CASE REPORT

Primary hepatic hemangioendothelioma in a patient with Budd-Chiari syndrome

Preet Mukesh Shah,¹ Vijay Waman Dhakre,² Aabha Nagral¹

¹Department of Medical Gastroenterology, Jaslok Hospital and Research Centre, Mumbai, India

²Department of Surgical Gastroenterology, Jaslok Hospital and Research Centre, Mumbai, India

Correspondence to
Dr Vijay Waman Dhakre,
vddrvijayd@gmail.com

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SUMMARY

A 36-year-old woman was diagnosed with compensated cirrhosis of liver secondary to Budd-Chiari syndrome (BCS) and had undergone stenting of a thrombosed left hepatic vein. Eight months later, she presented with jaundice and right upper quadrant pain. CT revealed multiple focal lesions in the liver, which on biopsy proved to be hepatic hemangioendothelioma (HHE). Her liver disease and ascites progressively increased. Four months later, magnetic resonance cholangiopancreatography showed an advanced stage of HHE with infiltration of the common bile duct and vascular invasion with a blocked stent, with metastasis to the spleen and dorsolumbar vertebrae. We believe this is the first reported case of an HHE developing in the background of BCS.

BACKGROUND

In patients with cirrhosis, the most commonly encountered liver tumours are hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma.¹

Hepatic hemangioendothelioma (HHE) is a very rare tumour with an incidence of <1 per 1 million. Furthermore, it is rare in the setting of chronic liver disease (CLD). We describe a case of HHE developing in the setting of cirrhosis, secondary to Budd-Chiari syndrome (BCS).

CASE PRESENTATION

A 36-year-old woman, with no history of consumption of alcohol or oral contraceptive pills or any other medications, first presented at another hospital in 2012 with right abdominal pain along with loss of appetite in the preceding 2 months. On examination, there was 3 cm palpable, soft to firm hepatomegaly, with no stigmata of CLD. Investigations revealed a haemoglobin of 11 g/dL (normal range is 12–16 g/dL for women), white cell (WBC) count of 11×10^9 /L (normal range is $4\text{--}11 \times 10^9$ /L), platelet count of 321×10^9 /L (normal range is $150\text{--}450 \times 10^9$ /L), total bilirubin of 1 mg/dL (normal range is 0–1 mg/dL), aspartate aminotransferase (AST) of 16 IU/L (normal range is 5–40 IU/L), alanine aminotransferase (ALT) of 19 IU/L (normal range is 5–40 IU/L), alkaline phosphatase of 121 IU/L (normal range is 30–185 IU/L), serum albumin of 3 g/dL (normal range is 3–5 g/dL), international normalised ratio of 1 and gamma-glutamyl transferase (GGT) of 66 IU/L (normal range is 5–45 IU/L for women). Serology for hepatitis viruses A, B, C and E was negative, antinuclear antibody was negative and serum ceruloplasmin was 32 mg/

dL (normal range is 15–60 mg/dL). Ultrasonography (USG) of the abdomen revealed hepatomegaly with coarse hepatic echotexture with hypertrophy of the caudate lobe and absence of any ascites or splenomegaly, all suggestive of cirrhosis of the liver. Doppler and contrast-enhanced CT (CECT) scan had not been done at that time.

The patient was asked to periodically monitor her liver function tests and follow-up. She was asymptomatic for 4 years, when she presented with an acute onset of right-sided abdominal pain. A CECT scan of the abdomen was done which showed abnormal enlargement and heterogeneous enhancement of the entire liver, with compression of the intrahepatic portion of the inferior vena cava (IVC), non-visualisation of the hepatic veins, normal portal vein, with mild splenomegaly and ascites, all suggestive of Budd-Chiari syndrome. For this, she was started on anticoagulants and diuretics, following which she improved. Her thrombophilia profile, consisting of factor V Leiden mutation, protein C and S activities, lupus anticoagulant, anticardiolipin and antiphospholipid antibodies, dilute Russell's viper venom screen, antithrombin III activity, JAK2 mutation and serum homocysteine levels, was normal.

She then underwent a hepatic venography where the left hepatic vein showed a filling defect suggestive of a thrombus and could be cannulated, whereas the right and middle hepatic veins were blocked and could not be cannulated. A balloon angioplasty with a stent placement in the left hepatic vein was done. She was on heparin followed by warfarin. Transjugular intrahepatic portosystemic stent shunt (TIPSS) was attempted but was not possible because of technical reasons.

Eight months later, she presented with abdominal pain and jaundice. USG of the abdomen and Doppler studies showed a patent stent in the left hepatic vein. A CECT of the abdomen was done which showed atrophy of the right lobe with heterogeneous parenchymal enhancement in the liver and large focal hypodense non-enhancing areas involving segments 2, 3, 4 and 8, multiple small hypodense lesions in the rest of the left lobe showing delayed enhancement, stent in the left hepatic vein in situ, the right hepatic vein not seen, compression of the intrahepatic IVC and mild ascites.

Tumour markers carcinoembryonic antigen, carbohydrate antigen (CA19-9) and alpha-fetoprotein were within normal limits.

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Figure 1 Tumour cells are present in cords and nests. The cells have moderate nuclear pleomorphism with a moderate amount of eosinophilic cytoplasm (A). There is no evidence of mitosis/necrosis. Prominent cytoplasmic vacuoles are seen, which contain red cells (B). Immunohistochemistry shows cells positively staining for cluster of differentiation (CD) 31 (C) and CD-34 (D). The staining pattern is membranous.

A CT-guided biopsy was taken from the liver lesion, which was suggestive of epithelioid hemangioendothelioma (tumour cells expressing cluster of differentiation 31 and 34 (CD31 and CD34), immunonegative for cytokeratin and epithelial membrane antigen on immunohistochemistry) (figure 1).

The patient was advised a liver transplant (LT), which she declined.

Four months later, she had developed increasing jaundice and abdominal distention and pain. She gave a history of multiple therapeutic abdominal paracentesis done outside, which was needed almost every 2 weeks. On examination, there was evidence of muscle wasting, and she was malnourished with icterus, pedal oedema and tense ascites.

INVESTIGATIONS

At last presentation, her haemoglobin was 10 g/dL, WBC count was $7 \times 10^9/L$, platelet count was $269 \times 10^9/L$, prothrombin time was >1 min (normal is up to 13 s), total bilirubin was 9 mg/dL with a direct component of 6 mg/dL (normal is 0–1 mg/dL), albumin was 2 g/dL, alkaline phosphatase was 831 IU/L, GGT was 187 IU/L, AST was 75 IU/L and ALT was 56 IU/L.

In view of her increasing jaundice and ascites, an MRI of the liver with a magnetic resonance cholangiopancreatography was done which showed gross hepatosplenomegaly, multiple nodular confluent delayed enhancing lesions completely replacing the left lobe with discrete nodules in the right lobe of the liver, suggestive of HHE. Liver and spleen lesions were hyperintense on T2-weighted imaging (T2WI). The liver lesions revealed nodular restricted diffusion with apparent diffusion coefficient drop. Delayed enhancement was seen with contrast retention after 45 min. The lollipop sign and capsular retraction sign were seen in our patient. The intrahepatic bile ducts showed dilatation secondary to encasement of the common hepatic duct by the lesions at the hilum. The common bile duct was normal.

In addition, there was encasement of the right and left hepatic arteries and the main, right and left portal veins. The hepatic veins were not visualised, and there was occlusion of the stent in the left hepatic vein with intrahepatic venovenous collaterals,

Figure 2 Contrast MRI shows typical low-intensity signal on T1-weighted image (WI) along with signs of 'capsular retraction' sign due to fibrous contraction (black arrow) and 'lollipop sign' (yellow arrow) hepatic/portal vein tapering and ending at the rim of the lesion (A). Contrast MRI in T2WI showing high-intensity signals in the hepatic hemangioendothelioma (HHE) lesions (C). HHE metastatic lesions were seen in the spleen (B) and vertebral bodies (D).

suggestive of Budd-Chiari syndrome. In addition, there were multiple centripetally enhancing splenic lesions suggestive of multiple hemangioendotheliomas and enhancing lesions in the bodies of multiple dorsal and lumbar vertebrae suggestive of bony metastases (figure 2). Ascitic fluid showed a high serum-ascitic fluid albumin gradient of 1.8 g/dL with no malignant cells on cytology, and a WBC count of 200 cells/high-power fields, predominantly lymphocytes.

DIFFERENTIAL DIAGNOSIS

1. Hepatic metastases have similar ring-like non-enhancement pattern but can be distinguished from HHE which have delayed enhancing patterns, lollipop sign and capsular retraction sign, which are absent in liver metastases.
2. Aggressive hemangiomas have typical arterial enhancement on imaging and also enhanced nodular edge during portal venous phase or delayed phase.

Treatment

She underwent multiple large volume paracentesis with supportive nutritional therapy and palliation for pain.

OUTCOME AND FOLLOW-UP

Currently, she is receiving palliative care and large volume paracentesis every week is needed.

DISCUSSION

Our patient had a CLD documented for 5 years. The aetiology of her CLD was Budd-Chiari syndrome as was evidenced by an enlarged caudate lobe at presentation on USG. She subsequently developed an HHE on this background of cirrhosis secondary to Budd-Chiari syndrome, which was untreated for 4 years. As TIPSS was not possible, the stented left hepatic vein may not have provided enough decompression, leading to progression of the disease. Literature search revealed only three cases of HHE developing in patients with cirrhosis: the first one in a patient with primary biliary cirrhosis; in the second one, it was

alcoholic cirrhosis and in the third, the aetiology was related to hepatitis C infection.²⁻⁴ HHEs are known to cause secondary Budd-Chiari syndrome as was described by Walsh *et al*⁵ On the other hand, there are no case reports of HHE developing in a background of Budd-Chiari syndrome, as we observed in our case where BCS was documented indirectly by an enlarged caudate lobe on USG and then subsequently on CECT. HHE was diagnosed on subsequent imaging.

HHE is an uncommon neoplasm with low incidence (<1 per 1 000 000) with female preponderance and peak incidence in third to fourth decade of life⁶ as was seen in our patient. The first series of 32 cases of HHE was first described by Ishak *et al* in 1984.⁷

Right upper quadrant pain, hepatomegaly and weight loss are the most common presenting symptoms overall, but often lesions can be incidentally picked up on imaging.

Aetiological factors contributing directly or indirectly to HHE such as oral contraceptives, vinyl chloride, asbestos, thorotrast, major trauma to the liver, viral hepatitis, primary biliary cirrhosis and alcohol consumption have been associated with HHE in literature⁶ but were not present in our patient.

HHE is considered to be slow-growing malignant tumours with metastatic potential.⁶⁻⁸ They present as nodular variety in the early stage of the disease, whereas diffuse involvement increase in size of lesion and hepatic vascular involvement represent the advanced stage of the disease² as was the case in our patient.

Grossly, the lesions of HHE are seen as solitary, which over a period of time coalesce to form multifocal or diffuse patterns.⁹⁻¹⁰

On CECT and contrast MRI studies, we get patterns such as capsular retraction (due to fibrous contraction) and lollipop sign (hepatic/portal vein tapering and ending at the rim of the lesion), both of which were present in our patient. CECT is more sensitive for large diffuse lesions with calcification. These are peripherally located slow-growing hypodense lesions with peripheral enhancing pattern on contrast administration, no traceable portal of hepatic vein and profound compensatory hypertrophy with splenomegaly.⁶⁻¹¹

On MRI, HHE shows low-signal intensity on T1WI and high-signal intensity on T2WI. On contrast-enhanced imaging, HHE creates what is called a black target or bull's eye sign lesion where the myxoid and hyaloplasm of the central zone is non-enhancing.

Extrahepatic involvement has been described and includes the lungs (8.5%), regional lymph nodes (7.7%), peritoneum-omentum (6.1%), bone (4.9%) and spleen (3.2%).⁶ Our patient had splenic and bone involvement.

Unlike an HCC, imaging findings are not specific,¹²⁻¹³ and hence a tissue diagnosis is warranted. HHE mainly originates from medium or large veins.⁷⁻¹⁴ The presence of Weibel-Palade bodies (storage granules of endothelial cells) and CD31 and CD34 positivity recognises its vascular origin.⁶ CD34 is an advanced glycation 1-type transmembrane protein highly specific for human haematopoietic stem cell, progenitor cell and endothelial cell. The metastatic nature of HHE can be predicted by the presence of factor VIII-related antigen on immunohistochemistry.⁶⁻¹² Our patient's biopsy was stained for CD34, but not for factor VIII-related antigen.

Unlike HCC, CLD is not recognised as an aetiological factor for HHE.⁶ In our case, the patient presented with cirrhosis secondary to BCS which we postulate was the cause of her cirrhosis but remained undiagnosed as CT/Doppler scan was not done at the initial presentation.

She had caudate lobe hypertrophy on USG (suggesting BCS), and all other aetiological markers were negative. As HHE was

not seen in the initial imaging, we can conclude from this observation that HHE lesions in the liver appeared in the background of cirrhosis (secondary to BCS), with subsequent metastasis to the spleen and dorsolumbar vertebrae after 1 year. This sequence of presentation is an unusual finding in our case and to the best of our knowledge, this presentation is the first of its kind in literature.

The mainstay of treatment remains liver resection (LR), when feasible, or LT. The aggressiveness of HHE increases substantially after resection. This behaviour of the neoplasm may be explained by the release of hepatotrophic growth factors during liver regeneration.⁶

LT has, therefore, become more acceptable as it has better outcomes. The outcome of LT for HHE has fairly good 5-year survival rates of 83% and 64% reported by the European Liver Transplant Registry and the United Network for Organ Sharing registry, respectively.⁷

In another analysis, Grotz *et al*¹⁵ compared the overall survival and disease-free survival in LR and orthotopic LT. The overall survival for LR at 1 and 5 years were 100% and 86% with disease-free survival of 78% and 62%, respectively. For orthotopic LT, a 1-year and 5-year overall survival of 91% and 73% and a disease-free survival of 64% and 46%, respectively, were seen. They mentioned certain factors favouring better disease-free survival such as size ≤ 10 cm, number ≤ 10 and extent of hepatic involvement ≤ 4 segments. Extrahepatic metastasis should not be considered an absolute contraindication for LR or orthotopic LT. Patients with >10 lesions and involving >4 liver segments and unresectable liver mass should be offered LT. A favourable overall outcome, with 5-year survival between 50% and 71% after LT even in the presence of extrahepatic disease, has been reported.⁶

Chemotherapy and radiotherapy have not been found to be beneficial.⁶ Transarterial chemoembolisation has been used as a bridge to LT. In addition, tumour regression and long-term stable disease with no treatment and only surveillance have been reported.⁶

Learning points

- ▶ Hepatic hemangioendothelioma (HHE) is a rare neoplasm of the liver with an uncertain natural history.
- ▶ HHE has not been previously described in the background of chronic liver disease secondary to Budd-Chiari syndrome.
- ▶ CT and MRI findings are suggestive of HHE, but histopathology and immunohistochemistry are needed for confirmation.
- ▶ Liver transplant remains the mainstay of the disease with good overall and disease-free survival.

Contributors PMS contributed in the writing of the case details, investigations and discussion, and provided histopathological and radiological photographs and figure legends. VWD made necessary corrections in the case report and formulated the discussion and references. AN contributed in the discussion and made significant corrections and finalisation of the complete draft.

Competing interests None declared.

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