Inflammatory Pseudotumor-like Follicular Dendritic Cell Sarcoma Mimicking A Colonic Polyp: Two Case Reports and Literatures Review

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Case Report

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Abstract

BACKGROUND: Follicular dendritic cell (FDC) sarcoma is a neoplastic proliferation of spindled to ovoid cells showing morphological and immunophenotypic features of FDCs. Inflammatory pseudotumor-like follicular dendritic cell sarcoma（IPT-FDCS）involves almost exclusively in the liver and spleen and are consistently associated with Epstein-Barr virus (EBV).Rarely, it selectively involves the gastrointestinal tract in the form of a polypoid lesion.

CASE SUMMARY: We report two cases of IPT-FDCS mimicking a colonic polyp that received high frequency electrocoagulation separately.The patients'main concern were whether to have chemotherapy or radiation after removal.After many consultations and literature review,The patients were treated by surgical resection, without adjuvant chemotherapy or radiation. Follow-up for 32 months showed no recurrence or metastasis.

RESULTS: The neoplasms usually had well—defined borders，composed of the neoplastic spindled cells are dispersed within a prominent lymphoplasmacytic infiltrate. The nuclei usually show a vesicular chromatin pattern and small but distinct nucleoli. Immunohistochemically，tumor cells showed the expression of at least one of the FDC markers，including CD21,CD35, CD23 and D2-40，with scattered positive EBER in situ hybridization.

CONCLUSION: IPT-FDCS could rarelly occur in the intestine with a polypoid appearance. Recognization of this disease could avoid being misdiagnosed as other common types of colonic polyposis. EBV-encoded mRNA (EBER) by in situ hybridization and FDC-related immunohistochemical markers plays an important role in differential diagnosis.

Introduction

Recently, some follicular dendritic cell(FDC) proliferation lesions in the liver and spleen have been reported, showing histological characteristics of inflammatory pseudotumors ,but expressing follicular dendritic cell differentiation markers.These tumors may represent a specific subtype of FDCS called inflammatory pseudotumor-like follicular dendritic cell sarcoma（IPT-FDCS）.In 1994, Delsol first noticed the presence of EBV and FDC marker expression in the spindle cells of an inflammatory pseudotumor of the liver, and the case was subsequently reported by Selves et al[1].Cheuk et al[2]define it as IPT-like FDCS in 2001.The IPT-like FDCS occurs predominantly in young to middle-aged adults, with a marked female predilection. It involves almost exclusively in the liver and spleen and are consistently associated with Epstein-Barr virus (EBV).

In this article, we present two rare case of IPT-like FDCS which occured in the intestinal tract with a polypoid appearance. To our knowledge, similar cases with an uncommon intestinal polyp-like clinical manifestations have been only reported in very few cases previously [3-5].

Patient Information

Case1

A 50-year-old postmenopausal female was admitted to our hospital for colonoscopy with the examination showing fecal occult blood test positive. The patient had no abdominal pain, distension or other clinical symptoms.No special history of hypertension or diabetes.Personal and family history was unremarkable.

Case2

A 56-year-old postmenopausal female was admitted to our hospital for resection of giant cell tumor of right tendon sheath, with the examination showing fecal occult blood test positive for many times during the hospitalization.The patient had no abdominal pain, distension or other clinical symptoms.Personal and family history was unremarkable.

Clinical Findings:

Case1

Colonoscopy showed a pedicled polyp with a diameter of 1.5 cm and 50 cm from the transverse colon to the anus, with a smooth surface (Fig. 1).

Case2

Colonoscopy showed a pedicled polyp with a diameter of 3.2 cm and 70 cm from the transverse colon to the anus. The surface was congested and lobulated with moss-like changes in

the base(Fig. 2).

Timeline:

Case1

fecal occult blood test positive——colonoscopy——surgical resection.

Case2

fecal occult blood test positive——colonoscopy——surgical resection.

Diagnostic Assessment:

Case1:

Microscopic features

Microscopically, local mucosa ulceration was observed with inflammatory exudate.

Inflammatory cells infiltrate the tissues, with a large number of plasmacytoid cells proliferating and gathering, with round nuclei of slightly different sizes. Large cells with lightly stained vesicular nuclei can be seen between plasmoid proliferative cells, which have unclear boundaries and scattered distribution. The pedunculated polypoid mass was composed of a well-circumscribed nodular,with negative resection margins(Fig. 3).

Immunohistochemistry and in situ hybridization findings

IHC studies showed that these large cells with lightly stained vesicular nucle expressed D2-40,but not CD21,CD23 and CD35. Meanwhile, they were positive for Ki67.CD20 showed scattered and clear lymphatic follicles.CD3 highlighted T cell proliferation between the follicles, mainly small to medium size, with no obvious cell atypia. κ/λ hinted polyclonal plasma cell reaction,with predominant CD38, CD138 and IgG expression but few cells positive for IgG4. CD31 and CD34 highlighted the blood vessels. S100, ALK, CD30, CD15, HMB45 and p53 staining were all negative. The large cells were partlyl positive for EBV-encoded mRNA (EBER) by in situ hybridization (Fig. 2).

Gene rearrangements in immunoglobulin for B cells

No amplification was observed.

Laboratory examinations or imaging examinations

Subsequently, the serum and urine immunofixation electrophoresis tests for monoclonal plasma cells became negative. Serum immunoglobulin k and l were increased, but no monoclonal increase was observed.

Case2:

Microscopic features

The morphology of this case was very similar to the first case under microscope.Colonic mucosal surface ulcer was observed, and obvious lymphoid tissue and plasma cell infiltration were observed in the mucosal layer and submucosal layer to form polypoid tumor-like lesions.Tumor cells were round, ovoid, fusiform, with grey-eosinophilic cytoplasm, thin nuclear membrane, evenly distributed chromatin, and centered nucleoli,occasionally seen binuclear or polynuclear.The cell morphology was mild with low mitotic activity.The tumor was arranged in a vague bundle. The background large number of lymphocytes and plasma cells were observed, scattered with a few eosinophil. Some lymphocytes were sprinkled with nodules or follicles, and the oval or fusiform tumor cells were covered. The pedunculated polypoid mass was composed of a well-circumscribed nodular,with negative resection margins(Figure.4).

Immunohistochemistry and in situ hybridization findings

FDC markers (D2-40, CD21, CD23, CD35) were all strongly expressed.SMA was weakly positive.CD20 showed scattered and clear lymphatic follicles. CD3 highlighted T cell proliferation between the follicles, mainly small to medium size, with no obvious cell atypia. κ/λ hinted polyclonal plasma cell reaction,with predominant CD38CD138 and IgG expression but few cells positive for IgG4. CD31 highlighted the blood vessels, as well as the plasma cells.CD34 highlighted blood vessels. S100,ALK,CD30 and BRAF were all negative.The spindle cells were all positive for EBV-encoded mRNA (EBER) by in situ hybridization,which supported the diagnosis of IPT-FDCS(Figure.4).

Gene rearrangements in immunoglobulin for B cells and TCR-β chain loci for T cells

No amplification was observed.

Laboratory examinations or imaging examinations

Subsequently, PETCT was performed and no other neoplastic lesions were found in the whole body.

1. .

Therapeutic Intervention:

Therapeutic Intervention:

Case1

The patient was treated by surgical resection, without adjuvant chemotherapy or radiation.

Case2

The patient was treated by surgical resection, without adjuvant chemotherapy or radiation.

Follow-up And Outcomes

Case1

Follow-up for 35 months showed no recurrence or metastasis.

Case2

Follow-up for 7 months showed no recurrence or metastasis.

Discussion

IPT-like FDC sarcoma generally occur in abdominal organs (such as liver and spleen). The ratio of male to female is 1:2. 2, with an average age of 54.5 years[6]. Patients are asymptomatic or present with

abdominal distension or pain, sometimes accompanied by systemic symptoms, such as significant weight loss, fever, weakness, etc., and often associated with EBV infection[7].

Histologically, the neoplastic spindled cells are dispersed within a prominent lymphoplasmacytic infiltrate. The nuclei usually show a vesicular chromatin pattern and small but distinct nucleoli. Nuclear atypia is highly variable; usually most cells are bland-looking, but some cells with enlarged, irregularly folded or hyperchromatic nuclei are almost always found. Some tumour cells may even resemble Reed-Sternberg cells [8]. Necrosis and haemorrhage are often present.In occasional cases, the tumour may be masked by massive infiltrates of eosinophils or numerous epithelioid granulomas[9].The neoplastic cells are often positive for follicular dendritic cell markers, such as CD21, CD35,CD23 and D2-40 ,with the staining ranging from extensive to very focal.The neoplastic cells are consistently associated with EBV[10].EBV provokes inflammation and neoplastic transformation, and most EBV-associated lesions share some histologic features observed in EBV + carcinoma with lymphoid stroma.Both of our cases had ulceration and a dense inflammatory background,but no monoclonal hyperplasia observed in immunohistochemistry or gene rearrangement .Meanwhile a large number of IgG positive plasma cells were observed, but the number of IgG4 positive cells was very little.

So far, a total of 5 cases of IPT-like FDCS were reported plus our two cases. Table 1 lists the clinical datas of these cases .Comparing to the first report[3],our patients had no obvious clinical symptoms.From the colonoscopy results and pathological features, our two cases and the first reported cases were highly similar.The difference is that FDC marker was only D2-40 positive in our first case.Most FDC sarcoma cases are positive for one or more FDC-associated antigens, such as CD21, CD23, or CD35. However, many cases showed only focal and/or weak staining for these markers [2, 11]. Xie et al[12]conclude that podoplanin (D2-40) is a sensitive and specific FDC marker, which is superior or equal to CD21 in evaluating both reactive and neoplastic FDCs.K-C et al[4] found spindle tumor cell growth pattern resembled GIST or meningioma in focal areas,with mitoses frequent for more than 10 per 10 high-power fields(HPF). and in-situ hybridizationstudy was negative for Epstein Barr virus RNA.Although the site and the gross morphology of this case is very similar to our two cases. We still saw that the histological morphology is more inclined to conventional FDCS.In our cases,the oval or fusiform tumor cells were covered by lymphocytes and plasma cells, with low mitotic activity. Kazemimood et al[5] found large, pleomorphic stromal cells with marked atypia, irregular to multilobed large nuclei, and hyperchromatic smudged chromatin pattern.Atypical mitoses were identified, and there were cells with Reed-Sternberg–like morphology. D2-40 was the only FDC marker expressed in IHC studies and Epstein-Barr virus-encoded mRNA (EBER) was negative. From clinicopathological features of the five cases ,we can see that the morphology of EBV positive IPT-like FDCS mimicking a colonic polyp is relatively mild with rare mitosis.To our knowledge, the cases we presented here were the second and third cases of EBV-positive IPT-like FDC sarcoma mimicking a colonicl polyp reported so far in the literatures.

Table I. Clinical datas of five cases of IPT-like FDCS mimicking a colonic polyp

Case No.	Age (year)/sex	Presentation	Site of involvement	Tumor size (cm)	EBV	Treatment	Outcome and follow-up (months)
1[3]	78/female	Abdominal discomfort and bloody stool	Transverse colon, 50 cm from the anal verge	3.9	+	polypectomy	no tumour 5 months after the operation
2[4]	35/female	Bloody stools for one year	60 cm above the anal verge	5	-	lymph node enlargement and right hemicolectomy	No tumor 7 months after the operation
3[5]	53/female	Abdominal discomfort	Right colon	3	-	right colectomy	No follow-up was recorded
4	50/female	bloody stool	50 cm from the transverse colon to the anus	1.5	+	radical resection	no tumour 32 months after the operation
5	56/female	bloody stool	70 cm from the transverse colon to the anus	3.2	+	radical resection	no tumour 4 months after the operation

Accordingly, this will require consideration of a wide differential diagnosis. (1)Inflammatory myofibroblast tumor(IMT):The tumor cells are fusiform fibroblasts and myofibroblasts with loose myxoid or edema in the stroma. The infiltrating inflammatory cells are mostly mature plasma cells, lymphocytes and eosinophil.but IPT-like FDC sarcoma is lack of myxoid stroma.The expression of immunoreactivity for ALK in IMT is high, and the positive rate can reach 89%, suggesting that ALK can be used as an indicator for the diagnosis of IMT.The ALK here ware all negative, so IMT could be excluded by combination of morphology and immunohistochemistry. (2) Hodgkin lymphoma (HL): It is common in middle-aged men and histologically typical in variable numbers of Hodgkin/

Reed-Sternberg (HRS) cells admixed with a rich inflammatory background.Classic diagnostic Reed-Sternberg cells are large, have abundant slightly basophilic cytoplasm, and have at least two nuclear lobes or nuclei.The HRS cells are positive for CD30 in nearly all cases and for CD15 in the majority.Follicular dendritic cell markers (e.g. CD35, CD21) are negative and could be excluded by immunohistochemistry and genetic testing.(3)IgG4-related disease:It is associated with autoimmune

diseases, and is characterized by systemic damage and elevated serum IgG4 level.Histopathological features include diffuse lymphoplasma cell infiltration, fibrosis, and obstructive phlebitis, as well as large amounts of IgG4-positive plasma cell infiltration.

Immunohistochemistry, clinical manifestations and laboratory examination of two cases were inconsistent with the disease, and the diagnosis could be excluded. (4) Interdigitating dendritic cell (IDC) sarcoma: It is difficult to distinguish from histological morphology, it requires more immunophenotypic analysis. The IDC sarcoma shows positive for S100 and Vim,but negative for FDC markers (such as CD2l, CD23, cD35, etc.) .(5)Inflammatory fibroid polyp (IFP): It consist of edematous spindle-shaped stromal cells and an inflammatory infiltrate rich in eosinophils,and stromal cells are diffusely positive for CD34 and fascin.They are negative for CD21, CD23, and EBER.

Epstein–Barr Virus (EBV), also known as human herpesvirus 4 (HHV-4), is a member of the

subfamily of Gammaherpesvirinae.EBV infects more than 95% of adults worldwide. EBV is transmitted through saliva and primarily infects B cells and epithelial cells, but macrophages and dendritic cells also play important roles in EBV infection[13].Previous studies revealed that EBV was clonally expanded in the tumor cells[14]FDC tumors can be recognized by their expression of CD21, to which EBV can bind[15].Moreover, the major oncogene of EBV, LMP1, was demonstrated in most cases of IPT-like FDC sarcoma[16] These findings support the idea that EBV is related to the pathogenesis of IPT-like FDC sarcoma. Lewis et al [17] suggested FDCs were of mesenchymal cell origin which was capable of differentiating along different pathways. Under stimulation of the Epstein-Barr virus(EBV),some of them would develop a myofibroblastic phenotype and be positive for SMA and vimentin. whereas others would acquire FDC characteristics and express CD21 and CD35.Similarly, Shia et al[18]proposed that under certain oncogenic stimuli,such as EBV infection, the mesenchymal cells in IPT-like conditions undergo transformation into FDCs, and as has been observed in Castleman's disease, such cells then undergo "dysplasia" and eventually become neoplastic.

Go et al[19] showed BRAF mutations were present in 18.5% of FDCS and 40% of inflammatory pseudotumor-like variants of FDCS cases. However, no cases with BRAF V600E were identified here. Han et al[20] found del-LMP1 might be involved in the tumorigenesis of inflammatory pseudotumour-like FDC tumour.Griffin et al[21] found mutations of the nuclear factor kappa B pathway and cell cycle regulatory genes in an approach of targeted re-equencing of FDC sarcomas.A study by Perry et al[22] demonstrated cytogenetic abnormalities of a near diploid clone with loss of chromosomes 3 and 14 in one FDCS case and a hypodiploid clone with loss of chromosomes 5, 6, 9, 14, 16, and 22 in another FDCS case.

0utcome data are limited,most cases are treated by surgical resection, with or without adjuvant chemotherapy and/or radiation.Ge et al[6]follow up thirty-four patients with IPT-like FDCS,one patient (2.9%) died of disease, 4 (11.8%) were alive with disease, 29 patients (85.3%) were alive with no evidence of disease.

In conclusion, IPT-like FDCS mimicking a colonic polyp is a low-grade malignant tumor having not been fully recognizedby pathologists and clinical physicians. Detection of EBV and FDC-related immune markers plays an important role in differential diagnosis. Radical resection is the best and preferred treatment option.The long-term follow-up needs to be carefully monitored.Strengthening the understanding of the disease might help to reduce misdiagnosis and missed diagnosis.

Patient Perspective

Case1

The patient underwent colonoscopy once a year, and no positive findings were found. The patient was satisfied with the plan of removing the tumor only without chemotherapy or radiation.

Case2

The patient was more tangled, went to each big hospital consultation, they gave different treatment plans.After repeated consultation and communication, the patient only accepted resection of the tumor and was in good condition.

Abbreviations

Follicular dendritic cell (FDC) ;Inflammatory pseudotumor-like follicular dendritic cell sarcoma(IPT-FDCS);Epstein-Barr virus (EBV);EBV-encoded mRNA (EBER);High-power fields(HPF);

Inflammatory myofibroblast tumor(IMT);Hodgkin lymphoma (HL); Interdigitating dendritic cell (IDC) ;Inflammatory fibroid polyp (IFP).

Declarations

Ethics approval and consent to participate: The study was done after agreement from the local ethics committee and with the patients'informed consent.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

CARE Checklist (2013) statement: The manuscript was prepared and revised according to the CARE Checklist (2013).

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Figures

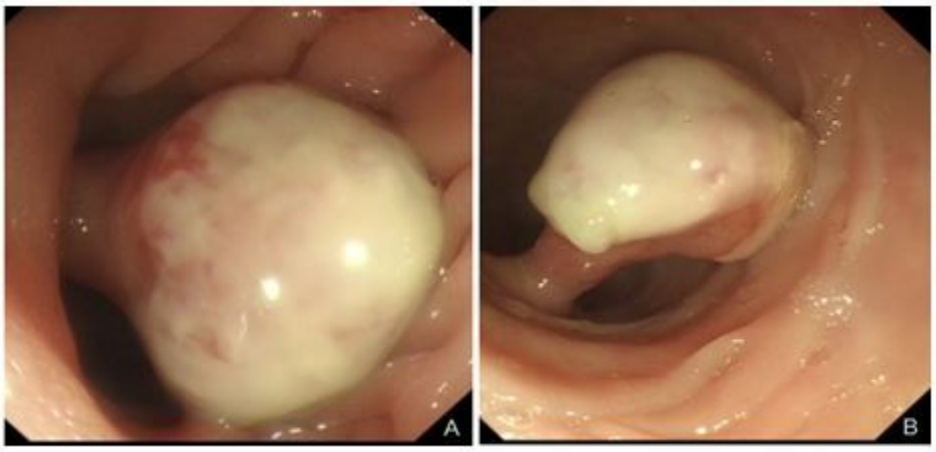

Figure 1

Endoscopy shows a pedunculated polyp in the colonic lumen (A) with a slender stalk (B).

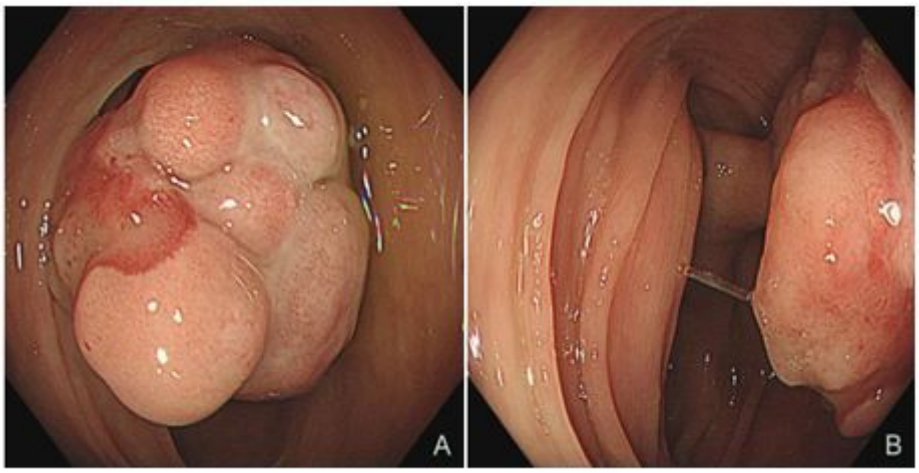

Figure 2

Endoscopy shows a pedunculated polyp in the colonic lumen (A) with a slender stalk (B).

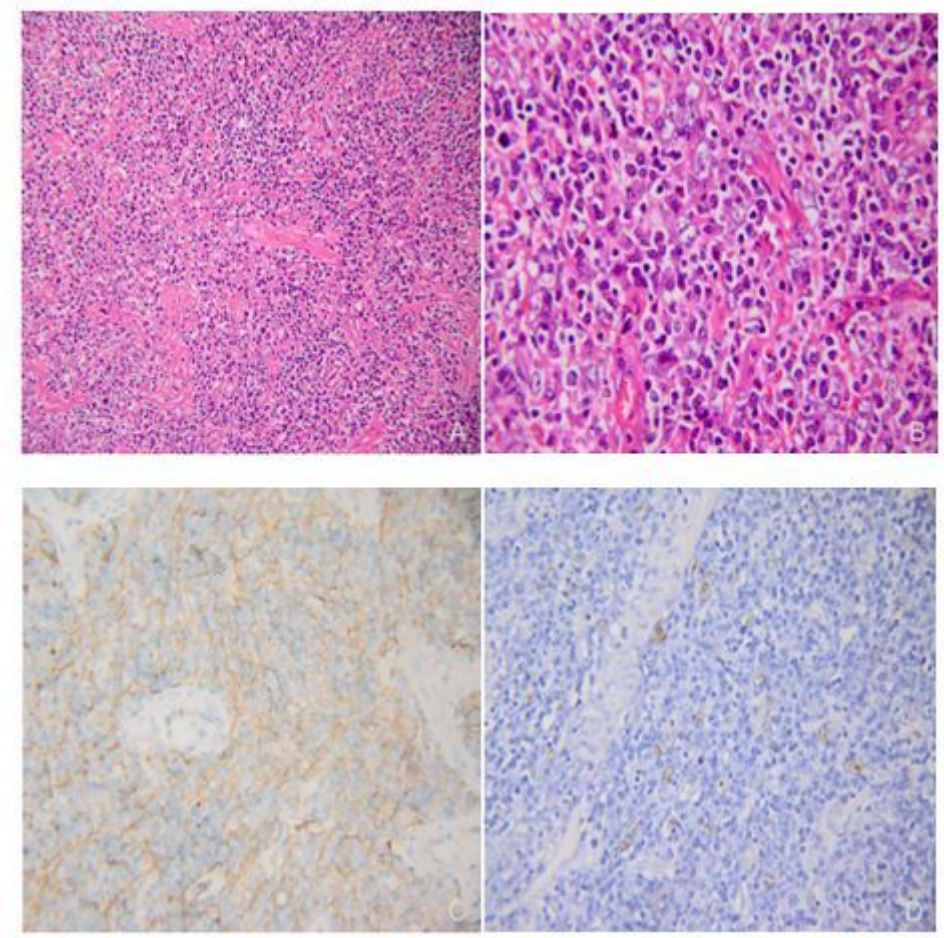

Figure 3

Inflammatory pseudotumor-like follicular dendritic cell sarcoma mimicking a colonic polyp. A: Haematoxylin and eosin stained image showing that the tumor tissue had a meshwork-like architecture (×200); B: On highpower field, the tumor was composed of oval to spindle cells with vesicular chromatin and distinct nucleoli. There was less degree of atypia. The background showed abundant lymphocytes and plasma cells (×400); C: D2-40 was detected on the membrane of tumor cells by immunohistochemistry (×400); D: Epstein-Barr virus-encoded small RNA-based in situ hybridization demonstrated positive nuclei of the neoplastic dendritic cells (×400).

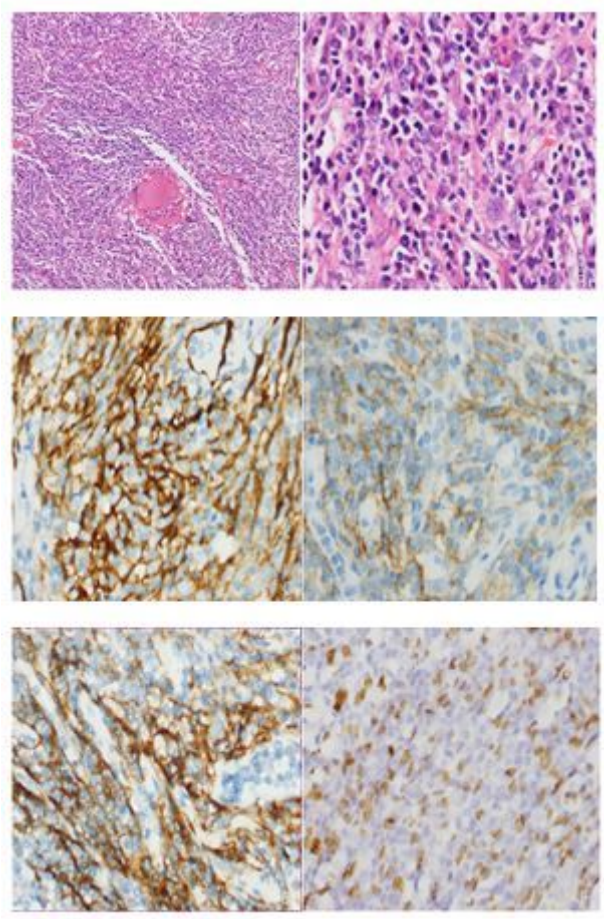

Figure 4

Inflammatory pseudotumor-like follicular dendritic cell sarcoma mimicking a colonic polyp. A: Haematoxylin and eosin stained image showing that the tumor tissue had a meshwork-like architecture (× 200); B: On highpower field, the tumor was composed of oval to spindle cells with vesicular chromatin and distinct nucleoli. The cell morphology was mild with low mitotic activity.The background large number of lymphocytes and plasma cells were observed, scattered with a few eosinophil(× 400); C: D2-40 was detected on the membrane of almost all of tumor cells by immunohistochemistry (× 400); D: CD21 was detected on the membrane of tumor cells by immunohistochemistry (× 400); E: CD35 was detected on the membrane of tumor cells by immunohistochemistry (× 400); F: Epstein-Barr virus-encoded small RNA-based in situ hybridization demonstrated positive nuclei of the neoplastic dendritic cells (× 400).

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