Littoral cell angioma of the spleen – a surprising cause of anemia

IULIA URSULEAC1,2, CRISTINA IOSIF3,4, RODICA BÎRLĂ1,5, CAMELIA DOBREA1,3, AMELIA MARIA GĂMAN6, D. ARSENE3, D. CORIU1,2

1)“Carol Davila” University of Medicine and Pharmacy, Bucharest
2)Center of Hematology and Marrow Transplantation, “Fundeni” Clinical Institute, Bucharest
3)“Victor Babes” National Institute, Bucharest
4)Department of Pathology
5)Department of Surgery
6)University of Medicine and Pharmacy of Craiova

Abstract
Littoral cell angioma is a rare tumor of the spleen, usually being considered benign and typically discovered incidentally. There are three different modalities of presentation: tumoral splenomegaly, long-standing iron deficient anemia or thrombocytopenia due to hypersplenism. However, some of its manifestations could generate the suspicion of a lymphoma or other more serious condition. We present the case of a 46-year-old man with splenomegaly and iron deficiency anemia. The tumor affected the whole spleen, which was surgically removed. The histopathological examination, together with immunophenotyping, established the diagnosis. Six months after the procedure, the patient is in very good condition. Several differential diagnoses were discussed, as well as the prognostic factors. The case illustrates a rare cause of anemia and the importance of pathology in uncovering such unusual causes for this.

Keywords: littoral cell angioma, splenomegaly, iron deficiency anemia, thrombocytopenia.

Introduction
Littoral cell angioma (LCA) was described for the first time in the ‘90s by Falk S et al. [1]. It is a unique and rare disorder of the spleen consisting of littoral cells proliferation. These special cells are placed between endothelial and histiocytic cells and line the venous sinuses of the normal spleen. In some circumstances, such as antigenic stimulation, littoral cells proliferate and undergo an increasing capacity of phagocytosis. The result is a tumoral vascular growth pattern; it can be limited to a simple area of the spleen or, in rare cases, extended to the entire organ. A strong association between this type of vascular tumor and other malignancies such as adenocarcinoma of the colon, liver or pancreas, chronic inflammatory bowel disease (e.g., Crohn’s disease) has been postulated [2].

Many cases are diagnosed due to imagistic features of isolated splenic masses [3].

The clinical course is usually benign, most patients being asymptomatic. When symptoms are present, there are several types of presentation at diagnosis: left flank-upper abdominal pain, weakness, fatigue and weight loss. Some patients may present splenomegaly or splenic nodular masses, long-standing anemia, iron deficient type and thrombocytopenia, either due to hypersplenism or to consume of the platelets into the vascular proliferated network [4].

We report a case of LCA of the entire spleen in a 46-year-old man, with a history of iron deficiency anemia, mild thrombocytopenia and splenomegaly.

Patient, Methods and Results
Clinical and radiological features
The patient, a man who practices martial arts, was admitted in Center of Hematology and Marrow Transplantation, “Fundeni” Clinical Institute, Bucharest, Romania, in April 2012, with one-year history of pallor, dyspnea on exertion, fatigue, sweats and progressive weakness. At physical examination, we noted splenomegaly (4 cm below costal margin), confirmed by abdominal ultrasound (14 cm mild splenomegaly, without any abnormality of the structure). A microcytic, hypochromic anemia, with ferricprive pattern (hemoglobin – 8 g/dL, sideremia – 12 µg/dL), and a mild thrombocytopenia (platelets – 140 000/dL) were revealed. The check-up for blood loss lesions was started.

Superior endoscopy was performed and a scary duodenal ulcer was discovered, but without active blood loss. Colonoscopy revealed a rectal polyp; it was resected and the histopathology infirmed any dysplasia or malignant features. The abdominal ultrasound was without specific images.

Martial therapy was initiated for six months with improve of hemoglobin level to 12 g/dL, but persistence...
of hypochromia and microcytosis. Thalassemia was excluded by a normal pattern of hemoglobin electrophoresis. The second abdominal ultrasound revealed multiple hyperechoic splenic nodular lesions. An intravenous contrast-enhanced CT scanning was performed (Figure 1).

![Figure 1](image1.png)

**Figure 1 – Abdominal CT scanning performed with intravenous contrast-enhanced (early portal phase): multiple, nodular, hypoenhancing, partially confluent splenic lesions.**

The maximal splenic length was 15 cm. The CT scanning confirmed the presence of multiple nodular lesions located at the inferior pole of the spleen, most of these lesions with a medium diameter of 33/21 mm. The spleen was intensely inhomogeneous and the aspect of tumoral nodular lesions was hypodense, hypocaptant and poorly circumscribed. The abdominal adenopathies (interaorticocaval, lomboaortic) were infracentimetric.

A splenic lymphoma was presumed, and a bone marrow trephine biopsy was done. The bone marrow examination do not revealed malignant infiltrates.

Splenectomy for diagnostic purposes was performed, with no incidents and fully recovered patient.

**Pathology**

**Gross examination**

The spleen was moderately enlarged (15/11/8 cm). The section of the spleen revealed multiple, large hemorrhagic nodules almost completely replacing the spleen tissue with spongy and brownish-red appearance. The diameters of the nodules varied from 10 mm to 35–40 mm. The nodules were dark-red, brown or black color, well defined from surrounding normal splenic tissue, but without evidence of a capsule. Several such nodules were harvested and routinely processed for histopathology and subsequent immunohistochemical examination.

**Histopathology**

The lesions were located in the splenic red pulp. The overall tumor pattern was cystic, with associated papillary structures extended into the vascular channel (Figure 2). The endothelial cells lining the cystic spaces had abundant cytoplasm; round shaped or slightly indented large nuclei. Some of these cells were observed into luminal spaces of vascular, dilated channels. No atypical mitosis, no atypical cells and no associated lymphoid proliferation were noted. The histopathological diagnosis was littoral cell angioma.

**Immunohistochemistry**

Immunohistochemistry was performed on the paraffin-embedded material using the EnVision+ Dual Link System Peroxidase Kit (Dako, Carpinteria, CA, USA), according to manufacturer’s instructions. Primary antibodies against the following antigens were used: CD68 (histiocytic marker), CD34 and CD31 (both vascular markers) (Dako, Glostrup, Denmark, 1:50 dilution). The endothelial cells lining the cystic spaces were positive for both, endothelial and histiocytic markers: CD31 (Figure 3), CD34 (Figure 4), and for CD68 (Figure 5), confirming the histopathological diagnosis of littoral cell angioma.

**Clinical outcome**

Six months after splenectomy, the patient is fully recovered, with a normal social life and works, without any complaint or sign of disease. A mild thrombocytosis found after the splenectomy was treated with low doses of acetylsalicylic acid for three months, until normal values were gained.

![Figure 2](image2.png)

**Figure 2 – Histopathology: global aspect of the tumor. The splenic parenchyma contains numerous cystic vascular spaces (HE staining, 100×).**

![Figure 3](image3.png)

**Figure 3 – The cells lining the vascular channels are strongly positive for CD31 (CD31 immunohistochemistry, 200×).**
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Discussion

Vascular tumor constitute the second most common primary neoplasms in spleen, commonest being lymphoid malignancies [5]. This was the reason for first suspecting a lymphoma in this patient. LCA of the spleen is a rare, usually benign cause of splenomegaly [2, 6], but rare metastasizing cases were described [7].

Sometime asymptomatic [8], LCA may be associated with hematological symptoms, like anemia, including iron deficient type [9, 10] or aplastic anemia [11]; and/or thrombocytopenia [12]. In our case, LCA was the cause of a chronic anemia, with persistent low iron levels, despite a correct martial treatment and without an active source of blood loss. The symptoms were induced by anemia and iron deficiency rather than by the splenomegaly itself. Imagistic examination (abdominal ultrasound, CT scan) for splenomegaly investigation are required, and isolated splenic masses are revealed [13, 14].

Imagistic investigations may be suspicious for a vascular tumor of the spleen, the diagnosis of LCA is a histopathological one. LCA are composed of anastomosing vascular channels resembling splenic sinusoids with cystic spaces. The absence of atypical cells and presence of low mitotic activity are common. The differential diagnosis of LCA include other splenic vascular tumors with indeterminate malignancy (hemangioendothelioma, hemangiopericytoma), but also benign (hemangioma, hamartoma, lymphangioma), and malignant (angiosarcoma) neoplasms [5]. Hemangiomas are the most common benign primary neoplasms of the spleen, but at CT scans, they are hypovascular lesions which may have a contrast enhancement pattern, similar to hepatic angiomas. The hemangioma lesion is more frequent localized than generalized and calcifications, cysts, fibrosis may be described within the hemangioma.

Lymphomas or metastatic lesions affect the entire spleen and at CT scan, it is difficult to differentiate them from LCA; the presence of adenopathies or specific organ lesions may contribute to diagnosis of malignancy. Infectious diseases, such as tuberculosis of the spleen, septic emboli during severe infectious diseases, fungal disseminated infections or opportunistic infections in immunocompromised hosts (Pneumocystis carinii, Mycobacterium complex) may have a similar imagistic pattern, but clinical condition is important for differential diagnosis [15]. Histological evaluation (abnormal architecture, nuclear atypia, necrosis) and close follow-up of LCA may be warranted due to the potential for their malignant transformation and distant metastasis several months after splenectomy [7]. Immunohistochemical, tumor cells express endothelial (CD31, factor VIII Ag) and histiocyte markers (CD68), a reflection of the distinct dual differentiation potential of LCA [10]. Unlike the data from the literature [10], our case was also strongly positive for CD34, aside the known positivity for CD31 and CD68. The pathogenesis of LCA remains unclear, but given its association with autoimmune disorders such as Crohn’s disease, immune system dysfunction has been postulated as a possible pathogenesis [2].

Conclusions

This case reflects the importance of a very rare, not fully understood cause of microcytic anemia with persistent low iron levels despite a correct treatment and without active source of blood loss in association with a tumor splenic mass. The diagnosis was entirely histopathological. Most of the tests and imagery were directed in order to exclude a concomitant neoplasia that may accompany a loss of iron. It also emphasized the need for complete check-up in such cases of anemia, this truly “Pandora’s box” of hematology.

References


Corresponding author
Iulia Ursuleac, MD, PhD, “Ștefan Berceanu” Center of Hematology and Marrow Transplantation, Fundeni Clinical Institute, 258 Fundeni Highroad, 022328 Bucharest, Romania; Phone +4021–275 07 00, Fax +4021–318 04 44, e-mail: iuliaursuleac@yahoo.com

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