Gastric Cancer (2022) 25:473–478
https://doi.org/10.1007/s10120-021-01253-x

CASE REPORT

Prophylactic laparoscopic total gastrectomy for gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS): the first report in Asia

Chihiro Matsumoto[1] · Masaaki Iwatsuki[1] · Shiro Iwagami[1] · Takeshi Morinaga[1] · Kohei Yamashita[1] · Kenichi Nakamura[1] · Kojiro Eto[1] · Junji Kurashige[1] · Yoshifumi Baba[1] · Yuji Miyamoto[1] · Naoya Yoshida[1] · Yoshihiro Komohara[2] · Hideo Baba[1]

Received: 2 July 2021 / Accepted: 15 September 2021 / Published online: 23 September 2021

Abstract

A 41-year-old woman was admitted to our hospital for epigastralgia. She had been admitted to another hospital for fundic gland polyposis (FGP) without any symptoms, and no malignancy had been noted in her previous endoscopy. However, a biopsy performed at our hospital revealed adenocarcinoma, and computed tomography (CT) revealed multiple liver and peritoneal metastases. We clinically suspected gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) and indicated genetic testing. The point mutation in exon 1B of *APC* was revealed. She was diagnosed with GAPPS with multiple liver metastases and underwent systemic chemotherapy. She has two older brothers who also have FGP. The same genomic mutation was observed in both brothers and their mother, and they were also diagnosed with GAPPS. The brothers underwent prophylactic laparoscopic total gastrectomy with D1 lymph-node dissection.

Keywords Gastric cancer · Polyps · Mutation · Gastrectomy

Introduction

Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) is an autosomal dominant syndrome that is characterized by polyposis localized in the gastric body and fundus with a high tendency of adenocarcinoma [1]. Subsequently, GAPPS cases have been reported mainly in western countries [2–6]. However, more recently, GAPPS has been reported in some families in Asia [7–9]. The diagnosis of GAPPS is based on Worthley's criteria [1]. Li et al. investigated one Australian family and five North American families met the diagnostic criteria for GAPPS and identified a point mutation in promoter 1B of *APC* using Sanger sequencing in all six families [10].

The prognosis of GAPPS remains unknown owing to insufficient data. Repak et al. reported on three sisters with GAPPS, one of whom died because of multiple metastases; the other two sisters underwent prophylactic gastrectomy and did not develop gastric cancer [2]. The prognosis of GAPPS may depend on malignant transformation.

The treatment strategy for GAPPS remains controversial. Logically, the basic concept must be based on the treatment of gastric cancer. As the concept and understanding of GAPPS has widened, a number of GAPPS cases have been diagnosed at an early stage with fundic gland polyposis (FGP) without malignant characteristics. The practice of performing prophylactic total gastrectomy for GAPPS without malignant characteristics has recently increased in Western countries [2, 4, 11].

Herein, we report two Asian cases of GAPPS diagnosed by preoperative genetic testing that were successfully treated via prophylactic laparoscopic total gastrectomy.

✉ Hideo Baba
hdobaba@kumamoto-u.ac.jp

[1] Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Chuo-ku, Kumamoto-city 860-8556, Japan

[2] Department of Cell Pathology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

Case presentation

The patient was a 41-year-old woman, who had been admitted to another hospital for FGP without any symptoms. Esophagogastroduodenoscopies (EGDs) revealed FGP localized in the gastric body and fundus (Fig. 1a, b), and a biopsy from the largest polyp in the gastric body revealed no malignant findings. She had no symptom and was not taking any medication, including proton pump inhibitors. After 10 months, she was presented to our hospital for epigastralgia. EGDs at our hospital revealed a Bormann type 2 tumor about 30 mm in diameter, which is hemorrhagic elevated lesion with central depression in the cardia (Fig. 1c, d). In pathological examination, biopsy from the cardiac lesion indicated that main component was papillary and well-differentiated tubular adenocarcinoma (Fig. 2a, b). Biopsy from polyps were diagnosed as fundic gland polyps with fundic gland hyperplasia (Fig. 2c) and dilated foveolar epithelium and polypoid lesions consistent with hyperproliferative aberrant pits (HPAP) (Fig. 2d). Carcinoma cells were strongly positive for MUC 5AC (Fig. 2e) and sporadically positive for MUC6 (Fig. 2f), and negative for MUC2, pepsinogen I, and H+/K+-adenosine triphosphatase, which indicated that carcinoma cells had foveolar phenotype. Notably, small proportion of micropapillary component was observed (Fig. 2g, h). Although no duodenal or colonic polyps were detected by endoscopy, CT revealed of paracardial lymph-node enlargement, multiple hypovascular nodules in the liver, and multiple peritoneal masses (Fig. 3). Suspecting GAPPS, genetic testing was indicated. Genetic testing revealed a point mutation in APC exon 1B and she was diagnosed with GAPPS. She was also diagnosed with advanced gastric adenocarcinoma cT4aN1M1 (HEP, PER) at stage IV according to the Japanese classification of gastric carcinoma [12] and underwent systemic chemotherapy (S-1 plus oxaliplatin). The patient had two older brothers (aged

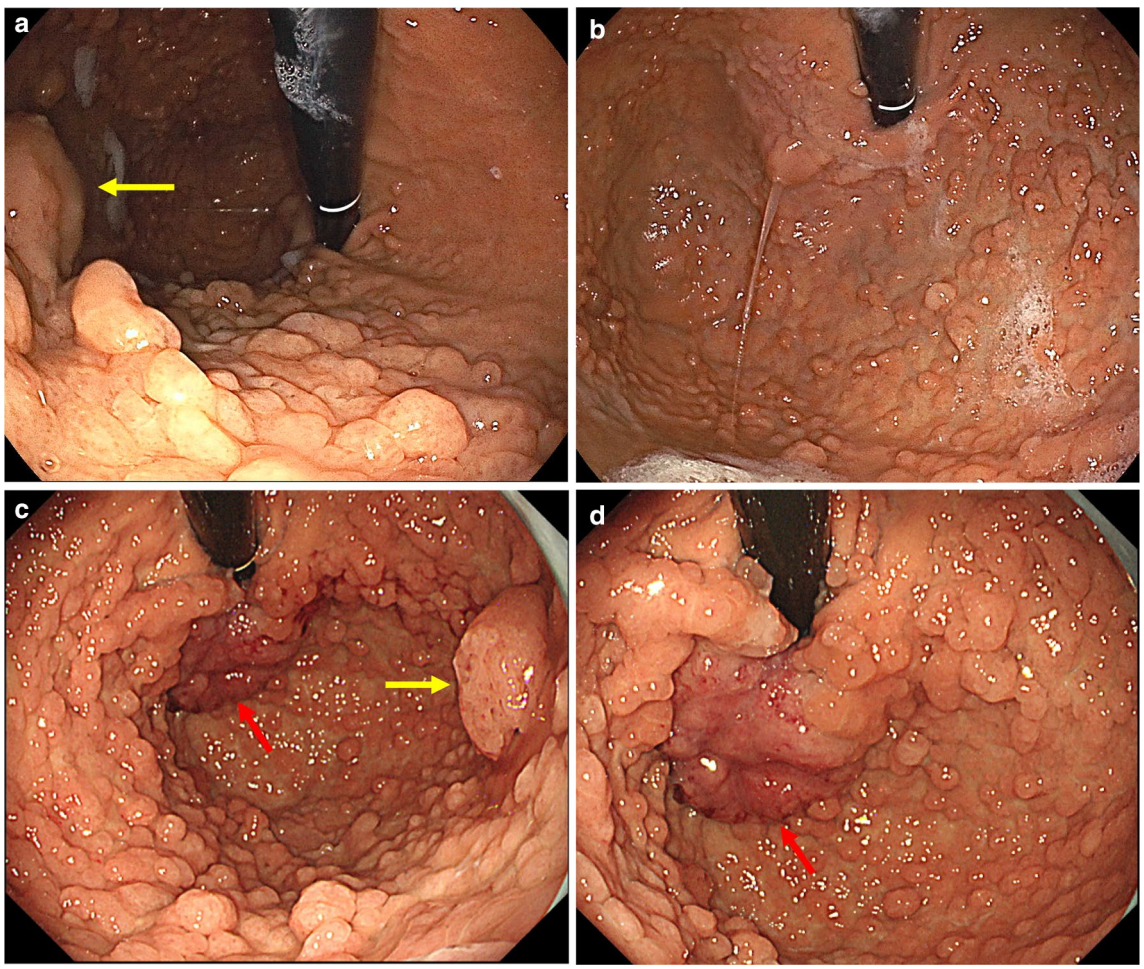

Fig. 1 Esophagogastroduodenoscopy of the proband patient **a**, **b** esophagogastroduodenoscopy of the female patient at another hospital (yellow allow points at the largest polyp in the gastric body), **c**, **d** esophagogastroduodenoscopy of the female patient at our hospital (red allow points at the elevated lesion with central depression in the cardia)

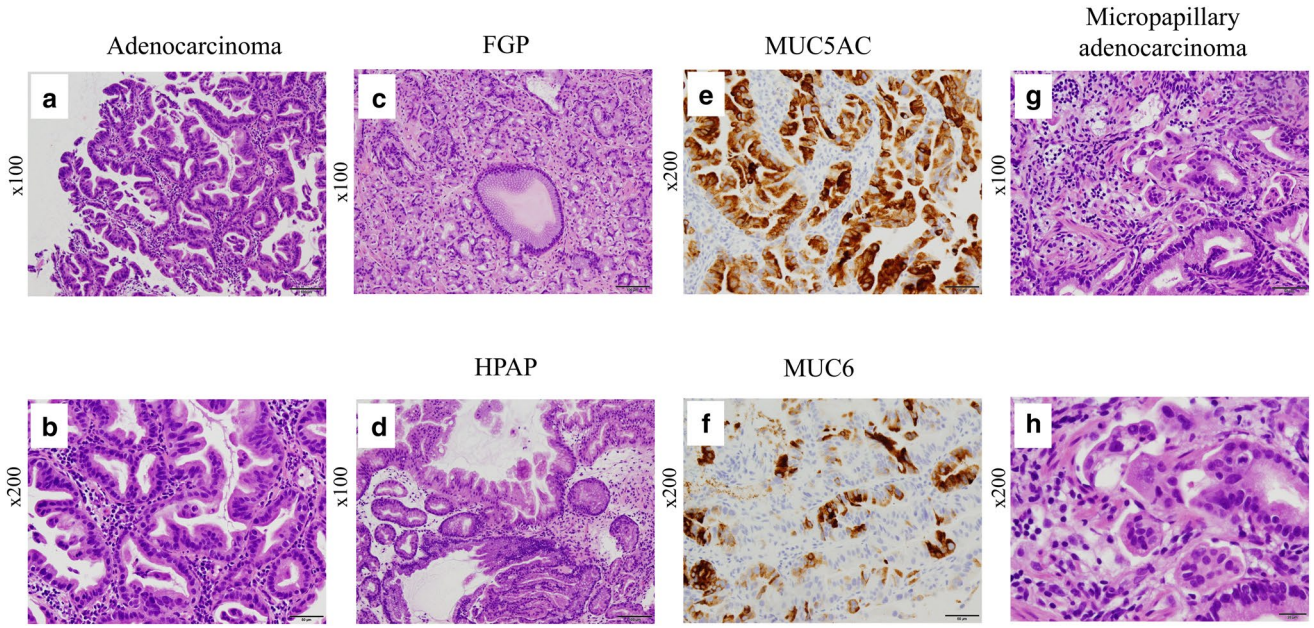

Fig. 2 Hematoxylin and eosin section and immunohistochemistry of gastric lesions **a**, **b** papillary and well-differentiated tubular adenocarcinoma, **c** fundic gland polyp (FGP), **d** hyperproliferative aberrant pits (HPAP), **e** immunohistochemistry of MUC5AC, **f** immunohistochemistry of MUC2, **g**, **h** micropapillary adenocarcinoma in a small part of biopsy specimen

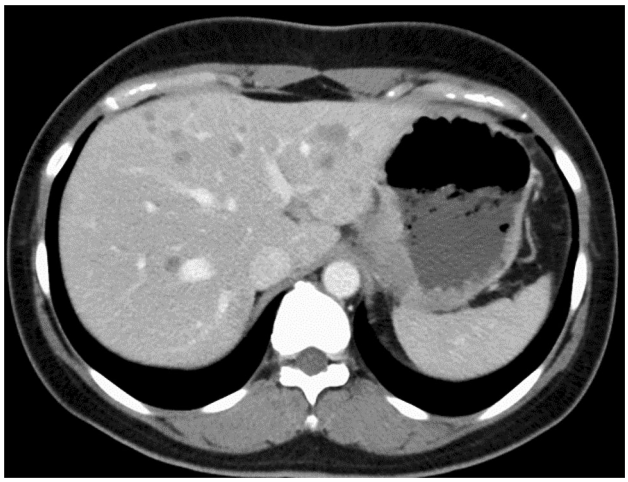

Fig. 3 Computed tomography of the female patient

43 and 45 years). EGD revealed that both of them had FGP (Fig. 4a, b); however, FGP was not detected in their parents. Although biopsy of the FGP revealed no malignancy or dysplasia, a mutational analysis of *APC* exon 1B using peripheral blood genomic DNA via polymerase chain reaction was performed after genetic counseling and obtaining informed consent. A point mutation in promoter 1B was detected in the patient's brothers and mother. They had no clinical symptom, and their endoscopic biopsies revealed no malignancies or dysplasia. However, considering the risk of malignant transformation, prophylactic laparoscopic total gastrectomy with D1 lymphadenectomy was performed after obtaining informed consent and ethical approval in her brothers. They were discharged 14 days after the surgery without postoperative complications. The histopathological findings of the resected specimen revealed FGP without malignant characteristics (Fig. 5a, b). The proband has received nivolumab as a third-line treatment due to disease progression after S-1 plus oxaliplatin followed by ramucirumab and nab-paclitaxel. Two relatives who underwent prophylactic gastrectomy are doing well.

Discussion

GAPPS is an autosomal dominant inherited disease with a high risk of massive polyposis limited to the gastric body and fundus. Worthley et al. published the first report of GAPPS in 2012 [1]. Since then, reports on GAPPS have increased, and the characteristic of this disease have been revealed. However, owing to the difficulty of evaluating the precise condition of FGP and predicting the timing of malignant transformation, the clinical management of GAPPS remains uncertain.

Upper gastrointestinal endoscopy is useful for the early detection of GAPPS, and endoscopic biopsy at regular intervals is necessary to prevent the development of gastric adenocarcinoma. However, some previous reports questioned a prolonged endoscopic surveillance in patients with GAPPS

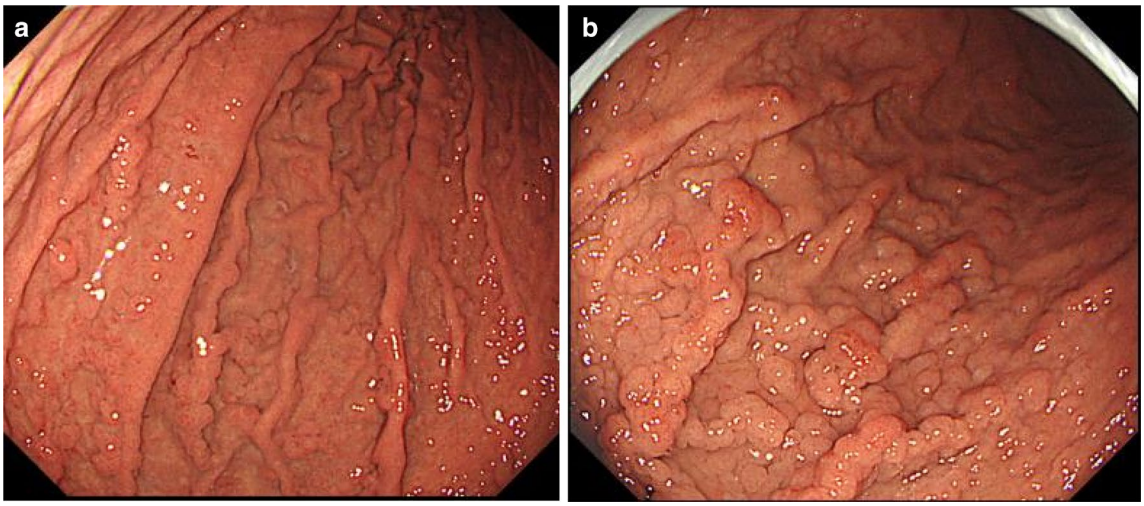

Fig. 4 Esophagogastroduodenoscopy of two older brothers: **a** the older brother and **b** the younger brother

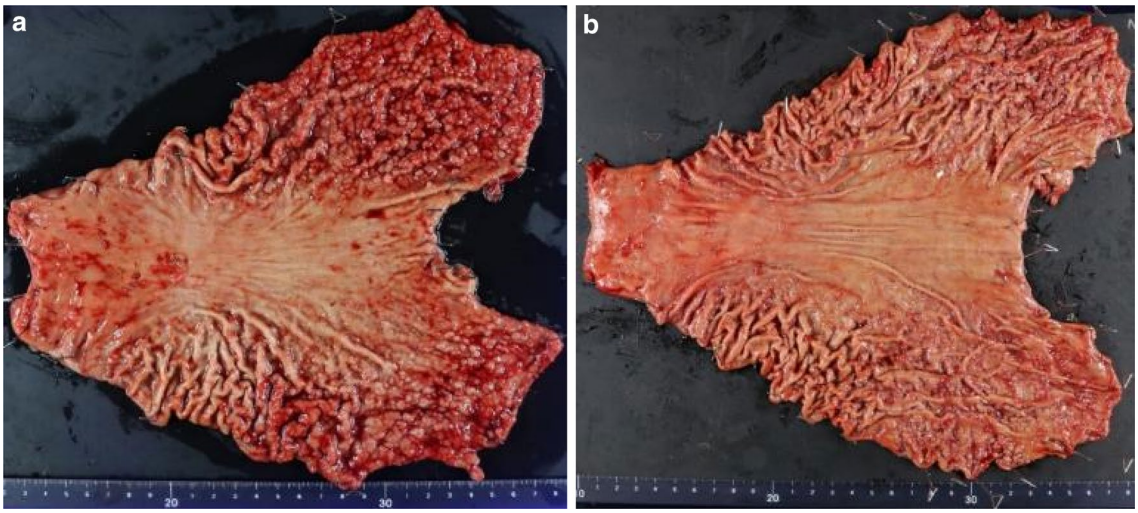

Fig. 5 Surgical specimen of two older brothers: **a** the older brother and **b** the younger brother

[2, 3]. One case of rapid progression to gastric adenocarcinoma with distant metastasis was reported despite frequent endoscopic surveillance [2]. In our case, the rapid progression to gastric adenocarcinoma with distant metastasis was observed in a brief period of 10 months. Micropapillary component was observed in the biopsy specimens, although the proportion was small. It is well known that micropapillary subtype had an unfavorable prognosis, and this component might be associated with the aggressive characteristic of our case.

Furthermore, sampling in cases of polyposis, which include FGP with different degrees of dysplasia, is challenging [3]. The timing of endoscopic surveillance initiation also remains controversial, particularly in young patients. A recent report suggested that the first-degree relatives of patients with GAPPS with a proven *APC* mutation should start undergoing the endoscopic surveillance at 15 years of age [13]. The interval or starting time of endoscopic surveillance should be flexible according to the disease condition.

Based on the recent molecular elucidation of GAPPS, prophylactic total gastrectomy is also a useful choice and the only curative treatment for GAPPS with malignant potential. We reviewed medical publication published in English on PubMed using the keywords "GAPPS" or "prophylactic total gastrectomy." The search yielded three available reports on prophylactic total gastrectomy for GAPPS (Table 1). To date, approximately 11 cases of 8 families undergoing prophylactic total gastrectomy have been reported in Western countries. In the available data, the median patient age was 38 (range 23–65) years and the sex ratio (male/female) was

Table 1 Summary of prophylactic gastrectomy from previous articles

Author	Year	Country	Cases (family)	Age	Sex	Preoperative genetic test	Reason for operation	Surgical approach	Lymph-node dissection	Pathological findings
Repak [2]	2016	Czech	2 (1)	23	F	No	Sister's death due to gastric cancer	N/A	N/A	Adenocarcinoma
				30	F	No	Sister's death due to gastric cancer	N/A	N/A	Adenocarcinoma
Beer [4]	2017	Austria	1 (1)	38	F	No	High-grade dysplasia	N/A	N/A	No malignancy
Foretova [12]	2019	Czech	8 (6)	29	F	Yes	Mother's death due to gastric cancer	N/A	N/A	Adenocarcinoma
				34	F	Yes	Mother's death due to gastric cancer	N/A	N/A	No malignancy
				42	F	Yes	Genetic diagnosis	N/A	D1	No malignancy
				50	M	Yes	Genetic diagnosis	N/A	D1	No malignancy
				51	F	Yes	Son's death due to gastric cancer	N/A	D2	No malignancy
				65	F	Yes	Genetic diagnosis	N/A	N/A	No malignancy
				27	M	Yes	Genetic diagnosis	N/A	N/A	No malignancy
				44	M	Yes	Genetic diagnosis	N/A	N/A	No malignancy
Our cases	2021	Japan	2 (1)	43	M	Yes	Genetic diagnosis	Lap	D1 +	No malignancy
				45	M	Yes	Genetic diagnosis	Lap	D1 +	No malignancy

F female, *M* male, *N/A* not available, *Lap* laparoscopic

3/8. Histological analysis of surgical specimens revealed adenocarcinoma in three cases. To our knowledge, this is the first Asian cases of GAPPS confirmed by preoperative genetic testing, who underwent prophylactic laparoscopic total gastrectomy with lymph-node dissection.

Several surgical indications have been proposed so far. Repak et al. stated that patients who fulfill the original GAPPS criteria and those with FGP progression to dysplasia should be tested for genetic mutations, so that prophylactic gastrectomy can be performed appropriately [2]. In addition, Tacheci et al. reported that in cases with dysplasia, prophylactic total gastrectomy is indicated promptly without delay, whereas in cases without dysplasia, prophylactic total gastrectomy should be performed at 30—35 years of age, or 5 years earlier than the age at which the youngest family member developed gastric cancer [13]. Furthermore, Foretova et al. recommended prophylactic total gastrectomy for cases with progressive massive stomach polyposis even without dysplasia [11]. The optimal timing of prophylactic gastrectomy is also an important issue. In the previous reports, the youngest case of prophylactic total gastrectomy was 23 years old [2]. Prophylactic gastrectomy should be considered when GAPPS is genetically diagnosed before it progresses to gastric adenocarcinoma. However, the timing of dysplasia and adenocarcinoma development varies widely. Foretova et al. reported that the development of massive polyposis was variable, with the earliest finding at 22 years of age, with a negative finding in a woman at 65 years, and no clinical symptoms in a man at 92 years. Out of a total of eight prophylactic gastrectomies performed, one case of gastric adenocarcinoma diagnosed in a histological specimen of a 29-year-old woman [11]. Therefore, determining when a patient should undergo prophylactic gastrectomy remains controversial.

The surgical procedure involves the risk of postoperative complications, including infection, dumping syndrome, and surgery-related death [14]. In general, patients who undergo prophylactic gastrectomy are younger and healthier than those who undergo curative gastrectomy for gastric cancer. However, van der Kaaij reported that the number of patients requiring a reintervention after prophylactic gastrectomy for hereditary diffuse gastric cancer was comparable to that in the curative setting [15]. Dumping syndrome and weight loss are common postsurgical complications of prophylactic total gastrectomy. Anastomotic strictures, bile reflux, and iron deficiency have also been reported as postsurgical complications within 5 years following prophylactic gastrectomy [16]. Sufficient follow-up after prophylactic gastrectomy is required for late complications such as osteoporosis and megaloblastic anemia.

Herein, we report the first GAPPS case in Asia to undergo genetic testing and prophylactic laparoscopic total gastrectomy with lymph-node dissection. However, clinical

concerns, such as the optimal timing of genetic testing and prophylactic gastrectomy, remain unclear. Therefore, further studies are warranted worldwide to resolve these issues.

Acknowledgements We thank Edanz (http://jp.edanz.com) for English language editing

Author contributions CM, MI, TM, and KY managed genetic testing. SI and KN performed operations. YK performed a pathological evaluation. KE, JK, YB, YM, NY, and HB supervised the management. CM and MI drafted manuscript and all authors approved the final manuscript.

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declarations

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

Ethics approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent Informed consent to be included in the study, or the equivalent, was obtained from all patients.

References

1. Worthley DL, Phillips KD, Wayte N, Schrader KA, Healey S, Kaurah P, et al. Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS): a new autosomal dominant syndrome. Gut. 2012;61:774–9.
2. Repak R, Kohoutova D, Podhola M, Rejchrt S, Minarik M, Benesova L, et al. The first European family with gastric adenocarcinoma and proximal polyposis of the stomach: case report and review of the literature. Gastrointest Endosc. 2016;84:718–25.
3. McDuffie LA, Sabesan A, Allgäeuer M, Xin L, Koh C, Heller T, et al. β-Catenin activation in fundic gland polyps, gastric cancer and colonic polyps in families afflicted by 'gastric adenocarcinoma and proximal polyposis of the stomach' (GAPPS). J Clin Pathol. 2016;69(9):826–33.
4. Beer A, Streubel B, Asari R, Dejaco C, Oberhuber G. Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)—a rare recently described gastric polyposis syndrome report of a case. Z Gastroenterol. 2017;55:1131–4.
5. de Boer WB, Ee H, Kumarasinghe MP. Neoplastic lesions of gastric adenocarcinoma and proximal polyposis syndrome (GAPPS) are gastric phenotype. Am J Surg Pathol. 2018;42(1):1–8.
6. Rudloff U. Gastric adenocarcinoma and proximal polyposis of the stomach: diagnosis and clinical perspectives. Clin Exp Gastroenterol. 2018;11:447–59.
7. Mitsui Y, Yokoyama R, Fujimoto S, Kagemoto K, Kitamura S, Okamoto K, et al. 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. Gastric Cancer. 2018;21(6):1058–63.
8. Ako S, Seiji K, Hiroyuki O. Gastric adenocarcinoma and proximal polyposis of the stomach occurring with ball valve syndrome. Clin Gastroenterol Hepatol. 2020; 23:S1542-3565(20)31006–5.
9. Kanemitsu K, Iwatsuki M, Yamashita K, Komohara Y, Morinaga T, Iwagami S, et al. Two Asian families with gastric adenocarcinoma and proximal polyposis of the stomach successfully treated via laparoscopic total gastrectomy. Clin J Gastroenterol. 2021;14(1):92–7.
10. Li J, Woods SL, Healey S, Beesley J, Chen X, Lee JS, et al. Point mutations in exon 1B of the APC reveal gastric adenocarcinoma and proximal polyposis of the stomach as a familial adenomatous polyposis variant. Am J Hum Genet. 2016;98:830–42.
11. Foretova L, Navratilova M, Svoboda M, Grell P, Nemec L, Sirotek L, et al. Gapps—gastric adenocarcinoma and proximal polyposis of the stomach syndrome in 8 families tested at Masaryk memorial cancer institute—prevention and prophylactic gastrectomies. Klin Onkol. 2019;32:109–17.
12. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer. 2011;14:101–12.
13. Tacheci I, Repak R, Podhola M, Benesova L, Cyrany J, Bures J, et al. Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)—a helicobactor-opposite point. Best Pract Res Clin Gastroenterol. 2021;50–51:101728.
14. Gjyshi O, Vashi P, Seewald L, Kohan M, Abboud E, Fowler E, et al. Therapeutic and prophylactic gastrectomy in a family with hereditary diffuse gastric cancer secondary to a CDH1 mutation: a case series. World J Surg Oncol. 2018;16:143.
15. van der Kaaij RT, van Kessel JP, van Dieren JM, Snaebjornsson P, Balagué O, van Coevorden F, et al. Outcomes after prophylactic gastrectomy for hereditary diffuse gastric cancer. Br J Surg. 2018;105(2):e176–82.
16. Kaurah P, Talhouk A, MacMillan A, Lewis I, Chelcun-Schreiber K, Yoon SS, et al. Hereditay diffuse gastric cancer: cancer risk and the personal cost of preventive surgery. Fam Cancer. 2019;18(4):429–38.