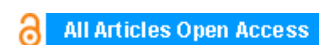


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**Daniel Gorman, Reece Bergstrom**

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Littoral cell angioma (LCA) of the spleen is a rare, benign vascular tumor first described in 1991. The etiology and pathogenesis continues to be unclear. Only a few dozen cases have been noted since its first original identification. This case report discusses a patient in which hypodense splenic lesions were incidentally found on computed tomography. The patient elected for a splenectomy and LCA was discovered on pathologic analysis. This case presents an interesting discussion due to the patients' complex medical history including a previous diagnosis of Ehlers-Danlos syndrome as well as chronic immunosuppression secondary to treatment for psoriatic arthritis. The possible pathogenesis of LCA is unclear. Current theories revolve around either increased or decreased levels of TNF $\alpha$  in disease progression. Altered immune response is linked to LCA, which is confirmed by the resolution of leukocytosis following treatment. Reticuloendothelial system fragility predisposes to structural anomalies such as LCA. Further etiologic studies of patients with this extremely rare vascular tumor will give further indication of the disease pathogenesis.



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**Littoral cell angioma (LCA) of the spleen is a rare, benign vascular tumor first described in 1991. The etiology and pathogenesis continues to be unclear. Only a few dozen cases have been noted since its first original identification. This case report discusses a patient in which hypodense splenic lesions were incidentally found on computed tomography. The patient elected for a splenectomy and LCA was discovered on pathologic analysis. This case presents an interesting discussion due to the patients' complex medical history including a previous diagnosis of Ehlers-Danlos syndrome as well as chronic immunosuppression secondary to treatment for psoriatic arthritis. The possible pathogenesis of LCA is unclear. Current theories revolve around either increased or decreased levels of TNF $\alpha$  in disease progression. Altered immune response is linked to LCA, which is confirmed by the resolution of leukocytosis following treatment. Reticuloendothelial system fragility predisposes to structural anomalies such as LCA. Further etiologic studies of patients with this extremely rare vascular tumor will give further indication of the disease pathogenesis.**

**Keywords: Hemangioma, Littoral cell angioma, Vascular tumors**

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## INTRODUCTION

Littoral cell angioma (LCA) of the spleen is a rare vascular tumor first described in 1991 by Falk [1]. The LCA is a primary vascular neoplasm and composed of littoral cells that line the splenic sinuses of the red pulp. Littoral cells can be described as cylindrical endothelial cells that project into the vascular lumen with very little mitotic activity [2]. While originally thought to be benign, recent reports suggest the potential for malignancy with both congenital and immunological pathogenic associations. The presentation is variable and often is found incidentally on imaging. Patients may present with vague abdominal pain, splenomegaly and hypersplenism [3]. In rare circumstances, LCA has been associated with extramedullary hematopoiesis [4]. The diagnosis of LCA is confirmed either histologically or through immunohistochemistry.

Patients with chronic autoimmune inflammatory conditions, such as Crohn's and psoriatic arthritis, are often treated with immunosuppression such as methotrexate and anti-TNF $\alpha$  antibody treatments like certolizumab or infliximab. Deep immunosuppression in patients with long term treatment of these diseases is

associated with an increased risk of lymphoma and has been reported in one case LCA [5]. The relationship of TNF $\alpha$  to the development of LCA remains unclear and will be discussed below.

Ehlers–Danlos syndrome (EDS) is an inherited connective tissue disease characterized by joint laxity, small blood vessels diameter, increased scar formation, abnormal wound healing, and excessive skin elasticity. It can also cause weak internal organs due to defects involving type 3 and type 5 collagen. The EDS is currently thought to be associated with the mutations in COL5A1 and COL5A2 genes [6]. This disease can cause a defect in multiple types of collagen and present itself in various forms throughout the body. In the vascular form, type 3 collagen is affected and patients demonstrate vascular instability. The reticuloendothelial system is composed primarily of a type 3 collagen meshwork, which could suggest a potential link between these two diseases.

This presents a case of littoral cell angioma in a patient on Biologic Immunosuppression for Psoriatic Arthritis with a previous additional diagnosis of Ehlers–Danlos syndrome. There exists a potential component of immune dysregulation and reticuloendothelial system fragility in the pathogenesis of LCA.

## CASE REPORT

A 54-year old female was presented to the emergency department following repeated syncopal episodes during a routine office visit with her dermatologist. On presentation, her white blood cell count was 22,000/ $\mu$ L. She was hypotensive, at 98/62, on presentation and remained hypotensive despite aggressive IV fluid resuscitation. The patient reported that five days prior to admission she experienced a bout of loose, watery diarrhea with occasional bright red blood per rectum. She was admitted to the hospital in accordance with sepsis criteria. Upon continued aggressive IV fluid resuscitation, she became normotensive. An abdominal/pelvis CT with contrast, ordered by the emergency department, demonstrated multiple lesions of the spleen (Figure 1), which were new compared to a study from 2014. The CT additionally demonstrated an adnexal cyst. On hospital day -3 the patients' platelet count was 392,000 and hemoglobin was 12.2.

The patient had an extensive past medical history including psoriatic arthritis, hypertension, hyperlipidemia, major refractory depression requiring hospitalization, and Ehlers–Danlos syndrome. During the hospital stay, the patient was consulted by hematology for chronic thrombocytosis and leukocytosis. Previous workup for the same presentation included a negative JAK2 mutation test. The thrombocytosis and leukocytosis was initially attributed to biologic immunosuppression with methotrexate and certolizumab (Cimzia). Due to increased risk of lymphoma associated with immunosuppressive medication, workup included

LDH, SPEP, beta-2 microglobulin, PET CT, and CT chest, all of which were negative for abnormalities. The patient reported exposure to parrots at home, prompting a negative workup for Psittococcal antibodies.

The patient verbal history included a diagnosis of Ehlers–Danlos syndrome. Clinically the patient exhibited hypermobility bilaterally at the elbow and hyperextension of the upper extremities. The patient history also included adnexal cysts, hepatic cyst, renal angio lipomas, all of which were confirmed on the initial admission CT. The patient has a family history of renal cell carcinoma and angiolipoma. Previous imaging revealed a hemangioma in the liver as well as multiple vascular skin lesions for which she visits a dermatologist (Figures 2 and 3).

## Management

The patient returned to the hospital one month later for an elective open splenectomy in order to rule out lymphoma. The patient elected to do the procedure with an open approach. The surface of the spleen showed no visible lesions. The procedure was done without complications and estimated blood loss was 100 ml. Pathology report of the specimen revealed a 12.2x7.4x4.0 cm spleen weighing 272.2 grams. The capsule was intact with multiple hemorrhagic appearing well-circumscribed, spongy lesions throughout the parenchyma (Figure 4). The sizes of the lesions ranged from 5 mm to 1.5 cm. The uninvolved spleen was normal. The diagnosis of littoral cell angioma was given by the pathologist following microscopic analysis.

The etiology of this particular case remains unclear. Due to the increased incidence of malignancy associated with this disease, the patient will be monitored closely in addition to age-appropriate screening [7]. The patient developed normocytic anemia post-splenectomy as expected and was placed on iron sulfate. Platelet counts increased slowly to as high as 637,000/ $\mu$ L on postoperative day-9. Leukocytosis peaked around 29,000/ $\mu$ L on postoperative day-4 and then trended to 22,000/ $\mu$ L by postoperative day-9. The patient was stable and discharged on postoperative day 11 with close follow-up scheduled to monitor for leukocytosis and thrombocytosis.

## DISCUSSION

This patient presented without any signs or symptoms related to LCA. The patient was given an abdominal CT as part of a sepsis workup which then demonstrated the splenic lesions. The patient was not hypersplenic at the time of presentation, which is often times associated with LCA. The patient did not display splenomegaly on physical examination, nor did the patient complain of abdominal pain. Asymptomatic presentation is not uncommon in littoral cell angioma and is often found incidentally such as with this patient [7].



Figure 1: Computed tomography scan abdomen/pelvis with contrast demonstrating multiple hypodensesplenic lesions that are well defined.

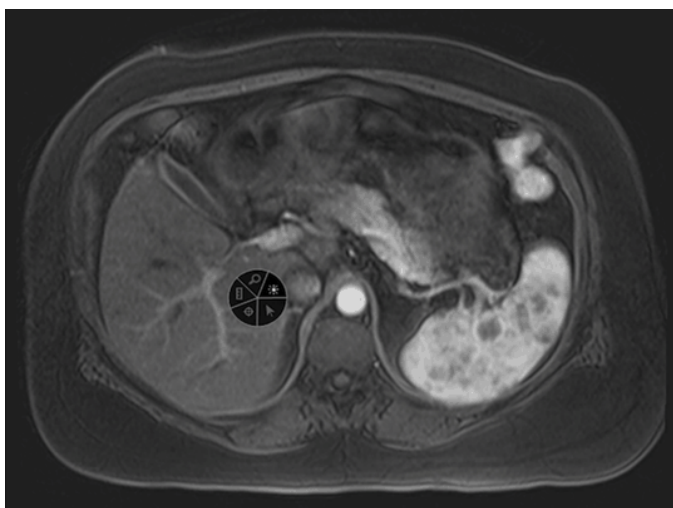


Figure 2: 3D Arterial magnetic resonance imaging demonstrating the hypodensesplenic lesions.

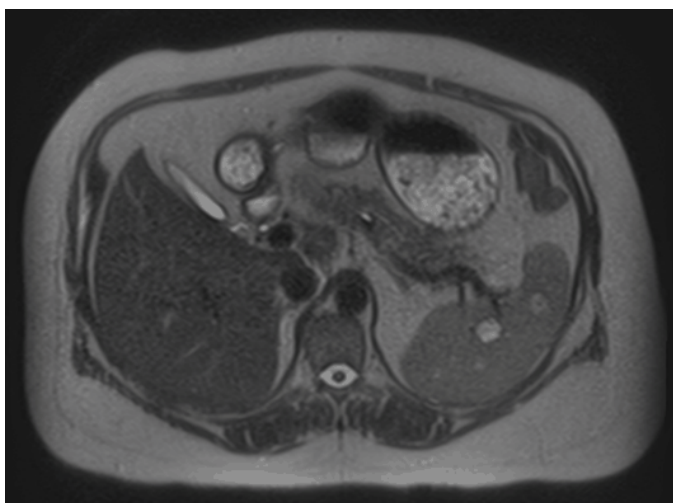


Figure 3: T2 magnetic resonance imaging demonstrating splenic lesions.

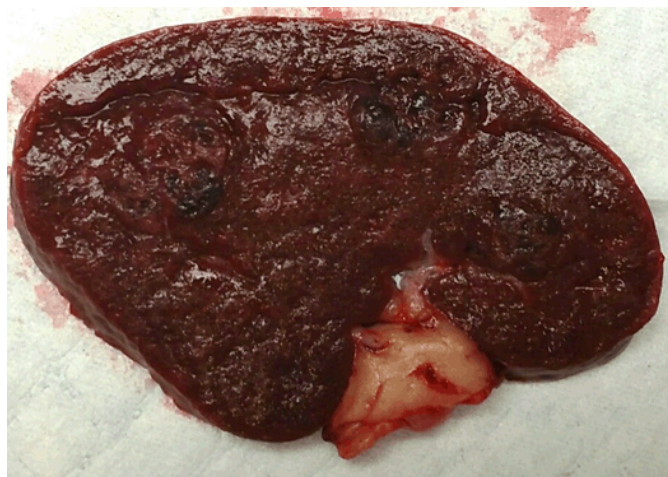


Figure 4: Gross section of spleen showing multiple hemorrhagic appearing well circumscribed and spongy lesions throughout the parenchyma.

The primary discussion point in this case relates to the chronic immunosuppression for psoriatic arthritis. Chronic  $\text{TNF}\alpha$  antibody treatments have a known link to an increased risk of lymphoid neoplasms. However, no link has been established with vascular neoplasms such as LCA. The pathogenesis is unclear and requires further investigation. Some previous reports link immunosuppression to LCA [5] and this case now represents another association of LCA to this possible pathogenesis.

A possible relationship exists between the development of LCA and patient serum levels of  $\text{TNF}\alpha$ .  $\text{TNF}\alpha$  has a pivotal role both in inflammation and immune response. LCA arises from splenic macrophages that line the vascular channels. As critical immune cells, these macrophages would be expected to have high levels of  $\text{TNF}\alpha$  receptors. Thus, littoral cells are expected to be extremely sensitive to fluctuating serum levels of this particular cytokine. Elevated serum levels of  $\text{TNF}\alpha$  are also known to have effects on tumor development, producing an attractive environment for growth by facilitating genomic instability and promoting angiogenesis [8].

There must be a relationship between LCA and an altered immune host response. Tan described chronic immunosuppression following renal transplant and development of LCA induced fever reflecting the altered host response. The fever resolved after the removal of the spleen [9]. The patient in this case was immunosuppressed secondary to the treatment of her psoriatic arthritis. The patient responded as expected based on previous reports. Her leukocytosis began down-trending following splenectomy from  $29,000/\mu\text{L}$  on postoperative day-4 to  $22,000/\mu\text{L}$  on discharge.

Reticuloendothelial system fragility appears to play a role in the pathogenesis of LCA. To date, there have been no studies suggesting this as a possible mechanism for

development of these benign lesions. Type 3 collagen has a high presence in splenic tissue and thus fragility would predispose to development of structural anomalies such as LCA. A weakened reticular network of the spleen would allow for the expansion and development of these vascular tumors.

The possible etiology of this particular manifestation of LCA is unclear. There are two separate hypothesis in place regarding the role of TNF $\alpha$  in disease pathogenesis. One hypothesis describes increased levels of TNF $\alpha$  as a pathogenic mechanism for development of the disease. A second hypothesis relates chronic immunosuppression with TNF $\alpha$  blocking medication to LCA development. The role of immune dysregulation is clear. However further investigation is needed into the exact role of the immune response and TNF $\alpha$  in the disease progression. The component of reticuloendothelial fragility compounded angioma development. The exact mechanism cannot be concluded at this point, but this represents the first case in which a combination of these two possible pathogenic mechanisms presented in the same patient.

## CONCLUSION

The possible pathogenesis of littoral cell angioma (LCA) remains a mystery. Current research into the disease indicates a strong correlation between LCA and either increase or decreased levels of TNF $\alpha$ . Fragility of the reticuloendothelial system predisposes to structural anomalies such as LCA. Immune dysregulation must play a role in the pathogenesis of LCA, which is confirmed by the resolution of leukocytosis following splenectomy. Etiologic studies are limited due to the extreme rarity of this disease. However, as the prevalence of the disease increases so will our understanding of the underlying mechanisms.

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## Author Contributions

Daniel Gorman – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Reece Bergstrom – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

## Guarantor

The corresponding author is the guarantor of submission.

## Conflict of Interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement

in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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