Diffuse gastric polyposis in a young patient with a giant retroperitoneal mass: A case report

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Abstract. Familial adenomatous polyposis (FAP) is characterized by hundreds of colonic adenomatous polyps and extraintestinal manifestations beginning in adolescence and early adulthood. It is also one of the most common hereditary colorectal cancer syndromes. In this case study, a rare phenotype of FAP associated with diffuse gastric polyposis, colon oligo-polyposis, and a massive retroperitoneal mass is described. The results expand on the current body of knowledge of FAP and may represent a new phenotypic expression of FAP. Accurate evidence-based surveillance and management recommendations for this disease require further research and evaluation.

Introduction

Polyps are common lesions found in digestive endoscopic screening. They are abnormal growths of tissues projecting from the gastric or colonic mucosal membrane (1). Familial adenomatous polyposis (FAP) is a rare autosomal dominant genetic disorder, characterized by hundreds or even thousands of colonic adenomatous polyps beginning in adolescence and early adulthood (2). The global prevalence of FAP is ~1/10,000 in individuals, with men and women being affected equally (3). It is also one of the most common hereditary colorectal cancer syndromes (4). Attenuated FAP (AFAP) is a less aggressive variant of FAP in that patients clinically develop fewer colonic polyps and at a later age (5). The emergence of colorectal cancer in AFAP is often delayed 10-20 years compared with typical FAP (6). In addition to the colonic manifestations, FAP-related complications such as cutaneous lesions and extracolonic tumors are common (7). Here, a unique case is reported describing a novel phenotype of FAP associated with diffuse gastric polyposis, colon oligo-polyposis, and a massive retroperitoneal mass. The following case report was performed in accordance with the CARE reporting checklist.

Case report

In October 2021, a 21-year-old male presented to Tongji Hospital of Tongji University (Shanghai, China) with a history of multiple gastrointestinal polyps for endoscopic surveillance (Fig. 1A). He denied prolonged use of proton pump inhibitors (PPIs), which increase the incidence of gastric polyps in a time and dose-dependent manner (8). The patient was symptom-free with no complaints of abdominal pain, bloating, nausea, dysphagia, recent weight loss, or gastrointestinal bleeding. He had 1-2 solid stools per day.

The patient completed the relevant evaluation and bowel preparation before the endoscopic examinations. The esophagogastroduodenoscopy displayed hundreds of gastric fundic gland-like polyps heaped up throughout the gastric fundus and body, and the size of the majority of them ranged from 0.3-0.8 cm. The polyps were considerably numerous, and some of them coalesced to form areas of irregular surface mucosa. However, the mucosa was intact and smooth in the gastric antrum and duodenum (Fig. 2A). The colonoscopy was significant only for 10-20 small (<0.5 cm) broad-based polyps distributing from the cecum to the rectum (Fig. 2C). All the polyps detected in his colon and rectum were removed by cold snare polypectomy or high-frequency electrocoagulation resection. Histopathological results showed fundic glands' polyps (in gastric polyps) and tubular adenomas (in colonic

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Abbreviation: AFAP, attenuated familial adenomatous polyposis; APC, adenomatous polyposis coli; CT, computed tomography; FAP, familial adenomatous polyposis; GAPPS, gastric adenocarcinoma and proximal polyposis of the stomach; GS, Gardner syndrome; PPIs, proton pump inhibitor

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polyps), while no evidence of dysplasia or carcinoma was present in any biopsy specimen. According to his medical history, the patient had undergone digestive endoscopies twice in the local hospital in the previous 2 years in which the lower endoscopy (Fig. 2D) contained 10-20 small (<0.5 cm) nondysplastic tubular adenomas and were only sampled for biopsy, and the results were similar to the current results. In the previous endoscopy, the upper endoscopy (Fig. 2B) contained ~100 gastric fundic polyps restricted to the stomach body and fundus, which was similar in distribution and histopathology but fewer in number compared to what was observed this time.

During the period of endoscopy examinations, the on-duty endoscopist incidentally noticed a palpable abdominal mass. The mass was ~15 cm in diameter, solid, painless, and immobile upon physical examination. An enhanced computed tomography (CT) examination was then performed, and it showed that the upper mid-abdominal cavity was occupied by a mass ~20x9.5 cm in size (Fig. 3A). However, the patient reported that there were no significant findings in the previous upper and lower abdominal CT examinations performed in October 2018. The patient was transferred to the Department of General Surgery for further investigation and treatment. On admission, a 'giant abdominal mass resection' was performed (Fig. 3B). The size of the retroperitoneal tumor was 23x15 cm, close to the ileal mesentery (Fig. 3C and D). The specimens were fixed in 10% neutral formalin at room temperature for 24 h, paraffin-embedded, and sliced into 4-μm-thick sections for hematoxylin-eosin staining (at room temperature; hematoxylin for 8 min and eosin for 8 sec) and immunohistochemical staining. The primary antibodies used were: β-catenin (clone β-catenin-1, 1:200; Dako; Agilent Technologies, Inc.), Vim (cat. no. UMAB159, 1:150; OriGene Technologies, Inc.), Desmin (cat. no. GTM2, 1:80; Gene Tech Co., Ltd.), SMA (cat. no. UMAB237, 1:150; OriGene Technologies, Inc.), CD34 (cat. no. 10C9, 1:150; OriGene Technologies, Inc.), CD117 (cat. no. YR145, ready to use; MXB Biotechnologies), DOG.1 (cat. no. SP31, ready to use; MXB Biotechnologies), S-100 (cat. no. 15E2E2+4C4.9, 1:150; OriGene Technologies, Inc.), and Ki67 (cat. no. UMAB107, 1:200; OriGene Technologies, Inc.). Immunohistochemical staining was performed using the EnVision two-step method on Dako automated instruments according to the manufacturer's protocol (Dako Autostainer Link48; Agilent Technologies, Inc.). The primary antibodies were incubated at 37˚C for 1 h followed by incubation with the EnVision FLEX/HRP secondary antibody (cat. no. SM802; Dako; Agilent Technologies, Inc.) at 37˚C for 30 min. Postoperative pathological analysis revealed that tumor cells were wavy and stellate in shape with bland nuclei, and were arranged in ill-defined fascicles. Immunohistochemical staining showed that the tumor cells were positive for nuclear β-catenin and Vim, and negative for Desmin, SMA, CD34, CD117, DOG.1, and S-100. Pathological results met the diagnostic criteria of desmoid fibromatosis (7) (Fig. 3E-G).

In addition, he had a history of an excision of nuchal fibroblastoma, plantar fibroma, epulis, and forearm adenoma at the age of 17. He also mentioned a history of nuchal fibroblastoma at the age of 2 without providing more details.

Given the patient's family history, his grandmother, a paternal uncle, and his uncle's son all died due to colon cancer. His father had also suffered a long history of gastrointestinal disturbance and died of colon cancer several years ago. Regrettably, further history of their endoscopic details was not known (Fig. 1B). To further confirm the diagnosis and determine possible therapeutic targets by mutation analysis, genetic testing was recommended for the patient and all his first-degree family members. Unfortunately, he declined due to lack of financial means, even though he was well informed that they may benefit from genetic counseling. He was suggested to undergo annual digestive endoscopy surveillance. The patient was discharged a week after the operation and went back to work after a month. No abnormalities were found in the follow-up for the next half a year.

Discussion

In this young male patient, the diagnosis of FAP-related disease was suspected since he had profuse gastric fundic gland polyposis, multiple intestinal tubular adenomas, and fibromatosis occurring earlier in life. The patient's condition was suggested to be inherited in an autosomal dominant pattern based on his family history.

Fundic gland polyps are the most prevalent types of polyps in the stomach, and account for ~74% of all gastric polyps and may be detected in 6% of patients undergoing upper gastrointestinal endoscopy (9). Fundic gland polyps rarely develop in *helicobacter pylori*-infected individuals and are generally regarded as benign lesions with a fairly low risk of gastric cancer. Genetic disorders such as FAP or gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) should be considered when presented with 100-1,000 s of fundic gland polyps in a young patient. Although FAP polyps may appear in any part of the gastrointestinal tract, there are no reports of numerous gastric polyposis in as early a stage of adulthood, to the best of our knowledge.. Patients with FAP are at an increased risk of gastric adenocarcinoma and the risk may be 2-4x higher in Asian patients (8,10). Gastric cancer may develop from dysplastic fundic gland polyps, especially those containing high-grade dysplasia. In ~14% of patients with FAP develop gastric adenomas, and 5% of these contain high-grade dysplasia (11). The American College of Gastroenterology guidelines recommends that upper endoscopy screening in patients with FAP with multiple gastric polyps should be performed every 3 years if adenomas are not found and annually if they are (4). Endoscopic resection was initially suggested to be feasible for dealing with high-grade dysplastic polyps, but they do not eliminate the risk of cancer. However, differentiating between these presumed high-risk polyps and the other hundreds of fundic gland polyps remains a significant challenge for endoscopists. Therefore, more practicable guidelines or criteria are required to assist endoscopists with gastric surveillance in FAP. In this case, the gastric fundic gland polyps rapidly progressed to a stage of hundreds within just a year, while no evidence of dysplasia or adenomas has been found so far. Patients with GAPPS have florid fundic gland polyposis, and polyps are restricted to the proximal stomach (12). However, the absence of colorectal or duodenal polyposis and the adenocarcinoma of the gastric body in these patients is an important clinical feature helping to distinguish between GAPPS and FAP (12,13). The intestinal polyposis in patients with FAP tends to undergo malignant changes by the mean age of 50 years if the colon is left intact (4,6). Due to the

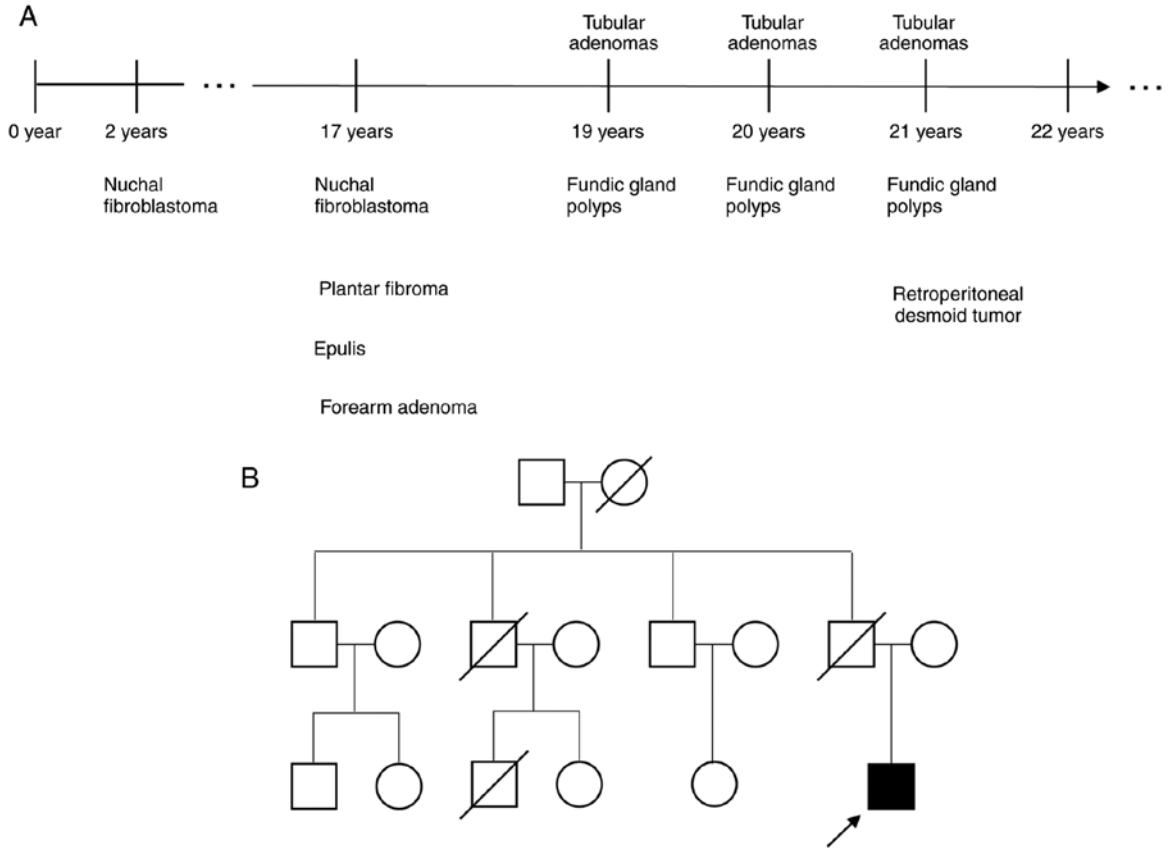

Figure 1. Timeline of the relevant clinical findings and family pedigree. (A) The timeline shows the relevant clinical findings in the patient since birth. (B) Family pedigree. Squares indicate males and circles represent females. A slashed symbol indicates that an individual succumbed to the colorectal cancer. The filled black symbol represents the patient reported in the current case. The empty symbols without slashes indicate unaffected individuals.

lesser colonic polyp burden in this patient, annual surveillance may be sufficient and negate the need for colectomy. However, prophylactic surgeries such as colectomy with ileorectal anastomosis are also considered appropriate for large adenomas (>1 cm), advanced polyp histology, or increasing polyp burden that is no longer manageable by colonoscopy (3,14).

Substantial evidence has suggested that there is an association between inflammation and gastrointestinal disorders such as ulcerative colitis, irritable bowel syndrome, and FAP (15-17). Chronic inflammation and the immune microenvironment can drive the progression of adenomas and gastric or colonic carcinomas (18,19). A well-designed randomized clinical study demonstrated that low-dose aspirin (a common non-steroidal anti-inflammatory drug) is safe to suppress the development of colorectal polyps and the reoccurrence of those polyps >0.5 cm in patients with FAP (20). Mesalazine treatment is reported to help reduce intestinal polyp diameter in FAP patients with ulcerative colitis (21). Adhering to a low-inflammatory dietary intervention may also play a potentially protective role in patients with FAP by reducing gastrointestinal markers of inflammation (17,22,23), whereas a high-fat diet can induce inflammation and alter metabolism, which is related to the occurrence of various digestive diseases and tumors (24). Furthermore, inflammation can act in FAP by influencing the microbiota containing tumorigenic bacteria. Gut microbiota can generate microbial metabolites such as butyrate, which have both anti-tumor effects in normal and tumor tissues (25). *E. coli* and *Bacteroides fragilis* were demonstrated to be highly enriched in colonic mucosa in patients with FAP patients, and the introduction of these bacteria exhibited could quicker tumor onset and increased mortality by increasing IL-17 levels in the colon and DNA damage in the colonic epithelium (26). The administration of prebiotics, probiotics, or antibiotics was found to have beneficial effects in reducing polyp development and colorectal cancer risk, which may involve inflammatory pathways (27). However, whether identifying tumorigenic bacteria in the diagnosis of FAP remains to be investigated. Together the above evidence highlights that anti-inflammatory support is promising in reducing the risk of adenomas and carcinomas in patients with FAP.

In addition to the gastrointestinal polyposis, it was also noteworthy that this young patient presented with several other extracolonic manifestations such as a large retroperitoneal mass along with a history of nuchal fibroblastoma, plantar fibroma, and epulis, which could not be explained by typical FAP. Abdominal desmoid tumors are not rare in patients with FAP, and they are locally aggressive. Although they have a relatively high recurrence rate, tumor surgical resection is still suggested for a symptomatic desmoid tumor when it affects organ function or grows rapidly (28). Patients with AFAP generally present with a lower overall polyp burden typically averaging <100 adenomatous polyps in their lifetime. Adenomas and cancer hardly emerge in early adulthood and the average age of diagnosis of AFAP is 45 years old (4). Gardner syndrome (GS) is a phenotypic variant of FAP, characterized by intestinal adenomatous polyps and extracolonic symptoms such as osteomas, epidermoid cysts, and dental anomalies (7).

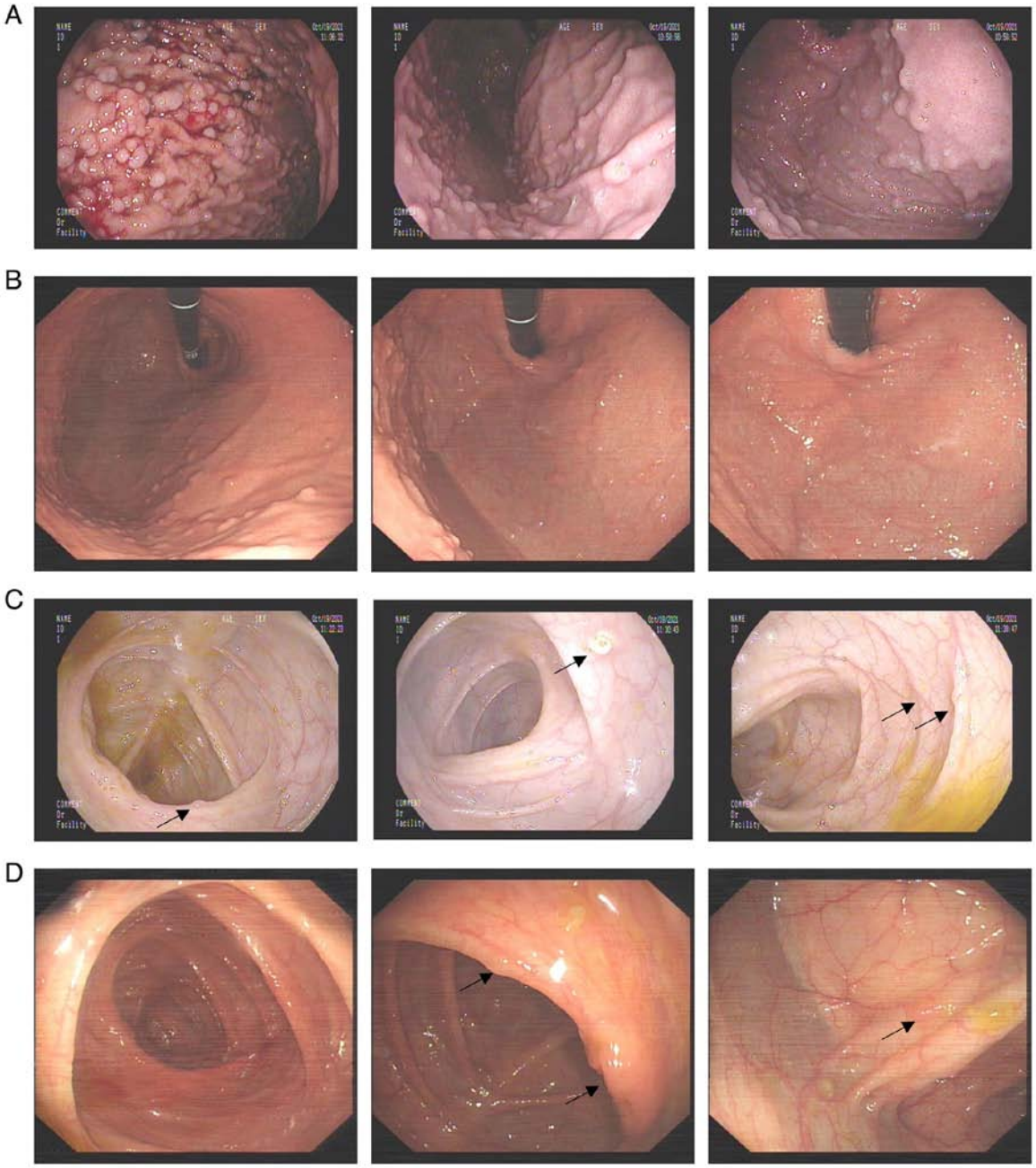

Figure 2. Endoscopic examinations. The esophagogastroduodenoscopies performed in (A) 2021 and (B) 2020 show diffuse polyps covering the entire gastric fundus and body. The colonoscopies performed in (C) 2021 and (D) 2020 show small broad-based polyps (black arrow) distributed from the cecum to rectum.

These characteristic manifestations are crucial for physicians to discern between GS and other differential diagnoses. Of note, in recent years, it has been suggested that the terms GS and AFAP no longer be used, as both of these syndromes are now known to be a part of the FAP spectrum (5,7).

Adenomatous polyposis coli (APC) is a tumor suppressor gene located on chromosome 5q21, playing a significant role in the adenoma-carcinoma sequence of colorectal cancer (29). Point mutations or frameshift mutations in the APC gene are detected in a majority of patients with FAP, and APC gene mutations are associated with FAP tumorigenesis (30). Sequencing approaches involving the genome or transcriptome have been used for molecular genetic diagnosis and in the prediction of therapeutic targets for the management of FAP (29,31). For patients with FAP without detectable pathogenic mutations, next-generation sequencing combined with bioinformatics tools may be effective to detect low-level somatic mosaic APC mutations in a single assay (32). Disciglio *et al* (33) described a novel FAP clinical variant, characterized by diffuse gastric polyposis in the stomach fundus and body, colon oligo-polyposis, and desmoid tumors. Genomic sequencing showed that this phenotype was associated with mutations in APC gene region B.

In conclusion, this case study described a rare phenotype of FAP characterized by diffuse gastric polyposis, colon oligo-polyposis, and a massive retroperitoneal mass. These results expand on the current knowledge of patients with FAP and may add a novel phenotypic expression of FAP. Moreover, the importance of a combination of upper and lower endoscopy

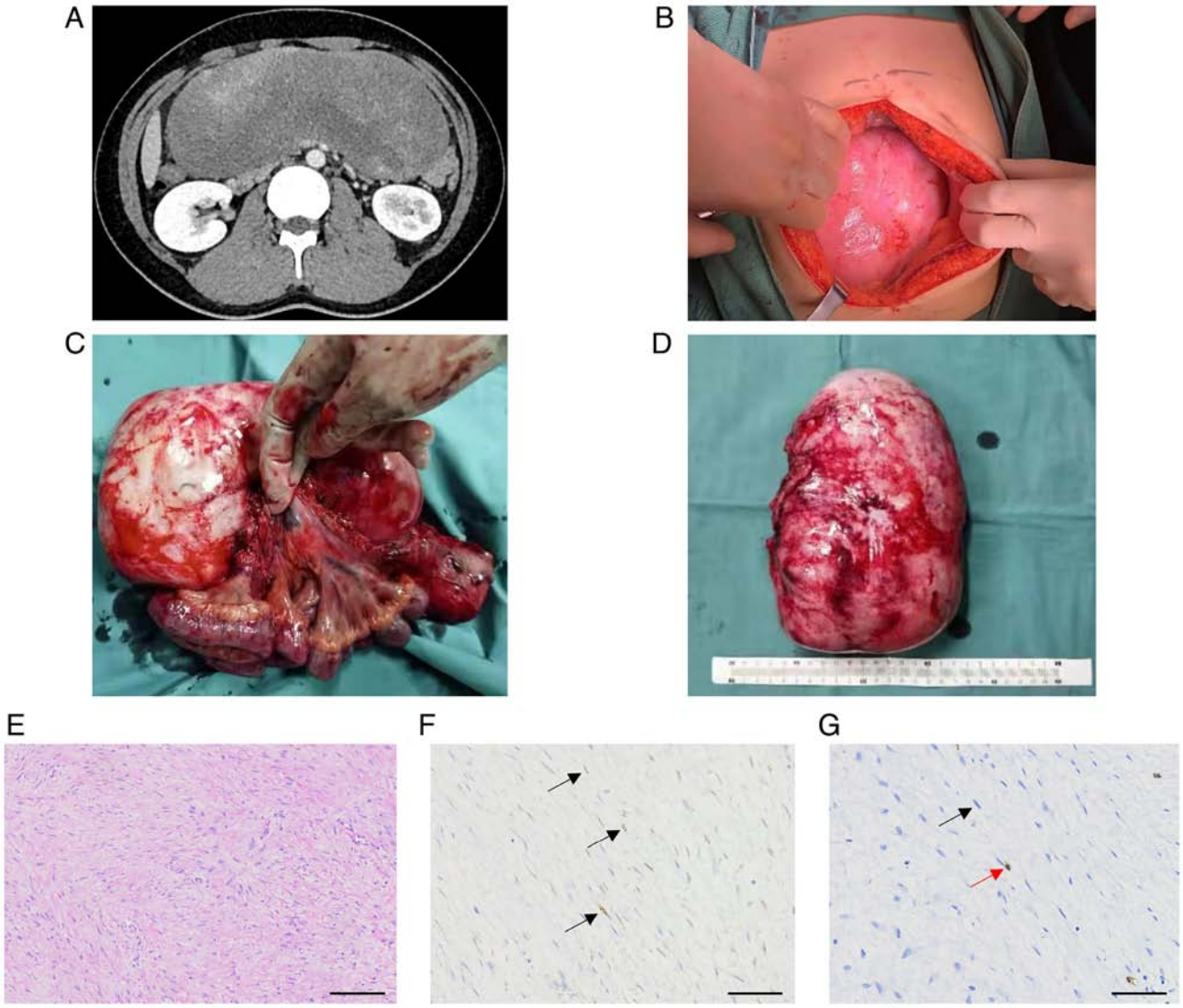

Figure 3. The large retroperitoneal mass. (A) Enhanced computed tomography examination showed that the upper mid-abdominal cavity was occupied by an aberrant mass. (B) Resection of the giant retroperitoneal mass. (C) The mass was located close to the ileal mesentery. (D) Removal of the specimen (23x15 cm). (E-G) Postoperative pathology revealed desmoid fibromatosis. (E) Tumor cells appeared wavy and stellate in shape with bland nuclei, and cells were arranged in ill-defined fascicles. (F) Staining for nuclear β-catenin was positive (black arrow). (G) CD117 was not expressed in the tumor cells (black arrow) but was expressed in the mast cells (red arrow). Magnification: (E) x200 and (F and G) x400.

examinations for patients with polyposis was highlighted. However, it remains a significant challenge to properly identify the interval of time for surveillance and sampling correctly for histological evaluation in the clinic. Therefore, accurate evidence-based surveillance and management recommendations for this disease require further research and evaluation. Studies on the role of inflammation and sequencing approaches in FAP will provide more targeted therapeutics and may serve as potential research hotspots in the future.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contribution

GBD and HHS conceived the study, collected the data, and wrote the manuscript. YZ performed the imaging and pathological review. SRJ and WFL performed the resection of the large retroperitoneal mass and performed the imaging. YC,

JWW, JX, and YC assisted in the acquisition, analysis, and interpretation of the data. WFL and SCX contributed to the conception of the study and revision of the manuscript. WFL and SCX confirm the authenticity of the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

Competing interests

The authors declare that they have no competing interests.

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