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

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Case Report

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Abstract

**Background:** Epstein-Barr virus positive (EBV+) inflammatory follicular dendritic cell (FDC) sarcoma is a neoplasm of spindled follicular dendritic cells with abundant lymphoplasmacyte infiltration and a consistent association with EBV. It usually involves the liver and spleen but rarely the digestive tract. Herein, we reported a special case of EBV+ inflammatory FDC sarcoma in colon with clonal immunoglobulin (IG) receptor gene rearrangement.

**Case presentation:** A 70-year-old man presented with abdominal distension for 1 month. A pedunculated polyp in ascending colon was revealed by colonoscopic examination. The patient then underwent endoscopic polypectomy. The colonic polyp had extremely prominent lymphoplasmacytic infiltrates with dispersed EBV+ neoplastic cells, highlighted by EBV-encoded small RNA in situ hybridization. The neoplastic cells were immunoreactive for FDC markers (CD21, CD35 and CD23). The tumor also showed an amplification of immunoglobulin heavy chain (IGH) gene rearrangement. Finally, its diagnose was EBV+ inflammatory follicular dendritic cell sarcoma.

**Conclusions:** We represented a rare case of EBV+ inflammatory FDC sarcoma presenting as a colonic polyp with clonal IGH gene rearrangement. The molecular change is first described in this tumor of colon. Awareness of this rare neoplasm in gastrointestinal tract is important for accurate diagnosis and well patient management.

Background

Follicular dendritic cell (FDC) sarcoma is a rare malignant neoplasm, with the morphologic and immunophenotypic characteristics of FDCs, which may originate from mesenchymal tissues. Epstein-barr virus positive (EBV+) inflammatory FDC sarcoma is a special subtype of FDC sarcoma. Its clinical and pathological features are different from those of traditional follicular dendritic cell sarcoma, with inflammatory pseudotumor-like histological features and consistent presence of EBV[1]. It most frequently occurs in the liver or spleen but uncommonly the digestive tract in the form of polypoid lesions.

Here, we reported a unique case of EBV+ inflammatory FDC sarcoma presenting as a pedunculated polypoid in the ascending colon, with clonal IGH gene rearrangement. In addition, we had a thoroughly review of the English literature and summarized the clinicopathologic features and outcomes of EBV+ inflammatory FDC sarcoma in the digestive tract.

Case Presentation

**Clinical findings**

The patient was a 70-year-old man, who presented with abdominal distension for 1 month, but no abdominal pain, vomiting, stool habit change, weight loss or fever. He had a past medical history of hypertension, fatty liver and empyema, but no history of haematolymphoid tumors. Laboratory data
showed a positive fecal occult blood test, but other blood tests including carcinoembryonic (CEA), carbohydrate antigen 199 (CA199), cancer antigen 125 (CA125), haemoglobin, thyroid hormone, blood coagulation function, renal function and liver function were all within normal limits. Contrast-enhanced computed tomography (CT) of the abdomen showed a polypoid hyperplasia in ascending colon with enhancement, which was inclined to tumor (Fig. 1A, 1B). Chest CT indicated changes of chronic empyema. Colonoscopic examination revealed a pedunculated polyp of 2.5 cm × 2.5 cm, 60 cm from the anal verge, with ulcer on the surface and local abundant dilated blood vessel showed by narrow-band imaging (NBI) (Fig. 1C, 1D). An endoscopic biopsy showed colonic tissues with chronic active inflammation. Endoscopic polypectomy was subsequently performed one week later. The patient was followed up for three months with no evidence of disease after polypectomy, without radiotherapy or chemotherapy.

**Pathological findings**

The resected tumor, measured 2.5 cm × 1.0 cm × 1.0 cm, was a pedunculated polypoid with surface ulceration. The cut surface was tan, solid and tough. Microscopically, the polypoid tumor showed focal ulceration and obvious lymphocytic infiltration, which were mainly lymphocytes and plasma cells, and few eosinophils. Focally hyperplastic blood vessels were also observed (Fig. 2A, 2B). In the inflammatory background, spindled-shaped to oval atypical cells with lightly eosinophilic cytoplasm and ill-defined cell borders were scattered separately, without forming intersecting cell fascicles. These dispersed neoplastic cells were more prominent beneath the area of ulceration. They possessed vesicular nuclei with stippled chromatin and centrally located distinct nucleoli. Highly variable nuclear atypia can be found, with some were slender, bland-looking nuclei, and some were enlarged, irregularly folded and hyperchromatic nuclei. Several large neoplastic cells might even resemble Reed-Sternberg cells, with binucleated and mummified forms (Fig. 2C,2D). Mitoses were rare.

**Immunohistochemical and Molecular finding**

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-2G). The background lymphocytes were composed of CD20 + B cells mixed with CD138 + plasm cells and CD3 + T cells. The plasma cells were polytypic by kappa and lambda staining (2:1 ratio). The ratio 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).

Clonality study based on polymerase chain reaction (PCR) for B-cell receptor gene rearrangement showed 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 study for T-cell receptor gene rearrangement was negative. All specimen control were well amplified in each detection.
Discussion And Conclusions

FDC sarcoma is a rare tumor of FDC origin. According to its morphology, it can be classified into conventional FDC sarcoma and EBV positive inflammatory FDC sarcoma[2, 3]. EBV positive inflammatory FDC sarcoma, also known as inflammatory pseudotumor-like FDC sarcoma (tumor), is featured with neoplastic FDC proliferation, abundant lymphoplasmacytic infiltrates and consistent association with EBV. It is mainly located in the liver and spleen, but rarely occurs in the gastrointestinal tract, with only 12 cases reported in English literatures. Summing up all 13 cases (including our present case) of gastrointestinal EBV+ inflammatory FDC sarcoma [4–9], the median age of 13 patients was 57 years old (range, 42 to 78 y). The male-to-female ratio was 6:7, with no significant sex predilection. All tumors present as polyp or mass in the colon. The clinical symptoms are usually not specific, such as abdominal discomfort, hematochezia or no abnormalities. The patient underwent enteroscopy because of abdominal distension and positive fecal occult blood, which revealed a pedicled polyp, but no systemic symptoms such as fever or weight loss was found. Because of the rarity of gastrointestinal EBV+ inflammatory FDC sarcoma, there is currently no common consensus on treatment. Since the existing clinicopathologic features indicate the indolence of the tumor to some extent, the prognosis after polyposis resection appears to be highly favorable, although follow-up information are limited.

EBV+ inflammatory FDC sarcoma always has a prominent lymphoplasmacytic infiltrate background, with inconspicuous neoplastic cells scattered, which is easy to mimick other tumors. Small to medium-sized blood vessels are often seen in the tumor, with fibrinoid deposits and hyaline degeneration of the vessel walls occasionally been observed. The neoplastic cells show immunoreaction for one or more FDC markers, including CD21, CD23, CD35, D2-40, CXCL13 and clusterin, but the staining can be diffuse or focal. There have been reported cases that lack FDC markers but are postive for non-FDC marker, such as SMA, exhibiting a fibroblastic/myoid immunophenotype[5, 10]. In addition to immunohistochemical staining, the neoplsam is associated consistenly with EBV infection, with a positive EBER expression in situ hybridization, suggesting the possible etiology of a common EBV-infected mesenchymal cell pathway.

The major differential diagnoses of EBV+ inflammatory FDC sarcoma include inflammatory myofibroblastic tumor (IMT) and malignant lymphoma, like low grade B-cell lymphoma and Hodgkin lymphoma. IMT, which has a similar morphology of atypical spindled cells and prominent lymphoplasmacytic infiltrates, usually does not express FDC markers such as CD21, CD23 and CD35, but often shows tyrosine kinase receptor gene (mostly ALK/ROS1) translocation, and lacks EBV[11]. Malignant lymphoma, like low grade B-cell lymphoma, usually has cytologic atypia in the lymphoid cells and immunohistochemical demonstration of clonal B cells or T cells, although it may have molecular alterations like clonal IGH gene rearrangement similar to our case. As to Hodgkin lymphoma, which has similar atypial neoplastic cells in inflammatory background, it can also be distinguished by immunohistochemistry. The large neoplastic cells of Hodgkin lymphoma commonly have a immunoreactivity for CD30/CD15, and do not express FDC markers. In addition, EBV+ inflammatory FDC sarcoma of colon needs to be differentiated from inflammatory polyp, inflammatory fibroid polyp (IFP)
and gastrointestinal stromal tumor (GSIT) occurring in colon. Inflammatory polyp is mainly composed of polytypic lymphoid cells, but lacking a component of atypical neoplastic cells. IFP does not exhibit such a dense lymphoplasmacytic infiltrate, but shows spindly to stellate neoplastic cells forming concentric whorls around blood vessels, with a large number of eosinophils infiltrate and an expression of CD34. GSIT usually lacks inflammatory background, and has an expression of CD34, CD117 and DOG1, but not FDC markers. All of them are negative for EBER.

EBV + inflammatory FDC sarcoma with abundant infiltration of plasma cells, has a variable expression of IgG4, sometimes leading to misdiagnosis of IgG4 related sclerosing diseases. Goh et al. [6] reports a case of colon EBV + inflammatory FDC sarcoma with obviously increased IgG4 + plasma cell infiltration, and without other pathological features of IgG4 related diseases, such as vasculitis obliterans and sclerotic stroma. Other studies have covered that several cases of EBV + inflammatory FDC sarcoma occurring in liver and spleen have a well IgG4 expression, satisfying the pathological criteria of IgG4 related disease, but lacking other evidence of IgG4 related diseases[12, 13]. In our case, IgG and IgG4 staining were performed, with only a very small amount of IgG4-positive plasma cells were seen.

At present, there are few studies on molecular changes related to FDC sarcoma. It has been reported that clonal IGH (+ IGK) gene rearrangements can occur in classical FDC sarcoma[12, 13], suggesting that a subset of FDC sarcoma may inherited B-lymphocyte genotypes and derives from committed B-cell progenitors. As to EBV + inflammatory FDC sarcoma, molecular researches are even less. Li et al. [12] describes a case of EBV + inflammatory FDC sarcoma in liver with clonal IG gene rearrangements, accompanied by clonal T cell receptor (TCR) gene rearrangements, while the underlying reason needs to be further explored. In the present study, we reported a case of EBV + inflammatory FDC sarcoma involving the descending colon and having a clonal IGH gene rearrangement. The molecular alteration of clonal IGH gene rearrangement is first described in EBV + inflammatory FDC sarcoma of colon.

In conclusion, we reported a rare case of EBV + inflammatory FDC sarcoma occurring in colon with clonal IGH gene rearrangement, which broadens the molecular characteristic of EBV + inflammatory FDC sarcoma in gastrointestinal tract, although more cases and studies are still needed. Recognizing the particularity of this tumor is the key to reach right diagnosis and related treatment.

**Abbreviations**

EBV+ Epstein-Barr virus positive

FDC follicular dendritic cell

IG immunoglobulin

IGH immunoglobulin heavy chain

NBI narrow-band imaging
Declarations

Ethics approval and consent to participate

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.

Consent for publication

The consent for publication has been obtained from the institutional board from the Second Affiliated Hospital Zhejiang University School of Medicine. All authors agree to publish.

Availability of data and materials

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors’ contributions

Xia Xu and Xiuzhen Li contributed to designing the study and writing original draft. Qun Deng communicated with patient and collected the case. Kaihang Yu Summarized the relative literatures. Jinfan Li revised the manuscript and edited it. All authors read and approved the submitted version.
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References


Figures
Figure 1

CT and Colonoscopy reveal polyp. (A) Abdominal enhanced CT shows a polypoid hyperplasia in ascending colon with enhancement (white arrow). (B) Colonoscopy reveals a 2.5 cm pedunculated polyp in the colonic lumen. (C) Narrow-band imaging (NBI) shows ulcer on the surface and local abundant dilated blood vessel.
Figure 2

Pathological features of EBV+ inflammatory FDC sarcoma. (A) A tumour 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×).

Figure 3

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

Supplementary Files

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