Sex Hormones and Hepatic Neoplasia

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Summary

The recent increase in hepatocellular neoplasms in women of child-bearing age taking oral contraceptives and in individuals of both sexes taking anabolic androgenic steroids is a phenomenon that requires urgent attention. Although most of the lesions are benign, reports of carcinomas in a few of these individuals and our own observation of an adenoma that shows borderline malignant transformation suggest that some of the adenomas are pre-malignant lesions.

The pathology of our own cases and those reported in the literature are reviewed, and hypotheses are offered for a carcinogenic role of synthetic steroid sex hormones. These speculations are based on known toxic and metabolic actions of the drugs and are amenable to experimentation.

Introduction

Beginning in 1973 with the 1st report of 7 cases of hepatic adenomas in women taking oral contraceptive drugs (6), there have appeared a number of full-length publications and Letters to the Editor describing localized hepatic lesions, including adenomas (1, 4, 15, 17, 29, 34, 35, 48), areas of FNH (40, 46), benign hamartomas (15), and finally a hepatocellular carcinoma (15) and hepatoblastoma (42), in women taking either combined or sequential progestogen and estrogen preparations for fertility control (Table 1). The potential seriousness of this problem was recently brought home to us when we reviewed our own experience and found 6 adenomas and areas of focal nodular hyperplasia in the short span of 2.5 years, all in women who had taken oral contraceptives (Table 2). Since 4 of our cases were adenomas, but only 5 such lesions were found at the Mayo Clinic between 1907 and 1954 (26), and only 1 patient was treated for a hepatic adenoma at the University of California, Los Angeles Hospital prior to 1965 (39), our experience, which is similar to that of others, reflects a marked increase in incidence of these tumors (1, 6, 15). Because 2 of the lesions in our series were discovered incidentally at laparoscopy for tubal fulguration and 3 other cases were found at the time of hysterectomy (15), the true incidence of these neoplasms is probably far greater than that reflected from the accumulated case reports. Also, since hepatocellular carcinomas (8, 20, 23, 25, 32, 41, 51) and an adenoma (12) have been reported in individuals treated with anabolic androgenic steroids, there is a possibility that other synthetic steroid hormones might also have induced hepatic neoplasms. It is the purpose of this brief review to summarize the accumulated reports, describe the pathological findings, and suggest a hypothesis of carcinogenesis and lines of further study that might help to identify the population at risk of developing hepatic neoplasms from these drugs.

Clinical and Pathological Features of the Benign Lesions

Table 1 lists the total number of benign and malignant hepatocellular lesions, including 6 of our own, that have been classified in patients taking synthetic sex steroid hormones. These cases have not been reviewed at a central registry. The diagnoses are those made by individuals reporting the cases. The benign lesions include hepatic adenomas, FNH, and benign hamartomas. Of the 3 types, the adenoma is the best described pathological entity. It is sharply demarcated from the surrounding parenchyma, although it is not always encapsulated, and is typically composed of sheets of glycogen-filled hepatocytes with small uniform nuclei having no mitoses and without bile ducts. These tumors are frequently quite large. In our own small series of 4 adenomas, they averaged 12 cm in greatest dimension. They frequently undergo central hemorrhagic necrosis, and the enlarging hematoma often ruptures through the capsule leading to hemoperitoneum with shock and signs and symptoms of an acute surgical abdomen (1, 6). FNH, in contrast to hepatocellular adenoma, contains bile ducts as well as hepatocytes. These lesions, usually much smaller than the adenomas, are often incidental findings at autopsy. The great confusion concerning the morphology and proposed etiology of this lesion is reflected in the variety of additional names used to describe it. These include focal cirrhosis, hepatic hamartoma, hamartomatous cholangiohepatoma, mixed adenoma, adenoma, and others.

As in the adenoma, the typical lesion is well demarcated from the surrounding liver, but it also has a large central dense scar and, frequently, thinner fibrous septa containing bile ductules and separating nodules of hepatocytes resulting in a distinctly lobulated appearance (7, 19). The parenchymal cells within the lesion are usually similar in appearance to those in the surrounding liver, but they are sometimes typically hyperplastic and arranged in 2- to 3-cell-thick hepatic plates. Occasionally, they contain abundant fat. Under the heading of FNH, some authors now include a lesion lacking a central scar but containing fibrous...
sex with proliferated bile ducts (31). Accordingly, I feel that there are probably at least 2 types of FNH. One type with the central scar could be a true hamartoma, while the other variety without the central scar could represent an area of reactive hyperplasia. Chart 1 shows this 2nd lesion as ?FNH, with arrows between it and the adenoma, suggesting a progression from one to the other. This speculation is based on our finding an adenoma and an area of ?FNH in the same patient (J. T. in Table 2). The patient was operated on for a bleeding adenoma that measured 12 cm in diameter. At surgery 3 other discrete lesions were found, one of which was removed and measured 1.5 cm in diameter with the lobulation and histological features typical of ?FNH. The simultaneous occurrence of ?FNH and adenoma in the same patient at the very least suggests a common etiology. However, I believe that the generally smaller size of ?FNH is consistent with progression from this lesion to the adenoma.

**Hepatocellular Carcinomas and Hepatoblastoma**

To date only 1 hepatocellular carcinoma has been reported in a woman taking oral contraceptives (15). In our series, however, we have 1 adenoma that shows features strongly suggestive of transition to hepatocellular carc-

<table>
<thead>
<tr>
<th>Oral contraceptives</th>
<th>Androgenic anabolic steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenomas</td>
<td>25 (4)*</td>
</tr>
<tr>
<td>Focal nodular hyperplasia</td>
<td>13 (2)</td>
</tr>
<tr>
<td>Liver hamartomas</td>
<td>3</td>
</tr>
<tr>
<td>Hepatic carcinomas</td>
<td>3*</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>1</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, number of cases from the University of Wisconsin Hospital.

Table 1: Neoplastic and hyperplastic hepatocellular lesions in patients who had received synthetic steroid hormones.

The cases were collected from the literature and include The University of Wisconsin Hospital cases. The survey was completed in September 1975.

Table 2: University of Wisconsin hospital cases

Patients receiving oral contraceptives, who had adenomas and areas of focal nodular hyperplasia that were seen at the University of Wisconsin Hospitals between January 1973 and July 1975.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Oral contraceptive (duration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. H.</td>
<td>33</td>
<td>Adenoma</td>
<td>Ovulen* (10 yr)</td>
</tr>
<tr>
<td>D. P.</td>
<td>23</td>
<td>Adenoma</td>
<td>Ovral® (2 yr, 10 mo.)</td>
</tr>
<tr>
<td>A. C.</td>
<td>36</td>
<td>?FNH</td>
<td>Oracon® (3 yr); Norlestin® (5 yr)</td>
</tr>
<tr>
<td>J. T.</td>
<td>35</td>
<td>Adenoma; ?FNH</td>
<td>C-Quens® (2 yr, then none for 7 yr)</td>
</tr>
<tr>
<td>M. Z.</td>
<td>40</td>
<td>Adenoma; (focal carcinoma?)</td>
<td>Ovral® (10 yr)</td>
</tr>
</tbody>
</table>

* Ethynodiol and mestranol.
® Norgestrel and ethinyl estradiol.
™ Dimethyosterone and ethinyl estradiol.
® Norethindrone and ethinyl estradiol.
± Chlormadinone acetate and mestranol.

Some areas show severe dysplasia (Fig. 1) similar in degree to the published lesion that is considered premalignant (3), while other areas show progressive hyperplasia with hepatocyte plates that in areas measure up to 5 to 8 cells in thickness (Fig. 2). Despite the absence of mitoses and vascular invasion, this marked thickening of hepatocyte plates and another focus of hepatocytes arranged in a glandular pattern (Fig. 3) are highly suspicious of malignant transformation. This case was reviewed by Dr. Hans Popper at the Mt. Sinai Medical Center in New York, who agrees that this adenoma shows considerably more atypia than the usual benign adenoma. He classifies it as an adenoma with focal tendency to transition to carcinoma, but not yet carcinoma.” Dr. Popper informed me of 2 additional cases of hepatocellular carcinoma that he has personally seen in women taking oral contraceptives, one in England and another at the Mt. Sinai Medical Center. A 4th case of hepatocellular cancer, a hepatoblastoma in a 19-year-old woman who had taken Ortho-Novum for 15 months (42), is unique, since it is the first reported instance of such a tumor in a female beyond the 1st decade of life (14).

Hepatocellular tumors described in patients taking anabolic androgenic steroids are much more difficult to analyze than those in women taking contraceptives p.o., since many of the case reports are very brief. However, I tend to agree with Dr. P. P. Anthony (2) that the long clinical courses, reversibility of the tumors, and absence of metastases suggest that a number of the tumors that are classified as malignant are probably benign hepatocellular lesions.
Additional Evidence Implicating the Steroid Sex Hormones

Since female rats are considerably more resistant to the chemical induction of hepatocellular neoplasms than are males (49), and since the hepatoma-susceptible C3H/1B mice actually show a decreased incidence of hepatomas after chronic feeding of Enovid (27), this might be taken as evidence against a role for female sex hormones in carcinogenesis. However, the synthetic progestational hormones, norethynodrel and norethisterone, alone or in combination with the synthetic estrogen mestranol, cause an increase in benign and in some instances malignant hepatic neoplasms in male rats, and megestrol and ethinyl-estradiol either alone or in combination cause an increase in hepatocellular carcinomas in female rats (13). Furthermore, the presence of crystals in many mitochondria in 1 adenoma in a woman on contraceptives (28), and a similar accumulation in the mitochondria of our own atypical adenoma, may be of some significance. This latter finding, although not specific, has been reported previously in the mitochondria of hepatocytes of women on the contraceptive pill (45).

There is a complete lack of experimental evidence suggesting a direct carcinogenic role for androgenic steroids in hepatic carcinogenesis. In contrast, the evidence is rather strong implicating a permissive or cocarcinogenic role for these hormones in chemical carcinogenesis (49). Additional evidence suggesting a role for anabolic androgenic steroids in hepatocarcinogenesis was the finding of peliosis hepatis and multiple hepatocarcinomas in the liver of a patient who had been treated with the anabolic steroid oxymetholone (8). This single case report is especially noteworthy, since peliosis hepatis is a very rare condition which is almost exclusively found in patients taking anabolic androgenic steroids (5).

Hypotheses

Since the synthetic sex hormones share a number of common metabolic and toxic effects on the liver, it is at least possible to suggest general hypotheses for hepatic carcinogenicity. These are outlined in Chart 2. As in the case of endogenous steroid hormones, the synthetic compounds undergo a very significant enterohepatic circulation (21). These steroids may themselves be low-grade carcinogens or they could be converted into carcinogenic compounds (a) through partial degradation by intestinal bacteria, or (b) by transformation by drug metabolizing enzymes.
systems in hepatocytes. Additionally, the steroids might contribute to the carcinogenicity of another compound (X) by competing for the biotransformation system in the liver in analogy with the inhibition of hexobarbital metabolism by progesterone (47). Conversely, they may aid in the more complete conversion of this compound to an ultimate carcinogen (X) by inducing microsomal drug-metabolizing systems (16). Again, the estrogenic compounds and anabolic androgenic steroids are known to decrease the biliary excretion of a number of anions including sulfobromphthalein (44), bile acids (24), and the synthetic estrogen, ethinyl estradiol (37). These toxic effects are most closely correlated with the molecular configurations of the compound and are dependent on an oxygen-containing group in position 3 of the phenolic A ring in estrogens (22) and a 17-α alkyl-substituted group in the synthetic estrogen and anabolic androgenic steroids (Chart 3; Refs. 18, 22). In its most severe form, this excretory block results in cholestatic jaundice, usually in predisposed individuals (43), but some degree of defective biliary excretion can also be demonstrated in women taking oral contraceptives (43) by using a bromsulfaphthalein infusion technique (50). Decreased bile acid excretion probably also accounts for the production of lithogenic bile in many women on the oral contraceptives (30). Thus, a block of this type could contribute to hepatic carcinogenesis by increasing the intrahepatic concentration of carcinogens that are either derivatives of the steroids or some other drug (Chart 2c).

It should also be noted that the addition of an alkyl group at the 17-α position might contribute to the carcinogenicity of these drugs in another way. This is suggested, since 16-α hydroxylation of estradiol, which results in products that are rapidly excreted, is markedly reduced in the case of ethinyl estradiol, the 17-α derivative of estradiol (11). Consequently, the alternate hydroxylation at the 2 position proceeds to a much greater extent in the case of the synthetic compound. The products formed via this pathway bind covalently with protein (10) to a far greater extent than the 16 hydroxyl derivatives, thus greatly increasing the biological half-life of the compound. Furthermore, these derivatives might still be shown to bind to DNA or RNA despite the negative results following incubation of the ethinyl estradiol with herring-sperm DNA and hepatic microsomes (9).

Conclusions and Recommendations

It may require several additional years of experimentation and epidemiological study to prove or disprove a carcinogenic or cocarcinogenic role of the synthetic steroid sex hormones. In the meantime, it might be wise to assume that individuals showing a marked decrease in biliary excretion of organic anions after synthetic steroid intake may be at increased risk for developing hepatic neoplasms. A high priority should, therefore, be placed on developing a simple test for defective excretion of organic anions. A postprandial serum bile acid determination (33) or an i.v. bile acid tolerance test (36, 38) may be found to meet these requirements.

References

25. Henderson, J. T., Richmond, J., and Sumerling, M. D. Androgenic-

Chart. 3. Steroid hormone nucleus with groups in boldface that are responsible for blocks in organic anion excretion.


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