Hepatic angiosarcoma presenting as acute liver failure in young adults. Report of two cases and review of literature

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ABSTRACT

Background: Hepatic angiosarcoma is a rare tumor of endothelial origin that accounts for up to 2% of all primary neoplasms of the liver. It is uncommon in young adults and acute liver failure is a very unusual presentation of this disease. Case Presentation: We report the cases of two young male adults who presented with acute liver failure. One of them was diagnosed with primary hepatic angiosarcoma after transplantation based on the complete evaluation of the hepatectomy specimen; while the other was diagnosed through a liver biopsy which was done as part of the work-up for transplantation. Both patients had a rapidly worsening clinical course and died within 2 months of diagnosis. Conclusion: Hepatic angiosarcoma is a poor prognosis disease with high and early mortality. Therefore, a high level of suspicion should be present to promptly diagnose it, especially when dealing with patients with a rapidly worsening liver disease.

Keywords: Liver; Hepatic Angiosarcoma; Acute Liver Failure

1. INTRODUCTION

Hepatic Angiosarcoma (HAS) is a malignant vascular tumor that accounts for up to 2% of all primary liver tumors [1]. It usually develops during the sixth and seventh decades of life, and is more frequent in males [2]. Given that HAS clinical, laboratory, and radiologic presentations are nonspecific, its diagnosis is difficult and often delayed. Therefore, this is considered as a poor prognosis disease, with a high mortality rate, and with few therapeutic options.

Even though it is a rare tumor, it has become a topic of great interest in occupational medicine due to the strong association with hepatic carcinogens like polyvinyl chloride, thorium dioxide, arsenic, among others [2-6]. However, most of the cases arise without any associated risk factors.

Herein, we report the clinical manifestations, pathologic evaluation, and treatment of two cases of young adults with HAS that came to our institution in the last 4 years. Both cases presented as acute liver failure (ALF), which is an extremely rare presentation of a primary liver tumor [7]. They had a progressively declining clinical course and died within 2 months of the diagnosis.

2. CASE REPORT 1

A thirty-one year-old male was referred to us from a local hospital to the Intensive Care Unit (ICU) for further management, after he suddenly developed severe hypoglycemia and acute liver failure.

Three days before admission he visited the local hospital complaining of asthenia, anorexia, progressive jaundice, and abdominal distention for one month. His past medical history included marijuana and cocaine consumption years before, but not recently. He reported possible occupational exposure to vinyl chloride while staining fabric material for making clothes for many years. Upon examination the patient was jaundiced, with edema, ascites, and hepatosplenomegaly.

Laboratory tests on admission showed a hemoglobin of 13.4 gr/dL; hematocrit 44%; WBCs: 4500; platelets: 44,000/cm³; PT: 22/11 seconds; INR: 2.2; total bilirubin: 26.4 mg/dL and direct bilirubin 16 mg/dL; AST: 646 IU/L and ALT: 302 IU/L; alkaline phosphatase 137 IU/L;
albumin 2.5 g/dL; creatinine: 0.7 mg/dL. Serology for hepatitis A, B, C and autoimmune markers were negative. An abdominal paracentesis was performed and the ascites fluid evidenced proteins of 2.3 g/dL and a serum-ascites albumin gradient (SAAG) of 1.1 g/dL. Doppler ultrasound (US) of the liver demonstrated a heterogeneous parenchyma with irregular borders, and no focal lesions. Plus, the portal vein, hepatic artery, and suprahepatic vein blood flow was within normal limits. Following these findings a liver biopsy was done and it revealed venous blood flow obstruction suggestive of Budd-Chiari syndrome.

The patient experienced rapid deterioration of his neurological status, renal failure, and he required hemodynamic and ventilatory support. As a consequence, he was listed for an urgent transplantation, and on the fifth day after his admission to our center, he underwent a successful liver transplantation.

The hepatectomy specimen weighed 2489 gr; it had a spongy appearance and multiple hemorrhagic areas (Figure 1).

Microscopically, there was massive invasion of the liver parenchyma by the tumor. Neoplastic cells were pleomorphic and spindle shaped with high mitotic activity (Figures 2 and 3), and they were positive for CD31, CD34, factor VIII, and CD10 immunohistochemistry markers (Figure 4). The proliferation index was established with the Ki67 marker (50%).

One month after the transplantation the patient had recurrence of the tumor involving the bone marrow. He received 3 cycles of chemotherapy, but he had a torpid clinical course and died 2 months later.

3. CASE REPORT 2

A twenty year-old male, who worked as a car technician, presented at the emergency room because of somnolence, disorientation, and disturbances of the sleep-wake cycle for 5 days. Additionally, he presented with upper abdominal pain and increased abdominal girth.

Initially, he was admitted to a local hospital and an abdominal US, a paracentesis, and a liver biopsy were performed. The results demonstrated a mass in the liver suggestive of hemangioendothelioma. His past medical history was unremarkable.

Physical examination on admission revealed a patient who had altered level of consciousness, mucocutaneous jaundice, ascites, hepatosplenomegaly, and edema of the lower limbs. Laboratory data: hemoglobin: 14.4 gr/dL; hematocrit: 43.2%; WBCs: 4900; platelets: 18,000/ cm³; PT: 39.5/27.5 seconds; INR: 1.7; AST: 446 IU/L and ALT 140 IU/L; alkaline phosphatase: 285 IU/L; total bilirubin: 17.65 mg/dL and direct bilirubin: 10.45 mg/dL; albumin: 0.94 g/dL. The abdominal CT scan showed hepatomegaly and multiple focal lesions that...
compromised most of the hepatic parenchyma; some of them showed a necrotic center.

As part of the work-up for transplantation, a new liver biopsy was taken. The histological and immunohistochemistry findings (positive CD31 and Factor VIII; Ki67: 50%) were consistent with angiosarcoma (Figures 5 and 6). Hence, the patient could not be listed for transplantation and he was referred for oncologic and palliative therapy. This was considered an occupational disease due to the chronic exposure to vinyl chloride.

The patient had rapid deterioration of his clinical course and 17 days after admission he died.

4. DISCUSSION

Hepatic angiosarcoma is a malignant neoplasia of mesenchymal origin that arises from endothelial and fibroblastic tissues, which grow and compromise the blood vessels [8]. It is a rare tumor which accounts for up to 2% of all primary hepatic malignancies [1,7]. However, it is the most common primary sarcoma of this organ [9]. The incidence and prevalence in the western world is estimated at 0.5 - 1 per million and 0.14 - 0.25 per million, respectively [10]. These patients have a poor prognosis and without treatment the median survival is less than 6 months [11,12].

It is most common during the sixth and seventh decades of life (50 - 59-year-old) [3,13]; although there are cases reported in children and young adults [14-18]. There is a male predominance with a ratio varying be-
tween 3:1 and 4:1 [3,4,14]. Metastases are usually to lung (38%), spleen (18%), and bone (18%), still there are cases described with metastasis to the stomach and left gastric vein [11,18].

In up to 75% of the cases its etiology is unknown and no associated risk factors are found [17]. Nevertheless, it has been related with the exposure to thiorium dioxide, polyvinyl chloride, arsenic and radium compounds, inorganic copper, anabolic steroids, and radiation [3-5, 8,19]. There is also an association with hemochromatosis and von Recklinghausen disease [7,13].

Thorotrast was a radiologic contrast medium used in the US, Europe, and Japan from 1930s until the late 1950s [2,3]. It is a colloidal solution composed of 25% thorium dioxide (Th\(^{232}\)) and dextrin [2,19]. After intra vascular injection, Th\(^{232}\) is stored in the reticulo-endothelial system, particularly the liver, spleen, and bone marrow [19].

Th\(^{232}\) is a radioactive isotope that emits α particles and it is the chronic α radiation the one responsible for the development of angiosarcoma [2,19]. The people affected have a mean latency of exposure to tumor of 24 - 42 years [3].

Vinyl chloride (VC) is a gas used in the production of plastic piping and conduit, floor covering, furniture, electrical applications, and packaging [3]. In 1974 in the US, the carcinogenicity of this compound was recognized, and since then the allowed exposure levels were reduced, reaching current levels of <1 ppm [2,3]. It is rapidly metabolized and it generates metabolites that react with the proteins, DNA and RNA, creating new mutations in K-ras and p53 [2,8]. The mean latency for vinyl-chloride-induced angiosarcoma is between 19 to 22 years [3].

The liver is a target of carcinogenesis from arsenic exposure [5]. Arsenic is absorbed in the gastrointestinal tract and the liver is the principal site for its detoxification [5]. Initially, it was used as a drug. Fowler’s solution (1% arsenic trioxide) was considered as part of the treatment for psoriasis, anemia, asthma, cholera, syphilis, among others [6]. Then, from 1931 until 1953, it was one of the first medications used for the management of chronic myelogenous leukemia [6]. Nowadays, Fowler’s solution, the consumption of contaminated water, and the exposure to pesticides made up of arsenic, have been reported as possible risk factors for angiosarcoma [4].

Clinical presentation may be variable. The most common initial symptoms are diffuse abdominal pain, asthenia, and weight loss [3,8]. Other systemic findings, like weakness and anorexia may be present in 25% - 50% of patients [4]. In a series of 5 patients reported by Molina and Hernandez, fever was documented as a presenting symptom in 2 patients for the first time. It is believed that the causes of this symptom are the hemorrhage and the necrosis related to the tumor [20]. Cases presenting as lower back pain, epigastric pain, abdominal discomfort, hemoptysis, chest discomfort, and dyspnea have been described as well [4,10,12,20]. Physical signs include ascites, hepatomegaly, splenomegaly, and jaundice [2,3,7]. Hemoperitoneum, due to the rupture of blood vessels or after instrumentation, happens in 17% to 27% of the cases and it is associated with a high morbidity and mortality [3].

Acute liver failure is a very unusual presentation of HAS [21]. This clinical syndrome is marked by encephalopathy and coagulopathy in a patient with no prior evidence of liver disease [7,22]. The most common causes for ALF are acetaminophen overdose (46%), drug toxicity (11%) and hepatitis (10%) [23]. In contrast, there are few case reports of infiltrative metastatic neoplasms affecting the liver that present as ALF, for example hematological malignancies, adenocarcinoma, melanoma, anaplastic tumors, breast, colon, gastric, and lung cancer [7,13,24-26]. There are even fewer cases of primary liver cancer presenting as ALF [21].

In HAS, ALF is thought to be a consequence of the combination of ischemia of the parenchyma, portal vein occlusion by tumor thrombi, non-occlusive infarct due to septic shock or cardiogenic dysfunction, and the replacement of the hepatocytes by malignant cells that lead to secondary necrosis [7,17].

4.2. Laboratory and Radiologic Findings

Laboratory data show elevation of liver enzymes with a predominance of cholestasis [8]. The most common finding is the increase of the alkaline phosphatase levels [2]. In more than 50% of the cases, thrombocytopenia and negative tumor markers are observed [3]. Also, cases of microangiopathic hemolytic anemia secondary to blood cell damage by passing through the tumoral vascular channels have been reported [2].

From a radiologic point of view, it is difficult to distinguish HAS from other hepatic tumors of mesenchymal or vascular origin [3,10].

Through imaging 4 growth patterns have been identified: multiple nodules, solitary mass, mixed pattern with a dominant mass and multiple nodules, and infiltrative micronodular type [1,10]. In most cases it appears as multiple lesions or as a heterogeneous dominant mass [1,2].
In certain cases, abdominal X-rays show a mass in the right upper quadrant (RUQ) and thorium dioxide deposits at the periphery of the liver [3]. The US may show a solitary mass or multiple nodules with different echogenicity depending on the necrosis and the hemorrhage [2,3,17].

The various morphologic appearances on CT and magnetic resonance explain why the differential diagnosis with other primary liver tumors is difficult [10]. In the CT scan without contrast, lesions are hypodense; however, when contrast media are used multiple patterns of enhancing may be observed [3,9]. On the other hand, the magnetic resonance with contrast demonstrates the hemorrhagic, heterogeneous and hypervascular characteristics of the dominant mass [1,2,27]. This image shows the different levels of attenuation in the arterial and portal phases [2].

4.3. Pathologic Findings

The final diagnosis is made with a histologic evaluation.

This is a tumor of endothelial origin [20]. Macroscopically, it is composed of brown-gray areas mixed with hemorrhagic foci and cavitations [17].

Microscopically it is characterized by the proliferation of neoplastic cells around preformed vascular channels: sinusoids, hepatic terminal venules and branches of the portal vein [17,27]. The growth of the sinusoids is related to their dilation and atrophy of the hepatic cells [3]. The tumor nests are made up of epithelioid, spindle and pleomorphic cells with small vascular spaces; mitotic figures are commonly seen [3,17]. In the solid areas, fibrosis and hemosiderin deposits may be found [1]. Areas of hemorrhage, infarction, calcifications and necrosis can be seen as well [17]. The immunohistochemistry stains reveal the expression of: vimentin, CD31, CD34, Factor VIII and Ki67 [3,8,17].

4.4. Treatment

Treatment options for HAS are few and there are no established regimens due to the low frequency and rapidly worsening course of the tumor [3,17].

Although complete resection is the best treatment, curative surgeries are difficult to perform. In most of the cases, by the time of diagnosis, the disease is in an advanced state, presenting as a large tumor or with metastasis [3,17].

This neoplasm is radioresistant and no chemotherapeutic regimen has been established for its treatment [3,12]. Chemotherapy is palliative and is indicated for patients with HAS that cannot be resected [8,12]. In this case, the recommendation includes 5FU-carboplatin with doxorubicin or ifosfamide [12].

Liver transplantation is an absolute contraindication for the management of HAS [10]. In those patients who received a transplant, they did not show improvement in their survival and it is the hepatic neoplasm with the highest rate of recurrence after transplantation [1,7,8]. According to information of the European Liver Transplant Registry median survival after transplant is less than 7 months [10].

5. CONCLUSIONS

Hepatic angiosarcoma is a very infrequent tumor in patients younger than 35-year-old, and acute liver failure is a very unusual presentation of this disease. This unusual combination of clinical characteristics was part of the two cases we reported. Both patients had a progressively worsening clinical course and died within 2 months of diagnosis. This demonstrates the rapid evolution, poor prognosis, and the need to find a therapy that improves survival.

We would like to mention that we had another case of a young (26-year-old) female patient with a diagnosis of HAS. Her case was not included as part of the case reports because her disease presented as usual, with an insidious onset of diffuse abdominal pain and weight loss for 3 months. Additionally, she was being studied for a concomitant myeloproliferative disorder.

Even though the clinical manifestations are nonspecific, one should think of HAS as part of the differential diagnosis when dealing with a young patient that has a worsening clinical course and a rapidly progressive liver disease. A diagnosis made soon, will make a difference in the treatment options, outcome and prognosis of these patients.

REFERENCES


