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Veno-occlusive disease and peliosis of the liver after thorotrast administration

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Summary. A case of veno-occlusive disease and peliosis of the liver without coexisting liver malignancy 35 years after thorotrast administration is presented.

In the liver four main widely distributed lesions were found: Veno-occlusive disease (VOD), peliosis, fibrosis and thorotrast deposits.

Whether the VOD and the peliotic lesions are pathogenetically related or totally independent cannot be determined in the present case. However, the VOD and the peliosis are possibly related to the protracted alpha-emitting effect of thorotrast deposited in the liver parenchyma.

Key words: Veno-occlusive disease – Peliosis hepatis – Thorotrast

Thorotrast, a roentgenographic contrast medium, is a colloid solution of alpha particle emitting thorium dioxide with a biological half-life of 400 years. It was widely used in diagnostic radiology between 1928 and the mid 1950's primarily for hepatosplenography, peripheral and cerebral angiography and visualization of body cavities (Looney 1960). The major known complications of thorotrast administration are atrophy of the lymphoid system, fibrosis and cirrhosis of the liver as well as neoplastic diseases, mainly liver malignancies and lymphoproliferative diseases (Faber 1979; Mori et al. 1979; Selinger and Koff 1975; Visfeldt and Poulsen 1972; Wegener 1979).

Recently, Okuda et al. (1981) published 5 cases of peliosis hepatis (characterized by numerous small blood filled cystic spaces in the liver) as a late complication of thorotrast administration. Two of these patients had no concomitant liver malignancy.

Veno-occlusive disease (VOD) of the liver is a condition with fibrotic obliteration of the minute efferent centrilobular and sublobular hepatic veins (Bras 1954).

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The following case is the first report of veno-occlusive disease of the liver and the third case of peliosis of the liver without coexisting malignant tumours, after thorotrast administration.

Case report

A 60 year old woman was admitted to our department in September 1981 because of rapidly increasing abdominal distention, oedema of the lower extremities and general malaise. No history of tuberculosis, transplantation or irradiation was given, and the patient had never been treated with steroids, alkaloids, cytotoxic or immunosuppressive agents. In 1946 a carotid angiography was performed with an unknown amount of thorotrast to elucidate the cause of a long lasting headache. In 1970 a tumour of the neck located at the site of the former thorotrast injection was resected. Microscopy revealed fibrotic tissue with deposits of thorotrast, but no signs of malignancy were found.

Physical examination at the time of admission revealed a tender, firm, irregularly enlarged liver five centimeters below the right costal margin. No splenomegaly was found but ascites and massive oedema of the lower extremities were evident. No other signs of cirrhosis were demonstrated.

Laboratory data: Haemoglobin 5.9 (7.1–9.9 mmol/l), aspartate-aminotransferases 117 (10–40 U/l), alkaline phosphatases 892 (51–275 U/l), clotting factor II, VII, and X 0.54 (0.7–1.3), bilirubin 58 (5–17 μmol/l), albumin 310 (540–800 μmol/l), alpha-1-fetoprotein < 5 ng/l.

An abdominal x-ray film demonstrated thorotrast deposits in liver, spleen and lymph nodes along the splenic vessels. Ultrasonic investigation showed a large liver of non-homogeneous parenchymal structure raising suspicion of liver metastases. Arteriography of the abdominal aorta and superior mesenteric artery demonstrated a diffuse irregular gritty pattern over the liver, especially in the late arterial phase.

Laparoscopy revealed white fibrotic bands at the surface of the liver interspersed with parenchymal nodules of dark red colour. Because of the highly vascular appearance no laparascopic biopsy was taken, but a transvenous liver biopsy was performed. The obtained specimen was too fragmentated to be diagnostic. No tumour cells could be demonstrated in the ascitic fluid. Liver vein catheterization showed marked elevation of the wedged hepatic venous pressure and post-sinusoidal resistance as in advanced cirrhosis.

The patient was treated with diuretics and paracentesis, but the liver function decreased, and at the 47th day of admission she went into hepatic coma and died three days later in hepatic failure.

Autopsy findings

The patient was slightly jaundiced. One and a half litres of haemorrhagic ascites was found. The liver measured $26 \times 20 \times 8$ cm. The surface was non-homogeneous with a whitish network of subcapsular fibrosis demarcating areas of dark red and yellow-greenish colour. On the cut surface numerous blood filled cystic spaces up to about 5 mm in diameter were found dispersed throughout the liver parenchyma. No normal tissue was present. No obliteration of the main hepatic veins, of the superior vena cava or of the portal veins was found.

The spleen weighed 40 g and the cut surface showed fibrosis and a few blood filled spaces of 2–5 mm unevenly distributed throughout the red pulp.

There was only slight atherosclerosis and all other organs were without significant changes, in particular no signs of tuberculosis or malignant diseases were found.

Light microscopy

In the liver four main, widely distributed lesions are found: Veno-occlusive disease (VOD), peliosis, fibrosis and thorotrast deposits.

The larger branches of the hepatic veins are without any lesion but for scattered thorotrast deposits which are located subintimally, within the walls or adjacent to the wall of the vessels (Fig. 1). In contrast, sublobular and central veins show varying degrees of subendothelial fibrosis, often with total obliteration of the lumen (Fig. 2). These lesions are found unevenly distributed in the liver parenchyma. In addition, focal slight perivenous fibrosis is seen. No recent thrombi are demonstrated and the endothelium appears normal.

The size of the thorotrast deposits are similar in the veins with VOD compared to those without this lesion. No inflammatory cells or liver cell herniations are demonstrated in the lumina of the veins.

In the parenchyma widely distributed cystic blood filled spaces of varying size (1–5 mm) are present without zonal predominance and without relation to the areas with VOD (Fig. 3). The spaces are lined either by hepatocytes circumscribed by slender reticulin fibres or by sinusoidal lining cells, or in some areas by newly formed connective tissue (Fig. 4). In many cysts fine trabeculae of liver cells similarly covered by reticulin fibres are present, but apart from this, reticulin fibres are absent from the cystic cavities (Fig. 4). Many of the cysts are filled by recent thrombi, and a few by orga-

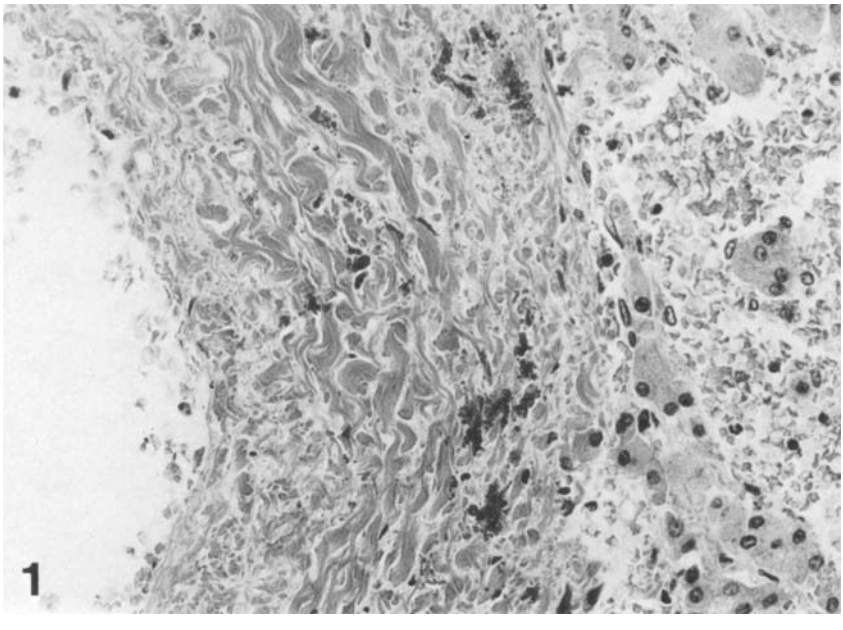

Fig. 1. Thorotrast deposits located within the wall of a larger branch of a hepatic vein

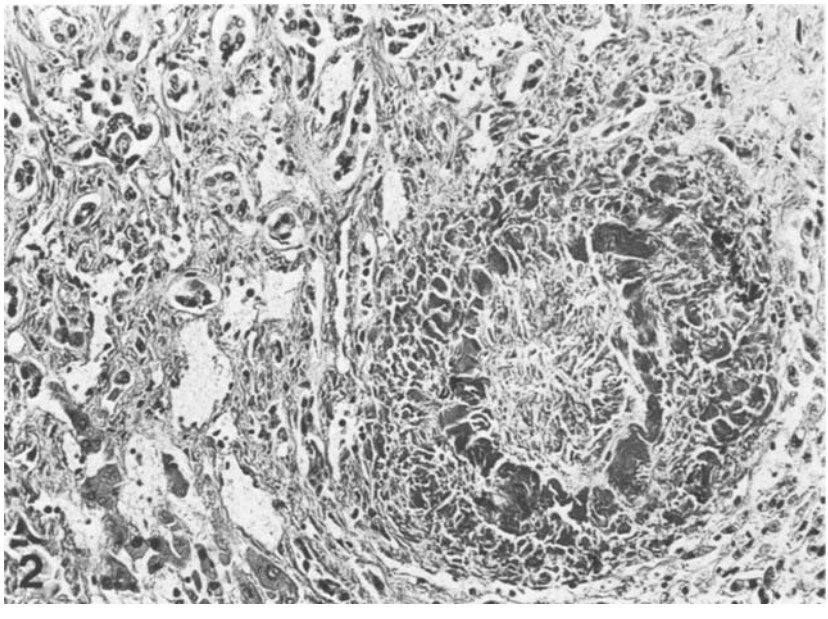

Fig. 2. A central vein in the liver parenchyma showing fibrosis and total obliteration of the lumen

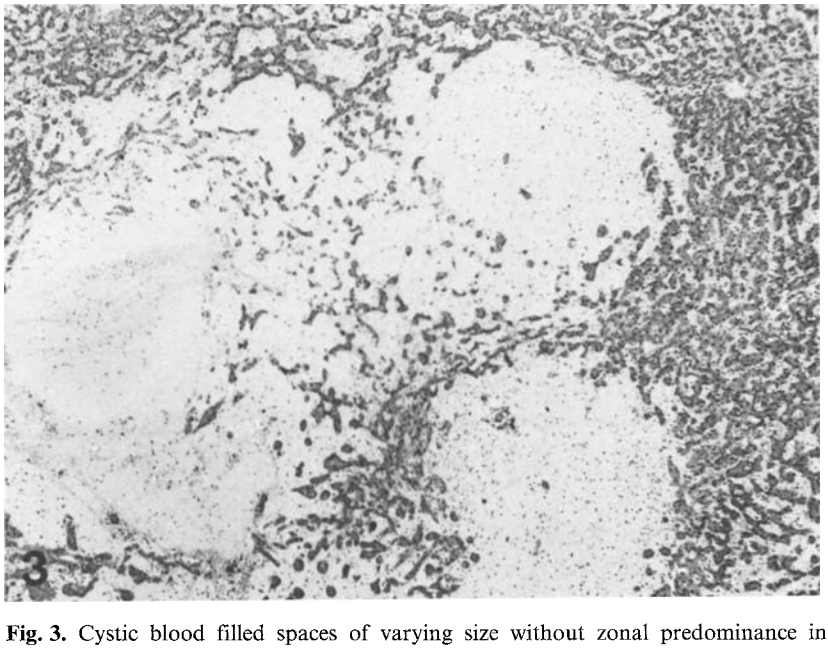

Fig. 3. Cystic blood filled spaces of varying size without zonal predominance in the liver parenchyma (peliosis)

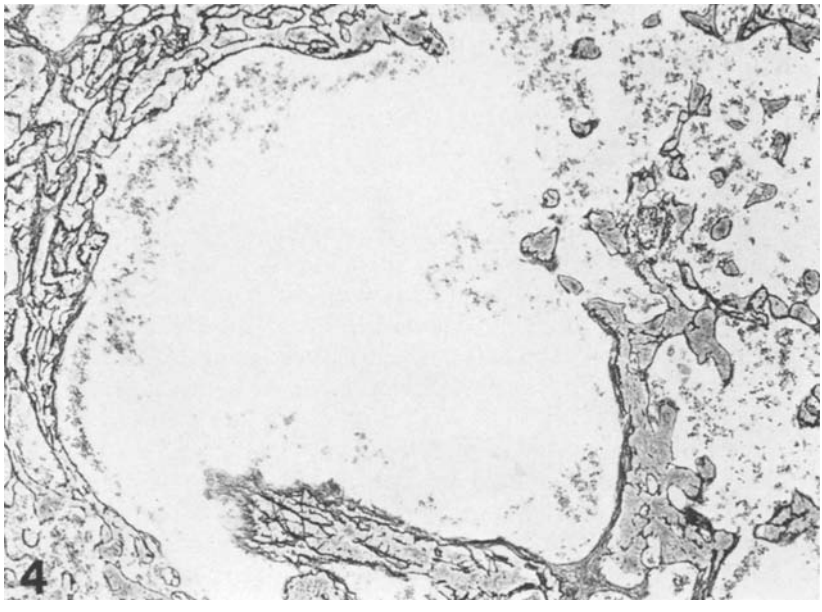

Fig. 4. Cystic spaces line by reticulin-circum-scribed hepatocytes. No reticulin fibres are seen in the cavities. (Reticulin staining)

nized ones. As mentioned above, no relationship between the central veins and peliotic cysts can be visualized, but in many areas gradual transition from sinusoidal dilatation to cysts is evident (Fig. 3).

The following patterns of fibrosis are seen: 1) Centrilobular fibrosis of varying degrees, in areas with extension into the liver parenchyma with partly or complete destruction of the lobules. These lesions are always found in relation to VOD, and in lobules with only partial destruction delicate plates of atrophic liver cells and bile duct proliferation are seen. 2) Slight focal perisinusoidal and pericystic fibrosis (Fig. 4). 3) A few slender portal-portal septa.

In general no or only minimal inflammation is seen.

The thorotrast deposits are of different size and irregularly distributed both in mature and in newly formed connective tissue. In addition, small amounts of thorotrast were demonstrated in scattered Kupffer cells.

Haphazardly small foci of liver cell necrosis are present, as well as foci of haemopoiesis. In hepatocytes, as well as in bile canaliculi, moderate bile pigment deposits are seen without zonal preference. No granulomas, Mallory bodies, alpha-1-antitrypsin globuli, ground-glass cells, orcein positive granules, iron deposits or signs of malignancy can be demonstrated.

Microscopy of the spleen reveals pronounced fibrosis with scattered thorotrast deposits and a few characteristic peliotic lesions. Specimens taken

from around the left carotid artery and the hilar lymph node contain thorotrast deposits, but there are no signs of venous occlusion, peliosis or malignancy.

Discussion

The term VOD was introduced by Bras et al. (1954) who described five cases possibly caused by ingestion of pyrrolozidine alkaloids.

Later VOD was ascribed to treatment with chemotherapeutic agents (Griner et al. 1976), irradiation (Fajardo and Colby 1980; Viala et al. 1981), immunosuppressive therapy (Degott et al. 1978, Weitz et al. 1982), oral contraceptives (Alpert 1976) and bone marrow transplantation (Berke et al. 1979; Schulman et al. 1980).

VOD has never been reported in man following the medical use of radioactive isotopes, however, in animal experiments it has been induced by radioactive colloidal gold (Hahn et al. 1951).

The pathogenesis of VOD is unknown. After ionizing radiation it is thought to be a consequence of endothelial injury of the central veins with focal deposition of fibrin and collagen resulting in fibrous occlusion of the veins (Fajardo and Colby 1980).

The symptoms of VOD are a consequence of postsinusoidal obstruction leading to portal hypertension and hepatic congestion. The condition should be suspected when there is a sudden onset of the symptoms, and can be diagnosed by needle aspiration biopsy (Sherlock 1981). The patients may recover from the acute stage (50%), die in liver failure (20%) or pass into a chronic stage which resembles any other type of chronic postsinusoidal obstruction (Stuart and Bras 1957). No specific therapy is available to prevent fibrosis or to hasten the recanalization of hepatic vein branches in VOD (Shulmann et al. 1980).

Peliosis was named by Schoenlank (1916) and was initially reported in patients with wasting diseases such as tuberculosis (Kent and Thompson 1961; Zak 1950) and malignant tumours (Orandi and Pirozynsky 1967; Yanoff and Rawson 1964). Later it has evolved into a clinical iatrogenic problem as a complication of anabolic steroid treatment (Bagheri and Boyer 1974; Groos et al. 1974; McGiven 1970; Nadell and Kosek 1977; Naiem et al. 1973; Taxy 1978) or to contraceptive steroid treatment (Winkler and Poulsen 1975). Recently it has been reported after thorotrast exposure (Okuda et al. 1981).

The pathogenesis of peliosis still remains enigmatic. Considering the numerous conditions in which it may arise it seems unlikely that one common pathogenic mechanism is responsible for development, and various pathogenic theories have been suggested including congenital malformations, vascular varicosites, ruptured vessels or hepatic necrosis (Kent and Thomson 1961; Zak 1950).

Okuda et al. (1981) have suggested that alteration of the reticulin framework is the initial lesion, followed by sinusoidal dilatation and thinning

of cell cords and influx of blood to form the characteristic blood filled cystic spaces.

The diagnosis of peliosis can be made where arteriography shows a characteristic pattern with multiple small accumulations of contrast medium in the late arterial phase (Pliskin 1975). Percutaneous liver biopsy is generally contraindicated considering the risk of peritoneal haemorrhage (Visfeldt and Poulsen 1972). Transjugular venous liver biopsy might be a good alternative method, even though the specimens obtained by this procedur often are small, fragmentated and inconclusive as in our case. Laparoscopy may be helpful in the diagnostic procedure.

In at least three reported cases of steroid induced peliosis (Groos et al. 1974; Nadel and Kosek 1977; Arnold and Kaplan 1979) remissions were reported after withdrawal of the drug, but in most cases the progression has been rapid and fatal with haemorrage or hepatic failure being the cause of death (Okuda et al. 1981; Taxy 1978). As in VOD the clinical symptoms of peliosis hepatis are uncharacteristic and patients will present with liver failure and portal hypertension in the terminal stage.

The concommitant occurence of VOD and peliosis hepatis have been reported earlier by various authors (Bras et al. 1954; Degott et al. 1978). In the present case the pathogenetic relation ship between VOD and peliosis can not be determined with certainty. A possible explanation of the findings would be that the protracted alpha emitting effect of thorotrast induces damage in the vascular lining cells, giving rise to VOD. The resulting post-sinusoidal obstruction causes portal hypertension which in the weakened parenchyma could leaf to the cyst formation characteristic of peliosis.

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