

# Hepatic angiosarcoma: Pitfalls in establishing a diagnosis

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Katerina Flabouris<sup>1,2</sup> , Suzanne McKeen<sup>2</sup>, Deborah Chaves Gomes<sup>3</sup>, Debajyoti Chaudhuri<sup>1</sup> and Patrick Russell<sup>2</sup>

## Abstract

Hepatic angiosarcomas are rare, deceptive and aggressive malignancies that remain notoriously difficult to diagnose and treat. This case report discusses some of the common challenges faced by clinicians, and potential clinical, radiological and histological clues to this often elusive diagnosis.

## Keywords

Hepatic angiosarcoma, liver, malignancy, bleeding

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## Introduction

Hepatic angiosarcomas are rare, high-grade and malignant vascular neoplasms that are particularly prone to bleeding. They account for roughly 2% of all primary liver cancers<sup>1</sup> and are typically seen during the sixth and seventh decades of life, with a male predilection of 3:1.<sup>2</sup>

Exposures to several agents have previously been implicated in the pathogenesis of hepatic angiosarcomas, including vinyl chloride,<sup>3</sup> arsenic,<sup>4</sup> anabolic steroids<sup>2</sup> and thorium dioxide,<sup>5</sup> but at least 60% of cases now have no known underlying causative factors.<sup>6</sup>

## Case

A 53-year-old woman was referred to the emergency department of a tertiary centre with a 4-week history of right upper quadrant abdominal pain. She had no relevant medical history or exposure history. She never smoked, rarely consumed alcohol and took no regular medications. Apart from tender hepatomegaly, physical examination was largely unremarkable. Her laboratory tests revealed normal haemoglobin and liver enzyme levels, but mild thrombocytopenia (platelet count =  $138 \times 10^9/L$ ,  $n=150-450$ ) and an elevated lactate dehydrogenase (LDH = 518U/L,  $n=120-250$ ). Her D-dimer was grossly elevated at 28.25 mg/L ( $n=0.0-0.5$  mg/L) with otherwise normal coagulation studies.

Multiphase computed tomography (CT) demonstrated multiple liver lesions with high attenuation on the non-contrast study compatible with intra-lesional haemorrhage

(Figure 1(a)). There were also scattered foci of nodular enhancement on the arterial phase and low attenuation on the portal venous phase (Figure 1(b)). There was no other significant abnormality. Three passes were made into the right lobe to obtain CT-guided core biopsies, but a pathological diagnosis was not able to be provided from these samples. Subsequent magnetic resonance imaging (MRI) showed no features of cirrhosis; the lesions were of low T1 and high T2 signal and did not show restricted diffusion (Figure 1(c) and (d)), aside from an isolated area in the right lobe which was felt to be related to haemorrhage (Figure 1(e)). Core biopsies were repeated under ultrasound guidance, but again did not yield any malignant cells. The case was presented at the relevant multi-disciplinary meeting and a possible diagnosis of peliosis hepatis was put forward, with differentials including hepatic epithelioid haemangioendothelioma. The patient was discharged for outpatient follow-up.

A few weeks later, the patient developed abdominal pain, hypotension and significant anaemia (haemoglobin = 74 g/L,  $n=115-155$ ). CT demonstrated acute intra-peritoneal haemorrhage but no active bleeding. It was clear that the liver lesions had significantly increased in size over the short time

<sup>1</sup>Adelaide Medical School, University of Adelaide, Adelaide, SA, Australia

<sup>2</sup>Royal Adelaide Hospital, Adelaide, SA, Australia

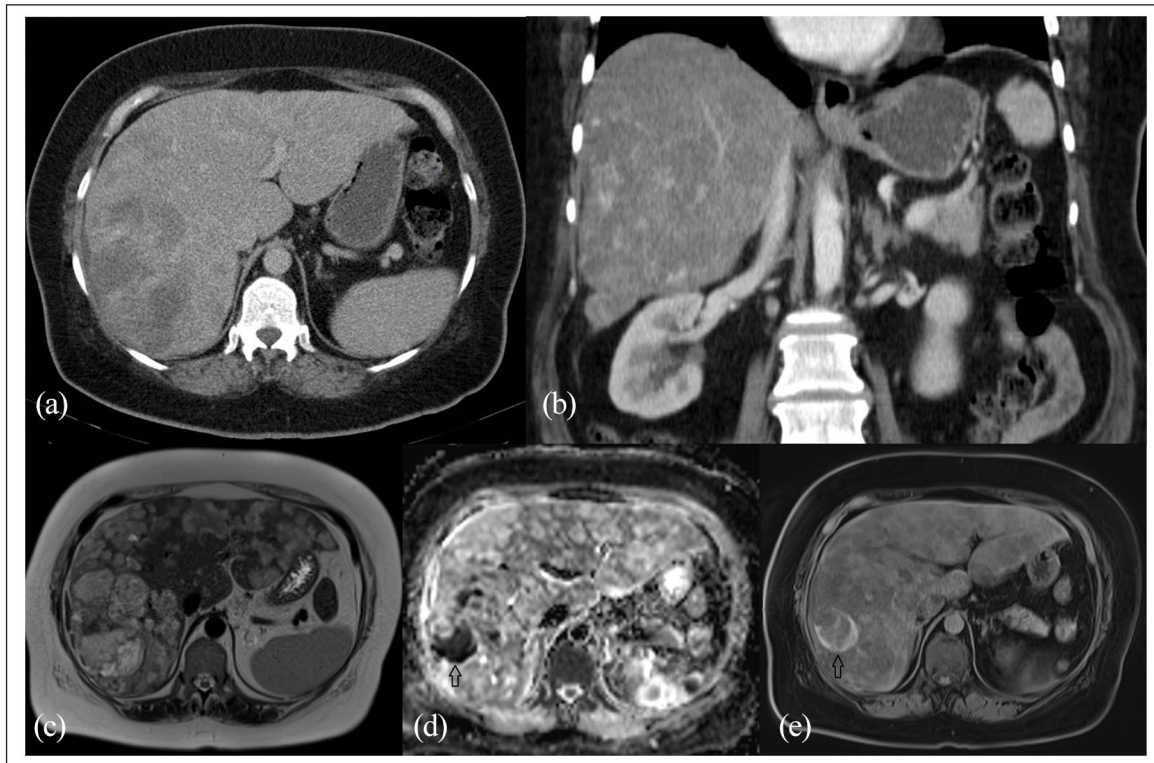
<sup>3</sup>SA Pathology, Adelaide, SA, Australia

## Corresponding Author:

Katerina Flabouris, Royal Adelaide Hospital, 1 Port Road, Adelaide, SA 5000, Australia.

Email: katerina.flabouris@adelaide.edu.au





**Figure 1.** (a) Non-contrast CT abdomen demonstrating multiple liver lesions with high attenuation. (b) Contrast CT abdomen demonstrating scattered foci with nodular enhancement. (c and d) MRI abdomen showing low T1 and high T2 signal. (e) MRI abdomen showing small area of high T1 signal and restricted diffusion in the right lobe of liver, likely representing haemorrhage.

interval (Figure 2(a)). A whole-body positron emission tomography (PET)/CT scan confirmed widespread malignant involvement of the liver and bones (Figure 2(b)–(d)), and a bone biopsy revealed a poorly differentiated large cell cancer of unclear source. The patient's condition continued to deteriorate from worsening liver failure, and she died 3 months after her first presentation.

At autopsy, there was marked hepatomegaly with extensive replacement of the liver parenchyma by tumour nodules at various stages of haemorrhage, thrombosis and necrosis (Figure 3(a)). Metastatic deposits were present in the spleen, lungs and vertebrae. Histological examination revealed a tumour composed of hyperchromatic and highly pleomorphic spindled and epithelioid cells. Brisk mitotic activity was evident, with numerous atypical mitoses. Immunohistochemistry demonstrated endothelial differentiation of the tumour cells, with strong and diffuse positivity for CD31, CD34 (Figure 3(b)) and ERG. A diagnosis of hepatic angiosarcoma with multiple distant metastases was made.

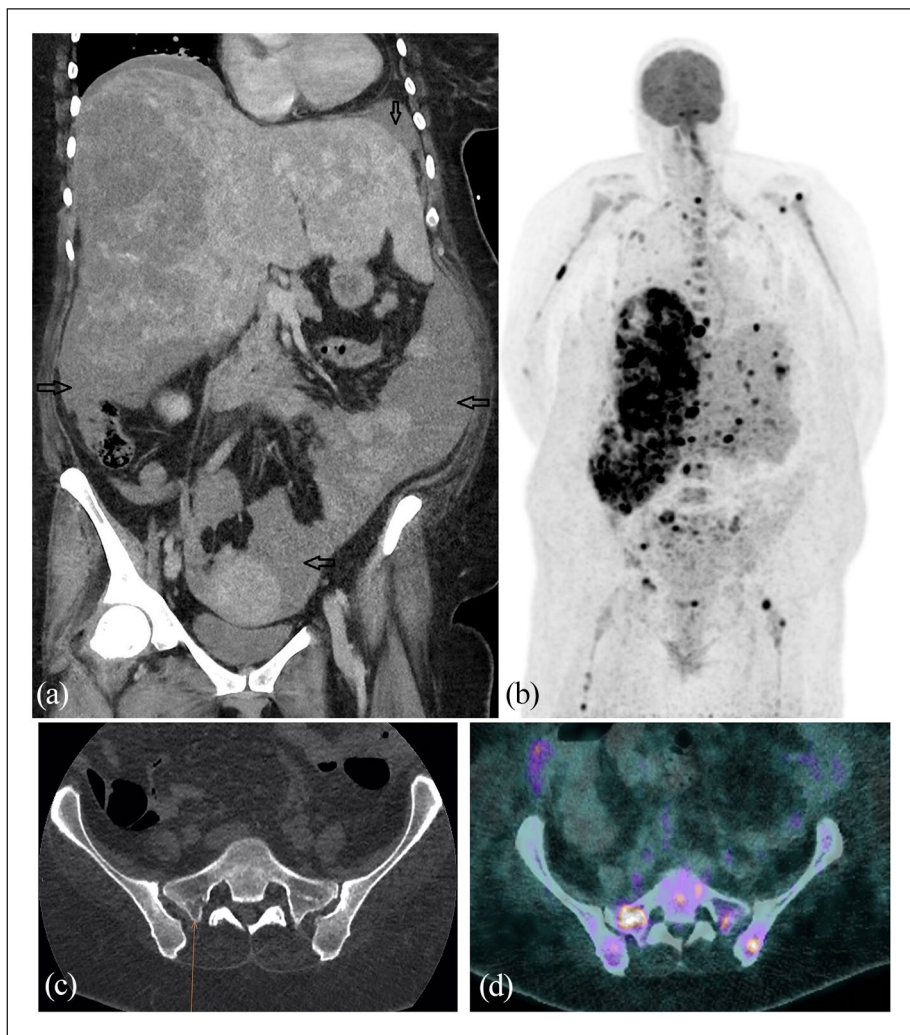
## Discussion

Hepatic angiosarcomas can be very difficult to diagnose antemortem. Clinical presentation and investigations can vary and be relatively non-specific.<sup>6–10</sup> The radiological features can also vary widely, therefore resulting in hepatic

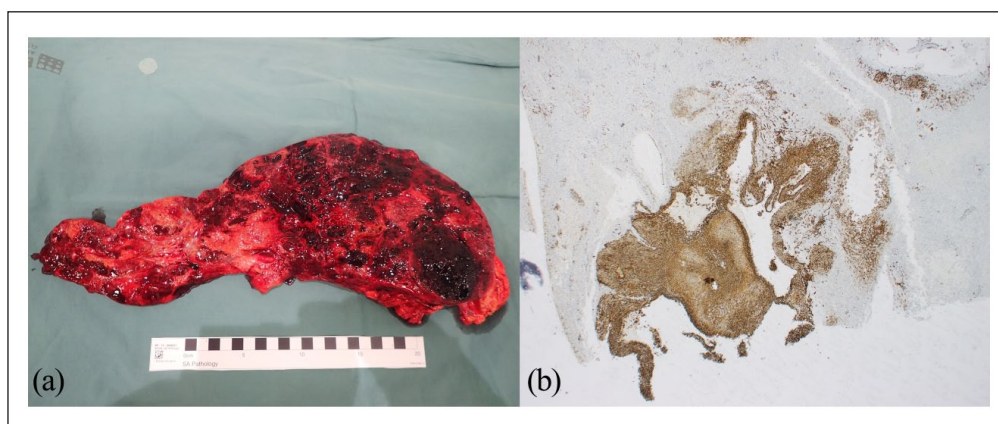
angiosarcomas commonly being mistaken for haemangiomas or other liver tumours.<sup>9,11</sup> They may present as multiple hypoattenuating nodules, or single dominant masses with necrosis and irregular hypervascularity, with an average size of 7–9 cm at diagnosis.<sup>6,11,12</sup> Furthermore, attempts at radiology-guided percutaneous biopsies may be met with limited diagnostic success due to the high rates of necrosis and haemorrhage with these tumours.<sup>8,13</sup> Alternative approaches such as open biopsy may need to be considered in this instance.

While there are some potential clues to the diagnosis, none are sufficient in isolation. A grossly elevated D-dimer may reflect high rates of intra-lesional thrombosis and haemorrhage.<sup>12</sup> Serial radiological imaging may reveal the particularly aggressive growth rate of the tumour, and MRI characteristics may prove more useful than those seen on CT or ultrasound. PET imaging has also proven to be enlightening.<sup>14–16</sup> Histologically, these tumours may be composed of pleomorphic spindle or epithelioid cells, often with bizarre or multinucleated forms and mitosis.<sup>7</sup> Immunohistochemistry is usually positive for vascular markers, including ERG transcription factor, CD31, CD34 and Factor VIII antigen.<sup>6</sup>

Hepatic angiosarcomas are as difficult to treat as they are to diagnose. They are frequently metastatic at the time of diagnosis due to their inherently aggressive nature and can rapidly progress to involve lymph nodes, lung, bone and spleen.<sup>8,17</sup> Early surgical intervention remains a cornerstone



**Figure 2.** (a) CT abdomen revealing rapid interval growth with haemoperitoneum. (b) PET scan demonstrating a grossly enlarged liver containing innumerable peripheral foci of radiotracer activity with a large photopaenic area in the right lobe, and further separate foci of tracer scattered in the left lobe. There are also innumerable FDG-avid bony deposits. (c) CT pelvis revealing a pathological fracture (arrow). (d) Corresponding PET image demonstrating FDG-avid lesion in the same area.



**Figure 3.** (a) Macroscopic view of the liver at autopsy revealing extensive tumour infiltration. (b) Microscopic view of section of liver at autopsy revealing strongly positive staining to CD34.

of treatment.<sup>8</sup> Unlike patients with certain hepatocellular carcinomas, hepatic angiosarcomas remain an absolute contraindication for liver transplantation.<sup>10,18</sup> There is, however, a potential role for trans-arterial chemoembolisation (TACE), particularly in cases complicated by acute bleeding.<sup>9,19</sup> Anthracycline-based chemotherapy regimens tend to predominate, and research is ongoing into alternative agents.<sup>20</sup> Nevertheless, overall median survival remains poor, even compared to other soft tissue sarcomas, with some estimates of as little as 6 months, even with treatment.<sup>8,21</sup> Death is usually due to liver failure or intra-abdominal bleeding.<sup>6,21</sup>

## Conclusion

Hepatic angiosarcomas are rare, aggressive and deceptive malignancies, frequently complicated by intra-abdominal bleeding. Radiological findings can be misleading but rapidly progressive, and histological findings on percutaneous biopsy can be ambiguous. This case emphasises the importance of careful and thorough diagnostic radiological evaluation prior to proceeding to biopsy, where more invasive approaches should be considered if percutaneous attempts are not enlightening. Early surgical resection is crucial, but often largely ineffective due to the high rates of metastasis at the time of diagnosis. Further research is required to guide future therapies.

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Our institution does not require ethical approval for reporting individual cases or case series.

## Informed consent

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## ORCID iD

Katerina Flabouris  <https://orcid.org/0000-0001-8923-824X>

## Supplemental material

Supplemental material for this article is available online.

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