



Case report

Case report: Haemoperitoneum secondary to acute rupture of primary hepatic angiosarcoma

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ABSTRACT

Introduction and importance: Primary hepatic angiosarcoma (PHA) is a rare and aggressive liver malignancy of endothelial cell origin and is associated with poor outcome. Pre-operative confirmation of the diagnosis is challenging, as clinical and radiological findings are generally non-specific. Very rarely, spontaneous haemoperitoneum may occur due to the spontaneous rupture of previously undiagnosed PHA.

Case presentation: We describe a case of a 28-year-old male with haemoperitoneum due to the rupture of previously undiagnosed PHA. After failing to respond to the non-operative measures, the patient underwent emergency partial liver resection and recovered without any post-operative complications. Histopathological examination of the specimen confirmed the diagnosis of PHA. Two months after the operation, the patient represented with advanced metastatic disease and disseminated intravascular coagulation (DIC). The patient died one month after discharge.

Clinical discussion: A patient with PHA presents a diagnostic challenge due to its rare incidence and non-specific clinical findings. Spontaneous intra-abdominal haemorrhage can occur due to PHA rupture and carries a dismal prognosis. In addition to emergency haemorrhage control, complete surgical resection with clear margins is the definitive treatment to date, however, most cases of PHA are unresectable at diagnosis and recurrence is common even after complete resection.

Conclusion: PHA is associated with very poor outcomes, due to its rapid progression, early recurrence, and metastatic nature. The median survival is approximately 5 months. Haemoperitoneum secondary to rupture of previously undiagnosed PHA is uncommon and is a poor prognostic indicator. Complete surgical resection of the disease is challenging and there is no established treatment.

1. Introduction and importance

Angiosarcoma, a rare soft tissue sarcoma, is an aggressive malignant disease of endothelial cells that line blood or lymphatic vessels [1,2]. Primary hepatic angiosarcomas (PHA) account for less than 5% of all angiosarcomas and are associated with poorer outcome, compared to other subtypes of angiosarcoma [3,4]. Although it is the most common primary malignant mesenchymal tumour of the liver, it only accounts for 0.1–2.0% of all primary liver malignancies [1,2]. PHA occurs predominantly in men, 60–80 years of age, with a male-to-female ratio of 3–4:1 [1]. Previously, 25% of PHA cases were associated with occupational or medicinal exposure to chemical carcinogens, however, most cases are now considered idiopathic [2,5]. Pre-operative confirmation of

the diagnosis is challenging, as clinical and radiological findings are generally non-specific [1,2,6]. Rarely, haemoperitoneum may occur due to the spontaneous rupture of previously undiagnosed PHA [1,6]. PHA carries a poor prognosis due to its rapid progression, high recurrence rate and early metastatic nature [1,7]. This is a case report of a 28-year-old male who presented with haemoperitoneum due to PHA rupture and underwent emergency partial liver resection. This work has been reported in line with the SCARE 2020 criteria [8].

2. Case presentation

A 28-year-old male presented to the Emergency Department (ED) with a 5-day history of severe abdominal pain on a background of

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intermittent abdominal pain for the last five weeks. There was no significant past medical or family history. On presentation, the patient was alert and oriented, with a blood pressure of 128/90 mm Hg, heart rate (HR) of 140 beats/min and oxygen saturations of 97% on room air. His temperature was 38.5 °C. On examination, his abdomen was soft with mild right upper quadrant tenderness, however there were no signs of peritonism. His initial laboratory results showed a white cell count (WCC) of $14.9 \times 10^9/L$, a neutrophil count of $12.4 \times 10^9/L$, haemoglobin (Hb) of 99 g/L, and platelet count of $179 \times 10^9/L$. C-reactive protein (CRP) was 23 mg/dL. Liver function tests (LFTs) showed gamma-glutamyl transferase (GGT) of 59 units/L, alkaline phosphatase (ALP) of 90 units/L, alanine transaminase (ALT) of 45 units/L, aspartate transaminase (AST) of 36 units/L. Lactate was 1.7 mmol/L. Tumour markers, such as carbohydrate antigen 19.9 (CA 19.9) 4 kU/L, carcinoembryonic antigen (CEA) $<1 \mu\text{g/L}$, and alpha-fetoprotein (AFP) 2.0 kU/L, were not elevated. Hepatitis B, hepatitis C serology and human immunodeficiency virus (HIV) results were all negative.

The initial computed tomography of abdomen pelvis (CTAP) revealed a $13 \times 10.6 \times 10.9$ cm irregular mass in liver segment 8 with rim enhancement and central necrosis, as well as moderate free fluid. The suspected initial diagnosis was haemangioma, however primary hepatic malignancy was not excluded. The patient commenced a trial of non-operative management and was provided with intravenous fluids and empirical antibiotics. After 48 h, the patient failed to respond to the non-operative measures. Further imaging with multiphase CT remained concerning for active bleeding secondary to the ruptured liver mass (Fig. 1).

The interventional transcatheter arterial embolisation (TAE) was not an available option at our centre and surgical control of bleeding was required. An emergency partial hepatic resection was performed. Intraoperatively, the ruptured mass of the right lobe of the liver and another small subcapsular mass in segment VI were found. There was significant intraperitoneal blood. Subsegmental resection of the lesion in segment VI and resection of the segment V and VIII were performed without complications (Fig. 2). The patient was admitted to the intensive care unit for post-operative care and subsequently discharged to the ward after two days. The initial histopathology result was suggestive of PHA. The specimen was sent to a tertiary centre in Sydney for further testing to confirm the diagnosis. The patient was discharged home on postoperative day 12.

Subsequent outpatient positron emission tomography (PET) for staging showed extensive residual tumours in the liver, and metastases in bilateral lungs and left ribs. On outpatient follow up with an oncologist, chemotherapy with weekly paclitaxel was suggested, however, the patient declined the treatment.

Two months after the operation, the patient represented to the ED with headache and toothache. Laboratory results showed Hb of 69 g/L, and platelet count of $117 \times 10^9/L$. Coagulation studies showed a

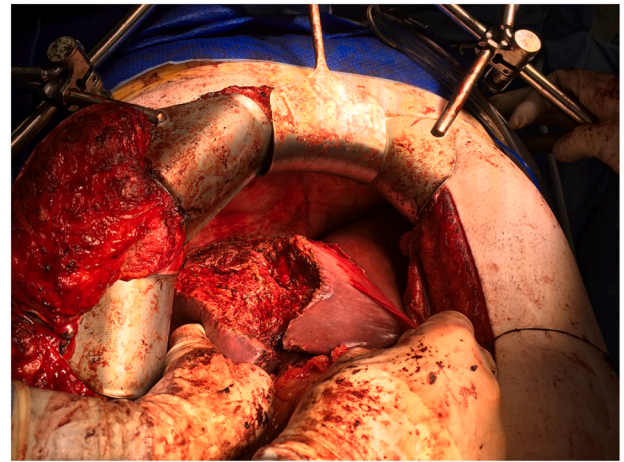


Fig. 2. Intraoperative appearance of the liver post resection.

positive d-dimer (>20), international normalized ratio (INR) of 1.6, prothrombin time (PT) of 23 s, fibrinogen of 1.2 g/L, activated partial thromboplastin time (APTT) of 46 s. Disseminated intravascular coagulation (DIC) was suspected. LFTs were more elevated, with a bilirubin of $22 \mu\text{mol/L}$, GGT of 362 units/L, ALP of 320 units/L, ALT of 149 units/L and AST of 119 units/L. Computed tomography of brain, chest, abdomen, and pelvis showed extensive disease progression throughout the liver and the omentum, and extensive pulmonary metastases with a right sided pleural effusion (Fig. 3). The patient was discharged to the palliative care unit at a private hospital nearby and survived for one month after the discharge.

2.1. Histopathology

Macroscopic examination of the liver segment V/VIII resection showed a disrupted capsule in association with a lobulated mass measuring $135 \times 90 \times 55$ mm with haemorrhagic, spongy cut surface and central necrosis (Fig. 4). Histological examination showed a lesion characterized by anastomosing vascular channels lined by multilayered endothelial cells with pleomorphic nuclei and frequent mitotic figures, solid nodules of similar atypical spindle endothelial cells and focal areas of epithelioid morphology were noted. Central necrosis was confirmed. The interface with the background liver parenchyma was well defined although limited extension of atypical endothelial cells into sinusoids and entrapped hepatocytes were seen at the periphery.

Immunohistochemistry showed strong and diffuse staining of tumour cells for CD31, CD34 (Fig. 5), ERG, Fli-1, and P53. Immunostains for AE-1+3, S100, Melan-A and HMB-45 were negative. Ki-67 immunostaining highlighted 30–40% of tumour nuclei. Histopathology was consistent



Fig. 1. Repeat CT abdomen with arterial, venous, delayed phase showed a large irregular mass in the liver and intra-abdominal free fluid.

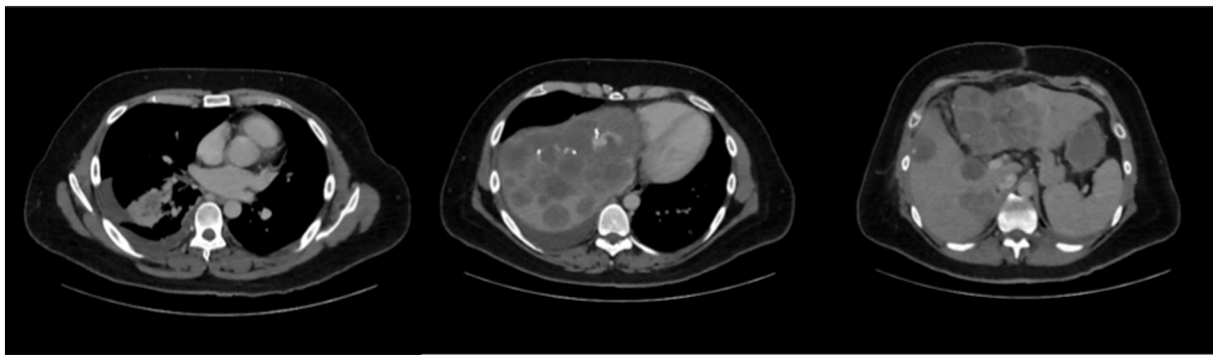


Fig. 3. CT chest and abdomen showed the recurrence and metastases of the disease.

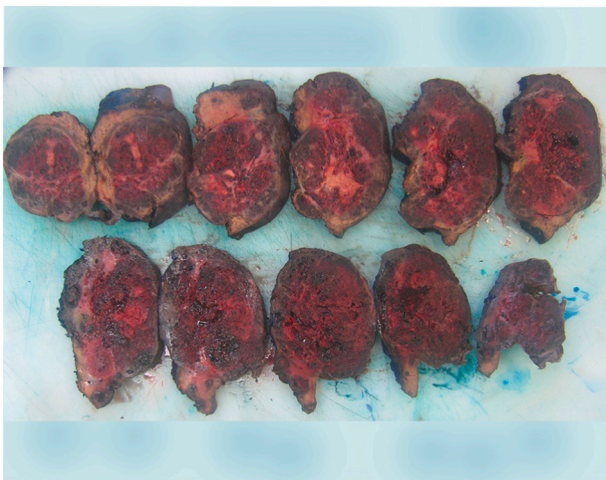


Fig. 4. Lobulated haemorrhagic tumour with central necrosis.

with PHA.

3. Clinical discussion

Primary hepatic angiosarcoma is a rare and aggressive liver malignancy of endothelial cell origin [1,2]. It is the third most common primary liver cancer, after hepatocellular carcinoma (HCC) and cholangiocarcinoma, and the most prevalent primary malignant mesenchymal tumour of the liver [1,2].

This report describes a case of a previously healthy 28-year-old male with spontaneous haemoperitoneum secondary to the rupture of PHA, who was managed at a regional centre. As demonstrated in our case, the diagnostic challenges in PHA are partly attributed to its rarity and non-specific clinical findings. Patients commonly present with vague symptoms such as abdominal pain, distension, weight loss, fatigue, and anorexia, but many cases can be asymptomatic [2,6]. As a result, the initial diagnosis is usually made at an advanced stage [1,2,6]. Common signs of advanced PHA include hepatomegaly, jaundice, and ascites [6]. 9% of patients with PHA will present with symptoms secondary to metastatic disease, the most common site being lung and spleen [9,10].

Laboratory results in the setting of PHA are usually non-specific, as was seen in our case. Non-specific elevations of liver enzymes and mild

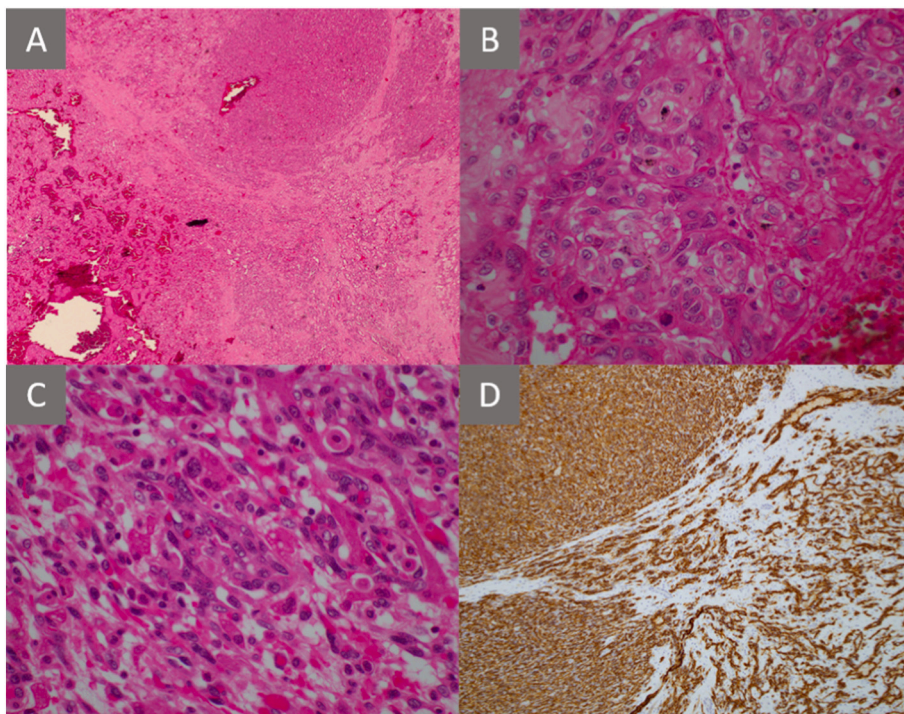


Fig. 5. A: Anastomosing vascular channels and solid nodules (H&E 4×).
 B: Focal epithelioid nodules (H&E 40×).
 C: Atypical spindle cells infiltrating sinusoids at periphery (H&E 40×).
 D: CD34 (4×).

hyperbilirubinaemia are common [2]. Thrombocytopenia is common, secondary to sequestration of platelets within the tumour, and this increases the likelihood of spontaneous rupture of the tumour and intra-abdominal bleeding [11]. Anaemia can result from the rupture of PHA and subsequent intraperitoneal bleeding. To date, there is no tumour marker specific for PHA. Tumour markers, such as CA 19-9, CEA, and AFP, are usually unremarkable or slightly elevated [4,10].

Radiological investigations in our case revealed non-specific findings mimicking hepatic haemangioma. PHA is associated with various enhancement patterns on imaging, due to its hypervascularity and pleomorphic tumour histology [12]. Although PHA is typically multifocal, its growth pattern can vary [10,13]. Thus, it is often difficult to differentiate from other hepatic tumours, such as HCC and hepatic haemangioma.

Acute intra-abdominal bleeding may occur secondary to the spontaneous rupture of PHA, as previously described by a few case reports [9,14–16]. Haemoperitoneum due to spontaneous tumour rupture occurs in 15–27% of PHA cases and DIC may develop subsequently [2]. This should be considered an indicator of a malignant tumour, as benign tumours such as hepatic haemangioma rarely undergo spontaneous rupture [2,9]. Furthermore, haemoperitoneum in PHA is a poor prognostic factor, as it leads to subsequent tumour cell spillage and peritoneal tumour seeding [2,9,16]. TAE is usually the first choice for emergency haemorrhage control because this eliminates the need for emergency liver surgery if successful and provides sufficient time to plan for elective liver resection [9,16]. Unfortunately, TAE was not an option in our case, due to limited access to interventional radiology services at our centre. Transfer to a tertiary centre for TAE was not feasible due to haemodynamic instability with ongoing tachycardia and decreasing haemoglobin level.

Pathological diagnosis is essential in PHA and this requires good understanding of a wide spectrum of morphological and pathologic patterns of PHA. A recent study by Yasir et al. reviewed 21 PHA cases and reported four different morphological patterns, with the mass-forming and vasoformative pattern being the most commonly observed [17]. On immunohistochemistry analysis, angiosarcoma usually expresses typical vascular markers, such as CD 31, CD 34, Factor VIII-related antigen, and ERG [18]. Other markers have been found to be variably positive in PHA, such as Pan-cytokeratin (CK), vimentin, GPC-3, desmin, Ki-67 [19].

PHA carries a dismal prognosis and there are no established treatment guidelines. The reported median survival is approximately 5 months, with only 3% of patients living for more than 2 years even after treatment [4,6]. The most common causes of death include liver failure, DIC, and haemorrhagic shock [2,4]. Complete surgical resection with clear margins remains the cornerstone of definitive treatment to date, however, most cases of PHA are unresectable at diagnosis and recurrence is common even after complete resection [1,2,6]. Transplantation has no role in the management of PHA due to its high recurrence rate and poor prognosis and evidence on adjuvant chemotherapy is limited [20].

4. Conclusion

PHA has a very poor prognosis, due to its rapid progression, early recurrence, and metastatic nature. This case demonstrates that a patient can rarely present with spontaneous haemoperitoneum secondary to the rupture of undiagnosed PHA and this is a poor prognostic factor. Complete surgical resection of the disease is challenging and there is no established treatment.

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.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Ethical approval

The case report was notified to the ethical committee of the hospital. Ethical approval has not been requested for this case report, according to hospital protocol.

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Boyoung Kim, Gratian J. Punch.

Research registration number

Not applicable.

CRediT authorship contribution statement

Boyoung Kim - data collection, analysis, writing – original draft, review, and editing.

Rebecca Reardon - data collection, writing – original draft, performed the surgery.

Jane Cross – review, performed the surgery.

Trafford Fehlberg – review, performed the surgery.

Ben Allanson – data collection, analysis, writing – original draft, review and editing.

Gratian J. Punch – study concept/design, data collection, analysis, review and editing, supervision, performed the surgery.

Declaration of competing interest

None.

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