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Original Article

Clinicopathologic characteristics of inflammatory pseudotumor-like follicular dendritic cell sarcoma

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Abstract: Inflammatory pseudotumor (IPT)-like follicular dendritic cell (FDC) sarcoma is a recently described rare tumor and considered a unique entity, with different histologic appearances and behavior from those of the classical FDC sarcoma. This study analyzed the clinical and pathological findings of two such cases that the authors encountered and 36 previously reported cases identified in the literature. Assessment of all 38 cases showed a slight female predominance (2.2:1) with a median age of 56.5 years. Seventeen patients complained of abdominal discomfort or pain, while fifteen patients had no clinical symptom. Almost all cases occurred in liver (n = 20) or spleen (n = 17). Except in one case, all patients underwent surgical resection of the tumor alone. Histologic features showed a mixture of chronic inflammatory cells and variable amounts of spindle cells with vesicular nuclei and distinct nucleoli. The tumor cells expressed conventional FDC markers such as CD21 (75%), CD35 (92%), CD23 (62%), clusterin (75%), and CNA.42 (100%). EBV was detected in thirty-five cases (92.1%) by Epstein-Barr virus (EBV)-encoded RNA in situ hybridization, and EBV-latent membrane protein-1 was expressed in 90% of the cases. With a median follow-up of 21 months, 29 patients (85.3%) were alive and well, 4 (11.8%) were alive with disease, one patient (2.9%) died of disease. Only four patients with hepatic tumors underwent recurrence or metastasis after initial treatment. Epstein-Barr virus is thought to play a role in the development of the tumor; however, the pathogenesis of the disease and the origin of tumor cells remain unclear.

Keywords: Follicular dendritic cell sarcoma, inflammatory pseudotumor, Epstein-Barr virus, spleen, liver

Introduction

Follicular dendritic cell (FDC) sarcoma was first described by Monde et al. in 1986 [1]. Since then, many reports have documented FDC sarcomas. In most of these cases, the sites affected are the lymph nodes [2-5]. Extranodal cases are uncommon, mainly arising in intra-abdominal organs and the upper aerodigestive tract [4, 5]. FDC sarcoma tends to affect young to middle-aged patients without gender predilection. The tumor displays a generally indolent behavior, but intra-abdominal cases can have an aggressive clinical course [6-8]. Histologically, FDC sarcoma shows storiform and fascicular arrangement of plump spindle cells, which are immunoreactive for one or more the FDC markers: CD21, CD35, CD23, CNA.42 and Clusterin.

The FDC sarcoma that characteristically demonstrates a conventional inflammatory pseudotumor (IPT)-like histology is uncommon neoplasm. Up to now, 36 cases of IPT-like FDC sarcomas have been published [5, 9-29]. Almost all reported cases have involved the liver or spleen, and are related to clonal Epstein-Barr virus (EBV) proliferation. The tumor with so-called IPT-like histology was recognized as a distinctive entity, and was defined as an 'IPT-like variant of FDC sarcoma' by the World Health Organization [4]. However, the clinicopathologic nature of the disease remains controversial.

There are only 15 cases of IPT-like FDC sarcomas in the spleen in the literature [5, 22-29]. Here, we present two cases of IPT-like FDC sarcomas occurring in the spleen, and discuss this rare neoplastic subtype of FDC sarcomas based on a review of the literature.

Materials and methods

Assessment of new cases

Two cases of splenic IPT-like FDC sarcomas were retrieved from the surgical pathology files

Table 1. Antibodies and results of immunostaining

Antibodies	Source	Dilution	Pretreatment	Results	
				Case 1	Case 2
CD21	Dako	1:50	HT	+	-
CD35	Dako	1:25	PC	+	+
CD23	Dako	1:50	PC	+	-
ALK1	Novocastra	1:25	HT	-	-
CD30	Dako	1:20	PC	-	-
EMA	Dako	1:50	HT	-	-
CD68	Dako	1:20	TP	-	-
S-100 pretein	Dako	1:800	HT	-	-
SMA	Dako	1:500	No pretreatment	-	+, focal
desmin	Dako	1:50	No pretreatment	-	-
CD1a	Novocastra	1:20	HT	-	-
CD3	Dako	1:800	PC	-	-
CD20	Dako	1:1600	HT	-	-

HT, heating at 95°C in citrate buffer (10 mmol/L, pH 6.0) for 30 min; PC, pressure cooking in EDTA for 2 minutes; TP, trypsinization with 0.1% trypsin for 20 min at room temperature.

of Ningbo Diagnostic Pathology Center. A detailed clinical history was obtained from the hospital records and the discussions with the responsible clinicians. Pathological materials were taken for routine histologic processing with formalin fixation and paraffin embedding. Four-μm sections cut from the tissue blocks were stained with hematoxylin and eosin (H&E), and were used for immunohistochemical staining and in situ hybridization. Immunohistochemical staining studies were performed using the EnVision method. The antibodies used are listed in **Table 1**. Appropriate positive and negative controls were evaluated simultaneously. In situ hybridization for Epstein-Barr virus (EBV)-encoded RNA (EBER) was performed in the two cases using an EBV probe in situ hybridization kit (Novocastra, Newcastle upon Tyne, UK). The manufacturer's instructions were followed with no modifications, and a known positive control was used to ascertain the sensitivity of the assay.

Literature review

Review of the literature was performed with MEDLINE search and China Biology Medicine disc (CBMdisc) using the terms "follicular dendritic cell sarcoma" or "follicular dendritic cell tumor" combined with "Inflammatory pseudotumor" or "Epstein-Barr virus". The articles that included the cases of the FDC sarcomas showing an inflammatory pseudotumor (IPT)-like histology were selected, and the references from these articles were also reviewed to identify other relevant publications. An effort was made to discern cases that were reported more than once in different settings and use the most updated information for such cases.

Results

Clinical histories of the two new cases

Case 1 was a 54-year-old female patient who presented with intermittent vague pain in the left upper quadrant for 4 months and with a 6-year past medical history of hypertension. Physical examination revealed multiple enlarged lymph nodes in the bilateral axillaries and neck region. Laboratory tests showed anemia (hemoglobin 87 g/L; normal range, 120-160 g/L) and renal inadequacy (blood urea nitrogen 13.3 mmol/L; normal range, 3.2-7.1 mmol/L). A workup including abdominal ultrasound and computed tomography scan revealed a well-defined, round mass measuring 3.5 cm in diameter in the spleen. The patient underwent a splenectomy with removal of splenic hilar lymph nodes, made a fine postoperative recovery and the laboratory tests normalized. Follow-up for 10 months showed no recurrence or metastasis.

In Case 2, the anamnesis of a 79-year-old man was negative except a short lasting dizziness 6 months ago. The splenic lesion was been found incidentally in the course of a routine clinical check up with ultrasound examination. At present he presented with persistent epigastralgia and physical examination showed left hypochondriac tenderness upon palpation. Computed tomography scan confirmed the existence of a solitary nodular 6 cm in diameter in the spleen. Blood picture and laboratory findings were in the normal range. A splenectomy was performed and no additional therapy was carried out. At last follow-up, 18 months after initial diagnosis, the patient remained alive with no evidence of disease.

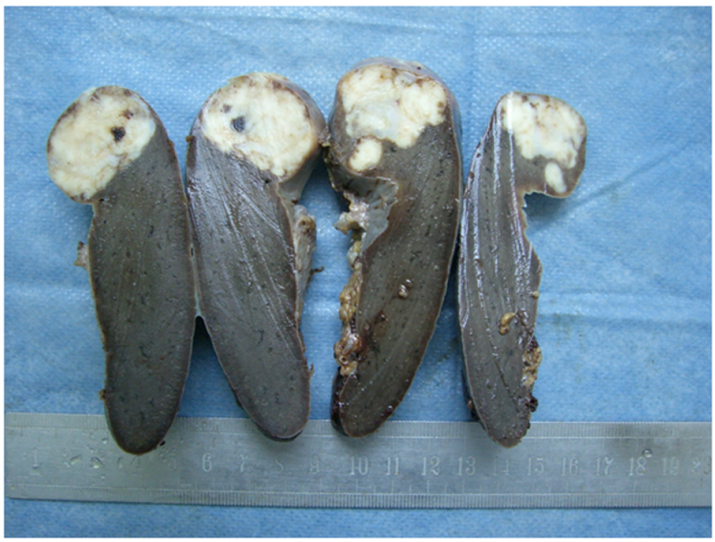

Figure 1. Gross picture of an inflammatory pseudotumor-like FDC sarcoma of the spleen (case 1). A well-circumscribed solid nodule is found in the spleen. Note the grayish-white colored cut surface with focal hemorrhage.

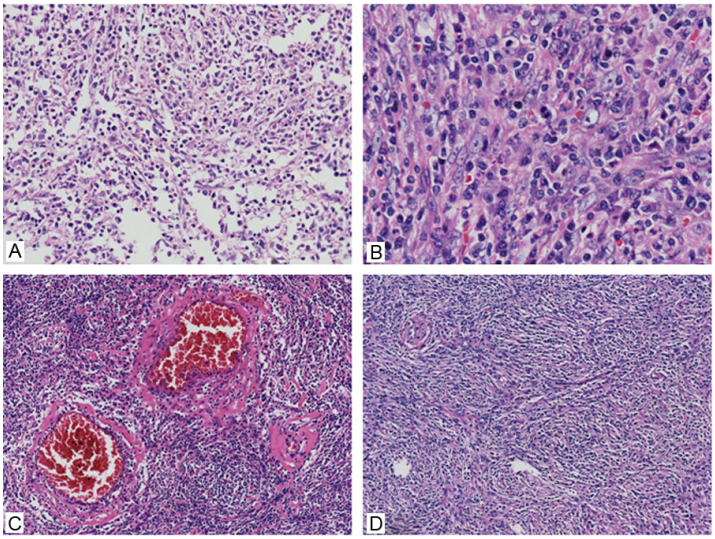

Figure 2. Microscopic appearance of inflammatory pseudotumor-like FDC sarcoma of the spleen. A: The tumor is mainly composed of an admixture of lymphocytes, plasma cells, and spindle cells. B: The tumor cells are plump with pink, vaguely fibrillary cytoplasm, vesicular nuclei and distinct nucleoli. Mitotic figures are seen. C: Blood vessels exhibit hyalinous thickening of the wall. D: The tumor has a short storiform and interlacing fascicle growth pattern.

Pathological findings of the two new cases

The resected spleen from Patient 1 measured 10 × 7 × 3.5 cm and weighed 380 g with smooth surface. The cut surface revealed a well-circumscribed but unencapsulated tumor measuring 3.5 × 3.5 × 3 cm, which was grayish-white colored and slightly firm consistency with area of hemorrhage (**Figure 1**). The tumor approached the splenic margin and a satellite nodule was present. The hilar lymph nodes were 0.8-1.5 cm in size. Microscopically, a thin fibrous layer separated the tumor from the surrounding splenic tissue in some places, but the tumor was not completely encapsulated and even involved the splenic capsule. The tumor was composed of an admixture of chronic inflammatory cells and uniform spindle cells (**Figure 2A**), which were dispersed or arranged in vague fascicles. The cytoplasms of the spindle cells were eosinophilic and slightly fibrillary, and the cytoplasmic membranes were indistinct (**Figure 2B**). The nuclei were elongated and vesicular, sometimes irregularly twisted, and contained distinct small nucleoli of central location. There was no significant cytologic atypia, and mitotic figures were not found. The inflammatory cells were predominantly mature lymphocytes and plasma cells. There were hyalinized fibrosis in some areas and fibrinoid deposits in the vessel wall (**Figure 2C**). A heavy paracortical and medullary polyclonal plasma cell reaction was present in the splenic hilar lymph nodes. The spleen specimen from Patient 2 measured 12 × 9 × 6 cm and weighed 600 g. Its capsule was undamaged, but uneven on the surface. It contained a 6 × 6 × 5 cm nodular mass without encapsulation, which had a grayish and soft cut surface with focal necrosis and cyst formation. Morphological features were generally similar to that viewed in Patient 1. Besides, the tumor cells were arranged in whorled, storiform or interlacing fascicle patterns (**Figure 2D**). Mitotic figures were seen, averaged 1/10 high power fields (HPF). A few multinucleated giant cells were observed, and Necrosis was prominent in some areas.

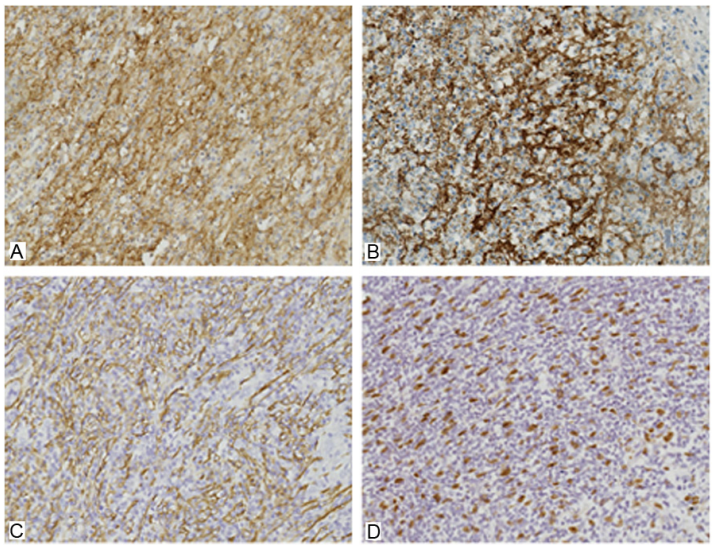

Figure 3. Immunohistochemistry of the tumor and In situ hybridization for EBER. A: CD35 is diffusely positive in the spindle cells (case 1). B: CD21 is diffusely positive (case 1). C: Some of the spindle cells are positive for smooth muscle actin (case 2). D: EBV is detected in almost all of the tumor cells with positive dark staining of their nuclei (case 2).

Immunohistochemically, the spindle cells in both cases were diffuse positivity for CD35 (**Figure 3A**), and case 1 showed positivity for CD21 (**Figure 3B**) and CD23. Focally, the spindle cells in case 2 were stained with SMA (**Figure 3C**), but not with CD21 and CD23. Both cases were negative for ALK, CD30, EMA, CD68, S-100 protein, desmin, CD1a, CD3 and CD20. Lymphocytes in the background were mostly CD3-positive. There were a few CD20-positive cells. In situ hybridization analysis for EBER showed that spindle cells in both cases were almost exclusively EBV-positive (**Figure 3D**), but not on the surrounding inflammatory cells.

Literature review

A total of 36 cases of IPT-like FDC sarcomas were retrieved from the literature. Clinical information on these 36 cases, along with the two new cases, is detailed in **Table 2**.

There were 26 women and 12 men (female to male ratio, 2.2:1). The age range was 19-82 years, with a median of 56.5 years and a mean of 54.5 years. Although the geographic distribution of the cases covered both Eastern and Western countries, more reports appeared to occur in Asian countries. The tumors mainly affected the liver and the spleen. Twenty cases involved the liver, seventeen the spleen and one the peripancreatic region between the wall of the duodenum and the head of the pancreas. The most common symptom was abdominal discomfort or pain (seventeen cases), although fifteen cases had no clinical symptom (six in the liver, nine in the spleen). Other common clinical features included weight loss (nine cases), anemia (six cases), fever (three cases), malaise (three cases), and dizziness (two cases).

Clinical management and patients' outcome

Except in one case (case 4), all patients underwent surgical resection of the tumor alone. Follow-up information was available in 34 cases. The follow-up time ranged from 2 to 108 months (mean, 30.0 months; median, 21 months). At last follow-up, 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. There is no recurrence or metastasis in the splenic cases, while 4 hepatic cases show recurrence or metastasis after initial treatment. Two patients had intra-abdominal recurrence at 8 and 108 months respectively. Two patients experienced repeated recurrence and one of them died of tumor dissemination at 95 months. Overall, the recurrence rate was 11.8% and the mortality rate was 2.9%.

Pathological findings

The average size of tumors of all sites was 9.2 cm, ranging from 2 to 22 cm (median, 8.3 cm). Hepatic tumors (n = 18) had an average tumor size of 11.1 cm (range, 2-20 cm; median, 12.3 cm), whereas the average tumor size of the splenic tumors (n = 17) was 7.1 cm (range, 3.2-22 cm; median, 6 cm).

The gross and microscopic findings of the reported cases were similar to those observed in our two cases as described above. The most helpful diagnostic characteristics were the fascicle arrangement of tumor cells with fibrillary cytoplasm and vague cellular borders and the presence of prominent inflammatory infiltrate.

Table 2. Summary of reported cases of inflammatory pseudotumor-like follicular dendritic cell sarcoma

Case	Sex/ age	Location	Maximum diameter (cm)	Presentation	Treatment	Last follow-up (months)	Outcome
1 [9]	F/68	Liver	11	Malaise, weight loss, anemia	Chemotherapy; Excision of liver mass	30	AW
2 [5, 10]	F/35	Liver	20	Epigastric discomfort, low-grade fever, weight loss	Right hemihepatectomy	95	Recurrence 3 times; Died from dissemination
3 [5, 11]	M/37	Liver	15	Malaise, weight loss, hepatomegaly	Right trisegmentectomy with caudate lobectomy	42	AW
4 [12]	F/57	Liver	9.5	Intermittent epigastralgia, anemia	Refused resection	36	AD
5 [12]	F/51	Liver	12	Abdominal fullness, weight loss, anemia	Left lobectomy	12	AW
6 [5]	F/19	Liver	12	Right upper quadrant pain, palpable abdominal mass, weight loss	Surgical excision	40	AW
7 [5]	F/56	Liver	15	Gastrointestinal upset	Right lobectomy	56	Recurrence 3 times, AD
8 [5]	F/40	Liver	12.5	Epigastric pain, weight loss	Left hepatectomy	108	Intra-abdominal recurrence, AD
9 [5]	F/49	Liver	4.2	Asymptomatic	Surgical excision	9	AW
10 [5]	F/31	Liver	15	Abdominal distension, weight loss	Right hemihepatectomy	60	AW
11 [13]	M/82	Liver	15	Weakness, occasional fevers, anorexia, weight loss, syncope, anemia, hypoalbuminemia	Right lobectomy	18	AW
12 [14]	F/30	Liver	5.5	Asymptomatic	Right lobectomy	24	AW
13 [15]	M/29	Liver	15	Abdominal distension, epigastric pain, weakness	Resection of left lateral and quadrate lobe	8	Intra-abdominal recurrence, AD
14 [16]	F/28	Liver	2	Epigastric discomfort	Resection of the tumor	NA	NA
15 [17]	F/57	Liver	13	Abdominal pain, vomiting, dizziness	Resection of the tumor	24	AW
16 [18]	M/40	Liver	NA	Asymptomatic	Excision of liver mass	3	AW
17 [19]	F/59	Liver	6	Asymptomatic	Partial hepatectomy	17	AW
18 [20]	M/75	Liver	NA	Asymptomatic, founding hepatic mass for cholecystitis	Excision of liver mass	6	AW
19 [21]	F/50	Liver	4	Asymptomatic	Excision of liver mass	6	AW
20 [28]	F/58	Liver	12.6	Intermittent right upper quadrant pain, weight loss	Left hepatectomy	30	AW
21 [5]	F/49	Peri-pancreas	9.5	Abdominal distension	Whipple's operation	NA	NA
22 [22]	M/70	Spleen	5.5	Asymptomatic, finding splenic mass for gallbladder disease	NA	NA	NA
23 [5]	F/58	Spleen	22	Abdominal fullness, easy bruising	Splenectomy	4	AW
24 [5]	F/39	Spleen	7.5	Malaise, weight loss, fever, splenomegaly	Splenectomy	2	Alive with persistent fever
25 [5]	F/61	Spleen	3.5	Asymptomatic	Splenectomy	NA	NA
26 [23]	M/54	Spleen	12	Asymptomatic	Splenectomy with splenic hilar lymph nodes removal	48	AW
27 [24]	F/77	Spleen	11	Epigastralgia	Splenectomy	36	AW
28 [25, 29]	F/64	Spleen	5.5	Asymptomatic	Splenectomy	78	AW
29 [26]	F/37	Spleen	9	Urgent micturition, painful urination, mild anemia	Splenectomy	5	AW
30 [27]	M/63	Spleen	7	Asymptomatic	Splenectomy	18	AW
31 [28]	F/67	Spleen	5	Progressive epigastric pain	Splenectomy	72	AW
32 [29]	F/72	Spleen	7.2	Asymptomatic	Splenectomy	18	AW
33 [29]	F/53	Spleen	3.2	Asymptomatic	Splenectomy	13	AW
34 [29]	M/76	Spleen	3.2	Asymptomatic	Splenectomy	8	AW
35 [29]	M/72	Spleen	6	Asymptomatic	Splenectomy	18	AW
36 [29]	M/75	Spleen	3.5	Abdominal pain	Splenectomy	30	AW
37	F/54	Spleen	3.5	Intermittent vague pain in the left upper quadrant, lymph nodes enlargement, anemia, renal inadequacy	splenectomy with splenic hilar lymphadenectomy	10	AW
38	M/79	Spleen	6	A short lasting dizziness	Splenectomy	18	AW

AW, alive and well; AD, Alive with disease; NA, not available.

The tumors had a low-grade histology with only mild atypia and rare mitotic figures. Binucleated and multinucleated neoplastic cells were seen occasionally. However, some cases showed obvious cytological atypia, such as enlarged irregular nuclei and coarsely condensed chromatin. There were abundant lymphocytes and plasma cells, and some histiocytes or eosinophils; a few multinucleated giant cells were also present. Focal necrosis and hemorrhage were noted in some cases. Around the central necrosis, some blood vessels exhibited hyalinous deposition of the wall.

Immunohistochemical study

CD21 and CD35 were usually used, and both had a high positive rate (75% for CD21 and 92% for CD35). The CD21/CD35 cocktail were detected in 100% of the cases, although the staining could be weak and focal. Other follicular dendritic cell markers were also noted: 18/29 (62%) for CD23, 14/14 (100%) for CNA.42, and 6/8 (75%) for clusterin. Vimentin showed uniform positivity, while CD68 was observed in 60% of the cases. Expression of muscle-associated antigens was detected, including 7/14 (50%) for HHF35 and 11/19 (58%) for SMA. The tumor cells were negative for desmin, ALK-1, CD30, EMA, CD34, HMB-45 and CD1a. T cells were more predominant than CD20- or CD79a- positive B Cells among the background inflammatory cells, except for one case. CD8-positive T cells clearly outnumbered or equaled CD4-positive T cells. The majority of the T cells also expressed intracellular T cell antigen 1 (TIA-1).

Detection of EBV and LMP-1 gene study

Of all the 38 tumors, thirty-five cases showed that the spindle cells were positive for the EBER as tested by in situ hybridization. The background small lymphocytes and plasma cells were completely negative for EBV. Immunostaining for LMP-1 was detected in 90% of the cases, although the positivity was only seen in a small proportion of the tumor cells. No expression of EBV nuclear antigen 2 (EBNA 2) was detected [10, 23]. DNA sequencing of PCR products were analyzed in three cases and showed a 30-bp deletion in exon 3 compared with the standard LMP1 sequence of the EBV from B95-8 cells. Besides, there were three point mutations at positions 168320 (A→G), 168308 (T→C), and 168225 (T→A) [9, 12, 24].

Ultrastructural examination

Ultrastructural findings were reported in four cases, and all showed the tumor cells with long villous cytoplasmic processes and well-formed desmosomes [10, 11, 13, 19]. No cytoplasmic interdigitations or Birbeck granules were detected [10, 19].

Discussion

IPT-like FDC sarcoma is a very rare neoplasm, and only 38 cases have been reported in the literature, including ours. Although its clinicopathologic features have not been fully investigated, it is generally considered to be a distinctive variant compared with conventional FDC sarcoma. First, IPT-like FDC sarcomas occur almost invariably in the spleen or liver. In contrast, conventional follicular dendritic cell FDC sarcomas can involve the lymph nodes and a broad range of anatomical sites [8]. Second, IPT-like FDC sarcomas show marked female predilection (female to male ratio, 2.2:1), whereas FDC sarcomas are not more prevalent in one sex than in the other [30]. Third, IPT-like FDC sarcomas have intense lymphoplasmacytic infiltrates, which make it difficult to discern them from inflammatory pseudotumors, contrasting with a sprinkling of inflammatory cells in the majority of conventional FDC sarcomas. Fourth, IPT-like FDC sarcomas are strongly associated with the presence of EBV, which is rare for conventional FDC sarcomas. Fifth, although both IPT-like FDC sarcomas and conventional FDC sarcomas show generally a indolent clinical behavior, intra-abdominal cases of conventional FDC sarcomas can be more aggressive than IPT-like FDC sarcomas, and may recur or metastasize and even lead to patient death [2, 30]. Conversely, IPT-like FDC sarcomas seldom recur or metastasize, especially in the splenic cases.

When suspected intra-abdominal inflammatory pseudotumor-like lesion, especially in the liver and the spleen, the diagnosis of IPT-like FDC sarcoma can become relatively easy. As illustrated in our study, IPT-like FDC sarcoma typically has distinct histological and immunohistochemical findings to allow a definitive diagnosis. However, sometimes it can be difficult to

consider the disease because the tumor shows bland spindle cells without nuclear atypia and the overshadowing chronic inflammatory infiltrate. Immunostaining for FDC markers is of great value for the diagnosis of IPT-like FDC sarcoma. Because the tumor cells usually lost at least one FDC marker, it is necessary to apply a panel of FDC markers. CD21 and CD35 have been widely used as the preferred FDC markers, and using a cocktail of both antibodies can increase the intensity of staining. Clusterin is also a highly sensitive and specific FDC marker [31]. The antibody CD23 is of limited utility for diagnosis because of the low positivity rate and only patchy or focal staining. CNA.42 has been shown to be very sensitive, but at the same time less specific. Reed-Sternberg cells in Hodgkin's disease and mononuclear cells in the background are also positive for CNA.42 [32]. Additionally, IPT-like FDC sarcomas may show variable staining for SMA, HHF-35, S100 protein, and CD68.

Discordant diagnoses can entertain at the time of initial evaluation. Overall, six cases were misdiagnosed at initial evaluation and these disease entities considered included: Hodgkin lymphoma (one case) [9], malignant fibrous histiocytoma (one case) [15], inflammatory myofibroblastic tumor (IMT) or IPT (four cases) [5, 10, 22, 28]. The disease is uncommon, and lack of a high index of suspicion is the main reason for misdiagnosis in most instances. When IPT-like FDC sarcoma occasionally contain some Reed-Sternberg–like cells or show a sarcomatoid appearance with a spindle cell-predominant morphology, it may be confused with Hodgkin's disease, malignant fibrous histiocytoma, or simply a stromal tumor not further specified [5, 28]. Immunoreactivity for FDC markers may help in making the distinction. However, it is difficult to distinguish IPT-like FDC sarcoma from IPT/IMT on account of striking histological resemblance. IPT/IMT can involve at virtually any anatomic sites of the body, including spleen and liver, and usually occurs in children and younger adults [33]. The diagnosis of IPT-like FDC sarcoma should be based on the recognition of FDCs from microscopic appearance. In fact the distinction of IPT-like FDC sarcoma from IPT/IMT is usually impossible without immunohistochemistry. IPT-like FDC sarcoma may be mixed with reactive myofibroblasts to a variable degree [29], because SMA, which stains myofibroblasts of IPT/IMT, is detected in more than half cases of IPT-like FDC sarcomas. IPT-like FDC sarcoma shows at least one FDC marker immunostaining, but negative for ALK, which is demonstrated by some IPT/IMTs.

EBV is thought to play a key role in the genesis of IPT-like FDC sarcoma. Almost all IPT-like FDC sarcomas exhibited positive EBER by in situ hybridization, whereas only one of 25 conventional FDC sarcomas cases tested was positive for the virus [2, 34]. LMP-1 gene, the major oncogene of EBV, is capable to transform rodent fibroblasts in vitro. EBV genome with a 30-bp deletion or point mutations in exon 3 of the LMP-1 gene was identified in three cases of IPT-like FDC sarcomas [9, 12, 24]. These alterations in the LMP-1 gene are prevalent in Asia, and it may be the reason that most reported IPT-like FDC sarcomas have been found in Asian patients. Southern blotting analysis demonstrated that the EBV infection occurred before the monoclonal proliferation of the neoplastic FDC [9, 10], indicating that there can be a pathogenetic difference between IPT-like FDC sarcoma and conventional FDC sarcoma. However, the pathogenic mechanism of EBV in IPT-FDC sarcoma remains unclear and further investigation is required.

Recently, there was an interesting observation that some IPT-like FDC sarcoma of the spleen accompanied by numerous $IgG4^+$ plasma cells [29]. According to the number of $IgG4^+$ plasma cells/high-power field and the ratio of IgG4/IgG, most cases in that study appeared to satisfy the criteria of IgG4-related disease proposed in the previous study [35]. However, those cases only showed a solitary, localized disease with focal sclerosis and obliterating vasculitis, and lacked more pathologic features supporting IgG4-related sclerosing disease. The study suggested that $IgG4^+$ cells can be closely linked with the IPT-like FDC sarcoma and might contribute to the development of the tumor.

In summary, IPT-like FDC sarcoma is receiving increasing attention and the diagnosis is becoming easy owing to advances in immunohistochemistry. In analyzing all reported cases, we have outlined the clinical and pathological characteristics of this disease entity, introduced associations between IPT-like FDC sarcoma and FDC sarcoma, brought forth differen-

tial diagnosis, and provide evidence for further exploration of the pathogenesis of the tumor.

Disclosure of conflict of interest

None.

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