First report of an Asian family with gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) revealed with the germline mutation of the *APC* exon 1B promoter region

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Abstract

A 48-year-old Japanese female with left hypochondralgia presented at our hospital. Esophagogastroduodenoscopy (EGD) revealed gastric cancers and carpeting fundic gland polyposis (FGPs) without *Helicobacter pylori* infection. Computed tomography showed multiple liver metastases. Total colonoscopy revealed a colonic tubular adenoma but not polyposis. She was diagnosed as having advanced gastric cancer with liver metastasis and received chemotherapy. Her mother had died from gastric cancer, and her elderly brother and niece had FGPs as revealed by EGD. Thus, the pedigree was diagnosed as gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS). Germline mutation analysis exhibited a point mutation in exon1B of the *APC* gene (c.-191T>C). Adenocarcinoma showed a gastric mucinous phenotype and was positive for a somatic mutation of *p53*, suggesting that *p53* mutation may play a role in FGPs carcinogenesis. This is the first family with GAPPS in Asia in whom germline mutation of *APC* exon 1B has been detected.

Keywords GAPPS · *APC* gene · Exon1B

Introduction

Fundic gland polyps are a common histological type of polyp in the stomach detectable by esophagogastroduodenoscopy (EGD). They usually exist in the gastric mucosa without *Helicobacter pylori* (HP) infection and are restricted to the

gastric body and fundus (fundic gland area). It is generally recognized that a sporadic fundic gland polyp is a benign lesion with little or no malignant potential [1, 2]. It is also well known that multiple or profuse polyps in the fundic gland area—i.e., fundic gland polyposis (FGPs)—occur in patients with familial adenomatous polyposis (FAP). FGPs associated with FAP is frequently associated with somatic mutations of the *adenomatous polyposis coli* (*APC*) gene [3]. In 1999, a case of gastric adenocarcinoma associated with FGPs of the stomach was reported, and since then FGPs has been considered to have malignant potential [1, 4].

Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) is an autosomal dominant disease characterized by gastric cancer and polyposis of the fundic gland [5]. Li et al. [6] reported that germline point mutations in *APC* exon 1B were positive in each of 6 families with GAPPS; however, the detailed etiology of GAPPS has not yet been fully clarified. In this paper, we report a family with GAPPS that had a germline mutation of *APC* exon 1B and gastric adenocarcinoma with a somatic mutation of the *p53* gene.

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Case report

A 48-year-old female presented to our hospital for investigation of left hypochondralgia. No notable past medical history or administration of a proton pump inhibitor were identified. Her mother had died from gastric cancer; however, it was unclear whether she had FGPs or not. Laboratory data indicated elevation of tumor markers (CEA, 27.2 ng/ml; CA19-9, 342 U/ml). EGD demonstrated FGPs (Fig. 1a) and 2 cancers in the gastric body (Fig. 1b); however, no polyposis or malignant tumors were identified in the antrum and duodenum (Fig. 1c, d). Atrophic mucosal change, observed only in the antrum, suggested the possibility of past infection with *HP*, which may be compatible with the negativity for serum *HP* test. A biopsy specimen obtained from the tumor of the gastric body showed moderately differentiated tubular adenocarcinoma and typical fundic gland polyp without any dysplasia from numerous gastric polyps. Total colonoscopy (TCS) demonstrated a single adenoma in the transverse colon. Computed tomography (CT) demonstrated regional lymph node swelling, ascites, and multiple liver tumors diagnosed as metastases based on typical CT findings. Therefore, she was diagnosed as having advanced gastric cancer cT3N2M1 HEP at stage IV according to the Japanese classification of gastric carcinoma [7]. She had received docetaxel, cisplatin, and S-1 (DCS) combination therapy, which had

resulted in a decrease in tumor size and disappearance of left hypochondralgia. However, after 5 courses of DCS therapy, her disease progressed. She subsequently received weekly paclitaxel plus ramucirumab combination therapy, followed by irinotecan monotherapy. However, the tumor size increased significantly, and she finally died on day 223 after hospitalization.

Figure 2 shows her family pedigree. Her elderly brother and niece had FGPs (Fig. 3a, b respectively), but her sister-in-law did not (Fig. 3c), as revealed by EGD. They had no apparent polyposis in the colon or small intestine as shown by TCS and capsule endoscopy. Thus, the patient and her relatives were diagnosed as having GAPPS.

It was assumed that the patient and her relatives had germline variants. Since point mutation *APC* exon 1B was reported to be positive in 6 families with GAPPS, we performed mutational analysis of *APC* exon 1B from the genomic DNA of peripheral blood, after performing genetic counseling and obtaining informed consent, using a polymerase chain reaction (PCR)-direct-sequencing method. We found a point mutation in the transcription factor Ying Yang (YY1) binding site in promoter 1B (exon 1B) of the *APC* gene (chr5: 112,043,224 T/C; c.-191T>C), which was present in the patient, her brother, and her niece (Fig. 4a–c), and was identical to the mutation described previously [6], but which was not detected in her sister-in-law (Fig. 4d). Accumulation of p53 protein was detected by immunohistochemistry (IHC) in the cellular nuclei of an adenocarcinoma specimen

Fig. 1 EGD image at the first medical examination and pathological examination of biopsy specimen. **a** Profuse fundic gland polyposis in the fundic gland area. **b** Adenocarcinoma in the gastric body classi-

fied as Type 3. **c, d** No polyp or tumor in the antrum and duodenum. **e** Fundic gland polyp with cystically dilated gland. **f** Adenocarcinoma (tub2)

Fig. 2 Pedigree of the family with/without *APC* exon 1B mutation

Fig. 3 EGD findings from related family members of the patient. **a** Fundic gland polyposis in her elderly brother. **b** Fundic gland polyposis in her niece. **c** No polyposis in her sister-in-law

but not in the nuclei of fundic gland polyps and normal epithelia (Fig. 5a–c). A mutation in exon 4 of the *p53* gene (c. 215C>G, p. Pro72Arg) was detected in the genomic DNA from the adenocarcinoma specimen by PCR-direct sequencing (Fig. 4e); while *p53* gene analysis in FPGs tissue could not be performed. No accumulation of β -catenin in the nuclei of the adenocarcinoma nor fundic gland polyps were identified (Fig. 5d–f). Moreover, both the adenocarcinoma and fundic gland polyps were positive for MUC5AC (Fig. 5i, n) but were negative for MUC2 and MUC6 (Fig. 5h, j, m, o).

Discussion

Most gastric cancers are sporadic and attributable to atrophic gastritis due to *HP* infection [8, 9]. However, familial clustering is observed in almost 10% of patients with gastric

cancer and heritability is seen in 1% of patients [10]. There have been several reports on familial gastrointestinal cancers such as, hereditary diffuse gastric cancer [11], FAP [1, 12], Lynch syndrome [13], Li-Fraumeni syndrome [14], Peutz-Jeghers syndrome [15], and juvenile polyposis [16]. In 2012, Worthley et al. [5] proposed GAPPs as a novel familial gastric cancer. Recently, Li et al. identified a point mutation in *APC* exon 1B in 6 families with GAPPs, suggesting that the gene mutation is responsible for the onset of GAPPs [6]. The phenotype of this pedigree could correspond to GAPPs from the viewpoint of having FPGs and gastric cancer without any colonic polyposis. Moreover, our pedigree showed autosomal dominant inheritance with a germline mutation in *APC* exon 1B.

A total of 10 Caucasian GAPPs families were identified based on a search of the PubMed database [5, 6, 17, 18]. Regarding gastric cancer associated with GAPPs, the mean

Fig. 4 An *APC* exon 1B germline mutation in the patient and her family and a *p53* somatic mutation in an adenocarcinoma specimen. A point mutation in exon 1B of the *APC* gene (191T>C) is shown, as revealed by polymerase-chain reaction (PCR)-direct sequencing. **a** The patient. **b** Her elderly brother. **c** Her niece. **d** Her sister-in-law. **e** A mutation in exon 4 of the *p53* gene (c. 215C>G) is shown

age of a total 14 patients was 49 (range: 23–75) years and the sex ratio (male/female/unknown) was 1/6/7. Only 3 of the patients received systemic chemotherapy, although their survival time was extremely short (range 0.5–5 months). The survival time of our case was also relatively shorter (7 months) as compared with sporadic gastric cancer in Japanese [19]. Although the number of cases who received systemic chemotherapy was very small, there is a possibility that an unresectable gastric cancer associated with GAPPS has a poorer prognosis.

The *APC* gene, which is responsible for FAP, codes for APC protein, which binds to Axin to degrade β -catenin [20, 21]. Mutated APC protein could lose the ability to bind Axin, resulting in the accumulation of β -catenin in the nucleus, leading to cell proliferation. The specific point mutations in the transcription factor YY1 binding site in promoter 1B of the *APC* gene reportedly results in the loss of binding potential with YY1 on the *APC* gene, leading to a decrease in the transcriptional activity of promoter 1B of the *APC* gene [6]. In this pedigree, family members with FGPs had identical mutations in *APC* exon 1B, but healthy individuals did not, suggesting that this mutation is pathogenic. Accumulation of β -catenin was not observed in either adenocarcinoma or fundic gland polyps consistent with findings reported by Li et al. [6] and Hassan et al. [22]. However, accumulation of p53 in the nucleus as well as mutation of the *p53* gene were observed in adenocarcinoma tissue, whereas there was no accumulation in the nucleus of fundic gland

Fig. 5 Immunohistochemical findings in normal gastric mucosa, fundic gland polyps, and adenocarcinoma of the patient. **a–e** Histology of the normal mucosa. **f, g** Immunohistochemistry for β -catenin and p53 without highlighting in nuclei. **h–j** Immunohistochemistry of fundic gland polyp presented positive for MUC5AC but not for MUC2 or

MUC6. **k, l** Immunohistochemistry showed nuclear staining for p53 but not for β -catenin (membranous pattern). **m–o** Immunohistochemistry of adenocarcinoma presented positive for MUC5AC but not for MUC2 or MUC6

polyps. These results raise the possibility that *p53* mutations are involved in the pathogenesis of GAPPS-related gastric cancer. Moreover, the adenocarcinoma in our case showed a gastric mucinous phenotype. This suggests that carcinogenesis was not associated with intestinal metaplasia, consistent with negativity for *HP* infection in this case.

GAPPS is a rare disease, particularly in Asia. To date, most GAPPS families have been reported in Western countries. Our case is the first case with GAPPS in Asia in whom germline mutation was detected in *APC* exon 1B. Henceforth, attention should be paid to FGPs among Asian people due to the heightened potential for malignancy. It is particularly notable that familial fundic gland polyps, such as GAPPS and FAP should be distinguished from sporadic fundic gland polyps because of the much higher risk of gastric cancers. Eventually, Nakamura et al. studied 22 patients with FAP and reported that the prevalence of *HP* seropositivity in patients with FGPs was significantly lower than in those without FGPs, suggesting that the FGPs phenotype was affected by *HP* infection [23]. Since the positivity rate for *HP* infection is relatively high in Asian countries including Japan [24], careful screening by EGD is necessary for patients with a family history of gastric cancer, in view of the phenotypic change of GAPPS associated with *HP* infection. In addition, suspected cases should be tested for mutation of *APC* exon 1B.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee and with the Helsinki Declaration. Informed consent to be included in the study was obtained from all patients.

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