Case report

Acute liver failure due to primary angiosarcoma: A case report and review of literature
Chandra S Bhati, Anand N Bhatt, Graham Starkey, Stefan G Hubscher and Simon R Bramhall*

Address: Liver Unit, Queen Elizabeth Hospital, Birmingham, UK
Email: Chandra S Bhati - c.s.bhati@bham.ac.uk; Anand N Bhatt - anb1234@hotmail.com; Graham Starkey - grahamstarkey@bigpond.com; Stefan G Hubscher - stefan.hubscher@uhb.nhs.uk; Simon R Bramhall* - simon.bramhall@uhb.nhs.uk
* Corresponding author

Abstract
Background: Hepatic angiosarcoma is a primary sarcoma of the liver, accounting for only 2% of all primary hepatic malignancies. Acute liver failure is an extremely rare presentation of a primary liver tumour.

Case presentation: We report a case of a seventy year-old man who presented with a very short period of jaundice leading to fulminant hepatic failure (FHF). On further investigation he was found to have primary angiosarcoma of liver.

Conclusion: The treatment outcomes for hepatic angiosarcoma are poor, we discuss the options available and the need for prompt investigation and establishment of a diagnosis.

Background

Hepatic malignancies include primary hepatocellular carcinoma, metastases and primary or metastatic sarcomas [1]. Hepatic angiosarcoma is a primary sarcoma of the liver which accounts for only 2% of all primary hepatic malignancies [2-5]. Angiosarcoma is associated with environmental or occupational exposure to carcinogens (thorium dioxide, vinyl chloride, arsenic and radiation). There is also an association with hemochromatosis and von Recklinghausen disease [1,2,4]. In most cases of primary hepatic angiosarcoma, no obvious risk factor can be identified.

The most common causes of fulminant hepatic failure (FHF) are drug toxicity and sero-negative hepatitis [6]; rarer causes include Bud-Chiari syndrome and acute Wilson's disease. FHF can also develop very rarely as a consequence of primary or metastatic liver tumour, this generally occurs as a result of massive neoplastic infiltration of the hepatic sinusoids leading to secondary necrosis of hepatocytes [7]. Rowbotham et al reported 4020 cases of FHF, malignant infiltration accounted for only 0.44% (18 cases) [8].

There have been a number of case series reporting FHF secondary to infiltration of the liver by malignant cells [7-15], haematological malignancies are the most common [7-10]. Other infiltrative metastatic malignancies that rarely cause FHF include adenocarcinoma, melanoma, and anaplastic tumours [11-15]. Although hepatic dysfunction due to malignancy such as hepatocellular carcinoma or metastatic infiltration is common, acute liver failure in these cases is rare. We report a case of primary angiosarcoma of the liver which presented with FHF.
Case presentation
A seventy year old Caucasian male, who had no significant previous medical history, was admitted to a local hospital with a history of sudden onset jaundice and weight loss. There was no previous history of jaundice or hepatitis. There was no significant history of alcohol intake or exposure to arsenic, vinyl chloride, or Thorotrast. He never used any hepatotoxic or herbal medications and his mother died of undiagnosed liver disease.

Upon examination the patient was jaundiced without encephalopathy or focal neurological findings. He had bilateral pedal oedema and hepatomegaly. The patient did not have any other signs of liver failure. Liver function tests at admission revealed a total bilirubin of 203 mmol/dL (normal, 5–17 mmol/dL), aspartate aminotransferase (AST) 52 IU/L (normal, 4–44 IU/L), alkaline phosphatase 170 IU/L (normal, 67–213 IU/L), albumin 2.0 g/dL, PT 22 seconds, APTT 51 seconds and platelets 113,000/cm³.

An urgent ultrasound scan demonstrated hepatomegaly with significant liver paranchymal alteration. A subsequent contrast enhanced abdominal CT showed gross replacement of liver with tumour tissue suggestive of a primary liver tumour (Figure 1). The patient was at this point referred to our centre.

The patient's initial evaluation in our Unit showed further derangement in the patient's liver function tests; total bilirubin had risen to 401 mmol/dL, AST to 132 IU/L, alkaline phosphatase to 370 IU/L and INR to 2.1. A local review of his CT scan raised the possibility of angiosarcoma. To confirm the diagnosis a transjugular biopsy was arranged as the clotting abnormality had been resistant to correction with fresh frozen plasma at the referring centre. Before this could be carried out patient rapidly deteriorated after admission and became progressively encephalopathic, consistent with FHF. He was treated conservatively with dextrose and broad spectrum antibiotics but deteriorated further and died two days after admission to the liver unit.

A post mortem liver biopsy was carried out confirming initial suspicions that this was a primary angiosarcoma of the liver. Microscopically, tumour was composed of poorly cohesive cells, oval to spindle shaped with high grade cytological atypia. The tumour had a sinusoidal growth pattern surrounding clusters of hepatocytes forming cholestatic rosettes (Figure 2a). Immunohistochemistry staining was strongly and diffusely positive for vascular endothelial markers (CD31, CD34) (Figure 2b) and vimentin. Stains for the cytokeratins and hepatocyte specific antigen highlighted the presence of entrapped non neoplastic hepatocyte and bile ducts. Staining for smooth muscle actin appeared to be confined to areas of fibrotic tissue.

Discussion
Angiosarcoma usually presents in late adulthood [2] with abdominal discomfort, distension, weight loss, and fatigue [4,16]. On examination, the patients may have jaundice, hepatomegaly, and ascites [4,16,17]. Our patient was admitted with similar symptoms. Fulminant hepatic failure (FHF) is defined as liver disease that results in encephalopathy within 28 days from the onset of jaundice in a patient with no prior evidence of liver disease. Presentation as FHF is rare, Table 1 shows published reports of clinical presentation and treatment of angiosarcoma in the current literature. In an adult FHF Study Group; acetaminophen overdose (46%), drug toxicity (11%) and hepatitis (10%) were found to be the most common causes for liver failure [18]. There are case reports where association of FHF with liver metastasis from other malignancies have been reported [7-15].

The liver is commonly involved in metastatic disease, and the degree of liver biochemistry derangement tends to reflect the extent of parenchymal replacement with tumour [19]. In this patient, liver function tests were only slightly abnormal two weeks before development of FHF. Although, alteration of liver function tests in these patients is very common [20], liver failure is extremely rare.
CT scan is often diagnostic, demonstrating multiple hypodense areas typical of angiosarcoma. Post contrast, the lesions become partly or completely isodense compared with normal hepatic tissue [1,21]. In our patient liver parenchyma was completely replaced with tumour tissue (Figure 1).

The mechanism of liver failure is multifactorial. Evidence suggests a combination of hepatic ischaemia leading to parenchymal infarction, vascular occlusion of portal vein by tumour thrombi and nonocclusive infarction of liver due to shock from secondary causes such as sepsis or cardiac dysfunction plays an important role in these patients [12,22]. In this patient, replacement of hepatocytes by malignant cells, leading to secondary necrosis of hepatocytes played a significant role in development of liver failure.

Angiosarcoma has very limited treatment options, without treatment the majority of patients die within 6 months of diagnosis [4]. Surgery has a limited role due to the advanced stage at which these tumours present. Liver

Figure 2
(A) Liver biopsy showing sinusoidal infiltration by pleomorphic spindle cells typical of hepatic angiosarcoma. There is disruption of the normal trabecular architecture with hepatocytes forming glandular structures containing bile plugs ("cholestatic rosettes"). (B) Spindle cells are strongly immunoreactive for the vascular endothelial marker CD34. (A = Haematoxylin and eosin, B = immunoperoxidase).
transplantation is contraindicated, as patients who have been transplanted incidentally have not shown any survival benefit. The data from European Liver Transplant Registry on 17 patients who had undergone transplantation for angiosarcoma had a median survival of only 7 months [23]. Hepatic resection has been reported in patients with limited disease but these results have also been poor. There are very few published case reports with good survival after liver resection (16 months [24] and 10 years [4]). The role of chemotherapy has been described with very limited improvement in overall length of survival [25]. Treatment with new techniques like transcatheter arterial chemoembolization (TACE) techniques has been described as a case report with very limited success in overall survival improvement [26].

**Conclusion**

Our patient presented with mild hepatic failure that rapidly progressed to FHF. In the absence of a clear aetiology for FHF primary liver tumour must be considered in the differential diagnosis and a biopsy should be arranged to reach definitive diagnosis.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

CSB – Contributions to case selection, analysis and drafting of the manuscript. ANB – Case analysis and initial drafting of manuscript. GS – Contributions to conception, arranging histopathology, revision of the manuscript. SGH – Histopathology evaluation, further study of slides and in depth analysis. SRB – Critical revision and final approval of the version to be published. All authors read and approved the final manuscript.

**Consent**

Written informed consent was obtained from the patient for publication of this case report.

**References**

1. Buetow PC, Buck JL, Ros PR, Goodman ZD: Malignant vascular tumours of the liver: radiologic-pathologic correlation. Radiographics 1994, 14:153-166.
2. Tanaka H, Yun Thioll D et al: Mesenchymal tumors of the liver. Clin Liver Dis 2001, 5(1):219-257.
3. Molina E, Hernandez A: Clinical manifestations of primary hepatic angiosarcoma. Dig Dis Sci 2003, 48(4):677-682.
4. Timaran CH, Grandas OH, Bell JL: Hepatic angiosarcoma: long-term survival after complete surgical removal. Ann Surg 2000, 266(12):1153-1157.
5. Budd GT: Management of angiosarcoma. Current Oncology Reports 2002, 4(6):515-519.
6. Lee W, Schiodt F: Fulminant hepatic failure. In Schiff's Diseases of the Liver Volume 1, Edited by: Schiff E, Sorrell M, Maddrey W. Philadelphia: Lippincott-Raven; 1999:879-895.
7. Emile JF, Azoulay D, Gornet JM, Lopes G, Delvart V, Samuel D, Remyes M, Bismuth H, Goldwasser F: Primary non-Hodgkin’s lymphomas of the liver with nodular and diffuse infiltration patterns have different prognoses. Ann Oncol 2001, 12:1005.
8. Rowbotham D, Wendon J, Williams R: Acute liver failure secondary to hepatic infiltration: a single centre experience of 18 cases. Gut 1998, 42(4):576-80.
9. Ghosh P, Fox IJ, Rader AM, Sorrell MF: Fulminant hepatic failure as the initial manifestation of non-Hodgkin's lymphoma. J Gastroenterol 1995, 90:2207-2209.
10. Zafarni ES, Leclercq B, Vernant JP, Pinaudeau Y, Chomette G, Dhumeaux D: Massive ductal infiltration of the liver: a cause of fulminant hepatic failure. Hepatology 1981, 3:428-432.
11. Alexopoulou A, Koskinas J, Deutsch M, Della Missia J, Kountouras D, Dourakis SP: Acute liver failure as the initial manifestation of hepatic infiltration by a solid tumor: report of 5 cases and review of the literature. Tumori 2006, 92(4):354-357.
12. Harrison HB, Middleton HM, Crosby JH 3rd, Crosby JH, Dasher MN Jr: Fulminant hepatic failure: an unusual presentation of metastatic liver disease. Gastroenterology 1981, 80:820-825.
13. Rajvanshi P, Kowdle KV, Hirota WK, Meyers JB, Keeffe EB: Fulminant hepatic failure secondary to neoplastic infiltration of the liver. J Clin Gastroenterol 2005, 39(4):339-43.
14. Ashanasakis E, Mouloudi E, Prinianakis G, Kostaki M, Tzardid M, Georgopoulos D: Metastatic liver disease and fulminant hepatic failure: presentation of a case and review of the literature. Eur J Gastroenterol Hepatol 2003, 15:1235-40.
15. Tanaka M, Watanabe S, Masaki T, Kurokohchi K, Kinekawa F, Inoue H, Uchida N, Kuriyama S: Fulminant hepatic failure caused by malignant melanoma of unknown primary origin. J Gastroenterol 2004, 39(8):804-6.
16. Forbes A, Portmann B, Johnson P, Williams R: Hepatic sarcomas in adults: a review of 25 cases. Gut 1987, 28(6):668-74.
17. Poggio JL, Nagorney DM, Nascimento AG, Rowland C, Kay P, Young RM, Donohue JH: Surgical treatment of adult primary hepatic sarcoma. Br J Surg 2000, 87:1500-1505.
18. Lee WM, Squires RH Jr, Nyberg SL, Doo E, Hoofnagle JH: Acute liver failure: Summary of a workshop. Hepatology 2008, 47(4):1-401-15.
19. Jaffe B, Donegan W, Watson F, Spratt W: Factors influencing survival in patients with untreated hepatic metastases. Surg Gynecol Obstet 1968, 127:1-11.
20. Roth A, Kolanic K, Dominis M: Histologic and cytologic liver changes in 120 patients with malignant lymphomas. Tumori 1978, 64:45-53.
21. Rademaker J, Widjaja A, Galinski M: Hepatic hemangiosarcoma: imaging findings and differential diagnosis. Eur Radiol 2000, 10(1):129-33.
22. Okuda K, Musha H, Kanno H, Igarashi M, Nakano M: Localized sub massive liver cell necrosis as a terminal event of liver carcinoma. Cancer 1976, 37:1965-1972.
23. Lerut J: Liver transplantation and vascular tumours, 7th World Congress of the International Hepato-Pancreato-Biliary Association In, Edinburgh UK 2006.
24. Arima-Iwasa S, Chijiwa K, Makino I, Tanabe R, Ohuchida J, Kondo K: A case of hepatic angiosarcoma surviving for more than 16 months after hepatic resection. Hepatogastroenterology 2007, 54(74):533-5.
25. Vennarecci G, Ismail T, Gunson B, McMaster P: Primary angiosarcoma of the liver. Minerva Chir 1997, 52(10):1141-6.
26. Stambo GW, Guiney MJ: Hepatic angiosarcoma presenting as an acute intraabdominal hemorrhage treated with transarterial chemoembolization. Sarcoma 2007:90169.
27. Husted TL, Neff G, Thomas MJ, Gross TG, Woodle ES, Buell JF: Liver transplantation for primary or metastatic sarcoma to the liver. Am J Transplant 2006, 6(2):392-7.
28. Weitz J, Klimestra DS, Cymes K, Jarnagin WR, D’Angelica M, La Quaglia MF, Feng Y, Brennan MF, Blumgart LH, Dematteo RP: Management of primary liver sarcomas. Cancer 2007, 109(7):1391-6.