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Calcification in the liver, an unusual feature of ductal cell hepatic carcinoma

*Report of a case**

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CALCIFICATIONS in the liver occur rarely. Roentgenographically, such deposits of calcium may appear as discrete, structured elements, or may be distributed diffusely and irregularly. Histologically the calcium may be deposited amorphously, as dystrophic calcification, or may be organized into new bone.

In the case reported in this paper, the patient had intrahepatic calcification as the first manifestation of a ductal cell carcinoma of the liver. In addition to malignant cells, the neoplasm contained areas of dense fibrosis, amorphous calcium deposits, and new bone. Since carcinoma of the liver as a cause of intrahepatic calcification is rare, the varied etiopathogenesis of the latter is discussed and a review of the pertinent literature is presented.

Report of a case

A 32-year-old Caucasian man was first examined at the Cleveland Clinic in March, 1965, because of weakness, and roentgenographic evidence of calcification of the liver. Four years previously, the patient was first noted to have asymptomatic enlargement of the liver. There was evidence of calcifications in the right upper part of the abdomen at the time of barium enema study in 1964 and again in January 1965. Varicella developed in February 1965, at which time the patient was noted to have an increase in alkaline phosphate, serum glutamic oxaloacetic transaminase (SGOT), and sulfobromophthalein sodium retention, but the serum bilirubin content was normal. On April 19, 1965, he was admitted to the Cleveland Clinic Hospital for further evaluation.

On physical examination the patient appeared to be well developed and well nourished. The temperature was 98 F, pulse rate 80, and blood pressure 130/80 mm Hg. Positive physical findings were the presence of icterus, bilateral gynecomastia, a hard, nodular, nontender liver extending 4.0 cm below the right costal margin, and an enlarged spleen palpable 3.0 cm below the left costal margin.

Laboratory studies disclosed a hemoglobin content of 14.0 g per 100 ml, and a leukocyte

* *Roentgenographic details of the case were previously reported in reference 1.*
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count of 5,600 per cubic millimeter, with a normal differential count. Urinalysis was normal. The serum determinations were as follows: total bilirubin 15.8 mg per 100 ml, with a direct fraction of 7.5 mg per 100 ml; alkaline phosphatase 85 King-Armstrong units; SGOT 120 units; calcium 10.6 mg per 100 ml; and phosphorus 3.2 mg per 100 ml; protein normal. The prothrombin time was normal. Electrolyte values, blood sugar concentration, serologic tests, lupus erythematosus cell preparation, and Casoni skin test were all within normal limits or negative. Stool examination for blood, ova, and parasites was negative.

Roentgenograms of the chest, and barium examination of the upper gastrointestinal tract were normal except for the presence of multiple 0.5- to 2.0-cm densities in the region of the liver (*Fig. 1*). A liver scintigram showed multiple filling defects scattered throughout both lobes. A selective celiac arteriogram was normal (*Fig. 2*). The vascularity of the liver appeared reduced, but no abnormal vessel or tumor stain was evident within the liver. Roentgenographic details of this case were previously reported.[1]

On April 23, 1965, the patient underwent abdominal exploration by one of us (R.E.H.). Both lobes of the liver were affected by a nodular, calcified, and fibrotic process that was extremely hard, making surgical biopsy difficult. The gallbladder was normal and collapsed. An operative cholangiogram via the gallbladder revealed a normal extrahepatic biliary tree. No surgical procedure other than resection of multiple liver biopsy specimens was attempted.

The heavy calcium deposits present in the biopsy material (*Fig. 3*) required decalcification for histologic preparation (*Fig. 4*). The normal architecture of the liver was completely destroyed in the areas of involvement. The hepatic lobules were replaced by a dense, hyaline, connective tissue in which were embedded variously sized patches and islands of calcification and bone formation. Portal tracts were identifiable, but were surrounded and infiltrated by the dense collagen. Bile ducts in the portal areas, and the larger collecting ducts were well preserved but did not appear to contain secretion. Arterial and venous vessels stood out in sharp relief against the dense hyaline and calcific background but were otherwise not remarkable. In no areas were there any atypical epithelial elements suggestive of neoplasm. The entire histologic picture suggested a bizarre form of scar formation complicated by extensive calcification.

The patient had an uneventful postoperative course, except for increasing jaundice. Because of the failure to diagnose a tumor conclusively by biopsy, and in the hope that the pathologic process might be inflammatory, the patient was given prednisone, 60 mg a day. During the next two months, there was a gradual increase in icterus, pruritus, anorexia, and weight loss.

On August 28, 1965, the patient was readmitted to the Cleveland Clinic Hospital. There were now severe icterus, ascites, and pitting edema to the knees. The liver was palpable 10.0 cm below the right costal margin. The hemoglobin content had decreased to 7.0 g per 100 ml. The serum alkaline phosphatase concentration was 119 King-Armstrong units; the total serum bilirubin content had increased to 30.6 mg per 100 ml; and the prothrombin time was 14 sec (control, 12 sec). In the hope that a dilated intrahepatic bile duct could be identified and the liver decompressed surgically, a percutaneous transhepatic cholangiogram was attempted, without success. A transfusion of 1000 ml of whole blood was given and the patient was discharged from the hospital to the care of his local physician. Prednisone, hydrochlorothiazide,* vitamin K, and multivitamins were prescribed.

During the next month and a half hepatic failures worsened, coffee-ground emesis occurred, and hepatic coma developed. The patient died at home on October 31, 1965.

At autopsy† the liver and porta hepatis were grossly abnormal; the liver weighed 2,140 g. A large nodular calcified mass occupied most of the right lobe. Biliary radicles could not be discerned within the mass, but within the liver more peripheral radicles were dilated and filled with inspissated material. Sections of the liver revealed biliary cirrhosis with portal fibrosis, extreme bile stasis, and dilatation of bile ducts. Sections from the hepatic mass were largely formed of dense, fibrous tissue that contained irregular areas of

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* *HydroDIURIL, Merck Sharp & Dohme.*

† *The postmortem examination was performed by Donald L. Cohen, M.D., pathologist, Sharon General Hospital, Sharon, Pennsylvania; we are indebted to him for the gross description and for microscopic sections which one of us (W.A.H.) reviewed.*

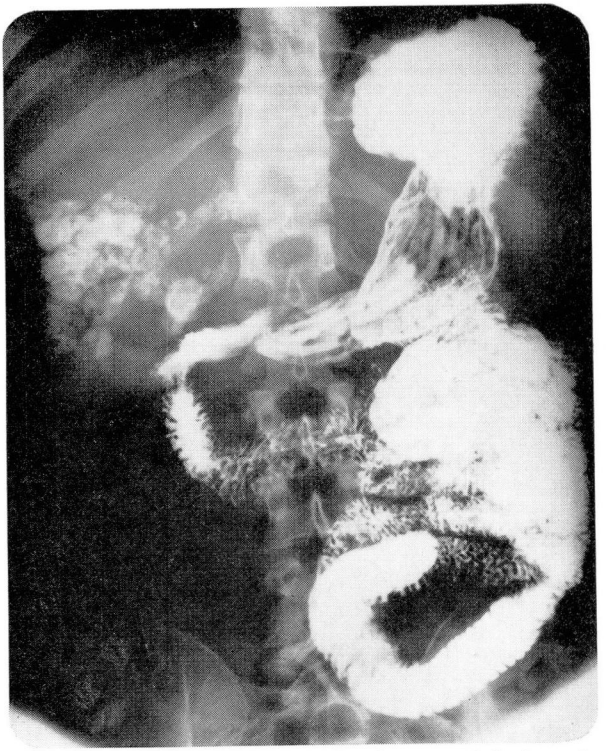

Fig. 1. Upper gastrointestinal roentgenogram showing rounded, irregular, dense, intrahepatic calcification.

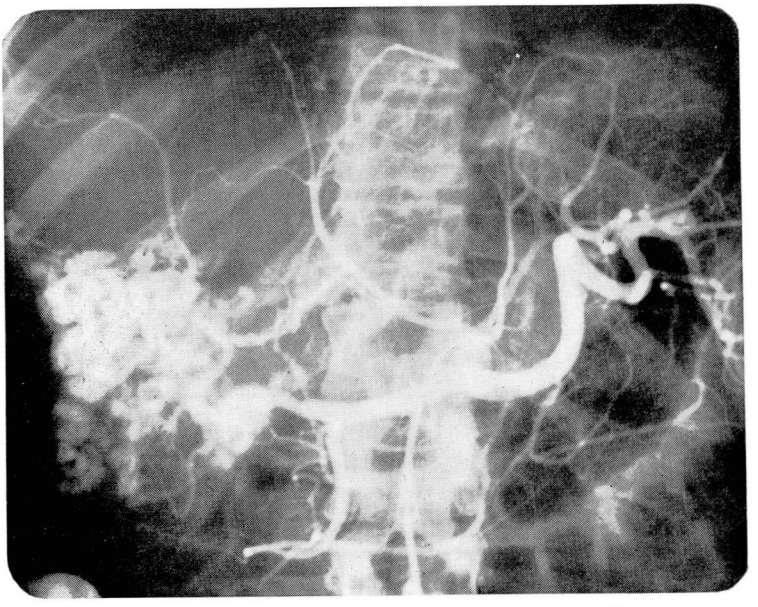

Fig. 2. Normal celiac arteriogram (note intrahepatic calcification).

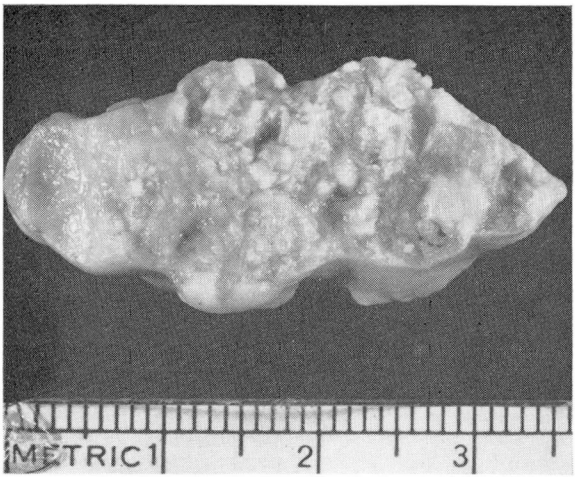

Fig. 3. Photograph of liver biopsy specimen. The whitish rounded projections are areas of calcification.

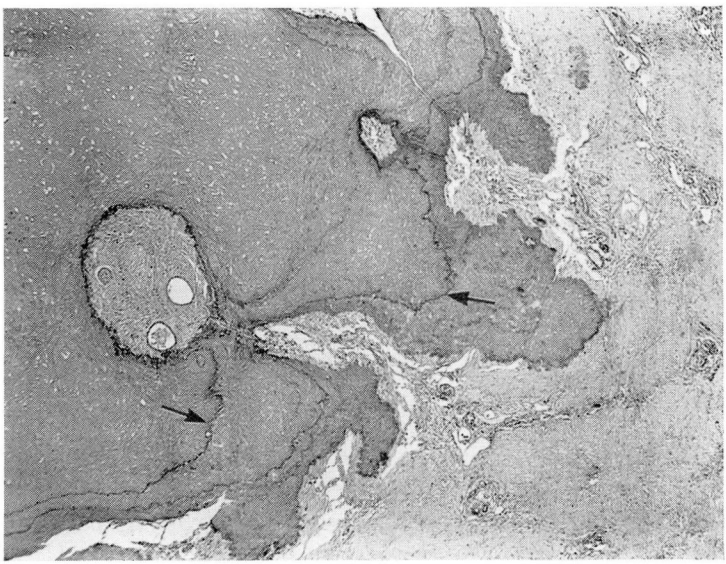

Fig. 4. Photomicrograph of a section showing a representative area of the first biopsy specimen. Note the extensive irregular zone of calcification showing "cement" lines (arrows). Magnification ×50.

neoplasm. The neoplasm itself (*Fig. 5 and 6*) was formed of atypical ductal cells enmeshed in a scirrhous calcified stroma. The cells were pleomorphic, having large irregular vesicular nuclei and abundant pink-staining cytoplasm. Tumor cells were in greatest number surrounding bile ducts and around entrapped nerves.

Secondary cholangiolar carcinoma was evident in sections of lung, omentum, and peritoneum. In addition, there were acute peritonitis, esophageal varices, and evidence of recent gastrointestinal hemorrhage.

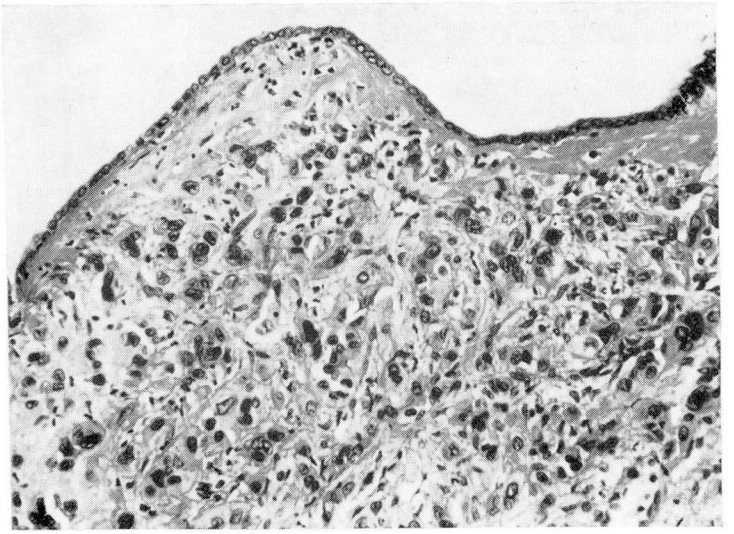

Fig. 5. Photomicrograph of a section of the cholangiolar carcinoma marginating a bile duct. The bile duct epithelium is intact; the neoplasm is highly dedifferentiated and at this site is less scirrhous than in most other locations. Magnification ×200.

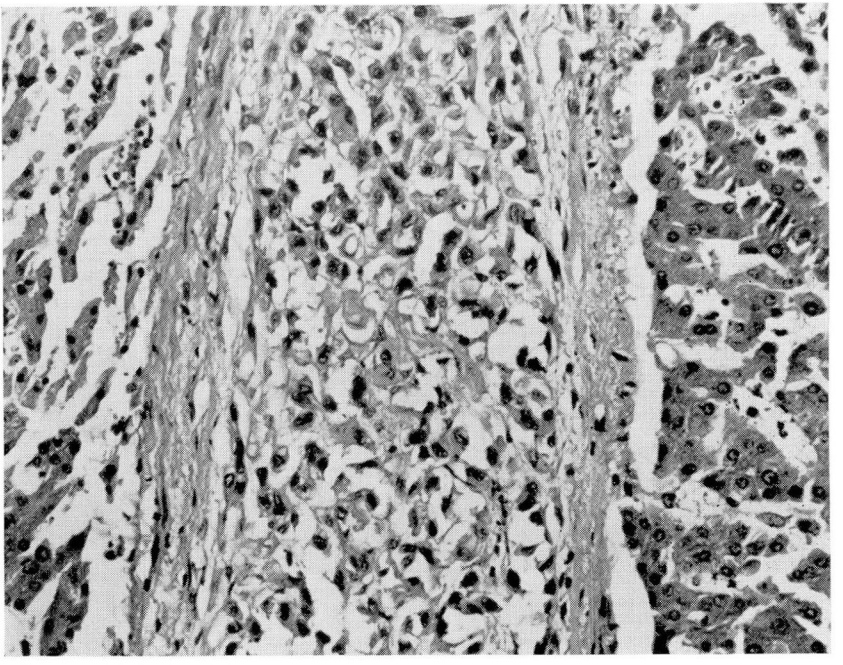

Fig. 6. Photomicrograph of a section showing the island of tumor cells that filled and distended a bile duct; it is remote from the zones of calcification. Magnification ×200.

Table 1.—Summary of data of 24 reported cases (including the one from the Cleveland Clinic) of hepatic neoplasms associated with intrahepatic calcium

Case number	Author (s)	Reported, year	Patient		Roentgenographic evidence of calcification	Hepatic neoplasm	
			Age	Sex		Gross description, site	Diagnosis-histopathologic description
1	Misick[30]	1898	6 weeks	M	None reported	Multinodular right lobe	Mixed cell tumor—liver cells, bone plaques, osteoblasts, blood vessels, bile ducts, embryonic liver tissue, epithelial cysts, spindle cells
2	Nakamura (cited by Milman and Grayzel[29])	1911	18 months	F	None reported	—	Mixed cell tumor—liver cells, bile ducts, bone
3	Yamagiwa (cited by Milman and Grayzel[29])	1911	12 months	F	None reported	Multinodular	Mixed cell tumor—liver cells, bile ducts, bone
4	Yamagiwa (cited by Milman and Grayzel[29])	1911	18 months	F	None reported	Multinodular	Mixed cell tumor—bone, connective tissue, epithelium, cartilage, mucous membrane
5	Idzumi (cited by Milman and Grayzel[29])	1913	7 months	M	None reported	Uninodular right lobe	Mixed cell tumor—glycogen-containing cells, bone, connective tissue, fat, cartilage, mucous membrane, epithelium
6	Saltykow[32]	1914	67 years	M	None reported	Uninodular right lobe	Mixed cell tumor—connective tissue, cartilage, bone, hepatic cells, spindle-shaped cells

7	Griffith[26]	1918	21 months	F	Present	Right lobe only without metastasis	Ductal cell carcinoma—epithelial cells without trace of normal liver tissue; early gland formation
8	Nissel[31]	1928	Newborn	F	None reported	Uninodular right lobe	Mixed cell tumor—liver cells in cords, connective tissue, spindle-shaped cells, osteoblasts, bone, cartilage, osteoid
9	Imai (cited by Milman and Grayzel[29])	1934	32 years	M	None reported	Uninodular right lobe	Mixed cell tumor—epidermis, sweat glands, eye connective tissue, fat, cartilage, bone marrow, blood vessels, gonads, bronchial and oral mucosa
10	Hamburger[27]	1938	5 years	M	Present after X-ray therapy to tumor in liver	"Small tumor size of shilling"	Hepatic cell carcinoma
11	Webster[37]	1938	6 months	M	None reported	Right lobe without metastasis	Mixed cell tumor—hepatic cells, osteoid, unsystematized calcium, blood vessels, keratinized epithelium
12	Leffers (cited by Milman and Grayzel[29])	1941	16 months	M	None reported	Multinodular to both lobes with pulmonary metastasis	Mixed cell tumor—adenomas, cartilage, bone, myxomatous connective tissue, liver cells, bile ducts, blood vessels
13	Wallace[36]	1941	23 years	F	Present—4-cm ring of calcium in liver area	Right lobe	Cord of hepatic type of cells—in lobular formation

Table 1.—*Continued*

Case number	Author (s)	Reported, year	Patient		Roentgenographic evidence of calcification	Hepatic neoplasm	
			Age	Sex		Gross description, site	Diagnosis-histopathologic description
14	Tomlinson and Wolff[35]	1942	18 months	M	Present—scattered throughout right lobe	Right lobe with pulmonary metastasis	Hepatic cell carcinoma—pleomorphic hepatic type of cells; calcium in shell-like configuration
15	Brick[24]	1950	26 years	M	Present—small flecks	Both lobes	Hepatic cell carcinoma—liver cell type with rare cholangiomatous elements; calcium deposited sporadically
16	Bigelow and Wright[23]	1953	8 months	F	Appeared 2½ months after diagnosis	—	Mixed cell tumor—hepatic type of cells, vascular channels, bile duct epithelium, hyalin, calcium in hyalin, osteoid, epithelial pearls, bone
17	Coleman, Haines, and Phillips[25]	1954	67 years	M	Present	—	Hepatic cell carcinoma—diagnosis made via Vim-Silverman needle biopsy
18	Margulis, Nice, and Rigler[21]	1956	6 months	F	Present	Right lobe only	Hepatic cell carcinoma
19	Kattan, Langer, and Sufrun[28]	1959	18 months	F	Present—multiple areas of granular calcified foci	Tumor mass replaced ⅘ liver	Hepatic cell carcinoma—liver type of cells arranged in adenomatous pattern with hyperchromatic nuclei

20	Schroder[33]	1959	70 years	F	Present—clumps of calcium in right and left lobes	Involvement of both lobes	Heavy fibrosis, areas of calcification, and mucus-producing adenocarcinoma, consistent with bile duct type
21	Shorter, Baggenstoss, Logan, and Hallenbeck[34]	1960	7 months	F	Present	Right lobe with renal and pulmonary metastasis	Mixed cell tumor—spindle cells, round cells, liver cells, myxomatous stroma, osteoid, calcium
22	Cruickshank[38]	1961	3 months	F	None reported	Right lobe only without metastasis	Mixed cell tumor—bone, myxomatous areas containing hematopoietic cells, hepatic type of cells
23	Karras, Cannon, and Zanon[12]	1962	65 years	M	Present—spherical and amorphous calcification	Right lobe	Well-differentiated seromucinous adenocarcinoma of bile duct type
24	Hall, Winkelman, Hawk, and Hermann (Cleveland Clinic)	1969	32 years	M	Multiple round 0.5 to 2.0 cm densities	Both lobes	Ductal cell carcinoma—destruction of normal architecture, dense fibrosis, areas of amorphous calcification, bone formation, atypical epithelial cells enmeshed in fibrous stroma

Discussion

The reported causes of hepatic calcification are several. Structured or discrete patterns of calcification occur most commonly in echinococcus cysts of the liver[2, 3] and intrahepatic calculi.[4] In the former, the calcium is deposited in the wall of the cyst and has a ringlike appearance;[5] in the latter, the calcium may appear as a solid round density or as rings of radiopaque material.[4] Calcified congenital nonparasitic hepatic cysts have also been reported.[6] Plachta[7] described a roentgenographic pattern of "linear or trabecular calcification radiating from a central point," and stated that this pattern, when present in the liver, is characteristic of calcified hepatic hemangiomas. Gallbladder fluid containing calcium ("limey bile," milk of calcium bile), can usually be diagnosed because it assumes the shape of the gallbladder.

Irregular, or unsystematized intrahepatic calcification has a more varied etiology; it has been reported to have occurred in Hodgkin's disease,[8] hepatic gumma,[9] and miliary tuberculosis;[10] it is said to occur in amebic abscess,[11] and in old hepatic or subphrenic abscesses.[12] Wilkins and Ravitch[13] reported the occurrence of an extensively calcified adrenal rest tumor of the liver, which produced virilism and Cushing's syndrome. Calcification has been found in malignant hepatic hemangioendotheliomas,[14] in hepatic metastases from a neuroblastoma,[15] and in pancreatic,[16] colonic,[17, 18] and breast[18, 19] neoplasms.

Primary hepatic neoplasms rarely contain calcium. In a review of the literature, we have found reports of only 30 cases of primary hepatic neoplasms containing calcification. Because of insufficient data, seven[20-22] cases were excluded from the summary in *Table 1*. Of the other 23 cases, nine were summarized earlier by Milman and Grayzel.[29] While in all 23 cases there was histologic evidence of calcium, in only 12 was roentgenographic evidence of intrahepatic calcium reported. In case 10, calcification appeared after X-ray therapy to the hepatic tumor. In only our case did the occurrence of intrahepatic calcification precede the onset of clinical symptoms.

Management was also difficult in the case we report, in that despite laparotomy no exact diagnosis could be made. Although a neoplasm was considered, there was no pathologic confirmation. Faced with progressive hepatic failure the patient was given prednisone, with the hope that there was an inflammatory process that could be arrested with a corticosteroid preparation. The last hope was that a duct could be found in order to allow decompression of the biliary system by a biliary drainage procedure. This was not possible and the patient was discharged from the hospital with the advice to follow a program of symptomatic treatment to alleviate the manifestation of progressive hepatic failure.

The principal feature of this case was the presence of extensive calcification in a malignant hepatic neoplasm of the ductal cell type. Of the various

primary hepatic neoplasms, the mixed cell type has been reported most often to contain calcium.[29, 34, 39] Such tumors contain both hepatic and cholangiomatous cell types, as well as new blood vessels, connective tissue, squamous epithelium, cartilage, osteoid, and calcium.[39] In those tumors, the calcium is deposited amorphously, as dystrophic calcification,[38] and in the form of new bone.[39] The former, resulting from the deposition of lime in dead or degenerating tissue, is independent of the level of calcium in the circulating blood, and is apparently dependent upon local tissue reactions. New bone formation results from the proliferation of tumor from mesodermal cells having a pleuropotential nature.

In the case we report, the histologic features of the tumor were those of a ductal cell neoplasm and not those of the mixed cell type; yet, both dystrophic calcification and ossification were present. Of the 23 other cases listed in *Table 1,* 13 were mixed cell tumors of the liver, seven cases were hepatic cell carcinomas, and three were carcinomas of the ductal cell type. None of these three cases had both dystrophic calcification and ossification; thus, these features in a hepatic ductal cell carcinoma occurring in an adult, makes the case we report unique.

Summary

A case is reported of an adult with intrahepatic calcification as the first manifestation of a ductal cell carcinoma of the liver. From a review of the literature we have presented the causes of intrahepatic calcification and have summarized the data of the 23 other reported cases of hepatic carcinoma associated with calcification. Intrahepatic calcification of any cause is uncommon; it is especially rare in primary hepatic carcinoma. This case is unique in that both dystrophic calcification and pathologic ossification were present in a ductal cell carcinoma of the liver in an adult.

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