

Recurrent giant hemangiomas of liver: Report of two rare cases with literature review

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pathogenesis of tumor progression and recurrence is unknown, as is the management of these patients with recurrent hemangioma, particularly when it is extensive and unresectable.

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Abstract

Most hepatic hemangiomas (HHs) are small, asymptomatic and do not require clinical intervention. Surgical resection is only indicated for symptomatic hemangiomas. We report here cases of recurrent HHs in 2 women of 37 and 40 years old, who initially presented with abdominal pain and mass. Radiological examination of each tumor revealed a solitary tumor of 14 and 20 cm in diameter, respectively. Surgical liver segmental resections were performed in both, and the diagnosis of cavernous hemangioma was confirmed. Both patients had recurrent tumor on subsequent radiological examination 4-5 years after the initial surgery. In the first patient, a 15 cm recurrent hemangioma was resected, but multiple hemangiomas were again detected 8 years later occupying the other hepatic lobe, which was not amenable for resection. In the second patient, a 16 cm hemangioma was seen on radiogram, and because the lesion was not symptomatic, conservative observation was offered. Recurrence after liver resection of giant hemangioma is extremely rare. The

INTRODUCTION

Hemangiomas are the most common hepatic neoplasm, occurring in up to 7% of population^[1]. They occur at all ages, but are most frequently seen in women in the third to fifth decades of life. They are usually small (< 1 cm), solitary, and well demarcated. Giant hemangiomas are larger than 4 cm and can give symptoms. Surgery is indicated only when there is spontaneous or traumatic rupture, consumption coagulopathy (Kasabach-Merritt syndrome), rapid growth, severe abdominal pain or when the diagnosis is uncertain^[2-4].

The natural history of hepatic hemangiomas (HHs) is variable. They can regress, have thrombosis, scarring (sclerosed hemangioma), or calcification^[1]. Tumor recurrence after liver resection is extremely rare and the underlying mechanism is still poorly understood. Steroids and sex hormones have been speculated to be associated

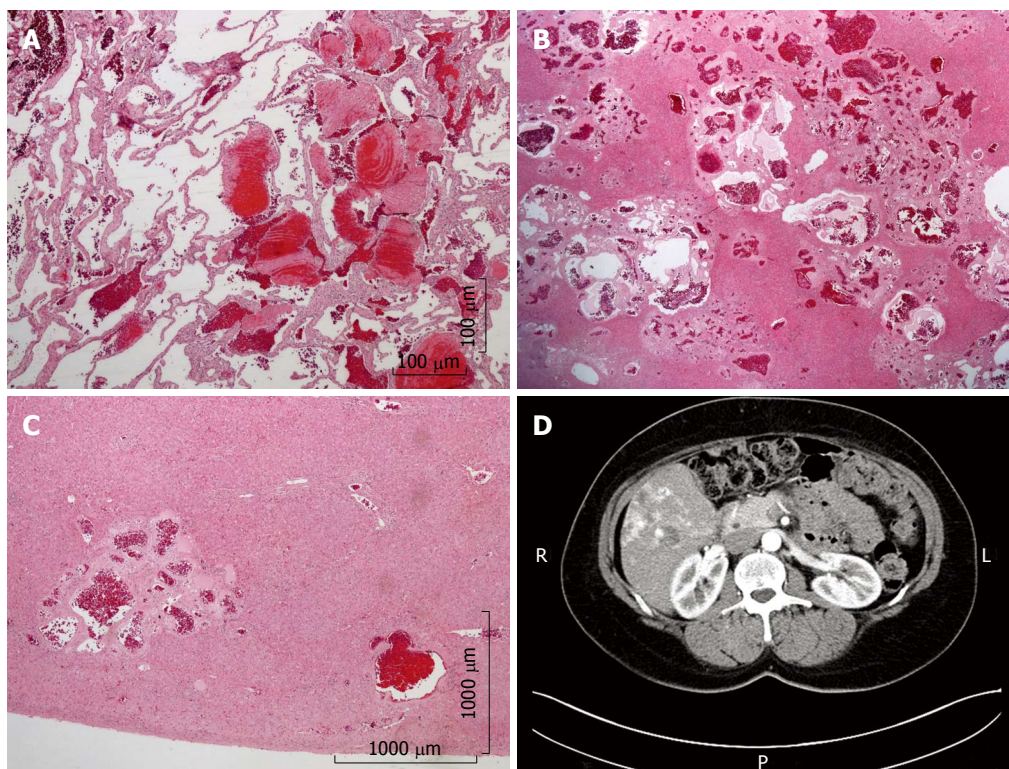


Figure 1 Case 1 (patient 6 in Table 1). Micrograph of the first recurrent hemangioma in the left hepatic lobe shows typical cavernous hemangioma (A: HE, $\times 100$); and multiple foci of hemangioma-like vessels adjacent to the main tumor (B: HE, $\times 40$) and at a distant from the main lesion (C: HE, $\times 40$). D: Magnetic resonance image reveals recurrent hemangiomas involving right hepatic lobe 7 yr after left lobe resection for recurrent hemangioma. R: Right; L: Left; P: Peripheral.

with tumor progression^[5-9]. Here, we report two unique cases of recurrent hemangiomas after liver resection. The pathogenesis and clinical management of recurrent giant hemangiomas are discussed.

CASE REPORT

Case 1

The first case involved a 37-year-old female presented with complaints of bloating and an abdominal mass. A computed tomography (CT) scan showed an 11 cm mass with peripheral enhancement. A tagged red blood cell uptake scan suggested hemangioma. She underwent a hepatic left lobectomy. The pathology diagnosis was a 14 cm \times 10 cm \times 9 cm well demarcated cavernous hemangioma.

A follow-up CT scan performed 5 years after initial diagnosis revealed a 12 cm \times 5 cm mass in the left hepatic lobe with peripheral enhancement suggestive of hemangioma. Seven years after initial diagnosis, the patient was referred to The Mount Sinai Medical Center for surgery. Gross examination of the resected tumor revealed a 15 cm, 581 grams sclerosing cavernous hemangioma with organizing thrombi (Figure 1A). Microscopically, the liver parenchyma adjacent to and distant from the main tumor had foci of dilated, congested vascular channels or hemangioma-like-vessels (HLVs) (Figure 1B and C). The resection margin was not involved by the HLVs. However, magnetic resonance image (MRI) performed 15 years after initial diagnosis revealed several hemangiomas in the

right lobe of the liver (Figure 1D). Liver function tests and complete blood count were within reference range. A repeat MRI 16 years after the initial diagnosis demonstrated increases in the size of the recurrent HHs. A liver biopsy was performed and confirmed the diagnosis of benign hemangioma. The tumors were unresectable, and the patient's symptoms were considered unrelated to the tumor. It was therefore decided to observe the patient. The patient's history of hormone use was not clearly stated in the medical record.

Case 2

The second case involved a 40-year-old female who was incidentally found to have a 10 cm \times 8 cm tumor, suggestive of hemangioma on MRI examination (Figure 2C and D). Two years after diagnosis, she underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO). History of hormone replacement therapy was not recorded. She was initially asymptomatic, but started to have right upper quadrant pain as well as right shoulder pain four years after diagnosis. On physical examination, the patient demonstrated abdominal distention and a readily palpable mass. Her laboratory results included a mildly decreased platelet count and a mild elevation of serum alkaline phosphatase. The patient underwent right hepatic lobectomy at The Mount Sinai Medical Center 5 years after initial diagnosis of hemangioma. The resected specimen was 1300 g and 25 cm \times 18 cm \times 4 cm. Pathological examination revealed a 20 cm \times 15 cm \times 4 cm

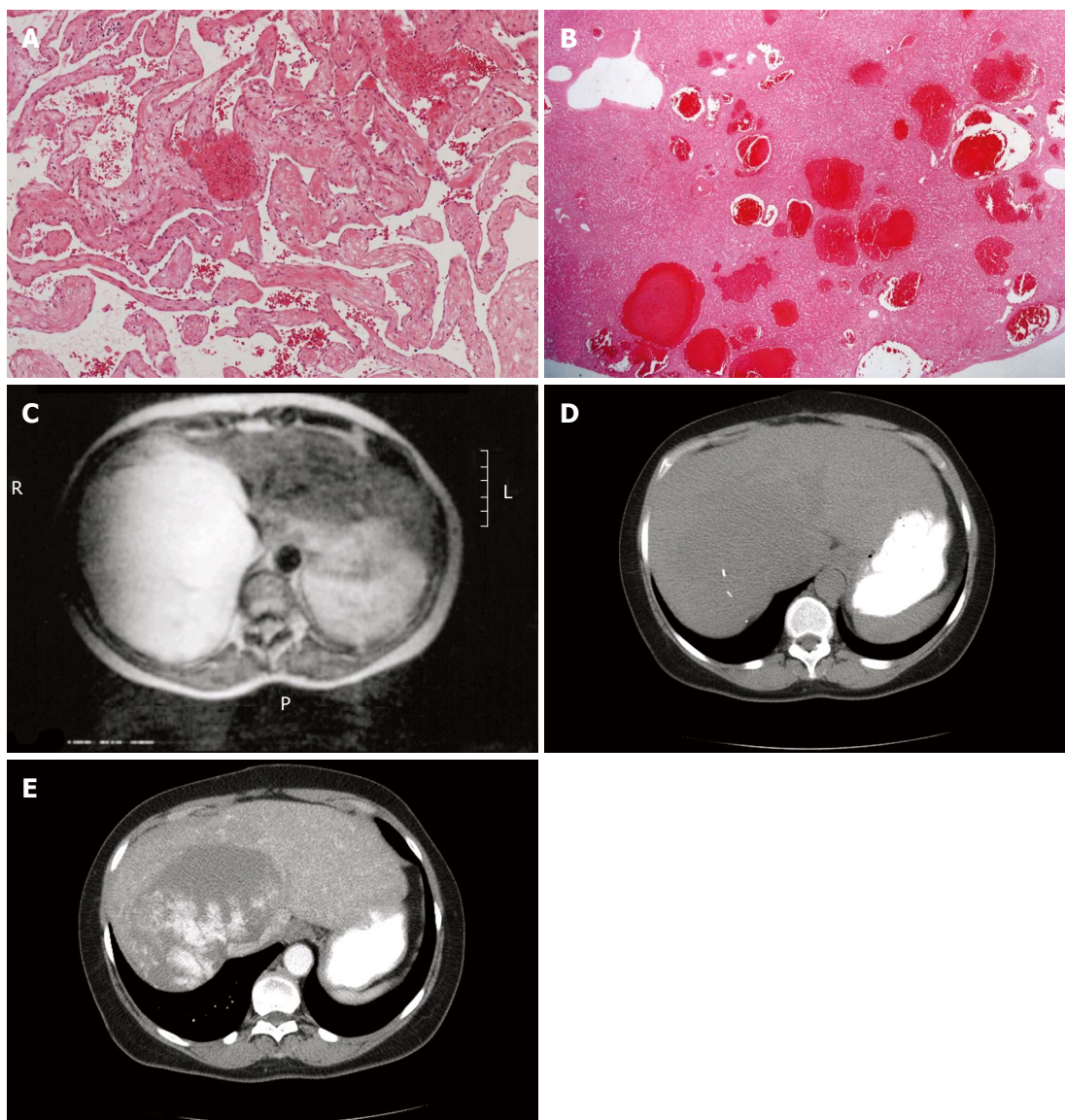


Figure 2 Case 2 (patient 7 in Table 1). A: Right lobe resection specimen of case 2 with cavernous hemangioma (HE, $\times 100$); B: Multiple hemangioma-like vessels in the surrounding liver parenchyma (HE, $\times 40$); C-E: Computed tomography scan images [initial giant hemangioma in the right hepatic lobe (C), image after resection shows no residual hemangioma (D), and recurrent hemangioma in right lobe of liver, 4 years after second resection (E)]. R: Right; L: Left; P: Peripheral.

spongy hemangioma with areas of hemorrhage, fibrosis and myxoid degeneration. Microscopic examination confirmed the diagnosis of cavernous hemangioma with areas of hemorrhage and fibrosis (Figure 2A). Scattered throughout the adjacent liver parenchyma were microscopic foci of HLVs (Figure 2B). Nine years after initial diagnosis (MRI), the hemangioma recurred (Figure 2E). The patient had nonspecific intermittent symptoms of abdominal and back pain that were thought unlikely related to the tumor. The patient is currently being managed with observation.

DISCUSSION

Hemangiomas are the most common benign tumors in the liver with reported incidence of 0.4%-7.3%. They occur predominantly in young adult women in the third to fifth decades of life with female to male ratio of 5:1^[1].

Most hemangiomas are small and asymptomatic and are usually discovered incidentally on radiographic or ultrasonic examination for other health issues. Multiple hemangiomas have been reported in 9%-22% of patients, and occasionally, there may be diffuse hemangiomatosis^[1,10,11]. Giant hemangiomas (> 4 cm) can become symptomatic. Surgery is indicated only when there is spontaneous or traumatic rupture, consumption coagulopathy (Kasabach-Merritt syndrome), rapid growth, severe abdominal pain or uncertain diagnosis^[2-4]. We report here two cases of giant hemangiomas with recurrence 4 and 5 years after initial hepatic resection. In the first case, multiple enlarging hemangiomas involving the right hepatic lobe were diagnosed on imaging studies 5 years after a second resection for recurrent left lobe giant hemangioma. In the second patient, a recurrent giant hemangioma was detected 4 years after resection.

Table 1 Comparison of six patients with recurrent giant hemangiomas

	Age (yr)	Sex	Original tumor No./size	Initial treatment	Recurrence in years	Recurrent tumor No./size	Treatment for recurrence	Hormone	Micro-hemangiomas	Follow up (yr)
1	59	F	1/large	Radiation	13	Multiple/950 g	Surgery	Premarin	N/A	8
2	49	M	Entire left lobe	Radiation	16	Multiple/810 g	Surgery	None	N/A	3
3	57	F	Multiple/900 g	Surgery	17	1/7 cm	Observation	Premarin	N/A	< 1
4	55	F	1/650 g	Surgery/incomplete	11	1/690 g	Surgery	Premarin	N/A	1
5	64	F	Unknown	Surgery	16	Multiple/35 cm	Surgery	Unknown	N/A	16
6 (case 1)	37	F	1/14 cm	Surgery	5	1/15 cm ¹	Surgery	Unknown	Yes	8
7 (case 2)	40	F	1/20 cm	Surgery	4	1/16 cm	Observation	Probable (TAH-BSO)	Yes	11

¹The patient had recurrence 8 yr after the second surgery with multiple hemangiomas and not amenable for another resection. M: Male; F: Female; TAH-BSO: Total abdominal hysterectomy with bilateral salpingo-oophorectomy; N/A: Not available.

The pathogenesis of cavernous hemangiomas is largely unknown. It was speculated that abnormal vasculogenesis and angiogenesis might be involved^[1,5]. Studies showed that hemangioma-derived endothelial cells were different from sinusoidal endothelial cells in morphology, phenotype, and function; exhibited more activated angiogenesis capacity; and had the ability to form abnormal capillary-like structures *in vitro*^[1,5,12]. Electron microscopy showed aberrantly enlarged endoplasmic reticulum in hemangiomas^[1]. Kim *et al.*^[13] described 84% of their 19 cases of hemangiomas to have irregular interface between the hemangiomas and their surrounding liver parenchyma. This irregular or spongy interface consisted of HLVs that were usually located 0.1-2.0 cm from the main tumor forming discrete single or clusters of satellite nodules. HLVs were grossly difficult to identify and microscopically they were characterized by dilated, blood-filled vascular spaces lined by single-layered endothelium. When HLVs formed clusters, the histopathologic appearance and the immunohistochemical characteristics were indistinguishable from cavernous hemangiomas. The clinical significance of HLVs and its association with tumor recurrence are still unknown. The authors proposed that they might be related to tumor progression or secondary vascular telangiectasia due to mass effect of adjacent space occupying hemangioma^[13]. The high frequency of HLVs in the reported cases compared to the extreme low recurrent rate of resected hemangiomas suggests that HLVs were unlikely the main source of tumor recurrence. Interestingly, both of our cases with recurrent giant hemangiomas had irregular boundaries between the main tumor and the adjacent liver parenchyma due to the presence of HLVs.

Tumor recurrence after resection is extremely low. To date, there are only five reported cases (four women and one man) of hemangiomas that have recurred, with average time of recurrence of 14 years (11 years to 17 years)^[6,9] (Table 1). It has been suggested that recurrent tumors are probably due to the result of growth of new cellular tissue instead of earlier suggestions of vascular ectasia^[1,8]. Interestingly, all 3 women were on chronic estrogen replacement therapy (Premarin) suggesting possible link between sex hormone and tumor progression. This supports the clinical observation of higher incidence in

women and of an accelerated tumor growth even rupture under condition of estrogen exposure such as puberty, pregnancy or hormonal replacement^[5-8]. Our patients have had a relatively shorter recurrence period and their histories of estrogen replacement use were unfortunately unknown. The second patient underwent TAH-BSO at the age of 37, and presumed to have received hormone replacement therapy. In both patients, immunostains of the tumors for estrogen and progesterone receptors were negative. Whether discontinuation of hormone replacement therapy would induce tumor regression is not known. Another medication, metoclopramide, to treat heartburn has also been associated with diffuse hemangiomatosis^[14].

The clinical management for symptomatic giant hemangiomas is controversial. The modalities for management of giant hemangiomas include radiofrequency ablation, intra-arterial embolization, anatomic liver resection, enucleation, and rarely liver transplantation when hemangiomas involve both lobes or in diffuse hemangiomatosis^[1,15,16]. The indications for surgical resection are tumors with continuous abdominal pain, worsening of pain symptoms, mechanical complaints or when malignancy cannot be excluded^[1]. Occasionally, liver transplantations are necessary when the giant hemangioma occupied the entire liver or ruptured^[15]. In our patient with second time recurrence, the tumor was multiple and occupying the other remaining hepatic lobe, therefore liver transplantation may need to be considered when necessary.

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