

Sinusoidal portal hypertension in hepatic amyloidosis

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Abstract

Hepatic venous catheterisation and transvenous liver biopsy were performed in five patients with hepatic amyloidosis. In three patients, hepatic venous pressures were normal and histological examination of the liver biopsy specimen showed discrete and sparse perisinusoidal amyloid deposits. In the other two, however, the gradient between wedged and free hepatic venous pressures was increased (12 and 16 mmHg; normal 1-4 mmHg) and amyloid deposits were abundant and diffuse in the Disse's space. This study shows that portal hypertension in patients with hepatic amyloidosis is of the sinusoidal type and is related to the reduction of vascular space of hepatic sinusoids by massive perisinusoidal amyloid deposits. Furthermore, portal hypertension is associated with a poor prognosis in patients with hepatic amyloidosis.

In patients with hepatic amyloidosis, hepatomegaly and moderate abnormalities of liver function tests are the most frequent findings.¹⁻⁴ Portal hypertension is an uncommon complication of this disorder and its mechanism remains unclear. In this study, we report the results of hepatic vein pressure measurements in five patients with hepatic amyloidosis, two of whom had portal hypertension. In addition, we evaluated the value of the hepatic venous pressure gradient to the degree of amyloidosis infiltration into the liver.

Case reports

PATIENT 1

A 62 year old woman was admitted to hospital on 15 May 1987 because of jaundice, weight loss, and fatigue of eight months' duration. Clinical examination showed jaundice, a firm hepatomegaly measuring 16 cm on the right mid-clavicular line, two spider angiomas, and moderate ascites. There was no splenomegaly. Results of liver tests are given in Table I. Proteinuria was 3 g/day. No M component was

TABLE I Biochemical features in five patients with hepatic amyloidosis

Patient	Serum bilirubin ($\mu\text{mol/l}$)	Alkaline phosphatases (IU/l*)	Prothrombin time (% of normal)	Serum albumin (g/l)
1	175	512	39	18
2	25	625	70	32
3	11	312	90	40
4	6	250	89	31
5	10	150	65	22

*Normal: <125 IU/l.

detected in the serum or urine. Endoscopy showed no oesophageal varices. Ultrasound showed a homogeneous enlarged liver with ascites and patent portal and hepatic veins. Hepatic venous catheterisation and transvenous liver biopsy were performed. Wedged and free hepatic venous pressures were found to be 19 and 7 mmHg respectively, with a pressure gradient of 12 mmHg (normal values, 1-4 mmHg). Right atrial pressure was 7 mmHg. Histological examination of the liver biopsy specimen showed massive amyloid deposits in the Disse's space with considerable compression atrophy of hepatic sinusoids and hepatocytes. A rectal biopsy specimen showed large subepithelial and vascular deposits of amyloid. Bone marrow biopsy tissue showed infiltration with lymphoplasmacytoid cells bearing IgM with kappa light chains and prominent interstitial deposits of amyloid. Primary AL type amyloidosis with severe liver, kidney, and bone marrow infiltration was diagnosed. Gastrointestinal bleeding from an unknown origin occurred. The patient died from sepsis and renal failure 15 days after admission to hospital.

PATIENT 2

A 66 year old man was admitted to hospital on 1 July 1987 for dyspnoea of two months' duration and hepatomegaly. Clinical examination showed a firm hepatomegaly measuring 19 cm on the right mid-clavicular line, tense ascites, ankle oedema, distended jugular veins, and tachycardia. Results of liver tests are given in Table I. An M component (IgA lambda) was present in the serum and lambda light chains in urine. Proteinuria was 0.6 g/day. No oesophageal varices were seen at endoscopy. Abdominal ultrasound showed a homogeneous enlarged liver with patent portal and slight dilated hepatic veins. Cardiac ultrasound showed hypertrophy of the interventricular septum and the posterior wall without ventricular dilatation and a moderate pericardial effusion. There was no detectable skeletal lesion on x ray examinations. A hepatic venous catheterisation and a transvenous liver biopsy were performed. Wedged and free hepatic venous pressures were 20 and 4 mmHg respectively, with a pressure gradient of 16 mmHg. Right atrial pressure was 4 mmHg. Histological examination of the liver biopsy specimen showed diffuse and massive perisinusoidal amyloid deposits (Fig 1). Submucosal deposits of amyloid were found in the gastric and duodenal biopsy specimens. Bone marrow biopsy tissue showed infiltration with mature plasmacytes bearing IgA with lambda light chains and interstitial deposits of amyloid. Primary AL type amyloidosis with severe liver

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and cardiac involvement, possibly associated with myeloma, was diagnosed. The patient was treated with melphalan and prednisone without improvement and died from arrhythmia five months after hospital admission.

PATIENT 3

A 50 year old man was admitted to hospital on 5 January 1987 because of abnormal liver tests over three months. Six months earlier he had developed nephrotic syndrome and renal failure due to renal amyloidosis associated with multiple myeloma. At this time chronic haemodialysis was started and he was treated with cyclophosphamide, vincristine, and prednisone every two or three months. At hospital admission, clinical examination showed neither hepatomegaly nor ascites. Results of liver tests are given in Table I. An M component (IgG lambda) was present in the serum. Hepatic venous catheterisation showed wedged and free hepatic venous pressures of 8 and 6 mmHg respectively, and a pressure gradient of 2 mmHg. Right atrial pressure was 5 mmHg. Histological examination of the transvenous liver biopsy specimen showed discrete and sparse perisinusoidal amyloid deposits. In January 1989, the M component (IgG lambda) was found to be decreased in the serum. Chronic haemodialysis and chemotherapy were continued.

PATIENT 4

A 34 year old man was admitted to hospital on 30 March, 1988 because of abnormal liver tests over a year. He had a 10 year history of chronic pelvic

suppuration of unknown origin. Clinical examination showed a slight hepatomegaly measuring 12 cm on the right mid-clavicular line; ascites was not detected on abdominal ultrasound. Results of liver tests are given in Table I. A moderate renal failure (creatinine: 146 $\mu\text{mol/l}$) had been found two years earlier. Hepatic venous catheterisation showed wedged and free hepatic venous pressures of 11 and 10 mmHg respectively, and a pressure gradient of 1 mmHg. Right atrial pressure was 8 mmHg. Histological examination of a transvenous liver biopsy specimen showed thin amyloid deposits in the Disse's space (Fig 2). One year later, he was in good condition.

PATIENT 5

A 70 year old man was admitted to hospital on 11 December 1978 for fatigue and anorexia that had lasted six months. Clinical examination showed a firm hepatomegaly measuring 15 cm on the right mid-clavicular line; ascites and splenomegaly were absent. There was no skeletal manifestation. Results of liver tests are given in Table I. An M component (IgG kappa) was present in the serum and kappa light chains in urine. A severe renal failure (creatinine: 1050 $\mu\text{mol/l}$) was present with proteinuria of 2.5 to 7 g/day. Endoscopy showed no oesophageal varices. Hepatic venous catheterisation showed wedged and free hepatic venous pressures of 10 and 7 mmHg respectively, and a pressure gradient of 3 mmHg. Right atrial pressure was 2 mmHg. Histological examination of transvenous liver biopsy specimen showed discrete perisinusoidal amyloid deposits. Submucosal deposits of

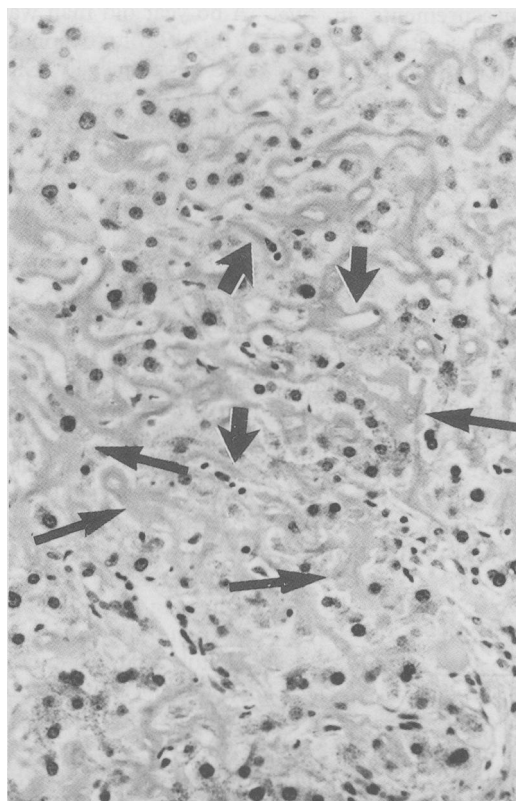


Figure 1: Patient 2: large and diffuse perisinusoidal amyloid deposits (thin arrows) with compression of hepatic sinusoids (large arrows). (Sirius red, original magnification $\times 400$.)

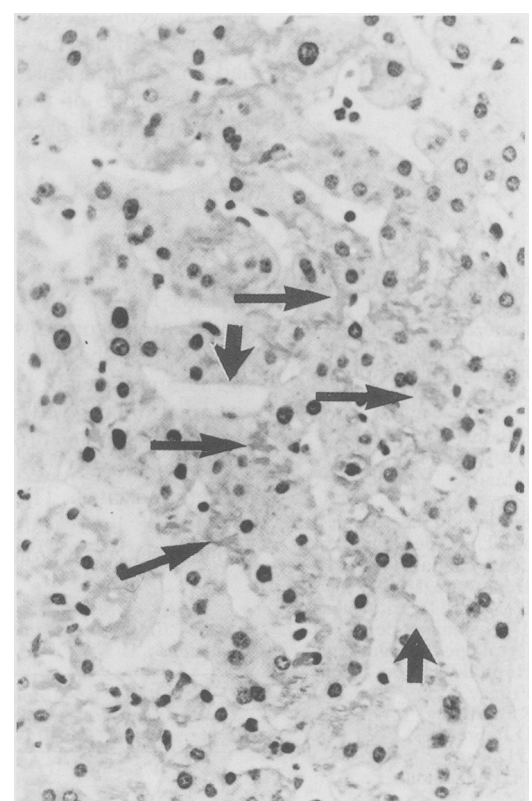


Figure 2: Patient 4: discrete and sparse amyloid deposits in the Disse's space (thin arrows) with normal lumen of hepatic sinusoids (large arrows). (Sirius red, original magnification $\times 400$.)

TABLE II Clinical features of 14 patients with hepatic amyloidosis and portal hypertension

Authors	Sex/ age (yr)	Ascites	Oesophageal varices	Gastrointestinal bleeding*	Delay between diagnosis and death (mths)	Cause of death
Melkebeke <i>et al</i> ⁵	F/71	-	+	+	5	Haemorrhage and renal failure
Atkinson ⁶	M/46	+	+	+	12	General inanition
Pocock <i>et al</i> ⁷	M/57	-	+	+	8	Haemorrhage
Czyzyk <i>et al</i> ⁸	F/43	+	+	+	18	Haemorrhage
Burgi ⁹	M/51	+	+	+	3	Hepatic failure
Kapp ¹⁰	M/46	-	+	+	36	Haemorrhage and renal failure
Brandt <i>et al</i> ¹¹	ns	ns	+	+	ns	Haemorrhage
Singh <i>et al</i> ¹²	M/47	+	-	+	1	Haemorrhage
Itescu ¹³	F/72	+	-	-	0.3	Renal failure
Prieto <i>et al</i> ¹⁴	M/46	+	+	+	0.2	Haemorrhage and renal failure
Case report, <i>N Engl J Med</i> ¹⁵	F/43	+	+	+	6	Haemorrhage and renal failure
Ayadi <i>et al</i> ¹⁶	M/61	+	+	-	2	ns
Our patient 1	F/62	+	-	+	0.5	Renal failure
Our patient 2	M/66	+	-	-	5	Renal failure

+ = present; - = absent; ns = not specified. *From ruptured oesophageal varices or other causes.

amyloid were not found in gastric biopsy specimens. Bone marrow biopsy tissue showed infiltration with mature plasmocytes and interstitial deposits of amyloid. Primary AL type amyloidosis with severe renal involvement was diagnosed. The patient received supportive treatment only and died from terminal renal failure one year after admission.

Discussion

The liver is affected in approximately 60% of patients with amyloidosis.¹⁻⁵ Portal hypertension, however, seems to be an uncommon complication of this disorder. It has previously been reported in only 12 patients with hepatic amyloidosis (Table II).⁵⁻¹⁶ We report two patients with portal hypertension complicating hepatic amyloidosis. In five reported patients, portal hypertension was present without clinical manifestations. In two patients, oesophageal varices were present at necropsy,^{6,8} and in two at endoscopy.^{5,16} In one patient, increased portal pressure was measured at laparotomy.¹³ In seven reported patients and in two of our patients, gastrointestinal bleeding due to ruptured oesophageal varices,⁷⁻¹¹ ascites with splenomegaly,¹⁴ or prominent abdominal veins¹² led to the diagnosis of portal hypertension. In our two patients, portal hypertension was shown by hepatic vein catheterisation performed for transvenous liver biopsy - transparietal liver biopsy being contraindicated in those patients with massive hepatic amyloidosis.^{17,18} The absence of oesophageal varices in our two patients and in two reported patients^{12,13} with hepatic amyloidosis complicated by portal hypertension, may be explained by a mild increase in portal pressure which does not allow collateral circulation to develop. A rapid deterioration in the patient's condition may also contribute to the absence of the development of oesophageal varices.

The prevalence of ascites is high in amyloidosis, ranging from 15 to 47%.^{12,19} In patients with hepatic amyloidosis, ascites may be the result of multiple causes, the commonest being hypoalbuminaemia due to the nephrotic syndrome and cardiac failure. The role of portal hypertension, however, was suggested by Levine, who found ascites in 21% of patients with and in only

8% of those without hepatic amyloidosis.¹ Hypoalbuminaemia in our patient 1 and cardiac failure in patient 2 were probably associated factors for ascites formation.

Portal hypertension in patients with hepatic amyloidosis is of the sinusoidal type since the gradient between wedged and free hepatic venous pressures in our patients 1 and 2 was high (12 and 16 mmHg respectively). Portal hypertension was related to the degree of hepatic infiltration. Sinusoidal portal hypertension is ascribed to the reduction in the vascular space of hepatic sinusoids by abundant and diffuse amyloid deposits in the Disse's space and a subsequent reduction in the sinusoidal lumen (Fig 1). Experimental observations have suggested that decreased intrahepatic vascular space caused by hepatic resection leads to portal hypertension.²⁰ Massive amyloid deposits in the Disse's space were found in our two patients with portal hypertension and hepatic amyloidosis as well as in other previously reported patients.^{5,7-9,13-16} Centrilobular vein lesions, periportal fibrosis, or regenerating nodules were absent in all these patients. In our three patients without portal hypertension, the amyloid deposits, although also present in the Disse's space, were, however, discrete and sparse (Fig 2). Deposition of amyloid predominates in the Disse's space in primary amyloidosis but is limited to walls of blood vessels in secondary amyloidosis.^{3,21} The morphological differences in the pattern of liver amyloid infiltration in primary and secondary amyloidosis may explain why portal hypertension developed mostly in patients with primary amyloidosis.⁵⁻¹²

Portal hypertension in patients with hepatic amyloidosis carries a poor prognosis - of nine patients suffering from gastrointestinal bleeding^{5-11,14,15} related to ruptured oesophageal varices, seven died.^{5,7,8,10,11,14,15} Death occurred between six days and 36 months after the recognition of hepatic involvement. Massive hepatic amyloidosis rarely leads to fatal hepatic failure.¹ In patients with amyloidosis, other factors can lead to gastrointestinal bleeding, including acquired clotting factor deficiencies,¹⁷ increased vessel permeability,⁸ and ulceration of the gastrointestinal tract due to amyloid infiltration.^{10,17}

In conclusion, portal hypertension is an uncommon complication of hepatic amyloidosis and is associated with a poor prognosis. In hepatic amyloidosis, portal hypertension is of the sinusoidal type and is related to the reduction of vascular space of hepatic sinusoids by massive perisinusoidal amyloid deposits.

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