CASE REPORT

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Cavernous liver hemangioma complicated with spontaneous intratumoral hemorrhage: a case report and literature review

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Abstract

Hemangiomas, the most common benign tumors of the liver, have a prevalence of approximately 20% and are more frequent in women. According to previous studies, the size and location of the tumor are correlated with the appearance of symptoms and complications. Cases of hemangiomas complicated by spontaneous intratumoral hemorrhage have been rarely reported in the literature. Here, we report the case of a 70-year-old woman admitted for persistent upper abdominal pain. The patient showed signs of anemia, inflammatory markers and a transient increase in creatinine levels, which were corrected by conservative treatment. Our patient denied the previous use of estrogen derivatives, smoking or alcohol consumption. Native computed tomography identified a liver mass measuring 73×63 mm, located in segment IV and bulging out of the anterior contour of the liver. The mass was surgically removed by hepatic segmentectomy, and histopathological examination identified a cavernous hemangioma complicated by intratumoral hemorrhage. The postoperative outcome was favorable. After a literature review, we identified 19 other cases of hepatic cavernous hemangioma complicated by intratumoral hemorrhage reported worldwide.

Keywords: cavernous liver hemangioma, spontaneous intratumoral hemorrhage, benign tumor.

Introduction

Cavernous liver hemangiomas are benign tumors arising from the mesenchymal tissue, with irregular structure and numerous vascular spaces [1] of different forms and sizes separated by interstitial tissue. These tumors are frequently incidentally discovered at imaging, as most of them are asymptomatic, and liver tests remain within normal ranges. According to clinical and autopsy studies, the prevalence of hemangioma does not exceed 20% [2, 3]. In the general population, the condition can be diagnosed in all age groups, but the highest incidence is between 30–50 years of age. Hemangiomas, including large-sized tumors, are more common in women (female/male ratio 4:1 to 6:1) [2–4], possibly due to women's hormonal characteristics, mainly estrogen levels [5]. Abnormal vasculogenesis followed by increases in angiogenic factors [6, 7], such as vascular endothelial growth factor (VEGF), have also discussed [3, 8].

Solitary or multiple cavernous hemangiomas are more frequently located in the right hepatic lobe [2]. Diagnosis is based on imaging studies, such as ultrasound (US), computed tomography (CT) or magnetic resonance imaging (MRI). Grossly, the lesions are well defined; microscopically, they are characterized by unevenly arranged vascular structures [9].

The increase in size of liver hemangiomas may be accompanied by symptoms and complications. Hemangiomas measuring over 4 cm in diameter were first defined as "giant" by Adam *et al.* in 1970 [2, 10]. While analyzing a series of 106 hepatic hemangioma patients, they found that no patient with a hemangioma not exceeding 4 cm in diameter become symptomatic [2, 10]. This limit has been used in most subsequent studies; however, according to a recently published review, some authors have suggested other size categories, namely, diameters of 5 cm, 8 cm, or even 10 cm [2]. Symptomatic or complicated hemangioma is the main indication for surgical intervention [9]. We report a case of cavernous liver hemangioma complicated with intratumoral hemorrhage in a 70-year-old woman and review the literature.

Case presentation

A 70-year-old woman presented at the hospital with persistent pain in the upper quadrant of the abdomen, with weakness and fever lasting for one week. Her history revealed the progressive course of the symptoms. She did not mention any notable pathological conditions in her family. She had three pregnancies, one of which was ectopic, and two births. The patient had been treated for high blood pressure for over 10 years, with the last schedule including a beta-blocker combined with an angiotensin-converting enzyme (ACE) inhibitor. She denied the previous use of estrogen derivatives, smoking or alcohol consumption. She is a retired civil servant. Her clinical presentation indicated abdominal obesity grade I [body mass index (BMI) of 32 kg/m^2 and abdominal circumference (AC) of 92 cm], fever (>38^{0}C), pale and dry skin with persistent skin folds, without evidence of

jaundice, with no abnormal cardiac murmur or pathological pulmonary auscultation. Her blood pressure (BP) was 120/80 mmHg, and her heart rate (HR) was 84 beats/min. Tenderness in the right upper quadrant of the abdomen and palpable liver below the costal margin were noted.

After admission, laboratory assessment showed a hemoglobin (Hb) level of 10.8 g/dL (normal range: 12–16 g/dL), a red blood cell (RBC) count of 3.9 million cells/mm^3 (normal range: 4.5–5.5 million cells/mm^3), a white blood cell (WBC) count of 7800 cells/mm^3 (normal range: 4000–9000 cells/mm^3), a platelet count of 346 000/mm^3 (normal range: 150 000–400 000/mm^3) and a C-reactive protein (CRP) level of 16.65 mg/dL (normal range: 0–10 mg/dL). Biochemical assays revealed the following: a fasting blood glucose level of 83 mg/dL (normal range: 70–100 mg/dL), an alkaline phosphatase (ALP) level of 86 U/L (normal range: 100–290 U/L), a gamma-glutamyltransferase (γ-GT) level of 48 U/L (normal range: 0–55 U/L), an aspartate aminotransferase (AST) level of 25 U/L (normal range: 0–35 U/L), an alanine aminotransaminase (ALT) level of 21 U/L (normal range: 0–45 U/L), a total bilirubin level of 1 mg/dL (normal: ≤1.1 mg/dL), a total cholesterol level of 134 mg/dL (normal: ≤200 mg/dL), a triglycerides level of 176 mg/dL (normal: ≤150 mg/dL), and a serum albumin level of 5.3 g/dL (normal range: 3.5–5.2 g/dL). No abnormalities in routine bleeding or coagulation tests were found. Assessment of renal function showed a transient increase in serum creatinine (2.3 mg/dL, normal range: 0.6–1.2 mg/dL), which was corrected by conservative treatment. Hepatitis B and C virus markers were negative, and serum alpha-fetoprotein was 5 ng/mL (normal range: 0–20 ng/mL).

A hepatic mass suggestive of cavernous hemangioma was detected by abdominal US, followed by native CT (contrast administration was contraindicated due to acute kidney injury). The CT appearance was of a round-oval, well-delimited mass, 73×63 mm in size, located in liver segment IV (Figure 1). The spleen was of normal size, and no peritoneal fluid was noted. The patient showed no improvement in general health status, remaining feverish and with persistent abdominal pain. To confirm the morphological diagnosis and to continue the treatment, the patient was transferred to a surgical clinic, where she underwent exploratory laparotomy followed by liver segmentectomy. The postoperative outcome was favorable.

On gross examination, the 60×45 mm mass had a nodular, encapsulated appearance, and on sections, bleeding areas were noted.

The collected tumor fragments were fixed in 4% formaldehyde and embedded in paraffin, and the histological sections were stained with Hematoxylin–Eosin (HE). Microscopically, the tumor was composed of vascular lobules containing numerous large vascular spaces joined by bands of connective tissue. The tumoral vascular spaces with different shapes and sizes were lined by normal endothelium and contain blood red cells (Figures 2 and 3). The tumor contains a chronic inflammatory infiltrate associated with edema in the connective tissue between the tumor blood vessels (Figure 4). Tumor tissue has an infiltrative character in the hepatic parenchyma, which has the appearance of liver steatosis (Figure 5). Figure 6 emphasizes the hemorrhage, which complicated the clinical evolution of the hemangioma.

Discussions

Cavernous hemangiomas are the second most common cause of liver tumor, following metastatic cancer, and the most common benign liver tumors [11, 12]. In the general population, variable prevalence rates of up to 20% have been reported [2], while the incidence in autopsy studies ranged from 0.4% to 7.3% [3]. These tumors are most commonly solitary, small, asymptomatic and discovered incidentally during routine imaging investigations or during examinations for associated diseases. According to the literature, multiple hemangiomas account for 9–22% of all liver hemangiomas [13]. Cases of diffuse hepatic hemangiomatosis have rarely been reported. They are characterized by the replacement of the hepatic parenchyma with numerous hemangiomatous lesions ranging in size from a few millimeters to several centimeters. Such cases have been seen mostly in children or in association with systemic hemangiomatous lesions, such as Osler–Weber–Rendu hereditary hemorrhagic telangiectasia, with adult cases of diffuse isolated liver hemangiomatosis being extremely rare [14].

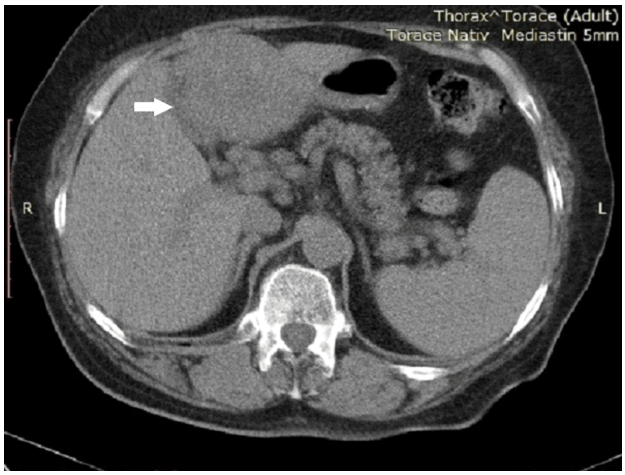

Figure 1 – ***Native computed tomography showing a round-oval, well-delimited liver mass (arrow).***

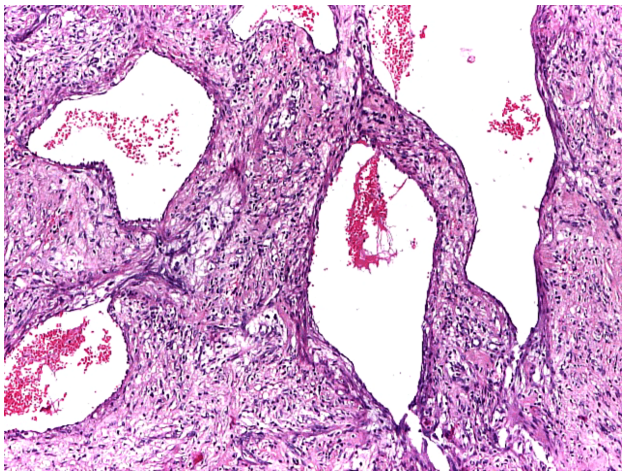

Figure 2 – ***Cavernous liver hemangioma composed of enlarged tumoral vascular spaces separated by connective tissue bands. The tumor vessels have normal endothelial cells (HE staining, ×100).***

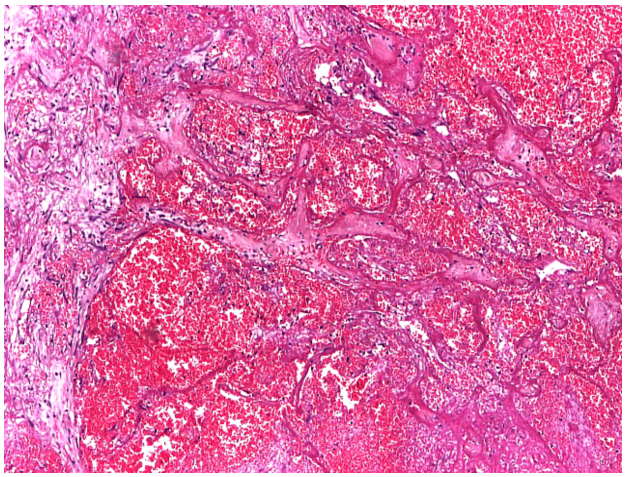

Figure 3 – ***Cavernous liver hemangioma composed of vascular spaces of different shapes and sizes (HE staining, ×100).***

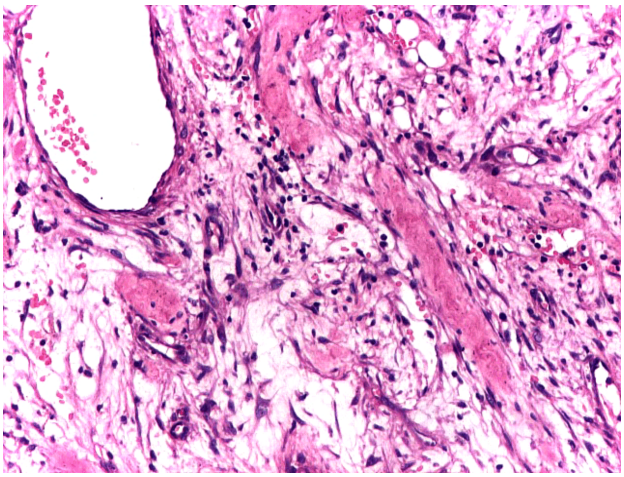

Figure 4 – ***Edema in the connective tissue bands of liver hemangioma (HE staining, ×200).***

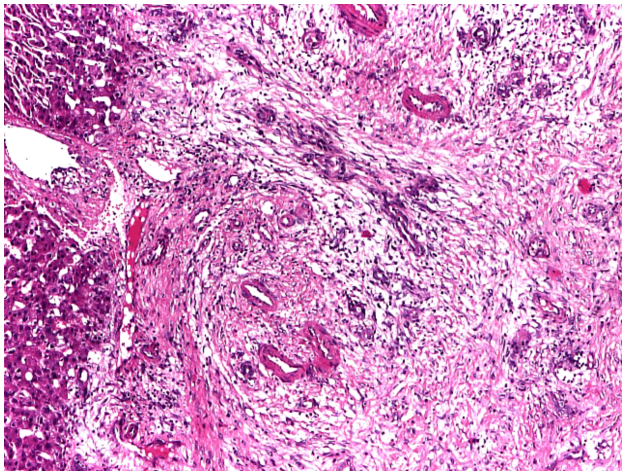

Figure 5 – ***Infiltration of liver parenchyma by hemangioma associated with fibrosis (HE staining, ×100).***

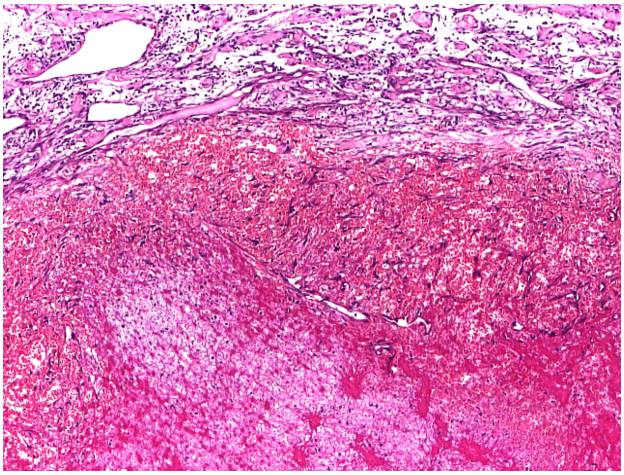

Figure 6 – ***Cavernous liver hemangioma with hemorrhagic areas (HE staining, ×100).***

In the reported case, the findings of preoperative imaging assessment were suggestive of cavernous liver hemangioma; given the persistent abdominal pain and the likelihood of complications at the hepatic lesion level, exploratory laparotomy and liver segmentectomy were performed. Macroscopically, the tumor size exceeded 4 cm in diameter. Histological examination was conclusive for cavernous liver hemangioma complicated by intratumoral hemorrhage. According to a retrospective study by Miura *et al.* [9], who identified 241 patients undergoing surgery for hepatic hemangiomas, the indications for surgery included persistent abdominal symptoms (85%), increasing tumor size (11.3%), patient anxiety (3.7%), and the presence of severe, life-threatening complications (1.2%). More recently, after reviewing 34 articles published between 1970 to 2014 that included data from a total of 4587 patients, Di Carlo *et al.* [2] identified a higher percentage of patients who underwent surgery due to persistent abdominal pain (96.2%), while only 3.8% had other indications for surgery, such as Kasabach–Merritt syndrome (44 patients, 2.2%), intratumoral hemorrhage (15 patients, 0.8%), traumatic or iatrogenic rupture (15 patients, 0.8%), compression on adjacent structures (seven patients, 0.4%), and spontaneous hemangioma rupture (four patients, 0.2%). However, the follow-up of these patient series confirmed the absence of the risk of malignant transformation.

In our case report, the histopathological examination identified areas of intratumoral hemorrhage. Spontaneous intratumoral hemorrhage is a severe complication, but it has been a rare finding in the liver hemangiomas' cases published thus far. A review of the available literature data identified 19 patients with liver hemangiomas complicated by intratumoral hemorrhage. Fifteen cases were reported in a study published by Iwatsuki & Starzl, in 1988, who retrospectively identified the indications for surgery in 411 partial liver resections performed over a 24-year period [15]. In this study, in all cases complicated by intratumoral hemorrhage within the hemangioma, the patients had severe, persistent abdominal pain, and dynamic CT was suggestive of the diagnosis [15]. In another series of 163 patients followed by Farges *et al.*, over a mean period of 92 months, one woman developed intrahepatic hemorrhagic complications. Histological examination of the specimen resected from this patient revealed that cavernous hemangioma was associated with adenoma of the liver [16]. The association with hepatocellular carcinoma or liver adenoma was cited among the predisposing factors for spontaneous hemorrhage of cavernous hemangioma [3, 16]. In our case, a tumor

exceeding 40 mm in diameter and bulging out of the anterior contour of the liver [1], as detected *via* CT, may predispose the patient to hemorrhagic complications. The patient had experienced no recent trauma, and her history did not reveal any administration of some estrogen derivatives, steroids, Metoclopramide or anticoagulant therapy. Increased frequency and risk of recurrence and possible significant enlargement of liver hemangioma have usually been reported in association with both endogenous and exogenous estrogens [3, 17–19]. Uncommonly, Metoclopramide use has been associated with diffuse hemangiomatosis [19, 20].

Another four cases of hepatic hemangiomas complicated by spontaneous hemorrhage have been reported separately in the literature [8, 21–23]; their characteristics and those of the case reported by us are summarized in Table 1.

Table 1 – ***Review of characteristics of hemangioma of the liver complicated with intratumoral hemorrhage***

Case No.	Age [years]	Gender	Size of hemangioma (diameter/measurement type)	Localization of hemangioma	Management	Outcome	Reference
1.	29	F (during pregnancy)	120 mm/angiography	Caudate lobe	Transcatheter arterial embolization	Survived	21
2.	56	F	105×75 mm/postsurgically	Left lobe	Resection	Survived	22
3.	39	M	Not available	Right lobe + left lobe	Drainage and suture	Survived	23
4.	54	F	44×28 mm/CT	IVth segment	Laparoscopically resection	Survived	8
5.	70	F	60×45 mm/postsurgically	IVth segment	Resection	Survived	Present case

F: Female; M: Male; CT: Computed tomography.

Current imaging modalities are integrated for the accurate diagnosis and follow-up of liver hemangiomas. In many cases, US imaging was the main option, as it is generally available and inexpensive. CT scanning, MRI, angiography, nuclear medicine studies and positron-emission tomography are other possibilities for imaging-based diagnosis [3, 24]. Patients with cavernous hemangiomas and associated fatty liver disease should undergo multiple imaging studies because of the increased prevalence of hepatocellular carcinoma and the risk of confusing it with benign lesions [25]. Overall, it is estimated that the sensitivities of CT, US and MRI for detecting hepatic hemangiomas exceed 90%, while the specificities range between 55% and 85% [8]. CT was also preferred in our case, though contrast enhancement was avoided because of the patient's high serum creatinine levels on admission.

The treatment options for complicated hemangiomas are still controversial. In our patient, exploratory laparotomy was followed by segmental resection. Available data in the literature have emphasized that transcatheter arterial embolization could be a successful alternative to surgery in select patients [3]. However, a limited number of reported cases have required liver transplantation, which is indicated restrictively in cases of giant liver hemangioma complicated by rupture, hemorrhage or Kasabach–Merritt syndrome [26–29]. Depending on the particular features of the tumor, the surgical methods applied have included enucleation, segmentectomy, sectorectomy or lobectomy. There are studies highlighting the advantages of using transcatheter arterial embolization in patients at high hemorrhagic risk but also its disadvantages, among them the increased risk of ischemia or intra-abdominal infection [3]. Transcatheter arterial embolization may also be used sequentially, before the surgical procedure, in hemangiomas complicated by rupture or at high-risk of bleeding. In one of the reported cases, consumptive coagulopathy was treated preoperatively using transcatheter arterial embolization [3]. In summary, transcatheter arterial embolization is a less invasive method of treatment for selected, stable patients with a permeable portal vein, preserved liver function, and no severe hemostatic function disturbances [3, 30, 31].

Conclusions

We reported a case of hepatic hemangioma complicated by intratumoral hemorrhage. Tumor size and location are factors that can influence the development of this complication. Currently, the treatment options for complicated hemangiomas are more diversified but still controversial. When the patient's condition become worse and imaging diagnosis is not decisive, exploratory laparotomy is indicated.

Conflict of interests

The authors declare that they have no conflict of interests.

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