CASE REPORT

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# Hyperplastic Polyposis Syndrome Identified with a *BRAF* Mutation

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Hyperplastic polyposis syndrome (HPS) is a rare condition characterized by the presence of numerous hyperplastic polyps (HPs) in the colon and rectum. Patients with HPS have an increased risk of colorectal cancer. This link is associated with gene mutations, especially B type Raf kinase (*BRAF*). However, a case of HPS associated with gene mutations has seldom been reported in Korea. Here, we describe a case of HPS in which a *BRAF* mutation was present in a 34-year-old woman. She had more than 110 HPs in the stomach and colorectum, which we removed. All of the polyps were diagnosed histologically as HPs, and no adenomatous or malignant changes were noted. We performed a *BRAF* and *K-ras* mutation analysis as well as a microsatellite analysis on the resected colon polyps. *BRAF* mutations were found in the resected colon polyps, but there was no evidence of *K-RAS* mutation or microsatellite instability. **(Gut Liver 2012;6:280-283)**

**Key Words:** Hyperplastic polyposis syndrome; *BRAF*

## INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers in the world. CRCs usually progress from adenomatous polyps, and the morphological and genetic progression of CRCs in an adenoma-adenocarcinoma sequence has been well described.[1,2] A hyperplastic polyp (HP) is the most common histological type found among colorectal polyps, but they have been considered to have no malignant potential. However, recent studies have demonstrated that some HPs can develop into CRCs, especially in patients diagnosed with hyperplastic polyposis syndrome (HPS).[3,4] Recent studies have proposed that HPs arising in HPS progress toward adenocarcinoma through a "serrated neoplastic pathway" and that a B type Raf kinase (*BRAF*) proto-oncogene mutation is one of the early genetic events in the initiation of this serrated pathway.[4-6] *BRAF* mutations have recently been found in 5% to 15% of CRCs.[7-9] We present a case of a 34-year-old young woman with HPS who had a *BRAF* mutation.

## CASE REPORT

A 34-year-old young woman visited our hospital for a general health check. She had no family or personal history of colorectal carcinoma or other bowel diseases. However, she underwent a fine-needle aspiration biopsy (FNAB) for incidentally discovered thyroid nodules 2 months previous. The FNAB of these nodules demonstrated bland-looking follicular cells. Her complete blood count showed no abnormal findings, and other laboratory tests and thyroid function tests were within the normal range. She underwent an esophagogastroduodenoscopy and colonoscopy. At the esophagogastroduodenoscopy, numerous 0.2 to 0.7-cm-sized polyps were seen in the body and antrum of the stomach (Fig. 1). However, no lesions were observed in the bulb or secondary portion of the duodenum. During the colonoscopy, numerous 0.2 to 1.0-cm-sized polyps were also observed in the transverse colon, sigmoid colon and rectum. The polyps were mainly distributed on the sigmoid colon and rectum. An upper gastrointestinal series showed no lesions in the small bowel. We removed 48 and 70 polyps from the stomach and colorectum, respectively. A histological examination of the resected polyps revealed HPs (Fig. 2). Based on our findings, the patient was diagnosed with coexisting HPS and gastric hyperplastic polyposis. We performed a *BRAF* and *K-RAS* mutation analysis as well as a microsatellite analysis on the representative HPs of the colon. *BRAF* mutations were found in the resected colon polyps (Fig. 3). The *BRAF* mutation identified was a missense mutation at codon 600, exon 15 replacing GTG (valine) with GAG (glutamic acid). A *K-RAS* mutation and microsatellite

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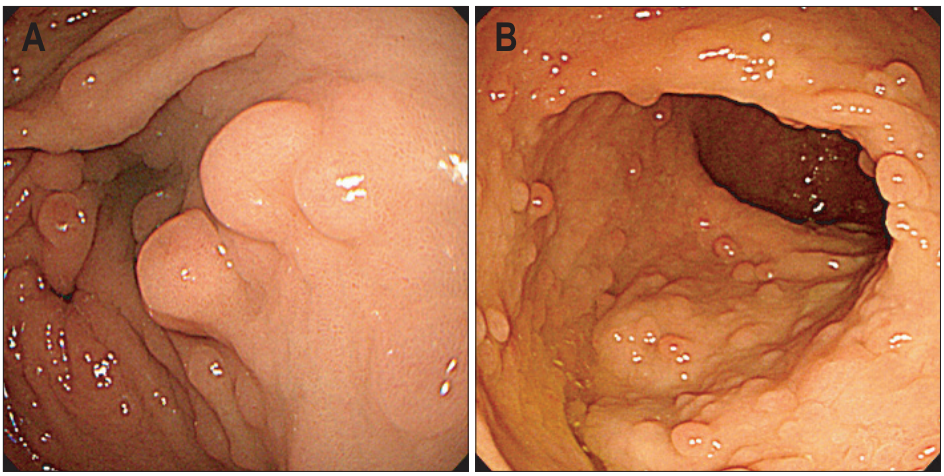


**Fig. 1.** (A) Esophagogastroduodenoscopic findings revealed numerous 0.2- to 0.7-cm-sized polyps on the antrum of the stomach. (B) The colonoscopic findings revealed numerous 0.2- to 0.6-cm-sized polyps on the rectum.

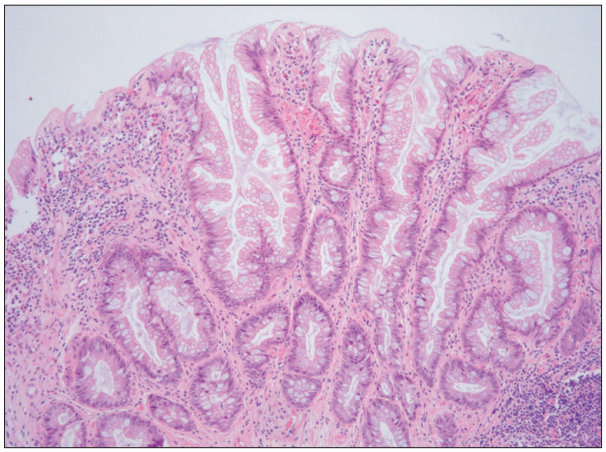

**Fig. 2.** Photomicrographs of a colon polyp. A hyperplastic polyp exhibiting crypt serration and regular architecture with minimal crypt branching (H&E stain, ×100).

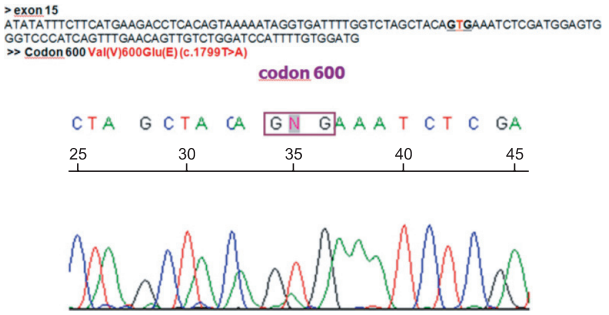


**Fig. 3.** B type Raf kinase (*BRAF*) mutation analysis. Direct DNA sequencing revealed a *BRAF* mutation at codon 600 and replacement in exon 15 of GAG (glutamic acid) with GTG (valine).

instability (MSI), however, were not detected. The patient was discharged without complications and is on regular follow-up.

## DISCUSSION

Sporadic HPs are of a benign nature and are usually small in size, multiply, increase with old age, and are mainly distributed in the sigmoid colon and rectum. However, CRCs arising in colorectal HPs or serrated adenomas (SAs), especially in patients diagnosed with HPS have been reported.[10-14] Additionally, recent studies proposed the HP-SA-carcinoma sequence as an alternative pathway for colorectal carcinogenesis.[4,15,16] HPS is an uncommon syndrome characterized by a diverse range of polyp types including multiple, large HPs and smaller numbers of SAs, traditional adenomas, and admixed hyperplastic/adenomatous polyps in the colon and rectum. In the World Health Organization (WHO) HPS diagnostic criteria, Burt and Jass[17] defined HPS as at least five histologically diagnosed HPs occurring proximal to the sigmoid colon and of which more than two are greater than 1 cm in diameter, or more than 30 HPs in the whole colon and rectum, or any number of HPs proximal to the sigmoid colon in an individual who has a first-degree relative diagnosed with HPS. In such patients, polyps are usually sessile and 1-7 mm in diameter, but larger and/or pedunculated HPs may also be observed. Some patients had adenomas or CRCs.[18-20] HPs of HPS progress to CRCs through the serrated pathway and a *BRAF* mutation is a key genetic event in the initiation of the serrated neoplastic pathway in the development of CRC.[4-6] The risk of malignant changes in HPs seems much higher when the HPs have histologically dysplastic features such as admixed polyps and SAs or when they are large, numerous, located on the right-sided colon, and present in younger patients.[21,22] Genetic and epigenetic alterations in colorectal carcinoma are present in HPS. These alterations include *BRAF* or *K-RAS* proto-oncogene mutations and MSI .[14,23,24] *BRAF* makes a protein called B-RAF which is one of the members of the RAF family of serine/threonine kinases. B-RAF mediates cellular responses to growth signals through the RAS-RAF-MEK (mitogen-activated protein/extracellular signal-regulated kinase)-ERK (extracellular signal-regulated kinase)-MAP (mitogen-activated protein) kinase pathway.[25,26] *BRAF* mutations have been found in various human cancers including CRCs and melanomas.[7,9,27-30] They have also been found in sporadic HPs and in SAs from patients with hyperplastic polyposis.[6,31,32] *BRAF* mutations are frequent in

CRCs with a high level of MSI, but uncommon in microsatellite-stable CRCs.[27-30] The frequency of *BRAF* mutations is much higher in HPS, especially younger patients and patients with large and right-sided polyps than in sporadic HPs which are predominantly present in the left-sided colon or rectum.[23] In contrast, *K-RAS* mutations are infrequent in HPS, but frequent in sporadic HPs.[14] Unlike *BRAF*, *K-RAS* mainly plays a key role in the development of CRC through the classical adenoma-adenocarcinoma sequence, allowing the growth and progression of adenomatous colorectal polyps.[33] Some reports have demonstrated that *BRAF* and *K-RAS* mutations are strongly inversely correlated.[7-9] It is rare that both *BRAF* and *K-RAS* mutations are present in different polyps from the same patient.[24] Therefore, molecular data such as *BRAF* or *K-RAS* can help in diagnosing HPS. In our case, the 34-year-old young woman had 48 and 70 0.2 to 1.0-cm-sized HPs in the stomach and large bowel respectively. We diagnosed HPS with gastric hyperplastic polyposis according to the WHO diagnostic criteria. We confirmed a *BRAF* mutation in the colon polyps. But, she had no *K-RAS* mutation and MSI. A case of HPS identified with a *BRAF* mutation has been reported in only one case in Korea until now.[34] Furthermore, HPS with multiple gastric HPs is very rare. We think that genetic alterations such as *BRAF* mutations in HPS may be frequently seen in patients who have hyperplastic polyposis in the stomach, colorectum or both. Although our case had no adenomatous or malignant changes, such patients may more frequently be accompanied with adenomatous or malignant changes in polyps. Because HPS with a *BRAF* mutation may carry a high risk for CRC, colonoscopic surveillance should be indicated. Endoscopic surveillance is recommended every 1 to 3 years for patients with hyperplastic polyposis.[18] This endoscopic surveillance interval may be modified by other risk factors such as age, family or personal history of CRC, histology of polyps, and genetic mutations such as *BRAF*, and so on.[35]

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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