BUDD—CHIARI SYNDROME AND HEPATIC ADENOMAS ASSOCIATED WITH ORAL CONTRACEPTIVES A CASE REPORT

Ho Kok Tong
Gloria Loke Keng Fai
Lenny Tan Kheng Ann
Ong Beng Hock

University Department of Medicine (II)
Singapore General Hospital

Ho Kok Tong, MBBS, M.Med, FRACP, FACG, AM
Senior Lecturer

Department of Medicine
Alexandra Hospital
Singapore

Gloria Loke Keng Fai, MBBS, DCH, MRCP, AM
Consultant Physician

Department of Radiology
Singapore General Hospital

Lenny Tan Kheng Ann, MBBS, DMRD, FRCR, AM
Consultant Radiologist

Department of Pathology
Singapore General Hospital

Ong Beng Hock, MBBS, DCP, AM
Consultant Pathologist

Address for Reprints:

Dr Ho Kok Tong
The Medical Polyclinic
Suites 1001-1004, 10th Floor
Mount Elizabeth Medical Centre
Mount Elizabeth
Singapore 0922

SYNOPSIS

A case of Budd-Chiari syndrome associated with liver cell adenomas in a young woman taking oral contraceptives is described. Her main complaints were of abdominal discomfort and massive ascites. Diagnosis of Budd-Chiari syndrome was established by hepatic venography and at laparotomy, multiple liver cell adenomas were discovered. It appears that oral contraceptives play a central role in the etiology of these conditions.

INTRODUCTION

Obstruction of the hepatic venous outflow leads to a clinico-pathological entity known as Budd-Chiari Syndrome. Although Budd and Chiari were credited by the eponym, neither of them were the first to describe the disease. The earliest known case was reported cases of thrombosis of hepatic vein resulting from intrahepatic abscesses (1). The clinical features of the disease were however not adequately described until fifty-three years later by Chiari in 1899 (2), who erroneously thought that the disease was the result of primary hepatic endophlebitis from syphilis.

The aetiology of the syndrome is unknown in two-thirds of cases. Of the known causes polycythemia rubra vera, hypernephroma and other tumours invading the inferior vena cava have been most often reported (3). Pregnancy (4, 5) and more recently oral contraceptives have also been implicated in the aetiology of the syndrome (6, 7, 8).

The present paper describes a young woman, previously on oral contraceptive pills for four months duration, who developed Budd-Chiari syndrome two weeks after delivery. She was also found to have multiple hepatic adenomas on laparotomy. Only one similar case has been reported in the literature (9).

Case History

L.S.H., a 32 year old Chinese woman was first seen in December 1976 with a five-day history of colickly abdominal pain, nausea, vomiting and progressive abdominal distension, two weeks after delivery of her second child. She had been taking an oral contraceptive (Norgestrel and Ethinyl Oestradiol) for four months prior to her second pregnancy.

On physical examination, she was in distress but was not jaundiced. There were no stigmata of chronic liver disease. There

was gross ascites with the liver palpable 4cm below the right costal margin. Her haemoglobin was 12.4gm/100ml. The white blood cell count was 8900/cm^3 with a normal differential count. She had a serum bilirubin of 0.7mg/100ml, alkaline phosphatase 218 I.U./litre, SGPT of 20 I.U./litre, serum albumin 2.8gm/100ml, and normal electrolytes. A hepatic scintiscan showed a grossly enlarged liver with heterogeneous uptake of I^{131}. The ascitic fluid was a transudate. She was thought to have portal vein thrombosis and was treated conservatively with diuretics with some improvement.

She defaulted follow-up and was not seen again till February 1977 when she presented with gross ascites, ankle oedema and abdominal discomfort. On examination, no organ enlargement could be detected because of the tense ascites. There was mild ankle oedema. Her serum bilirubin was 1.0mg/100ml, SGPT 40 I.U./litre, and alkaline phosphate 177 I.U./litre. Peritoneoscopy showed an enlarged but otherwise grossly normal liver. Celiac axis arteriography revealed a patent portal vein during the venous phase while inferior venocavography showed narrowing in IVC in the region of the liver but there was no significant obstruction (Fig 1). Repeated hepatic scintiscans revealed several filling defects in the liver and a hepatic arteriogram showed that the filling defects were multiple vascular tumours present in both lobes of the liver (Fig 2). Alpha fetoprotein was negative. Laparotomy was performed and an enlarged liver studded with multiple tumour nodules of varying size was found. A wedge biopsy of the nodule revealed benign liver adenoma (Fig 3). In the meantime, her symptoms had become more difficult to control and she was referred to the University Department of Medicine II for further evaluation.

Physical examination on admission revealed that she appeared to be in no acute distress and was not jaundiced. There were palmar erythema and spider naevi. Prominent collateral circulation was seen on the abdominal wall. Her abdomen was grossly distended with ascites. The liver and spleen were not palpable. Her Hb was 15.3gm%. Her white cell count 8400/cm^3 and platelets 120,000/cm^3. The urea and electrolytes were normal. Her bilirubin was 0.8mg/100ml, alkaline phosphatase 139 I.U./litre, SGPT 37 I.U./litre and serum albumin 2.2gm/100ml. Both the alpha fetoprotein and hepatitis surface antigen were negative. Oesophagoscopy showed presence of oesophageal varices. A hepatic venogram was performed (Fig 4). In contrast to the usual easy passage of catheter into the hepatic vein, the hepatic vein was wedged with some difficulty by an experienced radiologist and when the contrast medium was injected, the hepatic vein was shown to be almost completely obliterated with saccular collaterals distal to the obstruction. Thus a diagnosis of Budd-Chiari syndrome was established. Currently her ascites is fairly well controlled with Frusemide 120mg b.d. and Spironolactone 100mg tds.

DISCUSSION

Budd-Chiari syndrome is a rare disease characterised by massive ascites, hepatomegaly, abdominal pain and tenderness of variable degree. While nausea and vomiting occur at various times throughout the course of the illness, jaundice and splenomegaly are uncommon (3). Occasionally acute abdominal pain is the predominant symptom which increases rapidly in severity, leading to shock, coma and death from hepatic insufficiency. Rarely patients may present with haematemesis due to variceal bleeding as a result of portal hypertension.

The clinical features of the disease are not specific and the liver function tests are of little help in establishing the diagnosis. In the early stages they may be completely normal, and severe hepatocellular damage is seen only in the advanced state. The liver histology

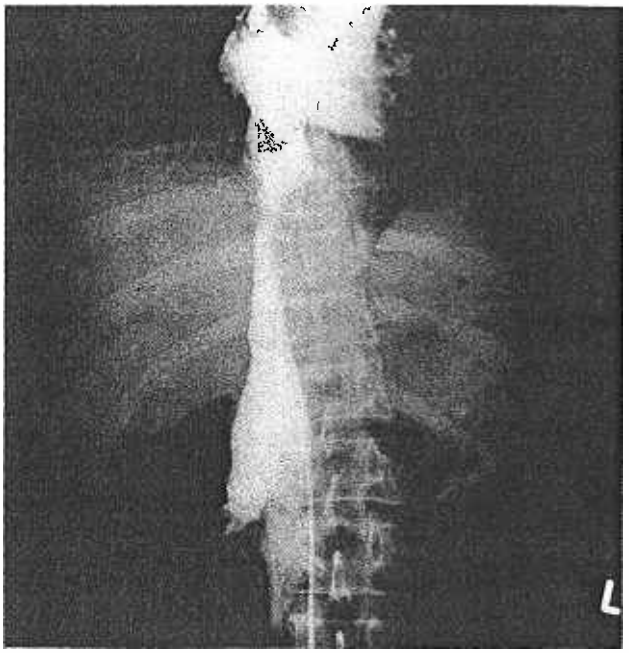

Figure 1 Inferior venocavograph showing narrowing of inferior vena cava in the region of the liver.

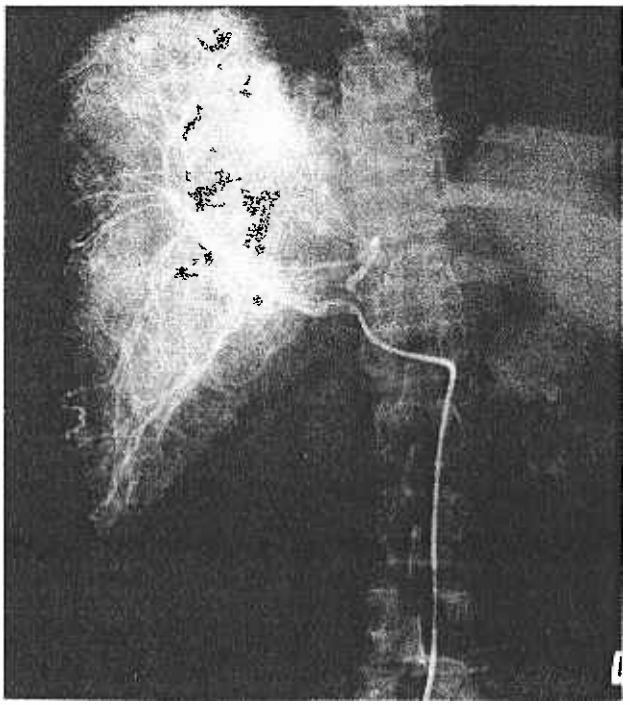

Figure 2 Hepatic arteriogram showing multiple tumour circulation.

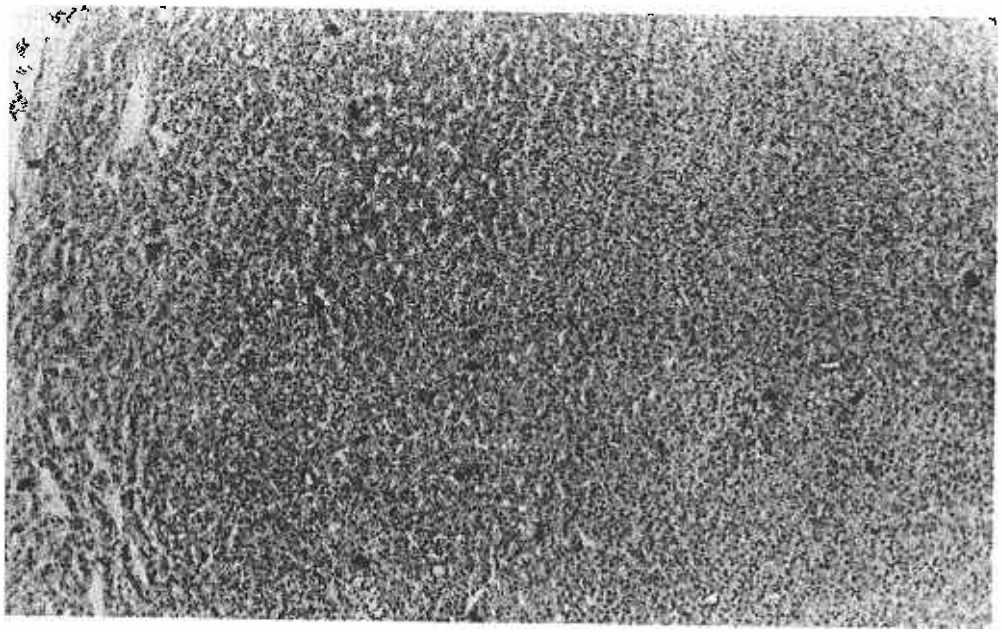

Figure 3 Photomicrograph of hepatic adenoma (H & E x100)

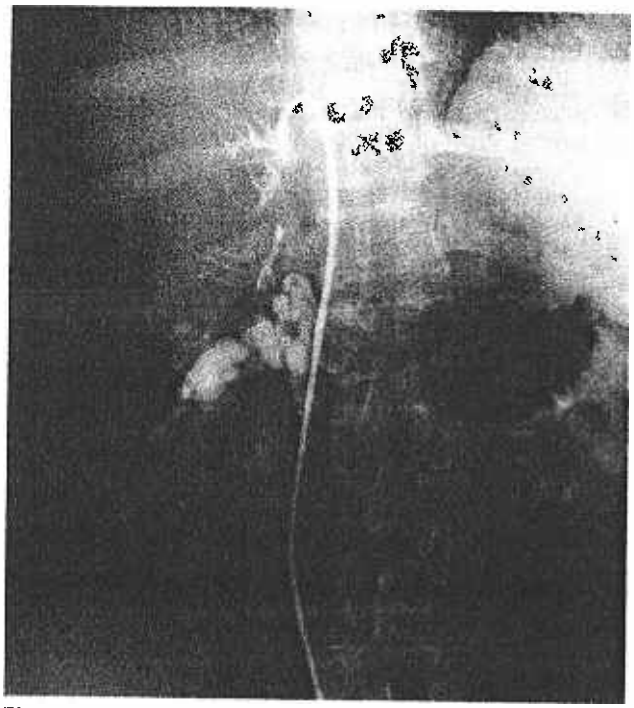

Figure 4 Hepatic venogram showing catheter wedged in the hepatic vein which is nearly obliterated with saccular collaterals distal to the obstruction.

may show non-specific sinusoidal congestion with centrizonal necrosis (10), seen also in patients with cardiac failure or constrictive pericarditis. The liver scan may show a characteristic concentration of isotopes in the central area of the liver (10), probably due to compensatory hypertrophy of the caudate lobe, which drains directly into the vena cava. The definitive diagnosis of the syndrome, however, must rely on radiological procedures to detect the level and extent of obstruction, and the presence or absence of collateral circulations. Two types of hepatic venous obstruction can be identified by hepatovenography and inferior venocavography (11). In type I, the obstruction is localised in the hepatic vein alone and the inferior vena cava is patent. In type II, there is a well-defined obstruction in the intrahepatic portion of the inferior vena cava or ostium of the hepatic vein. In Japan, congenital membranous obstruction in the hepatic portion of the IVC is the most frequent cause of Budd-Chiari syndrome and Japanese workers stress the importance of simultaneous superior and inferior venocavography to detect the presence of an IVC membrane (12). The hepatic vein and inferior vena cava may also be separately involved in the same patient (3). Side-to-side narrowing may be observed in inferior vena cavography but this non-specific appearance may be seen also in cirrhosis of liver (13).

Budd-Chiari syndrome seen shortly after delivery was first described by Thran (14) in 1899 and subsequently 7 other cases had been reported (15). Several factors have been postulated for its development. In late pregnancy the IVC is normally occluded when patient is lying in supine position and the venous return is via the azygos and vertebral veins (16). Furthermore, there is a hypercoaguability state in pregnancy due to increase in clotting factor VII and VIII, fibrinogen (5) and, in the puerperium there is a rise in platelet count with high level of fibrinogen and factor VII (15). Similar alteration in clotting mechanisms (17, 18), increased platelet sensitivity (15) and possible vasculitis due to changes in adreno-cortical steroid metabolism (19) as well as a primary endothelial defect (20) have also been postulated in women taking oral contraceptives. It has been estimated that the risk of venous thrombosis is increased six-fold during pregnancy and in the puerperium and three-fold with intake of oral contraceptives, although the actual mechanism remains speculative (21).

In our patient, the development of massive ascites, abdominal pain, hepatomegaly and the hepatic venographic finding of the hepatic venous occlusion confirm the diagnosis of Budd-Chiari syndrome. Although both pregnancy and the ingestion of oral contraceptives are implicated as causes, it appears that the latter is a more likely cause as the patient also has hepatic adenomas, which are recognised to have a close association with oral contraceptives.

Prior to the introduction of oral contraceptives, liver cell adenoma had been regarded as an extremely rare benign tumour. The association of liver cell adenoma and oral contraceptives was first suggested by Baum et al who collected 7 cases of liver cell adenoma, all in women taking oral contraceptives (22). Since then there has been a striking increase in the incidence of liver cell adenoma in parallel with the increased use of oral contraceptives and 237 published cases were reviewed by 1977 (23). The majority of women with liver cell adenoma had been taking oral contraceptives for more than 5 years but in 10% of patients the duration of oral contraceptive intake was less than 12 months. In 7% of cases the liver cell adenoma was discovered 6 months to 10 years after cessation of contraceptive pills (23). It appears that oral contraceptives of high hormonal potency carry greater risk particularly in patients over 30 years of age (24). The long term use of oral contraceptive pills have been estimated to be associated with an annual incidence of liver cell adenoma of 3 to 4 per 100,000 (25).

The clinical presentation of liver cell adenoma falls into 3 catagories (25, 26). About one-third to one-half of the patients present with a mass palpable at physical examination or discovered as an incidental finding at laparotomy. One-third of patients present with a painful tender mass and the remainder may present with a sudden, often fatal, intraabdominal haemorrhage due to rupture of the tumour. There appears to be a temporal relationship between menstruation and the rupture of the adenoma (24).

The diagnosis of liver cell adenoma is usually made at laparotomy although a liver scintiscan may show filling defects in lesions larger that 3cms in diameter. Before rupture hepatic arteriography is the best diagnostic aid (27). The hepatic artery is enlarged and the tumour shows up as filling defect with a clearly defined margin while numerous enlarged tortuous feeding vessels supply the mass from the periphery. The differentiation between the liver cell adenoma and hepatocellular carcinoma may occasionally be difficult. When liver cell adenoma is suspected, percutaneous liver biopsy is contraindicated because of the vascularity of the tumour and the increased risk of haemorrhage (27). Oral contraceptives are also implicated in the development of focal nodular hyperplasia and more rarely in hepatoma (27). The mechanism to the development of hepatic tumour following oral contraceptives is unknown. Present evidence suggests that the estrogen components of the oral contraceptive seem more incriminable than the progesterone components as estrogens are carcinogenic in other organs and promote liver cell regeneration in rats (16, 28). It has been suggested that estrogen by interference with the metabolism of oncogenic bile salt derivatives thereby exerts its oncogenic effect (6). Others suggest that these tumours may develop as a result of a steroid-induced stimulus to a preexisting developmental abnormality or a hyperplastic response to a chronic vascular injury (9).

The management of this patient is complicated by the dual pathology. Currently her symptoms are fairly well controlled by salt restriction and massive doses of diuretic. There is little evidence that anticoagulant or fibrinolysis therapy is of benefit in Budd-Chiari syndrome and it is particularly hazardous here as it may enhance the haemorrhage into the hepatic adenoma.

Surgery is controversial in the treatment of Budd-Chiari syndrome. Recently a number of favourable reports of side-to-side porta-caval (29) or mesoatrial shunt (30) have been advocated, but these operations will not influence the natural history of hepatic adenoma. Surgical resection on hepatic adenomas (31) is also unlikely to be successful as the adenomas are multiple and large. Oral contraceptives should never be used again as there are evidence that tumour may regress on stopping oral contraceptives. She is also advised against further pregnancy. Her final prognosis with regard to rupture of hepatic adenoma, liver cell failure and variceal haemorrhage, must be guarded.

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REFERENCES

1. Budd G: Disease of the Liver. Lea and Blandchard, Philadelphia, P151, 1846.
2. Chiari H: Ueber die Selbstandige phlebitis obliterans der Hauptstamme der Venae hepaticae als Todesursache. Beitr. Z. Path. Anat. U. Z. allg Path., XXVI, 1-17, 1899.
3. Parker R G F: Occlusion of the hepatic veins in Man. Medicine 1959; 38: 369-402.
4. Rosenthal T, Shani M, Deutsch V, Samra H: The Budd-Chiari Syndrome after pregnancy. Am. J. Obstet. Gynaecol 1972; 789-792.
5. Tiliacos M, Tsantoulas D, Tsoulias A, Kokka E, Eudaimon E, Aphentoglou S, Metzantonakis G: The Budd-Chiari Syndrome in pregnancy. Post-grad. Med. J 1978; 54: 686-691.
6. Golfard S: Sex hormones and hepatic neoplasm. Cancer Res 1976; 36: 2584.
7. Hines C Jr, Mitchell, W T Jr: Hepatic vein thrombosis in a woman taking oral contraceptives. A case report. J. LA State Med. Soc 1977; 129: 189-192.
8. Hoyumpa A, Schiff L, Helfman E L: Budd-Chiari Syndrome in women taking oral contraceptives. Am. J. Med 1971; 50: 137-139.
9. Alpert L I: Veno-occlusive disease of the liver associated with oral contraceptives. Case report and review of literature. Med. Intelligence 1976; 7: 709-718.
10. Chain D, Freston J, Kreel L, Sherlock S: Clinical Diagnosis of the Budd-Chiari Syndrome. Am. J. Med 1967; 43: 544-554.
11. Datta D V, Vashishta S, Samanta A K, Chhuttani P N: Diagnostic value of combined transhepatic venography and inferior vena cavography in the chronic Budd-Chiari syndrome. Am. J. Dig. Dis 1978; 23: 1031-1041.
12. Nakamura T, Nakamura S, Arkawa T. et al.: Obstruction of the inferior vena cava in the hepatic portion and the hepatic vein. Angiology 1968; 19: 479-500.
13. Petersen O, Tygstrup N and Winkler K: Inferior vena caval obstruction in hepatic cirrhosis. Acta. Radiol 1961; 55: 97.
14. Thran J H: Inaug. Diss. Kiel, 1899. Cited by Hanock, K.W. J. Obstet. Gynaecol. Br. Emp 1957; 64: 715.
15. Balton C H, Hampton J R, Mitchell J R A: Effect on oral contraceptive agents on platelets and plasma-phospholipids. Lancet 1968; 1: 1336-1341.

16. Aldercreutz H: Hepatic metabolism of estrogens in health and disease. New Engl. J. Med 1974; 290: 1081-1083.
17. Brakman P, Albrechtsen O K, Astrup T: Blood coagulation, fibrinolysis and contraceptive hormones. JAMA 1967; 199: 69-74.
18. Poller L: Progesterone and contraceptives and blood coagulation. Br. Med J 1969; 1: 554-556.
19. Rosenberg M: The link between norethynodrel and thromboembolism. Am. J. Obstet. Gynaecol 1964; 90: 747-752.
20. McIntyre N, Phillips M J, Voigt M J: Two cases of thromboembolic disease associated with oral contraceptives. Br. Med. J 1962; 2: 1029-1031.
21. Risk of thromboembolic disease in women taking oral contraceptives. A preliminary communication to the Medical Research Council by a subcommittee (Lord Platt, Chairman). Br. Med J 1967; 2: 355.
22. Baum J K, Holtz F, Bookstein J J and Klein E W: Possible association between benign hepatomas and oral contraceptives. Lancet 1973; 2: 926.
23. Klatskin G: Hepatic tumours: possible relationship to use of oral contraceptive. Gastroenterology 1977; 73: 386-394.
24. Edmondson H A, Henderson B and Benton B: Liver cell adenomas associated with use of oral contraceptives. New Engl. J Med 1976; 294: 470.
25. Rook J B, Ory H W, Ishark K G, Stranos L T, Greenspan J R, Hill A P, Tyler C W: Epidemiology of Hepatocellular Adenoma. J. Am. Med. Assoc 1979; 242: 644-648.
26. Ameriks J A, Thompson N W, Frey C F, Appelman H D and Walter J F: Hepatic cell adenomas, spontaneous liver cell rupture and oral contraceptives. Arch. Surg 1975; 110: 548.
27. Sherlock S: Hepatic adenomas and oral contraceptives. Gut 1975; 16: 753.
28. Editorial: Liver Tumours and Steroid Hormones. Lancet 1973; 2: 1481.
29. Matt R A, Dalton J C, Johnson R E, Gurewich V: Side-to-side portacaval shunt versus non-surgical treatment of Budd-Chiari syndrome. Am.J. Surg 1978; 136: 1387-1389.
30. Cameron J L, Maddrey W C: Masoatrial shunt: A new treatment for the Budd-Chiari syndrome. Ann. Surg 1978; 187: 402-406.
31. Chan K C, Detmer D E: Proper management of hepatic adenoma associated with oral contraceptives. Surg. Gynaecol. and Obstet 1977; 144: 703-706.