

Kidney Pathology and HCV

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Introduction

Hepatitis C virus (HCV) infection are a common and potentially serious health problem throughout the world with different variations depending the geographic area, between an 0'5% to 2'8%, in Europe and Western countries, 2'8% in USA or Canada, or more of the 20% of the population in Egypt or Romania. In addition the patients with chronic renal disease increase the prevalence because their frequent exposure to blood from transfusion, to HCV contaminated medical equipment exposure or immunodepressed status in transplanted kidney population.

The major complication of acute HCV infection is chronic hepatitis in up to 70% of cases. Chronic HCV infection has been associated with extrahepatic manifestations. The most of these extrahepatic manifestations with kidney repercussion is the mixed essential cryoglobulinemia. Typical renal manifestation of cryoglobulinemia includes proteinuria, hematuria, renal insufficiency with renal glomerular affectation.

HCV-related glomerular disease

HCV is probably a principal cause of idiopathic membranoproliferative glomerulonephritis (MPGN). This type of renal disease typically occurs in adults after a HCV liver affectation but the HCV also are related with different types of glomerular disease such as IgA nephropathys, membranous glomerulonephritis (MG), focal sclerosis, fibrillary or immunotactoid glomerulopathy, TMA and vasculitis.

The associations between MPGN and Essential Mixed Cryoglobulinemia (EMC) rise up 90% of the cases. Otherwise there is a wide variations related the frequency of this association. In our experience the 37% of MPGN there was an associations, but only in 1'7% of MG and 1'8 of IgA was possible to demonstrate a relationship between HCV and glomerular disease.

The pathogenesis of the glomerular injury in HCV infection is not known. The injury may be is the result from deposition of circulating immune deposits with participation of HCV, anti-HCV and Rheumatoid factor (RF) at the site of injury.

The HCV envelop protein E2, able to bind CD81 molecule expressed on B-lymphocytes, might be involved in the first steps of HCV-driven autoimmune phenomena. The interaction between HCV-E2 and CD81 may the frequency of VDJ rearrangement in antigen B-cell. The B-cell is responsible for autoantibody and immune-complex production, including mixed cryoglobulins and vasculitis.

HCV, Cryoglobulinemia and Membranoproliferative glomerulonephritis (MPGN). Histology characteristic.

The MPGN is the glomerular form more frequently associated to Essential mixed cryoglobulinemia (EMC) up 80% the cases. The typical clinic characteristic consists in:

hypocomplementemia, mild/moderate kidney insufficiency, proteinuria, microhematuria, and high blood pressure.

HCV RNA positivity was demonstrated in PMGN associated Cryoglobulinemias as so as in the cryoprecipitates.

The MPGN associated HCV usually is the type I, indistinguishable from the other MPGN not related with the virus, but some differences were related: presence of hyaline thrombi in capillary loops with less endocapillary proliferation, massive leucocyte/monocyte infiltration, small and medium vessels with fibrinoid necrosis. At the ultrastructural level, the presence of tubular deposits and/or dense round deposits in the mesangium or in subendothelial position has been described.

A lobular pattern was another light microscopy feature described in 20% of the cases. In our experience after to review a total of 32 MPGN in the 37.5% there were an association in the 37.5%, only we have seen hyaline thrombi in 2 cases.

The immune fluorescent observation, deposition of C3, IgM, IgG are usually finding but not invariably shown in mesangial and capillary wall.

In summary, HCV associated GN cryoglobulinemia glomerulonephritis has similar histologic characteristics to non cryoglobulinemic MPGN in the most of the cases, but the presence of large deposits filling the capillary lumen, fibrillary or crystalline structures by electron microscopy and the massive infiltration of monocytes are findings suggestive of the cryoglobulinemia glomerulonephritis.

Other forms of glomerulonephritis associated with HCV

An association with HCV infection and other glomerulonephritis has been described.

Membranous glomerulonephritis (MGN) has been documented in several series with a variation between 1.75%, in autopsy cases, to 8.3% in renal biopsies series. In our experience the MGN HCV association is the 1.7%.

Up to 80% HCV RNA positivity has been described in MGN associated HCV.

The IgA GN is other HCV associated glomerulonephritis. There is a classical relation between chronic hepatic disease and IgA glomerular deposits. It is possible the glomerular IgA deposits related with chronic hepatitis C has a different pathogenetic mechanism respect to cirrhosis HCV non related.

Postinfectious glomerulonephritis, focal and segmental glomerulonephritis, fibrillary/immunotactoid glomerulopathy and TMA, are different forms, also associated to HCV infection.

HCV in Kidney Transplanted Patients

There is not uniform data respect to HCV infection and its adverse relation with the follow up in kidney transplanted patients. Also there is significant rates variations. In USA series the variations range between 6% to 46%. In our transplanted kidney populations the 8.5% are HCV positive.

After a comparative study between HCV positive and HCV negative patients with allograft biopsies the differences with p significances were chronic allograft dysfunction, and chronic rejection. In 2.000 transplanted patients, non statistical ($p < 0.1$) differences we found related with other parameters as: clinical features, delayed graft function, acute cellular rejection or "de novo" or recurrent glomerular disease.

The recipients of HCV positive donors have a mortality independent risk as so as the presence of cirrhosis before transplantation.

Conclusions

- HCV infections with a variable incidence depending of geographic areas.
- Direct relation between HCV infection, essential mixt cryoglobulinemia and special form of MPGN.
- Less frequent association with other glomerulonephritis: IgA, Focal sclerosis, infectious glomerulonephritis, fibrillary/immunotactoid glomerulopathy and TMA.
- Non significant impact of HCV after transplantation except in long-term survival (10 to 20 years).
- More Incidence of chronic rejection related with HCV in our experience.

Tables

MPGN type I

Table 1. Histological findings (cryoglobulinemic vs non-cryoglobulinemic MPGN)

Cryoglobulinemic (4/12)			Non-cryoglobulinemic (8/12)			
	n	%		n	%	p
Lobular pattern	1	25	Lobular pattern	3	37.5	0.665
Celular crescents	0	0	Celular crescents	5	62.5	0.038
Hyaline thrombi	2	50	Hyaline thrombi	3	37.5	0.679
Fibrinoid necrosis	0	0	Fibrinoid necrosis	0	0	
Exocitosis/leucocytes	2	50	Exocitosis	2	25	0.386
Arteriolar hyalinosis	1	25	Arteriolar hyalinosis	1	12.5	0.584

MPGN type I

Table 2. Demographics, clinical and laboratorial features

Age (yr), mean±SD [min-max]	49 ± 16 [28-77]	Purpura	2 (16.7%)
Male/Female (n)	9/3	HBV/HIV co-infection (n)	3/1
Renal failure	9 (75%)	Creatinine mean±SD (mg/dl)	1.8 ± 0.9
Nephrotic syndrome	9 (75%)	Proteinuria mean±SD (g/day)	5.6 ± 3.0
Hypertension	8 (66.7%)	Cryoglobulins	4 (33.3%)
Microscopic haematuria	8 (66.7%)	Hypocomplementemia	8 (66.7%)
Nephritic syndrome	2 (16.7%)		

Table 3. Differences between HCV+ and HCV- in transplant patients.

	HCV positive (n=169)		HCV negative (n=169)		P
	n	%	n	%	
Causes of patient's death					
CVD	11	23.9	8	28.6	0.479
Neoplastic	6	13.0	5	17.9	0.759
Infectious	15	32.6	9	32.1	0.204
Others	8	17.4	4	14.3	0.239
Unknown	6	13.0	2	7.1	0.152
Graft outcome					
Functioning graft	86	39.1	76	46.1	0.276
Lost graft	57	33.7	61	37.0	0.648
Death of the recipient with functioning graft	46	27.2	28	17.0	0.018
Acute rejection					
Yes	45	26.9	43	26.2	0.881
No	122	73.1	121	73.8	
Diabetes before KT					
Yes	16	9,6	12	7,3	0.449
No	151	90,4	153	92,7	
NODAT					
Yes	24	14,4	18	10,9	0.343
No	143	85,6	147	89,1	

: Table 4 Graft survival: comparative study between HCV+ and HCV -

years	1	2	3	4	5	6	7	8	9	10
HCV +	88.7%	85.1%	80.5%	78.1%	75.1%	75.1%	72.9%	66.0%	61.9%	60.3%
HCV -	79.9%	77.8%	77.0%	74.7%	73.8%	71.8%	70.8%	68.6%	65.2%	60.1%

Patient survival

Log rank: 4.754 ; **p=0.029**

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**MGCGn+ hyalin thromby
+ exocitosis
+ monocytes
vasculitis**



