

Complete Regression of Hepatocellular Adenoma after Withdrawal of Oral Contraceptives

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Prolonged therapy with oral contraceptive (OC) drugs is associated with the development of benign hepatocellular adenomas (HCAs) (1-4). At present, the natural history of OC-associated HCA is not fully understood, and consequently no uniform guidelines concerning the optimal management of this disorder are available. All but a small minority of previously reported cases have been diagnosed at laparotomy and, in most patients, tumor resection was undertaken (1-6). However, recent observations have indicated that OC-associated HCAs frequently regress or even disappear following discontinuation of OCs (7-13). Based on these findings, it has been suggested that simple discontinuation of OCs and careful follow-up may be the preferred therapy in minimally symptomatic cases diagnosed without laparotomy or in cases where complete tumor removal is considered technically difficult (7-9). However, as complications such as hemorrhage have been reported many months after discontinuation of OC therapy (14), further experience with the nonsurgical approach is required before it can be regarded as established. We report a patient with a large OC-associated HCA which showed complete regression over a 12-month period following withdrawal of OC therapy.

CASE REPORT

A 28-year-old Caucasian woman was seen in the Outpatient Department of the Royal Victoria Hospital on February 23, 1978, because of upper abdominal pain of two days' duration. The pain had begun during sleep, was dull and steady in nature, but was exacerbated by deep respiration or sudden movements. The patient had noted decreased appetite, but no other relevant symptoms.

Her only child had been born ten years previously; since that time she had continuously taken an oral contraceptive containing 0.25 mg *d*-norgestrel and 0.05 mg ethinyl estradiol (Ovral®) except for a one-year interruption seven years previously. She took no other medications other than aspirin occasionally for headaches. Her past medical history included "iron-deficiency anemia" at age 12. She smoked three packages of cigarettes per week and rarely consumed alcoholic beverages. An oral cholecystogram gave normal results, while an upper gastrointestinal series revealed displacement of the stomach by a greatly enlarged liver. The patient was admitted for further investigation on March 6; by this time her pain had subsided, and she was completely asymptomatic.

Physical examination on admission revealed an obese female in no distress. A visible mass was noted in the epigastrium and right upper quadrant; on palpation this appeared to be an enlarged liver, with a span of 16 cm in the mid-clavicular line and a blunt edge. There was no abdominal tenderness. The remainder of the examination revealed no further abnormalities.

Results of laboratory investigations included hemoglobin concentration 10.4 g/d, WBC count 5300/ μ l, mean corpuscular volume 72 fl (normal 84-101), reticulocyte count 1.6%, platelet count 610,000/ μ l, and erythrocyte sedimentation rate 59 mm/hr (normal 0-20). The prothrombin time was normal. The serum alkaline phosphatase activity was 1038 IU/liter (normal 30-95) while all other tests on the SMAC automated biochemical profile gave normal results. The serum gamma-glutamyltransferase activity was 64 IU/liter (normal 5-30) and the 5'-nucleotidase activity 25.5 IU/liter (normal 0-12). Serum protein electrophoresis revealed a mild elevation of α 2 globulin levels to 1.33 g/dl (normal 0.45-0.91).

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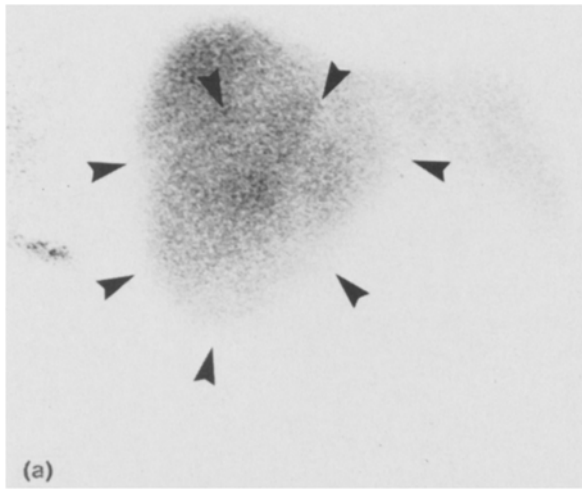


Fig 1. Scintiscans with ^{99m}Tc sulfur colloid showing regression of the tumor over a 12-month period (a,c). The tumor uptake of radiocolloid is similar to that of normal liver tissue; however, scanning with ^{99m}Tc HIDA defines the tumor as a distinct area of reduced uptake (b).

A ^{99m}Tc sulfur colloid liver-spleen scan revealed massive hepatomegaly with no focal defects (Figure 1a). Because no mass was identified on the radiocolloid scan, a percutaneous liver biopsy was performed using a 1.4-mm-diameter Menghini needle. This showed marked sinusoidal dilatation and irregularly distributed septae car-

rying vascular structures but no bile ducts. The hepatocytes were morphologically normal; however, biliary canaliculi were not seen. Kupffer cells were present (Figure 2). The initial pathologic diagnosis was peliosis hepatis; however, this was subsequently changed to "peliosis hepatis in a presumed adenoma." A ^{99m}Tc $N[N'(2,6\text{-dimethylphenyl})\text{carbamoylmethyl}]$ iminodiacetic acid (HIDA) scan disclosed a rim of normally functioning liver tissue around a large hypofunctioning mass (Figure 1b). Two days following the biopsy, a hepatic arteriogram was performed (Figure 3). The findings indicated a large vascular tumor occupying most of the right and central lobes, and probably the left lobe as well. Resection was considered technically impossible. Oral contraceptives were discontinued and, as the patient desired no further pregnancies, tubal ligation was performed two months later. The patient remained well in follow-up. Subsequent scintiscans documented complete regression of the tumor over a 12-month period (Figure 1c). The alkaline phosphatase level has also returned to normal.

DISCUSSION

This case is a unique demonstration of the fact that even large HCAs can regress completely following no therapy other than withdrawal of OCs. Most previous reports of apparent regression of HCA included patients who underwent partial resection, hepatic artery ligation, or chemotherapy as a part of their initial treatment. One previous case

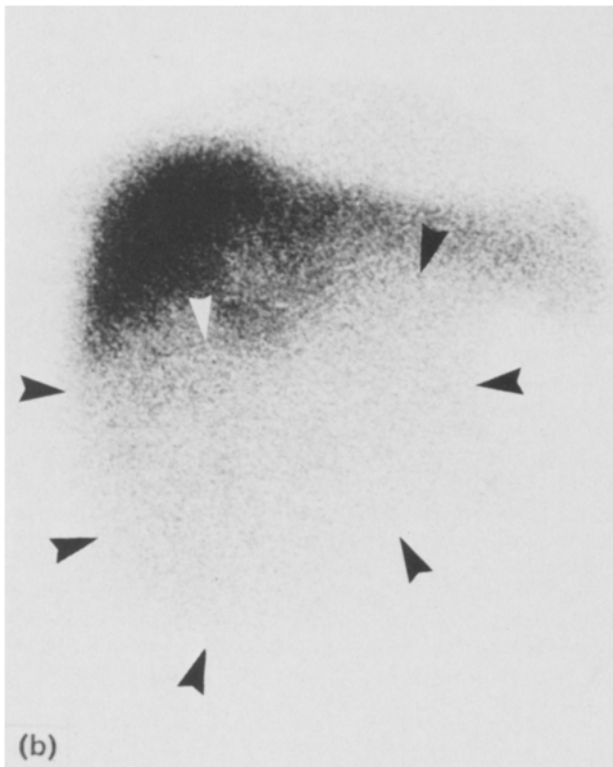


Fig 1. Continued.

REGRESSION OF LIVER TUMOR

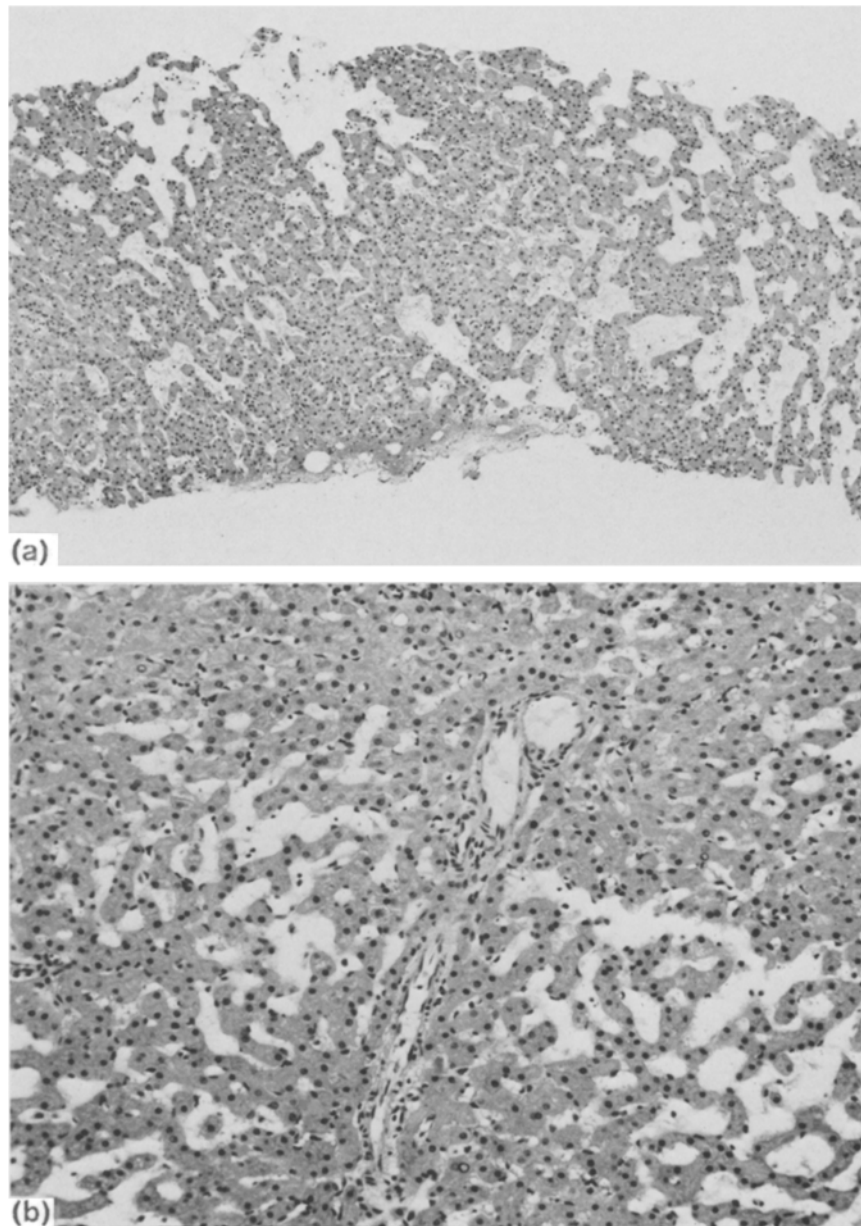


Fig 2. Needle biopsy of the tumor showing marked sinusoidal dilatation and irregular fine septae carrying vascular structures but no bile ducts. Hepatocytes are morphologically normal but canaliculi are not seen. Kupffer cells are present. Hematoxylin-eosin stain (a) $\times 63$; (b) $\times 150$.

was managed without laparotomy, but the tumor had not regressed completely at the time of the last reported follow-up examination (7). The outcome in the present case tends to support the suggestion of others (7-9) that simple observation after withdrawal of OC may be an alternative to resection in minimally symptomatic HCAs.

Radionuclide imaging techniques have an important role in the diagnosis of hepatic adenomas. However, conventional radiocolloid scans may give negative results even with large tumors (15). In some cases this is explained by the origin of the tumor from the inferior edge of the liver with minimal distortion of normal liver parenchyma. A

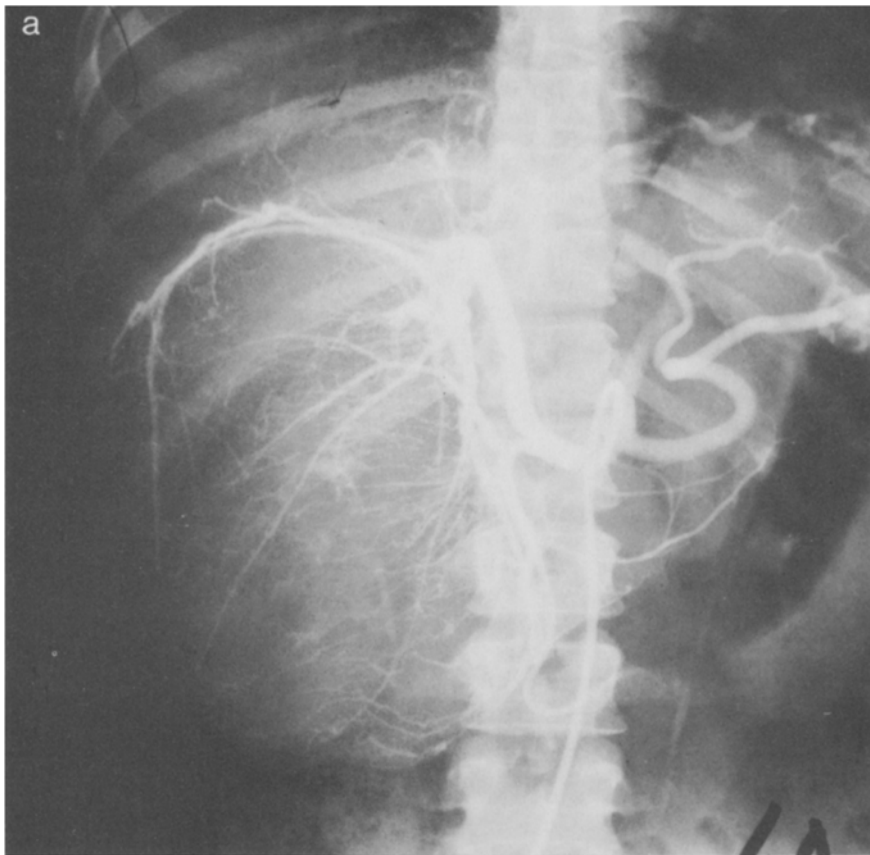


Fig 3. Hepatic arteriogram showing a large tumor with peripheral arterial supply occupying most of the right lobe (a). The early capillary phase film (b) shows contrast filling the site of the liver biopsy done 2 days previously (arrows).

second possible cause of false-negative scans is related to the presence of Kupffer cells within the adenoma; typically these cells are deficient, resulting in "cold" defects on radiocolloid scans, but in our patient, and in a previously reported case (16), Kupffer cells were present and radiocolloid uptake by the adenoma was normal. We found that imaging with ^{99m}Tc HIDA, a tracer which is taken up and excreted by hepatocytes rather than Kupffer cells, gave improved resolution of the tumor from adjacent normal parenchyma. Further studies of this radiopharmaceutical in the diagnosis of HCA are warranted.

The role of percutaneous liver biopsy in the diagnosis of HCA is controversial (7). Serious hemorrhage following this procedure has been reported in patients with HCA (17, 18). Although our patient escaped adverse consequences, we would be reluctant to recommend "blind" percutaneous biopsy in cases where HCA is strongly suspected. Angiogra-

phy would be the preferred initial diagnostic procedure and could be followed by open biopsy if the diagnosis remained uncertain.

Marked sinusoidal dilatation, similar to that seen in the biopsy of the present patient, has been a frequent histologic finding both in OC-associated HCA and in "normal" liver surrounding HCAs (4). The importance of this abnormality is uncertain—it may simply be a characteristic feature of HCA which contributes to the tendency of these tumors to bleed—but there is evidence that it may be a general effect of estrogen therapy. Sinusoidal dilatation in otherwise normal liver has been reported in patients receiving long-term OC therapy (19). The abnormality was reversible on withdrawal of OCs. Analogous lesions have been produced in rats given large doses of estrogens (20, 21). Further studies are required to elucidate the mechanism by which OCs produce these changes and to define their clinical importance.

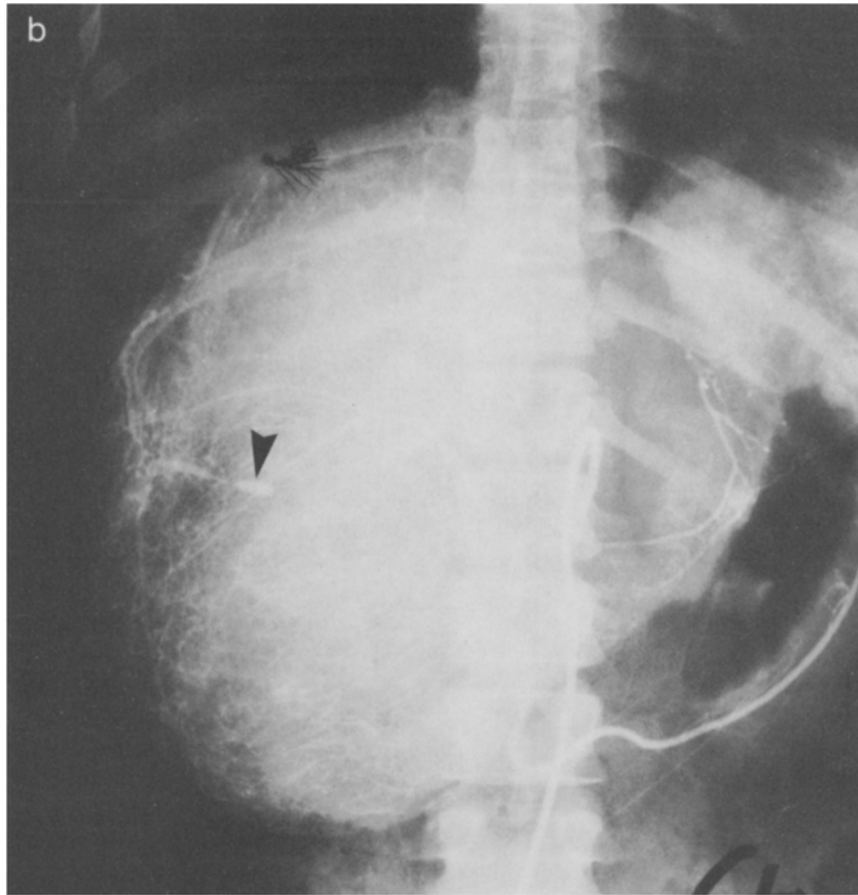


Fig 3. Continued.

SUMMARY

A 28-year-old woman who complained of mild abdominal pain was found to have a large liver tumor. Angiography and needle biopsy established the diagnosis of hepatocellular adenoma. The tumor was felt to be unresectable because of its size, and no treatment was given other than withdrawal of oral contraceptives. Subsequent hepatic scintiscans documented complete resolution of the tumor over a 12-month period.

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