

Hepatic Adenomas and Focal Nodular Hyperplasia of the Liver In Young Women on Oral Contraceptives: Case Reports

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Two cases of hepatic adenoma and one of focal nodular hyperplasia, presumably associated with the use of oral contraceptives, are reported. Special reference is made to their clinical presentation, which may be totally asymptomatic. Liver-function tests are of little diagnostic value, but valuable information may be obtained from both liver scanning and hepatic angiography. Histologic differences and clinical similarities between hepatic adenoma and focal nodular hyperplasia of the liver are discussed.

J Nucl Med 18: 263-266, 1977

The number of reported cases of hepatic adenoma and focal nodular hyperplasia of the liver has increased sharply in the last 5 years, and a possible relationship with the use of oral contraceptive pills has been suggested (1-4). Two cases of hepatic adenoma and one case of focal nodular hyperplasia

are presented here, with special emphasis on diagnosis.

CASE REPORTS

Case 1. A 32-year-old white woman had been taking oral contraceptive medication (Enovid-E) for 4 years since the birth of her fourth child. Her menstrual periods during this period were regular and she had no gynecologic complaints. While exercising, she noticed a palpable mass in the right upper abdominal quadrant. Her physician did not consider it clinically significant. Roentgenographic examination of the small bowel and gallbladder was normal, as were liver-function tests. She sought medical advice again because the mass had increased slightly in size, but she denied pain or other symptoms. On examination a nontender smooth mass about the size of a large lemon was felt in the right upper quadrant. The mass was intra-abdominal and moved with respiration. There was no rub or bruit. Repeat x-rays and liver-function tests were normal.

A liver-spleen scan showed two cold areas in the hilum of the liver (Fig. 1A). At surgery a mobile cystic well-confined mass was found attached to the

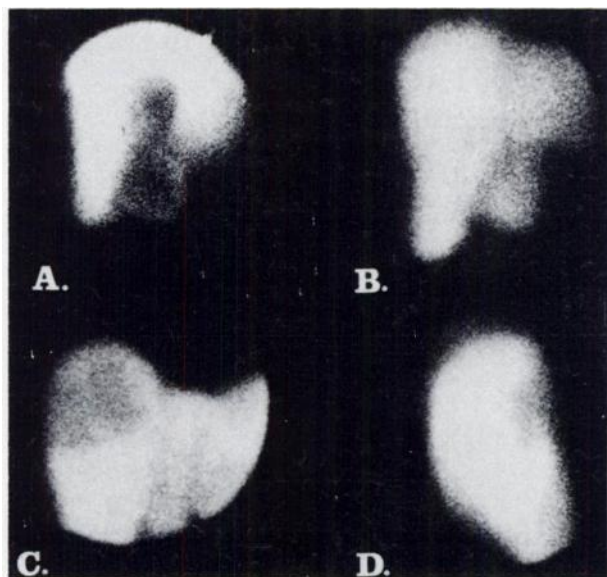


FIG. 1. Technetium-99m-sulfur colloid liver scintigrams. (A) Case 1: Anterior view showing two cold areas in hilum of liver. (B) Case 3: Anterior view showing large mass-like projection below anteroinferior margin of liver, with irregular concentration of tracer. (C, D) Case 2: Anterior and right lateral views showing single cold area in right lobe.

Received May 6, 1976; revision accepted Oct. 12, 1976.

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liver only on its posterior aspect. The second mass was located in the hilum and extended into the right and left liver lobes. Pathologic examination revealed a distinct border against the surrounding compressed slightly yellow liver parenchyma. The capsule of the liver was intact. Both masses were diagnosed as hepatic adenomas with large areas of hemorrhage. After surgery the patient did well and was discharged in good health.

Case 2. A 29-year-old black woman had enjoyed excellent health until July 1975 when she had an episode of acute crampy abdominal pain in the periumbilical area, followed by watery diarrhea. On the following day she developed chills, fever, and persistent right upper quadrant pain, for which she was admitted with the diagnosis of possible cholecystitis. She denied prior abdominal pain, weight loss, anorexia, or malaise. She had taken oral contraceptives (Ortho-Novum) for about 4 years before her admission to the hospital. On examination, moderate tenderness was noted in the right upper quadrant, with a positive Murphy's sign. The liver was just palpable. No bruit or rub was heard. Her white cell count was 10,000, with a mild left shift. Oral cholecystogram was normal. Chest x-ray revealed an elevated right hemidiaphragm that moved poorly with respiration.

Liver scanning revealed a single cold area in the right lobe (Figs. 1C and 1D), and hepatic angiogram revealed a mass with evidence of neovascularity and an area of possible infarction (Fig. 2A). Liver-function tests were normal except for an alkaline phosphatase of 112 units. At surgery a 5×7 -cm multilobular mass was removed from the right upper portion of the liver. It had several areas of hemorrhage, which occupied nearly 50% of the entire mass. The mass was compressing the surrounding hepatic parenchyma. A right lobectomy was performed. Histologic diagnosis of the tumor was hepatic adenoma with hemorrhage (Fig. 2C). The patient was discharged without symptoms and well.

Case 3. A 35-year-old white woman was admitted for elective total abdominal hysterectomy after 10 years of heavy menstrual bleeding. She had one child, 9 years old, and had had one subsequent spontaneous abortion. She had taken oral contraceptives (Norinyl) for about 3 years but had discontinued them about 4 months prior to her admission due to mild hypertension and frequent breakthrough bleeding. She had no other symptom. At hysterectomy, an incidental vascular tumor was found arising from the left lobe of the liver and projecting partly under the left half of the diaphragm. It was decided not to attempt immediate removal of the tumor. A few months later the patient returned to the hospital for

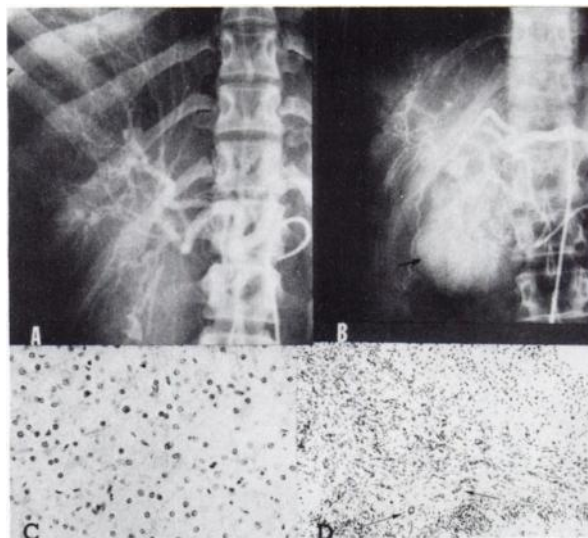


FIG. 2. (A) Case 2: Coeliac arteriogram showing mass in right upper lobe (arrow) with evidence of hypovascularity and area of possible infarction. (B) Case 3: Coeliac arteriogram showing hypervascular mass in lower portion of liver (arrow). (C) Case 2: Photomicrograph of hepatic adenoma shows proliferation of uniform hepatocytes without bile ducts. (D) Case 3: Photomicrograph of focal nodular hyperplasia shows central fibrous scarring with bile ducts (arrows).

removal of the liver mass. All liver-function tests were normal.

A liver scan revealed a large mass-like projection below the anteroinferior margin of the liver with irregular concentration of tracer (Fig. 1B). An abdominal aortogram showed a single 8×9 -cm vascular tumor, supplied by the left hepatic artery (Fig. 2B). At surgery one large and two small masses were found. Histologic diagnosis of the large mass was focal nodular hyperplasia (Fig. 2D). The small nodules found in the right and left lobes were hemangiomas.

DISCUSSION

In the last 5 years relatively large numbers of patients with hepatic-cell adenoma and focal nodular hyperplasia have been reported. Most of these patients are young women on oral contraceptives. This association is circumstantial but seems to be a common feature in the cases reported to date. The relative risk of developing hepatic adenoma has been reported to increase dramatically with prolonged use of oral contraceptives (4). In the series reported by Edmondson, the mean period of usage for the 29 patients who used oral contraceptive pills was 79.7 months. The comparable figure for the 26 controls was 37.8 ($p < 0.001$ by the paired t-test). The mechanism by which oral contraceptives give rise to neoplastic lesions is poorly understood. Mestranol and norethynodrel appear to be oncogenic to rats

(4,5). Both hepatic adenoma and focal nodular hyperplasia of the liver are of particular clinical concern since a delay in diagnosis may lead to complications such as intraperitoneal hemorrhage with irreversible shock, rapidly developing coagulopathies, and postoperative complications (2,3,6,7). Therefore, early surgical removal is recommended. The cases presented in this report also emphasize clinical importance of these two entities and illustrate some interesting aspects of their clinical presentation.

A totally asymptomatic presentation of hepatic adenoma is observed in about one-third of all patients, indicating slow tumor development as illustrated by Cases 1 and 3. Of the remaining symptomatic patients, half complain of acute or chronic abdominal pain, usually localized to the right upper quadrant. Laboratory studies are generally of little value. The literature mentions that raised levels of enzymes and bilirubin may occur in patients with hepatic adenoma after acute expansion or intrahepatic hemorrhage. Although our first and second patients had significant bleeding in and around the tumor, no change in SGOT, SGPT, or bilirubin was found.

Valuable information regarding the presence or absence of hepatic neoplasms can be obtained by angiography. Not only can a lesion be detected, but its blood supply can also be delineated, which aids significantly in surgical resection. In addition, angiography may help differentiate benign from malignant tumors. Arteriovenous shunting, vascular pooling, and venous invasion are more commonly seen with malignant lesions. The differentiation between benign and malignant lesions becomes more difficult when there are multiple lesions. Angiographic appearances indicative of a benign lesion are a spoke-wheel vascular pattern with vessels radiating to the periphery and linear lucencies in the hepatogram phase representing fibrous septa. Benign hepatoma can be differentiated from focal nodular hyperplasia of the liver by the presence of capsular arteries (8), the early arterial-phase blush, and marked neovascularity (9). Two of our three patients had angiographic examinations that clearly indicated the position and size of the tumors and correlated well with scintigraphic localization. In both, the tumors were shown to be highly vascular but no venous invasion was noted. The typical spoke-wheel pattern of benign lesions was not observed and the possibility of a malignant tumor, such as carcinoma of the liver, could not be ruled out on an angiographic basis.

Histologically, focal nodular hyperplasia of the liver is distinguished from hepatic adenoma by the lack of a true capsule, the presence of proliferating bile ducts, a central stellate scar, fibrous trabeculae

extending radially to the periphery, dividing the mass into pseudobules, and the presence of Kupffer cells (2,9). Focal nodular hyperplasia and regenerative nodules are the only mass lesions of the liver that contain Kupffer cells. Scintiscanning can be helpful in differentiating between focal nodular hyperplasia and hepatic adenoma since the colloids used in liver scanning are concentrated in the Kupffer cells (8). Focal nodular hyperplasia of the liver presents with a mottled radionuclide uptake (Fig. 1B) whereas hepatic adenoma presents with cold areas (Figs. 1A, 1C, and 1D). However, this difference in avidity for radiopharmaceuticals is not completely reliable since, for unknown reasons, focal nodular hyperplasia of the liver may occasionally present as filling defects, particularly after intrahepatic hemorrhage (10). Scintiscanning may be helpful in the differential diagnosis of hepatic adenoma and hepatoma. Hepatomas generally concentrate such radiopharmaceuticals as ^{75}Se -selenomethionine, ^{67}Ga , and ^{131}I -rose bengal to a greater degree than do the normal hepatocytes (11-16). In contrast, hepatic adenomas usually show decreased radionuclide uptake (17). Cases have been reported, however, in which hepatoma presented with decreased uptake of ^{131}I -rose bengal (18). Bloodflow and blood-pool studies using $^{99\text{m}}\text{Tc}$ -pertechnetate or $^{111}\text{InCl}$ may fail to show differences between hepatoma and hepatic adenoma (19-21). We believe that, for maximum diagnostic accuracy, hepatic scanning, should be correlated with the clinical, angiographic, and histologic data.

At present, about 20 million women in the United States use oral contraceptives. Considering this usage, the incidence of hepatic adenoma and focal nodular hyperplasia of the liver is low, but detailed prospective studies should be undertaken to determine the true incidence and prevalence of these clinical entities. The patients who develop hepatic adenoma or focal nodular hyperplasia should clearly stop using oral contraceptive pills. Additionally, the possibility of hepatic adenoma and focal nodular hyperplasia should be considered in any young woman taking oral contraceptives who has such clinical manifestations as acute or chronic right upper quadrant pain, unexplained blood loss, and anemia. Before the development of acute complications, hepatic scanning and angiography may be extremely useful in preventing significant morbidity.

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