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Pre-eclampsia presenting with deep jaundice

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SUMMARY Pre-eclampsia complicated by deep jaundice occurred in a previously healthy primigravida. The main aetiological factor was disseminated intravascular coagulation; this caused both haemolysis and liver cell necrosis. Liver biopsy showed fibrin thrombi in the capillaries with microhaemorrhages and loss of periportal liver cells. The jaundice was attributed to both haemolytic and hepatocellular processes. Organs other than the liver were relatively unaffected.

Jaundice is rare in eclampsia and usually complicates only the very severe or fatal case; even then plasma bilirubin rarely exceeds 100 μmol/l (5·8 mg/100 ml). It has been attributed to a microangiopathic anaemia secondary to disseminated intravascular coagulation, the mechanism being haemolytic due to trauma of the red cells against the intravascular fibrin and damaged vascular endothelium. Hepatocellular jaundice has been discounted (Antia *et al.*, 1958; Sheehan, 1961; Fletcher, 1971). This case report describes a patient who developed deep jaundice and a high serum aspartate transaminase level in association with relatively mild pre-eclampsia. The mechanism of the jaundice is thought to have been partly haemolytic, but in view of the fibrin thrombi in the hepatic capillaries and the liver cell necrosis a hepatocellular element is also implicated.

Case report

In July 1975 a 29-year-old primigravid Caucasian housewife was admitted to hospital when 37 weeks pregnant because of sudden onset of severe epigastric pain and vomiting. The pregnancy had previously been uneventful without oedema, hypertension or proteinuria. Blood pressure was 140/95 mmHg, the epigastrium was tender, there was moderate proteinuria, and the uterine size was compatible with her dates. A regular fetal heart was heard. The pain settled with intramuscular pethidine. Six hours later spontaneous uterine contractions started and the fetal heart was inaudible. She became jaundiced. Artificial rupture of membranes was performed and 15 hours later a stillborn male infant was delivered. There was no evidence of abruptio placentae but birth was complicated by a postpartum haemorrhage of about 3 litres. She was transferred to the Royal Free Hospital.

On arrival she was distressed but orientated. She was deeply jaundiced with a mild foetor hepaticus but had no evidence of chronic liver disease. Blood pressure was 130/100 mmHg. The liver was impalpable but by percussion was normal in size. A firm uterus was enlarged to the umbilicus. There was moderate proteinuria. The provisional diagnosis was mild pre-eclampsia with jaundice due either to acute fatty liver of pregnancy or to viral hepatitis.

INVESTIGATIONS ON ADMISSION

Haemoglobin 14·4 g/dl; white cell count 14·4 $\times$ 10^9/l with 84% polymorph neutrophils; platelets 40 $\times$ 10^9/l; the blood film was normal except for very occasional fragmented red cells; prothrombin ratio 1·5; plasma fibrinogen 1·5 g/l (150 mg/100 ml); blood urea 12·3 mmol/l (74 mg/100 ml); plasma potassium 5·0 mmol/l (5·0 mEq/l); plasma sodium 138 mmol/l (138 mEq/l); plasma osmolarity 282 mmol/l (282 mosm/kg); urinary potassium 18 mmol/l (18 mEq/l); urinary sodium 7 mmol/l (7 mEq/l); urinary osmolarity 142 mmol/l (142 mosm/kg); total bilirubin 336 μmol/l (19 mg/100 ml) (conjugated fraction 154 μmol/l (9·0 mg/100 ml)); aspartate transaminase 305 IU/l (normal range 4-15); alkaline phosphatase 36 King Armstrong units/dl (within normal range for last trimester of pregnancy); hepatitis B surface antigen negative; electroencephalogram 7 cycles/s (normal 9-12); liver scan normal.

Next day the prothrombin time had returned to normal after intramuscular vitamin K_1 and the platelet count had risen to 80 $\times$ 10^9/l. Needle liver biopsy showed the main abnormality to be fibrin thrombi in the capillaries of some of the portal tracts and periportal sinusoids, associated with micro-

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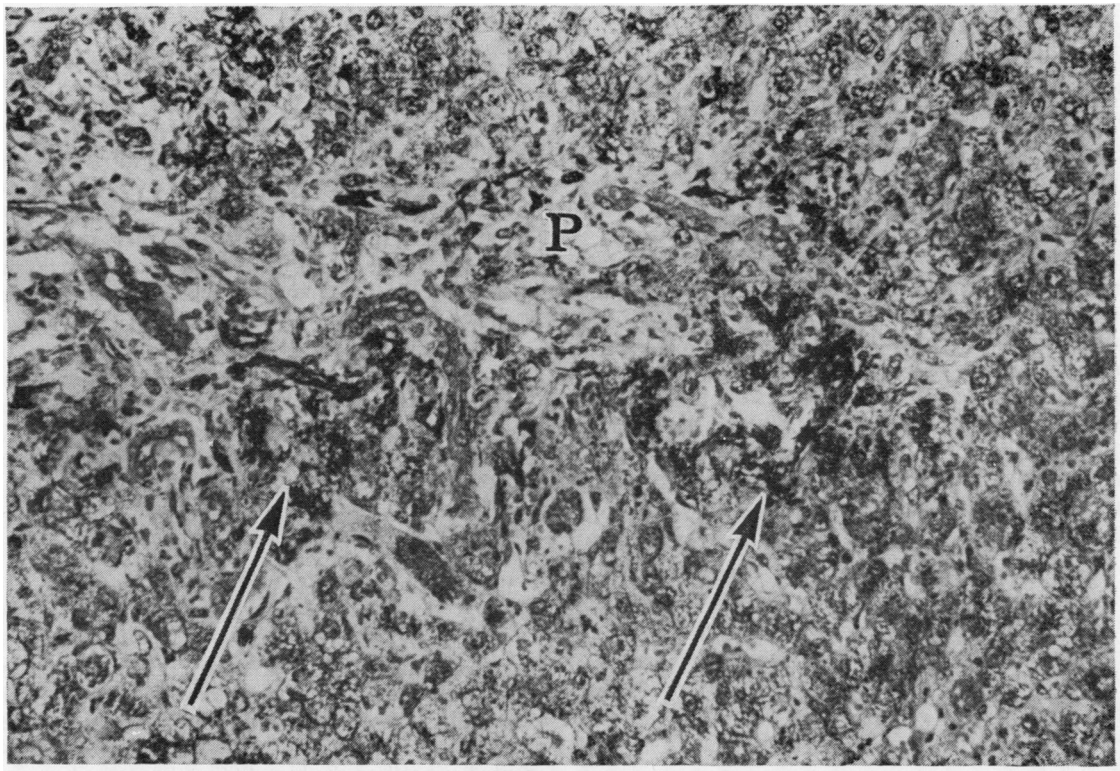

Fig. 1 *The needle liver biopsy section shows a portal tract (P) from which deposits of darkly stained fibrin (arrows) extend into the lobules. The fibrin is partly extravascular and there is liver cell necrosis. Phosphotungstic acid-haematoxylin* × *285.*

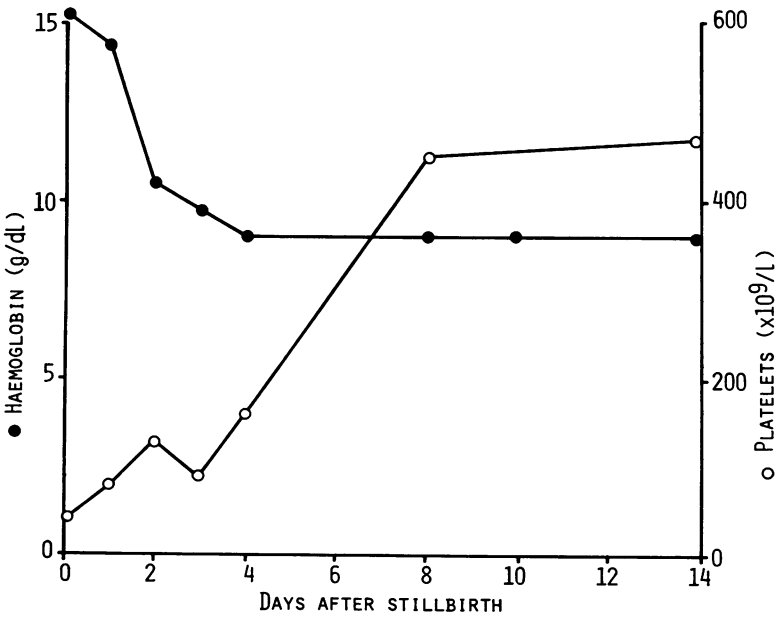

Fig. 2 *Haemoglobin concentration and platelet count.*

haemorrhages, neutrophil leucocytes, and loss of periportal liver cells (Fig. 1). Centrizonal liver cells were swollen and there were small bile thrombi in undilated bile canaliculi. The changes were not those of acute fatty liver of pregnancy or of viral hepatitis and a diagnosis of pre-eclampsia with disseminated intravascular coagulation was made. The bile thrombi were thought to be consistent with acute haemolysis.

She was treated with intravenous fluids, a low salt and a low protein diet, oral neomycin, and intramuscular vitamin K_1 and gradually improved. On the fourth day her haemoglobin had fallen to 9·0 g/dl (Fig. 2) and she subsequently developed a maximum reticulocytosis of 9%. The platelet count (Fig. 2) and white cells had become normal within eight days. In 10 days the serum bilirubin and aspartate transaminase had returned to normal (Fig. 3). The blood urea rose to 20 mmol/l (120 mg/100 ml) and the creatinine clearance fell to 9·2 ml/minute; both then improved (Fig. 4). The urinary sodium-potassium ratio deteriorated to 1:10 and the plasma renin activity nine days after delivery was 11·0 ng/ml/hour (normal range 0·2-1·5). A renal biopsy done 13 days postpartum showed some interstitial oedema as the only abnormality; the capillary lumina were patent without fibrin thrombi.

She was discharged home 16 days after admission. Three months later she felt well; the haemoglobin was 11·5 g/dl and renal and hepatic function tests were normal.

Discussion

This patient had pre-eclampsia with an elevated blood pressure and proteinuria but no clinically detectable fluid retention. Acute epigastric pain, possibly due to liver capsule stretching, is recognised as a symptom of pre-eclampsia. Plasma fibrinogen rises throughout pregnancy to a mean of 550 mg/dl at birth (Gillman *et al.*, 1959). A plasma fibrinogen of 150 mg/dl immediately after delivery in association with a prolonged prothrombin time, thrombocytopenia, and fibrin thrombi in the hepatic capillaries and sinusoids confirms disseminated intravascular coagulation. The high serum total bilirubin, the bile thrombi on liver biopsy, and the occasional fragmented red cell on the blood films show that haemo-

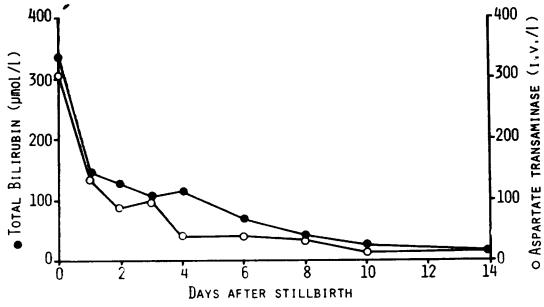

Fig. 3 *Plasma total bilirubin and aspartate transaminase. Conversion SI to traditional units—Total bilirubin: 1 μmol/l ≈ 0·06 mg/100 ml.*

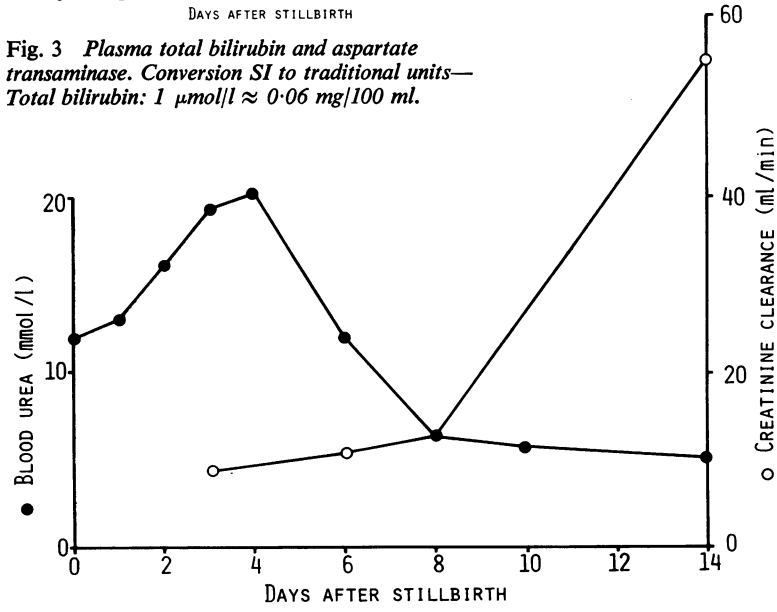

Fig. 4 *Blood urea and creatinine clearance. Conversion SI to traditional units—Blood urea: 1 mmol/l ≈ 6 mg/100 ml.*

lysis, as well as the postpartum haemorrhage, contributed to the fall in haemoglobin. The presence of superadded hepatocellular dysfunction is shown by the high serum aspartate transaminase, the very high serum unconjugated bilirubin fraction, and the capillary thrombi with liver cell necrosis on liver biopsy. It is concluded that haemolysis led to the rapid rise in serum total bilirubin and that clearance was slow because of poor liver cell function.

Raised plasma renins are reported throughout pregnancy (Brown *et al.*, 1963) and are associated with raised angiotensin levels (Massani, 1967). It has been suggested that renin and an increased vascular reactivity secondary to sodium retention may mediate the ill-effects of pre-eclampsia by causing generalised arterial vasoconstriction (Page, 1972). In view of the reversed urinary sodium:potassium ratio immediately after delivery and the very high renin on the ninth day, it is probable that the plasma renin was high at the time of delivery. A raised renin could have contributed to liver cell necrosis by causing hepatic artery vasoconstriction.

The evidence for fibrin deposits in the capillaries of other organs is incomplete. The patient had no fits and the transient electroencephalogram slowing may have been due to hepatic causes. Fibrin deposits in the glomerular capillaries are well described in pre-eclampsia and eclampsia (Vassalli *et al.*, 1963); if they were ever present in this patient they had resolved by the time of renal biopsy. Heparin has been advocated to prevent permanent renal damage for the disseminated intravascular coagulation of pre-eclampsia (Brain *et al.*, 1967); it was not used in this patient because of her spontaneous improvement. The Birmingham Eclampsia Study Group (1971) reported abnormal lung scans in both eclampsia and pre-eclampsia in association with platelet and coagulation factor consumption: this patient showed no clinical, chest *x*-ray or electrocardiographic changes of pulmonary involvement but lung scanning was not done.

We conclude that on rare occasions pre-eclampsia may be associated with deep jaundice. In this patient both haemolytic and hepatocellular mechanisms contributed to the jaundice. It is usual for such deep jaundice to be associated with fits, severe renal involvement, and a poor prognosis. The particular predilection for the liver in this patient and the relative sparing of other organs are atypical.

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