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Epidemiology of Cancer

HEPATIC ANGIOSARCOMA ASSOCIATED WITH ANDROGENIC-ANABOLIC STEROIDS

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Summary A retrospective epidemiological study of deaths from hepatic angiosarcoma (HAS) in the U.S. showed that during 1964–74 there were 168 such cases, of which 37 (22%) were associated with previously known causes (vinyl chloride, 'Thorotrast', and inorganic arsenic) and 4 (3·1%) of the remaining 131 cases with the use of androgenic-anabolic steroids. It is suggested that the long-term use of androgenic-anabolic steroids is the fourth cause of HAS, the majority of cases still being of unknown ætiology. Moreover, the presented cases serve as a link in a spectrum of hepatic disorders recently recognised to be caused by environmental agents such as vinyl chloride, arsenic, and thorotrast, and by contraceptive and anabolic steroids. Similar precursor stages, usually not recognised by clinical laboratory tests and consisting of areas of hyperplasia of hepatocytes and sinusoidal cells and sinusoidal dilatation, lead potentially to hepatic adenoma, carcinoma, peliosis, and angiosarcoma.

INTRODUCTION

THE discovery that vinyl chloride monomer induced hepatic angiosarcoma (HAS) in polymerisation workers increased interest in this rare tumour.[1-3] Recent studies of chemically induced and idiopathic cases have shown that, independent of ætiology, the tumour-precursor stage consists of areas of hyperplasia of hepatocytes and sinusoidal cells associated with excess of reticulin and sinusoidal dilatation.[4] With subsequent loosening of the lobular plate arrangement, HAS develops by increasingly severe atypia of sinusoidal lining cells. This is often associated with bloody cysts, mainly in sarcomatous areas.

So far, androgenic-anabolic steroids have been implicated in: cholestasis;[5] hepatocellular tumours (benign, malignant, and equivocal),[6-8] which are almost always accompanied by conspicuous sinusoidal dilatation; and peliosis—enlarged bloody cysts which develop in apparently normal liver.[9,10] Women taking oral contraceptive steroids have a small but increased risk for a range of hepatic lesions which includes benign adenoma,[11,12] focal nodular hyperplasia,[13] and hepatocellular carcinoma;[14] these conditions are often associated with sinusoidal dilatation and vascular abnormalities.

We describe here 4 cases of HAS in patients taking androgenic-anabolic steroids who were identified in a retrospective epidemiological study of HAS during 1964–74.

METHODS

The procedures have been presented in detail elsewhere.[15] Briefly, the Center for Disease Control obtained information about cases of HAS diagnosed in the U.S. during 1964–74 in a variety of ways which included a postal questionnaire to all pathologists in the country, a review of records at the Armed Forces Institute of Pathology (A.F.I.P.), and a review of death certificates with I.C.D.-A. code 197·8 (liver cancer, not specified whether primary or secondary). Pathology reports and specimens were reviewed for each identified case (all non-A.F.I.P. material was seen by L.B.T. and H.P.), and the final study group consisted of the 168 histologically confirmed cases who had died during 1964–74. Permission to review the patient's medical records was sought from the next of kin who were asked by telephone details of the patient's occupation, residence, and possible exposure to chemicals. Sometimes physicians, friends, or employers provided additional information.

RESULTS

Of the 168 cases of HAS in this study, 37 (22%) had been exposed to previously reported ætiological agents (vinyl chloride, 'Thorotrast', inorganic arsenic).[3,15] Of the remaining 131 cases, 4 (3·1%) had documented histories of treatment with androgenic-anabolic steroids. Because medical records were not always available and next of kin were often unaware of the patient's full drug

HEPATIC ANGIOSARCOMA ASSOCIATED WITH ANDROGENIC-ANABOLIC STEROID USE

Case no.	Age at death	Year of death	Underlying condition	Androgenic-anabolic steroids used	Duration	Latent period*
1	58	1974	Irregular menses	Testosterone enanthate ('Delatestryl')	2 yr	2 yr
2	56	1973	Multiple myeloma	Fluoxymesterone ('Halotestin')	10 yr‡	13 yr
3	52	1971	Hypogonadism	Testosterone Methyltestosterone Other unidentified androgens	23 yr†	35 yr
4	52	1967	Osteoporosis	Methandrostenolone Stanozolol ('Winstrol') Methyltestosterone ('Gynetone')	15 mo.†	2 yr

*Time elapsed from first taking androgenic-anabolic steroids to diagnosis of HAS.
†Not used continuously.
‡Discontinued 3 years before diagnosis of HAS.

history, the rates of androgenic-anabolic steroid use may be erroneously low.

Case-reports (Table)

Case 1.—A Black, female English teacher had irregular menses for approximately 10 years, and in the early 1960s she was given norethynodrel 5 mg plus mestranol 0·075 mg ('Enovid-5') daily for 2–3 years. The treatment was then changed to chlordiazepoxide 10 mg plus water-soluble esterified œstrogens 0·4 mg ('Menrium 10-4') daily, and in 1968 it was changed to 20 mg œstradiol valerate ('Delestrogen') intramuscularly every month. From early 1971 she received instead 100 mg testosterone enanthate ('Delatestryl') intramuscularly every 6 weeks. Menses ceased in July 1972. 2 months later she had a raised alkaline phosphatase level of 236 IU/l but she was symptomless and physical examination was negative. The testosterone injections were discontinued in January, 1973. In March, 1973, the liver was enlarged and activities of both alkaline phosphatase (450 IU/l) and lactic dehydrogenase (LDH) (305 IU/ml) were high. A liver scan showed multiple small filling defects, and a needle biopsy specimen of the liver revealed angiosarcoma. She received chemotherapy for 5 months with only transient response and died in January, 1974, with gross ascites and hepatic failure.

Case 2.—A White, male military officer had active pulmonary tuberculosis in 1957 which was successfully treated with isoniazid, para-aminosalicylic acid, and pyridoxine for 2 years. In 1958 he had multiple vertebral compression fractures. Protein electrophoresis and bone-marrow biopsy findings were consistent with multiple myeloma. Urethane therapy was started, but was discontinued by the patient after 4 months. In 1960 severe lumbar pain with radiation to the leg led to therapy with cyclophosphamide ('Cytoxan') 50 mg/day until July, 1973, and fluoxymesterone ('Halotestin') 30–40 mg/day until July, 1970. In July, 1973, he had abdominal swelling, weakness, a grossly enlarged liver, jaundice, ascites, and cachexia. Bilirubin was 7·6 mg/dl (direct, 5·2), serum glutamic oxaloacetic transaminase (SGOT) was 244 IU/ml, and LDH was 574 IU/ml. A liver scan showed multiple filling defects. He died 10 days after admission. HAS was first diagnosed at necropsy. There were peri-œsophageal metastases. The bone-marrow also revealed multiple myeloma.

Case 3.—A White man had a history of hypogonadism for approximately 50 years. He was cryptorchid as a child and corrective surgery at age 12 was followed by gonadal failure. By 1944, at age 25, he had received, because of bilateral atrophic testes and poor development of secondary sexual characteristics, hormone injections (not specified) for approximately 5 to 6 years, and methyltestosterone for 2 years, with limited benefit. He continued to be given testosterone irregularly for several years. From the late 1950s androgenic hormone preparations (mostly oral, but on occasion injectables) were given regularly. Specific information about the dosage and type of androgenic steroid given is not available. In June, 1971, he had nausea, vomiting, anorexia, and questionable hepatomegaly. The total bilirubin was 4·1 mg/dl, alkaline phosphatase was 210 IU/l, LDH was 225 IU/ml, and SGOT was 130 IU/ml. Multiple filling defects were seen on hepatic scan, and a biopsy specimen taken at laparotomy showed HAS. In the absence of demonstrable metastases an orthotopic liver transplantation was performed and immunosuppressive therapy was started. 2 months later liver function became abnormal, and during the final month of life septicæmia and uncorrectable acidosis developed. Necropsy showed widespread angiosarcoma that involved not only the transplanted liver, but also the lungs, adrenal glands, kidney, pancreas, spleen, bone-marrow, peritoneum, pleura, pericardium, lymph-nodes, and the abdominal incision scar. The patient was a designer-draftsman for radio and telephone companies for 22 years. During 7 of those years he was exposed to carbon tetrachloride (used for cleaning instruments) for approximately 15 min/week in a well-ventilated room. In the early 1950s he had a small farm and was briefly exposed to arsenical pesticides about once a year.

Case 4.—A White, male cook had a 19-year history of progressively severe back problems dating from an injury in 1948. Three lumbosacral fusion operations were not successful and compression fractures recurred. By early 1965, possibly even earlier, he had received anabolic steroids (methandrostenolone); information about the exact dates and dosage of this therapy was not available from the medical records. In October, 1965, because of multiple compression fractures and osteoporosis, he was given stanozolol ('Winstrol'), glutamic acid, calcium, and vitamin D for at least 3 months. In late 1966 the patient was placed on methyltestosterone plus ethinylœstradiol ('Gynetone'). In April, 1967, he had jaundice with a bilirubin of 8·5 mg/dl and an SGOT of 244 IU/ml. His liver was not enlarged. The methyltestosterone therapy was stopped. In May, 1967, progressive hepatic failure set in and he died 4 weeks later. At necropsy the liver was enlarged by multiple nodules of HAS; metastatic angiosarcoma was present in lymph-nodes. He had consumed alcohol excessively for several years in early adulthood, but drank little alcohol in subsequent years.

Except for the exposures noted in cases 3 and 4, the 4 patients did not abuse alcohol, and were not exposed to vinyl chloride, thorotrast, or arsenic.

Pathological Findings

The lesions in the livers of these 4 patients were nearly identical and conformed with the previously reported morphological description of HAS.[4] Briefly, the hepatic changes included complex precursor lesions and areas of multicentric angiosarcomatous transformation leading to many large nodules of angiosarcoma. The precursor lesions, best seen in portions of the liver not involved by angiosarcoma, consisted of areas with mixed nodular hyperplasia of hepatocytes and sinusoidal lining cells, with or without sinusoidal dilatation. In some parts of the specimens, angiosarcomatous transformation of the sinusoidal lining cells was associated with conspicuous sinusoidal dilatation and disruption of

Fig. 1—Trabecular angiosarcoma in case 3.

Note trabeculæ of hyperplastic hepatocytes or fibrous tissue in widened blood spaces. The trabeculæ are covered by angiosarcoma cells which are also found in portal connective tissue. Hæmatoxylin and eosin, 60×.

Insert—Close-up of hyperplastic hepatocytes and angiosarcoma cells. 250×.

hepatic plates so that large blood spaces formed (fig. 1). Hyperplastic hepatocytes were often found in plates two or more cells thick which were covered by angiosarcoma cells (fig. 1, insert). Both intralobular and trabecular patterns of angiosarcoma were contiguous with solid nodules of angiosarcoma. In case 3 a preoperative biopsy, as well as the resected liver, showed the same changes.

DISCUSSION

Further investigation of 168 deaths from HAS during 1964–74, of which 22% were associated with the 3 previously identified causative agents for this tumour, showed that 4 of the other 131 (3·1%) cases previously thought to be idiopathic had been exposed to large doses of androgenic-anabolic steroids. Although estimates of the extent of androgenic-anabolic steroid use are very crude because of scarcity of data, it is thought that considerably fewer than 1% of the general U.S. population are likely to have had androgenic-anabolic steroids for long periods (personal communication, Drug Use Analysis Branch, Division of Drug Experience, FDA). Thus, we suggest that these steroids are a fourth potential cause of HAS although, given the small number of cases and the difficulty in precisely quantifying the expected number, this association remains to be confirmed. At this time the risk of HAS developing after the use of these steroids would appear to be less than after exposure to vinyl chloride or thorotrast.

The suspicion that prolonged therapy with androgenic-anabolic steroids may cause HAS arose because of observations that: 1) sinusoidal dilatation, often with activation of sinusoidal lining cells, is present in the early stages of both steroid-induced and HAS precursor lesions;[4,16] (2) hepatocellular proliferation, which is an essential part of the precursor lesion of HAS, is also seen after exposure to androgenic-anabolic steroids and can result in tumour formation; and (3) peliosis hepatis has been increasingly reported in those receiving these steroids.

Women who are taking oral contraceptive steroids have an analogous, although very small, risk for the development of primarily benign hepatocellular tumours which are associated with sinusoidal dilatation or vascular anomalies.[12,17] Recently, a case was reported of HAS developing in an elderly male treated for 12 years with diethylstilboestrol because of prostatic carcinoma,[18] although it should be emphasised that so far an association between oral contraceptive or oestrogenic hormones and HAS has not been found in females.

Although the suggested association between androgenic-anabolic steroids and HAS remains to be confirmed, it may be a link in a spectrum of liver diseases which have attracted much attention in the past decade —these conditions, which appear related to the treatments and environmental agents discussed above, are hepatic adenoma, focal nodular hyperplasia (both often associated with intra-abdominal hæmorrhage), hepatocellular carcinoma in the absence of cirrhosis and with potential for regression, peliosis hepatis, and HAS.

The common feature in this spectrum of diseases seems to be the precursor lesion consisting of varying degrees of mixed hyperplasia of hepatocytes and sinusoidal cells and sinusoidal dilatation and which has been described in detail for HAS;[4] it has also recently been observed after long-term exposure to contraceptive steroids.[19] The potential for progression of the precursor stage is now becoming apparent, as exemplified by the present report, although the magnitude of the risk and the distribution of lesions seen will undoubtedly vary for different ætiological factors (fig. 2).

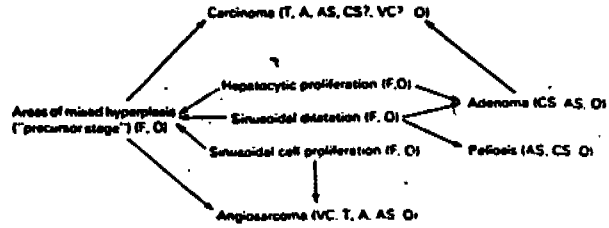

Fig. 2—Interrelated hepatic disorders caused by new treatments and environmental agents.

Aetiological agents: AS—androgenic-anabolic steroids; CS—contraceptive steroids; VC—vinyl chloride; O—other unidentified; A—arsenic; T—thorotrast; F—all of above.

The common morphological precursor stage, which may present as portal hypertension of the idiopathic or Banti syndrome type as observed after exposure to vinyl chloride or arsenic, is often symptomless and is not reliably detected by conventional hepatic laboratory tests. Thus its detection depends greatly on investigations such as liver biopsy. The dilatation of the sinusoids and other vascular lesions are key features in the clinical manifestations of the entire group. They account for the hæmorrhage into the hepatocellular tumours and subsequently into the peritoneal cavity seen with oral contraceptives, the grossly visible bloody cysts in the usually multicentric angiosarcoma, and the peliosis hepatis seen primarily with androgenic-anabolic steroids.

The androgenic-anabolic steroids, which appear to induce hepatic adenoma and hepatocellular carcinoma (a case of cholangiocarcinoma was also reported recently[20]) as well as peliosis and angiosarcoma, thus link the spectrum of hepatic disorders with potential for malignant transformation of both hepatocellular and sinusoidal cells. The most important purpose in calling attention to this range of conditions, however, is to encourage the search for the ætiological factors (endogenous, medicinal, and environmental/industrial) which are responsible for the cases considered so far to be idiopathic.

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