Liver Tumors and Oral Contraceptives: Pathology and Pathogenesis

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ABSTRACT

Since 1973, over 200 cases of liver masses associated with oral contraceptive usage have been reported. Nearly 100 have been liver cell adenomas and 11 have been hepatocellular carcinomas. Focal nodular hyperplasia (FNH) appears only coincidentally associated, but with a particular hemorrhagic tendency. Bile duct proliferation distinguishes FNH from liver cell adenoma. Two typical cases are presented. Right upper quadrant pain with intra-abdominal hemorrhage is the single most common clinical presentation. Mestranol-containing preparations appear more hazardous. Liver enzymes are usually normal or slightly elevated. Most cases are resectable. Lesions have regressed following discontinuation of pill use; however, close observation is required. Although mammalian liver possesses estrogen receptors, these agents have induced few or no liver tumors in numerous animal studies. Mutagenicity tests indicate that estrogenic compounds do not damage DNA. However, diethylstilbestrol can promote the growth of rat hepatomas initiated by a carcinogen. Further experimental studies may better characterize estrogens as hepatoma promoters.

Since 1973 over 200 cases of liver tumors associated with oral contraceptive usage have been reported. Over 100 have been identified as hepatocellular adenomas (HCA) and at least 11 hepatocellular carcinomas have been related to use of oral contraceptives. Focal nodular hyperplasia (FNH) appears only coincidentally associated but with a particular hemorrhagic tendency. Two cases are reported to illustrate the differing pathological features of HCA and FNH. Available experimental evidence suggests that estrogens act as tumor growth promoters rather than as carcinogens.

Case History

CASE 1

A 33 year old housewife on oral contraceptives for seven years presented with right upper abdominal pain of five months duration. For the last 30 months, she had taken C-Quens® which contains 2 mg of chlormadinone acetate and 80 μg of mestranol. Details of the radiologic features of her liver hepatocellular adenomas have been previously reported but without the history of oral contraceptive use.
Figure 1. Case 1. Hepatocellular adenomas in the right hepatectomy specimen: the larger, darker mass consists of viable tumor with a 2 cm diameter focus of lighter, necrotic tissue, the site of a previous operative biopsy. The smaller, lighter tumor has spontaneously undergone necrosis.

Serum alkaline phosphatase was slightly elevated (5.4 Bodansky units) and other serum indicators of liver condition were normal. Two masses in the right lobe of the liver were evident on liver scans with both sulfur colloid and rose bengal. A large 9 cm posterior-inferior mass took up tracer as readily as normal liver while a smaller 6 cm medial mass appeared as a defect. By arteriography, the first mass was highly vascular but the second avascular. A right hepatic lobectomy was performed, with successful outcome (figure 1). The patient is alive and well eight years later. Microscopically, the viable tumor consisted predominantly of large hepatocytes arranged in haphazard plates two to three cells thick accompanied by Kuppfer cells lining inconspicuous sinusoids (figure 2). Scattered dysplastic liver cells occurred with enlarged, dark nuclei and prominent nucleoli. Numerous endothelial lined vascular channels occurred but portal triads and especially bile ducts were absent. The only fibrosis present was the thick collagenous capsule which surrounded the tumor. Adjacent liver was normal except for compression and a band of diffuse hepatocellular hyperplasia along one edge (figure 3).

CASE 2

A 28 year old woman who died of carcinoma of the cervix had taken Ovulen 21® intermittently for nine years until ten months prior to death. A 1.5 cm diameter well demarcated lesion which proved to be focal nodular hyperplasia was an incidental finding in the liver at autopsy. Grossly, it was pale tan with a central stellate white scar. Microscopically it resembled a collection of regeneration nodules of cirrhosis (figure 4). Enlarged hepatocytes arranged into plates two cells thick formed round nodules which lacked central veins. Fibrous septa with prominent bile duct proliferation occupied much of the center of the lesion (figure 5). There was little vascularity and few foci of dysplasia. Adjacent liver was normal but frequently compressed.

Discussion

Hepatocellular adenomas are clearly associated with oral contraceptive use, but focal nodular hyperplasia appears only coincidentally associated. Of 88 cases of HCA occurring in women, in the files of the Armed Forces Institute of Pathology, 92 percent had taken oral contraceptives for one year or longer. In 1976, only an estimated 17 percent of all U.S. women aged 15 to 44 used oral contraceptives. Development of HCA is associated with prolonged pill use and, for women over 27 years old, the relative risk
rises rapidly with duration of pill use. In over one half of the cases, oral contraceptives have been taken for five years or more and in 90 percent of the cases for 14 months or more.\textsuperscript{3,19}

Mestranol-containing preparations are considered particularly hazardous.\textsuperscript{3,6} Right upper quadrant pain with abdominal hemorrhage is the single most common clinical presentation.\textsuperscript{3} Right upper quadrant masses with or without gastrointestinal symptoms account for two-thirds of cases.\textsuperscript{19} Liver enzymes are usually normal or only slightly elevated. Alpha-fetoprotein levels have not been elevated. The risk of hemorrhage precludes percutaneous liver biopsy. Liver masses found incidentally or because of pain require preoperative liver scan and arteriography. Abdominal ultrasound and CAT scan are also useful diagnostic aids. Over two-thirds of lesions have been solitary and resectable, although multiple lesions have occurred in nearly 10 percent of cases.\textsuperscript{3,19} Several lesions have regressed following discontinuation of oral contraceptive use, but careful observation is warranted especially after pregnancy when delayed rupture may occur.\textsuperscript{3,7,12} Approximately two-thirds of the HCA have occurred in the right lobe of the liver.

Microscopically, bile duct proliferation, usually in fibrous septa between nodules, distinguishes FNH from HCA.\textsuperscript{8} No lipofuscin pigment is usually found in the proliferating hepatocytes in both HCA and FNH. Granular diastase resistant periodic acid-Schiff positive deposits of alpha\textsubscript{1}-antitrypsin have been described in approximately two-thirds of cases of HCA and FNH in the absence of serum alpha\textsubscript{1}-antitrypsin abnormalities.\textsuperscript{13}

In most animal studies, female sex steroids alone induced few or no liver tumors.\textsuperscript{1,21} \textit{In vitro} mutagenicity assays indicate that estrogenic compounds do not damage DNA and should not be regarded as tumor initiators.\textsuperscript{5,11} Including mestranol.\textsuperscript{14} On the other hand, diethylstilbestrol can promote the growth of rat hepatomas initiated by a carcinogen.\textsuperscript{18} Mammalian liver is known to possess estrogen receptors\textsuperscript{9} which mediate gene regulation by estrogens in classic target tissues through relatively well-defined mechanisms.\textsuperscript{2}

A promoter or co-carcinogen is defined as a compound which increase the growth of tumors induced by another agent but which cannot induce tumors by itself. A current problem in the biology of tumors induced by carcinogenic chemicals is the mechanism of action of promoters.\textsuperscript{15} Such
agents are thought to promote tumor growth by altering the expression of genes. The two best studied promoters of rat hepatomas, partial hepatectomy and phenobarbital, have no obvious mechanism of gene regulation.15,22 Chemically induced rat hepatomas are the best studied animal model system for human chemical carcinogenesis and experimental identification of estrogens as rat hepatoma promoters should lead to information of broad significance in basic tumor biology.

References