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Liver-cell adenoma in an epileptic man on barbiturates

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Summary. The case of a 19-year-old epileptic man with a solitary hepatic adenoma is described. The tumor was 9 x 8.5 x 6.5 cm in size and microscopically consisted of cells similar in appearance to non-neoplastic hepatocytes, arranged in cords with slit-like sinusoids interposed. Bile ducts and portal tracts were conspicuously absent. Our patient was on antiepileptic drugs, among them phenobarbital which experimentally produces liver cell tumors in mice and rats.

Key words: Hepatic adenoma, Barbirutates, Epilepsy

Introduction

Liver-cell adenoma occurs almost exclusively in women, many of them on oral contraceptives (Scheuer, 1980). Hepatic adenomas have also been described in relation to anabolic steroid therapy, some of them occurring in men (see review by Pelletier et al., 1984). In the present article a liver-cell adenoma found in an epileptic man who was on barbiturates is described.

Materials and methods

Case report

A 19-year-old epileptic man was admitted to our hospital complaining of pain of the upper abdomen, nausea and weakness of three months duration. He had begun with a history of epileptic seizures at the age of seven. From the age of 10 to 13 he received valproic acid (Depakene®), and was asymptomatic until the age of 16, when the seizures reappeared and he began treatment with phenobarbital (daily dose of 150-200 mg), which he has been receiving up to the present. There was no androgen steroid use in this patient.

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On physical examination a smooth, non-tender mass was palpable in the left upper quadrant. There were no stigmata of chronic liver disease.

An abdominal CT scan showed a solitary, round, well-circumscribed 9 cm mass in the left lobe. Combined celiac and superior mesenteric arteriography demonstrated that the mass was hypervascular. The remainder of the liver was normal.

Laboratory tests disclosed a slight elevation of alkaline phosphatase (200 I.U.; N = 90) and γ-glutamyltransferase (170 I.U.; N = 60) values. Transaminases and bilirubin were within the normal limits.

Because of the nature of the mass was unclear, a fine needle aspiration biopsy was performed and it was diagnosed cytologically as a benign hepatic lesion. At surgery, the liver was found to be enlarged, and a tumor involving the left lobe was resected. The patient made an uneventful recovery and he is alive and well at the present time, 42 months later.

Results

The surgical specimen weighed 370 g and contained a 9 x 8.5 x 6.5 cm well-demarcated mass. On cut section a lobular, fleshy, yellowish tumor with a haemorrhagic area was observed (Fig. 1).

Histologically the tumor consisted of cells similar in appearance to non-neoplastic hepatocytes, arranged in cord pattern, with slit-like sinusoids interposed, often simulating normal hepatic architecture. The tumor cell cytoplasm varied from field to field: eosinophilic and granular; clear, containing a large amounts of glycogen (Fig. 2); vacuolated with lipid droplets. No mitoses were seen. Sinusoids were lined predominantly by flattened cells which were occasionally plumper and displayed a polygonal cytoplasm, suggesting Kupffer cells, particularly in PAS stained sections after diastase digestion. Some sections were stained for lysozyme by the peroxidase-antiperoxidase method which permitted

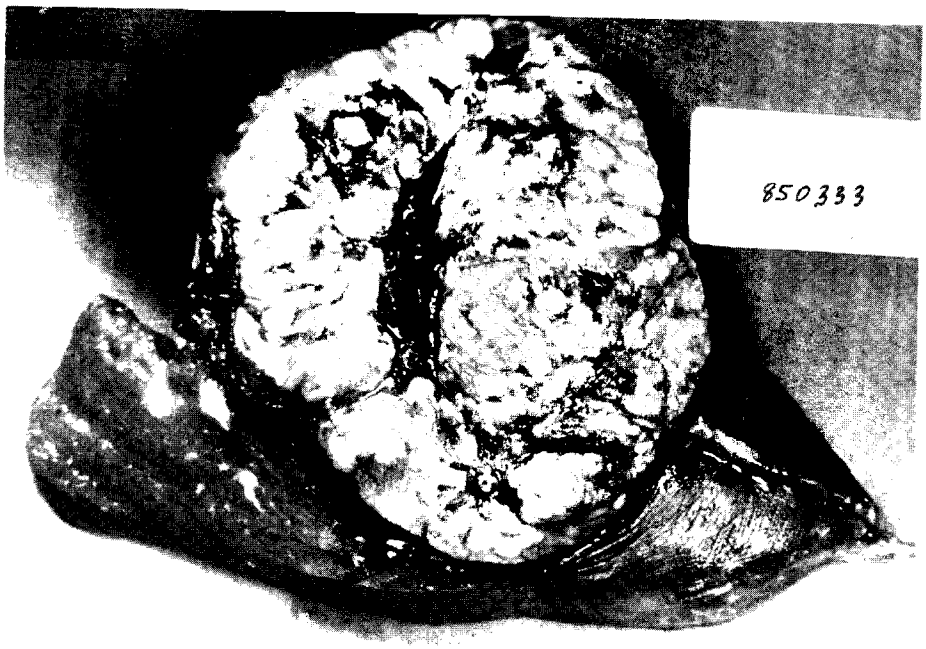

Fig. 1. Tumor found in the left lobe.

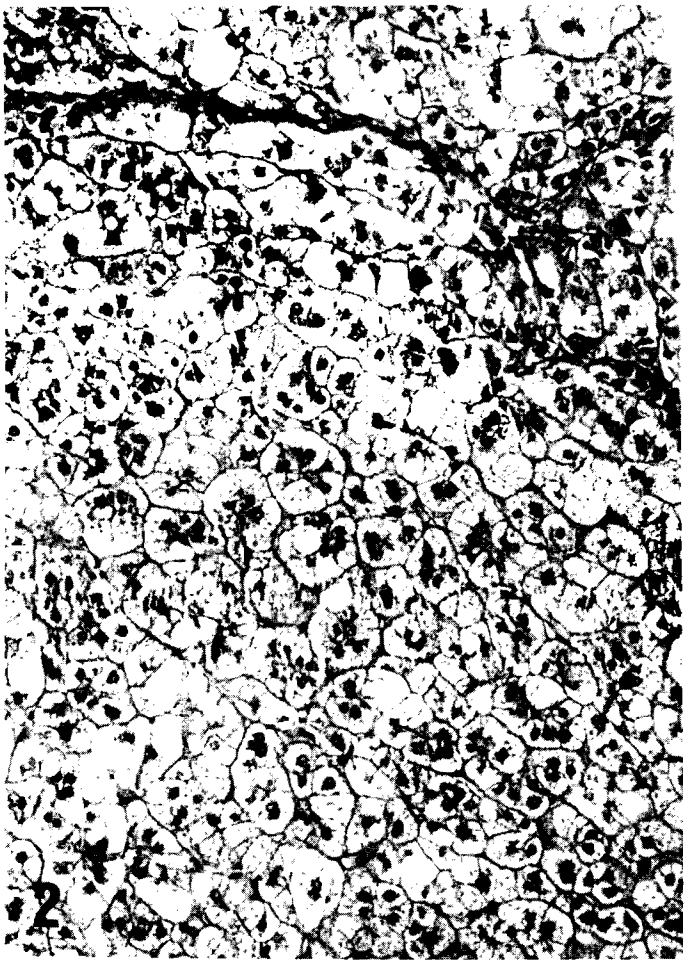

Fig. 2. Micrograph of the tumor tissue. Thickened liver-cell plates two or three cells thick. The tumor cells have a clear cytoplasm due to excess glycogen. Sinusoids appear compressed. H&E. × 150

a ready identification of such plump cells, as they are lysozyme-rich.

Bile ducts, portal tracts and central veins were conspicuously absent. At the periphery the tumor was partly encapsulated.

The remainder of the liver tissue was normal.

Discussion

The tumor of the patient here described had the characteristic pathological features of liver cell adenoma, which are quite different from those of focal nodular hyperplasia (FNH). Macroscopically it was a large, well-demarcated, partially encapsulated mass with a fleshy appearance. In contrast, FNH resembles a cirrhotic process, the parenchyma being divided into nodules by fibrous septa which arborize from a large stellate scar. Microscopically, bile ducts and central veins are absent in adenoma, whereas they are present in FNH, particularly the bile ducts which are numerous in the fibrous septa.

The histological features are the most important criteria for distinguishing adenoma from FNH, as an adenoma which undergoes hemorrhages and necrosis resulting in central scarring, may macroscopically closely resemble a FNH. Although the distinction of liver cell adenoma from hepatocellular carcinoma is not always easy, the present case must be considered as an adenoma because it was well-demarcated and composed entirely of normal appearing hepatocytes, without evidence of capsular or blood vessel invasion.

There is some controversy about the presence of Kupffer cells in the sinusoidal lining of hepatic adenomas. Some authors have described their presence, whilst other authors have asserted their total absence or do not comment on Kupffer cells at all (for references see Goodman et al., 1987). Very recently Goodman et al. (1987) clearly pointed out the existence of Kupffer cells in liver-cell adenomas. These authors emphasized the importance of lysozyme as a marker of Kupffer cells, which belong to the mononuclear phagocyte system.

In the present case the tumor was a solitary mass, located in the left lobe of an otherwise normal liver. Contrary to what occurs in women, liver cell adenomas in men are located more often in the left lobe (Pelletier et al., 1984), as in the present case, and are quite frequently multiple (12 out of 23 cases in which this fact is recorded).

Hepatic adenoma is an uncommon tumor in men. In a recent review Pelletier et al. (1984) collected 30 well-documented cases and they added one more. Eight of these 31 patients were on androgens for a long period of time. Our patient was on anticonvulsant drugs, principally phenobarbital. In this case the association

may be entirely fortuitous. Nevertheless, the possibility that barbiturates could play a role is not unlikely. Hepatocellular hyperplasia has been described after administration of antiepileptic drugs (Stromeyer and Ishak, 1981). On the other hand it has been shown that phenobarbital produces liver cell tumours in mice and rats after application of high dosages (Ponomarkov et al., 1976; Rossi et al., 1977).

Barbiturates, as inductors of drug-metabolising enzymes, stimulate cell growth and cell division (Schulte-Hermann et al., 1974; Benson et al., 1978). The induction process by itself has no proven carcinogenic effect. Moreover, it probably protects against carcinogenic effect when administrated before exposure to some carcinogens (McLean and Marshall, 1971; Peraino et al., 1971). However, the administration of phenobarbital after exposure to hepatocarcinogens seems to increase the tumor yield (McLean and Marshall, 1971; Peraino et al., 1971, 1977), having then a promoting action. We could not find any putative carcinogen in the history of this patient.

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