Fibrolamellar carcinoma versus scirrhous hepatocellular carcinoma : diagnostic usefulness of CD68

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Abstract

Background : **Fibrolamellar hepatocellular carcinoma (FL-HCC) is a rare variant of hepatocellular carcinoma that commonly affects young individuals without a prior history of liver disease. The principal differential diagnosis is conventional hepatocellular carcinoma especially the scirrhous variant. Despite their distinctive appearance, recent studies have demonstrated a lack of consistency in how FL-HCC are diagnosed by pathologists.**

Aim : **To investigate the diagnostic utility of CD68 in differentiating between FL-HCC and scirrhous hepatocellular carcinoma.**

Patients and Methods : **In our retrospective study, we reviewed four cases of FL-HCC that were diagnosed at the pathology department of Mongi Slim hospital over a thirteen-year period (2002-2014). Relevant clinical information and microscopic slides were available in all cases and were retrospectively reviewed. Immunohistochemical analysis was performed using the avidin-biotin complex technique with antibodies against CD68 and CK7.**

Results : **Our study group included one man and three women (sex ratio M/F = 0.33) aged between 23 and 34 years (mean = 28 years). All cases arose in non-cirrhotic liver. Immunohistochemically, all cases were positive for CK7 and for CD68 (n = 4).**

Conclusions : **CD68 immunostaining is a sensitive marker for FL-HCC that may be of use in routine diagnostic surgical pathology. Lack of CD68 staining should suggest caution in making a diagnosis of FL-HCC.** (Acta gastroenterol. belg., **2015**, 78, **393-398**).

Key words : liver, fibrolamellar carcinoma, scirrhous hepatocellular carcinoma, CD68, immunohistochemistry.

Introduction

Fibrolamellar hepatocellular carcinoma (FL-HCC) is an uncommon variant of hepatocellular carcinoma (HCC) accounting for less than 1% of primary liver tumours (1). It is defined by a triad of morphological features : polygonal tumour cells with eosinophilic cytoplasm, prominent macronucleoli and lamellar fibrosis. Despite its distinctive appearance, recent studies have demonstrated a lack of consistency in how FL-HCC is diagnosed by pathologists (2). In this paper, we report four cases of FL-HCC. Our aim was to highlight the clinicopathological features of this relatively uncommon neoplasm with special emphasis on the utility of immunohistochemistry in the differential diagnosis especially with scirrhous HCC.

Patients and methods

We undertook a retrospective study of four patients who were operated on for FL-HCC at the surgery department of Mongi Slim Hospital of Tunis between July 2009 and July 2014. The cases were retrieved from the files of the registry of surgery of the same hospital. Clinical records and microscopic slides of each patient were available for review in all cases. Clinical data, radiological investigations, treatment and outcome were retrospectively analyzed. All patients underwent imaging evaluation during the preoperative period. All specimens were surgically obtained. Tissues were fixed in 10% phosphate buffered formaldehyde, embedded in paraffin and sections were prepared for routine light microscopy after staining with hematoxylin and eosin. Immunohistochemical analysis was performed using the avidin-biotin complex technique with antibodies against CD68 and cytokeratin 7 (CK7).

Results

The clinical data of the patients of our series are summarized in table 1.

Clinical Findings

There were three female and one male patients (sex-ratio M/F = 0.33) aged between 23 and 34 years (mean = 28 years). The delay from onset of symptoms to diagnosis ranged between two weeks and one month. One patient was pregnant at 10 weeks of gestation (case 3). The most common presenting symptoms were abdominal and right upper quadrant pain (n = 4) followed by jaundice (n = 2) and altered general health (n = 1). Physical examination disclosed hepatomegaly in all cases (n = 4).

Biological tests

Serum tumour markers namely alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA) were performed in respectively four cases and two cases of our series. AFP was slightly elevated in only one case (9 ng/ml) and within normal range in three cases (< 6 ng/ml) ; whereas CEA was not elevated in all cases.

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Table 1. — **Clinical data in four patients with fibrolamellar carcinoma**

	Case 1	Case 2	Case 3	Case 4
Age / gender	25/F	23/M	30/F	34/F
Past medical history	–	–	cholecystectomy	Hypothyroidism
Tumour size	10 cm	6,5 cm	16 cm	18 cm
Location	Right hepatic lobe	Right hepatic lobe	Left hepatic lobe	Left hepatic lobe
Clinical Presentation	Right upper quadrant pain, jaundice. altered general health	Right upper quadrant pain, jaundice	Pregnant at 10 weeks Abdominal pain	Abdominal pain
Biological tests				
AFP	< 6 ng/ml	< 6 ng/ml	9 ng/ml	< 6 ng/ml
CEA	< 2.5 ng/ml	< 2.5 ng/ml	NP	NP
Hepatitis B & C serology	Negative	not performed (NP)	Negative	NP
Imaging Findings	CT scan : lobulated isodense mass with central stellate calcification	CT scan : lobulated hypodense mass	CT scan : well-delineated hypodense mass with central calcification	CT scan : hypodense mass
Lymph node status	No regional lymph node metastasis (N0)	Regional lymph node metastasis (N1)	Regional lymph node metastasis (N1)	Regional lymph node metastasis (N1)
Treatment	Chemoembolization and Palliative biliary drainage	No preoperative treatment Right hepatectomy and lymph node dissection	No preoperative treatment Left hepatectomy and lymph node dissection	No preoperative treatment Left hepatectomy and lymph node dissection
Evolution	Febrile after chemoembolization Lost to follow-up	Hemorrhagic shock on postoperative day 23 Still being followed up	No postoperative complications Still being followed up	Tumour recurrence, lymph node metastases and peritoneal carcinosis, 13 years after surgery

AFP, alpha-fetoprotein ; CEA, carcinoembryonic antigen ; F, female ; M, male ; NP, not performed.

Radiological findings

All patients underwent imaging evaluation during the preoperative period. Ultrasonography and computed tomography (CT) scan were performed in all cases, whereas magnetic resonance imaging (MRI) was realised in three cases. Imaging findings of the cases of our series are summarized in table 1.

Pathologic Findings

Macroscopic findings (Figs. 1b & 2a)

FL-HCC ranged in size from 6,5 to 18 cm (mean = 12.6 cm). On cut section, FL-HCC were yellow to pale and their consistency was firm. A central scar was found in two cases. Areas of hemorrhage were found in only one case (case 3).

Microscopic findings

Histological examination of the surgical specimen coupled with immunohistochemical study established the diagnosis of FL-HCC. The following triad of histological features were noted in all cases : large polygonal tumour cells with abundant eosinophilic granular cytoplasm, prominent macronucleoli and lamellar fibrosis. The tumour cells were separated by plate-like stacks of collagen lamellae of variable thickness (Figs. 1c, 2b & 2c). Areas of hemorrhage were found in one case (case 3), but necrosis was not detected. The adjacent liver parenchyma was not cirrhotic in all cases (fibrosis stage = 0 in all cases). Lymph node metastases were detected in three cases (cases 2, 3 & 4).

Immunohistochemical study

Immunohistochemically, the tumour cells were immunoreactive with CK7 (Fig. 1d) and CD68 (Fig. 2d) in all cases. Positive immunostaining with CD68 was characteristic, with a distinctive granular pattern (Fig. 2d).

Operative morbidity and postoperative complications

One patient developed hemorrhagic shock on postoperative day 23 (case 2). Local recurrence of the tumour with concomitant lymph node metastases occurred 13 years after surgery in another patient (case 4). In one case postoperative course was uneventful (case 3).

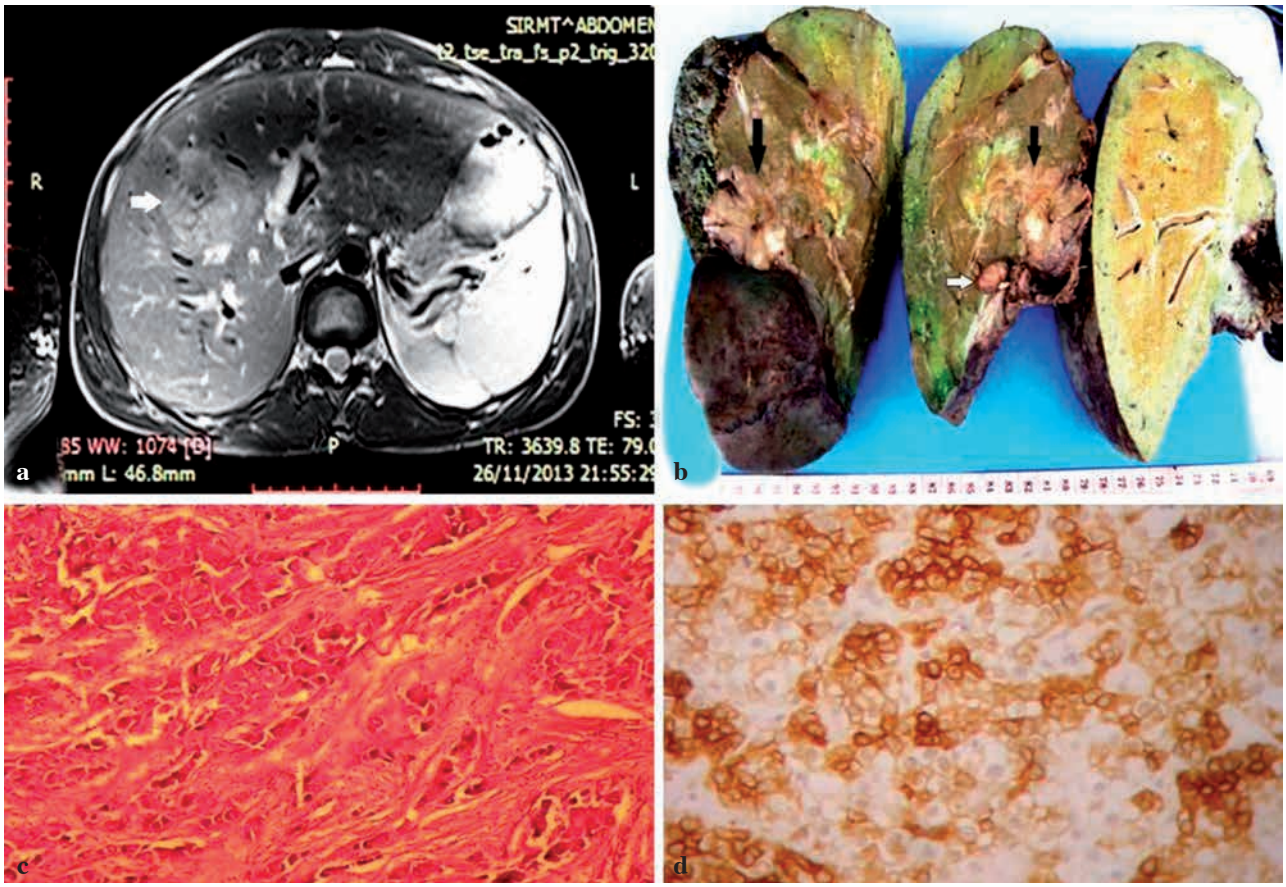

Fig. 1. — Pathological findings of fibrolamellar hepatocellular carcinoma (case 2). (a) Magnetic resonance imaging revealing an intrahepatic lesion measuring 7.5 × 5.3 cm developed in segment V and VIII. (b) Macroscopic appearance of fibrolamellar hepatocellular carcinoma. An ill-delineated and unencapsulated liver mass (black arrow). The tumour is brown with scalloped borders and it has a solid consistency. Note lymph node enlargement (white arrow). (c) Trabecular pattern of fibrolamellar hepatocellular carcinoma with a characteristic stroma comprising dense fibrous bands of varying thickness arranged as lamellae (Hematoxylin and eosin, magnification ×200). (d) Positive immunostaining of tumour cells for cytokeratin 7 (Immunohistochemistry ×100).

Follow-up and evolution

The mean follow-up period ranged between two months and 13 years. One patient was lost to follow-up (case 1) and two patients are still being followed-up (cases 2 and 3). Local recurrence of the tumour with concomitant lymph node metastases and peritoneal carcinosis occurred in one case, 13 years postoperatively (case 4).

Discussion

FL-HCC typically occurs in young adults (mean age, 26 years) while only 6% of patients are 50 years of age at diagnosis (3,4). In contrast, conventional and scirrhous HCC usually occur in older patients (mean age, 65 years). In our series, mean age at presentation was 28 years. A slight female predominance has been observed in FL-HCC, but both genders are equally affected in most series (5,6). In our series, there was a female predominance with a sex-ratio (M/F) = 0.33. FL-HCC often presents with non-specific signs and symptoms such as abdominal or right upper quadrant pain, anorexia, nausea, weight loss, hypoglycemia, abdominal mass and jaundice. FL-HCC can coexist with other medical conditions like pregnancy, Fanconi anemia, autoimmune cholangitis and primary sclerosing cholangitis (7-11). In our series, there was a pregnant woman with FL-HCC (case 3). While scirrhous HCC often occur in the setting of chronic liver disease and cirrhosis, FL-HCC is not associated with any definite risk factors and its etiology remains unknown. In our series, all cases of FL-HCC arose in non-cirrhotic liver.

Laboratory workup may help distinguish FL-HCC from conventional HCC. Serum levels of AFP are normal in most cases of FL-HCC and are often elevated in conventional and scirrhous HCC. Up to 10-15% of FL-HCC cases may exhibit mildly elevated AFP, usually below 200 ng/ml (12,13). Computerized tomography currently is the most accurate method for imaging, diagnosis and staging of FL-HCC. One-third to half of FL-HCC may exhibit punctate, nodular or stellate calcifications, typically in the central scar (14). FL-HCC is usually visualized as a lobulated well-defined mass with

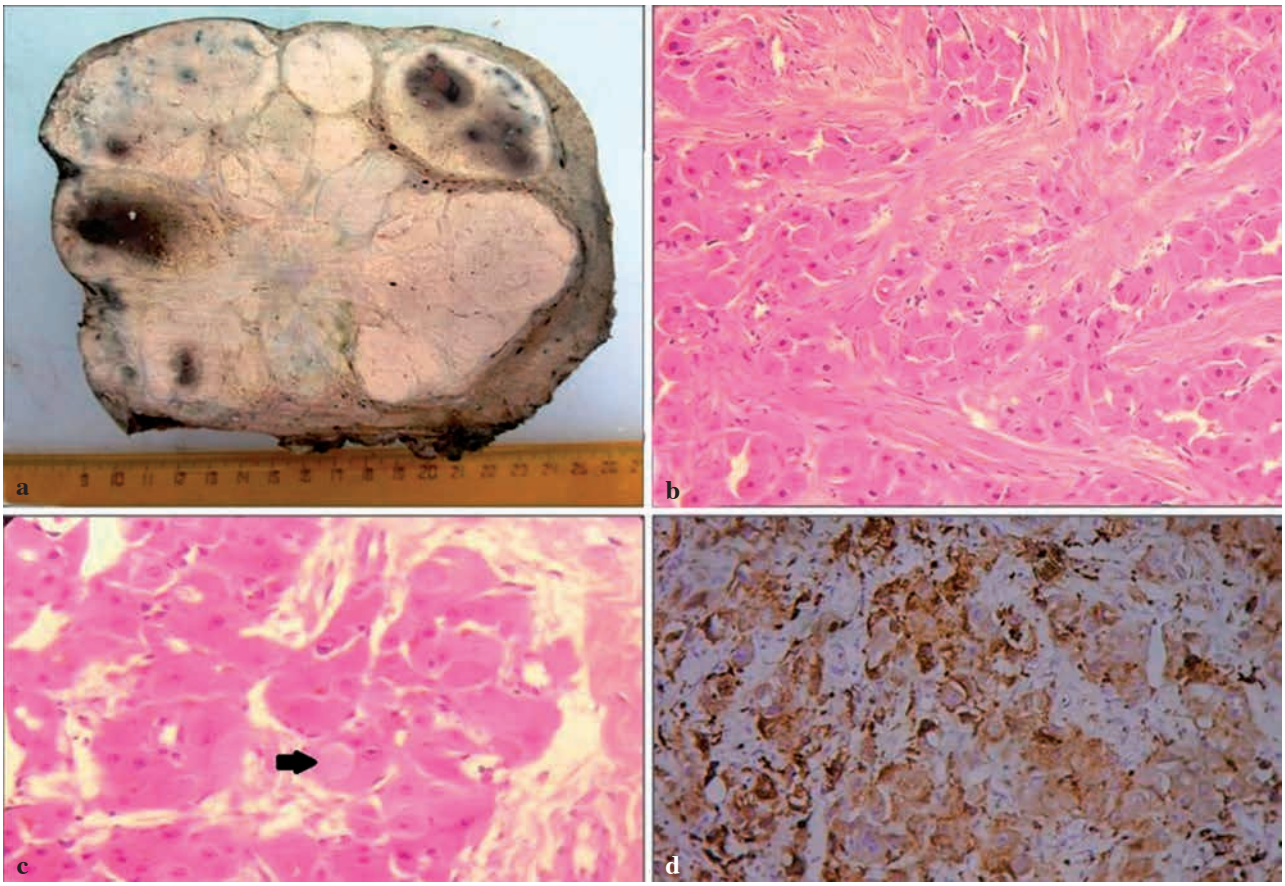

Fig. 2. — Pathological findings of fibrolamellar hepatocellular carcinoma (case 3). (a) Macroscopic appearance of fibrolamellar hepatocellular carcinoma. Multiple well-defined contiguous nodules present in non cirrhotic liver. Note the characteristic central fibrous scar. (b) The tumour was composed of large eosinophilic cells arranged in trabeculae with hyalinized lamellar fibrous stroma (Hematoxylin and eosin, magnification ×200). (c) The tumour cells were larger than normal hepatocytes and displayed abundant granular and deeply eosinophilic cytoplasm. Note the prominent nucleoli of tumour cells and the intra-cytoplasmic pale body (black arrow) (Hematoxylin and eosin, magnification ×400). (d) Fibrolamellar carcinoma expressed CD68 with a characteristic granular cytoplasmic staining pattern (Immunohistochemistry ×200).

mixed echogenicity on ultrasound and hypodensity on non-contrast CT scan (14,15). After contrast injection, the non-scar portion may show significant enhancement, raising the possibility of focal nodular hyperplasia (FNH). In contrast to FNH and cholangiocarcinoma, the scar of FL-HCC usually does not show enhancement (14, 15). By virtue of its mimicry to cholangiocarcinoma on imaging, scirrhous HCC is commonly radiographically mistaken for cholangiocarcinoma (16). Magnetic resonance imaging shows a hypointense scar in FL-HCC, in contrast to FNH. Recently, combined positron emission tomography scans performed with 2-fluoro-2-deoxyglucose and intravenous contrast has been used to identify primary and metastatic FL-HCC based on the anatomic and metabolic characteristics (17). One-third of FL-HCC patients present with regional or metastatic disease. Nodal and peritoneal metastases are more common than in conventional and scirrhous HCC (16,18). Lymph node involvement has been reported in up to 70% of cases and distant metastases occur in nearly half the cases (18). The preferred treatment is complete excision of the affected lobe. Relapse rate for FL-HCC is high (36-100%) with a median time to relapse of 10-33 months (18). The large tumour size and high incidence of nodal disease likely contribute to the high recurrence rate.

Hence, an aggressive surgical approach with lymph node dissection is recommended. Direct invasion into adjacent organs, nodal disease or limited metastatic disease should not preclude attempts at curative tumour resection (18-20). When resection is not possible due to the location or extent of tumour, liver transplantation may be considered although the outcome is less favourable compared to resection (20). Limited experience with chemotherapy in earlier studies indicates that it does not enhance survival in FL-HCC when used as adjuvant therapy with surgery, nor is chemotherapy efficacious for recurrent tumours (1,6,18). The efficacy of newer therapeutic agents like EGFR antagonists also requires further evaluation (1,6,18). The distinction between scirrhous HCC and FL-HCC is important as the diagnosis of FL-HCC can lead to consideration of extended hepatic resection and lymph node dissection. The correct diagnosis

also enables recruitment of patients in appropriate treatment trials. The main distinctive features of scirrhous and FL-HCC are summarized in table 2. Scirrhous HCC is subclassified by the WHO as HCC with marked fibrosis along the sinusoid-like blood spaces with varying degrees of atrophy of tumour trabeculae (21). Such fibrosis needs to be differentiated from nonspecific fibrotic changes that commonly occur after post-therapeutic ablation in any HCC (21). On gross and microscopic examination due to the dense fibrosis, scirrhous HCC may be confused with fibrolamellar carcinoma (21). Grossly, FL-HCC are yellow to pale tan in colour and their consistency can range from soft to firm and hard. In contrast to scirrhous HCC, a central scar is found in 60-70% of FL-HCC (1,6). In our series, a central scar was found in only two cases. FL-HCC tend to be more common in the left lobe of the liver (19), but frequently involve both lobes (1). In our series, the tumour involved the left lobe in two cases and the right lobe in two cases. At the time of resection, the average tumour diameter ranges between 9 and 14 cm in greatest dimension (1,6). In our series, the average tumour diameter was 12.6 cm. In 80-90% of cases, a single large tumour is present (20). Histologically, FL-HCC are usually arranged in cords, solid nests or rarely acinar structures. The tumour cells are large and polygonal with abundant eosinophilic cytoplasm, large vesiculated nuclei and large nucleoli (21). These three cytological findings in conjunction with the lamellar fibrosis are the defining features of FL-HCC and were encountered in all cases of our series. The scirrhous variant of HCC shows prominent fibrosis that can be mistaken for FL-HCC. The absence of lamellar type fibrosis and lack of cytological features of FL-HCC lead to the correct diagnosis. The term "sclerosing HCC" was used in some old reports to describe a variant of HCC with hypercalcaemia and marked stromal fibrosis (21,22). Both FL-HCC and scirrhous HCC express markers of hepatocellular differentiation like HepPar 1 and polyclonal CEA (canalicular pattern). AFP immunoreactivity is absent except for focal expression in a few tumour cells in rare cases (12). Glypican-3 is expressed in two-thirds of FL-HCC compared to 80% of scirrhous HCC, while CK7 is expressed in nearly 80% of FL-HCC compared to 20-30% of scirrhous HCC (12). FL-HCC are usually CD 68 positive whereas scirrhous HCC are often CD68 negative (2,16). In our series, all cases of FL-HCC were positive for CK7 and CD68. The CD68 gene encodes for a transmembrane glycoprotein located within lysosomes and endosomes. Macrophages as well as other cell types rich in lysosomes/endosomes are CD68 positive (2,23, 24). A recent study indicates that FL-HCC also have increased lysosomal or endosomal accumulations in their

Table 2. — **Clinicopathological features of fibrolamellar carcinoma and scirrhous hepatocellular carcinoma**

	FL-HCC	Scirrhous HCC
Incidence (percentage of primary liver carcinoma)	< 1-4%	< 1-2%
Clinical Features		
Mean age at presentation	26 years	65 years
Gender distribution	M:F = 1	M:F = 4
Serum AFP	Usually normal, mild increase in 10-15% of patients	Often increased (> 80% of patients)
Serum neurotensin	Often increased	Usually normal
Serum B12 binding protein	Often increased	Usually normal
Serum glypican-3	Insufficient data	Increased in 50%
Vascular invasion	Rare (< 5%)	Common
Pathologic Features		
Gross pathology	Well-circumscribed pale mass often with prominent central scar	Often subcapsular unencapsulated and lobulated whitish mass mimicking intrahepatic cholangiocarcinoma
Cirrhosis	Absent	Present in 80-85%
Central scar	Often present	Absent
Calcification	Present in 50%	Absent
Oncocytic cytoplasm	Present	Rare
Lamellar fibrosis	Present	Absent or focal
Pale bodies	Often present	Uncommon
Stainable copper	Often present	Uncommon
CK7 expression	Often present	Less common
AFP expression	Negative	Present in 30-50%
CD68 expression	Often present	Uncommon

cytoplasm, which may suggest that abnormalities in endosomal/ lysosomal trafficking are characteristic of fibrolamellar carcinomas (2). Over-expression occurs at the level of both mRNA and protein. Further analysis of previously reported gene expression studies showed a modest increase in the expression of CD68 (2,23,24). One study demonstrated a distinctive pattern of immunostaining for CD68 in FL-HCC (2). Nearly all cases showed a granular, stippled pattern or a dot-like pattern of positivity (2). Based on this multi-institutional series of cases, this staining pattern was highly sensitive for FL-HCC, but was not specific (2). According to the authors of this study, given its high negative predictive value, a diagnosis of FL-HCC in a primary liver carcinoma that is CD68 negative should be strongly reconsidered to ensure that FL-HCC is the appropriate diagnosis (2). They proposed that the reproductibility of the histological diagnosis of FL-HCC can be substantially improved by careful attention to the full pattern of histological features and that most cases should be CK7 and CD68 positive. In the absence of CK7 and/or CD68 positivity, a diagnosis of FL-HCC should be carefully re-considered (2). Many studies have reported that FL-HCC is a less aggressive neoplasm compared to conventional and scirrhous HCC (12). This has led to the widely held conclusion that FL-HCC has a relatively favourable natural history and is associated with a better outcome than conventional HCC. However, several well-designed studies have failed to confirm a better outcome in FL-HCC (12,13). Irrespective of how FL-HCC behaves compared to scirrhous HCC, it is important to realize that it is an aggressive malignant tumour with a 5-year survival of 50-60% in most series. In resected cases, the 5-year survival ranges from 25% to 75% and is even lower for cases with metastases at presentation (1,6).

In conclusion, FL-HCC are unique at the clinical, histological and molecular levels. Their aetiology is unknown and much of their molecular biology remains poorly described and awaits future investigation. FL-HCC are aggressive tumours with an overall low cure rate. Yet, there is hope that improvements in therapy will develop as advanced molecular biology tools are applied to the field and uncover the principle genetic lesions that drive tumour growth.

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