Development of Invasive Colon Cancer with Microsatellite Instability in a Patient with Hyperplastic Polyposis Syndrome

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The serrated pathway has recently been proposed as a route for the development of colorectal cancer with microsatellite instability. Hyperplastic polyposis syndrome is a rare syndrome defined by the presence of numerous serrated polyps, with a high risk of developing into colorectal cancer. We present here a case of hyperplastic polyposis syndrome developing into colorectal cancer with microsatellite instability from a serrated polyp.

BRAF mutation and the loss of MLH1 protein were observed in the colorectal cancer, but not in the other serrated polyps around the colorectal cancer, suggesting that colorectal cancer with microsatellite instability develops rapidly from a specific serrated polyp with distinct molecular properties.

Key words: hyperplastic polyposis – colorectal cancer – serrated pathway – microsatellite instability – BRAF mutation

INTRODUCTION

Hyperplastic polyps (HPs) traditionally have been considered to have little malignant potential. HPs are histologically ‘serrated polyps’ that are characterized by a sawtooth architecture. In 2003, Torlakovic et al. classified serrated polyps according to histologic features as HPs, traditional serrated adenomas and sessile serrated adenomas (SSAs) (1).

Among serrated polyps, SSAs have unique characteristics with regard to their clinical and genetic background, such as a proximal dominant location, a high frequency of BRAF mutations and a CpG island methylator phenotype (CIMP) (2). Therefore, SSAs have been claimed to represent precursor lesions for colorectal cancer (CRC) showing microsatellite instability-high (MSI-H), which has similar clinical and biological characteristics to SSAs (serrated pathway).

Hyperplastic polyposis syndrome (HPS) is a rare syndrome defined by the presence of numerous serrated polyps (mainly HPs and SSAs) and is associated with a high risk of developing CRC (3,4). The high incidence of CRC in HPS patients proved that the serrated polyp-MSI pathway definitely works. However, although SSAs have been reported to tend to show relatively rapid growth (5,6), few reports have elucidated the progression speed and morphological change during the transition from SSA to CRC. It is also largely unknown what type of polyps develops into CRC with MSI among the many polyps present in HPS.

We present here a case of HPS that developed rapidly into CRC with MSI, accompanied by a distinct morphological change from SSA. Moreover, molecular analysis of the tumor and the surrounding benign serrated polyps was performed to elucidate the key molecular mechanisms in the development of CRC with MSI from SSA.
CASE REPORT

CLINICAL FEATURES

A 62-year-old man had been followed up in Fukuyama Medical Center since 2007 due to the presence of numerous polyps throughout the colon, especially in the proximal colon. He had undergone surgical resection for rectal cancer in 2007 and endoscopic submucosal dissection for sigmoid colon cancer in 2008. He had no family history of CRC. In September 2008, a colonoscopy revealed multiple smooth, sessile polyps throughout the entire colon (ranging from 5 to 20 mm). A biopsy of three sessile polyps located in the cecum and one sessile polyp located in the ascending colon was performed, and the histological diagnosis of all of the specimens was HP at that time. However, the review of the histology afterwards revealed that the polyp which developed into cancer was diagnosed as SSA due to the presence of exaggerated serration, increased proliferation and mild nuclear changes.

This patient fulfilled the World Health Organization criteria for HPS. Therefore, colonoscopy was performed repeatedly for cancer surveillance. The serrated polyps in the cecum appear to show mild changes in June 2009. However, in November 2009, advanced CRC was found in the cecum (Fig. 1A). This patient underwent ileocecal resection soon after the colonoscopy.

PATHOLOGICAL AND MOLECULAR FEATURES

The CRC in the cecum macroscopically presented a depressed lesion with a circumferential embankment, 15 × 13 mm in diameter (Fig. 1B). The tumor consisted of histologically moderately differentiated adenocarcinoma invading into the muscularis propria. The resected specimen showed neither coexistence of adenoma nor serrated lesion, suggesting that such transitional phases had already diminished at resection. Mild lymphatic invasion, but no vascular invasion, was observed in the tumor (Fig. 1C). There were not significant lymphocyte aggregations which are typically shown in cancer with MSI. One of the eight dissected lymph nodes contained metastasis. In the resected specimen of the colon, there were five sessile polyps around the CRC.

We examined the molecular features of the CRC and five serrated polyps in the resected specimen (Fig. 2). Mutations in \( \text{BRAF} \) (V600E) and \( \text{Kras} \) (codon-12 and -13), methylation and protein expression of \( \text{MLH1} \), and MSI status were analyzed. The CRC showed \( \text{BRAF} \) mutation and wild-type \( \text{Kras} \), accompanied by extensive methylation of \( \text{MLH1} \) and loss of \( \text{MLH1} \) protein (Fig. 2A–D). MSI analysis of the tumor showed MSI-H (Fig. 2E). On the other hand, all five serrated polyps showed no \( \text{BRAF} \) mutation, no loss of \( \text{MLH1} \) and no MSI. Of the five serrated polyps, two had \( \text{Kras} \) mutation and three showed partial methylation of \( \text{MLH1} \) (Fig. 2B and C, and Table 1).

DISCUSSION

We experienced a case of HPS developing into CRC with MSI within a short interval accompanied by a distinct morphological change from SSA. MSI-H was observed with extensive methylation of \( \text{MLH1} \) and loss of \( \text{MLH1} \) protein in this CRC. In contrast, neither MSI nor loss of \( \text{MLH1} \) protein
was observed in any of the other serrated polyps examined. Because $MLH1$ silencing has been considered to be a critical, rate-limiting step in the development of CRC with MSI (7–9), the loss of $MLH1$ due to extensive methylation of the promoter region followed by microsatellite unstable status is highly likely to be responsible for the rapid growth (10) from SSA to advanced CRC. In addition, genetic analysis of HPs around the tumor revealed that HPs with or without $Kras$ mutation, but absolutely without $BRAF$ mutation, did not show morphological changes. Therefore, it is reasonable to consider that only SSA with $BRAF$ mutation can develop rapidly to CRC in HPS and probably in sporadic conditions. Moreover, $Kras$ mutation may be a marker of HPS that will never progress into CRC.

Previous reports also showed the progression of SSA into cancer within a short interval (5,6). Oono et al. (6) reported the progression of SSA into cancer with submucosal invasion within 6 months showing slight morphological change. Boparai et al. (5) reported that one case of interval cancer among the 77 HPS patients showed progression within
7.7 months into T3 cancer. However, these reports lacked genetic analysis and did not elucidate the molecular changes responsible for such rapid progression. Goldstein (8) reported eight cases of small SSAs with minimum invasive cancer or high-grade dysplasia with loss of MLH1, but that report did not show morphological changes of such lesions nor their speed of progression. Based on our case and these previous cases, we can conclude that SSA can proceed to CRC very rapidly through the serrated-MSI pathway.

Because of increased risk of malignant progression, HPS patients should undergo endoscopic surveillance with removal of polyps or surgical colonic resection. East et al. (11) proposed the following management strategy for HPS patients: colonoscopy every 1–2 years with removing all polyps > 5 mm in size, or colectomy with ileorectal anastomosis. Based on our findings in this case report, the critical polyps with a high risk of rapid progression are SSAs with BRAF mutation. Because most such polyps are located on the right side of the colon, the removal of polyps from the right-side colon or right hemicolectomy may be sufficient. In sporadic conditions, all polyps suspicious of SSA (larger in size, sessile morphology, coverage with abundant mucus, nodular or granular surface, irregular or vague margin) in the right colon should be resected (12).

Although we had performed colonoscopy within a short interval in this case, tumor at resection was proved to be an invasive cancer. In a retrospective point of view, detailed endoscopy such as chromoendoscopy with magnification may have revealed evidence of cancer at September 2008, or at least, June 2009. Thus, our case also suggests that surveillance for HPS patients requires an intensive work-up of endoscopic observation by using magnifying colonoscopy if removal of polyps is not immediately done.

In conclusion, we observed a case of HPS that rapidly progressed to CRC derived from proximal SSA. This case confirmed the following steps of progression in a serrated pathway: mutation of BRAF occurs first, then CIMP is established slowly, and once MSI develops, the genetic changes rapidly drive further malignant progression.

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Conflict of interest statement
None declared.

References