

CLINICAL NOTES

Hepatic angiosarcoma. Presentation of two cases

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ABSTRACT

Hepatic angiosarcoma is a rare primary tumor of the liver with a mesenchymal origin. Diagnosis is difficult because clinical manifestations and imaging studies are inconclusive. In many cases a diagnosis is obtained during necropsy, not being apparent during the course of disease. It is associated with several risk factors, but these contribute to explaining only a few of all reported cases. When clinical manifestations begin progression is often fast, and possibilities for curative treatment are limited.

We report two cases of hepatic angiosarcoma. In the first one, our patient had an insidious initial course, and then suddenly presented with hepatic failure followed by acute respiratory distress. A diagnosis was reached during necropsy. In the second case, we initiated the study of a chronic liver disease using fine-needle aspiration biopsy, which showed findings suggestive of hepatic angiosarcoma. In the following weeks the patient started on a torpid clinic course, and died from multiple organ failure.

Key words: Angiosarcoma. Gastrointestinal stromal tumor. Hepatic neoplasms. Chemically induced.

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INTRODUCTION

Hepatic angiosarcoma, also called Kupffer's sarcoma, is an infrequent, difficult-to-diagnose, rapidly progres-

sive disease that usually has a fatal outcome. Several risk factors and etiological agents have been described, but in up to 75% of cases the tumor origin remains uncertain. The condition is very hard to identify as its clinical presentation and both laboratory and image tests are extremely nonspecific. A great number of diagnoses are obtained in necropsies. There is no curative medical treatment, only palliative care at the end of life. Surgery is the definitive treatment, but is technically complex and the neoplasm is often disseminated at the time of diagnosis, making resection impossible.

We present two cases of hepatic angiosarcoma observed in our center during the last few months – one of them was diagnosed during necropsy, the other was diagnosed pre-mortem after a fine-needle aspiration biopsy.

CASE REPORT 1

A 65-year-old male presented at the emergency room because of jaundice, abdominal distension, and malaise.

He worked as assistant in a lawyer's office, and reported no toxic habits. For four years he had been intermittently followed by a gastroenterologist because of disturbed liver enzymes with a prevalence of mild cholestasis. In those years many laboratory tests were carried out, which only showed mild cholestasis and slight thrombopenia in some cases. Liver tests: AST: 31-56 U/l; ALT: 27-75 U/l; alkaline phosphatase: 213-456 U/l; GGTP: 150-185 U/l. Total bilirubin was within the range of 1.2-2.56 mg/dl. The remaining laboratory tests were always normal. Other studies, including autoimmunity, and serology for hepatotropic viruses and HIV were negative.

Many imaging studies were carried out, too. He underwent several abdominal echographies, all of them documented as normal except one performed four months before his admission to hospital, in which mild splenomegaly was observed. Two CT studies, the last one made seven months before admission, were also normal.

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During admission jaundice and ascites were evident, as was a mildly altered level of consciousness. Laboratory tests revealed: hemoglobin: 9.6 g/dl; platelets: 37,000; leukocytes: 3,800; total bilirubin: 27.5 mg/dl; AST: 88; ALT: 73; GGTP: 243; alkaline phosphatase: 305; prothrombin index: 33%; INR: 2.1; creatinine: 2.09 mg/dl; urea: 172 mg/dl; alpha-fetoprotein: 1 ng/ml. Serology for HBV, HCV, HIV, CMV and Epstein Barr virus was negative. A new abdominal echography was performed, which showed a liver with signs of chronic hepatopathy and multiple regeneration nodes, and an MRI scan unveiled images suggestive of macronodular *hepatic cirrhosis* and perihepatic and perisplenic ascites. Following these findings a transjugular hepatic biopsy was carried out.

The patient suddenly experienced a worsening of his clinical condition with respiratory failure that required invasive ventilation, and was moved to the Intensive Care Unit because of respiratory distress syndrome. He died 36 hours later.

The results of the liver biopsy were received after his demise, and showed non-regular dilation of hepatic sinusoids (*peylosis*) and proliferation of endothelial cells, with no mitoses at this level.

A necropsy was carried out that revealed, macroscopically, a macronodular external surface with pelyotic and spongy areas surrounded by normal parenchyma, but with macroscopic signs of intense cholestasis. Microscopically, *neoplastic proliferation* with sinusoid growth configuring cavernous spaces covered by atypical cells. Liver affectation was diffuse and discontinuous, and neoplastic intravascular growth was seen (Fig. 1). Cells were intensely positive for endothelial markers CD-31 and CD-34 (Fig. 2). This is all compatible with *primary hepatic angiosarcoma*.

CASE REPORT 2

A 73-year-old male who suffered from tuberculosis when he was young and had no other history of interest.

He fell accidentally at home and injured his right leg. The injury had abnormally high bleeding, and this alerted the doctor who was attending him. Laboratory tests showed the following findings: hemoglobin: 10.6 g/dl; platelets: 115,000; leukocytes: 3,450; total bilirubin: 7.1 mg/dl; AST: 45; ALT: 53; GGTP: 293; alkaline phosphatase: 286; prothrombin index: 61%. A study for chronic liver disease was carried out, with the result of viral serology, serum proteinogram and autoimmunity tests being all negative. Several imaging tests were also performed: abdominal CT: enlarged liver, with multiple nodes suggestive of *hepatic metastases*. Some of them are big and they appear all over the parenchyma. Slight amount of ascites with atypical distribution (Fig. 3); abdominal MRI scan: *liver cirrhosis* with multiple images suggestive of regeneration nodes; other etiologies such as *metastases* cannot be ruled out. Presence of ascites; PET/CT: pathological findings in both hepatic lobes; abdominal echography: some space-occupying lesions with *metastatic appearance*. With these findings, and suspecting a neoplastic disease, a fine-needle biopsy was obtained of hepatic lesions. The histological study revealed: tumor of mesenchymal origin with hyperchromatic nuclei positive for various endothelial markers, compatible with *hepatic angiosarcoma*.

Forty-eight hours after biopsy the patient was admitted to hospital because of peritoneal bleeding. He required no surgery, and the episode resolved under observation. The patient went home a few days later with no more complications. Nevertheless, in the following

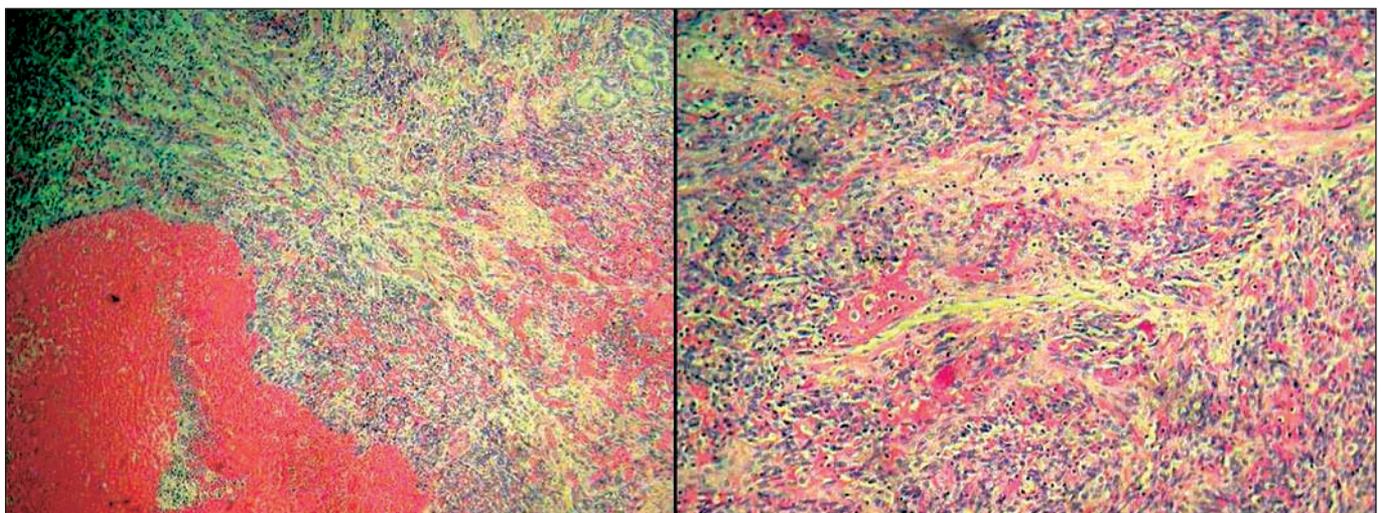


Fig. 1. A histological study with hematoxylin and eosin in which we can see sinusoid proliferation and the formation of cavernous spaces covered by atypical cells.

Corte histológico teñido con hematoxilina-eosina en el que se pone de manifiesto la proliferación sinusoidal y la formación de espacios cavernosos tapizados por células.

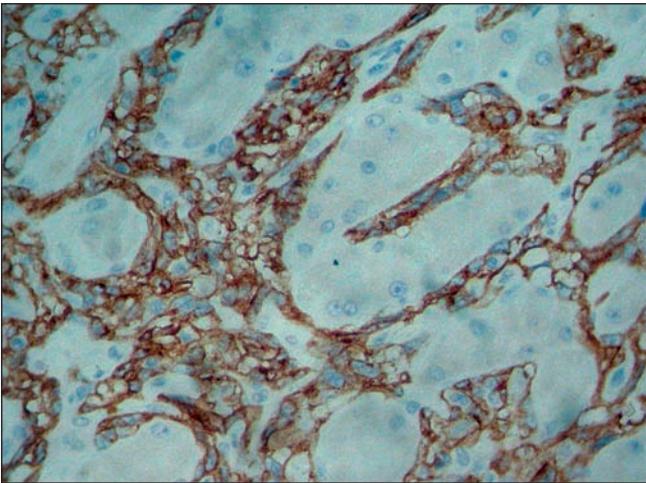


Fig. 2. A histological view in which tissue positivity for endothelial markers is apparent. Some isolated hepatocytes may be seen.
Imagen histológica en la que se aprecia la positividad de la muestra para los marcadores endoteliales. Se observa escasa cantidad de hepatocitos aislados.

weeks he experienced a progressive, severe deterioration, and developed both hepatic and respiratory failure associated with liver encephalopathy with no response to medical treatment. Finally, he died from multiple organ failure.

DISCUSSION

Hepatic angiosarcoma or Kupffer's sarcoma is a malignant tumor of mesenchymal origin and a low frequency (0.5-2% of all primary neoplasms of the liver). It arises from endothelial and fibroblastic tissues, which grow and compromise the blood vessels. The most frequent ages at presentation are between the 6th and 7th decades of life, but the ratio is wide (among the 2nd and the 8th decades) with a higher incidence in males (4:1). When diagnosed, the course of the disease is often fast, with not many options for treatment.

It has been associated with different toxics and carcinogenic substances. The etiological agent more clearly implicated is thorium dioxide (Thorotrast), a contrast widely used in radiology up to the 50's. Other not-so-common etiologies also mentioned in the medical literature include exposure to vinyl chloride monomer (VCM), chronic arsenic intoxication, use of oral contraceptives, use of androgenic steroids, and exposure to stilbestrol or ionizing radiation. Systemic diseases such as hemochromatosis or von Recklinghausen's neurofibromatosis have been also related to hepatic angiosarcoma. Anyway, most cases show no clear exposure antecedents, and the origin of the disease remains uncertain (58-75% of the cases).

In the last few years several investigations have suggested the role of different genes and their mutations in the origin of these tumors. It has been demonstrated that exposure to VCM causes mutations on K-ras-2 and protein p53 in a very particular mode, and this alteration is

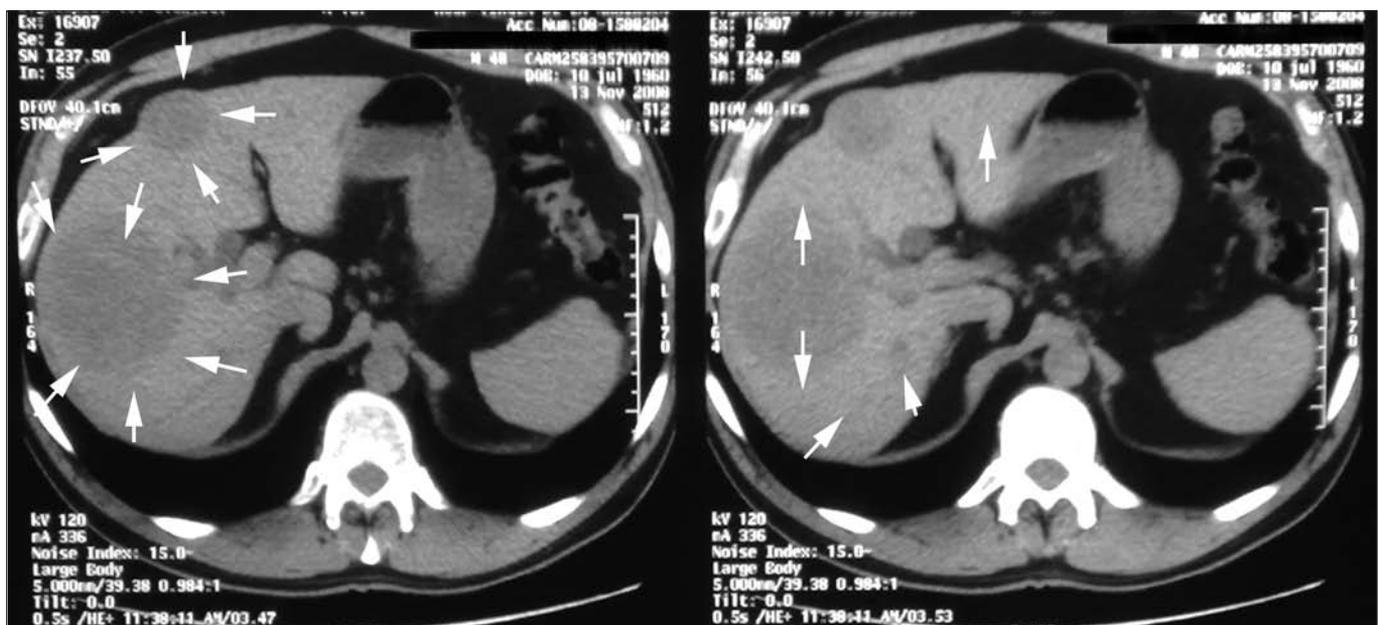


Fig. 3. CT images showing multiple hepatic lesions all over the parenchyma. Two big lesions are shown on the left side (arrows). Several smaller lesions may be seen to the right (arrows). They were identified as metastases.
Imágenes de tomografía computarizada en la que se aprecian múltiples lesiones hepáticas, distribuidas por la totalidad del parénquima. En la imagen izquierda se señala con flechas dos lesiones de gran tamaño. En la derecha se indica también mediante flechas la localización de varias lesiones más pequeñas. Fueron interpretadas como metástasis en un primer momento.

often seen in liver angiosarcomas. In other works investigators have concluded that the inactivation of p16 through methylation of its promoter also plays a decisive role in the pathogenesis of angiosarcomas because it is a frequent defect found in this neoplasm. At any point, these mutations cannot be considered risk or prognosis factors, and further studies are needed.

In these patients clinical findings will not help for diagnosis. Symptoms and signs are extremely nonspecific – diffuse abdominal pain; asthenia and weight loss; malaise and fever of uncertain origin; hepatomegaly and jaundice; digestive or peritoneal bleeding; and progressive anemia. In laboratory tests it is usual to find altered hepatic enzymes with predominating cholestasis, and iron deficiency anemia, which in some cases have been described accompanied by micro-angiopathic hemolysis and mild thrombopenia. It is also important to investigate prior exposure to potential etiologic agents.

The utility of imaging tests is also limited, and they only show the characteristic alterations of the disease in final stages. As these tumors have a low frequency, the typical findings in imaging tests have been described only in several cohorts of cases, and there are not many exhaustive studies. Abdominal echography may show unique or multiple masses and heterogeneous cystic alterations, and a differential diagnosis with metastases, hydatidosis, etc. is then feasible. Hepatomegaly and splenomegaly with no signs of portal hypertension are also encountered. Abdominal CT may reveal heterogeneous hepatosplenomegaly with irregular liver morphology, showing alternate hyperdense and hypodense areas. We may see isolated big lesions, multiple nodes or images of diffuse infiltration consistent with a possible diagnosis of hemangioma, metastases, or hepatocellular carcinoma. In the last few years other techniques have been proposed for the diagnosis of liver angiosarcomas, including MRI and PET (positron emission tomography), but experience is still limited.

The definitive diagnosis is always given by pathology techniques. Histology reveals the presence of endothelial neoplastic cells with epithelioid appearance, pleomorphic and hyperchromatic nuclei and prominent nucleoli, and formation of cytoplasmic vascular spaces with cavernous morphology. Immunohistochemistry shows tissues to be positive for endothelial markers, specially CD-31 and CD-34. On many occasions specimens obtained by fine-needle biopsy are inconclusive, so recommendations are issued to carry a liver biopsy when possible. Anyway, both techniques should be carried out under ultrasonographic or radiographic guidance, and very carefully because these tumors are rich in vessels and potential intraperitoneal bleeding may occur.

In general the prognosis of these patients is fatal. At the time of diagnosis the liver disease often affects all the parenchyma and has spread to other organs in a great number of cases. Metastases of hepatic angiosarcoma usually affect the lungs and spleen. Disease progression

is fast after becoming clinically apparent, and survival is 6 months at most after diagnosis without treatment. On many occasions patients die undiagnosed, and a diagnosis is obtained during necropsy.

There is no curative medical treatment, only supportive and palliative care. Nowadays surgery is the definitive treatment and may improve survival in some cases. However, it is technically complex, a great number of cases are nonresectable due to tumor size and extension, and recurrence after surgery is high. Depending on lesion size and intrahepatic extension, liver resection or liver transplantation offer curative possibilities to these patients and should be both taken into consideration, although angiosarcoma is the hepatic neoplasm with the highest rate of recurrence after transplantation.

There is little experience in using adjuvant therapies after surgery for hepatic angiosarcoma, and no data support its routinely use. In general recommendations include post-resection radiotherapy for localized smaller sarcomas, but it is unclear whether this can reduce local recurrence since hepatic angiosarcoma is particularly resistant to radiation. There is no evidence either that chemotherapy may be useful. Limited data come from small cohorts of patients treated with local resection plus adjuvant chemotherapy, and conclusions are that no improvement in survival is seen.

Nevertheless, as recurrence after surgery is high, especially for big angiosarcomas, effective multidisciplinary therapies are needed, including local and systemic treatments, in order to improve survival. Ongoing follow-up after resection is also required to detect local or systemic recurrence early, and to treat it if possible.

CONCLUSIONS

As has been previously said, hepatic angiosarcoma is an infrequent tumor that is difficult to diagnose. It is easily overlooked in patients with suspicion of chronic hepatopathy or liver lesions. It also presents with a fast, fatal outcome, so not all cases are diagnosed when the patient is still alive, and treatment options are limited or nonexistent.

In our two patients we may see some of the typical characteristics of this tumor: both of them presented with nonspecific symptoms; laboratory tests and imaging techniques suggested liver cirrhosis or metastases; diagnoses were reached in histological studies, and there was previously no suspicion of a mesenchymal tumor; in both cases progression proved rapidly fatal.

It is important to carry out more studies in order to define the clinical and radiological characteristics of these tumors, so that early diagnosis will be possible. It is also necessary to develop more effective treatment options, emphasizing the importance of multidisciplinary strategies.

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