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CASE REPORT

Primary Hepatic Malignant Fibrous Histiocytoma Mimicking Hepatocellular Carcinoma: Report of Two Cases with Immunohistochemical Detection of Ezrin, and Ultrastructural and K-*ras* Mutation Analysis

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We reported two primary malignant fibrous histiocytoma (MFH) cases (cases 1 and 2) strikingly simulating hepatocellular carcinoma with immunohistochemical (IHC) stains, and ultrastructural and K-*ras* mutation analysis. Cases 1 and 2 both included only men, aged 65 and 72 years, respectively. Case 1 presented with abdominal pain, fever, and bilateral legs edema. Case 2 was found to have a liver tumor during routine heath examination. Computed tomography scan showed hepatic mass with fine tumor vessels. Case 1 had one $16 \times 15 \times 13$ cm^3 liver mass with tumor rupture in the right lobe, and case 2 had one $3 \times 2.5 \times 1$ cm^3 liver tumor in segment 6. Microscopically, the tumors were composed of spindle, pleomorphic, and multinucleated giant cells arranged in storiform, sheet-like, and fascicular patterns. Strong immunoreactivity for CD68 and vimentin in tumor cells in both cases was noticed. Ezrin immunoexpression in tumor tissue from case 1 was diffusely strong; in contrast, case 2 showed sparse and weak ezrin expression in tumor cells. Ultrastructurally, cells with fibroblasts and histiocytic characteristics were present in both cases. K-*ras* gene analysis of exon 2codon 12 or 13 showed no mutation. This is the first report describing K-*ras* gene analysis of liver MFH. We emphasize that ezrin immunoreactivity may be correlated with poorer prognosis.

1. Introduction

In Taiwan, hepatocellular carcinoma (HCC) is the most common liver tumor, which is associated with hepatitis virus infection and liver cirrhosis. Primary sarcomas of the liver are rare neoplasms.[1] Primary hepatic malignant fibrous histiocytoma (MFH) is extremely rare,[2–4] and only 49 cases have been reported to date in the literature.[5–27]

Ezrin is a novel cytoskeleton linker protein that is involved in regulating cellular growth and metastatic potential of various types of malignancies.[28–30] Point mutation of the K-*ras* oncogene is a frequent event in many gastrointestinal carcinomas.[31,32] However, little is known about the occurrence of this mutation in primary hepatic MFH.

In this report, we present two cases of primary hepatic MFH. We investigated extensive immunohistochemical (IHC) stains, electron microscopic studies, and K-*ras* mutation analysis to describe the possible histological prognostic factor in hepatic MFH.

2. Case reports

2.1. Case 1

A 65-year-old male patient suffered from abdominal pain, fever, and bilateral legs edema for 1 month. No history of previous operation, alcohol consumption, or smoking was found. Laboratory data showed slightly increased glutamic-oxaloacetic transaminase (GOT) (50 IU/L; normal, 5–40 IU/L), carbohydrate antigen 19-9 (64.40 U/mL; normal, <37.00 U/mL), and anemia (hemoglobin = 7.3 g/dL; normal, 14–18 g/dL). Serologic anti-hepatitis C virus (anti-HCV) antibody and hepatitis B virus (HBV) surface antigen were positive. Serum alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA) were within normal limits.

Preoperative abdominal computed tomography (CT) showed a heterogeneously enhancing mass ($16 \times 15 \times 13$ cm^3) in the right hepatic lobe, with suspicious invasion of right portal vein and tumor rupture (Figure 1). Under the impression of huge HCC with suspected rupture, the patient underwent extended right

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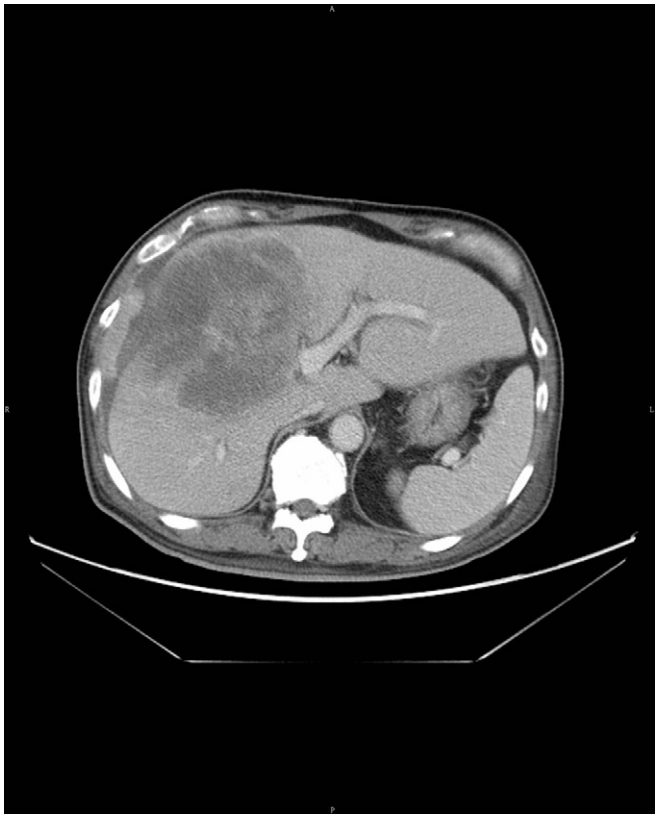

Figure 1 CT scan of case 1. A lobulated mass ($16 \times 15 \times 13$ cm^3) occupying segments 4, 5, and 8 of liver, with an initial peripheral and gradual fill-in enhancement pattern, and central areas of necrosis were found. Tumor had ruptured at its lateral margin, with blood clot in right perihepatic space. CT = computed tomography.

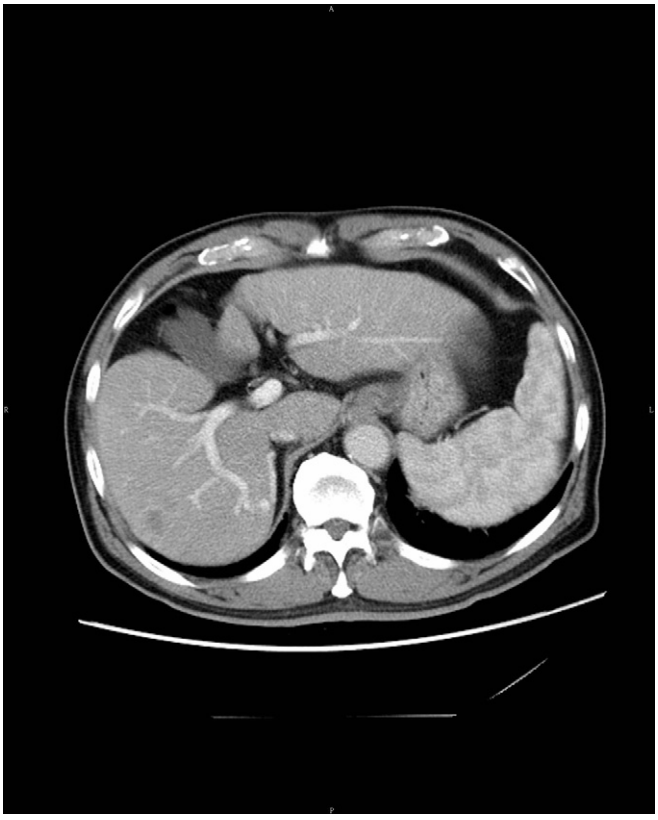

Figure 2 CT scan of case 2 showed a solitary mass ($3 \times 2.5 \times 1$ cm^3) with irregular margin in segment 6 of liver, with a peripheral enhancement pattern and central area of necrosis. CT = computed tomography.

lobectomy of the liver, omentectomy, and cholecystectomy. Written informed consent was obtained.

The patient complained of right shoulder and neck pain 1½ month after operation. Abdominal and pelvis CT scan showed numerous variable-sized heterogeneously enhanced masses at right resection margin of liver with diffuse peritoneal seeding. Bilateral metastatic lung masses with right pleural effusion and massive ascites were also noted. The patient expired 2 months after surgery.

2.2. Case 2

A 72-year-old male patient was incidentally found to have a hepatic tumor during routine medical examination. The patient had no history of previous operation, alcohol consumption, or smoking. Laboratory data showed anemia with hemoglobin of 12.4 g/dL, a decreased platelet count of $72 \times 10^3/\mu$L (normal, $130-400 \times 10^3/\mu$L), slightly increased GOT (63 IU/L), glutamic-pyruvic transaminase (60 IU/L; normal, 5—40 IU/L), and Indocyanine green retention test (ICG) 16.0% (normal, <10%). Serologic anti-HCV antibody and HBV surface antigen were negative. The AFP level was within normal limit.

Preoperative CT scan showed a hypervascular liver mass ($3 \times 2.5 \times 1$ cm^3) in segment 6 of liver with patent portal vein (Figure 2). Under the impression of HCC, the patient underwent laparoscopic segmentectomy of segment 6. Written informed consent was obtained. The postoperative course was smooth.

2.3. Macroscopic and light microscopic findings

These two tumors were solitary and well circumscribed, but unencapsulated whitish to yellow tan mass with areas of hemorrhage and necrosis (Figures 3A and B). Rupture of tumor is present

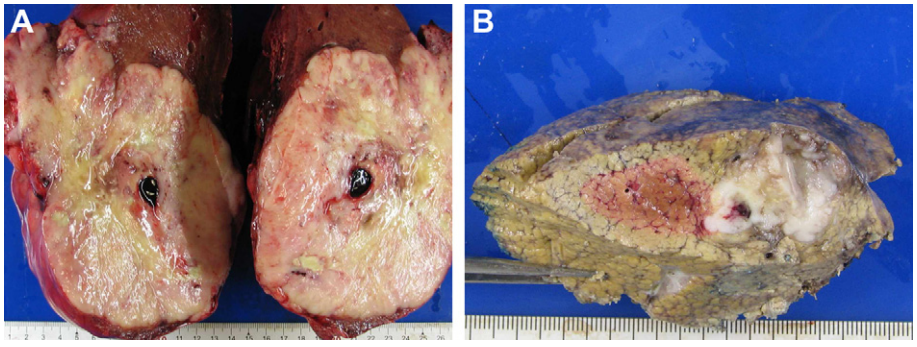

Figure 3 Macroscopic findings of the cut surface of the tumor in (A) case 1 and (B) case 2.

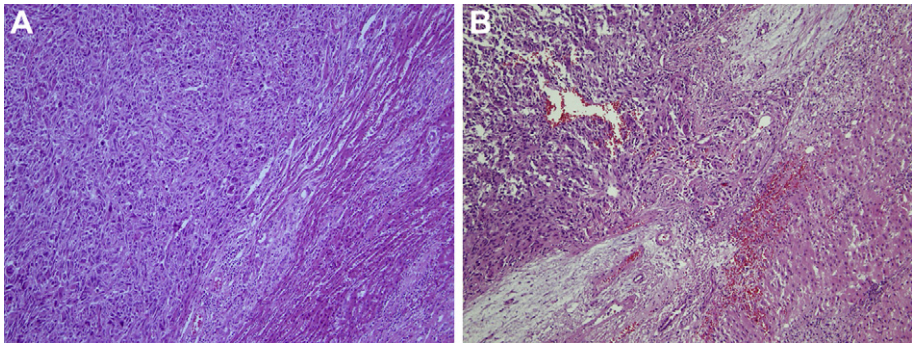

Figure 4 Microscopic features of hepatic MFH in (A) case 1 and (B) case 2. The storiform–pleomorphic growth patterns were similar in both cases (hematoxylin and eosin staining, original magnification in A and B, ×100). MFH = malignant fibrous histiocytoma.

in case 1. Histopathological findings of the hepatic tumors from cases 1 and 2 (Figures 4A and B) were similar. Proliferation of spindle, pleomorphic, and multinucleated giant cells arranged in storiform, sheet, and/or fascicle patterns was noticed. In both cases, marked nuclear pleomorphism, prominent mitoses (five in 10 fields of high-power view), and foci of inflammatory cellular infiltration were noticed. The tumor stages of case 1 and case 2 were stage IVB and stage I, respectively.

2.4. Immunohistochemistry findings

IHC staining was performed on paraffin-embedded tissue sections (Table 1). Positive control for ezrin (small bowel mucosa) and negative controls by omitting primary antibodies were performed.

Table 1 Primary antibodies used in the two cases of primary hepatic malignant fibrous histiocytoma

Antibody	Manufacturer	Clone	Dilution
Actin	DAKO	1A4	1/400
AFP	DAKO	Polyclonal	1/250
ALK-1	Novocastra	Polyclonal	1/500
β-Catenin	DAKO	Polyclonal	1/200
Bcl-2	Novocastra	3.1	Predilute
Calretinin	Novocastra	5A5	1/100
CD1a	Novocastra	MTB-1	Predilute
CD21	Cell Marque	Polyclonal	1/200
CD23	Biocare	1B12	1/200
CD31	DAKO	JC70A	1/200
CD34	DAKO	QBEnd10	1/200
CD56	DAKO	Polyclonal	1/100
CD68	DAKO	PG-M1	Predilute
CD117	DAKO	C-kit	1/200
CEA	Zymed	Polyclonal	1/1000
Cytokeratin	DAKO	Polyclonal	1/400
Cytokeratin 7	DAKO	OV-TL 12/30	1/200
Cytokeratin 19	DAKO	RCK108	1/200
Desmin	DAKO	D33	1/100
EGFR	Novocastra	EGFR.25	1/100
Epithelial membrane antigen	DAKO	E29	1/200
Estrogen receptor	Novocastra	6F11	1/200
Ezrin	Epitomics	EP886Y	1/250
HMB-45	DAKO	HMB-45	1/500
Hep Par-1	DAKO	OCH1E5	1/100
Ki-67	DAKO	MIB-1	1/100
Progesterone receptor	Novocastra	16	1/200
p53	Novocastra	DO-7	Predilute
S-100	DAKO	Polyclonal	1/200
Thyroid transcription factor 1	DAKO	8G7G3/1	1/200
Vimentin	DAKO	V9	1/400

AFP = alpha-fetoprotein; CEA = carcinoembryonic antigen; EGFR = epidermal growth factor receptor.

Staining intensity was assessed by an arbitrary value of 0 (no staining, <5%), 1 (weak staining, 5–33%), 2 (moderate staining, 33–66%), or 3 (strong staining, >66%).

Tumor cells in both cases were positive for vimentin and CD68. Cellular proliferative indexes (Ki-67 stain) were 75% and 80% in cases 1 and 2, respectively. Faint immunoreactivity (<5% of tumor cell) was found for smooth muscle actin and epidermal growth factor receptor (EGFR) in both cases. Ezrin immunoexpression showed diffuse and strong cytoplasmic and/or membranous staining in case 1 (Figure 5A). In contrast, the immunoreactivity against ezrin in tumor cells of case 2 was weak and showed a scattered distribution (Figure 5B). The other immunostains were negative in both cases.

2.5. Electron microscopy findings

Tumor tissue sections were fixed in 2.5% glutaraldehyde and 1% osmium tetroxide, progressively dehydrated in graded acetones, and then embedded in epoxy resin. After staining with uranyl acetate and lead citrate, ultrathin sections were analyzed with a transmission electron microscope (Hitachi H-600). In our cases, predominantly fibroblast-like cells with well-developed rough endoplasmic reticulum and some histiocyte-like cells with lysosomes and Golgi apparatus were observed (Figures 6A and B).

2.6. K-ras mutation analysis

Mutation analysis of the K-*ras* oncogene (exon 2 codon 12 or 13) was performed using the polymerase chain reaction (PCR)-dependent preferential homoduplex formation assay. The K-*ras* gene was amplified by PCR with a forward primer (huKRAS2 ex2F: 5′-GAA TGG TCC TGC ACC AGT AA-3′) and reverse primer (huKRAS2 ex2R: 5′-GTG TGA CAT GTT CTA ATA TAG TCA-3′). All sequencing reactions used ABI standard reagents and protocols for the ABI 3100 automated DNA sequencer. The K-*ras* mutation analysis failed to demonstrate any single-point mutation in both cases (Figure 7).

3. Discussion

Primary hepatic MFH is a rare entity.[3,4] It is a disease of adult patients (mean age: 57.6 years) without sex predilection (male:female ratio is 18:16). Most reported cases were solitary lesions, with tumor size ranging from 5.5 to 20 cm (average 12 cm). To the best of our knowledge, the size of the tumor of case 2 ($3 \times 2.5 \times 1$ cm^3) in our present report was the smallest in hepatic MFH. The diagnosis of primary hepatic MFH is often delayed because of nonspecific clinical symptoms.

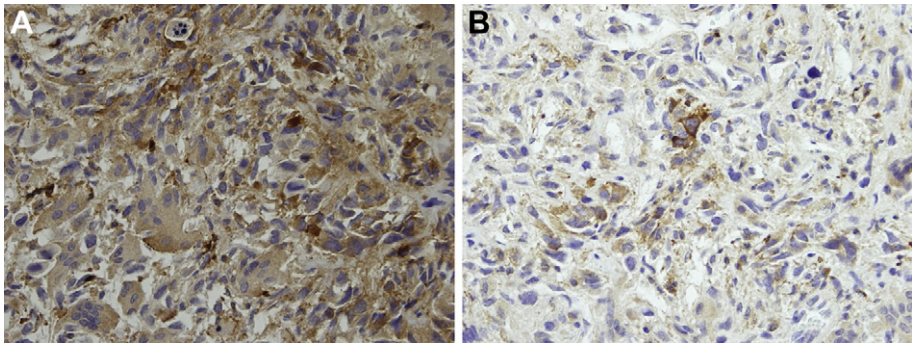

Figure 5 Ezrin immunoexpressions in tumor cells from (A) case 1 and (B) case 2. Immunohistochemical staining with hematoxylin counterstained was shown (original magnification in A and B, ×400).

Most hepatic MFHs demonstrate a well-defined mass with a complex pattern on radiology image studies.[10,19] Marginal tumor staining without a central feeding artery is a characteristic feature of MFH on hepatic angiography. However, no specific radiologic features are diagnostic of hepatic MFH. The conclusive diagnosis of hepatic MFH relies on histological examination only.

Histopathological section of hepatic MFH was usually well circumscribed, without encapsulation, and with firm consistency. About 32% of tumors presented with local invasion, most commonly into diaphragm and lung. Histologically, the tumor consisted of bundles of spindle cells arranged in storiform and fascicle patterns, intermingled with bizarre and multinucleated giant cells. Most tumor cells expressed vimentin and CD68 IHC stains. The absence of antigens for epithelial tumors of the liver and the lack of expression of CD45 suggest the diagnosis of primary hepatic MFH.[25]

Primary hepatic MFH is a diagnosis of exclusion. A history of viral hepatitis infection, an elevated serum AFP level, a rich blood supply from hepatic artery, and a frequent portal vein invasion on imaging are the clinical factors that favor the diagnosis of HCC in Taiwan. A previous report showed that cirrhosis has never been reported in hepatic MFH.[33] However, liver cirrhosis was found in case 1 of our present report, which was probably related to hepatitis virus infection. Therefore, the preoperative diagnostic challenge of case 1 was more difficult. Intrahepatic cholangiocarcinoma is the second primary epithelial neoplasm that needs to be included in the differential diagnosis. Cytokeratin 7 IHC stain is useful to exclude intrahepatic cholangiocarcinoma.

HCCs vary architecturally and cytologically. Special variants of HCC include fibrolamellar carcinoma, scirrhous HCC, undifferentiated carcinoma, lymphoepithelioma-like carcinoma, and sarcomatoid HCC. Immunohistochemically, HCC is characterized by cytoplasmic positivity with antibodies to carbamoyl phosphate synthetase-1 (HepPar1). Canalicular patterns with IHC staining of polyclonal antibodies to CEA or antibody to CD10 may be seen. Besides, HCC is also positive for AFP and pan-cytokeratin, but usually negative for cytokeratins 19 and 20 and epithelial membrane antigen. Occasionally, HCC is partially or fully comprised of malignant spindle cells, and may be difficult to distinguish from various sarcomas. Some sarcomatoid HCC with undifferentiation may show storiform pattern resembling MFH, especially in case 1 of our recent report. Although in case 1, the tumor was arising from an

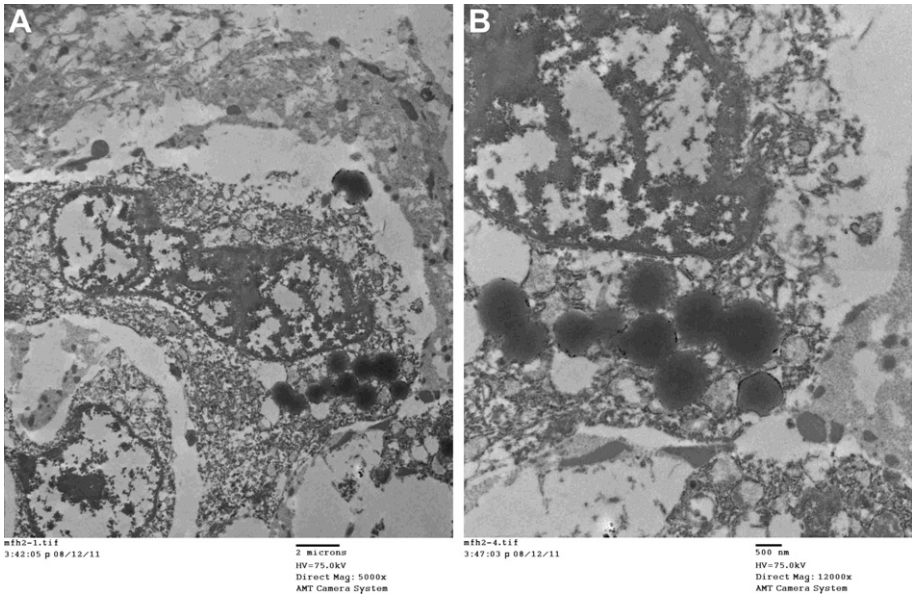

Figure 6 Representative electron microscopic images of the tumor from (A) case 1 and (B) case 2. Fibroblast-like cells with prominent cytoplasmic rough endoplasmic reticulum and histiocyte-like cells with prominent lysosomes were noticed (original magnification in A, ×5000; in B, ×12,000).

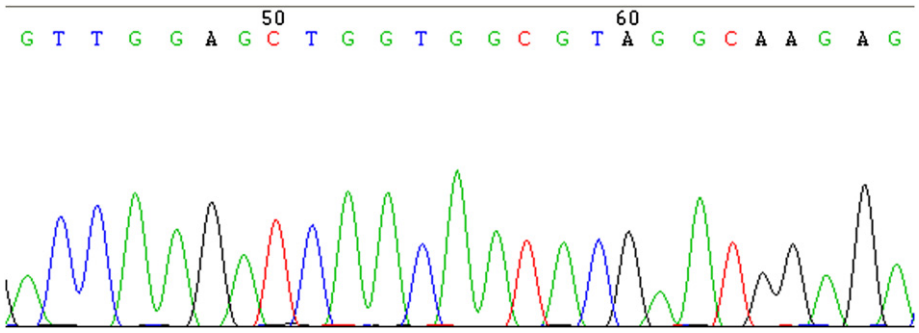

Figure 7 The K-*ras* exon 2 codon 12 or 13 mutation analysis is not detectable.

HBV- and HCV-positive cirrhotic liver, we were convinced that this was not a sarcomatoid HCC because we could not find areas of more typical HCC by extensive gross and histological sampling. In addition, thorough IHC stains (up to 32 antibodies) were performed and the results were not compatible with sarcomatoid HCC.

Metastatic MFH from other sites or invasion from retroperitoneal MFH should be considered. Liver metastases from extrahepatic MFH usually occur until late stages. The primary MFH becomes large and, therefore, the primary location could easily be discovered. In our two cases, no tumors were found in any other organs on radioimaging examinations or intraoperative gross examination. The fourth differential diagnosis of primary mesenchymal neoplasms of the liver includes angiosarcoma, dedifferentiated liposarcoma, rhabdomyosarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, and fibrosarcoma. The immunoexpression of certain specific lineage markers is useful. We could use S100 for malignant peripheral nerve sheath tumor and liposarcoma; CD31 and CD34 for angiosarcoma; and desmin and actin for skeletal and smooth muscle tumors, respectively. Inflammatory pseudotumor, a rare entity, is the fifth disease that mimics primary hepatic MFH. In microscopic examination, the lack of significant nuclear pleomorphism and the presence of a large number of inflammatory cells throughout the background should help differentiate it from primary hepatic MFH.

Many patients survived less than 1 year, which was associated with large tumor size, late clinical stage, and a high ezrin expression score.[25,26,28,29] Our observation of higher ezrin immunoreactivity score associated with poorer prognosis is consistent with previous reports. Akatsu et al[32] first reported K-*ras* mutation in pancreatic MFH. However, similar genetic analysis showed no mutation.[31] In soft tissue MFH, Wilke et al[34] and Bohle et al[35] found *ras* point mutation at codon 12. Our patients carried K-*ras* wild-type sequences, which clearly differed from the most frequent malignant tumor of digestive organs.

In conclusion, primary hepatic MFH has certain characteristic clinicopathologic features that differentiate it from other more common neoplasms in the liver. Ezrin immunoexpression was probably correlated with poorer outcomes in patients with primary hepatic MFH.

Conflict of interest

None.

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