California Tumor Tissue Registry

65th Semi-Annual Slide Seminar

Tumors of The Liver

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June 4, 1978

Los Angeles, California

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CASE 1. MYOSARCOMA, PRIMARY IN LIVER

CONTRIBUTOR: Herbert C. Sillman, M.D.
Tarzana, California
Tissue from: Liver
(LUS167-78)

June 4, 1978
ACCESSION NO. 22777
(173)

1.1 CASE SUMMARY

CLINICAL ABSTRACT

History: This 12 year old Chinese male had a long history of recurrent abdominal pains and was in his usual state of health until July 1977 when he began experiencing nausea and occasional vomiting. By September, he had lost 5 pounds.

Physical Examination: The liver was found to be enlarged 5 cm. below the right costal margin. It was firm and nodular, suggesting a tumor.

Laboratory: Liver function tests were reported as within normal limits. The alpha-fetoprotein was negative.

Radiographs: Delta scan of abdomen showed a partly calcified mass in the right lobe of the liver, which was confirmed by liver-spleen scan. Arteriography demonstrated the mass to be large and highly vascular.

SURGERY (September 7, 1977)

An exploratory laparotomy demonstrated an inoperable hepatic tumor involving much of the right lobe and extending into the middle lobe of the liver. The tumor extended into the porta hepatis involving the hepatic vessels and common duct. Multiple biopsies were taken.

GROSS PATHOLOGY

The specimen consisted of three segments of liver tissue ranging from 1.5 to 2.3 cm. in greatest dimension. They were composed mostly of firm, homogenous, gray tissue with some softer reddish-tan tissue near the surface resembling liver parenchyma.

Porta hepatis lymph nodes appeared uninvolved with tumor.

FOLLOW-UP

The patient was started on triple chemotherapy with Vincristine, Actinomycin-D, and Cytoxan on September 28, 1977.

1.2 CASE DISCUSSION

DIAGNOSIS

Myosarcoma

HISTOLOGIC DESCRIPTION

In the section of liver there is widespread infiltration, particularly of the centrolobular areas, by neoplasm. The latter consists of interlacing strands of tightly compacted spindle-shaped cells with a multitude of fibrils. The tumor cells do not have clear cut cell borders, the nuclei vary from oval to spindle in shape and their cytoplasm varies considerably in quantity. The nuclei are not particularly hyperchromatic, many do have small acidophilic nucleoli and mitoses are difficult to find. In some areas the intercellular fibrils are rather dense and coarse. Much of the intercellular substance is almost amorphous and constitutes a major portion of the tumor. Throughout most of the neoplasm there are areas of round cell infiltration consisting of lymphocytes and many plasma cells. Central veins and hepatic veins appear to be obliterated. The triads are still present although many of them are enlarged by neoplastic involvement. Portal veins are difficult to identify. The hepatocytes for the most part are rather large and where not involved by neoplasm, a fairly normal cord structure is seen.

CHARACTERIZATION OF TUMOR

This neoplasm, with its predominant cigar-shaped nuclei and abundant intercellular fibrillae, represents a low-grade leiomyosarcoma that could well have arisen in the hepatic venous system. The latter seems to have been obliterated. However, there also seems to be involvement of the portal veins as only bile ducts and hepatic artery branches are identified with certainty in the triads. It has been postulated that malignant smooth muscle tumors that arise in the liver come from either the vascular system or from muscle in the walls of the bile ducts. If this tumor did arise in the hepatic venous system, metastasis might be expected at some future date in the lungs. The lack of mitotic activity probably indicates rather slow growth of the neoplasm. Leiomyosarcomas of the liver are massive, slow growing tumors that arise in adults.[1] The chief complaint is RUQ pain. The chief physical finding is hepatomegaly, often marked. Liver scans disclose one or more cold areas. Surgery is recommended even if metastases are present. The prognosis is better than observed in HCC. A patients with leiomyosarcoma may live for more than a year, occasionally two to four years.

One report of hepatic artery ligation and infusion chemotherapy for a sarcoma of the liver has been reported.[2]

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes the various spindle cell sarcomas (discussed with Case 10). Electron microscopy has proven to be helpful in the diagnosis of smooth muscle tumors. Morales lists ultrastructural criteria of leiomyosarcoma as follows: 1) the presence of intracytoplasmic myofilaments; 2) dense bodies, both in the cytoplasm and in association with the plasma membrane; 3) pinocytic vesicles and invaginations of the plasma membranes; and 4) remnants of basal lamina or an extensive cell coat.[3]

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CASE 2. HISTIOCYTIC LYMPHOSARCOMA

CONTRIBUTOR: Walter F. Coulson, M.D.
Los Angeles, California
TISSUE FROM: Liver
(LUS291-78)

June 4, 1978
ACCESSION NO. 22807
(176)

2.1 CASE SUMMARY

CLINICAL ABSTRACT

History: This 48 year old Caucasian male had a history of intravenous drug use and a 27 pound weight loss. He was initially hospitalized in late October 1977, when he developed acute onset of sharp right upper quadrant pain radiating to the back.

Physical examination revealed an enlarged liver 10 cm. below the right costal margin, not associated with icterus or lymphadenopathy. There was a mild elevation of SGOT, SGPT, and alkaline phosphatase with a normal serum bilirubin.

An emergency laporatory showed hepatosplenomegaly and a wedge biopsy showed "necrosis and features of granulomatosis inflammation" although a specific diagnosis was not established.

Pain persisted during the two months following discharge and the patient's increasing problems with anorexia, night sweats, low grade fevers, and hematemesis lead to readmission in December of 1977. Scleral icterus was noted and the liver span was 27 cm. by percussion. Vascular ectasia of the trunk, face, and extremities were present. Endoscopy showed gastritis and esophageal varices.

Laboratory Data: "Liver enzymes" were elevated, an unspecified amount, with a billirubin of 13. Peripheral blood smears were unremarkable and HBsAg was negative.

Radiographs: Hepatic angiogram and ultrasound examination showed a mixed cystic and solid 7 cm. diameter mass involving the right and left hepatic lobes.

SURGERY (December 10, 1977)

An exploratory laporatomy for possible partial hepatic resection showed a huge liver which appeared cirrhotic. The left lobe was completely replaced by tumor extending to the hepatoduodenal ligament. Multiple biopsies were performed.

GROSS PATHOLOGY

The specimen consisted of several wedges of bile-stained parenchyma averaging 2 x 0.5 x 0.5 cm. in greatest dimensions. One section was nodular and other sections appeared grossly cirrhotic.

FOLLOW-UP

Following surgery the patient's course was complicated by staphylococcus aureus sepsis and metabolic encephalopathy. Two courses of chemotherapy were administered and follow-up ultrasound examination of the liver on April 13, 1978, showed disappearance of the left lobe mass. Bone marrow examination was normal and no abdominal or peripheral lymphadenopathy was noted.

2.2 CASE DISCUSSION

DIAGNOSIS

Lymphosarcoma, pleomorphic histiocytic type, apparently primary in liver

HISTOLOGIC DESCRIPTION

The segment of liver is almost replaced by primitive tumor cells that are not entirely uniform but are large with oval and irregularly shaped, vesicular nuclei and scanty, faintly eosinophilic cytoplasm. Nucleoli are prominent and irregular. Some of the tumor cells have indented nuclear membranes with pseudopodia. Occasional multi-nucleated forms are found, in addition there are some smaller cells with pyknotic nuclei, others with nuclei undergoing mitosis. Most have shrunkened eosinophilic cytoplasm. Occasionally normal bile duct structures are found trapped in the tumor tissue. In some areas, normal lymphocytes

are pushed to the periphery by the proliferating immature cells.

CHARACTERIZATION OF TUMOR

Fifty percent of patients dying of lymphoma at the USC-John Wesley Medical Oncology Unit, had liver involvement. However, only between 16-22% of patients have hepatic involvement at staging operations.[1,2]

The occurance of lymphomas presumed to be primary in the liver has been limited to relatively few reports,[3-6] in 48,000 autopsies from LAC/USCMC and John Wesley Hospital performed from January 1949 through August 1972, only three could be identified as candidate cases. Freeman et al[5] only identified 6 primary hepatic non-Hodgkin's lymphosarcomas in a study of 2194 extranodal lymphosarcomas extracted from a total of 8767. (fig. 1) It is obviously difficult to pinpoint any primary site for malignant lymphoma; lymphoid tissue of many organs seems to be involved simultaneously, and involvement of all reticuloendothelial tissues may be so prominent at autopsy that a primary site, if there really was one, can no longer be defined. The liver is a normal organ site for lymphopoiesis, precursers to T-cells can be identified in the portal areas of human embryo's from 12-17 weeks.[7] When a lymphosarcoma involves the liver, it apparently always arises in the portal lymphoid tissue, the same areas initially affected in Hodgkin's disease of the liver. The typical pattern is effacement and widening in a relatively uniform involvment of most of the portal areas. Occasionally, as in this patient, the tumor mass will be a large bulging tumor that may bulge and displace parenchyma, grossly resembling a metastatic neoplasm. Apparently, on occasion, a rapid growth from one or several portal areas gives rise to a true compressing mass. According to Kim et al, staging biopsies show that nodular and diffuse lymphosarcomas of the histiocytic type involve the liver relatively less frequently than poorly differentiated lymphocytic lymphosarcoma.[8] This may be because histiocytic lymphosarcomas present as mass lesions in the liver more often than other types, and staging biopsies may fail to give an accurate picture.

DIFFERENTIAL DIAGNOSIS

Hodgkin's Disease may be confused with histiocytic lymphosarcoma when a mass of the size encountered in this patient has developed. However the prominent bright red nucleolus of the Reed-Sternberg cell is lacking in histiocytic lymphosarcoma cells. The latter tumor is also typically more cellular and less polymorphic. The distinction between involvement of the liver by histiocytic lymphoma or Hodgkin's disease, might be quite difficult early in the disease. Hodgkin's involvement of portal areas is usually preceeded by nonspecific infiltration of enlarged and polymorphous non-neoplastic cells, some of which are lymphocytes and immature histiocytes. The limiting plate is usually destroyed early in Hodgkin's disease and a prominent Kupffer cell hyperplasia throughout the lobule can ordinarily be found. Histiocytic lymphosarcoma, on the other hand, is from it's onset, a monomorphous cellular infiltrate which effaces many of the components within the portal areas but while widening the portal space, usually spares the limiting plate until late in the the course of the disease. The Kupffer cell hyperplasia throughout the sinusoids is not a typical feature in lymphosarcoma. Striking Kupffer cell proliferation will be found in livers of patients with malignant histiocytosis (histiocytic medullary reticulosis).

Nonspecific **Lymphoid hyperplasia** must be distinguished from lymphosarcoma. Lymphoid hyperplasia is particularly pronounced in patients who have autoimmune type disorders such as rheumatoid arthritis, inflammatory bowel disease, or lupus erythematosus.

Primary biliary cirrhosis is characterized by lymphoid hyperplasia that may be profound with development of follicles. However the limiting plate and biliary radicals are destroyed early in primary biliary cirrhosis, the lymphocytes are normal and generously interspersed with plasma cells.

A **pseudolymphoma** pattern may occasionally develop in patients who are intravenous drug users. Presumably the lymphoid hyperplasia is related to the continued innoculation of foreign material. None such diseases enter into the differential diagnosis of the solid mass lesion found in this patient.

Salmonelloses as well as **typhoid fever** may result in diffuse reticulosis but not a mass lesion.

Metastatic tumor can be indistinguishable from histiocytic lymphosarcoma, the distinction may depend on the cytologic features, as in this case.

Lesions that appear to be granulomas or abscesses may occasionally mask the presence of necrotic tumor. Lymphosarcomas undergo spontaneous necrosis much less frequently than metastatic neoplasms however. The reaction to necrotic tumor tissue may be granulomatous in character.

DIAGNOSTIC METHODS

Evaluation of lymph nodes is of critical importance when the question of lymphoma has been raised in the liver biopsy. Patients with lymphoma often manifest autohemolytic features and may be chronically anemic even without marrow involvement by lymphoma. There may be increased iron stores in the hepatic parenchymal cells should the chronic anemia have been present for some time. However patients with solid lymphosarcoma mass lesions in the liver, usually have neither marrow involvement or chronic anemia.

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CASE 3. CHOLANGIOLOCELLULAR CARCINOMA

CONTRIBUTOR: Robert L. Peters, M.D.
Los Angeles, California
TISSUE FROM: Liver
(JWA123-74)

June 4, 1978
ACCESSION NO. 22872
(159)

3.1 CASE SUMMARY

CLINCIAL ABSTRACT

History: This 80 year old male retired butcher was said to be in good health until one month prior to hospitalization for weakness and increased abdominal girth, in October of 1974. Additional history revealed that the patient experienced confusion for several months, diarrhea for one month, and anorexia of one week's duration.

Laboratory data: Glucose ranged from 155 to 235, BUN 43 to 63, serum alkaline phosphatase 6.5 to 8.1, creatinine less than 1.4, albumin 2.2, globulin 2.6, total bilirubin 0.7, SGOT 45 and SGPT 20. A liver biopsy was interpreted as liver cell carcinoma.

CLINICAL COURSE

The patient was transferred to John Wesley Hospital in a moribund and cachectic state. There was no icterus. The abdomen was distended and there was said to be an enlarged nodular hard liver. There was 3+ ascites. On October 25, 1974, the patient expired.

GROSS PATHOLOGY (Autopsy)

The liver weighed 1425 gm., was granular and contained retracted white tumor foci averaging 0.2 cm. in diameter. The lower 10-15% of the liver was involved by a poorly defined, irregularly shaped sclerotic tumor with a lobulated surface. The intrahepatic bile ducts were nondilated. Small nodules averaging 0.1 cm. in diameter were also present in the peripancreatic fat.

The duodenum and jejunum had numerous small 0.1 to 0.3 cm. plaques on the serosal surface. Sclerotic tumor nodules covered the serosa of the ileum and jejunum and the fat of the cecum. Several polyps were present in the cecum; one large and cauliflower-like, one sessile, and two peduculated.

3.2 CASE DISCUSSION

DIAGNOSIS

Cholangiolocellular carcinoma

HISTOLOGIC DESCRIPTION

The liver is involved by solid cords of uniform but primitive cells, the tumor cord size is somewhat larger than the usual liver cord. The tumor cells have no clear-cut basement membrane on the outer side and a canalicular space is only occasionally recognizable. The cells are uniform and fairly small with round and oval nuclei that generally lack nucleoli. The nuclear characteristics are similar to those of cholangioles. The scanty cytoplasm is poorly defined and is polychromatophilic. Rarely a small focus of what appears to be bile can be identified between the tumor cells. There are moderate number of mitotic figures and many pyknotic nuclei. The tumor is uniform in all areas although the cohesiveness is occasionally lost. In some areas the clusters of tumor cells are larger.

CHARACTERIZATION OF TUMOR

The cholangiolocellular carcinoma was introduced as a new subdivision of primary liver cancer by Steiner in 1957[1] and described further in 1959.[2] The tumor resembles the cholangiole (Canal of Hering) in contrast to the ductal carcinoma (cholangio carcinoma) which resembles duct structures at the interlobular radicle or larger. Whereas it is not established that the tumor actually has any different histogenesis, the basis of it's description was its similarity to cholangioles and not its proven or even hypothesized histogenesis. It has been speculated that all carcinomas of the liver arise from cells that have the potential to form either ducts or hepatocytes, explaining the fairly common finding of ductal carcinoma in otherwise hepatocellular carcinomas. The cholangiolocellular carcinoma differs from

primitive and poorly differentiated cholangiocarcinomas in that it has uniform resemblance to the cholangioles throughout, and it is not pleomorphic as the poorly differentiated cholangiocarcinoma may be. Many cholangiocarcinomas have areas that resemble cholangioles but have other areas with ductal or even adenocarcinoma patterns.

Steiner indicated that the cholangiolocellular carcinoma was quite rare. He considered it to represent 1% of liver cancers. In the 250 primary tumors in the liver from LAC/USCMC and John Wesley Hospital, only two were believed represent cholangiolocellular carcinoma,[3] this case being one example. Cholangiolocellular carcinomas do not have a predilection of originating in cirrhotic livers nor in livers with cystic disease, biliary tract obstruction nor parasites as far is as known. However the tumor is too uncommon to easily make correlations with other underlying diseases.

DIFFERENTIAL DIAGNOSIS

Cholangiolocellular carcinoma must be distinguished from carcinomas of the bile duct system but even more so from metastatic carcinoma. Occasionally carcinomas that metastasize to the liver will grow into the sinusoids in such a fashion that a pseudotrabecular or cord like pattern may be assumed. In this patient, such a problem in differential diagnosis arises because there is a leiomyoma of the jejunum involved by carcinoma. There is a sharp distinction between the leiomyomatous tissue and the carcinoma. In other sites of metastases of this tumor, such as in bone marrow, the tumor tends to have the same cord-like configuration; whereas it might be difficult to distinguish from bronchogenic oat-cell carcinoma, it does not have the pattern of leiomyosarcoma. In one focus of the marrow, the tumor does have larger more epithelioid appearing cells, a metastatases in the adrenal glands has configuration similar to that in the liver.

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CASE 4. HILAR CHOLANGIOCARCINOMA

CONTRIBUTOR: Robert L. Peters, M.D.
Los Angeles, California
TISSUE FROM: Right hepatic duct
(JWA49-71)

June 4, 1976
ACCESSION NO. 22890
(164)

4.1 CASE SUMMARY

CLINICAL ABSTRACT

History: This 68 year old Caucasian male had a 40 year history of chronic alcoholism. He first developed ascites in 1969. He was presented to John Wesley Hospital in January 1971.

Physical examination: The patient was cachetic and deeply icteric. The liver was palpable and very tender.

Laboratory data: His albumin was 4.2, globulin 4.0, bilirubin 6.0, alkaline phosphatase 7, SGOT 184, SGPT 134. His bilirubin rose progressively until February 17 when bilirubin was 31.1, alkaline phosphatase was 15.2 and alpha-fetoprotein was negative.

A liver biopsy revealed a striking duct proliferation. Hepatic vein catheterization revealed a right lobe wedge pressure of 45 and a left lobe pressure in the range of 12. Peritoneal fluid examination failed to reveal malignant cells.

The patient subsequently expired on March 23, 1971.

GROSS PATHOLOGY (Autopsy)

The liver weighed 2200 gms. and was deep green in the left lobe and in the median portion of the two left lobes. The right lobe, lateral to the line of the gallabladder was extensively sclerotic and pale. Scattered over the capsular surface of the liver were thin-walled cystic structures, ranging from 2 cm. down to .1 cm. The sclerotic areas of the right lobe also had some cystic structures. The lateral portion of the right lobe cut with

marked difficutly. It was densely sclerotic. The biliary tree on the left was dilated with clear mucinous material and at the point where the common hepatic duct bifurcated, the common hepatic duct was entirely sclerotic and occluded by material extending from the right duct. On the intrahepatic side of the area of occlusion, the entire biliary tree was quite dilated. The right side of the duct to the lateral portion was not generally recognizable, although there were some areas where dilated cut structures could be followed clear into the median lateral portion. The branches of the hepatic duct to the median portion of the true left lobe were dilated as were those to the lateral portion of the left lobe. The intrahepatic portion of the rest of the liver had a markedly accentuated lobular pattern by deep bile staining of the perivenular areas and a pale fibrous discoloration of the portal regions. The hepatic vein branches, even into the sclerotic lateral right lobe portion were patent.

The extrahepatic biliary system was not stained. The gallbladder did contain some pale, golden bile, which did not distend the gallbladder. The gallbladder wall was unthickened. There was no tumor. There were no calculi. The extrahepatic biliary tree was neither thickened nor dilated. The mucosa was pale and there were no obstructions. It emptied into the duodenum in a normal fashion.

No evidence of tumor metastasis was detected.

4.2 CASE DISCUSSION

DIAGNOSIS

Cholangiocarcinoma of right hepatic duct extending to common hepatic duct, with right lobe atrophy. Multiple hepatic cysts.

HISTOLOGIC DESCRIPTION

The true right lobe of the liver is almost completely atrophic with only occasional clusters of viable hepatocytes remaining. However the basic lobular configuration is maintained with regularly spaced portal structures. The intervening tissue is made up of proliferating cholangiolar structures, the terminal hepatic vein is obliterated, and there is dense fibrosis of the intervening stroma. The true ducts in the portal areas are not dilated, cholestasis is non-existent. Scattered randomly, are

microcystic ductal structures, occasionally forming cysts up to 1 cm diameter.

The left lobe of the liver has marked bile duct proliferation, with dilatation, the liver parenchyma is invaded by the proliferating ducts but considerable parenchyma remains. There is striking cholestasis within canaliculi. Scattered small cystic malformations of ducts may be found.

The right main hepatic duct is obliterated by dense fibrosis and by proliferating columns of tumor cells in a very restricted area of about .5 cm diameter and 2-3 cm long.

CHARACTERIZATION OF TUMOR

Carcinoma arising in the hilum of the liver from hepatic duct epithelium has variously been dubbed "hilar carcinoma", "Klatskin tumor" or "cholangiocarcinoma of hepatic duct bifurcation". Most tumors arising near the hepatic duct bifurcation, occlude both major branches of the hepatic duct nearly simultaneously, resulting in jaundice and all the features of complete mechanical duct obstruction. Unless this tumor is kept in mind considerable confusion may be engendered by the surgical finding of a shrunken gallbladder and a small extra hepatic duct in association with the changes in the liver characteristic of mechanical duct obstruction. Fortunately, most surgeons rely strongly upon the T-tube cholangiogram taken at surgery. Case 4, however, represents a variant of the pattern of such tumors in that the tumor arose in the right hepatic duct, completely occluding it for an unknown period of time before extending to the point of involving the juncture of the right and left ducts. The one sided occlusion resulted in complete atrophy of the true right lobe (demonstrating the true division between the two lobes by a line drawn from the gallbladder bed to the hepatic veins). Since the left duct initially remained patent, no symptoms developed from the right duct occlusion. By the time the common hepatic duct was involved, there remained no functioning hepatocellular tissue on the right, there was no dilatation of right sided intrahepatic ducts and no cholestasis or significant bile on the right side. The residual left lobe on the other hand, was deeply bile stained.

Cholangiocarcinomas of the bifurcation of hepatic ducts occurred in only .013 percent of patients in the LAC/USCMC, John Wesley autopsy series of 84,986 as compared with an incidence of .27% of autopsy cases in Japan.[1] The statistic may be deceptive, however, since more recent medical practices are oriented toward autopsies of selected patients only and patients with carcinoma

are apparently more frequently selected for autopsy studies than patients dying of other diseases. However, Okuda described approximately the same number of patients with hilar cholangiocarcinoma as those with peripheral cholangiocarcinoma, a feature out of line with the experience at LAC/USCMC.

Although hilar cholangiocarcinoma was uncommon in Edmondson's and Steiner's study of liver carcinomas from 1918-1958 at LAC/USCMC[2,3] in which only six cases from 48,900 necropsies were identified (.01%), Klatskin brought the tumor to greater medical awareness by reporting thirteen cases he had studied between 1947 and 1963, ten of whom were studied at Yale,[4] an incidence far in excess of that at LAC/USCMC. However Yale medical school, and particularly Dr. Klatskin's service, functions as a referral center for a rather broad population area and cases are highly selected. Dr. Klatskin divided the hilar cholangiocarcinomas into three groups: 1) intramural sclerosing tumor, 2) bulky invasive tumor, and 3) papillary tumor. All of these same tumor patterns may be seen also as peripheral cholangiocarcinomas. Six of thirteen of Dr. Klatskin's patients had scanty metastases at autopsy although the duration of illness ranged from 1.5 to 71 months after diagnosis. The prolonged survival of patients who develop this tumor has led to many instances of misdiagnosis.

In addition to the duct carcinoma, patient #4 had numerous asymptomatic hepatic microcysts and cyst complexes (of von Meyenburg). Cholangiocarcinomas have been reported to be associated with anomalies of the duct system that include: congenital saccular dilatation of the duct system (Caroli's disease),[5] congenital hepatic fibrosis,[6,7,8] Meyenburg complexes,[9] choledochal cyst,[10] and congenital biliary atresia.[11] Ordinarily the intrahepatic cystic diseases are associated with peripheral cholangiocarcinoma, in this instance the carcinoma arose in the major duct.

Other diseases associated with cholangiocarcinoma of major ducts in unusually high frequency include Clonorchis sinensis infestation[12] and chronic ulcerative colitis. The latter relationship was first recorded by Parker and Kendall in 1954[13] and has been emphasized in recent years.[14,15,16] In one series of such patients, the carcinoma was at the hilum of the liver in five patients but more distal in the extrahepatic duct system in three.[15]

DIAGNOSTIC METHODS AND DIFFERENTIAL DIAGNOSIS

With the popularization of the percutaneous cholangiogram and the endoscopic retrograde cholangio-pancreatic-ductogram (ERCP), the diagnosis of hilar cholangiocellular carcinoma should usually be made preoperatively. If such preoperative procedures are bypassed, the surgeon may be stymied by the "normal" extrahepatic duct system and collapsed gallbladder in the face of a tense, deeply bile-stained liver. A wedge biopsy at surgery may be interpreted by the pathologist to represent **primary biliary cirrhosis**, undoubtedly a diagnosis influenced by the knowledge of surgical findings.

Sclerosing cholangitis is often mistakenly diagnosed after duct biopsy attempts at laparotomy have yielded only fibrous tissue, and T-tube cholangiogram have shown a strictured area. The long period from diagnosis to death in some patients, found at autopsy to have duct carcinoma rather than sclerosing cholangitis, has led some investigators to consider hilar cholangiocarcinoma to have arisen from pre-existing sclerosing cholangitis. Peck, Kern and Mikkelson have shown that <u>most</u> patients diagnosed on radiological ground as having sclerosing cholangitis, actually have a sclerosing hilar cholangiocarcinoma.[17] Generous curettement of the hilar area at surgery is necessary to allow definite diagnosis of hilar cholangiocarcinoma.

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CASE 5. HEPATOCELLULAR CARCINOMA ARISING IN B-VIRAL CIRRHOSIS

CONTRIBUTOR: J. Brewster Gere, M.D.
Prescott, Arizona
TISSUE FROM: Right lobe of liver
(JWS5259-76)

June 4, 1978
ACCESSION NO. 22901
(151)

5.1 CASE SUMMARY

CLINICAL ABSTRACT

History: This 53 year old male had a past history of hospitalization for 11 months in 1948 because of persistent right upper quadrant pain and intermittent episodes of scleral icterus. There was a prior history of dental work as well as contact with a prison guard who later developed hepatitis. From 1949 - 1956, there was a history of substantial ethanol intake. Between 1951 and 1966, he was hospitalized several times because of right upper quadrant pain and nausea as well as intermittent episodes of scleral icterus and dark urine. In 1973, an exploratory laporatomy was performed and a cholecystectomy at that time revealed two large gallstones. At surgery the liver was described as hard, but non-nodular, with a cobblestone surface. In 1973 he was found to be hepatitis B surface antigen positive and was placed on steroids.

He was again hospitalized in March 1976 and physical examination revealed a firm palpable liver, 4 cms. below the right costal margin with a span of 15 cms. The spleen was palpable 5 cms. below the left costal margin. There was no detectable ascites, although he was icteric.

Laboratory data: CBC was within normal limits except for a hemoglobin of 10.6 and a hematocrit of 34; SGOT as high as 129, total bilirubin was 14.1 with a direct component of 8.1 and alpha-fetoprotein was normal. Hepatitis B surface antigen was positive; albumin 0.9 on one occasion; alkaline phosphatase was as high as 123 I.U.

Radiographs: A liver scan was normal, although celiac

angiography revealed a large hepatic tumor.

Course: The patient was discharged on 5 FU treatment. His condition gradually deteriorated and he expired in June of 1976.

GROSS PATHOLOGY (Autopsy)

At post mortem examination, the liver weighed 1940 gms. The right lobe was adherent to the diaphragm. There was also a large blood clot over the right lateral aspect where the serosal surface of the liver was shaggy and dark red. It was grossly distorted by two processes: 1) numerous well circumscribed, but nonencapsulated tumors, the largest measuring 17 x 10 cm. 2) diffuse, coarse nodularity, varying from 0.2 to 0.7 cm. in diamter. The nodules were green to yellow and separated by strands of green, fibrous tissue. Other areas were hemorrhagic. The only other gross findings were emaciation, 4+ jaundice, 1500 cc. of bloody ascites, esophageal varices with superficial erosion and hemorrhagic atelectasis of the right lower lobe with bronchopneumonia. Microscopic tumor emboli were present within pulmonary vessels.

5.2 CASE DISCUSSION

DIAGNOSIS

Hepatocellular carcinoma in B-viral cirrhosis

HISTOLOGIC DESCRIPTION

The tumor mass is made up of nodules that simulate cirrhosis in their growth pattern. Each nodule consists of irregularly sized trabecula of neoplastic hepatocytes without significant stroma, imparting a papilliform pattern to the tumor. The trabecula are generally only 4-5 cells thick, but occasional areas have thick plates or macrotrabecula. The tumor cells have poorly defined, deeply eosinophilic cytoplasm, irregularly sized and shaped cells, and irregular nuclei, most of which are vesicular with sharp chromatin-parachromatin demarcation. The non-tumor liver is cirrhotic, the nodules are large with very little inflammatory reaction ongoing necrosis. In a few areas, ground glass bodies (of Hadziyannis) in non-neoplastic hepatocytes can be found. Stains for hepatitis B surface antigen (HBsAg) show many

foci of cytoplasmic HBsAg, but no hepatitis B core antigen (HBcAg) is found in the single area studied.

REVIEW OF BIOPSIES

The first liver biopsy on the patient was performed in 1949. It showed some very subtle areas of bulging of parenchyma without distorting the lobules, there was no necrosis nor exudate. The portal areas were not significantly widened and lymphoid activity was quiescent. The tinctorial characteristics, hepatocytic size and regularity of cord pattern differed from one area to another and bore no relationship to lobular architecture. By 1966 there had been considerable destruction resulting in the pinching off of isolated islands of hepatocytes. By 1973 and 1974 the liver was frankly cirrhotic. In 1976 the patient had hepatocellular carcinoma.

CHARACTERIZATION OF TUMOR

Hepatitis B virus has now been recognized as the most important single etiologic agent in the genesis of hepatocellular carcinoma (HCC) on a world-wide scale. It is unquestionably more important in this regard in the United States than previously recognized.[1,2] The reported incidence of HBsAg positivity in HCC from several parts of the world is listed in table 1.

Table 1
Relative incidences of HBsAg in patients with hepatocellular carcinoma

Country (ref)	HCC % HBsAg +
Greece (5)	76%
Senegal (6)	61%
Gr Brit (7)	23%
Taiwan (8)	80%
Vietnam (9)	70%
California (4)	35.5%

In the United States where alcoholic cirrhosis is so common, even the relatively low figure of HCC in 4% of patients dying of alcoholic liver disease, makes alcoholic liver disease constitute a high percentage of the predisposing hepatic lesion in patients with HCC in the United States. The percentage of cases of HCC in cirrhotic livers that is due to alcoholism differs widely in different demographic areas at LAC/USCMC, about 50% of the cases

of cirrhosis that underlie HCC are alcoholic type.[4] In most countries, the large number of patients with alcoholic cirrhosis as the basis of HCC is non-existent; particularly is this so in West Africa, Asia and Greece which represent regions of exceedingly high incidence of HCC. Similarly, most countries with high incidence of carcinoma, have a relatively low incidence of HCC arising in normal liver although there are poorly documented statements that the livers are often "not cirrhotic".[10] Thus if we were to subtract from the series, the cases of HCC arising in the normal livers and those HCC complicating alcoholic cirrhosis, the percentage of those patients with HCC in Southern California who have serum or tissue evidence of HBV infection is 75%, as high in Southern California as nearly anywhere. This suggests that the high level of HCC in some countries is due to the high rate of B-viral disease, not to co-carcinogenesis.

At the John Wesley Hospital, HCC is found in 38% of patients dying with B-viral cirrhosis. Carcinoma of the liver has marked differences in sex incidence. As shown in Table 2 patients with HCC arising in alcoholic cirrhosis or in chronic B-viral disease have a male:female ratio in the range of 10:1. On the other hand patients with HCC arising in normal liver have about equal sex incidence while patients with HCC in cryptogenic cirrhosis have a female preponderence.[4]

Table 2

Sex preponderance of HCC as related to underlying hepatic condition

Underlying disease	M:F	Incidence
Alcoholic cirrhosis	10:1	4%-10%
B-viral cirrhosis	6.5:1	38.5%
Cryptogenic cirrhosis	1:4	38.5%
Normal liver	3:5	0.1%

The true relationship of the hepatitis B virus to liver cancer is unknown. Whether the neoplasm develops as a direct oncogenic effect of the virus or as a natural sequence of cirrhosis is unknown. However at least one group of investigators has been successful in producing hepatitis B surface antigen in tissue explants from hepatocellular carcinoma that arose in the liver of a patient with B-virus cirrhosis, indicating that the virus is apparently still present in the tumor.[11]

The fashion in which the carcinoma develops in B-viral

cirrhosis, in contrast to other types of cirrhosis, is pertinent. Carcinoma may develop in any stage of B-viral cirrhosis or precirrhosis accounting for the many reports of carcinomas arising in noncirrhotic livers. Shikata pointed out many years ago that it almost appeared as though the carcinoma and the cirrhosis arose simultaneously.[12] In support of this is the observation by Omata et al[14] that the age of patients dying from carcinoma arising from B-viral cirrhosis is the same as the age of patients dying of B-viral cirrhosis alone. Patients dying with carcinoma arising in alcoholic cirrhosis, in contrast, are ten years older than those dying with alcoholic cirrhosis alone, and carcinoma in the alcoholic only arises in advanced cirrhosis.

Differences in the incidence of carcinoma in different types of cirrhosis needs some further study. To date we have found no patients with lupoid cirrhosis who had hepatocellular carcinoma.

Diagnostic Methods

Of patients who enter the hosptial and die of HCC, only 15% have had symptoms of a "hepatitis like" illness in the past. Thus testing for **HBsAg** and **anti-HBc** is manditory in order to recognize the relationship of HBV to HCC. Since Omata et al has shown that 32% of patients with previously "cryptogenic cirrhosis" have hepatitis B antigens in tissue and anti-HBc in sera, an accurate evaluation of the relationship of hepatitis B to HCC requires testing for anti-HBc in patients who have no other basis for the cirrhosis underlying their HCC.[4,13]

Alpha-fetoprotein is elevated to levels above 350 ng./ml. in about 75% of the patients with hepatocellular carcinoma arising in B-viral cirrhosis. The incidence of alpha-fetoprotein is thus somewhat higher in patients who have B-viral cirrhosis and HCC (73%) than it is in patients whose hepatocellular carcinoma arises in alcoholic cirrhosis (about 66%) cryptogenic cirrhosis (43%) or in noncirrhotic liver (about 30%). Okuda showed that patients with a wide variety of hepatic disorders had alpha-fetoprotein levels between 20-400 ng./ml. (normal less than 20 ng./ml.) and that a few had alpha-fetoprotein in the range of 500-1000 ng./ml. About 10% of the hepatocellular carcinoma patients had alpha-fetoprotein detectable only in the ranges of 20-400 ng./ml. Okuda further showed that if one serially quantitated the levels of alpha-fetoprotein in patients with chronic active hepatitis type B, increases in levels occur concomittantly with the recognition of small tumors that could be detected by selective arteriograms.[14]

Hepatic scans are quite useful in identifying filling defects that represent hepatocellular carcinoma. However in the cirrhotic liver, false scan defects can be identified. Tumors less than 2.5 cm. may not be found and multiple small foci of hepatocellular carcinoma may be overlooked on the liver scan.

Selective arteriogram is one of the most useful radiologic tools for identifying hepatocellular carcinoma. Typically the arterial vessels leading to the tumor are markedly enlarged. They are also bowed or displaced to the side, and as they enter the neoplasm they lose their regular size and numerous pools of contrast material may be identified in the arterial phase of the injection. Often the portal vein branches may fill during the arterial phase. In the venous phase the contrast remains in the highly vascular neoplasm.[15] In the tumor that is growing in a nodular (cirrhoto-mimetic) fashion, the residual contrast will have a nodular pattern. Although there is little radiologic experience to relate the kind of background liver in which carcinoma arises, from the autopsy - characteristics of hepatocellular carcinomas that arise in cirrhotic liver as contrasted to that arising in noncirrhotic liver, the pseudolobular character of the residual contrast should suggest that the tumor is arising in chronic liver disease even is the liver is not completely cirrhotic.

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CASE 6. LIVER CELL ADENOMA

CONTRIBUTOR: Roy L. Byrnes, M.D.
South Laguna, California
TISSUE FROM: Liver
(LUS1580-78)

June 4, 1978
ACCESSION NO. 22896
(156)

6.1 CASE SUMMARY

CLINICAL ABSTRACT

History: This 25 year old female first noted a slightly tender abdominal mass in March 1973. She had been on oral contraceptives (Ovulen 21) for four years, and she reported a 20 pound weight loss over the preceeding year.

On physical examination she was found to have a firm, slightly tender right upper quadrant mass which moved with respiration.

Radiographs: Aortography showed an avascular area of the inferior aspect of the right lobe of the liver, which by liver scan was interpreted as a "non-functioning mass lesion".

SURGERY (April 10, 1973)

An exploratory laparotomy revealed a 6 x 6 cm. mass confined to the right lobe of the liver. A partial hepatectomy was performed.

GROSS PATHOLOGY

The specimen consisted of a 380 gm., 12 x 10 x 7 cm. piece of liver almost completely covered by a smooth glistening capsule. On sectioning, the tissue was almost completely replaced by a fleshy ovoid 10 x 9 x 7 cm. discrete mass which on sectioning had a yellow-tan surface. The lesion appeared to have a thin capsule separating it from the adjacent parenchyma.

FOLLOW-UP

The patient was last seen in January 1974 and was doing well. She reported weigh gain and was using an IUD for contraceptive.

6.2 CASE DISCUSSION

DIAGNOSIS

Liver cell adenoma.

HISTOLOGIC DESCRIPTION

The tumor is composed of benign hepatocytes arranged in cords similar to the arrangment of normal liver cells. The hepatocytes are fairly normal in size and appearance. They have a rather clear base and are more granular in their central portions where they form canaliculi. There is a remarkable uniform quality to all of the hepatocytes. Many of the cells are binucleated but mitoses are not seen. The sinusoidal system is similar to that of the normal liver except the lining cells do not appear quite as large and there is no evidence of phagocytosis. The vascular supply is abundant. Often the arteries and veins accompany one another. There are no bile ducts and no cholestasis. A well-defined capsule is present.

CHARACTERIZATION OF TUMOR

Liver cell adenomas (LCA) consist of fairly normal appearing hepatocytes that are arranged in cords. A canalicular pattern is common, sometime with small acini. Bile formation is evident in about 25 percent of cases. Mitoses are rarely seen, apparently the cells undergo amitotic cell division. In nearly every case of LCA there is a well-defined capsule. There are no bile ducts.

Infarction and hemorrhage are noted in about two-thirds of the tumors. In some adenomas the infarcts are old and have been replaced by scar tissue. In other cases hemorrhage and necrosis is more recent and rupture through Glisson's capsule may be occurred. Malignant change is a rare complication but does occur.[1]

GROSS PATHOLOGY

Adenomas in their early stages are homogeneous appearing light, tan-brown encapsulated tumors. They are not as a rule lobulated. After necrosis and hemorrhage, the centers of the tumors may show extensive degenerative changes with pigmentation, softening and a mild degree of fibrosis. Occasionally, small areas of adenomatous change may be seen just outside the capsule or in other parts of the liver. These small multiple lesions may be nonencapsulated.

CLINICAL FEATURES AND HISTORY

Adenomas of the liver were a rare occurrence before the era of oral contraceptive (1960). I had difficulty getting material for the liver fascicle that was published in 1958, either from local sources or from the Armed Forces Institute of Pathology. With the use of oral contraceptive hormone (OCH) there has been an increase of frequency of LCA.[2] In my material which now numbers over 50 cases, about one-third of the women had a symtomless mass in the right upper quadrant, another third had pain and discomfort produced by infarction and/or hemorrhage, another third had a rupture that led to emergency surgery. A few deaths have been reported. Hemorrhage rarely occurs in an adenoma in a nonuser. Although most of the cases published to date are associated with the use of menstranol, women on ethinyl estradiol are also subject to LCA. The relative risk factor in long continued use of OCH is shown in the following table.

Table 2

Duration of Use of Oral Contrceptives for
30 Case-Control Pairs

Months	Cases	Controls	Risk Ratio*
Up to 12	6	15	1.0
13-36	4	8	1.3
37-60	7	7	2.5
61-84	4	2	5.0
85-108	3	1	7.5
109+	10	1	25.0

*Compared to use up to 1 yr. Similar relative risks are obtained if a matched analysis is performed.

In recent years much smaller doses of the synthetic estrogens are being used. It remains to be seen whether or not women are less susceptible to LCA on the reduced dosage schedule.

In the nationwide study conducted by the American College of Surgeons, the peak incidence of LCA due to OCH occurred at 25-30 years of age and thereafter falls quickly. This survey did not show an increased risk that was related to duration of OCH use.

A few examples of spontaneous regression of LCA have been noted when women with known tumors that were too large to remove surgically have discontinued the pill.[3] The dissapearance of tumors 10-12 cm in diameter is difficult to understand. On the contrary, in a few cases LCA has become clinically manifest or has ruptured months or years after discontinuance of OCG.[4] Nevertheless, it appears that in some instances LCA is hormone dependent to an extraordinary degree.

DIFFERENTIAL DIAGNOSIS

Adenomas have to be differentiated primarily from focal nodular hyperplasia. The helpful features are as follows:

	ADENOMA	FNH
Capsule	+	-
Broad sheets of hepatocytes	+	-
Excess glycogen storage	+	- +
Central scar	-	+
Bile ducts	-	+
Pseudolobules	-	+

DIAGNOSTIC METHODS

Liver scans disclose a cold lesion. On angiogram about one-half are hypovascular and one-half hypervascular. However, a septate blush is never seen.

TREATMENT

The treatment of an adenoma that is complicated by infarction and hemorrhage is necessarily surgical excision. However, the patient with a symptomless mass might be treated by discontinuance of the pill. The only risk in this case would be whether or not this should be done without a needle biopsy. Occasionally large mutiple masses are present in the liver that can not be removed at surgery and conservative managment is the only mode of therapy.

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CASE 7. MIXED HEPATOBLASTOMA

CONTRIBUTOR: W. Leonard Taylor, M.D.
Redlands, California
TISSUE FROM: Left lobe of liver
(LUS1586-78)

June 4, 1978
ACCESSION NO. 20546
(158)

7.1 CASE SUMMARY

CLINICAL ABSTRACT

History: This one year old girl was noted to have a left flank mass on physical examination for a upper respiratory infection.

Radiographs: IVP revealed the mass to be calcific and distorting the upper calyceal system. Cytoscopy and left retrograde pyelogram were normal. Tentative diagnosis of Wilm's Tumor was made.

SURGERY (January 4, 1972)

At laparotomy the left kidney and spleen were found to be normal. However, there was a large mass involving the left hepatic lobe. A lobectomy was performed.

GROSS PATHOLOGY

The specimen consisted of a 350 gm. well demarcated tumor measuring 10.5 x 9.0 x 6.0 cm. The external surface was nodular (2.0 to 2.5 mm). Sectioning revealed soft, nodular yellowish-tan, focally hemorrhagic tissue. Firm gray gritty areas were present as well.

FOLLOW-UP

No treatment was given untl 6 months postoperative when hepatomegaly developed. The patient received Cytoxan, Vincristine, and Actinomycin D with good results, however the patient returned in November 1973 with hepatomegaly and a right lower lobe pulmonary lesion, considered to be metastatic. Five FU was begun without benefit. Later Adriamycin and DTIC were added to the regimen also without benefit. Methotrexate also had no effect. Vinblastine sulphate was then given weekly. However by April 1974 she had developed increasing cyanosis and dyspnea with a huge tumor filling the entire right chest, displacing the mediastinal structures. Nodular infiltrates were present in the left chest. Abdominal radiographs demonstrated a liver mass extending half way down to the iliac fossa, crossing the midline in the lower thoracic upper lumbar areas. The patient expired on April 8, 1978, no autopsy was performed.

7.2 CASE DISCUSSION

DIAGNOSIS

Mixed hepatoblastoma

HISTOLOGIC DESCRIPTION

This neoplasm is composed of a mixture of neoplastic hepatocytes, primitive mesenchyme and osteoid tissue. The hepatocytes differ greatly in various parts of the tumor. In the better differentiated areas (fetal type cells) a cord arrangement is seen but canaliculi are not clearly seen. Many of the cells contain fat vacuoles. There are numerous areas of extramedullary hematopoiesis noted. The more immature cells (embryonal type) have scanty cytoplasm, the nuclei are more hyperchromatic and a cord arrangement is not evident. These foci of light staining cells stand out in sharp contrast to other parts of the neoplasm. Among these cells there is considerable mitotic activity. The stroma consists of rather widely spaced mesenchymal cells that have short, oval to spindle-shaped nuclei and a considerable amount of intercellular stroma. Throughout the stroma there are islands of osteoid. These seem to be surrounded by a thin layer of connective tissue. In some of the islands of osteoid there is

calcification. Many areas of necrosis and hemorrhage are present as well as deposition of hemosiderin. An incomplete capsule is present. Many blood vessels that contain tumor cells are present in various parts of the tumor.

CHARACTERIZATIÓN OF TUMOR

This is an example of a mixed hepatoblastoma of the liver. These occur almost exclusively in the first five year of life with an almost equal frequency between boys and girls. Most of the patients present with abdominal enlargement but pain, jaundice, fever and rare findings such as hemihypertrophy and endocrine symptoms have been reported. There is no explanation for the various elements in the mixed hepatoblastoma, one must assume that both primitive mesenchyme and the hepatocytes undergo neoplastic change. The metastases usually do not contain osteoid.

DIAGNOSTIC AIDS

The radioactive isotope scans will accurately localize most lesions. Arteriography most often shows the increased vascularity of the tumor. The laboratory findings often include an increase in SGOT. The alpha-fetoprotein may be normal.

GROSS PATHOLOGY

The tumors that have been resected may vary from a few centimeters to 18 cm in diameter and weigh as much as 800 gms. They are usually lobulated, variegated in appearance due to degenerative change and have a pseudocapsule.

TREATMENT

Surgical resection has proven to be the most successful. According to Foster and Berman's review, 21 or 36 patients under two years of age have survivied without evidence of disease for a mean of 53 months and 4 of 11 over two years old have a mean survival of 81 months.

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CASE 8. METASTATIC CARCINOMA FROM PANCREAS

CONTRIBUTOR: A. Wittman, M.D.
Los Angeles, California
TISSUE FROM: Liver
(LUS3610-77)

JUNE 4, 1978
ACCESSION NO. 22902
(161)

8.1 CASE SUMMARY

CLINICAL ABSTRACT

History: This 57 year old Caucasian male with a 15 year history of diabetes mellitus complained in Jaunary 1977 of weight loss of 6 months' duration. This was in conjunction with a postprandial epigastric pain which radiated to his back

Significant laboratory studies included a normal CEA, Hct 36, WBC 9,400, HAA negative, AFP Negative, liver functions completely within normal limits including an alkaline phosphatase.

Work-up in June 1977 revealed several filling defects in liver scan in the right lobe. ERCP, on May 31, 1977, showed a normal biliary tree but inadequate visualization of the pancreatic ducts. An EMI body scan on June 10, 1977, showed no definite lesions in the pancreas but low density filling defect seen in the right lateral region of the liver. Barium enema and upper gastrointestinal series were within normal limits. Liver biopsy was interpreted as a moderately well differentiated hepatocellular carcinoma arising in a noncirrhotic liver.

The tumor was unresectable, and the patient was placed on chemotherapy (Adriamycin and CCNU). He did well until August 3, 1977, when he was readmitted for fever, chills, nausea, vomiting and leukopenia (WBC=2,400). No obvious source of infection was noted, and he was placed on Keflin and Gentamycin. The patient's condition progressively deteriorated (his bilirubin rose to 12.5) and he expired on August 29, 1977.

GROSS PATHOLOGY (Autopsy)

The right lobe of the liver had a 10 x 9 x 9 cm. irregular yellow-gray-white tumor mass extending to the porta hepatis and compressing the vessels and bile ducts. There were two smaller but otherwise similar tumor masses in the liver, one in the left lobe. The portal vein was thrombosed, the hepatic artery, vein and common bile ducts were compressed by tumor.

The pancreas was distorted by a 10 x 8 x 7 cm. rock hard mass replacing the head of the body. The pancreatic tail was small, hard and had a gray-white and yellow mottled cut surface.

Additional tumor was grossly seen to involve the ampulla of Vater, both lungs, both kidneys, both adrenal glands, and the right pectoral muscle.

8.2 CASE DISCUSSION

DIAGNOSIS

Liver, metastatic ductal carcinoma, primary in pancreas.

HISTOLOGIC DESCRIPTION

The liver biopsy revealed that part of the liver was replaced by cords of plump tumor cells with large nuclei and prominent nucleoli. No canaliculi were detectable and there was no trabecular pattern to the tumor. The tumor did not invade into the sinusoids of the liver. There were numerous mitoses.

At autopsy, the carcinoma had much the same cytologic pattern but could be found extending through the sinusoids interdigitating with the cords. In many areas there were well formed duct structures and in the liver adjacent to the tumor the bile duct elements were atypical and proliferative.

Segments of the pancreas taken at autopsy were sclerotic and extensively infiltrated by duct forming carcinoma that lacked the solid cords of tumor that were identifiable in the initial liver biopsy.

CHARACTERIZATION OF TUMOR

This patient's tumor is classically pancreatic carcinoma metastatic to liver. The initial liver biopsy reflected how metastatic pancreatic carcinoma may be misinterpreted as primary liver cancer, particularly when sclerosing duct structures are not present. Those areas of sclerosis were found, but only in the autopsy liver.

In the USC Oncology service at John Wesley Hospital, carcinoma of the pancreas has been the most common origin of hepatic metastatic tumors that, until autopsy, were of unknown origin. Eighty-four percent of patients with carcinoma of the pancreas have liver metastases at autopsy (80% of those arising in the head of the pancreas and 87.5% of those with tumors arising in body and tail). Carcinoma of the pancreas frequently is mistaken for cholangiocarcinoma, a tumor that is found in much lower frequency than carcinoma of the pancreas. Tumors that infiltrate into the hepatic sinusoids are rarely cholangiocarcinomas and instead are metastatic.

DIFFERENTIAL DIAGNOSIS AND DIAGNOSTIC TECHNIQUES

Carcinoma of the pancreas is a prime suspect when carcinoma is found in a noncirrhotic liver of a jaundiced patient. Most metastatic tumors do not produce jaundice except as a terminal event. Carcinoma of the head of the pancreas usually heralds it's onset by to invasion of the common bile duct. Carcinoma of the neck of the gallbladder which also produces jaundice as a first symptom by invading along the cystic artery to obliterate the hepatic ducts at the bifurcation, tends not to extensively involve the liver parenchyma in contrast to carcinoma of the fundus of the gallbladder which does not usually produce jaundice early in the disease.

The diagnosis of carcinoma of the body or tail of pancreas can now more readily be made due to the advances in contrast radiography and in "skinny needle" aspiration. Pancreatic ductograms (ERCP) will demonstrate many early carcinomas of the pancreas and thin needle aspiration, guided radiographically into the areas of suspicion can allow a very early diagnosis of the neoplasm. Unfortunately clinical symptoms that would bring about such relatively expensive diagnostic approaches, are usually lacking early in the development of this neoplasm.

CASE 9. INFANTILE HEMANGIOENDOTHELIOMA, LIVER

CONTRIBUTOR: Francis S. Buck, M.D.
Los Angeles, California
TISSUE FROM: Liver
(1581-78)

JUNE 4, 1978
ACCESSION NO. 17251
(146)

9.1 CASE SUMMARY

CLINICAL ABSTRACT

History: This child was born on August 4, 1967, weighing about 2 pounds 5 ounces, with a crown-heel length of 38 cm. Both the baby and her mother were O, Rh positive. The infant received exchange transfusions on the third and fourth days of life because of hyperbilirubinemia. The etiology was undertermined. Blood and urine cultures were sterile. She failed to thrive, with subsequent development of chronic anemia and hydrocephalus. She expired on January 2, 1968.

GROSS PATHOLOGY

Autopsy demonstrated hydrocephaly; marked atrophy of adrenal, thyroid and thymus glands; multiple tumors of the liver; and peritonitis caused by coliform organisms.

The liver weighed 102.5 gm., was yellow-tan, and contained many small, pearl-like, gray-white tumors up to 0.4 cm. in diameter.

9.2 CASE DISCUSSION

DIAGNOSIS

Infantile hemangioendothelioma

HISTOLOGIC DESCRIPTION

The section of liver contains numerous circumscribed areas of involvement by a vasoformative tumor. The vessels in the tumor have rather small lumens and are lined with benign endothelial cells that are for the most part a single layer in thickness. Most of the vascular lumens within the tumor are bloodless. Between the newly formed vessels there is loose fibrous stroma that contains primitive mesenchymal cells, some of which are obviously fibroblasts that are actively forming collagen. Mitoses are not seen in either the endothelial cells or stroma. In the stroma there are many islands of extramedullary hematopoiesis. As the small tumors have expanded in size and replace portions of the liver lobules, there is considerable transformation of hepatocytes to bile duct epithelium so that in most of the lesions there is a mixture of bile ducts. In some of the larger, older appearing nodules the blood vessels are a bit wider and there is more collagen deposition in the stroma.

Many of the neoplastic foci appear to be located in the vicinity of portal tracts but do extend well into the lobules, sometimes apparently replacing an entire lobule or more.

In the liver parenchyma not involved by tumor, some of the portal tracts appear more fibrotic than normal. A few of them show mild bile duct hyperplasia.

CHARACTERIZATION OF TUMOR

Infantile hemangioendotheliomas arise in early life, usually before the age of six months. They usually grow rapidly causing enlargement of the abdomen and marked hepatomegaly. Arteriovenous shunts within the tumor may cause cardiac hypertrophy, a cardiac murmur and even heart failure. Cutaneous hemangiomas are present in many of the patients, as well as hemangiomas of other organs. Grossly, the lesions are usually multicentric involving the entire liver. Although individual nodules may reach a size of 15 cm, the average size is about 4 cm or so. Occasionally the lesions are solitary and more solid in appearance. In a few cases cavernous angiomatous change has occurred. Ishak describes two histologic types, an orderly proliferative type and a more aggressive tumor in which the endothelial cells are larger and more hyperchromatic.

DIFFERENTIAL DIAGNOSIS

Hemangioendotheliomas are distinguished from malignant tumors of blood vessels in that the endothelial cells lining the newly formed vesssels are benign. On rare occasions a mesenchymal hamartoma may be excessively vascular, and shunts occur that are followed by heart failure. The edematous mesenchymal background of the hamartoma in pathognomonic. Hepatic cavernous hemangiomas in the newborn or in the first weeks of life may require surgery but the gross and microscopic differentiation is easy.

DIAGNOSTIC METHODS AND LABORATORY FINDINGS

Related features may include a normocytic normochromic anemia, leukocytosis, hyperbilirubinemia, microangiopathic hemolytic anemia and occasional thrombocytopenia with bleeding complications. With the use of i.v. urograms, liver scans and angiography, a diagnosis can usually be made.

PROGNOSIS

This should be guarded as the course of the disease may be complicated by the presence of congenital anomalies, congestive failure, hepatic failure, etc. About one-half of the reported cases have survived. On rare occasions the tumors become malignant.

TREATMENT

One or more modes of treatment include partial hepatectomy for localized lesions, radiation, hepatic artery ligation and corticoids.

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the liver: Report of three cases. Pediatrics 19:596-606, 1957.

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CASE 10. METASTATIC EPITHELIOID LEIOMYOSARCOMA (LEIOMYOBLASTOMA)

CONTRIBUTOR: Albert Garib, M.D.
Huntington Beach, California
TISSUE FROM: Liver
(LUS1582-78)

JUNE 4, 1978
ACCESSION NO. 21847
(160)

10.1 CASE SUMMARY

CLINICAL ABSTRACT

History: This 32 year old male patient presented on May 6, 1976, with a nine month history of progressive weight loss and hepatosplenomegaly.

Laboratory studies included a normal bilirubin, LDH, SGOT, SGPT. Alkaline phosphatase was 117 IU (normal 30-100). Alpha-fetoprotein and HAA were negative.

Radiographs: Liver scan revealed multiple hepatic filling defects. An upper GI series revealed a gastric mass with central ulceration.

A gastroscopy was performed and a 3 cm. diameter sessile polyp with a central area of ulceration was biopsied. A needle biopsy of the liver was also obtained.

SURGERY

In order to help determine the nature of the tumor, an exploratory laporatory was performed on May 17, 1976. The liver was massively enlarged due to tumor in both the left an right lobes. Although obscured by the enlarged liver, at no point was the liver contiguous with the stomach. A biopsy of the liver was taken.

GROSS PATHOLOGY

The specimen consisted of an irregular rectangle of tissue measuring 4 x 3 x 2.8 cm. in maximum dimension. The surface of the liver was irregularly lobulated with numerous subcapsular confluent gray nodules, measuring up to 3 cm. in diameter. On section the parenchyma was partially replaced by numerous confluent gray nodules, which were fleshy, finely granular, soft and bulging on section. The nodules, were sharply demarcated from adjoining liver parenchyma and ranged in size from 0.3 to 1.6 cm. in maximum dimension.

FOLLOW-UP

The patient did not respond to chemotherapy and moved out of the area in January 1977. He was alive in April 1978, although his state of health was unknown.

10.2 CASE DISCUSSION

DIAGNOSIS

Metastatic epithelioid leiomyosarcoma (leiomyoblastoma)

HISTOLOGIC DESCRIPTION

This section discloses a malignant neoplasm that has grown most prominently within the lumens of blood vessels, apparently branches of the portal vein. Most of the tumor cells tend to be arranged in clusters. The cells have a rather plump, spindle shape with frequent areas of palisading. The nuclei of the cells are oval with smooth nuclear membranes. Some of the nuclei are surrounded by a halo. Nucleoli are not prominent. A few mitoses are noted. The cytoplasm varies considerably in amount. In much of the tumor it appears to form an elongated mass that encases the nucleus in its center. Fibrils can be seen in cytoplasm. Cell membranes are not clearly delineated.

CHARACTERIZATION OF TUMOR

This is a malignant leiomyoblastoma or epithelioid leiomyosarcoma that arose in the stomach. The presence of small clusters, as well as the appearance of the closely packed nuclei and a scattering of clear cells are characteristic of this particular tumor. These tumors occur mostly in the stomach and retroperitoneal area.[1]

Appelman and Helwig have classified the round cell myogenic tumors of the stomach into two groups: 1) epithelioid leiomyomas, and 2) epithelioid leiomyosarcomas (leiomyoblastomas).[2] In the first group, the cells have abundant eosinophilic cytoplasm so that the nuclei appeared widely separated. Several microscopic patterns were recognized. In the second group, the leiomyosarcomas, the cells were similar to the benign tumors, but the cytoplasm was less quantitatively and the nuclei were more closely packed. Two cellular subgroups were recognized. In the second malignant pattern, a clustering similar to Case 10 was frequently noted. Extensive palisading was not mentioned. Metastases were seen in some 65 percent of cases, usually in the liver.

Electron microscopy is helpful but none of the criteria indicative of smooth muscle mentioned in Case 1 may be seen. However, intracytoplasmic filaments have been observed.[1] Where the diagnosis of leiomyosarcoma is made from biopsy material the pathologist should always inquire as to the gross and/or clinical findings. Metastatic leiomyosarcoma is much more prevalent than primary. Primary leiomyosarcoma is extremely rare. The presence of sarcoma in the branches of the portal veins is a clue as to whether or not the neoplasm is primary in the liver. In the study of malignant tumors of the liver that are not obviously of hepatic origin, the growth of cells in the branches of the portal is indicative at least of extrahepatic origin and the clinician should be alerted as to this possibility.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes all other spindle-cell sarcomas of the liver. Fibrosarcomas are rare but the dense collagenous deposition is helpful. Neurogenic sarcomas are rarely seen in the liver but may have a palisade arrangment similar to this tumor. Liver cell carcinoma may be associated with a spindle-cell component that shows no evidence of differentiation into any specific sarcoma. Some sarcomas in adults are undifferentiated and many terms have been used for them, including

non-differentiated sarcoma,[3] malignant mesenchymoma and mesenchymal sarcoma.

DIAGNOSTIC METHODS

Liver scans and angiograms would not differ from any other metastatic cancer.

10.3 REFERENCES

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2. Appelman HD and Helwig EB: Gastric epithelioid leiomyoma and leiomyosarcoma (leiomyoblatoma). Cancer 38:708-728, 1976

3. Mattila S, Keskitalo E and Makinen J: Primary non-differentiated sarcoma of the liver. Acta Chir Scand 140:303-307, 1974

CASE 11. MULTILOCULAR CYSTADENOMA

CONTRIBUTOR: Marvin Retsky, M.D.
Van Nuys, California
TISSUE FROM: Liver

June 4, 1978
ACCESSION NO. 22839
(159)

11.1 CASE SUMMARY

CLINICAL ABSTRACT

History: This 67 year old Caucasian female presented with a complaint of pain and swelling in the right upper quadrant of the abdomen, approximately two weeks' duration. The pain radiated to the back. The gallbladder had been removed in 1946.

Physical examination: A palpable mass was present in the right upper quadrant of the abdomen, extending downward to the lower abdomen. It was nontender, nonpulsatile and slightly mobile.

Laboratory data including alkaline phosphatase, SGPT, SGOT, bilirubin and CEA were within normal limits. Alpha-fetoprotein was not determined.

SURGERY (February 25, 1978)

A hepatic lobectomy removing a large mass occupying the left lobe of the liver and extending to the right lobe was performed.

GROSS PATHOLOGY

The mass weighed 2,670 gms. and measured 21 x 17.5 x 10 cm. The mass was externally lobulated with a narrow rim of grossly identifiable liver tissue present. The mass consisted of one large cyst filled with cloudy mucoid fluid. Multiple smaller cysts up to 1.5 cm. were present in the wall.

11.2 CASE DISCUSSION

DIAGNOSIS

Multilocular cystadenoma with questionable malignant change.

HISTOLOGIC DESCRIPTION

The tissue slide on this case is taken from the wall of the large cyst. The epithelial lining of the cyst varies considerably, but for the most part the cells are columnar and have much centrally placed, clear cytoplasm. A few of the cells contain large mucoid globules in the cytoplasm. In much of the wall the subepithelial connective tissue is densely cellular. An unusual feature is the presence of many large, thick-walled arteries just beneath the epithelium. In part of the tissue submitted there has been a papillary change in the epithelial lining and multiple glandular structures are present in the wall. The individual cells are somewhat larger and have hyperchromatic nuclei. However, no mitoses are observed nor is there evidence of invasion of the underlying connective tissue. Outside the large cyst are many small cysts and duct-like structures lined with a benign type of columnar epithelium. Mucinous material is noted in some of the small cysts, also a few contain neutrophils. Occasionally, the epithelial lining is absent and the wall of the small cyst appears somewhat hyalinized and acellular. Peripheral to the subepithelial tissue is a more mature type of connective tissue that carries larger blood vessels.

CHARACTERIZATION OF TUMOR

In this multilocular cystadenoma the area of atypical proliferative change raises the question of cystadenocarcinoma. Ishak, in 1977, reported eight cases of cystadenoma and six of cystadenocarcinoma.[1] In addition he noted there were ten published cases. In my material of 18 cases, six had undergone malignant change. Some 80% of multilocular cystadenomas have been noted in women, usually in the middle age group. They may reach a large size, occasionally enclosing up to 10 or 11 liters of mucinous fluid. Some have been noted in the bile duct system. The mucinous character of the fluid distinguishes cystadenomas from simple cysts of the liver. Occasionally there will be one cyst that composes most of the tumor, and rarely they are unilocular. These tumors bear some gross resemblance to cystadenomas of the

pancreas.

Unusual features on microscopic examination include evidence of hemorrhage in nearly every case and deposition of hemosiderin in the subepithelial tissue. Occasionally calcification is seen in the connective tissue around the cysts.

The histogenesis of multilocular cystadenomas is unknown. They are presumed to arise from the bile ducts yet the mucin-producing type of epithelium that lines the cysts is not a normal component of bile ducts. Any theory of origin should take into account their similarity to cystadenomas of the pancreas. It is difficult to relate any feature of cystadenoma to the embryologic development of the liver or pancreas.

DIFFERENTIAL DIAGNOSIS

This includes primarily simple nonparasitic cysts. These contain clear watery fluid and are not multilocular. Occasionally, however, there may be two or more simple cysts in a cluster. Their walls are usually thinner and more transparent than the walls of multilocular cystadenomas. Echinococcal cyst has a thick chitinous wall, is usually unilocular and the clinical diagnosis is made before surgery.

DIAGNOSTIC PROCEDURES

Sonograms are helpful in diagnosing cystic lesions of the liver. Liver scans show a filling defect and arteriograms disclose an avascular lesion.[2]

TREATMENT

Surgical excision is the only recommended treatment. Only rarely is a cystadenoma so large that it cannot be removed.

11.3 REFERENCES

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CASE 12. ANDROGEN PRODUCING TUMOR, PRIMARY IN LIVER

CONTRIBUTOR: Albert Stanek, M.D.
Brooklyn, New York
TISSUE FROM: Liver
(LUS1736-78)

JUne 4, 1978
ACCESSION NO. 22906
(159)

12.1 CASE SUMMARY

CLINICAL ABSTRACT

History: This 23 year old woman was in good health until seven months prior to admission (1978) when she experienced amenorrhea, hirsutism, weight gain and voice deepening, all of which grew progressively worse.

Physical examination revealed cushingoid facies, hepatomegaly, clitoral enlargement, and a male pattern of body hair distribution.

Laboratory studies: Morning and afternoon cortisol were 26.1 and 21.0 mcg./dl. respectively (normal 5-25 mcg.). After 8 mg. of dexamethasone the morning and afternoon levels were 26.8 and 20.2 mcg./dl. The serum testosterone level was 393 ng./dl. (normal 30-60 ng./dl).

Radiographs: An intravenous pyelogram was normal. Sonography disclosed a large mass in the right suprarenal region, most likely in the liver. Liver scan revealed a large hepatic mass. Catheterization of the inferior vena cava was done to evaluate focal levels of cortisone and testosterone. Cortisol levels from 13 sites, including the left and right hepatic veins, failed to demonstrate significantly elevated levels above those found in the right atrium (18.9 mcg./dl.). Testosterone levels from the same sites ranged from 105 to 156 ng./dl. except for the right hepatic vein levels of 799 ng./dl.

COURSE

A laparoscopy was planned; however, the patient suddenly became cyanotic, had a cardio-respiratory arrest and expired.

GROSS PATHOLOGY (Autopsy)

The liver weighed 2,650 gm. A single, large white mass, measuring 18 x 15 x 14 cm., was found to occupy most of the right lobe as well as considerable portion of the left lobe of the liver. The tumor margins were well demarcated and in most areas the mass could be easily separated from the liver. The hepatic tissue surrounding the tumor was compressed and along both the superior and inferior aspects measured no more than 3-4 mm. in thickness. Nowhere, however, was the tumor actually contiguous with Glisson's capsule. Other than the deformity from the compression, the liver showed no abnormalities. No evidence of cirrhosis was present. In spite of a very careful search, no metastases were found. A large pulmonary embolus was found in the left pulmonary artery which was the cause of death.

12.2 CASE DISCUSSION

DIAGNOSIS

Androgen producing primary hepatic tumor.

HISTOLOGIC DESCRIPTION

The neoplasm in the liver is composed of malignant cells that tend to form cord-like masses of variable width that are separated by bands of collagenous connective tissue and blood vessels. The neoplastic cells vary considerably in appearance, from round to spindle-shaped forms. Most of them have rather irregularly shaped, finely stippled nuclei that are moderately hyperchromatic. Some cells do have larger, more hyperchromatic nuclei. Mitotic activity is present, particularly in the latter cells. In many of the tumor cells a small nucleolus is seen but these are not prominent. The cytoplasm of the tumor cells is moderate in quantity, being somewhat less than that of a normal hepatocyte. The cytoplasm has a very fine granular quality. It is difficult to say whether or not any of the tumor cells are forming acini or canaliculi. No Reinke crystals are observed. The neoplastic

cells are intimately related to fibrous stroma. The latter not only forms bands but also in many areas individual neoplastic cells and oblong masses are surrounded by fine, fibrillar connective tissue and blood vessels. Throughout the tumor, small remnants of liver parenchyma remain, both bile ducts and hepatocytes being seen. At its margins the tumor is obviously invading liver tissue, apparently displacing the hepatocytes. No invasion of the blood vessels is seen.

CHARACTERIZATION OF TUMOR

This tumor is difficult to categorize. I have not had a similar case. It does not resemble hepatocellular carcinoma, nor are there any bridging forms between the hepatic parenchyma and the neoplasm. There is some resemblance to normal adrenal cortex, especially in regard to the appearance of the nuclei and cytoplasm and also the relationship to connective tissue. The question of whether or not adrenal rest tumors may arise in the liver has not been decided. Hamperl did not think this could occur.[1] The presence of a small right adrenal gland in this patient rules out origin from a displaced gland. Aberrant liver tissue has been noted in the adrenal, therefore, it seems logical that extremely rarely, aberrant adrenal cortex might be present in the liver. Structurally the tumor resembles adrenal more than it does any ovarian tumor that produces virilism. Futhermore, displacement of ovarian tissue in the liver has not been reported. I believe the tumor should be diagnosed as a low-grade carcinoma. Virilism produced by adrenal cortical carcinoma (ACC) is nearly always accompanied by an increase of urinary ketosteroids. The slight increase in this patient is therefore equivocal. Hepatoblastoma may produce virilism but in the reported cases, all boys, there was an increase of urinary gonadotropins in three of four cases and Leydig cell hyperplasia.[2]

A good review of virilism due to various tumors is that of Jones.[3]

Table 1
(from Jones[3])

Steroid-Secreting Tumors That Produce Sexual Changes

Tumor	Virilization	Feminization
Testis		
Leydig cell tumors	+	+
Sertoli cell tumors	-	+
Androblastomas	-	+
Ovary		
Granulosa-theca cell tumors	+	+
Gynandroblastomas	+	+
Lipid cell tumors	+	+
Adrenal		
Adrenal cortical carcinoma	+	+
Germ cell tumors	-	+

Virilism produced by adrenal cortical carcinoma (ACC) is always accompanied by an increase of 17-KS.[4] The slight increase in this patient is therefore equivocal. Eight cases of hepatoblastoma produing virilism have been reported, all in boys, average age of 2 3/4 years. There was an increase of serum or urinary gonadrotropin in five of the patients. In six patients there was Leydig cell hyperplasia. In Braunstein's case[5] the tumor cells grown in vitro produced hCG (human chorionic gonadotropin) and alpha-fetoprotein.

12.3 REFERENCES

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virilizing hepatoblstoma. J Clin Endocrin and Metabol 35:857-862, 1972

CASE 13. EMBRYONAL RHABDOMYSARCOMA, PRIMARY IN LIVER

CONTRIBUTOR: E. R. Jennings, M.D.
Long Beach, California
TISSUE FROM: Liver
(LUS1583-78)

June 4, 1978
ACCESSION NO. 20065
(173)

13.1 CASE SUMMARY

CLINICAL ABSTRACT

History: This 7 months old Caucasian male was admitted for terminal care following the diagnosis of a malignant liver tumor made two months previously. He had received Cytoxan 300 mg, Vincristine 1.5 mg, and Actinomycin as well as radiotherapy. He had marked respiratory difficulty due to pulmonary metastases and a protuberant abdomen with known peritoneal metastases. He expired on January 22, 1972.

Laboratory data: Blood: WBC 9,100 with 52 segs, 5 bands, 27 lymphs, 14 monos, 1 metamyelocyte and 1 myelocyte; Na 144, K 3.5, CL 104, CO_2 22, pH 7.31. There was 1 nucleated RBC/100 WBC's. Urinalysis: specific gravity 1.028 with 1+ protein, otherwise negative. VMA was negative.

GROSS PATHOLOGY (Autopsy)

The liver was markedly enlarged weighing 640 gms. The left lobe was replaced by tumor. This tumor extended into the medial 1/4 of the right lobe, along with a few isolated 1.0 cm. nodules. Cut sections showed the tumor to have a ropy mucinous appearing much of it being necrotic. Tumor was also present in the lungs, which were massively involved by metastatic nodules, thoracic lymph nodes, peritoneum and pleura.

13.2 CASE DISCUSSION

DIAGNOSIS

Liver embryonal rhabdomyosarcoma

HISTOLOGIC DESCRIPTION

In this section there is a malignant tumor composed of rather round, plump cells with a hyalin matrix background. The nuclei are round to oval and hyperchromatic. A few mitoses are noted. The size of the cells varies greatly, from rather small cells with a halo around the nucleus to larger discrete cells with fairly abundant acidophilic cytoplasm and even multinucleated cell. The larger cells usually have a nucleus that occupies an eccentric position within the cell. The mass of cytoplasm is rather round but in occasional cells it has a streamer-like appearance and may be deeply acidophilic. In the cytoplasm of some of the cells there are tiny fibrils but cross striations are not evident. In much of the tumor there is a dense homogeneous intercellular matrix that contains a few fibrils. Many areas of calcification are seen that appear to represent calcification of necrotic tumor cells. At the margin of the tumor there are extensive intravascular growths. Within blood vessels the tumor cells seem to lie free with the matrix being absent.

The trichrome stain does not stain the cytoplasm of the tumor cells red.

CHARACTERIZATION OF TUMOR

This is an embryonal rhabdomyosarcoma. The diagnosis is usually made without there being evidence of cross striations. The embryonal appearance of cells and the eccentric location of the nucleus, plus the acidophilic character of the cytoplasm are the most useful criteria. EM examination has shown myofibril formation.

In children there are several reported cases of embryonal rhabdomyosarcoma that have arisen along the bile ducts. These often have a botryoid appearance. The course of the disease is usually short, but with radical excision, radiation and chemotherapy, two patients have survived for nine months and four years without evidence of recurrence.[1] The presenting symptom is

usually jaundice.

It is presumed that in cases such as the one presented here that the neoplasm arose in the intrahepatic bile ducts. Reported cases of intrahepatic embryonal rhabdomyosarcoma are rare. Landing reports one, and there are two in our accession file.

DIFFERENTIAL DIAGNOSIS

A non-pigmented melanoma may have an eccentric nucleus and simulate an embryonal rhabdomyosarcoma but melanomas are not seen in this young age group. The absence of sharp cell borders, cord formation and canaliculi or acini rules out hepatoblastomas and hepatocellular carcinomas.

13.3 REFERENCES

1. Nagaraj HS, Kmetz DG and Leitner C: Rhabdomyosarcoma of the bile ducts. J Ped Surg 12(6):1071-1074, 1977

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3. McAllister RM, et al: Cultivation in vitro of cells derived from human rhabdomyosarcoma. Cancer 24(3):520-526, 1969

CASE 14. FOCAL NODULAR HYPERPLASIA

CONTRIBUTOR: R. W. Purvis, M.D.
Modesto, California
TISSUE FROM: Liver
(LUS1584-78)

June 4, 1978
ACCESSION NO. 22846
(153)

14.1 CASE SUMMARY

CLINICAL ABSTRACT

History: This 21 year old female patient presented in June of 1967 with complaints of "a hard lump" in the mid upper abdomen. She had generally been in good health except for a case of mumps three months prior to admission.

Physical examination was unremarkable except for an irregular mass in the mid upper abdomen which became more prominent upon standing or straining. The patient was on oral contraceptives.

Laboratory data were noncontributory.

SURGERY

On June 6, 1967, the patient was operated on and a firm nodule was removed from the lateral aspect of the left lobe of the liver, just lateral to the falciform ligament. The mass was not attached to adjacent organs and the remainder of liver was normal in appearance.

GROSS PATHOLOGY

The specimen consisted of tissue weighing 100 gms. and measuring 8 x 6 x 6.4 cm. A narrow rim of liver tissue partly surrounded a firm, apparently well encapsulated nodule of firm, yellowish-tan tissue. It was approximately the same color or slightly paler than the adjacent liver. It had a central fibrous area and coarse bands of fibrous tissue radiating toward the center of the nodule.

FOLLOW-UP

The patient recovered without incident, has two children and no longer lives in the area.

14.2 CASE DISCUSSION

DIAGNOSIS

Focal nodular hyperplasia

HISTOLOGIC DESCRIPTION

This lesion is composed of hepatocytes and radiating bands of connective tissue that originate from a central scar. The connective tissue bands contain blood vessels, many of which have thick walls and, to a variable degree, many small ductules. The basic unit upon which the diagnosis can be based, particularly when viewed with a scanning lens, is a tiny pseudolobule that has in its center blood vessels and ductules. These units are best seen at the periphery of the nodule where they abut the adjacent parenchyma. In some sections the line of demarcation between the hyperplastic complex and the adjacent liver is difficult to discern. However, in other sections the line is fairly sharp and there appears to be a small amount of connective tisue present. Within the central stellate scar, small pseudolobules are often sharply demarcated and some do not have a central area of ductules. A few inflammatory cells are seen within the connective tissue framework. The cords formed by the hepatocytes and the sinusoidal complex is similar to that of normal liver. The outflow veins are scattered throughout the hyperplastic units but do not seem to collect and drain along the radiating connective tissue.

CHARACTERIZATION OF TUMOR

Focal nodular hyperplasia (FNH) arises particularly in women during the menstrual age, however, typical nodules may be seen in men, older women and in children. The nature of the hyperplastic process in unknown. Whether or not there has been an increase in FNH among women on the pill is questionable. Many cases were noted previous to the use of oral contrceptive hormone (OCH). FNH arising in women on the pill do seem to bleed more often than

nodules in non-users. The differential features between FNH and LCA are given in the table in the discussion on Case 6. In patients with FNH there are usually no symptoms, only the finding of a palpable mass, or perhaps even more frequently an irregular gray-white to gray-brown mass is noted beneath Glisson's capsule at surgery for some nonhepatic disorder. A surgeon may mistake such a nodule for metastatic cancer and ask the pathologist to do a frozen section. The tumors are usually single but may be multiple. As most of them are subcapsular, they are usually easily resected. On occasion the tumors are too large to remove. So far as can be determined, these large masses do not undergo malignant change or affect the general health of the patient. It has been noted at surgery and on angiograms that FNH has an abundant arterial blood supply, sometimes with a single large branch of the hepatic artery being the chief supply. Studies with the electron microscope discloses no essential difference between FNH hepatocytes and normal hepatocytes. Likewise, the sinsusoidal lining cells are similar in that the cells are phagocytic and the lesions often show on liver scan.

DIFFERENTIAL DIAGNOSIS

Liver cell adenoma and adenomatous hyperplasia in cirrhosis are the chief considerations. IN LCA the absence of bile ducts, the presence of a capsule and hepatocytes that are usually different in appearance from those of the surrounding liver are the important distinguishing features. In adenomatous hyperplasia the remainder of the liver is diseased and small bile ducts with a variable amount of connective tissue are usually present somewhere in the nodule.

DIAGNOSTIC METHODS

Angiograms show a hypervascular lesion with a capillary blush. During the capillary phase a septate appearance is seen in about one-half of the cases. This is probably due to the radiating septa seen so well on gross examination of FNH.

Liver scans shows either a normal uptake or a decrease.

PROGNOSIS

Prognosis is good, rarely are there complications unless the nodule is preduculated. Malignant change has not been reported.

TREATMENT

Surgical if there is easy access. Cessation of OCH apparently does not cause regression.

14.3 REFERENCES

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CASE 15. YOLK SAC (ENDODERMAL SINUS) TUMOR

CONTRIBUTOR: Frank J. Glassy, M.D.
Sacramento, California
TISSUE FROM: Liver
(LUS4010-77)

June 4, 1978
ACCESSION NO. 22613
(163)

15.1 CASE SUMMARY

CLINICAL ABSTRACT

History: This 2 1/2 year old child was noted to have some prominence of his right lower rib cage for about a year. The patient was hospitalized in September of 1977.

Physical examination revealed a prominent mass in the right lower chest and upper abdomen measuring approximately 10 x 5 x 3 cm. No masses were noted in the scrotum.

Laboratory data: WBC was 10,400, Hgb 10.8, and Hct. 32.0. Chemistry panel was normal except for ablumin 4.0 gm., globulin 4.0 gm, glucose 134 mg/dl (non fasting), and LDH 435 units. Alpha-fetoprotein was positive.

Radiograph: CT scan revealed a large irregular lesion occupying the right lobe of the liver. A liver scan showed a solitary, moderately vascular lesion confined to the right lobe. Hepatic arteriogram revealed a large, partly vascular mass in the right lobe of the liver, radiographically most likely a hepatoma. An intravenous pyelogram showed flattening of the right kidney consistent with pressure from the liver. A chest film was negative.

SURGERY (September 21, 1977)

A tumor mass felt to be about 12 cm. in diameter was removed by an extended right hepatic lobectomy with an en bloc resection of a portion of the right diaphragm, rib cage and abdominal wall. The left lobe of the liver looked normal.

GROSS PATHOLOGY

The specimen consisted of a large mass of liver, associated tumor, and attached gallbladder, measuring 16.5 x 9.5 x 9.5 cm. The hepatic surface was smooth and glistening. The tumor was irregular, nodular and bossellated and externally was cream-gray to gray-purple, measuring 12.5 x 9 x 7 cm. Some nodules were up to 1.5 cm. in diameter. Sectioning showed the tumors to be well circumscribed from the liver parenchyma with a suggestion of a narrow capsule 1 mm. in thickness. Some cystic changes were present, as was necrosis, hemorrhage and viscid mucoid material, which exuded easily. Other areas were pale yellow and granular, separated by translucent foci. Several hilar lymph nodes were grossly normal.

FOLLOW-UP (Surl Nielsen, M.D.)

The patient was placed on chemotherapy in November 1977, beginning with Vincristine, Actinomycin and Cytoxan. As of February 1978, there was no evidence of metastases.

15.2 CASE DISCUSSION

DIAGNOSIS

Liver yolk sac

HISTOLOGIC DESCRIPTION

Nine sections of tumor and adjacent liver were available for review. A representative area was selected for the study set and it contains a large area of necrosis, myxoid stroma in broad bands and a variety of distinctive patterns including transitions from loose edematous stroma with prominent vascular spaces lined by thin endothelial cells to thin epithelial bands which become

broader into large sheets of cells. In the myxoid edematous stroma, the vascular spaces have a variety of shapes from round to oval and variable sizes from very small capillary-like spaces to large vascular channels with multiple papillary projections. Some of these papillary projections resemble small glomerular bodies and the epithelial lining of the vascular space takes on a hob-nail shape thus producing the so-called Schiller-Duval body. The larger bands of epithelial cells are composed of polygonal basophilic cells often with indistinct cell borders and oval to elongated nuclei with prominent mitotic figures. Some small areas resemble pleomorphic seminoma. Adjacent to the bands of polygonal cells, there are areas of myxoid poorly cellular stroma with many vascular spaces and these cells often contain hyaline globules varying in size from a few microns to more than 20 microns. The globules are pink, usually solitary and some form elonagted masses that appear to be extracellular. Many of these myxoid areas containing hyaline globules have few nuclei and other areas have many polygonal cells with clear cytoplasm and resemble portions of the clear cell carcinoma of Mullerian origin as in ovarian tumors. The junction of this tumor with the adjacent normal liver is thick fibrous band. Prominent vessels are within the fibrous band but no tumor extension is found within these vascular spaces nor within the adjacent liver.

To summarize the histologic features of this tumor, several patterns are apparent which include 1) an epithelial component with cuboidal and hob-nail shape cells, 2) a stomal component with prominent vacularity and many endothelial and stromal structures incldung gland formation and papillary structures forming the so-called Schiller-Duval body. These histologic components are characteristic and diagnostic of yolk sac carcinoma.

HISTOLOGIC DIFFERENTIAL DIAGNOSIS

The first major diagnostic consideration is metastatic yolk sac carcinoma. Of primary ovarian tumors that metastasize, virtually 100% are found within the liver and occasionally the patients are hosptilized for evaluation of an enlarged liver with an unrecognized ovarian tumor. This male patient could have a primary testicular tumor, but is considered unlikely as careful examination of the scrotum failed to reveal a testicular mass. Whereas adult testicular tumors may be occult and nonpalpable, the yolk sac carcinoma in young males is almost always noted as large scrotal masses. Listed in Table 1 are additional histologic differential diagnoses.

Table 1

Histologic Differential Diagnosis

1. Metastatic yolk sac carcinoma
2. Teratoma
3. Germinoma
4. Choriocarcinoma
5. Hepatoblastoma

Primary hepatic teratomas are rare and many sections must be reviewed to exclude this occurrence.[2] Extragonadal yolk sac tumors have been reported in association with teratoma.[3] In the series of 71 ovarian endodermal sinus tumors reported by Norris and Kurman, 10 patients had ovarian teratomas associated with this tumor.[1] Extragonadal primary yolk sac carcinomas have also been associated with teratomas. To date none of the teratomas arising in liver have been noted to have a component of yolk sac carcinoma. In this case, no teratoma element was detected in the many slides examined. Another diagnosis to consider is germinoma and Huntington et al describes some areas of the testicular yolk sac tumors as being seminomatous. The present case has a few very small foci of large polygonal cells resembling germinoma, but these areas are too pleomorphic.[4] Choriocarcinoma is another alternative consideration but no cytotrophoblastic areas were noted. Immunoperoxidase staining for HCG in patients with yolk sac carcinoma has revealed no positive staining. A hepatoblastoma must be considered as this is a primary liver tumor within a young patient. The histologic pattern of osteoid production is clearly absent. Hepatoblastomas do often have solid sheets of polygonal and embryonal-like cells which certainly do resemble the solid areas of the yolk sac carcinoma. However, the racemose pattern of vascularity of the the yolk sac carcinoma is not a typical feature of hepatoblastomas. The vascular lining of yolk sac carcinoma typically shows as in this case, the hob-nail endothelial lining cell, whereas the vascular spaces of malignant infantile hepatic tumors often are elongated endothelial cells. The histiologic components of the yolk sac carcinoma are listed in Table 2 as summarized by Huntington.[4]

Table 2

Histologic Components Yolk Sac Carcinoma

1.	Epithelial:	Cuboidal
		Columnar
		Polygonal
2.	Stromal:	Fibrous
		Myxoid
		Vascular
3.	Epithelial and Stromal:	Cysts
		Papillary fronds
		Glomerular-like

These multiple components have been given many names by different observers and in the recent review of ovarian endodermal sinus tumors by Kurman and Norris, the histologic patterns were described as listed in Table 3.[1]

Table 3

Histologic Pattern: Yolk Sac

1. Reticulum
2. Festoon
3. Polyvesicular
4. Solid
5. Mixed

However, the number of slides reviewed may influence the predominent histologic pattern and in the series by Kurman and Norris, an average of 12 slides per case were studied. This represented one block for each 1.9 cm. of maximal tumor diameter. The predominant histologic patterns are listed with reticular most common in 30% of the tumors. A festoon pattern was noted in 20% and is the pattern showing the typical Schiller-Duval bodies with prominent hob-nail cells. The polyvesicular vitelline pattern predominated in 10% of cases and is recognized by dense spindle stroma and cysts with thin lining. However, the most common pattern, was a mixture of all types, which was noted in 35% of the 71 ovarian tuumors.

This histologic interpretation and nomenclature or yolk sac carcinoma is confusing because of reports which include cases

representing different types of tumors yet given the same name.[5] Minimal histologic criteria of yolk sac carcinoma are 1) solid areas of proliferated endothelial cells and 2) glomerular-like bodies. However, in the review by Kurman and Norris, only 75% of the tumors had the Schiller-Duval bodies and they considered the presence of hyaline droplets pathognomonic. These distinctive hyaline globules have been identified by immunofluorescence and immunoperoxidase as containing alpha fetoprotein.[1,6] In addition, immunofluorescence has identified many other components within these globules as listed in Table 4.

Table 4

Yolk Sac Hylaine Globules

1. Alpha fetoprotein
2. Alpha-1-antitrypsin
3. Tranferrin
4. Orosomucoid
5. Haptoglobin
6. Gc-globulin
7. Alpha 2 maroglobulin
8. Ceruloplasmin
9. IgG
10. IgA

In the five yolk sac tumors tested all had hyaline globules staining for albumin, alpha-1-antitrypsin, transferrin, and alpha fetoprotein. The other protein components listed in the table were present in only some of the five tumors. Hyalin droplets, (intra- or extracellular) are commonly found in a variety of non-germinal tumors including hepatocellular carcinoma, lung carcinoma, colon carcinoma and normal adrenal cortex.

CHARACTERIZATION OF TUMOR

After several decades of research and multiple reports, it is the current opinion that yolk sac carcinoma is a tumor of germinal epithelium with differentiation as extraembryonic mesoderm. Conceptially, it is derived from prohyperation of villous stroma.

The extragonadal location may be attributed to sequestration of germ cells during migration from yolk sac into the gonadal ridge during embryonic life.[7]

Terminology of the tumor has been confusing as the search for

histogenesis has required many studies. Various names in the literature for this tumor are listed in Table 5.

Table 5

Nomenclature of Yolk Sac Carcinoma

1. Schiller's mesonephomas
2. Distinctive adenocarcinoma of infant testes
3. Variant of embryonal carcinoma
4. Endodermal sinus tumor
5. Yolk Sac tumor

The early report by Schiller included germinal and non-germinal clear cell carcinomas. He reported the similarity of the glomerular-like body to fetal glomeruli and suggested mesonephric origin.[8] In 1944, Saphir and Lackner emphasized the clear cell component of mesonephric carcinoma and described a non-germinal form of Schiller's mesonephric carcinoma. Schiller later realized the confusion as discussed in a paper cited by Teilum.[5]

In 1946 and 1959, Teilum related the origin of these distinctive tumors to extraembryonic structures. He indicated that the tumor was of germinal origin and histogenetically related to embryonal carcinoma, teratocarcinoma and trophoblastic tumors.[10]

Subsequently in 1959, Teilum reported the comparative histology of rat placenta and these Schiller mesonephric tumors and concluded that the mesonephric glomeruli were in fact very similar to the endodermal sinuses described by Duval in 1894.[5] These Schiller-Duval bodies are in fact diverticula of the yolk sac endoderm that expand the labyrinth of the rat placenta. Pierce et al reported numerous mouse experiments and demonstrated that the mouse parietal yolk sac carcinoma could be derived by transplantation of a murine testicular embryonal carcinoma. The characteristics of this tumor were studied by electron microscopy and immunohistochemical procedures, and found to be of parietal yolk sac origin. Subsequently, Pierce, Huntington and Bullock reported the comparative histology of two mouse testicular yolk sac carcinomas and 15 human tumors.[11] In 1977, comparison of the ultrastructural features of human yolk sac with human yolk sac caricnoma was reported. The most prominent feature of the tumor was voluminous basement membrane material which corresponded to the PAS positive hyaline globules seen by light microscopy.[12]

CLINICAL CORRELATION

The prognosis of yolk sac tumor has been related to site of origin and the age of the patient. The testicular tumors are common in early childhood and those treated by orchiectomy before age 2 have a hopeful prognosis with a five year survival range at 40-60%.[7] On the other hand, ovarian tumors are more common in young women, (mean age 19 in the 71 cases by Kurman and Norris) and in these ovarian tumors, in patients under 2 years of age, a fatal outcome is always noted. Prognostic factors in the ovarian tumors included: generally smaller tumors had better prognosis, but no specific histologic pattern was associated with longer survival.[1] Rupture of an ovarian tumor was not necessarily an adverse event as even in a case with spill and no subsequent therapy, the patient had a prolonged survival. The duration of symptoms in this tumor is often very short and in the case of the ovarian tumors, two-thirds of the patients had symptoms less than 2 weeks. Several patients had delivery and normal pelvic exams within several weeks of diagnosis.

The extragonadal yolk sac tumors have been reported in a variety of sites as listed in Table 6.

Table 6

Endodermal Sinus Tumor
Extragonadal origin

vagina
saccro coccygeal area
Retroperitoneum
anterior mediastinum
C.N.S. - Pineal
stomach
liver
prostate

The extragonadal tumors are usually unresectable and occasionally associated with other germ cell components. Two, five year survivals have been reported, of which one arose in the vagina and the other in the pineal gland.[11]

The previously reported case of hepatic yolk sac carcinoma occurred in an 18 month old male with abdominal distension and fever for eight days. A solid 15 to 20 cm. mass in the liver was found in the right lobe. During surgery the friable tumor was

spilled and one month post-surgery, a pelvic mass was noted. Widespread metastasis to the chest wall, lung, abdomen and pelvis were observed during the 6 1/2 months until death.[14]

TREATMENT

The previously reported liver yolk sac carcinoma did not show any change in clinical course following triple chemotherapy (actinomycin, methotrexate, cyclophosphomate) even though chemotherapy was instituted soom after surgery. Subsequently supervoltage radiation appeared to cause some shrinkage of tumor. Radiation therapy has not been beneficial in treatment of the ovarian tumors.[1] As expected best survival is recorded in those patients who require only surgery for removal of the entire tumor.

LABORATORY DIAGNOSIS

Serum alpha fetoprotein is a helpful diagnostic test as it is positive in the yolk sac carcinoma including the previously reported liver case.[14] A value of the serum alpha fetoprotein in following the course of the patient and observing recurrence has been helpful in liver cell carcinoma but also in examples of gonadal yolk sac carcinomas.[15] Many reports indicate the alpha fetoportein is increased prior to removal.[13] Early published reports beginning in 1968 indicated many patients with malignant teratoma had elevated serum alpha fetoprotein and it is expected that upon careful histologic review of these tumors, some portion would reveal yolk sac carcinoma. Previous reports in the literature indicate that yolk sac endoderm can produce alpha fetoprotein as well as several other protein components. This patient was tested and found to have alpha-fetoprotein present.

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CASE 16. UNDIFFERENTIATED MALIGNANT TUMOR, PRIMARY IN LIVER

CONTRIBUTOR: J. G. Harmeling, M.D.
San Bernardino, California
June 4, 1978
ACCESSION NO. 22827
(170)
TISSUE FROM: Liver
(LUS4890-77)

16.1 CASE SUMMARY

CLINICAL ABSTRACT

History: This 78 year old white male who was hospitalized in November of 1976 because of several days of fever and abdominal pain.

He was hospitalized in March 1976 for right upper quadrant pain which was diagnosed as hiatus hernia and reflux esophagitis. The liver was palpable 2 finger breadths below the right costal margin and was tender.

He was found to have hepatomegaly, and technetium scans of the liver, spleen, and skeleton demonstrated multiple hepatic filling defects, with right hepatic lobe enlargements, and displacement of a small right kidney inferiorly.

Laboratory data: WBC 6,500, Hbg 8.6 with normal differentials, SGOT 58, alkaline phosphatase 110, LDH 908, Albumin 2.8, and total protein 7.1.

SURGERY

The patient underwent exploratory surgery on November 24, 1976. A 15-20 cm. cystic lesion involved almost the entire right lobe of the liver. The interior of the lesion was soft, cystic, and filled with "old blood fluid". In addition, a small area of tumor was found in the "mesenteric area of the small bowel". The mass was drained and a biopsy was obtained. The right hepatic artery was ligated and an infusion catheter was inserted.

GROSS PATHOLOGY

The specimen consisted of several fragments of tissue, the largest of which measured 4.7 x 2.1 x 1.4 cms. The tissue was delicately nodular, tan and soft with a membranous smooth lining or surface.

FOLLOW-UP

The patient subsequently received 5 FU for ten days followed by a ten month course of 5 FU as an outpaitnet. As of May 1978, his condition was deteriorating. He continued to receive intermittent 5 FU.

16.2 CASE DISCUSSION

DIAGNOSIS

Undifferentiated malignant tumor, apparently primary in liver

HISTOLOGIC DESCRIPTION

The tumor is made-up of primitive oval and spindle-cells with poorly defined cytoplasm and a round to oval nuclei. The tumor grows in poorly defined fescicular patterns. Each fasicle is separated from the others by fine reticulum fibers. The tumor is highly vascularized but on reticulum stain the tumor cells do not seem oriented toward the vascular channels. In a few areas the tumor cells are more plump with abundant clear or pale eosinophilic cytoplasm. There is no glandular character. In a few areas there is large numbers of plasma cells, nearly filling the entire field in such areas. Electron microscopy fails to show either neurosecretory granules or a relationship to basement membranes or endothelial cells.

CHARACTERIZATION OF TUMOR

This tumor differs from the cases of undifferentiated sarcoma that Edmondson described in the AFIP fasicle, in that there is a definite pattern to many areas in this tumor with a creation of the small poorly defined fasicle. Several tumors might be considered:

1. Hemangiopericytoma is a tumor composed of the "pericytes" of Zimmerman. Occasionally hemangiopericytomas are arranged in clusters of this type, however reticulum stains generally show fine reticulum fibers that encircle individual cells. Such reticulum fibers were not demonstrable in tumor of this patient. Instead the reticulum fibers include the entire nest of the tumor.

2. **Alveolar** soft part sarcoma. This group of neoplasms which has been considered at various times to represent malignant forms of granular cell myoblastoma or nonchromaffin perigangliomas consist of a fairly rigid arrangement of polyhedral cells surrounded by a reticulum network not usually consisting of the spindling form seen in the tumors of patient #16. Electron microscopy is said to reveal that many alveolar soft part sarcomas have a crystaline shaped body or lattice not present in the rhabdomyosarcomas or nonorganoid granular cell tumors nor in carotid body tumors. The cytoplasmic granules are a distinctive part of the histologic feature and the granules are always PAS positive. The granules were not found in this patient's tumor.

3. **Paragangliomas** The typical periganglioma apparently arises in periganglia associated with arterial vessels. Typically such tumors give a chromaffin reaction, based on the oxidation of catacholamines to brown polymers that are similar to melanin. Paragangliomas in the abdomen are usually nonchromaffin reacting. Formalin induced flourescence may often depict scattered chief cells that indicate the presence of catacholamines.

4. Epithelioid leiomyoblastomas may bear a resemblance to a pattern seen in this patient. However in the major portion of the tumor the spindling cells are more stiking that the small oval plump cells. Leiomyoblastomas have been described in livers although primary leiomyoblastomas rising in the liver are extremely rare.[3]

DIAGNOSTIC TECHNIQUES

The identification of tumors that arise in the paraganglion is, according to Glenner,[3] a complex and difficult matter. One of the early distinguishing features of paragangliomas is the ability of many of the tumor cells to develop a brown color resulting from the oxidation of catacholamines by chromic acid and thus the term chromaffin reaction. However it became clear that frequently paraganglia did not exihibit a chromaffin reaction, either because the concentration of the catacholamine was to low for detection, or the suceptibility of depletion of catacholamines by histologic preparation was to great. Glenner recommends formaldehyde induced flourescence as a more sensitive identifying technique but this requires fresh frozen tissue exposed to formaldehyde vapors, ordinary formalin fixation leaches out the relatively soluble catacholamine material. Electron microscopy may show neurosecretory granules that allows identification of the secretory character of the tumor thus distinguishing it from some of the neoplasms listed above in differential diagnosis.

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CASE 17. GIANT CELL CARCINOMA, PRIMARY IN LIVER

CONTRIBUTOR: John R. Craig, M.D.
Los Angeles, California
June 4, 1978
ACCESSION NO. 20230
(154)
TISSUE FROM: Liver
(LUS1341-78)

17.1 CASE SUMMARY

CLINICAL ABSTRACT

History: This 23 year old Caucasian female presented with right upper quadrant pain of eight months' duration and fever of recent onset. She was treated with antibiotics which did not relieve her symptoms.

On physical examination, her liver was palpated 5 cm. below the costal margin. It was firm and nontender.

Laboratory data included a hemoglobin of 10.1, albumin of 3.4, negative alpha-fetoprotein, and negative HAA.

Radiographs: Liver scan revealed a circumscribed right lobe filing defect.

SURGERY (January 24, 1972)

Following a needle biopsy, a partial hepatectomy and cholecystectomy were performed.

GROSS PATHOLOGY

The 20 x 20 x 9 cm. liver segment weighed 1550 gms. It contained multiple subcapsular light yellow nodules up to 5 cm. in diameter. On section there was a central necrotic, variegated yellow-white 12-15 cm. tumor. Multiple bands coursed through the tumor dividing the mass into small discrete lobules. There were shiny and granular areas as well as mucoid foci. Although the intervening liver parenchyma was normal, tumor was found within

the portal vein.

FOLLOW-UP (N. Friedman, M.D.)

The patient was rebiopsied for recurrent disease on June 9, 1975. She developed portal hypertension and after numerous bleeds a portosystemic shunt was performed. She did well for a number of months and then was re-admitted to the hosptial with jaundice and E. coli septicemia. The patient finally expired approximately 4 years after her initial right hepatic lobetomy. An autopsy was not performed.

17.2 CASE DISCUSSION

DIAGNOSIS

Giant cell carcinoma in noncirrhotic liver

HISTOLOGIC DESCRIPTION

The tumor is made-up of pleomorphic giant tumor cells with poor cohesiveness. The tumor cell cytoplasm is eosinophilic. Often a body in the cytoplasm seems to displace the nucleus and the nuclei are often bizarre and multiple, frequently containing prominent nucleoli. There are many mitotic figures. Occasional forms have phagacytosed inflammatory cells. Between the tumor cells, smaller neoplastic cells with eccentric nuclei are found. There is no gland formation. There is a moderate amount of inflammatory reaction to the tumor. Most inflammatory reaction is at the margins, infiltrating into the neighboring liver parenchyma. The parenchyma around the tumor is not cirrhotic, there is neither fibrosis nor irregular regeneration. No tumor is found in the intrahepatic portal vein branches.

The liver biopsy taken later was quite different. There was dense fibrosis that encased scattered ductal structures and a few isolated dysplastic cells apparently of ductal origin.

CHARACTERIZATION OF TUMOR

Hepatocellular neoplasms made-up exclusively of giant cells are extremely rare (0.4% of hepatocellular carcinoma). Hepatocellular carcinomas made-up predominently of giant cells but with areas of otherwise typical hepatocellular carcinoma constituted 2.2% but 11.5% of hepatocellular carcinomas may have some areas of gigantic neoplastic hepatocytes.[1] Ninety percent of otherwise typical hepatocellular carcinomas with some giant cell component arise in cirrhotic livers. Those made-up almost entirely of giant cells are too few in number to extablish an accurate relationship but those studied have occurred in non cirrhotic livers, both men and women, and in patients in their thirties and forties.

Hanot and Gilbert in 1888 pictures a giant-cell carcinoma of liver in which the largest cells were up to 100 microns in diameter[2] and White described one in 1899 with cells in the range of 30-40 microns.[3]

Giant cell carcinomas occur in many organs (lung, thyroid gland, pancreas). They are uncommon or rare in all organs in which they arise but their occurence in liver is sufficiently uncommon that if otherwise typical hepatocellular carcinoma cannot be recognized, metastatic tumor should be suspected until proven otherwise. From the clinical data presented on this patient, it would seem that the most likely primary was indeed the liver.

It is not clear what the basis for the development of portal hypertension was in this patient, since an autopsy was not performed. However, according to injection studies by Nakashima et al[4] the hepatic neoplasms which receive their blood supply from the hepatic artery only, empty ensuing venous supply into the portal vein rather than into the hepatic venous outflow. Thus the development of portal hypertension is often an early sign in patients with silent but large hepatocellular carcinomas. This ready flow of arterial blood into the portal vein is probably a more important feature than intrahepatic occlusion of the portal vein bed by tumor growth, a factor that was also apparently present in this patient. The sclerosing dysplastic duct cells in the follow-up biopsy resemble irradiated cells. Since radiation has not been adminstered, we must assume these to be neoplastic cells. The ductal character of the cells on biopsy could reflect a duct origin of this tumor but conversely may indicate the mutipotent capacity of transformation of tumor cells.

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CASE 18. SCLEROSING HEPATOCELLULAR CARCINOMA

CONTRIBUTOR: Robert L. Peters, M.D.
Los Angeles, California
June 4, 1978
ACCESSION NO. 20228
(155)
TISSUE FROM: Liver
(JWA94-73)

18.1 CASE SUMMARY

CLINICAL ABSTRACT

History: This 46 year old Caucasian female was admitted for increasing abdominal pain and girth. During the previous 6 months she had had several episodes of right upper quadrant pain associated with alcohol which was abused and spicy foods. She had lost 12 pounds in the previous 3-4 months. She had been on birth control pills since 1967. Prior to her final hospitalization, a cholecystectomy had been performed and a liver biopsy had been interpreted as showing possible Budd-Chiari syndrome.

Physical exmiantion: There were two spiders on her back. The abdomen was distended with venous stasis. The right upper quadrant was tender to palpation.

On admission all **laboratory data** were normal including liver profile. Terminally, the prothrombin activity dropped to 5% with SGOT 230, SGPT 111, alkaline phosphatase 13.0, calcium 11.3 and phosphate 2.5 and she expired.

Radiographs: A liver scan showed a filling defect in the superior aspect. Angiography showed a stricture of the inferior vena cava at the level of the diaphragm. The hepatic vein could not be entered.

GROSS PATHOLOGY

Autopsy showed 4 liters of ascitic fluid with thrombosis of the inferior vena cava, right renal vein and left intrahepatic branch of the portal vein. The inferior vena cava also showed probable congenital web defect. The liver had an 8 cm. markedly umbilicated tumor on the diaphragmatic surface, predominantly in the medial portion of the left lobe with extension into the porta hepatis and caudate lobe. Bisection revealed a 12 x 7 cm. sclerotic bosselated tumor involving thrombosed hepatic vein outflow tracts.

18.2 CASE DISCUSSION

DIAGNOSIS

Sclerosing hepatocellular carcinoma

HISTOLOGIC DESCRIPTION

The tumor is made-up of a densely sclerotic tissue in which is embedded atrophic cords of hepatocytes. On paraffin section these resemble duct cells but on plastic sections they have an eosinophilic cytoplasm of hepatocytes with large vesicular nuclei and prominent nucleoli. There is no basement membrane formed around the tumor. A few of the tumor cells have polyploid and somewhat pleomorphic nuclei. At the margins of the tumor the hepatocytes are blended insidiously with the tumor cells. In regions away from the tumor, the perivenular regions of each hepatic lobule are obliterated by fibrous tissue and hemorrhage. As much as two-thirds of the lobule is involved. In some areas the erythrocytes extravasate into the spaces of Disse. There are no thromboses of the terminal hepatic vein radicles however.

CHARACTERIZATION OF TUMOR

Sclerosing hepatocellular carcinoma is a little recognized variety of liver tumor, probably because it has frequently been interpreted as representing cholangiocarcinoma. Edmondson did not set aside this variety of carcinoma as a different type but recognized it in his figure 40 as liver cell carcinoma with dense stroma.[1] It is not uncommon to have areas of sclerosis in ordinary hepatocellular carcinoma. Such tumors by their behavior

are no different than hepatocellular carcinomas without sclerosis. However, the sclerosing liver cell carcinomas were set aside of the group because of the occurance of a relatively small number of neoplasms that grossly resembled bile duct carcinoma and which had a high incidence of hyperparathormone-like effect. In reviewing patients dying with hepatocellular carcinoma at LAC/USCMC from 1949 through 1974, 15 sclerosing carcinomas primary in the liver were found, some of which could be identified as hepatocellular and some which appear to be cholangiocarcinoma. Others could not be clearly differentiated. In the entire autopsy series there were nine patients who had clinically recognized and unexplained hypercalcemia. Six of the nine were associated with sclerosing carcinomas. The distinction between sclerosing cholangiocarcinoma and sclerosing hepatocellular carcinoma is made on basis of the more granular and somewhat more abundant cytoplasm of the hepatocellular carcinoma with nuclei that are vesicular and have prominant nucleoli. This is contrasted with the more watery cytoplasm, cuboidal cells and the basement membrane of the cholangiocarcinoma. It may be that both cholangiocarcinomas and hepatocellular carcinoma originate from a common primitive cell type and that similarity of origin is manifest in these cases. All of the sclerosing tumors cholangiocarcinoma, hepatocellular carcinoma or the rare cholangiolocellular carcinoma, tend to act similarly in that they metastasize to a more widespread pattern than does the hepatocellular carcinoma, and many of the tumors are associated with hypercalcemia.

The sclerosing hepatocellular carcinoma is morphologically distinct from a sclerosing cholangiolocellular carcinoma. The cholangiolocellular carcinoma, as described by Steiner,[3,4] was characterized as a rare neoplasm that throughout it's entirety had the appearance of cholangiole (the canal of Hering) differentiating into neither bile duct cells or hepatocytes. Only two neoplasms met that criteria in the 248 primary liver tumor autopsy cases studied at LAC/USCMC.[2]

The question of the basis of the parathormone-like effect of certain hepatocellular carcinomas as been fairly extensively investigated but not settled. The first evidence of the capacity of tumors to secrete a parathromone-like substance was reported in 1964 by Tashjian et al.[5] Root and his collegues[6] demonstrated several varieties of parathyroid hormone-like activities associated with malignant tumors, one being indistinguishable from a normal hormone another immunologically distinct and a third in which the parathormone-like material is also associated with <u>normal</u> calcium levels. However, about half of the patients with hypercalcemia associated with malignant tumors do not have parathromone or parathromone-like material that can be

demonstrated in the serum.[6] More recently several investigators have related the hypercalcemia to prostoglandins.[8,9] One of the best documented cases of demonstration of a immunologically reactive parathyroid hormone secreted by a liver tumor was in the report by Knill-Jones et al, in which a cholangiocarcinoma was found to be associated with hypercalcemia. Immunologically reactive parathyroid hormone (PTH) was demonstrated in the tumor tissue and the circulating concentration of the elemented levels of immunoassayable parathyroid hormone, elevated before surgery dropped to normal ranges after liver transplatation.[10] Most investigators have found that in the majority of patients with malignancy related hypercalcemia, a hormone secreted by the tumor is chemically distinct from PTH, prostaglandins may play a part.[11]

Budd Chiari's syndrome was confusing in this setting since there is a reported increased incidences of hepatocellular carcinoma in patients with chronic idiopathic Budd Chiari disease, at least in the Bantu.[12] Apparently, however, such neoplasms usually arise in patients who have congenital webb lesions that traverses the hepatic vein structures including part or all of them and thus the Budd Chiari lesion is extremely chronic. Since the cases reported are from Africa where the incidences of hepatocellular carcinoma in antigen positive patients is high, the significance of Budd Chiari disease alone as a preneoplastic lesion is open to question. Involvement of the hepatic veins secondary to the tumor without production of symptoms on the other hand is relatively common, occuring in 23% of patient with HCC arising in cirrhotic liver and 18% of those arising in noncirrhotic livers but rarely producing a Budd Chiari syndrome in either instance. The Budd Chiari syndrome when it does occur is usually rather late in the course of the patient with known hepatocellular carcinoma involving a considerable amount of the liver.

DIFFERENTIAL DIAGNOSIS

Grossly, the sclerosing hepatocellular carcinoma is difficult to distinguish from cholangiocarcinoma or metastatic carcinoma. Histologically the same differential diagnosis applies and sections which allow relatively little shrinkage of the tumor cells or the collagen are required in order to identify the tumor cells as hepatocytes.

DIAGNOSTIC TECHNIQUES

Alpha fetoprotein seems only uncommonly associated with sclerosing hepatocellular carcinomas or for that matter carcinomas arising in noncirrhotic livers. Studies of serum calcium level may increase the suspicion of presence of this neoplasm as may parathromone assays, nephrogenic cyclic AMP studies, and prostaglandin E_2 analysis. However, according to Rude et al,[12] in a study of eleven patients with hypercalcemia associated with malignancy but with no bony metastases, no elevations were found in serum immunoreactive PTH nor in prostaglandin E_2 . Nephrogenic AMP was elevated. The authors believed some yet unknown hormonal substance was responsible.

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CASE 19. MIXED HAMARTOMA OF LIVER

CONTRIBUTOR: Roger Terry, M.D.
Los Angeles, California
TISSUE FROM: Liver
(LUS1343-78)

June 4, 1978
ACCESSION NO. 21247
(153)

19.1 CASE SUMMARY

CLINICAL ABSTRACT

History: This 4 month old Mexican-American female patient was noted to have a right upper quadrant abdominal mass on routine physical examination at a well-baby clinic in February of 1975. The infant's past history was unremarkable, with no history of maternal infections or familial disorders.

Physical examination revealed a firm nodular 5 x 7 cm. mass palpable 7 cm. below the costal margin, presumably in the left lobe of the liver. The spleen was not palpable. A capillary hemagioma was also noted in the left axilla.

Laboratory data: Hgb 11.3, Hct 32, WBC 19,500, normal differential, platelets normal to slightly increased. Total protein 6.5, albumin 4.0, total bilirubin 0.5, direct bilirubin <0.1, SGOT 45, SGPT 10, alkaline phosphatase 6.0, CPK 60, LDH 760, alpha-1-antitrypsin negative, alpha-1-antitrypsin negative, VMA normal.

Radiographs: Liver scan showed filling defect left lobe posterior aspect, angiograms showed a vascular lesion of the liver, felt by the pediatric radiologists to be either hamartoma or hepatoblastoma.

SURGERY (March 5, 1975)

Exploratory laparotomy revealed one liter of milky chylous ascites. A liver tumor was identified which appeared to arise from the caudate lobe and involved mostly the superior aspect of the left and caudate lobes. However, it also extended into the right lobe behind the portal structures which were free of tumor. The tumor was not encapsulated. It was intimately attached to the vena cava, around which it was wrapped. An incomplete resection was performed and the vena cava was freed.

GROSS PATHOLOGY

The specimen consisted of a 7 x 5 x 4 cm. piece of red-brown tissue, thinly encapsulated except over the amputated surface. The tissue was quite firm and rubbery with pearly-white connective tissue bands. No cysts or necrotic areas were present. After fixation it had a distinctive gray color and a lobulated or nodular pattern.

FOLLOW-UP

The patient was discharged on March 27, 1975 to be followed in clinic. The child was doing well as of July, 1977.

19.2 CASE DISCUSSION

DIAGNOSIS

Mixed Hamartoma of the liver

HISTOLOGIC DESCRIPTION

The slide in this case discloses abnormal hepatic tissue that is composed of nodules, most of which have a portal tract in their center with radiating branches that subdivide the nodules. Some of the nodules are ill-defined but many have fibrous tissue around their periphery. Large outflow veins may be noted in this location. Two changes are noted along the portal tracts. First, the larger tracts are widened by compact collagen which tends to form coarse bundles. The thick connective tissue has involved the walls of blood vessels and encompassed the small bile ducts. A

second change is present along the smaller branches of the portal system where the connective tissue is more cellular and a remarkable ductular proliferation is noted that spreads into the pseudolobules. It is apparent that the connective tissue alongside the liver cords is associated with conversion of hepatocytes to bile duct epithelium. Variable amounts of this fibroductular complex is noted in the nodules, in some it approaches 50 percent. The sinusoids and Kupffer cells appear fairly normal. The majority of hepatocytes have nuclei of normal size and a diffuse granular acidophilic cytoplasm. At the point where the canalicular lumen joins the ductules a tubular expansion is often present. The transition area between canaliculi and ductules are apparently of bile duct origin.

DISCUSSION

Although different terms have been used for benign mixtures of hepatocytes and bile ducts that have an abnormal arrangement, we have chosen to call this lesion a mixed hamartoma.[1] The lesion undoubtedly has its inception in abnormal development. In the embryo, bile ductular transformation occurs as the mesoderm grows into the primitive liver to form the triads. In a mixed liver hamartoma the conversion process continues, apparently in concurrence with the formation of abnormal nodules. This finally results in broad areas of fibroductular tissue. Grossly, the mixed hamartoma in this case resembled an accessory lobe of the liver. The presence of arterial branches coming directly from the aorta indicate its misplacement and congenital nature.

DIFFERENTIAL DIAGNOSIS

The only lesion to be seriously considered in differential diagnosis is focal nodular hyperplasia. This should present no problem as FNH has such a characteristic gross and microscopic pattern, especially the small pseudolobules with centrally placed connective tissue and bile ducts. Angiograms are helpful in delineating the tumor in cases such as this but do not help in differential diagnosis.

TREATMENT

If possible, a mixed hamartoma should be surgically resected, but if symptomless, it is doubtful that any complications would ever develop.

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CASE 20. EOSINOPHILIC HEPATOCELLULAR CARCINOMA WITH LAMELLAR FIBROSIS

CONTRIBUTOR: Karen Cove, M.D.
Los Angeles, California
TISSUE FROM: Right lobe of liver
(LUS1344-78)

June 4, 1978
ACCESSION NO. 22650
(157)

20.1 CASE SUMMARY

CLINCIAL ABSTRACT

History: This 22 year old Caucasian female presented in August of 1977 with sharp intermittent right upper quadrant pain associated with nausea and vomiting.

The patient first experienced abdominal pain and nausea in 1971 following the use of birth control pills (Ovral). She discontinued their use; although, pain recurred several times between 1974 and 1976. Following a nonvisualizing cholecystogram in June of 1976, an uneventful cholecystectomy was performed. No stones were present and a diagnosis of chronic cholecystitis was made.

In June 1976, the patient resumed use of birth control pills which she continued until her August 1977 admission.

Physical examinaiton: The abdomen was slightly tender in the right upper quadrant, without guarding or rigidity. The liver edge was palpable 10 cm. below the costal margin, was smooth and nontender.

Laboratory data:

	SGOT	SGPT	LDH	Alk. Phos.	Bili.	HAA	FP	A/G
11-73	25		48	24	0.4			
5-76	26	16			0.4			
8-77	49	33		41	0.3			
9-77	54			49	1.5	Neg.	Neg.	3.4/3.5

Radiographs: Cholangiograms was within normal limits. Liver scan showed a very abnormal huge liver with multiple prominent filling defects and two large cold filling defects in the right upper quadrant. Angiograms demonstrated a large vascular tumor in the right lobe. This tumor was confirmed by sonography.

SURGERY (September 26, 1977)

A right lobe resection was performed.

GROSS PATHOLOGY

The specimen was 1700 gms. of multinodular tumor. The largest portion measured 15 x 10 x 12 cm. Multiple small satellite tumors were present at the periphery. It was tan-green and focally degenerated. The adjacent liver parenchyma appeared normal (i.e., non-cirrhotic). The capsule was smooth without breach of umbilication.

FOLLOW-UP

On January 31, 1978, liver scan for routine follow-up was reported an no activity in the majority of the lower right side due to old surgery. The liver tissue picking up the isotope was enlarged and had a mottled irregular uptake. No discrete filling defect was noted. The spleen was enlarged. SMA 12 done in February 1978, which included SGOT, alkaline phosphatase, bilirubin, cholesterol, uric acid, BUN, phosphate, calcium, albumin and total protein was unremarkable.

She had been seen multiple times as an outpatient. When last seen on March 27, 1978, she was doing well and a 20 lb. weight gain was noted.

20.2 CASE DISCUSSION

DIAGNOSIS

Lamellar fibrosis

HISTOLOGIC DESCRIPTION

Most of the section is a tumor composed of two components, with polygonal to round eosinophilic hepatocytes composing approximately 75% of the tumor and thin to moderately thick fibrous bands arranged as thin lamellar fibers compose the remaining 25% of the tumor. The eosinophilic hepatocytes have prominent nuclei that are usully round to oval, and have dense chromatin with prominent nuclei. An occasional intranuclear inclusion which is an invagination of cytoplasm is noted and occasional mutinucleated form is present. The epithelial cytoplasm is eosinophilic and finely granular with small intracellular hyaline globules present in several areas. These hyaline globules are reminiscent of those seen in the yolk sac carcinoma. Many foci of the hepatocytes have a finely vaculated form of fat. No significant cholestasis is present. Often the small nests of hepatocytes are divided by the lamellar fibrosis but in other areas larger sheets of many hepatocytes are common. There is no hepatocellular necrosis in this section but it is evident in other areas. The margin of the tumor with adjacent normal liver is a thin fibrous band and the adjacent liver has hepatocytes oriented in trabeculae suggesting compression. These histologic features are characteristic of a newly recognized variant of hepatocellular caricnoma referred to as eosinophilic hepatocellular carcinoma with lamellar fibrosis.

HISTOLOGIC DIFFERENTIAL DIAGNOSIS

The tumors to consider upon review of histologic sections of such a tuumor are listed in Table 1.

Table 1
HISTOLOGIC DIFFERENTIAL DIAGNOSIS

1. Focal nodular hyperplasia
2. Cirrhosis with HCC
3. Metastatic malignancy
   - islet cell
   - paraganglioma
   - squamous carcinoma
4. Ectopic adrenal

Focal nodular hyperpalsia is a consideration as the fibrous bands in some of these tumors may become very prominent and form a "central scar" in the small tumor nodule. One example has already been reported as a potentially malignant form of focal nodular hyperplasia associated with oral contraceptive.[2] Secondly, a case has been reported as cirrhosis with hepatocellular carcinoma.[3] Thirdly, metastatic tumors must be considered and include metastatic islet cell carcinoma which may have thin fibrous bands although not usually the lamellar fibrosis variety. Islet cell carcinoma has epithelial components that resemble hepatocytes but the lack of a prominent nucleolus is an important feature of islet cell origin. Metastatic paraganglioma to the liver can mimic this tumor in part by the division of the tumor cells into nests. The paraganglioma cells are typically smaller with less cytoplasm and often lack the eosinophilic staining seen in this tumor. Invasive squamous carcinoma from a gallbladder primary may produce significant sclerosis and be so poorly differentiated that the squmous origin can be difficult to find in selected areas. Multiple sections should be examined. The fibrous tissue in squamous carcinoma can also cause this form nests, and prominent nucleoli are a feature of squamous carcinoma. The keratin pearl formation is distinctive however, whereas the eosinophilic hepatocellular carcinoma is fairly uniformly polygonal and does not become elongated in cell shape. A fourth tumor to consider may be the ectopic adrenal in which clear cells are predominant. Eosinophilic hepatocellular carcinoma may have areas of prominent clear cells. Lamellar fibrosis and single file trabeculae of hepatocytes between fibrous bands was absent in the only case of ectopic adrenal in our files.

CHARACTERIZATION OF TUMOR

Eosinophilic hepatocellular carcinoma with lamellar fibrosis is a unique variant of liver cancer first recognized by Edmondson in the fascicle on Liver Tumors written in 1956. During the years since that time, He has accumulated a number of consultation cases and we have collated the series obtain from the consultation file of Robert L. Peters, M.D. and that at LAC/USCMC and found 21 such patients. This tumor is typically found in young people between 5 and 35 years of age and usually occurs in a noncirrhotic liver. Because the tumor may produce symptoms and be recognized before distant spread it is amenable to surgical therapy and thus the histologic recognition and therefore opportunity for surgical resection and potential cure is of utmost importance.

Previous reports of this tumor are shown in Table 2.

Table 2

PREVIOUS REPORTS OF EOSINOPHILIC HCC WITH LAMELLAR FIBROSIS

1956 Edmondson	Case report	No name
1958 Edmonsdon	Fascicle	No name
1965 Ohlsson et al	Large series	Polymorphous
1967 Misugi et al	Childhood cancer	"cirrhosis"
1973 Anthony	Childhood cancer	Scirrhous stroma
1975 Lieberman et al	Case report	No name
1976 Peters	Large series	E HCC with L.F.
1977 Christopherson	One patient	FNH
1977 Berman et al	Large series	P.C.F.S.
1978 Craig et al	Large series	E HCC with L.F.

The first large series in which many tumors of this variant were probably reported is the one by Ohlsson et al. Unfortunately, the histologic features were not described in enough detail to be certain that the tumors were pure. A subsequent report by Misugi et al indicated one tumor with this pattern that was illustrated. The series of primary carcinoma of the liver in Ugandan patients reported by Anthony indicated five scirrhous variants of liver cell carcinoma out of the total series of 263 tumors of liver cell origin. One of the patients in our series was previously reported by Lieberman et al as a case report of alpha-1-antitrypsin deficiency associated with hepatocellular carcinoma.[6] The case report of Davis is a 21 year old woman on oral contraceptive for two years who had a tumor suggestive of focal nodular hyperpasia but is a hepatocellular carcinoma.[7] The first published series of these patients was by Peters et al in the book HEPATOCELLULAR CARCINOMA.[8] In a series of steroid-related liver tumors Christopherson reported one patient with focal nodular hyperplasia with a probable malignant tumor which upon review of the slides by Robert L. Peters, M.D. confirms that the tumor, in fact, is eosinophilic liver cell carcinoma with lamellar fibrosis.[2] A large series of these patients was reviewed and described by Berman et al in the book entitled SOLID LIVER CANCER. We have recently summarized 21 cases from the consultation files of Hugh Edmondson M.D., Robert L. Peters, M.D., the California Tumor Tissue Registry and the autopsy files of LAC/USC Medical Center.

The age at diagnosis is indcated in Table 3.

Table 3
AGE AT DIAGNOSIS

0-9	1
10-19	5
20-29	9
30-39	3
40-49	0
50+	2
Unknown	1

The young age at diagnosis of these patients is most unusual for hepatocellular carcinoma in our experience. However, the percent of patients with primary hepatocellular carcinoma under the age of 40 is quite variable. In Hong Kong, Sweden and Los Angeles the reported series indicate the incidence at less than 6% but in Uganda the incidence increased to 51%. Other reported series in the United States show the incidence at 30-40% but these reports include childhood tumors including hepatoblastomas which dilute the average age. The typical sex breakdown of this tumor is 50% males and 50% females, which is similar for most hepatocellular carcinomas arising in noncirrhotic liver. The duration of symptoms of this tumor is variable with approximately one-third having symptoms for less than one month and yet another third having symptoms for an average of 6 months and a few patients up to one year. The symptoms that led to diagnosis were typical symptoms for liver cancer and included abdominal pain (9 patients), malaise (4 patients), jaundice (2 patients), incidental findings (2 patients). Laboratory results were not widely available to us in the consultation cases. The hemoglobin average was 12.0 grams percent in a range of 8.8 to 14.4. The transaminases were abnormal in 11 but generally only slightly elevated with 6 patietns having levels at 100 to 400 units/liter. The bilirubin was normal in 10 patients and elevated in 3.

The gross morphology of this tumor is intriguing as the majority of patients have the tumor in the left lobe (8 patients). Patients with only right lobe involvement were 4 and one patient had both lobes involved. No data was recorded in 7 patients. The tumor was solitary in 6 patients and multiple nodules noted in 7.

DISTINCTIVE HISTOLOGIC FEATURES

The distinctive features of this case in tumor type are listed in Table 4.

Table 4

HISTOLOGIC FEATURES

1.	Hepatocytes:	oval - polygonal cholestasis common clear cells often hyaline droplets
2.	Nuclei:	prominent nucleoli mitosis rare
3.	Stroma:	thin fibrosis common thick bands and scars
4.	Necrosis:	often in large areas
5.	Other HCC pattern:	Pelioid

The arrangement of the hepatocytes may be solid sheets with a few fibrous bands dissecting these sheets into very large nodules. On the other end of the spectrum is thin lamellar fibrous bands dissecting individual trabeculae into thin lines. Intermediate forms would be small nests of several hepatocytes. Cholestasis is variable and in some instances very large bile plugs are noted. The hyaline droplets are PAS positive and diatase resistant. Other patterns of hepatocellular carcinoma include the pelioid pattern noted in 4 of our patients. The pelioid nature may be a small portion or noted in many blocks. Transition forms of the typical eosinophilic hepatocellular carcinoma with lamellar fibrosis and pelioid pattern may be intermixed or there may be abrupt transition. The adjacent liver was normal in most instances although some degree of fibrosis, even suggesting cirrhosis, was present in 4 patients. Associated diseases included general hepatic fibrosis, (1 patient) alpha-1-antitrypsin deficiency (MZ phenotype - 2 patients) and hepatocellular adenoma (1 patients).

TREATMENT

At the time of diagnosis 14 patients were considered operable and 4 not operable. Some form of hepatic resection was performed in 8 patients and no resection was performed after observing the tumor in 6. Eleven patients in the series had a biopsy only. Based on operative findings and other evidence the clinical stage at the time of diagnosis indicated only liver involvement in 9 patients, liver and limited abdominal involvement in 9 patients and liver involvement with distant metastasis in 1 patient. Other forms of therapy included chemotherapy in 10 patients. Seven patients were treated with 5 FU and no improvement in clinical condition was noted. Radiation therapy was given to one patient and no significant improvement in clinical condition was noted. Of the 16 patients with follow-up information available, 11 are dead and 5 are alive. Patients alive include survival at 12 months, 14 months, 66 months, 10 years and 20 years plus. When metastasis has been found it occurred in adjacent lymph nodes, peritoneum, lung, and spleen. The expected survival of hepatocellular carcinoma after diagnosis is generally several months. If the three long term survivals of 5, 10 and 20 years are excluded, the survival of all patients in our series is 12 months.

20.3 REFÈRENCES

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CASE 21. HEPATOCELLULAR CARCINOMA, CLEAR CELL VARIANT

CONTRIBUTOR: John J. Gilrane, M.D.
Duarte, California
TISSUE FROM: Liver
(LUS1345-78)

June 4, 1978
ACCESSION NO. 9828
(151)

21.1 CASE SUMMARY

CLINICAL ABSTRACT

History: This 75 year old Caucasian female entered the hospital in January 1958, with complaints of right upper quadrant abdominal pain of one month's duration. The pain started suddenly after a fatty meal but without attendant vomitting or fever. No other gastrointestinal symptoms were elicited.

Pertinent physical examination showed an afebrile, obese, elderly woman with an exquisitely tender mass, 8 x 6 x 4 cm., extending three finger breadths below the right costal margin and moving with deep inspiration.

Laboratory data:

BSP (normal less than 6% retention)	14%
Albumin (normal 4 - 6)	4.4
Globulin (normal 1.6 - 3)	1.3
AG ratio (normal 1.7/1 - 3/1)	3.3/1
Total protein (normal 6.5 - 8.0)	5.7 gram%
Alkaline phosphatase (normal 0.8 - 2.3)	1.7

Radiographs showed a functioning gallbladder and medial displacement of hepatic flexure of the colon. An IVP showed "no definite kidney pathology".

SURGERY (January 24, 1958)

An 8 x 10 x 8 cm. polypoid mass was found in the right lobe of the liver, protruding from the inferior aspect of the right lobe and lying just to the right of adjacent gallbladder bed. Approximately 200 cc. of old blood was found in the peritoneal cavity which appeared to have come from a ruptured cyst on the inferior surface of the liver adjacent to this mass. There was an inflammatory reaction of the retroperitoneal tissues below and contiguous to this with many adhesions of the small bowel. After frozen section, the mass was resected with a good cuff of adjacent normal liver. The inflammatory reaction on contiguous peritoneal surfaces was also resected. The remaining liver was unremarkable.

GROSS PATHOLOGY

Specimen received was a 10 x 7 x 6 cm. wedge of liver containing a 6 cm. in diameter circumscribed but unencapsulated, yellow, glistening somewhat softened, bulging, tumor resembling fatty tissue.

FOLLOW-UP (John Waken, M.D.)

The patient was last seen on April 11, 1958 when she moved to the east coast and was lost to follow-up.

21.2 CASE DISCUSSION

DIAGNOSIS

Clear Cell

HISTOLOGIC DESCRIPTION

The tumor is composed of sheet of polygonal to oval cells with distinct cell margins, clear cytoplasm, small nuclei with smudged chromatin and no definite nucleolus. Mitotic figures are infrequent. The sheets of tumor occasionally form finger-like broad trabeculae interdigitating with large vascular spaces and at the edge of the tumor a thin capsule is occasionally noted. The adjacent liver is altered by compression change but no cirrhosis is noted. Histologic features absent in this tumor are necrosis,

calcification, cholestasis, and hyalin formation. The histologic features present are compatible with a clear cell variant of a hepatocellular carcinoma. The clear areas are PAS positive diastase sensitive indicating glycogen.

HISTOLOGIC DIFFERENTIAL DIAGNOSIS

Clear cell carcinoma metastatic from several sites must be considered as possible explanation for the tumor in this patient. A primary renal cell carcinoma and a primary thyroid carcinoma look identical to the features noted in this cancer. Furthermore there is no clinical or surgical evidence that the tumor began in an adrenal cortex. The IVP which indicated no definite histopathology is important negative evidence, although, an arteriogram is required for better proof as some renal cell carcinomas may be associated with a normal IVP (or poorly performed IVP).

CHARACTERIZATION OF TUMOR

Clear cell carcinoma as a primary liver tumor has been recognized for several decades and a recently reported series of patients have allowed comparison of histologic and clinical features of these tumors to more typical hepatocellular carcinomas. In the review of 150 patients with hepatocellular carcinoma seen at Memorial Sloan-Kettering Cancer Center over a 25 year period, 13 patients (8.7%) were classified as clear cell carcinoma.[2] The histologic features of these 13 cases indicated that at least one slide showed significant numbers of vacuolated clear tumor cells and resembled clear cell varieties of renal, adrenal, or endocrine cancer. Additional sections of these same tumors revealed a typical hepatocellular carcinoma pattern which was trabecular in 8 patients, alveolar in 7, and adenomatoid in 2. Cholestasis was noted in 4. In 10 of the 13 cases, clear cells of the tumor were randomly scattered among more typical hepatocellular carcinoma cells and in the remaining 3 cases, clear cells were in aggregates whcih were distributed throughout the hepatocellular carcinoma. In the isolated foci of clear cells, the concentration of the clear cell was 30% to nearly 100% of the lesion. In the review of Ugandan patients with hepatocellular carcinoma, Anthony reported 4 examples in the series of 263 hepatocellular tumors. The clarity of the cytoplasm was related to glycogen storage and one of the patients had profound hypoglycemia. Foster and Berman recored 7 clear cell hepatocellular carcinomas in their series of 112 hepatocellular carcinomas. Two of six arose in noncirrhotic livers and the

prognosis was similar (and grave) as in non-clear cell hepatocellular carcinomas. The clinical and pathologic differential diagnosis of metastatic tumor is the most challenging aspect of this case. The liver is a common metastatic site for renal cell carcinoma. In such examples of metastatic tumor to the liver, multiple nodules would be more characteristic rather than a solitary large well circumscribed mass as noted in the current case. The clear cell hepatocellular carcinoma typically arises in a noncirrhotic liver and often is a solitary mass. At autopsy, the mass may be so extensive as to be consistent with multiple metastatic nodules coalescing. In most tumors of clear cell variety, there are typical areas of hepatocellular carcinoma which assures the diagnosis. One interesting autopsy case at the John Wesley Hospital was a patient with two primary tumors of which the renal cell carcinoma was clear cell in variety as well as the hepatocellular carcinoma. In review of the series at the John Wesely Hospital, there were no examples of hepatocellular carcinoma with metastasis to the kidney in the survey of 247 cases.[3] However, 2 of the patients with liver cell carcinoma also had renal cell carcinoma.

21.3 REFERENCES

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CASE 22. SQUAMOUS CELL CARCINOMA, PRIMARY IN LIVER

CONTRIBUTOR: Harriet Davis, M.D.
Edmund M. Y. Low, M.D.
Los Angeles, California

June 4, 1978

ACCESSION NO. 12652
(159)

TISSUE FROM: Liver
(LUS1346-78)

22.1 CASE SUMMARY

CLINCIAL ABSTRACT

History: This 75 year old female was hospitalized in August 1962 for weakness, weight loss and anorexia. There was considerable elevation of the serum alkaline phosphatase. A contracted gallbladder was seen on cholecystogram. The patient was taken to surgery and extensive spread of tumor was encountered in the liver. The patient expired several months later.

GROSS PATHOLOGY (Autopsy)

The liver was described as being remarkably enlarged with multiple nodules varying in size from 1 to 10 cm. in diameter. The largest nodules was in the right lobe. Cut surfaces of the tumor exhibited a granular grayish-white to greenish-brown tissue with central necrosis in the larger nodules. Several mucus containing cysts and dilated intrahepatic bile ducts were encountered which measured up to 2 cm. Multiple infarcts and thromboemboli were seen in the lungs. No tumors was found in any site other than the liver.

22.2 CASE DISCUSSION

DIAGNOSIS

Squamous cell carcinoma primary in liver, possibly arising in hepatic cyst.

HISTOLOGIC DESCRIPTION

The main tumor in the section is encapsulated but there is extension beyond the capsule so that pleomorphic tumor extends into the liver but is bounded by a sharp margin. The the tumor is made-up of pleomorphic squamous cells with intercellular bridges, epithelial pearls and some keratin material may be found. There is polyploidy and gigantism of the nuclei. There are no gland formation, nor bile. In a few regions there are undifferentiated tumor cells with a spindling or stellate pattern.

CHARACTERIZATION OF TUMOR

Squamous cell carcinoma of the liver is a rare lesion.[1-4] The tumors in reported cases seem to have arisen from hepatic cysts[1-3] except one arising in a teratoma.[4] Adenosquamous carcinomas and muco-epidermoid carcinomas have also been reported but may represent squamous metaplasia of pre-existing carcinoma arising from duct epithelium.[5,6]

There are a number of reports of cholangiocarcinomas arising in the liver of patients who have congenital cysts, Meyenberg complexes and Caroli´s disease (see case #4), although cholangiocarcinoma have not been demonstrated arising within the cyst (as do the squamous cell carcinomas) or from the Meyenberg complexes themselves.

DIAGNOSTIC METHODS

None of the cases of squamous cell carcinoma have been reported to be associated with alpha-fetoprotein and there are no reports of surgical resection of primary hepatic squamous cell carcinoma. All cases of squamous cell carcinoma in the liver must be first considered to be metastatic tumors until proven otherwise.

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CASE 23. PERIPHERAL CHOLANGIOCARCINOMA

CONTRIBUTOR: William E. Cowell, M.D.
Oceanside, California
TISSUE FROM: Liver
(LUS1349-78)

June 4, 1978
ACCESSION NO. 15800
(152)

23.1 CASE SUMMARY

CLINICAL ABSTRACT

History: This 65 year old male entered the hospital on July 10, 1967 with the complaint of mid-epigastric pain for 3 to 4 weeks. This was a different pain from the discomfort of a bowel hypermobility that he had off and on for years. Two years ago he had a questionable pyloric ulcer which healed and repeat G.I. series failed to reveal any ulcer.

Radiographs: In 1965 a barium enema was reported as "negative". A gallbladder visualization at this (July 10, 1967) admission revealed cholelithiasis.

SURGERY

On July 10, 1967 an exploratory laparotomy revealed a tumor confined to the right lobe of the liver, extending to the bed of the gallbladder. A right hepatic lobectomy with cholecystectomy was performed.

GROSS PATHOLOGY

The specimen consisted ot a right lobe of the liver weighing 890 gm. and measured 17 x 16 x 7 cm. The gallbladder was attached, and immediately lateral to this was a gristly tumor in the liver weighing 3.5 cm. in diameter. The gallbladder mucosa was intact, but adjacent to the liver it was thickened measuring up to 6 mm. It was indurated. No calculi were present.

COURSE

Following surgery he had evidence of internal bleeding and was reoperated. The bleeding was from the cut edge of the coronal ligament. He continued on a precarious recovery course, lapsed into coma with a sustained hypotension and expired on the 4th post-operative day.

An autopsy revealed the lobectomy site to be healing. There was no collection of fluid or infection. Approximately 500 gm. of orange liver remained. There was no evidence of cancer. There were no arterial or venous thrombi, but microscopically the greater portion of the remaining liver was necrotic.

23.2 CASE DISCUSSION

DIAGNOSIS

Cholangiocarcinoma, peripheral, small duct type

HISTOLOGIC DESCRIPTION

The tumor is fairly well circumscribed and separated from the liver parenchyma by a margin of lymphocytes. Non-tumor liver is not cirrhotic but does have lymphoid hyperplasia in portal areas and a few scattered foci of lymphocytes and hepatocytolysis elsewhere. There is perivenular parenchymal pigment around each terminal hepatic vein but only rarely can a true bile plug be identified. The lymphoyctes that form the margins of the tumor are mixed with pigmented histiocytes and the lymphocytes seem to invade neither the liver nor the tumor. The tumor is made-up of orderly, well organized ductal structures separated into small clusters by dense collagen. There is variation regarding the density of collagenosis from one area to another. There is secretory material in the lumen formed in the small ducts but no bile. The tumor epithelial cells are cuboidal or low columnar and are faintly eosinophilic. The tumor nuclei are round to oval. Nucleoli are not prominent. The tumor has very little pleomorphism.

CHARACTERIZATION OF TUMOR

The tumor in this instance had the appearance of arising from the interlobular ducts rather than from larger duct structures. Of interest is its separation from the remaining liver by an inflammatory border. Whereas a tumor of this type could have arisen from gallbladder or pancreas, the dense hard collagen separating clusters of ductal structures is a little more consistent with primary duct tumor in the liver.

Although the residual liver was described as necrotic at autopsy, the material submitted showed a fatty change but hepatocytes that were viable and were apparently undergoing attempts of regeneration. There were a few small clusters of hepatocytes that produced an irregularity to the entire lobular character by some proliferation and bulging. Cholestasis was prominent.

In a patient of this age whose liver has been resected to a level of 500 gms., the cellular activity of replication is in conflict with the cellular function, and hepatic failure may develop after a period of time. Frequently such patients have marked cholestasis by the time death occurs. (See also appendix #B)

CASE 24. HEPATOCELLULAR CARCINOMA, ADENOID, IN HEMOCHROMATOSIS

CONTRIBUTOR: D. R. Dickson, M.D.
Santa Barbara, California
TISSUE FROM: Liver
(LUS1348-78)

June 4, 1978
ACCESSION NO. 17868
(151/124)

24.1 CASE SUMMARY

CLINICAL ABSTRACT

History: This 85 year old Caucasian male first presented with a 2 to 3 week history of mild epigastric pain, anorexia, nausea and vomiting associated with a 10 pound weight loss in July 1968. He had diabetes mellitus for 12 years treated with Diabinase. Physical examination revealed the liver to be 4 to 5 fingers below the right costal margin and possibly nodular. An exploratory laporatomy was performed and a large subhepatic hematoma was found. There was a suggestion of liver nodularity but a biopsy was not performed and the patient was discharged.

Three months later, the patient was again admitted with swelling of his abdomen and legs. The clinical diagnosis was Budd-Chiari syndrome. His condition steadily deteriorated and he died on December 30, 1968.

Laboratory Data: RBC 3.7 million, hemoglobin 12.1 gm., WBC 5,300 with normal differential. Prothombin time was 75%, SGOT was elevated to 195 units but the alkaline phosphate was elevated to only 19 units on admission and fell to normal levels by December 2, 1968.

GROSS PATHOLOGY

At autopsy, the liver weighed 2180 gm. and contained dense adhesions over the peritoneal surfaces. The right lobe was enlarged and multinodular with surface mottled yellow nodules up to 2 cm. in greatest dimensions. On cut sections the entire right lobe of the liver was replaced by nodules which varied from 0.3 cm. to 0.4 cm. These nodules were dry, light green-brown to green-red with scattered hemorrhages in the larger nodules. A 2.0 cm. diameter extension of tumor was seen in the portal vein, but there was no evidence of hepatic vein involvement. The left lobe of the liver was normal.

Metastatic tumor was found only in the lungs and death was attributed to bilateral bronchopneumonia.

24.2 CASE DISCUSSION

DIAGNOSIS

Hepatocellular carcinoma, adenoid type arising in hemochromatotic liver

HISTOLOGIC DESCRIPTION

The liver is cirrhotic with poorly defined nodules and large amount of parenchymal hemosiderin. Kupffer cells contain a small amount of iron and macrophages in portal areas are heavily iron laden. There is striking bile duct proliferation and some of the duct epithelial cells contain hemosiderin also. However, there are numerous areas where hepatocytes have become more plump and atypical and fail to incorporate iron. There are large areas of hepatocellular carcinoma in which there is no hemosiderin. The tumor has an unusual pattern. It ranges from ordinary trabecular carcinoma in a few areas, to a pattern that resembles thyroid follicle formation in most areas. The follicular structures are not surrounded by connective tissue but often do have endothelial cell structures around them. Even the follicular lining cells are made-up of hepatocytes with little pleomorphic change. The nuclei have prominent nucleoli and the scanty brown pigment that is recognizable in tumor cells is apparently formalin pigment, giving a negative reaction to iron although a few cells have pigment that closely resembles iron on H & E. There is an occasional microcystic area. In many areas of the liver, bulging parenchymal

nodules free of hemosiderin appear to be undergoing low grade neoplastic or at least paraplastic change. Each of these foci are seemingly arising denovo. Some of the tumor structures can be found within vascular channels, often as a budding acinar elements.

CHARACTERIZATION OF TUMOR

Hemochromotosis has been an uncommon hepatic lesion in our material at Los Angeles Country USC Medical Center and at John Wesley Hospital. Only two hepatocellular carcinomas and one cholangiocarcinoma arising in hemochromatosis were found in 39,000 autopsies. This number and the total number of hemochromatosis cases is too small for any statistical analysis but between 10% to 20% hemochromatosis patients are said to develop hepatocellular carcinoma.[1] The effect of removal of hemosiderin on the development of carcinoma has not been entirely settled, at Kings College Hospital Liver Unit in London, carcinoma of the liver is the leading cause of death in patients with hemochromatosis who have had repeated venasection. In addition, a higher incidence of other neoplasms were found. Of 45 repeatedly phlebotomized patients, 13 died of hepatocellular carcinoma (28.9%) and 10 (22%) of other cancers.[3] On the other hand Powell's experience for 15 years included 44 patients, 24 had all of their iron removed by phlebotomy and none of those developed hepatocellular carcinoma, whereas four of the remaining 20 developed hepatocellular carcinoma (20%).

Recent work by Willson et al[3] has resulted in the hypothesis that tissue damage and carcinogenesis are the result of iron becoming decompartmentalized. The presumption is that iron combines with thiol groups to result in the formation of oxidative free radicles. The free radical generally produces cell death but if free radical activity is partially neutralized by the presence of either low intracellular oxygen tension or the presence of an incomplete anti-oxidant, such as copper, the cell may survive but neoplastic change may result. Zinc seems to compete with iron for combination with thiol groups and prevent free radical formation. Thus much of the damage effect produced by iron is prevented.[4] Zinc has been shown to protect from the effect of radiation induced free radicals, a reverse of the action of iron. Zinc tends to be depleted in the cirrhotic patient. The effect of repeated phlebotomies and loss of hemosiderin may take place after carcinogenesis is initiated, accounting for the high incidence of HCC, but in addition the phlebotomized hemochromatosis patient no longer dies of his heart failure and thuse lives long enough to develop his HCC. In addition, phlebotomy also depletes further

the levels of zinc which may be a critical factor in preventing neoplasia.

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CASE 25. PERIPHERAL CHOLANGIOCARCINOMA LARGE DUCT TYPE

CONTRIBUTOR: David J. Francis, M.D.
Torrance, Caliofornia
June 4, 1978
ACCESSION NO. 22569
(152)
TISSUE FROM: Liver
(LUS1349-78)

25.1 CASE SUMMARY

CLINICAL ABSTRACT

History: This 60 year old Filipino female was in her usual state of health until May 1977 when she first noted the onset of right upper quadrant fullness. This persisted until July 1977 when she presented to a physician who found her liver to be enlarged 8 to 9 cm. below the right costal margin.

Laboratory data: Prothombin time, partial thromboplastin time, bilirubin, alkaline phosphatase, LDH, SGOT and SGPT were all within normal limits. Alpha-fetoprotein was normal. The CEA was 7.8 ng. per ml. (this was interpreted as elevated). Albumin was 3.8 and globulin was 3.9.

Radiographs: Liver scan and ultrasound both demonstrated a 6-8 cm. solitary mass of the right lobe of the liver. Arteriograms showed this lesion to be hypovascular.

SURGERY (August 5, 1977)

A partial hepatectomy with en bloc removal of the gallbladder and cystic duct was performed.

GROSS PATHOLOGY

The specimen consisted of a 13 x 8.5 x 10 cm., 550 gm. portion of the right lobe of the liver with attached 5.8 x 2.7 cm. gallbladder. Seventy-five percent of the liver was occupied by a firm, whitish mass with a multilobular well-circumscribed border extending to Glisson's capsule. The remaining hepatic parenchyma was brown-red and was grossly compressed. A few small satellite nodules were present within the remaining hepatic parenchyma, and gross tumor was found at the line of resection as well as in the portal vein. The attached gallbladder had a smooth, mottled, gray-green wall normal thickness lined by a finely granular, dark green mucosa. The cystic duct was of normal caliber, and no stones were noted.

FOLLOW-UP

The patient was last seen on March 29, 1978 when she was reported as well and free of disease. She is being treated with 5 Fluorouracil and BCG.

25.2 CASE DISCUSSION

DIAGNOSIS

Peripheral cholangiocarcinoma, large duct type, with inflammatory reaction.

HISTOLOGIC DESCRIPTION

The segment of liver is almost completely replaced by well formed ductal structures separated from adjacent ducts by connective tissue and inflammatory cells. The ducts all have prominent lumina. The epithelial cells are large with prominent nuclei. There are numerous neutrophils in duct lumina.

CHARACTERIZATION OF TUMOR

This tumor would appear to have arisen from more major duct radicles than Case #23 but still from peripheral areas. The pattern is somewhat unusual in view of the rather scanty fibrosis and the intense inflammatory reaction which is largely plasmacytic and neutrophilic. The cytoplasm of the tumor cells resembles hepatocytes to a certain extent and the type of carcinoma in this patient resembles those often found in patients who have hepatocellular carcinoma with ductal elements. (see also appendix B)

APPENDIX A. HEPATOCELLULAR CARCINOMA

Primary malignant tumors of the liver were only characterized and subdivided near the beginning of the 20th Century. Hanot and Gilbert divided primary liver cancers into those that arose from bile duct origin as well as those that arose from hepatocytes.[1] However, although Hanot and Gilbert's work included detailed microscopy, the morphologic classification of cirrhosis still used in large part today, is based on the classic work of Eggel in 1901.[2] Eggel's classification divided the tumors into "massive" "diffuse" and "nodular". Although Eggel made no distinctions in these three classes, as to whether there are not there were different patterns based on the underlying liver disease, his review of the gross descriptions of 163 cases of primary carcinoma included the information that cirrhosis was positively identified in 57 of 99 patients with hepatocellular carcinoma (57.6%) but that in those not specifically identified as having cirrhosis, only 9 times was the statement made excluding cirrhosis. One might conclude that cirrhosis was present in 86.4% of the 66 patients with hepatocellular carcinoma in which the liver adequately described or in 57.6% of the total group in which cirrhosis was positively diagnosed. However it seems that cirrhosis was much less frequently associated with carcinoma of the liver, and that carcinoma of the liver was a much less common neoplasm at the turn of the century that it is today. In 18,500 necropsies at Guy's Hospital, Hale White[3] found 24 cases of primary liver cancer (.13%). Eggel[2] estimated that primary carcinoma occured once in 2,000 autopsies or .05%. This is in sharp contrast to the percent incidence of carcinoma of the liver in current data in this country. It seems unlikely that we can ascribe the differences that carcinoma bears to cirrhosis simply on incomplete data. In 1888 Hanot and Gilbert indicated that only 1/3 of their patients who had HCC had cirrhosis and in 1881 Sabourin had felt that the relationship of carcinoma to cirrhosis was sufficiently atypical that an entirely different tumor class was devised for those patients in whom the carcinoma developed in a cirrhotic liver, many investigators at that time believing that the tumors were actually multiple adenomas. Sabourin apparently is the first to use the term "hepatoma".[4] Rolleston reported in 1912 that 10 of 41 patients with liver cell carcinoma at Middlesex hospital had cirrhosis of the liver. In 1959 Shikata objected to the usual manner of quotation of cirrhosis vs. noncirrhosis in patients with carcinoma and pointed out that many reports indiscriminately included all primary liver cancers (hepatocellular and

cholangiocarcinoma) and their relationship to cirrhosis and that since cholangiocarcinoma represented a higher relative percentage of primary liver cancers in countries with low total incidences of hepatocellular carcinoma and that since such tumors were less frequently associated with cirrhosis, the relationship between hepatocellular carcinoma and cirrhosis became somewhat warped by such reporting. Shikata also pointed out that, at least in Japan, carcinomas frequently arose in livers that, although not characterized as cirrhotic, were certainly not normal. A more valid distinction might be made if investigators separated carcinomas that arose in normal livers compared with those that arose in liver that had cirrhotic or precirrhotic changes. He even conjectured that it often appeared as though the cirrhosis developed simultaneously with the carcinoma.[6]

At LAC/USCMC the percentage of patients with chronic liver disease, underlying the hepatocellular carcinoma, has been in the range of 80-90%[7] (see table 1) but if one only included patients with nodular cirrhosis described grossly in the autopsy protocol and confirmed microscopically, the incidence of cirrhosis was only 67%.

Table 1
Changing of HCC in indigent population of Los Angeles

	Guy's Hospital pre-1900	LAC-USCMC 1918 to 1953	LAC-USCMC and JWCH 1954 to 1963	1964 to 1973
Number of autopsies	18,500	49,915	23,476	15,380
HCC	24	81	78	147
Autopsies (%)	0.13	0.17	0.33	0.96
HCC with Cirrhosis (%)	25 to 50	85	90.8	81.8
Admitted alcoholism (%)	?	50+	48	48

The racial-ethnic-cultural differences in incident of cirrhosis and of carcinoma has been of interest in our material at LAC/USCMC. (table 2) Ten percent of the autopsy population from the LAC/USCMC and John Wesley Hospitals had cirrhosis and about 5.5% of those with cirrhosis had hepatocellular carcinoma whereas approximately .1% of patients without cirrhosis had hepatocellular carcinoma. Negroes had about 1/2 the expected incidences of cirrhosis based on the percent of negroes in the autopsy series. Of Negroes with cirrhosis, however, twice as many had hepatocellular carcinoma compared with Caucasians. Orientals had an anticipated 10% incidence of cirrhosis based on the total number in the population, but a ten-fold higher incidence of

carcinoma arising in those cirrhotic livers.

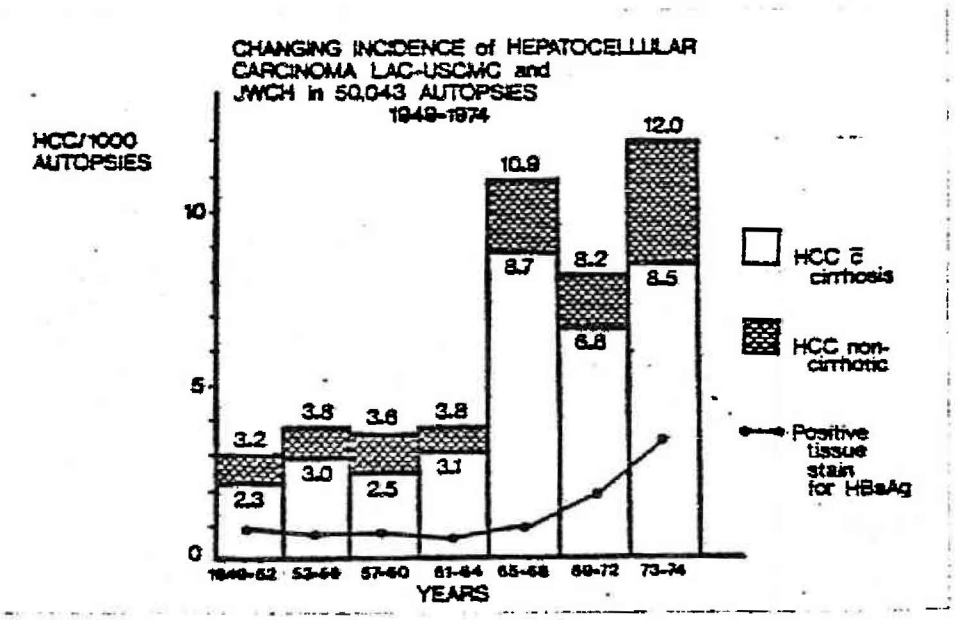
Table 2

Hepatocellular Carcinoma
Racial Incidence
LAC-USC-MC & JWCH 1949-73

	#Autopsies 50,043	% Cirrhotic 10.%	% of cirrh. & HCC 4.4%	% of HCC in cirrhosis that are HBsAg 21%
Caucasian	32,027	11.0%	3.2%	10%
Negro	10,509	5.7%	8.3%	25%
Mexican	7,006	12.2%	3.6%	12%
Oriental	500	10.0%	47.9%	46%

The etiology of the cirrhosis that underlies carcinoma of the liver varies in different parts of the world, the incidence of B-viral cirrhosis as an underlying disease to hepatocellular carcinoma seems to have changed in the United States in recent years. Studies by hepatitis B antigen staining have shown that the incidence of HBsAg positivity has risen but no more so than the total incidence of carcinoma of the liver has risen, carcinoma in otherwise normal liver has also increased in incidence suggesting an etiology not yet studied.[8]

Table 3



Recently Omata and others have shown that the hepatitis B core antigen may be demonstrable in hepatocyte nuclei of patients who do not have circulating HBsAg but only anti-HBc in their serum and that some of the patients with what had heretofore been considered cryptogenic cirrhosis, actually have B-viral cirrhosis without circulating HBsAg.[9]

Table 4

Correlation Between Serum HBV Markers and Tissue Antigens in 20 HCC Patients with Non-Alcoholic Chronic Liver Disease

SERUM		TISSUE		NO. OF SUBJ.
HBsAg	Anti-HBc	HBsAg	HBcAg	
+	+	+	+	6
+	+	+	-	3
+	+	-	-	2
+	-	+	+	1
-	+	-	+	2
NT*	NT	+	+	1
-	-	-	-	5
12	13	11	10	20

At least one positive - 15

* Not Tested

Other pre-existing diseases have been reported in association with hepatocellular carcinoma but their incidence is low. There had been a number of reports dealing with the association of protease inhibitor type ZZ in carcinoma of the liver.[10] However, at least in the United States, type ZZ protease inhibitor is not a significant underlying anomaly in patients with hepatocellular carcinoma. To date we have found no patients in nearly 160 serum specimens in patients with hepatocellular carcinoma who were type ZZ. The incidence of MZ has been about twice that of normals (6.8% instead of 3.1%) but it is doubtful that this is in the range of significant differences.[7]

Many patients with carcinoma arising in a pre-existing chronically diseased liver have atypical changes that we have characterized as paraplastic. This may be the same change that Farber has referred to as "initiated cell alteration" in experimental animals.[11] The variety of "nearly neoplastic" alterations, early neoplastic change and well established carcinoma that often occurs in the same liver has led to the impression that hepatocellular carcinoma arising in the cirrhotic liver may often be multifocal in origin. Such a concept of mutifocal origin seems reasonable when one considers that the entire liver is exposed to the same carcinogen. However the question of whether or not the pre-neoplastic or early neoplastic change lingers for sufficient time to allow a similar change to develop in other areas has not been settled. Okuda believes that

multifocal sites of tumor in the liver are always or nearly always from intrahepatic metastatic spread. The metastatic spread of other carcinomas to involve liver have a markedly different morphology. The multifocular or unifocal origin of the carcinoma is not yet settled. Carcinoma arising in alcoholic cirrhotic livers tend to develop from areas of cirrhotic regeneration in which there is little cellular dysplasia. The hepatocytes instead have assumed a very regular a somewhat atropic appearance and from these normal appearing hepatocytes, a spurt of growth develops, and often within that a neoplastic change. In carcinomas arising in B-viral cirrhosis, however, striking dysplastic cellular changes occur in about 50% of the cases in contrast to only 5% of those who do not have carcinoma.[12]

The metastatic patterns of hepatocellular carcinomas are monotonously similar. The metastatic patterns of HCC and cholangiocarcinoma are compared in table 5.

Table 5

METASTATIC PATTERNS of PRIMARY LIVER CARCINOMAS

	HCC Non-cirrhotic (39 cases)	HCC Cirrhotic (188 cases)	Peripheral Cholangioca. (18 cases)
No metastases	33%	54.8%	25.0%
Single metastases	25%	19.1%	18.8%
Lung	41%	38.8%	25.0%
Lymph node (portal)	43.6%	16.5%	68.8%
Portal vein	23%	37.2%	12.5%
Hepatic vein	18%	22.9%	18.8%
Skin	0	2.7%	0
Serosa	23.1%	7.4%	25%
Adrenal gland	3.0%	6.9%	18.0%
Bone marrow	7.7%	8.0%	25%
Heart	2.6%	1.6%	0
Spleen	7.7%	2.1%	6.3%
Pancreas	0	1.1%	0
CNS	2.6%	1.1%	0
Kidney	0	0	0
Diaphragm	2.6%	3.7%	6.3%
Gallbladder	10.3%	5.3%	0
Other	5.1%	3.2%	6.3%

Paraneoplastic syndromes have become recognized with increasing frequency in patients with hepatocellular carcinoma. Often the symptoms of the associated features will be what brings the patients to seek medical care.[13]

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APPENDIX B. CHOLANGIOCARCINOMA

Cholangiocarcinoma is malignant tumor arising from the epithelium of bile duct. Usually the term has been reserved for intrahepatic tumors, but the term may correctly be applied to extrahepatic carcinomas of the bile duct. Intrahepatic cholangiocarcinomas are separated into **hilar** and **peripheral** origins, hilar arising in the common hepatic duct or a major duct near the bifucation, peripheral arising at the lobular level. Most large studies have non-selectively grouped the cholangiocarcinoma and its epidemiologic features with hepatocellular carcinoma.

The original division of primary liver cancer into tumors that arose from hepatic cells and those that arose from bile duct epithelium was by Hanot and Gilbert.[1] Bile duct carcinomas were referred to as "cancer alveolaire". In 1901 Eggel, whose gross classification has persisted to this time, divided his 162 cases of primary liver cancer into "carcinoma solidum" and carcinoma adenomatosum.[2] While many carcinomas fall distinctly into hepatocellular or cholangiolar types, there are many tumors that have a mixture of both; most tumors with hepatocytic elements act like hepatocellular carcinomas except for the few that seem to have two separate primary cancers. Although cholangiocarcinomas have a much less frequent relationship with cirrhosis of the liver, there is no question that a higher percentage of patients with cholangiocarcinoma have cirrhosis than would be expected by chance alone.

Intrahepatic cholangiocarcinoma represents between 5-25% of the total numbers of primary liver tumors, 13 cholangiocarcinomas were identified in 248 cases of primary liver cancer at LAC/USCMC in the years from 1953 to 1974. A nearly equal number (10) were classified as mixed cholangio-hepatocellular carcinomas. In contrast to hepatocellular carcinoma, over 60% of cholangiocarcinomas arise in noncirrhotic, normal livers. About a fourth arise in alcoholic cirrhosis with a small number of less than 10% arise in pre-cirrhotic alcoholic liver disease or in liver disease associated with chronic ulcerative colitis. In those patients with mixed cholangiocarcinoma - hepatocellular carcinoma, 10% arose in hemachromatosis, 10% in hemasiderosis, 40% in cirrhotic liver and 40% in "normal" liver.

Reported relative incidence of cholangiocarcinoma in series of primary liver cancers has varied between 7% and 25%.[3,4,5] There does not appear to be the male sex preponderance in patients with cholangiocarcinoma in patients with hepatocellular carcinoma, although in this small series there were 8 men and 5 women.

Grossly, cholangiocarcinomas tend to be grayish-white firm and solid with dense fibrosis. The tumor does not have a cirrhotomomentic nor nodular growth pattern.

DIAGNOSTIC TECHNIQUES

Cholangiocarcinoma does not have an association with hepatitis B surface antigen nor with alpha-fetoprotein. The diagnostic tools available include selective celiac angiogram and liver scan. It must be distinguished from carcinoma of the pancreas which metastasizes to produce a very similar histologic pattern and from carcinoma of gallbladder which on invasion of the liver may also produce a similar reaction. However carcinoma of the gallbladder is more frequently a mucin producing tumor resembling carcinoma of the colon, only a minority of gallbladder carcinomas producing the sclerosing ductal pattern so frequently seen with carcinoma of the bile duct system.

Metastases from carcinoma of the breast may closely resemble cholangiocarcinoma if it is the sclerosing ductal type of tumor. However carcinoma of the breast is rarely an occult primary lesion.

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