Diagnostic Pathology

REVIEW

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Family adenomatous polyposis come across dome type adenocarcinoma: a case report and literature review

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Abstract

Dome-type carcinoma (DC), also referred as Gut-associated lymphoid tissue (GALT) carcinoma, is a rare variant of colorectal adenocarcinoma which has been seldomly reported up to now. We report a case of a DC lesion developed in a 33-year-old male diagnosed with family adenomatous polyposis (FAP). A 1.5 × 1.5 cm well-demarcated lesion exhibited a 0-Is + IIc figure was detected near the anastomotic stoma during regular colonoscopic polypectomy. Surgical specimen showed well-differentiated adenocarcinoma consisted of dilated cystic glands and the lymphoid stroma with reactive germinal centers exhibited a destructive manner of infiltration into SM2 level. The immunohistochemical findings revealed MUC1 positive but MUC2 negative of the carcinomas epithelial which retained all the 4 mismatch repair proteins (MMRs) (MLH1, PMS2, MSH2, and MSH6) and was negative for EBV-encoded small RNA-1 (EBER). Considered a rare category of colorectal adenocarcinoma, more cases will help uncover the nature of GALT/dome-type carcinoma. Clinicians and pathologists should be aware of recognizing this special type of carcinoma and making necessary differential diagnostics.

Background

Dome-type carcinoma (DC) is a rare variant of colorectal adenocarcinoma first described in 1999 [1]. This kind of carcinoma is characterized by neoplastic intestinal epithelial within the gut-associated lymphoid tissue (GALT) which is also referred to as "lymphoglandular complexes" (LGCs) [2]. As such, the umbrella term "GALT/dome-type carcinoma" was applied to nominate this special kind of carcinoma [3]. Some previous cases have reported a certain evolvement of DCs from adenomatous background [4]. However, there was only one case mentioned the relationship between DC and family adenomatous polyposis (FAP) [5]. In this case report, we describe a DC lesion which is derived from a background of FAP.

Case presentation

Family members with FAP are indicated with Shading. Squares and circles denote males and females respectively. Individuals labeled with diagonal lines represent deceased. The black arrow denotes the proband (diagnosis age indicated), solid symbols indicate affected individuals, and open symbols indicate unaffected individuals. I, II, III and IV indicate generations. A total of three members were diagnosed with FAP showing the typical autosomal dominant inheritance pattern of FAP.

Figure 1 shows a four generation Chinese pedigree with 12 members, among whom 3 individuals were affected

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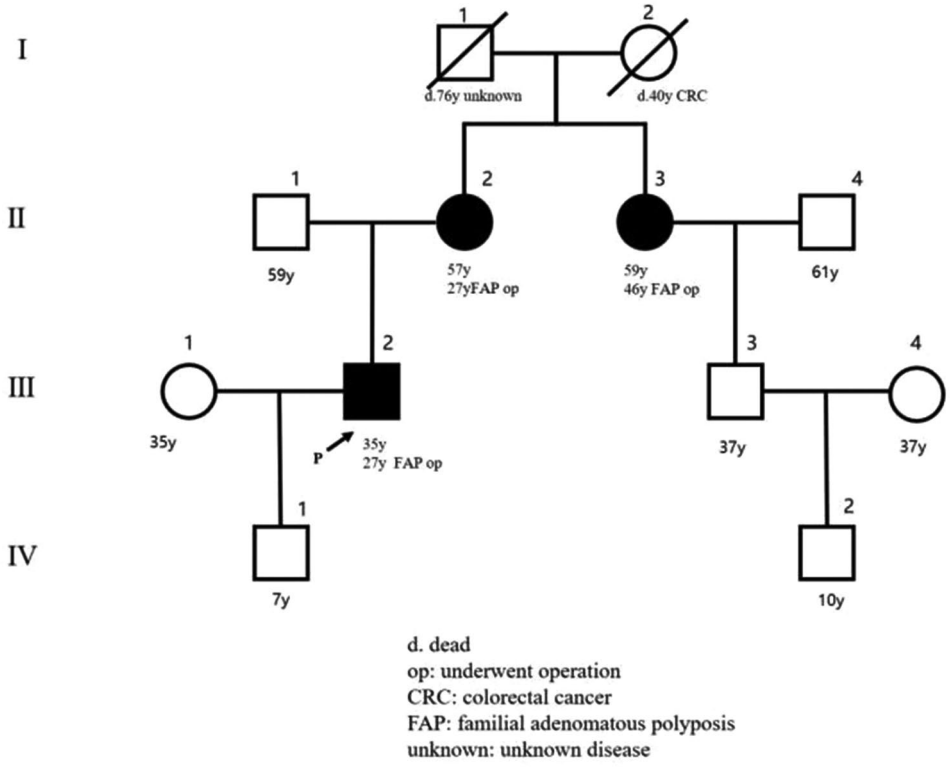

Fig. 1 Pedigree structure of the FAP family

by FAP and underwent operation. The self-reported age of onset ranged from 27 to 46 years. Another 1 affected family members (I-1) died of colorectal cancer (over a background of polyps) at the age of 40. The index case (III-2, black arrow), was diagnosed with adenomatous polyposis of definite familial heritability at age 27 and underwent right hemicolectomy. Since then, he came to our center for colonoscopy and polypectomy regularly. 7 years later, he suffered intermittent hematochezia but without weight loss, fever, chills or fatigue. He accepted colonoscopy again, during the screening, a 1.5 × 1.5 cm lesion located near the anastomotic stoma of remnant ascending colon caught our sight because of a 0-Is + IIc outlook. The near field observation showed that in the middle of this lesion the capillaries were lack of uniformity with blind ending (Sano IIIA type [6]). Meanwhile, the glandular tubes were irregular as well and some parts seemed no structure (Kudo Vn type [7])(Fig. 2). Interestingly, the capillaries and glandular tubes of the surrounding epithelial were extremely uniformed as normal mucosa. Biopsy histology of this lesion revealed tubulous adenoma with low-grade and locally high-grade intraepithelial neoplasia, UL (+), lymph tissue proliferation. In suspicion of invasive cancer, we recommend this patient to undergo surgical resection again.

The histological manifestation of the resected specimen showed a background of abundant adenomas mucosa which was consist with the FAP diagnosis. Besides, a well-differentiated adenocarcinoma developed on the adenomas background was spotted (Fig. 3). This lesion exhibited expansive growth associated with a dense lymphocytic stroma within which well-developed germinal centers could be identified. Under magnifying view, no doplastic stroma was observed and the tumor was covered with mucosa of low-grade intraepithelial neoplasia. Meanwhile, right beneath the main lesion, a cluster of glandular epitheliums confining to lymphoid stroma (LGC) was observed. The epithelium lined by well differentiated eosinophilic columnar cells showed high-grade intraepithelial neoplasia and formed dilated cysts containing abundance necrotic and eosinophilic debris (Fig. 4A-D) that was positive with periodic acid-Schiff diastase (PAS-D) (Fig. 4E). The final pathologic examination showed no lympho-vascular and perineural invasion, no metastasis was observed in 9 regional lymph nodes.

Additional immunohistochemical staining was performed for a better understanding of this lesion. The desmin staining showed a destructive manner of infiltration and the forward of tumor was deep inside the submucosal layer (SM2 level) (Fig. 5A-B). CD20 staining showed lymphoid follicles with germinal centers and T-lymphocyte were labeled with CD3 (Fig. 5C-D).The carcinomas epithelial was MUC1 (Fig. 6A) positive but negative for MUC2 (Fig. 6B) indicating the derivation of intestine

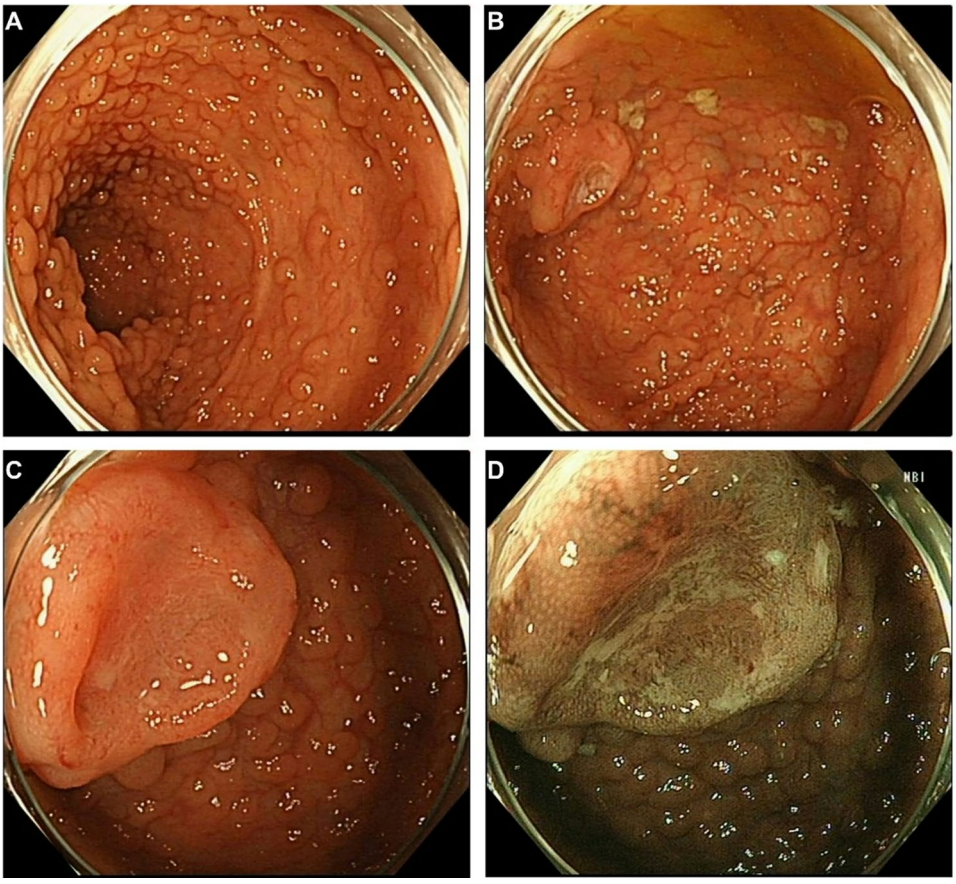

Fig. 2 **A** FAP background of numerous adenomas throughout the residual colon. **B** the gross appearance of a 0-Is + IIc lesion detected near the anastomotic stoma. **C**. near field observation of the lesion. **D** NBI observation of the lesion

epithelial but in absent of goblet cells [8]. In addition, the MMR proteins expressions were retained and in situ hybridization for EBV-encoded small RNA-1 (EBER) was negative which suggested microsatellite stability (MSS) (Fig. 6C-F) of this tumor and no relation with EBV infection (Fig. 6G).

Postoperatively, the patient recovered steadily and was discharged 6 days after surgery. Colonoscopy at 6 months and annual follow-up within two years to date revealed a healed lesion without recurrence.

Discussion

GALT/dome-type carcinoma is considered deriving from the M-cells involving lymphoglandular complex(LGC) which is a special part of intestinal mucosa [9]. M-cells may regenerate in response to inflammation, grow into colorectal mucosa-associated lymphoid tissues to form LGCs which may be the ultimate histologic basis for the formation of DCs.

To our knowledge, there are over 20 cases of GALT/dome-type carcinomas up to now [10]and recently, a multi-institutional international cohort including 20 lymphoglandular complex-like carcinoma (LGCC), which are characterized as colorectal carcinomas with associated prominent lymphoid infiltrates, listed the most 12 cases of DCs [11]. However, even fewer reports demonstrated the relation between this rare type carcinoma with FAP.

One previous report mentioned a DC patient's daughter suffered FAP as family history for the patient himself which actually offered no evidence of interaction between FAP and DC [5]. Since then, FAP has been considered a probable pathogenesis for GALT/dome-type carcinoma all by mistake. Here, we reported an DC case absolutely developed on the background of FAP. Nevertheless, it is worth noting that nearly half of DC lesions showed relation with adenomatous mucosa [4]. Combined with our findings, this phenomenon may not be interpreted as accidents. As we all know, GALT mucosa is scattered throughout the intestine mucosa [12] and one previous study have revealed that about 38% non-protruding adenomas were accompanied with GALT aggregates [13]. Therefore, it is reasonable to speculated that diffuse adenomatous mucosa might gain more opportunities for dome epithelial to form DCs.

According to previous reports, DC lesions usually exhibited plaque-like, sessile, polypoid and mostly

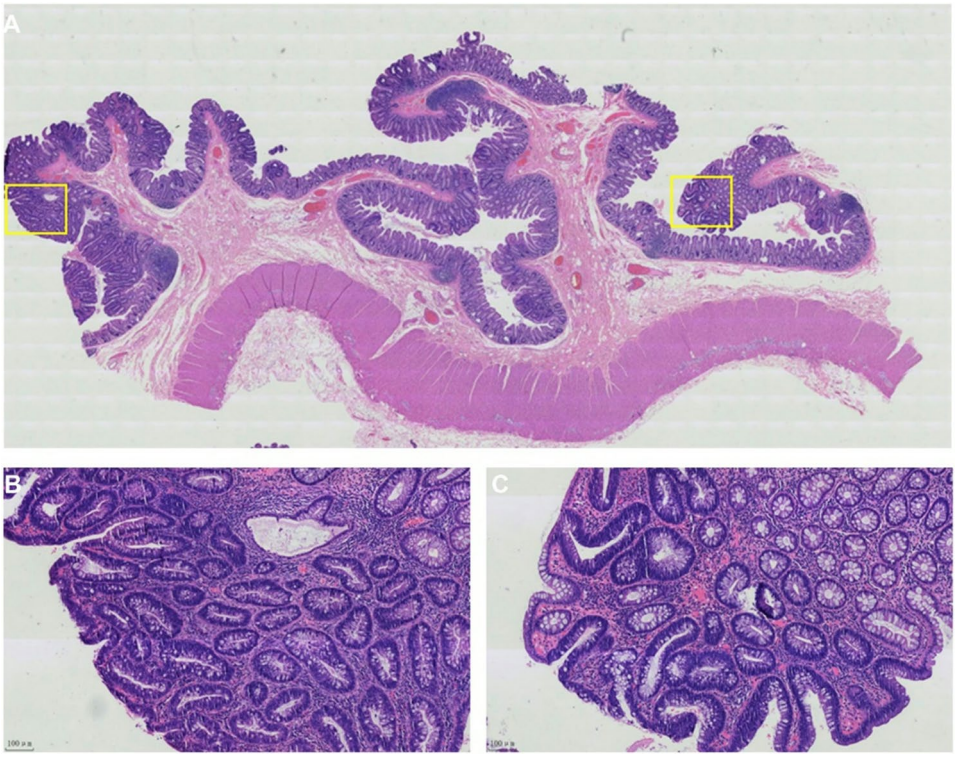

Fig. 3 **A** Panoramic view of peripheral mucosa. **B** and **C** high-power view of the tubular adenoma with mild dysplasia in the yellow boxes of A (H&E, ×100)

SMT-like appearances endoscopically [3], lesions of 0-Is + IIc type as was showed in our case have been seldomly reported. However, due to the natural of expending growth [5], it is comprehensible of DCs to manifest raised figures no matter in what state or stage of the lesions. The mucosa of LGCs is known to protrude through gaps in the muscularis mucosae into the submucosa, accompanied by prominent lymphoid nodules [14]. Thus, DC lesions derived from LGCs, which are surrounded by benign lymphoid aggregates, must be identified apart from adenoma with dysplasia herniation and invasive adenocarcinoma with lymphoid aggregates. Generally, adenoma with dysplasia herniation, which is also called pseudo-invasion, are often seen at the edge of the specimen and may result from tangential sectioning or tissue processing artifacts. Meanwhile, invasive adenocarcinoma with lymphoid aggregates, which is also referred as true invasion, also shows neoplastic glands within or beyond the muscularis mucosa with Crohn's disease-like reaction. However, true invasion is also present discontinuous or irregular pattern of glandular growth, cytological atypia within the invading glands and stromal desmoplasia and discrete inflammatory infiltrate [15]. Therefore, careful examination of adjacent sections, structural and cytological dysplasia are important to differentialize LGC-derived DCs from true invasion and pseudo-invasion.

However, under some special situation, pseudo-invading adenoma involving LGCs, as a rare phenomenon, brings diagnostic challenge in distinguishing from DCs. Generally, LGC-associated adenomas harbor the features of neoplastic glandular epithelium such as relative regular cell and gland morphology with dysplasia, reserved goblet cells expression (MUC 2 positive). The most important feature of pseudo-invading adenoma is an intact rim of muscularis mucosae surrounded the adenoma which forms 'herniation' structure. Histological characteristics, such as gland angulation, gland fusion, and occasionally single-cell infiltration, stromal desmoplasia, and high-grade cytologic atypia, and lack of crypt rupture, mucin without epithelial cells, fibroinflammatory stromal reaction, hemosiderin, and granulation tissue, suggest diagnosis of DCs [11].

As were showed in our case, all these features such as well-differentiated adenocarcinoma consisted of dilated cystic glands, the lymphoid stroma with reactive germinal centers, MUC1 positive but MUC2 negative suggested DC derived from FAP background. In order to differentiate from medullary-like carcinoma, Lynch syndrome and microsatellite instability-high (MSI-H) CRC, necessary exams such as MMRs identification, in situ hybridization for EBER and CD3/CD20 IHC staining [3] were also performed. Due to the presence of intact muscularis mucosae and basic findings above, it is reasonable

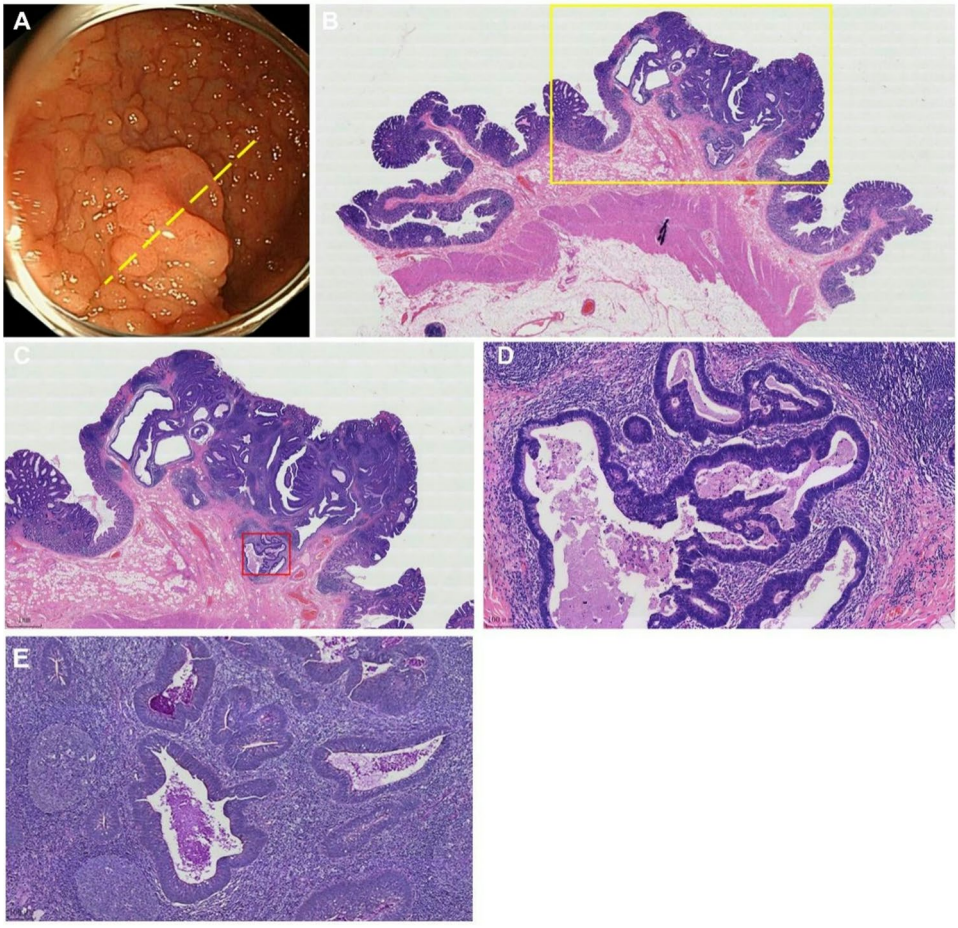

Fig. 4 **A** split path of the lesion; **B** Panoramic view of the lesion. **C** Higher-power magnification of the yellow box in B (H&E, ×10). **D** Higher-power magnification of the red box in C The neoplasia epithelium lined by well differentiated eosinophilic columnar cells and formed dilated cysts containing abundance necrotic and eosinophilic debris (H&E, ×100). **E** The intraglandular eosinophilic debris showed intensive PAS-D positive (×100)

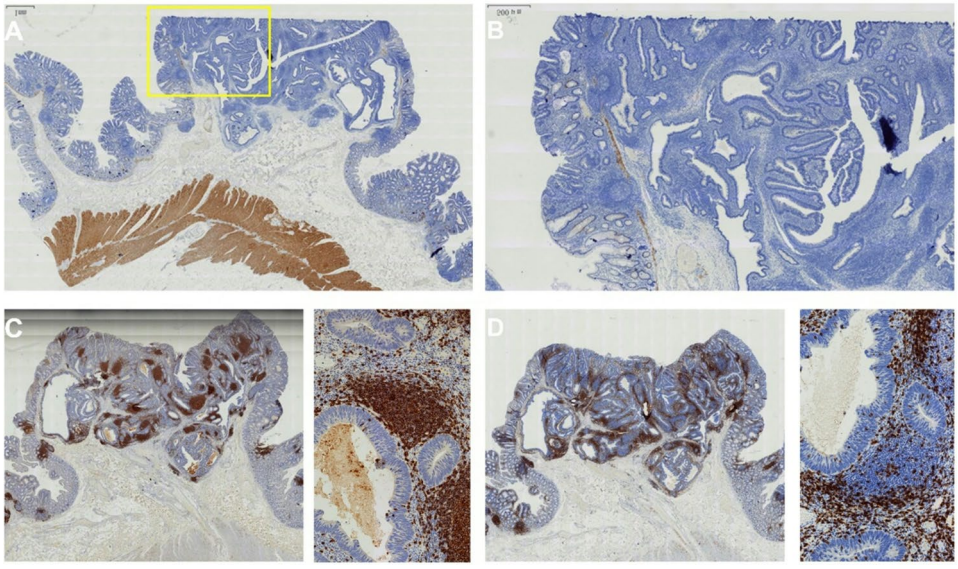

Fig. 5 **A** desmin staining outlined muscularis mucosae. **B** higher-power magnification of the yellow box in A (IHC, ×40). **C** CD20 staining labeled lymphoid follicles (lower power in left panel, higher-power in the right panel, ×200). **D** CD3 staining labeled T-lymphocyte in the tumor-infiltrating lymphoid tissue (lower power in left panel, higher-power in the right panel, ×200)

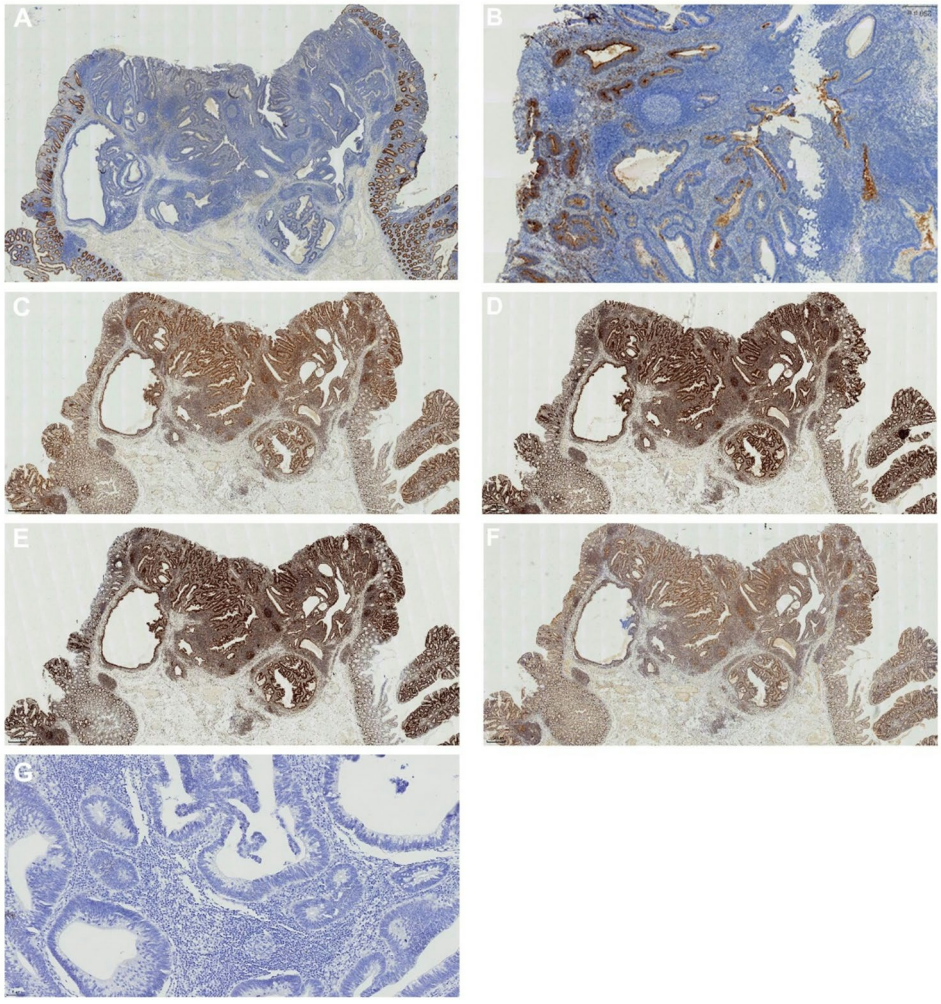

Fig. 6 **A** MUC2 staining (IHC, ×10). **B** MUC1 staining (IHC, ×20). **C** MLH1 staining (IHC, ×10). **D** MSH2 staining (IHC, ×10). **E** MSH6 staining (IHC, ×10). **F** PMS2 staining (IHC, ×10). **G** negative expression of EBER (×100)

to interpreted DC as dysplasia of dome epithelia invaded into submucosal lymphoid tissue.

DCs are generally regarded as malignant tumors with a favorable prognosis, this conclusion is also suitable for our case after a long period follow-up and observation. this perspective was primarily supported by the following clinical and pathological observations: (1) well-differentiated carcinomatous glands structures, (2) the majority of cases exhibited confinement to the submucosal layer despite the presence of MMR deficiency, (3) few documented metastases to lymph nodes or to distant sites, (4) no reported recurrences or disease-related deaths to date, (5) the expanding dome area predominantly consists of lymphoid tissue rather than carcinomatous epithelium, suggesting a poorer proliferative potential of DC compared with conventional CRCs [16, 17]. One recent report presented several DCs (necessary diagnostic and differential diagnostic information was intact) with T3 invasion (2 of 12 cases) and lymphoid nodule invasion (at least 3 of 12) [11], but there was still limit evidence of poor prognosis for DCs. All these histological characteristic implied that the lymphoid tissue might play a role in inhibiting aggressive behavior of DCs.

Taken together, we deem that DC presents a good biological behavior. In clinical practice, patients may benefit from minimally invasive treatment approaches. It is considerable to take colonoscopy follow-up after colectomy without further chemo- or radio- therapies as implemented in the present case. As a result, the short-term follow-up showed no adverse event and the sustained attention will be paid to observe long-term survival.

Conclusions

We report an additional case of dome/GALT carcinoma on the background of FAP. This case indicated that adenomatous mucosa may be a suitable soil for DC development which is consist with most cases reported up to now. However, more cases and adequate follow-up are

needed to further elucidate the nature of such lesions clinically and pathologically.

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Author contributions
YH W analyzed and interpreted the histopathological and immunohistochemical results; XL Z, YY C collected the clinical information and wrote the manuscript; TS L revised the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All methods in this study were carried out following relevant guidelines and regulations. Ethical approval was obtained from the Ethics Committee of Jiangsu Provincial Hospital of Chinese Medicine. All data were handled confidentially and in compliance with relevant privacy laws and regulations. The study protocol ensured that the research objectives could be achieved without compromising patient privacy or the ethical standards of medical research.

Consent for publication
Written consent for publication of the case was obtained from the patient.

Competing interests
The authors declare no competing interests.

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