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Early postsurgical lethal outcome due to splenic littoral cell angioma: A case report and literature review

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BACKGROUND

Littoral cell angioma (LCA) is a rare benign vascular tumor of the spleen. Given its rarity, standard diagnostic and therapeutic recommendations have yet to be developed for reported cases. Splenectomy is the only method of obtaining a pathological diagnosis and providing treatment to obtain a favorable prognosis.

CASE SUMMARY

A 33-year-old female presented after one month of abdominal pain. Computed tomography and ultrasound revealed splenomegaly with multiple lesions and two accessory spleens. The patient underwent laparoscopic total splenectomy and accessory splenectomy, and splenic LCA was confirmed by pathology findings. Four months after surgery, the patient presented with acute liver failure, was readmitted, rapidly progressed to multiple organ dysfunction syndrome and died.

CONCLUSION

Preoperative diagnosis of LCA is challenging. We systematically reviewed online databases to identify the relevant literature and found a close relationship between malignancy and immunodysregulation. When a patient suffers from both splenic tumors and malignancy or immune-related disease, LCA is possible. Due to potential malignancy, total splenectomy (including accessory spleen) and regular follow-up after surgery are recommended. If LCA is diagnosed after surgery, a comprehensive postoperative examination is needed.

Key Words: Littoral cell angioma; Imaging features; Malignancy; Immunodysregulation; Treatment; Case report

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Core Tip: Littoral cell angioma (LCA) is a rare benign vascular tumor of the spleen. No standard diagnostic and therapeutic recommendations are available. We report a patient with LCA and without comorbidities who died of multiple organ dysfunction syndrome 4 mo after surgery, which is extremely rare. Systematic analysis of relevant cases in the PubMed, Embase, Web of Science and the Cochrane Library databases revealed that LCA has a close relationship with malignancy and immunodysregulation. The possibility of LCA should not be overlooked when a patient presents with splenic tumors and malignancy or immune-related disease. Considering its potential malignant behavior, total splenectomy (including accessory spleen) and regular follow-up after surgery are recommended.

INTRODUCTION

Littoral cell angioma (LCA) is a very rare benign nonhematological vascular neoplasm of the spleen that originates from the cells lining the splenic red pulp sinuses[1]. Only approximately 300 cases have been published since LCA was first described in 1991 by Falk *et al*[2]. Standard diagnostic and therapeutic recommendations are not available to date. As imaging examination is insufficient for diagnosing LCA, splenectomy remains the only method of obtaining a pathological diagnosis and providing treatment to achieve a favorable prognosis. However, we describe an LCA patient without obvious preoperative comorbidities who died of multiple organ dysfunction syndrome (MODS) four months after splenectomy, which is extremely rare.

CASE PRESENTATION

Chief complaints

A 33-year-old female complained of abdominal pain in the left upper quadrant and discomfort without any obvious cause for 1 mo prior.

History of present illness

The pain presented as intermittent dull pain. Occasionally, she felt abdominal distention and experienced acid regurgitation without nausea, vomiting, fever, jaundice, diarrhea, or constipation. Other complaints included poor sleep and loss of appetite. There was no change in weight or bowel habits.

History of past illness

The patient reported that she had no history of past illness.

Personal and family history

The patient reported no family history of malignant tumors.

Physical examination

Physical examination revealed an enlarged spleen with an irregular edge and tough quality; the inferior margin of the spleen extended to 4 cm below the left costal margin.

Laboratory examinations

Laboratory findings included a low red blood cell count (3.4×10^{12}/L) and low hemoglobin level (93 g/L), which suggested anemia, without evidence of thrombocytopenia (platelet count: 9.7×10^{10}/L) and hypersplenism. Other blood tests, including those for tumor markers, liver and renal function, and coagulation, were within normal limits.

Imaging examinations

Imaging examination showed splenomegaly with an irregular shape. Computed tomography (CT) showed that the density of the spleen was uneven. The lesions exhibited hypodensity (31 HU), isodensity (40 HU) or hyperdensity (55 HU). Contrast-enhanced CT (CECT) revealed that the degree of enhancement ranged from moderate to high (100-150 HU), gradually decreased in the venous or delayed phase (100-120 HU), and was nearly equal to the splenic parenchyma (78 HU) around the lesions (80-90 HU) in the delayed phase. There were also some lesions with no obvious enhancement (Figure 1).

Ultrasound (US) showed multiple hyperechoic lesions with unclear boundaries. Some were integrated, and some were heterogeneous. The largest lesion was 5.4 cm × 5.0 cm, protruding to the outside of the spleen. Two accessory spleens were displayed, and the diameter of the larger accessory spleen was 1.1 cm. The features of the lesions varied on contrast-enhanced US (CEUS) (Figure 2).

Given the negative results of cervical, axillary, inguinal and abdominal lymph node ultrasounds and the bone marrow biopsy, no typical sign of hematologic malignancy was observed.

FINAL DIAGNOSIS

As malignant disease could not be excluded, laparoscopic total splenectomy and accessory splenectomy were performed for diagnosis and treatment. The whole operation time was 3.5 h, and the blood loss was 50 mL.

Pathological examination confirmed splenic LCA. Grossly, the spleen measured 17 cm × 13 cm × 7 cm. A longitudinal section exhibited multiple brownish-red nodules, and the texture was soft. Microscopically, the lesions were in the red pulp of the spleen and consisted of multiple vascular cavities. The normal structures of the splenic parenchyma among the lesions could not be detected in the hematoxylin and eosin (HE)-stained section, and almost all the tissue was invaded by tumor cells. Immunohistochemical analysis confirmed benign LCA, with the cells positive for the

endothelial markers factor VIII (FVIII), CD31, CD34, ETS-related gene and the histiocytic markers CD68 and CD21. The Ki-67 Labeling index was no more than 20%, and the cells were negative for cytokeratin (Figure 3).

TREATMENT

Laparoscopic total splenectomy and accessory splenectomy were performed for the purpose of diagnosis and treatment.

OUTCOME AND FOLLOW-UP

Red blood cell counts and hemoglobin levels were within normal limits 6 d after the surgery. The patient was discharged on the 8th d and underwent regular follow-up after the surgery.

After 4 mo, the patient was readmitted to the hospital with systemic edema and jaundice. The patient was diagnosed with acute liver failure (ALF). Multiple examinations failed to detect atypical results. In addition, the clinicians were unable to acquire pathological results of the liver tissue because of the poor condition of the patient, which made it more difficult to acquire a definite diagnosis and carry out effective etiological treatment. During the course of the disease, the patient suffered from hypocalcemia and hypokalemia. Calcium gluconate and potassium chloride were given to correct the ionic disorders. Blood gas analysis was performed to determine whether there was acid-base imbalance. Given the coagulation dysfunction, the patient was supplemented with plasma. Hypoproteinemia was treated with supplemental albumin. To treat ALF, liver-protecting and cholagogic drugs were administered. For pulmonary infection and respiratory failure, spectrum antibiotic treatment and oxygen support treatment were given. Although multiple treatments were administered, the patient's condition deteriorated rapidly, and she developed renal insufficiency and respiratory failure; ultimately, she died of MODS. Laboratory examination results and disease progression are shown in detail in Figure 4.

DISCUSSION

LCA is a rare benign vascular tumor of the spleen. To obtain a better understanding of LCA, we systematically searched the PubMed, Embase, Web of Science and Cochrane Library databases for relevant data between 1991 and November 1st, 2022. The search terms for benign tumors included "littoral cell angioma" [MeSH Terms] OR "littoral cell angioma" [All Fields]. Other relevant records were also retrieved, including conference abstracts, references of the eligible studies and clinical trials that mentioned LCA. Two reviewers (Fan Jia and Han Lin) independently screened the literature according to the inclusion and exclusion criteria and extracted relevant data from the articles. Disagreements were resolved by consensus; if consensus was not achieved, then a third author (Yi-Long Li) provided an assessment of eligibility.

We included 167 studies containing 319 cases of LCA. According to our review, LCA usually occurs in middle-aged adults (range of age at onset: 28 d to 86 years)[3,4], with no obvious sex differences. The lesions may be solitary or multiple, and the diameters range from 0.1 cm to 21.0 cm[5,6]. Symptoms and signs are usually not specific and include splenomegaly, abdominal pain, thrombocytopenia, anemia, fatigue, and fever.

Some patients are asymptomatic; in such patients, LCA is usually detected by routine physical examination or incidentally. LCA can be easily misdiagnosed as hemangioma or (sometimes) as hamartoma before surgery. The CECT imaging features of our case presented characteristics similar to hemangioma, which was why the lesions were misdiagnosed at the local hospital. Thus, when a patient presents with several of the following features, the possibility of LCA should not be overlooked: splenomegaly, hypersplenism, multiple lesions, hypodensity in CT and hypo/hyperenhancement in CECT, and hypo/isoechoic in US as well as specific magnetic resonance imaging features (*i.e.*, low signals in T1-weighted images, high signals in T2-weighted images and diffusion-weighted images (DWI), and/or sign of "freckles"). Splenic infarction may occur[7], especially when hemangioma is highly suspected because of an absence of typical features.

LCA is closely related to malignancy (78/319 cases) (hematological malignancy, gastrointestinal cancer, genitourinary cancer, and endocrine cancer as well as immunodysregulation (47/319 cases) (vital hepatitis, liver cirrhosis[8], Crohn's disease, and immune thrombocytopenia), and has the potential for recurrence and malignant transformation.

During postoperative follow-up, some LCA cases showed potential malignancy. One case had recurrence of LCA in the accessory spleen 7 years later[9]. Two cases had hepatic recurrence and metastases of LCA after 8 and 10 years[3,10]. A patient who was diagnosed with LCA after splenectomy died of multiple metastases of littoral cell hemangioendothelioma (LCHE) 4 years later[11]. One patient had both LCA and primary splenic angiosarcoma (PSAS) cells in the same lesion[12].

Eleven (3.6%) patients, including our patient, died after splenectomy; details are listed in Table 1. No case was similar to ours. In our case, a young woman without obvious preoperative comorbidities died of MODS 4 mo after surgery, emphasizing the complexity and potential lethality of LCA and the importance of regular postoperative follow-up. Unfortunately, due to the local customs and beliefs of the patient's family members, autopsy results could not be obtained, and the cause of MODS was unknown.

Clinicians from different departments convened to analyze the diagnostic experience and discuss the possible causes of MODS. Based on the clinical characteristics, disease progression (Figure 4) and the results of the literature review, the possibility of lymphoma was proposed.

Common causes of ALF are viral infection (especially hepatitis virus), drugs, toxins, bacteria and parasites, other liver diseases (such as autoimmune liver disease), biliary diseases, metabolic disorders and circulatory failure. However, given the results of the examination, none of them could explain the patient's condition. Hepatic invasion of malignancies can also lead to ALF, which is an independent predictive factor for 30-d mortality[13]. Considering that no typical images were observed, solid tumors could be excluded. However, hematologic malignancies cannot be ignored, especially lymphoma. Hepatic infiltration of tumor cells can be observed in 15%-22% of

hematological malignancies[14], rarely leading to significant liver dysfunction[15-19], which usually occurs in the terminal stage of the disease[15,16,20,21] and is closely related to high mortality (67%-100%)[15]. Although rare, some case reports have described this course of disease. Liver biopsy was not acquired because of serious coagulopathy, but given the positive bone marrow biopsy and expected clinical features (ALF, hepatomegaly, and elevated lactate dehydrogenase), lymphoma should be highly suspected[14-17,22]; among malignancies, it has a high rate of cooccurrence with LCA.

Our patient had fever, decreased blood cells and fibrinogen, and increased sCD25 (Figure 4). Thus, four of the eight diagnostic criteria[23] for hemophagocytic lymphohistiocytosis (HLH) were met. Not all symptoms are displayed at the early stage, and many diseases can lead to HLH, including malignancies (leukemia, lymphoma, and other solid tumors), infections and rheumatoid disorders[23]. HLH should be highly suspected. Combined with the analysis in the previous paragraph and negative results of the bone marrow biopsy, the possibility of lymphoma was proposed again.

In our experience, if the patient is diagnosed with ALF after splenectomy without other obvious causes, lymphoma should be considered, and liver biopsy should be performed as soon as possible for early diagnosis and etiological treatment if the patient's situation allows. If LCA is diagnosed after surgery, standard postoperative long-term follow-ups should be strictly observed[27].

CONCLUSION

These recommendations are based on the disease characteristics of the patient and a literature review; thus, more studies are needed. Although we cannot provide clear diagnostic criteria for LCA because its imaging features are similar to those of other splenic tumors, when a patient suffers from both splenic tumors and malignant or immune-related diseases, LCA should be considered given the close relationship of LCA with malignancy and immunodysregulation. In view of the potential recurrence and malignant transformation of LCA, the recommended treatment is total splenectomy

(including the accessory spleen). If LCA is diagnosed after surgery, a comprehensive postoperative examination is needed. In addition, standard postoperative long-term monitoring should be strictly observed.

Figure 1 Computed tomography. A: Larger lesions with hypo/iso-density were patchy or nodular enhanced from the peripheral part of the lesions, gradually centripetally full-filled in the venous or delayed phase with decreased degree of enhancement, finally presented with iso-enhancement, and central part of the lesion presented with no enhancement; B: Smaller lesions with hypo/iso-density were fully enhanced in the arterial or venous phase presenting hyper-enhancement, then gradually decreased and became iso-enhancement in the delayed phase; C: Some lesions showed hyper-density and presented with no obvious enhancement; D: Branches of the splenic arteries extending into the larger lesion; E: A peripheral wedge shaped hypo-density area in the spleen showed no obvious enhancement (white arrow).

Figure 2 Contrast-enhanced ultrasound. A-H: White arrow: Contrast-enhanced ultrasound showed some larger lesions, especially hyper-echoic part of the lesion, presented with nodular enhancement in the early arterial phase, then quickly became full-filly enhancement, then gradually decreased in the venous phase with slightly hyper-enhancement; red arrow: Some small hyper-echogenic lesions presented with nodular or completely enhancement in the arterial phase, then fast decreased to iso-enhancement, or just slowly slightly decreased and still presented with hyper-enhancement in the venous phase; blue arrow: Some small lesions with hypo-echoic presented with hypo-enhancement; and yellow arrow: One heterogeneous lesion, with slight posterior acoustic shadow, presented with iso-enhancement during the process.

Figure 3 Pathological examination. A: The lesion was located in the splenic red pulp, nearly all the surrounding tissues were invaded by the tumor cells (H&E magnification × 20); B: The lesion consists of a large amount of variably sized sinuses with anastomosing vascular channels lined by relatively plump round to columnar histiocytic-endothelial littoral cells, some cells with small nucleus with deep chromatin, some columnar cells with large nucleus with vacuolated chromatin, some exfoliated into the expanded sinuses (H&E magnification × 400); C-F: Immunohistochemical staining confirming endothelial differentiation with CD31, CD34, ERG, and FVIII (magnification × 200); G and H: Immunohistochemical staining confirming histiocytic differentiation with CD68 and CD21 (magnification × 200); I: Ki-67 labeling index was no more than 20% (magnification × 200).

Figure 4 Results of the laboratory examinations and disease progression of the patient. FCM: Fluorescence confocal microscopy; PCR: Polymerase chain reaction; CEUS: Contrast-enhanced ultrasound; CECT: Contrast-enhanced computed tomography; AST: aspartate aminotransferase; RBC: Red blood cell; PLT: Platelet; Cr: Creatinine; Hb: Hemoglobin; TBIL: Total bilirubin; FIB: Fibrinogen.

Table 1 Information about dead patients

Ref.	Age (yr)	Gender (M/F)	Weight (g)	Length (cm)	Number (S/M)	Diameter (cm)	Splenomegaly (Yes/No)	Died after splenectomy	Cause of death	The details of the dead patient
Falk *et al*[2], 1991	42	F	145	NA	NA	NA	No	3 yr	Disseminated lymphoma	The patient suffered from malignant lymphoma, and died of disseminated lymphoma 3 yr after splenectomy
Ref.	77	M	2404	NA	M	18	Yes	2 wk	NA	The patient's splenic lesion were discovered incidentally during surgical repair of a dissecting aneurysm, and

										died 2 wk after splenectomy
Priego *et al*[25], 2008	83	F	NA	NA	M	NA	Yes	2 d	Great stress of operation	The patient suffered from myelodysplastic syndrome, and died 2 d after splenectomy because of the great stress of operation
Hansen *et al*[26], 2010	67	M	213	14	S	2.1	Yes	> 6 mo	Advanced liver failure, additional renal failure	The patient suffered from colon carcinoma, hepatocellular carcinoma and LCA, simultaneously. Hemicolectomy and

										splenectomy were performed first, and partial hepatectomy was performed 6 mo later. The patient died of advanced liver failure and additional renal failure a few weeks after surgery
Kranzfelder *et al*[13], 2012	62	M	110	NA	M	NA	No	8 mo	NA	Splenectomy was performed because of rupture of the spleen, and the pathology was LCA and PSAS. The patient died

										8 mo after splenectomy
Peckova *et al*[3], 2016	62	F	310	19	M	1	Yes	6 yr	NA	The patient suffered from endometrioid endometrial adenocarcinoma and died of unknown cause 6 yr after splenectomy
Ref.	83	M	200	14	M	1.2	Yes	NA	Multiple myeloma	The patient was performed renal resection because of renal cell carcinoma in 2005, and splenectomy because of LCA in 2006, and was diagnosed

										as multiple myeloma in 2011, adenocarcinoma of ascending colon (the time was unclear). The patient died of multiple myeloma
CAO Zhong *et al.*[25]	NA	NA	NA	NA	NA	NA	NA	NA	Recurrence of malignant tumors	Two patients died of recurrence of malignant tumors (1 patient with gastric diffuse large B-cell lymphoma, 1 patient with ovarian serous

										cancer) after splenectomy
Takayoshi *et al*[11], 2018	61	F	NA	NA	S	NA	NA	10 yr	Hemorrhagic cerebral infarction	After 10 yr of splenectomy, the patient sufferred from metastatic LCA recurrence and multiple liver metastases, and died of hemorrhagic cerebral infarction
Our patient	33	F	NA	17	M	5.4	Yes	4 mo	MODS	The patient died of MODS after 4 mo after splenectomy without any obvious evidence of

comorbidities

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M/F: Male/female; S/M: Single/multiple; NA: Not available; LCA: Littoral cell angioma; PSAS: Primary splenic angiosarcoma; MODS: Multiple organ dysfunction syndrome.

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12	Man-Jiang Li, Xuan Zhou, Jing-Yu Cao, Cheng-Zhan Zhu, San-Shun Zhou, Yun-Jin Zang, Li-Qun Wu. "Laparoscopic splenectomy for littoral cell angioma of the spleen", Medicine, 2019 Crossref	10 words — < 1%
13	Yun-Hua Zhang, Li-Min Liu, Wen-Ping Wang, Hong Ding, Xiu-Nan Wang, Han-Sheng Xia. "Littoral Cell Angioma of the Spleen", Journal of Ultrasound in Medicine, 2013 Crossref	10 words — < 1%
14	siriuscoin.com Internet	10 words — < 1%
15	Jan-Inge Henter. "HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic	9 words — < 1%

lymphohistiocytosis", Pediatric Blood & Cancer, 02/2007
Crossref

16 Yang, Ling, Shuang Zhao, and Rong-Bo Liu. "Unicentric mesenteric Castleman's disease with littoral cell angioma, anemia, growth retardation and amenorrhea: A case report", Oncology Letters, 2015.
Crossref
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19 "Letters to the Editor", Leukemia & Lymphoma, 2009
Crossref
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8 words — < 1%

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