Epstein-Barr virus+ inflammatory follicular dendritic cell sarcoma with clonal immunoglobulin heavy chain gene rearrangement: A case report and literature review

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Abstract. Epstein-Barr virus+ inflammatory follicular dendritic cell sarcoma (EBV+ IFDCS) is a tumor with relatively inert biological behavior and low malignancy. Due to the lack of clinical features and non-specific imaging examinations, EBV+ IFDCS is difficult to diagnose preoperatively. The histological morphology and immunophenotype of EBV+ IFDCS are very broad, in which the presentation of EBV+ IFDCS with marked granulomatous changes is rare and can be confused with other granulomatous diseases. The present study reported a case of EBV+ IFDCS with marked granuloma formation. Notably, the present case report detected gene rearrangements using PCR-capillary electrophoresis and identified an amplification peak in the DH7-JH region of the immunoglobulin heavy chain, which has rarely been reported in previous cases, to the best of our knowledge. We hypothesized that this rearrangement may be associated with background B cells.

Introduction

Epstein-Barr virus (EBV)+ inflammatory follicular dendritic cell (FDC) sarcoma (EBV+ IFDCS) is an inert malignant tumor characterized by neoplastic FDC hyperplasia, markedly reactive lymphoplasmacytic infiltration and association with the EBV virus. EBV+ IFDCS most commonly occurs in the liver and spleen, predominantly affecting females (F:M=1.14:1), with an age range spanning 29 to 79 years (median age of 62 years) (1). The tumor has a large volume, clear boundaries and a gray-white cross-section. Microscopically, the tumor cells are spindle-shaped, ovoid, scattered or loosely bundled, accompanied by obvious lymphoplasmacytic infiltration. Certain cases may have notable granulomas, while a few cases may also have a large number of eosinophils or plasma cell infiltration (2-5).

In 1986, Monda *et al* (6) described a non-lymphomatous primary lymph node malignancy originating from FDC. In 1996, Shek *et al* (7) first reported a case of primary FDC tumor of the liver, which was revealed to be associated with a clonal proliferation of EBV+ neoplastic FDC. In 2001, Cheuk *et al* (8) proposed that inflammatory pseudotumor-like FDC tumors are a unique variant of FDC tumors, morphologically mimicking inflammatory pseudotumors, but with tumor cells expressing FDC markers and positive *in situ* hybridization of RNA encoded by EBV. In 2023, the 5th edition of the World Health Organization Classification of Haematolymphoid Tumours reclassified inflammatory pseudotumor-like follicular/fibroblastic dendritic cell sarcoma as EBV+ IFDCS and categorized it as mesenchymal dendritic cell neoplasms (9). The present study reports a rare case of EBV+ FDCS with clonal immunoglobulin heavy chain (IGH) gene rearrangement, aiming to help pathologists to better recognize the disease.

Case report

Case presentation. A 50-year-old man was admitted to Suining Central Hospital (Suining, China) in July 2024 due to the identification of a splenic space-occupying lesion during a physical examination, with no uncomfortable symptoms. MRI of the epigastric region revealed a round-like abnormal signal in the spleen, ~35 mm, with a slightly high signal in T1-weighted image (WI), a slightly high signal in T2WI, a slightly high signal in diffusion-WI, a high signal in apparent diffusion coefficient (Fig. S1) and the enhancement appeared to be mildly intensified (Fig. 1A). The CEA (6.43 ng/ml, normal range: <4.5 ng/ml) and CA19-9 (38.92 U/ml, normal range: <30 U/ml) of the patient were slightly elevated. In July 2024, the patient underwent a total splenectomy. The surgical specimen revealed a mass of the spleen, size 3.5x3.3x3 cm, gray-white, solid, medium texture and a clear border with the surrounding tissue (Fig. 1B).

Histopathological features. Tissue specimens were fixed in 10% neutral formalin at room temperature for 24 h. The

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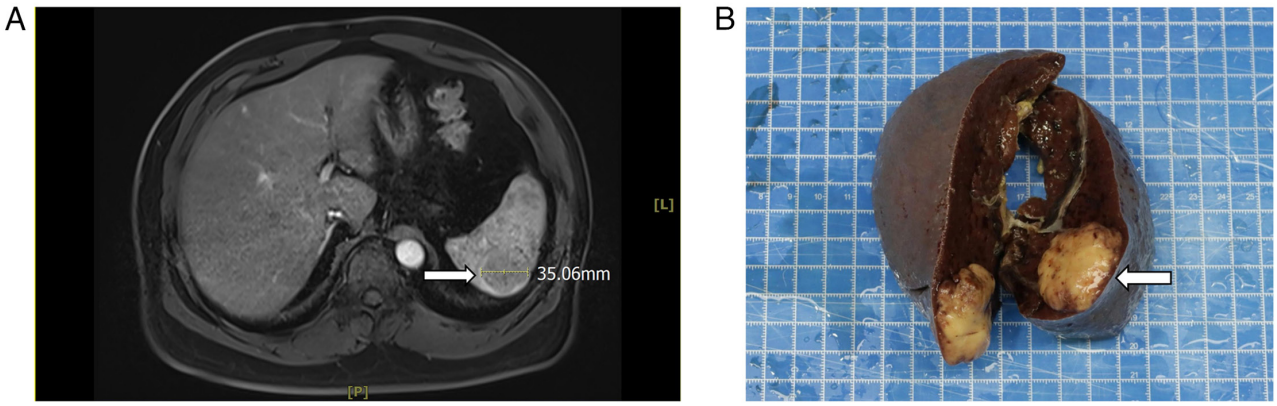

Figure 1. Upper abdominal MRI and surgical specimen image. (A) A circular mass was observed in the spleen, which (indicated by the arrow) shows mild enhancement on contrast-enhanced MRI. (B) A mass (indicated by the arrow) with a size of 3.5x3.3x3 cm can be seen under the membrane at the edge of the spleen, and it appears as a gray-white solid in cross-section (July 2024). MRI, magnetic resonance imaging.

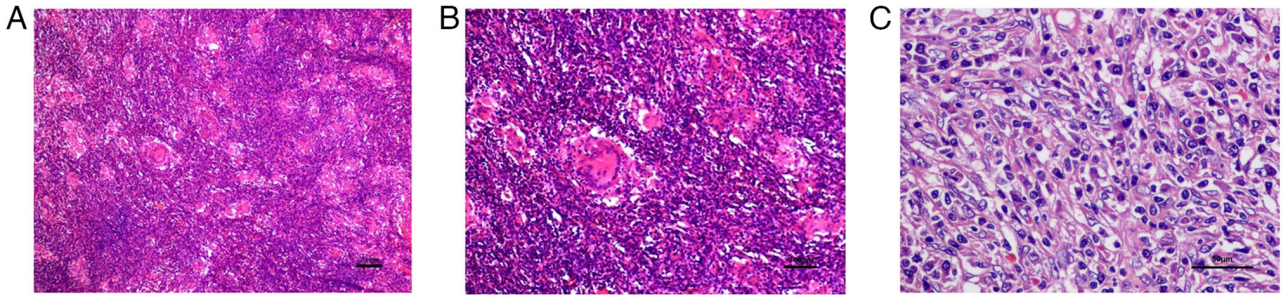

Figure 2. H&E staining results. (A) The normal structure of the spleen was destroyed and the tumor cells were arranged in bundles (x40 magnification; scale bar, 200 μm). (B) A large number of lymphocytes and plasma cells infiltrate the tumor and granuloma formation can be seen (x100 magnification; scale bar, 100 μm). (C) Tumor cells have unclear borders, little eosinophilic cytoplasm, spindle-shaped and ovoid nuclei, clear nuclear membranes, vacuolated chromatin and obvious nucleoli (x400 magnification; scale bar, 50 μm). H&E, hematoxylin and eosin.

tumor tissues were cut into small pieces, which were subjected to dehydration, clearing and wax infiltration. Subsequently, the tissues were made into sections with a thickness of 4 μm. Hematoxylin-eosin staining was performed using a Leica automatic stainer (Leica Microsystems, Inc.). Under the microscope (BX43; Olympus Corporation), the normal structure of the spleen appeared to be destroyed, and round, ovoid and spindle-shaped cells were seen scattered in the background of a large number of lymphocytes and plasma cells. The tumor cells were arranged in bundles and cords, with unclear boundaries. The cytoplasm is sparse and eosinophilic. The nuclei of the tumor cells were rounded and ovoid. The tumor contains a large number of non-caseous epithelioid granulomas (Fig. 2A).

Immunophenotypic findings. Using 4 μm tissue sections, after dewaxing and rehydration, staining was performed using a fully automated immunohistochemistry machine (Roche BenchMark ULTRA; Roche Diagnostics). Primary antibodies employed included: Smooth muscle actin (SMA; cat. no. UMAB237) and CD23 (cat. no. UMAB101) purchased from Wuxi Origene Biotechnology Co., Ltd., CD3 (cat. no. MAB-0740), CD5 (cat. no. MAB-0827), CD8 (cat. no. RMA-0514), CD20 (cat. no. Kit-0001), CD21 (cat. no. RMA-0811), CD35 (cat. no. RMA-0768), S-100 (cat. no. RMA-1075), podoplanin monoclonal antibody (D2-40; cat. no. MAB-0567), C-X-C chemokine ligand 13 (CXCL13; cat. no. GAB-0616) and anaplastic lymphoma kinase (ALK; cat. no. MAB-0848), all procured from Fuzhou Maxin Biotechnology Development Co., Ltd. After adding the primary antibody, incubation was performed at 37˚C for 60 min. Subsequently, samples were incubated with the UV-HRP-UNIV MULT and UV-DAB kits (Ventana Medical Systems) separately at 37˚C for 8 min each. Following color development, counterstain with hematoxylin was performed. All reagents were ready-to-use and required no dilution during the procedure. After sealing with neutral gum, slides were observed and imaged under an optical microscope. Immunohistochemical results revealed that tumor cells expressed CD21, CD35, CXCL13 and SMA (Fig. 3A-D). Background lymphocytes were partially positive for CD20, CD3, CD5 and CD8 (Fig. 3E-H). ALK, CD23, D2-40 and S-100 results were negative (data not shown).

In situ hybridization. Epstein-Barr encoding region (EBER) *in situ* hybridization is the methodology of choice for the detection of the EBV in tissue sections (10). All operating procedures were performed in accordance with the instructions of the EBV probe *in situ* hybridization kit (cat. no. ISH-7001; OriGene Technologies, Inc.). After dewaxing with xylene and anhydrous ethanol, the slices were air-dried for 5-10 min.

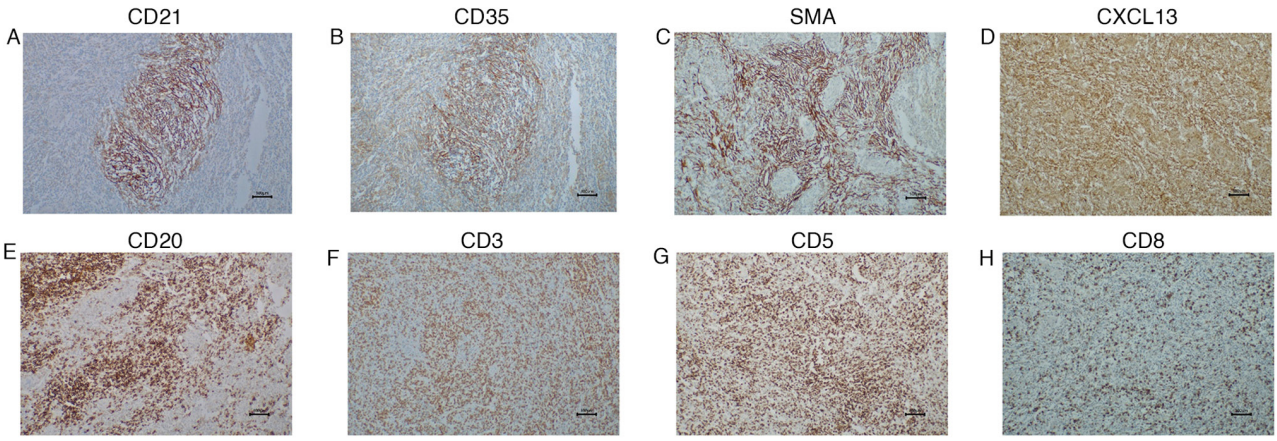

Figure 3. Immunohistochemical results. Tumor cells differentially express (A) CD21, (B) CD35, (C) SMA and (D) CXCL13. Background lymphocytes were partially positive for (E) CD20, (F) CD3, (G) CD5 and (H) CD8 (x100 magnification; scale bar, 100 μm). SMA, smooth muscle actin; CXCL13, C-X-C motif chemokine ligand 13.

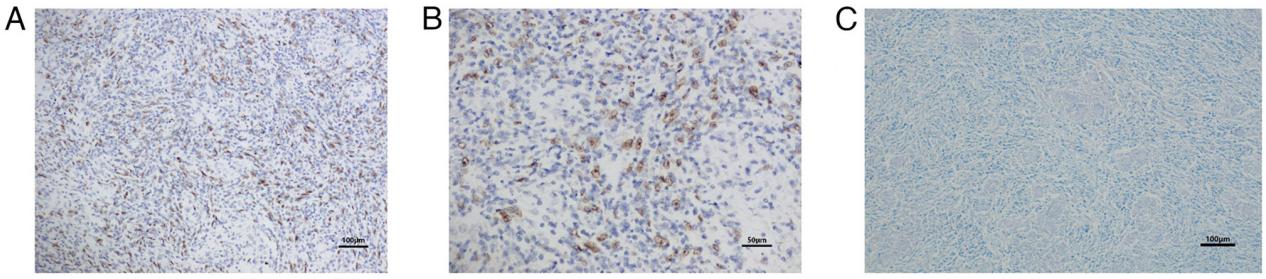

Figure 4. *In situ* hybridization and acid-fast staining results. (A) Tumor cells were positive for Epstein-Barr virus *in situ* hybridization (x100 magnification; scale bar, 100 μm). (B) Brown granules appeared in the cell nucleus (x200 magnification; scale bar, 50 μm). (C) Tumor cells were negative for acid-fast staining (x100 magnification; scale bar, 100 μm).

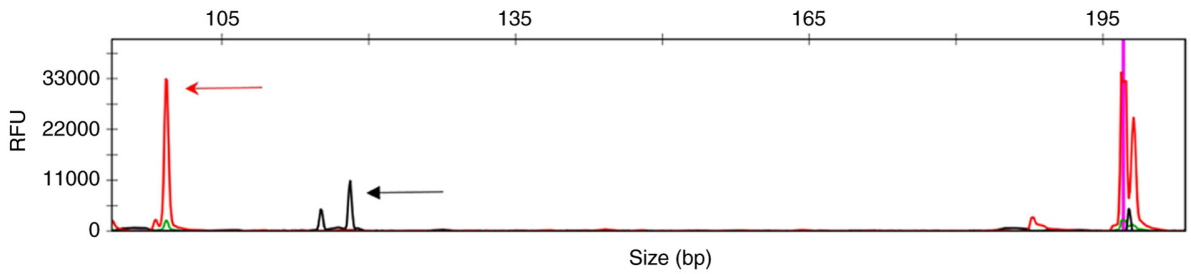

Figure 5. Results of PCR-capillary electrophoresis. Gene rearrangement detection revealed an amplification peak in the DH7-JH region of immunoglobulin heavy chain C (black arrow) and the red arrow represents the positive control. RFU, relative fluorescence units.

Subsequently, 50-100 μl of gastric enzyme working solution was added dropwise and incubated at 37˚C for 30 min. After discarding the gastric enzyme working solution, gradient ethanol dehydration (75, 95 and 100% for 2 min each) was carried out and samples were air-dried. Drops of 10 μl digoxigenin-labeled EBER probe were added, coverslips were added and sealed with rubber cement, and they were placed in an *in situ* hybridizer (Thermobrite) and incubated at 37˚C for 2 h. The coverslips were removed and an appropriate amount of HRP-labeled digoxin antibody was added dropwise and incubated at 37˚C for 30 min. After washing in PBS, DAB working solution was added, samples were counterstained with hematoxylin staining solution, dehydrated, cleared and sealed. The results demonstrated that the tumor cell nuclei appeared brownish yellow, indicating the presence of EBER (Fig. 4A and B).

Acid-fast staining. All procedures were performed according to the instructions provided in the acid-fast staining kit (cat. no. BA4090; Zhuhai Beiso Biotechnology Co., Ltd.). After deparaffinization of the slices, without alcohol treatment, a solution of stone carbonate was added to the slices and they were stained at room temperature for 10-15 min. They were washed with water and an acidic alcohol solution was added to decolorize for 1-2 min. Subsequently, they were washed again with water and methylene blue solution was added to stain for 20-30 sec, and they were finally washed with water and blown dry, and sealed with neutral gum. The results indicated

that Ziehl-Neelsen special stain did not detect acid-fast bacilli (Fig. 4C).

Molecular assays for gene rearrangements. Human genomic DNA was extracted from paraffin samples according to the instructions for nucleic acid extraction and purification reagents (cat. no. W006; Shanghai Yuanqi Biotechnology Co., Ltd.). DNA purity and concentration were measured using a NanoDrop 2000C microvolume spectrophotometer. Patient T-cell receptor (TCR) and immunoglobulin (IG) gene rearrangements were detected using the BIOMED-2 multiplex PCR system (Thermo Fisher Scientific, Inc.). Multiplex PCR reactions were performed as described previously (11). Detectable primers included three VH-JH, two DH-JH, two Ig κ (IGK), one Ig λ, three TCR β, two TCR γ, one TCR δ (12). A reaction system of 20 μl was prepared. PCR amplification conditions on the PCR amplifier (Hangzhou Bori Technology Co., Ltd.) were set as follows: Pre-denaturation at 95˚C for 7 min, followed by 40 cycles of denaturation at 95˚C for 45 sec, annealing at 60˚C for 45 sec and extension at 72˚C for 90 sec. A final extension step was performed at 72˚C for 10 min. Following the manufacturer's instructions, the PCR amplification products were denatured at 95˚C for 3 min and immediately placed on ice for 3 min. The products were analyzed by capillary electrophoresis on a 3500DX Gene Analyzer (Thermo Fisher Scientific, Inc.) and electrophoresis patterns were analyzed using GeneMapper software (version 6.0; Thermo Fisher Scientific, Inc.). All experiments included appropriate positive and negative controls. The results revealed that an amplification peak appeared in the DH7-JH region of IGH (Fig. 5).

Pathological diagnosis. According to the 5th edition of the World Health Organization Classification, the patient was diagnosed with EBV-positive inflammatory follicular dendritic cell sarcoma (August 2024).

Follow-up. The patient received anticoagulant therapy after splenectomy surgery, taking aspirin enteric-coated tablets (0.1 g, orally, once daily) and did not undergo radiotherapy or chemotherapy postoperatively. Monthly telephone follow-ups were conducted, and the patient is currently in good condition. As of the date of this case submission (August 2025), the patient has survived for one year.

Discussion

EBV+ IFDCS is a rare disease that exhibits morphological and immunophenotypic features of FDCs and the exact etiology and pathogenesis remain to be fully elucidated (13). FDCs are major members of primary and secondary lymphoid follicles, which present antigens in a spatially defined form to B cells and maintain humoral immune responses. They are derived from the mesenchyme and express markers of FDC differentiation (14).

EBV+ FDCS is prevalent in the young to middle-aged population, with a predominance in women and most reports from Asian countries. It often involves the liver and spleen, with a few cases occurring in the colon and other sites (4,15). Patients are usually asymptomatic; certain patients present with abdominal pain, abdominal discomfort and a few present with systemic symptoms such as fever and weight loss (15). Based on morphological features, they are classified into classic, lymphomatoid and hemangiomatoid subtypes (13). The classic type has distinct EBV+ tumor cells with a fascicular or columnar growth pattern, variable lymphoplasmacytic infiltration and vascularity. The lymphoma-like subtype has a prominent lymphoplasmacytic infiltrate and monodisperse distinct EBV+ tumor cells. The hemangioma-like subtype has prominent blood vessels, accompanied by transparent and/or fibrinoid degeneration, dispersed individual EBV+ tumor cells and limited lymphoplasma cell infiltration (13).

Tumor cells specifically express FDC markers, of which CD21, CD23 and CD35 are extensively used as preferred FDC markers. Other markers such as SMA, fascin, β-3 tubulin, clusterin, D2-40, γ-synuclein and CXCL13 may also be positive. Tumor cells do not express ALK, desmin, CD31, CD34 and S100 (16-18). EBV+ IFDCS is an entity with an extensive morphological spectrum and immunophenotype and tumor cells typically lose at least one conventional FDC marker. Using a set of FDC markers is more advantageous for diagnosis than relying on a single marker (16). In the present case, tumor cells expressed FDC markers (CD21, CD35 and CXCL13) to varying degrees. EBV+ IFDCS exhibited a fibroblast/myoid immunophenotype with positive expression of SMA (14). Positive expression of CD3, CD5, CD8 and CD20 suggested that the background lymphocytes were a mixture of T and B cells.

EBV is considered to serve a key role in the occurrence of IFDCS (19). EBER *in situ* hybridization is a key method for the accurate diagnosis of EBV+ IFDCS, with a positive result suggesting the diagnosis of EBV+ IFDCS. Chen *et al* (20) reported a 30 bp deletion of exon 3 of the latent membrane protein-1 (LMP-1) gene in hepatic FDC tumors. It has been reported that EBV preferentially infects B lymphocytes by binding to the CD21 receptor on the surface of B cells via the envelope glycoprotein (gp)350 and binding gp42 to human leukocyte antigen class II (21,22). The pathogenesis of EBV infection in EBV+ IFDCS remains to be elucidated. Abe *et al* (23) speculated that EBV initially infects human B lymphocytes in lymphoid follicles. EBV lurks in B cells and begins to infect FDCs. EBER or EBV-encoded LMP-1 is released from EBV into FDCs, leading to inhibition of apoptosis and FDC proliferation by amplifying the CD40 signaling pathway. EBV can infect any resting B cells, driving them out of their resting state and becoming activated proliferating lymphoblasts. EBV-encoded LMP-1 (CD40 homolog of EBV) and LMP2A (B-cell receptor homolog of EBV) are considered to provide signals independent of antigen-driven interactions with helper T cells or FDCs and can utilize the normal pathway of B cell differentiation to transform EBV-infected B progenitor cells into resting memory cells (24,25). LMP-1 is the main oncogene of EBV, which can activate various cellular signaling pathways and upregulate anti-apoptotic proteins, thereby inhibiting apoptosis and promoting tumor development (25,26).

Previously, Lorenzi *et al* (27) investigated FDCS using whole-genome and whole-exome sequencing, observing CDK inhibitor 2A deletion and frequent mutations on retinoblastoma 1, BRCA2, Werner syndrome RecQ-like helicase and tumor protein 53. The accumulation of inactivating mutations on these genes was associated with poor

prognosis. Currently, there is limited molecular research on EBV-associated IFDCS. Li *et al* (13) identified clonal TCR rearrangements in three cases of lymphoma-like subtypes, one of which was accompanied by clonal IG gene rearrangement. Xu *et al* (28) also reported a case of EBV$^+$ IFDCS with clonal IGH gene rearrangement occurring in the colon. The underlying mechanisms of these findings warrant further investigation. The present study reported a case of EBV$^+$ IFDCS with clonal IGH gene rearrangement. There are three main hypotheses regarding clonal receptor gene rearrangement in histiocytic and dendritic cell tumors, including dedifferentiation, common progenitor and transdifferentiation (29). 'De-differentiation' occurs by returning to the pluripotent progenitor stage and then re-differentiating along the histiocytic/dendritic lineage. 'Common progenitor' refers to the existence of a common premalignant progenitor cell, particularly a pluripotent progenitor, that differentiates at different times along the B cell and histiocytic/dendritic lineages. 'Transdifferentiation' bypasses the progenitor cell stage and directly differentiates from tumor B cells into malignant histiocytes or dendritic cells (30-32). In 2009, Chen *et al* (33) reported that a high frequency of clonal IG receptor gene rearrangements was detected in sporadic histiocyte/dendritic cell (H/DC) sarcomas and 4 cases of IGH/IGK$^+$ H/DC sarcomas were positive for organic cation transporter 2, indicating that these H/DC sarcomas may inherit the B cell genotype and may originate from stereotyped B-cell progenitor cells. Huang *et al* (34) detected not only clonal IGH/IGK but also TCRβ/γ gene rearrangements in 33 cases of H/DC sarcomas, which seems to support the idea that H/DC tumors develop from lymphoid stereotyped progenitor cells. The two different types of tumors may derive from a common precursor and differentiate in two different directions under pathological conditions. In 2004, Xie *et al* (35) reprogrammed B cells into macrophages and reported that the reprogrammed macrophages exhibited heavy and light chain IG rearrangements. Barone *et al* (36) reported a case of mantle cell lymphoma with an apparent lineage transition to EBV$^+$ T-cell lymphoma, indicating that a lineage transition from a mature B-cell phenotype to a mature T-cell phenotype is possible.

Based on the aforementioned findings, we hypothesized the following: i) EBV latent in B cells infects FDCS and EBER or LMP-1 is released from EBV into FDCS, leading to inhibition of apoptosis and FDC proliferation by amplifying the CD40 signaling pathway; ii) EBV infects resting B cells and turns them into activated proliferating lymphoblasts that then differentiate along FDCs; and iii) EBV-infected B cells differentiate directly into FDCs. The clonal IGH gene rearrangement detected in the present case may also be associated with differentiation of clonal EBV-infected B cells to FDC. The existing data could not draw a clear conclusion and the mechanism of occurrence still warrants further exploration in future research.

The main differential diagnoses of EBV$^+$ IFDCS include inflammatory myofibroblastoma (IMT) and classic Hodgkin's lymphoma (CHL). IMT demonstrated elongated or polygonal myofibroblasts with eosinophilic or biphasic cytoplasm, infiltrated by plasma cells, lymphocytes and eosinophils. The histological morphology is similar to that of EBV$^+$ IFDCS, but IMT is prevalent among children ranging from 2 months to 24 years of age (median age, 9.5 years) and the majority of cases express ALK, desmin and SMA but not FDC markers and are EBER- (37,38). CHL is a lymphoblastic neoplasm with a small number of diagnostic Reed-Sternberg cells and their variants scattered in a characteristic reactive cellular background. CD30 and CD15 are usually expressed (39). Furthermore, the present case exhibits prominent granulomas, necessitating differential diagnosis from granulomatous diseases such as sarcoidosis and tuberculosis. Sarcoidosis typically involves multiple systems, particularly the lungs, but FDC immunomarkers and EBER are negative, while tuberculosis demonstrates positive acid-fast staining (2).

Due to the rarity of this disease, there is no standard treatment. Saygin *et al* (14) conducted a comprehensive analysis of 462 cases of dendritic cell sarcoma and reported that surgery was the most effective treatment method. Adjuvant radiotherapy had no significant impact on the overall survival of patients and the role of chemotherapy in the treatment of advanced diseases is controversial. By contrast, Pang *et al* (40) observed a significantly lower local recurrence rate in patients receiving surgery plus radiotherapy compared with those undergoing surgery alone when studying FDCS of the head and neck. In clinical practice, chemotherapy is often used for patients with metastatic FDCS, although there is no consensus on the most effective regimen (41). At present, due to the lack of consensus on the specific roles of chemotherapy and radiotherapy in the management of FDCS, surgical resection remains the main treatment method. In the future, large-scale multicenter prospective studies are warranted to effectively evaluate adjuvant therapy.

In conclusion, the present study described a rare case of EBV$^+$ IFDCS occurring in the spleen with clonal IGH gene rearrangement. Two hypotheses were proposed: i) Clonal EBV-infected B cells differentiation to FDC; and ii) IGH gene rearrangement occurring in the background B cells. The key principles behind the present case finding still warrants further research in the future.

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Availability of data and materials

The data generated in the present study are included in the figures of this article.

Authors' contributions

WZ evaluated the samples cytologically and histologically and clarified the diagnosis. JH completed the relevant experiments. QY and JZ participated in the analysis and interpretation of the results. QY, JZ, JH and WZ confirmed the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of anonymized data and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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