GASTROENTEROLOGY

Clinicopathologic features of hyperplastic/serrated polyposis syndrome in Japan

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Abstract
Background and Aim: Hyperplastic/serrated polyposis syndrome (HPS) is a condition characterized by multiple hyperplastic/serrated colorectal polyps. The risk of colorectal cancer (CRC) is increased in HPS. The clinicopathologic characteristics of HPS in Japanese patients are unknown.

The aim of this study is to clarify the clinicopathologic features of HPS in Japanese patients.

Methods: We retrieved records of patients diagnosed with HPS between April 2008 and March 2011 from the endoscopy database of Hiroshima University Hospital. In addition, we mailed a questionnaire to the hospital’s 13 affiliated hospitals in July 2012. Data collected from the database and questionnaires included patient age, sex, number of hyperplastic/serrated polyps and tubular adenomas, size of the largest polyp, polyp location, resection for polyps, coexistence of HPS with CRC, and the diagnostic criterion met.

Results: Of the 73 608 patients who underwent colonoscopy, 10 (0.014%) met the criteria for HPS. The mean age of these patients was 58.3 years, and 6 (60%) were men. No subjects had a first-degree relative with HPS. Four (40%) HPS patients had more than 30 hyperplastic/serrated polyps, and average size of the largest polyp was 19 mm. Three (30%) HPS patients had coexistence of HPS with CRC. In these 3 patients, polyps were observed throughout the colorectum.

Conclusions: Although HPS was a rare condition in the overall study population, patients with the disease may have high risk of CRC. HPS should be diagnosed correctly and followed up carefully.

Introduction

Hyperplastic polyps, either solitary or multiple, are one of the most common lesions of the colorectum. Hyperplastic polyps have traditionally been considered not to have malignant potential. However, recent studies have demonstrated that some hyperplastic polyps can develop into colorectal cancers (CRCs), especially in patients diagnosed as having hyperplastic/serrated polyposis syndrome (HPS).1

HPS is associated with an increased incidence of CRC. In the published series, about 25–70% of patients with HPS have CRC at the time of diagnosis or during follow-up. Increased CRC risk is observed not only in the patients but also in their first-degree relatives. The relative risk of CRC in first-degree relatives compared with the general population has been reported to be 5.4.2 Because HPS has such a high malignant potential, endoscopists need to pay much more attention to the disease.

Until recently, it was thought that adenoma–carcinoma pathway initiation with a mutation of the APC gene accounted for nearly all CRCs, but it has been found that this pathway accounts for only approximately 70–80% of CRCs. The remaining CRCs are thought to follow the serrated pathway (i.e., hyperplastic polyp–serrated adenoma–carcinoma sequence), leading to CpG island methylator-phenotype carcinoma with BRAF mutation and with or without microsatellite instability. In HPS patients, CRCs may arise via the serrated pathway.3–6

Although HPS is such an important disease, there are few reports on its clinicopathologic features. In addition, these reports are all from Western countries; none are from Asian countries such as Japan. Therefore, we evaluated the clinicopathologic characteristics of HPS in Japan, an Asian country.

Methods

We retrieved records of patients diagnosed with HPS between April 2008 and March 2011 from the endoscopy database of Hiroshima University Hospital. In addition, we mailed a questionnaire to the hospital’s 13 affiliated hospitals in July 2012. The
questionnaire comprised questions covering numbers of total colonoscopies performed during the period and numbers of patients diagnosed as having HPS.

A patient was diagnosed as having HPS if at least one of the following criteria (modified from WHO criteria [1, 2, and 3, respectively]) was met: (i) at least five hyperplastic/serrated polyps proximal to the sigmoid colon, two of which were greater than 10 mm in diameter; (ii) any number of hyperplastic/serrated polyps occurring proximal to the sigmoid colon in an individual who had a first-degree relative with hyperplastic polyposis; or (iii) more than 20 hyperplastic/serrated polyps of any size distributed throughout the colon. Magnifying narrow-band imaging (NBI) was used for diagnosis of small (<5 mm in diameter) polyps.\(^5\)^\(^9\) Data collected from the database and questionnaires included patient age, sex, number of hyperplastic/serrated polyps and tubular adenomas, size of the largest polyp, polyp location, resection for polyps, coexistence of HPS with CRC, and the diagnostic criterion met (Table 1).

Table 1 Clinicopathologic features of patients with hyperplastic/serrated polyposis

| Patient no. | Sex | Age | No. of polyps in the colon | Size of largest polyp (mm) | Treatment method | Colorectal cancer | Diagnostic criterion\(^i\) |
|-------------|-----|-----|---------------------------|---------------------------|-----------------|------------------|----------------------|
| 1           | Male| 73  | 20                        | 20                        | ER              | –                | i                    |
| 2           | Male| 82  | >30                       | 10                        | ER              | –                | i                    |
| 3           | Female| 51  | >30                       | 10                        | ER              | –                | iii                  |
| 4           | Male| 87  | 10                        | 20                        | ER              | –                | i                    |
| 5           | Female| 50  | >30                       | 40                        | ER              | +                | iii                  |
| 6           | Male| 64  | 15                        | 15                        | ER              | –                | iii                  |
| 7           | Female| 49  | 15                        | 15                        | ER              | –                | i                    |
| 8           | Female| 46  | >30                       | 20                        | ER              | +                | iii                  |
| 9           | Male| 57  | 10                        | 15                        | Surgical        | –                | i                    |
| 10          | Male| 24  | 10                        | 25                        | Surgical        | +                | i                    |

\(^{i}\)Criterion i: at least 5 hyperplastic/serrated polyps proximal to the sigmoid colon, 2 of which are greater than 10 mm in diameter; criterion iii: more than 20 hyperplastic/serrated polyps of any size distributed throughout the colon. ER, endoscopic resection.

Relative with HPS. Four (40%) HPS patients had more than 30 hyperplastic/serrated polyps, and the average size of the largest polyp was 19 mm.

Three (30%) HPS patients had coexistence of HPS with CRC—in the right colon in two patients and in the left colon in the remaining patient. There were no differences in number of polyps between HPS patients with and without CRC. In these three patients, polyps were observed throughout the colon and were not restricted to the right-side colon. All CRCs were diagnosed at initial colonoscopy. Two of the patients underwent surgery and one patient underwent endoscopic resection. These three CRCs were serrated adenocarcinomas histopathologically (Fig. 3). Three CRC patients have been followed up over 204, 48, and 5 months, respectively, and no recurrences have been detected during the follow-up periods.

Eight (80%) HPS patients were diagnosed in Hiroshima University Hospital, where 14 935 subjects underwent colonoscopy during the study period and 2096 (2.0%) patients were treated endoscopically. The other two (20%) HPS patients were diagnosed in one affiliated hospital, where 8022 colonoscopies were performed. A total of 64 021 colonoscopies were performed in the other 12 hospitals, and no patients were diagnosed as having HPS.

A total of 91 polyps were excised in the 10 HPS patients (2008–2011, mean 9.1 polyps/person, mean 3.0 polyps/person-year). Hyperplastic polyposis comprised 26 (28.5%), SSA/P 34 (37.3%), TSA 7 (7.6%), and tubular adenoma 24 (26.4%) of the 91 polyps. Distinct distribution of polyps was observed in 7 (70%) patients, and proximal colon distribution was seen in the remaining 3 (30%) patients.

Discussion

This is, to our knowledge, the first report on clinicopathologic features of HPS patients in an Asian country. There appeared to be a difference between the previous reports, all from Western countries, and ours in terms of the diagnostic criteria met by the patients, suggesting a difference in the underlying mechanism of HPS.

Recently, Rosty et al.\(^{13}\) reported characteristics of 100 HPS patients. In their report, there were no differences between men and women, and most patients presented with a pancolonic
distribution of polyps. Among the serrated polyps, SSA/Ps were predominant compared with TSAs. Similar findings were observed in the present study: There were no differences between men and women. The pancolonic distribution was predominant (70%), and among the serrated polyps, SSA/Ps were predominant. According to the Rosty et al. report, most patients met WHO criterion 3 (72%) rather than criteria 1 (12%) or 2 (0%). However, in the present study, such a finding was not observed: 5 (50%) patients each met criteria i and iii. There is a significant difference between the frequencies ($P = 0.017$ by Fisher’s exact probability test), and this may be one of the differences between Western and Asian populations.

HPS has been associated with an increased incidence of CRC. In the published series, about 25–70% of patients with HPS had CRC at the time of diagnosis or during follow-up. Boparai et al. reported that CRC occurred in 6.5% of patients during a mean follow-up of 5.6 years. In another report, the total number of polyps was higher in HPS patients with CRC than in those without.

Figure 1  Representative example of hyperplastic/serrated polyposis from patient No. 2. (a) Conventional endoscopic findings. Many polyps are observed in the ascending colon. (b) Endoscopic findings with indigo carmine staining. The largest polyp shows a “pinecone-like” appearance. (c) Histopathologic findings of the largest polyp, original magnification, x40. The crypts show dilation, serration, and irregular branching. (d) Histopathologic findings, original magnification, x400. A uniform population of dysplastic epithelial cells is observed. This polyp is diagnosed as a traditional serrated adenoma.

Figure 2  Another representative example of hyperplastic/serrated polyposis from patient No. 8. (a) Conventional endoscopic findings. Two sessile polyps are observed in the ascending colon. (b) Endoscopic finding with indigo carmine staining. The larger polyp shows a “star-like” appearance. (c) Histopathologic findings of the larger polyp, original magnification, x40. The crypts show dilation, serration, irregular branching, and horizontally arranged L-shapes, inverted T-shapes, or anchor shapes at the base. (d) Histopathologic findings, original magnification, x400. A uniform population of dysplastic epithelial cells is observed. This polyp is diagnosed as a sessile serrated adenoma/polyp.
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CRC, and conventional adenoma was comorbid at a high rate.10 In our study, 30% of HPS patients had CRC, and all had CRC combined with conventional adenoma. As for colorectal polyps in HPS patients, Edelstein et al.14 reported that surveillance colonoscopy of HPS patients revealed that every patient had additional polyps at the next surveillance colonoscopy (mean interval of 1.8 years), with an average 40% increase over the baseline per year in polyp number. Based on these reports, there may be significant risks to HPS patients of CRC developing via the serrated pathway. Therefore, many reports recommend close surveillance colonoscopy and resection of polyps. We recommend that patients undergo an annual colonoscopy and that polyps of 5 mm or more be resected as much as possible, because polyps of 5 mm or more have a risk of developing into cancer.15

Although HPS was initially considered to be non-familial, previously published case series reported that up to 50% of HPS patients have first-degree relatives with CRC.16,17 Based on these reports, a yet unidentified underlying genetic defect would appear to play a role in at least some HPS patients. Recently, it was reported that the relative risk of CRC in first-degree relatives compared with the general population was 5.4.2 In addition, the probability that other family members have HPS when one of them is diagnosed as having HPS is high. Boparai et al.2 reported that the projected relative risk of HPS in first-degree relatives was 39. None of the first-degree relatives of HPS patients in our study were diagnosed as having HPS. This may be because not all of the family members underwent colonoscopy in the present study.

Orłowska et al.18 reported the frequency of HPS to be 0.06% (28/50 148) in asymptomatic subjects who underwent colonoscopy. Lockett and Atkin19 reported a rate of 0.03% (13/40 674) in subjects who underwent flexible sigmoidoscopy. Compared with these reports, the frequency observed in the present study was lower. The frequency of HPS in Asian populations may be lower than that in Western populations; however, there are other possible reasons for this lower rate of observation. One is that Japanese endoscopists may overlook HPS. Although 14 hospitals were included in the present study, patients with HPS were diagnosed in only two hospitals—the university hospital and one affiliated hospital—whereas in the remaining 12 affiliated hospitals, no HPS patients were observed. Knowledge of HPS may not be adequate in Japanese endoscopists. Krishna and Rex20 reported that HPS was common in a cohort of patients with large sessile colorectal polyps and that it was frequently unrecognized. In their study, among 20 patients who met the WHO criteria,1 only one (5%) patient was suspected of having HPS by a referring physician. These data suggest the need for better detection of sessile polyps, better awareness of HPS, and more consistent application of HPS criteria to findings regarding the polyps of individual patients.

In patients who underwent index screening colonoscopy based on fecal occult blood testing, HPS appeared to be more common than in subjects who underwent total colonoscopy (Biswas et al.,21 0.66% [1/151]; Moreira et al.,22 0.34% [1/294]) (Table 2). In patients with large (≥ 2 cm in diameter) sessile colorectal polyps, 4% of the patients were reported to have HPS.10 The frequency of HPS in patients who underwent endoscopic resection was 0.38% in the present study. As described previously, many instances of HPS may be underdiagnosed, and the frequency may be much higher than that in the previous reports and the present study. Further examinations are needed to confirm the frequency.

A recent report showed the presence of large serrated polyps to be a risk factor for CRC.23 HPS patients have many large hyperplastic/serrated polyps. Hyperplastic/serrated polyps arising in HPS progress toward adenocarcinoma through the serrated pathway. The mechanism by which carcinomas arise from this pathway is thought to begin with an activating mutation of the BRAF proto-oncogene, especially in the presence of relatively few,
large, right-sided polyps. This BRAF mutation provokes the development of serrated lesions that are mainly microvascular hyperplastic polyps or sessile serrated polyps.11 These lesions are prone to methylation of CpG islands in the promoter regions of genes such as p16, IGFBP7, and p53, resulting in their epigenetic silencing.24,25 The best-characterized gene silenced by this mechanism is hMLH1. This gene is one of the mismatch repair genes, and its epigenetic silencing results in sporadic tumors with microsatellite instability. However, there is another pathway, associated with KRAS mutation. Serrated adenomas with KRAS mutations are more frequently microsatellite-stable and are frequently associated with MGMT silencing. BRAF mutations have recently been found in 5% to 15% of all CRCs.26

In conclusion, HPS appeared to be a rare condition in the overall study population. However, in patients who underwent endoscopic resection, HPS appeared not to be so rare. Because the disease carries a high risk of developing into CRC, HPS should be diagnosed correctly and followed up carefully. For example, annual colonoscopy may be needed.

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Table 2 Reported prevalence of hyperplastic polyposis

| Author | Frequency (%) | No. of subjects | Screening method |
|--------|---------------|-----------------|-----------------|
| Lockett and Atkin (2001, UK) | 1/3000 (0.03) | 40,674 | Flexible sigmoidoscopy, followed by colonoscopy if > 20 distal polyps were found |
| Orlowska et al. (2012, Poland) | 1/1791 (0.06) | 50,148 | Total colonoscopy |
| Biswas et al. (2013, USA) | 1/151 (0.66) | 755 | Index screening colonoscopy after positive gFOBT |
| Moreira et al. (2013, Spain) | 1/294 (0.34) | 2355 | Index screening colonoscopy after positive gFOBT |
| Present study (2012, Japan) | 1/7361 (0.01) | 73,608 | Total colonoscopy |

gFOBT, stool guaiac test for fecal occult blood.
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