Fibrolamellar Carcinoma of the Liver

Review of Three Cases and the Presentation of a Characteristic Set of Tumor Markers Defining this Tumor

DANIEL H. TEITELBAUM, M.D., STEVEN TUTTLE, M.D., LARRY C. CAREY, M.D., KATHRYN P. CLAUSEN, M.D.

From the Departments of Surgery and Pathology, The Ohio State University Hospitals, Columbus, Ohio

This study demonstrates the unique clinical and histologic aspects of fibrolamellar hepatic carcinoma, a rare variant of hepatocellular carcinoma. Three cases are reviewed and an extensive study of immunologic and intracellular substances defining this tumor is presented. Length of survival was considerably longer than typical hepatoma. The cause of death generally is due to a lack of control of the primary tumor. Successful treatment appears to relate to the ability to perform a total excision of the primary hepatic tumor. Chemotherapy should be used only in the presence of metastatic disease. Surgical resection of metastatic disease, unlike the usual hepatocarcinoma, may have some beneficial use. Fibrinogen was found in all tumors. It is possible that this tumor produces fibrinogen to create its unique histologic appearance. Carcinoembryonic antigen is described for the first time in this tumor. Both deposits of alpha-1 antitrypsin and copper were found in most of the tissues studied. The presence and amounts of these substances differ markedly from the common type of hepatoma. This unique composition of intracellular components may both facilitate histologic diagnosis, particularly if the amount of tissue is limited, and give further insight into the etiology of this tumor.

FIBROLAMELLAR CARCINOMA (FLC), a variant of hepatocellular carcinoma (HCC) comprises less than one per cent of cases in most series of HCC.[1,2] Only 43 cases of FLC have been described in a review of the world literature. The distinct morphology was originally described by Edmonson in 1958: "It consists of polygonally-shaped tumor cells with a highly eosinophilic cytoplasm. Bands of fibrous stroma, arranged in parallel lamellae, surround clusters of these tumor cells. The clinical aspects of these tumors differ significantly from the typical trabecular type of HCC. The tumor predominates in adolescents and young adults; the incidences between males and females are equal; and usually no past history of cirrhosis or exposure to hepatitis B virus (HBV) is given."[2] The prognosis for such a patient is considerably good; average survivals for FLC compared to other primary liver tumors are 44 to 68 months and 6 months, respectively.[1,3] Because of the relative rarity of this tumor, little or no literature is available on the clinical management of these patients. Recent attempts to study this tumor have used both electron microscopy and several special staining techniques.[4] Vitamin B_{12} binding protein in FLC tumor cells may be a characteristic marker.[5] In addition, the presence of intracytoplasmic copper and copper-binding protein, in one case report,[6] and fibrinogen[7] may also be associated with the tumor. Such associations, however, are hampered by the rarity of this tumor.

This report presents three new cases of FLC found in a review of 58 patients with a diagnosis of HCC from 1966 to 1981. The clinical cases are reviewed, as is the gross and microscopic histology. A discussion of surgical and nonsurgical management is given. In addition, the most extensive investigation to date of the presence of specific antigens and other markers in FLC is presented. A highly sensitive immunoperoxidase technique was employed, along with other special stains from the study, the results of which add to the present knowledge of this tumor.

Materials and Methods

All tissue was fixed in 10% buffered formalin and parafin embedded. Immunohistochemical localization of fibrinogen, carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), alpha-1-antitrypsin (A-1-AT), hepatitis B surface antigen (HB_sA_g), and human blood group antigens A, B, and H (O) was accomplished with an

Dr. Tuttle was an American Cancer Society Fellow.

Reprint requests: Larry C. Carey, M.D., Professor and Chairman of the Department of Surgery, The Ohio State University Hospitals, 410 W. 10th Avenue, Columbus, OH 43210.

Submitted for publication: December 11, 1985.

avidin-biotin peroxidase (ABC) technique, which was slightly modified from that originally described.[8] The following immunoreagents were used in the study: (1) Rabbit anti-fibrinogen, anti-A-1-AT, anti-HB_sA_g, and normal rabbit serum (Immunlok Laboratories, Carpenteria, CA); (2) Rabbit anti-CEA and anti-AFP (Dakopatts, Copenhagen, Denmark); (3) Mouse monoclonal anti-A, -B, and -H (O) (provided by Chembiomed, Ltd., University of Alberta, Edmonton, Canada); (4) Normal mouse ascitic fluid (Cappel Laboratories, Cockranville, PA); and (5) Biotinylated anti-rabbit immunoglobulin, biotinylated anti-mouse immunoglobulin, and avidin-biotin peroxidase complex (ABC) (Vector Laboratories, Burlingame, CA). Substitution of the primary antibody by nonimmune serum served as a negative control in each case. Site of peroxidase localization in tissue sections was shown using amino-ethyl-carbazole (Sigma Chemical Co., St. Louis, MO). Each tumor was also stained with routine hematoxylin and eosin (H & E), rhodadine stain (copper), Gomori's stain (iron), Fraser-Lendrum stain (fibrin), and periodic acid Schiff (PAS) histochemical stains.

Case Reports

Patient 1

A 16-year-old white female was referred to our medical center with a 1-month history of a painful abdominal mass and a liver-spleen scan localizing this mass in her liver. On physical exam, a smooth, nontender, 8-cm epigastric mass was noted. All liver function tests and hematologic parameters were normal. Hepatic angiography showed a well-circumscribed mass in the left lobe, which contained tortuous vessels arranged in a septated pattern. Neovasculature was noted, but no artereovenous shunting was presented. A tentative diagnosis of focal nodular hyperplasia was made based on angiographic findings and a lack of oral contraceptive use. At laparatomy, an 11×13 cm discrete nodular mass occupied the left lobe of the liver. A left hepatic lobectomy was performed. This was complicated by an injury of the right hepatic bile duct, which was repaired along with placement of a t-tube catheter. The patient did well after surgery, and has been followed in our outpatient clinic. Immediate postoperative CEA serum level was 20 ng/ml, but subsequently decreased to 1.9 ng/ml. Alpha fetoprotein has been normal. Because of the complete excision of her hepatoma and her young age, chemotherapy has been withheld. She is currently alive without evidence of recurrent disease 45 months after removal of the tumor.

Patient 2

A 26-year-old white man presented with a 5-month history of gastrointestinal discomfort, pyrosis, and puritis, with an abdominal mass subsequently discovered by the patient 2 months later. He gave a history of hepatitis 3 years prior to admission. Physical examination showed a nontender, 8-cm epigastric mass extending to the left of the midline. Liver function and hematologic tests were normal. Serus AFP and HB_sA_g were negative and preoperative CEA level was 9.2 ng/ml. Hepatic arteriography showed a highly vascular tumor in the left and intermediate lobes. A few vascular areas were noted, suggesting necrosis, and a tentative diagnosis of hepatoma was made. Initial surgical exploration located a tumor in the left and intermediate hepatic lobes with extension onto the stomach wall and gastric and paraortic lymph node involvement. The tumor was felt to be unresectable at this time, and the hepatic artery was cannulated for the continuous administration of fluorouracil for 1 month. On reexploration, some reduction in tumor size was noted. An extended left hepatic lobectomy was performed, along with total gastrectomy, splenectomy, and dissection of gastric and paraortic nodes. He did well after surgery and was placed on multiple chemotherapeutic drugs and a short course of external beam radiation. His CEA levels declined to as low as 2.2 ng/ml, but began to rise 14 months later to 6.8 ng/ml. On the basis of this elevation, he underwent an exploratory laparotomy and metastatic tumor to the retroperitoneum was found and removed. He did well with CEA levels declining to 0.5 ng/ml. Liver function tests, however, began to rise: LDH 594; SGOT 45; SPGT 33; and alkaline phosphatase 71. Three months later he developed multiple pulmonary emboli from left leg thrombophlebitis. During this admission, he subsequently developed bilateral hydronephrosis secondary to metastatic tumor. His CEA levels were 12.5 ng/ml and his right lobe of the liver was infiltrated with tumor by percutaneous biopsy. The patient expired 1 month later, 18 months after his initial resection. No autopsy was performed.

Patient 3

This 21-year-old white woman had a 5-month history of epigastric discomfort, nausea, vomiting, and fever. She was referred to our center after a liver mass was detected by liver scintigraphy. She had used oral contraceptives for 1 year. Physical examination was normal, as were hematologic and liver function tests. Hepatic arteriography showed a moderately vascular tumor of the left lobe. A neovascular pattern was noted, but no A-V shunting was present. An 8-cm tumor was found in the left lobe of the liver. No evidence of intraabdominal metastasis was noted, and a left hepatectomy was performed without complication. Because frozen section of the tumor showed HCC, a hepatic artery catheter was inserted, and chemotherapy was given through it for 1 week. The patient was then started on monthly I.V. chemotherapy. AFP was normal and immediate postoperative CEA level was 2.2 ng/ml. After surgery, several noncalcified, bilateral pulmonary nodules were seen. Chemotherapy was discontinued 8 months later, when the patient became pregnant, and subsequently delivered a healthy, full-term girl. During the withholding of chemotherapy, the pulmonary nodules increased in size. After delivery, she underwent sequential hemithoracotomies for the removal of metastatic tumors in her lungs. Throughout these events, her CEA levels stayed consistently low (0.7–1.3 ng/ml). She was restarted on monthly I.V. chemotherapy, but despite therapy, new pulmonary metastases developed. She became markedly jaundiced (total bilirubin 13.2 mg/dl), which was believed to be secondary to tumor occluding the intrahepatic biliry tree. The patient died 44 months after her initial laparotomy. No autopsy was performed.

Results

Gross and Microscopic

The three tumors varied in weight from 400 to 800 gms. The color varied from pale yellow to green. They consisted of smooth, fine nodules and were well-circumscribed. On cross-sectioning, however, two of the specimens (Patients 1 and 3) contained numerous satellite nodules. Variable amounts of central necrosis and hemorrhage were present. One tumor had a central scar with

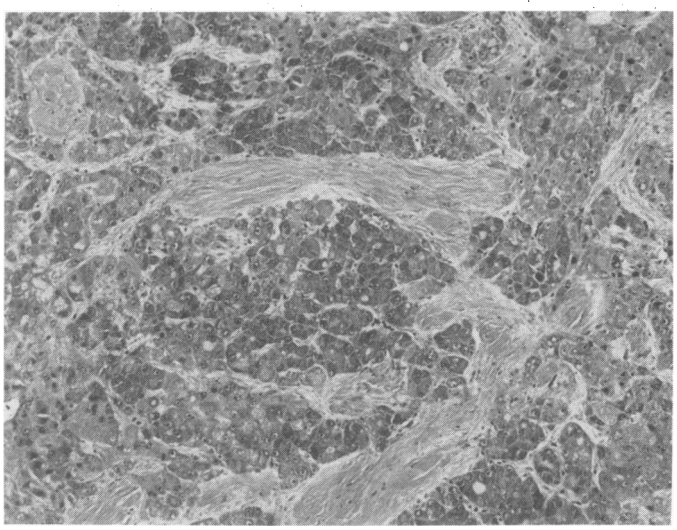

FIG. 1. Typical light microscopy morphology of fibrolamellar carcinoma. Note the large tumor cells surrounded by broad bands of collagen fibers. H & E stain ×100.

radiation to the periphery similar to that described for focal nodular hyperplasia.

The tumor cells were large, eosinophilic, and contained a large nucleus with prominent nucleoli (Fig. 1). Mitoses were uncommon in two cases; however, in one case (Patient 1), 5 per hpf were noted in some areas. Variable numbers of tumor cells were oriented into parallel strands with intervening broad fibrous bands (Fig. 1). Pale bodies, as previously described, were found occasionally in all three cases.[1] A small degree of bile production was noted in the tumors, including metastatic tumor to one patient's lung. Small amounts of ground glasslike cells were found, particularly in Patient 2. Nonneoplastic liver contained variable amounts of chronic inflammatory infiltrate, but no cirrhosis was present. Invasions into vascular spaces were noted in Patients 2 and 3, and invasion of the bile ducts and nerves in Patient 1.

Immunperoxidase and Special Stains

The results of several of the stainings were shown in Table 1. The cytoplasm of many tumor cells and a few nontumor cells stained mildly to strongly positive using the Fraser-Lendrum stain for fibrin. The results of the immunoperoxidase studies for fibrinogen showed strongly positive staining to the cytoplasm of those hepatoma cells with a fine ground glasslike pattern (Fig. 2). In addition, the fibrous stroma, particularly at the edges, were moderately positive for fibrinogen. Metastatic tumors were also mildly to moderately positive. Adjacent normal liver tissue was either negative for fibrinogen, or in a few cells, only mildly positive.

CEA was found in all three tumors using immunoperoxidase staining (Fig. 3). The antigen was exclusively confined to the bile canaliculi in both tumor and nontumor areas of the liver. Tumor cells were consistently negative. Studies on a metastatic lung tumor did not show any CEA, despite the fact that bile production was found on histologic exam.

Immunoperoxidase staining for alpha-1 antitrypsin (A-1-AT) was moderately to strongly positive in all three tumors (Fig. 4). Its presence varied from a patchy to homogeneous distribution, depending on the case. Individual tumor cells contained granular particles in the cytoplasm which were somewhat coarser than those for fibrinogen. Similar granules were found with PAS staining and were diastase-resistant, thus supporting the presence of A-1-AT at these tumors. Normal liver tissue and metastatic tumor were positive, but stained less positively. Immunoperoxidase staining for AFP, HB_sA_g were entirely negative both in the tumor and normal liver tissues. ABH isoantigens were not detected in either the tumor or adjacent liver; isoantigens were, however, found on biliary mucosa.

The Rhodadine stain for copper was moderately to markedly positive in two cases (Patients 1 and 3). The normal adjacent liver of these two cases did not stain for copper. The other case had only a rare positive tumor cell containing copper. Cells contained copper in coarse clusters throughout the cytoplasm. The tumors did not stain for hemosiderin: the normal liver stained moderately in the Kupffer's cells. Gomori's stain for these compounds was generally negative, except for a few rare positive cells in Patient 3.

Discussion

These three cases of FLC demonstrate the unique aspects of this variant of HCC—particularly the young

TABLE 1. *Results of Immunoperoxidase and Special Stains of Fibrolamellar Hepatocarcinoma Cells**

Patient No.	Special Stains				Immunoperoxidase Stains					
	Copper	Iron	Fibrin	PAS	Fibrinogen	A-1-AT	CEA†	HB_sA_g	AFP	ABO
1	3+	0	4+	3+	1–3+	4+	0	0	0	0
2	0–1+	0	2–3+	3+	1–2+	4+	0	0	0	0
3	4+	2+	4+	3–4+	2–3+	3–4+	0	0	0	0

* Degree of positivity expressed from 0 to 4+.

† CEA was located only in bile canaliculi, not in tumor cells.

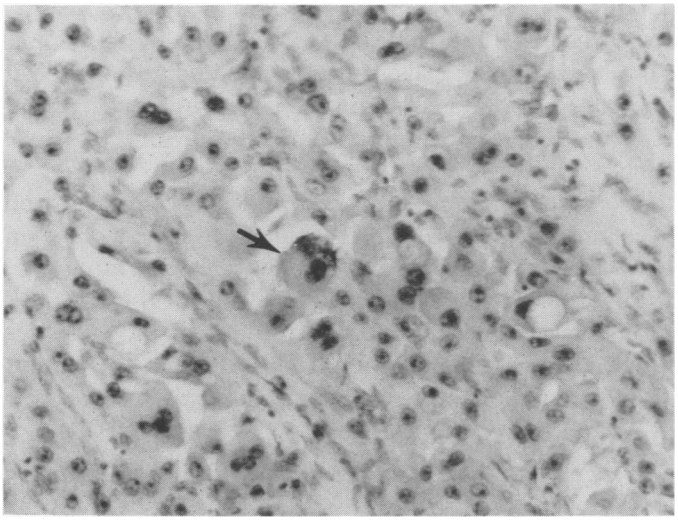

FIG. 2. Immunoperoxidase stain of fibrinogen in hepatoma cell (arrow). The cell is quite large and has a ground glasslike appearance. H & E ×250.

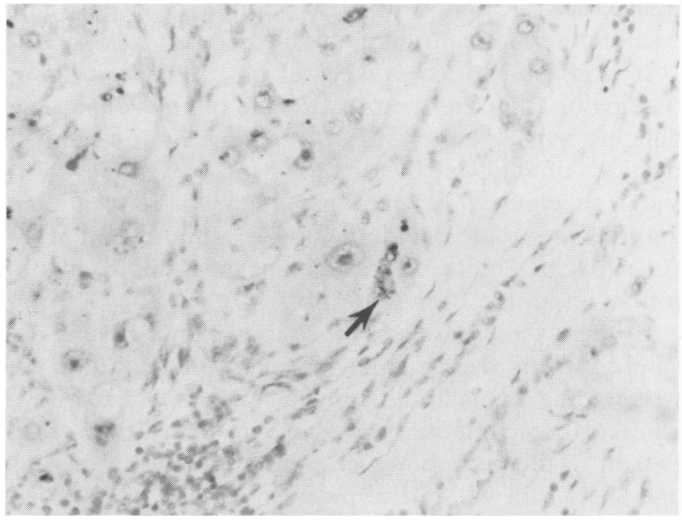

FIG. 3. CEA detected in FLC by immunoperoxidase staining. CEA was confined to the bile canaliculi (arrow), without intracellular involvement. H & E stain ×250.

age of the patients and their prolonged survival, despite two patients with metastatic disease at the time of their diagnosis. In addition, we have shown that the tumor contains a set of antigens and other intracellular substances that are distinct from the more common HCC.

Clinical Aspects

The clinical symptoms were generally nonspecific. It was not until a mass was found on physical exam or detected with radionucleotide scanning that the patients were referred to our center. Routine laboratory data was not contributory to making the diagnosis. Usefulness of hepatic angiography was limited to defining the extent and anatomical relationship of the tumor. Preoperative diagnosis of hepatoma, based on angiography, was correct in only one case. All three were vascular tumors, with moderate amounts of neovasculature; no arteriovenous shunting was present, despite a previous claim that this may be a diagnostic feature of FLC.[9]

The benign appearance by angiographic interpretation and the young age of the patients lead to the preoperative diagnosis of a benign tumor in two cases. Because of this, little preparation was made for a wide hepatic resection, and preoperative investigation for metastatic disease was not performed. We strongly recommend that FLC be considered in the physician's differential diagnosis of a young patient presenting with a hepatic mass. The fact that these patients achieve a prolonged survival, despite metastatic disease, emphasizes the low aggressiveness of FLC. In addition, persistent local disease was responsible for the death of two of our patients. Because of this and the young age at which patients present, we strongly advise that all attempts be made to resect the primary tumor. The use of chemotherapy in the hepatic artery may enable, in cases of a large tumor (Patient 2), a complete resection. Embolization of the tumor at the time of hepatic angiography has also been attempted as a way of reducing tumor size and, thus, facilitating resection.[9]

It is difficult to assess the benefit of resecting metastases. In Patient 3, no conclusion can be made because her tumor was subsequently found to have spread to the remaining lobe of her liver, as well as her lungs. Pulmonary resection for other types of tumors may prolong survival.[10,11] The resection of her metastases was performed without complications. In a patient with pulmonary metastases, lacking evidence for other recur-

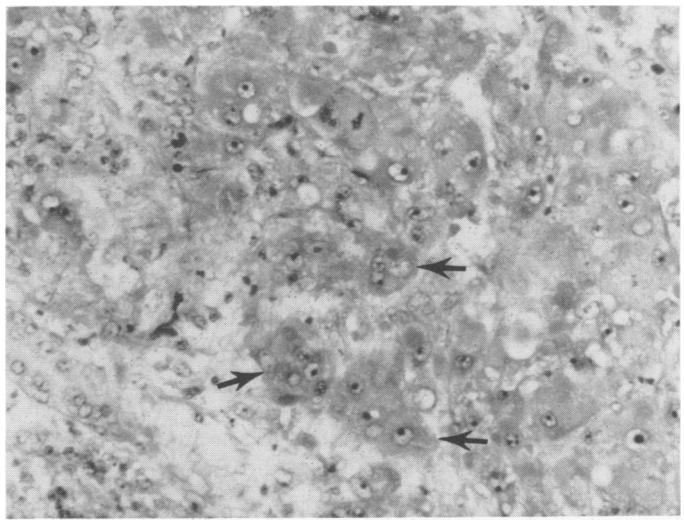

FIG. 4. Diffuse distribution of A-1-AT deposits in tumor cells (arrows), as shown by imnmunoperoxidase technique. H & E stain ×250.

rent disease, resection of these pulmonary lesions may be a safe way to contribute to increased survival in FLC.

It is difficult to assess whether postoperative chemotherapy or radiation treatments were of any benefit. No data are available on adjuvant therapy for FLC. Investigations of adjuvant therapy for typical HCC, however, show generally poor response rates to conventional administration of chemotherapy.[11] Administration of Adriamycin®, however, has significantly improved objective responses 10 to 25%.[12,13]

In these three patients, no serious complications developed from the adjuvant therapy. In addition, the withholding of chemotherapy in Patient 3 may have allowed her pulmonary disease to increase in size. Patient 1 did not, however, receive adjuvant therapy and she is still without recurrent disease. However, her prolonged survival is most likely due to the fact that no metastatic disease was initially found in her. At this time, adjuvant therapy seems most appropriate in those who concomitantly have known metastatic disease. The role of complete surgical removal of the tumor appears far more important than the use of adjuvant therapy.

In postoperative follow-up, liver-spleen scan, chest roentgenographs, and CT scanning were generally useful in detecting recurrence. CEA levels were also found to be helpful. Contrary to a previous report suggesting CEA levels to be of little value in patients with typical hepatomas,[14] in two cases (Patients 1 and 2), CEA levels correlated closely with their clinical course. The reexploration that found metastatic tumor in Patient 2 was based solely on elevation of his CEA, while other concomitant tests for recurrence were negative. Thus, CEA levels may be a useful way of monitoring those patients with FLC who have preoperative elevated CEA levels.

Immunoperoxidase and Special Stains

Both fibrinogen and fibrin were found in moderate to large amounts in all three tumors. Fibrinogen is found in normal hepatocytes;[15] this amount, however, is considerably less than the amounts found in these tumors, both in number of cells containing fibrinogen and the amount of fibrinogen in each cell. In addition, there was no to very little fibrinogen in the normal liver adjacent to the tumor. The finding of fibrinogen in FLC agrees with the findings of Stromeyer et al. (1980) in three other cases of FLC. Typical HCC, to the contrary, does not contain significant amounts of fibrinogen.[7] This strongly suggests that fibrinogen may be specific for FLC and may be useful in the diagnosis of more difficult cases. This may be particularly useful if tissue is limited in amounts, as with a transcutaneous biopsy. The location of fibrinogen was also interesting. Fibrinogen was located in ground glasslike cells. Our study also located fibrinogen in the lamellar stroma. This suggests that some cells in the tumor function to deposit fibrinogen around the tumor cells, and thus might contribute to the unique lamellar stroma of FLC. Whether the presence of fibrin and fibrinogen contributes to the development of a hyperfibrinogen condition found in some cases of HCC is unclear; nor is it known whether such a condition may have been responsible for the thrombophlebitis in Patient 2. Fibrin and fibrinogen levels, when obtained, were normal, but were not followed during these patients' clinical courses. Perhaps such hematologic values may be of some use in diagnosis or in finding recurrent disease.

Immunoperoxidase stains showed CEA in all three tumors. No previous study has investigated the presence of CEA in FLC; however, CEA is found in 30% of typical HCC.[16] The distribution of CEA in HCC corresponds with our own findings of CEA in the bile canaliculi of FLC. The source of this CEA may be either secondary to inflammation induced by the tumor or from hepatoma cells themselves. CEA has not been found in the cytoplasm of hepatocytes or hepatoma cells. Levels in individual cells may be too low to be detected by immunoperoxidase techniques, and may only be found once CEA is secreted into the biliary system and concentrated.[15] This would explain the detection of CEA in the bile canaliculi in both areas of tumor and normal liver.

Moderate to large amounts of A-1-AT were found in all three tumors. A-1-AT is found in approximately 73% of tumors of the common type HCC.[16] One of two tumors, examined for A-1-AT by another investigator, was found to contain A-1-AT.[17] With the inclusion of our findings, the antigen appears to be found with similar frequency in both typical HCC and FLC. The etiology of the deposits of A-1-AT is unknown. It may be due to increased production or an inability to remove A-1-AT; it may also be secondary to genetic predisposition.[18] Accumulation of A-1-AT may be found in any liver disease in which biliary stasis or cirrhosis is present. Thus, the finding of A-1-AT in the liver and in the serum of one case (Patient 2) does not imply an alpha-1 antitrypsinase deficiency. However, it is of interest that Pi MZ type A-1-ATase deficiency was found in all three cases of FLC studies in one series of HCC. Because of the rarity of this phenotype, an association with FLC may be present. It may be a useful diagnostic method to identify FLC before surgery.

Immunoperoxidase stains for AFP and HB_sA_g antigens were negative in these tumors. These results differ markedly from the typical HCC, in which AFP and HB_sA_g are found in 35% and roughly 33%, respectively.[16,19] The lack of characteristic tissue markers, such

as AFP and HB_sA_g, suggests a unique etiology of FLC. ABO isoantigens were not present in either tumor cells or normal hepatocytes. Previous studies have not detected these isoantigens in normal liver cells; thus, no significance is carried in the absence of these antigens in FLC.[21]

Moderate amounts of copper were present in areas of normal liver in all three cases. This appears to be somewhat typical for most hepatomas.[19] Of greater interest was the finding of moderate to large amounts of copper in the tumor itself (Patients 1 and 3). Typical HCC contains low levels of copper in the tumor cells.[20] The presence of these copper deposits in FLC appears to be unique compared to other hepatocellular carcinomas. The etiology of these increased intracellular copper deposit is uncertain. Lefkowitch et al. (1983) has reported the presence of increased levels of copper binding protein in a single case of FLC. Elevated levels of this protein may be the cause of this accumulation of copper, but this remains to be proven.

Gomori's stain for iron compounds showed no to very small amounts of iron in the tumor. This finding is similar to typical HCC, in which only low levels of iron and ferritin are present.[20]

The presence of HCC in a young patient should arouse suspicion of FLC. Both the young age and long-term survival in patients with this tumor should prompt the surgeon to make a more aggressive attempt at resection of the primary tumor; possibly even when distant metastases are present. Preoperative diagnosis of this would allow the surgeon to prepare for such a resection. The use of sensitive immunoperoxidase stains and other special stains may facilitate the identification of this tumor. Recently, serum levels of neurotensin have been shown elevated in FLC; this may be a useful tumor marker.[22] In our study, fibrinogen, copper, CEA, and perhaps A-1-AT staining may not only allow accurate preoperative diagnosis (when the amount of tissue is limited), but may eventually lead to an understanding of the etiology of this tumor.

References

1. Craig JR, Peters RL, Edmonson HA, Omata M. Fibrolamellar carcinoma of the liver: a tumor of adolescents and young adults with distinctive clinico-pathologic features. Cancer 1980; 46: 372–379.
2. Edmondson HA. *In* Tumours of the liver and intrahepatic bile ducts. 1st ed. Washington, DC: Armed Forces Institute of Pathology, 1958; 90–104.
3. Berman MM, Libbey P, Foster JH. Hepatocellular carcinoma; polygonal cell type with fibrous stroma-An atypical variant with favorable prognosis. Cancer 1980; 46:1448–1455.
4. Farhi DC, Shikes RH, Silverberg SG. Ultrastructure of fibrolamellar oncocytic hepatoma. Cancer 1982; 50:702–709.
5. Paradinas FJ, Melia WM, Wilkinson ML, et al. High serum vitamin B_{12} binding capacity as a marker of the fibrolamellar variant of hepatocellular carcinoma. Br Med J 1982; 285:840–843.
6. Lefkowitch JH, Muschel R, Price JB, et al. Copper and copper-binding protein in fibrolamellar liver cell carcinoma. Cancer 1983; 51:97–100.
7. Stromeyer FW, Ishak KG, Gerber MA, Mathew T. Ground glass cells in hepatocellular carcinoma. Am J Pathol 1980; 74:254–258.
8. Hsu SM, Raine L, Fanger H. Use of avidin-biotic peroxidase complex (ABC) in immunoperoxidase techniques: a comparison between ABC and unlabled antibody (PAP) procedures. J Histochem Cytochem 1981; 29:277.
9. Wong LK, Link DP, Frey CF, et al. Fibrolamellar heptocarcinoma: radiology, management and pathology. American Journal of Radiology 1982; 139:172–175.
10. McCormack PM, Manjit SB, Beattie EJ, Martini N. Pulmonary resection in metastatic carcinoma. Chest 1978; 73:163–166.
11. Rosenberg SA, Flye MW, Conkle D, et al. Treatment of osteogenic sarcoma. II. Aggressive resection of pulmonary metastases. Cancer Treat Rep 1979; 63:753–756.
12. Falkson G, Moertel CG, Lavin P, et al. Chemotherapy studies in primary liver cancer: a prospective randomized clinical trial. Cancer 1978; 42:2149–2156.
13. Vogel CL, Bayley AC, Brooker RJ, et al. A phase II study of Adriamycin® (NSC 123127) in patients with hepatocellular carcinoma from Zambia and the United States. Cancer 1977; 39:1923–1929.
14. Macnab FM, Urbanowicz JM, Kew MC. Carcinoembryonic antigen in hepatocellular cancer. Br J Cancer 1978; 38:51–54.
15. Forman WB, Barnhart MJ. Cellular site for fibrinogen synthesis. JAMA 1964; 187:168–172.
16. Thomas P. Studies on the mechanisms of biliary excretion of circulating glycoproteins. The carcinoembryonic antigen. Biochem J 1980; 192:837–843.
17. Thung SN, Gerber MA, Sarno E, Popper H. Distribution of five antigens in hepatocellular carcinoma. Lab Invest 1979; 41:101–105.
18. Govindarajan S, Ashjcavai M, Peters RL. A-1-Antitrypsin phenotypes in hepatocellular carcinoma. Hepatology 1981; 1:628–631.
19. Nazarewicz-de Mezer T, Slusarczyk J, Krawczynski K, Nowoslawski A. Localization of hepatitis B virus antigens in hepatocellular carcinoma. Prog Med Virol 1981; 21:66–76.
20. Linder MC. Iron and copper metabolism in cancer, as exemplified by changes in ferritin and ceruloplasm in rats with transplantable tumors *In* Morris HP, Criss WE, eds. Morris hepatomas: mechanisms of regulation. New York: Plenum Press, 1978; 643–644.
21. Mathew T, Gupta RK. Isoantigens A, B and H in primary liver malignancies. Pathology 1981; 13:571–577.
22. Collier NA, Bloom SR, Hodgson HJF, et al. Neurotensin secretion by fibrolamellar carcinoma of the liver. Lancet 1984; 1:538–540.