pISSN: 2508-5778 • eISSN: 2508-5859
Ann Hepatobiliary Pancreat Surg 2023;27:1-5
https://doi.org/10.14701/ahbps.22-062

AHBPS
Annals of Hepato-Biliary-Pancreatic Surgery

Editorial

Littoral cell angiomas: Benign lesion with a penchant for visceral malignancies

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Littoral cell angiomas are rare vascular tumors of the spleen. Because of their rarity, unclear etiopathogenesis, and association with other malignancies, these tumors can pose diagnostic and therapeutic challenges. Due to paucity of published literature on this entity often limited to case reports, relevant data on this topic were procured and synthesized with the aid of a comprehensive Medline search in addition to oncologic, pathologic, radiologic, and surgical literature review on littoral cell angiomas. This article provides an in-depth review into postulated etiopathogenesis, pathology, clinical manifestations, associated malignancies, and prognostic features of littoral cell angiomas.

Key Words: Spleen; Splenic neoplasms; Littoral cell angioma; Surgery; Cells

Littoral cell angioma (LCA) is a primary vascular neoplasm of the spleen with less than 200 cases reported in literature to date. LCA is a rare benign lesion, taking its origin from littoral cells (Latin: '*littoralis*' meaning seashore) of the trabeculated mesh in the reticuloendothelial system lining splenic red pulp sinuses. First described in 1991 by Falk et al. [1], LCA tumor cells display a unique myriad of endothelial-histiocytic immunological phenotype, the key to a definitive diagnosis of this tumor. LCA has been reported in every age group, from a 26-day old neonate to a woman aged 83 years, without any sex-based predilection [2,3]. Two variants of LCA (littoral cell hemangioendothelioma and littoral cell angiosarcoma) have malignant potential and hence warrant more understanding into the etiopathogenesis, management, and follow-up screening of this seemingly benign lesion.

Most patients are asymptomatic, with LCA presenting as an incidental radiological finding.

While some present with vague clinical complaints such as abdominal pain, fever, fatigue, bleeding diathesis, or weight loss, further workup of patients usually reveal splenomegaly, anemia, and thrombocytopenia (Fig. 1). This can be probably explained by hemophagocytosis (removal, destruction, and subsequent siderosis) by this neoplasm. It is also supported by the fact that these resolve after splenectomy [4]. Magnetic resonance imaging (MRI) characteristics vary with the amount of hemosiderin within the tumor. Unenhanced and contrast-enhanced sequences of MRI can aid distinguish LCA from other angiosarcomatous (potentially malignant) vascular lesions [5]. However, definitive diagnosis often warrants tissue diagnosis. A high biopsy-related complication rate (10.3%) reported for patients with refractory thrombocytopenia or vascular splenic neoplasms and fear of seeding malignant cells at the time of percutaneous splenic biopsy have led to splenectomy being both diagnostic and therapeutic [6]. Splenectomy can be performed both laparoscopically or in open fashion with attention to avoid splenic capsular disruption and tumor spillage.

Grossly, LCA is a meshwork of solid tissue, dilated cavernous vessels, and numerous narrow vascular channels with occasional microthrombi in lumen in a very organoid form reminiscent of normal sinuses in the spleen, appearing as well-defined blood or hemosiderin-filled spongy lesions in the spleen, existing either as solitary or multiple lesions, ranging in size from 1 mm to 21 cm (Fig. 2) [7,8]. These are well demarcated without

Received: August 5, 2022, **Revised:** August 31, 2022,
Accepted: September 7, 2022, **Published online:** November 16, 2022

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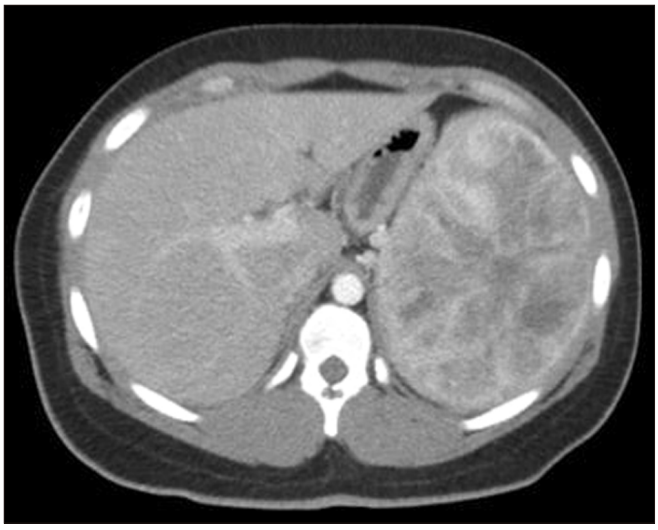

Fig. 1. Early contrast-enhanced helical computed tomography scan showing enlarged spleen containing innumerable small, focal, low-density lesions.

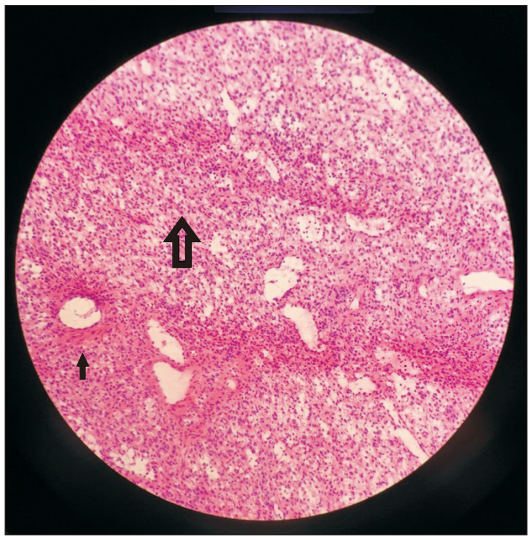

Fig. 3. Histologic specimen showing normal splenic parenchyma (large arrow) and adjacent vascular proliferation of cavernous, blood-filled spaces (small arrow) (H&E, ×20).

capsule, compressing against the normal splenic parenchyma (Fig. 3). LCA is characterized by positive reactivity to a myriad of endothelial and histiocytic cell markers, including D56, synaptophysin, CD10, alpha-1-antitrypsin, CD31, CD163, CD4, CD8, CD68, BMA120, patchy CD34, ERG, CD68, CD21, vWF/FVIII related antigen, D2-40, Mac-387, Ham-56, vimentin and lysozyme, LYVE-1, FLI-1, vascular endothelial growth factor receptor (VEGFR-2), VEGFR-3, claudin-5, and LMO2. While WT1 is positive in normal endothelium (and normal littoral cells), LCA is WT-1 negative, emphasizing immunophenotypic transformation of neoplastic cells from normal cells [9].

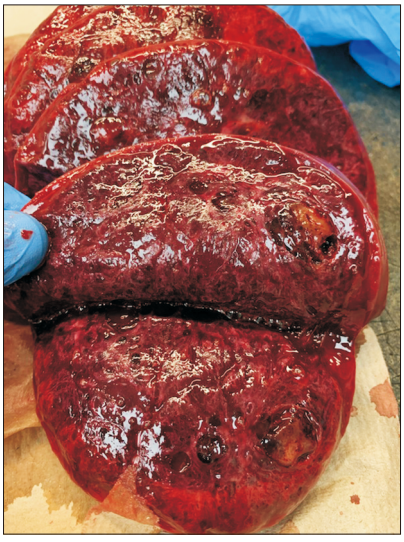

Fig. 2. Serial sections of spleen showing that the parenchyma is notable for multiple hemorrhagic cystic lesions diffusely spread throughout the parenchyma.

Although the etiopathogenesis of LCA is unclear, its association with a myriad of conditions (apart from malignancies) including congenital and immunologic conditions points towards the role of a dysregulated immune response (Table 1) [2,8,10-22]. Immunosuppression was a notable risk factor in several of reported LCA cases that included renal transplantation [10,11], steroid refractory immune thrombocytopenic purpura [12], Myelodysplastic syndrome on pulse steroid therapy [13], systemic lupus erythematosus [14], pulmonary sarcoidosis [15], and Ehlers-Danlos syndrome on biologic immunosuppression for psoriatic arthritis [16], although the duration of immunosuppression and the kind of drugs varied widely amongst them. It has been hypothesized that LCA and the resulting splenomegaly can create an altered immune state of the body, with resolution of leukocytosis after excision being proof of same [16]. Varying levels of tumor necrosis factor (TNF)-alpha have also been speculated to be the cause of LCA [15]. Several reported cases in the literature had co-existing LCA with inflammatory bowel disease, further strengthening the link of LCA with TNF-alpha [23-25].

LCA is frequently associated with a wide range of malignancies, including epithelial, mesenchymal, and hematological tumors. To date, there have been at least 24 reports of LCA associated with a malignancy (8 patients had a pre-existing malignancy years before; 13 at the time of diagnosis of LCA) (Table 2) [3,5,7,8,13,17,23,26-40]. The wide range of tumors associated with LCA makes it difficult to draw any conclusions regarding its possible pathogenesis. Genetic associations (for instance, with BRCA1 or BRCA2—being frequently associated with

Table 1. Speculated etiopathogenesis of littoral cell angioma (LCA)

Speculated pathogenic factor	Reference	Condition associated with LCA
Immune dysregulation	Tan et al. (2004) [10]	Immunosuppression (renal transplant)
	Erçin et al. (2005) [13]	Immunosuppression (Myelodysplastic syndrome)
	Mühlfeld et al. (2008) [11]	Immunosuppression (renal transplant)
	Mac New and Fowler (2008) [14]	Immunosuppression (SLE)
	Cordesmeyer et al. (2011) [15]	Immunosuppression (Pulmonary sarcoidosis)
	Gorman and Bergstrom (2016) [16]	Immunosuppression; Connective Tissue Disorder (Ehler Danlos)
	Gardner and Devitt (2017) [12]	Immunosuppression (steroid refractory ITP)
	Roldan-Vasquez et al. (2021) [18]	Hypothyroidism and diabetes mellitus
Environmental Carcinogen	Ziske et al. (2001) [19]	Worked in a chemical industry
	Collins et al. (2003) [17]	Exposure to boiler fumes of ship during WW2
Macrophage Colony Stimulating Factor	Gupta et al. (2001) [20]	Gaucher's disease
	Forest et al. (2010) [21]	Gaucher's disease
Congenital	Gakenheimer-Smith et al. (2018) [2]	LCA in an infant
	Antón-Pacheco et al. (2000) [22]	LCA in an infant
Reactive disorder	Truong et al. (2019) [8]	Clear cell RCC

SLE, systemic lupus erythematosus; ITP, immune thrombocytopenic purpura; WW2, World War II; RCC, renal cell carcinoma.

Table 2. Associated malignancies with littoral cell angioma (LCA)

Malignancy	Year	Author	Age/sex	Time of diagnosis of associated malignancy
Malignant melanoma	2000	Schneider et al. [5]	66/M	At the same time
	2007	Bhatt et al. [26]	56/M	(*Not mentioned*)
	2011	Pilz et al. [27]	73/M	25 years before
Colon adenocarcinoma	2000	Steensma and Morice [28]	54/F	3 years before
	2020	Opatrny et al. [29]	53/F	At the same time
Pancreatic tumors				
Malignant cystic neuroendocrine neoplasm of pancreas	2000	Veillon et al. [7]	53/M	At the same time
Pseudopapillary tumor of the pancreas	2011	Bhavsar et al. [30]	30/F	At the same time
Lymphoma				
CNS large cell lymphoma	2000	Heese and Bocklage [31]	33/M	At the same time
Nodular Sclerosis Hodgkin's & diffuse large T cell lymphoma	2005	Floyd et al. [32]	42/M	*(Not mentioned)*
Myelodysplastic syndrome	2005	Erçin et al. [13]	36/F	1 year after
Plasmablastic B cell lymphoma	2012	Melzer et al. [33]	67/M	At the same time
Chronic myeloproliferative disorder	2015	Marzetti et al. [34]	79/F	At the same time
Splenic marginal zone lymphoma and villous lymphocytic leukaemia	2002	Chatelain et al. [35]	50/F	At the same time
Urologic tumors				
Seminoma of testis	2003	Yano et al. [36]	33/M	1 year before
Transitional cell carcinoma bladder	2006	Harmon et al. [37]	74/F	2 years before
Renal cell carcinoma	2011	Shah et al. [38]	78/M	2 years before
Non-metastatic Prostate cancer	2012	Melzer et al. [33]	67/M	2 years before
Clear cell RCC	2019	Truong et al. [8]	42/M	At the same time
Lung adenocarcinoma	2003	Collins et al. [17]	64/M	1 year after
Papillary thyroid carcinoma	2005	Mohan et al. [39]	25/M	2 years before
Sarcoma	2014	Sarandria et al. [23]	32/M	At the same time
Thigh leiomyosarcoma	2007	Bhatt et al. [26]	56/M	At the same time
Scapular sarcoma	2008	Priego et al. [3]	55/F	13 years before
Giant cell tumor of femur	2011	Shah et al. [38]	57/M	At the same time
Breast cancer	2022	Yaney et al. [40]	63/F	At the same time

M, male; F, female; RCC, renal cell carcinoma.

breast, prostate, and pancreatic cancer) and familial clusters (even though a case of siblings was reported—one with LCA, and another with primary splenic angiosarcoma) have not been established for LCA [41]. The follow-up in reported cases of LCA in the literature varied from two weeks to ten years, with a mean follow-up of 15 months.

In spite of several associations with malignancies at the time or before the diagnosis of LCA, only three reported cases in the literature (all above the age of 61 years) have described metastatic or recurrent LCA post splenectomy [42-44]. Two [42,43] of these studies reported atypical histology (presence of solid areas with/without necrotic foci) in the primary splenic LCA with subsequent metastatic histology labelling it as littoral cell hemangioendothelioma. Thus, the histologic diagnosis of LCA in primary splenic lesion is questionable in these two cases. Metastases in these cases appeared at eight and four years after the index case, involving the liver, periaortic, and retroperitoneal lymph nodes. Patients survived for less than four months. The third patient [44] was the only reported case of true LCA with recurrence noted 10 years later in the liver and periportal lymph nodes. The patient underwent chemotherapy for 21 months before death.

LCA by the sheer size of the spleen or history of associated malignancies/immunological conditions at the time of LCA diagnosis poses a diagnostic dilemma which often warrants a splenectomy [45]. Precise histologic diagnosis of LCA carries a good prognosis. Presence of ominous histological features such as abnormal architecture, solid areas, necrotic foci, or nuclear atypia should raise the suspicion for alternative diagnosis including littoral cell hemangioendothelioma and littoral cell angiosarcoma and warrant a closer follow-up protocol for recurrence/metastasis. Owing to the rarity of splenic angiomas and wide spectrum of associated malignancies, implementation of a generalized screening protocol is generally impractical. Continued efforts are needed to better understand the role of immune dysregulation and facilitate early detection of associated malignancies. The association of these splenic lesions with other visceral malignancies calls for close clinical follow-up and surveillance which are not very well defined yet [46,47].

FUNDING

None.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Conceptualization: AV. Data curation: SG, AV. Methodology: SG, AV. Visualization: SG, AV. Writing - original draft: SG, AV. Writing - review & editing: HJ, AV.

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