

Recurrent Pancreatic Follicular Dendritic Cell Sarcoma: A Case Report and Literature Review

Jia Li

Shengjing Hospital of China Medical University

Wenyang Zhou

Shengjing Hospital of China Medical University

Ying Lv

Shengjing Hospital of China Medical University

Rong Hu (✉ cmuhr@qq.com)

Shengjing Hospital of China Medical University

Case Report

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Abstract

Background: Follicular Dendritic Cell Sarcoma (FDCS) is a rare malignant tumor originated from follicular dendritic cells. Presently radical resection is the standard treatment; however there is no clear optimal chemotherapy for unresectable lesions. We presented the clinical data, pathological features, imaging features, diagnosis and treatment of a very rare patient with recurrence and metastasis after radical resection of pancreatic FDCS.

Case presentation: A 64-year-old male patient was delivered to hospital due to intermittent chest tightness and pain. A pancreatic mass was found after thorough physical examination. Enhanced MRI showed a round solid mass in the head and neck of pancreas. The patient underwent radical resection. The pathological diagnosis was FDCS. CHP regimen was used for consolidation chemotherapy for 6 cycles. Two years later, due to a large amount of effusion, the patient was confirmed to have relapse and extensive abdominal metastasis. Both CHOP regimen and bendamustine were ineffective.

Conclusions: FDCS of pancreas is very rare, and its imaging findings are not specific. If the disease relapses or metastases, though applies a variety of chemotherapy regimens, it is difficult to obtain satisfactory curative effect, and long-term prognosis is pessimistic. This is the first reported case that bendamustine was ineffective in the treatment of FDCS.

Background

Follicular Dendritic Cell Sarcoma (FDCS) is a rare tumor of lymphatic hematopoietic system. The incidence rate is low, and less than 200 cases have been reported in literature [1]. WHO defines it as a spindle or oval cell tumor with similar histomorphology and immunophenotype to follicular dendritic cells [2]. The tumor cells usually express the markers of follicular dendritic cell differentiation, including CD21, CD23 and CD35. FDCS usually occurs in lymph nodes, especially in cervical lymph nodes. About 30% of FDCS occurs in extranodal sites, including pharynx, tonsil, peritoneum, spleen, stomach, liver, pancreas and lung [3]. Pancreatic FDCS is very rare. So far, only 5 cases have been reported in the literature, including 2 cases of recurrence. Surgery is the main treatment strategy for FDCS, but the efficacy of radiotherapy and chemotherapy is still unclear.

The ensample in our report was a 64-year-old male patient with pancreatic FDCS, who recovered well after surgery and postoperative chemotherapy. Unfortunately, the patient relapsed and had a wide range of metastases after two years. Although a variety of chemotherapy regimens were used, the curative effect was pessimistic. Through analyzing these unique clinicopathological characteristics combined with the discussion of related literature, this study is targeted to enrich the understanding of FDCS of pancreas, provide experience and basis for establishing state-of-the-art treatment strategy.

Case Presentation

The 64-year-old male patient was delivered to the Department of Cardiology of Shengjing Hospital of China Medical University, due to intermittent chest tightness and pain lasted 3 months. He planned to undergo coronary angiography. The patient had no abdominal discomfort. After admission, abdominal color doppler ultrasound showed a 7.9 x 7.4 x 7.6cm mass in the upper abdominal pancreatic area, displayed clear boundary and heterogeneous low echo. CDFI detected abundant blood flow signals. As coronary angiography showed no stenosis and PCI wasn't needed, the patient was transferred to the surgical ward for further diagnosis and treatment. Enhanced MRI of the pancreas showed round and equal T1, slightly longer T2 signal shadow at the junction of the

head and neck of the pancreas. The dimension was approximately 8.8 x 7.4 x 8.6cm. The signal was slightly uneven, the enhanced scan was gradually strengthened, and the area of necrosis was not strengthened locally (Fig. 1a and 1b). The patient was diagnosed as solid occupying position of the head and neck of the pancreas, and the imaging was considered to be the solid pseudopapilloma of the pancreas. In three-dimensional endoscopic ultrasonography, the probe was placed in the body of stomach and duodenal bulb for scanning. A round hypoechoic mass in the head and neck region of pancreas was found with uneven internal echo (Fig. 1c). The section dimension was about 81mm x 75mm. Alpha fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 19 – 9 (CA19-9), carbohydrate antigen 125 (CA-125) and carbohydrate antigen 724 (CA-724) were normal. Amylase, lipase and lactate dehydrogenase (LDH) were normal. The patient underwent pancreatic tumor resection under general anesthesia, no metastatic nodules were found in the liver, spleen, stomach, small intestine, colon, mesentery and pelvic cavity. The tumor size was 7.5 x 6.5 x 6cm with smooth outer surface, and crisp white matter (Fig. 1d). Microscopically, the tumor cells were short spindle with obvious nucleoli, nodular lobular arrangement, and a large number of lymphocytes between the lobules (Fig. 2a and 2b). Immunohistochemical (IHC) examination showed that CD23, CD21, CD35 and vimentin were positive (Fig. 2c-2f); Ki-67 was 20%; CK, SMA, S-100, CD117, dog-1 and CD34 were negative. According to the above pathological results, a final diagnosis of pancreatic FDCS was made. After operation, the patient received six cycles of CHP (cyclophosphamide, adriamycin, prednisone) chemotherapy.

Subsequent to the treatment, no metastasis or recurrence was found by CT or ultrasound during follow-up examinations. Unfortunately, the patient was hospitalized in our department because of severe abdominal distension after two years. Physical examination showed that the abdomen was distended, and the mobile voiced sound was positive. Abdominal CT examination showed that pancreatic postoperative changes, abdominal cavity mesentery, retroperitoneum, greater omentum and right psoas major muscle multiple lesions, multiple intrahepatic space occupying lesions, were all considered for metastasis. There was a large amount of effusion in abdomen and pelvis. Bone marrow examination showed that bone marrow hyperplasia was obviously active, and no abnormal cells were found. CA-125 was increased significantly to 659.2u/ml, yet LDH was normal. Considering the recurrence and extensive metastasis of the disease, abdominal tumor puncture biopsy was performed. A pile of 0.3cm strip-shaped tissue was taken. Microscopically, short spindle cells were found in the strip-shaped tissue arranged in bundles (Fig. 3a and 3b). IHC examination showed that CD21 and CD35 were positive; Ki-67 was approximately 10%; CD23, SMA, S-100, CD117 and dog-1 were negative (Fig. 3c-3e). Combined with immunohistochemistry and medical history, the recurrence of FDCS was confirmed. In the meanwhile, the result of PD-L1 in IHC staining was negative (Fig. 3f). Due to a large amount of effusion, the patient underwent ultrasound-guided peritoneal effusion puncture and catheterization, the ascites drainage was unobstructed. Pathological examination of effusion showed that mesothelial cells and histiocytes were distributed in clusters or scattered manners, many lymphocytes were seen in the background. IHC examination showed that Ber-EP4 and MOC31 were negative, D2-40 and calrelinin were positive, and no tumor cells were found in effusion. After receiving one cycle of CHOP (cyclophosphamide, vincristine, doxorubicin, prednisone) chemotherapy, CA-125 decreased to 150.4u/ml. By the time the second cycle of CHOP chemotherapy was completed, abdominal CT showed multiple abdominal pelvic metastases, and liver metastases were the same as before. Considering the inefficacy of CHOP regimen, we chose bendamustine (90mg/m², day 1 and day 2 out of 28 days cycle) combined with prednisone for two cycles. Both considered as the 1st and 2nd tier drugs for the treatment of malignant lymphoma, bendamustine was tried in FDCS. After 2 cycles, abdominal CT showed that abdominal, liver, and pelvic multiple metastases were roughly the same as before. In the meanwhile, the patient had a large amount of effusion again, and CA-125 was even higher than before, all indicated curative ineffectiveness and disease progression. Because of deteriorative status of the patient, he discontinued receiving any other treatments.

Discussion

FDCS is a rare tumor, usually with a localized slow-growing painless mass as the first symptom, accompanied with multiple lymph node enlargement. In recent years, the incidence rate of extranodal FDCS is increasing [4]. Pancreas is a very rare site for FDCS. So far, only 5 cases of pancreatic FDCS have been reported in the literature. Most of them are female, the ratio of male to female is 1:4, mainly involving middle-aged and elderly patients, with an average age of 59 years old [5–9](Table 1). FDCS is considered as a low-grade malignant tumor because of its slow clinical course. However, due to its potential risk of local recurrence and metastasis, it has recently been considered to be at least moderately malignant [10]. Saygin et al. [11] followed up the clinical data of 224 patients with FDCS, approximately 44.6% of the patients had local recurrence and / or metastasis. Recurrence occurred in 2 out of 5 cases of pancreatic FDCS reported in the literature. The patient of our case had extensive metastasis 2 years after the first treatment.

Table 1
Summary of Previously Reported Cases of Pancreatic Follicular Dendritic Cell Sarcoma.

Case No.	Age (years)	Gender	Site	Tumor Size(cm)	IHC positivity	Initial treatment	Follow-up	Status
1	67	Male	pancreatic head	10.5×9.0×6.5	CD21, CD23, CD35, S-100, clusterin, Fascin	Surgery	18 months	Recurrence (hepatic metastases)
2	49	Female	pancreatic tail	4.0×5.0	CD21, CD23, CD138, SMA, Des	Surgery	12days	Death
3	70	Female	pancreatic tail spleen	7.0×4.2×4.0 3.0×2.7×2.8	CD21, CD23, CD35, CD68, EBER	Surgery	NA	NA
4	67	Female	pancreatic tail	4.0×4.0×4.5	CD21, CD23	Surgery	NA	NED
5	42	Female	pancreatic tail	NA	CD21, CD23, CD68, vimentin, clusterin, Fascin	Surgery	5 months	Recurrence (liver and lymph nodemetastasis, peritoneum dissemination)
Notes: IHC, immunohistochemistry; NA, not available; NED, no evidence of disease.								

Due to the slow growth of FDCS, patients with abdominal FDCS usually have no specific clinical symptoms and physical signs, our patient did not have any abdominal discomfort, thus some patients found it out only during physical examination. FDCS is often misdiagnosed as other tumors, because of its lack of characteristic imaging findings. Mao et al. [12] retrospectively analyzed CT and MRI imaging features of 20 patients with FDCS confirmed by pathology: among which 6 cases of nodal FDCS showed a small homogeneous mass, while the rest 14 cases of extranodal FDCS in mediastinum or abdomen showed a large heterogeneous mass with necrosis and calcification, possibly accompanied by local lymph node enlargement. The results showed that most FDCS were isolated and had well-defined masses. Angiogenesis and progressive enhancement can be seen in most tumors, nevertheless, the

diagnoses of FDCS were not considered in the initial radiological evaluation of all these 20 patients. Although the enhanced MRI images of our patient were consistent with the above features, our initial imaging diagnosis considered it as a solid pseudomastoid tumor of the pancreas, it was confirmed to be FDCS by surgery and pathology eventually.

Microscopically, FDCS was composed of spindle cells, arranged in a variety of manners, mainly in mat like and diffuse flaky arrangement; some of which were fasciculate, nodular and lobular arrangement, with a large number of lymphocytes and plasma cells in the background [13]. The tumor cells of this case were short spindle, nodular lobular arrangement, with a large number of lymphocytes between the lobules. Chan et al. [14] studied 17 cases of FDCS, the results of IHC examination showed that CD21 (17/17), CD35 (17/17), desmosin (10/17), epithelial membrane antigen (14/16), S-100 (6/17) and CD68 (2/17) were positive in varying degrees. Lu et al. [1] studied 9 cases of FDCS, CD21 (6/9), CD35 (6/9), CD23 (7/9) tumor cells were positive in varying degrees: among which 3 cases were positive for 3 antibodies, 4 cases were positive for 2 antibodies, and 2 cases were positive for only 1 antibody. In the meanwhile, a small number of IgG4 positive plasma cells were found in FDCS. The Ki-67 index of 9 cases ranged from 10–50%, with an average of 25%. The positive expressions of CD23, CD21 and CD35 in our case were consistent with the typical immunohistochemical characteristics of FDCS. Two years after the first treatment, the patient's imaging examination showed that the disease recurred. In order to make the pathological diagnosis clear, the patient underwent abdominal tumor puncture biopsy. Microscopically, the short spindle cells were arranged in bundles in the strip tissue. IHC examination showed positive expression of CD21 and CD35, negative expression of CD23, consistent with FDCS recurrence.

Surgical resection is the main treatment of FDCS, and most patients can achieve long-term disease-free survival via this treatment. The necessity of radiotherapy and chemotherapy during the treatment of FDCS is unclear. De PAS et al. [15] showed that the recurrence rate of 83 patients with FDCS after surgical resection was 46.3%, and the overall recurrence rate of patients receiving adjuvant therapy such as chemotherapy or radiotherapy was 35%. Therefore, some scholars believe that for the patients with Ki-67 > 20%, tumor diameter > 6cm or located in the abdominal cavity, in addition to complete tumor resection, adjuvant chemotherapy and / or radiotherapy may be beneficial to the residual or locally recurrent tumor [16]. Five cases of pancreatic FDCS reported in the literature were treated with surgery without adjuvant therapy. Two patients recurred 5 months and 18 months after operation, respectively. Another patient died of myasthenia gravis and paraneoplastic pemphigus 12 days after operation, due to unable to expectorate and respiratory obstruction. In our case, the 64-year-old patient in this report received 6 cycles of CHP chemotherapy after the operation, extensive abdominal metastasis still occurred 2 years after operation. Because of extensive abdominal metastases, it is impossible to operate again. Up to now, CHOP regimen is the most widely reported salvage treatment for FDCS. Choi et al. [17] reported a case of FDCS with extensive lymph node involvement, patient received 2 cycles of CHOP regimen chemotherapy and achieved partial remission. Shinagare et al. [18] reported a case of huge FDCS in the liver with a diameter of 11cm, after 4 cycles of chemotherapy with CHOP regimen, the tumor was successfully removed by portal vein embolization. In our case, the patient received two cycles of CHOP regimen after recurrence, but the curative effect was pessimistic. Therefore we speculate that the 6 cycles of CHP regimen the patient received 2 years ago may also be ineffective. Sasaki et al. [9] reported the pancreatic FDCS case of extensive abdominal metastasis 5 months after operation, both the CHOP regimen and Chemotherapy drugs, such as ifosfamide, ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine) and paclitaxel, were ineffective. The patient then received bendamustine treatment eventually. After one cycle treatment, the tumor index decreased. Unfortunately, the patient was unable to continue treatment due to intolerable adverse reactions. This is the first case of FDCS treated with bendamustine, and the curative effect has been observed. Bendamustine has anti-tumor effect and low cross resistance with other alkylating agents. It is very effective for low-

grade B-cell lymphoma, and also the standard chemotherapy for low-grade B-cell lymphoma. In recent years, it has been widely used in the invasive lymphoma such as diffuse large B-cell lymphoma and recurrent multiple myeloma [19]. In our case, the 64-year-old patient received two cycles of bendamustine after the CHOP regimen failed. Although the treatment was well tolerated, the disease progression was still observed. This is the first study to report the inefficacy of bendamustine in the treatment of FDCS. More cases are needed in order to verify whether bendamustine can become the key drug in the treatment of FDCS. Additionally, it is worth noting that studies have shown that the PD1 / PD-L1 checkpoint pathway plays an important role in the regulation of the immune environment of FDCS. In FDCS, the expression levels of PD-1 and PD-L1 are increased [20–21]. Therefore, for unresectable FDCS, immune checkpoint inhibitors may be a promising neoadjuvant therapy. Lee et al. [22] reported 2 cases of PD-L1 positive FDCS with good response to immune checkpoint inhibitors treatment, and the tumor shrank within 8 to 12 weeks. PD-L1 immunohistochemistry was also performed in this case after the recurrence of the disease, but the result was negative, so immunotherapy was not available. In the future, more prospective multicenter clinical trials were needed to verify the anti- PD1/ PD-L1 treatment on FDCS.

Abbreviations

FDCS
Follicular Dendritic Cell Sarcoma; AFP:Alpha fetoprotein; CEA:carcinoembryonic antigen; CA19-9:carbohydrate antigen 19 – 9; CA-125:carbohydrate antigen 125; CA-724:carbohydrate antigen 724; LDH:lipase and lactate dehydrogenase; IHC:Immunohistochemical

Declarations

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Not applicable.

Authors' contributions

All authors contributed to the writing of the manuscript and approved the final version of the manuscript.

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Availability of data and materials

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

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Shengjing Hospital of China Medical University.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Authors' Information

¹Department of Hematology, Shengjing Hospital, China Medical University, Shenyang 110022, Liaoning China. ²Department of Pathology, Shengjing Hospital, China Medical University, Shenyang 110022, Liaoning China.

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Figures

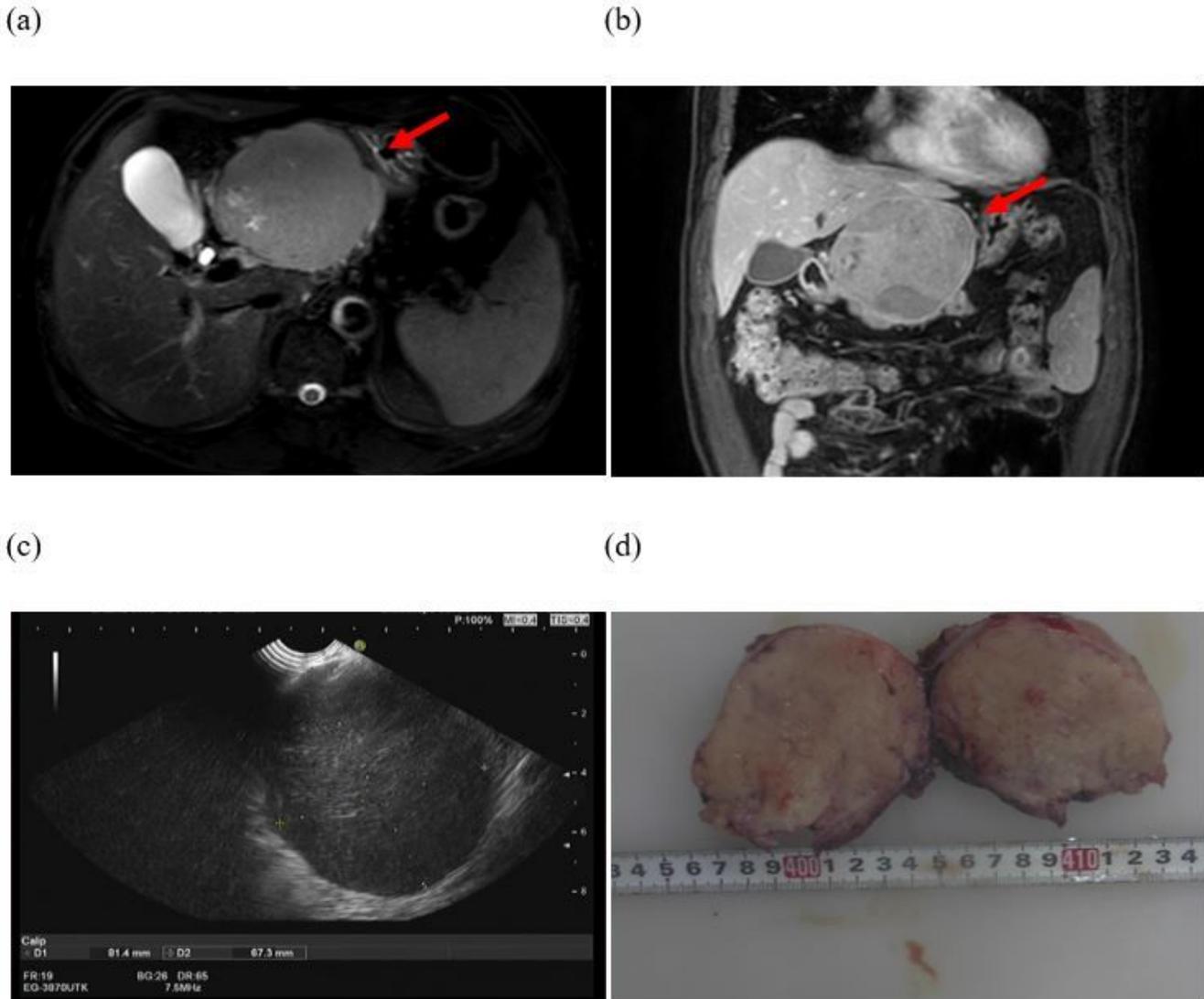


Figure 1

Imaging findings and macroscopic features of tumor. (a) Axial view of enhanced MRI showed a mass in pancreas measuring 8.8 x 7.4 x 8.6cm. (b) Coronal view of enhanced MRI showed the close association of the mass with the head and neck of pancreas. (c) Three-dimensional endoscopic ultrasonography showed a round hypoechoic mass. (d) The cut surface of the pancreatic FDCS without obvious necrosis or hemorrhage. Written informed consent was obtained from the individual for the publication of this image.

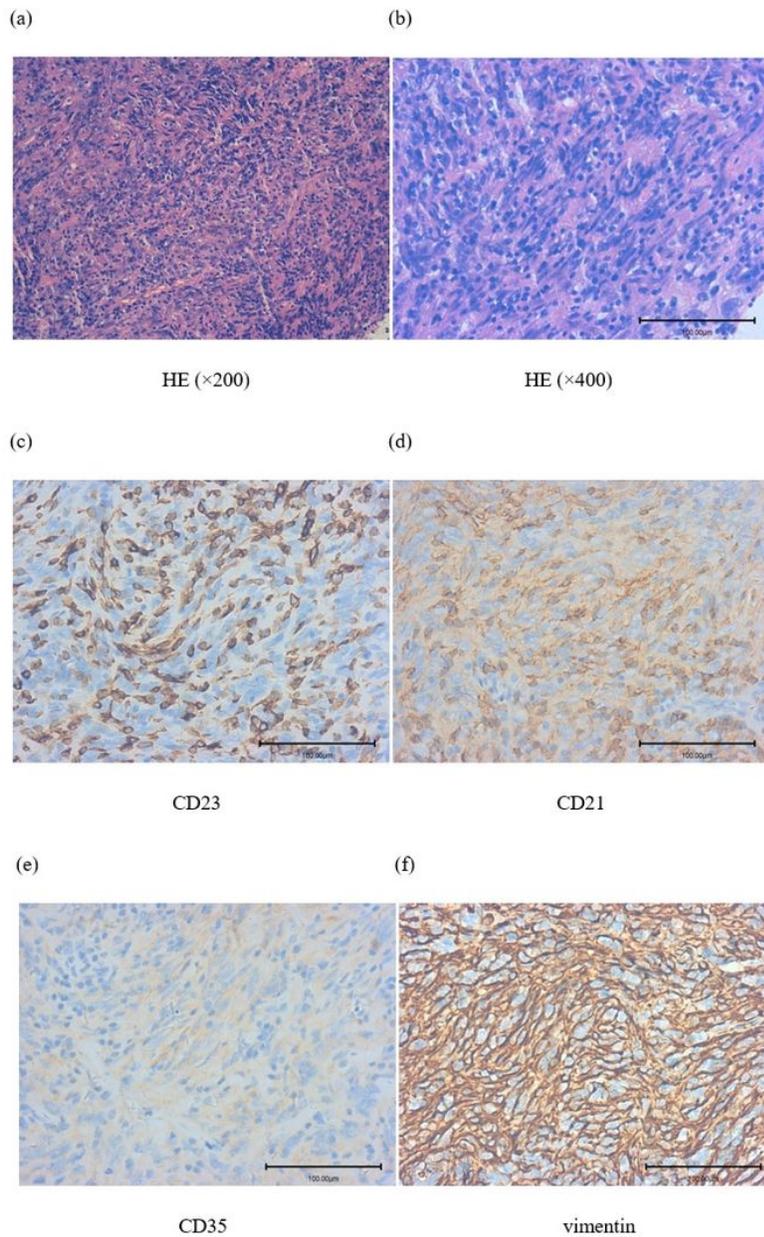


Figure 2

Cytomorphology and immunohistochemistry of the tumor. The tumor cells were short spindle with obvious nucleoli, a large number of lymphocytes between the lobules. [hematoxylin and eosin stain, original magnification $\times 200$ (a) and $\times 400$ (b)]. Immunohistochemical examination showed the tumor cells were positive for CD23 (c), CD21 (d), CD35 (e), and vimentin (f) (Original magnification $\times 400$). Written informed consent was obtained from the individual for the publication of this image.

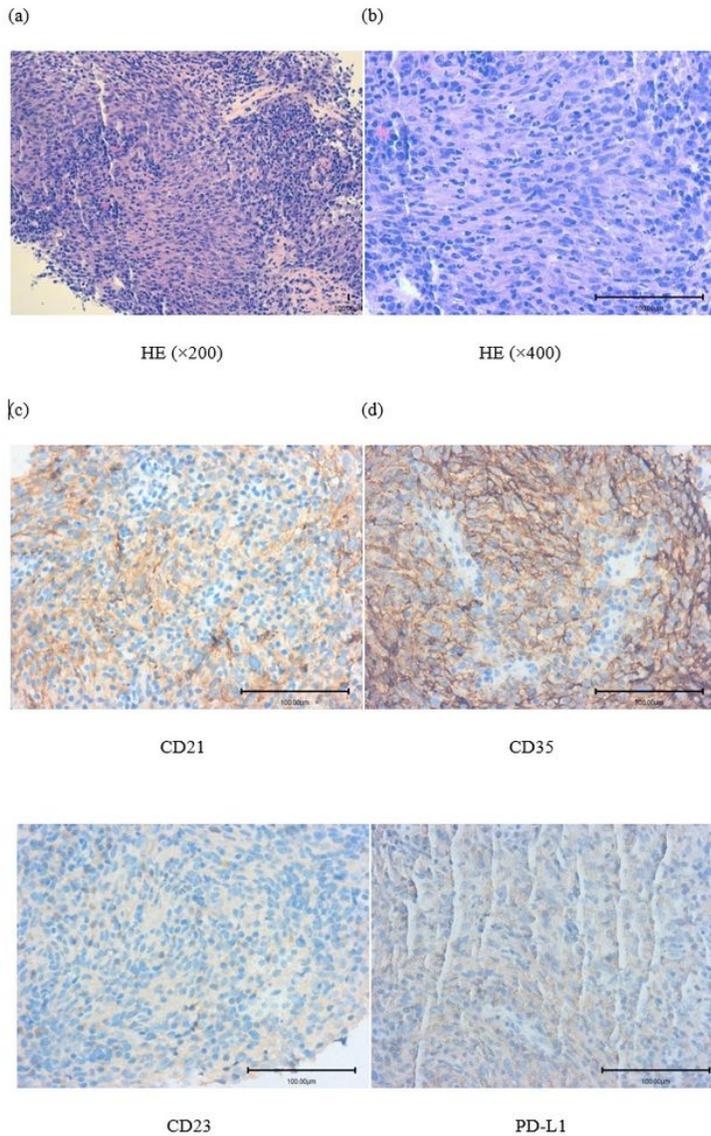


Figure 3

Cytomorphology and immunohistochemistry of the puncture tissue. The tumor cells were short spindle arranged in bundles. [hematoxylin and eosin stain, original magnification $\times 200$ (a) and $\times 400$ (b)]. Immunohistochemical examination showed the tumor cells were positive for CD21 (c) and CD35 (d), negative for CD23 (e) and PD-L1 (f). (Original magnification $\times 400$). Written informed consent was obtained from the individual for the publication of this image.