

Early detection and integral resection are keys to extend survival in patients suffered from primary angiosarcoma of the spleen

A care-compliant case report and literature review

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Abstract

Rationale: Primary angiosarcoma of the spleen (PAS) is a very rare malignant neoplasm that originates from endothelial cells of the splenic blood vessels. Without typical clinical presentations and specific radiological features, PAS is very difficult to be early identified and 1-year mortality is extremely high. Late detection and spleen rupture are considered as the most important risk factors for early metastasis.

Patient concerns: Without any obvious symptom, a 35-year-old woman was admitted with splenic neoplasm that was accidentally discovered through a routine physical examination.

Diagnoses: The patient was first diagnosed as lymphoma by laboratory tests and imaging studies, but changed to PAS by histological examinations after the surgery.

Interventions: After careful preoperational assessment, a laparoscopic-assisted splenectomy was scrutinously performed and the entire spleen was removed without any rupture.

Outcomes: The postoperative followed-up was uneventful until 3 years later, when she sought medical attention due to persisting back pain. Bone metastasis was consequently identified and the symptom was quickly alleviated after radiation therapy. However, intra-abdominal metastases leading to intestinal obstruction occurred 4.5 years after surgery. Following short palliative treatment, the patient passed away 4 years and 9 months after the operation due to multiple organ failure.

Lessons: PAS is an uncommon and aggressive splenic disease. Once suspected, PAS require prompt and precise surgical procedures to remove the tumor origin. Laparoscopic-assisted splenectomy was technically feasible and therapeutically harmless for PAS treatment compared with open surgery as long as the spleen was removed intact. However, more evaluation of this option will be needed due to limited experience by now. Early discovery, precautionous plan, meticulous operation, close follow-up, and comprehensive treatment may significantly prolong the living period of this fatal disease.

Abbreviations: AFP = α -fetoprotein, CA = carcinoma antigen, CEA = carcinoembryonic antigen, CT = computed tomography, MRI = magnetic resonance imaging, PAS = primary angiosarcoma of the spleen, PET = positron emission tomography, SMA = smooth muscle actin, US = ultrasound sonography.

Keywords: early detection, follow-up, integral resection, laparoscopic- assisted splenectomy, primary angiosarcoma of the spleen

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1. Introduction

Primary angiosarcoma of the spleen (PAS) is an extremely rare and aggressive malignant neoplasm arising from splenic vascular endothelium, with a total of approximately 200 cases presented in relevant literatures.^[1-4] First reported by Langhans in 1879,^[1] the incidence is only 0.14 to 0.25 cases per million population.^[2,3] The mean age at presentation is 59 years with a range between 14 months and 89 years.^[2-4] Histologically, mesenchymal-derived elongated endothelial cells lining the spleen's spongy network of sinusoids is the most common finding. The differential diagnosis should include lymphoma, metastatic tumors, and other splenic vascular lesions such as hemangioma.^[5]

PAS is very aggressive as most patients died within 1 year after the treatment, regardless which approach was applied. Late diagnosis and spleen rupture are considered as the most significant risk factors for poor prognosis. We herein present a PAS of a 35-year-old woman who was early identified by routine physical examination and received a laparoscopic-assisted

splenectomy, and lived relatively longer (4 years and 9 months) than most other patients. Relevant literatures on this rare entity are also reviewed.

2. Case presentation

A 35-year-old woman was hospitalized with splenic tumor after a routine physical examination. Her appetite was normal and she had no history of abdominal pain, distension, or dyspnea. There was no pertinent medical or surgical history. On examination, she was well nourished with stable vital signs, and showed no pallor or any significant lymphadenopathy. Abdominal examination revealed enlarged spleen, which reached 4 cm under left costal arch by palpation, without tenderness.

Laboratory investigation was unremarkable including hematological findings, serum electrolyte levels, liver function markers, and urine and stool examination results. Serum levels of tumor-associated antigen including carcinoembryonic antigen, α -feto-protein, and carcinoma antigen (CA)19-9 were within normal range, while CA125 was increased to 67.22 U/mL (0–35 U/mL). Serum α 1-globulin protein was measured as 5.2% (normal range 1.7–4.1) by electrophoresis. Multiple nodules sized in 2 to 5 cm were shown in the spleen by both abdominal ultrasound sonography and contrast-enhance abdominal computed tomography (CT). The density of these nodules was highly increased on the arterial phase (Fig. 1). No evidences of lymphadenopathy in the abdominal cavity were noted. No abnormal findings were detected by chest x-ray photography.

With a preoperative diagnosis of spleen lymphoma, the patient was referred for surgical consultation and laparoscopic-assisted splenectomy was subsequently performed. During operation, several nodules were found within the spleen, located in the upper area of the splenic body. Intra-abdominal cavity was explored thoroughly and neither metastases nor direct invasion to the other organs was identified. In a sequential order, the spleen–stomach, spleen–colon, spleen–kidney, and spleen–diaphragm

ligaments were dissected with ultrasound shears. After a 10-cm incision was made in the left costal margin, the splenic artery and vein were all ligated, and then the entire spleen was excised intact. During the whole procedure, extensive care was taken not to injure the splenic capsule and neighboring pancreatic parenchyma.

The removed spleen was checked by both macroscopic and microscopic approaches. On gross examination, the spleen was measured as $14 \times 7 \times 5$ cm in size and an intact external surface was maintained. The specimen was then cut into slices with 1-cm thickness, and multiple nodules with variable sizes were identified in the spleen. The largest node was measured to be 6.0 cm in the maximum dimension, with grayish yellow color (Fig. 2). Under microscope, a cavernous vasoformative pattern was shown in the splenic nodules, which were lined by neoplastic endothelial cells. A “2-tube” pattern was also observed in some areas. In addition, diffusive proliferation of atypical cells with an epithelioid appearance and slit-like vascular spaces were observed in the solid component. Immunohistochemically, the tumor cells show strong cytoplasmic positivity for the endothelial markers including CD31, CD34, Vimentin, CD68, and smooth muscle actin. In contrast, they were negative for cytokeratins, factor VIII-related antigen, and S-100 (Fig. 3).

Postoperative follow-ups were routinely carried out. The patient was well until 3 years after surgery, when she suffered back pain and was diagnosed with bone metastasis by emission computed tomography examinations. After radiation therapy, the symptoms were quickly alleviated. Four and a half years after surgery, symptoms of intestinal obstruction occurred and abdominal cavity metastases were confirmed by the CT scan (Fig. 4). Long tube intestinal drainage was applied and the patient was discharged once the symptoms were improved. Unfortunately, the patient passed away 3 months later due to multiple organ failure. Compared with other patients with an average 1 year of survival time, this patient lived relatively longer after the treatments.

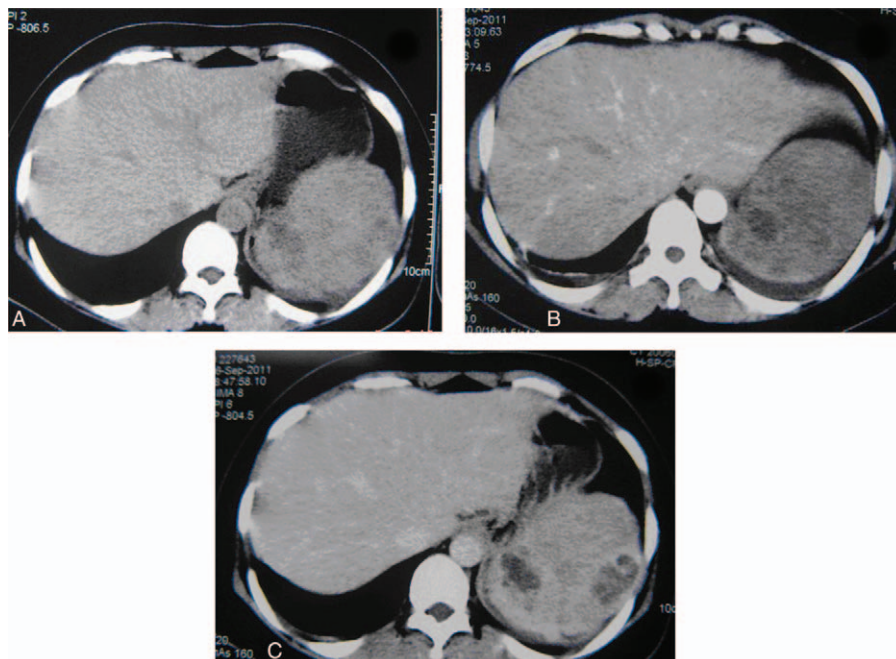


Figure 1. (A) Plain CT scan showing multiple low-density nodules in the spleen. (B) CT scan (contrast-enhance arterial phase) showing peripheral enhancement around the nodules. (C) CT scan (portal venous phase) still showing peripheral enhancement. CT = computed tomography.



Figure 2. Macroscopic view of remove spleen. The capsule of the spleen is intact and multiple nodules can be seen bulging out of the surface. After splitting along the long axis, the largest node in the spleen was measured to be 6.0cm in the maximum dimension with grayish yellow color.

3. Discussion

It is still unclear about the pathogenesis of PAS. There were few cases reported after receiving radiation therapy for other malignancies such as breast cancer and ovarian cancer.^[6] However, there is no clear relationship of the PAS with exposure to radiation, chemotherapy, and other toxic substances as seen in hepatic angiosarcomas.^[7] There are some hypotheses that PAS may transform from other benign splenic tumors, such as hemangiomas, lymphangiomas, and hemangioendotheliomas^[2,3,8-10] According

to the literature, this tumor has a high incidence of early metastasis rates of 69% to 100%,^[2] with the most common sites being the liver, lungs, bones or bone marrow, lymph nodes, gastrointestinal tract, brain, and adrenal glands. Furthermore, there are some reports of synchronous PAS combined with malignancies of the breast, colon, odontogenic myxofibroma of the temporomandibular joint,^[11] skin, and kidney.

The clinical manifestations of PAS range from asymptomatic to splenic rupture which leads to lethal hemorrhage. There are no specific presentations for this rare entity. Upper abdominal

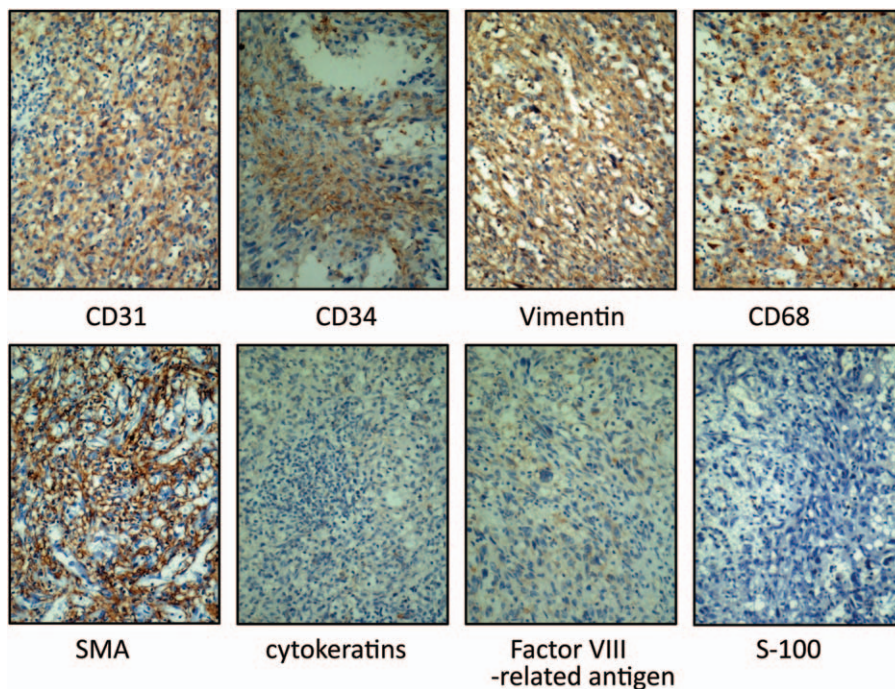


Figure 3. Tumor cells showing positive immunohistochemistry staining for CD31, CD34, Vimentin, CD68, SMA, but negative for cytokeratins, Factor VIII-related antigen, and S-100 (magnification $\times 20$). SMA=smooth muscle actin.

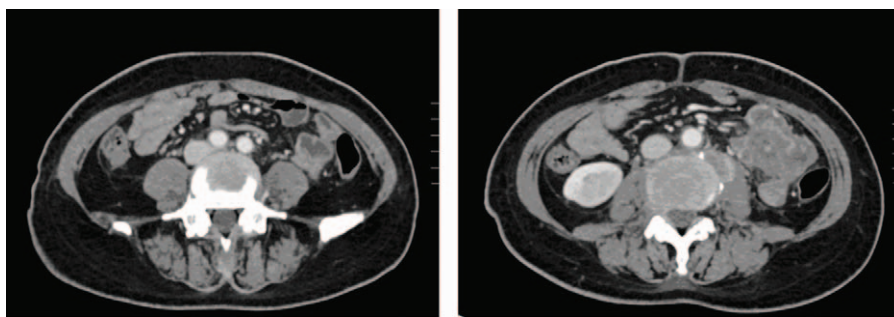


Figure 4. CT scan revealing vertebral body damage (left) and intrabdominal metastatic tumors (right), at 4.5 years after the initial surgery.

discomfort is the predominant presenting symptom in >80% of cases. Fever, fatigue, and weight loss have also been observed, but these initial symptoms constitute <10% of the cases.^[2,3,12,13] Splenic rupture, however, was reported in 13% to 32% of all cases, and is the most serious complication, usually leading to fatal hemoperitoneum.

Upon physical examination, splenomegaly is frequent (in 68% of cases)^[3] and hepatomegaly is also common. By palpation, a mass often can be identified in left hypochondrium. These patients usually have normal bowel sounds by auscultation.

Anemia is the most common (70%) laboratory abnormality in PAS patients. Other abnormal laboratory findings include cytopenia (91%), leukocytosis (20%), thrombocytopenia (10%–40%), and elevated erythrocyte sedimentation rate (15%), respectively.^[2–4] Laboratory examinations in our case showed normal values of hemoglobin, total white blood cell, and platelets, but slightly increased α 1-globulin and almost doubled CA125, which are not reported by others.

It is very difficult to confirm the diagnosis of PAS just relying on the imaging studies. No specific radiological characteristics are valuable to differentiate PAS from other benign or malignant splenic tumors. In common, splenomegaly can be found by ultrasound, CT, and magnetic resonance imaging. Inside of the enlarged spleen, either hypoattenuating or hyperattenuating nodules may be found on CT plain scans. These splenic nodules can be heterogeneously enhanced after injecting contrast material, such as observed in our case. Massive splenic calcifications is not a specific sign of PAS as it may also be found on benign lesions such as a hemangioma.^[14] Therefore, significance of calcification is controversial in the diagnosis of splenic angiosarcoma.^[15,16] ¹⁸F-2-fluoro-2-deoxy-D-glucose (¹⁸FDG) positron emission tomography (PET) provides a means of diagnosing cancer based on altered metabolism in malignant tissues. ¹⁸F-FDG PET-CT scans may usually reveal an abnormal uptake in the splenic angiosarcoma, the SUVmax value of which may be >6.0.^[11]

Biopsy is contraindicated in the PAS due to high risk of rupture, and diagnosis can be only made by histopathologic examinations after splenectomy. Macroscopically, hemorrhage and necrosis are frequently seen within PAS. A diffuse pattern of involvement and replacement of the entire splenic parenchyma with neoplasm are frequently observed while solitary mass is less common.^[2,3] The microscopic appearance of angiosarcoma may be quite variable. These neoplasms show a focal or diffuse cavernous vasoformative component, which are lined by atypical endothelial cells, exhibiting solid sarcomatous, papillary, and epitheloid growth patterns. Immunoprofiles often aid to confirm

the histological diagnosis. Immunohistochemical studies typically demonstrate positive for at least 2 endothelial markers (CD34, FVIIIIRAg, VEGFR3, or CD31) and 1 histiocytic marker (CD68 or lysozyme).^[3] Expression of these markers confirms the endothelial phenotype of this malignant vascular tumor.

PAS has a very poor prognosis. It is usually treated with open splenectomy, although it is rarely curative due to its aggressive nature and high metastatic occurrence.^[2,3] Neuhauser et al^[3] reported a study about PAS, in which 28 patients with PAS were analyzed. Only 2 patients were alive at last follow-up, 1 was lost to follow-up, and the other 25 died of disseminated disease. The longest duration of survival in a patient with PAS is 16 years in a pediatric patient who was treated with splenectomy alone at 7 years of age.^[9] There is no evidence that chemotherapy has any benefit in the treatment of PAS.^[3] In our case, the patient has no obvious symptoms and the splenic tumor was accidentally found by routine medical examination, indicating that she might be in the early phase of pathological development. Laparoscopic-assisted splenectomy was performed after careful preoperational assessment. The entire spleen was removed without any rupture, eliminating the risk of surgical metastasis. The patient lived well through the first 3 years after the surgery, proving that this procedure is technically possible and not detrimental to the survival. However, further data would be required to define the outcomes of patients treated this way.

4. Conclusion

PAS is a rare and aggressive neoplasm that is difficult to be early discovered and precisely diagnosed. Its pathogenesis remains unclear, and its clinical and radiological diagnoses are challenging. Although rare, the possibility of hemangiosarcoma should be taken into consideration when assessing for splenic tumors. Laparoscopic-assisted splenectomy can be chosen to reduce the surgical injury if the splenic integrity was ensured. Early detection and precise treatment might be the keys to expect a relatively longer duration for this aggressive disease.

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