Case Report

Schistocytes, Echinocytes, Iron Deficiency Anemia, and Thrombocytopenia – Hematologic Manifestations of Splenic Angiosarcoma

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Abstract

Splenic angiosarcoma is a rare and aggressive malignancy with an incidence of less than one per million and a fatality rate over 90%. Early diagnosis is of great importance for optimal management. Here, we report the case of a patient with splenic angiosarcoma who presented with prominent schistocytes, echinocytes, thrombocytopenia, and iron deficiency anemia, which in combination with radiographic evidence of a splenic mass, raised the suspicion for angiosarcoma and resulted in a prompt surgical intervention with curative intent. Resolution of the hematologic findings following splenectomy suggests that patients with this malignancy should be monitored for recurrent hematologic abnormalities as they may herald recurrence of the disease. We present a literature review on the hematologic manifestations that is associated with this malignant disease.

Keywords: Anemia, angiosarcoma, echinocytes, schistocytes, splenic angiosarcoma

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Introduction

A splenic angiosarcoma arises from atypical vascular endothelium of the spleen as it forms large masses with solid sarcomatous and hemorrhagic cystic components.[1] Immunostaining with CD34, CD31, FVIIIRAg, and VEGFR3 illustrate the vascular component and histiocytic differentiation is also present.[1] The masses can become extremely large with a mean spleen weight of 1073g (normal spleen weight is 50–250 g); weights over 3200 g have been reported.[1] With this degree of massive splenomegaly, 32% of patients present with spontaneous splenic rupture which has an immediate mortality of 50% and a median short survival time of 4.4 months for those who survive the initial event.[2]

For those cases identified prior to splenic rupture, the outcomes remain grim as 80% of patients have metastatic disease at the time of presentation and the mean survival time ranges from 10.3–14.4 months.[2] As with other forms of angiosarcomas, splenic angiosarcoma has a propensity for early multifocal metastasis through hematogenous spread.[3] However, compared with other angiosarcomas, splenic angiosarcoma has an increased potential for bone marrow infiltration.[4] Splenectomy for localized disease appears to be the only cure. Adjuvant treatments of anthracyclines, taxanes, vinca alkaloids, vascular endothelial growth factor modulators, and antiangiogenic agents have been used, but most reserve chemotherapeutics for metastatic and inoperable disease.[5]

Here, we present a case of a localized splenic angiosarcoma, initially suspected based on multiple hematologic findings that characterize the disease in an appropriate clinical context. These abnormalities resolved following surgery, and may thus provide a low-risk and low-cost method of monitoring for disease recurrence.

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Case Report

The patient was a sixty-year-old male from Grenada with no significant past medical history who presented to the hospital after a witnessed seizure. Physical examination was notable for a mild pallor and splenomegaly 10 cm below the costophrenic margin. Computerized tomography (CT) showed a large mass in the spleen measuring 12 × 11 cm and a 4 cm pituitary mass (Figure 1). The splenic mass appeared as a heterogeneous solid mass with multiple cystic components and septal enhancements (Figure 1). His laboratory data demonstrated pancytopenia with a white blood cell count of 2.3 × 10^9/L, hemoglobin level of 7.1 g/dL, and a platelet count of 105 × 10^9/L. The peripheral blood smear was notable for at least five schistocytes per high power field, echinocytes, and target cells (Figure 2A). Because of symptomatic anemia, the patient was transfused in the emergency room. Further studies (after transfusion) revealed a mean corpuscular value (MCV) of 69 fL (normal 80–96), plasma iron level of 96 mcg/dL (normal 59–158), total iron-binding capacity (TIBC) of 299 mcg/dL (normal 112–346), percent iron saturation of 32%, ferritin of 77 ng/mL (normal 30–400), vitamin B12 level of 246 pg/mL (normal 211–946), and folate level of 7.0 ng/mL (normal 3–17.5). A direct Coombs test was negative, with lactate dehydrogenase of 298 units/L (normal 110–210), haptoglobin of 131 mg/dL (normal 36–195), reticulocyte count of 64 K/mcL (normal 28–150), and a reticulocyte percent of 1.4% (normal 0.59–2.8). A hemoglobin electrophoresis showed 98% hemoglobin A. He had normal coagulation studies and ADAMTS13 (a disintegrin and metallopro-

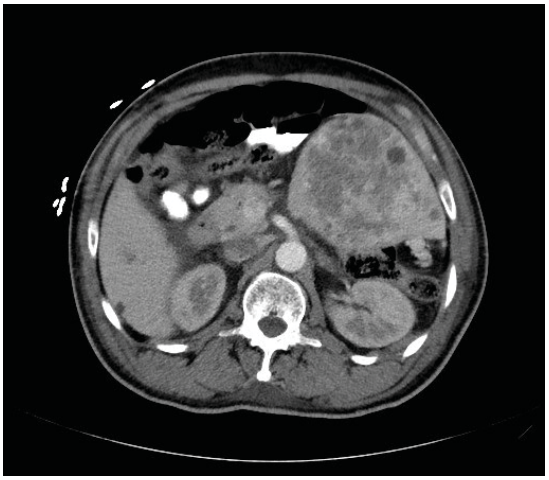

Figure 1. Computerized tomography of the abdomen showing replacement of the spleen by a heterogeneous solid mass with small cystic components and with peripheral and septal enhancements.

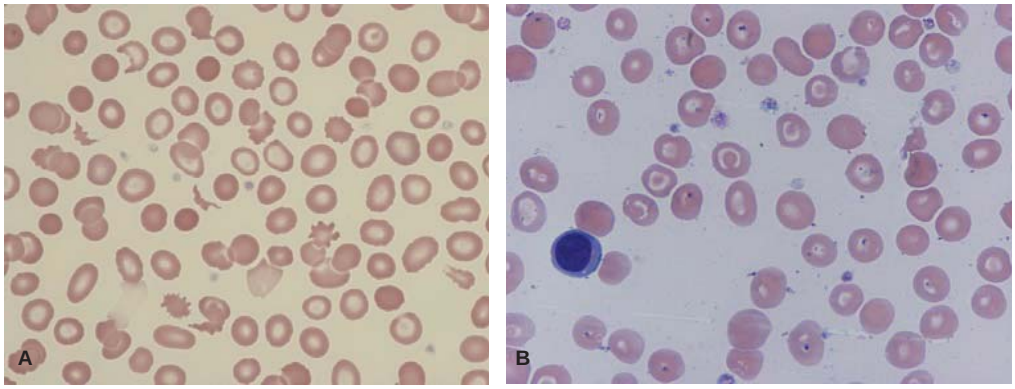

Figure 2. Peripheral smears before **(A)** and after **(B)** splenectomy. **A)** The smear shows frequent fragmented red blood cells including schistocytes and helmet cells. Several echinocytes are present. In addition, the red cells are microcytic and hypochromic, consistent with iron deficiency. **B)** The smear shows frequent target cells. The red cells are normocytic and normochromic. Fragmented red cells are not present.

teinase with a thrombospondin type 1 motif, member 13) profile.

Given the findings on the peripheral smear indicating microangiopathy and the absence of hemolysis and the presence of radiographic findings of the large splenic mass, angiosarcoma was highly suspected and it was recommended that the patient undergoes emergent splenectomy. The splenic mass pathology revealed a 12.9 cm and 739 gram well-circumscribed, hemorrhagic, and necrotic mass. Histologic examination demonstrated a cellular, spindle cell lesion that was positive for vascular endothelial markers, CD34 and CD31, supporting the diagnosis of angiosarcoma (Figures 3A, 3B, 3C, 3D). The splenic sinusoids showed significant red cell congestion (Figure 3B), likely as a consequence of neoplastic endothelial proliferation. Evaluation for metastatic disease was completed with CT of chest, abdomen, and pelvis, bone marrow biopsy, and bone scan. No metastatic disease was detected. The bone marrow biopsy showed normal trilineage hematopoiesis, 50% cellularity, 3:1 myeloid to erythroid ratio, and a CD31 stain did not show proliferating vessels. Given the history of seizures, the pituitary mass was partially removed and was compatible with adenoma.

By postoperative day 8 from the splenectomy, the patient's platelet count had increased to 211×10^9/L, and his hemoglobin to 8.8 g/dL. Subsequent peripheral smear demonstrated resolution of schistocytosis, a significant reduction in the number of spiculated red blood cells, and a concurrent increase in target cells (Figure 2B). Postsurgery, the patient developed bowel obstruction. Laboratory tests were repeated a few weeks later and showed an iron level of 15 mcg/dL, TIBC of 334mcg/dL, and ferritin of 53 ng/mL. He was started on iron replacements. Approximately fifteen months after surgery, the patient is alive with no radiographic evidence of malignancies and has returned to work. His most recent blood work revealed a hemoglobin of 10.7 g/dL, ferritin of 234 ng/mL, iron level of 88 mcg/dL, and an MCV of 74fL.

Discussion

Hemangiosarcomas are far more frequent in dogs than humans, accounting for 5%–7% of malignancies in the canine species, with common sites being splenic, atrial, and subcutaneous.[6] While the literature on the canine presentation of the disease focuses on hematologic manifestations of anemia with acanthocytes and schistocytes, there is little reported on significant red cell changes in humans.[7] Previous reports in humans have mentioned anemia, thrombocytopenia, leukopenia, and leukocytosis as hematologic manifestations.[1,2,8,9] However, there is little documentation in the literature of red cell changes, such as fragmentation, spiculation, formation of targets, and changes associated with iron deficiency.[2] This report highlights these changes to enhance our understanding of splenic angiosarcomas.

The development of a microangiopathic process in splenic angiosarcoma is a consequence of the irregular malignant endothelium; however, only 5% of cases are reported to have these

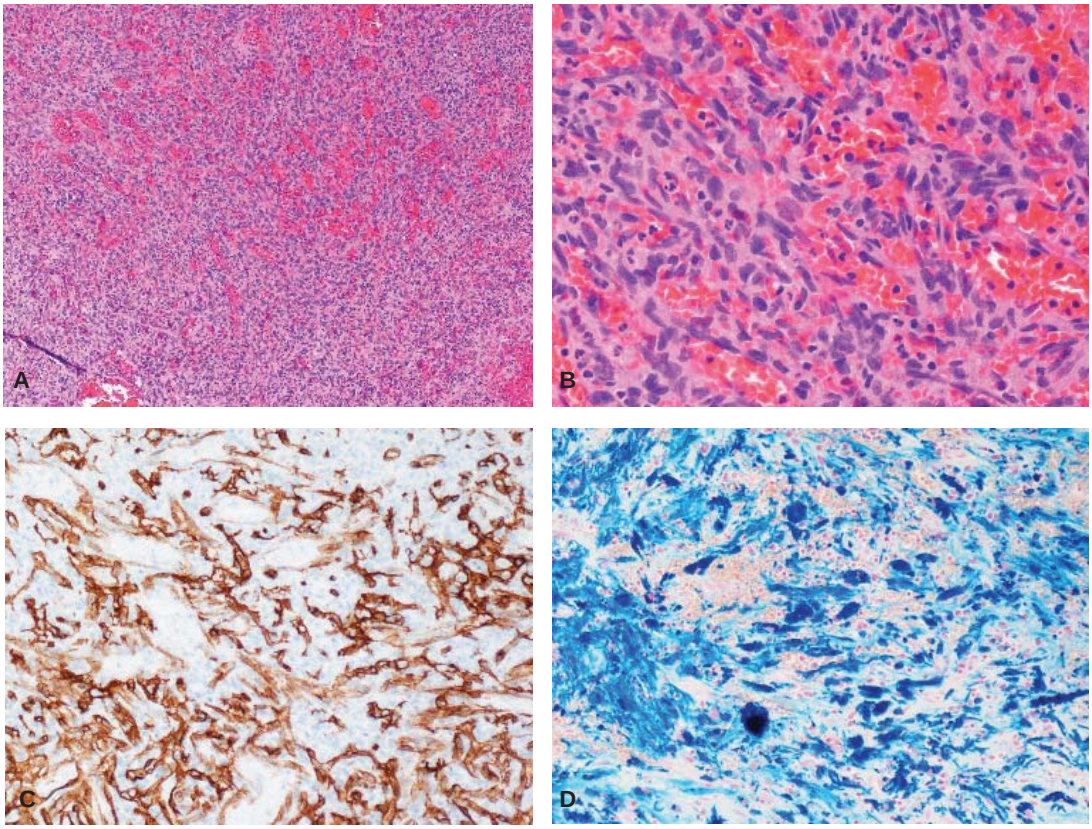

Figure 3. (A and B) H&E-stained sections of splenic angiosarcoma. Cellular and highly vascular spindle cell neoplasm with congestion and large atypical cells consistent with splenic angiosarcoma (A. low power 100x; B. high power 400x). **C)** Neoplastic cells demonstrate membrane staining with vascular endothelial marker CD34. **D)** Neoplastic cells with increased iron deposition.

findings.[2] It is not clear if the entity is truly not present or simply not looked for in most cases. In other entities, such as dysfunctional heart valves and malignant hypertension, it has been demonstrated that vascular damage causes fragmentation of red cells by two mechanisms. First, the shear forces along the irregular endothelium cause breakage of the red blood cell. Next, the shear forces also cause inflammation of vessel walls that generate fibrin strands that guillotine passing red cells. It is believed that a combination of these mechanisms as a result of the abnormal blood vessels associated with the splenic angiosarcoma is responsible for the schistocytes observed in this case.

Echinocytes, also known as burr cells, are red blood cells with uniformly spaced short spiculations. Echinocytes form in the presence of renal dysfunction, liver failure, vitamin E deficiency, pyruvate kinase deficiency, after exposure to 2-mercaptoethane sulfonate sodium (MESNA), 5-fluorouracil, and benzodiazepines and artifacts in smear preparation.[10] Echinocytes form due to lipoproteins and other plasma factors binding to the cell membrane causing conformational changes. Altomare et al. reported a case of a patient with a benign splenic hemangioma that had echinocytosis of 60% prior to splenectomy and resolution of echinocytosis after the procedure.[10] It was suggested that the changes may occur due to movement through the abnormal littoral cell endothelium, but the full mechanism has yet to be explained. Similar resolution of echinocytosis following the removal of the spleen was observed in this report.

The spleen removes excess cell membrane from red cells. Target cells form due to redundant cell membranes that culminate in increasing the surface area to volume ratio when the spleen is not removing the excess membrane. The splenectomized patient can have up to 10% target cells.[11] Our patient had initial target cells, perhaps due to the hypofunctioning spleen, and then had increases in target cells following splenectomy due to the complete absence of splenic tissue.

Anemia occurs in 46%–70% of patients with splenic angiosarcomas and is believed to be the result of chronic disease, splenic sequestration, and myelophthisis.[1,2,5] While most patients with splenic angiosarcoma have a normocytic anemia, multiple reports of microcytic anemia with iron deficiency in the blood and marrow but excess iron in the splenic tissue have been reported.[5,12] Persistent microcytosis with near normal hemoglobin and normal hemoglobin electrophoresis in a patient originally from Grenada, suggest the diagnosis of asymptomatic alpha-thalassemia.

Thrombocytopenia was seen in four of the 28 cases studied by Neuhauser et al.,[1] but has been as high as 33%–40% in other series.[8,13] Hemangiomas that present with thrombocytopenia, anemia, and coagulopathy can be classified as Kasabach-Merritt syndrome and the thrombocytopenia is believed to be due to peripheral destruction.[10] Splenic angiosarcomas likely have a similar mechanism as well as a component of distributional thrombocytopenia from sequestration due to the massive splenomegaly. Given the normal coagulation studies, normal ADAMTS13, and lack of hemolysis, disseminated intravascular coagulation (DIC) and thrombotic thrombocytopenic purpura (TTP) were ruled out.

In summary, the hematologic manifestations of a splenic angiosarcoma can be diverse. While anemia and thrombocytopenia are well documented, red blood cell changes of echinocytosis, fragmentation, and target cell production are possible. These hemato-

logic findings along with radiographic changes resulted in early diagnosis and a prompt splenectomy in this patient. Surveillance for hematologic abnormalities is ongoing to assist in early detection of relapse.

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