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Epithelial Liver Hamartoma, Systemic Arterial Hypertension and Renin Hypersecretion

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Summary. The case of a 14-year old girl presenting with headaches, severe progressive hypertension and high plasma renin levels, in whom a voluminous epithelial liver hamartoma or adenoma was discovered at surgery is documented. The morphological characteristics of the hamartomatous abnormality are described and evidences are put forward which would suggest that the liver lesion might have been the site of the abnormal renin production which was responsible for the systemic arterial hypertension.

Key words: Epithelial Liver Hamartoma — Adenoma — Renin, Plasma Renin Activity — Hypertension.

Introduction

Primary tumours of the liver in childhood are rare, and among them malignant epithelial tumours are much more frequent than the hamartomatous malformations. Hepatoma is known to manifest itself in certain cases with systemic manifestations by ectopic hormone production such as parathyroid hormone or erythropoietin (Margolis and Homey, 1972).

In children hepatoblastoma may secrete gonadotrophins leading to the appearance of precocious puberty (Omenn, 1971). The association of liver tumours and severe systemic hypertension has, to our knowledge, not been described. This report describes the case of a 14-year old girl with a voluminous epithelial hamartoma of the liver in which the first manifestation was a severe hypertension with increased serum renin levels. The girl was successfully operated upon and the hypertension subsided. After a follow-up of three years, the girl is well and has a normal blood pressure.

Case Report

A 14-year old girl was admitted to the hospital suffering from severe headaches, vomiting, and pain in the neck and dorsal spine, which had appeared 4 days earlier. Two years prior to admission, the girl complained of headache. She was examined by her physician one year before admission and the physical examination was normal; the blood pressure was 110/70 mm Hg. Four weeks before admission, the headaches were more frequent and more severe. They were often accompanied by epistaxis which seemed to relieve the pain.

On admission the patient was conscious. Her weight was 42.4 kg for a height of 151 cm. She complained of severe headaches. The neck was stiff, Kernig and Brudzinski signs were present. The deep tendon reflexes were present, and sensitivity was normal. The fundoscopic examination did not reveal signs of papilledema, nor haemorrhage. Blood pressure was 160/130 mm Hg. The liver was 6 cm below the costal margin. There were no physical signs of puberty, and no hirsutism or acne. A lumbar puncture was performed and the CSF was xanthochromic with numerous red cells. The proteins were 0.66 g/l and the glucose 0.74 g/l.

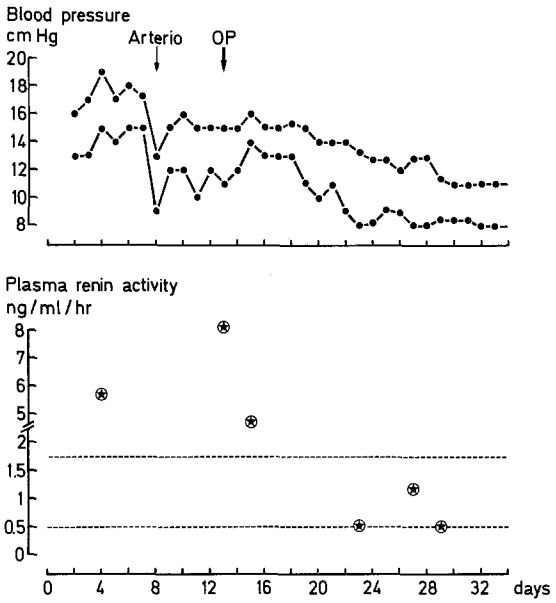

Fig. 1. Systolic and diastolic blood pressure and plasma renin activity before and after surgery. The normal range for PRA is indicated

Pandy reaction was positive. The day following admission, the blood pressure rose to 180/150 mm Hg. Haemoglobin was 15 g/100 ml and haematocrit 44%. The leucocyte count was 10,550/mm^3 and the blood smear was normal. Platelets were elevated at 500000/mm^3. Prothrombin time, partial prothrombin time and fibrinogen were normal. There was 1 g/l of protein in the urine with few erythrocytes and leucocytes in the sediment. The clinical condition worsened during the following days. The headaches became more severe; the patient became lethargic, semicomatose and developed a left side hemiparesia. The fundoscopic examination revealed bilateral papilledema. Arteriography of both carotids was performed and found normal.

Serum glucose phosphate transaminase (SGPT) which was normal (8 mEz/l) on admission became elevated 8 days later at 151 mEz/l and SGOT was then 435 mEz/l. Prothrombin time was 70%, total bilirubin 8.3 mg/l and alcaline phosphatase 43 mEz/l. Serum electrolytes (Na = 140 mEq/l, K = 5.2 mEq/l, CO_2 = 20.2), as well as blood glucose and urea nitrogen, were normal. The 24-hour urinary excretion of epinephrine, norepinephrine and vanilmandelic acid were normal. Plasma renin activity (PRA)[1] however was quite elevated at 5.71 ng/ml/h.

The liver on palpation was found to be greatly increased to 18 cm below the costal margin on the eight hospital day and chest roentgenograms revealed a markedly elevated right diaphragm. Intravenous pyelogram showed normal excretion of the dye on both sides. The nephrographic picture appeared simultaneously in both kidneys but the right kidney was slightly displaced downwards. A hepatic scintiscan revealed a voluminous mass within the right lobe which did not capture the colloid (^{198}Au). This mass seemed to displace the left lobe further to the left. Arteriography of the superior mesenteric and coeliac arteries confirmed the presence of a large "tumour" with abnormal vascularisation (Fig. 2). Surgery was undertaken and a voluminous greenish yellow tumour occupying almost the totality of the right liver lobe was resected. Blood drawn from the hepatic vein had much higher PRA (26.5 ng/ml) than blood from the systemic circulation (8.4 ng/ml/h). The blood pressure

1 Renin activity was measured by radioimmunoassay which determines the production of angiotensin I released during incubation (Vallotton, 1970).

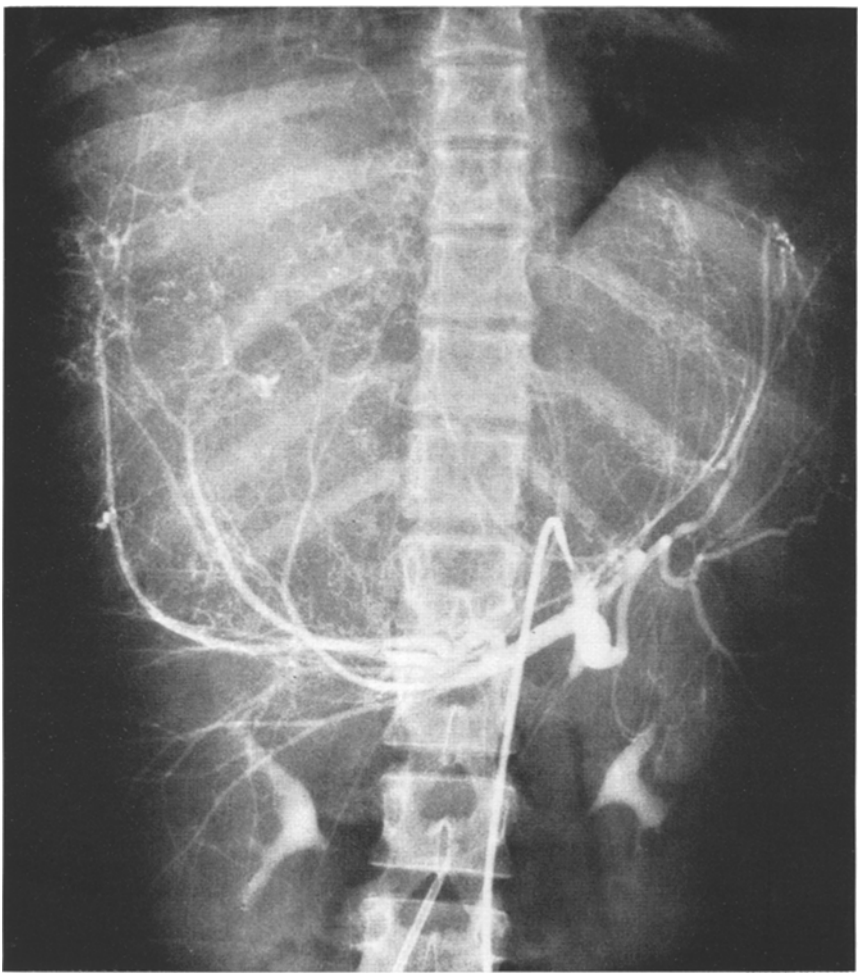

Fig. 2. Arteriography of coeliac trunk showing large round area poorly vascularized with a net-work of fine vessels. The arteries are lengthened and pushed towards the periphery. The right kidney is slightly displaced downwards

and plasma renin returned to normal values within two weeks of surgery (Fig. 1). The patient was discharged 21 days after her operation. Since, she has been regularly controlled over the last 3 years and found to develop normally.

No secondary growths have been detected. Her blood pressure remains normal; serum transaminases (SGOT, SGPT), alcaline phosphatase, prothrombin time, bilirubin are all within normal limits. A liver scan showed an important regeneration of the remaining liver lobe.

Pathology

The gross specimen consisted of the right lobe of the liver, a portion of the left lobe and the gall-bladder. The resected segment weighed 2750 g and measured $25 \times 22 \times 20$ cm (Fig. 3). The vessels on the surface were quite prominent. The

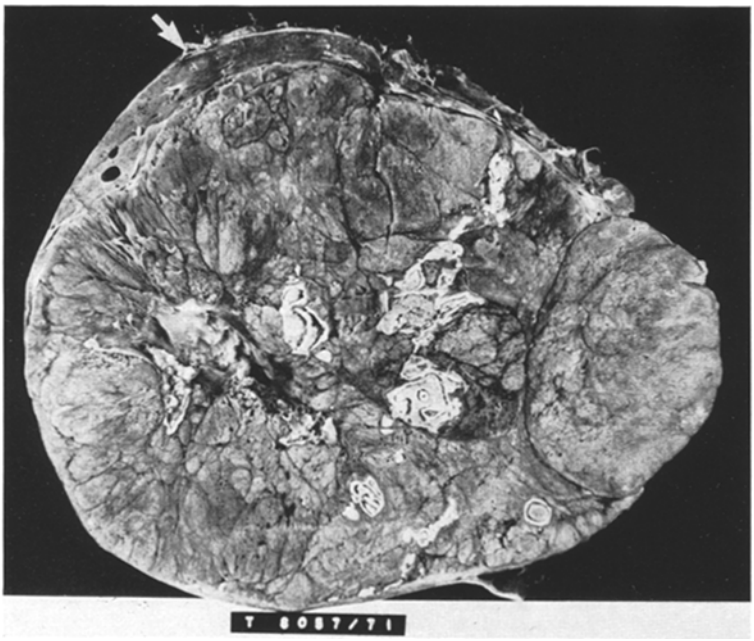

Fig. 3. Cut surface of tumour made up of lobules of various sizes and compressing the narrow rim of normal hepatic tissue (↗) to the periphery. Note the necrotic central areas

Table 1. Blood values of plasma renin activity, renin substrate and plasma renin concentration before (9. 7. 71) and after (8 and 24. 9. 71) surgery. The high plasma renin activity is mainly due to a high plasma renin concentration. Normal values: Plasma renin activity: 0.57 ± 0.4 (SD) ng/ml/hour. Substrate: 1335 ± 217 (SD) ng angio I/ml

	9. 7. 1971[a]	8. 9. 1971	24. 9. 1971
Plasm renin activity (ng/ml/hr)	26.5	1.0	0.98
Substrate (ng angio I/ml)	1612	919	656
Plasma renin concentration Goldblatt Units $\times 10^{-4}$	4.08	0.22	0.279

[a] Hepatic vein.

greater portion of the resected liver was occupied by a tumourous mass approximately 21 cm in diameter. This was surrounded in parts by apparently normal hepatic parenchyma forming a thin compressed outer shell varying between 0.2 to 3 cm in thickness. The cut surface was moderately firm, lobulated with many irregular nodules variable in size. The colour varied between a light green and yellow hue, interrupted by greyish-white necrotic areas predominantly in the central region. Within the normal hepatic parenchyma were many dilated vessels, especially adjacent to the tumour, but much less conspicuous within the latter.

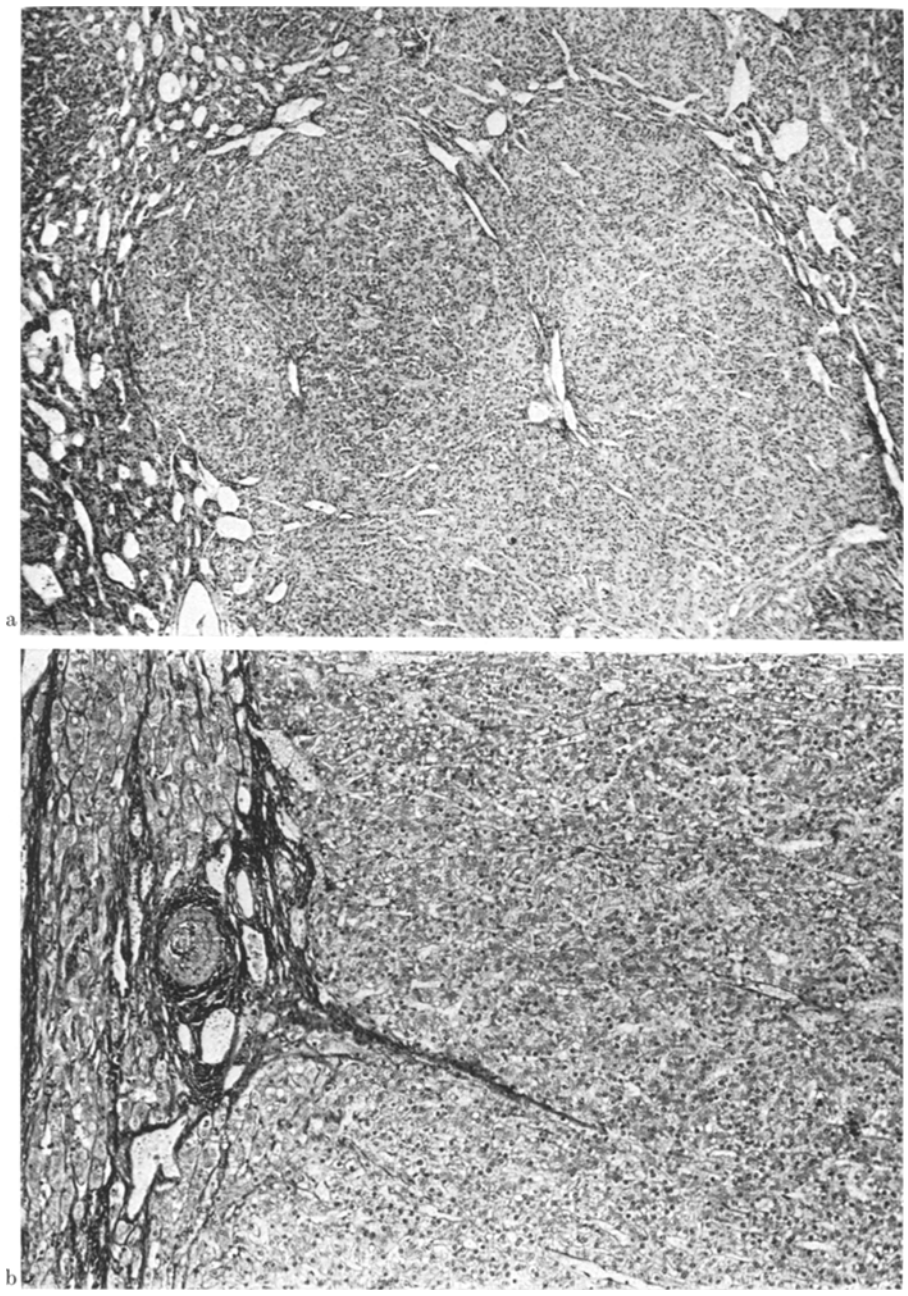

Fig. 4. (a) The appearance of large regenerative nodules is shown with prominent dilated vessels and sinusoids at the junction with the normal liver parenchyma (H. E. × 30). (b) The compressed peripheral liver cells are atrophic, held within thin connective tissue bands (pseudo-capsule) in which there are numerous dilated sinusoids and veins. The arteries show marked hypertrophy of their media with partial obliteration of their lumen. Some are thrombosed (Gomori, × 60)

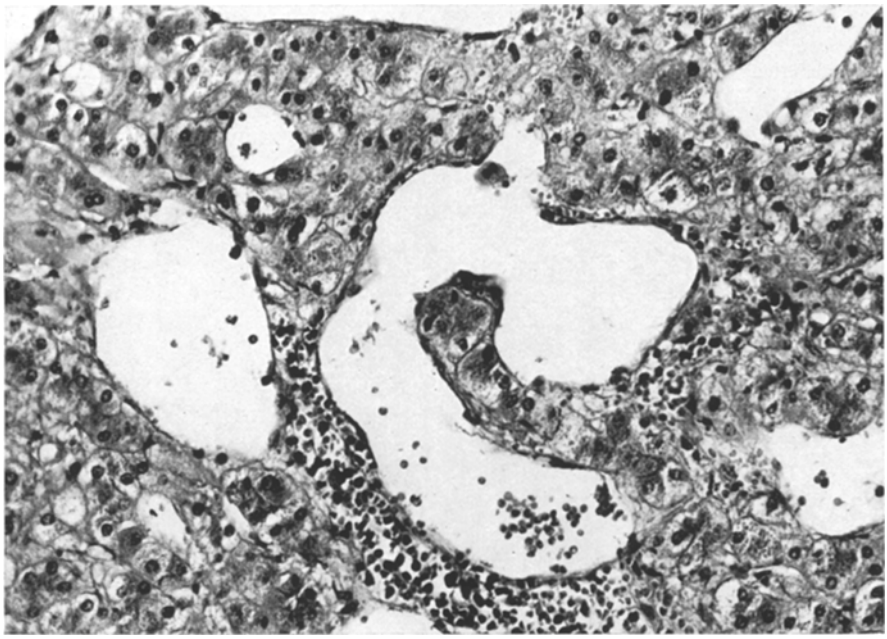

Fig. 5. Tumour showing well differentiated liver cells. The sinusoids are dilated giving an angiomatous appearance. Note the haematopoietic elements (HE, × 180)

Histology

The material was fixed in 10% formalin, embedded in paraffin and cut at 5 μ. Sections were stained with H-E, VG-Verhoff, Gomori, PAS, PAS-diastase, Masson-trichrome, VG-Fouchet and Giemsa.

The tumour presented as numerous large regenerative nodules compressing the normal liver parenchyma at its periphery (Fig. 4a). The compressed liver cells were flattened and atrophic lying within thin connective bands connecting the sclerosed enlarged portal tracts showing some bile duct proliferation. Together, this formed a "pseudo-capsule" heavily infiltrated, in areas, by chronic inflammatory cells, and containing markedly dilated vascular channels connecting the portal venous system. Many of the arteries in this region showed thickening of their media together with an important endofibrous proliferation leading to almost complete obliteration of their lumen (Fig. 4b).

The tumour mass outside the necrotic areas was characterized by cords and tubules of well differentiated liver cells, sometimes forming disorganized plates (Fig. 5). The cells had a fine granular cytoplasm, with an irregular distribution of glycogen, or a clear cytoplasm, thus resembling vegetal cells. There were no diastase resistant globules. The nuclei were centrally located with prominent nucleoli. Numerous cells contained two or more nuclei, but there were no atypical mitotic elements. Broad, loose fibro-hyalin trabecular bands including islands of cells, sometimes undergoing pycnotic changes, separated the lobules (Fig. 6a and b). In these bands, there were macrophages laden with haemosiderin pigment.

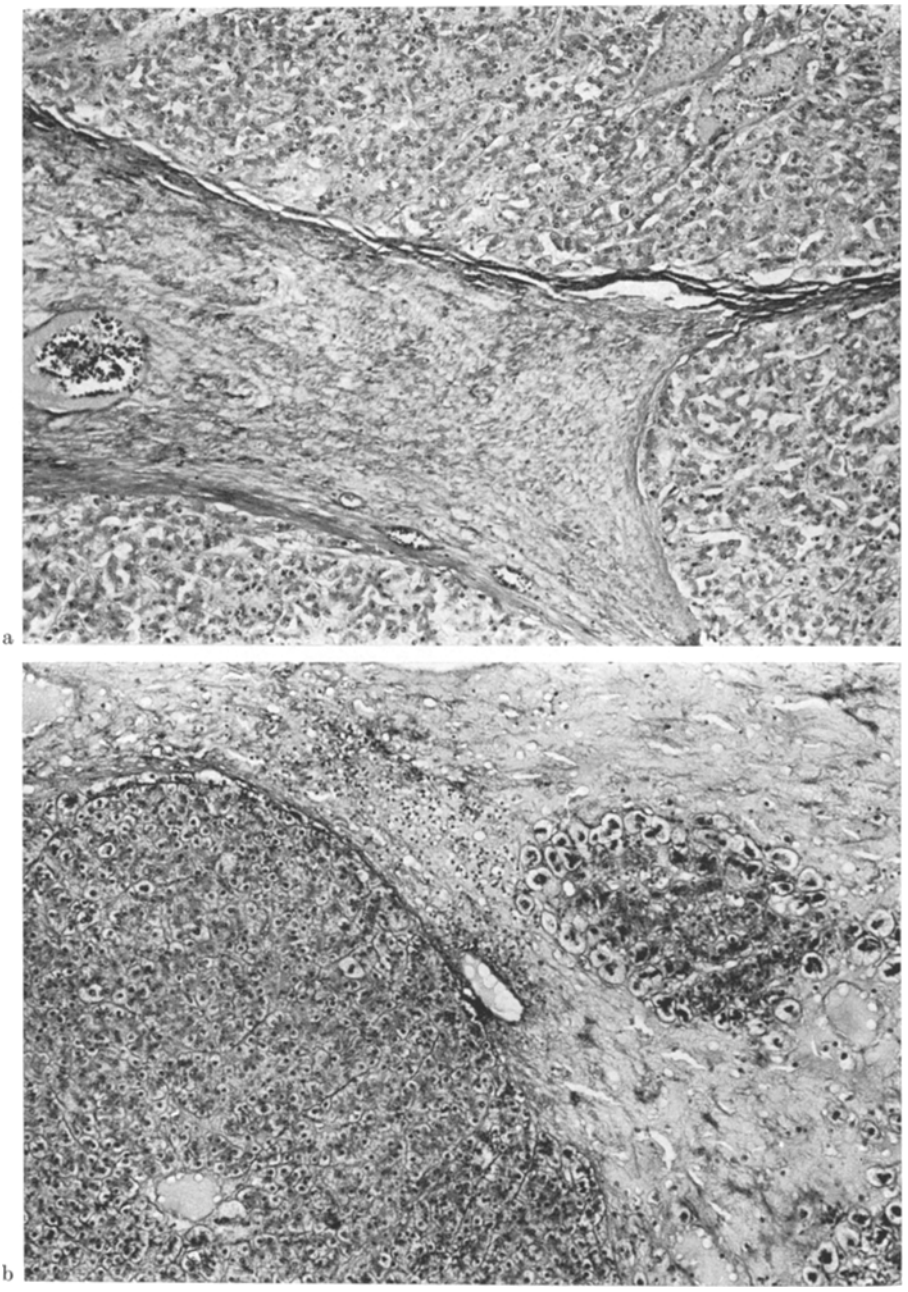

Fig. 6. (a) Large connective tissue bands separating the proliferative lobules principally in the central areas of the tumour (H.E. × 120). (b) Lobule undergoing necrosis with formation of connective bands (H.E. × 120)

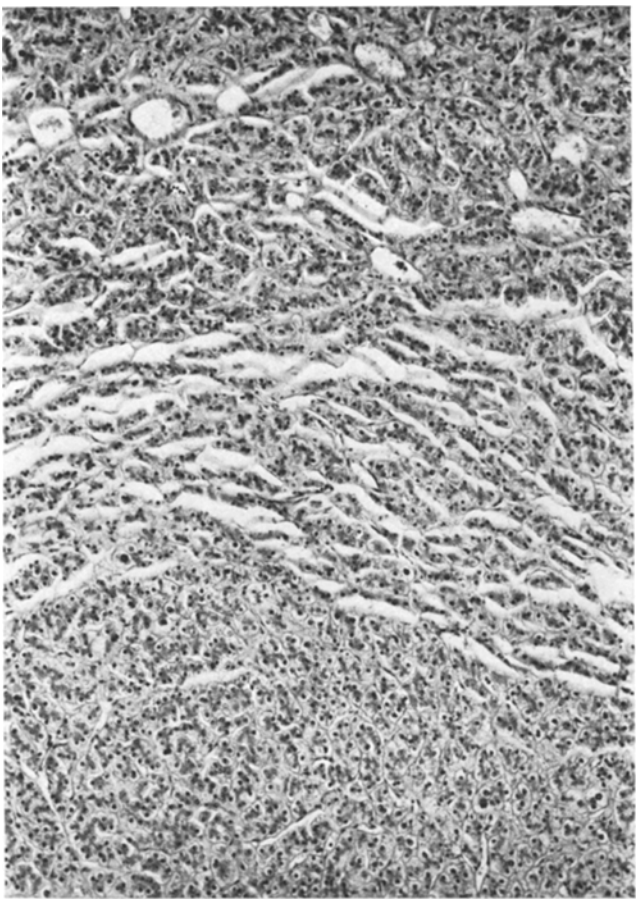

Fig. 7. Compression with atrophic changes of a pre-existing nodule by newly regenerating tissue (lower left). (HE, × 60)

The normal lobular architecture of the liver was absent. There were no bile ducts nor central veins, but here and there were dilated vascular channels, veins and sinusoids, having an angiomatous appearance.

Small foci of haematopoietic elements were sometimes observed among the cords of cells within areas. Some of these vessels, like those at the periphery, presented thickened walls, but only few organized mural thrombosis, principally within and around the central necrotic areas. There were no calcifications.

Some of the nodules were well formed while others were in formation sometimes within the already formed nodule which was pushed outward with the formation of a second pseudocapsule within the nodule (Fig. 7). No vascular invasion or local infiltration was observed.

Within the normal liver parenchyma, and principally about the hilum, there was an important dilatation of the portal vein and its tributaries, some of which contained fresh thrombi. The nuclei of the liver cells were often glycogenic.

Discussion

Primary tumours of the liver in infancy and childhood are rare when compared to other solid tumours arising in other organs (Ishak and Gluntz, 1966; Keeling, 1970). Malignant epithelial tumours are more frequent than the hamartomatous malformations and among the latter the parenchyma or epithelial hamartoma is still less frequent than the mesenchymal variety (Keeling, 1970; Nikaidoh *et al.*, 1970; Ramchaud *et al.*, 1970). The latter has been designated in the literature under such names as: adenoma, hamartoma, benign hepatoma, solitary hyperplastic nodule, focal cirrhosis, or focal nodular hyperplasia (Albritton *et al.*, 1974; Benz and Baggenstoss, 1953; Edmondson, 1956; Wilson and McGregor, 1969) and this has resulted in the discrepancy in the number of cases listed by some authors in their review of the literature (Roy and Bremner, 1971; Tate *et al.*, 1972).

The histological appearances in the case under discussion are consistent with those of an epithelial hamartomatous lesion or adenoma of the liver as described by the above authors.

Various theories have been postulated as to the aetiology and pathogenesis of these lesions, but there is still doubt as to their true nature (de Saint-Maur and Delaître, 1973; Whelan *et al.*, 1973). Sometimes, these lesions are small and discovered accidentally at post-mortem or on abdominal exploration for other reasons. However, they often present, especially in infancy and childhood, as rapidly growing abdominal masses with little or no other symptoms. Torsion of the pediculated tumour and spontaneous rupture of the large rapidly growing mass resulting in an acute abdomen and collapsus are among the complications listed in the literature (Davis *et al.*, 1973; Veyrières and Flabeau, 1974).

The association of a liver tumour and hypertension is very rare; only one case report, to our knowledge, mentions this association (Alexandre *et al.*, 1971). Tumours arising in non endocrine tissues may secrete substances with hormonal activity (Omenn, 1971). This phenomenon, referred to as "ectopic hormone production by tumours" (Liddle *et al.*, 1969) is well known in certain liver tumours. In young children, hepatoblastoma and hepatoma may produce gonadotrophins and parathormone (Omenn, 1971).

In the case under discussion, the dominant manifestation was arterial hypertension, associated with high plasma renin activity before removal of the rapidly growing liver "tumour". It has been demonstrated in man and animals that the kidney is the major site for renin secretion, and the liver the major site for renin clearance. Thus, plasma renin is the resultant of both renin secretion by the kidney and renin clearance by the liver (Christlieb *et al.*, 1968).

Although all the mechanism controlling renin release could not be studied in this patient, the following factors can be eliminated as major causes of the high renin blood levels:

Serum potassium levels were consistently normal.

24-hour urinary excretions of catecholamines were normal.

Renal artery compression or renal ischemia induced by the liver tumour is unlikely. The intravenous pyelogram was normal and the dye appeared simultaneously and promptly in both kidneys, despite displacement of the right kidney,

which was moderate but without apparent modification of the calibre of its artery similar to the cases described by Weidmann *et al.* (1969).

In the present case, since the blood sample from the hepatic vein contained a higher level of plasma renin activity than that of the peripheral sample, it is very likely that the existing liver tumour was the site of renin production. If excessive plasma renin activity were due to defective renin clearance by the liver, the renin level in the hepatic vein should not be higher than that in the systemic blood.

Primary overproduction of renin by tumours has been described in such cases as juxta-glomerular cell tumours (Brown *et al.*, 1973; Conn *et al.*, 1972), nephroblastoma (Wilm's tumour) (Ganguly *et al.*, 1973; Mitchell *et al.*, 1969) and "oat-cell" carcinoma of the lung (Hauger-Klevene, 1970), but not in liver tumours.

In this patient, slightly elevated renin substrate levels were demonstrated in the serum before surgery and returned to normal within 9 days thereafter. Since renin substrate is a plasma globulin which is synthesized in the liver, the question should be raised as to the participation of the elevated renin substrate in the high plasma renin activity found. It is generally agreed that the normal concentration of renin substrate in man is very close to the nominal values of the K_m of renin. Thus, the kinetics of renin *in vivo* and *in vitro* is not of zero order, but at best of mixed zero and first orders (Favre and Vallotton, 1973). Nevertheless, from such a normal value any elevation of renin substrate could at the most, everything else being equal, double the plasma renin activity. In the present case these values were 5 to 20 times normal. Since the true renin concentration by internal calibration could not be measured in the present case for lack of material, it was derived by application of the integrated Michaelis-Menton equation (Gould and Green, 1971; Haas and Goldblatt, 1967). For this purpose, the values of K_m and velocity constant found in our laboratory were applied (Favre and Vallotton, 1973). Table 1 shows the plasma renin concentration thus obtained. The value found preoperatively is markedly elevated while post-operatively normal values were obtained within 9 days following a steady decrease. These results further support the view that abnormal production of renin was responsible for the systemic arterial hypertension.

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