mixed pattern of crypt openings are independent diagnostic features for colorectal SSL-D$^+$s.

Research perspectives

This finding is expected to improve the immediate diagnostic accuracy of endoscopists in SSL-D$^+$s in order to inform them to use appropriate endoscopic treatment modalities.

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