Fibrolamellar Hepatocellular Carcinoma

18

Contents

Abstract

Fibrolamellar hepatocellular carcinoma (FL-HCC) is a distinct variant of hepatocellular carcinoma (HCC) that differs from classical HCC at histological, cytological, immunohistochemical, and molecular levels. FL-HCC is typically a tumor of adolescents and young adults, but may also occur in older individuals. In contrast to most HCCs, FL-HCC is not associated with liver cirrhosis. The neoplasm is histologically characterized by strands of large, eosinophilic hepatocyte-like cells embedded in a collagenous stroma forming striking lamellae. Clear cell and glandular variants are known. Clinically, the tumor often presents as a large solitary mass in the absence of elevated serum alpha-fetoprotein levels. FL-HCC may be associated with several metabolic paraneoplastic syndromes that include disorders of vitamin B12-binding protein, sex steroid metabolism, ammonia handling, neurotensin synthesis, and gonadotropin production. In contrast to previous views, there is now evidence that the biological behavior of FL-HCC is not different from that of classical HCC. The neoplasm shows a distinct genomic landscape characterized by a recurrent DNAJB1-PRKACA chimeric transcript arising from a deletion on chromosome 19, but the tumor also showed other molecular abnormalities.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_18

Introduction

Fibrolamellar hepatocellular carcinoma (FL-HCC) is a distinct malignant liver cell tumor that differs from classical HCC at histological, cytological, immunohistochemical, and molecular levels. It mainly occurs in adolescents and young adults and is histologically characterized by strands of large, eosinophilic hepatocyte-like cells embedded in a fibrous stroma forming collagen-rich lamellae. FL-HCC was first described in 1956 (Edmondson 1956) and subsequently confirmed by Craig et al. (1980) and Berman et al. (1980). The typical clinicopathologic and molecular features of this tumor entity have been reviewed (Soreide et al. 1986; Vecchio 1988; Saab and Yao 1996; McLarney et al. 1999; El-Serag and Davila 2004; Torbenson 2007; Liu et al. 2009; Lim et al. 2014; Darcy et al. 2015a). After the first description, it took a rather long time period until the tumor entity was defined and accepted. Several alternative terms had been employed to denote this lesion, including hepatocellular carcinoma with laminar fibrosis, hepatocellular carcinoma with polygonal cell type and fibrous stroma, oncocytic hepatocellular carcinoma, and eosinophilic hepatocellular carcinoma with lamellar fibrosis.

Epidemiology

FL-HCC accounts for 1–9 % of HCCs overall, this impressive frequency range being caused by markedly variable prevalences in different geographic niches and differences in diagnostic criteria used (Craig et al. 1980; McLarney et al. 1999). Among 46,392 cases of HCC registered in the SEER program between 2000 and 2010, 191, tumors were FL-HCC, with an incidence of clearly less than 0.1 per 100,000 people (Eggert et al. 2013). In contrast to conventional HCC, FL-HCC is not associated with cirrhosis of the liver and other typical risk factors, although a relation to genetic syndromes has been suggested in part of the cases, e.g., Gardner syndrome (Gruner et al. 1998) and Fanconi anemia (LeBrun et al. 1991). FL-HCC is typically a tumor of adolescents and young adults, but rarely also occurs in older individuals. FL-HCC is rare in infants and small children (Cruz et al. 2008), but FL-HCC in older children has more often been encountered (Dellaportas et al. 2011). There is usually no gender predominance, but a predominance of the female gender has also been reported (Chagas et al. 2015). The tumor has been diagnosed during pregnancy (Kroll et al. 1991; Louie-Johnsun et al. 2003). In reviewing studies there is an age range of 5–69 years (mean in Western patients : 23 years), and most patients present in their second and third decades (McLarney et al. 1999). In contrast, conventional HCC is less common than FL-HCC in individuals younger than 40 years (Hernandez-Castillo et al. 2005).

The incidence of FL-HCC is relatively high in Western countries, but is rare in Oriental countries. Analysis of Japanese cases revealed an age range of 15–45 years, with a mean of 21.9 years, findings similar to those in Western countries (Kohno et al. 1988; Haratake et al. 1990; Tanaka et al. 1994; Hoshino et al. 1996; Nojiri et al. 2000; Magata et al. 2001; Yoshimi et al. 2002; Yoshinaga et al. 2002; Kanai et al. 2004; Morise et al. 2005). FL-HCC is apparently not uncommon in sub-Saharan Africa (Moore et al. 2004; Bhaijee et al. 2009) and Latin America (Arista-Nasr et al. 2002).

Clinical Features

FL-HCC characteristically manifests as a large hepatic mass in the absence of liver cirrhosis, elevated serum AFP values, or known risk factors for HCC. In most cases, FL-HCC presents with vague and nonspecific clinical signs and symptoms, often with abdominal discomfort or pain, malaise, and weight loss (Craig et al. 1980; Saab and Yao 1996; Hemming et al. 1997; reviews: Torbenson 2007; Chun and Zimmitti 2013). Due to its mass effect, FL-HCC can cause recurrent obstructive jaundice (Albaugh et al. 1984; Soyer et al. 1991a). It can, similar to ordinary HCC, invade large bile ducts and cause obstructive

Table 1 Metabolic disorders in fibrolamellar hepatocellular carcinoma

Increased serum vitamin B12-binding capacity
Increased neurotensin synthesis with increased serum levels
Paraneoplastic gynecomastia caused by increased aromatase P450 activity
Paraneoplastic production of beta-HCG
Paraneoplastic hyperammonemia with encephalopathy

jaundice, sometimes with subsequent migration of tumor fragments to the common bile duct and distal biliary obstruction (intrabiliary tumor thrombus; Eckstein et al. 1988; Kunz et al. 2002; De Gaetano et al. 2013; Arora 2015). FL-HCC reveals invasion of large liver veins less commonly than conventional HCC, but Budd-Chiari syndrome has been observed as the first manifestation of FL-HCC (Lamberts et al. 1992; Asrani and LaRusso 2012). Caval compression syndrome has been reported as a complication of FL-HCC (Kanai et al. 2004). Additional and usually less common or rare disorders sometimes associated with FL-HCC include severe anemia (Tanaka et al. 1994), nonbacterial thrombotic endocarditis (Vaideeswar et al. 1993), tumor-induced ascites in the case of peritoneal spread (Gupta et al. 1999), a clinical syndrome mimicking hepatic pyogenic abscess (Debray et al. 1994), and cold agglutinin disease (Al-Matham et al. 2011). FL-HCC has been observed in association with ulcerative colitis with primary sclerosing cholangitis (Snook et al. 1989).

FL-HCC patients can show complex patterns of metabolic disorders (Table 1).

The tumor shows abnormalities in the metabolism of vitamin B12 (cobalamin). An increase of serum levels of vitamin B12-binding capacity in patients with FL-HCC has first been reported in 1982 (Paradinas et al. 1982) and confirmed in later analyses (Sheppard et al. 1983; Wheeler et al. 1986; Lildballe et al. 2011). Increasing vitamin B12-binding capacity has been found in postoperative recurrence of FL-HCC (Kanai et al. 2004). However, elevation of vitamin B12 and B12-related proteins seems to be a common feature in HCCs and not only in FL-HCC (Simonsen et al. 2014). Transcriptional profiling of FL-HCC revealed an endocrine signature, in that 4 of the 16 genes most significantly overexpressed in pure FL-HCC were neuroendocrine genes, i.e., prohormone convertase 1/PCSK1, neurotensin, delta/notch-like EGF repeat containing, and calcitonin (Malouf et al. 2014). Serum neurotensin levels (especially levels of the C-terminal part) may be elevated in patients with FL-HCC, caused by secretion of this peptide by the tumor (Collier et al. 1984; Read et al. 1991). Neurotensin was originally isolated from bovine hypothalamus and is an important gastrointestinal regulatory peptide that affects pancreatic secretion, gut motility, gut mucosal growth, and the translocation of fatty acids from the intestinal lumen. The neurotensin gene is expressed in fetal human liver (but not adult liver) and in FL-HCCs (Ehrenfried et al. 1994). In the tumor itself, the neurotensin (6–13) peptide was detectable (Read et al. 1991).

FL-HCC can be associated with gynecomastia (McCloskey et al. 1988; Hany et al. 1997; Agarwal et al. 1998; Sher et al. 1998), mainly in cases of large tumor mass/metastasis. Gynecomastia may be the presenting sign of FL-HCC (McCloskey et al. 1988). Gynecomastia in this tumor is caused by increased aromatase P450 activity in the neoplasm (hyperaromatase syndrome; Hany et al. 1997; Agarwal et al. 1998; Muramori et al. 2011), which gives rise to markedly elevated serum levels of estrone and estradiol-17 beta, suppressing FSH and LH, respectively, and consequently testosterone (Agarwal et al. 1998). Northern analysis indicated the presence of P450 aromatase transcripts in total RNA from FL-HCC but not in the adjacent liver (Agarwal et al. 1998). FL-HCC can rarely produce beta-HCG and by this cause vaginal bleeding (Dahan and Kastell 2002). In part of patients, FL-HCC is associated with a recurrent non-hepatic/non-cirrhotic form of hyperammonemia (paraneoplastic hyperammonemia) complicated by encephalopathy. This complication may mimic a disorder of urea synthesis, e.g., ornithine transcarbamylase deficiency (Sulaiman and Geberhiwot 2014).

Imaging Features

Abdominal imaging shows a well-circumscribed, lobulated, heterogeneous mass that may resemble focal nodular hyperplasia (FNH). CT images document that FL-HCCs are predominantly solitary, well-delineated, and hypervascular lesions which are predominantly hypoattenuating compared with the liver (Bedi et al. 1988; Soyer et al. 1991b; Ichikawa et al. 2000; Marrannes et al. 2005; Selaru et al. 2007; Yen and Chang 2009; Terzis et al. 2010). Almost all tumors were heterogeneous on non-enhanced CT images. In portal venous phase and relative to enhanced liver, FL-HCCs appeared isoattenuating in 48 %, hyperattenuating in 16 %, and hypoattenuating in 36 % (Ichikawa et al. 1999). A central scar resembling the stellate scar seen in FNH is present in CT images in about a third to about 70 % of the cases (the "scar sign"; Kane et al. 1987; Soyer et al. 1991b; Ichikawa et al. 1999). In one study, 82 % of the scars showed a stellate morphology on CT images (Ichikawa et al. 1999). However, central or eccentric scars are also found in conventional HCC, cholangiocarcinoma, and some hepatic metastases (review: Kim et al. 2009). Among 31 cases, CT revealed well-defined margins in 77 % and ill-defined margins in seven cases (Ichikawa et al. 1999). PET-CT scans are a valuable modality in the diagnosis of FL-HCC (Liu et al. 2011). Tumor calcifications in FL-HCC have been reported in 15–68 % of cases at CT and occur in a wide variety of patterns (Soyer et al. 1991b; Stoupis et al. 1998; Ichikawa et al. 1999). Calcifications are more frequent in FL-HCC than in FNH (Caseiro-Alves et al. 1996).

Classification

FL-HCC has been divided into two separate entities, i.e., pure FL-HCC and mixed FL-HCC, differing in clinical presentation and course (Malouf et al. 2012). Pure FL-HCC typically occurs in patients younger than 30 years of age and is often complicated by lymph node metastasis at the time of diagnosis and more frequently shows extrahepatic recurrence. So far, combined or mixed FL-HCC has been regarded as rare lesion. However, in a more recent investigation of 54 patients, the mixed form was found in 25 % of the patients. In contrast to pure FL-HCC, the mixed variant appeared to resemble HCC, occurring in patients aged >40 years, often involving the liver as primary site of disease recurrence, and imparting an increased risk of death (Malouf et al. 2012). Pure FL-HCCs have a distinct transcriptomic signature characterized by strong expression of neuroendocrine genes, including prohormone convertase 1, neurotensin, delta/notch-like EGF repeat containing, and calcitonin, suggesting a complex cellular lineage (Malouf et al. 2014).

Pathology

Macroscopy

The tumors tend to be more common in the left liver lobe (about two thirds of cases; Craig et al. 1980), but relatively often involve both lobes (Ichikawa et al. 1999). In one study, 55 % of the cases had involvement of three or more hepatic segments, and 32 % had involvement of two segments (Ichikawa et al. 1999). Multifocality, gross vascular invasion, and cirrhosis are typically absent, but the tumor often demonstrates aggressive local invasion and nodal and distant metastases (Wong et al. 1982; Friedman et al. 1985; Francis et al. 1986; Gibson et al. 1986; Brandt et al. 1988; Ruffin 1990; Ichikawa et al. 1999; McLarney et al. 1999; Smith et al. 2008). Macroscopically, the tumors are well-delineated masses with a polycyclic border and an expansive growth pattern. A tumor capsule (usually incomplete) is seen in approximately half of the neoplasms. In a study of 31 cases, tumor diameter ranged from 3 to 27 cm, with an average of 13 cm (Ichikawa et al. 1999). In 80–90 % of the

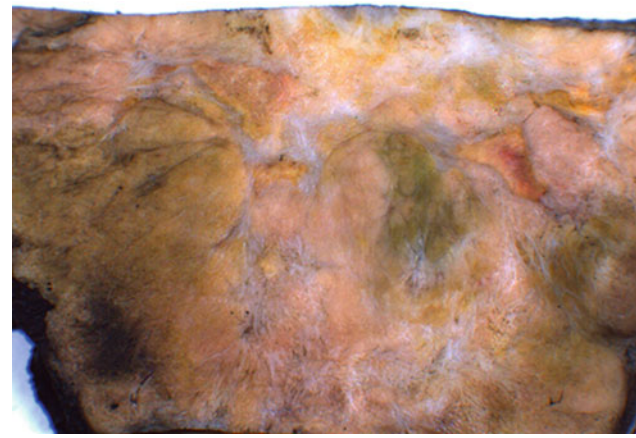

Fig. 1 Fibrolamellar hepatocellular carcinoma. On cut surfaces, the neoplasm exhibits a lobulated texture, lobules, or nodules separated from each other by fibrous septa

cases, a solitary tumor is present. In the remaining cases, there is a mass with small peripheral satellite lesions (10–15 %), a bilobed mass (5 %), or rarely a diffusely/multifocal mass (less than 1 %). Up to 20 % of the tumors show some degree of pedunculation. On cut surfaces, the neoplasms are yellow to tan and often show a nodular or radiated structure caused by radiating fibrous band that originates from central fibrous scar-like areas (Figs. 1 and 2).

In case of marked bile accumulation, a greenish discoloration of the tumor is seen. The neoplasms are encapsulated in about half of the cases, the pseudocapsule being mostly incomplete. A central scar-like structure resembling that seen in focal nodular hyperplasia was detected in about three quarters of cases (Ichikawa et al. 1999). Small necroses and/or hemorrhages may be noted, but are grossly visible in only about 10 %. Rare examples of tumors have revealed massive necrosis and/or hemorrhage, resulting in a multicystic morphology mimicking a primarily cystic liver tumor, but primary multicystic variants of FL-HCC also occur (Pombo et al. 1993). The adjacent liver does not show cirrhosis.

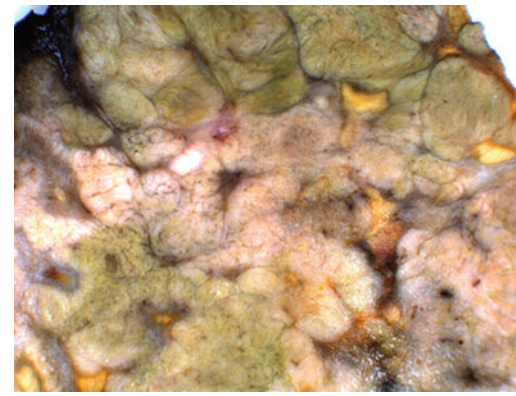

Fig. 2 Nodular structures in fibrolamellar hepatocellular carcinoma can form intertwining ribbons, resulting in a gyriform pattern

Histopathology

The typical cell of FL-HCC is a large polygonal cells having an abundant, deeply eosinophilic, faintly granular cytoplasm and well-defined cell borders . These oxyphilic cells are, however, cytologically different from oncocytes (Altmann 1990). The nuclei are large, round to ovoid and vesicular, and usually single, and they show a peripheral condensation of chromatin and a prominent, centrally placed amphophilic nucleolus. The typical morphologies of the cells and nuclei, together with lamellar fibrosis, are the three main criteria for diagnosis (Figs. 3, 4, 5, 6, and 7).

A part of the nuclei display intranuclear cytoplasmic pseudoinclusions (cytoplasmic invaginations). Large invaginations cause so-called empty nuclei. Mitotic figures are much less common

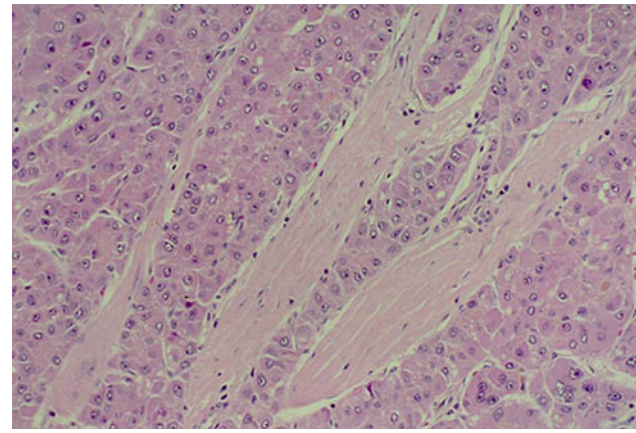

Fig. 3 Fibrolamellar hepatocellular carcinoma. Solid strands and ribbons of large eosinophilic tumor cells are separated by fibrous hypocellular tracks, the fibrolamellae (hematoxylin and eosin stain)

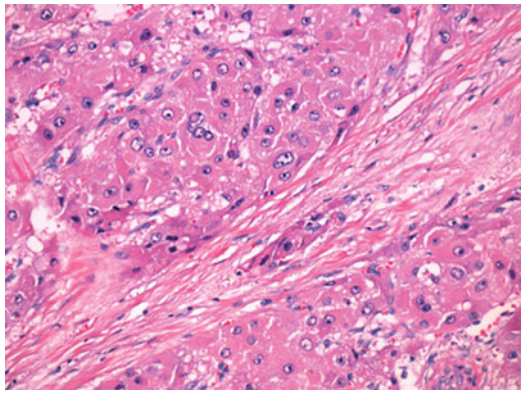

Fig. 4 Fibrolamellar hepatocellular carcinoma. The epithelial tumor cells are in direct contact with collagenous bands, without a visible interposed cellular stroma (hematoxylin and eosin stain)

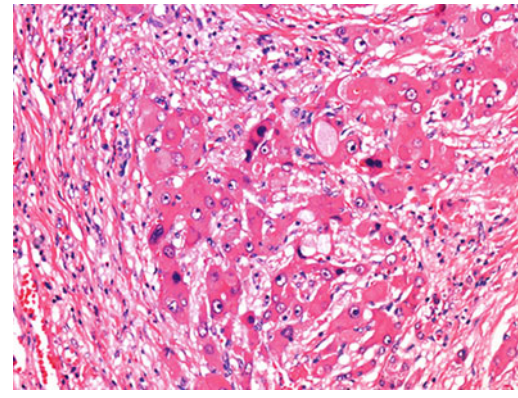

Fig. 5 Fibrolamellar hepatocellular carcinoma. Focally, stroma of slightly higher cellularity can occur, sometimes associated with dissociation of tumor cells (hematoxylin and eosin stain)

than in ordinary HCC (Farhi et al. 1983) and may have previously suggested that the tumor is of low malignancy, what is not the case. Less than 10 % of the cells exhibit PAS-positive globular cytoplasmic inclusions (2–7 μm in diameter; Farhi et al. 1982). About half of the tumor cells contain large ovoid cytoplasmic inclusions that are much less eosinophilic or are amphiphilic, the so-called pale bodies (Fig. 8) .

Pale bodies sometimes show a central hyaline core. Cholestasis is often seen. The tumor cells commonly show canaliculus-like lumina present between adjacent cells containing bile. Tumor cholestasis is, like in ordinary HCC, associated with deposition of copper (copper-binding protein in many cases (Lefkowitch et al. 1983). Small calcifications are sometimes seen, mostly in the central scar and within the fibrous bands. In a minority of FL-HCC, a mild macrovesicular steatosis may be found.

The solid components of medium- to large-sized polygonal cells are irregularly subdivided by connective tissue bands rich in collagen (the "fibrolamellae" that have given the tumor's name). The amount of collagen in the bands varies markedly, ranging from sclerosed bands to bands with a loose texture of tissue rich in glycosaminoglycans and higher spindle cell

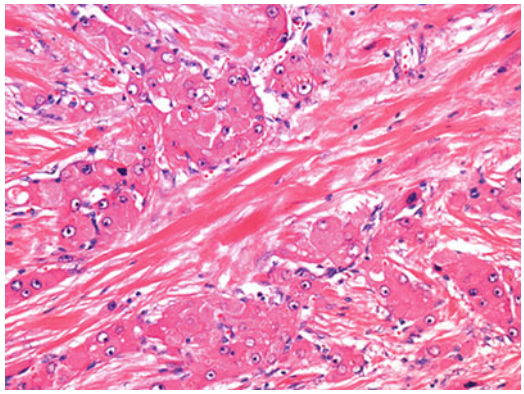

Fig. 6 Fibrolamellar hepatocellular carcinoma. In the fibrous lamellae, collagen-rich connective tissue may undergo hyaline change (hyaline sclerosis of stroma, center of figure; hematoxylin and eosin stain)

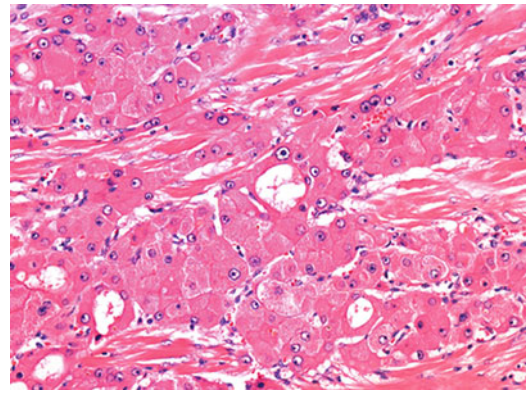

Fig. 7 Fibrolamellar hepatocellular carcinoma. The typical tumor cell is large, with abundant oxyphilic and granular cytoplasm. Nuclei are spherical to ovoid, with a hyperchromatic periphery and less dense center, and with prominent nucleoli. Pseudotubular lumina can be present (hematoxylin and eosin stain)

cellularity. However, it has been shown that the connective tissue content in FL-HCC is overall greater than in other liver tumors (Sarosi et al. 1991). The bands stain red in the van Gieson stain and bright blue with the trichrome stain. In the silver stain, the stroma shows a fine, dense, and complex network of reticulin fibers. The fibrolamellae often end in frayed edges. The fibrous matrix is predominantly composed of collagens I, III, and V, tenascin, and (less abundantly) basement membrane proteins such as laminin. In situ hybridization studies have shown that the fibroblastoid cells embedded in the matrix express collagen III-mRNA (Nerlich et al. 1992). FL-HCC cells may develop apparently intracellular lumina or spaces containing erythrocytes (Fig. 9).

Rare variants of FL-HCC, or certain regions in these tumors, may display a markedly solid component (Kojima et al. 2004). Based on the distinct cellular features and the distinct epithelial-stromal composition of FL-HCC, this neoplasm has been diagnosed by cytological methods (Suen et al. 1985; Perez-Guillermo et al. 1999; Jain et al. 2002; Kunz et al. 2002; Sarode et al. 2002; Mansouri et al. 2006; Gulati and Saran 2009). FL-HCC is an angioinvasive neoplasm that tends to invade large veins. Vascular invasion is present in about 40 % of the tumors (Farhi et al. 1983; Kakar et al. 2005). It was reported that FL-HCC arose in a background of focal nodular hyperplasia (Imkie et al. 2005). In a patient with generalized AA amyloidosis, amyloid was also deposited in the stroma of an FL-HCC (Llortea et al. 1994).

Ultrastructure

The neoplastic cells are rich in organelles and contain nuclei with often prominent cytoplasmic invaginations, the latter corresponding to the clear nuclear pseudoinclusions seen in light microscopy. The cytoplasm frequently contains numerous and densely packed, swollen mitochondria which are uniform in size and shape and often contain dense inclusions, resulting in a picture resembling oncocytes (Andreola et al. 1986). The endoplasmic reticulum is prominent, sometimes with dilated profiles. Dense cytoplasmic inclusions have been noted (Farhi et al. 1982; Andreola et al. 1986; Hasegawa 1996). Fully developed Mallory-Denk bodies are absent, but filamentous material resembling that found in these bodies has been detected (Caballero et al. 1985). Between two adjacent cells, lumina with microvilli can be found, representing abortive biliary canaliculi (Sato et al. 1997). The pale

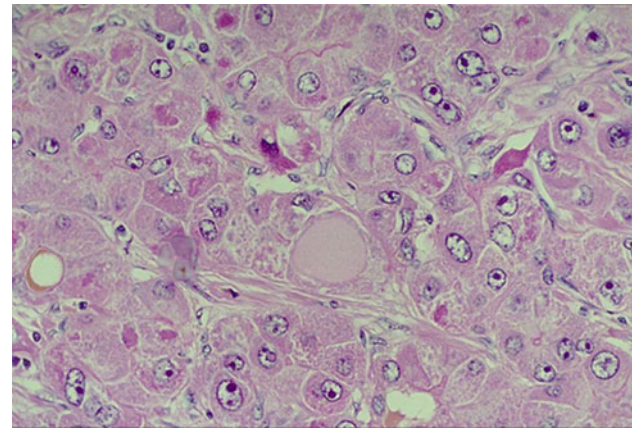

Fig. 8 Fibrolamellar hepatocellular carcinoma. Part of neoplastic cells contain large pale cytoplasmic inclusions (pale bodies, center of figure, hematoxylin and eosin stain)

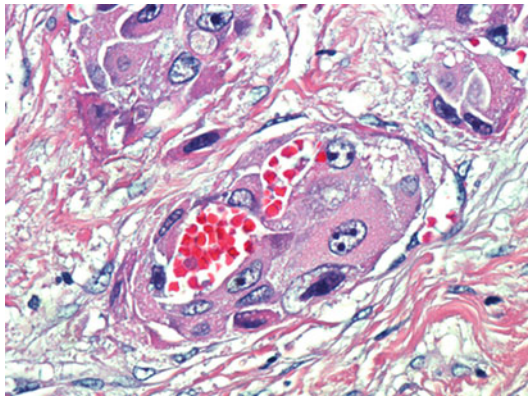

Fig. 9 Fibrolamellar hepatocellular carcinoma. Neoplastic cells can develop apparently intracellular lumina or spaces that contain erythrocytes (hematoxylin and eosin stain)

bodies seen at light microscopy ultrastructurally represent intracellular lumina lined with numerous microvilli. The central hyaline cores seen in part of the pale bodies are depositions of fine granular material (An et al. 1983). In part of the tumors, ultrastructural signs of neuroendocrine differentiation have been found (Payne et al. 1986; Garcia de Davila et al. 1987; Lloreta et al. 1994). The tumor cells are separated by broad, homogeneous bands of dense collagen with characteristic periodicity. The bands of collagen are lined by spindle cells with the features of fibroblasts or myofibroblasts, and these cells are interposed between collagen and tumor cells (Farhi et al. 1982).

Immunohistochemistry of the Epithelial Component

The immunophenotype of epithelial cells in FL-HCC has been analyzed in detail (Caballero et al. 1985; Teitelbaum et al. 1985; Berman et al. 1988). The cells of FL-HCC are positive for HepPar [hepatocyte paraffin 1] (Wennerberg et al. 1993; Klein et al. 2005; Ward et al. 2010; Patonai et al. 2013), suggesting that a hepatocyte-like differentiated cell is involved. Similar to conventional HCC, FL-HCC expresses the heparan sulfate proteoglycan, glypican-3, the positivity rate ranging from 17 % (Abdul-Al et al. 2010) to 59 % (Ward et al. 2010) and 64 % of cases (Shafizadeh et al. 2008). The tumor cells display canalicular membrane expression of pCEA (Ward et al. 2010). Interestingly, FL-HCC cells show a circumferential staining for pCEA, suggesting a loss of the normal apical-basolateral polarization of hepatocytes (own observations). The tumor cells may be positive for copper and copper-binding protein (Lefkowitch et al. 1983). The cells of FL-HCC typically and strongly express cytokeratin-7 in the cytoplasm (Van Eyken et al. 1990). Positivity for cytokeratin-7 has been confirmed in later studies (Gornicka et al. 2005; Klein et al. 2005; Abdul-Al et al. 2010; Fig. 10).

In one study, all cases of FL-HCC were positive for epithelial membrane antigen (EMA), and 36 % of FL-HCCs showed staining for cytokeratin-19, B72.3, and EpCAM (Ward

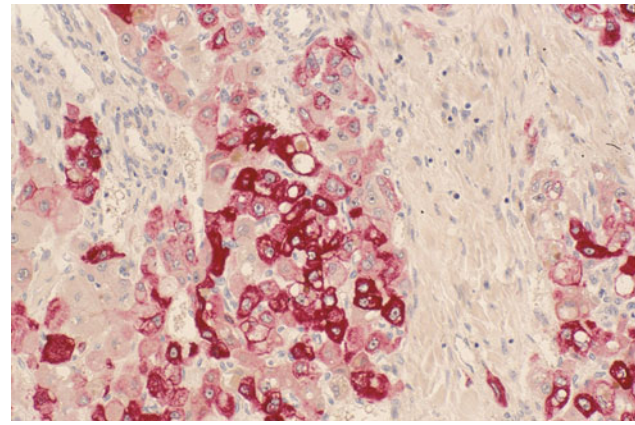

Fig. 10 Fibrolamellar hepatocellular carcinoma. Cells typically express cytokeratin-7 (CK7 immunostain)

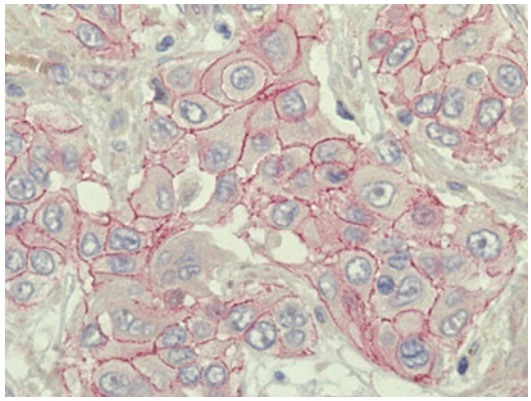

Fig. 11 Fibrolamellar hepatocellular carcinoma. The tumor cells show membranous reactivity for beta-catenin (beta-catenin immunostain)

et al. 2010). It has, however, been shown that FL-HCC is less often positive for CK19 than ordinary HCC (Abdul-Al et al. 2010). In ordinary HCC, expression of CK19 and EpCAM is associated with worse prognosis and the potential involvement of a bipotential progenitor cell (see the respective chapter). Cells of FL-HCC usually show a beta-catenin staining pattern similar to that of hepatocytes (Fig. 11).

Interestingly, the cells of FL-HCC are positive for CD68, a marker of lysosomal/endosomal membranes and typically positive in macrophages. The CD68 immunostaining, which involves almost all cases of FL-HCC, presents a distinctive granular, dot-like, or stippled pattern of the cytoplasm and had a sensitivity of 96 % and a specificity of 80 % (Ross et al. 2010). A part of FL-HCCs are immunoreactive for CD99 (Vasdev and Nayak 2003). Cells of FL-HCC produce several proteins that are also typical products of normal hepatocytes, including ferritin (Caballero et al. 1985) and alpha-1 antitrypsin, the latter sometimes accumulated in cytoplasmic globular inclusions or around such inclusions. FL-HCCs more often than ordinary HCCs express claudin-2 and claudin-5 (Patonai et al. 2011). FL-HCCs demonstrate hepatocyte growth factor receptor (c-met) levels similar to normal (Schoedel et al. 2003). In contrast to common HCC, FL-HCC has not been shown to express survivin (Kannangai et al. 2005). Similar to HCC, FL-HCC can express the CCK-B/gastrin receptor Caplin et al. 1999).

Immunohistochemistry of the Matrix Component

Immunohistochemically, the abundant extracellular matrix of FL-HCCs has been shown to contain large amounts of tenascin (Scoazec et al. 1996) and fibronectin (Jagirdar et al. 1985), whereas basement membrane proteins such as laminin seem to be less expressed. As FL-HCC cells more often express TGF-beta than HCC, it was suggested that fibrosclerosis and matrix protein production may be regulated by this fibrokine (Nerlich et al. 1992; Orsatti et al. 1997). The

tumor cells express a set of surface proteins that are important for cell-matrix interactions. The large epithelial cells are positive for alpha-1 integrin, E-cadherin, and the hepatocyte N-related cadherin, but lack beta-4 integrin (Scoazec et al. 1996). The tumor cells display a strong expression of CD44 (Washington et al. 1997), a widely distributed integral membrane protein and cell adhesion protein that has been implicated in cell-matrix contact, invasion, and metastatic spread. Most FL-HCCs revealed increased expression of active matrix metalloproteinase-2, in contrast to ordinary HCC (Schoedel et al. 2003). The sinusoid-like vascular channels of FL-HCC have diffusely CD34-positive endothelia (Abdul-Al et al. 2010).

Growth Features of FL-HCC

FL-HCCs typically grow with broad pushing borders. Invasion of adjacent parenchyma may be seen histologically, and portal tracts may be entrapped in the growing tumor front. FL-HCC has a very low mitotic activity, mitotic figures being normally structured in most cases. In a study of seven cases, the mitotic index was very low, i.e., 0–1 mitotic figure/10 high-power fields. The percentage of Ki-67 nuclear staining ranged from 1.0 to 29.7 %. There was no reactivity for S-phase kinase-associated protein (Skp) 2; all cases showed moderate to strong nuclear p16INK4 positivity (Dhingra et al. 2010).

Clear Cell Variant of Fibrolamellar Hepatocellular Carcinoma

A clear cell variant of FL-HCC has been described (Cheuk and Chan 2001). A 59-year-old female known to be a hepatitis B virus carrier was found to have a liver mass on routine checkup, visualized at CT as a solitary mass in the right liver lobe. Serum AFP was not elevated. The lesion was resected via right hepatectomy, and the patient was without of recurrence 13 months later. Grossly, the tumor was circumscribed, bosselated and formed a tumor measuring up to 50 mm in diameter. Histologically, the tumor consisted of oxyphilic cells and clear cells of about 50 % each, embedded in stroma consisting of strands of hyalinized collagen. Transitional forms between the two main cell types were seen. Pale bodies were found in part of the cells. Both the oxyphilic cells and the clear cells showed diffuse immunostaining for HepPar1, whereas antimitochondrial antibody stained the oxyphilic cells but weakened the clear cells. This variant has also been diagnosed by fine needle aspiration cytology (Kaplan and Hoda 2007.)

Glandular Variant of Fibrolamellar Hepatocellular Carcinoma

This probably rare and somewhat intriguing variant of FL-HCC is characterized by components of acinar or pseudoglandular structures, sometimes with mucin production (Goodman et al. 1985; Tanaka et al. 2005). The cells lining the gland-like spaces are structurally similar to other FL-HCC cells, but are usually smaller. Mucin is detectable within the neoplastic cells but also in the lumina of acinar profiles, and the mucinous substance is positive for mucicarmine and alkaline alcian blue (Goodman et al. 1985). The cells lining the pseudoglandular spaces immunohistochemically share features with cholangiocellular elements, i.e., positivity for biliary-type cytokeratins. This phenotype was also found in lymph node metastases of the tumor, a phenomenon which may exclude a collision tumor (Tanaka et al. 2005). This is the reason why such neoplasms were also termed, combined fibrolamellar carcinoma and cholangiocarcinoma, with biphenotypic antigen expression (Tanaka et al. 2005). This cholangiocyte-like differentiation is not associated with other histologic features of true cholangiocarcinoma; the biologic behavior of such combined tumors seems to be more in keeping with pure FL-HCC.

Combined Patterns

Combined tumors, albeit very rare, are of some theoretical interest because they may shed light on the cell of origin of FL-HCC. Exceptionally,

FL-HCC occurred in combination with conventional HCC (Hasegawa 1996; Okano et al. 1998; Seitz et al. 2002), the FL-HCC component being cytokeratin-7 positive, in contrast to the HCC component (Seitz et al. 2002; Zermani et al. 2005). In the tumor described by Hasegawa (1996), a common HCC element with trabecular structure existed at the periphery of the FL-HCC. In contrast, the tumor described by Seitz et al. (2002) showed HCC at the center of a large FL-HCC. In few cases, FL-HCC transformed into common HCC in recurrent lesions of the residual liver and in a remote metastasis (Yamamoto et al. 1999; Chang et al. 2003). FL-HCC has also been found to be associated synchronously with common HCC located in another part of the liver (Okada et al. 1993).

FL-HCC has been observed 5 years after hepatocellular adenoma in a 14-year-old girl (Terracciano et al. 2004). Nodular hyperplasia associated with or surrounding FL-HCC has been observed (Saul et al. 1987; Saxena et al. 1994). In a 14-year-old girl, a 9 cm subcapsular nodule was present in the right lobe of the liver, with a distinct zonation: ca central grayish white area of FL-HCC and peripheral fleshy, tan-colored rim of nodular hyperplastic liver parenchyma resembling FNH. It was suggested that the hyperplasia was a reaction to an abnormal arterialization of the tissue, the arteries originating from the central FL-HCC (Saxena et al. 1994). It has been assumed that FL-HCC may be the malignant counterpart of FNH (Vecchio et al. 1984), but there is no convincing evidence for this.

Biology of Disease

FL-HCC reveals a metastasizing pattern different from ordinary HCC. FL-HCC tends to metastasize within the abdominal cavity. This may lead to intriguing and misleading patterns, such as metastasis to the pancreatic head (Thirabanjasak et al. 2009) or the skeletal muscle (Kutluk et al. 2001). FL-HCC can metastasize to the ovaries (Benito et al. 2012) and has been shown to produce ovarian Krukenberg tumor as first tumor manifestation (Montero et al. 2007; Bilbao et al. 2008). FL-HCC is also a primary liver tumor that typically metastasizes to locoregional lymph nodes (Stipa et al. 2006; Tsilividis et al. 2010; Gras et al. 2012, Fig. 12), lymph node positivity representing a negative prognosticator and considered to be an indication for lymph node dissection (Yamamoto et al. 1995; Hiramatsu et al. 1999; Jaeck 2003).

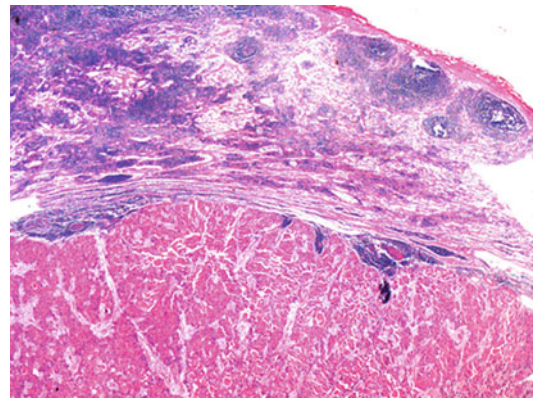

Fig. 12 Lymph node metastasis of fibrolamellar hepatocellular carcinoma. The typical tumor morphology, with strongly eosinophilic cells and fibrous bands, is recapitulated in metastatic disease (hematoxylin and eosin stain)

As ordinary HCC, FL-HCC can invade large vessels, including the inferior vena cava, and spread to the heart cavities and pulmonary arteries (Asrani and LaRusso 2012; Knudson et al. 2012).

Several studies have advocated that FL-HCC is less aggressive than conventional HCC (Berman et al. 1980; Craig et al. 1980; Lack et al. 1983; Wetzel et al. 1983; Nagorney et al. 1985; Hodgson 1987; Kaczynski et al. 1996; Pinna et al. 1997; Okuda 2002; El-Serag and Davila 2004; Meriggi and Forni 2007), and even in textbooks it is or was mentioned that FL-HCC is associated with a favorable prognosis (Everson and Trotter 2003; Sherlock and Dooley 2003; Ferrell 2004). There are single reports of long-term survival after surgery alone (Ishikawa et al. 2007), but in contrast to older suggestions, there is now evidence that the biology of FL-HCC in comparison with ordinary HCC is a complex issue, the presence or absence of differences in part being affected by artifacts of methodology (Njei 2014). For example, in patients with FL-HCC, the better outcome

in some patients is due to the absence of cirrhosis in these patients, and the presentation at a non-advanced stage, rather than its distinct clinicopathologic features (Stevens et al. 1995; Zografos et al. 1997). There is also evidence that tumor stage was in fact the most significant factor for prognosis in patients treated with resection and transplantation (Ringe et al. 1992; El-Gazzaz et al. 2000). The biology of FL-HCC shows, nevertheless, striking differences in comparison with conventional HCC, mainly what regards metastatic patterns and causes of death (Epstein et al. 1999). A study of the Pediatric Oncology Group (Pediatric Intergroup Hepatoma Protocol), analyzing 46 patients, showed that children with FL-HCC did not have a favorable prognosis and do not respond any differently to current therapeutic regimens than patients with common HCC (Katzenstein et al. 2003). In a study of 20 resected cases, the 5-year survival was 45 %, the overall mortality was 60 %, and mortality of FL-HCC was higher with metastatic disease at presentation. Age, gender, and tumor size did not correlate with survival (Kakar et al. 2005). In another retrospective investigation, however, age was a prognosticator, in that patients diagnosed before 23 of age had a worse outcome than those diagnosed after age 23 (Moreno-Luna et al. 2005). In a study on 41 patients, median tumor size in 28 patients treated with resection was 9 cm, 50 % of the patients had lymph node metastases, and nodal metastases were the only negative prognostic factor. Seventeen of these patients (61 %) underwent a second resection for recurrent disease. The 5-year survival of resected patients was 76 %, but 5-year recurrence-free survival was only 18 %, illustrating that this tumor has a characteristic tendency for recurrence (Stipa et al. 2006). In a series of ten patients, FL-HCC was treated with resection followed by close surveillance and aggressive management of relapse. Relapse occurred in all ten cases at a median of 2.2 years. With a combination of re-resection, systemic chemotherapy, and radiotherapy, the overall median survival was 9.3 years (Maniaci et al. 2009). FL-HCC is different from common HCC in its recurrence pattern after liver transplantation. Late recurrence (>1000 days) is typical for FL-HCC, and the tumors tend to be associated predominantly with extrahepatic or combined extra- and intrahepatic recurrence, while well-differentiated HCCs tended to recur within the liver (Schlitt et al. 1999). In the recent SIOPEL/Childhood Liver Tumour Strategy Group study on 24 patients with FL-HCC, long-term overall survival in FL-HCC and ordinary HCC was similar (Weeda et al. 2013). In contrast, the results of a nationwide survey using SEER data show that surgically treated patients with FL-HCC had better long-term outcomes than those with conventional HCC (Mayo et al. 2014). In the setting of a systematic review and meta-analysis of 368 FL-HCC patients, it turned out that overall there was a significant increase in 5-year survival for FL-HCC versus conventional HCC, but this difference was not detectable in the subgroup of non-cirrhotic patients (Njei et al. 2014).

Differential Diagnosis

There are conventional HCCs having a central scar and a scalloped tumor margin resembling FNH and FL-HCC. In one study, such tumors predominantly occurred in non-cirrhotic livers of patients in their 60s and were associated with a good surgical outcome (Yamamoto et al. 2006). There are other primary liver carcinomas with a marked stromal component, which may cause diagnostic problems (Malouf et al. 2009). Histologically, sclerosing hepatocellular carcinoma may mimic FL-HCC, but these tumors have smaller epithelial cells, the stroma is more cellular and not band-like, and the tumors occur in middle-aged persons, show a male predominance, and are associated with the typical HCC risk factors (Haratake and Horie 1989).

Pathogenesis

Cell Lineage(s) Involved

The cell lineage of FL-HCC is still not well known, despite the fact that the tumor cells resemble hepatocytes with oxyphilic features and that

the cells share with hepatocytes immunoreactivity for a hepatocyte marker, HepPar. Other findings that support a hepatocyte-like lineage in FL-HCC is the positivity for glypican-3, a canalicular staining pattern with polyclonal CEA/pCEA (see above), and the positivity for albumin mRNA by in situ hybridization (Ward et al. 2010). In contrast to normal hepatocytes, FL-HCC cells are usually positive for cytokeratin-7 and sometimes for cytokeratin-19 and for epithelial membrane antigen (EMA), normally expressed in cholangiocytes of the normal liver. These results have been interpreted to suggest that FL-HCCs show a dual differentiation, i.e., both hepatocellular and cholangiocellular (Ward et al. 2010). There is also immunohistochemical evidence for a stem cell-associated phenotype of FL-HCC. The tumor cells were positive for the stem cell markers CD133 and CD44, revealed reduced cell cycle progression, and displayed evidence of reduced differentiation (Zenali et al. 2010).

Cytogenetic Findings

FL-HCC generally reveals less ploidy and chromosomal aberrations than ordinary HCC and hence a greater genomic homogeneity (Lapis et al. 1990; Orsatti et al. 1994; Sirivatanauksorn et al. 2001; Ward and Waxman 2011). Specifically, 8p- and 17q+, which are typical for HCC, hardly occur in FL-HCC (Terraciano and Tornillo 2003). Also allele loss seems to be much less common that in conventional HCC (Ding et al. 1993). FL-HCCs with chromosomal alterations seem to behave more aggressively than tumors without cytogenetic abnormalities (Kakar et al. 2009). By the use of comparative genomic hybridization, chromosomal imbalances were identified in 6 out of 11 (55 %) of cases, and the mean number of aberrations per case was 3.9 for all cases and 7.2 in abnormal cases. The most common abnormalities were found in chromosomes 1, 7, 8 and 18, with gains in 1q and 8q and loss of 18q being the most common alterations (Kakar et al. 2009; review: Ward and Waxman 2011). As outlined in the next paragraph, 7p has a gene (AGR2) that is overexpressed in FL-HCC and affects cancer cell spread. Some of the tumors show complex chromosomal patterns, such as a nearly triploid karyotype (Hany et al. 1997). Genomic hybridization (CGH) studies demonstrated striking differences in recurrent cytogenetic aberrations between FL-HCC and common HCC (Wilkins et al. 2000). Loss of heterozygosity (LOH) on 6q at the mannose 6-phosphate/insulin-like growth factor II receptor locus has found in 33 % of FL-HCCs, in comparison with 69 % in common HCCs, suggesting that this gene may act as a tumor suppressor in HCC and FL-HCC (DeSouza et al. 1995). Previously (and in apparent contrast to conventional HCC), epigenetic instability manifesting as methylation of tumor suppressor promoters had been reported to be rare in FL-HCC (Vivekanandan and Torbenson 2008). In a later study, it was shown that FL-HCCs display frequent and distinct gene-specific hypermethylation in the absence of significant global hypomethylation. Frequent aberrant hypermethylation was found for the cyclin D2 and the RASSF1A genes as well as for the microRNA genes mir-9-1 and mir-9-2 (Tränkenschuh et al. 2010). The genomic features of FL-HCC loose homogeneity as a function of the tumor's spread, and recurrent metastatic tumors have complex karyotypes (Lowichik et al. 1996).

Molecular Findings

FL-HCC displays a distinct genomic landscape (Darcy et al. 2015b) and shows a unique genomic profile uncovering three robust molecular classes, i.e., a proliferation class, an inflammation class, and an unannotated class (Cornella et al. 2015). Recently, a recurrent DNAJB1-PRKACA chimeric transcript, arising as a result of a ~400 kb deletion on chromosome 19, was detected in FL-HCC. The chimeric RNA was predicted to code for a homolog of the molecular chaperone DNAJ, fused in frame with PRKACA, the catalytic domain of protein kinase A. The chimeric protein is expressed in tumor tissue and retains kinase activity (Honeyman et al. 2014; Xu et al. 2015).

FL-HCCs display various other molecular abnormalities. FL-HCC overexpresses epidermal growth factor receptor (EGFR), similar to conventional HCC (Buckley et al. 2008), probably due to polysomy 7 rather than gene amplification. Immunohistochemically, EGFR was strongly overexpressed on the cell membranes of more than 90 % of tumors tested (Buckley et al. 2006). FL-HCC exhibits overexpression of genes in the RAS, MAPK, PIK3, and xenobiotic degradation pathways (Kannangai et al. 2007) and reveals mTORC1 activation and FGFR1 overexpression (Riehle et al. 2015). FL-HCC cells express anterior gradient 2 (AGR2; Vivekanandan et al. 2009), a protein that is critical for normal embryonic development. AGR2 is located on chromosome 7p21.3 (Petek et al. 2000) and encodes the human homolog of a secreted protein identified in *Xenopus* (cement gland-specific gene), where it determines the formation of anterior structures during the generation of ectoderm. In the adult mammalian organism, AGR2 is mainly expressed in cells of the gastrointestinal tract. In the small intestine of mice, expression is found predominantly in Paneth, neuroendocrine, and goblet cells (Komiya et al. 1999; Wang et al. 2008). It has been shown that AGR2 encodes a protein disulfide isomerase (enzymes that aid protein folding and assembly), which is essential for the production of the intestinal mucin MUC2 (Park et al. 2009). A critical interacting protein of AGR2 is the ATP-binding protein, reptin (Maslon et al. 2010). AGR2 is expressed in several cancers, including pancreatic cancer, breast cancer, and lung cancer, where it affects cancer cell survival (via the p53 pathway), cancer cell motility, and cancer spread. Specifically, AGR2 promotes metastatic spread and its expression is associated with poor survival. This metastasis-promoting activity of AGR2 is repressed by ErbB3-binding protein 1 (Zhang et al. 2010). In FL-HCC, overexpression of AGR2 is associated with several polymorphisms, but no mutations (Vivekanandan et al. 2009). In contrast to ordinary HCC, where missense mutations and interstitial deletions of the beta-catenin gene and nuclear accumulation of beta-catenin are common, beta-catenin gene alterations were not yet detected in FL-HCCs (Terris et al. 1999), so that the Wnt-beta-catenin signaling pathway does not seem to be involved in the carcinogenesis of this tumor.

FL-HCC reveals alterations of mitochondrial structure and function. It is well known that ordinary HCCs show mitochondrial DNA mutations. In one molecular study, approximately 50 % of ordinary HCCs had lower levels of total mitochondrial DNA than paired nonneoplastic tissue, associated with deletions of the mitochondrial DNA control region. Despite their apparently increased numbers of mitochondria, primary FL-HCCs had lower levels of total mitochondrial DNA, while metastatic FL-HCCs had greatly increased mitochondrial DNA levels. Complete sequencing of the entire mitochondrial genome in FL-HCC identified several somatic mutations, but no consistent pattern of mutations was found (Vivekanandan et al. 2010).

HBV Infection

Ordinary HCC has an etiologic association with HBV in numerous cases. It was therefore of interest to test whether FL-HCC is also related to HBV infection, although this tumor is not associated with liver cirrhosis. The finding of integrated HBV DNA in certain instances of FL-HCC tissue may be consistent with an oncogenic role of HBV in at least a subset of the tumors (Davison et al. 1990; Dadke et al. 2002). This question has to be addressed in more detail with larger numbers of tumors.

References

Abdul-Al HM, Wang G, Makhlouf HR, Goodman ZD (2010) Fibrolamellar hepatocellular carcinoma: an immunohistochemical comparison with conventional hepatocellular carcinoma. Int J Surg Pathol 18:313–318

Agarwal VR, Takayama K, Van Wyk JJ, Sasano H, Simpson ER, Bulun SE (1998) Molecular basis of severe gynecomastia associated with aromatase expression in a fibrolamellar hepatocellular carcinoma. J Clin Endocrinol Metab 83:1797–1800

Albaugh JS, Keeffe EB, Krippaehne WW (1984) Recurrent obstructive jaundice caused by fibrolamellar hepatocellular carcinoma. Dig Dis Sci 29:762–767

Al-Matham K, Alabed I, Zaidi SZ, Qushmaq KA (2011) Cold agglutinin disease in fibrolamellar hepatocellular carcinoma: a rare association with a rare cancer variant. Ann Saudi Med 31:197–200

Altmann HW (1990) Some histological remarks on the fibrolamellar carcinoma of the liver. Pathol Res Pract 186:63–69

An T, Ghatak N, Kastner R, Kay S, Lee HM (1983) Hyaline globules and intracellular lumina in a hepatocellular carcinoma. Am J Clin Pathol 79:392–396

Andreola S, Audisio RA, Lombardi L (1986) A light microscopic and ultrastructural study of two cases of fibrolamellar hepatocellular carcinoma. Tumori 72:609–616

Arista-Nasr J, Gutierrez-Villalobos L, Nuncio J, Maldonado H, Bornstein-Quevedo L (2002) Fibrolamellar hepatocellular carcinoma in Mexican patients. Pathol Oncol Res 8:133–137

Arora R (2015) Fibrolamellar hepatocellular carcinoma presenting as obstructive jaundice: uncommon presentation of a rare entity. Pol J Radiol 80:168–171

Asrani SK, LaRusso NF (2012) Fibrolamellar hepatocellular carcinoma presenting with Budd-Chiari syndrome, right atrial thrombus, and pulmonary emboli. Hepatology 55:977–978

Bedi DG, Kumar R, Morettin LB, Gourley K (1988) Fibrolamellar carcinoma of the liver: CT, ultrasound and angiography. Case report. Eur J Radiol 8:109–112

Benito V, Segura J, Martinez MS, Arencibia O, Lubrano A (2012) Fibrolamellar hepatocellular carcinoma metastatic to the ovary. J Obstet Gynaecol 32:200–202

Berman MM, Libbey NP, Foster JH (1980) Hepatocellular carcinoma: polygonal cell type with fibrous stroma – an atypical variant with a favorable prognosis. Cancer 46:1448–1455

Berman MA, Burnham JA, Sheahan DG (1988) Fibrolamellar carcinoma of the liver: an immunohistochemical study of nineteen cases and a review of the literature. Hum Pathol 19:784–794

Bhajee F, Locketz ML, Krige JE (2009) Fibrolamellar hepatocellular carcinoma at a tertiary centre in South Africa: a case series. S Afr J Surg 47:108–111

Bilbao I, Vilallonga R, Allende E, Montero A, Quiroga S, Viladomiu L, Charco R, Margarit C (2008) Krukenberg's tumor as the first clinical manifestation of fibrolamellar hepatocarcinoma (in Spanish). Gastroenterol Hepatol 31:341–346

Brandt D, Johnson CD, Stephens DH, Weiland LH (1988) Imaging of fibrolamellar carcinoma. Am J Roentgenol 151:295–298

Buckley AF, Burgart LJ, Kakar S (2006) Epidermal growth factor receptor expression and gene copy number in fibrolamellar hepatocellular carcinoma. Hum Pathol 37:410–414

Buckley AF, Burgart LJ, Sahai V, Kakar S (2008) Epidermal growth factor receptor expression and gene copy number in conventional hepatocellular carcinoma. Am J Clin Pathol 129:245–251

Caballero T, Aneiros J, Lopez-Caballero J, Gomez-Morales M, Nogales F (1985) Fibrolamellar hepatocellular carcinoma. An immunohistochemical and ultrastructural study. Histopathology 9:445–456

Caplin M, Khan K, Savage K, Rode J, Varro A, Michaeli D, Grimes S, Brett B, Pounder R, Dhillon A (1999) Expression and processing of gastrin in hepatocellular carcinoma, fibrolamellar carcinoma and cholangiocarcinoma. J Hepatol 30:519–526

Caseiro-Alves F, Zins M, Mahfouz AE, Rahmouni A, Vilgrain V, menu Y, Mathieu D (1996) Calcification in focal nodular hyperplasia: a new problem for differentiation from fibrolamellar hepatocellular carcinoma. Radiology 198:889–892

Chagas AL, Kikuchi L, Herman P, Alencar RS, Tani CM, Diniz MA, Pugliese V, Rocha MS, D'Albuquerque LA et al (2015) Clinical and pathological evaluation of fibrolamellar hepatocellular carcinoma: a single center study of 21 cases. Clinics (Sao Paulo) 70:207–213

Chang YC, Dai YC, Chow NH (2003) Fibrolamellar hepatocellular carcinoma with a recurrence of classic hepatocellular carcinoma: a case report and review of Oriental cases. Hepatogastroenterology 50:1637–1640

Cheuk W, Chan JK (2001) Clear cell variant of fibrolamellar carcinoma of the liver. Arch Pathol Lab Med 125:1235–1238

Chun YS, Zimmitti G (2013) Fibrolamellar variant of hepatocellular carcinoma. Recent Results Cancer Res 190:101–110

Collier NA, Weinbren K, Bloom SR, Lee YC, Hodgson HJ, Blumgart LH (1984) Neurotensin secretion by fibrolamellar carcinoma of the liver. Lancet 1:538–540

Cornella H, Alsinet C, Sayols S, Zhang Z, Hao K, Cabellos L, Hoshida Y, Villanueva A, Thung S, Ward SC, Rodriguez-Carunchio L et al (2015) Unique genomic profile of fibrolamellar hepatocellular carcinoma. Gastroenterology 148:806–818

Craig JR, Peters RL, Edmondson HA, Omata M (1980) Fibrolamellar carcinoma of the liver: a tumor of adolescents and young adults with distinctive clinicpathologic features. Cancer 46:372–379

Cruz O, Laguna A, Vancells M, Krauel L, Medina M, Mora J (2008) Fibrolamellar hepatocellular carcinoma in an infant and literature review. J Pediatr Hematol Oncol 30:968–971

Dadke D, Jaganath P, Krishnamurthy S, Chiplunkar S (2002) The detection of HBV antigens and HBx-transcripts in an Indian fibrolamellar carcinoma patient: a case study. Liver 22:87–91

Dahan MH, Kastell P (2002) Fibrolamellar hepatic carcinoma with a presentation similar to that of septic pregnancy. A case report. J Reprod Med 47:47–49

Darcy DG, Malek MM, Kobos R, Klimstra DS, DeMatteo R, La Quaglia MP (2015a) Prognostic factors in fibrolamellar carcinoma in young people. J Pediatr Surg 50:153–156

Darcy DG, Ciaroni-Clarke R, Murphy JM, Honeyman JN, Bhanot U, laQuaglia MP, Simon SM (2015b) The genomic landscape of fibrolamellar hepatocellular carcinoma: whole genome sequencing of then patients. Oncotarget 6:755–770

Davison FD, Fagan EA, Portmann B, Williams R (1990) HBV-DNA sequences in tumor and nontumor tissue in a patient with the fibrolamellar variant of hepatocellular carcinoma. Hepatology 12:676–679

De Gaetano AM, Nure E, Grossi U, Frongillo F, Russo R, Vecchio FM, Lirosi MC et al (2013) Fibrolamellar hepatocellular carcinoma with biliary tumor thrombus: an unreported association. Jpn J Radiol 31:706–712

De Souza AT, Hankins GR, Washington MK, Fine RL, Orton TC, Jirtle RL (1995) Frequent loss of heterozygosity on 6q at the mannose 6-phosphate/insulin-like growth factor II receptor locus in human hepatocellular tumors. Oncogene 10:1725–1729

Debray D, Pariente D, Fabre M, Foucaud P, Valayer J, Bernard O (1994) Fibrolamellar hepatocellular carcinoma: report of a case mimicking a liver abscess. J Pediatr Gastroenterol Nutr 19:468–472

Dellaportas D, Lykoudis P, Tsagkas A, Voros D, Kondi-Pafiti A (2011) A large fibrolamellar hepatocellular carcinoma in a 17-year-old male body builder. J BUON 16:780

Dhingra S, Li W, Tan D, Zenali M, Zhang H, Brown RE (2010) Cell cycle biology of fibrolamellar hepatocellular carcinoma. Int J Clin Exp Pathol 3:792–797

Ding SF, Delhanty JD, Bowles L, Dooley JS, Wood CB, Habib NA (1993) Infrequent chromosome allele loss in fibrolamellar carcinoma. Br J Cancer 67:244–246

Eckstein RP, Bambach CP, Stiel D, Roche J, Goodman BN (1988) Fibrolamellar carcinoma as a cause of bile duct obstruction. Pathology 20:326–331

Edmondson HA (1956) Differential diagnosis of tumors and tumor-like lesions of liver in infancy and childhood. Arch Dis Child 91:168–186

Eggert T, McGlynn KA, Duffy A, Manns MP, Greten TF, Altekruse SF (2013) Fibrolamellar hepatocellular carcinoma in the US, 2000–2010: a detailed report on frequency, treatment and outcome based on the surveillance, epidemiology, and end results database. U Eur Gastroenterol J 1:351–357

Ehrenfried JA, Zhou Z, Thompson JC, Evers BM (1994) Expression of the neurotensin gene in fetal human liver and fibrolamellar carcinoma. Ann Surg 220:484–489

El-Gazzaz G, Wong W, El-Hadary MK, Gunson BK, Mirza DF, Mayer AD, Buckels JA, McMaster P (2000) Outcome of liver resection and transplantation for fibrolamellar hepatocellular carcinoma. Transpl Int 13 (Suppl 1):S406–S409

El-Seraq HB, Davila JA (2004) Is fibrolamellar carcinoma different from hepatocellular carcinoma? A US population-based study. Hepatology 39:798–803

Epstein BE, Pajak TF, Haulk TL, Herpst JM, Oder SE, Abrams RA (1999) Metastatic nonresectable fibrolamellar hepatoma: prognostic features and natural history. Am J Clin Oncol 22:22–28

Everson GT, Trotter JF (2003) Transplantation of the liver. In: Schiff ER, Sorrell MF, Maddrey WC (eds) Diseases of the liver, vol 2, 9th edn. Lippincott, Williams and Wilkins, Philadelphia, pp 1585–1614

Farhi DC, Shikes RH, Silverberg SG (1982) Ultrastructure of fibrolamellar oncocytic hepatoma. Cancer 50:702–709

Farhi et al (1983) PubMed PMID 6311397

Ferrell LD (2004) Benign and malignant tumors of the liver. In: Odze RD, Goldblum JR, Crawford JM (eds) Surgical pathology of the GI tract, liver, biliary tract and pancreas. Souanders, Philadelphia, p 1012

Francis IR, Agha FP, Thompson NW, Keren DF (1986) Fibrolamellar hepatocarcinoma: clinical, radiologic, and pathologic features. Gastrointest Radiol 11:67–72

Friedman AC, Lichtenstein JE, Goodman Z, Fishman EK, Siegelman SS, Dachman AH (1985) Fibrolamellar hepatocellular carcinoma. Radiology 157:583–587

Garcia de Davila MT, Gonzalez-Crussi F, Mangkornkanok M (1987) Fibrolamellar carcinoma of the liver in a child: ultrastructural and immunohistologic aspects. Pediatr Pathol 7:319–331

Gibson AA, Soreide O, Hemingway AP, Carr DH, Blumgart LH, Allison DJ (1986) The radiology of fibrolamellar carcinoma. Clin Radiol 37:355–358

Goodman et al (1985) PubMed PMD 2578078

Gornicka B, Ziarkiewicz-Wroblewska B, Wroblewsi T, Wilczynski GM, Koperski L, Krawczyk M, Wasiutynski A (2005) Carcinoma, a fibrolamellar variant – immunohistochemical analysis of 4 cases. Hepatogastroenterology 52:519–523

Gras P, Truant S, Boige V, Ladrat L, Rougier P, Pruvot FR, Hebbar M (2012) Prolonged complete response after GEMOX chemotherapy in a patient with advanced fibrolamellar hepatocellular carcinoma. Case Rep Oncol 5:169–172

Gruner BA, DeNapoli TS, Andrews W, Tomlinson G, Bowman L, Weitman SD (1998) Hepatocellular carcinoma in children associated with Gardner syndrome or familial adenomatous polyposis. J Pediatr Hematol Oncol 20:274–278

Gulati G, Saran RK (2009) Fine needle aspiration cytology of fibrolamellar hepatocellular carcinoma: recognizing the oncocytic hepatocyte. Indian J Pathol Microbiol 52:288–289

Gupta P, Dhar S, Strickland NH (1999) Fibrolamellar carcinoma :an unusual clinico-radiological presentation. Eur J Radiol 32:119–123

Hany MA, Betts DR, Schmugge M, Schönle E, Niggli FK, Zachmann M, Plüss HJ (1997) A childhood fibrolamellar hepatocellular carcinoma with increased aromatase activity and a near triploid karyotype. Med Pediatr Oncol 28:136–138

Haratake J, Horie A (1989) A histopathologic comparative study of European cases of fibrolamellar carcinoma and

Japanese cases of sclerosing hepatocellular carcinoma (in Japanese). Gan No Ronsho 35:793–798
Haratake J, Horie A, Lee SD, Huh MH (1990) Fibrolamellar carcinoma of the liver in a middle-aged Korean man. J UOEH 12:349–354
Hasegawa A (1996) Fibrolamellar hepatocellular carcinoma: a report of a resected case with an electron microscopic and flow cytometric analysis. Pathol Int 46:84–90
Hemming AW, Langer B, Sheiner P, Greig PD, Taylor BR (1997) Aggressive surgical management of fibrolamellar hepatocellular carcinoma. J Gastrointest Surg 1:342–346
Hernandez-Castillo E, Mondragon-Sanchez R, Garduno-Lopez AL, Gomez-Gomez E, Ruiz-Molina JM et al (2005) Hepatocellular carcinoma in the youth. A comparative analysis with hepatocellular carcinoma in adulthood. Hepatogastroenterology 52:903–907
Hiramatsu K, Okamoto K, Uesaka K, Muakiyama H, Seno T (1999) Surgical management for lymph node recurrence of resected fibrolamellar hepatocellular carcinoma: a case report. Hepatogastroenterology 46:1160–1163
Hodgson HJ (1987) Fibrolamellar cancer of the liver. J Hepatol 5:241–247
Honeyman JN, Simon EP, Robine N, Chiaroni-Clarke R, Darcy DG, Lim II, Gleason CE et al (2014) Detection of a recurrent DNAJB1-PRKACA chimeric transcript in fibrolamellar hepatocellular carcinoma. Science 343:1010–1014
Hoshino H, Katada N, Nishimura D, Imada J, Morita K, Yoshida N, Sano H, Okamoto K, Kato K (1996) Case report: fibrolamellar hepatocellular carcinoma in a Japanese woman: a case report and review of Japanese cases. J Gastroenterol Hepatol 11:551–555
Ichikawa T, Federle MP, Grazioli L, Madariaga J, Nalesnik M, Marsh W (1999) Fibrolamellar hepatocellular carcinoma: imaging and pathologic findings in 31 recent cases. Radiology 213:352–361
Ichikawa T, Federle MP, Grazioli L, Marsh W (2000) Fibrolamellar hepatocellular carcinoma: pre-and posttherapy evaluation with CT and MR imaging. Radiology 217:145–151
Imkie M, Myers SA, Li Y, Fan F, Bennett TL, Forster J, Tawfik O (2005) Fibrolamellar hepatocellular carcinoma arising in a background of focal nodular hyperplasia: a report of 2 cases. J Reprod Med 50:633–637
Ishikawa T, Kamimura H, Tsuchiya A, Watanabe K, Seki K, Ohta H, Yoshida T, Musya N et al (2007) A resected case of fibrolamellar hepatocellular carcinoma with chronic hepatitis(type B) (in Japanese). Nippon Shokakibyo Gakkai Zasshi 104:1076–1081
Jaeck D (2003) The significance of hepatic pedicle lymph nodes metastases in surgical management of colorectal liver metastases and of other liver malignancies. Ann Surg Oncol 10:1007–1011
Jagirdar J, Ishak KG, Colombo M, Brambilla C, Paronetto F (1985) Fibronectin patterns in hepatocellular carcinoma and its clinical significance. Cancer 56:1643–1648
Jain M, Niveditha SR, Bharadwaj M, Pathania OP (2002) Cytological features of fibrolamellar variant of hepatocellular carcinoma with review of literature. Cytopathology 13:179–182
Kaczynski J, Gustavsson B, Hansson G, Wallerstedt S (1996) Fibrolamellar hepatic carcinoma in an area with a low incidence of primary liver cancer: a retrospective study. Eur J Surg 162:367–371
Kakar S, Burgart LJ, Batts KP, Garcia J, Jain D, Ferrell LD (2005) Clinicopathologic features and survival in fibrolamellar carcinoma: comparison with conventional hepatocellular carcinoma with and without cirrhosis. Mod Pathol 18:1417–1423
Kakar S, Chen X, Ho C, Burgart LJ, Sahai V, Dachrut S, Yabes A, Jain D, Ferrell LD (2009) Chromosomal changes in fibrolamellar hepatocellular carcinoma detected by array comparative genomic hybridization. Mod Pathol 22:134–141
Kanai T, Takabayashi T, Kawano Y, Kuramochi S, Miyazawa N (2004) A case of postoperative recurrence of fibrolamellar hepatocellular carcinoma with increased vitamin B12 binding capacity in a young Japanese female. Jpn J Clin Oncol 34:346–351
Kane RA, Curatolo P, Khettry U (1987) "Scar sign" on computed tomography and sonography in fibrolamellar hepatocellular carcinoma. J Comput Tomogr 11:27–30
Kannangai R, Wang J, Liu QZ, Sahin F, Torbenson M (2005) Survivin overexpression in hepatocellular carcinoma is associated with p53 dysregulation. Int J Gastrointest Cancer 35:53–60
Kannangai R, Vivekanandan P, Martinez-Murillo F, Chori M, Torbenson M (2007) Fibrolamellar carcinomas show overexpression of genes in the RAS, MAPK, PIK3, and xenobiotic degradation pathways. Hum Pathol 38:639–644
Kaplan JS, Hoda RS (2007) Clear cell variant of fibrolamellar hepatocellular carcinoma: diagnosis of recurrence by fine-needle aspiration. Diagn Cytopathol 35:459–462
Katzenstein HM, Krailo MD, Malogolowkin MH, Ortega JA, Qu W, Douglass EC, Feusner JH et al (2003) Fibrolamellar hepatocellular carcinoma in children and adolescents. Cancer 97:2006–2012
Kim T, Hori M, Onishi H (2009) Liver masses with central or eccentric scar. Semin Ultrasound CT MR 30:418–425
Klein WM, Molmenti EP, Colombani PM, Grover DS, Schwarz KB, Boitnott J, Torbenson MS (2005) Primary liver carcinoma arising in people younger than 30 years. Am J Clin Pathol 124:512–518
Knudson JD, Goldberg JF, Ayres NA (2012) Fibrolamellar hepatocellular carcinoma with cardiac spread causing severe inferior vena cava obstruction in a 9-year-old child. Pediatr Cardiol 33:872–873
Kohno H, Nagasue N, Taniura H, Nakamura T, Nagaoka S (1988) Fibrolamellar carcinoma of the liver – a case report from Japan and a review of the literature. HPB Surg 1:77–80
Kojima M, Kunimura T, Inagaki T, Hayashi R, Morohoshi T, Shiokawa A, Ohta Y, Ohike N (2004) A

fibrolamellar carcinoma of the liver with a marked solid component. J Gastroenterol 39:905–907
Komiya T, Tanigawa Y, Hirohashi S (1999) Cloning of the gene gob-4, which is expressed in intestinal goblet cells in mice. Biochim Biophys Acta 1444:434–438
Kroll D, Mazor M, Zirkin H, Schulman H, Glezerman M (1991) Fibrolamellar carcinoma of the liver in pregnancy: a case report. J Reprod Med 36:823–827
Kunz G, Chung J, Ali SZ (2002) Hepatocellular carcinoma-fibrolamellar variant: cytopathology of an unusual case. Diagn Cytopathol 26:257–261
Kutluk MT, Yalçin B, Büyükpamukçu N, Kale G, Büyèkpamukçu M (2001) Fibrolamellar hepatocellular carcinoma with skeletal metastases. Pediatr Hematol Oncol 18:273–278
Lack EE, Neave C, Vawter GF (1983) Hepatocellular carcinoma. Review of 32 cases in childhood and adolescence. Cancer 52:1510–1515
Lamberts R, Nitsche R, de Vivie RE, Peitsch W, Schauer A, Schuster R, Tebbe U, Kreuzer H, Creutzfeldt W (1992) Budd-Chiari syndrome as the primary manifestation of a fibrolamellar carcinoma. Digestion 53:200–209
Lapis K, Schaff Z, Kopper L, Karacsonyi S, Ormos J (1990) Das fibrolamelläre Leberkarzinom. Zbl Allg Pathol Anat 136:135–149
LeBrun DP, Silver MM, Freedman MH, Phillips MJ (1991) Fibrolamellar carcinoma of the liver in a patient with Fanconi anemia. Hum Pathol 22:396–398
Lefkowitch JH, Muschel R, Price JB, Marboe C, Braunhut S (1983) Copper and copper-binding protein in fibrolamellar liver cell carcinoma. Cancer 51:97–100
Lildballe DL, Nguyen KQ, Poulsen SS, Nielsen HO, Nexo E (2011) Haptocorrin as marker of disease progression in fibrolamellar hepatocellular carcinoma. Eur J Surg Oncol 37:72–79
Lim II, Farber BA, LaQuaglia MP (2014) Advances I fibrolamellar hepatocellular carcinoma: a review. Eur J Pediatr Surg 24:461–466
Liu S, Chan KW, Wang B, Qiao L (2009) Fibrolamellar hepatocellular carcinoma. Am J Gastroenterol 104:2617–2624
Liu S, Wah CK, Tong J, Wang Y, Wang B, Qiao L (2011) PET-CT scan is a valuable modality in the diagnosis of fibrolamellar hepatocellular carcinoma: a case report and a summary of recent literature. QJM 104:477–483
Lloreta J, Vadell C, Fabregat X, Serrano S (1994) Fibrolamellar hepatic tumor with neurosecretory features and systemic deposition of AA amyloid. Ultrastruct Pathol 18:287–292
Louie-Johnsun M, Hewitt P, Perera D, Morris D (2003) Fibrolamellar hepatocellular carcinoma in pregnancy. HPB (Oxford) 5:191–193
Lowichik A, Schneider NR, Tonk V, Ansari MQ, Timmons CF (1996) Report of a complex karyotype in recurrent metastatic fibrolamellar hepatocellular carcinoma and a review of hepatocellular carcinoma cytogenetics. Cancer Genet Cytogenet 88:170–174
Magata S, Kitahara K, Watanabe K, Miyazaki K (2001) Fibrolamellar hepatocellular carcinoma – a case report (in Japanese). Acta Hepatol Jpn (Kanzo) 42:414–419
Malouf G, Falissard B, Azoulay D, Callea F, Ferrell LF, Goodman ZD, Hayashi Y, Hayashi HC et al (2009) Is histologic diagnosis of primary liver carcinomas with fibrous stroma reproducible among experts ? J Clin Pathol 62:519–524
Malouf GG, Brugières L, Le Deley MC, Faivre S, Fabre M, Paradis V, Aerts I, Le Tourneau C et al (2012) Pure and mixed fibrolamellar hepatocellular carcinomas differ in natural history and prognosis after complete surgical resection. Cancer 118:4981–4990
Malouf GG, Job S, Paradis V, Fabre M, Brugières L, Saintigny P, Vescovo L, Belghiti J et al (2014) Transcriptional profiling of pure fibrolamellar hepatocellular carcinoma reveals an endocrine signature. Hepatology 59:2228–2237
Maniaci V, Davidson BR, Rolles K, Dhillon AP, Hackshaw A, Regent RH, Meyer T (2009) Fibrolamellar hepatocellular carcinoma – prolonged survival with multimodality therapy. Eur J Surg Oncol 35:617–621
Mansouri D, Van Nhieu JT, Couanet D, Terrier-Lacombe MJ, Brugières L, Cherqui D, Suciu V, Vielh P (2006) Fibrolamellar hepatocellular carcinoma: a case report with cytological features in a sixteen-year-old girl. Diagn Cytopathol 34:568–571
Marrannes J, Gryspeerdt S, Hapseslagh M, van Holsbeeck B, Baekelandt M, Lefere P (2005) Fibrolamellar hepatocellular carcinoma in a 65-year-old woman: CT features. JBR-BTR 88:237–240
Maslon MM, Hrstka R, Vojtesek B, Hupp TR (2010) A divergent substrate-binding loop within the pro-oncogenic protein anterior gradient-2 forms a docking site for reptin. J Mol Biol 404:418–438
Mayo SC, Mavros MN, Nathan H, Cosgrove D, Herman JM, Kamel I, Anders RA et al (2014) Treatment and prognosis of patients with fibrolamellar hepatocellular carcinoma: a national perspective. J Am Coll Surg 218:196–205
McCloskey JJ, Germain-Lee EL, Perman JA, Plotnick LP, Janoski AH (1988) Gynecomastia as a presenting sign of fibrolamellar carcinoma of the liver. Pediatrics 82:379–382
McLarney JK, Rucker PT, Bender GN, Goodman ZD, Kashitani N, Ros PR (1999) Fibrolamellar carcinoma of the liver: radiologic-pathologic correlation. Radiographics 19:453–471
Meriggi F, Forni E (2007) Surgical therapy of hepatic fibrolamellar carcinoma (in Italian). Ann Ital Chir 78:53–58
Montero A, Allende H, Tallada N, Ramon y Cajal S, Margarit C, Viladomiu L (2007) Fine needle aspiration cytology of massive bilateral ovarian metastasis of fibrolamellar hepatocellular carcinoma. Acta Cytol 51:682–683
Moore SW, Millar AJ, Hadley GP, Ionescu G, Kruger M, Poole J, Stones D, Wainwright L et al (2004)

Hepatocellular carcinoma and liver tumors in South African children: a case for increased prevalence. Cancer 101:642–649

Moreno-Luna LE, Arrieta O, Garcia-Leiva J, Martinez B, Torre A, Uribe M, Leon-Rodriguez E (2005) Clinical and pathologic factors associated with survival in young adult patients with fibrolamellar hepatocarcinoma. BMC Cancer 5:142

Morise Z, Sugioka A, Mizoguchi Y, Fujita J, Hoshimoto S, Kato T, Hasumi A (2005) Fibrolamellar carcinoma of the liver in a Japanese hepatitis B virus carrier. J Gastroenterol Hepatol 20:1136–1138

Muramori K, Taguchi S, Taguchi T, Kohashi K, Furuya K, Tokuda K, Ishii E (2011) High aromatase activity and overexpression of epidermal growth factor receptor in fibrolamellar hepatocellular carcinoma in a child. J Pediatr Hematol Oncol 33:e195–e197

Nagorney DM, Adson MA, Weiland LH, Knight CD, Smalley SR, Zinsmeister AR (1985) Fibrolamellar hepatoma. Am J Surg 149:113–119

Nerlich AG, Majewski S, Hunzelmann N, Brenner RE, Wiebecke B, Müller PK, Kreig T, Remberger K (1992) Excessive collagen formation in fibrolamellar carcinoma of the liver: a morphological and biochemical study. Mod Pathol 5:580–585

Njei B (2014) Fibrolamellar hepatocellular carcinoma versus conventional hepatocellular carcinoma: better 5-year survival or artifactual result of research methodology ? Gut 63:1374–1375

Njei B, Konjeti VR, Ditah I (2014) Prognosis of patients with fibrolamellar hepatocellular carcinoma versus conventional hepatocellular carcinoma: a systematic review and meta-analysis. Gastrointest Cancer Research 7:49–54

Nojiri T, Mitsumori N, Yoshida T, Shinohara T, Asakura J, Doi N et al (2000) A case of fibrolamellar hepatocellular carcinoma (in Japanese). Jpn J Gastroenterol Surg 33:1905–1909

Okada K, Kim YI, Nakashima K, Tada I, Yoshida T, Kobayashi M, Yokoyama S (1993) Fibrolamellar hepatocellular carcinoma coexistent with a hepatocellular carcinoma of common type: report of a case. Surg Today 23:626–631

Okano A, Hajiro K, Takakuwa H, Kobashi Y (1998) Fibrolamellar carcinoma of the liver with a mixture of ordinary hepatocellular carcinoma: a case report. Am J Gastroenterol 93:1144–1145

Okuda K (2002) Natural history of hepatocellular carcinoma including fibrolamellar and hepato-cholangiocarcinoma variants. J Gastroenterol Hepatol 17:401–405

Orsatti G, Greenberg PD, Rolfes DB, Ishak KG, Paronetto F (1994) DNA ploidy of fibrolamellar hepatocellular carcinoma by image analysis. Hum Pathol 25:936–939

Orsatti G, Hytiroglou P, Thung SN, Ishak KG, Paronetto F (1997) Lamellar fibrosis in the fibrolamellar variant of hepatocellular carcinoma: a role for transforming growth factor beta. Liver 17:152–156

Paradinas FJ, Melia WM, Wilkinson ML, Portmann B, Johnson PJ, Murray-Lyon IM, Williams R (1982) High serum vitamin B12 binding capacity as a marker of the fibrolamellar variant of hepatocellular carcinoma. Br Med J (Clin Res Ed) 285:840–842

Park SW, Zhen G, Verhaeghe C, Nakagami Y, Nguyenvu LT, Barczak AJ, Killeen N, Erle DJ (2009) The protein disulfide isomerase AGR2 is essential for production of intestinal mucus. Proc Natl Acad Sci U S A 106:6950–6955

Patonai A, Erdélyi-Belle B, Korompay A, Somoracz A, Straub BK, Schirmacher P et al (2011) Claudins and tricellulin in fibrolamellar hepatocellular carcinoma. Virchows Arch 458:679–688

Patonai A, Erdélyi-Belle B, Korompay A, Somoracz A, Törzsök P, Kovalszky I, Barbai T et al (2013) Molecular characteristics of fibrolamellar hepatocellular carcinoma. Pathol Oncol Res 19:63–70

Payne CM, Nagle RB, Paplanus SH, Graham AR (1986) Fibrolamellar carcinoma of liver: a primary malignant oncocytic carcinoid? Ultrastruct Pathol 10:539–552

Perez-Guillermo M, Masgrau NA, Garcia-Solano J, Sola-Perez J, de Agustin P (1999) Cytologic aspect of fibrolamellar hepatocellular carcinoma in fine-needle aspirates. Diagn Cytopathol 21:180–187

Petek E, Windpassinger C, Egger H, Kroisel PM, Wagner K (2000) Localization of the human anterior gradient-2 gene (AGR2) to chromosome band 7p21.3 by radiation hybrid mapping and fluorescence in situ hybridization. Cytogenet Cell Genet 89:141–142

Pinna AD, Iwatsuki S, Lee RG, Todo S, Madariaga JR, Marsh JW, Casavilla A et al (1997) Treatment of fibrolamellar hepatoma with subtotal hepatectomy or transplantation. Hepatology 26:877–883

Pombo F, Rodriguez E, Arnal-Monreal F (1993) Multicystic fibrolamellar carcinoma. CT appearance. Clin Imaging 17:67–69

Read D, Shulkes A, Fernley R, Simpson R (1991) Characterization of neurotensin (6–13) from an hepatic fibrolamellar carcinoma. Peptides 12:887–892

Riehle KJ, Yeh MM, Yu JJ, Kenerson HL, Harris WP, Park JO, Yeung RS (2015) mTORC1 and FGFR1 signaling in fibrolamellar hepatocellular carcinoma. Mod Pathol 28:103–110

Ringe B, Wittekind C, Weimann A, Tusch G, Pichlmayr R (1992) Results of hepatic resection and transplantation for fibrolamellar carcinoma. Surg Gynecol Obstet 175:299–305

Ross HM, Daniel HD, Vivekanandan P, Kannangal R, Yeh MM, Wu TT, Makhlouf HR, Torbenson M (2010) Fibrolamellar carcinomas are positive for CD68. Mod Pathol 24:390–395

Ruffin MT (1990) Fibrolamellar hepatoma. Am J Gastroenterol 85:577–581

Saab S, Yao F (1996) Fibrolamellar hepatocellular carcinoma. Case reports and a review of the literature. Dig Dis Sci 41:1981–1985

Sarode VR, Castellani R, Post A (2002) Fine-needle aspiration cytology and differential diagnoses of fibrolamellar hepatocellular carcinoma metastatic to the mediastinum: case report. Diagn Cytopathol 26:95–98

Sarosi I, Kiss A, Schaff Z, Lapis K (1991) Connective tissue content of fibrolamellar carcinoma and other human liver tumors. Acta Morphol Hung 39:321–331

Sato S, Masuda T, Oikawa H, Satodate R, Suzuki K, Sato S, Suzuki A, Monma N (1997) Bile canaliculi-like lumina in fibrolamellar carcinoma of the liver: a light- and electron-microscopic study and three-dimensional examination of serial sections. Pathol Int 47:763–768

Saul SH, Titelbaum DS, Gansler TS, Varello M, Burke DR, Atkinson BF, Rosato EF (1987) The fibrolamellar variant of hepatocellular carcinoma. Its association with focal nodular hyperplasia. Cancer 60:3049–3055

Saxena R, Humphreys S, Williams R, Portmann B (1994) Nodular hyperplasia surrounding fibrolamellar carcinoma: a zone of arterialized liver parenchyma. Histopathology 25:275–278

Schlitt HJ, Neipp W, Weimann A, Oldhafer KJ, Schmoll E, Boeker K, Nashan B, Kubicka S et al (1999) Recurrence patterns of hepatocellular and fibrolamellar carcinoma after liver transplantation. J Clin Oncol 17:324–331

Schoedel KE, Tyner VZ, Kim TH, Michalopoulos GK, Mars WM (2003) HGF, MET, and matrix-related proteases in hepatocellular carcinoma, fibrolamellar variant, cirrhotic, and normal liver. Mod Pathol 16:14–21

Scoazec JY, Flejou JF, D'Errico A, Fiorentino M, Zamparelli A, Bringuier AF, Fedlmann G et al (1996) Fibrolamellar carcinoma of the liver: composition of the extracellular matrix and expression of cell-matrix and cell-cell adhesion molecules. Hepatology 24:1128–1136

Seitz G, Zimmermann A, Friess H, Büchler MW (2002) Adult-type hepatocellular carcinoma in the center of a fibrolamellar hepatocellular carcinoma. Hum Pathol 33:765–769

Selaru FM, Cross R, Drachenberg C, Cross R (2007) Electronic clinical challenges and images in GI. Fibrolamellar carcinoma. Gastroenterology 133: e1–e3

Shafizadeh N, Ferrell LD, Kakar S (2008) Utility and limitations of glypican-3 expression for the diagnosis of hepatocellular carcinoma at both ends of the differentiation spectrum. Mod Pathol 21:1011–1018

Sheppard KJ, Bradbury DA, Davies JM, Ryrie DR (1983) High serum vitamin B12 binding capacity as a marker of the fibrolamellar variant of hepatocellular carcinoma. Br Med J (Clin Res Ed) 286:57

Sher ES, Migeon CJ, Berkovitz GD (1998) Evaluation of boys with marked breast development at puberty. Clin Pediatr (Phila) 37:367–371

Sherlock S, Dooley J (eds) (2003) Malignant liver tumors. In: Diseases of the liver and biliary systems, 11th edn. Blackwell, Malden, pp 537–562

Simonsen K, Rode A, Nicoll A, Villadsen G, Espelund U, Lim L, Angus P, Arachchi N et al (2014) Vitamin B12 and its binding proteins in hepatocellular carcinoma and chronic liver diseases. Scand J Gastroenterol 49:1096–1102

Sirivatanauksorn Y, Sirivatanauksorn V, Lemoine NR, Willimason RC, Davidson BR (2001) Genomic homogeneity in fibrolamellar carcinomas. Gut 49:82–86

Smith MT, Blatt ER, Jedlicka P, Strain JD, Fenton LZ (2008) Best cases from the AFIP: fibrolamellar hepatocellular carcinoma. Radiographics 28:609–613

Snook JA, Kelly P, Chapman RW, Jewell DP (1989) Fibrolamellar hepatocellular carcinoma complicating ulcerative colitis with primary sclerosing cholangitis. Gut 30:243–245

Soreide O, Czerniak A, Bradpiece H, Bloom S, Blumgart L (1986) Characteristics of fibrolamellar hepatocellular carcinoma: a study of nine cases and a review of the literature. Am J Surg 151:518–523

Soyer P, Roche A, Levesque M (1991a) Fibrolamellar hepatocellular carcinoma presenting with obstructive jaundice. A report of two cases. Eur J Radiol 13:196–198

Soyer P, Roche A, Levesque M, Legmann P (1991b) CT of fibrolamellar hepatocellular carcinoma. J Comput Assist Tomogr 15:533–538

Stevens WR, Johnson CD, Stephens DH, Nagorney DM (1995) Fibrolamellar hepatocellular carcinoma: stage at presentation and results of aggressive surgical management. AJR Am J Roentgenol 164:1153–1158

Stipa F, Yoon SS, Liau KH, Fong Y, Jarnagin WR, D'Angelica M, Abou-Alfa G, Blumgart LH, DeMatteo RP (2006) Outcome of patients with fibrolamellar hepatocellular carcinoma. Cancer 106:1331–1338

Stoupis C, Taylor HM, Paley MR, Buetow PC, Marre S, Baer HU, Vock P, Ros PR (1998) The rocky liver: radiologic-pathologic correlation of calcified hepatic masses. Radiographics 18:675–685

Suen KC, Magee JF, Halparin LS, Chan NH, Greene CA (1985) Fine needle aspiration cytology of fibrolamellar hepatocellular carcinoma. Acta Cytol 29:867–872

Sulaiman RA, Geberhiwot T (2014) Fibrolamellar hepatocellular carcinoma mimicking ornithine transcarbamylase deficiency. JIMD Rep 16:47–50

Tanaka J, Baba N, Arii S, Fujita K, Tamura J, Kawakami Y, Tsuji S, Imamura M et al (1994) Typical fibrolamellar hepatocellular carcinoma in Japanese patients: report of two cases. Surg Today 24:459–463

Tanaka K, Honna T, Kitano Y, Kuroda T, Tanaka K, Morikawa N, Matsuda H, Kawashima N et al (2005) Combined fibrolamellar carcinoma and cholangiocarcinoma exhibiting biphenotypic antigen expression: a case report. J Clin Pathol 58:884–887

Teitelbaum DH, Tuttel S, Carey LC, Clausen KP (1985) Fibrolamellar carcinoma of the liver. Review of three cases and the presentation of a characteristic set of tumor markers defining this tumor. Ann Surg 202:36–41

Terracciano L, Tornillo L (2003) Cytogenetic alterations in liver cell tumors as detected by comparative genomic hybridization. Pathologica 95:71–82

Terracciano LM, Tornillo L, Avoledo P, Von Schweinitz D, Kühne T, Bruder E (2004) Fibrolamellar hepatocellular

carcinoma occurring 5 years after hepatocellular adenoma in a 14-year-old girl: case report with comparative genomic hybridization analysis. Arch Pathol Lab Med 128:222–226

Terris B, Pineau P, Bregeaud L, Valla D, Belghiti J, Tiollais P, Degott C, Dejean A (1999) Close correlation between beta-catenin gene alterations and nuclear accumulation of the protein in human hepatocellular carcinomas. Oncogene 18:6583–6588

Terzis I, Haritanti A, Economou I (2010) Fibrolamellar hepatocellular carcinoma: a case report with distinct radiological features. J Gastrointest Cancer 41:2–5

Thirabanjasak D, Sosothikul D, Mahayosnond A, Thorner PS (2009) Fibrolamellar carcinoma presenting as a pancreatic mass: case report and review of the literature. J Pediatr Hematol Oncol 31:370–372

Torbenson M (2007) Review of the clinicopathologic features of fibrolamellar carcinoma. Adv Anat Pathol 14:217–223

Tränkenschuh W, Puls F, Christgen M, Albat C, Heim A, Poczkaj J, Fleming P, Kreipe H, Lehmann U (2010) Frequent and distinct aberrations of DNA methylation patterns in fibrolamellar carcinoma of the liver. PLoS One 5:e13688

Tsilividis B, Huet E, Lubrano J, Lacaze L, Lestrat JP, François A, Riachi G, Scotté M (2010) Late supradiaphragmatic lymph node recurrence following resection of a fibrolamellar hepatocarcinoma: an unusual case. Surg Radiol Anat 32:123–127

Vaideeswar P, Pandit MJ, Deshpande JR, Sivaraman A, Vora IM (1993) Fibrolamellar carcinoma of the liver – an unusual presentation. J Postgrad Med 39:159–161

Van Eyken P, Sciot R, Brock P, Casteels-Van DM, Ramaekers FC, Desmet VJ (1990) Abundant expression of cytokeratin-7 in fibrolamellar carcinoma of the liver. Histopathology 17:101–107

Vasdev N, Nayak NC (2003) CD99 expression in hepatocellular carcinoma: an immunohistochemical study in the fibrolamellar and common variant of the tumour. Indian J Pathol Microbiol 46:625–629

Vecchio FM (1988) Fibrolamellar carcinoma of the liver: a distinct entity within the hepatocellular tumors. A review. Appl Pathol 6:139–148

Vecchio FM, Fabiano A, Ghirlanda G, Manna R, Massi G (1984) Fibrolamellar carcinoma of the liver: the malignant counterpart of focal nodular hyperplasia with oncocytic change. Am J Clin Pathol 81:521–526

Vivekanandan P, Torbenson M (2008) Epigenetic instability is rare in fibrolamellar carcinomas but common in viral-associated hepatocellular carcinomas. Mod Pathol 21:670–675

Vivekanandan P, Micchelli ST, Torbenson M (2009) Anterior gradient-2 is overexpressed by fibrolamellar carcinomas. Hum Pathol 40:293–299

Vivekanandan P, Daniel H, Yeh MM, Torbenson M (2010) Mitochondrial mutations in hepatocellular carcinomas and fibrolamellar carcinomas. Mod Pathol 23:790–798

Wang Z, Hao Y, Lowe AW (2008) The adenocarcinoma-associated antigen, AGR2, promotes tumor growth, cell migration, and cellular transformation. Cancer Res 68:492–497

Ward SC, Waxman S (2011) Fibrolamellar carcinoma: a review with focus on genetics and comparison to other malignant primary liver tumors. Semin Liver Dis 31:61–70

Ward SC, Huang J, Tickoo SK, Thung SN, Ladanyi M, Klimstra DS (2010) Fibrolamellar carcinoma of the liver exhibits immunohistochemical evidence of both hepatocyte and bile duct differentiation. Mod Pathol 23:1180–1190

Washington K, Telen MJ, Gottfried MR (1997) Expression of cell adhesion molecule CD44 in primary tumors of the liver: an immunohistochemical study. Liver 17:17–23

Weeda VB, Murawski M, McCabe AJ, Maibach R, Brugières L, Roebuck D, Fabre M et al (2013) Fibrolamellar variant of hepatocellular carcinoma does not have a better survival than conventional hepatocellular carcinoma – results and treatment recommendations from the Childhood Liver Tumour Strategy Group (SIOPEL) experience. Eur J Cancer 49:2698–2704

Wennerberg AE, Nalesnik MA, Coleman WB (1993) Hepatocyte paraffin 1: a monoclonal antibody that reacts with hepatocytes and can be used for differential diagnosis of hepatic tumors. Am J Pathol 143:1050–1054

Wetzel WJ, Costin JL, Petrino RL (1983) Fibrolamellar carcinoma: distinctive clinical and morphologic variant of hepatoma. South Med J 76:796–798

Wheeler K, Pritchard J, Luck W, Rossiter M (1986) Transcobalamin I as a "marker" for fibrolamellar hepatoma. Med Pediatr Oncol 14:227–229

Wilkens L, Bredt M, Flemming P, Kubicka S, Klempnauer J, Kreipe H (2000) Cytogenetic aberrations in primary and recurrent fibrolamellar hepatocellular carcinoma detected by comparative genomic hybridization. Am J Clin Pathol 114:867–874

Wong LK, Link DP, Frey CF, Ruebner RH, Tesluk H, Pimstone NR (1982) Fibrolamellar hepatocellular carcinoma: radiology, management, and pathology. AJR Am J Roentgenol 139:172–175

Xu L, Hazard FK, Zmoos AF, Jahchan N, Chaib H, Garfin PM, Rangaswami A, Snyder MP (2015) Genomic analysis of fibrolamellar hepatocellular carcinoma. Hum Mol Genet 24:50–63

Yamamoto H, Watanabe K, Takayama W, Yamada S, Fujita Y, Honda I, Watanabe S et al (1995) Surgical management for lymph node recurrence of resected fibrolamellar carcinoma of the liver: a case report. Jpn J Clin Oncol 25:282–285

Yamamoto H, Watanabe K, Nagata M, Yano Y, Akai T, Honda I, Watanabe S, Soda H, Matsuzaki O (1999) Transformation of fibrolamellar carcinoma to common hepatocellular carcinoma in the recurrent lesions of the rectum and the residual liver: a case report. Jpn J Clin Oncol 29:445–447

Yamamoto M, Ariizumi S, Yoshitoshi K, Saito A, Nakano M, Takasaki K (2006) Hepatocellular carcinoma with a central scar and a scalloped tumor margin resembling focal nodular hyperplasia in macroscopic appearance. J Surg Oncol 94:587–591

Yen JB, Chang KW (2009) Fibrolamellar hepatocellular carcinoma – report of a case. Chang Gung Med J 32:336–339

Yoshimi F, Asato Y, Amemiya R, Itabashi M, Nakamura K (2002) Fibrolamellar hepatocellular carcinoma in a Japanese man: report of a case. Surg Today 32:174–179

Yoshinaga Y, Okazumi S, Takayama W, Makino H, Iwasaki K, Kondou S et al (2002) A resected case of fibrolamellar hepatocellular carcinoma in a 15 year old woman (in Japanese). Shoukaki Gazou 4:97–103

Zenali MJ, Tan D, Li W, Dhingra S, Brwon RE (2010) Stemness characteristics of fibrolamellar hepatocellular carcinoma: immunohistochemical analysis with comparisons to conventional hepatocellular carcinoma. Ann Clin Lab Sci 40:126–134

Zermani R, Charfi L, Kourda N, Farah F, Rammeh S, Trabesli O, Zaouch A, Ben Jilani S (2005) A particular hepatocellular carcinoma combining the ordinary and the fibrolamellar variant (in French). Tunis Med 83:419–421

Zhang Y, Ali TZ, Zhou H, D'Souza DR, Lu Y, Jaffe J, Liu Z, Passaniti A, Hamburger AW (2010) ErbB3 binding protein 1 represses metastasis-promoting gene anterior gradient protein 2 in prostate cancer. Cancer Res 70:240–248

Zografos GN, Palmer S, Papastratis G, Habib NA (1997) Aggressive surgical management of fibrolamellar hepatocellular carcinoma in puberty. Eur J Surg Oncol 23:570–572