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Case report

Primary angiosarcoma of the spleen, a rare indication for splenectomy: a case report

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ABSTRACT

Introduction and importance: Primary angiosarcoma of the spleen is a rare condition with a nonspecific clinical presentation and is associated with a poor prognosis. We describe two patients with primary splenic angiosarcoma successfully treated with splenectomy and adjuvant chemotherapy.

Case presentations: Case 1: A 50-year-old female presented with fatigue and left-sided rib, shoulder, and abdominal pain. A CT scan demonstrated a large splenic mass, and biopsy was diagnostic of angiosarcoma. An open en bloc resection of the spleen was performed, and pathologic examination confirmed high-grade angiosarcoma; the surgical margins were negative. The patient received pegylated liposomal doxorubicin (PLD) and ifosfamide; she demonstrated no evidence of recurrence with four years of follow-up. Case 2: A 70-year-old male presented with acute back pain. A CT scan demonstrated a splenic mass; biopsy was diagnostic of angiosarcoma. The patient underwent open splenectomy, and pathology revealed high-grade angiosarcoma; the surgical margins were positive. The patient received PLD and ifosfamide but presented three years later with metastatic tumor to the spine. The patient had a favorable tumor response to pembrolizumab. The patient's tumor burden remains stable at 5 years following splenectomy.

Clinical discussion: Angiosarcoma of the spleen is a rare clinical entity and is often challenging to diagnose early. Moratality is high, especially in the case of metastasis or spontaneous rupture.

Conclusion: Due to the rare nature of this tumor, optimal treatment is not known. Here, we show excellent response in two patients to surgery combined with adjuvant therapy.

1. Introduction

Primary splenic tumors are rare, with an overall lifetime incidence of 0.1% [1]. Metastasis of other tumors to the spleen is also rare but can occur with breast, lung, ovary, and colon cancers as well as with melanoma. Primary tumors of the spleen are categorized as benign or malignant. Benign primary tumors include hemangioma, littoral cell angioma, lymphangioma, and hamartoma; these tumors are frequently asymptomatic and are most often discovered incidentally [1,2]. When symptomatic, benign splenic tumors may present with early satiety, abdominal pain, or anemia [2].

Primary malignant tumors of the spleen are exceedingly rare. The annual incidence of primary splenic angiosarcoma is approximately one case per four million persons and is often challenging to diagnose early [3,4]. It is usually diagnosed in the sixth or seventh decade of life, [3] and presenting symptoms may include fatigue, weight loss, and left-sided abdominal or chest pain. Bleeding secondary to gastric involvement has also been reported [4]. Splenic angiosarcoma may rupture in up to 30% of patients and is associated with a poor prognosis and high mortality, especially when metastasis is present [5]. Due to the rarity of this malignancy, the optimal treatment of angiosarcoma of the spleen remains under investigation. Initial treatment frequently involves

Abbreviations: CT, computed tomography; ERG, ETS-related gene; FVIIIAg, factor VIII-related antigen; PLD, pegylated liposomal doxorubicin.

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surgical resection; however, survival after surgery remains low, especially in the setting of possible metastases that may be undetected at the time of surgery. The role of adjuvant chemotherapy is unknown. We describe two patients who presented with primary splenic angiosarcoma to our academic medical center, and both had excellent long-term survival. These two cases add to the existing literature regarding this rare entity because of the patients' favorable outcomes; they are reported in accordance with SCARE criteria and PROCESS guidelines [6,7].

2. Case presentations

2.1. Patient 1

A 50-year-old healthy woman, with a negative medical history for serious illness, presented to an outpatient clinic with fatigue associated with chronic left-sided rib, shoulder, and abdominal pain. She had a history of *H. pylori*-associated gastric ulcers and a total abdominal hysterectomy with bilateral salpingo-oophorectomy at age 30 for a benign indication. The patient reported a history of cigarette smoking for 10 years but quit smoking 15 years prior to diagnosis. She had no significant family history. Physical exam failed to reveal abnormal findings. Laboratory evaluation was significant for an elevated C-reactive protein at 175 mg/L (normal range: 0.0–8.0 mg/L). White blood cell count was 8.4×10^9/L (normal range: 4.0–11.0 $\times$ 10^9/L) and hemoglobin 110 g/L (normal range: 117–157 g/L). Her presenting symptoms were initially considered to be musculoskeletal in nature due to overuse, and the patient completed a 5-day course of prednisone, which temporarily relieved her rib and shoulder pain. However, the patient's left-sided abdominal pain persisted, and she developed early satiety. An abdominal CT scan demonstrated a large splenic mass (Fig. 1). A percutaneous core needle biopsy was diagnostic for a high-grade angiosarcoma. Immunohistochemical staining was positive for ETS-related gene (ERG), Factor VIII-related antigen (FVIIIAg), and CD31, with focal positivity for CD34. Nonspecific staining for CD61 and CD117 was also present.

The patient was scheduled for a laparoscopic splenectomy, which was converted to open surgery due to dense adhesions in the area of the stomach, liver, diaphragm, and omentum. The short gastric vessels and the splenic artery were ligated and divided prior to the full mobilization of the spleen. Controlling the splenic artery early during the surgical procedure was performed to reduce intraoperative hemorrhage and potential spread of the tumor. The spleen and adherent tissues were removed *en bloc* and a staging lymph node dissection was performed. Despite the dense adhesions, pathologic examination revealed a 19.6 cm pseudo-encapsulated angiosarcoma with negative surgical margins and no local tissue invasion. Gross cross-sectional examination of the splenic tumor revealed a variegated, tan-yellow and red cut surface with a necrotic center. Microscopic findings were consistent with high-grade angiosarcoma (Fig. 2). Four retrogastric lymph nodes were negative for malignancy. The patient's postoperative course was uncomplicated, and she was discharged home on hospital day seven. The patient completed fur cycles of pegylated liposomal doxorubicin (PLD) and ifosfamide followed by eight cycles of PLD [8]. The patient has had no evidence of tumor recurrence at four years after surgical resection.

2.2. Patient 2

A 70-year-old man presented to the emergency department with a one-day history of acute back pain with no other accompanying symptoms. His family history was non-contributory, and he had no significant past medical history. He did not use alcohol, tobacco, or illicit drugs. Physical exam failed to reveal abnormal findings. Laboratory evaluation demonstrated a white blood cell count of 8.5×10^9/L (normal range: 4.0–11.0 $\times$ 10^9/L) and a hemoglobin of 117 g/L (normal range: 133–171 g/L). An abdominal CT scan demonstrated a large, highly irregular splenic mass (Fig. 3). A percutaneous core needle biopsy was diagnostic for a high-grade angiosarcoma. Histologic examination demonstrated a vascular tumor composed of anastomosing vascular channels lined by atypical hyperchromatic cells. Immunohistochemical staining was positive for CD31 and CD34 but was negative for pankeratin, CD21, and CD68 (Fig. 4). Analysis by flow cytometry excluded a diagnosis of lymphoma.

Open splenectomy was performed using a left subcostal incision. Inflammatory omental adhesions to the left hemidiaphragm and the abdominal wall were taken down with electrocautery. A large, organized hematoma was evacuated from the space between the omental adhesions and the lower pole of the spleen. The spleen was mobilized

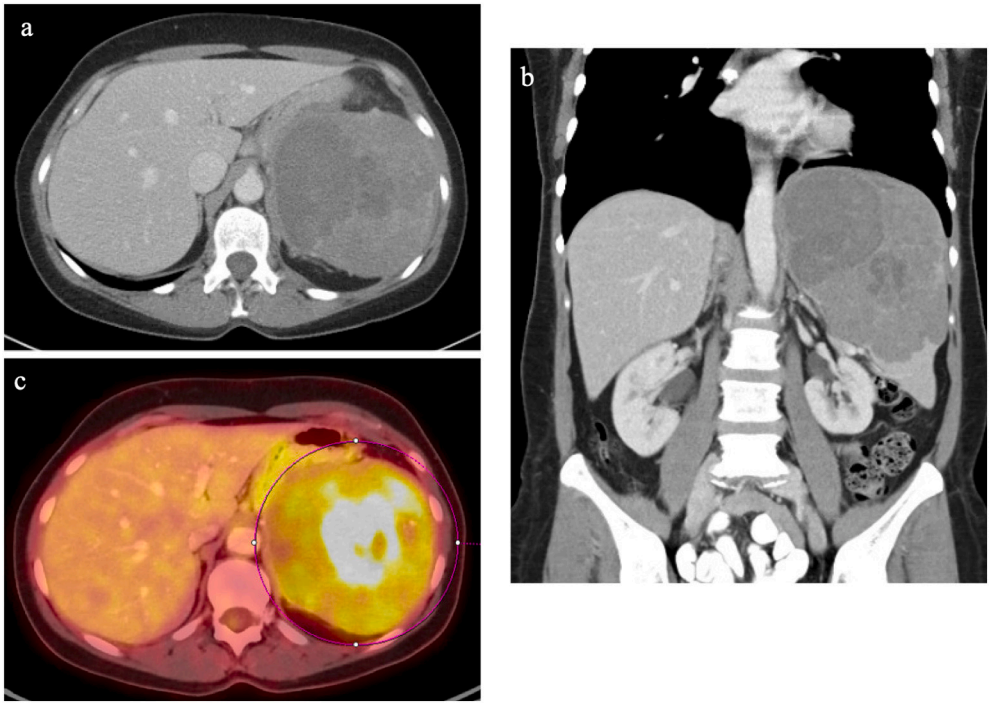

Fig. 1. Radiographic images from Case 1.
a, b) Transverse and coronal sections from a CT of the abdomen and pelvis demonstrating a low-density mass in the spleen that measures 14.6 $\times$ 11.0 $\times$ 11.2 cm. The lesion involves the majority of the spleen sparing the inferior tip. More superiorly there is an 8 cm rounded area of slightly decreased density that could represent an area of necrosis or fluid.
c) Fluorodeoxyglucose (FDG) positron emission tomography (PET) scan reveals a large heterogenous mass in the spleen. There is necrosis in the medial aspect of the lesion and the solid portion demonstrate a maximum standardized uptake value (SUV) of 8.0.

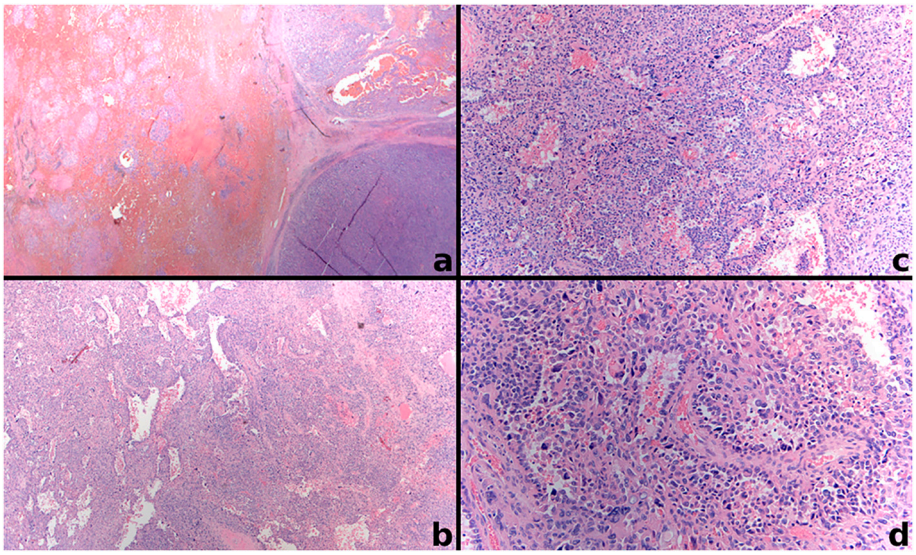

Fig. 2. Pathologic images from Case 1.
a) Low power (4× objective H&E) demonstrating congested spleen on left and cellular blue, nodular area on right representing tumor.
b) Low power (4× objective H&E) of tumor represented sheets of cells with intervening dilated vascular spaces containing blood.
c–d) High power (10× and 20× objective) demonstrates sheet-like as well as vasoformative growth of pleomorphic, hyper chromatic, malignant endothelial cells.

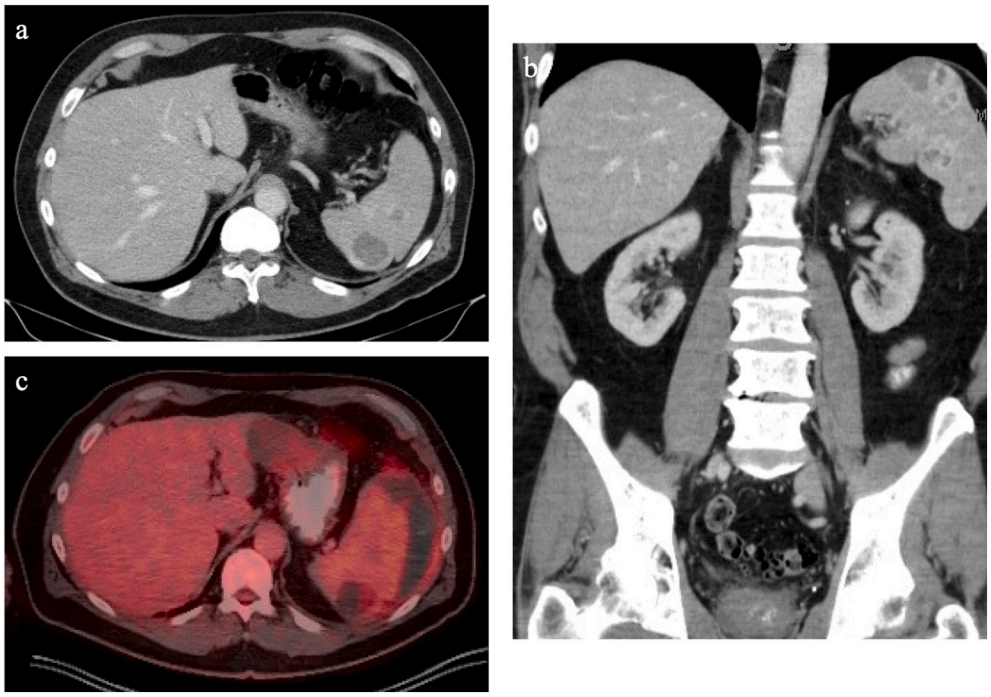

Fig. 3. Radiographic images from Case 2.
a, b) Transverse and coronal sections from CT of the abdomen and pelvis demonstrating multiple rim-enhancing lesions seen throughout the spleen, measuring up to 5 cm in size.
c) PET scan reveals multiple non- FDG avid, low-density masses throughout the spleen. There is an iatrogenic perisplenic hematoma (from CT-guided biopsy).

from the colonic and diaphragmatic attachments; the short gastric vessels and the hilum were ligated and divided. Open splenectomy was completed without complication and a port-a-cath access device was secured in the subcutaneous tissue of the upper chest.

A gross cross-section of the tumor revealed a necrotic tumor with variegated, tan-yellow, and dark red hemorrhagic areas. The tumor was 7.5 cm in greatest dimension and demonstrated replacement of the splenic parenchyma with extracapsular involvement of the perisplenic tissue. Microscopic features were consistent with high-grade angiosarcoma (Fig. 4). An ectopic spleen was identified, which also contained high-grade angiosarcoma. Although surgical margins were positive, three hilar splenic lymph nodes were negative.

The patient completed six cycles of PLD and ifosfamide followed by six cycles of PLD. Three years following splenectomy, multiple deposits of metastatic angiosarcoma were identified in the spine (Fig. 5a). The patient demonstrated a durable tumor response to pembrolizumab (Fig. 5b); the patient received 35 infusions of pembrolizumab over the course of two years. The metastatic disease to the spine has remained stable and the patient demonstrates no disease progression at five years after surgical resection.

3. Discussion

All primary splenic tumors are rare [1]; although benign splenic tumors are more common, several malignant splenic tumors, including angiosarcoma carry a high mortality rate unless diagnosed and treated early (Table 1) [5]. Patients with angiosarcoma of the spleen often present with nonspecific symptoms, making it difficult to detect the disease early [3]. Acute or subacute symptoms such as fever, fatigue, weight loss, upper abdominal pain, left flank pain, or chest wall pain usually prompt imaging studies.

Laboratory evaluation may reveal anemia, leukocytosis, or

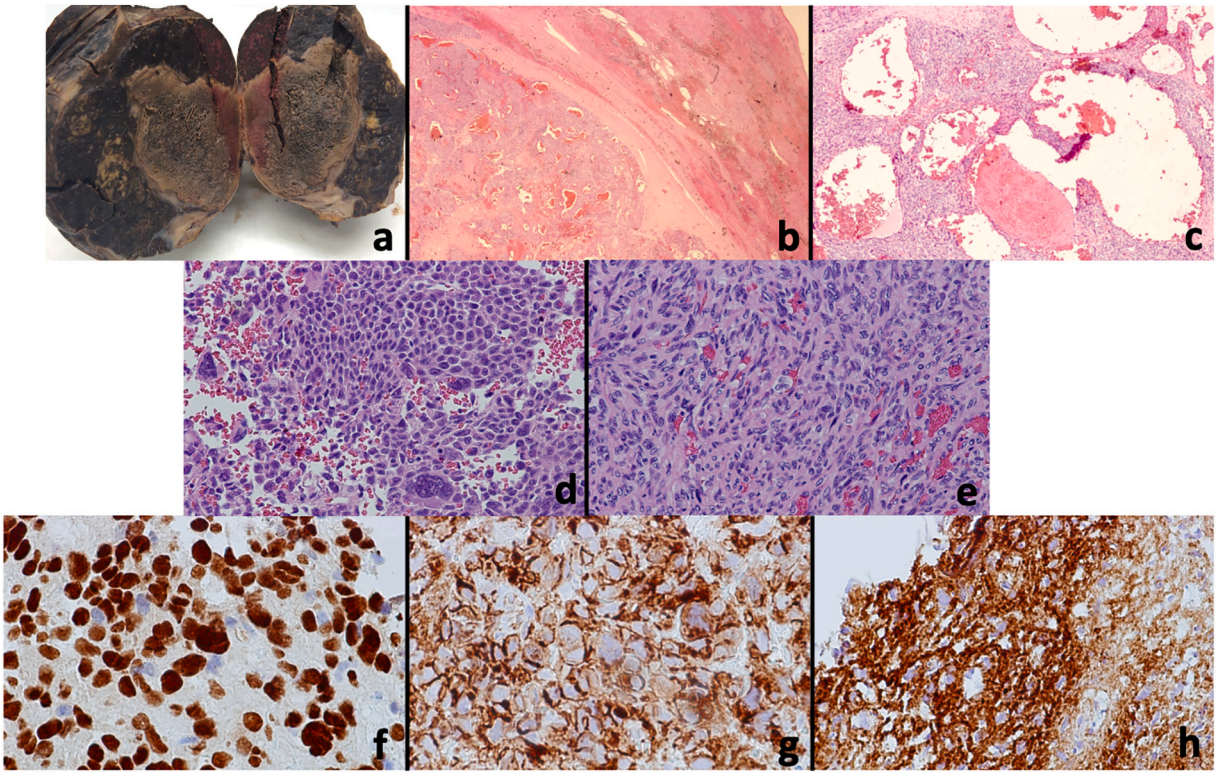

Fig. 4. Images from Case 2.
a) Post-fixation gross splenectomy specimen.
b) Low power (1× objective, H&E) magnification of spleen (right) demonstrating chronic congestive changes including hemorrhage with hemosiderin deposition as well as artefactual reduction in white pulp due to compression from angiosarcoma (left).
c) Low power (4× objective, H&E) magnification of anastomosing vascular channels lined by large epithelioid tumor cells. At higher (20× objective, H&E) magnification, high grade epithelioid cells with severe cytologic atypia (d), and small scattered foci of spindled cells are seen (e). f–h) Immunohistochemistry. Tumor cells are diffusely and strongly positive for the vascular endothelium marker and nuclear stain ERG (f), cytoplasmic staining for Factor VIII-related antigen (g), and membranous staining with CD31 (h).

thrombocytopenia [4]. CT imaging most often demonstrates a hypodense mass, which may be either homogeneous or heterogeneous [9]. In rare patients, angiosarcoma of the spleen may be misinterpreted as a suprarenal mass [9]. Ultrasound examination can also be informative, demonstrating nodularity, splenomegaly, or vascular filling defects [10]. Occasionally, splenic angiosarcomas are discovered as "incidental findings" on CT scans obtained for indications unrelated to the splenic tumor [3].

Pathologic examination of tissue is essential in the diagnosis of splenic angiosarcomas. Performing percutaneous biopsy of a potentially malignant lesion remains controversial due the possibility of tumor seeding of the needle tract; however, needle tract seeding has been reported in the literature as less than 1% of patients in whom biopsies have been obtained. This outcome is true for tumors located in the extremities, in the peritoneal cavity, or in the retroperitoneum [11]. Percutaneous biopsy of the spleen has been shown to be a safe and effective technique to obtain accurate diagnoses, including for the diagnosis of splenic tumors, which are most commonly lymphomas [12]. Concern regarding percutaneous core needle biopsies of vascular tumors is relevant, as one of our patients developed a splenic hematoma; however, the patient remained stable, and the hematoma was evacuated without further complication during the tumor resection. Because of the potential benefits of obtaining a tissue diagnosis, percutaneous core needle biopsies were obtained for both patients in this report. On histologic examination, angiosarcomas demonstrate anastomosing irregular vascular channels lined by malignant endothelial cells. The tumor architecture may be solid or papillary with a high grade epithelioid or spindled cells lining vascular channels. High mitotic rates and tumor necrosis are typically present. Vascular differentiation is poor in some cases, and immunohistochemical studies may be required to confirm angiosarcoma as the diagnosis. Immunohistochemistry usually demonstrates positive staining for vascular markers including ERG, FLI1, CD31, CD34, FVIIIAg, and VEGFR3. Additional markers include CD68, lysozyme, and high Ki-67 [3]. Substantial overlap exists for these markers and other tumor types, including littoral cell angioma and lymphangioma [13]. Correlation with routine histologic morphology is critical.

Patients with angiosarcoma of the spleen should undergo early splenectomy whenever possible to avoid splenic rupture [9,14]. Adjuvant therapy may include both radiation and chemotherapy. Systemic chemotherapy regimens have not been standardized due to the rare nature of this tumor. Regimens may include doxorubicin, ifosfamide, paclitaxel, gemcitabine, or docetaxel [15–19]. It is not known if primary splenic angiosarcomas respond to pegylated-liposomal doxorubicin (PLD) and paclitaxel with the same efficacy as is seen in angiosarcomas of other sites [8,17]. Both of our patients received chemotherapy regimens that included ifosfamide and PLD, suggesting the feasibility and effectiveness of this particular regimen. The response of the patient to pembrolizumab in Case 2 demonstrates that immunotherapy may also be useful, especially for metastatic disease. The role of splenectomy in patients who present with widely disseminated disease has not been established [15].

Despite surgical intervention and adjuvant radiation and chemotherapy, the prognosis for patients with angiosarcoma remains poor [5,10]. Retrospective studies have reported 30-month mortality rates up to 93% [3,4]. A majority of patients with angiosarcoma of the spleen die

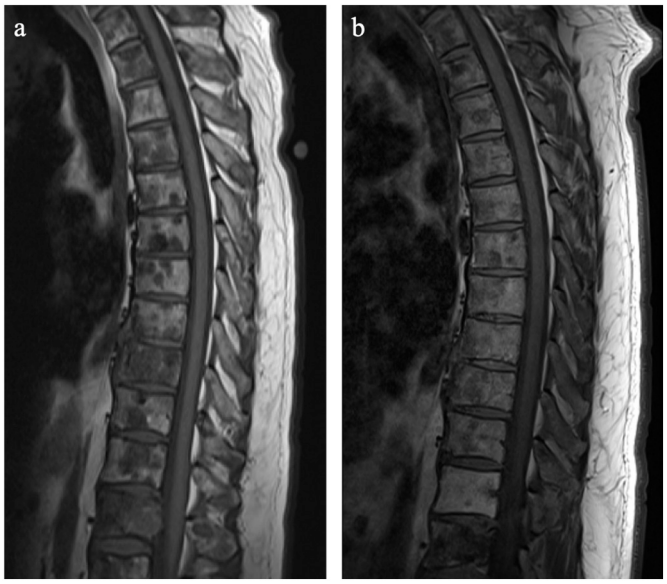

Fig. 5. Bone metastasis demonstrating the tumor response following pembrolizumab administration.
a) Sagittal section from MR thoracic imaging obtained 3 years post-splenectomy demonstrating T1 hypointense lesions within the vertebral bodies throughout the spinal axis.
b) Sagittal section from MR thoracic imaging obtained 6 months later following administration of pembrolizumab demonstrating stable or resolved T1 hypointense lesions of the spine.

from disseminated tumor at a median interval of six months from diagnosis even when they have undergone splenectomy, adjuvant chemotherapy, and radiation. Metastatic disease can involve the liver, lungs, lymph nodes, bones, gastrointestinal tract, brain, adrenals, abdominal wall, heart, and pancreas [3,4]. In patients presenting with widely metastatic disease, it is often impossible to identify the site of the primary origin of tumor.

In summary, angiosarcoma of the spleen is a rare tumor with a nonspecific presentation. Early diagnosis and splenectomy avoid splenic rupture and associated sequelae. Optimal treatment of primary splenic angiosarcoma is a combination of surgery, adjuvant chemotherapy, and radiation. We describe two patients with primary angiosarcoma of the spleen who both promptly underwent surgical resection and who both received adjuvant chemotherapy. Despite the poor prognosis for primary splenic angiosarcoma reported in the existing literature, these two patients have now survived four and five years, respectively following tumor resection and chemotherapy.

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None.

Ethical approval

Ethics approval is not required for case reports at our institution.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Table 1
Literature review of primary angiosarcoma of the spleen.

Study	Study design	Summary of findings
Neuhauser et al. (2000) [3]	Clinicopathologic study of 28 cases	28 cases of primary angiosarcoma of the spleen are described. Median age was 63 years. Most common physical exam finding was splenomegaly in 71% of patients. Immunohistochemical studies showed that a majority of tumors were immunoreactive for at least two markers of vascular differentiation (CD34, FVIIIRA, VEGFR3, CD31) and at least one marker of histiocytic differentiation (CD68 and/or lysozyme). Metastasis developed in 100% of patients. 26 patients died within 29 months from diagnosis. One patient remained alive with disease at 8 years and the other patient was disease-free at 10 years.
Falk et al. (1993) [4]	Clincopathologic study of 40 cases	40 cases of primary angiosarcoma of the spleen were included in the study. Median age was 59 years. Presenting symptoms include splenomegaly, abdominal pain, fatigue, fever, and weight loss. Metastases were present in 69% of patients and most often went to the liver, followed by bone, lymph nodes, and brain. 79% of patients were dead on follow-up at a median interval of 6 months with the remaining patients alive 5–21 months after diagnosis.
Naka et al. (1996) [5]	Retrospective study	55 patients from hospitals in Japan were reviewed for cases of angiosarcoma including head and neck, trunk, extremities, spleen, breast, and other. Median age was 69 years. Overall 2-year survival rate was 21%. Multivariate analysis revealed that age, tumor size, and mode of treatment, and mitotic counts were significant independent prognostic factors.
Hamid et al. (2010) [10]	Case report	70-year-old woman with shortness of breath and chest discomfort secondary to left-sided pleural effusion. Laparoscopic splenectomy was performed and final diagnosis revealed primary splenic angiosarcoma. Subsequent CT scan showed metastasis to liver and lung. Patient received ifosfamide and doxorubicin. Patient reported with stable disease 9 months later.
Hai et al. (2000) [14]	Case Report	56-year-old male presented with substernal chest pain, dyspnea, generalized weakness, and lower back pain. The patient underwent splenectomy and was found to have an enlarged spleen and multiple small accessory spleens. Final pathology confirmed angiosarcoma of the spleen. The patient was treated paclitaxel and doxorubicin with unknown follow-up.
Ferreira et al. (2012) [15]	Case report	Two patients with splenic angiosarcoma were described. The first patient was a 57-year-old woman with metastatic splenic angiosarcoma. She received 4 cycles of weekly paclitaxel prior to metastatic resection and 4 cycles of the same drug as adjuvant therapy. She was found to have recurrent angiosarcoma and was treated with pazopanib followed by doxorubicin and a novel agent within

(*continued on next page*)

Table 1 (*continued*)

Study	Study design	Summary of findings
		a Phase II trial. She was reported alive 2 years after diagnosis. The second patient was a 30-year-old male who presented with metastatic high-grade splenic angiosarcoma and was treated with 2 cycles of weekly paclitaxel. He developed a gastrointestinal bleeding secondary to metastatic angiosarcoma to his stomach. He was treated with radiation and gemcitabine and docetaxel. The patient died 8 months from diagnosis.
Vakkalanka et al. (2010) [16]	Case report	69-year-old female presented with high-grade splenic angiosarcoma. She was initially not considered a surgical candidate due to extent of local spread. She received three cycles of single agent Paclitaxel and subsequently underwent successful resection of the tumor.
Smith et al. (1985) [20]	Case Report	63-year-old male presented with left-sided abdominal pain. Physical exam revealed splenomegaly. CT scan demonstrate a diffuse infiltrative process of the spleen. The patient underwent exploratory laparotomy due to suspicion for metastatic carcinoma or lymphoma. Histopathology was consistent with primary angiosarcoma of the spleen. The patient received a regimen of cyclophosphamide, doxorubicin and methotrexate. The patient died 13 months after splenectomy from metastatic disease.
Duan et al. (2013) [21]	Case Report	65-year-old man presented with abdominal pain, anemia, thrombocytopenia, palpable abdominal mass and unstable blood pressure. Laparotomy revealed a large, actively bleeding spleen. Splenectomy was performed and histopathology was consistent with primary angiosarcoma of the spleen. The patient was discharged 10 days post-operation with no complications and unknown follow-up.
Myoteri et al. (2014) [22]	Case report	82-year-old woman with left pleural effusion and palpable left upper quadrant abdominal pass. Classic open splenectomy was performed with angiosarcoma of the spleen identified as final histopathologic diagnosis. Adjuvant chemotherapy was not reported. Patient was reported as disease-free 6 months later.
Badiani et al. (2013) [23]	Case report	30-year-old man with severe abdominal pain and distention, hypotension, and splenomegaly. Imaging revealed splenomegaly with acute hemorrhage. Laparoscopic splenectomy was performed but was complicated by intra-operative cardiorespiratory arrest. The patient was resuscitated but then fatally arrested post-operatively in the intensive care unit.

CRediT authorship contribution statement

Author #1: data curation, investigation, writing — original draft, writing — review & editing.

Author #2: data curation, investigation, writing — original draft, writing — review & editing.

Author #3: supervision, writing — review & editing.

Author #4: data curation, writing — review & editing.

Author #5: supervision, writing — review & editing.

Author #6: conceptualization, supervision, writing — review and editing.

Research registration

These case reports do not meet the Research Registry's criteria of "first used in man" as all of these described chemotherapeutic agents have been utilized previously in other settings and for other purposes.

Guarantor

Author #6 (anonymized).

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

The authors report no declarations of interest.

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