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Case Report

Isolated hepatic hemangiomas in 2 septuagenarians

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ABSTRACT

We report 2 cases of isolated hepatic hemangiomas: a 76-year-old woman who is, to our knowledge, the oldest person with this diagnosis, and a 74-year-old woman. Magnetic resonance imaging of the abdomen showed T2 hyper intense lesions throughout the liver, peripheral nodular arterial enhancement, and filling of contrast on the portal venous and delayed phases. Computed tomography showed liver lesions with peripheral nodular enhancement in the early phase and a centripetal pattern or “filling in” during the late phase; the lesions opacified after a delay of 3 or more minutes and remained isodense or hyperdense on delayed scans. Both images were consistent with hepatic hemangiomas. These cases help increase awareness about benign and unusual liver lesions with radiologic characteristics similar to those of malignant liver tumors. The authors also present a review of 15 other cases of isolated hepatic hemangiomas reported in English literature from 1970 to present.

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Introduction

Hepatic hemangioma is the most prevalent type of benign liver tumor with an incidence reaching 20% in the overall population [1]. Conversely, hepatic hemangiomas, a term used to describe the presence of innumerable hemangiomas, is a rare presentation of liver hemangiomas and is more frequently seen in neonates [2,3]. Isolated hepatic hemangiomas, without extrahepatic involvement, is uncommon, particularly in the adult population [4]. We report 2 cases:

76-year-old and 74-year-old women, both diagnosed with isolated hepatic hemangiomas, with a review of 15 other cases reported in English literature from 1970 to 2018.

Case reports

Patient 1

A 76-year-old woman with a past medical history of hypertension, hyperlipidemia, postherpetic neuralgia, and

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gastroesophageal reflux disease was seen for abdominal pain. She had a history of cigarette smoking more than 35 years ago and denied any alcohol or illicit drug use. Her medications included Atenolol, Lisinopril, Gabapentin, Omeprazole, ASA, and Ativan. The patient saw her primary care provider for right upper quadrant abdominal pain, described as nonradiating, moderate in severity, that she was unable to characterize. Her physical exam was normal and her laboratory tests, including complete blood count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin, albumin, and prothrombin time were normal. Alpha-fetoprotein was 1.0 ng/mL. Magnetic resonance imaging (MRI) of the abdomen with and without contrast showed multiple T2 hyperintense lesions throughout the liver, and a liver biopsy was performed to exclude a neoplastic process. With a diagnosis of hepatic hemangiomas, she was referred to our center in 2018 for specialized care. Upon her visit to our institute, she reported that she was previously diagnosed with liver lesions and had a biopsy performed at a hospital in Iowa in 2009; at that time, she was told she had benign liver tumors.

Her most recent MRI showed multiple hyperintense T2 liver lesions. On the postcontrast images, the hepatic lesions demonstrated peripheral nodular arterial enhancement and slowly fill with contrast on the portal venous and delayed phases. This pattern is consistent with hemangiomas (Fig. 1). The liver biopsy showed multiple dilated vascular spaces scattered within the otherwise benign liver tissue. The portal areas had a mild chronic inflammatory infiltrate consisting of lymphocytes and plasma cells. The dilated thin-walled vascular channels were lined by bland endothelium. The biopsy confirmed the diagnosis of hepatic hemangiomas (Fig. 2).

Patient 2

A 74-year-old woman with a past medical history of primary biliary cholangitis, hyperlipidemia, and hypothyroidism presented to our facility for primary biliary cholangitis follow-up. Her medications include Ursodiol, Obeticholic acid, Pravastatin, ASA, Levothyroxine, magnesium, vitamin D, fish oil, and multivitamin. Her physical exam was normal, including no hepatomegaly, and her laboratory tests including ALT, AST, ALP, bilirubin, albumin, and prothrombin time were normal. Alpha-fetoprotein was 5.2 ng/mL. A computed tomography (CT) of the abdomen with and without contrast in June 2018 showed multiple liver lesions, the 2 largest ones measuring 2.7 cm and 4.1 cm, both of which were unchanged from prior CT in 2017. The lesions showed a peripheral nodular enhancement in the early phase, and a centripetal pattern or “filling in” during the late phase. The lesions opacified after a delay of 3 or more minutes and remained isodense or hyperdense on delayed scans. These characteristics were consistent with the diagnosis of liver hemangiomas and biopsy was not performed.

Discussion

Hepatic hemangiomas are also known as cavernous hemangiomas given the cavernous vascular space seen on liver biopsy [5]. Liver hemangiomas are typically isolated lesions, but can be seen in both liver lobes in 40% of cases. The diameter of the hemangioma can vary from only a few millimeters to greater than 20 cm, and the larger lesions are referred to as giant hemangiomas [6]. Hemangiomas, or the occurrence of innumerable hemangiomas, is a less common presentation of hepatic hemangiomas and is more commonly seen in neonates diagnosed with hereditary hemorrhagic telangiectasia or systemic hemangiomas [2,7,8]. Hepatic hemangiomas have also been described in association with giant cavernous hemangiomas. In 2011, Jhaveri et al. described hepatic hemangiomas in 18 out of 41 patients who were diagnosed with giant cavernous hemangiomas [7]. Additional reports of hemangiomas-associated giant hemangiomas have been described [4,15,18,21,24,30]. Isolated liver hemangiomas, without any extrahepatic involvement or association with giant hemangioma, is uncommon in children and even more so in the adult population.

Both of our patients were reassured about the benign nature of the liver lesions and plans were made for consistent follow-up appointments. They were advised against the use of hormonal replacement therapy, and it was recommended that they carry medical alert bracelets with the diagnosis. This would avoid unnecessary liver biopsies and a potential delay in the diagnosis of ruptured hemangiomas.

Demographics and clinical presentations

Table 1 depicts the clinical characteristics of our patients and the other 15 cases of isolated hepatic hemangiomas reported in English literature from 1970 to present. The age of patients at the time of publication varied from 21 to 76 with a mean age of 46.4. Of the 17 total cases reported, 13 were women, which is consistent with the previously described predominance of hepatic hemangiomas in women [9–11]. Our patients were 74 and 76 years old and are the oldest patients in this review.

While the etiology of hepatic hemangiomas remains unknown, one study suggests a role of the vascular endothelial growth factor in its development [12]. In addition, there is a case report that found an association of hemangiomas with the use of metoclopramide, as well as regression of the hepatic lesions with discontinuation of the drug [13]. In patients with hepatic hemangiomas, enlargement of the lesions during pregnancy and with estrogen or progesterone therapy, with subsequent regression after the medication is discontinued, suggests hormonal influence over tumor growth. This has not been described in patients with hepatic hemangiomas. However, 4 of the 13 women with hepatic hemangiomas reported to date had previously taken some form of estrogen [13,14,16]. Our patients were not on hormonal replacement; however, our first patient had 3 full-term pregnancies and our second patient had 2 full-term pregnancies.

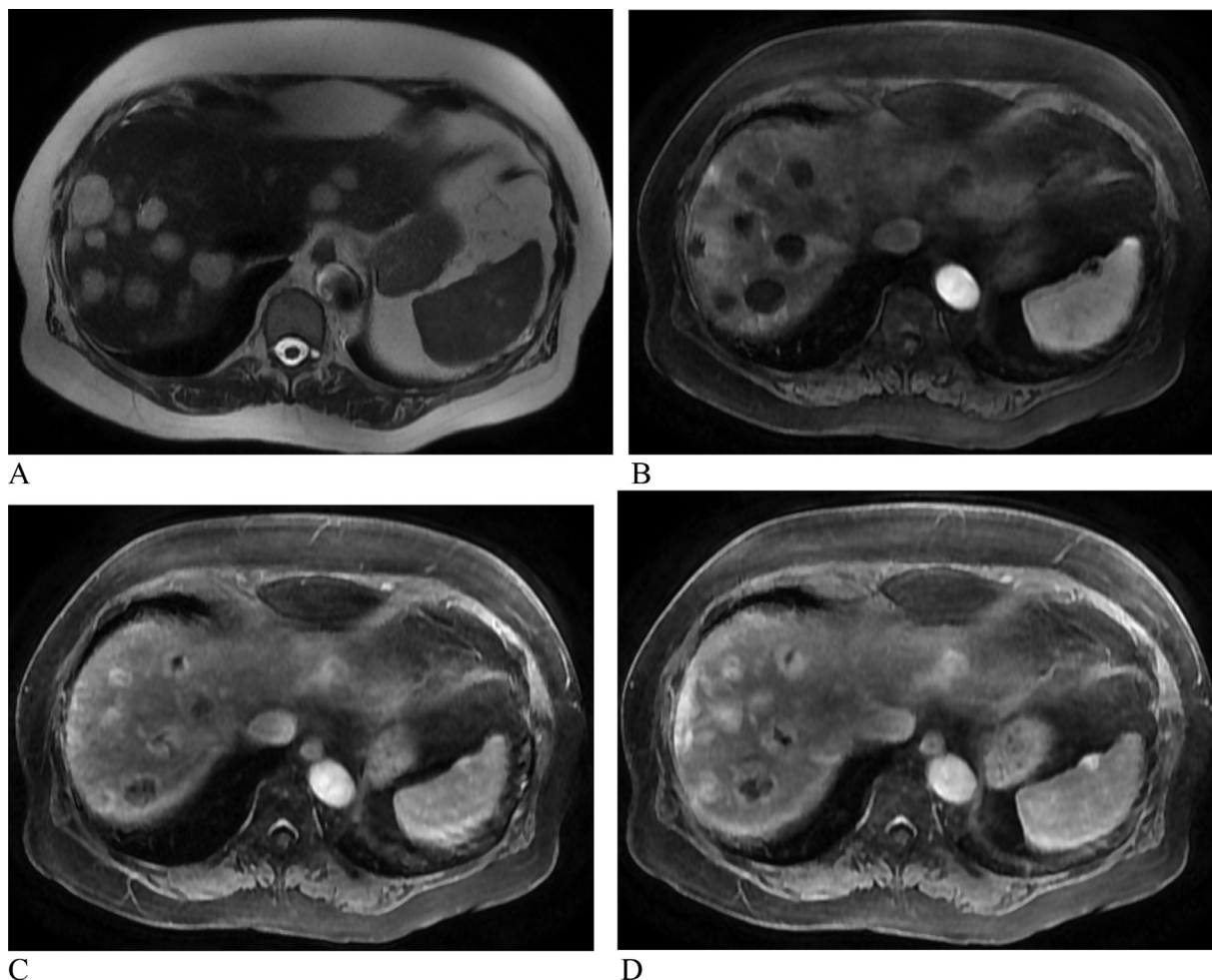


Fig. 1 – MRI of the abdomen with a pattern consistent with hemangiomas. A: The multiple hepatic lesions demonstrate hyperintense T2 signal. B: On the postcontrast images, the lesions demonstrate peripheral nodular arterial enhancement. C: The lesions slowly fill in with contrast on the portal venous phase. D: The lesions slowly fill in with contrast on the delayed phase.

Out of the 17 cases reported, 13 patients had symptoms of upper abdominal pain and/or sensation of fullness and/or abdominal mass, in either the right upper quadrant and/or epigastrium. Other common symptoms included dyspnea and systemic symptoms of fevers and night sweats. Fatigue was also a reported symptom [17]. The most common finding on physical exam was hepatomegaly [19–21] reported in 8 of the 17 patients.

Laboratory values and imaging studies

Few of the reported cases included laboratory tests; of those who did, the liver chemistry tests, that is, ALT, AST, ALP, GGT, and bilirubin were normal in the majority of patients. Alpha fetoprotein was reported in 6 cases and was normal in all.

Abdominal ultrasound was performed in 8 out of the 17 cases. On ultrasound exam, the characteristic finding was hyper- or hypoechoic nodules diffusely distributed throughout the liver. Other imaging modalities included CT, MRI, and CT angiography. On CT, performed in 9 out of 17 cases, the

lesions of hepatic hemangiomas were described as heterogeneous nodular enhancement and hypodense hepatic lesions. MRI, performed in 7 out of 17 cases, showed low signal intensity on T1-weighted images, high signal intensity on T2-weighted sequences, and delayed enhancement in the contrast images.

Differential diagnosis

While the characteristics of the cross-sectional images described above are consistent with the diagnosis of liver hemangiomas, there are no definitive radiologic features that will diagnose liver hemangiomas with certainty. Therefore, a detailed clinical history and physical exam are paramount. Other liver lesions that may present with similar characteristics are liver angiosarcomas, hepatic epithelioid hemangioendothelioma, and multicentric hepatocellular carcinoma. Table 2 describes the different clinical characteristics of the tumors that should be considered in the differential diagnosis of hepatic hemangiomas.

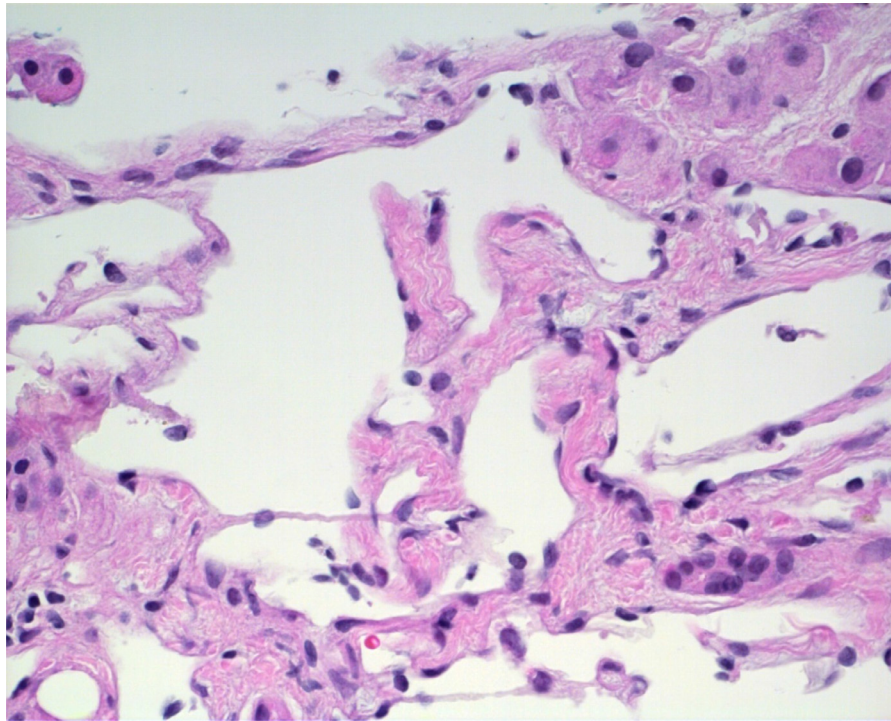


Fig. 2 – Liver biopsy showed multiple-dilated vascular spaces scattered within the otherwise benign liver tissue. The portal areas contained mild chronic inflammatory infiltrate consisting of lymphocytes and plasma cells. The dilated thin-walled vascular channels were lined by bland endothelium.

Table 1 – Clinical characteristics of our patients and 15 cases of isolated hepatic hemangiomas reported in English literature from 1970 to present.

Author	Age	Sex	Hormone use	Symptoms	Hepatomegaly
This manuscript	76	F	N	Abdominal pain	N
This manuscript	74	F	N	None	N
Gruttadauria et al. 2015	37	F	N	Abdominal pain, fatigue, anemia	Unk
Batista et al. 2014	68	M	N	None	Y
Ramos and Coelho, 2014	66	M	N	None	N
Supakul et al. 2013	53	M	N	Fatigue, dyspnea on exertion	Y
Kim et al. 2008	33	F	N	Abdominal distention, edema	Y
Kim et al. 2008	33	F	N	Abdominal distention, shortness of breath	Y
Bakhshi et al. 2008	65	M	N	Mass in right hypochondrium and epigastrium	Y
Ozakyol and Kebapci, 2006	47	F	Y	Abdominal pain	N
Ozakyol and Kebapci, 2006	42	F	Y	Abdominal pain	N
Tanaka et al. 2002	32	F	N	Abdominal pain, lower back pain, dyspnea on exertion	N
Jayanthi et al. 2000	21	F	N	Abdominal pain, dyspnea	Y
Moon et al. 2000	50	F	N	Postprandial abdominal pain and indigestion	N
Lehmann et al. 1999	35	F	N	Abdominal pain, weight loss, night sweats, fever	Y
Feurle, 1990	22	F	Y	Abdominal pain radiating to right shoulder	N
Kositckek and Cullen, 1970	36	F	Y	Abdominal fullness and pain, distention, postprandial fullness, constipation	Y

Unk: unknown.

Histology

In 12 out of the 17 reported cases, a liver biopsy was performed to confirm the diagnosis of hepatic hemangiomas. As seen in our 76-year-old patient (Fig. 2), the histologic findings of those patients for whom a liver biopsy was performed

showed multiple-dilated vascular spaces scattered within the otherwise benign liver tissue. The portal areas contained mild chronic inflammatory infiltrate consisting of lymphocytes and plasma cells. The dilated thin-walled vascular channels were lined by bland endothelium. However, for patients presenting with the characteristic findings on image tests, particularly

Table 2 – Clinical characteristics of tumors that should be considered in the differential diagnosis of hepatic hemangiomas.

Diagnosis	Age	Sex	History of chronic liver disease	Symptoms	References
Hepatic hemangiomas	30-50	F	N	Abdominal pain and fullness	[11,31,32]
Angiosarcoma	>60	M	Unk	Abdominal pain, jaundice, ascites, weight loss	[33–36]
Epithelioid hemangioendothelioma	50's	F	N	Abdominal pain, mass, weight loss	[37–40]
Hepatocellular carcinoma	50-60	M	Y	Upper abdominal pain, weight loss, early satiety, mass in upper abdomen, signs of decompensation (ascites, jaundice, variceal bleeding, encephalopathy)	[41,42]

Unk: unknown.

cross-sectional image, liver biopsy should be avoided, given the vascular nature of these lesions with an increased risk of bleeding.

Follow-up and outcomes

Given the few number of cases reported to date, it is not possible to make statements on the natural history or outcome of hepatic hemangiomas. Our patients have done very well and have remained asymptomatic since the diagnoses, 9 years prior to this publication. Other reports described similarly favorable outcomes, although most patients were followed for less than 5 years [13,14,16,22,23,25,26]. Nonetheless, not all reported cases had the same uneventful course. There has been a report of a patient who developed liver failure and eventually expired 10 days after hospitalization [27]. Three other fatalities were reported, but no clear relationship between the hemangiomas and the cause of death. One patient was diagnosed with deep venous thrombosis during admission and expired after 1 week [28]. Additionally, there was a patient who was admitted with lactic acidosis and expired after cardiopulmonary arrest [29]. Another patient expired after hemorrhagic shock due to a duodenal ulcer that was present for a few years prior to hospital admission [19].

The scarce number of cases reported and the diversity of the outcome of this unique presentation of isolated liver hemangiomas explain the lack of recommendations for treatment, or if any treatment should be considered. Based on the reports of some hemangiomas increasing in size when the patients were exposed to estrogen, recommendations against the use of oral contraceptives and hormonal replacement therapy should be considered. Given the report of an association between metoclopramide and hepatic hemangiomas [13], discontinuing this medication may be considered. Otherwise, the treatment approach should be individualized for each patient, based on the symptoms and radiologic findings at presentation. There are reports of patients treated with arterial embolization and hepatectomy [19,30], and a case of a patient who developed progressively growing hemangiomas on the remaining liver parenchyma after left hepatectomy

[26]. The above anecdotal reports illustrate the need to individualize the care based on each patient's presentation.

Conclusion

We present 2 cases of isolated hepatic hemangiomas: a 76-year-old woman, who is, to our knowledge, the oldest person reported to date with this diagnosis, as well as a 74-year-old woman. These case reports help increase awareness about a benign liver lesion that has radiologic characteristics similar to those of malignant liver tumors. The literature review confirms the rarity of this entity, which is seen more frequently in women and are often asymptomatic. The finding of hepatomegaly on physical exam is likely to prompt imaging of the liver. The importance of a detailed clinical history for the evaluation of these patients cannot be over emphasized. The absence of chronic liver disease, normal laboratory tests, and careful evaluation of the cross-sectional imaging of the liver may obviate the need to perform a liver biopsy. Given the vascular nature of these lesions, liver biopsy is likely to carry an increased risk of bleeding, similar to that seen in biopsies of liver hemangiomas.

Author contributions

Both authors reviewed the information of the patients in the report, reviewed the published literature, and wrote the manuscript.

Informed consent statement

The patients involved in this study gave written informed consent authorizing the use and disclosure of their protected health information.

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