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Case Report

Littoral cell angioma of spleen: three cases report and literature review

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Abstract: Littoral cell angioma (LCA) is a rare primary splenic vascular neoplasm which arises from the sinusoidal lining or littoral cells of the splenic red pulp. Although it is considered to be a benign lesion, there have been case reports of malignant degeneration. Due to its non-specific clinical and imaging features, splenic LCA has posed a diagnostic challenge and may necessitate histopathological confirmation with splenectomy or image-guided tissue sampling. Herein, we reported three cases of LCA confirmed by histology after splenectomy. Patients remained asymptomatic at 8, 7 and 6 years after operation. In addition, a brief discussion about the histopathological features, clinical behavior and treatment of LCA, and review of the relevant literature are presented.

Keywords: Spleen, littoral cell angioma, indeterminate tumor, diagnosis, immunohistochemical

Introductiom

Littoral cell angioma (LCA) is a rare vascular neoplasm of the spleen, which was first described by Falk *et al* in 1991 [1]. The tumor originates from the littoral cells in the splenic red pulp sinuses and exhibits both epithelial and histiocytic properties. LCA is usually thought to be a benign lesion, but it has malignant potentiality [2, 3]. Being lack of typically clinical manifestations and radiological features, the preoperative diagnosis of LCA is difficult. Herein, we presented three cases of LCA of the spleen and reviewed the related literature.

Case report

Case 1

A 43-year-old man was presented to our hospital with recurrent left upper quadrant pain for two months. He had multiple hyperechoic lesions in the spleen on ultrasound (US) a year ago. Physical examination and laboratory test showed no positive findings. Grayscale sonogram displayed multiple masses of mixed echogenicity scattering in the spleen and color Doppler image revealed multiple heterogenous lesions, suggesting the possibility of hemangioma (**Figure 1A and 1B**). The patient underwent laparoscopic splenectomy (LS). Multiple nodules measuring 1.0 to 4.5 cm in diameter were obtained as the surgical specimen. Histological examination showed that the tumor consisted of anastomosing vascular channels lined by tall and flat endothelial cells with papillary structures. Immunohistochemical staining was positive for CD31, CD68 and FVIII and negative for CD21 and CD34. The diagnosis of LCA was established. The patient's postoperative course was uneventful and was well 8 years after operation.

Case 2

A 57-year-old woman was admitted to our hospital with recurrent left upper quadrant pain for eight months. The patient had a previous history of schistosomal cirrhosis with splenomegaly for 16 years. Physical examination found splenomegaly with 5 cm below the left costal margin. Routine laboratory tests were within normal ranges. Abdominal ultrasound showed splenomegaly with multiple hyperechoic masses scattering in the spleen, and the largest being approximately 5.1 cm in diameter. Splenomegaly and multiple hypodense nodules

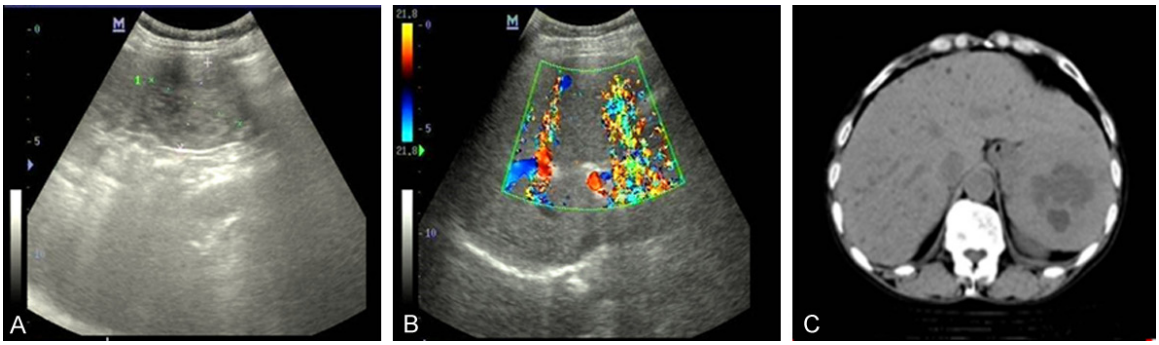

Figure 1. A: Grayscale sonogram showing multiple masses of mixed echogenicity scattering in the spleen (Case 1); B: Color Doppler image showing multiple heterogenous lesions (Case 1); C: Unenhanced CT showing splenomegaly with multiple hypodense nodules scattering in the spleen (Case 2).

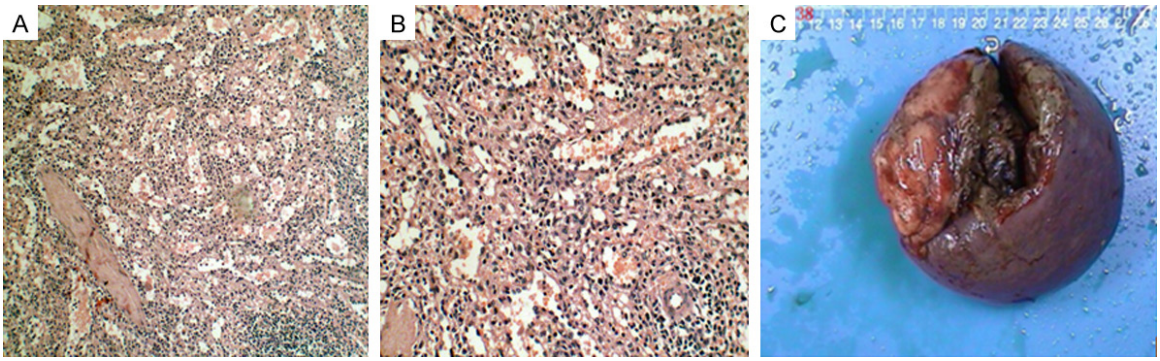

Figure 2. A: Low-power view shows the lesion composed of anastomosing vascular channels (HE staining, 100×) (Case 2); B: High-power view shows the vascular channels are lined by tall, plump endothelial cells (HE staining, 400×) (Case 2); C: The spleen was moderately enlarged with a laceration about 8 cm in length (Case 3).

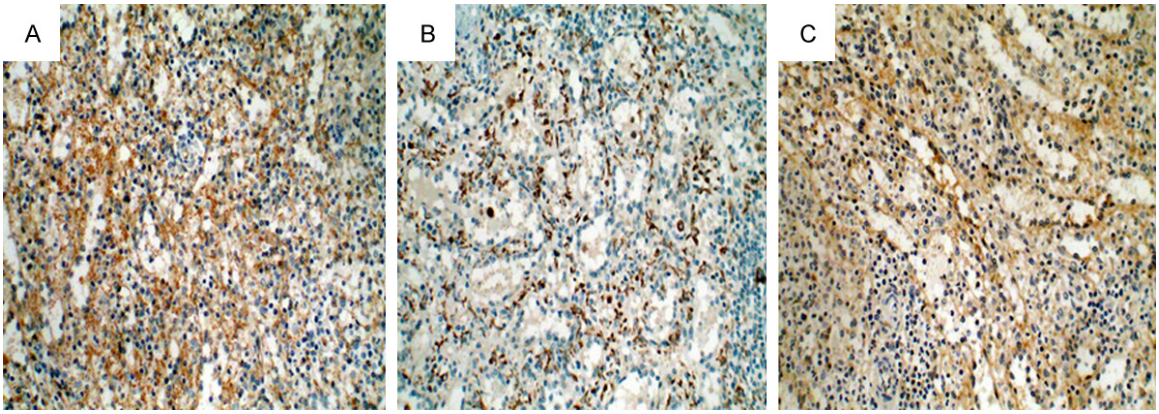

Figure 3. Immunohistochemistry for CD31, CD68 and FVIII of Case 3, A: Positive staining for CD31 (100×); B: Positive staining for CD68 (100×); C: Positive staining for FVIII (100×).

were also found in the spleen on unenhanced CT (**Figure 1C**). A diagnosis suspicious of splenic lymphangioma was made before operation. Subsequently, open splenectomy was performed. Histopathologic examination showed multiple anastomosing vascular lesions which vaguely resembled splenic sinusoids lined by tall endothelial cells (**Figure 2A and 2B**). No atypical cells or mitosis were seen. Immunohistochemistry was positive for CD31, CD68, FVIII and α-AT, and negative for CD21 and CD34. Based on the histopathological and immunohistochemical findings, the diagnosis of LCA was confirmed. The postoperative course was

Table 1. LCA of spleen in the literature with more than 3 cases

Author	Year	N	Sex (F/M)	Age (mean)	Immunophenotype	Associated malignancy (n)	Follow-up (months)
Cao	2017	13	6/7	54.2	CD31(+), CD68 (+), CD21 (+), FVIII (+), ERG (+) CD34 (-), CD8 (-)	2	2 dead, 11 alive (10-62 months)
Peckova	2016	25	9/16	56.2	FVIII (+), ERG (+), CD31 (+), lysozyme (+), CD4 (+) CD8 (-), FXIIIa (-)	15	5 dead, 10 alive (24-228 months), 10 LFU
Du	2015	3	0/3	53.7	CD31 (+), CD68 (+), FVIII (+) CD34 (-)	0	NA
Zhang	2013	7	5/2	37	CD31 (+), CD68 (+), FVIII (+), CD34 (+)	0	NA
Lin	2011	3	2/1	48	CD31 (+), CD68 (+), FVIII (+), CD21 (+)	0	3 alive (13-27 months)
Shah	2011	3	0/3	61.7	CD31 (+), CD68 (+), CK (+)	0	NA
Bi	2009	17	5/12	47	CD31 (+), polyclone FVIII (+) CD34 (-), monoclone FVIII (-)	0	17alive (1-168 months)
Levy	2004	8	3/5	52.8	FVIII (+), CD68 (+), lysozyme (+)	0	NA
Falk	1991	17	9/8	48.8	FVIII (+), UEA-1, CD68 (+)	1	2 dead, 15 alive (6-96 months)

NA: not available, LFU: lost follow-up

uneventful and the patient was discharged on the 7th postoperative day. Currently, the patient is alive without recurrence about 7 years after operation.

Case 3

A 28-year-old female, who had two months of pregnancy, presented with continuous left upper quadrant pain for 5 days. The findings of physical examination were unremarkable. Laboratory tests were within normal ranges. CT scan showed a 3.8×7.2 cm heterogeneous lesion located at the hilum of the spleen, and high density fluid in the abdomen, which indicated the possibility of hemoperitoneum. An emergency hand assisted laparoscopic splenectomy (HALS) was performed. The spleen measured 3×12×15 cm and weighted 830 g. There was a laceration about 8 cm in length at the surface of spleen (**Figure 2C**). Histopathologic examination revealed that the lesion was characterized by anastamosing vascular channels lined by cuboidal or columnar cells, which blended with normal splenic sinuses at the periphery of the tumor nodule. Immunohistochemistry was positive for CD31, CD68 and FVIII (**Figure 3A-C**), and negative for CD34. The Ki67 index was less than 1%. This confirmed the diagnosis of LCA. The patient had uneventful postoperative recovery and has remained tumor free for 6 years since operation.

Discussion

Primary splenic vascular tumors are rare but represent the majority of non-hematolymphoid splenic tumors, which are considered benign, indeterminate or malignant [4]. LCA arises from the specialised lining cells of the venous sinuses of the red pulp known as “littoral cells”, previously thought to be benign. Since several cases of malignancy were reported recently, LCA has been considered as an indeterminate tumor. Furthermore, about one-third patients of LCA have an association with malignancy, including lymphoma, colorectal adenocarcinoma, lung adenocarcinoma, pancreatic adenocarcinoma, renal cell carcinoma, melanoma, leukemia, and papillary thyroid carcinoma (**Table 1**) [1, 5-12]. Up to now, two subtypes of LCA with malignant potential have been described: littoral cell angiosarcoma and littoral cell hemangioendothelioma [13-15].

The exact incidence of LCA is unknown due to few reported cases in the literature. There is no gender or age predilection although the median age of the patients is 49 years [16, 17]. Clinically, most patients (> 55%) are asymptomatic and discovered incidentally. The remaining patients may present with left flank upper abdominal pain, fatigue, splenomegaly, hyperthermia of unknown origin, and hypersplenism [18]. In addition, LCA may also be detected during the workup of abdominal emergencies, including spontaneous splenic rupture. Routine laboratory tests were within normal limits except for hemoglobin and platelets in most cases, which may be hypersplenism-associated anemia and thrombocytopenia [19].

Radiologically, LCA can be evaluated by several imaging modalities including US, CT, MRI, or nuclear medicine studies such as Tc-99m

labeled RBC scintigraphy. On ultrasound, LCA usually presents as lobular splenomegaly and solitary or multiple echogenic nodules [20, 21]. Consistent CT features of splenic LCA include the presence of hypodense lesions and low-attenuating lesions on contrast-enhanced images [10, 21]. On MRI, LCA usually appears isointense to slightly hypointense on T1-weighted images and hyperintense on T2-weighted images [22]. In a minority of cases, the lesions of LCA seemed hypointense on both T1- and T2-weighted images and may remained hypointense after gadolinium administration [4, 20]. It has been proposed that this was due to the presence of significant amount of hemosiderin within the tumor that caused magnetic susceptibility artifact. Tc-99m labeled RBC scintigraphy can be used to differentiate splenic lesions from splenic hemangiomas [23].

LCAs were often misdiagnosed before operation for the limited number of reported cases, and nonspecific clinical signs and radiological features. The definitive diagnosis of LCA is based on histopathological and immunohistochemical findings in tissue samples obtained either cytologically or after splenectomy. Histopathologically, LCA is composed of anastomosing vascular channels of variable sizes and irregular lumina, often displaying papillary projections and cyst-like spaces. The cells usually sloughed off into the vascular lumina and may show macrophage-like morphology and exhibit hemophagocytosis [17, 19]. Typically, few mitosis and no cytologic nuclear atypia are seen. The tumor demonstrates immunoreactivity with endothelial markers (FVIII and CD31) and histiocytic markers (CD68), but negative response to CD8, CD34, and S-100 on immunohistochemical staining [24]. In our three cases, the tumors were all positive for CD31, FVIII and CD68, and negative for CD21 and CD34. These specific histopathological features can differentiate LCA from other primary splenic vascular tumors.

LCA with clinical symptoms are often treated with splenectomy. Considering that the LCA is associated with malignancies, splenectomy is both diagnostic and therapeutic. At the same time, close follow-up of LCA may be warranted due to the potential of malignant transformation [2]. Because of the low risk of fine-needle biopsy for hemorrhage, pneumothorax, and other complications [25, 26], Leung *et al* [27] proposed that diagnosis should also be made by fine-needle biopsy without splenectomy. However, surgery is still considered the gold standard for the treatment of LCA, due to the suspected malignancy of LCA [2, 3]. The present three patients underwent open or laparoscopic splenectomy with no surgical complications, and no recurrence and malignancies were found during the follow-up for 6 to 8 years.

In summary, LCA is a rare primary splenic vascular neoplasm. Histopathological and immunohistochemical findings on tissue samples are the most important for the diagnosis of LCA. Splenectomy is the most effective treatment for LCA, and close postoperative follow-up is necessnary.

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Disclosure of conflict of interest

None.

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