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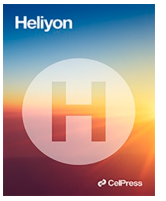

Case report

EBV-positive inflammatory follicular dendritic cell sarcoma of the colon with clonal immunoglobulin gene rearrangement: A case report and literature review

Xia Xu [a], Xiuzhen Li [a], Qun Deng [b], Kaihang Yu [a], Jinfan Li [a,*]

[a] Department of Pathology, Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China
[b] Department of Surgical Oncology, Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China

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ABSTRACT

Introduction: Epstein-Barr virus-positive (EBV+) inflammatory follicular dendritic cell (FDC) sarcoma is a rare neoplasm characterized by spindle-shaped follicular dendritic cells, marked lymphoplasmacytic infiltration, and a consistent link to EBV. While it typically affects the liver and spleen, it is exceptionally rare in the digestive tract. We present a special case of EBV + inflammatory FDC sarcoma arising in the colon with clonal immunoglobulin (IG) gene rearrangement.

Case presentation: A 70-year-old man presented with a one-month history of abdominal distension. Colonoscopy revealed a pedunculated polyp in the ascending colon, which was subsequently removed via endoscopic polypectomy. Histological examination of the colonic polyp demonstrated a pronounced lymphoplasmacytic infiltrate with scattered EBV + neoplastic cells, as evidenced by EBV-encoded small RNA in situ hybridization (EBER ISH). The neoplastic cells were positive for FDC-specific markers, including CD21, CD35, and CD23. Additionally, the tumor exhibited clonal rearrangement of the immunoglobulin heavy chain (IGH) gene. The diagnosis was confirmed as EBV + inflammatory follicular dendritic cell sarcoma.

Conclusions: We described an exceptional case of EBV + inflammatory FDC sarcoma presenting as a colonic polyp, featuring a clonal IGH gene rearrangement not previously documented in this colonic tumor type. Heightened awareness of this rare neoplasm within the gastrointestinal tract is essential for both accurate diagnosis and effective patient management.

1. Introduction

Follicular dendritic cell (FDC) sarcoma is a rare malignant neoplasm that exhibits the morphological and immunophenotypic characteristics of FDCs, potentially arising from mesenchymal tissues. A special subtype, Epstein-Barr virus-positive (EBV+) inflammatory FDC sarcoma, presents with clinical and pathological features that distinguish it from the more conventional FDC sarcoma. This variant is characterized by histological features reminiscent of inflammatory pseudotumors and is consistently associated with EBV [1]. While it is most commonly encountered in the liver or spleen, it is exceptionally rare within the digestive tract, where it may present as a polypoid lesion.

* Corresponding author.
E-mail address: 2307024@zju.edu.cn (J. Li).

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We reported an unusual case of EBV + inflammatory FDC sarcoma that appeared as a pedunculated polyp in the ascending colon, accompanied by a clonal IGH gene rearrangement. Furthermore, we conducted an extensive review of the English literature, summarizing the clinicopathological features and outcomes of EBV + inflammatory FDC sarcoma within the digestive tract.

2. Case presentation

2.1. Clinical findings

A 70-year-old man presented with a one-month history of abdominal distension, yet without experiencing abdominal pain, vomiting, alterations in bowel habits, weight loss, or fever. His medical history included hypertension, fatty liver, and empyema, but was notably free of any haematolymphoid tumor diagnoses. Laboratory investigations revealed a positive fecal occult blood test; however, other blood work, including levels of carcinoembryonic (CEA), carbohydrate antigen 199 (CA199), cancer antigen 125 (CA125), hemoglobin, thyroid hormone, blood coagulation function, renal function tests, and liver function tests, were all unremarkable. Contrast-enhanced abdominal computed tomography (CT) depicted polypoid hyperplasia with enhancing features in ascending colon, suggestive of a neoplastic process (Fig. 1A and B). Chest CT scans were consistent with changes associated with chronic empyema. Colonoscopic examination revealed a pedunculated polyp of 2.5 cm × 2.5 cm located 60 cm from the anal verge, characterized by surface ulceration and prominent dilated blood vessels evident upon narrow-band imaging (NBI) (Fig. 1C and D). Endoscopic biopsy of the colonic tissues demonstrated chronic active inflammation. The patient underwent endoscopic polypectomy one week following the biopsy. During the subsequent four-month follow-up period, there were no signs of disease recurrence post-polypectomy, and the patient did not receive radiotherapy or chemotherapy.

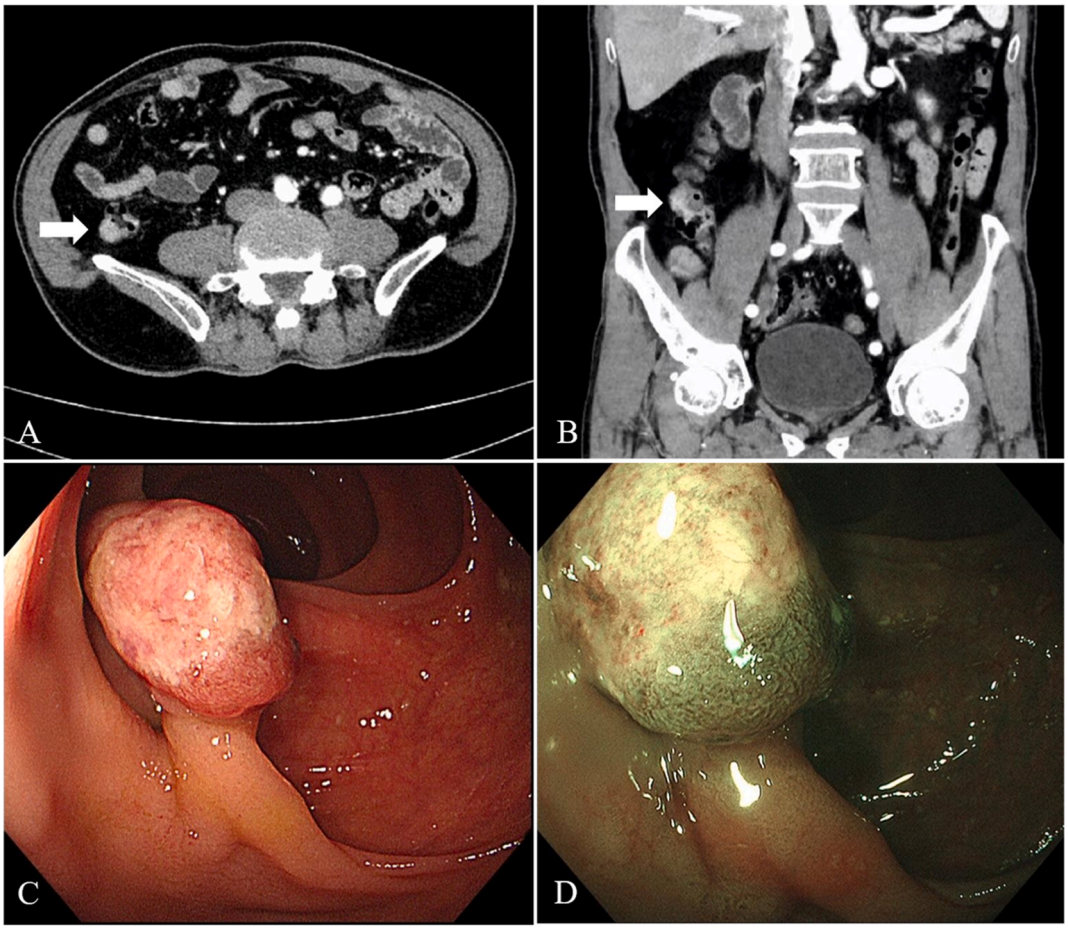

Fig. 1. CT and Colonoscopy reveal a polyp. (A.B) The right posterior wall of the ascending colon shows localized thickening with a nodular protrusion into the lumen, the serosal surface is smooth, measuring approximately 12mm by 13mm by 14mm, with uniform density, and progressive persistent enhancement following contrast (white arrow). (C)Colonoscopy reveals a 2.5 cm pedunculated polyp in the colonic lumen. (D) Narrow-band imaging (NBI) shows ulcers on the surface and locally abundant dilated blood vessels.

2.2. Pathological findings

The resected tumor, measuring 2.5 cm × 1.0 cm × 1.0 cm, was a pedunculated polyp with areas of surface ulceration. The cut surface appeared tan, indicating a solid and firm consistency. On microscopic examination, the polypoid lesion exhibited focal ulceration and pronounced lymphocytic infiltration, predominantly composed of lymphocytes and plasma cells, with only a sparse presence of eosinophils. Additionally, there was evidence of focal hyperplastic blood vessels (Fig. 2A and B). Within the inflammatory background, atypical cells with a spindled to oval shape, containing lightly eosinophilic cytoplasm and ill-defined cell borders, were scattered separately, not organizing into intersecting fascicles. These dispersed neoplastic cells were particularly prominent in the region beneath the area of ulceration. They possessed vesicular nuclei with stippled chromatin and distinct, centrally located nucleoli.

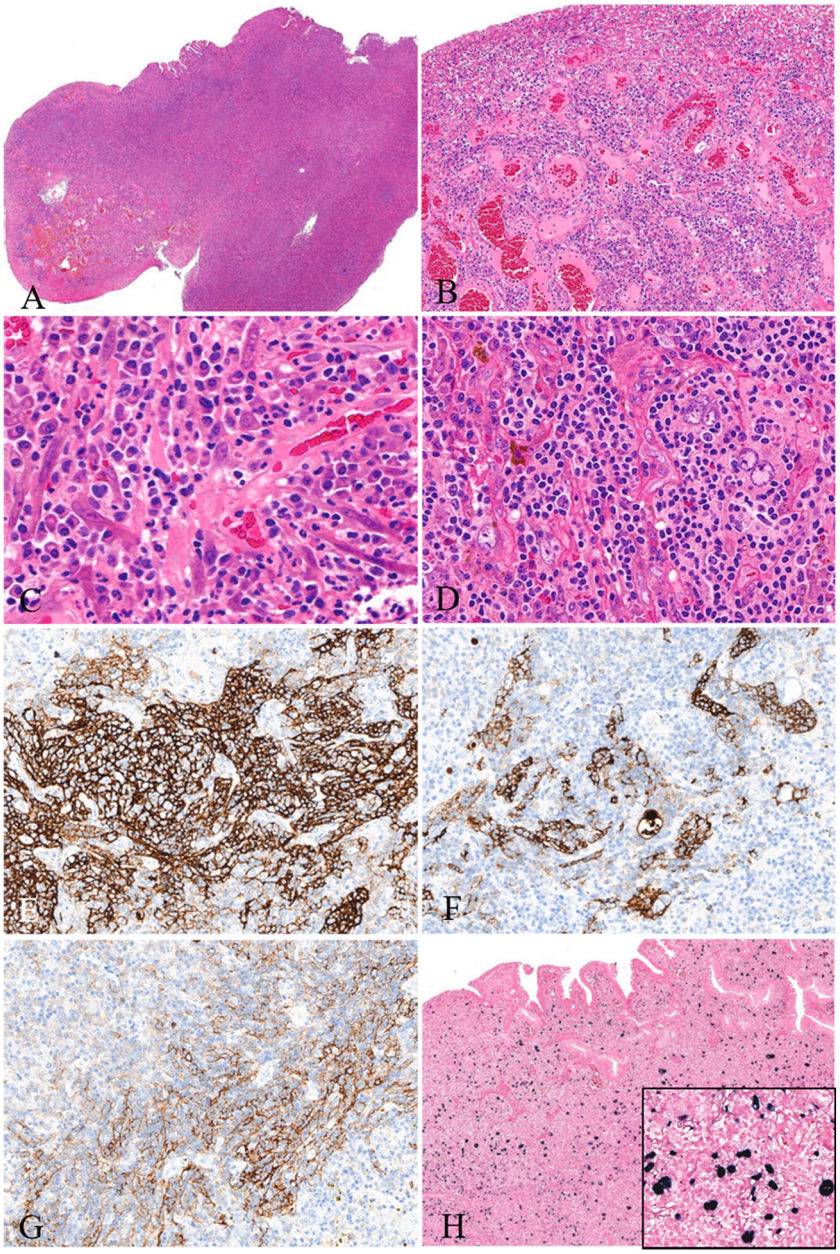

Fig. 2. Pathological features of EBV + inflammatory FDC sarcoma. (A) A tumor of the colon presents as a polyp (10 ×). (B)The tumor shows focal ulceration, hyperplastic blood vessels, and a prominent lymphocytic infiltration (100 ×). (C)Some tumor cells have large, spindled nuclei (400 ×). (D)Some tumor cells are mononuclear or binucleated with prominent nucleoli, resembling Reed-Sternberg cells (400 ×). (E–G) Immunohistochemistry shows that the tumor cells express (E)CD21, (F)CD23, and(G)CD35 (200 ×). (H)The tumor cells are positive for Epstein-Barr virus in situ hybridization (100 × , 400 ×).

Highly variable nuclear atypia can be found, with some slender, bland-looking nuclei, and some enlarged, irregularly folded, and hyperchromatic nuclei. Occasionally, large neoplastic cells resembled Reed-Sternberg cells, with binucleated and mummified forms (Fig. 2C and D). Mitoses were sparse.

2.3. Immunohistochemical and molecular findings

Immunohistochemical studies showed that these atypical spindled or oval cells expressed CD21, CD35, CD23, CD45, and focally expressed epithelial membrane antigen (EMA), smooth muscle actin (SMA), and desmin, but not D2-40, anaplastic lymphoma kinase (ALK), CD30, CD163, and pan-cytokeratin (Fig. 2E–G). The inflammatory background consisted of a mix of $CD20^+$ B cells, CD138+ plasm cells, and $CD3^+$ T cells. The plasma cells were polytypic by kappa and lambda staining (2:1 ratio). The proliferation index, as measured by the percentage of Ki-67-positive cells within the tumor, was about 10 %. These atypical large cells were also positive for in situ hybridization, highlighting the slightly atypical to bizarre nuclei (Fig. 2H).

A clonality assessment utilizing polymerase chain reaction (PCR) for B-cell receptor gene rearrangement demonstrated a positive amplification of immunoglobulin heavy chain (IGH) gene rearrangement, using FR2 and DH primers (Fig. 3), and negative results for immunoglobulin k-light chain (IGK) and immunoglobulin λ-light chain (IGL) gene rearrangement amplification. The PCR-based clonality analysis for T-cell receptor gene rearrangement was also negative. For each test, all control specimens were well amplified.

3. Discussion

FDC sarcoma is an uncommon tumor that originates from FDCs. According to its morphology, it can be classified into two types: conventional FDC sarcoma and EBV-positive inflammatory FDC sarcoma [2,3]. EBV-positive inflammatory FDC sarcoma, also referred to as inflammatory pseudotumor-like FDC sarcoma (tumor), is featured with neoplastic FDC proliferation, abundant lymphoplasmacytic infiltrates, and a consistent association with EBV. It is predominantly found in the liver and spleen, but it is exceptionally rare in the gastrointestinal tract, with only 12 cases documented in English medical literature (Table 1). When including the current case, a review of all thirteen cases of gastrointestinal EBV + inflammatory FDC sarcoma [4–9] shows that the median age of the patients is 57 years old (ranging from 42 to 78 years). The gender distribution is fairly even, with a male-to-female ratio of 6:7, indicating no significant sex predilection. These tumors typically manifest as polyps or masses within the colon. Clinical presentations are usually not specific, including symptoms such as abdominal discomfort and hematochezia, or may even be asymptomatic. In the case presented, the patient underwent enteroscopy due to abdominal distension and a positive fecal occult blood test, which led to the discovery of a pedunculated polyp. However, systemic symptoms like fever or weight loss were absent. Given the rarity of gastrointestinal EBV + inflammatory FDC sarcoma, there is no widely accepted standard of treatment to date. The existing clinicopathologic features indicate a somewhat indolent nature of the tumor, and the prognosis following polyposis resection appears to be highly favorable, although long-term follow-up data remains scarce.

EBV + inflammatory FDC sarcoma is characterized by a prominent lymphoplasmacytic background infiltrate, with the neoplastic cells being inconspicuously scattered, which can lead to confusion with other tumor types. The tumor often features small to medium-sized blood vessels, and it is not uncommon to observe fibrinoid deposits and hyaline degeneration affecting the walls of these vessels. The neoplastic cells typically exhibit immunoreactivity to one or more FDC markers, such as CD21, CD23, CD35, D2-40, CXCL13, and clusterin, although the staining pattern may vary from diffuse or focal. There are documented cases that, while lacking FDC markers, show positivity for non-FDC markers, such as smooth muscle actin (SMA), which can present with a fibroblastic/myoid immunophenotype [5,10]. Beyond immunohistochemical staining, the neoplasm is consistently linked to EBV infection, evidenced by a

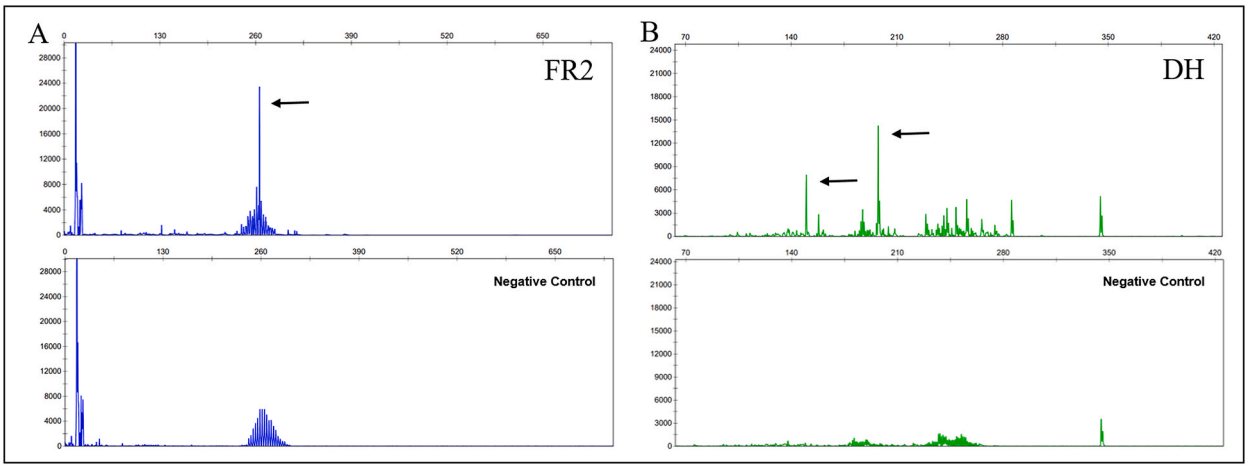

Fig. 3. Clonal immunoglobulin heavy chain rearrangement. (A.B) The 3 indicated peaks (black arrow) represent the rearranged PCR products of the IGH gene, using FR2 and DH primers.

Table 1
Clinicopathological features of 13 colon EBV-positive inflammatory FDC sarcomas.

Case	Age(y)	Size	Immunohistochemistry				Clonal	Clonal	Treatment	Outcome	Reference
No.	/Sex	(cm)	CD21	CD23	CD35	D2-40	IG	TCR		(month)	
1	78/F	3.9	+	+	+	+	–	NR	Polypectomy	NED, 5	Pan et al. [4]
2[a]	42/F	4.5	–	–	–	NR	NR	–	Polypectomy	Normal	Gong et al. [5]
3	46/F	4	+	+	+	+	NR	NR	Surgery	NED, 5	Goh et al. [6]
4	54/M	2.4	+	+	–	+	–	NR	Surgery	Uneventful	Chen et al. [7]
5	68/M	2	+	+	–	+	NR	NR	Polypectomy	Uneventful	Chen et al. [7]
6	53/M	1	+	+	+	+	–	–	Polypectomy	NED,11	Ke et al. [8]
7	48/F	4.5	+	+	+	+	–	–	Surgery	NED, 7	Ke et al. [8]
8	53/M	3.5	+	+	+	+/−	NR	NR	Surgery	NED, 18	Jiang et al. [9]
9	77/F	3	+	–	+	+	NR	NR	Polypectomy	NED, 14	Jiang et al. [9]
10	59/F	2.5	+	+	+	+	NR	NR	Polypectomy	NED, 84	Jiang et al. [9]
11	57/M	0.8	+	–	+	+	NR	NR	Polypectomy	Died of PP	Jiang et al. [9]
12	64/F	2.4	+/−	–	–	+	NR	NR	Surgery	NED, 122	Jiang et al. [9]
13	70/M	2.5	+	+	+	–	+	–	Polypectomy	NED, 4	Present case

NED, no evidence of disease; NR, not recorded; PP: Paraneoplastic Pemphigus.
[a] The case is negative for FDC markers but positive for SMA.

positive EBER expression in situ hybridization, which hints at a potential etiology involving a common pathway for EBV-infected mesenchymal cells.

The primary differential diagnoses of EBV + inflammatory FDC sarcoma encompass inflammatory myofibroblastic tumor (IMT) and various malignant lymphomas, including low-grade B-cell lymphoma and Hodgkin lymphoma. IMT, which resembles EBV + inflammatory FDC sarcoma in its atypical spindled cell morphology and prominent lymphoplasmacytic infiltration, typically lacks expression of FDC markers such as CD21, CD23, and CD35. It is often associated with tyrosine kinase receptor gene translocations, mostly *ALK/ROS1*, and is not linked to EBV [11]. Malignant lymphomas, such as low-grade B-cell lymphoma, generally exhibit cytological atypia within the lymphoid cells and immunohistochemical evidence of clonal B or T cells. These may also present with molecular alterations, including clonal IGH gene rearrangements akin to our case. Hodgkin lymphoma, with its atypical neoplastic cells in an inflammatory background, can be distinguished through immunohistochemical means. The large neoplastic cells in Hodgkin lymphoma commonly have an immunoreactivity for CD30/CD15 and do not express FDC markers [12].

Furthermore, EBV + inflammatory FDC sarcoma of the colon must be differentiated from other colonic lesions such as inflammatory polyps, inflammatory fibroid polyps (IFP), and gastrointestinal stromal tumors (GIST). Inflammatory polyps are predominantly composed of polytypic lymphoid cells but do not contain an atypical neoplastic cell component. IFPs lack the dense lymphoplasmacytic infiltrate seen in EBV + inflammatory FDC sarcoma and instead display spindle to stellate neoplastic cells arranged in concentric whorls around blood vessels, accompanied by a significant eosinophilic infiltrate and expression of CD34 [13]. GISTs usually do not present with an inflammatory background and are characterized by the expression of CD34, CD117, and DOG1, but not FDC markers [14]. Notably, all these alternative diagnoses are negative for EBER.

EBV + inflammatory FDC sarcoma, notable for its abundant infiltration of plasma cells, can exhibit varying levels of IgG4 expression, potentially leading to an erroneous diagnosis of IgG4-related sclerosing diseases. Goh et al. [6] reported a case of colonic EBV + inflammatory FDC sarcoma with a marked increase in IgG4+ plasma cell infiltration. However, this case lacked other pathological features of IgG4-related diseases, such as vasculitis obliterans and sclerotic stroma. Several studies have documented that cases of EBV + inflammatory FDC sarcoma occurring in the liver and spleen may meet the pathological criteria of IgG4-related disease due to elevated IgG4 expression, yet they do not present additional evidence of IgG4-related diseases [15,16]. In our case, staining for IgG and IgG4 was performed, revealing only a minimal presence of IgG4-positive plasma cells.

Currently, research into the molecular changes of FDC sarcoma is limited. Reports have indicated that classical FDC sarcoma can exhibit clonal IGH (±IGK) gene rearrangements, leading to the speculation that a subset of these tumors may possess B-lymphocyte genotypes and could originate from committed B-cell progenitors [17,18]. Molecular investigations into EBV + inflammatory FDC sarcoma are particularly scarce. Li et al. [15] described three cases of EBV + inflammatory FDC sarcoma in the liver, each with clonal T cell receptor (TCR) gene rearrangements; one of these cases also featured clonal IG gene rearrangements, although the rationale behind this finding requires further investigation. In this study, we report a case of EBV + inflammatory FDC sarcoma involving the descending colon and characterized by a clonal IGH gene rearrangement. This molecular alteration, specifically a clonal IGH gene rearrangement, is newly described in the context of colonic EBV + inflammatory FDC sarcoma. Although we propose that the clonal IGH gene rearrangement could be associated with the proliferation of background B cells and/or plasma cells, which may not represent neoplastic hyperplasia, additional research is essential to confirm this assessment.

In conclusion, we have described a rare case of EBV + inflammatory FDC sarcoma occurring in the colon with clonal IGH gene rearrangement. This finding expands our understanding of the molecular characteristics of EBV + inflammatory FDC sarcoma within the gastrointestinal tract. However, further cases and in-depth studies are necessary to fully elucidate the molecular spectrum of this condition. Accurately recognizing the unique features of this tumor is crucial for establishing an accurate diagnosis and determining the appropriate therapeutic approach.

Data availability statement

Data will be made available on request.

Funding

Not applicable.

Ethics statement

This case report has been performed in accordance with the Declaration of Helsinki and approved by the Ethics committee of The Second Affiliated Hospital of Zhejiang University School of Medicine. Written informed consent was obtained from the patient for publication of this report and accompanying images.

CRediT authorship contribution statement

Xia Xu: Writing – original draft. **Xiuzhen Li:** Writing – original draft. **Qun Deng:** Data curation. **Kaihang Yu:** Data curation. **Jinfan Li:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not applicable.

Abbreviations

EBV+	Epstein-Barr virus positive
FDC	follicular dendritic cell
IG	immunoglobulin
IGH	immunoglobulin heavy chain
NBI	narrow-band imaging
SMA	smooth muscle actin
PCR	polymerase chain reaction
EBER	EBV-encoded small RNA
IGK	immunoglobulin k-light chain
IMT	inflammatory myofibroblastic tumor
IFP	inflammatory fibroid polyp
GSIT	gastrointestinal stromal tumor
TCR	T cell receptor

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