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Recurrent Hepatoblastoma and early-onset colorectal cancer in a child with familial adenomatous polyposis: a case report

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Case Report

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Abstract

Introduction:

Familial adenomatous polyposis (FAP) is the most common hereditary polyposis syndromes in pediatric population. This hereditary cancer predisposition syndrome characterized by colonic adenomatous polyposis. Without prophylactic intervention, the risk of progression to colorectal cancer (CRC) approaches 100% by the fourth decade of life. Meanwhile, there is also risk of multiple childhood malignancies including hepatoblastoma (HB).

Case presentation:

We describe an 11-year-old male with a history of HB treated at ages 1 and 8, who presented with recurrent episodes of incomplete intestinal obstruction. Although postoperative adhesions or HB recurrence was considered according to imaging. Emergency laparotomy revealed an obstructing ascending colon mass and the distal bowel was carpeted with innumerable polyps. Frozen biopsy suggested adenocarcinoma, and a radical right hemicolectomy with lymphadenectomy was performed. Histology confirmed a poorly differentiated adenocarcinoma with extensive lymph node metastasis and the polyps were tubular adenomas with diffuse adenomatous polyposis. Further evaluation identified a paternal germline adenomatous polyposis coli (APC) mutation, confirming FAP. The patient is currently receiving palliative chemotherapy with 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) and bevacizumab.

Conclusion:

Screening for HB is warranted for children with a family history of FAP. Furthermore, the occurrence of HB in infancy should be regarded as a sentinel marker for aggressive FAP phenotypes, necessitating an intensified and individualized colorectal surveillance strategy initiated at an earlier age.

Introduction

Familial adenomatous polyposis (FAP) is one of the most common polyposis syndromes diagnosed in the pediatric population, affects approximately 1 in 10,000 live births and follows an autosomal dominant inheritance pattern with 100% penetrance[1]. It is caused by heterozygous constitutional pathogenic variants in the tumor suppressor adenomatous polyposis coli (APC) gene[2, 3]. FAP characterized by hundreds to thousands of colorectal adenomatous polyps, and the colonic manifestations of FAP present as a spectrum correlated with the specific APC mutation site[4]. This ranges from attenuated FAP, characterized by a lower polyp burden and delayed malignancy (variants from 5' to codon 157 or 3' to codon 1595), to the phenotype with early-onset severe polyposis (variants

between codons 1250 and 1464)[4]. Mutations located in the rest regions generally result in the classic FAP phenotype.

In FAP patients, who do not receive prophylactic treatment, polyps would develop to colorectal cancer (CRC) with a median of 35–45 years[3, 5]. Therefore, FAP patients should undergo regular surveillance and prophylactic surgery to avoid. However, malignant development to CRC within the first two decades of life is an uncommon occurrence, even in high-risk populations.

Besides CRC, FAP patients carry lifetime risk of extraintestinal malignancies. For pediatric FAP patients, extraintestinal malignancies including hepatoblastoma (HB) in liver, papillary cancer in thyroid, desmoid tumor, and medulloblastoma in central nervous system[4].

The incidence rate of HB is only about 1% with most occurring before the age of 3 years[5]. Although the guidelines for clinical surveillance and management of gastrointestinal polyposis in FAP patients has been well established, standardization in the pediatric surveillance and management of in extraintestinal malignancies in FAP children should be enhanced. Uncertainty and diabetes in screening HB remains.

Here in this study, we describe an extremely rare case, a FAP child with recurrent HB and early-onset CRC to underscore the possible necessity and raise awareness of screening HB and performing advanced prophylactic surgery.

Case presentation

A 11-year-old boy presented with paroxysmal abdominal pain and bilious vomiting, admitted by general surgery department in our hospital, a tertiary pediatric medical center, with repeated incomplete intestinal obstruction. His parents told us this is the fourth occurrence of similar condition in six months. He experienced three separate admissions in local hospital for conservative treatment, which included fasting, gastrointestinal decompression, and intravenous antibiotic therapy. On each occasion, his condition improved significantly within a week, resulting in discharge. He had a past medical history of HB which was diagnosed at the age of one. He received neoadjuvant chemotherapy followed by surgery, which ultimately met the criteria for complete response (CR) (Fig. 1A). At the age of 8, the patient experienced a tumor recurrence. He underwent surgical resection followed by adjuvant chemotherapy, again achieving CR (Fig. 1B).

On admission, physical examination revealed typical signs of intestinal obstruction, with abdominal distension and hyperactive bowel sounds. Laboratory investigations demonstrated a mild increase in inflammatory markers and serum tumor markers was unremarkable. An abdominal computed tomography (CT) revealed stenosis close to hepatic flexure of ascending colon and dilation in ascending colon and terminal ileum (Fig. 2). Combined with his medical history and the recurrent symptoms, the diagnosis of postoperative adhesive intestinal obstruction was initially made. However, given the presence of calcifications on imaging, the possibility of HB recurrence or local metastasis was also included in consideration.

An emergency exploratory laparotomy was performed. Intraoperative exploration revealed a palpable, hard mass located in the mid-ascending colon, which had penetrated the bowel wall and invaded the adjacent mesentery. This mass caused nearly complete obstruction in lumen, resulting in marked dilation of the proximal cecum and terminal ileum (Fig. 3A). The resected specimen confirmed a circumferential mass creating a tight stricture. Notably, the distal colon to the mass was carpeted with innumerable polyps (Fig. 3B). Intraoperative frozen section analysis of the mass revealed glandular structures with nuclear atypia and necrosis, consistent with adenocarcinoma. Consequently, a radical right hemicolectomy with regional lymphadenectomy was performed.

Postoperative histopathological examination confirmed a poor-differentiated adenocarcinoma with the malignant glands penetrated the visceral peritoneum (Fig. 3C). Lympho-vascular invasion was observed with cancer cell detected in more than 7 regional lymph nodes. The distal polyps are confirmed as tubular adenomas (Fig. 3D). The surgical resection margins were free of tumor. The background colonic mucosa exhibited diffuse adenomatous polyposis with varying degrees of dysplasia. An additional positron emission tomography-CT illustrated extensive intra-abdominal metastases. These findings suggested IVc stage according to American Joint Committee on Cancer (AJCC) staging system for CRC. To elucidate the etiology of metachronous HB and CRC, we conducted a detailed re-evaluation of the patient's family history. This inquiry revealed a significant genetic burden: the patient’s father had undergone a total colectomy 10 years ago due to diffuse colonic polyposis, and the patient’s grandmother had succumbed to CRC. However, the family had never undergone genetic testing to establish a definitive diagnosis. Genetic testing identified a heterozygous pathogenic variant in APC (NM_000038.5; c.2804dup; p.Tyr935*), consistent with autosomal dominant inheritance. Segregation analysis showed that the variant was present in his father but absent in his mother. This finding established the definitive diagnosis of FAP as the etiology for the patient's extraintestinal malignancies.

Figure 3 General presentation of the resected specimen and histological analysis. **(A)** The specimen revealed a mass located in the mid-ascending colon (circle), resulted in dilation of the proximal cecum and ascending colon (asterisk); **(B)** The opened specimen revealed a circumferential stricture caused by the mass (circles), penetrated the bowel wall and invaded the mesentery. Innumerable polyps in the distal colon could be noticed (arrows); **(C)** High-power view of tumor revealed disordered glands with nuclear atypia and loss of normal tissue structure (H&E staining, magnification x200); **(D)** Low-power view of the polyp revealed a polypoid lesion characterized by dysplastic glands exhibiting tubular and branching structure (H&E staining, magnification x40).

The patient was treated with chemotherapy of 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) plus bevacizumab. Despite evidence of systemic disease progression, the patient remains alive and is currently undergoing chemotherapy at the time of manuscript preparation.

Discussion

In this study, we report a case of an 11-year-old boy who eventually confirmed FAP, developed advanced CRC following two episodes of HB in infancy and at age of eight. The occurrence of such metachronous multiple childhood malignancies is exceptional in pediatric oncology and strongly present an underlying genetic predisposition. Pediatric CRC is an exceedingly rare entity, with an incidence of 0.12 per million in the 0–14 age group and typically characterized by a poor prognosis and a late-stage diagnosis[6]. In all CRC, hereditary factors have a role in around 5–15% of all cases which FAP accounts for only 1%[7]. However, in the past thirty years, an increase in CRC have led to a transition in adolescents and young adults marking a significant epidemiological change[8]. Therefore, to fit this trend, it is imperative for pediatric surgeons to raise clinical awareness and maintain a high index of suspicion, particularly when managing patients with a family history of malignancy or those with FAP.

Multiple studies and review have demonstrated that FAP patients participating in screening programs benefit from a reduction in CRC incidence and mortality. However, currently, the pediatric management remains inconsistent, under researched, and insufficiently standardized, due to the variation in the recommended timing, frequency, and methods of surveillance between different regions[9]. Although colonoscopy is a cornerstone of management, its implementation in pediatrics remains challenging of its invasive nature, the requirement for multiple anesthesia, and the anxiety provokes in both patients and parents[4, 9]. Nevertheless, individualized surveillance plans remain of significant benefit. The widely recommended time point to start surveillance is at ages 10 to 15 years[2, 5, 10].

Colectomy is inevitable for patients with FAP, yet the it is crucial to determine the precise optimal timing and indications for prophylactic surgery. The decisions are complex and should be discussed with patient, parent, doctors, and psychosocial providers based on multiple factors, including polyp burden and histology, understanding of risks and benefits, life quality, and socio-economic factors.[4, 11]. The recent surgical indications are adenomas > 10 mm, > 500 of polyps > 2 mm, carpeting of the colon of polyps and high-grade dysplasia identified which beyond the ability for endoscopic removal[12]. Although the early-onset severe polyposis always associates with variants between codons 1250 and 1464, studies have reported cases of exceptionally early-onset malignancies that do not mutations within this specific region. Even among individuals sharing the identical pathogenic variant, the phenotype can exhibit variable regarding the onset, severity, and timing of clinical presentation. Lazzareschi et al reported a parallel case involving a patient diagnosed with HB at 11 months and subsequently CRC at 14 years of age[13]. Taken together with our present case, while being speculative, an earlier timeline for colonic surveillance and prophylactic intervention may be considered to perform in patients with germline APC mutation who have been treated for HB[14].

The relative risk of HB in children with FAP is 750 to 7500 times higher, yet the prevalence remains low, reportedly less than 2%[12]. The necessity of routine surveillance remains debate. Given this discrepancy between high relative risk and low absolute incidence, the European Society for Pediatric Gastroenterology Hepatology and Nutrition advises against routine screening for HB in children with FAP [12]. In contrast, the American Association for Cancer Research advocates for active surveillance for HB

in this patient population[4]. The recommended screening strategy consists of liver ultrasound and serum alpha-fetoprotein

(AFP) depends on the guidance's decision every 3 or 6 months between 6 months to 5 years[2, 5, 15, 16]. Herein, we posit that surveillance for HB is imperative, given that early detection may correlate with lower PRETEXT staging and the potential to guide subsequent follow-up strategies for CRC.

Taken together, although established guidelines provide a framework for the general FAP population, clinical management should be tailored to the unique phenotype and needs of the individual patient.

A pivotal lesson from this case is the missed opportunity for early intervention. Our retrospective inquiry revealed the father's history of total colectomy for polyposis. Had this crucial information been linked during the patient's initial HB diagnosis at age 1 or HB recurrence at age 8, it could have prompted early genetic testing, colonoscopy surveillance and advanced prophylactic colectomy, thereby preventing the tragedy of Stage IV carcinoma. This serves as a reminder that for any pediatric cancer patients, the importance of a thorough family history cannot be overstated.

Conclusions

In conclusion, this case highlights the importance of a thorough family history taking when managing a pediatric cancer patient, and underscores the necessity of screening for HB in children with a family history of FAP. Furthermore, HB may serve as an early warning sign for a severe FAP phenotype. Therefore, for FAP patients with a history of HB, clinicians should remain high attention regarding the risk of early-onset CRC. Implementing a more aggressive surveillance strategy, begins earlier than current guideline recommendations, should be considered.

Abbreviations

FAP
Familial adenomatous polyposis
HB
Hepatoblastoma
APC
Adenomatous polyposis coli
CRC
Colorectal cancer
CT
Computed tomography
AJCC
American Joint Committee on Cancer
AFP
Alpha-fetoprotein

CR
Complete response
FOLFOX
5-fluorouracil, leucovorin and oxaliplatin

Declarations

Institutional Review Board Statement:

Not applicable.

Consent for publication:

Written informed consent has been obtained from the parents of the patient to publish this paper.

Clinical trial number:

Not applicable

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The authors declare no conflict of interest

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Author Contribution

Hao Shi provided medical care for this patient, drafted the initial manuscript, confirmed revisions, and submitted the final manuscript; Jiangbin Liu and Xiang Ren provided medical care for this patient, reviewed and revised the manuscript; Guogang Ye and Zhibao Lv provided medical care for this patient, provided figures and collected data of the article.All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Data Availability

The datasets used during the current study are available from the corresponding author upon reasonable request.

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Figures

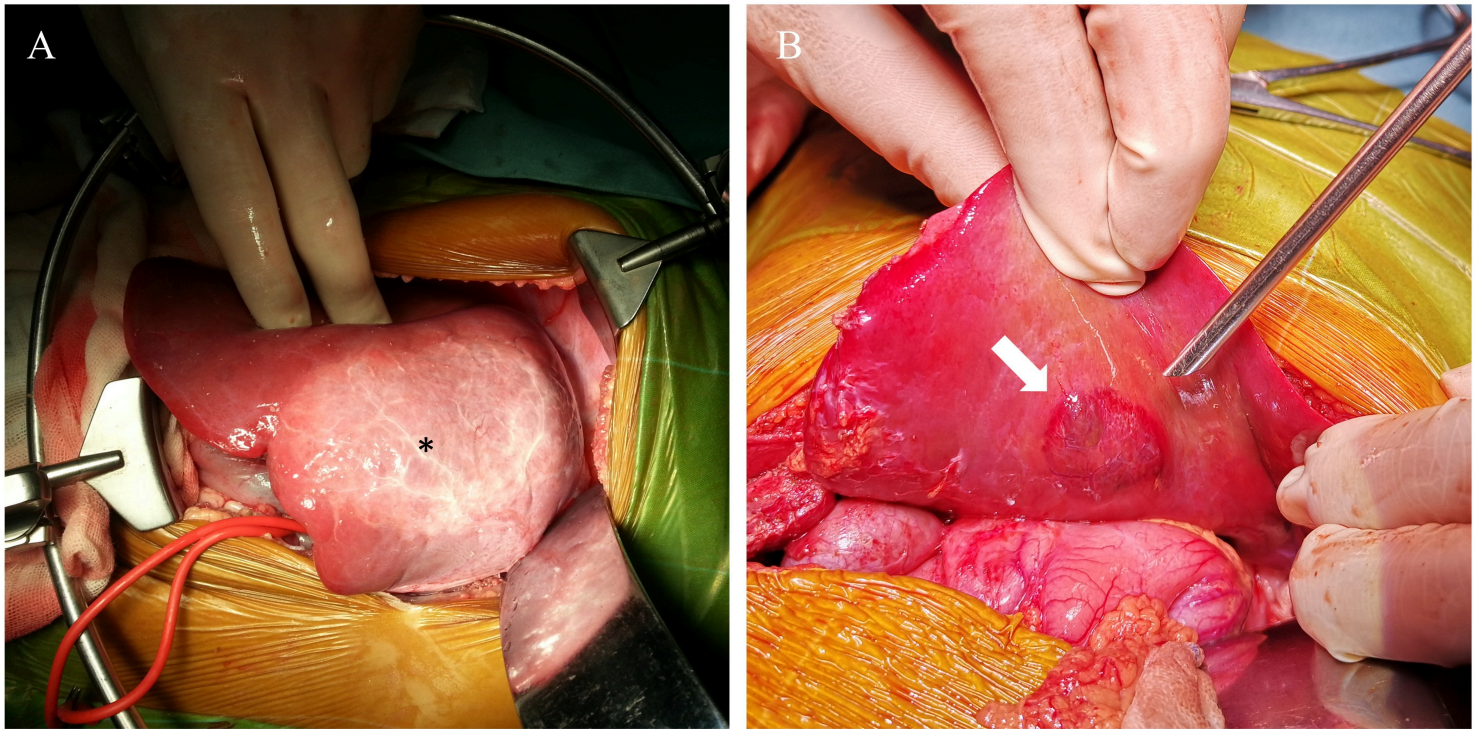


Figure 1

Intraoperative photographs in two HB surgeries. **(A)** The primary HB identified in liver segments IV, V, and VIII (asterisk); **(B)** The recurrent HB identified during the second surgery, located in liver segment III (arrow).

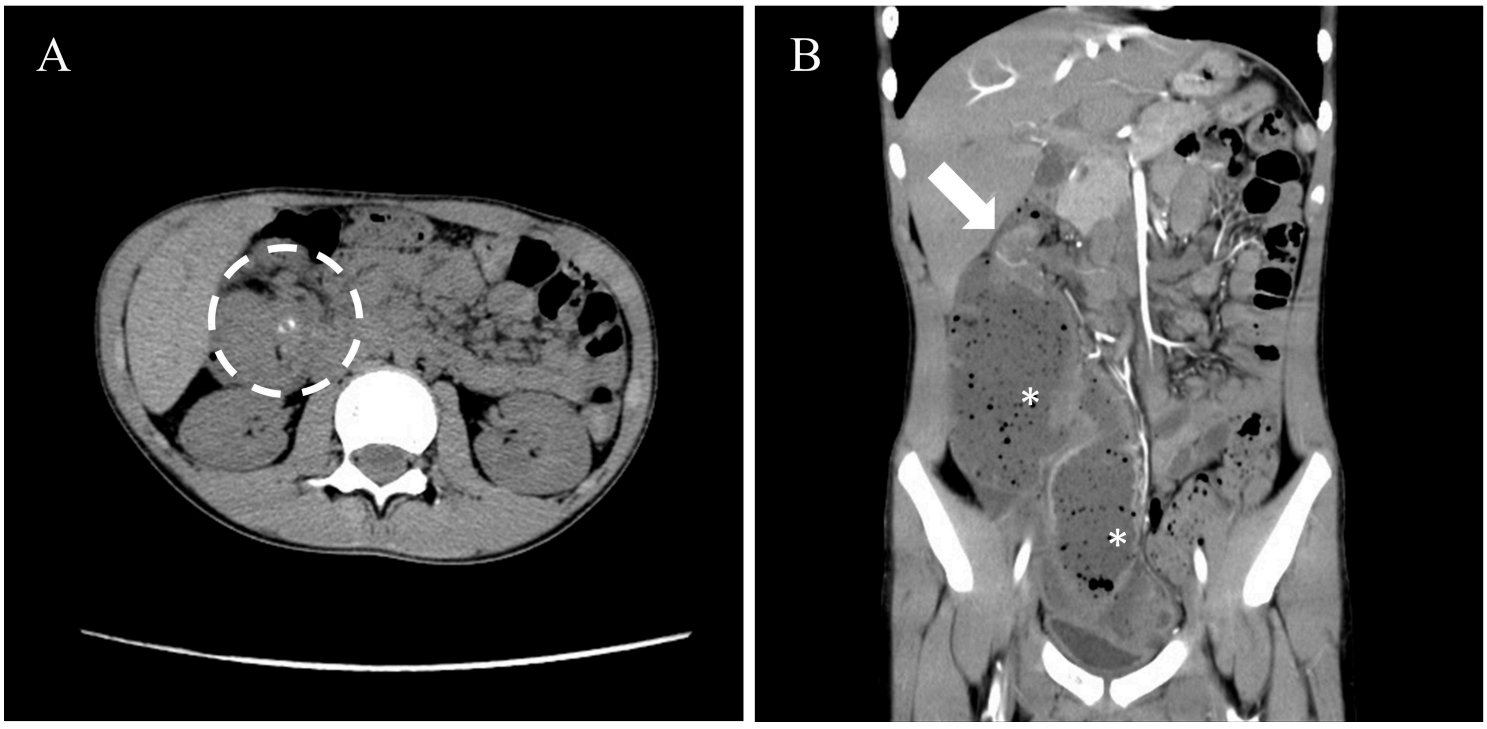


Figure 2

Abdominal CT images upon admission. **(A)** Cross-sectional image revealed calcification on mesentery near the hepatic flexure (circle), distinct from the liver; **(B)** Coronal images revealed a transition point at the hepatic flexure (arrow) with significant upstream dilation of the ascending colon and terminal ileum (asterisks).

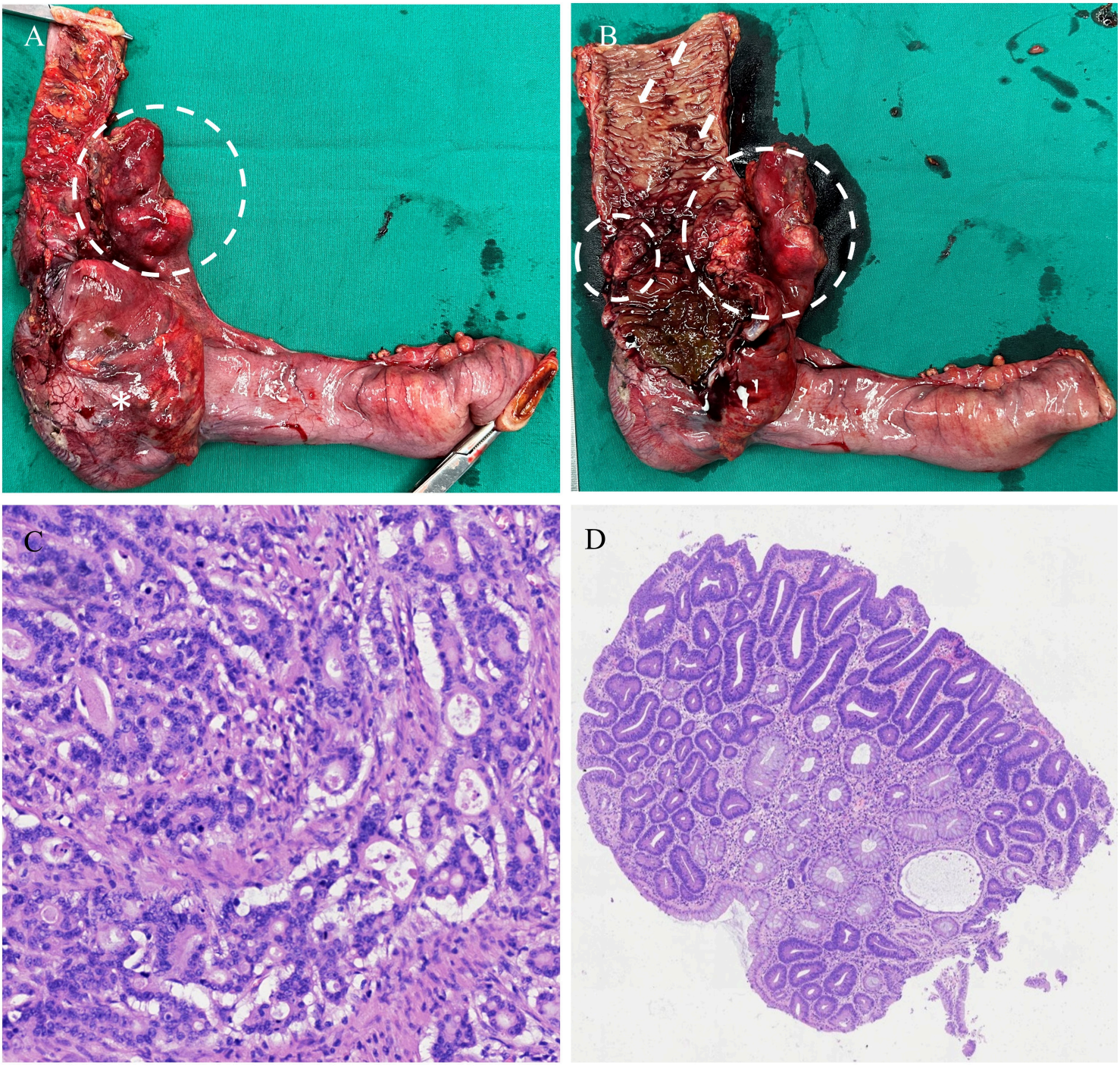


Figure 3

General presentation of the resected specimen and histological analysis. **(A)** The specimen revealed a mass located in the mid-ascending colon (circle), resulted in dilation of the proximal cecum and ascending colon (asterisk); **(B)** The opened specimen revealed a circumferential stricture caused by the mass (circles), penetrated the bowel wall and invaded the mesentery. Innumerable polyps in the distal

colon could be noticed (arrows); **(C)** High-power view of tumor revealed disordered glands with nuclear atypia and loss of normal tissue structure (H&E staining, magnification x200); **(D)** Low-power view of the polyp revealed a polypoid lesion characterized by dysplastic glands exhibiting tubular and branching structure (H&E staining, magnification x40).