Hereditary Nonpolyposis Colorectal Cancer Associated with Duodenal Carcinoma: a Case Report

Kazuho Konishi1,4, Hisao Tajiri1, Takahiro Fujii1, Narikazu Boku1, Atushi Ohtu1, Shigeaki Yoshida1, Masaru Konishi1, Takahiro Hasebe3, Kiyoshi Mukai3 and Reiko Makino4

1Endoscopy Division and 2Surgery Division, National Cancer Center Hospital East, Kashiwa, Chiba, 3Pathology Division, National Cancer Center Research Institute East, Kashiwa, Chiba and 4Second Department of Internal Medicine, Showa University School of Medicine, Tokyo, Japan

Hereditary nonpolyposis colorectal cancer is an autosomal, dominantly inherited disease, characterized by an early age of onset, right colon predominance and an association with various extracolorectal malignancies. We present a case of a 47-year-old woman who met the clinical criteria for the diagnosis of hereditary nonpolyposis colorectal cancer from her past and family histories. She had undergone operations for uterine cancer (histology not confirmed) at age 35 and for advanced cancer of the ascending colon at age 45. Gastroendoscopy revealed a flat elevated lesion, 20 mm in size, with a protrusion (type IIa + IIs) in the second portion of the duodenum in March 1996. Additionally, colonoscopy showed a flat elevated lesion, 30 mm in size, with an irregular and nodular surface (type IIa, laterally spreading tumor) in the descending colon. After the operation, the resected specimen of the duodenum histologically showed a well-differentiated adenocarcinoma associated with a tubulo-villous adenoma which had invaded the submucosal layer. The tumor of the colon was histologically confirmed to be a moderately-differentiated adenocarcinoma with submucosal invasion. A high frequency of replication error positivity (4/5 loci) was detected in both of the tumors. Reports of early cancer of the duodenum, associated with extracolorectal malignancies in hereditary nonpolyposis colorectal cancer, are very rare in the literature. Although it is difficult to determine which extracolorectal tumor sites should be taken into consideration by screening programs, we believe that careful observation by upper gastrointestinal endoscopy, which includes the duodenum, is necessary for patients with hereditary nonpolyposis colorectal cancer.

Key words: hereditary nonpolyposis colorectal cancer – early duodenal carcinoma – replication error

INTRODUCTION

Hereditary nonpolyposis colorectal cancer (HNPPC), which is known as Lynch syndrome, is a common autosomal dominant condition which predisposes a patient to cancer of the colon and rectum (1,2). In addition, a high frequency of certain specific extracolonic malignant neoplasms have been found in families with HNPPC. Significantly increased risks have been reported for cancer of the endometrium, stomach, small bowel, upper urological tract (ureter and renal pelvis) and ovary in HNPPC (3). However, reports of early cancer of the duodenum, which is associated with HNPPC, are very rare. In this report, we describe a case of HNPPC associated with an early duodenal cancer, with a discussion of the relevant literature.

CASE REPORT

The patient was a 47-year-old woman who had occasionally suffered from epigastralgia in December 1995. She consulted a local physician in February 1996. The duodenal tumor was detected by an upper gastrointestinal endoscopy. She was therefore admitted to the National Cancer Center Hospital East for further examination on March 7, 1996. The patient's past history revealed that she had undergone operations for uterine cancer (histology not confirmed) at age 35, and for advanced cancer in the ascending colon at age 45. Her pedigree included three patients with advanced cancer of the colon, two patients with uterine cancer and one patient with hepatocellular carcinoma.
HNPCC associated with duodenal carcinoma

(Fig. 1). Therefore, a diagnosis of HNPCC was made, according to the clinical criteria, based on her past and family histories (4).

The physical examination revealed a slight tenderness in the epigastrium. Her laboratory data including tumor markers were all within the normal ranges.

Hypotonic duodenography showed an irregularly elevated lesion with a depression, 20 mm in diameter, in the second portion of the duodenum. The view of the lateral side showed a deformity of the wall (Fig. 2). Endoscopy revealed the lesion as a flat elevation, a part of which had large nodules, and was diagnosed as being a IIa + Ia type early duodenal cancer (Fig. 3) (5).

Colonoscopy for the preoperative screening program showed a flat elevated lesion, measuring approximately 30 mm in diameter, with a smooth surface, in the descending colon. After spraying with indigocarmine, the irregular and nodular surface of the lesion was clearly demonstrated (Fig. 4). A double contrast study of this lesion showed a flat elevation with an irregular margin. This lesion was diagnosed as early colonic cancer [type IIa; laterally spreading tumor (LST) in Kudo’s classification of early colorectal cancer (6)], associated with an adenomatous component. The patient underwent a distal duodenectomy and partial colectomy in March 1996. No swelling of the regional lymph nodes was observed intraoperatively.

Macroscopically, the duodenum had an irregularly flat elevation with a large protrusion in the anal margin (type IIa + Ia), measuring 20 × 20 mm in size (Fig. 5a). Histologically, the tumor was a well-differentiated adenocarcinoma with tubulo-villous adenoma. Cancer cells were located in the flat elevation and had invaded the submucosal layer (Fig. 5b). The resected specimen of the large intestine showed a superficially elevated lesion with a central shallow depression, measuring 28 × 21 mm in size (type IIa; LST) (Fig. 6a). Stereomicroscopic pictures showed a type IIIa + IV pit pattern (6). Histologically, the central shallow depressed portion of the lesion consisted of moderately-differentiated adenocarcinoma which had invaded the submucosal layer, and the other part showed features of tubular adenoma with severe atypia (Fig. 6b).

RER ANALYSIS

In this case, analysis of microsatellite instability (replication error, RER) was carried out on both the duodenal and the colonic tumors. Serial 10 μm paraffin sections of these tumors were microscopically dissected to separate the cancerous or adenomatous region from the normal region. DNA was obtained from these sections with a DNA isolator PS kit (Wakko Pure Chemical Industries Ltd., Japan). Polymerase chain reaction (PCR) was performed to amplify DNA from the tumors and the correspond-
Figure 4. Colonoscopic examination in the descending colon. Endoscopic findings after spraying indigocarmine dye reveal a flat elevated lesion with an irregular and nodular surface.

Figure 5. (a) Resected specimen of the duodenum reveals an irregularly flat elevation with a large protrusion in the anal margin (type IIa + IIs), measuring 20 × 20 mm in size. (b) Low power view of the tumor showing cancer cells in the flat area and invasion of the submucosal layer.

Figure 6. (a) Resected specimen of the descending colon shows a superficial elevated lesion (type IIa; LST) with a central shallow depression, 28 × 21 mm in size. (b) Histological findings show moderately differentiated adenocarcinoma in the center of the lesion with submucosal invasion.

Figure 7. (a) Resected specimen of the duodenum reveals an irregularly flat elevation with a large protrusion in the anal margin (type IIa + IIs), measuring 20 × 20 mm in size. (b) Low power view of the tumor showing cancer cells in the flat area and invasion of the submucosal layer.

The criteria for HNPCC have been proposed by the International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer (ICG-HNPCC) (11). These are known as the ‘Amsterdam criteria’ and are as follows: 1, three or more relatives with histologically verified colorectal cancer (CRC), one of whom is

**DISCUSSION**

The criteria for HNPCC have been proposed by the International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer (ICG-HNPCC) (11). These are known as the ‘Amsterdam criteria’ and are as follows: 1, three or more relatives with histologically verified colorectal cancer (CRC), one of whom is
a first-degree relative of the other two; 2, CRC involving at least two generations; and 3, one or more CRC cases diagnosed before age 50. All of these criteria are essential for the diagnosis of HNPCC. These criteria are used internationally to obtain more uniform data from different institutions. It has been estimated that HNPCC, fulfilling the Amsterdam criteria, accounts for approximately 5% of all colorectal cancer cases (1,2). In Japan, the frequency is approximately 0.2%, as estimated by the survey of the 34th Japanese Society for Cancer of the Colon and Rectum (12).

In Japan, Clinical Criteria for HNPCC have also been proposed by the Japanese Research Society for Cancer of the Colon and Rectum (4). These criteria are different from the Amsterdam criteria in the elimination of pathologic diagnosis and existence of subcriteria in high risk patients, together with relaxation of the family history requirement. That was intended to identify as many HNPCC patients as possible and to overcome the difficulty or impossibility of obtaining a complete family history. In this case, the patient fulfilled the clinical criteria. Since World War II, families in Japan have tended to be smaller. Small families seldom meet the Amsterdam criteria, when one or more of the family members have had an extracolonic malignancy. Japanese clinicians should consider not only the Amsterdam criteria but the clinical criteria when a family shows some features of HNPCC.

CRC of HNPCC develops earlier than in sporadic CRC, and the incidence of CRC is 61–64% (1). A large American series of patients with HNPCC had synchronous CRC in 18.1% and metachronous CRC in 24.2% of the patients (13). It has been described that adenomas in HNPCC are not numerous but tend to be large, with a villous growth pattern and a higher degree of dysplasia than sporadic adenomas (14,15). The proclivity to multiple tumors, including extracolonic tumors such as cancers of the endometrium, stomach, urologic system, ovary, brain and small bowel, is one of the main features of HNPCC (3,16). There has been no overrepresentation of duodenal cancer associated with HNPCC in Medline from 1986 to 1996. However, duodenal cancer may have been included in the group of small bowel cancers in HNPCC, because the frequency of primary duodenal cancer is excessively low. The incidence of tumors of the endometrium, stomach, urologic system, biliary tract, small bowel and ovary are 9–12%, 4–6%, 2–5%, 2–4%, 1–3% and 1–3% respectively (1). With respect to extracolonic cancers in Japan, stomach cancer in males and uterine cancer in females are the most common secondary cancers in HNPCC (12).

An effective screening program is required for the early detection of easily treatable lesions in HNPCC patients and their families. The screening of colorectal carcinoma includes an initiation of a full colonoscopy by age 20–25, with repeated procedures every other year through age 30, and annually thereafter (17). Mecklin et al. suggested that gynecologic examinations (pelvic examination, transvaginal ultrasonography and endometrial biopsy) should be performed for women older than 30 to 35 years (1). Screening of other extracolonic malignancies should be considered individually in each country or institution. For examination of the stomach, endoscopy is readily available, especially in Japan. In contrast, the examination of areas such as the small bowel or the urinary tract is difficult. In Japan, practical screening programs for HNPCC may primarily include surveillance for colorectal cancer, gastric cancer and endometrial cancer. Although it is difficult to decide which extracolorectal tumor sites should be screened, we suggest that careful observation by upper gastrointestinal endoscopy, which includes the duodenum, is necessary for patients with HNPCC.

The frequency of flat adenoma has been found to be extremely high in HNPCC patients (18). One of the most remarkable features of flat adenomas is a high malignancy rate, as compared with that of other types of polyps in the colon and rectum (19,20). In addition, Adachi et al. reported that patients with flat adenoma have a significant hereditary background (20). Therefore, flat adenoma may be a morphologic marker for the identification of at least one subset of HNPCC. Moreover, it has been reported that the flat adenoma may play an important role in the development of colorectal carcinoma in some groups of HNPCC patients (18). The duodenal tumor in our case was a flat elevated type with submucosal invasion which was similar to the tumor in the colon detected at the same time. Both lesions were composed histologically of an adenoma component and cancer component. This fact was consistent with the above assumption.

In a recent study, genetic instability was observed to be one of the most important predispositions for human multistep carcinogenesis. Microsatellite instability caused by RER has been found in several colorectal carcinomas, including those from patients with HNPCC (21,22). HNPCC is caused by inherited mutations in DNA mismatch repair genes such as hMLH1 (23), hMSH2 (24), hPMS1 and hPMS2 (25). Severe microsatellite instability in a tumor with alterations in 3–5 loci supports the presence of hereditary defects in one allele of the DNA mismatch repair gene in an HNPCC microsatellite instability (26). In our case, both the duodenal and the colonic tumors demonstrated severe RER positive (RER+) (altered loci: 4 of 5). The portion of the adenoma which was included in these RER+ tumors showed pronounced RER-positivity. Muta et al. reported that the clinical criteria proved a good alternative for identifying legitimate
HNPCC patients who were excluded by the minimum criteria (27). The presence of severe RER+ tumors in this case, which fulfilled the clinical criteria, may provide additional evidence that these criteria are appropriate for identifying as many HNPCC patients as possible. Inactivation of the TGF-βRII gene is frequently observed in RER+ colon cancer cell lines in association with tumor progression (28). It has been reported that mutations of the BAT-RII pA tract are shown in about 90% of RER+ colorectal carcinomas, whether from HNPCC or sporadic carcinomas (9). However, abnormal patterns of alleles in BAT-RII were not detected in the present study. It is possible that some HNPCC tumors have other components of a mutated (A)10 repeat in TGF-βRII, because not all HNPCC tumors have been detected by the mutations of BAT-RII (9,26). Recently, several somatic mutations in the highly conserved serine/threonine kinase domain other than the (A)10 repeat of TGF-βRII were found in the RER+ colorectal carcinoma cell line and HNPCC (9,28,29). To clarify the exact cause for carcinogenesis in HNPCC, further molecular genetic studies are necessary.

Acknowledgment

This work was supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health and Welfare of the Japanese Government.

References

18. Watanabe T, Muto T, Sawada T, Miyaiki M. Flat adenoma as a precursor of colorectal carcinoma in hereditary nonpolyposis colorectal carcinoma. Cancer 1996;77:627-34.