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Primary hepatic malignant fibrous histiocytoma: A case report and review of the literature

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Summary. Primary malignant fibrous histiocytoma (MFH) of the liver remains extremely rare with only several cases having been reported in literature. We report a case of hepatic MFH in a 53-year-old man who presented with upper abdominal pain, and weight loss for one month. Ultrasound and computed tomography (CT) scan showed a large mass with fine tumor vessels over the left lobe of the liver. Histopathological findings indicated a mesenchymal tumor consisting of spindle cells in storiform pattern intermingled with histiocyte-like cells and giant cells. Immunohistochemically, most tumor cells expressed vimentin, alpha-1 anti-chymotrypsin, alpha-1 antitrypsin and CD68. Morphological and immunohistochemical findings support that the tumor should be classified as a primary malignant fibrous histiocytoma. The literatures is briefly reviewed.

Key words: Malignant fibrous histiocytoma, Sarcoma, Liver

Introduction

Malignant fibrous histiocytoma (MFH) is one of the common soft-tissue sarcoma, firstly described as "malignant fibrous xanthoma" by O'Brien and Stout in 1964. The term malignant fibrous histiocytoma, synonymous with pleomorphic malignant fibrous histiocytoma, is now reserved for a small group of undifferentiated high grade pleomorphic sarcoma. Most undifferentiated high grade pleomorphic sarcomas occur in patients over age 40, with peak incidence in the 6th and 7th decades. There is a male predominance of approximately 1.2:1. The tumors often occur in the extremities (especially the lower limb) and less in the trunk (Fletcher et al., 2002). Its occurrence has been reported in almost all parts of the body including head and neck (Sadati et al., 2004), intracranial (Ozhan et al., 1999; Fujimoura et al., 2002), lung (Wang et al., 2003), heart (Okamoto et al., 2001), breast (Yao et al., 2005), pancreas (Akatsu et al., 2005), gallbladder (Gruttadauria et al., 2001), conjunctiva (Arora et al., 2006), ovary (Dilek et al., 2006), glans penis (Katona et al., 2006), or the alimentary tract (Wright et al., 1988; Farinon et al., 1999), and so on. Though MFH was firstly described as "malignant fibrous xanthoma" by O'Brien and Stout in 1964, its histogenesis is still uncertain. It is thought to originate from undifferentiated mesenchymal cells, which are capable of multidirectional differentiation; this may explain why it has the potential to be found in all organs (Kempson et al., 1972). However, Primary MFH of the liver is extremely rare, with only a few cases reported in literature. Here, informed by patient's consent, we have a case of MFH arising in the liver presented and the literature is briefly reviewed.

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Material and methods

Case history

A 53-year-old man complained of upper abdominal pain for one month, with 5- kilogram weight loss. Pain and tenderness over the mass were noted. The patient had a history of viral hepatitis for 10 years. Physical examination on admission disclosed a hard liver was felt 8 cm below the right costal margin, with deep tenderness.

Laboratory data showed that serum albumin was 29.4 g/L (reference range (RR), 35-55 g/l); Serum aspartate aminotransferase (AST) was 72 U/L (RR, 0-40 U/L); Serum alanine aminotransferase (ALT) was 39 U/L (RR, 0-50 U/L); Lactate dehydrogenase (LDH) was

509 U/L (RR, 120-230 U/L); Alkaline phosphatase was 208 U/L (RR, 30-140 U/L); Gamma-glutamyl transferase (GGT) was 188 U/L (RR, 0-40 U/L); Alpha-Fetoprotein (AFP) was 0.7 g/l(RR, <25 g/l); Carcinoembryonic antigen (CEA) was 1.6 g/l (RR, <5 g/l). Viral Hepatitis Testing revealed HbsAg(+), HBeAb(+) and HBcAb(+). Prothrombin time (PT), peripheral blood cell count were in normal range.

Initial ultrasound revealed a large mass in the left lobe of liver, with subtle contour, measuring 13.7 cm in maximal diameter. The echogenicity was inhomogeneous, and color Doppler study showed pulsative flow signals, suggesting high vascularity in mass (Fig. 1).

Subsequent CT-scan confirmed a mass in the left lobe of liver, which had a slightly demarcated contour. Compared with surrounding parenchyma, the mass was hypodense or equi-dense (Fig. 2a). The mass was partly enhanced by the contrast, especially in the periphery. However, its density was lower than surrounding parenchyma (Fig. 2b).

Exploratory laparotomy was performed on April 24, 2006. A soft mass was located at the left lobe of liver. It had already penetrated the liver capsule, and was enwrapped by greater omentum. The rest of the exploration was negative. Left hepatectomy and segmentectomy of segment V was performed.

Tissue sample

The surgical specimen measured 20.0x16.0x11.0 cm in size, with a dark brown in color. The cut surface showed a large mass measuring 16.0x15.0x8.0 cm in size, which was irregular with greyish-white or yellowish color. The mass was soft to firm variably. Lesional tissues and the surrounding hepatic tissues were routinely sampled and processed. Serial sections (4 μm) were stained with haematoxylin and eosin, then the pathological diagnosis were reviewed by two pathologists individually.

Immunohistochemistry

Immunohistochemistry was performed on 4 μm thick sections cut from the paraffin embedded blocks using the Dako EnvisionTM system according to the manual. The primary antibodies were selected to help pathological diagnosis, including vimentin (DakoCytomation, Glostrup, Denmark; 1:200 dilution); cytokeratin 18 (DakoCytomation; 1:100 dilution); cytokeratin 19 (DakoCytomation; 1:100 dilution); HMB45 (DakoCytomation; 1:100 dilution); CD117 (DakoCytomation; 1:100 dilution); desmin (DakoCytomation; 1:100 dilution); alpha-fetoprotein (AFP) (DakoCytomation; 1:300 dilution); α-smooth-muscle actin (SMA) (DakoCytomation; 1:100 dilution); S-100 protein (DakoCytomation; 1:200 dilution); CD-68 (DakoCytomation; 1:200 dilution); α1-antitrypsin (DakoCytomation; prediluted); α1-antichymatrypsin (DakoCytomation; prediluted). Heat antigen retrieval was performed for each antibody in citrate buffer (0.01 M, pH 6.0) with a boiler (40min, 98°C). Appropriate positive experiments for all antibodies were performed. Negative controls were included in each case by substituting the primary antibodies with ChemMate™ washing buffer (DakoCytomation). The immunohistochemical stain was evaluated based on percentage of positive neoplastic cells. The immunostaining with each antibody in at least 10% of neoplastic cells was defined as a positive reaction.

Results

Pathological findings

The tumor was infiltrative and displayed a multinodular architecture that was separated by fibroconnective tissue septa (of varying thickness). The nodules were composed of pleomorphic spindle-shaped and histiocyte-like cells. In some area, osteoclastic giant cells were prominent and massive necrosis was observed. The morphological appearance was varied with these cells. There were some areas showing a prominent storiform pattern with spindle cells (Fig. 3a) and some arranged in a haphazard growth pattern with spindle and pleomorphic cells. Numerous tumor giant cells had single or multiple hyperchromatic and pleomorphic nuclei and eosinophilic cytoplasm. The mitotic activity was frequent. The osteoclastic giant cells had multiple small uniform nuclei and copious eosinophilic cytoplasm, with absence of malignant cytological features and osteoid tissue nearby (Fig. 3b). The stroma was rich in blood vessels, partially dilated, sometimes combined with haemangiopericytoma-like

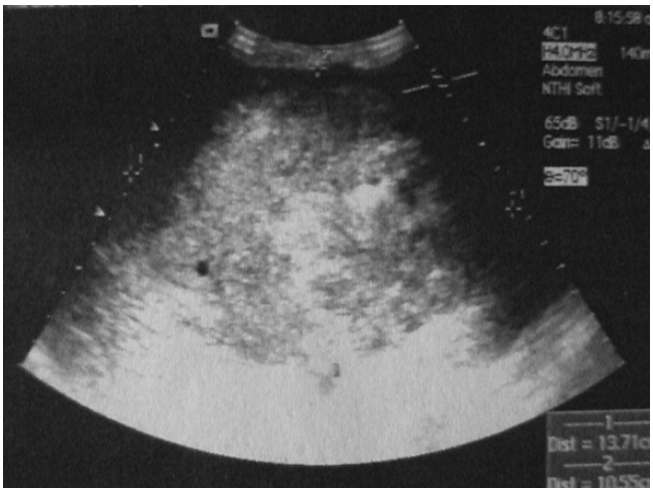

Fig. 1. Abdominal US showed a large hepatic mass with subtle contour, measuring 13.7 cm in maximal diameter. The echogenicity was inhomogeneous, and color Doppler study showed pulsative flow signals, suggesting high vascularity in the tumor.

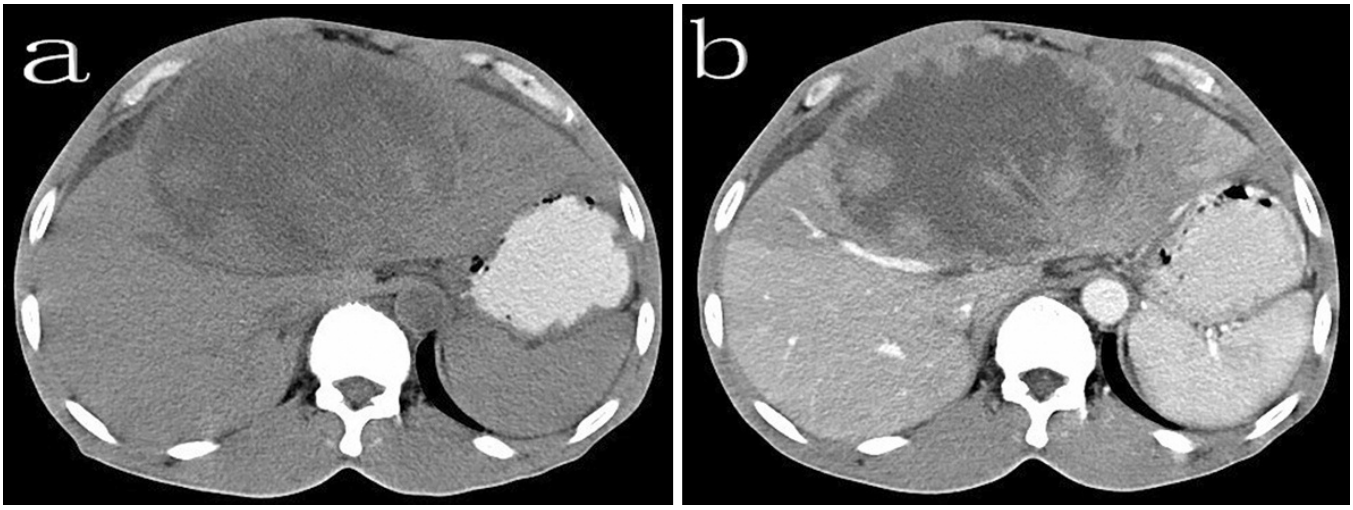

Fig. 2. a. Pre-contrast CT scans showed a mass in the left lobe of the liver, which has a subtle marginal contour. Compared with surrounding hepatic tissue, the mass was hypodense. **b.** After the contrast injection, the mass was slightly enhanced, especially on the edge. Its density of central area was as same as before that, being lower than the surrounding tissue.

Table 1. Reported cases of malignant fibrous histiocytoma of the liver.

Authors (yr)	case	Age/Sex	Location	Tumor size (cm)	Type of Histology	Immunohistochemistry	Clinical Course
Conran and Stocker (1985)	1	61/M	Left & right	22.4x23.5x12	Storiform/ pleomorphic		Dead,18 days after admission; metastasis(-)
Alberti-Flor et al. (1985)	1	59	Right & left	Round 18x15x14	Storiform/ pleomorphic		Dead, 2 wk after operation metastasis(-)
Fukuyama and Koike (1986)	1	38/F	Left	Round 6x6x7	Storiform/ pleomorphic	Ferritin(+) α1-antitrypsin(+) α1-antichymatrypsin(+)	Alive 4 yr after operation metastasis(-)
Arends and Willebrand (1987)	1	78/F	Left & right	Large mass (size not given)	Storiform/ pleomorphic	Vimentin(+) α1-antitrypsin(+) α1-antichymatrypsin(+)	Dead, 6 days after admission;metastasis(-)
Honda et al. (1988)	1	71/F	Right	Round (size not given)	Storiform/ pleomorphic	Vimentin(+) α1-antitrypsin(+) α1-antichymatrypsin(+)	Dead, 5 mo after admission; metastasis(-), operation(-)
Katsuda et al. (1988)	1	61/M	Right	Round(8.5x8x8)	Storiform/ pleomorphic	Vimentin(+)Lysozyme(+); α1-antitrypsin(+)	Dead, 6 mo after operation metastasis(±)
Akifuji et al. (1992)	1	79/M	Left	Round(8x8x6)	Storiform/ pleomorphic	Vimentin(+) α1-antichymatrypsin(+)	Alive , 8 mo after operation metastasis(+)
Ferozzi and Bova (1998)	3	62/F	Right	Large (size not given)	Myxoid		
		67/F	Right & left	Large (size not given)	Storiform/ pleomorphic		
		69/M	Right & left	Large (size not given)	Storiform/ pleomorphic		
Maekawa et al. (1999)	1	68/M	Right	Round(6x6x5.5)	Storiform/ pleomorphic	CD-6 (+)	
Chou (2002)	1	72/M	Right	Round(16x10x10)	Storiform/ pleomorphic	CD-68 (+)Vimentin(+)	Alive, 6 mo after operation and Adjuvant chemotherapy; metastasis(-)
Anagnostopoulos et al. (2005)	1	57/F	Right	Round(12x8)	Storiform/ pleomorphic	Vimentin(+) α1-antichymatrypsin(+)	Dead, 6 mo after admission; metastasis(-), operation(-)
Ding et al. (2006)	1	50/M	Left & righ	Large(9.5x14.2)	Storiform/ pleomorphic	CD-68 (+)Vimentin(+)	Dead, 2 mo after operation metastasis(-)
The present case	1	53/M	Left	Large(16x15x8)	Giant cells	CD-68 (+) α1-antitrypsin(+) α1-antichymatrypsin(+)	Dead, 4 mo after operation Recurrence(+), metastasis(-)

areas. Myxoid change was also seen. The surrounding hepatic tissue did not show any evidence of cirrhosis.

Immunohistochemistry

Most of the spindle-shaped cells, histiocyte-like cells, and osteoclastic giant cells were vimentin-positive (Fig. 3c). Several pleomorphic tumor cells, including osteoclastic giant cells, showed positive for alpha-1 antichymotrypsin, alpha-1 antitrypsin and CD68. Stains for desmin, cytokeratin 18, 19, CD117, HMB45, alpha-fetoprotein, SMA and S-100p were negative.

Clinical course

Postoperative course was satisfactory, but a recurrence was confirmed in the right lobe of liver and the hepatogastric space one month later (Fig. 4). The patient had lost the second chance for surgery, and unfortunately died 3 months later.

Discussion

MFH has been regarded as a common malignant soft tissue sarcoma. Based on its morphological pleomorphism, five histologic subtypes have been described by Enzinger and Weiss: storiform/pleomorphic (65% of cases), myxoid (15%), giant cell (10%), inflammatory (8%), and angiomatoid (2%) (Weiss et al., 1978). The pleomorphic MFH has been regarded as the prototypical form of MFH, characterized as pleomorphic spindle cells in a storiform pattern with fibroblastic and facultative histiocytic differentiation. It is now widely accepted that the so-called pleomorphic MFH may be shared by a wide variety of poorly differentiated malignant neoplasms (Fletcher, 1992). It is also agreed

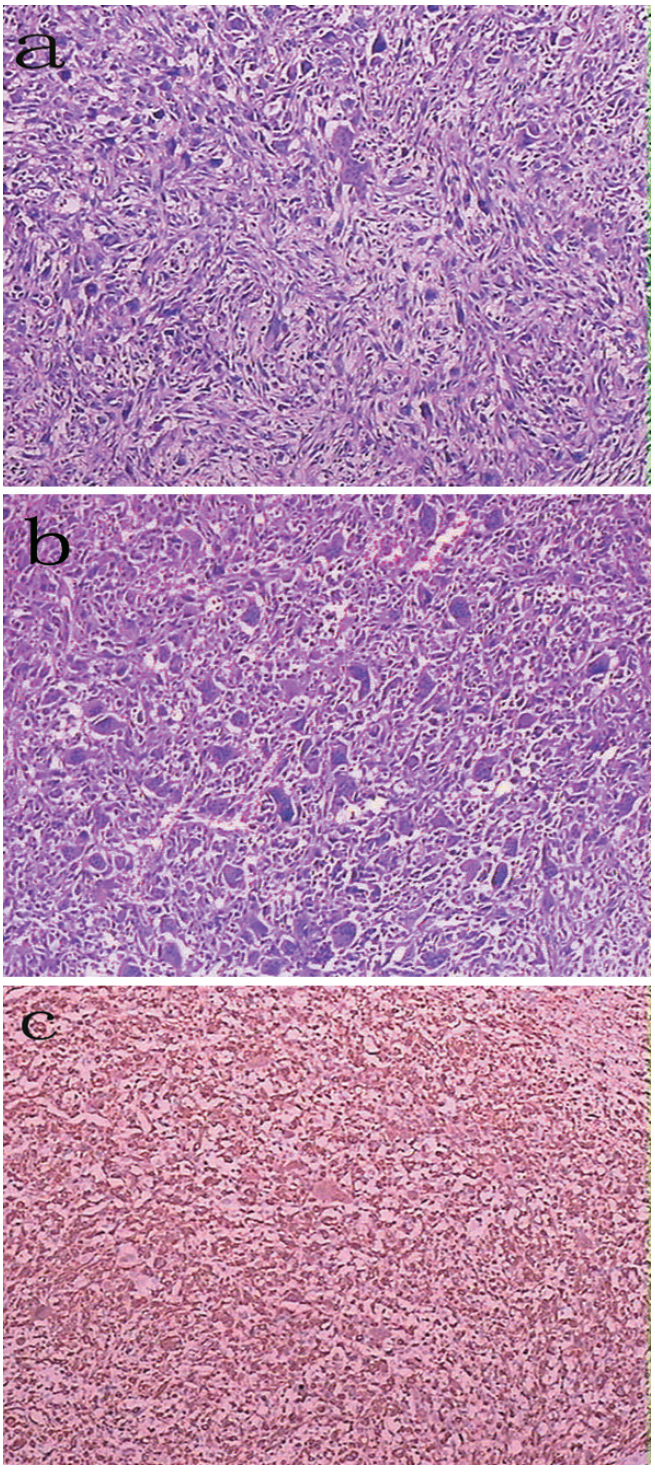

Fig. 3. a. The tumor showed a prominent storiform pattern composed of spindle cells. **b.** The neoplastic giant cells and the osteoclastic giant cells were prominent. (H&E x100). **c.** Immunostaining for vimentin was present in the cytoplasm of most neoplastic cell. x 100

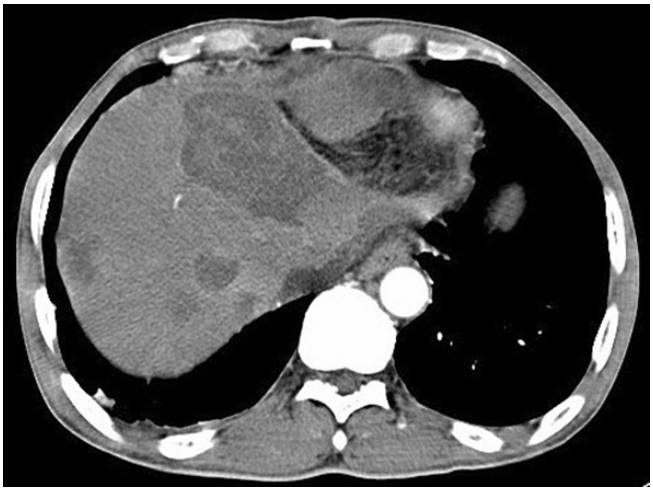

Fig. 4. Multifocal recurrences of the tumor in the right lobe of the liver were revealed by CT scan after one month of surgery.

that these tumors show no evidence of true histiocytic differentiation. So the term pleomorphic MFH is now reserved for the much smaller group of pleomorphic sarcomas, which by current technology, show no definable line of differentiation (Weiss et al., 2001). According to WHO Classification, the term malignant fibrous histiocytoma, pleomorphic malignant fibrous histiocytoma, and undifferentiated high grade pleomorphic sarcoma are synonyms (Fletcher et al., 2002).

Primary MFH of the liver is very rare. It was first reported in 1985 (Alberti-Flor et al., 1985). Table 1 lists 14 cases of primary hepatic MFH previously reported in English literature and one case here. Clinical symptoms include chest pain, right upper or diffuse abdominal pain, weight loss, fever, jaundice, anorexia, malaise and palpable abdominal mass. Some have leukocytosis and abnormal liver transaminases, alkaline phosphatase and gamma-glutamyl transferase.

Sonography shows hypoechoic, iso-echoic or hyperechoic occupation in liver with variable anechoic areas, depending on the pathological changes such as necrosis, hemorrhage or myxoid degeneration. The CT features of hepatic MFH include low-attenuation density areas of necrosis and a poorly defined border of solid component with liver parenchyma on precontrast scans. After contrast injection, the solid component shows variable enhancement depending on the tumor vascularity and the extent of tumor necrosis. Tumor sizes range from 6 to 23.5 cm in diameter, the mean diameter is 12 cm, but no predilection for one lobe or the other as the origin site. In our patient, the tumor's maximum diameter was 16 cm, and located at the left lobe of the liver.

Histopathologically, the tumors are very heterogeneous in appearance and also in cellularity. These tumors have in common marked cytological and nuclear pleomorphism, often with bizarre tumor giant cells, spindle cells and round histiocyte-like cells (Fletcher, 1992). WHO Classification of Tumor recommends two special MFH types: MFH with giant cells and with inflammatory. The former is for undifferentiated pleomorphic sarcoma with prominent osteoclastic giant cells, the latter with prominent inflammation (Coindre, 2002; Fletcher, 2002). The case here was the type of MFH with giant cells, or called undifferentiated pleomorphic sarcoma with giant cells.

Immunohistochemical stain shows positive results for vimetin, alpha-1 antichymotrypsin and alpha-1 antitrypsin indicating the presence of sarcomatous, fibrous, myofibroblastic and histiocytic differentiation. The absence of antigens characteristic of epithelial markers, such as keratin, desmin, alpha-fetoprotein, CEA, S-100p, indicates against the origin of epithelial cells. In our patient, most tumor cells express vimentin, alpha-1 antichymotrypsin, alpha-1 antitrypsin and CD68.

The pathological diagnosis of hepatic MFH in adults is not very difficult. Other malignancies with mimic pleomorphic appearances should be excluded when this diagnosis is made. The histomorphology of malignant fibrous histiocytoma is characterized by the presence of a typical storiform pattern composed of spindle-shaped fibroblasts and scattered, highly polymorphic bizarre or multinucleated neoplastic cells. The stroma has scattered inflammatory cell infiltration and abundant vessels. Stromal fibrosis is absent. Necrosis is commonly observed. Usually, immunochemical phenotypes of neoplastic cells including CD68, alpha-1 antitrypsin and alpha-1 antichemotrypsin expression, play an important role in pathological diagnosis and differential diagnosis. Considering the differential diagnosis in visceral organs, sarcomatous carcinoma and carcinosarcoma with epithelial component should firstly be included. In this case, no expression of cytokeratin 18, 19 and alpha-fetoprotein in the neoplastic cells supported the mesenchymal differentiation of the neoplasm. Distinction between the neoplasm and other pleomorphic sarcomas was also important, and sometimes quite difficult. Pleomorphic liposarcoma, rhabdomyosarcoma and leimyosarcoma could be excluded because the neoplastic cells lacked the expression of desmin, S-100 protein and SMA. Finally, metastatic malignant melanoma appearing with pleomorphic cellular pattern was excluded because of the absence of S-100 protein and HMB45 expression.

Surgery is the only effective treatment for MFH. Chemotherapy and radiotherapy have been used, but without success (Weiss et al., 1978). Most people with primary hepatic MFH reported in the literature were treated surgically, but the prognosis was poor. Only two patients (of 14 patients listed in the table) survived without any evidence of local recurrence or distant metastasis. Our patient presented a local recurrence in the right lobe of liver and the hepato-gastric space one month later, probably resulting from the tumor penetration. The outcome for this patient was poor despite aggressive therapy.

In conclusion, hepatic MFH is a rare malignant mesenchymal tumor. The variable features of clinical presentations and images make the diagnosis difficult. Histopathological findings and immunocytochemical stain has been the mainstay of the diagnosis. Clinicians must remember this while establishing differential diagnosis for patients with large liver lesions.

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