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Multiple Hepatocellular Tumours in a Patient Treated with Oral Contraceptives

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Summary. A case of multiple hepatic tumours in a patient treated for four years with high doses of oral contraceptives is described. Solitary hepatocellular lesions associated with conventional doses of oral contraceptives have been reported previously in twenty nine cases. Haemorrhage has been a common mode of presentation and is attributed to the marked vascularity of the lesions, an appearance referred to as peliosis hepatis. Radiographic studies show this term to be inappropriate as the vessels are of arterial origin. Another finding not previously reported is the presence of diffuse hyperplasia in the non-tumourous parts of the liver.

Key words: Liver-neoplasms — Oral contraceptives.

Introduction

Since 1972 twenty-nine cases of liver tumours associated with oral contraceptives have been reported (Horvath *et al.*, 1972; Baum *et al.*, 1973; Contostavlos, 1973; Hermann and David, 1973; Kelso, 1974; Knapp and Ruebner, 1974; Berg, *et al.*, 1974; Tountas *et al.*, 1974; Meyer *et al.*, 1974; Mays *et al.*, 1974; Model *et al.*, 1975; Stenwig and Solgaard, 1975; Stauffer *et al.*, 1975). These patients had been taking conventional doses of oral contraceptives for between six months and eight years. With the exception of two cases in which there were two masses (Berg *et al.*, case 4 and Model *et al.*,) the tumours have been solitary. Fourteen patients presented with spontaneous haemorrhage from the tumour and eight of them died. Several authors have noted the presence of abnormal thin-walled tumour vessels to which some have applied the term peliosis hepatis.

It is our purpose to describe a case of multiple hepatic tumours in a patient treated for four years with large doses of oral contraceptives. A possible pathogenesis is suggested by the coexistence of diffuse and focal hepatocellular hyperplasia. Post-mortem arteriography was used to clarify the true nature of the abnormal tumour vessels which in our view are not peliotic.

Case Report

(British Medical Journal, 1975)

A 24 year old houswife was admitted to hospital in November 1965 for investigation of oedema and proteinuria. She had moderately impaired renal function (Creatinine clearance 56 ml/min) and renal biopsy showed membrano-proliferative glomerulonephritis. She was treated with diuretics, prednisolone 30 mg/day reducing over 6 weeks to 10-15 mg/day, azathioprine 50-100 mg daily and norethandrolone 10 mg twice/day. She showed no improvement and after eight weeks the azathioprine and norethandrolone were stopped but the prednisolone (10-15 mg/day) was continued for a further six months. Her renal function steadily deteriorated and in July 1967 she was started on hospital haemodialysis.

A year later she developed menorrhagia which was exacerbated by the anticoagulation required for dialysis. She was given a three months course of cyclical hormone therapy using Minovlar (norethisterone acetate 1.0 mg, ethinyloestradiol 0.05 mg). After a further two years she again developed almost continuous uterine bleeding which was treated with norethisterone 15 mg daily for 3 months. When this proved ineffective, hysterectomy was advised but was refused. For the last four years of her life she was treated with oral contraceptives in doses sufficient to control her vaginal bleeding (see Table 1).

Table 1. Summary of oral contraceptive treatment

Minovlar (Norethisterone acetate 1 mg, Ethinyloestradiol 0.05 mg).	1 per day	Aug-Nov. 1968
Norethisterone	15 mg per day	July-Oct. 1970
Norinyl 1 (Norethisterone 1 mg, Mestranol 0.05 mg).	1 per day 2 per day upto 6 per day	Oct-Dec. 1970 Dec. 1970-Jan. 1971 Jan-March
Norinyl 2 (Norethisterone 2 mg, Mestranol 0.1 mg).	2 per day	March 1971-July 1974

Towards the end of 1973 hypertension necessitated bilateral nephrectomy. During the months following operation she developed severe anaemia (Hb 3.6 g/100 ml), mild leukopenia and thrombocytopenia (WBC = 4,300/ml, platelets 158,000/ml.) In April 1974 a 99 m Tecnetium Colloid liver/spleen scan showed a markedly and diffusely enlarged liver (estimated weight 2.9 kg, normal weight 1.3 kg) with no focal defects, and a slightly enlarged spleen. Liver function tests were normal with the exception of a raised alkaline phosphatase (22 King Armstrong units). Red cell survival studies showed a greatly diminished half life of 6.6 days (normal red cell half life for patients on dialysis 19.5 days (Laurent, 1974)), with significant sequestration of red cells in the spleen. Splenectomy was therefore performed on 2nd July, 1974.

While still in hospital she developed sudden severe upper abdominal pain associated with distension and shock. Coagulation studies were normal. Emergency laparotomy revealed a massive haemoperitoneum due to rupture of the right lobe of the liver. The bleeding area was packed and the abdomen closed. Hepatic arteriography showed an appearance suggesting multiple tumours. She was intensively treated with blood transfusions but bleeding continued and, despite further surgery, caused her death two days later.

Post Mortem

The post mortem examination, delayed until three days after the patient died, confirmed that the cause of death was haemorrhage due to spontaneous rupture of the right lobe of the liver.

Liver

(*i*) *Macroscopic Findings.* The liver weighed 4,945 gm including a subcapsular haematoma overlying the anterior and lateral surfaces of the right lobe. The cut surfaces showed tumours from 2–60 mm in diameter scattered throughout both lobes of the liver, and a haematoma, partly fresh and partly old, in the centre of the left lobe (Fig. 1). The tumours were clearly defined but not encapsulated and were pale brown and homogeneous, in contrast to the darker, lobulated pattern of the intervening liver. Foci of haemorrhage, and large vessels, often barium-

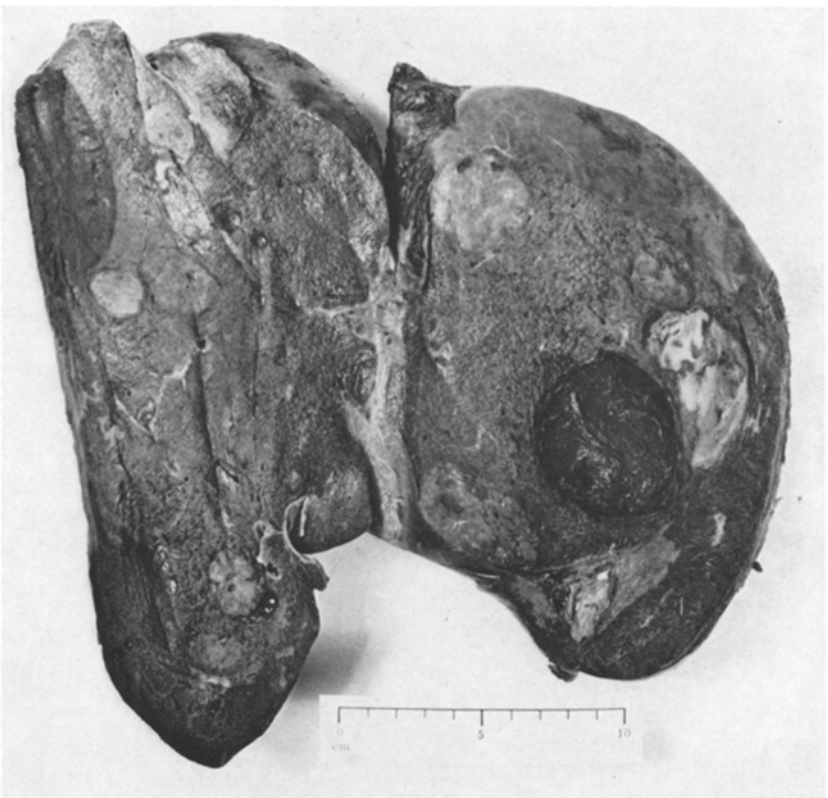

Fig. 1. The cut surface of the liver showing part of the subcapsular haematoma of the right lobe, (extreme left) and the central fresh haematoma of the left displacing an old haematoma laterally. Several tumours can be seen in each lobe

filled (see below), could be seen on the cut surfaces. Planimetry using photographs of the cut surfaces of the liver similar to Fig. 1, showed that 64% (± 64) of the specimen was macroscopically normal liver, which therefore weighed a minimum of 2,700 gm.

(*ii*) *Radiography.* A left hepatic artery angiogram was prepared by a slow infusion of equal parts of "Micropaque" and normal saline at a pressure of 40 mm of mercury. This showed an avascular filling defect in the left lobe corresponding to the haematoma described above, and several foci of abnormal vessels corresponding to the tumours seen on the cut surface of the liver (Fig. 2).

(*iii*) *Microscopy.* The tumours resembled liver cell adenomas as described by Edmondson (1958), except that they had no capsule. They contained no portal tracts, bile ducts or central veins and showed no lobular pattern (Fig. 3). They were composed of normal looking-liver cells, arranged in cords and plates two or three cells wide, separated by sinusoids with Kupffer cells. There were numerous, large, thin-walled blood vessels many of which were filled with barium. Their walls consisted of endothelial cells with a minimum of supporting tissue often

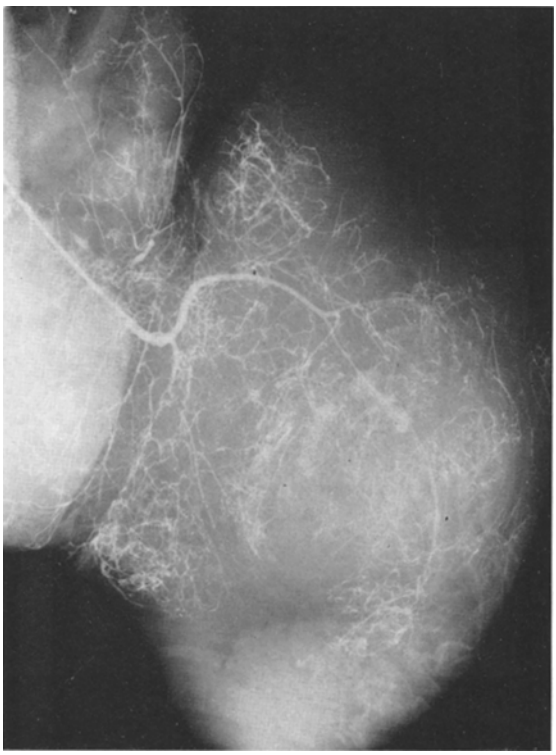

Fig. 2. Left lobe hepatic arteriogram (post mortem)

amounting to only a single reticulin fibre. None showed any muscle or elastic tissue (Fig. 4).

The remaining liver showed no evidence of a generalised vascular abnormality or cirrhosis. A high proportion of the liver cell plates were two cells wide and the liver lobules were enlarged though architecturally normal. The portal tracts were normal and there was barium in hepatic arteries and arterioles, but not in central veins, portal veins or sinusoids. Autolysis affected normal hepatocytes more severely than tumour cells emphasising the presence of foci of cells indistinguishable from those of the tumours, scattered in the parenchyma (Fig. 5). These ranged from small clumps of cells to nodules 2–3 mm in diameter compressing surrounding liver. The abnormal thin-walled vessels described above were seen only in tumours over 3 mm across.

Discussion

There appears to have been a real increase in the incidence of hepatic lesions in young women taking oral contraceptives and a causal relationship has been suggested. But in spite of reports of a total of 30 cases, the true nature of these lesions remains unclear. Mays *et al.* (1974) regarded their cases as focal nodular hyperplasia but the patient described by Model *et al.* presented nine months after the oral contraceptive had been withdrawn, suggesting that the lesion was auto-

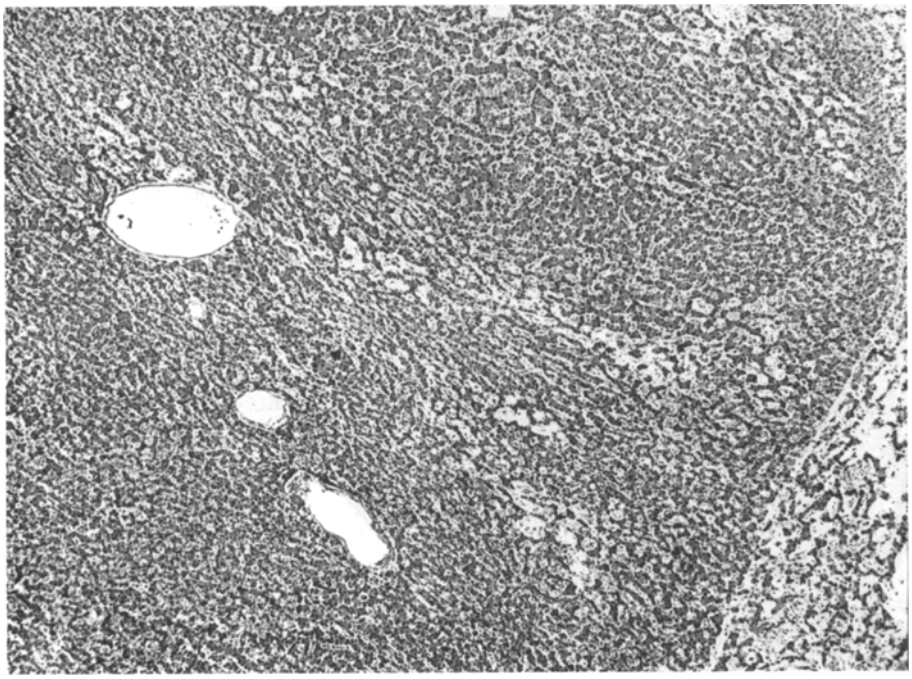

Fig. 3. Part of an adenoma including its edge. (H and E × 40)

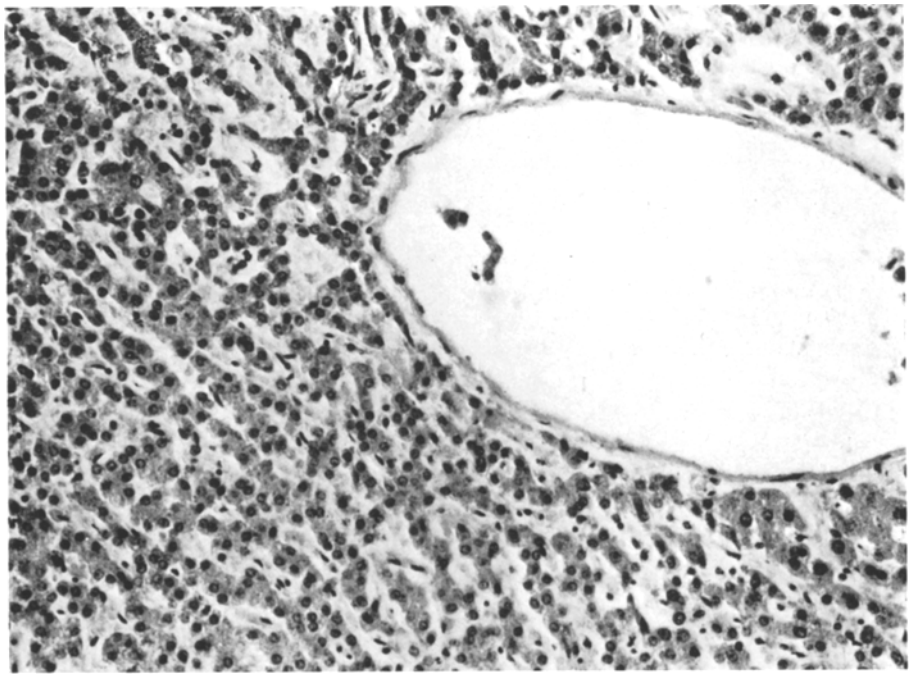

Fig. 4. Detail of the cytology and vessel structure in an adenoma. (H and E × 100)

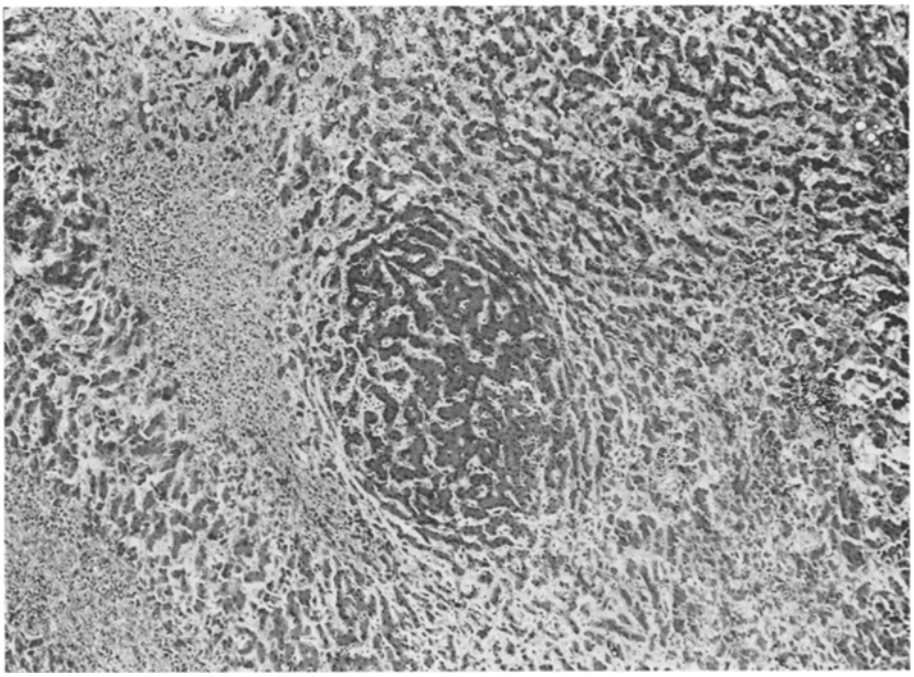

Fig. 5. A "nodule" of hyperplastic hepatocytes contrasting with adjacent autolytic liver. (H and E × 45)

nomous and therefore truly neoplastic. Histological evidence of malignancy has been reported but not metastatic spread. We believe that this reflects the problems of terminology of liver tumour pathology rather than fundamental differences in the individual cases. Rather are we impressed by the similarities in the reports. Common histological features include normal cytology, lack of a lobular pattern and the presence of thin walled vessels or blood lakes.

In our case we observed that the whole liver was abnormal. The scan four months before death showed that the liver was diffusely enlarged and at the time of death the non-tumorous liver was twice the expected weight. We have shown that this was due to diffuse hyperplasia coupled with focal nodularity. The former lesion was not immediately apparent for the architecture remained normal, each lobule being equally affected. It was only by comparison with normal livers at a fixed magnification that the lobule hyperplasia was seen. It is tempting to suggest that this represents a pathogenic progression from hyperplasia to neoplasia, but this conclusion would not be justified on the basis of a single case and previous authors do not report similar observations.

Scheuer (1973) divides hepatotoxicity into "predictable" and "unpredictable" types. The former is dose-related and is reproducible in experimental animals. The Report by the Committee on the Safety of Medicines (1972) showed that some oestrogen/progestogen preparations in high doses had a dose-related oncogenic effect on the livers of male rats. The present case of multiple tumours associated

with oral contraceptive therapy at four times the usual dose, compared to the previous reports of single tumours with conventional doses, suggests a similar dose-related response in humans. We can therefore expect to see more cases, though as Mays *et al.* point out, this may be prevented by the trend towards lower dose preparations.

Contostavlos (1973) was the first to use the term peliosis hepatis to describe the abnormal vascular spaces commonly seen in these tumours. In this condition blood-filled spaces are distributed throughout the whole liver though often unevenly. According to Yanoff and Rawson (1964) "the peliotic cavity appears to be a dilatation of a portion of the central vein." We know of no tendency to haemorrhage. Our radiographic studies showed that the abnormal vasculature of the tumour was readily filled by an arterial injection, and histology confirmed that filling was achieved without involvement of sinusoids or veins. Furthermore the abnormal vessels were confined to the tumour. We conclude that these vessels are derived from arterioles and are probably subjected to relatively high pressure. This would account for the prevalence and severity of haemorrhage, and makes the use of the term peliosis hepatis inappropriate and misleading.

References

Baum, Janet, K., Holtz, F., Bookstein, J.J., Klein, E.W.: Possible association between benign hepatomas and oral contraceptives. Lancet **1973II**, 925–929

Berg, J.W., Ketelaar, R.H., Rose, E.F., Vernon, R.G.: Hepatomas and oral contraceptives. Lancet **1974II**, 349–350

British Medical Journal, Clinico-pathological Conference. A Patient's Life. Brit. med. J. **1975II** 209–213

Carcinogenicity tests of oral contraceptives. A Report by the Committee of Safety of Medicines, London (1972)

Contostavlos, D.L.: Benign hepatomas and oral contraceptives. Lancet **1973II**, 1200

Edmonson, H.A.: Tumours of the liver and intrahepatic bile ducts, p. 18, Washington D.C.: Armed Forces Institute of Pathology (1958)

Hermann, R.E., David, T.E.: Spontaneous rupture of the liver caused by hepatomas. Surgery **74**, 715–719 (1973)

Horvath, E., Kovacs, K., Ross, R.C.: Ultrastructural findings in a well differentiated hepatoma. Digestion **7**, 74–82 (1972)

Kelso, D.R.: Benign hepatomas and oral contraceptives. Lancet **1974I**, 315–316

Knapp, W.A., Reubner, B.H.: Hepatomas and oral contraceptives. Lancet **1974I**, 270–271

Laurent, C., Wittek, M., Vercerstraetin, P., Troussaint, G., Naets, J.P.: Red cells life span, splenic sequestration and transfusion requirements in chronic bilateral nephrectomy. Clinical Nephrology **1974II**, 35–40

Mays, E.T., Christopherson, W.H., Barrows, G.A.: Focal nodular hyperplasia of the liver. Possible relationship to oral contraceptives. Amer. J. clin. Path. **61**, 735–746 (1974)

Meyer, P., LiVolsi, V.A., Cornog, J.L.: Hepatoblastoma associated with oral contraceptive. Lancet **1974II**, 1387

Model, D.G., Fox, J.A., Jones, R.W.: Multiple hepatic adenomas associated with an oral contraceptive. Lancet **1975I**, 865

O'Sullivan, J.P., Wilding, R.P.: Liver harmartomas in patients on oral contraceptives. Brit. med. J. **1974III**, 7–10

Scheuer, P.J.: Liver biopsy interpretation, 2nd ed. p. 40. Baltimore: The Williams and Wilkins Company 1973

Stauffer, J.Q., Lapinski, M.W., Honold, D.J., Myers, J.K.: Focal nodular hyperplasia of the liver and intrahepatic haemorrhage in young women on oral contraceptives. Ann. Int. Med. **83**, 301–306 (1975)

Stenwig, A. E., Solgaard, T.: Ruptured benign hepatoma associated with an oral contraceptive. A case report. Virchows Arch. A Pathol. Anat. and Histol. **367**, 337–343 (1975)

Tountas, C., Paraskevas, G., Deligeorgi, H.: Benign hepatoma and oral contraceptives. Lancet **1974I**, 1351–1352

Yanoff, M., Rawson, A. J.: Peliosis hepatis. An anatomic study with demonstration of two varieties. Arch. Path. **77**, 159–165 (1964)

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