Papers and Originals

Liver in Felty's Syndrome

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British Medical Journal, 1970, 1, 131-135

Summary: Liver function and histology, together with the haematological changes, were investigated in 12 patients with Felty's syndrome. Six of them were anaemic. The red cell mass was either normal or increased, and the anaemia was due to a considerable increase in the plasma volume. Two patients had increased haemolysis associated with red cell sequestration by the enlarged spleens.

In eight patients liver function tests were abnormal, while in five the liver histology showed lymphocytic infiltration of the sinusoids and portal tracts together with portal tract fibrosis. One of these was later found to have a macronodular cirrhosis. In another there were apparent nodules without a true cirrhosis, and this appearance was also seen in two other patients with Felty's syndrome in whom histology was available. An increased blood flow through the spleen was found in the two patients examined.

Introduction

Chauffard and Ramond (1896) described splenomegaly in rheumatoid arthritis, and the occurrence of neutropenia in such patients was first reported by Felty (1924) in a description of five cases. Hanrahan and Miller (1932) described a patient as suffering from "Felty's syndrome," and this eponym has survived until now. Since then isolated cases have been reported of patients with Felty's syndrome who were found at operation or at necropsy to have abnormal liver histology (Hutt, Richardson, and Staffurth, 1951; Ellman, Cudkowicz, and Elwood, 1955), consisting in the main of lymphocytic infiltration and fibrosis of the portal tracts.

We here describe studies of liver function and histology in 12 patients with Felty's syndrome seen during the past three years, together with two other patients in whom liver histology was available. The haematological effects of the enlarged spleen, and in two patients the changes in splanchnic haemodynamics, were also examined.

Material and Methods

All the patients had classical or definite rheumatoid arthritis according to the criteria of the American Rheumatism Association (1959), and the main clinical and laboratory findings are shown in Tables I and II. Five were treated by splenectomy. Routine liver function tests were carried out and

bromsulphalein retention at 45 minutes was determined after an intravenous injection of 5 mg./kg. body weight; the initial concentration was obtained from extrapolation of the values at 5 to 15 minutes back to zero on semilog paper. Red cell mass and plasma volume were estimated with ⁵¹Cr-labelled red cells and ¹²⁵I human serum albumin. After injection of the radioactive marker serial venous samples were taken at regular intervals for 60 minutes via a polyethylene catheter in an antecubital vein. Radioactivity over the spleen was monitored simultaneously by an external scintillation counter. In normal subjects activity over the spleen rises sharply to a plateau within one or two minutes of the injection of labelled red cells, indicating their complete mixing within the spleen. In patients with splenomegaly the splenic activity may rise more slowly and reach a plateau only after 10 to 20 minutes, owing to a second and slower-mixing compartment of red cells within the enlarged spleen (Motulsky, Casserl, Giblett, Brown, and Finch, 1958). The weight of the spleen was obtained either at splenectomy or from the area of the spleen on an anteroposterior abdominal radiograph according to the method of Blendis, Williams, and Kreel (1969).

In one patient in whom oesophageal varices were present on barium swallow and in another with pronounced splenomegaly the spleen blood flow was measured, expressed as ml./100g. of spleen tissue. Radioxenon (dissolved in saline) was injected into the splenic artery via a catheter inserted by percutaneous femoral artery puncture and the clearance curve of the isotope determined by surface counting (Williams, Condon, Williams, Blendis, and Kreel, 1968). From this measurement and the weight of the spleen the total spleen blood flow was calculated. After the flow measurements a selective coeliac arteriogram was performed, including a late venous filling phase to opacify any collateral vessels present. Hepatic blood flow was estimated from the hepatic extraction of a constant infusion of indocyanine green; the wedged and free hepatic vein pressures were also recorded and the postsinusoidal resistance was calculated (Blendis, Banks, Ramboer, and Williams, 1970).

Results

Eight of the patients were women, giving a female/male ratio of 2:1. Three were closely related—a mother, son, and daughter (Cases 3, 2, and 9 respectively). The mean age at onset of rheumatoid arthritis was 44 years, and the mean duration of arthritis before Felty's syndrome was diagnosed was 12 years (range 0-36 years). Three patients had clinical signs of active arthritis (Cases 4, 5, and 7), while the others had apparently quiescent disease, though the sedimentation rates were usually raised. Five patients had hepatomegaly. Splenomegaly or neutropenia was not noted before the onset of joint symptoms.

Five patients were treated by splenectomy. Three operations had been done before the period of this study—for profound neutropenia and splenic infarct; for neutropenia and recurrent skin sepsis; and for abdominal pain, neutropenia, and splenomegaly. Two of these patients had had normal white cell counts four years and five years later, but in the third neu-

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TABLE I.—Clinical Features of Rheumatoid Arthritis

Case No.	Age	Sex	Age at Onset		Sheep Cell Agglutination Test	L.E. Cells	Anti-nuclear Factor	Nodules	E.S.R. (mm./hr.)	Splenectomy	Complications
			Arthritis	Felty's							
1	68	F	28	64	1,024	+	+	0	70	1965	Sjögren's, leg ulcers
2	61	M	54	55	256	0	0	+	129	—	Pleuritis
3	85	F	71	82	1,024	0	—	+	123	—	Sjögren's
4	65	F	40	63	256	—	—	+	87	1968	Raynaud's, pulmonary fibrosis, skin sepsis
5	50	M	38	48	1,024	0	+	+	139	1968	Vasculitis, recurrent paronychia
6	61	M	45	54	1,024	+	+	+	31	—	Leg ulcers, pleuritis
7	31	M	29	30	1,024	0	+	+	25	—	pericarditis
8	49	F	30	39	1,024	+	+	+	118	—	Skin sepsis
9	31	F	42	42	1,024	0	0	0	40	1967	Leg ulcers
10	73	F	49	69	512	0	0	+	128	1964	Leg ulcers
11	75	F	61	73	128	0	0	+	137	—	Leg ulcers
12	74	F	66	66	128	0	0	0	107	—	Rheumatic heart disease, terminal septicaemia
									100		

tropenia and recurrent mild skin sepsis continued. Two patients underwent splenectomy during the period of study—Case 4 for neutropenia and progressive haemodilutional anaemia and Case 5 for neutropenia, progressive haemodilutional anaemia, skin sepsis, and deteriorating general health. One (Case 4) felt that her general health had improved, and 18 months later her haemoglobin and white cell count remained within normal limits. The other (Case 5) died from Gram-negative septicaemia two weeks after operation, at which time his neutrophil count was 20,500/cu. mm. One other patient died (Case 12), eight years after the onset of her disease, from progressive cachexia and a terminal beta-haemolytic streptococcal septicaemia. One patient (Case 11) was given prednisolone because of haemolytic anaemia with improvement, but no other patient was receiving systemic corticosteroid therapy.

All patients had had a neutropenia at some stage of their illness (less than 2,000/cu. mm.), but only two had a platelet count below 100,000/cu. mm., neither of them suffering from purpura. Six patients were anaemic, with haemoglobin concentrations of 7-11 g./100 ml. In four of these the red cell indices were normal. In the other two (Cases 4 and 11) there was increased haemolysis with a reduced $T_{1/2}$ for ^{51}Cr -labelled red cells of 8 and 10 days respectively, compared with the lower limited of normal of 25 days (Dacie and Lewis, 1968). In both patients the curve of radioisotope uptake over the spleen was delayed in reaching a plateau, indicating the presence of a slower-mixing red cell pool within the spleen.

The total red cell mass in the six anaemic patients was either normal or, in one patient (Case 5), increased at 35.8 ml./kg., the normal range being 22-34 ml./kg. In the two patients with increased haemolysis the subtraction of the red cell pool in the spleen from the total left a reduced circulating red cell mass. In five of these patients, including one with haemolysis, the anaemia was due to an increase in the plasma volume from 61.8 to 111.1 ml./kg. (normal range 34 to 48 ml./kg.), this leading to a dilution of the red cell mass. The increase in plasma volume showed a close correlation with the extent of the splenic enlargement.

One patient (Case 5) was observed for two years before undergoing splenectomy, during which time his general health deteriorated, with repeated infections. His spleen enlarged further and he became progressively anaemic, the haemoglobin concentration dropping from 12 to 9.4 g./100 ml. Repeat radioisotope studies showed that the red cell mass remained unchanged at between 2,100 and 2,200 ml., the increasing anaemia being due to a gradual increase in plasma volume from 4,175 to 6,990 ml. (Fig. 1).

Liver Function and Histology

Serum bilirubin levels were not increased, but both the alkaline phosphatase and aspartate transaminase were raised in three patients, and in two others one or the other was in-

creased (Table II). Three of these five patients had an increased bromsulphalein retention at 45 minutes; this was also found in three other patients, in whom the routine liver function tests were normal. All but one of the patients with abnormal liver function had severe long-standing arthritis. The exception (Case 7) had a raised transaminase level and only a one-year history of rheumatoid arthritis. An increase in gammaglobulin concentration was usually present with values of up to 4.3 g./100 ml., but it was impossible to decide whether this was due to the liver or joint disease. Serum

FIG. 1.—Changes in plasma volume and red cell mass over 20 months in Case 5.

albumin (2.2-2.6 g./100 ml.) was low in Cases 1, 5, and 8. There was no relation between the level of any of the protein fractions and the increase in plasma volume.

Liver histology was available either by needle aspiration biopsy or from necropsy material in 8 of the 12 patients. In five patients (Table II) the most striking features found were a diffuse infiltrate of mature lymphocytes within the sinusoids and a variable degree of Kupffer cell prominence (Fig. 2). In two of the four patients (Cases 1 and 9) in whom surgical biopsies were taken at splenectomy and in whom further needle biopsies were performed 18 months and three years later no significant decrease in the sinusoidal infiltration had occurred. Three patients (Cases 1, 6, and 9) had periportal fibrosis and lymphocytic infiltration in addition to the sinusoidal infiltration (Table II). Case 1, whose liver biopsy was fragmented, was later found at splenectomy to have classical

macronodular cirrhosis. This was confirmed on histological examination of a wedge biopsy, which, in addition to fibrosis and regeneration nodules, showed piecemeal necrosis.

Histological examination in one of the five patients (Case 5) in whom wedge biopsies or necropsy material were available showed apparent "nodules" without fibrosis or disruption of

FIG. 2.—Needle biopsy of Case 9 showing infiltration of sinusoids by lymphocytes. (H. & E. x 335.)

lobular architecture. This was due to variation in cellular size, the central areas being composed of large cells compressing peripheral columns of small cells (Fig. 3). In the two additional liver biopsies that were available from previous patients with Felty's syndrome similar apparent "nodule" formation was seen (Fig. 4) and lymphocytic sinusoidal infiltration was present in one.

The patient (Case 1) with a definite cirrhosis had abnormal liver function tests, but in the remainder there was no correlation between liver function and the histological findings. Special staining techniques failed to show amyloid infiltration in any of the sections of liver or spleen obtained.

Haemodynamic Studies

The two patients (Cases 5 and 6) examined had raised intra-splenic pressures of 20 and 15 mm. Hg. respectively. In Case 5 this was associated with oesophageal varices on barium swallow and a considerable collateral circulation was shown by arteriovenography. In both patients the spleen blood flow per

FIG. 3.—Surgical biopsy specimen of Case 5 stained for reticulin to show apparent nodule formation with retention of overall lobular architecture. (Gordon and Sweet. x 43.)

100 g. of tissue was normal or low, but the total spleen blood flow was greatly increased, with values of 712 and 1,060 ml./min. for Cases 5 and 6 respectively, compared with the normal range of 100 to 300 ml./min. (Williams *et al.*, 1968). These were associated with estimated total liver blood flows of 690 and 1,600 ml./min./sq.m., the normal range being 300-800 ml./min./sq.m. (Leevy, Mendehall, Lesko, and Howard, 1962). Thus in Case 5 a considerable part of the increase in blood flow through the spleen was being diverted into the collateral circulation.

A difference of more than 5 mm. Hg between the intra-splenic and wedged hepatic vein pressures has previously been defined as evidence of an increased presinusoidal resistance (Williams, Parsonson, Somers, and Hamilton, 1966). This was present in Case 6 who had large increases in total spleen and liver blood flows. In Case 5 the wedged hepatic vein pressure was 20 mm. Hg, the upper limit of normal being 12 mm. Hg. The calculated postsinusoidal resistance was increased at 800 dynes sec. cm.⁻⁵ (normal less than 400 dynes sec. cm.⁻⁵). These findings may be related to the apparent "nodule" formation which was the main change observed in the hepatic histology; only slight portal tract fibrosis was present. Liver function tests were also abnormal in this patient, with a raised alkaline phosphatase of 35 K.A. units and bromsulphalein retention of 9%. In contrast, in Case 6, in whom the wedged hepatic vein pressure and postsinusoidal resistance were normal, no nodules were present on liver histology though there was dense

FIG. 4.—Higher-power view of reticulin preparation from the surgical biopsy specimen of one of the additional patients showing apparent nodule formation with great variation in width of the liver cell plates. (Gordon and Sweet. x 73.)

fibrosis and lymphocytic infiltration of the portal tracts which may have accounted for the increase in presinusoidal resistance.

Discussion

Forty-five years after the first description of Felty's syndrome argument continues about whether it is a specific entity. The occurrence of three cases in one family of the present series is of interest, since a family history of Felty's syndrome is rare. Most patients with Felty's syndrome have long-standing seropositive nodular rheumatoid arthritis and the sedimentation rate is usually considerably raised. Neutropenia, splenomegaly, and arthralgia are common in systemic lupus erythematosus. The distinction between this disease and Felty's syndrome is made on clinical grounds, for rheumatoid factors are present in many patients with systemic lupus, and positive L.E. cell preparations and anti-nuclear antibodies are found in some patients with uncomplicated rheumatoid arthritis. Rheumatoid nodules, however, are found only in rheumatoid arthritis, and erosive arthritis is rare

TABLE II.—Liver Function and Histology Together with Haematological Changes. (The Presplenectomy Values are Recorded in those Patients Having a Splenectomy)

Case No.	Body Weight (kg.)	Haematology						Spleen Weight (g.)	Liver Function			Histology		
		Hb (g./100ml.)	W.B.C. (/cu. mm.)	Platelets ($\times 10^3$ /cu. mm.)	Red Cell Mass (ml./kg.)	Plasma Volume (ml./kg.)	Packed Cell Volume (%)		Alkaline Phosphatase (u./100ml.)	Aspartate Transaminase (i.u./100ml.)	Bromsulphthalein (% Ret.)	Sinusoids	Portal Tracts	Fibrosis
												Lympho-cytic Infiltrate	Lympho-cytic Infiltrate	
1	62	11.6	600	106	24.2	47.2	38	1,050	20	76	11	+	++	++
2	54	12.4	1,800	200	27.6	52.0	40	400	11	19	—			
3	36	11.9	1,100	120	28.3	60.5	38	300	8	19	—			
4	42	7.2	600	106	24.6	72.3	25	1,230	12	12	—	+	0	0
5	63	9.4	1,700	99	35.8	111.1	27	1,500	35	50	9	0	0	+
6	81	11.0	3,300	200	27.7	61.8	40	1,520	13	6	7	+	++	++
7	73	14.4	3,300	200	34.0	42.5	41	850	5	54	5	0	0	0
8	41	9.6	2,000	200	27.0	67.4	31	380	22	72	1	+	0	+
9	67	11.7	1,700	200	24.7	42.5	43	530	10	19	—	+	+	+
10	48	11.8	1,500	200	26.8	34.7	35	—	10	38	10	0	0	0
11	73	7.0	900	86	25.4	45.1	31	470	8	16	11			
12	39	7.8	1,700	200	27.5	69.5	28	480	22	24	7	++	++	0

in systemic lupus. Only three patients in this series did not have subcutaneous nodules, and two of these had an erosive arthritis. None of the patients had glomerulonephritis or other features of systemic lupus erythematosus.

The occurrence of splenomegaly in rheumatoid arthritis has been put as high as 5 to 10% (Short, Bauer, and Reynolds, 1957). The commonest cause is a non-specific hyperplasia of the spleen resulting in a small increase in size, but it may also be due to amyloidosis (Missen and Taylor, 1956). The incidence of more pronounced splenomegaly with neutropenia is said to be less than 1% (Green and Fromke, 1966). Leucopenia is commonly found in other diseases with splenomegaly the suggested mechanisms being decreased leucocyte production (Welch and Dameshek, 1950), increased destruction by the spleen (Wright, Doan, Bouroncle, and Zollinger, 1951), or the presence of neutrophil antibodies (Calabresi, Edwards, and Schilling, 1959). The mechanism, however, may be similar to that of the thrombocytopenia associated with splenomegaly—namely, pooling of neutrophils in the spleen.

Several factors may be implicated in the anaemia of Felty's syndrome, including those found in uncomplicated rheumatoid arthritis—namely, inadequate iron utilization for haemoglobin synthesis (Weinstein, 1959) and abnormalities of folate metabolism (Gough, McCarthy, Read, Mollin, and Waters, 1964)—as well as iatrogenic causes such as gastrointestinal bleeding from salicylate therapy. In addition, in Felty's syndrome, because of the splenomegaly, there may be increased haemolysis due to sequestration of red cells within the spleen (Hume, Dagg, Fraser, and Goldberg, 1964), as found in two of our patients. The present findings also show the importance of haemodilution, due to a large increase in plasma volume with a normal red cell mass. A similar haemodilutional anaemia is seen in other diseases with splenomegaly (Bowdler, 1963; Weinstein, 1964). The increase in plasma volume is proportional to the increase in spleen size, and there seems to be a generalized increase in vascular capacity, though the exact mechanism is uncertain (Blendis, Ramboer, and Williams, 1970). Beneficial effects of splenectomy will be a fall in plasma volume towards normal and a rise in haemoglobin concentration.

Changes in liver function and histology have been reported in patients with apparently uncomplicated rheumatoid arthritis. Lefkowitz and Farrow (1955), however, found that the abnormality of liver function tests was related to the severity of the rheumatoid disease and that most changes could be explained by the alteration in the plasma globulins. Nevertheless, 2 of their 15 patients had abnormal liver histology on biopsy material, with periportal fibrosis and chronic inflammatory cell infiltration. In contrast Movitt and Davis (1953) found only slight to moderate fatty infiltration in 4 out of 17 patients with rheumatoid arthritis examined by liver biopsy. Whether the histological abnormalities found in the present patients are distinct to Felty's syndrome or an

exaggeration of a process common to rheumatoid disease cannot be decided on available evidence. The main changes observed were lymphocytic infiltration of both sinusoids and portal tracts together with portal tract fibrosis. The apparent "nodule" formation which was also observed and the associated granularity of the surface of the liver in one patient have not received previous mention, though they may have accounted for the macroscopic appearances of the liver in one of the cases of Felty's syndrome reported by Ellman *et al.* (1955).

The cause of these histological changes is unknown. Similar lymphocytic infiltration of the sinusoids is described in idiopathic tropical splenomegaly (Marsden *et al.*, 1965; Pitney, Pryor, and Smith, 1968). Enlargement of the spleen from whatever cause is usually accompanied by considerable increases in spleen and liver blood flow (Blendis *et al.*, 1970). It is of interest, therefore, that experimentally increasing liver blood flow in dogs by arterializing the portal vein leads to portal fibrosis and lymphocytic cell infiltration (Siderys, Tyson, Herendeen, and Glover, 1964).

One of the two patients in whom haemodynamic measurements were made had an increased hepatic presinusoidal resistance in association with greatly increased liver and spleen blood flow. This may also be found in other "big spleen" syndromes occurring in the tropics and in this country. Occasionally, as in the other patient, an increased postsinusoidal obstruction is found (Blendis *et al.*, 1970). This is usually thought to be characteristic of cirrhosis, but it is possible that in blood dyscrasia and in the present case with Felty's syndrome the differential regeneration and apparent "nodule" formation may have acted in the same way, though there were no true regeneration nodules.

Fortunately, however, the portal hypertension in Felty's syndrome is rarely severe enough to cause the formation of oesophageal varices, but further studies of the relation between splenomegaly, increased spleen blood flow, and the development of histological abnormalities would be of value.

We thank the physicians of King's College Hospital Group for referring patients and Dr. M. S. Kataria for his helpful co-operation. We are grateful to the King's College Hospital Research Fund and the Abbeydale Trust for financial assistance.

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Renal Effects of Calcitonin

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British Medical Journal, 1970, 1, 135-137

Summary: Porcine calcitonin in a slow-release gelatin vehicle was given by intramuscular injection to 10 patients—four with primary hyperparathyroidism, four with Paget's disease, and two with carcinoma of the breast and hypercalcaemia. All cases showed a fall in serum calcium with an immediate rise in urine calcium. All except three patients with primary hyperparathyroidism showed a fall in serum phosphorus, but an immediate rise in urine phosphorus occurred in all cases. Urine hydroxyproline output fell in three patients with severe Paget's disease. Urine sodium rose in all cases, but the effects on potassium, magnesium, water, and pH were not appreciably different from results obtained in four control subjects who were given the gelatin vehicle alone.

The data suggest that calcitonin caused a decrease in the tubular resorption of calcium and phosphorus. The hypocalcaemic effect appeared to be due to a decrease in bone resorption in the patients with Paget's disease but in the remaining cases could be accounted for in part or entirely by the rise in urine calcium.

Introduction

Observation in rats has established that calcitonin lowers serum calcium by inhibition of bone resorption (Milhaud *et al.*, 1965; Robinson *et al.*, 1967; Wallach *et al.*, 1967), and this effect has also been demonstrated in tissue culture (Friedman and Raisz, 1965; Aliapoulis *et al.*, 1966; Nisbet and Nordin, 1968). Cooper *et al.* (1967) and Copp and Kuczerpa (1968)

showed that the hypocalcaemic action is greatest in young animals with a rapid bone turnover. The effect of calcitonin on urinary hydroxyproline in Paget's disease in man (Bijvoet *et al.*, 1968) has confirmed the inhibitory action of calcitonin on bone resorption when the resorption rate is high.

Some workers have also shown that calcitonin has a phosphaturic action on the kidney (Kenny and Heiskell, 1965; Milhaud *et al.*, 1966; Robinson *et al.*, 1966), and others have noted that it also tends to increase the calcium output in the urine (Ardaillou *et al.*, 1967; Singer *et al.*, 1968). The present paper reports the results of acute calcitonin studies in 10 patients where particular attention was paid to the renal action of the hormone.

Patients and Methods

The 10 patients comprised four with primary hyperparathyroidism without evidence of bone disease (one man and three women), four with Paget's disease (three men and one woman), and two with hypercalcaemia associated with carcinoma of the breast and bone secondaries. The relevant initial data are shown in Table I. It will be noted that six of the cases had hypercalcaemia. One patient (Case 1) had very mild Paget's disease, only one vertebra being involved.

After an overnight fast the subjects were given 1 litre of

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TABLE I.—Clinical Data and Initial Serum and Urine Values

Case No.	Age and Sex	Weight (Kg.)	Diagnosis	Serum			Urine				
				Alkaline Phosphatase (K.A. units/100 ml.)	Calcium (mg/100 ml.)	Phosphorus (mg/100 ml.)	Creatinine Clearance (ml./min.)	CaE (mg./100 ml. G.F.)	PE (mg./100 ml. G.F.)	Sodium (mEq/100 ml. G.F.)	Hydroxyproline (μg/min.)
Normal range				2-12	9.0-10.6	2.5-4.5	80-120	0.03-0.15	*	0.043-0.236	5-25
1	53 M	65	Paget's disease	14	9.70	3.35	103	0.12	0.19	0.007	11
2	59 M	91	"	260	9.05	3.15	86	0.03	0.33	0.043	333
3	59 M	62	"	188	9.95	3.65	104	0.05	0.34	0.120	88
4	62 F	60	"	160	9.65	3.65	93	0.08	0.43	0.148	173
5	55 M	53	Hyperparathyroidism	8	11.45	2.50	75	0.26	0.64	0.083	22
6	67 F	61	"	8	11.60	2.30	56	0.23	0.62	0.097	17
7	47 F	85	"	10	12.85	1.50	100	0.23	1.25	0.099	15
8	54 F	62	"	14	13.20	2.15	78	0.45	0.85	0.076	20
9	61 F	54	Carcinoma of breast	24	12.40	3.65	41	0.36	0.59	0.043	17
10	49 F	68	"	49	16.20	4.80	18	1.18	2.39	0.348	21

* Determined by serum phosphorus