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Fibrolamellar Hepatocellular Carcinoma

Case Reports and a Review of the Literature

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Fibrolamellar hepatocellular carcinoma is an uncommon malignancy seen in young adults without underlying liver disease. Physical signs are minimal and laboratory values are noncontributory. Diagnosis is suggested by clinical history, supported by radiographic studies, and confirmed by histologic examination. Individuals with fibrolamellar carcinoma generally have a greater survival than those with hepatocellular carcinoma. Although most patients with fibrolamellar carcinoma undergo curative surgery, two of the three patients we report had inoperable tumors.

KEY WORDS: fibrolamellar hepatocellular carcinoma.

In 1956 Hugh Edmondson remarked on the atypical histological features in hepatocellular carcinoma (HCC) resected from a 14-year-old girl (1). The stroma was profuse, and the tumor cells bore "striking" similarities to normal hepatocytes. He later reported the absence of recurrence almost five years after resection (2). Since his original description, this histologic variant of HCC has been confirmed and referred to as either hepatocellular carcinoma with laminar fibrosis, hepatocellular carcinoma with polygonal cell type and fibrous stroma, oncocytic hepatocellular tumor, or eosinophilic hepatocellular carcinoma with lamellar fibrosis (3–6). The term that is currently agreed upon is fibrolamellar hepatocellular carcinoma (FLHCC). The clinical impact of this variant was not fully appreciated until 1980 when both Craig et al and Berman et al separately showed a prolonged survival in patients diagnosed with FLHCC (5, 7). They also showed patients with FLHCC differed from those with HCC in terms of age at presentation, absence of underlying liver disease, and tumor markers.

Since Edmondson's initial description, there have been less than 150 cases of FLHCC reported in the medical literature written in English. Unfortunately, data regarding its clinical presentation, treatment, and outcome are limited. We were nevertheless able to identify 32 United States-based patients from case reports and case series with sufficient information to describe its epidemiology, clinical presentation, disease course, and therapy (4, 8–21). In the context of the these 32 cases, we will discuss three additional patients with FLHCC who presented with large, bulky tumors.

MATERIALS AND METHODS

Patient 1. A 31-year-old Hispanic woman, who had been in her usual state of health until August of 1993, developed severe intermittent right upper quadrant abdominal pain. By June of 1994, she had lost 15 kg in weight. She denied jaundice, abdominal distension, melena, or change of bowel habits. She also denied receiving blood transfusions or using medications or illicit drugs. There was no personal or family history of liver disease.

On physical examination an enlarged liver measuring 16 cm and palpable 8 cm below the costal margin was appreciated. The rest of her examination was normal.

Her hemoglobin was 9.3 g/dl and her platelet count was 550,000/mm^3. Aspartate (AST) and alanine (ALT) amin-

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otransferases were 42 units/liter and 20 units/liter (normal, 10–45 units/liter), respectively. Her alkaline phosphatase (ALP) was 72 units/liter (normal, 30–130 units/liter), her total bilirubin 2.6 mg/dl (normal, less than 1.2 mg/dl), and albumin 3.2 mg/dl (normal, 3.3–5.0 mg/dl). Alpha-fetoprotein (AFP) was undetectable. Hepatitis B surface antigen, surface antibody, and core antibody were negative. Hepatitis C antibody was also negative. An abdominal ultrasound (US) and computed tomography (CT) scan revealed a 15-cm mass in the right liver lobe. A percutaneous liver biopsy revealed areas of lamellar fibrosis consistent with FLHCC.

In August of 1994, the patient underwent an exploratory laparotomy. The tumor was confined to the right lobe with no evidence of metastasis. A well-circumscribed mass measuring 23 cm × 20 cm × 8 cm was resected, as were regional lymph nodes. The mass was found to be consistent with FLHCC, and the lymph nodes showed no evidence of malignancy. The patient is alive and well 18 months following resection.

Patient 2. A 23-year-old Portuguese man was in good health until March of 1994 when he developed exertional, progressive right upper quadrant abdominal pain. The patient denied subjective fever, chills, or night sweats. He also denied blood transfusions and illicit drug usage. There was no personal or family history of liver disease.

His physical examination in May of 1994 was remarkable for an enlarged liver measuring 18 cm. The liver edge was palpable 8 cm below the costal margin, and was firm and tender to palpation.

Hematologic blood values were normal. His AST, ALT, and ALP were 248 units/liter, 202 units/liter, and 358 units/liter, respectively. His total bilirubin and albumin were 0.9 mg/dl and 3.6 mg/dl, respectively. The AFP was 27 ng/ml. Hepatitis B surface antigen, surface antibody, and core antibody were negative. Serologies were also negative for hepatitis A and C.

An abdominal US revealed a hypoechoic mass in the right hepatic lobe measuring 6.8 cm × 11.3 cm and showed complete occlusion of the left portal vein. An echoic mass was present at the head of the pancreas extending into the lesser sac. An abdominal CT scan confirmed the large homogenous mass with multiple similar satellite lesions. A magnetic resonance imaging (MRI) showed a large 13-cm × 8-cm × 11-cm mass appearing hypointense on T1-weighted image and hyperintense on T2-weighted image. Extensive periportal and peripancreatic adenopathy was also seen on MRI. He underwent a percutaneous liver biopsy that was diagnostic of FLHCC. A bone scan and CT scan of the thorax showed no evidence of metastatic disease.

In June of 1994, his liver-associated blood values remained stable with the exception of AFP, which increased to 79 ng/ml. A repeat abdominal CT scan revealed a new thrombosis in the portal vein and an increase in the tumor size. Because of portal vein thrombosis and the increased size of the tumor, he was not considered a candidate for liver transplantation or resection. The patient was lost to follow-up after November of 1994.

Patient 3. A 20-year-old white woman was doing well until June of 1994 when she abruptly experienced daily episodes of nausea and vomiting. She also developed right upper quadrant and right nonpleuritic chest pain that radiated to her right shoulder. She was consistently diagnosed with costochondritis on several visits to the emergency room and prescribed nonsteroidal antiinflammatory drugs.

In early August of 1994, the patient presented to our medical center with worsening abdominal pain, intractable nausea, and weight loss. She had taken oral contraceptives for a one-week period in 1992 but denied the use of alcohol or nonprescription drugs. The patient also denied personal or family history of liver disease.

On physical examination, she was in distress from her abdominal pain. The examination was unremarkable with the exception of her liver edge extending 4 cm below the costal margin, and percussed to 18 cm.

Her hemoglobin was 9.3 g/dl. Her AST, ALT, and ALP were 110 units/liter, 343 units/liter, and 208 units/liter, respectively. Her albumin and total bilirubin were normal. Her AFP was unmeasurable. Serologies for hepatitis A, B, and C were negative.

An abdominal US revealed a large inhomogenous mass involving the right lobe, caudate, and possibly the left lobe. An abdominal CT scan also found a mass in the right hepatic lobe that measured 9 cm × 5 cm × 11 cm. There was no evidence of adenopathy. A celiac angiogram showed patent portal and hepatic vessels. Results of a percutaneous liver biopsy were consistent with FLHCC.

She underwent exploratory laparotomy, which revealed a bulky tumor in the portal hepatis. Biopsies were consistent with the tumor infiltrating beyond the confines of the liver and involvement of resected lymph nodes. Because of the tumor's extent, she was not considered for liver transplantation or resection. The patient refused palliative chemotherapy and opted for homeopathic remedies. She died in October of 1995 with progressive cachexia, jaundice, and ascites.

DISCUSSION

Fibrolamellar hepatocellular carcinoma is generally a malignancy of young adults. We obtained 32 cases of FLHCC from the United States-based medical literature with data on epidemiology, presentation, diagnosis, clinical course, treatment, and follow-up (4, 8–20). These cases, in addition to the three cases we are reporting, serve as the basis for this paper.

The mean age of diagnosis of FLHCC was 22 years, and there was a slight gender predominance of women (ratio, 1 to 1.3). Most cases of FLHCC were diagnosed in whites. Table 1 lists the symptoms manifested in patients with FLHCC. The most common complaint was abdominal pain, occurring in 71% of the patients. The mean duration of symptoms was eight months. The most frequent physical findings are hepatomegaly and an abdominal mass (Table 2). Because FLHCC does not occur in the setting of chronic liver disease, the usual physical stigmata of liver disease are absent. The physical signs and symptoms

TABLE 1. SYMPTOMS IN FIBROLAMELLAR HEPATOCELLULAR CARCINOMA (35 PATIENTS)*

Symptom	*Number (%)*
Abdominal pain	25 (71)
Nausea/vomiting	7 (20)
Weight loss	6 (17)
Fever	4 (11)
Fatigue	4 (11)
Diarrhea	4 (11)
Chest pain	3 (9)
Pruritis	2 (6)
Abdominal distension	2 (6)
Dyspepsia	2 (6)
Hematochezia	2 (6)
Others†	

* Two patients were incidentally found to have fibrolamellar hepatocellular carcinoma.

† Dysphagia, amenorrhea, early satiety, chills, night sweats, dark urine, hypochondrial pain, and weight gain each found in 3% of the patients.

summarized may be limited by the small number of patients and potential bias introduced by selected cases.

Laboratory tests in FLHCC are nonspecific and usually not helpful. Mildly elevated ALP and aminotransferases are seen in approximately half the patients with FLHCC. Significantly elevated liver function tests may be associated with mechanical obstruction of the biliary ducts (10).

Of the six patients tested for hepatitis B surface antigen (HBsAg), one was seropositive. Worldwide, chronic hepatitis B infection is the leading risk factor for HCC (22–25). Whether chronic hepatitis B infection also represents a potential risk factor for FLHCC is uncertain.

Tumor markers are usually absent in FLHCC, although small series have reported potential associations. AFP was present in three of the 21 patients who were tested; the peak abnormal value was 139 ng/ml. Carcinoembryonic antigen (CEA) was present in three of 12 patients tested. Elevated neurotensin and vitamin B_{12} binding capacity levels have also been described in patients with FLHCC (26–28). In one series, elevated neurotensin levels was described in patients with FLHCC, while patients with other liver cancers had normal levels (27). In another series, elevated neurotensin levels normalized in five of nine patients with FLHCC after surgery (28).

TABLE 2. PHYSICAL FINDINGS IN FIBROLAMELLAR HEPATOCELLULAR CARCINOMA (35 PATIENTS)*

Physical finding	*Number (%)*
Abdominal mass	16 (46)
Nontender	12 (34)
Tender	4 (11)
Hepatomegaly	9 (26)
Nontender	8 (23)
Tender	1 (3)
Normal physical examination	3 (9)
Peripheral edema	3 (9)
Gynecomastia	3 (9)
Ascites	2 (6)
Hepatosplenomegaly	1 (3)
Adenopathy	1 (3)
Hepatic bruit	1 (3)

* Two patients were incidentally found to have fibrolamellar hepatocellular carcinoma.

FLHCC usually appears as a large focal tumor and measures a mean of 12.6 cm across its greatest dimension. Most patients reviewed had focal tumors, without predominance of either lobe. Tumors appear on US as areas of low or mixed echogenicity, on CT as areas of low attenuation, and on angiography as vascular lesions (29). FLHCC appears on MRI as a well-defined homogenous mass that is isointense on T1-weighted images and usually on T2-weighted images as well (20, 30). Although a hypointense central signal on both images suggests lamellar fibrosis, the central scar may also appear as hyperintense on the T2 image as in our patient 2 (31).

Information regarding survival of patients with FLHCC was reviewed from case series (5, 7, 19, 28, 32–38). Although length of follow-up and the patient number differed among the studies, patients with FLHCC generally appear to have a better survival rate than those with HCC. Even when the age at presentation, number of hepatic tumors, presence of vascular invasion, and the presence of cirrhosis are stratified, patients with FLHCC survived longer (19, 37). Overall median survival of patients with FLHCC is between 28 and 32 months (5, 32). However, with surgical resection, the five-year survival is between 56% and 65%, and the survival range is between 2 and 252 months (Table 3) (5, 7, 19, 26, 27, 32, 37). Without resection, the survival rate is between 3 and 36 months (5, 19, 26, 27, 32, 37). Increased survival of patients with FLHCC may be related to its better resectability (19, 37).

Patients with FLHCC who have undergone subtotal resection tend to have a better survival than those who are treated with orthotopic liver transplantation (OLT) (34, 35, 39, 40). With OLT, the median survival is between 19 and 29 months, and the five-year survival ranges from 30% to 46% (33, 35, 36, 38, 40). The tumor recurrence rate is higher in patients who have undergone OLT as compared to those who are treated with partial resection. Large tumor size or multiple foci may reflect more aggressive tumors or

TABLE 3. SURVIVAL IN PATIENTS WITH FIBROLAMELLAR HEPATOCELLULAR CARCINOMA WITH HEPATIC RESECTION AND TRANSPLANTATION

Series	*Patients (N)*	*Partial resection*	*Transplantation*	*Outcome*
Craig (5)	23	11	0	Overall mean survival 32 months
Berman (7)	12	12	0	Mean survival of 68 months; 2-year survival at 82% and 5-year at 63%
Soreide (28)	9	0	9	With resection: 56% survival at 5 years; without resection: no survival at 5 years
Lack (32)	5	3	0	Overall mean survival 28.5 months, 4/5 died secondary to metastatic disease
Ringe (33)	20	14	6	With resection: median survival 44.5 months; with transplant: median survival 28.5 months
Starzl (34)	14	8	6	With resection: all patients alive at 11 months; of patients followed for more than 24 months, 5/5 alive; with transplant: of patients followed for more than 24 months, 2/4 alive
Iwatsuku (35)	22	12	10	With resection: 64.8% at 5 years; with transplantation: 37% at 5 years
Ismail (36)	6	0	6	Median survival 18.5 months
Yokoyama (38)	9	0	9	At 1 year survival of 89%; at 3 and 5 years 46%

micrometastasis, which in the presence of immunosuppression, could accelerate recurrence. Base on the data reviewed, patients with FLHCC should be treated with resection, if possible. OLT should be reserved for extensive tumor without vascular invasion or metastasis.

In summary, we presented a review of clinical signs and symptoms in 35 patients with FLHCC and a survey of the surgical treatment from various case series. Although most patients with FLHCC undergo surgery, two of our three case reports presented with aggressive bulky tumors and were found to be inoperable. Patients with resectable tumors should undergo partial hepatectomy as the treatment of choice, while those patients with extensive tumors may be considered candidates for OLT. Research is needed to help identify risk factors for the development of FLHCC and further investigate the utility of tumor markers.

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