CASE REPORT

Hepatic haemangiomatosis: multinodular liver in an asymptomatic elderly man

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SUMMARY

A 66-year-old man, overweight and a heavy drinker, was sent to our clinic to investigate multiple liver nodules detected on ultrasound. The patient had no symptoms, and physical examination was unremarkable. Laboratory evaluation disclosed an isolated two-fold increase of γ -glutamyltransferase. The MRI revealed multiple millimetric hypervascular nodules suggestive of liver haemangiomatosis, though malignancy could not be ruled out. Liver biopsy was consistent with hepatic haemangiomatosis. We discuss the differential diagnosis and therapeutic approach of a patient with hepatic haemangiomatosis involving the entire liver without associated symptoms or liver dysfunction.

BACKGROUND

Liver haemangiomatosis is a rare condition classically described in infants with diffuse neonatal haemangiomatosis syndrome, a life-threatening congenital disorder.¹ In adults, it is extremely uncommon, there are few reports in the literature² and there lies the challenge of the differential diagnosis, namely with malignancy, and of establishing the adequate treatment.

CASE PRESENTATION

We present the case of a 66-year-old man, a former seller of tapestry, with hypertension, dyslipidaemia, overweight, persistent atrial fibrillation and chronic obstructive pulmonary disease. The patient was medicated for several years with lisinopril 20 mg + hydrochlorothiazide 12.5 mg, warfarin 5 mg, pravastatin 20 mg, aminophylline 225 mg, and salmeterol and fluticasone inhaler. He was also a heavy drinker consuming >120 g of alcohol per day. There was no family history of cancer or hereditary haemorrhagic telangiectasia. The patient was sent to our outpatient clinic to further investigate the hepatic nodules detected in an ultrasound which was ordered to study an elevated γ -glutamyltransferase. He denied any symptoms or using recently introduced drugs or natural products. Aside from a body mass index (BMI) of 29 kg/m² and an irregular heartbeat, the physical examination was unremarkable.

INVESTIGATIONS

In the haematological and biochemical studies, which included protein electrophoresis and sedimentation rate, there was an expected prolonged prothrombin time (international normalised ratio of 1.98) and a two-fold elevation of γ -glutamyltransferase (normal <49 IU/L) with normal alkaline phosphatase,

bilirubin and albumin. The α -fetoprotein level was normal (α -FP 2.5; normal <10 ng/mL). The abdominal ultrasound showed a normal-sized liver with several hyperechoic, millimetric and ill-defined nodules. There were no findings suggestive of chronic liver disease. Contrast CT demonstrated a heterogeneous liver with multiple small nodules, very difficult to characterise and without apparent dynamic alterations. To clarify these findings, an abdominal MRI was ordered. It depicted a normal-sized liver without fatty infiltration or fibrosis. Scattered throughout the liver were countless millimetric hypervascular nodules surrounded by normal parenchyma, hypointense in the T1-weighted images, hyperintense in the T2-weighted sequences and with delayed enhancement in the contrast study. The larger nodules, under 1 cm, were located in the right hepatic lobe (figure 1). There were no enlarged lymph nodes or pancreatic, bowel or spleen abnormalities. These findings were suggestive of liver haemangiomatosis.

DIFFERENTIAL DIAGNOSIS

On the one hand, the imaging findings were suggestive of haemangiomatosis, and it is known that small hepatic lesions (<15 mm) detected in abdominal CT scan and MRI are common, and the probability of being malignant is extremely low in patients without a history of cancer or chronic liver disease.³ On the other hand, malignancy, namely angiosarcoma and hepatic epithelioid haemangioendothelioma (HEH), could not be dismissed specially considering the rarity of hepatic haemangiomatosis in adults and the age of the patient.

Liver angiosarcoma is an aggressive tumour that represents only <2% of primary hepatic tumours, although it is the most common malignant mesenchymal tumour of the liver.⁴ It is more common in white elderly men, and is usually symptomatic with abdominal distension and discomfort, weight loss, anorexia and fatigue.⁵ It usually presents as multiple masses or as a dominant heterogeneous mass, with MRI showing similar signal intensity characteristics to a haemangioma, since both tumours contain several blood-filled vascular spaces.⁶ Though unusual, this tumour can also have a diffusely infiltrating micronodular pattern.⁷

HEH is also a very rare vascular tumour, which does not arise in a background of chronic liver disease and has a variable clinical course, including slow progression to a rapidly fatal course.⁴ The presentation is heterogeneous, from absence of symptoms to portal hypertension and liver failure. HEH is most commonly a multifocal tumour with

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Figure 1 Abdominal MRI: multiple millimetric ill-defined nodules, diffusely replacing the liver parenchyma, (A) hyperintense in fat-suppressed T2-weighted sequence with arterial and (B) delayed enhancement on gadolinium-enhanced T1-weighted image.

variable-sized nodules from <1 cm to several cm in diameter disseminated in the entire liver parenchyma.⁸ On MRI, like haemangiomas, HEH nodules are hypointense in unenhanced T1 sequences and heterogeneously hyperintense in T2-weighted images and may have peripheral and delayed central enhancement after gadolinium administration.⁸

OUTCOME AND FOLLOW-UP

In order to obtain a definitive diagnosis, we performed a percutaneous ultrasound-guided biopsy in the right hepatic lobe. Histological examination depicted eight portal spaces with preserved architecture, focal macrosteatosis and a low-grade chronic inflammatory infiltrate. There were several areas of enlarged sinusoidal, periportal and acinar vessels lined by normal endothelium and filled with red blood cells. These findings were consistent with liver haemangiomatosis (figure 2).

In adults, liver haemangiomatosis can be associated with Rendu-Osler-Weber disease⁹ or systemic haemangiomatosis.¹⁰ Our patient did not have epistaxis, telangiectasias or a family history of hereditary haemorrhagic telangiectasia, making this diagnosis extremely unlikely. However, there was no involvement of other organs such as skin, bones and other viscera, thereby ruling out systemic haemangiomatosis.

For these reasons, we concluded that the patient had an isolated liver hepatic haemangiomatosis.

After 3 years follow-up, the patient remains asymptomatic and the γ -glutamyltransferase level normalised after alcoholic abstinence. In addition, in the MRI study performed after 2 years, the hepatic lesions remained unaltered.

Figure 2 Liver biopsy: H&E stain, $\times 40$ showing sinusoidal ectasia lined by endothelial cells without atypical features and filled with red blood cells.

DISCUSSION

Haemangiomas are the second most common hepatic tumour, following metastatic cancer, with a prevalence of 1–2% in the general population¹¹ and a female/male ratio of 2:1 to 5:1.¹² They are usually well-defined solitary masses, but can be multiple in up to 10% of cases.¹¹ Liver haemangiomatosis is an atypical presentation of haemangiomas, where the liver parenchyma is diffusely replaced by ill-defined haemangiomatic lesions that are multiple and range from a few millimetres to several centimetres of diameter.² It has been reported in four main settings: infants with diffuse neonatal haemangiomatosis characterised by haemangiomas of the skin and at least two visceral organs,¹ this group represents most cases of haemangiomatosis; as a manifestation of hereditary haemorrhagic telangiectasia⁹ or systemic haemangiomatosis¹⁰; and less commonly involving only the liver, in paediatric¹³ and adult patients.² To the best of our knowledge, there are only 20 reported cases of isolated liver haemangiomatosis in adults in the English literature.^{2 14–17} The majority of patients were women ($n=13$), and the median age was 43 years ranging from 21 to 82 years.

Similar to typical haemangiomas, a role for metoclopramide and oral contraceptives has been proposed, but most cases do not have a known causative factor.^{2 4} Although the pathogenesis of liver haemangiomas remains largely unknown, some studies suggest a role for the vascular endothelial growth factor (VEGF). In a transgenic rabbit model, the increased hepatic expression of human VEGF₁₆₅ transgene induced many features of human haemangiomatic disorders, including the Kasabach-Merritt syndrome.¹⁸ In one report, an infant with infantile liver haemangiomatosis had high serum and urine levels of VEGF compared with controls, which normalised with corticosteroid therapy, paralleling the regression of liver haemangiomas.¹⁹

The most common symptoms of liver haemangiomatosis were abdominal pain, distension or mass mainly due to hepatomegaly. Other symptoms included amenorrhoea and virilisation, fever and night sweats due to intratumoural haemorrhage²⁰ and congestive heart failure.^{15 17} Only two patients were asymptomatic.

On ultrasound, haemangiomatosis lesions can be hypoechoid or form confluent hyperechoic masses; on noncontrast CT, they are hypoaattenuating; and on MRI, they are found hypointense in T1 sequences and hyperintense on T2-weighted images with a peripheral and/or delayed enhancement in contrast studies.^{2 12} However, there are no definitive clinical or radiological features

and histological confirmation remains of paramount importance, especially to exclude rare vascular tumours such as epithelioid haemangioendothelioma and angiosarcoma.

As typical haemangiomas, the histological diagnosis is based on the observation of large blood-filled vascular channels, lined by normal endothelial cells and supported by fibrous tissue, in a normal-appearing hepatic parenchyma.²⁰

Reported complications included spontaneous rupture, intratumoural haemorrhage, thrombocytopenia and Kasabach-Merritt syndrome characterised by coagulopathy, thrombocytopenia and hypofibrinogenemia. Three patients demonstrated intrahepatic arteriovenous shunting, and one patient developed hepatic vessels obstruction.^{2 20}

Management depended on the extension of the diseased liver and the clinical severity. Radiotherapy was only used in the first four described cases where a 1500–2500 rads dose was targeted to the right upper quadrant and epigastrium. Two of these patients were lost to follow-up and two did not progress at 5 and 25 years follow-up.²¹ Discontinuation of oral contraception and metoclopramide was followed by regression of lesions. Arterial embolisation and partial liver lobectomy were other therapeutic options with a good outcome. Five of the six patients managed medically died, three from liver failure, one with sudden cardiac arrest and another due to deep vein thrombosis. In contrast, both asymptomatic patients were only observed without any events in 1-year follow-up.^{2 14–17}

Learning points

- ▶ Liver haemangiomatosis is an extremely rare presentation of haemangiomas in adults that affects both genders and all age groups.
- ▶ Unlike typical haemangiomas, it is rarely asymptomatic, and patients report abdominal pain or distension and have anaemia and thrombocytopenia.
- ▶ Liver biopsy is warranted to exclude malignancy, namely angiosarcoma and hepatic epithelioid haemangioendothelioma.
- ▶ The outcome is extremely variable, and liver failure and death are not uncommon for which referral to a transplant centre should be considered.
- ▶ Treatment options include discontinuing metoclopramide and oral contraceptives, arterial embolisation, partial liver lobectomy and liver transplant.

Competing interests None.

Patient consent Obtained.

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REFERENCES

- 1 Lopriore E, Markhorst DG. Diffuse neonatal haemangiomatosis: new views on diagnostic criteria and prognosis. *Acta Paediatr* 1999;88:93–7.
- 2 Maeda E, Akahane M, Watadani T, *et al*. Isolated hepatic hemangiomatosis in adults: report of two cases and review of the literature. *Eur J Radiol Extra* 2007;61:9–14.
- 3 Mueller GC, Carlos RC, Francis IR. Effectiveness of MR imaging in interpretation. *Am J Roentgenol* 2003;180:673–80.
- 4 Bioulac-Sage P, Laumonier H, Laurent C, *et al*. Benign and malignant vascular tumors of the liver in adults. *Semin Liver Dis* 2008;28:302–14.
- 5 Chien C-Y, Hwang C-C, Yeh C-N, *et al*. Liver angiosarcoma, a rare liver malignancy, presented with intraabdominal bleeding due to rupture—a case report. *World J Surg Oncol* 2012;10:23.
- 6 Buetow PC, Buck JL, Ros PR, *et al*. Malignant vascular tumours of the liver: radiologic-pathologic correlation. *Radiographics* 1994;14:153–66.
- 7 Koyama T, Fletcher JG, Johnson CD, *et al*. Primary hepatic angiosarcoma: findings at CT and MR imaging. *Radiology* 2002;222:667–73.
- 8 Mehrabi A, Kashfi A, Fonouni H, *et al*. Primary malignant hepatic epithelioid hemangioendothelioma: a comprehensive review of the literature with emphasis on the surgical therapy. *Cancer* 2006;107:2108–21.
- 9 Wu JS, Saluja S, Garcia-Tsao G, *et al*. Liver involvement in hereditary hemorrhagic telangiectasia: CT and clinical findings do not correlate in symptomatic patients. *Am J Roentgenol* 2006;187:W399–405.
- 10 Sugimura H, Tange T, Yamaguchi K, *et al*. Systemic hemangiomatosis. *Acta Pathol Jpn* 1986;36:1089–98.
- 11 Gandolfi L, Leo P, Solmi L, *et al*. Natural history of hepatic haemangiomas: clinical and ultrasound study. *Gut* 1991;32:677–80.
- 12 Vilgrain V, Boulos L, Vullierme MP, *et al*. Imaging of atypical hemangiomas of the liver with pathologic correlation. *Radiographics* 2000;20:379–97.
- 13 Bishop P, Nowicki M, Parker P. Hepatic hemangiomatosis. *Arch Pediatr Adolesc Med* 2000;154:743–4.
- 14 Kim EH, Park SY. Diffuse hepatic hemangiomatosis without extrahepatic involvement in an adult patient. *Korean J Radiol* 2008;9:559–62.
- 15 Kim JD, Chang UI, Yang JM. Clinical challenges and images in GI. Diffuse hepatic hemangiomatosis involving the entire liver. *Gastroenterology* 2008;134:1830, 2197.
- 16 Bakhshi G, Shaikh A, Borisa A, *et al*. Diffused liver haemangiomatosis in an adult. *Bombay Hosp J* 2008;50:669–71.
- 17 Supakul R, Vakili ST, Liangpunsakul S. Adult diffuse hepatic hemangiomatosis: a rare cause of dilated cardiomyopathy and sudden cardiac arrest. *J Gen Intern Med* 2014;29:244–5.
- 18 Kitajima S, Liu E, Morimoto M, *et al*. Transgenic rabbits with increased VEGF expression develop hemangiomas in the liver: a new model for Kasabach-Merritt syndrome. *Lab Invest* 2005;85:1517–27.
- 19 Schweigerer L, Pavlakovic H, Havers W. Infantile liver hemangiomatosis: evidence for molecular heterogeneity. *J Pediatr* 2000;136:419–20.
- 20 Lehmann FS, Beglinger C, Schnabel K, *et al*. Progressive development of diffuse liver hemangiomatosis. *J Hepatol* 1999;30:951–4.
- 21 Adam YG, Huvois AG, Fortner JG. Giant hemangiomas of the liver. *Ann Surg* 1970;172:239–45.

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