

## Case Report

# Littoral cell angioma associated with extramedullary hematopoiesis and renal cell carcinoma: case report and review

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**Abstract:** Littoral cell angioma (LCA) is a rare primary vascular neoplasm of the spleen that originates from the endothelial littoral cell lining of the red pulp sinuses. LCA has mostly benign behavior with a few reported cases of malignancy. LCA is associated with comorbid visceral organ cancers and immunosuppressive states. We report a case of LCA with synchronous renal cell carcinoma and features of extramedullary hematopoiesis. Histologically, multiple splenic lesions were found with anastomosing vascular channels lined by plump round cells. Within channels there were atypical hyperchromatic cells, later identified as hematopoietic elements, including erythroid precursors and megakaryocytes. Diagnosis was confirmed by the endothelial/histiocytic phenotype of tumor and of the megakaryocytes. To the best of our knowledge, this case is the fourth description of LCA associated with extramedullary hematopoiesis or renal cell carcinoma. Additionally, recognition of megakaryocytes in these tumors is vital to avoid false positive malignant diagnoses. Further clinical and molecular studies of LCA are needed to understand the pathogenesis and association to visceral organ cancers to provide appropriate surveillance recommendations.

**Keywords:** Littoral cell angioma of the spleen, extramedullary hematopoiesis, megakaryocytes, renal cell carcinoma

## Introduction

Littoral cell angioma is a rare vascular tumor first described in 1991 by Falk in a surgical review of splenic vascular lesions [1]. Unique to the spleen, it develops from littoral cells that line sinus channels in the splenic red pulp. Due to unknown stimuli, littoral cells transform and proliferate into bulky papillary projections creating anastomosing vascular channels with cyst-like spaces that obliterate normal splenic parenchyma.

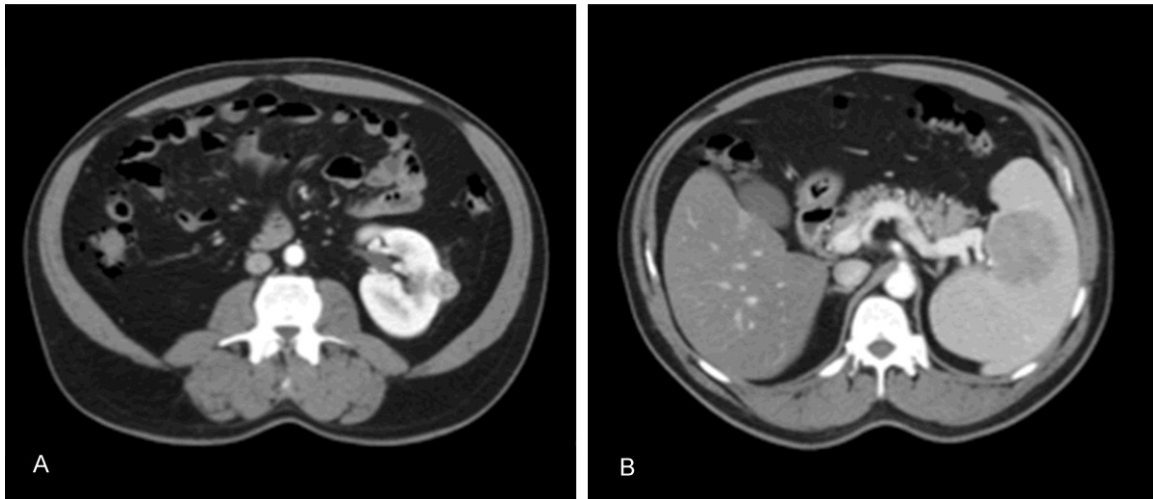
Given its rarity, our understanding of LCA is largely through descriptions in case series. To date, 220 cases have now been reported. LCA may occur at any age with mean age of diagnosis at 48 years and has equal gender predilection [2]. Initial presentation of LCA is variable. A meta-analysis of 180 cases found that LCA most often has a subclinical presentation and is incidentally found on imaging studies for an unrelated condition [3]. It may manifest clinically

as abdominal pain or mass from splenomegaly, or with symptoms of hypersplenism such as thrombocytopenia and anemia [4]. Infrequently it is associated with constitutional symptoms such as fever and fatigue, and in rare cases with splenic rupture and subsequent hemoperitoneum [5, 6].

LCA is largely benign; however, several reports have described malignant features of LCA [7, 8]. Splenectomy should be performed for diagnostic and therapeutic purposes. Due to its frequent association with cancers and potential for recurrence, subsequent careful surveillance is required. In this report, we present a case of LCA with features of extramedullary hematopoiesis and synchronous clear cell renal cell carcinoma.

## Case report

A 61-year-old male nonsmoker presented to our emergency department with intermittent left



**Figure 1.** Computer tomography scan of the abdomen with intravenous contrast. A. Imaging demonstrated a heterogeneously enhancing mass in the left kidney measuring  $2.2 \times 1.9 \times 2.2$  cm. B. Imaging demonstrated heterogeneously enhancing masses in the spleen with the largest measuring  $5.8 \times 5.7 \times 5.7$  cm.

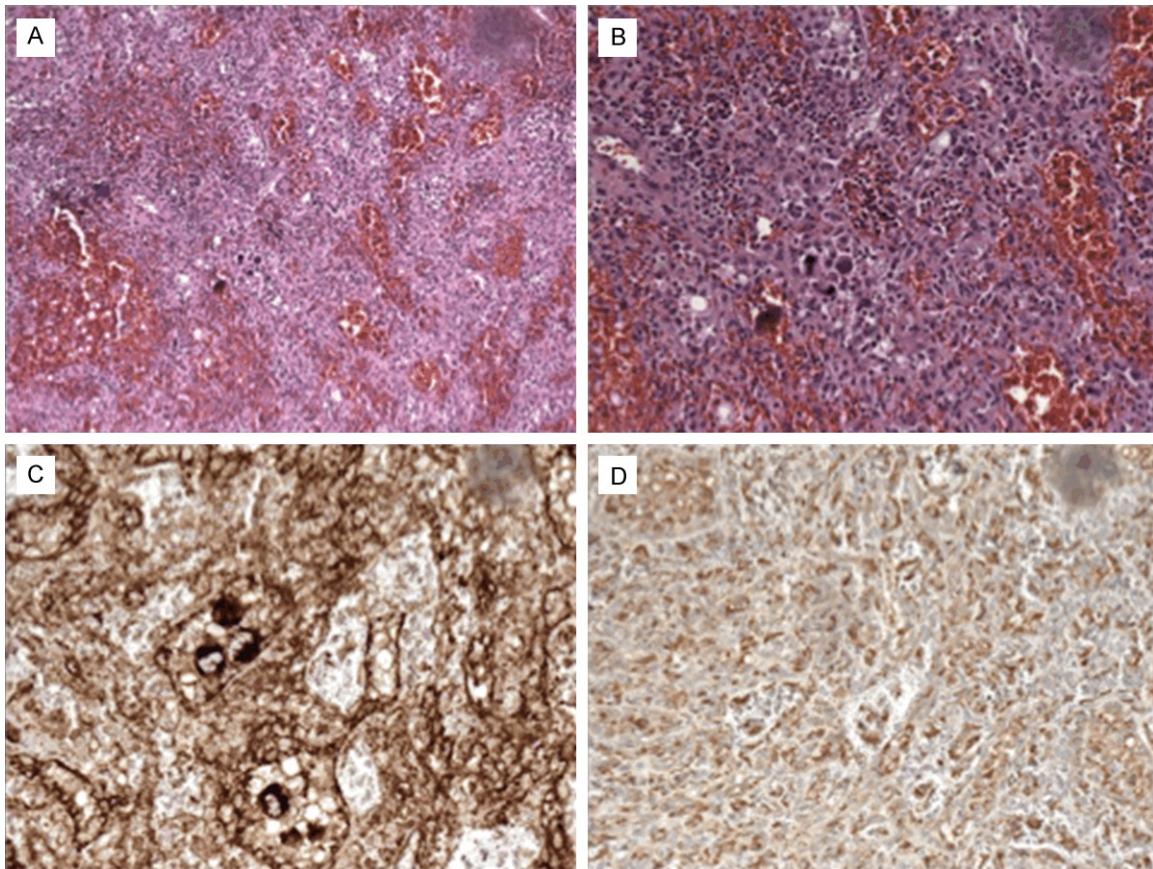
upper quadrant abdominal pain of one-month duration. Past medical history was notable for a fifteen-year history of splenomegaly and recent history of a thyroid nodule. Bone marrow biopsy, imaging and hematologic studies had been previously performed, and splenomegaly was attributed to his history of *Plasmodium vivax*. A fine needle aspiration of the thyroid nodule revealed a follicular lesion of undetermined significance.

At admission, the patient denied fever, weight loss or other constitutional symptoms. Physical examination demonstrated splenomegaly and was otherwise unremarkable. Laboratory values, including complete blood count and metabolic panel were within normal limits. A CT abdominal scan demonstrated multiple findings including 2 heterogeneously enhancing splenic masses with the largest measuring  $5.8 \times 5.7 \times 5.7$  cm, and a heterogeneously enhancing mass in the left kidney measuring  $2.2 \times 1.9 \times 2.2$  cm (**Figure 1**). Additionally, CT showed an incidental 5 mm lung nodule. Given the concern of malignancy and metastatic renal cell carcinoma, the patient underwent an open splenectomy and left partial nephrectomy. The five-day postoperative course was complicated by fever and leukocytosis on the second postoperative day as well as rebound thrombocytosis, which resolved without treatment.

On gross examination the spleen was threefold enlarged at 623 grams and measured  $14.0 \times$

$13.5 \times 4.5$  cm with smooth surfaces. Sectioning revealed two hemorrhagic tan-red to tan-brown intraparenchymal lesions. The largest measured  $5.5 \times 4.7 \times 4.5$  cm and a second measured  $0.9 \times 0.9 \times 0.8$  cm. Microscopically, the lesions were located in the red pulp and composed of anastomosing vascular channels that obliterated the normal splenic parenchyma (**Figure 2**). The channels were lined by plump round cells that sloughed into lumens of the lesion. Of note, within the vascular channels of the lesion there were enlarged, atypical cells with hyperchromatic nuclei and nuclear pleomorphism. The atypia was concerning for a malignant vascular neoplasm and/or metastatic disease (**Figure 3**).

On immunohistochemistry, the neoplastic cells had positive expression for endothelial markers CD31 and Factor VIII, as well as the histiocytic marker CD68, confirming a diagnosis of littoral cell angioma (**Figure 2**). The littoral cells were negative for CD34, CD8 and CD21. The large atypical cells concerning for malignancy were determined to be megakaryocytes by immunohistochemistry, proven with positive expression for CD61, CD31 and Factor VIII (**Figure 3**). Further investigation demonstrated small, hyperchromatic hematopoietic cells, some of which resembled erythroid precursors. These cells were highlighted by CD117, glycophorin-A and E-cadherin, confirming their erythroid lineage. Overall, the findings were consis-



**Figure 2.** Littoral cell angioma of the spleen. (A) H&E staining reveals the anastomosing vascular channels obliterating normal splenic parenchyma (100 × magnification). Higher power demonstrates tall, plump round cells sloughed into the cystic-like spaces of the lesion and scattered hyperchromatic atypical cells (B). Littoral cells showed positive expression of CD31 (C) and CD68 (D) (200 × magnification).

tent with littoral cell angioma with extramedullary hematopoiesis and prominent megakaryocytes. The solitary left kidney mass was diagnosed as clear cell renal cell carcinoma with margins negative for carcinoma.

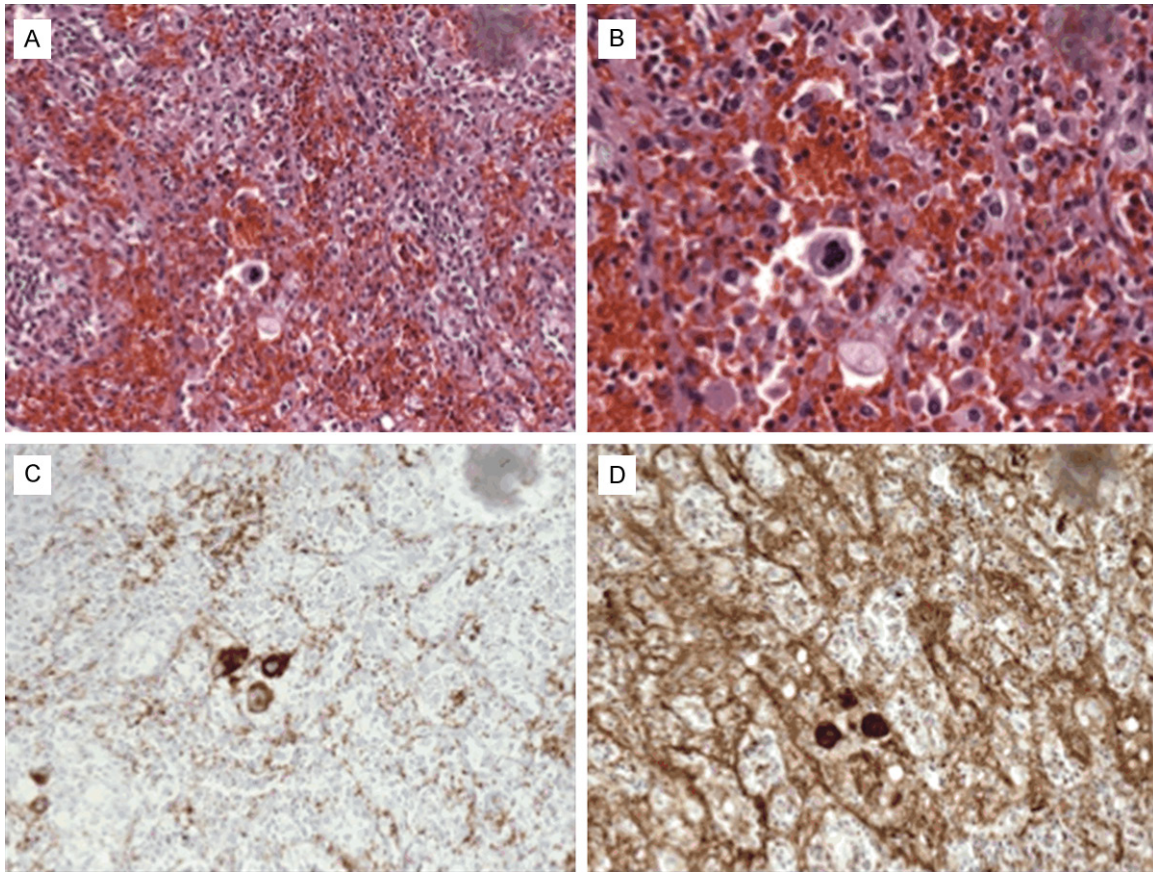
### Discussion

Primary tumors of the spleen are uncommon lesions that are characterized as lymphoid, non-lymphoid, tumor-like or vascular. Of these, vascular tumors are the most frequent solid tumor of the spleen. Vascular tumors arise from veins or sinus channels in the red pulp depending on the lesion, while lymphoid tumors conversely arise from lymphoid tissue in the white pulp. Secondary splenic tumors are unusual given the absence of afferent lymphatics to the spleen; however, they may occur in malignant melanoma, lung, breast or ovarian carcinomas [9]. In order to differentiate LCA from other

potential splenic lesions, pathologic assessment of tumor histology and immunophenotyping is necessary for diagnosis. At initial presentation, the differential diagnosis of splenic tumors is broad and includes lesions with variable degrees of aggressiveness from benign neoplasms, such as hamartoma, lymphangioma and hemangioma, to malignant tumors, such as lymphoma, angiosarcoma, and even Kaposi sarcoma.

Microscopic analysis of LCA demonstrates lesions with anastomosing vascular channels lined by tall, plump endothelial cells with exfoliated hemophagocytic cells in cystic lumens. Normal littoral cells appear flat and express only endothelial markers, including CD31 and Factor VIII. Neoplastic littoral cells are characterized by a dual histiocytic and endothelial phenotype, expressing both macrophage markers, CD68, CD168, and lysozyme, as well as





**Figure 3.** Extramedullary hematopoiesis in littoral cell angioma of the spleen. H&E staining reveals large atypical cells initially concerning for malignancy (A, 200 × magnification; B, 400 × magnification). Immunohistochemistry demonstrated these cells to be megakaryocytes with positive expression of CD61 (C) and FVIII (D) (200 × magnification).

endothelial markers, CD31 and Factor VIII. Additionally, LCA is characteristically negative for CD8, and may have low S100 expression. Several studies have sought other markers to delineate LCA from benign tissue and other splenic vascular tumors. Formin homology domain protein 1 (FHOD1) expression may be useful in differentiating LCA and normal littoral cells; FHOD1 has been reported in normal littoral cells and not in LCA [10]. LCA has been shown to have high expression of Ets Related Gene (ERG) and no expression of Wilms Tumor-1; however, this pattern is nonspecific and observed in other splenic lesions, including cavernous hemangiomas [11].

Originally, LCA was thought to have benign behavior. Recently, several reports have found LCA to have a variable potential for malignancy. Two subtypes of malignant LCA have been described as littoral cell hemangioendothelio-

ma (LCHE) and littoral cell angiosarcoma (LCAS). Metastatic lesions have been shown to occur years after splenectomy in these variant forms of LCA. In LCHE, 3 out of 4 cases metastasized to the liver or other organs resulting in patient death at 6 weeks, 4 years and 8 years post-splenectomy [8, 12]. Interestingly, in LCHE, original tumors have been described as typical of LCA or with mildly atypical solid areas with focal necrosis. Recurrent LCHE had increased solid architecture and higher proliferation indices measured by Ki-67 immunohistochemistry [12]. Several cases of LCAS have also been described with liver metastases [13-15]. In LCAS, 2 out of 4 patients died due to recurrence within one year of splenectomy [14, 16]. These tumors resembled typical LCA cases; however, they have solid areas of bland spindle cells which are immunophenotypically identical to LCA [17]. A recent meta-analysis of 180 cases found massive splenomegaly to be

associated with malignant variants of LCA (1655 vs 704 grams) [3]. Further studies are needed to risk stratify LCA lesions. Prognosis of variant littoral cell tumors is poor.

Radiologic methods are of some value and may potentially characterize the tumor as vascular; however, present imaging methodologies do not yield consistent results and may only narrow the differential. Ultrasound has a wide variability of findings in the evaluation of vascular splenic tumors. The sonographic appearance of LCA ranges from a hypoechoic to hyperechoic mass with a mottled texture [12]. If hyperechoic, the differential may be narrowed to include hemangiomatosis, hamartoma and Kaposi sarcoma [18]. On abdominal CT with and without contrast, LCA appears isodense to hypodense compared to normal splenic parenchyma in both arterial and early portal venous phase [19]. Such lesions have a broad differential diagnosis, including other splenic vascular tumors, other malignancies, infection, and systemic diseases such as sarcoidosis [20]. If the lesions enhance and isoattenuate on delayed contrast-enhanced CT, the differential may be narrowed [21]. MR imaging of the spleen demonstrates a hypodense mass on both T1-weighted and T2-weighted imaging due to the hemosiderin content of neoplastic littoral cells [20]. Thus, surgical intervention with excision is necessary for final pathologic diagnosis.

Currently, standard treatment of LCA is open splenectomy or hand-assisted laparoscopic total splenectomy. The procedure is diagnostic and therapeutic. Biopsy, using fine needle aspiration (FNA) or core needle biopsy (CNB), is not usually performed prior to total splenectomy due to the dangers of retroperitoneal hemorrhage. However, in certain instances biopsy may be beneficial in order to confirm the lesion as benign or malignant, thereby reducing unnecessary surgical procedures [22]. A retrospective study of ultrasound-guided splenic biopsy found FNA and CNB to be mostly safe and effective for the assessment of focal lesions [23]. Splenectomy does have significant long-term risks for patients including infections by encapsulated bacterial organisms, thromboembolism and increased risk of malignancy. In a cohort of 8,149 cancer-free American veterans, malignancy occurred in 13% of splenectomy cases, including lymphoma and visceral

organ cancers, within 10 years [24]. Partial splenectomy has been reported in two cases of localized LCA [25, 26]. However, given the multifocal nature of the disease in 71-89% of cases, total splenectomy may be necessary in this setting [3]. In cases of unifocal disease, a conservative approach using partial splenectomy may be warranted. There is no consensus guideline recommendation for the type of surgical resection. Both laparoscopic and open procedures are well tolerated with few complications. In a study of 27 patients comparing splenectomy techniques, Cai et al found that laparoscopic total splenectomy had shorter hospital duration versus an open procedure and the morcellation of specimens did not affect diagnosis in these patients [27]. In one case, rebound thrombocytosis occurred post-splenectomy and a subsequent pulmonary embolism occurred. In our patient, rebound thrombocytosis similarly occurred; however, it resolved without necessitating treatment.

LCA has an apparent association with visceral organ cancers and immune-mediated diseases. Approximately half of cases occur with synchronous cancer or an immunosuppressed state [28]. Several cases of LCA have occurred after long-term immunosuppression for renal transplantation, systemic lupus erythematosus, and Crohn's disease. Recently, TNF- $\alpha$  has been suggested to have a role in the pathogenesis of LCA [29, 30]. A familial case of LCA and primary splenic angiosarcoma has been described supporting potential genetic predisposition as well as the possibility for malignant transformation of LCA tumors to variant littoral cell tumors. It is not understood if variant LCA represents a distinct entity or arises from LCA in a stepwise manner.

This report is the fourth known description of LCA associated with renal cell carcinoma. The majority of cases are associated with gastrointestinal cancers. The association of LCA with synchronous cancer has been reported from 27 to 36% [30, 31]. Interestingly, in our case, the multifocality of the splenic lesions on imaging raised a strong concern for metastases from the patient's ipsilateral renal mass, although it is well known that LCA is commonly multifocal. Histologically, the finding of enlarged, atypical cells within the LCA was of concern for a malignant vascular neoplasm arising from the

LCA. Though initially concerning, careful evaluation and immunophenotyping recognized the cells as megakaryocytes within extramedullary hematopoiesis, which is a relatively rare finding in LCA. Interestingly, extramedullary hematopoiesis has been demonstrated with renal cell carcinoma, and may also occur with perirenal liposarcoma, spindle cell lipoma of the neck, myelofibrosis, hepatic angiomyolipoma, and other hepatic tumors [32]. In summary, LCA's are largely benign splenic neoplasms which hold variable potential for malignancy. The presence of multifocal splenic masses in the setting of visceral carcinoma should raise suspicion for LCA. Given the possibility of metastases, primary malignant vascular lesions and variant LCA of the spleen, careful assessment of the histology should be made, taking note of atypia, solid areas, and the presence of necrosis. Extramedullary hematopoiesis may be present and may mimic malignancy in this setting. Once the diagnosis of LCA is made, appropriate follow up with imaging should be recommended.

## Disclosure of conflict of interest

None.

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