Hepatic angiosarcoma five years following spontaneous intraperitoneal bleed of a hepatic mass

Jessica L. Cioffi-Pretti,1 Alexandra N. Kalof,2 George Ebert,3 Laurence E. McCahill4
1Department of Surgery, University of North Carolina at Chapel Hill, Chapel Hill; 2Department of Pathology, Fletcher, Allen Health Care/University of Vermont, Burlington; 3Department of Radiology, Fletcher Allen Health Care/University of Vermont, Burlington; 4Lacks Cancer Center, St. Mary’s Health Care, Grand Rapids, Michigan, USA

Abstract

Primary hepatic angiosarcoma is a rare and rapidly fatal disease. We present the highly unusual identification of this lesion five years after the initial clinical presentation.

In 2003, a 32-year-old man presented with abdominal pain, tachycardia, and evidence of hemorrhage. A CT scan showed a hepatic mass with intralesional hemorrhage, intraperitoneal blood, and splenomegaly. The patient was stabilized clinically. Laparoscopic core biopsies demonstrated no malignancy, only findings consistent with an old hemorrhage. Contralateral lobe biopsies revealed normal liver tissue. A metastatic workup was negative and the decision was made to observe the patient clinically with radiographic imaging, four to six months with radiographic imaging, and demonstrated a rounded hypovascular lesion based on CT. The mass abutted on the dense fibrosis and approximately 60% tumor necrosis (Figure 1). The patient became stable hemodynamically after a transfusion with two units of blood. In addition to Cohn’s disease, his past medical history was notable for splenomegaly since the age of 18 years and persistent thrombocytopenia (platelet count, 40,000-50,000). He denied drinking alcohol and subsequent hepatitis serology tests were negative.

A fine needle aspiration of the left hepatic mass was performed and demonstrated rare clusters of atypical cells with a background of necrotic debris, suggestive of malignancy. The paucity of cells present, however, precluded immunohistochemical workup and a definitive diagnosis. Laparoscopic needle core biopsies were performed subsequently and revealed an organizing hematoma without evidence of malignancy. Biopsies of the contralateral lobe demonstrated normal liver parenchyma without cirrhosis. A full metastatic workup was negative. Hepatic angiography was performed and demonstrated a rounded hypovascular lesion without a characteristic tumor blush. Hepatic venous wedge pressures (8 torr) failed to support a diagnosis of portal hypertension. A bone marrow biopsy was unremarkable and platelet function assays were normal. A decision for close observation was made secondary to the patient’s long-standing splenomegaly and thrombocytopenia and the concern for his suitability for resection.

The patient was monitored closely every four to six months with radiographic imaging, which documented an interval decrease in the size of the lesion (Figure 1B). He remained asymptomatic, fully active, and otherwise healthy. A surveillance CT scan performed four years after the initial presentation (April 2007) demonstrated the lesion had diminished to 3.0 cm in maximum dimension, but with newly identified asymptomatic esophageal varices and thrombosis of the left portal vein. Over the following eight months, the lesion increased in size from 3.0 cm to 4.8 cm, and developed prominent intralobular septations (Figure 1C).

A malignant process was considered and repeat core biopsies demonstrated an atypical vascular proliferation with features suggestive of an epithelioid hemangioendothelioma. Subsequently the patient underwent a left hepatic lobectomy (Couinaud segments 2-4) that revealed a highly vascular lesion involving the left lateral and left medial lobes with fibrosis of the porta hepatis. Pathologic examination demonstrated a high-grade primary hepatic angiosarcoma with negative histological margins. The patient’s postoperative course was complicated by the development of significant ascites. He recovered well from surgery, and the ascites resolved. A three-month follow-up CT scan demonstrated a single pulmonary lesion suggestive of metastasis. The patient underwent a video-assisted thoracoscopic procedure, with the pathologic examination demonstrating a 1 cm focus of a high-grade metastatic epithelioid angiosarcoma. He rapidly developed a port site chest wall recurrence, for which he has received systemic taxane-based chemotherapy, with a durable partial response of twelve months. Currently he remains free of disease in the liver.

Pathologic findings

Grossly, the resected liver specimen contained a tan, hemorrhagic well-demarcated mass (6.0x5.5x0.9 cm), with a peripheral rim of fibrous tissue and approximately 60% tumor necrosis (Figure 2). The mass abutted on the capsular surface with adjacent fibropurulent...
serositis. Surgical resection margins were normal tissue.

Microscopically, the liver mass revealed a high-grade malignant neoplasm composed of epithelioid cells exhibiting marked cellular pleomorphism, brisk mitotic activity (>50 mitotic figures/10 high power fields) and extensive geographic tumor necrosis (Figure 3). The cells were arranged in cohesive sheets, focally forming anastomosing vascular channels with prominent hob-nailing and scattered intracytoplasmic lumina. The tumor infiltrated the surrounding hepatic parenchyma with entrapment of benign bile ducts and hepatocytes. Lymphovascular invasion was not identified. Positive immunohistochemical stains included: CD31, CD34, Podoplanin (D2-40), EMA, and Factor VIII Ag, while Keratin CAM 5.2, Keratin MAK 6, Keratin AE1-AE3, and HepPar1 were negative. The immunohistochemical findings support vascular differentiation with high-grade morphology, extensive necrosis, and epithelioid morphology characteristic of an epithelioid angiosarcoma.

**Discussion**

Angiosarcomas are rare, malignant vascular tumors that may occur in any area of the body, but are most common in the region of the head and neck. Sarcomas of the soft tissues constitute less than 1% of all cancers, with angiosarcomas compromising approximately 2% of soft tissue sarcomas. Predisposing factors include a prior history of radiation therapy, chronic lymphedema, exposure to Thorotrast (thorium dioxide, a radiologic contrast medium), use of anabolic steroids or synthetic estrogens, insecticide exposure, and long-term exposure to vinyl chloride. Typically angiosarcomas are high-grade, aggressive tumors that tend to recur and metastasize despite treatment. Current therapies include surgical resection, with radiation therapy and/or adjuvant chemotherapy depending on the anatomic location and size. Overall prognosis is poor for soft tissue angiosarcomas, with a five-year survival reported in the range of 10-35%.

Hepatic angiosarcoma is very rare, constituting 2% of all primary hepatic cancers. The average incidence of hepatic angiosarcoma is estimated to be 25 cases per year in the United States. There is a male to female predominance of 3:1 with the majority of patients diagnosed in their sixth decade of life. Approximately 60% of patients have evidence of metastatic disease at the time of diagnosis.

Clinical presentation is nonspecific typically, with presenting symptoms including abdominal pain, weakness, fatigue, and weight loss; while physical examination findings may include hepatomegaly, ascites, and jaundice. Acute abdominal bleeds occur spontaneously or following percutaneous biopsy in 15-27% of cases, and thus hepatic angiosarcoma should be considered in the differential workup of a patient with spontaneous hemoperitoneum. Associated laboratory findings tend to be non-specific, although more than half of the patients have unexplained thrombocytopenia and elevated alkaline phosphatase levels. The remaining liver function tests are normal and tumor markers are negative. To date, there has not been any association with known viral markers identified.

Radiographically, hepatic angiosarcomas have a varying appearance. There may be one dominant focus or multiple masses that correlate with the gross appearance. Metastases are common at the time of presentation, with the most usual metastatic sites being the lung and spleen. Unenhanced CT images of these masses are observed to be hypodense when compared to normal hepatic parenchyma, while lesions observed with contrast-enhanced CT may be either hypo- or hyperdense, depending on the presence of hemorrhage within the tumor. Optimal imaging techniques for the diagnosis of hepatic angiosarcoma include unenhanced, multiple-phase enhanced, and delayed CT or MR imaging to adequately capture all phases of the tumor and eliminate potentially benign mimickers.

Pathologically, hepatic angiosarcomas of the deep soft tissue and in visceral locations generally are high-grade malignant neoplasms.
that have an epithelioid to spindled appearance. As in the current case, angiosarcomas of the liver are characterized by nests and solid sheets of malignant cells of high nuclear grade that form irregular vascular channels and exhibit invasion of the adjacent liver parenchyma. Tumor necrosis is a common finding. Grossly, the tumor may appear with one of four different growth patterns: multiple nodules, a single dominant mass, mixed patterns of a dominant mass with smaller nodules, or an infiltrating micronodular tumor.

For the past 40 years, a link has been established between hepatic angiosarcoma and environmental toxins, including Thorotrast, vinyl chloride, arsenic, radiation, and exogenous estrogens or anabolic steroids. However, in nearly 75% of cases, no causative agent is identified. In all cases of environmental exposure, a prolonged latency period has been established of 20-30 years on average, yet the gross and microscopic pathology of idiopathic angiosarcomas and those caused by environmental toxins remain identical.

Treatment for hepatic angiosarcoma is delayed often owing to the nonspecific symptoms with which the tumor typically presents. The average time until diagnosis is six months from the initial presentation to a health care professional; however, many patients do not seek medical attention for several months following the onset of symptoms. Thus, a large tumor size and the presence of metastases are common on diagnosis. Median survival time following diagnosis is six months, with near 100% mortality by one year. Improved prognosis has been observed with a single tumor mass, a smaller tumor size, lack of metastases, a low-grade lesion, and negative surgical resection margins; however, owing to the infrequent nature of the tumor, this still has to be quantified. Given the poor prognosis for patients diagnosed with hepatic angiosarcoma, surgical resection is the only definitive treatment; however, this is not possible in many cases either because of multifocal disease or the extent of the liver involvement. Adjuvant treatment remains undefined owing to the rarity of the tumor. Chemotherapy has not been well studied except on a case report basis, and in general angiosarcomas are resistant to radiation therapy. Liver transplantation has been attempted, but the tumor recurrence rate remains high (64%) and long-term survival has not been observed (average survival time, 23 months). If definitive resection can be achieved prior to microscopic spread of the disease, long-term survival is possible. This has been reported in three adult cases that were without evidence of recurrence at 64 months, 38 months, and 10 years.

Although our patient’s tumor was amenable to resection, the associated hepatic fibrosis documented by previous core biopsies and the clinical diagnosis of portal hypertension portends a worse prognosis. Pathologic examination results including high-grade nuclear features with epithelioid morphology are additional unfavorable findings. Paradoxically, the radiographic finding of a tumor mass that had been present for the previous five years in our patient would suggest a less aggressive clinical course of the disease.

In hindsight, this patient’s splenomegaly appears to be a result of periporal fibrosis and the splenomegaly and thrombocytopenia were long standing. These clinical findings have been reported previously as precursors to the development of angiosarcoma in other patients. An analysis of patients with significant polyvinyl chloride exposure by Lee et al. (1996) described a patient with a history of splenomegaly and thrombocytopenia, who later presented with esophageal varices and presinusoidal hypertension via a screening program. Ultimately a core needle biopsy lead to the diagnosis of presinusoidal hepatic fibrosis. The patient later sustained a fatal gastrointestinal hemorrhage, and at autopsy was found to have primary hepatic angiosarcoma. In the case of our patient, liver biopsies of the uninvolved liver in 2003 failed to demonstrate characteristic periporal fibrosis, but this was identified on repeat liver biopsies in 2007, after the patient developed esophageal varices.

We are unaware of any previous reports suggesting such a prolonged natural history of a hepatic angiosarcoma. This case may represent the possibility of malignant transformation of a lower grade vascular neoplasm, such as hepatic epithelioid hemangioendothelioma, to a more aggressive angiosarcoma. While angiosarcoma may present with spontaneous and often catastrophic intraperitoneal bleeding, this patient’s spontaneous intraperitoneal bleed was five years prior to eventual resection of the tumor. The patient had well-documented radiographic gradual reduction in size of the lesion over four and a half years, before its rapid enlargement just prior to excision; a very unusual progression in the natural history of a high-grade angiosarcoma, thus raising the possibility of malignant transformation of a benign precursor.
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