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ABSENCE OF IgA IN THE GLOMERULAR DEPOSITS OF PATIENTS WITH CIRRHOSIS OF THE LIVER AND GLOMERULOPATHY

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Summary

Twelve HBsAg negative patients with histologically documented cirrhosis of the liver of either alcoholic (8 of 12) or cryptogenic (4 of 12) origin underwent renal biopsy to investigate proteinuria, haematuria and/or renal failure. Immunofluorescence was positive for IgA in two patients with mesangiocapillary glomerulonephritis (MCGN), immunofluorescence was not undertaken in two additional patients with the same diagnosis. However, in the remaining eight patients, immunofluorescence was negative for IgA and frequently positive for C_3, IgG, IgM and/or fibrinogen. These eight patients without IgA were classified as follows: MCGN with subendothelial electron dense deposits (2), IgM-IgG cryoglobulinaemia with diffuse endocapillary glomerulonephritis (1), membranous nephropathy (1), diffuse endocapillary proliferative glomerulonephritis (1), and vasculitis with focal segmental necrotizing glomerulitis and rapidly progressive glomerulonephritis (2).

These results show that cirrhosis of the liver can be associated with a wide variety of glomerular disorders. Contrary to previous belief, IgA is absent in two of three of patients with cirrhosis and glomerulopathy and therefore the pathogenetic importance of IgA in the development of glomerular disease in such patients is doubtful.

Introduction

Cirrhosis of the liver is known to be associated with the development of several types of glomerular disease [1]. It has been emphasized that in such cases IgA is almost always the immunoglobulin predominantly deposited in the renal glomerulus [2,3].

This article reports the results of renal biopsies in 12 cases of cirrhosis of the liver with glomerulopathy and points out that, in contradiction to previous reports, IgA deposits were found in only a minority of cases.

Methods

From 1977 to 1985, 12 patients (8 males and 4 females) with cirrhosis of the liver of either alcoholic (8 of 12) or cryptogenic (4 of 12) origin underwent renal biopsy. Reasons for renal biopsy were proteinuria, haematuria and/or renal insufficiency in various combinations. In all cases, cirrhosis of the liver had been documented histologically. All patients were HBsAg negative.

All renal biopsies were examined by light microscopy, 10 by immunofluorescence and six by electron microscopy. Routine laboratory procedures were followed. Renal biopsy slides were interpreted according to conventional histological criteria.

Standard techniques were used for laboratory determinations. Unfortunately no serum immunoglobulin or circulating immune complex measurements were made in a meaningful number of patients.

Results

Table I shows age, sex, liver disease and main laboratory data at the time of renal biopsy.

There were four main clinical forms of presentation: asymptomatic proteinuria (cases 1, 2, 6, 11 and 12), nephrotic syndrome (cases 4 and 7), renal failure (cases 8 and 10) and cutaneous vasculitis with renal failure (cases 3, 5 and 9). The three patients in the latter group presented with palpable purpura of the lower extremities and rapidly progressive renal failure with proteinuria and haematuria. In all three, skin biopsy of a purpuric lesion disclosed leucocytoclastic vasculitis. One of them had cryoglobulinaemia type II (monoclonal IgM-kappa against polyclonal IgG) and a diffuse proliferative glomerulonephritis (case 5, see Table II). The other two patients with vasculitis (cases 3 and 9) had focal necrotizing glomerulitis with extracapillary proliferation in 60 per cent and 75 per cent of glomeruli respectively. Cryoglobulins were negative in all patients but number 5.

Histology Table II shows data on light microscopy, immunofluorescence and electron microscopy when available.

Renal biopsy specimens were classified by light microscopy as follows: mesangiocapillary glomerulonephritis (MCGN – 6 cases) (Figure 1), membranous nephropathy (1), endocapillary proliferative glomerulonephritis (2), and the three patients with vasculitis and associated glomerulopathy described above.

Of the 10 renal biopsies in which immunofluorescence was undertaken, IgA was present in two cases with MCGN (cases 1 and 10) and totally absent or present only in trace amounts in cases 2 and 7 with MCGN, case 4 with membranous nephropathy, cases 6 and 8 with endocapillary proliferative glomerulonephritis and in the three patients described above with vasculitis and glomerulopathy (cases 3, 5 and 9). In the eight patients without significant IgA deposition, immunofluorescence for other immunoglobulins or complement components was frequently positive for C_3, IgM or IgG, whereas fibrinogen was

TABLE I. Clinical data at the time of renal biopsy

Case number	Age	Sex	Liver cirrhosis	Platelets/mm³†/ prothrombin time*	Serum albumin (g/L)	Serum (μmol/L) bilirubin mg/dl	C_3** (mg/dl)	HBsAg/ANA/ cryoglobulins	Peak serum (μmol/L) creatinine mg/dl	Proteinuria g/24hr
1	48	M	alc (Bx)	122/75%	31	1.4 (24)	50	-/-/-	1.8 (159)	1.8
2	33	M	crypt (Bx)	50/70%	26	1.6 (27)	44	-/-/-	1.9 (168)	2
3	74	M	alc (Aut)	196/60%	32	0.9 (15)	ND	-/-/-	9.4 (831)	1.5
4	41	M	alc (Bx)	235/100%	15	0.6 (10)	70	-/-/-	1 (88)	5.8
5	61	M	crypt (Bx)	112/100%	28	1.6 (27)	26	-/-/++ type II***	2.7 (239)	3.4
6	37	F	alc (Bx)	84/100%	38	0.7 (12)	106	-/-/-	1 (88)	3
7	49	F	alc (Bx)	121/93%	23	0.5 (9)	36	-/-/-	1.3 (115)	8.8
8	38	M	alc (Bx)	136/60%	36	2.5 (43)	78	-/-/-	7.3 (645)	3.9
9	73	M	alc (Aut)	110/90%	16	4.1 (70)	42	-/-/-	9.6 (849)	2.4
10	65	F	crypt (Bx)	170/85%	27	0.4 (7)	28	-/-/-	9 (796)	4
11	53	F	crypt (Bx)	185/100%	33	0.7 (12)	40	-/-/-	1.5 (133)	0.8
12	53	M	alc (Bx)	115/90%	26	1.6 (27)	63	-/-/-	1 (88)	1.9

†=values x 10^3; *=percent of normal values; **=normal values 50–125mg/dl; ***=monoclonal IgM-kappa-polyclonal IgG
M=male; F=female; alc=alcoholic; crypt=cryptogenic; Bx=biopsy; Aut=autopsy; ND=not done; (-)=negative; (+)=positive; ANA=antinuclear antibodies

TABLE II. Main histological data

Case number	Histological diagnosis	Immunofluorescence for IgA	Immunofluorescence for others	Electron microscopy
1	MCGN	+	C_3++	Subendothelial EDD
2	MCGN	+/-	C_3++ C_4+ C_1q+ IgM++	Subendothelial EDD
3	Focal necrotizing GN with crescents	-	IgM+ Fibrinogen	ND
4	Membranous nephropathy	-	C_3++ IgG+ C_1q+	Subepithelial EDD
5	Endocapillary proliferative GN	-	C_3++	ND
6	Endocapillary proliferative GN	-	C_3++ IgM+	ND
7	MCGN	-	C_3++ C_1q++ IgM++ IgG+	ND
8	Endocapillary proliferative GN and 40% extracapillary proliferation	+/-	C_3++	Subendothelial EDD
9	Focal necrotizing GN with crescents	-	Fibrinogen	ND
10	MCGN	+++	C_3+++ IgG+	Subendothelial EDD
11	MCGN	ND	ND	Subendothelial EDD
12	MCGN	ND	ND	ND

GN=glomerulonephritis; MCGN=mesangiocapillary glomerulonephritis; EDD=electron dense deposits; Immunofluorescence is graded from (-)= negative or (+/-)=trace to (+++) strongly positive. ND=not done

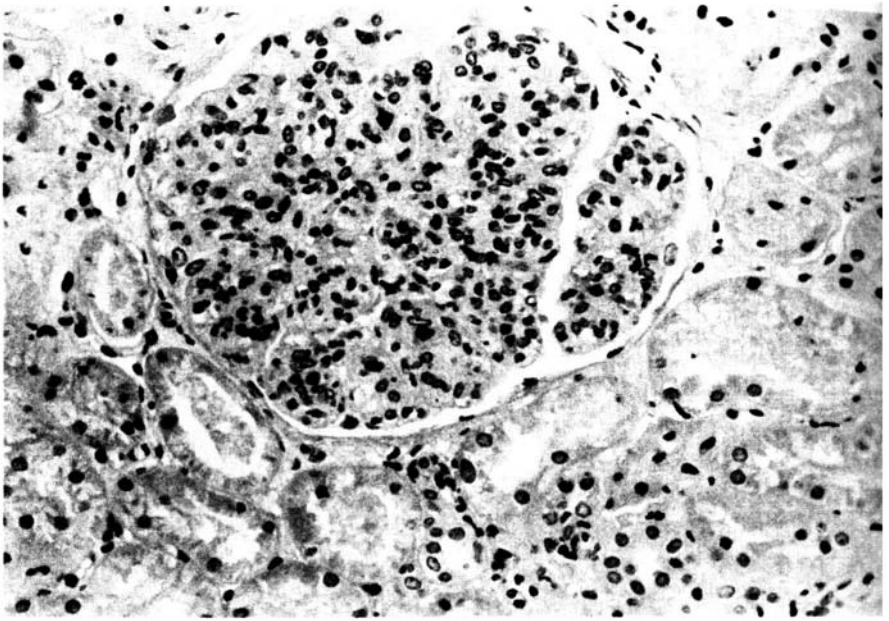

Figure 1. Mesangiocapillary glomerulonephritis with increase in mesangial matrix and cellularity and lobular appearance (case 7) (H&E x 300). IgA was absent on immunofluorescence

present in the cases of focal necrotizing glomerulitis and extracapillary proliferation (Table II).

Electron microscopy showed subepithelial deposits in the case of membranous nephropathy and predominantly subendothelial deposits in five additional cases classified as MCGN. As seen in Table II significant IgA deposition could be lacking even in patients with demonstrable electron dense deposits.

Follow-up Three patients (cases 3, 9 and 10) died during the acute phase of the disease of septicaemia or advanced liver failure. Seven patients (cases 1, 2, 5, 6, 7, 11 and 12) maintain stable serum creatinines after a mean follow-up of 58 months, although proteinuria persists in all. The patient with membranous nephropathy has been followed for 22 months. He is still nephrotic and serum creatinine has climbed to 5.2mg/100ml. Patient 8 was lost to follow-up.

Discussion

Our results demonstrate that cirrhosis of the liver can be associated with a wide variety of glomerular disorders, that range from membranous nephropathy to proliferative glomerulonephritis, MCGN being particularly frequent. In general, these results are in accordance with those obtained by other authors [4]. The

peculiar syndrome of vasculitis with renal involvement developing in cirrhosis of the liver has been previously reported by ourselves [5].

The very low prevalence of IgA deposits found in our study differs significantly from previous series. Of a total of 12 biopsies IgA was present in two, absent in eight and not investigated in the remaining two cases. The IgA negative biopsies were frequently positive for IgG, IgM and particularly C_3. Moreover, electron dense deposits could also be demonstrated in the absence of IgA positive immunofluorescence. These data suggest immune complex deposition without the participation of IgA. Earlier studies had demonstrated a high prevalence of IgA deposits in patients with liver disease and glomerular changes. IgA was nearly always present in the glomerular deposits found by Callard in patients with cirrhosis of the liver and portal hypertension, even in the absence of clinical manifestations of renal disease [1]. Similarly, Berger et al found IgA in the glomeruli of 61 of 100 cirrhotic patients autopsied, 98 of whom had no clinically apparent renal disease [3]. Sancho et al were able to show polymeric IgA in the serum and kidneys of six patients with cirrhosis of the liver [6]. In studies concerning patients with cirrhosis and clinical evidence of active glomerular disease in the form of proteinuria, haematuria and/or renal failure, IgA was also the predominant immunoglobulin deposited. IgA was present in nine of the 11 glomerulonephritic patients biopsied by Berger et al [3] and in 26 of the 34 patients reported in another paper [2]. However, in the latter study it should be noted that IgA was absent in two patients with pure endocapillary glomerulonephritis and in one with membranous nephropathy, in spite of positivity for C_3 and IgG respectively. Thus, it appears that in cirrhotic patients, glomerular IgA deposits are particularly frequent in MCGN, but can be absent in other forms of glomerular disease. Even in this series, of the four patients who had some IgA deposits, including minor and insignificant trace amounts, three had MCGN.

The reasons for the discrepancy between the prevalence of IgA deposits in our patients and those of previous series are unclear at the moment. We believe our data, although limited to a small number of patients, casts some doubt on the pathogenetic importance attributed to IgA in the development of glomerular disease in patients with cirrhosis of the liver, which in any case seem to have a notably increased incidence of a wide array of glomerulopathies. The exact pathogenesis of glomerular disease in cirrhotic patients is unknown, but probably involves immune complex deposition. The hypothetical origin of the immune complexes could be the absorption of intestinal antigens not necessarily coupled with IgA from the intestinal mucosa and inadequate reticuloendothelial clearance due to either portosystemic shunts or impaired Kupffer cell function in the diseased liver [7,8].

References

1 Callard P, Feldmann G, Prandi D et al. *Am J Pathol 1975; 80:* 329
2 Nochy D, Callard P, Bellon B et al. *Clin Nephrol 1976; 6:* 422
3 Berger J, Yaneva H, Nabarra B. *Adv Nephrol 1978; 7:* 3
4 Epstein M (ed). *The Kidney in Liver Disease.* New York: Elsevier. 1983. 119–145
5 Montoliu J, Darnell A, Grau JM et al. *Proc EDTA–ERA 1984; 21:* 677
6 Sancho J, Egido J, Sanchez-Crespo M, Blasco R. *Clin Exp Immunol 1981; 47:* 327
7 Triger DR, Alp MH, Wright R. *Lancet 1972; i:* 60
8 Bjorneboe B, Prytz H, Orskov F. *Lancet 1972; i:* 58