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Case Reports

Ruptured Benign Hepatoma Associated with an Oral Contraceptive

A Case Report

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Summary. A ruptured benign hepatoma is described in a woman at full-term pregnancy. The patient had used an oral contraceptive for eight years before she became pregnant. According to several recent reports it seems likely that there is a relationship between the use of oral contraceptive agents and the development of liver cell tumours. Twentythree such cases have been found in the literature. Fourteen of these were not diagnosed before rupture. The present tumour differed from previously described lesions by containing foci of haematopoietic cells. As there were no signs of blood or bone marrow disease, it is suggested that the extramedullary haematopoiesis is a constituent of the tumour tissue.

Key words: Contraceptives, Oral — Liver Neoplasms.

Introduction

During the last years several cases of liver cell tumours or tumour-like lesions in women using oral contraceptives have been reported (Baum *et al.*, 1973; Contostavlos, 1973; Hermann and David, 1973; Berg *et al.*, 1974; Horvat *et al.*, 1974; Kelso, 1974; Knapp and Ruebner, 1974; Mays *et al.*, 1974; Meyer *et al.*, 1974; O'Sullivan and Wilding, 1974; Tountas *et al.*, 1974). The lesions have been solitary and well circumscribed, mostly benign and variously diagnosed as benign hepatoma, liver cell adenoma, nodular hyperplasia, and hamartoma. A few have shown signs of malignancy (Hermann and David, 1973; Berg *et al.*, 1974; Meyer *et al.*, 1974).

As the incidence of benign hepatomas in earlier literature was considered to be very low (Edmondson, 1958), several authors have proposed a relationship between these liver tumours and the use of contraceptive agents (Lancet, 1973; Berg *et al.*, 1974; Brit. med. J., 1974; Solheim, 1975). No connection with other liver diseases have been demonstrated.

Dilated sinusoids and blood-filled spaces (peliosis hepatis) (Zak, 1950; Scheuer, 1973) have been a prominent feature in many cases (Contostavlos, 1973; Knapp and Ruebner, 1974; Mays *et al.*, 1974; O'Sullivan and Wilding, 1974; Tountas *et al.*, 1974). Because of the high vascularity the tumours are apt to bleed and rupture. Among 23 such cases reported, 14 were not diagnosed before rupture, and seven patients died. The tumours are therefore of great clinical importance.

We have recently seen a ruptured benign hepatoma in a patient who used oral contraceptives. To our knowledge this is the first reported case from Scandinavia. Microscopically, the tumour differed from those previously described by containing foci of haematopoietic cells.

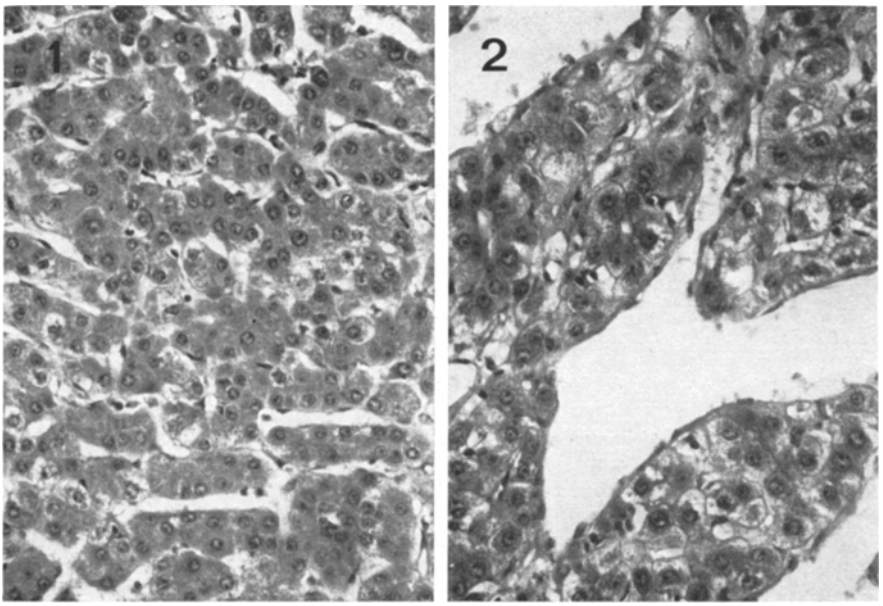


Fig. 1. Part of the lesion resembling normal liver tissue. HE, × 330

Fig. 2. Thick cords of liver cells and dilated sinusoids. HE, × 530

Case Report

A 31 year-old previously healthy woman had taken an oral contraceptive (lynestrenol—mestranol, "Lyndiol") for eight years. One month after she stopped using the agent she became pregnant. The pregnancy was uneventful. She was on iron medication and the lowest haemoglobin value measured was 12.5 g. per 100 ml.

At the time of expected delivery she suddenly got severe abdominal pain which started under the left costal margin and later spread to the whole abdomen. On admission to hospital she was in a relatively good condition. Within a few hours she got worse and because of impending shock and foetal bradycardia, a laparotomy was performed. The abdominal cavity contained about 1500 ml of fresh blood which came from a rupture in the left liver lobe. The child was lifeless and resuscitation unsuccessful. The left liver lobe was greatly enlarged and covered by blood clots. Beneath the clots there was a ruptured haemorrhagic lesion of about 10 cm in diameter. The pathological tissue was removed and the bleeding stopped. The liver was pale, probably because of the blood loss. Otherwise, no abnormalities could be observed or palpated. The patient received 1500 ml of blood during the operation. The postoperative course was uneventful and she has later remained well.

The haemoglobin was 15 g per 100 ml before the operation. For some time postoperatively the haemoglobin values and red blood cell counts were low and the reticulocyte values high. White blood cell counts, serum iron, iron-binding capacity and liver function tests (SGOT, SGPT, alkaline phosphatase, thymol turbidity test, bilirubin, and thrombotest) were normal. Blood and bone marrow smears did no reveal abnormalities. After some months on iron medication the haemoglobin was 15.8 g per 100 ml. Two weeks after the operation a liver scanning showed a defect in the left liver lobe. An arteriogram of the liver was normal.

Histopathology

Microscopical examination of the removed material revealed liver cells partly arranged in thin trabeculae resembling normal liver tissue (Fig. 1) and partly in

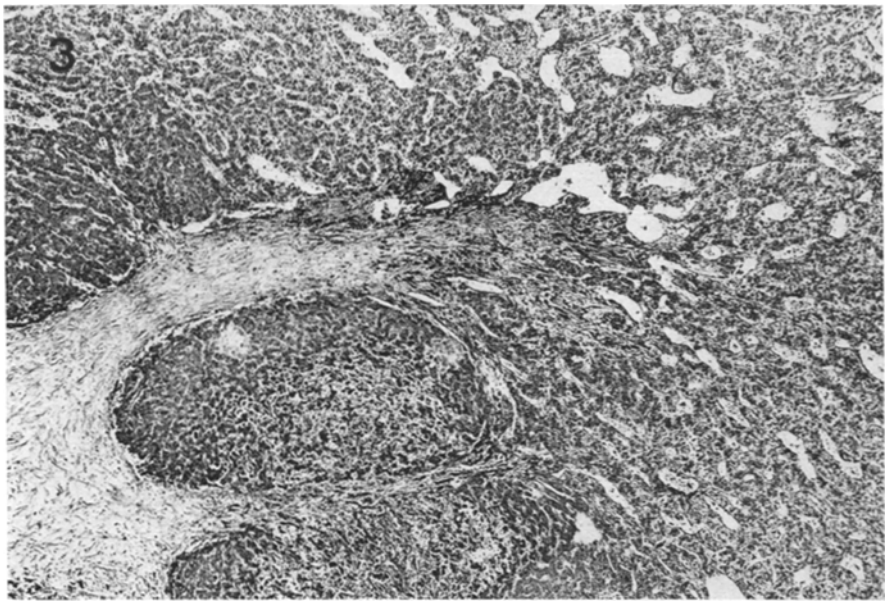


Fig. 3. Nodular growth and fibrous scar. Dilated sinusoids. HE, × 33

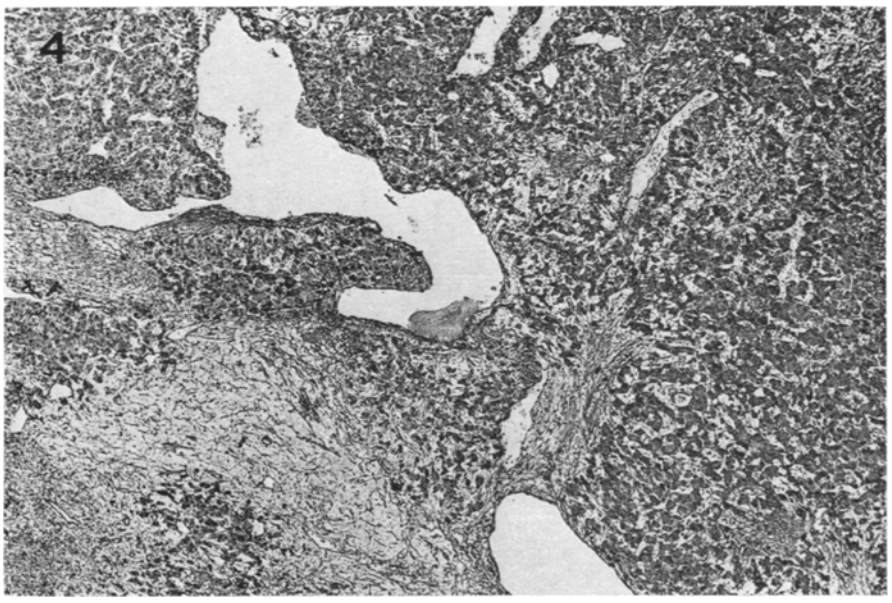
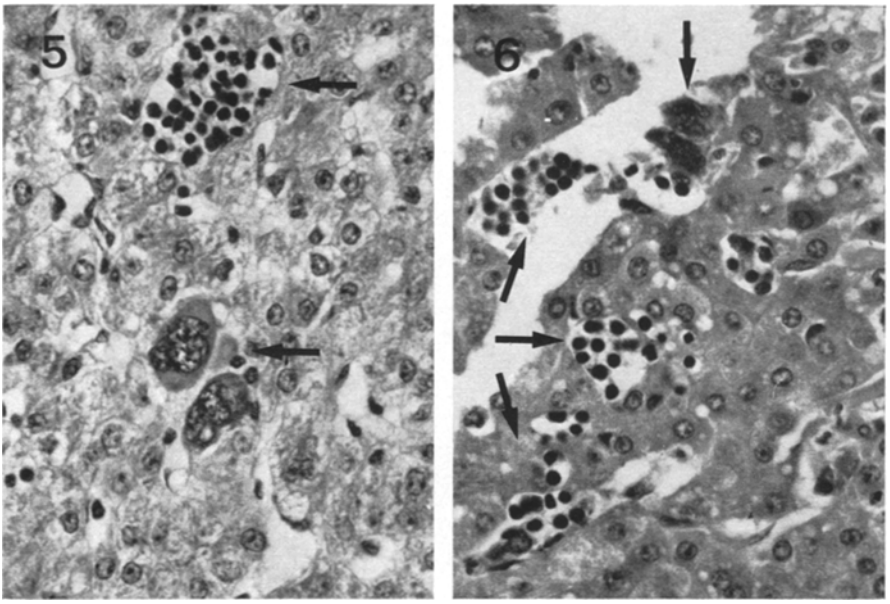


Fig. 4. Large blood spaces. HE, × 53

thicker cords and nodules (Figs. 2 and 3). There was no cellular atypia. No bile ducts, and no portal or central veins were seen but in some parts there were numerous wide sinusoids (Figs. 2 and 3) and large blood spaces (Fig. 4). Broad



Figs. 5 and 6. Haematopoietic cells (arrows), readily recognized by the presence of megakaryocytes. HE, × 530

fibrous scars containing many haemosiderin macrophages crossed the nodular areas (Fig. 3). The tissue was partly necrotic and large haematomas were present. Close to the necrotic fields the sinusoids contained recent thrombi. No other thrombosed vessels were observed. Foci of haematopoietic cells, readily recognized by the presence of megakaryocytes, were irregularly scattered throughout the tumour tissue. They were especially numerous in areas with recent and old haemorrhages (Figs. 5 and 6). There were no signs of tumour capsule or normal liver tissue in the specimen.

Discussion

The histological picture was that of a benign hepatoma with some degree of peliosis hepatis. As in most reported cases of this type bile ducts and portal and central veins were not found. Foci of haematopoietic cells have not been described in other cases.

Although the patient had stopped using the contraceptive agent ten months earlier, it seems likely, on the basis of previous reports, that there is a relationship between the use of the agent and the development of the tumour.

Liver cell tumours have also been described after the use of other steroids. Thus, malignant hepatomas have developed during treatment with androgenic-anabolic steroids for aplastic anemia (Bernstein *et al.*, 1971; Johnson *et al.*, 1972; Bagheri and Boyer, 1974; Meadows *et al.*, 1974) and other diseases (Farrel *et al.*, 1975). In animals there is a well-known effect of gonadal steroids on liver tumour development (Beaconsfield, 1974; Christoffersen, 1974; Lingeman, 1974). It is

uncertain whether the steroids have a direct carcinogenic effect on the liver cells or whether they potentiate the effect of other carcinogenic substances (Brit. med. J., 1974).

Peliosis hepatis is a condition with blood-filled spaces of varying size in the liver (Zak, 1950; Scheuer, 1973). It may occur with or without tumours and it has been reported after the use of oestrogenic (Contostavlos, 1973; Naeim *et al.*, 1973; Knapp and Ruebner, 1974; Mays *et al.*, 1974; Tountas *et al.*, 1974) as well as androgenic-anabolic steroids (Bernstein *et al.*, 1971; Naeim *et al.*, 1973; Bagheri and Boyer, 1974; Groos *et al.*, 1974). A reversible type of sinusoidal dilatation, probably an early state of peliosis, has also been observed during the use of oral contraceptives (Poulsen and Winkler, 1973). It is uncertain whether the condition is related to tumour development.

It has been suggested that intrahepatic vein thrombosis may be the primary cause of both peliosis and tumour formation. According to this concept the tumours should be regarded as nodular hyperplasias, secondary to infarction necrosis (Mays *et al.*, 1974). This would place the lesions among the well-known thrombotic complications to oral contraceptives. However, it seems more likely that the thrombosed vessels that occur in such cases are secondary events.

It is also worth notice that primary hepatic vein thrombosis—Budd-Chiari's syndrome—has been reported in women on oral contraceptives (see Hoyumpa *et al.*, 1971; Langer *et al.*, 1975). In one case with a localized venous thrombosis the liver ruptured (Frederick *et al.*, 1974). No tumours were observed in these cases. However, one may wonder whether the case with a localized lesion after all may have represented an undiagnosed tumour. The histological distinction between normal liver tissue, regenerative nodules, benign and highly differentiated malignant neoplasms may, indeed, be difficult, especially when the tissue is partly necrotic. Further studies concerning the nature of these lesions are therefore necessary.

As previously mentioned, extramedullary haematopoiesis has not been described in the other reported cases. It is well known that haematopoietic cells may be found in the liver of adults with severe anemia, especially in macrocytic types, and in anemias caused by bone marrow diseases, e.g. leukemia, myelofibrosis, widespread metastatic invasion, and toxic injuries (Brannan, 1927; Winthrobe, 1967). Our patient was not anemic and had no signs of blood or bone marrow disease. Thus, there was no reason to expect haematopoiesis in the liver.

Another mechanism that must be considered is whether the haemorrhages within the tumour may have acted as a local stimulus for the formation of haematopoietic tissue. This has never been reported in peliosis hepatis but it may have been overlooked. In mice fed on a diet containing oxazepam a high frequency of liver cell adenomas and peliosis hepatis was found, and microscopy revealed extramedullary haematopoiesis as well (Fox and Lahcen, 1974). The authors do not comment on this observation. Oxazepam, a benzodiazepine tranquilizer, has no known effect on the bone marrow (Jarvik, 1970), and haematopoiesis is not a normal finding in the liver of adult mice (Rubarth, 1958). However, since nothing is known about the blood and bone marrow of these animals, no definite conclusion can be drawn. At present it seems more likely that the haemato-

poietic cells may represent a constituent of the tumour. Absence of these cells in a biopsy from the uninvolved part of the liver would have supported this hypothesis. Unfortunately, no such tissue was removed.

Whatever the cause and nature of these tumours, they are of great clinical importance because of the serious complications. In most reported cases the contraceptive medication had lasted for more than five years. In one patient it occurred after only six months (Baum *et al.*, 1973). One half of the cases had no obvious symptoms before rupture, and some of them were erroneously diagnosed as acute cholecystitis or perforated peptic ulcer. When diagnosed before rupture, most cases presented with a palpable mass in the upper abdomen. Pains because of bleedings into the tumour tissue, occurred in some patients.

Liver scanning or arteriography have usually disclosed a localized mass in the liver. Most of the tumours have been large, 15 cm or more in diameter, and situated in the right lobe.

The prognosis is good when the diagnosis is made before rupture. Although the incidence is very low, it seems important to be aware of the possibility in all women on oral contraceptive agents who present with upper abdominal symptoms.

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