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Unusual Obliterative Disease of the Hepatic Veins in an Infant

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Summary. Hepatic fibrosis with obliterative lesions of the small hepatic veins occured in a three month old infant with fatal congenital leukaemia treated with cytostatic drugs. The vascular changes were characterized by an unusual, hitherto unreported angiomatoid, proliferation of the endothelium. The process is compared with the more common subendothelial-fibrous type of the "veno-occlusive disease". An etiological interpretation is difficult, possibly the process is a secondary reaction of the endothelium to a cytostatic-induced lesion with hepatic fibrosis.

Key words: Hepatic veins – Hepatic fibrosis – Budd-Chiari-Syndrome – Congenital leukaemia – Side effects of cytostatic drugs.

Zusammenfassung. Es wird berichtet über ein 3 Monate alt gewordenes Kind mit einer zytostatisch behandelten konnatalen Leukämie, bei dem im Bereich der kleinen Lebervenen ein obliterativer Gefäßprozeß beobachtet wurde. Die Gefäßveränderungen waren durch eine bisher nicht beschriebene angiomatoide, polsterförmige Endothelproliferation charakterisiert. Diese wird dem häufiger beobachteten subendothelial-fibrösen Typ, wie er charakteristisch für die Lebervenen-Verschluß-Krankheit („veno-occlusive disease") ist, gegenübergestellt. Eine ätiologische Deutung ist schwierig, möglicherweise handelt es sich um eine sekundäre Reaktion des Endothels im Rahmen einer Zytostatika-induzierten Leberschädigung mit Leberfibrose.

Introduction

The hepatic veins are a part of the venous system distinguished by an abundance of pathological changes with characteristic clinical consequences. This has given them a special position in the general pathology of the venous system (Bützow et al., 1976).

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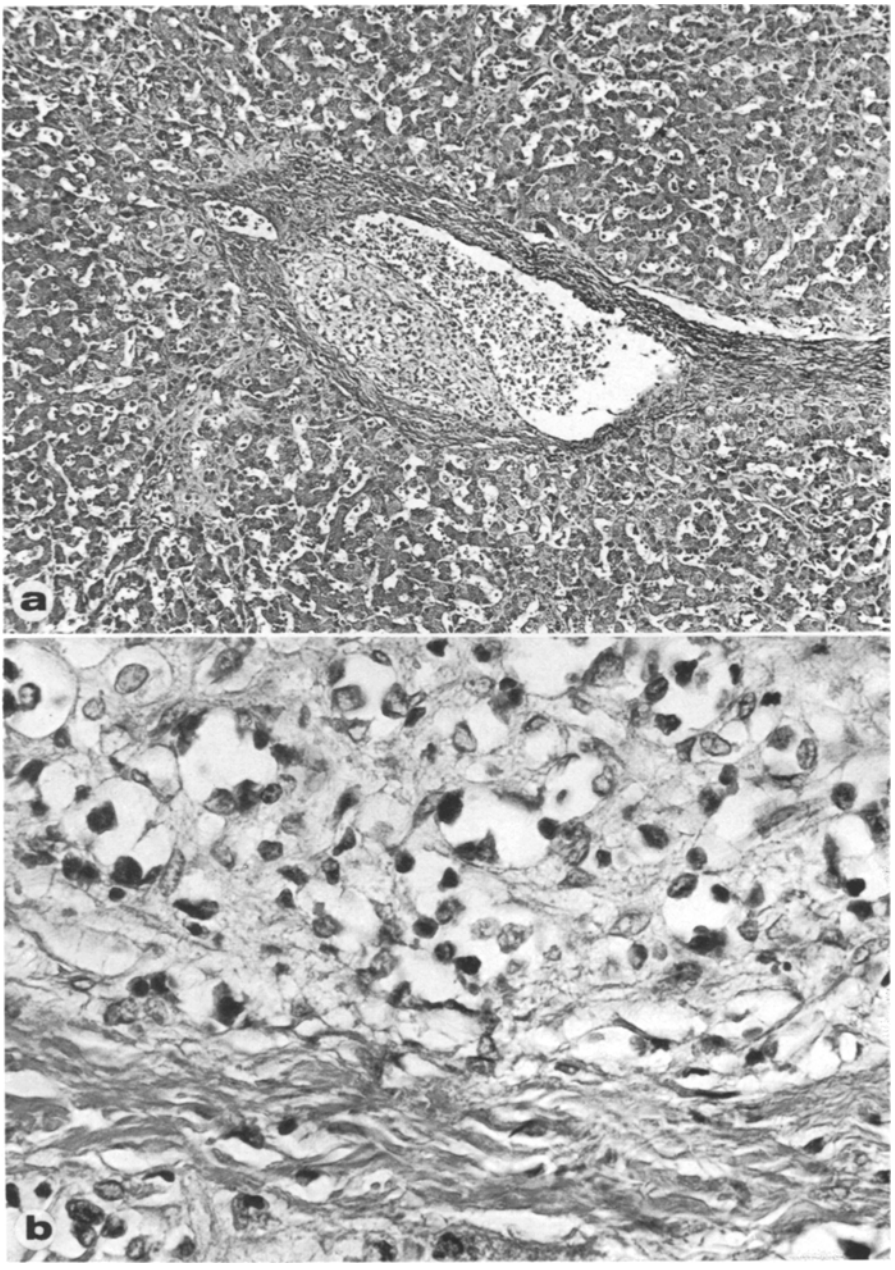

Fig. 1. a Partial occlusion of a sublobular hepatic vein through a cushion-like endothelial proliferation. Masson-Goldner; ×75. **b** Detail at higher magnification; capillary-like endothelial proliferation with only tender fibrous tissue. Hematoxilin-Eosin; ×480

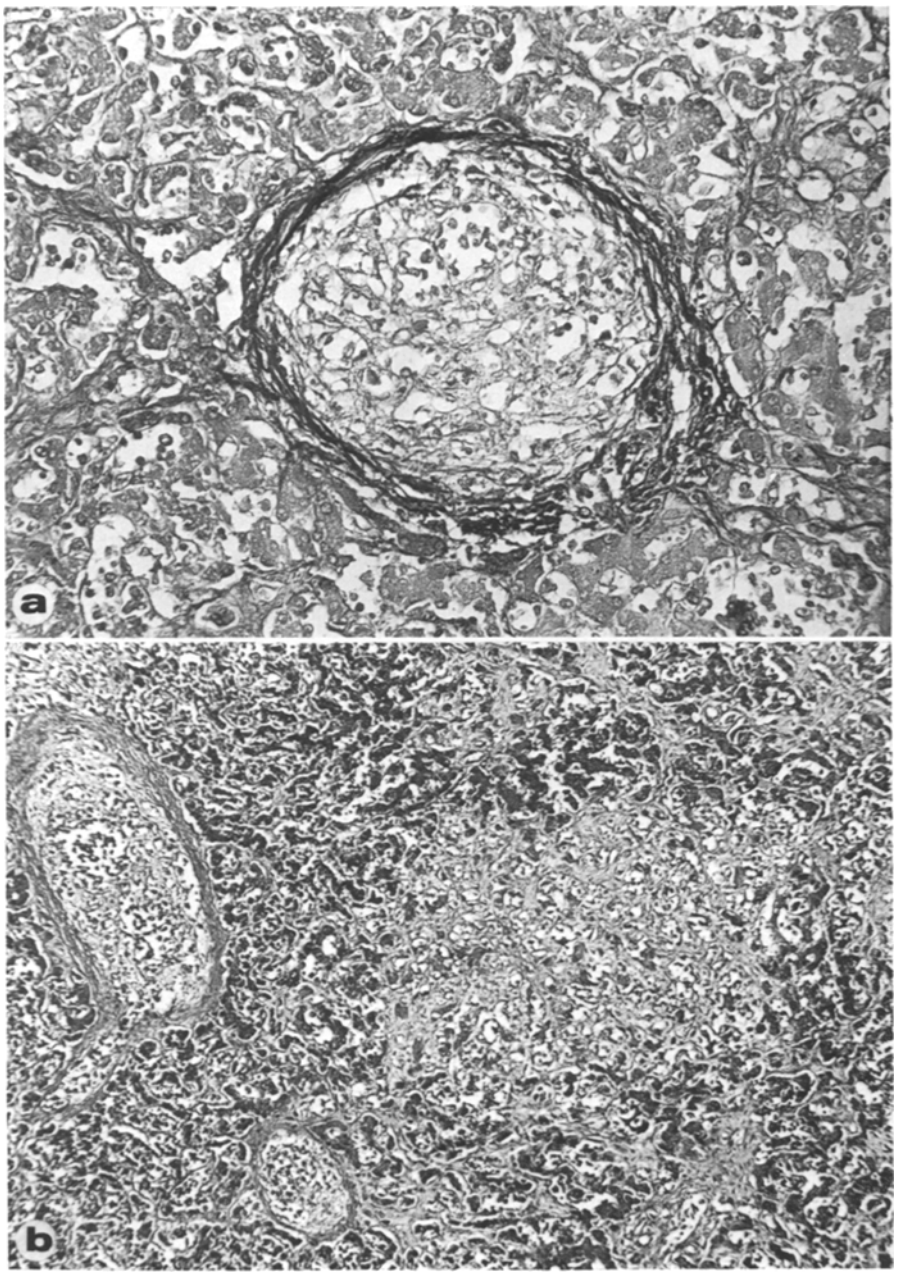

Fig. 2. **a** Totally occluded sublobular hepatic vein. Elastica van Gieson; ×190. **b** Perisinusoidal fibrosis in the vicinity of occluded hepatic veins. Masson-Goldner; ×75

Obliterative processes of the hepatic veins (Budd-Chiari-Syndrome; Budd, 1845; Chiari, 1899) are divided into secondary symptomatic occlusions and primary occlusions, essentially confined to the liver (so-called Chiari's Disease; Thaler, 1963; Bützow et al., 1976). The pathogenesis of the former group is characterized mostly by thrombosis, rarely by a general vasculitis. The most common causative diseases are hematological disorders, tumors, and malformations of the vena cava (Parker, 1959). The less frequent primary occlusions can be separated into lesions of the hepatic vein orifices (cp. Rössle, 1933; Coronini and Oberson, 1936) and lesions of the small hepatic veins (Bützow et al., 1976). The latter commonly show a specific microscopical picture with subendothelial fibrous proliferation.

The paper describes an uncommon obliterative process in the small hepatic veins of a newborn suffering from congenital leukaemia, treated with cytostatic drugs.

Case Report

A male child was born after an uncomplicated pregnancy. Four days after birth hepatosplenomegaly was noted. Because of the blood picture and the bone marrow cytology, a *congenital myeloic leukaemia* of the juvenile type was diagnosed. Serological tests for syphilis were negative. *Cytostatic therapy* was carried out with Cytosin-Arabinosid (total dose 185 mg) and Vincristin total dose 0.8 mg). In addition high doses of antibiotics, antimycotics and steroids were necessary. In spite of the therapy, the general condition of the infant deteriorated, high temperatures developed, and 14 days before death therapy was stopped. The infant died at the age of 3 months of respiratory failure.

The *autopsy* (S.N. 77/75, Institute of Pathology, University of Hamburg) confirmed the clinical diagnosis of leukaemia, with infiltrates in the bone marrow, liver, spleen, lymph nodes, thymus and lungs.

The extensive interstitial infiltrates in both lungs had caused death through respiratory failure. In the bone marrow, spleen and liver there was marked fibrosis.

The histological changes in the small hepatic veins were unusual. The predominant finding was partial or total occlusion of the sublobular veins by an endothelial proliferation (Fig. 1 and 2). This often showed a characteristic focal pattern (Fig. 1). The endothelium formed small capillary-like formations with only a few networks of young fibrous tissue in between. Leukaemic infiltrates were not seen in these lesions and could not be demonstrated by enzyme histochemistry. No evidence of a thrombotic pathogenesis was found. The liver parenchyma in the vicinity showed a marked perisinusoidal fibrosis (Fig. 2b). The lesions were confined to the small efferent hepatic veins. Neither in the branches of the portal vein nor in the large hepatic veins, the ostia, or the vena cava were similar alterations found. Only a few splenic veins exhibited subendothelial fibrosis, but no lesions similar to those in the hepatic veins.

Discussion

The obliterative process constitutes a secondary finding in the case presented, a congenital leukaemia, treated with cytostatic drugs. However, the unusual morphology of the venous lesions found in the liver deserves attention, as it does not fit into the patterns of obliterative diseases of hepatic veins described so far (cp. Bützow et al., 1976).

The liver in this case showed a non-thrombotic occlusion of the small hepatic veins. A similar picture of so-called "veno-occlusive disease" of the liver is found in Jamaica with a known etiology. It is caused by intoxication with

pyrrolizidine-alkaloids in the locally consumed "bush teas" made from Crotalaria-plants (Selzer and Parker, 1951; Bras et al., 1954; Bras and Hill, 1956; Bras, 1973). In Europe similar lesions had already been described by Wurm (1937 and 1939) in 8 infants following feeding with milk heavily contaminated by bacteria. There are also case reports from other countries (Burkhardt, 1938; König, 1944; Stein and Isaacson, 1962; Heinicke, 1967; Auger and Lefebvre, 1973; Bützow et al., 1976; Lyford et al., 1976; Mellis and Bale, 1976), without demonstration of etiological factors in all cases. In those cases without proven Crotalaria-exposition, toxic or toxic-allergic and rheumatic factors have been considered. Morphologically all these cases are characterized by a generally concentric, subendothelial fibrous proliferative process of the vascular wall of the small hepatic veins, with predominantly centrifugal expansion. In its terminal stages fibrous obliteration of the lumen is seen (Bras and Hill, 1956; Stirling et al., 1962; Brooks et al., 1970). The lesion must be classified as a proliferative endophlebitis (cp. Coronini and Oberson, 1936). Wurm (1939) defines it as a sero-fibrillar inflammation of the vessel wall. In "veno-occlusive disease", a non-thrombotic pathogenesis could be unequivocally proved in early cases (Stirling et al., 1962) and experimentally (Lidberg, 1966; Allen and Carstens, 1971). The process is initiated by an endothelial lesion followed by subendothelial edema and fibrous organization.

The case described above shows a clearly different histological picture. Here subendothelial fibrous proliferation does not play an important role. We find instead, a focal cushion-like proliferation of the endothelium itself, with only few accompanying fibrils. This leads to loose angiomatoid occlusion of the vessels. Congenital hepatic fibrosis accompanied by changes of the branches of the portal vein (McCarthy et al., 1965) can be ruled out, as the other typical features of this disorder are missing (diffuse periportal fibrosis, hyperplastic and dilated bile ducts).

In five cases with symptomatic occlusions of the large hepatic veins and ostia, Leopold et al. (1970) described a plexus of capillary channels in the walls of central and sublobular veins with aneurysmal and polypoid intraluminal expansions as a collateral system. However, in the case presented here, there was no distal venous outflow block and no capillary plexus in the adventitia or media of the vessel wall.

The etiology of the vascular lesions in this case must remain uncertain in view of the complex clinical picture and therapy. However, two factors may play a role in the pathogenesis:

(1) the leukaemic infiltration of the liver,

(2) cytostatic therapy, with damage of the liver parenchyma and secondary reactions of the venous system to tissue necrosis and fibrosis.

A direct connexion with the primary disease is possible but not probable. The intimal proliferations do not contain leukaemic infiltrates. Possibly, however, it could be a reaction of the endothelium to infiltrates destroyed by the cytostatic drugs.

Graff (1938) described an atypical "cirrhosis" with fibrosis and calcification in a case of chronic lymphatic leukaemia, but alterations of the hepatic veins are not mentioned.

Hill and Jüngst (1969) reported a case of a juvenile leukaemia with lesions of the hepatic veins. However, these were of the subendothelial-fibrous type. They regard cytostatic therapy as the cause of the lesions in their case and postulate a toxic-allergic reaction to necrotic and degraded tissue components. Brodsky et al. (1961) saw a fibrous obliteration of the central and hepatic veins and perisinusoidal spaces following administration of urethane in a patient with myeloma. Scott et al. (1962) report a fibrotic occlusion of the smaller hepatic veins similar to "veno-occlusive disease" in an adult with metastatic seminoma, treated with irradiation and nitrogen mustard. Similar progressive fibrous obliterations occur also after radiation injury without additional cytostatic treatment (Reed and Cox, 1966).

Altman and Klinge (1972) described mesenchymal occlusions of the branches of the portal vein following therapy with methotrexate. It is noteworthy that in these cases, in most cases of classic "veno-occlusive disease", and in our case the vascular lesions are confined to the hepatic veins. The role of the liver in metabolizing toxic substances and the local accumulation of toxic metabolites must be considered to be important factors in the pathogenesis. Altered metabolizing capability of the liver in leukaemia with infiltrates could aggravate this effect.

Frequent occurrence of hepatic fibrosis and cirrhosis following medication with cytostatic drugs – especially methotrexate – has been described by a number of authors (Colsky et al., 1965; Hutter et al., 1960; Talerman and Thompson, 1966; Nesbit et al., 1969; Nyfors and Poulsen, 1976). In a retrospective study of 333 cases of juvenile leukaemia Hutter et al. (1960) found an increase of hepatic fibrosis from 31% before to 80% after introduction of cytostatic therapy and noticed in addition an increase in the severity of fibrosis.

In the case reported here, therapy with Vincristin and Cytosin-Arabinosid was carried out, no methotrexate was administred. It would be interesting to see how often the cytostatica-induced hepatic fibrosis or cirrhoses are accompanied by venous lesions, but apart from the cases mentioned, no observations on this point are reported. Hutter et al. (1960) described, in their cases of cytostatica-induced hepatic fibroses, endothelial and capillary proliferations in the fibrous tissue, without further comment on this subject.

Focal endothelial proliferations with subsequent thrombosis, developing simultaneously with hepatic fibrosis, can be seen in experimental intoxication of rats with carbon tetrachloride, methylcholanthrene and dimethyl nitrosamine (Reuber and Glover, 1967; Reuber et al., 1968; Reuber, 1975).

The venous lesions reported in this paper are probably a special and localized expression of toxicity of cytostatic drugs, which promoted the hepatic fibrosis. The developing of the vascular changes could be favoured by the high proliferative capability of the endothelium in infants.

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