Fibrolamellar Carcinoma

8

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Abstract

Fibrolamellar carcinomas are unique primary liver malignancies that are distinguished from ordinary hepatocellular carcinoma by their distinct clinical features, as well as their unique morphologic, immunohistochemical, and molecular findings. All of these characteristics, along with prognostic factors and serum markers, are discussed in detail and illustrated in this chapter. The chapter also examines key features that help differentiate fibrolamellar carcinoma from other neoplasms and proposes the best diagnostic approach for recognizing this unique neoplasm, with special attention to common diagnostic pitfalls.

Keywords

Lamellar fibrosis • Mitochondria • Lysosome • Lamellar fibrosis • Pale bodies • Hyaline bodies • CD68 • CK7 • Pseudoglands • Mucin • *DNA-JB* • *PRCACA1*

8.1 Definition

Fibrolamellar carcinomas are primary hepatic carcinomas that arise in non-cirrhotic livers with no underlying liver disease. The tumor cells have abundant eosinophilic cytoplasm, prominent nucleoli, and intratumoral fibrosis.

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8.2 Etiology

The etiology of fibrolamellar carcinoma is unknown. Fibrolamellar carcinomas do not arise in the setting of chronic liver disease and the background liver tissue lacks significant inflammation or fibrosis [1]. While occasional reports have described the presence of hepatitis B viral proteins or DNA in fibrolamellar carcinoma [2–5], this is most likely a chance observation, given the high world-wide prevalence of chronic hepatitis B infection. There is no data to suggest hepatitis B is an etiological agent. No histological precursor lesion to fibrolamellar carcinoma has been identified to date. Rare cases of fibrolamellar

T. Mounajjed et al. (eds.), *Surgical Pathology of Liver Tumors*,
DOI 10.1007/978-3-319-16089-4_8, © Springer International Publishing Switzerland 2015

carcinoma have been reported in association with well-defined inherited syndromes (Table 8.1). While fibrolamellar carcinoma is not a major component of any of these syndromes, its occurrence in these patients suggests shared molecular pathways. For example, activation of the protein kinase A complex occurs in both fibrolamellar carcinoma and Carney syndrome, but through mutations of different subunits of the kinase.

8.3 Demographics

Overall, fibrolamellar carcinomas make up approximately 1 % of all hepatocellular carcinomas. Prior studies suggested a frequency of around 5 %, but more recent data from larger studies indicates a frequency closer to 1 % (Table 8.2). Fibrolamellar carcinomas have been reported from a wide variety of geographical locations, including most parts of the world. One study found no strong correlates between fibrolamellar carcinoma and white, black, Hispanic, or Asian ethnicities living in the USA [6]. However, many clinicians and scientists believe that fibrolamellar carcinomas are less common overall in Asian countries. There appears to be a small predilection in fibrolamellar carcinomas for males, but there is no evidence for a striking male dominance, as is seen in typical hepatocellular carcinoma.

One of the most distinctive and well-recognized features of fibrolamellar carcinoma is its occurrence in younger individuals. In fact, 50 % of cases occur between the ages of 17 and 30 and 80 % occur between the ages of 10–35 [7]. Nonetheless, an important diagnostic point is that fibrolamellar carcinomas are not the most frequent form of liver cancer in children and young adults. Instead, typical hepatocellular carcinomas are still the most common and account for 60–80 % of cases [1, 8–10]. Thus, young age is not a finding on which a diagnosis of fibrolamellar carcinoma can be based.

Table 8.1 Fibrolamellar carcinoma can rarely occur in the setting of inherited syndromes

Syndrome	Genes
Carney [35]	*PRKA* (protein kinase A)
Fanconi anemia [36]	About 15 different known genes, all involved in DNA repair
Familial adenomatous polyposis [53]	*APC* or less commonly *MUTYH*

Table 8.2 Representative studies of the prevalence of FLC in various populationsy

Nation	Prevalence (%)	Number of study cases (FLC/total)	Study time frame	Comment
Sweden [43]	0.4	2/532	1958–1979	From Ostra Sjukhuset
USA [6]	0.4	191/46,731	2000–2010	From SEER database
Thailand [44]	0.6	1/180	1991–1998	From Songkhla
USA [45]	0.9	68/7896	1986–1999	From SEER database
Germany [46]	1.1	13/1108	1998–2010	From Mainz
South Africa [47]	3	9/274		Pediatric cancer registry data; includes all pediatric cancers and not just HCC
Rochester, MN, USA [15]	4	10/280	1987–1993	From Mayo clinic
USA [19]	5	3/58	1966–1981	From Ohio State
Mexico [48]	5.8	7/121	1987–2001	From Mexico City
Mexico [49]	8.6	15/174	1990–2003	From Mexico City
United Kingdom [50]	7	8/107	Not stated	From London
France [51]	7.3	5/68		From Villejuif; HCCs in non-cirrhotic livers
USA [16]	8.9	41/477	1968 and 1995	From Pittsburgh, PA; Patients undergoing liver transplant for HCC
Canada [52]	9	10/NS	1982–1995	From Toronto. Referrals to a tertiary care center for HCC with intent to treat from

8.4 Clinical Findings

Fibrolamellar carcinoma most often presents with vague, nonspecific abdominal pain, weight loss, and malaise. However, there is a wide variety of less common findings at presentation. Of these, one recurrent theme is biliary obstruction secondary to direct tumor growth into the biliary tree or to compression by metastatic deposits in hilar lymph nodes. Gynecomastia in males is also a rare but distinctive finding at presentation.

8.5 Serum Findings

Serum alpha-fetoprotein (AFP) levels are normal in essentially all cases and an elevated serum AFP level makes the diagnosis of fibrolamellar carcinoma unlikely. There are some reports of fibrolamellar carcinomas with significantly elevated serum AFP levels, and it is possible that this might occur in rare cases, but overall it seems likely that most of these cases are misdiagnosed.

A number of serum proteins are elevated in individuals who have fibrolamellar carcinoma, but none are sufficiently sensitive or specific to be widely used clinically. These proteins include transcobalamin I, transcobalamin 2, fibrinogen, and neurotensin. In addition, PIVKA-II (protein induced by vitamin K absence/antagonist-II) is commonly elevated in both typical hepatocellular carcinomas and in fibrolamellar carcinoma. While these serum findings are not useful for diagnosis, they can be useful in individual cases to monitor for response to tumor therapy and to monitor for tumor recurrence.

8.6 Prognostic Factors and Tumor Spread

Prognostic factors are shown in Table 8.3. After resection of primary disease, approximately 55 % of cases will recur within the first 5 years [11]. Recurrent disease is intrahepatic in about 40 % of cases, involves extra-abdominal organs such as the lungs in about 40 % of cases, and presents with peritoneal and/or lymph node disease in about 20 % of cases [11].

Table 8.3 Prognostic factors in fibrolamellar carcinoma

Prognostic factor	Comment and representative reference
Gender	Females have better prognosis [45]
Age	Younger age at presentation has better prognosis [45, 49]
Absence of elevated liver enzymes	Better prognosis [49]
Absence of large vessel invasion or thrombosis	Better prognosis [49]
Lymph node disease at presentation	Worse prognosis [14, 16]
Metastatic disease at presentation	Worse prognosis [16]
Stage	Higher stages have worse prognosis [16, 45, 52]
Vascular invasion	Worse prognosis [16]

Lymph node metastases are identified at presentation in approximately two thirds of fibrolamellar carcinoma cases [12–15]. In fact, lymph node metastases at the time of presentation are more common in fibrolamellar carcinoma than in typical hepatocellular carcinoma [3]. The involved lymph nodes are commonly regional nodes [16–18], including celiac [16, 18], gastric [19], and para-aortic lymph nodes [16, 19].

Direct extension outside of the liver is also common at presentation. In one study, 42 % of fibrolamellar carcinomas extended into the adjacent fat planes by imaging studies [13]. Direct extension into adjacent organs can also be seen, including the stomach [19], diaphragm [13], and pancreas [13, 20]. A subset of cases can also demonstrate widespread peritoneal disease at presentation [13–16, 21–23]. Other cases tend to spread by isolated or a small number of metastases, a pattern that can often be treated with surgery.

8.7 Gross Findings

Overall, fibrolamellar carcinomas tend to be more common in the left lobe of the liver, but frequently involve both lobes. In 80–90 % of cases a single large tumor is present. In cases

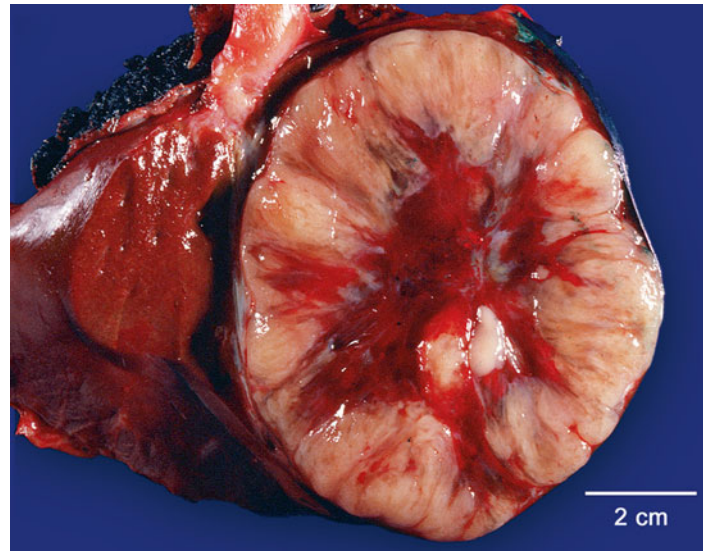

Fig. 8.1 Fibrolamellar carcinoma, gross. The tumor is yellow with a central area of fibrosis

with multiple tumor masses, there tends to be one dominant mass. Fibrolamellar carcinomas tend to be large at the time of resection, commonly measuring 10 cm or more in greatest dimension. Fibrolamellar carcinomas range in color from yellow to pale tan (Fig. 8.1) and range in consistency from soft to firm. The tumors can feel gritty when microcalcifications are prominent. In cases with prominent pseudoglands, the tumor can have areas that are grossly tacky and mucinous. A central scar is found in about two thirds of cases. Occasionally, the tumors may contain small foci of necrosis or areas of intratumoral hemorrhage. Gross vascular invasion is seen in up to 25 % of cases [16]. The background liver is non-cirrhotic, but a rim of inflamed and fibrotic tissue is often present at the interface of the fibrolamellar carcinoma with the non-tumor parenchyma. Sections from this area are helpful and important for looking for angiolymphatic invasion, but are not useful for examining the background liver for underlying liver disease.

8.8 Histologic Findings

Tumor cells are large and polygonal, with abundant eosinophilic cytoplasm that is rich in mitochondria and lysosomes (Fig. 8.2). The nuclei often have vesiculated chromatin and large nucleoli (Fig. 8.3). These distinctive cytological findings, when combined with the intratumoral fibrosis, are the defining H&E features of fibrolamellar carcinoma.

There are a variety of other histological findings that are common in fibrolamellar carcinoma, but they are neither necessary nor specific for the diagnosis. The most distinctive are pale bodies. Pale bodies are round amphophilic inclusions found in approximately 50 % of cases (Fig. 8.4). Pale bodies do not show any clear spatial relationships with fibrosis, the center or periphery of the tumor, or tumor vasculature. They are immunoreactive for a number of different proteins, including vimentin, but the principal protein component is not known. Their cause is also not known, but presumably reflects a defect in protein folding or protein secretion. Hyaline bodies can also be found in 20–30 % of cases, but can be more subtle histologically than pale bodies, and their true frequency is not clear. Hyaline bodies are eosinophilic cytoplasmic inclusions of unclear etiology and composition (Fig. 8.5). Similar to pale bodies, there does not appear to be any strong spatial correlates and hyaline bodies appear to be somewhat randomly found in tumors. Pale bodies and hyaline bodies can be found in the same tumor, but are generally not found in the same areas within a tumor.

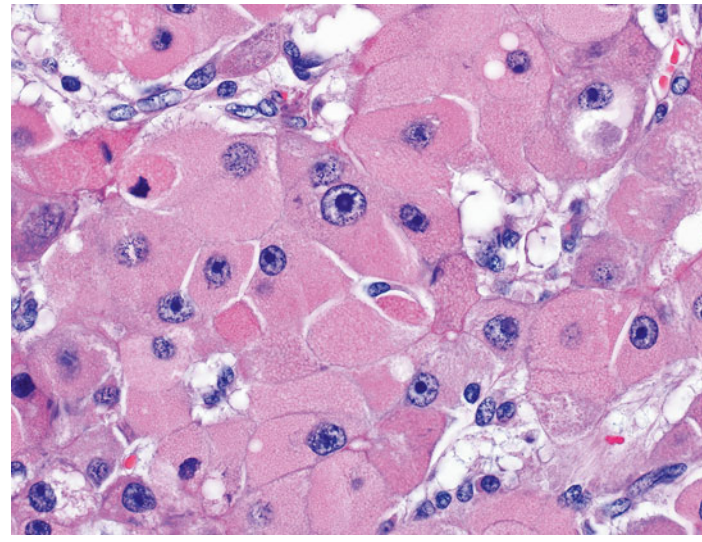

Fig. 8.2 Fibrolamellar carcinoma, cytoplasm. Fibrolamellar carcinomas have large eosinophilic tumor cells

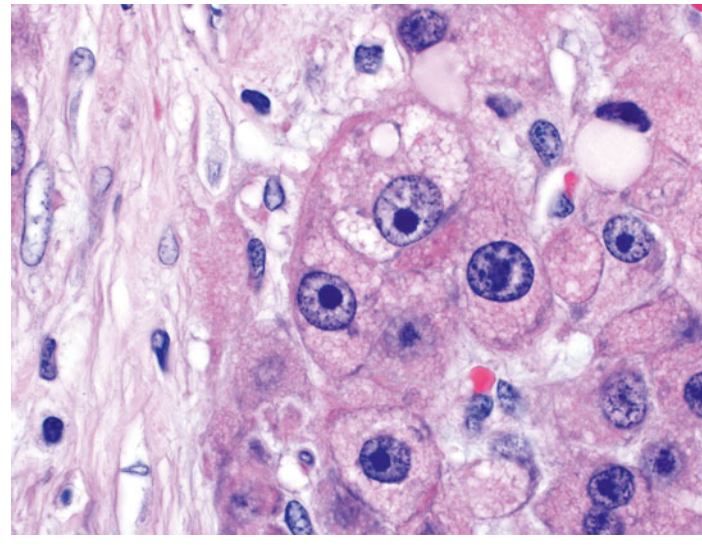

Fig. 8.3 Fibrolamellar carcinoma, nucleoli. Many of the tumor cells in fibrolamellar carcinoma have prominent nucleoli. The nucleoli can be either eosinophilic or basophilic, depending on the staining preparation

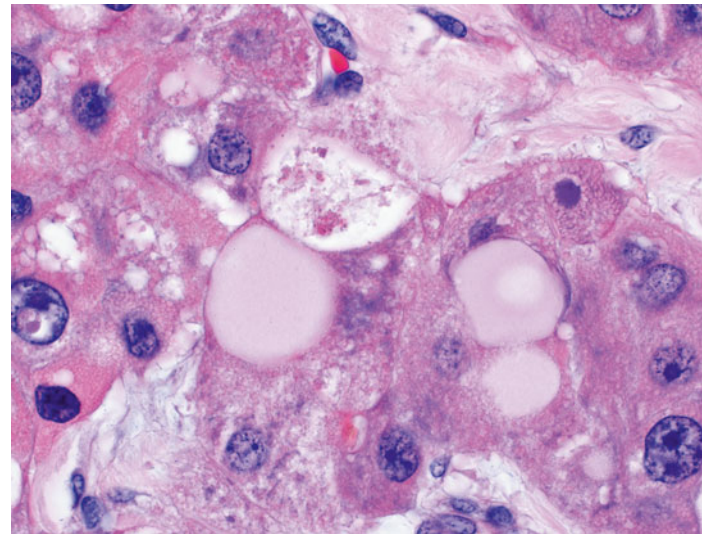

Fig. 8.4 Fibrolamellar carcinoma, pale bodies. Pale bodies are large amphophilic cytoplasmic inclusions. They are common in fibrolamellar carcinoma, but not specific

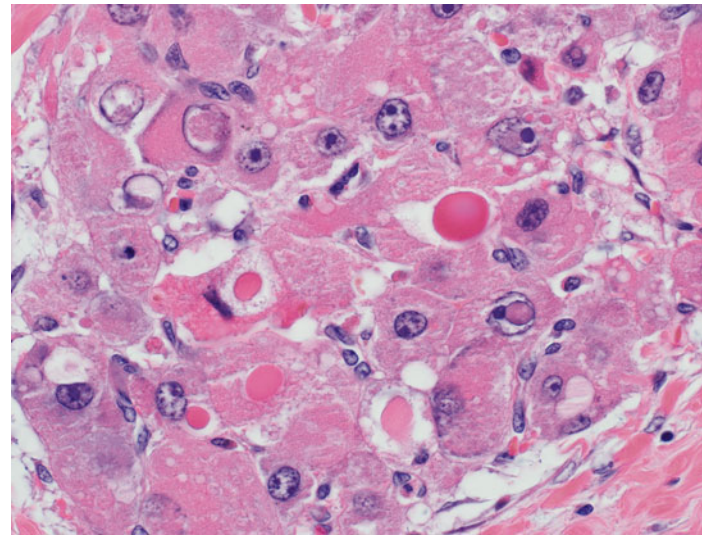

Fig. 8.5 Fibrolamellar carcinoma, hyaline bodies. Hyaline bodies can range considerably in size, but are dense eosinophilic inclusions, found mostly in the cell cytoplasm, but in some cases appear to be extracellular

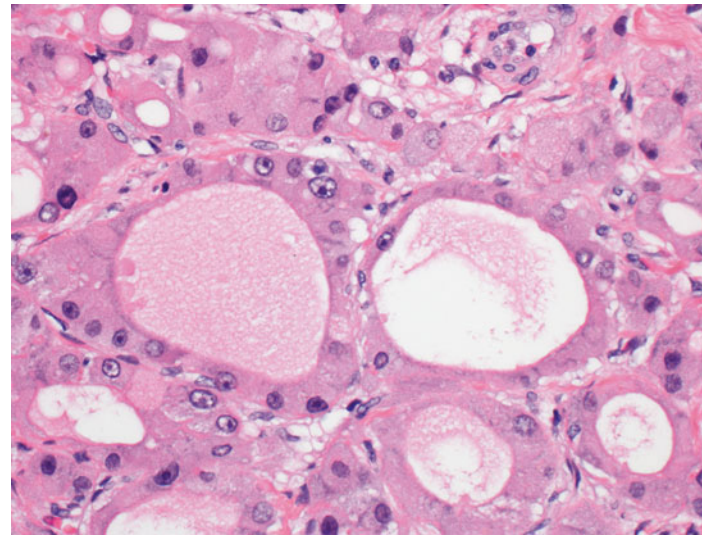

Fig. 8.6 Fibrolamellar carcinoma, pseudoglands. Sometimes, variation in size can be seen, with the smallest appearing to arise from dilated canalicular like structures

Approximately 10 % of fibrolamellar carcinomas can have gland-like structures, or pseudoglands (Fig. 8.6). The pseudoglands are ovoid cystic structures lined by tumor cells, have a wide range of sizes, and in some cases appear to arise from dilated canalicular like structures. The secretions within the pseudoglands are mucicarmine positive in about half the cases and are Alcian blue positive in most cases. Because of the mucicarmine positivity, some have suggested these are true glands and not pseudoglands, leading to diagnoses of combined fibrolamellar carcinoma and cholangiocarcinoma. Despite the mucicarmine staining, the data at this point suggests they should be classified as ordinary fibrolamellar carcinomas and not as combined tumors.

Metastases to lymph nodes and other organs typically look like the primary tumor, but in some cases metastatic disease can have a prominent pseudoglands component (Fig. 8.7). Since these pseudoglands can produce mucin, they can be mistaken for a cholangiocarcinoma. However, a history of fibrolamellar carcinoma is often present and will aid in the proper diagnosis. In other cases, immunostains can be used to differentiate fibrolamellar carcinoma from adenocarcinoma,

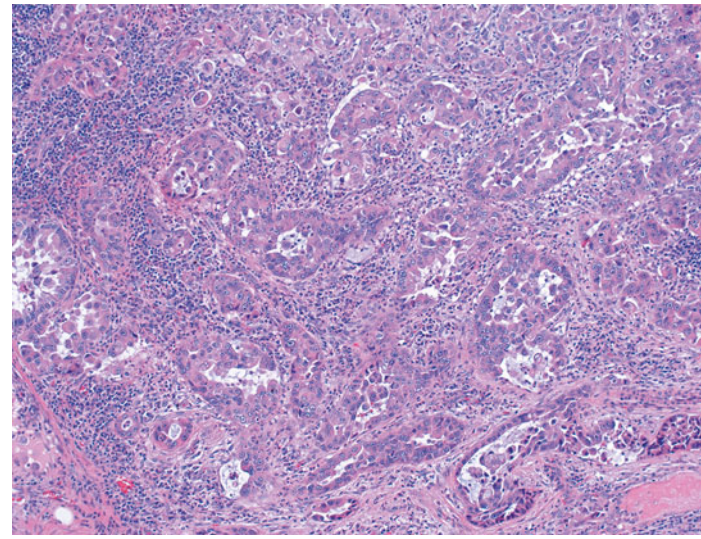

Fig. 8.7 Fibrolamellar carcinoma, metastatic to lymph node. The presence of pseudoglands in this case mimics cholangiocarcinoma

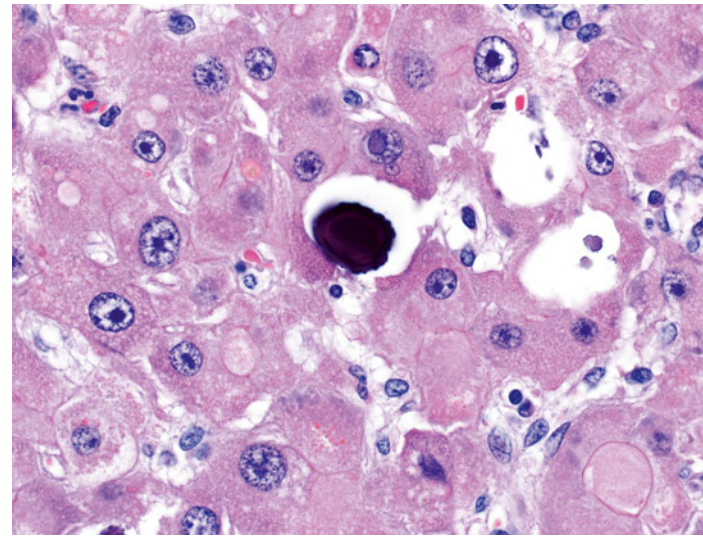

Fig. 8.8 Fibrolamellar carcinoma, microcalcifications. This microcalcification appears to represent a single dead, calcified cell

as fibrolamellar carcinomas will be positive for HepPar1, arginase, CK7, and CD68.

Other common tumor findings include microcalcifications. The calcifications can be dystrophic, featuring irregular deposits in areas of remote necrosis, fibrosis, or the walls of larger vessels. In other cases, the microcalcifications appear to represent calcification of single tumor cells (Fig. 8.8). Mild macrovesicular steatosis can occasionally be seen, even in cases without fat in the background liver (Fig. 8.9). Sometimes small pseudoglands can be similar in size to fat droplets and the two can appear similar at low power, but higher power examination readily separates the two findings. Tumor cholestasis is also common, with bile located within the cytoplasm of tumor cells or within canalicular like structures between tumor cells (Fig. 8.10). This frequent cholestasis is commonly associated with copper accumulation within tumor cells. However, copper accumulation is also found in ordinary hepatocellular carcinomas that are cholestatic and thus is not a specific finding. Finally, occasional benign isolated bile ducts can be found entrapped within the growing front of the tumor (Fig. 8.11).

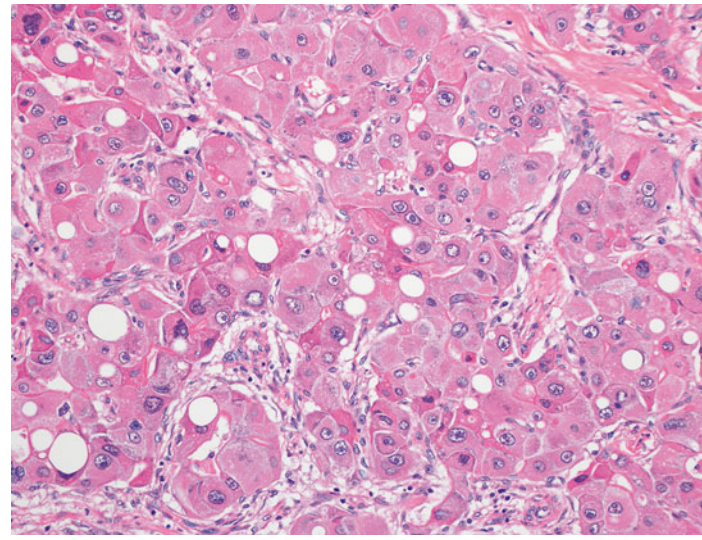

Fig. 8.9 Fibrolamellar carcinoma, fatty change. Mild macrovesicular steatosis is seen

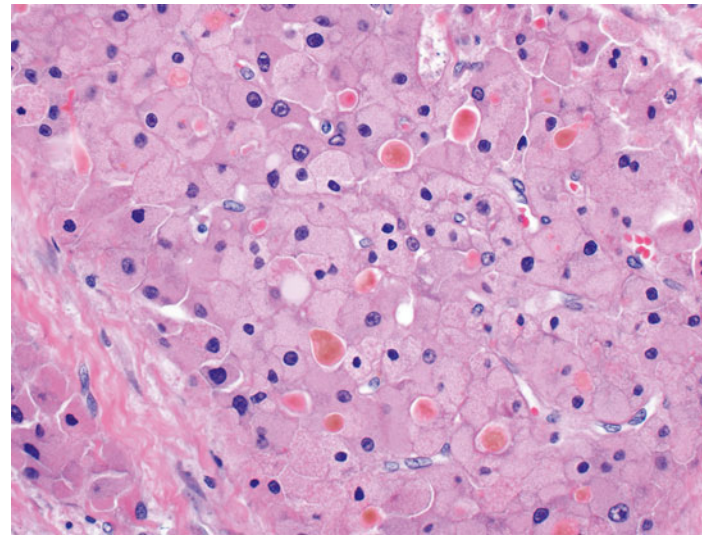

Fig. 8.10 Fibrolamellar carcinoma, cholestasis. Canalicular cholestasis is present in this tumor

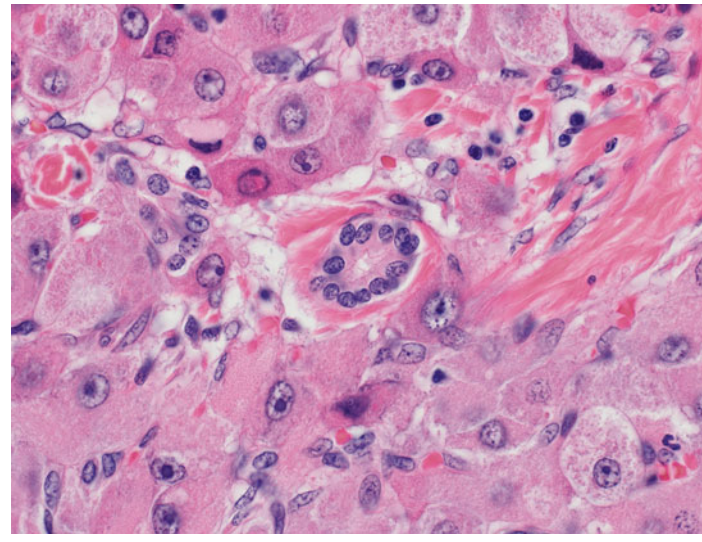

Fig. 8.11 Fibrolamellar carcinoma, entrapped bile duct. An entrapped benign bile duct is seen in the center of this image

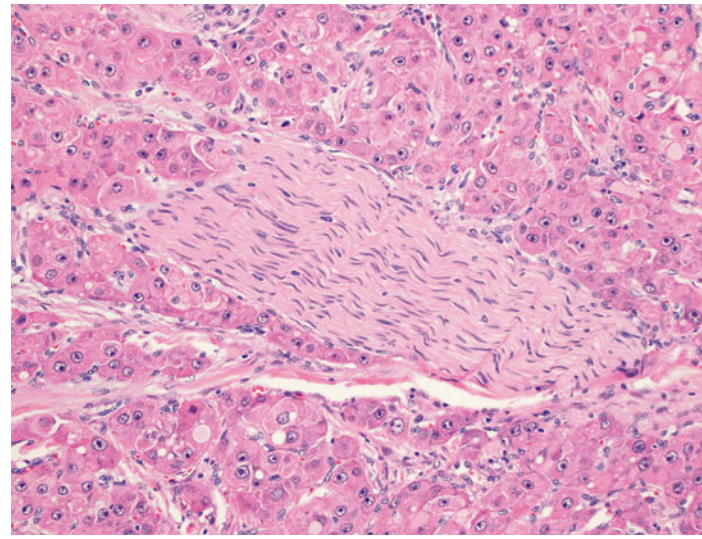

Fig. 8.12 Fibrolamellar carcinoma, perineural invasion. Perineural invasion is seen most commonly in tumors involving the liver hilum

Vascular invasion is present in 40–50 % of fibrolamellar carcinomas on histological analysis [8, 14, 16]. Vascular spread into the portal veins of nearby portal tracts is a common pattern of angiolymphatic invasion. The best place to identify vascular invasion is sections taken at the tumor–nontumor interface.

Perineural invasion can be seen when tumors involve the hilum of the liver (Fig. 8.12). In addition, tumor spread into the soft tissue of the liver hilum is a common finding and one that does not readily fit into current tumor staging systems. Nonetheless, both perineural invasion and invasion of the liver hilum soft tissue can be included in pathology reports and presumably indicate a worse prognosis.

8.8.1 Grading

Fibrolamellar carcinomas are histologically homogenous and lack the range of differentiation, from well differentiated to poorly differentiated, that is seen in ordinary hepatocellular carcinomas. Nonetheless, tumor templates demand a tumor grade; in that context, essentially all primary fibrolamellar carcinomas are moderately differentiated, as well as most recurrent and metastatic tumors. In fact, poorly differentiated cytology is sufficiently unusual for fibrolamellar carcinomas that any poorly differentiated tumor should be carefully examined before making a diagnosis of fibrolamellar carcinoma.

8.8.2 Intratumoral Fibrosis

Intratumoral fibrosis is a characteristic component of fibrolamellar carcinoma (Fig. 8.13) and is found in essentially all primary tumors and in many metastatic tumors. Nonetheless, the amount of intratumoral fibrosis varies and there often can be areas with a more solid growth pattern that lack intratumoral fibrosis, but retain the otherwise typical cytological findings (Fig. 8.14). These cases should be diagnosed as fibrolamellar carcinoma and not as a combined hepatocellular carcinoma and fibrolamellar carcinoma. Also of note, the fibrosis will be deposited in parallel, or "lamellar," bands in many cases of fibrolamellar carcinoma, but some cases will have more irregular patterns of intratumoral fibrosis. The fibrosis in about two third of cases coalesces into a larger central scar.

8.9 Immunohistochemistry

Fibrolamellar carcinomas show unequivocal hepatocellular differentiation by immunohistochemistry, but also show expression of proteins more

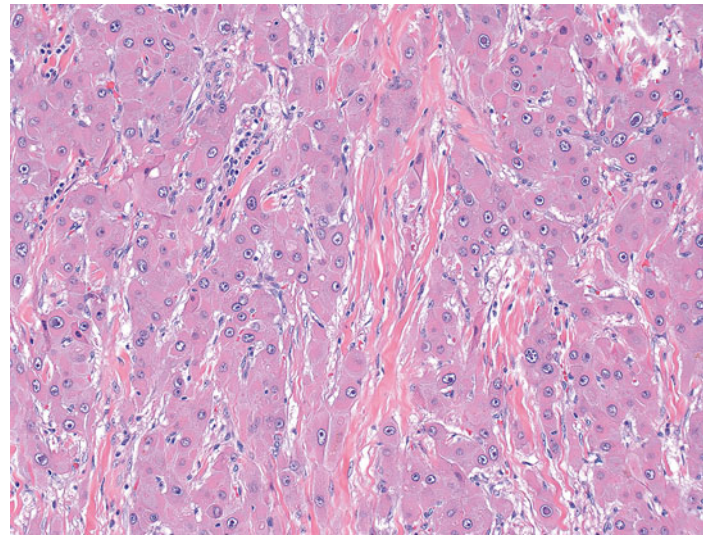

Fig. 8.13 Fibrolamellar carcinoma, lamellar intratumoral fibrosis

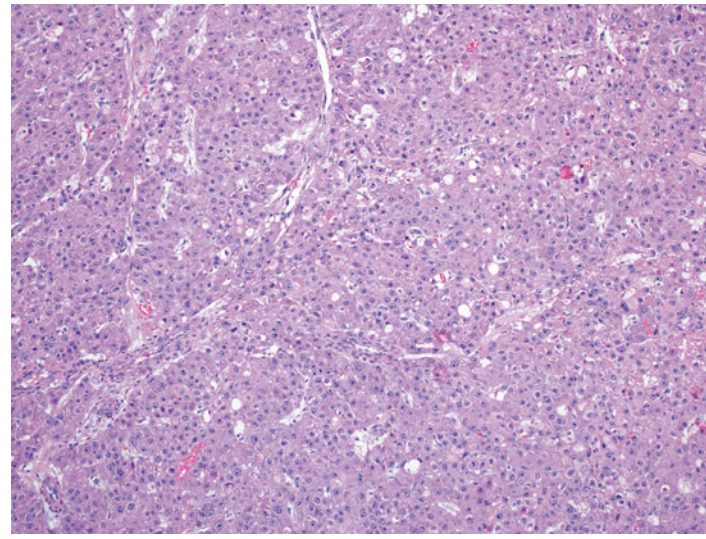

Fig. 8.14 Fibrolamellar carcinoma, solid growth. In this tumor, large areas had limited or no intratumoral fibrosis

commonly associated with biliary differentiation. The frequency of staining with commonly used diagnostic immunostains is shown in Table 8.4. Neuroendocrine features have been noted in some fibrolamellar carcinomas by several authors [24–26]. Most fibrolamellar carcinomas are negative for chromogranin and synaptophysin by immunohistochemistry [27, 28], but occasional cases are chromogranin positive [17].

8.10 Diagnostic Approach to Fibrolamellar Carcinoma

The H&E findings of large pink tumor cells, prominent nucleoli, and intratumoral fibrosis are very sensitive for suggesting the diagnosis of fibrolamellar carcinoma. Nonetheless, some hepatocellular carcinomas will have areas that

Table 8.4 Immunostains in fibrolamellar carcinoma

Immunostain	Frequency of positive staining (%)	Comment and representative reference
Markers of hepatic differentiation		
HepPar	100	[1, 27, 54]
Arginase 1	100	
Glypican-3	20–60	[27, 55]
Albumin-ISH	100	[27]
Polyclonal CEA	90	Canalicular pattern [27]
CD10	30	Canalicular pattern [27]
Keratin expression		
CK8 and 18	100	[56, 57]
CK7	100	[1, 26, 27, 55, 56, 58]
CAM5.2	100	[59]
CK19	0–25	[1, 27, 55–57]
Other stains		
EMA	100	[27]
CD34	100	Sinusoidal staining [55]
CD68	100	[29]
CD56	90	Most cases with focal staining [27]
EGFR	80–100	[57, 60, 61]
Ep-CAM (MOC-31)	20	[27]
Monoclonal CEA	10	[27]
CA19-9	0	[27]
AFP	0	[27, 28, 62]. The occasional reported cases with AFP positivity may be misdiagnosed

closely resemble fibrolamellar carcinoma, leading to misdiagnosis. Scirrhous hepatocellular carcinoma is the most common mimic, but other hepatocellular carcinomas can also have areas that mimic fibrolamellar carcinoma. In addition, a subset of neuroendocrine tumors can have tumor cytology and intratumoral fibrosis that is essentially identical to the H&E findings of fibrolamellar carcinoma and are important diagnostic pitfalls.

Because the H&E findings are sensitive but not entirely specific, the use of additional tests to confirm the H&E impression of fibrolamellar carcinoma is important, in particular if there are unusual clinical or histological findings. A useful approach is to stain cases that have consistent H&E findings with CK7 and CD68 (Figs. 8.15 and 8.16). Those cases that are negative for either CK7 or CD68 are most likely not fibrolamellar carcinoma and should not be diagnosed as fibrolamellar carcinoma without further molecular studies. Molecular detection of the DNA-JB1/PRACA transcript can also be used to confirm the H&E impression of fibrolamellar carcinoma. However, immunostains are more widely available and thus more practical for most medical centers. It is important to use the CK7 and CD68 immunostains together, as a small proportion of typical hepatocellular carcinomas can be CD68 positive [29], and a significant minority of typical hepatocellular carcinomas are CK7 positive.

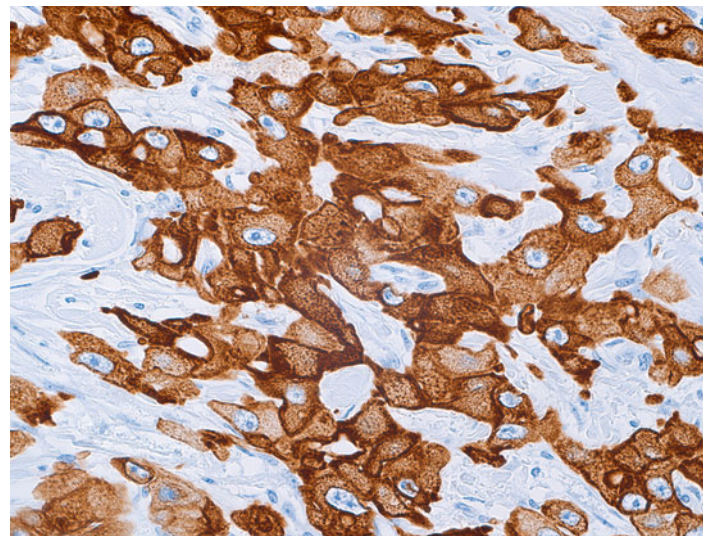

Fig. 8.15 Fibrolamellar carcinoma, CK7. The tumor cells are strongly positive

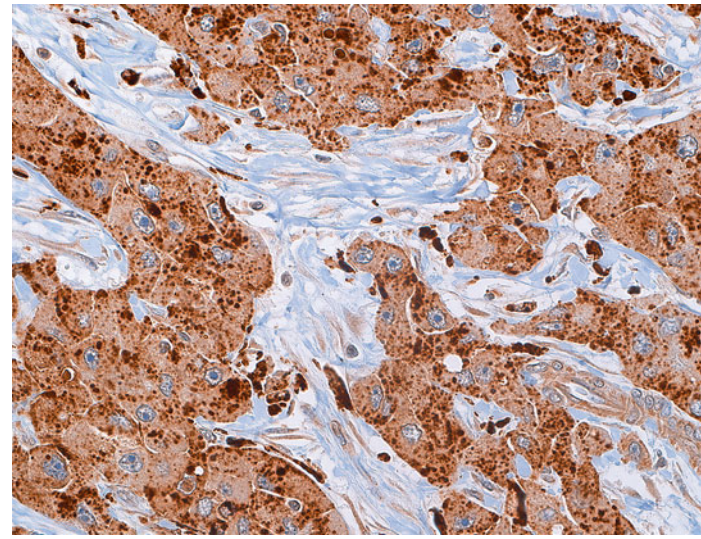

Fig. 8.16 Fibrolamellar carcinoma, CD68. The tumor cells are strongly positive

8.11 Diagnostic Pitfalls

The histological features of fibrolamellar carcinoma are distinctive and in many cases the H&E findings are classic. Nonetheless, there can be a variety of histological mimics that historically have made misclassification of fibrolamellar carcinoma a problem. These diagnostic pitfalls fall into several major themes:

1. *Uneven distribution of intratumoral fibrosis in fibrolamellar carcinoma*: Fibrolamellar carcinomas often have variation in the amount of intratumoral fibrosis, ranging from densely fibrotic areas with almost no residual tumor cells to areas with relatively inconspicuous or absent fibrosis. More classic morphology will be evident with sufficient tumor sampling.
2. *Intratumoral* (*sometimes striking*) *fibrosis also occurs in hepatocellular carcinomas*: Scirrhous hepatocellular carcinoma is a well-recognized mimic of fibrolamellar carcinoma because of the prominent intratumoral fibrosis, but other typical hepatocellular carcinomas can also have focal areas of prominent and sometimes lamellar fibrosis. In these cases, immunostains are an important tool to help confirm or refute a diagnosis of fibrolamellar carcinoma, especially on small tumor samples.
3. *Neither pale bodies nor eosinophilic bodies are specific for fibrolamellar carcinoma*: In addition, neither are necessary to make the diagnosis of fibrolamellar carcinoma.
4. *Fibrolamellar carcinomas with pseudoglands can mimic cholangiocarcinoma*: Identifying the typical cytology of fibrolamellar carcinoma is very helpful, as well as looking for other areas with more typical solid growth pattern of fibrolamellar carcinoma. Immunostains are an important tool to clarify the diagnosis in difficult cases: fibrolamellar carcinomas will be negative for CK19, but positive for HepPar, arginase, CD68, and CK7. In contrast, cholangiocarcinomas will typically be CK7 and CK19 positive, but negative for HepPar, arginase, and CD68. As discussed previously, mucin production in the context of fibrolamellar carcinoma should not lead to a diagnosis of cholangiocarcinoma or of mixed cholangiocarcinoma-fibrolamellar carcinoma.
5. *Young age is a typical but not a specific feature for fibrolamellar carcinoma*: In fact, most primary liver carcinomas in children and young adults are typical hepatocellular carcinomas, even in the absence of an underlying liver disease.
6. *Metastatic disease can mimic fibrolamellar carcinoma*: This pitfall is overall less commonly

encountered than the others because most individuals with metastatic disease to the liver tend to be older and outside the age range of most fibrolamellar carcinomas. However, metastatic neuroendocrine tumors and metastatic chromophobe renal cell carcinoma can both mimic many of the H&E findings of fibrolamellar carcinoma.

While not diagnostic pitfalls by H&E, there are several additional findings that should lead to careful consideration before making a diagnosis of fibrolamellar carcinoma. If these features are present, the diagnosis of fibrolamellar carcinoma is most likely incorrect. First, fibrolamellar carcinomas arising in individuals younger than 5 years of age or in individuals older than 60 years of age are very unusual and should lead to careful consideration of the diagnosis. Second, evidence for underlying chronic liver disease is atypical for fibrolamellar carcinoma. As mentioned above, however, sections taken within a centimeter of the tumor often show nonspecific inflammatory changes and fibrosis; evaluation for background liver disease should be done on sections taken far from the tumor. Mild fatty liver disease without fibrosis, however, can be seen in the background liver of some cases. Third, elevated serum AFP levels (more than 400 IU/L) or AFP positivity in the tumor cells by immunohistochemistry indicate that the tumor is most likely not fibrolamellar carcinoma. Finally, tumors that lack CD68 and CK7 immunostaining are unlikely to be fibrolamellar carcinoma.

8.12 Association with Other Liver Tumors

Fibrolamellar carcinoma does not share the same risk factors for ordinary hepatocellular carcinoma or hepatic adenoma, but rarely fibrolamellar carcinomas occur together with these tumors. The two lesions are typically clearly separate tumor nodules, even if they are adjacent. Rare cases have been reported where a resection for a typical hepatocellular carcinoma was followed by a recurrent tumor diagnosed as fibrolamellar carcinomas, or the opposite, where the recurrence following resection for fibrolamellar carcinoma was a typical hepatocellular carcinoma [30, 31]. Some studies have also reported combined hepatocellular carcinoma and fibrolamellar carcinoma in the same tumor [32–34]. It is currently unclear if this is a rare but true finding, or if some of these cases are misdiagnosed, and either represent ordinary fibrolamellar carcinomas with areas that lack intratumoral fibrosis or are typical hepatocellular carcinomas with focal areas that mimic fibrolamellar carcinoma. Specific studies addressing this issue and using modern methods to definitely classify fibrolamellar carcinomas (CK7, CD68, FISH for *DNA-JB* and *PRCACA1* fusion) have not been performed to date, but the weight of the data currently suggests that true combined fibrolamellar and typical hepatocellular carcinoma is very rare, if it occurs at all. Rare reports have also described hepatic adenoma in association with fibrolamellar carcinoma [7, 35, 36].

Also of note, early studies reported cases of fibrolamellar carcinomas associated with focal nodular hyperplasia [37–39]. It is now recognized that reactive nodular hyperplasia can develop around the rim of a small subset of fibrolamellar carcinomas, but the nodular hyperplasia is a reactive process and not a precursor lesion.

8.13 Key Molecular Findings

Essentially all fibrolamellar carcinomas have a fusion transcript between the *DNA-JB* gene and the *PRCACA1* gene. The fusion is caused by a micro-deletion on chromosome 19 [40]. *PRCACA1* is one of the catalytic units of a larger kinase called protein kinase A. Protein kinase A is a serine/threonine kinase that can phosphorylate a large number of cytoplasmic and nuclear proteins. The target of the kinase in fibrolamellar carcinoma is not known, but protein kinase A regulates many downstream targets, including those involved in glucose and lipid metabolism. Mutations in other subunits of protein kinase A are also associated with tumors in other organ systems (Table 8.5). For example, germ line mutations in one of the regulatory units of protein kinase A, called *PRKARA1*, are strongly associated with the

Table 8.5 Mutations in protein kinase A are associated with several tumor types

Gene	Location	Role in protein kinase A	Associated tumors/syndromes
PRKACA	19p13.12	Catalytic subunit	Adrenocortical adenoma with Cushing syndrome due to activating L206R point mutations [63, 64] or gene duplication [64]
			Fibrolamellar carcinoma through fusion gene with DNA-JB1
PRKACB	1p31.1	Catalytic subunit	Carney complex (growth hormone secreting pituitary adenomas, thyroid tumors, testicular tumors, and primary pigmented nodular adrenocortical disease) through gene duplication [65]
PRKAR1A	17q24.2	Regulatory subunit	Inactivating germ line mutations associated with Carney complex [66]
PRKACG	9q21.11	Catalytic subunit	Mouse models with haploinsufficiency develop hepatocellular carcinomas [67]
			Chimeric transcript with RET gene in thyroid carcinoma [68]
			Fusion gene with RARA in acute promyelocytic leukemia [69]
			Retroposon-derived gene of unclear function
PRKAR1B	7p22.3	Regulatory subunit	None to date
PRKAR2A	3p21.13	Regulatory subunit	None to date
PRKAR2B	7q22.3	Regulatory subunit	None to date

Carney syndrome. Interestingly, there has been a case report of fibrolamellar carcinoma occurring in a patient with the Carney syndrome [35].

In terms of other genetic findings, most fibrolamellar carcinomas are either aneuploid (about 50 % of cases) or tetraploid (about 50 % of cases) [41]. In addition to the ploidy changes, fibrolamellar carcinomas have several recurrent cytogenetic abnormalities (found in 20 % or more of cases), including gains of chromosome 1q and 8q and loss of chromosome 18q [42]. However, fibrolamellar carcinomas show less overall chromosomal changes than typical hepatocellular carcinoma. Fibrolamellar carcinomas do not have the common gene mutations found in typical hepatocellular carcinoma, including *CTNNB1*, *TP53*, *ARID1*, *ARID2*, and *PTEN*. Fibrolamellar carcinomas are also microsatellite stable by PCR analysis.

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