# Sclerosing angiomatoid nodular transformation of the spleen: A case report

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## Abstract

Sclerosing angiomatoid nodular transformation is a benign vascular pathology of the spleen, developed from the red pulp. Its etiology is unknown, although it is suggested that it may be related to immunoglobulin four disease and Epstein-Barr virus infection. Most cases are asymptomatic, constituting incidental imaging findings. We present the case of a 41-year-old male patient with a history of thyroidectomy for papillary carcinoma who consulted for fever. He received symptomatic treatment, and an abdominal computed tomography scan was performed due to non-specific abdominal symptoms. The image showed a lesion of solid aspect, with faint peripheral contrast enhancement, measuring 62 by 52 by 51 millimeters in the lower pole of the spleen. Splenectomy was performed. The macroscopic study showed a 14 by 11 by 4 centimeters spleen that weighed 284 grams. A solid, well delimited nodular formation with a central fibrous area and whitish tracts dividing violaceous regions was identified. Microscopy showed round coalescent nodules of angiomatoid appearance, in which a slit-like vascular proliferation was lined by endothelial cells without atypia, interspersed with spindle cells and infiltrates of lymphocytes and macrophages. The stroma surrounding the nodules showed myofibroblastic proliferation with lymphocytes, plasmacytes, and siderophages. Regarding immunohistochemistry, the vessels were CD34 9 (+) and CD31 (-), and some areas were CD8(+) and CD34 (-). One cell was positive for immunoglobulin 4 (IgG4) by high magnification field. The study for Epstein-Barr by polymerase chain reaction was negative. Imaging studies are non-specific to diagnose sclerosing angiomatoid nodular transformation, so the histopathological study is the gold standard. Splenectomy is curative, and there are no reported malignant transformation or recurrence cases. To date, risk factors are unknown, except for a suggested association with IgG4 and Epstein-Barr virus. As this entity is new, it is necessary to compile large series and review differentials of previous cases to achieve a higher understanding of the disease.

## Main messages

- Sclerosing angiomatoid nodular transformation is a rare benign pathology. Histopathologic and immunohistochemical studies are the gold standard for diagnosis.
- Sclerosing angiomatoid nodular transformation diagnosis is challenging due to the low specificity of imaging and laboratory tests.
- This clinical case shares the main features of this disease so that physicians may consider it in the differentials of splenomegaly.
- The documentation of this case will enrich the pool of evidence over sclerosing angiomatoid nodular transformation.

# Introduction

Sclerosing angiomatoid nodular transformation, first described by Martel et al. in 2004 [1], is rare. The existing evidence is based predominantly on less than 150 case reports [2], many of which focus on radiological images [3]. These lesions are usually solitary, but about six multifocal cases have been reported [4].

This lesion is a benign vascular pathology of the spleen, developed from the red pulp. The etiopathogenesis is unknown, although it is suggested that it may be related to immunoglobulin four (IgG4) disease [1]. Diagnostic criteria for IgG4 disease-related sclerosing angiomatoid nodular transformation consists of the presence of a mass, nodular lesion or organ dysfunction, serum IgG4 concentration greater than 135 micrograms per deciliter (reference value between one and 135 micrograms per deciliter), more than 10 IgG4-positive cells per high-magnification field, and an IgG4/IgG ratio greater than 0.4 [5]. Another likely cause is Epstein-Barr virus infection, and some isolated cases are associated with Mafucci syndrome [6]. Most cases are asymptomatic and present as incidental findings in radiological studies [7].

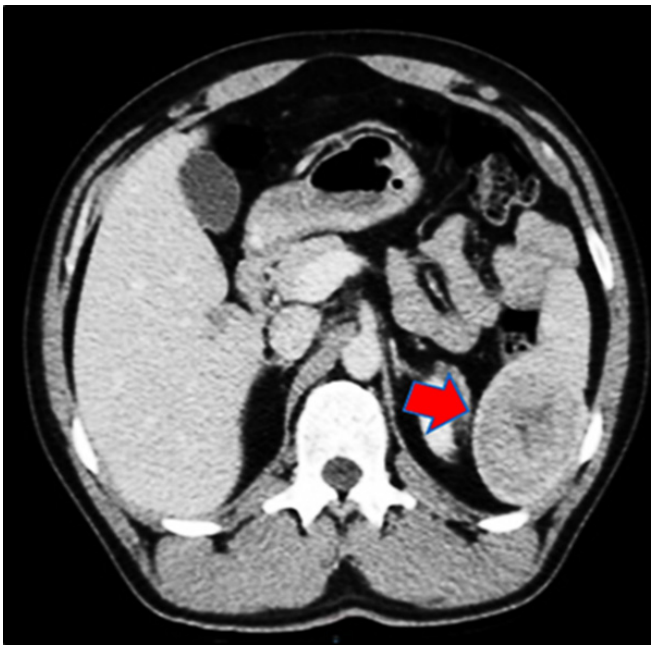
## Case report

A 41-year-old male patient (engineer by profession) consulted in 2018 for a non-specific febrile syndrome. He received symptomatic treatment for intermittent non-specific abdominal symptoms. As he continued with symptomatology, physicians in charge decided to perform an abdominal computed tomography. He had a history of hypothyroidism treated with levothyroxine 175 micrograms per day due to thyroidectomy for a classic variant papillary carcinoma in the right lobe and papillary microcarcinoma in the left lobe. He had surgical treatment in 2015 and later received radioactive iodine.

On physical examination, he had a blood pressure of 140/80 millimeters of mercury, a heart rate of 68 beats per minute, a respiratory rate of 15 breaths per minute, and a temperature of 37.3 degrees Celsius. In addition, he had cervical lymphedema linked to previous surgery (total thyroidectomy and cervical lymphadenectomy) and pain on palpation in the right flank, without peritoneal reaction. Laboratory tests revealed 4 960 000 red blood cells per cubic millimeters, 13 880 leukocytes per cubic millimeters (neutrophils 85%), hemoglobin of 14.5 grams per deciliter, hematocrit of 42.1%, 246 000 platelets per cubic millimeters, urea 30.6 micrograms per deciliter, creatinine 0.90 micrograms per deciliter, total bilirubin 0.6 micrograms per deciliter, aspartate aminotransferase 19.5 international units per liter, alanine aminotransferase 23.3 international units per liter and erythrocyte sedimentation rate 7 millimeters per hour. Serology for hydatidosis, HIV 1 and 2, hepatitis B virus, and hepatitis C were negative. The electrocardiogram was normal.

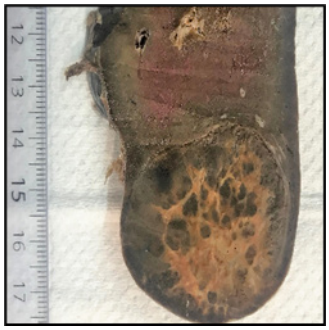
Abdominal computed tomography findings showed an abnormal image of the spleen. Given this finding, a consultation with oncology and a contrasted abdominal and pelvic computed tomography were indicated (Figure 1). The new image showed a solid lesion at the lower pole of the spleen measuring 62 by 52

**Figure 1.** Computed tomography, axial section.



Source: Prepared by the authors of this study.

**Figure 2.** Macroscopic image of sclerosing angiomatoid nodular transformation.



Source: Prepared by the authors of this study.

by 51 millimeters with a hypodense center that slightly enhanced peripherally with contrast.

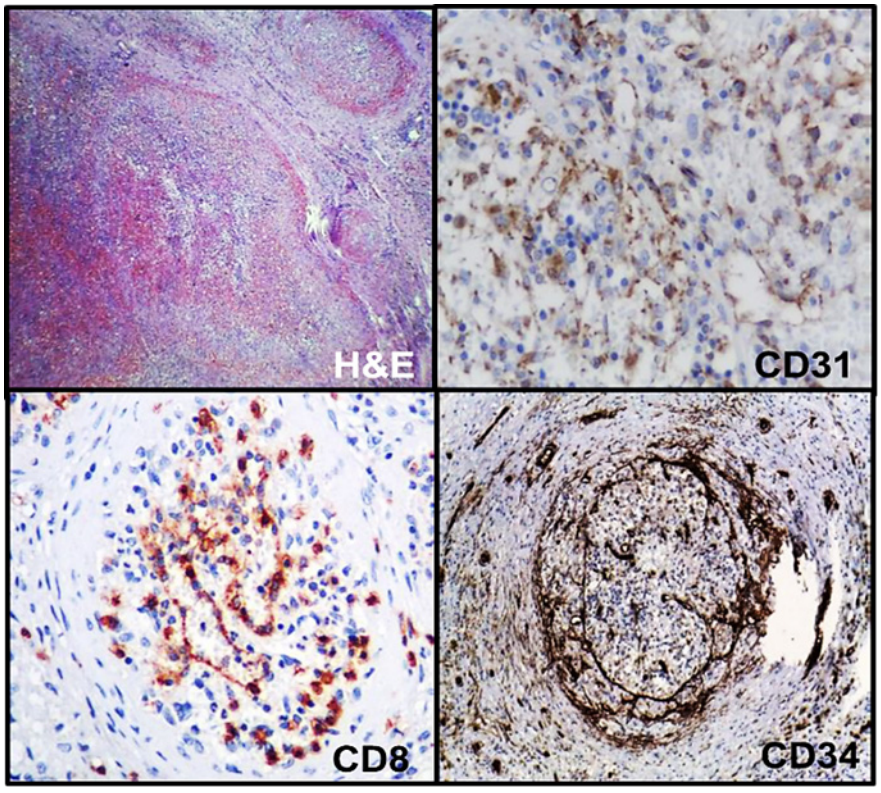
The risk of malignancy encouraged a splenectomy with a laparoscopic approach. Before surgery, the patient received vaccination against influenza, *pneumococcus*, *meningococcus*, and *Haemophilus influenzae*.

In the macroscopic study, the organ measured 14 by 11 by 4 centimeters and weighed 284 grams. A solid nodular formation was observed at the subcapsular level in the lower pole. This mass was well-circumscribed, with a central whitish area of fibrous aspect and whitish tracts defining violaceous areas measuring 4.5 by 4 centimeters (Figure 2).

Microscopic findings showed round coalescent nodules of angiomatoid appearance, in which a slit-like vascular proliferation was lined by endothelial cells without atypia. The vessels were interspersed with spindle cells and inflammatory cells, including lymphocytes and macrophages. The stroma surrounding the nodules was myxoid, and some sectors were fibrous, with a myofibroblastic proliferation accompanied by lymphocytes, plasmacytes, and siderophages. Regarding immunohistochemistry, the vessels were positive for CD34 and CD31, and some areas were positive for CD8 and negative for CD34 (Figure 3). The number of IgG4-positive cells was one per high magnification field, and the IgG4/IgG ratio was less than 0.4. The polymerase chain reaction (PCR) test for Epstein-Barr virus was negative.

The patient evolved favorably after surgery with no surgical or infectious complications to date and remained on the usual medication without requiring adjuvant treatment. Post-surgical laboratory studies showed 4 535 000 red blood cells per cubic millimeters, 7600 leukocytes per cubic millimeters (neutrophils 72%), hemoglobin of 13.2 grams per deciliter, hematocrit of 41%, 301 000 platelets per cubic millimeters, aspartate aminotransferase 17 international units per liter, and alanine aminotransferase 18.5 international units per liter.

**Figure 3.** Photomicrographs: hematoxylin-eosin and immunohistochemistry.




Source: Prepared by the authors of this study.

## Discussion

Sclerosing angiomatoid nodular transformation is a rare benign pathology with a slight female predominance that usually appears between 22 and 74 years of age (mean age: 50 years). They are asymptomatic lesions that usually appear as incidental findings on imaging studies.

These lesions are solitary masses that can measure from 0.9 to 17 centimeters. Radiologic features are non-specific, and histopathologic study is the gold standard for diagnosis. Macroscopically, they are well delimited non-encapsulated nodular lesions that present a central fibrous scar-like area, from which tracts radiate delimiting pseudo-nodules. The histological study is characterized by angiomatoid coalescing nodules composed of capillaries, venules, and sinusoids, divided by fibroconnective tracts. The internodular stroma consists of dense fibrous tissue with areas of myxoid appearance, scattered myofibroblasts, plasma cells, lymphocytes, and hemosiderophages.

Although the histologic image is distinctive, it is necessary to rule out more frequent pathologies. Immunohistochemistry is very useful, since these lesions have a distinctive immunophenotypic pattern characterized by CD34 (-) CD31 (+) CD8 (+) in the sinusoids, CD34 (+) CD31 (+) CD8 (-) in the capillaries and CD34 (-) CD31 (+) CD8 (-) in small veins. CD68 is positive in macrophages, and some cells are CD68 (+) and SMA (+) [8,9]. Some cases reported CD30 (+), others had Epstein-Barr virus expression by in situ hybridization (Epstein-B virus-encoded small RNA, EBER), and some were negative for both [10,11].

The proliferation rate with Ki67 is low (approximately less than 4%). The etiopathogenesis of proliferation seen in sclerosing angiomatoid nodular transformations may be related to the sclerosing lesions of IgG4 disease since fibroconnective stroma have increased IgG4-positive plasma cells. In our case, the number of IgG4 positive cells was one (measured by high magnification field), and the ratio of IgG4 positive cells to immunoglobulin positive cells was less than 0.4. Therefore, we considered that the lesion is not related to IgG4 disease. The negative marking for the Epstein-Barr virus by PCR would also exclude the association with this virus.

Lymphoid tumors are the most common spleen malignancies, while non-lymphoid tumors are scarcely reported [2,7] and generally of vascular origin. Although pre-surgical studies may suggest many diseases, once macroscopy and histology are reviewed, the lesions are usually diagnosed as hamartoma, conventional hemangioma, hemangioendothelioma, littoral cell angioma, and carcinoma metastases [7].

Within the nodules, endothelial lining cells are negative for D2-40, which confirms a vascular instead of a lymphatic origin. Cao et al. reviewed publications in English and found that 30 of 127 cases (23.6%) coexisted with other diseases, including idiopathic myelofibrosis, bile duct and pancreatic cancer, acute pyelonephritis, and malignant tumors [4]. The authors compared these findings with Martel's original report and concluded that patients with sclerosing angiomatoid nodular transformation have a relatively high prevalence of synchronicity with diseases in other organs. Therefore, clinicians and radiologists should not automatically assume a splenic lesion coexisting with a malignant neoplasm as tumor metastasis and should evaluate differentials such as sclerosing angiomatoid nodular transformation or other – more frequent – pathologies [1,4].

Splenectomy is curative, with no reported malignant transformation or recurrence cases to date. Some authors propose laparoscopic hemisplenectomy as the treatment of choice instead of open splenectomy. They suggest that the laparoscopic approach shortens hospitalization days, reduces medical expenses, has fewer wound complications, and offers better cosmetic results.

Although sclerosing angiomatoid nodular transformation has relatively specific imaging findings, the differential diagnosis with other benign or malignant splenic tumors is challenging.

This disease is only recently described in the literature (2004). Therefore, it is necessary to collect a more extensive series of cases and reevaluate differential diagnoses of previous cases to understand sclerosing angiomatoid nodular transformation better. As discussed by Agrawal et al. through their own two case reports and review of the literature (one of them associated with extensive extramedullary hematopoiesis), tumors with the characteristic morphology of sclerosing angiomatoid nodular transformation have been reported (at least) since 1978. Many were previously diagnosed as exuberant splenic granulation tissue, hamartomas, multinodular hemangiomas, or even inflammatory pseudotumors. The disease has been reported intermittently, but new cases with even newer associations appear from time to time.

In Ecuador, Fernandez and Lara published in 2018 a case of sclerosing angiomatoid nodular transformation in a 76-year-old patient with a spleen mass. A laparotomy with splenectomy confirmed the diagnosis by microscopy and immunohistochemistry (CD31+, CD34+), presenting similarly to our case [12].

A case of a 72-year-old male patient diagnosed by an ultrasound-guided puncture was also published. The pathologic study showed fibroblast proliferation, lymphocytes and plasma cells infiltration, and areas with small slit-like blood vessels. Immunohistochemistry revealed the presence of CD31 (+) and CD34 (+) cells in small blood vessels [13].

There are no known risk factors, except for the association with IgG4 and Epstein-Barr virus. In the title of a paper, it has been proposed whether sclerosing angiomatoid nodular transformation is *"A new entity or a new name?"* [14]. Perhaps this latter possibility is the most appropriate point of view.

## Conclusion

Sclerosing angiomatoid nodular transformation is a rare and benign pathology, usually diagnosed through incidental

findings. Physicians should keep it in mind in the differential diagnosis of spleen tumors.

## Notes

### Contributor roles

JBCL, LMTC, PCMS, AARC: clinical case data collection, conceptualization, writing-reviewing and editing of the draft and writing-reviewing and editing of the final article.

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### Competing interests

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### Ethics

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# Transformación nodular angiomatoide esclerosante del bazo: Reporte de caso


## Abstract

La transformación nodular angiomatoide esclerosante es una patología vascular benigna del bazo, desarrollada a partir de la pulpa roja, de etiología desconocida. Se postula que puede estar relacionada con la enfermedad por inmunoglobulina 4 y la infección por el virus de Epstein-Barr. La mayoría de los casos son asintomáticos, constituyendo hallazgos incidentales en estudios por imágenes. Presentamos el caso de un paciente masculino de 41 años con antecedentes de tiroidectomía por carcinoma papilar que consulta por fiebre. Recibió tratamiento sintomático y se realizó tomografía computarizada de abdomen por síntomas abdominales inespecíficos. La tomografía evidenció una imagen de aspecto sólido, con tenue realce periférico con el contraste que mide 62 por 52 por 51 milímetros en el polo inferior del bazo. Se realizó esplenectomía que midió 14 por 11 por 4 centímetros y pesó 284 gramos. Se identificó una formación nodular sólida, bien delimitada, con área central de aspecto fibroso, con tractos blanquecinos que delimitan áreas violáceas. La microscopía presentó nódulos coalescentes redondeados de aspecto angiomatoide, con proliferación vascular revestida por células endoteliales sin atipia, entremezclados con células ahusadas, infiltrado de linfocitos y macrófagos. El estroma entre los nódulos mostró proliferación miofibroblástica con linfocitos, plasmocitos y siderófagos. Inmunohistoquímica tuvo marcación positiva en los vasos para CD34 y CD31, sectores positivos para CD8 y negativos para CD34. Una célula positiva para inmunoglobulina 4 (IgG4) por campo de gran aumento. El estudio para Epstein-Barr por reacción en cadena de la polimerasa fue negativo. Para el diagnóstico los estudios de imagen son inespecíficos, por lo que la confirmación diagnóstica la da el estudio histopatológico. La esplenectomía es curativa sin casos reportados hasta la actualidad de transformación maligna o recidiva. No se conocen factores de riesgo y no se han comprobado factores desencadenantes, excepto la asociación de casos con IgG4 y virus de Ebstein-Barr. Por ser una entidad patológica recientemente descrita es necesario recopilar series grandes y revisar nuestros archivos, reevaluando algunos de sus diagnósticos diferenciales para lograr una mejor comprensión de la misma.