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Case Report

Inflammatory pseudotumor-like follicular dendritic cell sarcoma: a rare presentation of a hepatic mass

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Abstract: Follicular dendritic cell (FDC) sarcoma is a rare, low-grade malignant tumor originating from follicular dendritic cells in germinal centers that accounts for 0.4% of all soft tissue sarcomas. FDC sarcoma is classified into two types, the classic FDC sarcoma and inflammatory pseudotumor (IPT)-like follicular dendritic cell (FDC) sarcoma, the latter of which is rarer. IPT-like FDC sarcoma mainly involves the spleen and liver with non-specific clinical and imaging manifestations. It is often misdiagnosed as an inflammatory disease such as a liver abscess or a malignant tumor such as hepatocellular carcinoma, with a pathological morphology similar to inflammatory pseudotumors. IPT-like FDC sarcoma mainly consists of a large number of inflammatory and round, oval and spindle cells with less pleomorphism. These tumor cells are arranged in a whorled, storiform, or sheet pattern. The immunophenotype of IPT-like FDC sarcoma is the same as that of FDC sarcoma and is positive for CD21, CD23, and CD35, and positive for EBER in situ hybridization (ISH). This disease is easily misdiagnosed because it is so rare that clinicians and pathologists may not consider it in diagnosis. Here, a case of IPT-like FDC sarcoma in the liver was reported, and the related literature was reviewed to summarize the clinicopathological features, treatment, and prognosis of this rare new type of FDC sarcoma, providing new knowledge of this rare neoplasm.

Keywords: Inflammatory pseudotumor, epstein-barr virus, inflammatory pseudotumor-like follicular dendritic cell sarcoma, follicular dendritic cell sarcoma, liver, pathogenesis

Introduction

Follicular dendritic cell (FDC) sarcoma was first described by Monda in 1986. It is a low-grade malignant tumor found across a wide range of ages, but mostly in adults. Follicular dendritic cell (FDC) sarcoma can be divided into the intranodal and extranodal types based on the involved sites, of which the intranodal tumor develops mostly in the neck and axillary lymph nodes and the extranodal one in the tonsil, spleen, mouth, gastrointestinal tract, and liver [1-4]. According to the histological morphology, FDC sarcoma can be classified into two types, the classic FDC sarcoma and the IPT-like FDC sarcoma, and the latter is a new type defined by Cheuk et al. [1]. in 2001. In 1994, Delsol first discovered this inflammatory pseudotumor (IPT) in the liver and found that follicular dendritic cell markers were expressed in these tumor cells. Since then, a case of this disease was first reported by Selves et al. in 1996 [5]. IPT-like FDC sarcoma is a very rare tumor, and 63 cases have been reported in the English literature to date [2, 6-12], of which 30 cases developed in the liver [6, 12-16]. IPT-like FDC sarcoma is considered an entity completely different from classic FDC sarcoma in histological morphology and biological behavior, and it is often associated with Epstein-Barr (EB) virus infection.

Materials and methods

Case report

The patient (female; 67 years old) was admitted to our hospital because of a persistent cough, expectoration, and progressive aggravation for 2 weeks. A chest CT and an enhanced MRI were performed, showing that there was a mass in the left lobe of the liver. The mass was resected uneventfully. Routine H&E. staining was performed. The patient underwent a resection of the left hepatic tumor in Shanghai East Hospital in March 2017.

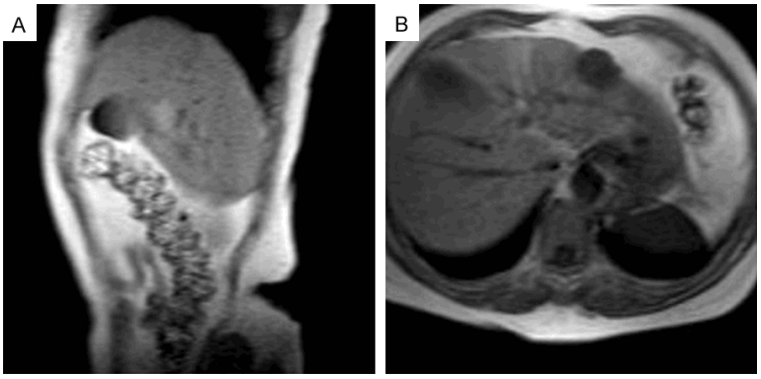

Figure 1. MR images of hepatic IPT-like FDCT. A. A well-defined heterogeneous mass 40 × 30 × 26.8 mm in size was situated in the left lobe of the liver. B. Some of which was out of the liver.

Immunohistochemistry and EBER in situ hybridization

A specimen of the liver parenchyma was examined histopathologically, and immunohistochemical staining for CD4, CD8, CD38, CD138, Kappa, Lambda, CK19, CD20, CD15, CD23, CD21, CD30, IgG4, CK, CD1a, ALK, and Ki67 were performed on formalin-fixed, paraffin-embedded (FFPE) tissue sections following routine procedures, on a Ventana Benchmark automated stainer (Ventana Medical Systems, Tucson, AZ). EBV-encoded small RNA (EBER) in situ hybridization was performed according to a published protocol [17].

IgH gene and TCR gamma gene rearrangement

DNA was extracted from FFPE tissue and PCR amplified for the detection of IgH gene and T-cell receptor (TRG locus) gene rearrangements. A multiplexed PCR reaction was performed following a published protocol [18].

Results

Chest CT and enhanced MRI findings

A chest CT showed chronic bronchitis accompanied by infection in both lungs. An enhanced MRI showed that the proportion of liver lobes was normal, and nodular abnormal signals were seen in the left lobe of the liver, some of which were out of the liver, with a range of about 40 × 30 × 26.8 mm, and slightly low, high, and high signal intensities were detected on the T1W, T2W, and DWI images respectively. A slightly inhomogeneous circular enhancement was found after the enhancement, but no abnormal changes were observed in the morphology or the signal from the intrahepatic and extrahepatic bile ducts. Therefore, a malignant tumor was suspected, with liver cancer the most likely cause (**Figure 1**).

Microscopic, immunohistochemical features, and EBER in situ hybridization (ISH)

Microscopically, the hepatic lesion was mainly composed of a large number of lymphocytes and plasma cells, with lymphatic follicle-like structures and bile ductule hyperplasia found, and a small amount of neutrophil infiltration and fibrous proliferation were observed in the local focus. The immunohistochemical results demonstrated that CD4 (+), CD8 (+), CD38 (+), CD138 (+), Kappa (+), Lambda (+), CK19 (bile duct epithelium +), CD20 (focus +), CD15 (partial +), CD23 (+), CD21 (+), CD30 (-), IgG4 (-), CK (-), CD1a (-), ALK(-), Ki67 proliferation index (about 30%). In situ hybridization for EBV (EBER) showed abundant EBV-infected cells that included the proliferating cells (**Figure 2**).

IgH gene and TCR gamma gene rearrangement study

Sizing control reactions indicated that the quality of the extracted DNA was adequate for all PCR reactions. Both IgH and TCR PCR revealed several peaks, within a polyclonal background suggestive of a restricted but not clonal gene rearrangement pattern (**Figure 3**).

DNA extracted from the FFPE tissue was subjected to multiplexed PCR amplification of the TRG gene locus. The products were analyzed by capillary electrophoresis. TRG PCR revealed several moderate peaks, within a polyclonal background, indicating a restricted but not clonal TCR gene rearrangement pattern. Duplicate PCR reactions were performed showing similar results.

We finally diagnosed the patient with inflammatory pseudotumor-like follicular dendritic cell (FDC) sarcoma.

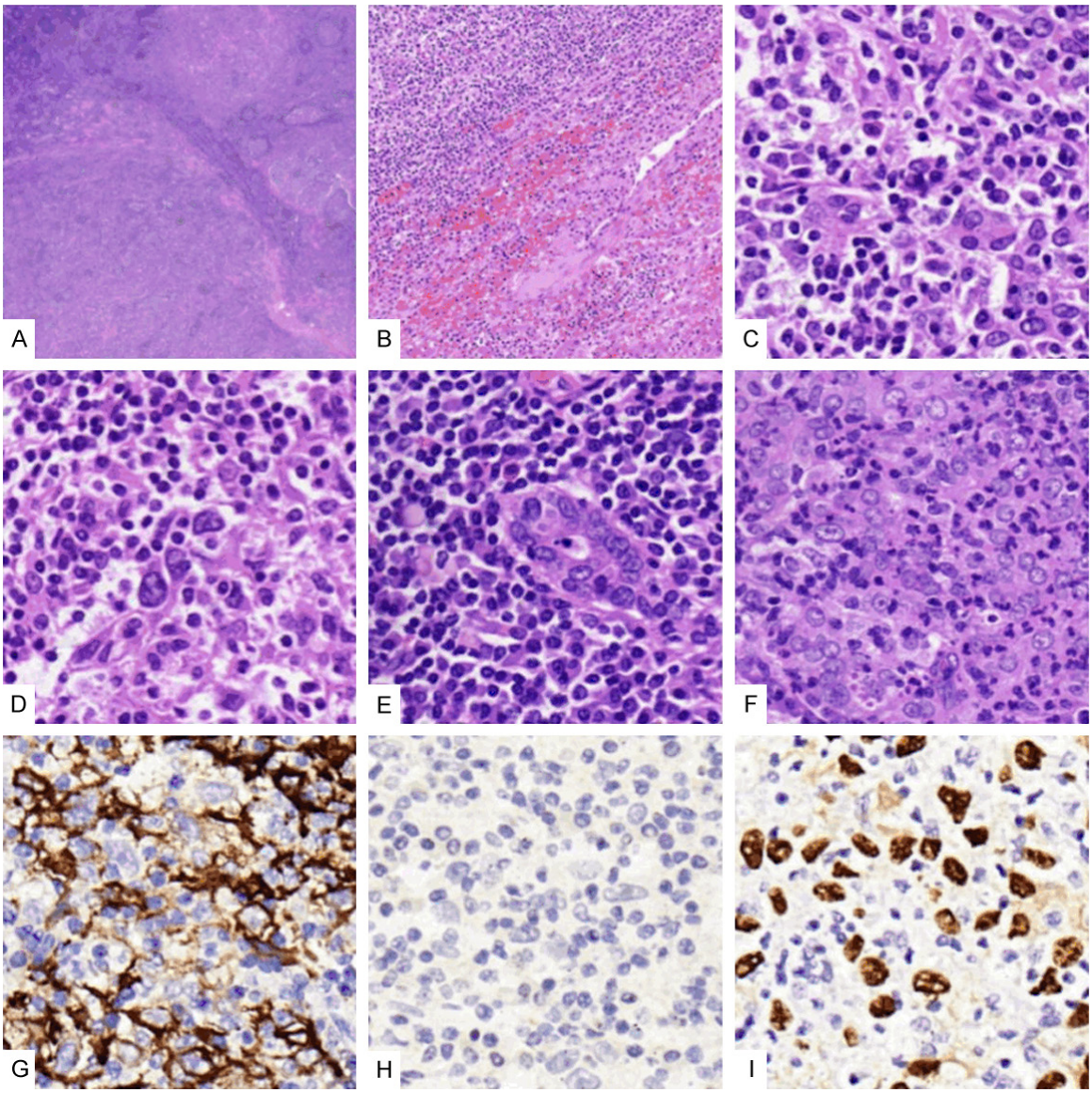

Figure 2. Microscopic, immunohistochemical features, and EBER in situ hybridization (ISH) of a case of hepatic IPT-like FDC sarcoma. (A) The lesion was composed of a dense lympho-plasmacytic infiltrate. It sometimes contains small lymphoid follicles. (B) The mass is well demarcated from the surrounding liver parenchyma, with an incomplete fibrous capsule. (C) High magnification demonstrating the tumor cell component. The tumor cells have indistinct cell borders and had a short spindle or oval shape with an irregular nucleus and the cytoplasms are moderately abundant and lightly eosinophilic. (D) Sometimes giant cells can be found, with large hyperchromatic nuclei. (E) The inflammatory cells in the background are histologically composed of lymphocytes, with a predominance of mature plasma cells, with bile ductule hyperplasia. (F) The cell borders are generally indistinct, imparting a syncytial appearance, and scattered neutrophils are focally present in the tumor. (G) Immunohistochemical staining indicates CD23 positive, suggesting that the proliferating stromal cells are of dendritic cell origin. (H) In this case, staining for IgG4 was negative. (I) The nuclei of the tumor cells are positive for EBV-encoded small RNA (EBER) by in situ hybridization detection (hematoxylin-eosin, original magnifications, × 20 (A), × 100 (B), × 400 (C-F); immunohistochemical staining, original magnifications × 400 (G, H); EBV-encoded small RNA ISH, original magnification × 400 (I)).

Discussion

Follicular dendritic cell (FDC) sarcoma is a very rare neoplasm which commonly involves the lymph nodes and less commonly involves extranodal organs such as the liver, spleen, bowel and pancreas. A subgroup of FDC sarcoma called the IPT-like FDC sarcoma is even rarer. In 2014 the largest study on the disease was a retrospective review with thirty-eight patients

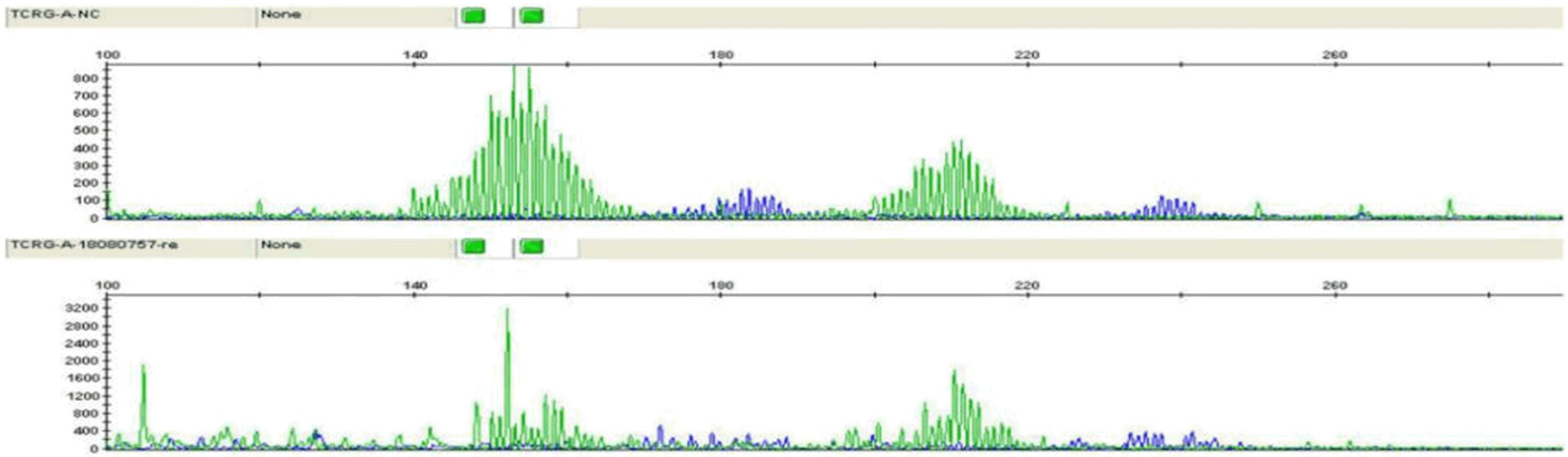

Figure 3. T-cell receptor γ-chain (TRG) gene rearrangement studies.

[2]. The assessment of all 38 cases showed a slight female predominance (2.2:1) with a median age of 56.5 years (range 19-82). Almost all the cases occurred in the liver (n = 20) or the spleen (n = 17). Although the study included cases from both Eastern and Western countries, there tend to be more reports from Asian countries. The main presentations of IPT-like FDC sarcoma include abdominal discomfort and pain, abdominal distension, a low fever, and an abdominal mass. Some patients are asymptomatic and the disease is found during a physical examination with color Doppler ultrasound or in CT findings showing well-defined space-occupying lesions in the liver or spleen.

The clinicopathological nature of IPT-like FDC sarcoma remains unknown. Chen et al. [19]. confirmed the presence of the EBV genome in 2 patients with FDC sarcoma reported by detecting the LMP-1 gene in tumor cells using a polymerase chain reaction. LMP-1 is an intramembrane protein encoded by the BNLF gene of EBV. The LMP-1 gene is a viral oncogene and also a target for T cell-mediated cytotoxicity. The mutation in this gene allows the virus to escape from the immune response of T cells. Meanwhile, a 30-bp deletion and point mutation at individual loci have been found in exon 3 of the LMP-1 gene, which helps the EBV-infected FDC sarcoma to develop tumoric hyperplasia and escape from host immune surveillance rather than to impair the transcriptional function of the protein, thereby enhancing the tumorigenicity of the cells. In hepatic IPT-like FDC sarcoma, the EBV infection occurs before the monoclonal proliferation of the neoplastic FDCs. The specific mechanism remains unclear, but all IPT-like FDC sarcoma patients, however, are positive for EBER ISH. The IPT-like FDC sarcoma patient reported in the present study was also confirmed to be EBV-positive.

Histologically, a clear boundary can be observed between IPT-like FDC sarcoma tissue and the surrounding normal tissue. The tumor cells are spindle, oval or round RS-like cells with 2 or more nuclei. Nucleoli are seen in some cells and the nuclear division phase is rarely noted. The tumor cells are arranged in whorled, storiform or interlacing fascicle patterns or individually scattered. The tumor background consists of a large number of diffusely distributed inflammatory cells, mainly including plasma cells, lymphocytes, and a small number of neutrophils, sometimes with lymphoid follicle formation. Fibrous tissue proliferation is seen at the margin of the tumor. For the patient in this report, the tumor morphology also showed a clear boundary between the tumor tissue and the surrounding normal tissue, with some tumor cells scattered in the inflammatory background. The tumor cells were short spindle or oval in shape with irregular nuclei.

On immunohistochemistry, the characteristic markers of IPT-like FDC sarcoma mainly include CD21, CD23, and CD35, and the most sensitive and reliable marker for this tumor is CD35. To demonstrate an FDC antigens, a panel of markers including CD21, CD35, clusterin, CAN.42, CXCL13, and D2-40 rather than a sole marker should be included in the immunohistochemical staining, as IPT-like FDC tumors are often positive for only 1 of the FDC markers and the staining can be patchy and focal [20, 21]. The tumor cells are often negative for desmin, caldesmon, CD31, CD34, S100, anaplastic lymphoma kinase (ALK), and CD30. The patient reported here was CD21- and CD23- positive. EBER ISH and EBV detection should be used as a first-line method for the diagnosis of IPT-like FDC sarcoma. In this case, EBER-positive tumor cells were prominent in the inflammatory background. Ki-67 is the most sensitive indicator for tumor proliferative activity. The expression level of Ki-67 reliably reflects the proliferation rate of malignant tumors and is related to the development, metastasis and prognosis of malignant tumors [22]. The Ki-67 labeling index for our patient was about 30%, indicating that IPT-like FDC sarcoma is an invasive and low-grade malignant neoplasm which is less invasive than other malignant tumors of the digestive system.

IPT-like FDC sarcoma needs to be differentially diagnosed from the following diseases. (1) Classic FDC sarcoma: IPT-like FDC sarcoma can express FDC markers such as CD21 and CD35 and is positive for EBV. The differential diagnosis of IPT-like FDC sarcoma from classic FDC sarcoma depends on its unique clinicopathological features with specific presentations as follows: IPT-like FDC sarcoma is mostly diagnosed in women, and no such pattern is seen in classic FDC sarcoma; inflammatory cells are abundantly distributed in IPT-like FDC sarcoma and rarely in classic FDC sarcoma. Most spindle cells in IPT-like FDC sarcoma are EBV-posi-

tive, but the tumor cells in classic FDC sarcoma are usually EBV-negative, and although IPT-like FDC sarcoma may relapse, the biological behavior of this tumor is relatively inert, and patients can survive for many years after disease recurrence. The biological behavior of classic FDC sarcoma may also be inert, but the recurrence rate, however, is as high as 40-50%, and the clinical process of intra-abdominal FDT sarcoma is invasive. (2) Inflammatory pseudotumor (IPT): The histological morphology of IPT is similar to that of IPT-like FDC sarcoma. Both tumors consist of spindle cells mixed with abundant inflammatory cells, and the morphology of spindle cells is the same as that of classic FDC sarcoma. Therefore, it is difficult to distinguish IPT-like FDC sarcoma from IPT. However, an immunohistochemical staining assay suggests that IPT-like FDC sarcoma are positive for CD21 and CD23 (markers for FDCs) as well as positive for EBEV ISH, and this is not noted in IPT. EBEV ISH is the key criteria for the differential diagnosis. (3) IgG4-related sclerosis: IgG4-related sclerosis is associated with autoimmune diseases. This disease is characterized by systemic injuries and elevated serum IgG4 levels as major clinical features and diffuse lymphoplasmacytic infiltration, fibrosis, obstructive phlebitis and a large number of IgG4-positive plasma cell infiltration in lesions in histopathological findings. For our patient, the serum IgG4 level was in the normal range, and the tumor tissue immunohistochemical staining was negative for IgG4. In addition, the clinical manifestations and laboratory tests didn't meet the criteria for the diagnosis of IgG4-related sclerosis, so the diagnosis of this disease was ruled out.

In treatment, no standard treatment for patients with IPT-like FDC sarcoma has been established to date. Surgical resection is usually the preferred treatment for patients with localized lesions and chemotherapy and/or radiation therapy is applied for recurrent or failed surgery patients [12]. The recurrence rate of IPT-like FDC sarcoma is very low, and patients survive for a long time even after the relapse. Ge et al. [2] followed up 34 patients with IPT-like FDC sarcoma and only 4 (about 11.8%) relapsed, and 1 (about 2.9%) died of the disease, revealing the relatively inert biological behavior of this disease.

Conclusions

In conclusion, IPT-like FDC sarcoma is a very rare tumor that mainly involves the liver and spleen. Despite the similar pathological morphology of IPT-like FDC sarcoma and IPT, IPT-like FDC sarcomas are positive for FDC markers and EBV, which contribute to the relatively easy diagnosis of this disease by immunohistochemistry. IPT-like FDC sarcoma is often misdiagnosed as inflammatory diseases such as liver abscess or malignant tumors such as liver cancer and is seldom considered in diagnosis because of the rarity and nonspecific clinical and imaging manifestations of this disease. We should increase the awareness of this rare type of FDC sarcoma in clinical practice.

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Disclosure of conflict of interest

None.

Abbreviations

FDC sarcoma, follicular dendritic cell sarcoma; IPT, inflammatory pseudotumor; enhanced MRI, Hydrography of mid-upper abdomen + hepatobiliary and pancreatic ducts; IPT-like FDC Sarcoma, inflammatory pseudotumor-like follicular dendritic cell sarcoma; EBV, Epstein-Barr virus; EBER, EBV-encoded small RNA.

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