

Case Records of the Massachusetts General Hospital



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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Case 36-2000

PRESENTATION OF CASE

A 22-year-old man was admitted to the hospital because of a hepatic mass.

The patient had been well until three weeks earlier, when he injured the right side of his chest and shoulder, with subsequent pain that was ascribed to a rib contusion. The pain disappeared after nine days, at which point he consulted a physician for clearance to return to work. Examination showed numerous spider angiomas, which were of unknown duration.

For several years, the patient had had difficulty gaining weight, with intermittent night sweats. They had become much more severe during the three nights before the examination, saturating the bedclothes. During the two years before admission, his weight had dropped from 79.5 to 69.0 kg. During the year before admission, the patient had vomited in the morning about every third day and had received antibiotics for several episodes of pneumonia. During the month before admission, he had had pain in the right upper abdominal quadrant during sexual activity.

The patient smoked one pack of cigarettes daily. He had drunk alcohol in binges, consuming a liter of whiskey once or twice weekly, until recently, when drinking had provoked nausea and he had stopped ingesting alcohol. In past years, he had had multiple sexual partners, without protection, but was currently in a monogamous relationship. He had had a single seizure at the age of 15 years and took carbamazepine daily thereafter. He did not have a history of viral hepatitis, receipt of blood products, or intravenous drug abuse.

Shortly before admission, the patient was seen at another hospital. The temperature was 37°C, the pulse was 88, and the respirations were 20. The blood pressure was 115/80 mm Hg.

TABLE 1. BLOOD CHEMICAL AND ENZYME VALUES.

VARIABLE	SHORTLY BEFORE ADMISSION	ON ADMISSION
Urea nitrogen	Normal	Normal
Creatinine	Normal	Normal
Protein (g/dl)		7.2
Albumin	3.1	2.9
Globulin		4.3
Bilirubin		
Total	Normal	Normal
Conjugated	Normal	Normal
Electrolytes		Normal
Aspartate aminotransferase (U/liter)	111 (Normal range, 8–42)	41 (Normal range, 10–40)
Alanine aminotransferase (U/liter)	130 (Normal range, 5–50)	
Alkaline phosphatase (U/liter)	97 (Normal range, 33–100)	134 (Normal range, 45–115)
Lactate dehydrogenase (U/liter)		22 (Normal range, 110–210)

TABLE 2. RESULTS OF IMMUNOLOGIC TESTS PERFORMED SHORTLY BEFORE ADMISSION.

TEST	RESULT
Carcinoembryonic antigen	Normal
Alpha-fetoprotein	Normal
Antibodies against the human immunodeficiency virus	Negative
Antibodies against hepatitis viruses A, B, and C	Negative

On examination, the patient was slender. Numerous spider angiomas were scattered over the thorax. The lungs and heart were normal. The liver descended 5 cm below the right costal margin. No splenomegaly was detected.

The urine was normal. The results of other laboratory tests are shown in Tables 1 and 2. A computed tomographic (CT) scan of the abdomen, obtained after the oral and intravenous administration of contrast material, revealed diffuse enlargement of the liver and a mass, 17 by 16 by 12 cm, in the right lobe that showed heterogeneous enhancement (Fig. 1). The spleen was normal.



Figure 1. CT Scan Obtained after the Intravenous Administration of Contrast Material, Showing a Mass with Heterogeneous Enhancement in the Right Lobe of the Liver.

TABLE 3. HEMATOLOGIC LABORATORY VALUES ON ADMISSION.

VARIABLE	VALUE
Hematocrit (%)	43
White-cell count (per mm ³)	6,300
Platelet count (per mm ³)	349,000
Prothrombin time	Normal
Partial-thromboplastin time	Normal

The patient was referred to this hospital, where the findings on physical examination were unchanged.

Laboratory tests were performed (Tables 1 and 3). A thoracic CT scan, obtained after the intravenous administration of contrast material, showed no abnormalities except for the mass, which involved the entire right hepatic lobe.

A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

DR. JOHN F. REINUS*: May we review the radiographs?

DR. MICHAEL E. ZALIS: The CT scan of the abdomen (Fig. 1) shows a mass with heterogeneous enhancement in the right lobe of the liver.

DR. REINUS: The differential diagnosis of a mass in the liver is a common clinical challenge in this era of widely used cross-sectional body imaging. A lesion

is often found incidentally in an asymptomatic patient. The most important initial question in a case of this type is whether chronic liver disease or an extrahepatic disorder may have led to the development of a focal liver lesion, such as a regenerative nodule,¹ hepatocellular carcinoma, a metastatic mass, or an abscess.

Could this patient's spider angiomas and abnormal results of blood chemical tests signal the type of chronic liver damage that might predispose him to hepatocellular carcinoma? He had a history of drinking a liter of whiskey (approximately 317 g of alcohol) once or twice a week. The amount required for the development of cirrhosis varies greatly, but most patients with alcohol-induced liver disease have consumed between 80 and 160 g of alcohol a day for more than 10 years.^{2,3} This patient is only 22 years old, he probably did not drink every day, and he does not have the aminotransferase values associated with alcohol-related liver disease. Therefore, I do not think he has hepatocellular carcinoma due to alcoholic cirrhosis.

Hepatocellular carcinoma often complicates longstanding hepatitis C virus infection^{4,5} and may be diagnosed in a young person with chronic hepatitis B even before cirrhosis develops.⁵ Each of these viral diseases can cause abnormal results of blood chemical tests, but this patient does not have chronic viral hepatitis, at least not an identified type, since serologic tests were negative for both hepatitis B and C viruses.

Could this patient have a much less common type of chronic liver injury? Any type of cirrhosis can confer a predisposition to the development of hepatocellular carcinoma, although the potential for hepatocarcinogenesis varies considerably from one type of cirrhosis to another and is minimal with some types. Thus, in rare cases, autoimmune hepatitis, Wilson's disease, alpha₁-antitrypsin deficiency, or another, even less common disorder causing cirrhosis in a young person is complicated by hepatocellular carcinoma.

It is important to consider a diagnosis of autoimmune hepatitis in a young person with an abnormal serum alanine aminotransferase level, because many affected patients have a dramatic response to treatment. Patients with autoimmune hepatitis may present with cirrhosis, spider angiomas, and hyperglobulinemia; the last finding is especially common in persons with this disease. The patient under discussion had both hyperglobulinemia and spider angiomas. Type 1, or classic, autoimmune hepatitis is usually diagnosed in girls and premenopausal women, however, and type 2 autoimmune hepatitis is almost always diagnosed in girls under 15 years of age. Cirrhosis due to autoimmune hepatitis with secondary hepatocellular carcinoma in this 22-year-old man is therefore very unlikely. The results of antinuclear and anti-smooth-muscle antibody tests and other tests for autoimmune hepatitis are not reported.

Patients with Wilson's disease have hepatic copper accumulation and secondary chronic liver injury due

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to mutations of the *ATP7B* gene that result in decreased biliary copper excretion. Wilson's disease is often asymptomatic, and the diagnosis is frequently made when serum aminotransferase abnormalities are found incidentally in a young person. A person between 3 and 40 years of age who has unexplainedly abnormal results of blood chemical tests should be screened for Wilson's disease by measurement of the serum ceruloplasmin concentration and ophthalmologic examination. The results of these studies are not reported in this case, but hepatocellular carcinoma is very unlikely in a young person who has cirrhosis due to Wilson's disease and no other signs or symptoms of that disorder, such as central nervous system complications.

This patient's history of several episodes of pneumonia during the year before admission is unusual for a 22-year-old, despite the fact that he smoked. Could he have had alpha₁-antitrypsin deficiency or cystic fibrosis, which are inherited diseases with pulmonary and hepatic manifestations? Cystic fibrosis is the most common lethal genetic disorder in whites. Although the diagnosis is usually made during the first year of life, up to 25 percent of affected persons present after the age of five years. Infections of the respiratory tract may be the first sign of the disorder in young adults. Between 1 and 5 percent of persons with cystic fibrosis have clinical manifestations of liver disease due to ductular obstruction by inspissated bile, with secondary biliary cirrhosis, which is characterized by portal hypertension and abnormal results of blood chemical tests, especially those reflecting the presence of cholestasis.⁶ In rare cases, liver disease is the only manifestation of cystic fibrosis.⁷ Sclerosing cholangitis and cholangiocarcinoma have been described in patients with this disorder^{8,9}; hepatocellular carcinoma, however, has not been reported.

Could the liver mass in this patient be cholangiocarcinoma? In patients with underlying bile-duct disease such as sclerosing cholangitis, cholangiocarcinoma usually appears at the lower end of the common bile duct or within the major bile ducts, near their bifurcations. If the tumor develops within the hepatic parenchyma, the location of the lesion in this case, it usually occurs in the absence of chronic liver disease, although it may be associated with Oriental cholangiohepatitis, cystic disease, liver-fluke infestation, or exposure to thorium dioxide, none of which are pertinent to this case. The average age of patients with cholangiocarcinoma at presentation ranges from 50 to 60 years. The serum carcinoembryonic antigen level is elevated in a minority of cases, but it is normal in this case.¹⁰ Thus, it is unlikely that this patient's lesion is a new central cholangiocarcinoma.

Patients with alpha₁-antitrypsin deficiency may also have asymptomatic, unexplained serum aminotransferase elevations and a history of respiratory disease. Two percent of patients with alpha₁-antitrypsin defi-

ciency who are 20 to 40 years old have liver disease, and cirrhosis is found in over 12 percent of all affected patients at autopsy. Hepatocellular carcinoma and, in rare cases, cholangiocarcinoma may develop.¹¹ Measurement of the serum alpha₁-antitrypsin level should be part of the evaluation of a young adult with high serum aminotransferase levels after other, more likely explanations have been ruled out. The alpha₁-antitrypsin level is not reported in this case, but a malignant liver tumor would be unlikely in a young person with cirrhosis due to alpha₁-antitrypsin deficiency and no other manifestations of the disorder — for example, parenchymal lung disease.

Could this patient's disease be due to treatment with carbamazepine for seven years? This drug causes abnormal results of blood chemical tests but has not been reported to cause cirrhosis. Treatment with carbamazepine can cause pseudolymphoma, with fever, lymphadenopathy, pneumonitis, a morbilliform skin eruption, and hepatitis, but it does not result in a large hepatic mass.¹² Thus, I do not think this patient's disease is iatrogenic.

Although 90 percent of patients with primary liver cancer have hepatocellular carcinoma, the common type is unlikely in this case. Hepatocellular carcinoma rarely develops in a person as young as this patient or in the absence of cirrhosis, unless the patient has chronic hepatitis B. Moreover, when cirrhosis is present, hepatocellular carcinoma is usually not the first clinical manifestation of liver disease. The common type of hepatocellular carcinoma is characterized by a shrunken, nodular liver surrounding the mass and other changes suggestive of cirrhosis on abdominal CT scans — findings that are absent in this case. Similarly, the serum alpha-fetoprotein level is abnormal in more than 70 percent of patients with the common type of hepatocellular carcinoma, but the value is normal in this case.

If this patient does not have chronic hepatitis and cirrhosis, why are the serum alanine aminotransferase and albumin levels abnormal, and why does he have spider angiomas? Spider angiomas are probably due to a relative excess of estrogen in persons with acute or chronic liver disease and in pregnant women.¹³ They have also been reported in association with elevated serum estrogen levels and as paraneoplastic manifestations of cancers, disappearing after the tumor has been resected.¹⁴ The spider angiomas in this patient are not diagnostic of chronic liver disease, but they may have developed in conjunction with the liver lesion, a possibility that suggests the malignant nature of the mass. The abnormal serum alanine aminotransferase level shortly before admission may have resulted from trauma to the large mass, with secondary blood clotting and tissue necrosis. I believe the abdominal CT scan shows signs of focal necrosis within the liver mass, just beneath the ribs on the right side. Since the serum aspartate aminotransferase level was almost

within the normal range when the patient was evaluated on admission, and I assume the same was true for the serum alanine aminotransferase level by then, the levels were probably not chronically elevated, as they would have been if he had had long-standing liver disease of most types. The serum albumin concentration is not a reliable test of liver function, and the value is typically low in a variety of diseases.

Is there any evidence that this patient had a primary extrahepatic illness that caused a liver mass? Night sweats and weight loss are common symptoms of extrahepatic diseases that are often associated with liver lesions, such as tumors (especially lymphomas) and infections. These findings occur in 25 to 30 percent of persons with Hodgkin's disease, which is common in males who are 15 to 30 years old, but this patient had no evidence of lymphadenopathy or splenomegaly.

Could the liver be the primary site of Hodgkin's disease in this case? Hepatic Hodgkin's disease usually has an infiltrative pattern, with multiple, or occasionally single, lesions that are well defined, large, and uniformly low in density, unlike the lesion in this case. The findings in this case are also not consistent with the diagnosis of primary hepatic non-Hodgkin's lymphoma, an uncommon disorder that is almost always aggressive, rarely causing symptoms of over two years' duration, and that is usually manifested as multiple low-density lesions on CT scans.

Hepatic metastases are approximately 30 times more frequent than primary liver cancer. Gastric, colonic, and pancreatic adenocarcinomas account for over 40 percent of cases of hepatic metastases, but none of the findings in this case suggest the presence of one of these tumors. Nor is there evidence of metastatic melanoma, which often metastasizes to the liver but almost always has a rapid clinical course once the liver is involved.

Could this patient have had an amebic liver abscess? Such an abscess typically develops in the right hepatic lobe of a young adult (median age, 29 years) and appears as a well-defined lesion on imaging studies.¹⁵ This patient did not report diarrhea, which would have suggested the presence of amebic colitis, but fewer than half the patients with an amebic liver abscess report antecedent diarrhea or have amebic trophozoites or cysts in their stools. Infection can be diagnosed serologically, but serum IgG antibody to *Entamoeba histolytica* was not measured in this case. Patients with an amebic liver abscess do not have spider angiomas, however, and their abdominal CT scans typically show well-defined, round, low-density lesions, unlike the lesion in this patient.

A pyogenic liver abscess may be primary, or it may be secondary to bacterial superinfection of an amebic liver abscess or another liver lesion. When this patient injured the right side of his chest, did a hemangioma or other primary hepatic lesion become infected? I doubt it. A pyogenic liver abscess is not a likely diag-

nosis, because of the duration of the patient's symptoms, the presence of spider angiomas, the absence of a history of clinically significant fever and rigors, and the absence of evidence of a source of infection on the abdominal CT scan. Rare nonpyogenic infectious causes of focal liver lesions include parasites other than *E. histolytica*, fungi,¹⁶ and *Mycobacterium tuberculosis*.¹⁷ A test for antibody against the human immunodeficiency virus was negative in this case, ruling out immunosuppression due to the acquired immunodeficiency syndrome and hepatic lesions such as Kaposi's sarcoma or peliosis hepatis.

Having ruled out chronic liver diseases and systemic diseases, I must consider new masses that arise in an otherwise normal liver. The most common primary hepatic lesions, in decreasing order of frequency, are hemangiomas, cysts, focal nodular hyperplasia, and hepatic adenomas. Small benign cysts and hemangiomas account for most lesions seen on imaging and at autopsy.^{18,19} A cavernous hemangioma, which is more common in men than in women, is generally asymptomatic, although it occasionally causes abdominal pain, and it is not associated with the constellation of findings in this patient. The lesion is usually easy to identify on imaging, but the features may be atypical, prompting a more detailed investigation. Similarly, most hepatic cysts are asymptomatic and are easily diagnosed on the basis of imaging studies.

Focal nodular hyperplasia, the third most common benign hepatic lesion, is usually detected incidentally in an asymptomatic person. The lesion is typically less than 5 cm in diameter, solitary, unencapsulated but well circumscribed, and homogeneous, with a central scar that contains an arteriovenous malformation. Occasionally, large lesions have caused abdominal discomfort and have been mistaken on imaging for malignant tumors, especially fibrolamellar carcinoma. Hepatic adenoma occurs almost exclusively in young women, particularly those taking oral contraceptives. It also occurs in patients with tyrosinemia, type I or IV glycogen storage disease, or familial diabetes mellitus and in those who use anabolic steroids. None of these predisposing factors are present in this case. Hepatic adenomas may become large enough to cause abdominal discomfort, but their clinical importance lies in their potential for rupture and malignant change. Intraleisional hemorrhage may result in a heterogeneous appearance on CT scanning that is suggestive of cancer.

A diagnosis that can explain most of the clinical features of this case is fibrolamellar carcinoma,²⁰ a slow-growing cancer that typically occurs in young adults; the median age of affected persons is 25 years.²¹ Although usually considered a variant of hepatocellular carcinoma, fibrolamellar carcinoma may be a separate entity.^{20,22} Unlike typical hepatocellular carcinoma, it has no known connection with cirrhosis or chronic inflammatory liver disease and is usually not associated with an elevated serum alpha-fetoprotein level. The se-

rum des-carboxy prothrombin level is abnormal in nearly all cases of fibrolamellar carcinoma.²³ Because the tumor generally has an indolent course, there may be a protracted prodromal period characterized by nonspecific symptoms, including abdominal discomfort, weight loss, and night sweats. Jaundice is uncommon. On CT scans, fibrolamellar carcinoma is heterogeneous, with a hypodense, occasionally calcified scar. Marked enhancement is seen after the administration of contrast material, and this finding may result in a misdiagnosis of focal nodular hyperplasia.

In addition to focal nodular hyperplasia, the differential diagnosis of fibrolamellar carcinoma includes typical hepatocellular carcinoma, adenosquamous carcinoma of the gallbladder with extension into the liver, and metastatic tumors associated with fibrosis — for example, breast cancer, islet-cell tumor, carcinoid, and cholangiocarcinoma, all of which are ruled out in this case by the clinical findings. The diagnosis of fibrolamellar carcinoma can be difficult to establish by examining a needle-biopsy specimen, and several passes or an open-wedge biopsy may be necessary to obtain adequate tissue. Complete surgical resection is curative in 50 to 75 percent of cases.²⁴ If partial hepatectomy is not feasible because of the size of the tumor or because it extends into adjacent organs, orthotopic liver transplantation is required. The lesion in this man is very large, but it appears to be resectable, since the remaining liver tissue is not cirrhotic and the left portal vein appears to be patent. I would attempt to establish the diagnosis by performing a percutaneous liver biopsy.

DR. PAUL P. BERGERON: As this patient's primary physician, I had examined him for shoulder pain and noticed the hepatic mass and cutaneous manifestations of hepatic disease. My impression was that he had a hepatocellular disorder such as hepatocellular carcinoma or lymphoma.

CLINICAL DIAGNOSIS

Hepatocellular carcinoma or lymphoma.

DR. JOHN F. REINUS'S DIAGNOSIS

Hepatocellular carcinoma, fibrolamellar variant.

PATHOLOGICAL DISCUSSION

DR. KENNETH TANABE: No source of metastatic disease was found, and I therefore performed a laparotomy. A percutaneous needle biopsy would not have revealed any findings that might have contraindicated an exploration for potential resection.

Intraoperative ultrasonographic examination of the liver showed the relation between the mass and major vessels. The left hepatic lobe appeared to be normal, and there was no evidence of extrahepatic cancer. I therefore resected the lesion, including segments 4 through 8.

DR. RHONDA K. YANISS: The specimen contained a tan–yellow, bile-stained mass, 17 cm in diameter, that was well circumscribed but unencapsulated, with a scalloped margin and a very small, stellate scar, 2.3 cm long, at the center. Microscopical examination revealed that the mass consisted predominantly of sheets of large polygonal cells with well-defined borders, abundant granular eosinophilic cytoplasm, and large, atypical nuclei with prominent, single, central nucleoli; intracanalicular and intracellular deposits of bile were present (Fig. 2). Many of the cells contained intracytoplasmic hyaline globules and faintly eosinophilic, pale bodies (Fig. 3). In some areas, there were broad zones of necrosis surrounded by inflammatory cells and nests of neoplastic cells within a desmoplastic stroma. We interpreted these features to be diagnostic of hepatocellular carcinoma that was moderately to well differentiated. In a minor portion of the tumor, however, nodules and nests of tumor cells were separated by dense, fibrous septa (Fig. 4). This part of the tumor was characteristic of so-called fibrolamellar hepatocellular carcinoma. Therefore, we classified the tumor as hepatocellular carcinoma, moderately to well differentiated, with a focal fibrolamellar pattern.

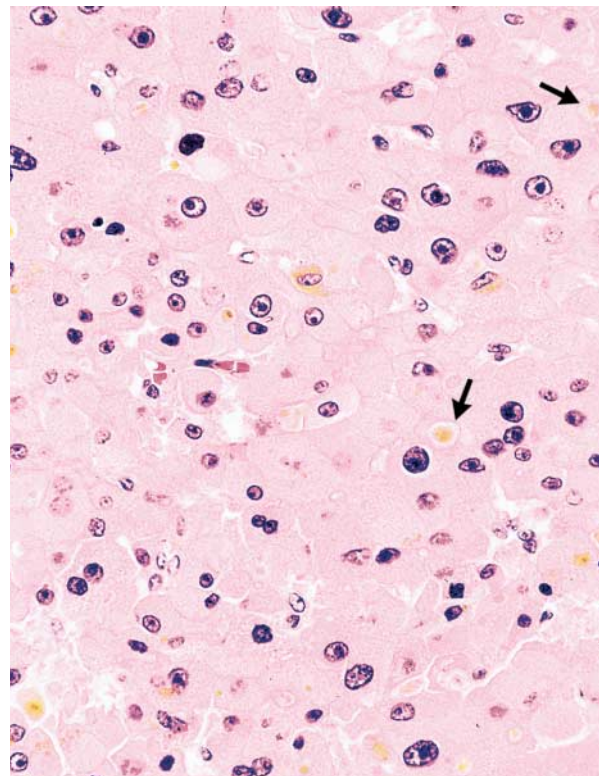


Figure 2. Large Tumor Cells with Abundant Pink, Granular Cytoplasm, Distinct Cell Membranes, and Nuclei Containing Single, Prominent Central Nucleoli (Hematoxylin and Eosin, $\times 350$). Intracanalicular deposits of bile (arrows) are present, as well as intracellular deposits.

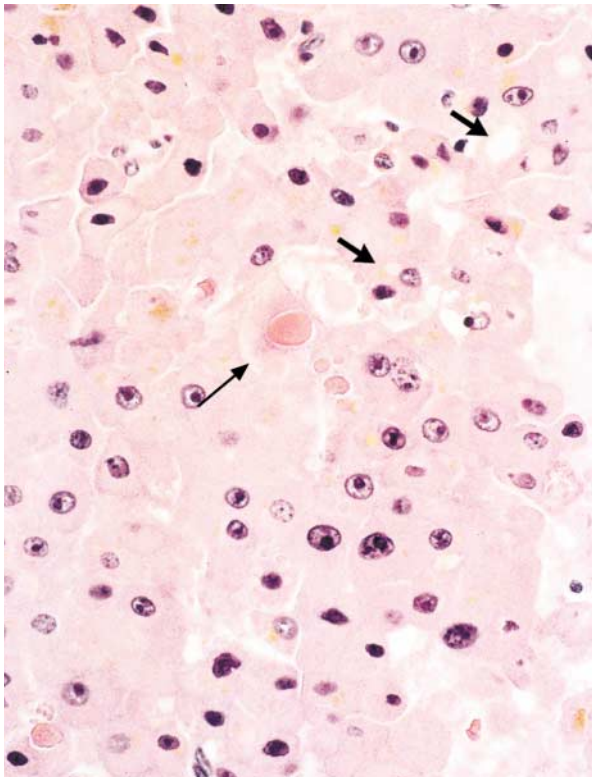


Figure 3. Eosinophilic Hyaline Globules (Long Arrow) and Faintly Eosinophilic, Pale Bodies (Short Arrows) in the Cytoplasm of Tumor Cells (Hematoxylin and Eosin, $\times 350$).

Until very recently, hepatocellular carcinoma with predominantly fibrolamellar features has generally been viewed as a distinctive entity and designated as fibrolamellar hepatocellular carcinoma. Many of the clinical and pathological characteristics of this type of tumor have been noted by Dr. Reinus. It is said to account for only 1 to 2 percent of all cases of hepatocellular carcinoma but for as many as 40 percent of those in patients 35 years of age or younger.²² Fibrolamellar hepatocellular carcinoma occurs in approximately equal numbers of males and females, whereas typical hepatocellular carcinoma occurs predominantly in men over the age of 35.

Fibrolamellar hepatocellular carcinoma typically appears as a solitary, well-circumscribed nodule with a prominent central, stellate scar. The characteristic histologic findings are cords and trabeculae of large hepatic cells in a dense, collagenous stroma composed of lamellae of collagen between nests of tumor cells (Fig. 4). Other features include eosinophilic hyaline globules, which are composed of accumulations of α_1 -antitrypsin; pale bodies, which are composed of fibrinogen; and intranuclear cytoplasmic pseudo-inclusions.^{20,22} In addition to the laboratory features

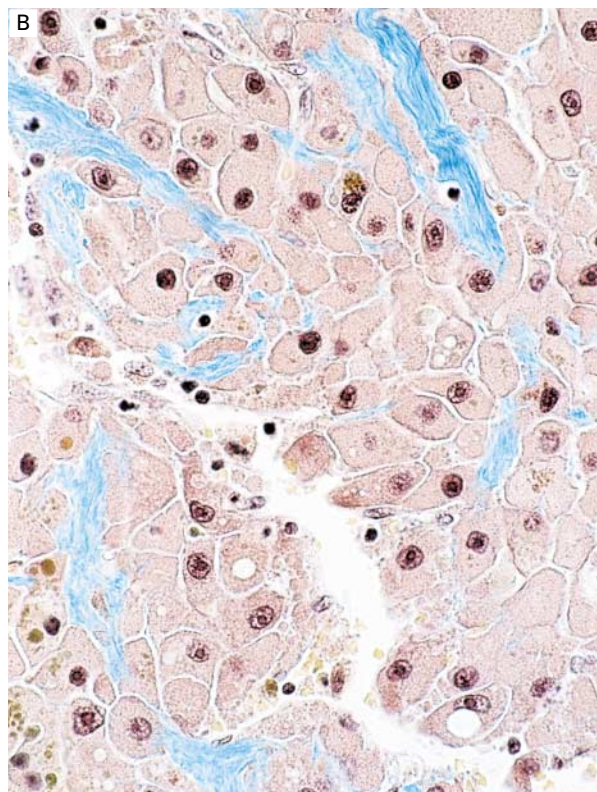
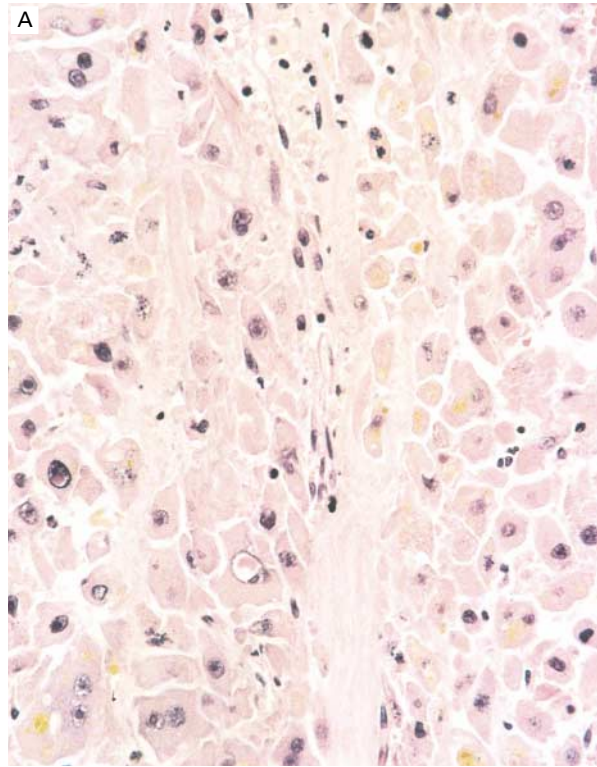


Figure 4. Dense, Fibrous Lamellae between Aggregates of Tumor Cells (Panel A, Hematoxylin and Eosin; Panel B, Masson Trichrome Stain, $\times 350$).

mentioned by Dr. Reinus, the tumor has been reported to be associated with an elevated plasma level of vitamin B₁₂, an unsaturated vitamin B₁₂-binding capacity, and an elevated level of neurotensin.²⁵⁻²⁷

The prognosis for patients with fibrolamellar hepatocellular carcinoma is better than that for patients with typical hepatocellular carcinoma. The former tumor is resectable in 50 to 75 percent of cases, whereas the latter tumor is resectable in only 17 percent of cases. Patients with fibrolamellar hepatocellular carcinoma have a survival rate of 34 percent at five years, and the rate rises to 63 percent if the tumor has been completely resected.²⁰ Moreover, among patients whose tumors either are not resectable or have metastasized at the time of diagnosis, the mean survival rate is 32 months for those with fibrolamellar hepatocellular carcinoma but only 6 months for those with typical hepatocellular carcinoma.²⁸ Patients with fibrolamellar hepatocellular carcinoma that is not resectable may be treated by liver transplantation, but recurrences develop in about half of them within 40 months after receipt of the transplant.²⁴

Recent findings suggest that fibrolamellar hepatocellular carcinoma may not be a distinct entity, but only a form of well-differentiated hepatocellular carcinoma, and that the relatively good prognosis for patients with this type of tumor stems from its resectability in most cases, its tendency to occur in young patients, and the absence of associated liver disease. A study of low-grade hepatocellular carcinoma without fibrolamellar features in young patients who did not have cirrhosis showed that the prognosis for these patients was similar to that for patients with fibrolamellar hepatocellular carcinoma.²⁹ In a recent study of 15 otherwise unselected cases of hepatocellular carcinoma in patients under 45 years of age, a colleague and I identified a fibrolamellar pattern in 8 tumors; 7 were well differentiated, and 1 was moderately to well differentiated.³⁰ The fibrolamellar component occupied less than half the lesion in five tumors and more than half in three, two of which were entirely fibrolamellar. Two of the patients who had tumors with a fibrolamellar component also had cirrhosis related to either alcohol abuse or hepatotropic viral infection. These findings suggest that fibrolamellar hepatocellular carcinoma is not a distinct entity but a morphologic variant of hepatocellular carcinoma with a prognosis similar to that of low-grade typical hepatocellular carcinoma.

DR. REINUS: Did the spider angiomas in the patient under discussion disappear after the tumor had been resected?

DR. TANABE: When I saw the patient 14 months after the resection, they were still present, although there was no evidence of recurrent cancer.

DR. REINUS: Spider angiomas have been described as a paraneoplastic manifestation, with resolution after resection of the tumor.¹⁴ Their presence in patients

with liver diseases is probably a complex phenomenon related to a preponderance of estrogens over androgens, which probably depends on the amount of gonadotropin-binding protein that is produced, or at least the amount released from the liver into the blood. In patients with non-neoplastic diseases, particularly alcoholic liver disease, a number of other effects on the reproductive organs may contribute to an excess of estrogen.

ANATOMICAL DIAGNOSIS

Hepatocellular carcinoma, with a focal fibrolamellar pattern.

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35-MILLIMETER SLIDES FOR THE CASE RECORDS

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