Hirschsprung’s Disease in a Patient with Familial Adenomatous Polyposis

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Abstract
The case of a 14-year-old Japanese female who had a past history of Hirschsprung’s disease is reported. Five members of her family had been diagnosed as having familial adenomatous polyposis (FAP). She had multiple polyps in her large intestine, stomach, and duodenum. She was also diagnosed as having FAP and underwent surgery at our hospital. To the best of our knowledge, this is the first report of Hirschsprung’s disease associated with FAP.

Key words: familial adenomatous polyposis, Hirschsprung’s disease, adenomatous polyposis coli gene

Introduction
Hirschsprung’s disease is a disorder characterized by absence of intrinsic ganglion cells in the distal gastrointestinal tract. Familial occurrence of Hirschsprung’s disease has been reported, and mutations in several susceptibility genes have been identified. On the other hand, familial adenomatous polyposis (FAP) is an autosomal-dominant inherited colorectal cancer predisposition syndrome and is known to be caused by germline mutations in the adenomatous polyposis coli (APC) gene. A young female patient who underwent surgery for treatment of FAP 14 years after she had undergone surgery for treatment of Hirschsprung’s disease is presented.

Case Report
A 2-month-old female who had been diagnosed as having Hirschsprung’s disease underwent a sigmoid colostomy. Sigmoideotomy with a narrowing segment resection (Duhamel method) was performed at the age of 12 months. Microscopic examination of the resected specimen showed that ganglionic cells were not present in the nervous plexus of the resected colon tissue, supporting the diagnosis of Hirschsprung’s disease. However, there were no polyps in the specimen. At the age of 14 years, the patient was seen at our hospital for gastrointestinal tract examination because five of her family members had been diagnosed as having FAP (Fig. 1). She had not undergone any gastrointestinal examinations after the operation for Hirschsprung’s disease. On barium enema and endoscopy of the colon, multiple polyps were seen throughout her large intestine (Fig. 2a, c), suggesting FAP. Endoscopic examination of the upper gastrointestinal tract also showed the presence of multiple polyps in the stomach and duodenum (Fig. 2d). Examination of biopsy samples from the polyps in the stomach and duodenum revealed tubular adenomas. Subsequent computed tomography showed a 7-cm-diameter ovarian cyst in the pelvic cavity and remnant staples in the rectum wall that had been used during the operation to treat Hirschsprung’s disease (Fig. 2b). The patient was diagnosed as having FAP and underwent a total colectomy and mucosal proctectomy with a 15-cm, ileal J-pouch-anal anastomosis and ileostomy. Pathological examination of the large intestine polyps revealed that they were tubular adenomas with no evidence of malignant change. Her postoperative
Fig. 1 Pedigree of the patient's family. The patient's grandfather, father, uncle, and two brothers were diagnosed as having FAP, and no members of her family had been diagnosed as having Hirschsprung's disease. ○=female (living); □=male (living); ◯=female (deceased); ×=male (deceased). The numbers are the ages at death.

Fig. 2a Barium enema examination showing multiple polyps in the rectum. The arrows indicate remnant staples that had been used during surgery to treat Hirschsprung's disease.

b CT image showing an ovarian cyst (arrow heads). The arrows indicate the remnant staples.

c Colonoscopic image showing the presence of multiple polyps throughout the large bowel.

d Gastroduodenoscopic image showing the presence of multiple polyps in the duodenum.
Hirschsprung’s disease with FAP

course was unremarkable, and the ileostomy was closed 1 year later.

Discussion

FAP is one of the most well-characterized inherited bowel diseases; it presents clinically with multiple adenomatous polyps in the gastrointestinal tract. The adenomatous polyposis coli (APC) gene has been identified as the gene responsible for FAP. The APC gene is one of the components of the Wnt signaling pathway and regulates the stability of cytoplasmic β-catenin in the Axin complex, acting as an onco-suppressor gene. Mutations in the APC gene have been found not only in cases of FAP but also in most cases of sporadic colorectal cancer. It is believed that patients with FAP showing an autosomal dominant mode of inheritance have a germline mutation or loss of heterozygosity in one allele of the APC gene, and that a somatic mutation in the APC gene occurs in another allele. Loss of function of APC results in accumulation of β-catenin protein in cells, promotion of cell proliferation, and, in some cases, the development of multiple adenomas. FAP is characterized by the development of multiple adenomatous polyps in the colon and rectum. Several other extra-colonic manifestations, including stomach and duodenal polyps, as were observed in the present case, have been reported. However, there are no reports of an association between FAP and congenital megacolon or aganglionicism. Hirschsprung’s disease is an early childhood disease characterized by megacolon and a following narrow segment of large bowel as a result of the absence of intramural ganglion cells. It has been reported that Hirschsprung’s disease occurs familiarly in approximately 4% of cases. Mutations in the RET gene have been identified both in familial and sporadic cases of Hirschsprung’s disease. Furthermore, transgenic mice studies have demonstrated the importance of RET in Hirschsprung’s disease. In the present case, the diagnosis of FAP was evident from the patient’s family history. Judging from her family history, the Hirschsprung’s disease might not have been familial, although genetic analyses were not performed. To the best of our knowledge, there have been no reports of an association between FAP and aganglionicism or congenital megacolon, or an association between Hirschsprung’s disease and intestinal polyposis. Based on the present patient’s clinical features and family history, she might be a case of FAP with incidental, sporadic Hirschsprung’s disease. We believe that this is the first report of a case of FAP associated with Hirschsprung’s disease.

References