

Renal pathology in HCV infected patients – Report of 148 patients and review of the literature

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ABSTRACT

Background: Hepatitis C virus infection (HCV) is a major public health problem with a reported incidence of 3-4 million cases per year. Renal injury secondary to HCV was initially observed in autopsy studies and later in kidney biopsies. Several types of renal disease have been recognized in association with HCV patients. **Objectives:** Characterize the type of renal disease found in HCV-infected patients and established as possible relation with clinical presentation. **Methods:** Unicentric retrospective study of HCV patients with a renal biopsy from January 1988 to December 2015. The clinical data at biopsy time was analyzed according to histological diagnosis. **Results:** HCV infection was present in 148 cases. Male gender was predominant (76.7%), as was Caucasian race (79.1%). Mean age was 41.46 ± 11.47 years. Histological study of renal biopsies revealed membranoproliferative glomerulonephritis (MPGN) type 1 to be the commonest lesion encountered (37.2%), followed by proliferative glomerulonephritis (16.9%), focal segmental glomerulosclerosis (FSGS) (10.1%), and tubulointerstitial nephropathy (10.1%). Other patterns (amyloidosis, diabetic nephropathy, membranous nephropathy, IgA nephropathy) were observed. Hypocomplementaemia and cryoglobulinaemia showed correlation with MPGN diagnosis. A statistically significant correlation was observed with human immunodeficiency virus (HIV) infection and FSGS diagnosis. Amyloidosis diagnosis was associated with advanced age. No other significant correlations were found. **Conclusions:** Renal disease in HCV patients has a broad spectrum. No strong correlations between clinical data and pattern of renal disease have been established and it seems that is not possible to predict the renal disease based on clinical criteria alone. Renal biopsy remains the gold standard for diagnosis.

Key Words: hepatitis C virus infection; renal biopsy; renal disease

INTRODUCTION

Hepatitis C virus (HCV) infection is a major public health problem with a reported incidence of 3-4 million cases per year¹. It is known that 3% of the world's population is currently infected with HCV². Hepatitis C is a major cause of liver-related morbidity³ and accounts for over 1 million deaths as a result of cirrhosis and liver cancer^{4,5}.

HCV infection leads to chronic liver disease⁶, but also should be considered as a systemic disorder which is often associated with a number of extrahepatic manifestations^{7,8}. These include porphyria cutanea tarda, type 2 diabetes mellitus, lymphoproliferative disorders, cryoglobulinaemia and renal diseases⁹. Almost 40% of patients with HCV develop at least one extrahepatic manifestation during the course of the disease².

Several types of renal disease have been recognized in association with HCV infection^{10,11}. Membranoproliferative glomerulonephritis (MPGN), is thought to be the most common histological pattern, whether cryoglobulinaemic or noncryoglobulinemic^{12,13}. An association between HCV infection and FSGS^{13,14}, IgA nephropathy^{15,16} and membranous nephropathy¹⁷ has also been reported. Other forms of renal disease have been previously linked to chronic HCV infection, including proliferative glomerulonephritis¹⁸, fibrillary and immunotactoid glomerulopathy, thrombotic microangiopathies and postinfectious glomerulonephritis^{9,19}. However, glomerular disease is not the only type of renal manifestation of chronic viral hepatitis. Tubular injury may also be present²⁰.

This retrospective study aims to characterize the type of renal disease found in Portuguese HCV-infected patients and establish possible relationships between clinical and laboratory data.

PATIENTS AND METHODS

We performed a retrospective study, reviewing all native biopsies of patients with positive HCV serology (n=148) analyzed in our Nephropathology Department, between January 1988 and December 2015. All had renal dysfunction and/or abnormal findings on urinalysis. Proteinuria was defined as protein urinary excretion of more than 300mg/24h and haematuria was defined as urine sedimentary red blood cell counts of more than five in microscope x400 visual field.

Tissues for optical microscopy were stained with haematoxylin-eosin, periodic acid Schiff, Masson's trichrome, methenamine silver and Congo red. Immunofluorescence (IF) was performed in frozen sections, using labeled human immunoglobulin (IgA, IgG, IgM), light chains (λ e κ), complement (C1q, C3), and fibrinogen. When no frozen fragment was available, indirect immunoperoxidase using formalin-fixed paraffin embedded section was performed. Amyloid substance was characterized using immunofluorescence or immunohistochemistry staining for SAA or κ and λ light chains. When required, electron microscopy was performed.

Clinical and laboratory data at the time of biopsy were obtained: demographic (age, gender), clinical (presence of renal failure, nephrotic syndrome, hypertension, microscopic haematuria, nephritic syndrome, purpura, other viral co-infections, chronic hepatic

disease), laboratory (serum creatinine, proteinuria, haematuria, cryoglobulins, hypocomplementaemia). We searched for relationships between renal histological findings and clinical data.

Mean and standard deviation were used to characterize quantitative variables. Qualitative variables were analyzed using absolute and relative frequencies. Background factors were compared with the different histological patterns by using the chi-square test for categorical variables and the Kruskal-Wallis test for comparison among the groups. A p value <0.05 was considered significant. All tests were performed using SPSS, version 22.

RESULTS

From January 1988 to December 2015, 148 biopsies of native kidney of HCV-infected patients were analyzed in our department. The baseline clinical characteristics of HCV patients are summarized in Table I.

Table I

Characteristics and laboratory data of HCV-infected patients. Data are the number (%) or mean \pm SD (range).

Characteristic	Patients	
Number	148	100%
Age (yr)	41.46 \pm 11.47 years	
Gender (male)	117	79.1%
Caucasian	140	94.6%
Clinical features		
Renal Failure*	86	58.1%
Nephrotic syndrome	51	34.5%
Hypertension	75	50.7%
Haematuria (\geq 6/HPF)	66	44.6%
Nephritic syndrome	20	13.5%
Purpura	4	2.7%
HBV infection	17	11.5%
HIV infection	50	33.8%
Intravenous drug use	82	55.4%
Diabetes mellitus	15	10.1%
Chronic liver disease	8	5.4%
Neoplasia	5	3.4%
Laboratory features		
Creatinine (mg/dl)	2.72 \pm 2.47	
Proteinuria (g/day)	6.74 \pm 6.9	
Positive cryoglobulins	22	14.9%
Hypocomplementaemia	34	23.0%

* Acute (defined as a rise in serum creatinine \geq 1.5 fold from the reference value) or chronic (defined as decreased glomerular filtration rate of less than 60 mL/min/1.73 m² for 3 or more months)

Table II

Renal histopathologic findings of renal biopsy in HCV patients

Histological diagnosis	n (%)
MPGN	55 (37.2%)
PGN	25 (16.9%)
FSGS	15 (10.1%)
TIN	15 (10.1%)
Amyloidosis	10 (6.8%)
Diabetic nephropathy	9 (6.1%)
IgAN	6 (4.1%)
MN	4 (2.7%)
Nephroangiosclerosis hypertensive	3 (2.0%)
Others	6 (4.1%)

MPGN – membranoproliferative glomerulonephritis; PGN – proliferative glomerulonephritis; FSGS – focal and segmental glomerulosclerosis; TIN – tubulointerstitial nephropathy; IgAN – IgA nephropathy; MN – membranous nephropathy.

Male gender (79.1%) and Caucasian race (94.6%) were predominant. Mean age was 41.46 ± 11.47 years. 10.1% (n=15) of the patients had diabetes mellitus and 5.4% (n=8) had chronic liver disease. Co-infections with HIV and hepatitis B virus (HBV) were present in 33.8% (n=50) and 53.3% (n=17), respectively. 82 patients (55.4%) had past or present history of intravenous drug use.

The mean serum creatinine level was 2.72 ± 2.47 mg/dl (0.4 – 12.0), 24-hour protein excretion was 6.74 ± 6.9 g (0.30 – 30.6), and haematuria was positive in 66

of the 148 patients (44.6%). Cryoglobulinaemia was detected in 22 patients (14.9%) and hypocomplementaemia in 34 patients (23.0%).

Ten different histological findings were recognized (Table II).

The predominant lesion was MPGN (n=55, 37.2%), followed by PGN (n=25, 16.9%), FSGS (n=15, 10.1%) and tubulointerstitial nephropathy (n=15, 10.1%). Amyloidosis was the histological diagnosis in 10 patients and diabetic nephropathy in nine.

The histological and clinical features and the major cause for performing renal biopsy are summarized in Table III and Table IV, respectively.

■ Histological feature

1. MPGN

MPGN was diagnosed in 55 of the 148 patients. All patients were Caucasian and eighteen patients were co-infected: 12 had HIV and six had HBV. Intravenous drug use was identified in 37 of 55 patients. No patients had clinical or serological signs for lupus. Mean Scr was 2.0 ± 1.02 mg/dl, and mean proteinuria was high (6.5 ± 5.38 g). Haematuria was present in 29 (53%) patients.

Table III

Renal histopathologic findings and association with age, viral co-infection, diabetes mellitus, creatinine, eGFR and proteinuria. Data are the number (%) or mean \pm SD [range].

Histological diagnosis	Age (yr)	Diabetes mellitus (n/%)	IV drug use (n/%)	Creatinine (mg/dl)	Proteinuria (g/day)	Cryoglobulins (n/%)	HypoC' (n/%)
MPGN (n=55)	40.05 \pm 11.67	1/1.81%	37/67.3%	2.0 \pm 1.02	6.5 \pm 5.38	19/35%	21/38%
PGN (n=25)	37.92 \pm 10.92	1/4%	16/64%	2.2 \pm 1.50	5.0 \pm 5.46	2/8%	8/32%
FSGS (n=15)	36.93 \pm 9.69	1/6.7%	12/80%	2.6 \pm 2.83	6.1 \pm 4.01	1/6.7%	0
TIN (n=15)	45.20 \pm 9.83	1/6.7%	4/26.6%	3.9 \pm 2.52	1.3 \pm 0.61	0	1/6.7%
Amyloidosis (n=10)	51.80 \pm 12.76	0	6/60%	2.4 \pm 1.55	10.5 \pm 8.29	0	1/10%
DM (n=9)	46.00 \pm 10.40	9/100%	2/22.2%	2.5 \pm 2.42	6.3 \pm 2.88	0	1/11.1%
IgAN (n=6)	43.50 \pm 9.52	1/16.7%	1/16.7%	2.8 \pm 2.67	4.1 \pm 3.41	0	2/33.3%
MN (n=4)	41.75 \pm 12.84	0	2/50%	2.9 \pm 1.55	10.1 \pm 10.45	0	0
p value*	p=0.018	p<0.001	p=0.003	p=0.063	p=0.114	p<0.001	p<0.013

MPGN – membranoproliferative glomerulonephritis; PGN – proliferative glomerulonephritis; FSGS – focal and segmental glomerulosclerosis; TIN – tubulointerstitial nephropathy; DM – diabetes mellitus; IgAN – IgA nephropathy; MN – membranous nephropathy; IV – intravenous. *p<0.05 (χ^2 -test and Kruskal-Wallis test).

Table IV

Causes for doing the renal biopsy according to histopathologic diagnosis.

Indication for biopsy	Nephrotic syndrome (n)	Proteinuria (n)	Nephritic syndrome (n)	AKI (n)	RPRI (n)	CKD (n)
MPGN (n=55)	20	15	11	9	0	0
PGN (n=25)	7	4	6	6	8	0
FSGS (n=15)	5	6	0	0	2	2
TIN (n=15)	0	1	1	13	0	0
Amyloidosis (n=10)	8	2	0	0	0	0
DM (n=9)	5	0	2	0	2	0
IgAN (n=6)	1	3	0	0	0	0
MN (n=4)	3	0	1	0	0	0
Others (n=9)	2	2	0	1	4	1

MPGN – membranoproliferative glomerulonephritis; PGN – proliferative glomerulonephritis; FSGS – focal and segmental glomerulosclerosis; TIN – tubulointerstitial nephropathy; DM – diabetes mellitus; IgAN – IgA nephropathy; MN – membranous nephropathy; AKI – acute kidney injury; RPRI – rapid progressive renal injury; CKD – chronic kidney disease.

Cryoglobulinaemia was present in 35% (n=19 patients) of the group and hypocomplementaemia in 38% (n=21 patients). Three patients presented purpura, all with cryoglobulinaemia and one with hypocomplementaemia.

2. Proliferative glomerulonephritis

Caucasian race was predominant (92%). Seven patients were co-infected with HIV and two with HBV. Sixteen patients (64%) were intravenous drug users. Mean Scr was 2.2 ± 1.50 mg/dl, mean proteinuria was high (5.0 ± 5.46 g), and two thirds had haematuria. No patients had clinical or serological signs for lupus. Cryoglobulinaemia was present in two patients and hypocomplementaemia in eight patients.

Renal histology was characterized by two different findings. In 23 patients, diffuse proliferative endocapillary glomerulonephritis, with hypercellularity of all glomeruli, no significant interstitial infiltration or tubular atrophy, and positive IMF for C3, IgG and IgM were found. In two patients, crescentic glomerulonephritis, and positive IMF for C3 and IgM was observed. ANCA was negative.

3. FSGS

Fifteen patients had a histological pattern of focal and segmental glomerulosclerosis (FSGS). Mean age of these patients was 37 ± 9.69 years and Caucasian race was predominant (93.3%). We found significant

proteinuria (6.1 ± 4.91 g), with 80% of patients having nephrotic proteinuria. HIV co-infection was present in ten patients and HBV in five (all intravenous drug users). Sclerotic lesion location was extremely heterogeneous, without specific histologic variant. IMF was positive with segmental deposits of C3, IgM and IgG in 8/15 patients.

Collapsing FSGS was found in one HCV-infected patient. This biopsy was obtained from a 28-year-old black male, intravenous drug user and HIV co-infected. He presented with heavy proteinuria (20g/day) and rapidly progressive renal insufficiency (Scr 8.6 mg/dl). Renal histology was characterized by microcystic distortion of the tubules. IMF was not available.

4. Tubulointerstitial nephropathy

A predominant interstitial pathology was present in 15 patients. All patients had normal glomeruli and marked interstitial nephritis. Eight biopsies had features of chronicity.

The proteinuria was non-nephrotic in 54% of the cases (1.3 ± 0.61 g/24h), 5 patients had haematoproteinuria and in all patients renal function was significantly deteriorated (3.90 ± 2.52 mg/dl).

5. Amyloidosis

Amyloidosis was found in ten HCV-infected Caucasian patients. All presented with nephrotic proteinuria (mean proteinuria 10.5 ± 8.29 g), including 8 with nephrotic

syndrome. The majority of these patients were male (n=9) and this diagnosis mainly occurred in older patients (51.80±12.76 years). Renal function was deteriorated: Scr 2.4±1.55mg/dl. Two patients had primary amyloidosis. In the patients with AA amyloidosis (n=8), six had pulmonary tuberculosis or chronic respiratory disease (obstructive pulmonary disease and bronchiectasis). Six patients were intravenous drug users, all with amyloidosis AA. Glomeruli were sclerosed and had mesangial nodules. Fibrosis and interstitial infiltrates were moderate.

6. Diabetic nephropathy

This lesion was present in nine HCV-infected patients. Caucasian race was pre-dominant (78%). All patients had renal insufficiency (mean Scr 2.5±2.42mg/dl). Mean proteinuria was 6.3±2.88g and HBV co-infection was present in one patient.

7. IgA nephropathy

Six of the 148 patients were diagnosed as having IgAN. A small amount of C3 was detected in 4 of the 6 patients. All patients had proteinuria (4.1±3.41 g/24h), 50% in the nephrotic range and one had normal renal function. Haematuria was detected in three patients. Co-infection with HIV was identified in two patients, one of which had severe renal impairment (Scr 8.0 mg/dl).

8. Membranous nephropathy

Four patients were diagnosed as having membranous nephropathy. All patients had proteinuria (3 in nephrotic range and with nephrotic syndrome) and 1 had also microhaematuria and presented with nephritic syndrome. Renal failure (Scr >1.5mg/dl) was present in all patients (2.9±1.55 mg/dl). Two patients were co-infected with HIV. IF showed diffuse granular deposits of IgG and C3 in the capillary walls.

9. Other renal diseases

- Nefroangiosclerosis: three male patients, one presented with anuric kidney injury due to malignant nephroangiosclerosis
- Minimal change lesion: two HCV-infected patients, one with a Hodgkin lymphoma
- Microscopic polyarteritis: two HCV-infected females, without any viral co-infections. Patients had crescent formation and IF showed no deposition of immunoglobulins or complement. All cases had positive anti-myeloperoxidase-neutrophil cytoplasmic antibodies (MPO-ANCA).
- Anti-GBM disease: one 43-year-old Caucasian male, without any viral co-infections
- Acute tubular necrosis (ATN): one HCV-HIV co-infected male, with chronic liver disease

■ Comparison between histological and clinical data

The clinical findings within distinct histological types were compared.

Statistically significant results were found between patients' ages and histological diagnosis (p=0.018). The data suggested that older patients had a higher frequency of amyloidosis (M=51.80, SD=12.76), while younger patients had a higher frequency of FSGS (M = 36.93, SD = 9.69), PGN (M = 37.92, SD = 10.92), or even MPGN (M = 40.05, SD = 11.67).

The incidence of hypocomplementaemia was twice as high in the MPGN group (61.8%), a statistically significant difference (p=0.013). No patient with FSGS or MN presented hypocomplementaemia.

A statistically significant association was found between the histological diagnosis and the presence of cryoglobulinaemia (p<0.001). Patients with this condition had a much higher prevalence of MPGN (86.4%) than patients without cryoglobulinaemia (28.6%).

HIV co-infected patients had a lower prevalence of MPGN diagnose (24%) than non-HIV patients (43.9%). On the other hand, HIV infection seems to be related to the diagnosis of FSGS (20.0%) and TIN (18.0%). The association between histological diagnosis and HIV infection was statistically significant (p=0.004).

Intravenous drug use presented a statistically significant relationship with histological diagnosis (p=0.003). Patients with drug addiction had a higher prevalence of MPGN diagnose (45.1%) than patients without drug dependence (27.3%).

The diagnosis of type 2 diabetes mellitus presented a statistically significant relationship with histological diagnosis (p<0.001). Diabetic nephropathy represented 60% of the total diagnosis in diabetic patients.

Regarding gender there was a predominance of males in the MPGN group (40.2%) although statistically non-significant (p=0.408).

The serum creatinine level was not significantly different between the groups. Nevertheless all patients with TIN diagnose had plasma creatinine levels >1.5 mg/dl.

There was statistically no significant difference regarding incidence of chronic liver disease, HBV

infection and proteinuria level ($p=0.561$, 0.889 , and 0.119 respectively).

DISCUSSION

Chronic HCV viraemia is present in 150–170 million people worldwide²¹.

Kidney disease is regarded as one of the most important of the extrahepatic manifestations of HCV infection²². With the current availability of direct-acting antivirals (DAA), which can achieve a viral remission of >95% for most HCV genotypes, the prevalence of glomerular disease in this population should progressively decline in the coming decade²³.

HCV-associated glomerular disease is primarily a consequence of viral antigen – immune complex formation with glomerular basement membrane deposition²¹. The expansion of HCV-reactive B-cells leads to antibody production, including cryoprecipitating antibodies²⁴. The classic pathologic hallmark of HCV renal disease is type 1 MPGN as a consequence of type 2 mixed cryoglobulinaemia (MC), although the same renal lesion may also develop from noncryoglobulinaemic immune complexes²⁵. In addition, HCV is also an important cause of polyarteritis nodosa (PAN) from immune complex deposition in medium size blood vessels leading to renal ischaemia and infarction similar to HBV PAN and idiopathic PAN²¹. The pattern of glomerular injury will depend on the physico-chemical characteristics of the immune-complexes such as their size and charge, their rate of production and factors such as phagocytic clearance and quantity of complexes reaching the kidney¹¹.

The typical renal manifestations in HCV-infected patients include proteinuria, microscopic haematuria, hypertension, acute nephritis and nephrotic syndrome. However, mostly the renal disease is asymptomatic, and thus patients with HCV infection should be screened for proteinuria, haematuria, hypertension and cryoglobulinaemia⁹.

Various other forms of histological types of renal diseases have been described in HCV patients, mesangial proliferative and focal proliferative GN, IgA nephropathy, membranous nephropathy (MN), focal segmental glomerulosclerosis (FSGS), fibrillary glomerulonephritis, immunotactoid glomerulopathy, renal thrombotic microangiopathy, vasculitic renal involvement and interstitial nephritis albeit far less commonly than MPGN^{9,17,19,21}.

It is important to note that renal dysfunction in a patient with HCV is rarely a result of GN (<10%) and hospital admissions for MPGN from HCV have been decreasing for the past decade²⁶. The majority of renal diseases in HCV patients with liver disease are a consequence of acute tubular necrosis, hepatorenal syndrome, prerenal azotaemia, and CKD and therefore it is essential to be familiar with the typical presentation and characteristics of acute GN in HCV patients and how to differentiate them from the more common diagnoses causing AKI in this population^{21,26}.

In our review, the histological lesions associated with HCV infection were MPGN (55 cases), followed by PGN (25 cases), FSGS (15 cases) and tubulointerstitial nephropathy (15 cases). Amyloidosis was the histological diagnose in 10 patients and diabetic nephropathy in nine. IgA nephropathy was found in six cases and membranous nephropathy in two.

The prevalence of HCV infection in MPGN varies between 15% and 60% in different series and rises to 96% when cryoglobulinaemia is also present^{11,19}.

In our patients with HCV-associated MPGN, hypertension and microscopic haematuria were the main clinical features followed by renal failure and nephrotic syndrome. These clinical findings are consistent with those described in the literature²⁷.

In cases of cryoglobulinemic glomerulonephritis, one-third of these patients may have vasculitis of small renal arteries however extracapillary crescents are rarely seen¹⁹. IF microscopy may reveal C3, IgM and IgG depositions on the capillary wall and mesangium. Intraluminal and subendothelial deposits may have a fibrillary pattern on electron microscopy probably representing cryoglobulin deposition^{1,19}.

In our study, cryoglobulinaemia was present in 35% of all HCV-positive patients. The clinical presentation was not different from that of patients without cryoglobulinaemia, and there were no differences in levels of plasma creatinine and proteinuria. A statistically significant correlation was observed between cryoglobulinaemia and the diagnosis of MPGN. Johnson *et al.*²⁸ found similar results in a group of 35 patients with MPGN, 31.4% having cryoglobulinaemia.

Interestingly, classical signs/symptoms of cryoglobulinaemia such as palpable purpura, arthritis, or neuropathy, are present in only 30–50% of patients with HCV and a MPGN^{19,29}. In our patients palpable purpura was

identified only in four patients, three of them with diagnosis of MPGN and positive cryoglobulins. Many questions remain unanswered on the relationship between the occurrence of cryoglobulinaemia and the duration of HCV infection, viral load, viral genotype, the number of mutations and cytokine profile^{19,21}.

Hypocomplementaemia is a distinguishing feature of MPGN, with C4 being low in 93% of patients, whereas C3 is depressed in only 53%^{6,21}. In our study, hypocomplementaemia was present in 38% of all HCV-positive MPGN patients, a feature statistically significant.

Proliferative glomerulonephritis was the second most frequent histological diagnosis. About one-third of patients had hypocomplementaemia but only a small percentage had positive cryoglobulins.

Reports about the association between HCV and FSGS have been published³⁰⁻³². Confounding factors must be stressed for FSGS. For example, intravenous drug abuse and HIV infection are common causes of both FSGS and HCV infection^{19,31}. In this study, FSGS was the histological diagnosis in 10% of patients and nephrotic proteinuria was the main clinical feature. Two thirds were co-infected with HIV and 80% were intravenous drug user. These concurrent predisposing conditions could explain a much higher prevalence of the FSGS diagnosis in our patients. Furthermore, HIV infection showed a significant association with the diagnosis of FSGS.

Association of IgA nephropathy with HCV infection has also been described in several reports^{15,16,33}. Fabrizi *et al.*³⁴ reviewed the association of HCV infection and glomerulonephritis and found that 6% of patients with IgA nephropathy were HCV-positive. On the other hand, Ström *et al.*³⁵ analysed the association between IgA and HCV infection from an autopsy series in cirrhotic patients: of 27 patients, 13 had IgA nephropathy and only two were HCV infected, suggesting that HCV does not play a role in the pathogenesis of IgA nephropathy associated with cirrhosis. These contradictory findings suggest that confounding factors must be taken into account, such as HBV infection and alcohol consumption¹⁹.

Regarding IgA nephropathy, our prevalence in HCV infection was lower than in other reported series. Several authors have suggested that the cases of IgA nephropathy were probably secondary to chronic hepatic disease and not directly related with the HCV infection¹¹. However, in our study no association was found between the presence of chronic liver disease and the diagnosis of IgAN.

Several cases of MN have been described in HCV-infected patients^{36,37}. The clinical presentation and the histological findings are usually similar from that occurring in HCV-negative patients. Nevertheless, atypical features, such as glomerular hypercellularity and/or mesangial and subendothelial immuno-complexes, are more often associated with the secondary form of membranous nephropathy related to HCV-infection than with the idiopathic disease¹¹. Published series (38, 39) support a possible pathogenic role of HCV in the development of MN. However, there was no increased prevalence of MN associated with HCV in the cohort of renal transplants in the Saint Etienne study⁴⁰, as well as in the Maiza *et al.* series⁴¹. As with IgA nephropathy, the possibility of confounding factors, such as HBV infection and causes of secondary membranous glomerulopathies must be taken into consideration^{11,19}. In our patients a much lower percentage of MN (2.7%) was found. No association with HBV infection was established.

The prevalence of HCV positivity in type 2 diabetic population ranges between 1.7% and 12.1%⁴². A high prevalence of HCV infection has also been observed in patients with diabetic nephropathy⁴³. After kidney transplantation, HCV infection has been identified as a predictive factor for DM⁴⁴. HCV infection might also alter the progression of diabetic-related nephropathy^{45,46}.

In our study, 10% of patients had diabetes mellitus and 9 were diagnosed as having diabetic nephropathy. The high prevalence of HCV-positive patients with diabetes mellitus and diabetic nephropathy may reflect the association between HCV and diabetes.

There are reports of renal amyloidosis in HCV infected patients. AA amyloid was described in patients with hepatosplenic schistosomiasis and HCV infection^{47,48}.

Renal AA amyloidosis is most seen in intravenous drug users with a history of skin-popping and suppurative skin infections⁴⁹. Intravenous drug abusers are also a population at risk for developing HCV infection and multiple others risk factors for renal disease (HBV and HIV infection). The state of immunosuppression of this population makes it also more susceptible to serious infections that may also contribute to the development of secondary amyloidosis⁵⁰.

HCV is a well-known risk factor for lymphoproliferative disorders^{51,52}. In AL amyloidosis, it is possible that the proliferation of monoclonal B cells resulted from HCV

infection associated with chromosomal rearrangement, which led to the production of amyloid proteins.

In our study, ten patients were diagnosed with amyloidosis, two with primary amyloidosis. In all patients with AA amyloidosis risk factors were identified for development of secondary amyloid deposition. Advanced age was related to amyloidosis diagnosis.

Regardless of the tubulointerstitial injury associated with different glomerular lesions, HCV may lead to tubular injury in its own right⁴⁸. Kasuno *et al.*²⁰ report that tubulointerstitial changes are observed frequently in HCV-infected patients, and the viral antigen and RNA of HCV were detected in the tubulointerstitium of these patients.

TIN was identified in 10% of our patients. It is interesting to note that all patients presented serum creatinine levels > 1.5 mg/dl, though without statistical significance. These results support the literature findings that HCV infection is a potent pathogenic factor of tubulointerstitial injury.

Although current findings suggest that HCV infection is a potent pathogenic factor of tubulointerstitial injury, further prospective studies are required to prove the causal roles of HCV in the initiation or progression of TIN.

Other types of glomerulopathy in association with HCV have been described, but they are mainly case reports. Six cases of fibrillary-immunotactoid glomerulopathies have been described in association with HCV infection^{53–55}. Thrombotic microangiopathy has been found associated with cryoglobulinaemic MPGN and hepatitis C in two patients⁵⁶. Antineutrophil cytoplasmic antibodies (ANCA) are frequently found patients HCV infected^{57,58}. No correlation has been found between ANCA positivity and the presence of clinically active vasculitis in these patients⁵⁹ and only a paucity of cases of ANCA-associated vasculitis in patients with HCV have been reported⁶⁰. The rarity of these glomerulopathies makes the causal relationship with HCV infection difficult to demonstrate and would require multi-centre studies¹⁹.

CONCLUSION

Patients infected with HCV can develop diverse renal pathologies. No strong correlations between clinical data and pattern of renal disease have been seen and

it seems that is not possible to predict the renal disease based on clinical criteria alone. Renal biopsy remains the gold standard for establishing the diagnosis and can help predict renal prognosis.

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