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Case Report

Peliosis Hepatis as a Result of Endogenous Steroid Hormone Production

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Summary. A case of peliosis hepatis in a 3 year old child with steroid hormone producing adrenal tumour is presented. The diagnosis of the adrenal tumour and peliosis hepatis was settled on the basis of surgical material examination. This case of peliosis hepatis due to endogenous steroid production lends more support to the earlier reported cases of iatrogenically produced peliosis due to exogenous steroid treatment.

Key word: Liver – Peliosis hepatis – Adrenal gland tumour – Endogenous steroids.

Introduction

Peliosis hepatis used to be an accidental finding in autopsy material in patients dying after long protracted illnesses as tuberculosis or cancer (Zak, 1950). Recently Taxy (1978) emphasized that peliosis is an iatrogenic problem resulting from anabolic steroid therapy. Peliosis have been produced in experimental animals by viruses (Bergs and Scotti, 1967), by oral administration of steroid hormones; Gordon et al. (1960), Bagheri et al. (1973), Delage and Lagacé (1973), Sale and Lerner (1977) and some hormone producing tumour transplantation; Furth and Sobel (1946), Wolstenholme and Gardner (1950).

Two cases of peliosis have been reported in children; Neuernberger and Ramos (1975), Usatin and Wigger (1976).

This paper discusses the effect of endogenous steroid hormone production in the development of peliosis. A child with adrenal tumour developed peliosis hepatis which was diagnosed in biopsy material. The value of angiography in the diagnosis of peliosis is discussed.

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Material and Methods

The assessment of the 17-hydroxy corticosteroids was carried out by the Birke-Diczfalusy-Plantin method (1958), a procedure estimating all corticosteroids possessing a 17-hydroxylgroup, including thus 17,20,21-triols, 17,20-glycols, 17,20-ketols and 17,21-diol-20-ones.

For the determination of total 17-ketosteroids, the Vestergaard (1951) rapid micro-modification of the Zimmermann/Callow procedure for urine was used. This method estimates dehydroepiandrosterone, the sume of androsterone and etiocholanolone, 3α,11β-diohydroxyetiocholan-17-one, 3α-hydroxy-etiocholane-11,17-dione and 3α-hydroxy-9-etiocholen-17-one (Birke et al., 1958). – Urinary pregnane-diol and pregnanetriol determination was carried out according to Goldzieher and Nakamura (1962).

The subject of this study is a girl born in December 1970, the second child to healthy parents. Since birth the mother noticed that the childs clitoris was unusually large. She developed pubic hair at two years and consequently she was taken for medical advice. Urinary pregnantriol and 17-hydroxy-corticoids were normal, 17 ketosteroids were 14,0 mg/24 h, a value which is markedly increased (normal 0–5 mg). The condition was thought to be an adrenogenital syndrome and the child was given Cortone® (cortisone acetate) from June 1973.

In December 1973 no supression of the adrenal cortical function was achieved in spite of the administration of 15 mg Cortone® three times daily. The validity of the earlier diagnosis was thus doubted and at the end of January 1974 the patient was readmitted to hospital for further investigation. Pregnantriol was still normal while both 17-keto and 17-hydroxysteroids were raised (18 mg/24 h and 13 mg/24h resp.). General examination revealed a well built female child with a status corresponding to a child much older than 3 years. Secondary sexual characters were prominent, axillary and pubic hairs were well developed and the back and legs were also covered by hair. The labia majora were darkly pigmented, the clitoris was large and the child's voice was harsh.

Intravenous urography showed flattening of the pole of the right kidney and renal angiography revealed a tumour mass, 6 cm in diameter, in the site of the right adrenal gland. A conglomerate of vessels 2 cm in diameter was seen in the lower part of the right lobe of the liver. Roentgenographic examination of the hands showed an acceleration of skeletal growth two years ahead of the patients age.

In February 1974 an encapsulated tumour mass, 6 cm in diameter, was removed from the right suprarenal area. The mass was loosely adherent to the inferior vena cava and easily resected from it. Normal adrenal tissue was macroscopically seen in one pole of the tumour. Wedge resection of liver tissue containing the roentgenographic lesion was performed. The postoperative period was uneventful and Corton® therapy was progressively diminished until it was completely stopped in March 1974. The patient was followed up periodically and in December 1978 almost 47 month after sugery she was healthy with normal steroid levels in urin. Secondary sexual characters, the body built and the harsh voice were however still unchanged.

Tissues from the adrenal gland and liver were fixed in 10% neutral buffered formalin, processed in a routine fashion and paraffin sections were cut at 5 μm. In addition to haematoxylin and eosin staining, Gordon & Sweet impregnation method was used to demonstrate the reticular fibre network in the liver. Frozen sections of the adrenal tumour were stained with Sudan black B and Oil-red-O (ORO) for the demonstration of lipids.

Results

Macroscopically the main tumour mass was rounded, well circumscribed, encapsulated, greyish in colour and measured 6 × 4 × 5 cm. The cut surface was solid, greyish brown and did not show any necrosis. At one pole of this mass a band like normal looking adrenal tissue 3 × 1 cm was attached. The liver biopsy measured 6 × 3 × 2,5 cm and centrally contained a cyst like structure measuring

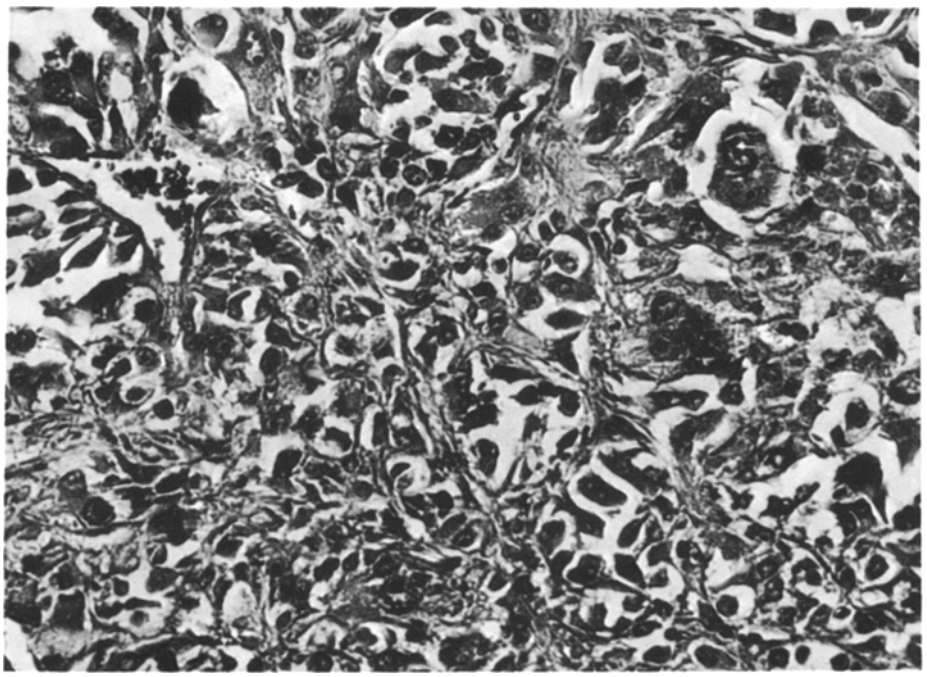

Fig. 1. Adrenal tumour cells with large cytoplasm, large nuclei and prominent nucleoli. H & E ×225

4 × 2 × 1 cm. This lesion was very rich in large blood spaces and had ill defined borders.

Microscopically the adrenal tumour was composed of relatively regular large cells with neutral lipids in the cytoplasm. A few giant cells showing nuclear polymorfism and prominent nucleoli were also present (Fig. 1). The cells were arranged in solid sheets and cords with a fasciculate pattern around dilated sinusoid vascular spaces lined by flattened endotheloid cells. There was no sign of mitosis, vascular invasion or infiltration into the adrenal capsule. Focal necrosis was seen in the tumour cell mass.

The liver biopsy showed normal liver parenchyma peripherally. The central cyst-like structure histologically proved to be blood spaces, mostly dilated sinusoids, but even dilated central or portal veins occurred. The blood lakes showed preserved endothelial lining, but endothelial cells were partly illdefined or completely absent (Fig. 2). Gordon and Sweet silver impregnation method demonstrated intact reticular fibre network in the walls (Fig. 3). Hepatocellular necrosis was noted in some cells and thus did not constitute a prominent feature. Focally, the blood lakes contained desquamated hepatocytes, amorphous debris, endothelial cells, erythrocytes as well as white blood cells. Thrombi in various stages of development and organisation were observed. No proliferating vascular channels were seen.

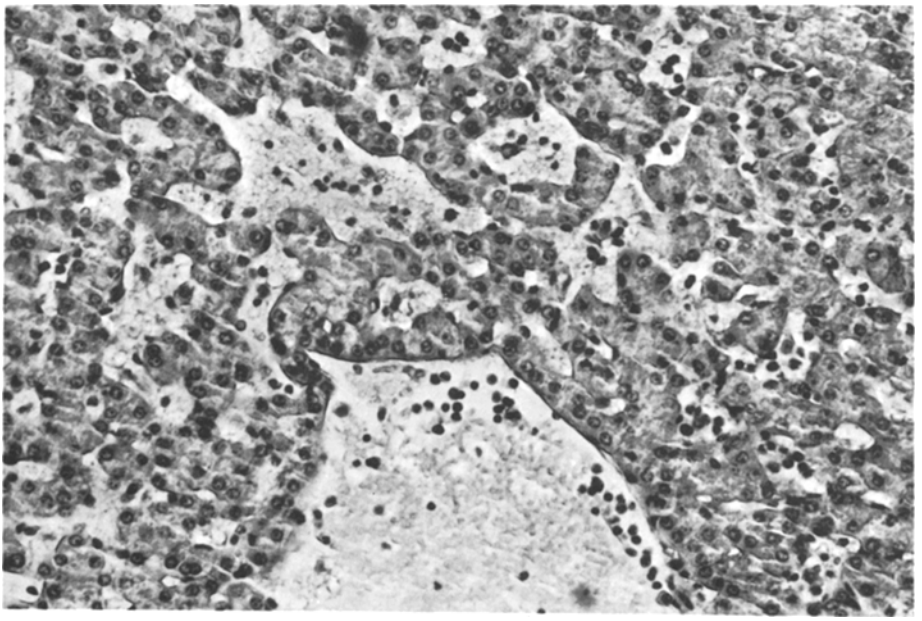

Fig. 2. Liver parenchyma with dilated sinusoids. The endothelial lining is partly preserved. H & E ×225

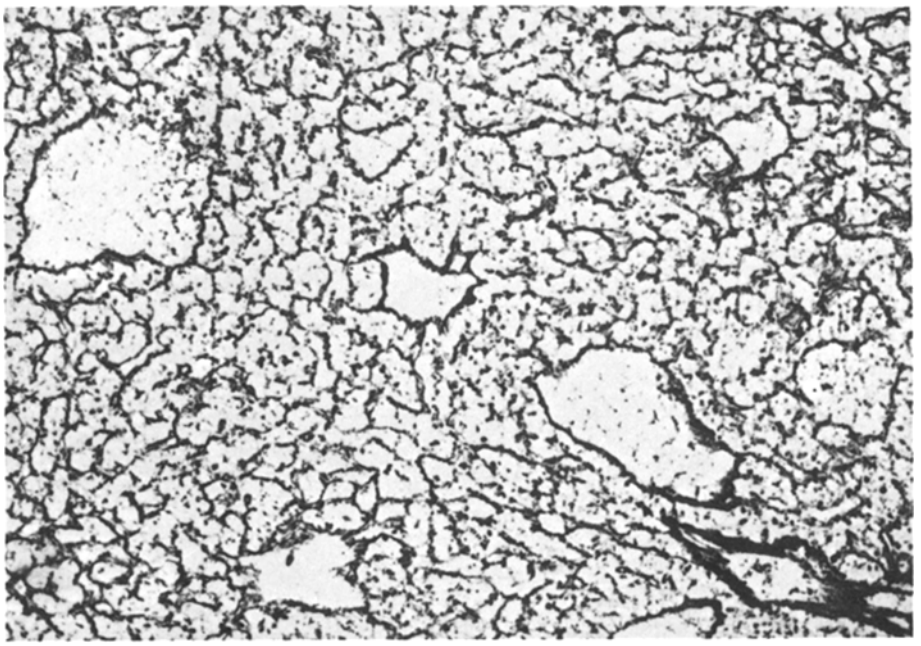

Fig. 3. Blood lakes shows reticulum lining. There is a communication among sinusoids. Gordon-Sweet reticulum stain ×250

Discussion

Peliosis hepatis is characterized by angiomatoid change of the liver with blood-filled spaces distributed irregulary all over the liver parenchyma. Yanoff and Rawson (1964) attempted to classify reported peliosis cases on the basis of the established criterium into two morphologic types; parenchymal and phlebectatic. Parenchymal peliosis was characterized by the absence of endothelial lining of the irregular blood spaces, hepatocellular necrosis and cholestasis. The phlebectatic type showed a more regular centrilobular distributed blood lakes with intact endothelial lining but hepatocellular necrosis was not a prominent feature. According to McGiven (1970) and Taxy (1978) a morphological subclassification of peliosis is unnecessary. Both phlebectatic and parenchymal patterns appear often together; Bagheri et al. (1974), Usatin and Wigger (1976).

Zak (1950), Gordon et al. (1960), McGiven (1970) and Naeim et al. (1973) emphasize the occurrence of disseminated foci of hepatic necrosis as a prerequisite for the formation of the blood-filled spaces of peliosis of the liver. One case revealed both phlebectatic and parenchymal patterns. Peliosis hepatis was associated in earlier reports with fatal tuberculosis, usually pulmonary (Zak, 1950). Neuernberger and Ramos (1975) describe a 15 months old infant with *E. coli* septicemia and peliosis hepatis. The most probable mechanism of peliosis in this case was endotoxin-induced hepatic necrosis followed by formation of vascular lakes.

Peliosis hepatis was also produced in experimental animals. Bergs and Scotti (1967) induced peliosis in rats by intraperitoneal injections of the 9 H virus isolated from leuchemic rat tissue. Peliosis appeared to be the result of focal hepatic necrosis followed by hermorrhage. The virus was recoverable from the peliotic livers. Wolstenholme and Gardnar (1950) developed blood sinusoid dilatation in the liver of mice by transplanting testicular intestinal cell tumour (3 AC, SS) subcutaneously and intraperitoneally. Fürth and Sobel (1946) measured the blood volume of mice bearing grafted granulosa cell tumour and found one to fivefold increase over that of normal mice. They suggested that secondary cavernous dilatation of the liver and other abdominal viscera was caused by hypervolemia. Peliosis hepatis was also induced in mice by oral administration of sodium lithocholate which has a structural similarity to etiocholanolone, a neutral steroid metabolite of testosterone (Bagheri et al., 1973). Both drugs can produce fever, inflammation and cell necrosis in man as well as in animals.

In man peliosis is considered by many authors to be an iatrogenic problem (Taxy, 1978) resulting from testosterone and anabolic steroid treatment of different disease conditions. Table 1 review reported cases of peliosis hepatis in humans following exogen administration of steroid drugs. In our case the occurrence of peliosis hepatis in a child with a steroid hormone producing tumour lends further evidence to the role of these compounds in the production of peliosis. We agree with Taxy (1978) that the lesion may be reversible following an interruption of the hormonal influence upon the liver tissue.

In the differential diagnosis liver vascular tumours and subcapsular malformations in infancy and childhood must be considered. They are defined either by several layers of plump endothelial cells, and various amount of myxomatous,

Table 1. Review of reported steroid drug administration in humans associated with peliosis hepatis

Authors	Main disease	Drug	Date and dosage	Material	Visceral peliosis
Delage et al., 1973	65y M Chronic myeloid leukemia	prednisone	6 weeks 500 mg/daily last twelve days of life	Autopsy	Liver
Gordon et al., 1960	43y M Pemphigus vulgaris osteoporosis	prednisolone norethandrolone	Aprox. 9 months 40–100 mg/daily	Autopsy	Liver
	57y F Chronic pancreatitis with pancreatic insufficiency	prednison norethanodrolone	13 months 2,5–5 mg/daily 20 mg/daily	Autopsy	Liver
McGiven, 1970	75y M Rheumatoid artritis with phenylbutazon depression of bone marrow	methadienone oxymetholone	Unknown	Autopsy	Liver
Naeim et al., 1973	26y M Fanconi's anemia	fluoxymesterone	11 days 50 mg/daily	Autopsy	Liver
	65y F Diabetes mellitus postmenopausae complaints	estrone sulfate	18 months 0,625 to 1,25 mg/daily	Autopsy	Liver
Ross et al., 1972	57y M Cardiac transplantation	azothioprine prednisone	Three years unknown	Perentaneous biopsy	Liver
Sale et al., 1977	37y M Idiopathic aplastic anemia	androgen and prednisone	4,5 years up to 100 mg/daily	Autopsy	Liver
Taxy, 1978	35y M Nodular sclerosing Hodgkin disease	fluoxymesterone	6 months 10 mg/daily	Autopsy	Liver
	42y F Nodular sclerosing Hodgkin disease	glucocorticoids	Unknown	Biopsy	Liver and spleen
	73y M IgD myeloma and bone marrow	oxymethalone	3 years 30–50 mg/daily	Autopsy	Liver and spleen
Usatin et al., 1976	11y M Cystic fibrosis	methandrostendone	1 years unknown	Autopsy	Liver
Yanoff et al., 1964	73y F Parkinsons disease and osteoporosis septic shock	norethandrolone	Aprox 1 month 20 mg/daily	Autopsy	Liver

y = years m = months M = male F = female

fibrous or collagen tissue changes. Frequently the presence of small bile ductules often prolifirating simultaneusly with the vessels, are seen (Dehner and Ishak, 1971).

In our case, however, the Gordon-Sweet reticular staining method demonstrated dilated vascular spaces with preserved reticular pattern (Fig. 3), lined

by a single raw of endothelial cells or no endothelial cells at all. No enhancement of collagen fibers was noted in the V. Gieson stain. We therefore considered this case a genuin example of peliosis hepatis.

The nature of the adrenal cortex tumour judge by its size, histological appearance and the postoperative course favours an adenoma.

Two cases of peliosis hepatis in children are on record. Beside Neuernberger's case of a 15 months old female infant who had *E. coli* sepsis a second case developed in an 11 years old boy with cystic fibrosis treated by steroids (Usatin and Wigger, 1976).

Initially the clinical condition was thought to be an androgenital syndrom. When no improvement was achieved following 15 mg Cortone® three times daily for 6 months, that hypothesis had to be omitted and further clinical investigations were initiated.

Angiography in this case helped in the localization of the peliotic laesion in the liver. Only two cases of peliosis hepatis were earlier reported diagnosed in surgical material (Ross et al., 1972; Taxy, 1978).

The mechanism underlying the production of peliosis hepatis remains obscure. However, hypervolemia and hepatotoxicity seem to play an important role in the production of peliosis.

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