

Oesophageal variceal bleeding in Felty's syndrome associated with nodular regenerative hyperplasia

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SUMMARY Four patients with Felty's syndrome developed massive upper gastrointestinal bleeding due to oesophageal varices. The underlying hepatic pathology in all 4 was nodular regenerative hyperplasia. This appears to be a difficult histological diagnosis to make, having been initially reported as normal on percutaneous biopsy or as fibrosis or cirrhosis on wedge biopsy. This series brings the total number of cases reported in the English literature of this association to 12, suggesting a definite symptom complex. The portal hypertension seems to be due to a combination of increased splenic blood flow and postsinusoidal resistance. The clinical importance of this syndrome is that the appropriate therapy for bleeding oesophageal varices appears to be shunt procedure such as a splenorenal shunt with splenectomy, which should be well tolerated.

In the past few years increasing interest has been shown in the hepatic abnormalities in Felty's syndrome. Abnormal liver function tests were found in 8 of 12 consecutive patients with this syndrome, 4 of whom had lymphocytic infiltration of sinusoids and portal tracts and 1 macronodular cirrhosis (Blendis *et al.*, 1970a). There have since been reports of associated portal fibrosis (Barnes *et al.*, 1971), and cirrhosis (Ritland, 1973) in patients with Felty's syndrome. Recently, 5 patients with Felty's syndrome were described who had nodular regenerative hyperplasia of the liver (Blendis *et al.*, 1974).

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One of these died from massive haemorrhage from oesophageal varices.

We have collected 4 cases of Felty's syndrome with oesophageal variceal bleeding. 3 of the patients have been reported previously, 2 with incorrect liver diagnoses, showing the changes of nodular regenerative hyperplasia.

Case reports

CLINICAL FEATURES

Details of the haematological and rheumatological investigations on the 4 patients are given in Table 1, which illustrates the pancytopenia, the nodular seropositive form of rheumatoid arthritis, and the high incidence of multiple system involvement. The

Table 1 Clinical data of 4 patients with rheumatoid arthritis and Felty's syndrome

Case no.	Age (years)	Sex	Duration of arthritis (years)	Nodules	SCAT (Latex)	ESR (mm/h)	Complication, multisystem involvement	Hb (g/dl)	WBC ($\times 10^9/l$)	Neutophils ($\times 10^9/l$)	Platelets ($\times 10^9/l$)
1	74	F	20	+	256 (+)	132	Rheumatoid lung; renal amyloidosis	7.1	1.8	0.54	80
2	54	F	9	+	256 (+)	68	Sjögren's syndrome; rheumatoid lung	10.1	2.2	0.79	61
3	72	M	6	+	(-)	25	Transient renal tubular acidosis	11.5	2.1	1.36	74
4	65	F	21	+	(+)	17	—	11.1	1.8	0.83	50

hepatological features are given in Table 2. None of the 4 patients had clinical stigmata of chronic liver disease. 3 patients had hepatomegaly in addition to splenomegaly but little alteration of liver function. 3 of the 4 had significant portal hypertension on measurement of portal pressure.

CASE 1*

A 74-year-old woman was known to have had rheumatoid arthritis for at least 20 years. Proteinuria due to renal amyloidosis had been present for 7 years. In 1971 she was admitted as an emergency after a haematemesis. Laparotomy showed large tortuous veins in the falciform ligament. The surface of the liver appeared normal. After gastrostomy large oesophageal varices were seen. A bleeding point was identified and under-run, but the patient continued to bleed, and since her clinical condition precluded further surgery a Sengstaken tube was passed. This controlled the bleeding for a further 3 days, but she then had a massive haematemesis when the balloon was deflated, and died.

CASE 2†

A 54-year-old woman had had seropositive erosive rheumatoid arthritis for 9 years. In 1965 she had an episode of erythema, pleuritic pain, and developed a pleural effusion which cleared spontaneously. The following year she was found to have hepatosplenomegaly. Investigation shows a pancytopenia and slightly abnormal liver function tests but all other tests, including a liver biopsy, were normal. Persistent inflammatory polyarthropathy and fever, together with the previous findings, led to a trial of cyclophosphamide therapy. 2 years later she was admitted with a massive haematemesis and required transfusion with 20 pints of blood. At laparotomy the portal pressure was found to be markedly raised (Table 2). Splenectomy and splenorenal anastomosis

were performed. The liver was not cirrhotic in appearance and histological examination subsequently showed nodular regenerative hyperplasia. (Fig. 1).

CASE 3

A 72-year-old man had had rheumatoid arthritis for 6 years and Felty's syndrome for 3 years. In June 1975, he presented with sudden onset of haematemesis and melaena shown to be due to oesophageal varices on oesophagoscopy. On examination, in addition to rheumatoid changes, he had a palpable spleen but the liver was not enlarged. Liver scan showed no evidence of cirrhosis. Laparoscopy was performed, a normal liver was seen and a biopsy taken. After further haematemesis, he developed a transient mild hyperchloraemia acidosis. Serum bicarbonate 20 mmol/l, chloride 112 mmol/l, sodium 141 mmol/l, potassium 3.2 mmol/l; an inappropriately alkaline urine of pH 8.3 to 8.5 associated with increased urinary bicarbonate excretion of 10 and 8 mEq/24 h on two successive days (normal 0-5). Before further studies could be performed, the acidosis disappeared associated with a return of urinary pH to 6. He was discharged from hospital well, only to be admitted to another hospital with a further haematemesis. A portacaval shunt was performed but he died in the postoperative period.

CASE 4‡

A woman, aged 65 years, began to complain of joint symptoms 20 years previously. She was treated with phenylbutazone for 2 years in doses between 600 and 200 mg daily, and was admitted with a history of anaemia and chronic gastrointestinal bleeding. Examination showed hepatosplenomegaly, and pancytopenia attributed at the time to phenylbutazone. 3 years later she had a haematemesis. Splenic venography showed oesophageal varices and

*First reported by Blendis *et al.* (1974).

†First reported by Barnes *et al.* (1971).

‡First reported by Ritland (1973).

Table 2 *Clinical and biochemical findings relevant to the liver involvement in Felty's syndrome*

Case no.	Hepatomegaly (cm below costal margin)	Serum bilirubin (mg/100 ml)	Alkaline phosphatase (KAU/100 ml)	BSP % retention 45 min	Varices	Spleen wt (g)	Portal pressure (mmHg)	Initial liver biopsy	Drugs
1	8	1.0	6.0	<5	++	650	27	Nodular regeneration hyperplasia	Salicylates
2	5	0.1	16.3	<5	++		28	Portal fibrosis	Corticosteroids; cyclophosphamide
3	2	0.7	27	—	++		—	Nodular regeneration hyperplasia	Indomethacin
4	5	0.8	19	8	++	450	31	Cirrhosis	Phenylbutazone
Normal range		1.0	<13	<5		120-300	4-12		

BSP = bromsulphalein. Conversion: Traditional units to SI—Bilirubin: 1 mg/100 ml \approx 17.1 μ mol/l.

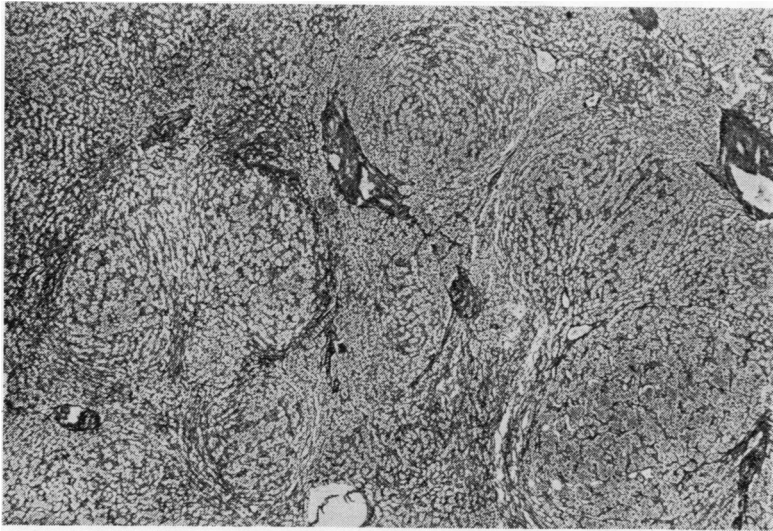


Fig. 1 Case 2. Photomicrograph showing an apparently marked liver nodularity, due to condensation of reticulin fibres but with no increase in collagen. Reticulin stain $\times 25$.

the intrasplenic pressure was raised (Table 2). Splenectomy and splenorenal anastomosis were performed. Liver biopsy was initially interpreted as cirrhosis (Ritland, 1973) (Fig. 2). Postoperatively, the leucocyte count rose to $9.0 \times 10^9/l$ and the platelets to $165 \times 10^9/l$. 4 years later there has been no deterioration in liver function and no further bleeding.

Discussion

Nodular regenerative hyperplasia (NRH) as originally described (Steiner, 1959) is a difficult histological diagnosis to make as confirmed in the present report

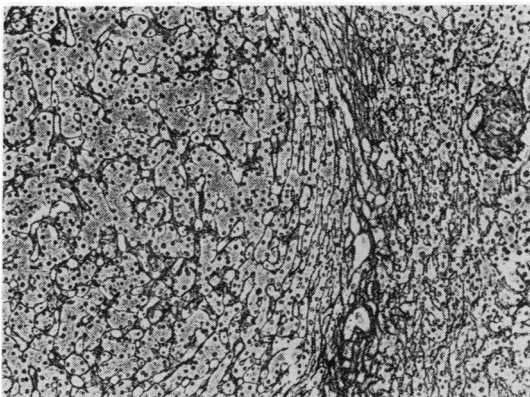


Fig. 2 Case 4. High power photomicrograph of a 'nodule' showing retention of architecture with compression and realignment of cells at periphery of nodule. Reticulin stain $\times 55$.

in which 2 of the 4 cases were originally diagnosed as portal fibrosis (Barnes *et al.*, 1971) or cirrhosis (Ritland, 1973). The surface of the liver may appear normal, finely granular or nodular, and on histology the 'nodules' are not outlined by true fibrosis giving a negative stain for collagen with Mallory's trichrom. Another important feature is the reversal pattern of the hepatic vein radicle and the lobule, so that the vein may be found in the periphery of the nodule within the circular compressed columns of hepatocytes. This histological pattern is usually not apparent on the small amount of tissue produced by a percutaneous liver biopsy when the liver may appear normal. The aetiology of NRH remains obscure.

Recent publications have drawn attention to the association of a related noncirrhotic nodular condition of the liver, focal nodular hyperplasia, with oral contraceptives (Stauffer *et al.*, 1975). However, all 4 patients in this series were on different drugs.

The association of NRH with Felty's syndrome is becoming increasingly recognised. In addition to the 3 new cases in this report, we have heard of 2 further patients with this association (Knowles *et al.*, 1975; Reisman *et al.*, 1977), bringing the total number of cases in the English literature up to 12 out of approximately 26 cases of NRH so far reported (Blendis, 1978). 12 of the remaining patients had congestive cardiac failure, 1 had subacute bacterial endocarditis (Knowles *et al.*, 1975), and 1 had rheumatoid arthritis with no evidence of Felty's syndrome (Harris *et al.*, 1974). This last patient presented with ascites, developed encephalopathy after abdominal paracentesis, and at necropsy the liver was small.

She was atypical in many respects from the patients described in this report, none of whom developed encephalopathy even after massive gastrointestinal bleeding.

Thus the question as to whether Felty's syndrome and NRH is a definite syndrome complex will depend on whether Felty's is a specific syndrome complex within the spectrum of rheumatoid arthritis. Although this question remains controversial, a recent report of the occurrence of NRH in 3 members of one family with Felty's syndrome (Blendis *et al.*, 1976) supports the suggestion that it is a definite entity. However, the association of Felty's syndrome and NRH cannot explain the splenomegaly and 'hyper-splenism' in most patients with this syndrome. For example, only one of 6 Felty's patients coming to necropsy had NRH on histological examination of the liver (Barnes *et al.*, 1971).

The mechanism of portal hypertension in this condition has previously been shown to be due partly to increased splenic blood flow (Blendis *et al.*, 1974), which particularly in noncirrhotic patients results in an increase in portal blood flow (Blendis *et al.*, 1970b), and partly to an unexplained post-sinusoidal resistance. The latter may be due to distortion and compression of the intrahepatic venous radicles or to microthrombi, as recently shown using corrosive case techniques in patients with idiopathic portal hypertension (Boyer *et al.*, 1974).

The importance of making the diagnosis of NRH in Felty's patients with oesophageal variceal bleeding is its indication for correct surgical treatment. In the light of our present knowledge, this should optimally be a splenectomy with a shunt procedure or perhaps, in the elderly and severely arthritic patient, a splenectomy alone.

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