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Research Article

Clinical Correlations and Patient's Prognosis in Glomerular Disease Associated with Hepatitis C Virus Infection

Delia Georgiana Tudorovici[1,2*] and Mircea Penescu[1,2]

[1]*Carol Davila, Clinical Hospital of Nephrology, Bucharest, Romania*

[2]*Carol Davila, University of Medicine and Pharmacy, Bucharest, Romania*

***Corresponding author:** Delia Georgiana Tudorovici, Carol Davila, Clinical Hospital of Nephrology, Bucharest, Carol Davila, University of Medicine and Pharmacy, Bucharest, Romania.

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Abstract

Hepatitis C virus infection is a systemic disorder that has been associated with extrahepatic manifestations. Our study had the goal to help understand the association between glomerulonephritis and virus C infection and its consequences and to identify prognostic factors. We retrospectively reviewed medical records of 59 patients with biopsy proven glomerulonephritis and hepatitis C virus infection diagnosed between 2007-2022 in "Dr. Carol Davila" Clinical Hospital of Nephrology. A high baseline creatinine increased 9 times the risk of ESRD (end stage renal disease), but nor proteinuria nor age were risk factors for ESRD. No correlation between viremia and eGFR (estimated glomerular filtration rate) or proteinuria were found. Furthermore, the clinical severity of glomerular disease didn't correlate with the severity of liver damage, so we concluded that the hepatic disease wasn't influenced by immunosuppression in terms of hepatotoxicity or a very high viral replication.

As for laboratory abnormalities, all cryoglobulinemic patients had a high rheumatoid factor and a positive cryoglobulinemic test and all lupus patients had anti dsDNA antibodies positive at the end of the follow-up. This ongoing immunologic activity (despite antiviral therapy and/or immunosuppression) could be a risk factor for future relapses. In conclusion, the association of glomerulonephritis and hepatitis C virus is heterogenous and more studies are necessary to help the clinician in order to decide the most appropriate therapy for each patient.

Keywords: Virus C infection, ESRD, Glomerulonephritis, Immunosuppression, Antiviral

Introduction

Hepatitis C virus infection is a systemic disorder that has been associated with extrahepatic manifestations. Renal involvement has a large spectrum of histopathological lesions [1]. Proteinuria and/or microscopic hematuria with/without a reduction in eGFR (estimated glomerular filtration rate) are the main clinical manifestations of the glomerular disease associated with hepatitis C virus infection. Studies found that genes polymorphism could be responsible for the kidney involvement in cryoglobulinemic patients, but it is unclear why only a small number of patients with hepatitis C virus infection develop renal abnormalities [2-4]. Furthermore, kidney disease has been reported in the absence or in the presence of significant hepatic disease [5,6].

KDIGO recommends evaluating all patients for renal disease at the time of hepatitis C virus infection diagnosis and to screen for kidney disease (urinalysis and eGFR). Also, all CKD (Chronic Kidney Disease) patients with a history of hepatitis C virus infection, whether HCV-RNA positive or not, should be followed up regularly to evaluate for progression of kidney disease [7]. Our study had the goal to understand the association between glomerulonephritis

and virus C infection and its consequences, to identify prognostic factors and to individualize the clinician's approach of these category of patients.

Materials and Methods

Study Design and Patients' Selection

The study retrospectively reviewed the medical records of 59 patients with biopsy proven glomerulonephritis and hepatitis C infection who were followed in Clinical Hospital of Nephrology "Dr. Carol Davila", Bucharest, from 2007 to 2022. The patients were followed up from the date of their first presentation (usually around the date of their renal biopsy), at least two times per year until they began dialysis, or they were lost to follow-up.

Statistical Analysis

Statistical analysis was performed using SPSS software. Statistical significance was assumed at $p<0.05$. Descriptive statistics included the mean (±SD) as appropriate for continuous variables and frequency (percentage for categorical variables). Survival analysis was performed using the logistic regression and Cox proportional hazard models as appropriate. Pearson correlation coefficient was used to correlate quantitative variables.

Patients' Baseline Characteristics

We included patients with virus C infection (serological diagnosis – Anti HCV and HCV RNA) and biopsy-proven glomerulonephritis. We excluded patients with type 2 diabetes, systemic atherosclerosis, nephroangiosclerosis, hepatic cirrhosis, patients with incomplete medical records, who refused to participate to study, who didn't show up or died during follow up. We recorded demographics, presenting characteristics, complications, response to medical therapy, timing of relapses, histologic features, outcome data and laboratory investigations. Laboratory parameters included serum creatinine, complete urinalysis, urine culture, serum uric acid, triglycerides and cholesterol, complete blood count, liver function test, serum glucose, complement levels, HCV RNA levels, anti-dsDNA antibodies levels. All laboratory values were recorded at each follow up.

Characteristics of Renal Presentation

Median period between hepatitis C infection diagnosis and renal disease diagnosis was 11.76 years ± 8.05. The mean age at diagnosis was 64 years ± 8, 75% of patients had hypertension, 80 % had microscopic hematuria. Mean proteinuria level was 4.28g/day ± 3.48 and 45.8% of patients had nephrotic range proteinuria. Renal dysfunction (eGFR <60ml/min/1.73m2) was observed in 44% of patients at the time of diagnosis. The most frequent type of glomerulopathy associated with hepatitis C virus was cryoglobulinemic glomerulonephritis, followed by lupus nephritis. Extracapillary cell proliferation was found in 10 of the 59 biopsies and 5 of them had eGFR<15/ml/min/1.73m2 at the end of the study. As classic markers of negative prognosis, interstitial fibrosis and tubular atrophy were described in 39% of patients with renal disease (23 patients had histopathological signs of chronicity in more than 20% of the glomeruli) and 20% of them had ESRD at the last follow-up.

Outcome

Clinical and Renal Response to Therapy

Actual treatment for renal disease in this specific association is determined by the severity of renal failure and proteinuria (or extrahepatic manifestations in cryoglobulinemic and lupus patients). All patients received antihypertensives (angiotensin-converting enzyme inhibitors, calcium channel blockers and diuretics) and supportive medication as albumin, calcium carbonate, erythropoiesis-stimulating agents. As for immunosuppressive treatment, 52 patients received corticosteroids in combination with cyclophosphamide, ciclosporin or rituximab as induction treatment and mycophenolate mofetil, azathioprine, ciclosporin and/or corticosteroids as maintenance treatment. Two patients received plasmapheresis to treat peripheral neuropathy, arthralgia and kidney involvement.

Most patients received induction treatment and the period of maintenance treatment was between 12-60 months. Seven patients didn't receive immunosuppression because they were stable at the beginning of the follow-up and they remained stable until the end of it. Minimal change disease, as well as IgA nephropathy had a favorable outcome at the end of the follow-up, with no patient reaching ESRD. Five of the patients with FSGS (focal segmental glomerulosclerosis), representing 50% of this subgroup, and 9 patients with cryoglobulinemic glomerulonephritis reached ESRD (representing 56% of this subgroup) (Table 1).

Table 1: Patients with eGFR <15ml/min/1.73m^2 at the end of follow-up.

Glomerulonephritis Type	Number of Patients with ESRD (from each type of GN)
MCD	0
Lupus nephritis	1 (9%)
FSGS	5 (50%)
Membranous glomerulonephritis	2 (22%)
Cryoglobulinemic glomerulonephritis	9 (56%)
Membranoproliferative glomerulonephritis	3(75%)
Ig A nephropathy	0

***Note:** *MCD – Minimal Change Disease, FSGS – Focal Segmental Glomerulosclerosis, ESRD – End Stage Renal Disease.

A logistic regression analysis was performed to examine the influence of baseline creatinine, proteinuria and age on the evolution towards ESRD. The analysis showed that a high baseline creatinine increased by 9 times the risk of ESRD ($Chi^2(1) = 14.99$, $p < .001$). Proteinuria also increased the risk of ESRD, but the influence wasn't statistically significant ($p>0.05$). In minimal change disease patients, mean therapy duration was 20 weeks, with no patient being corticoresistant, corticodependent or corticointolerant and none of the patients relapsed (relapse defined as reappearance of proteinuria >3.5g/day in patient with anterior complete or partial remission). Most of the patients with IgA nephropathy only received nephroprotection (antiproteinuric treatment consisting in angiotensin-converting enzyme inhibitors, statins, omega 3 acids), with only one patient receiving oral prednisone.

In patients with membranous nephropathy, classic and modified Ponticelli regimen were used. At the end of follow-up, 3 patients had complete remission (proteinuria <0.3g/day), 5 had partial remission (proteinuria <3.5g/day) and one patient didn't respond to the treatment (proteinuria >3.5g/day) after he was initially in partial remission. Maintenance treatment consisted in prednisone 15-20mg/day. Six patients had at least one relapse (reappearance of proteinuria >3.5g/day after complete remission or an increase in proteinuria by >50% during partial remission) and rituximab, Ponticelli scheme or oral ciclosporin were used.

In patients with FSGS, patients had frequent relapses. Five of them were treated with monthly pulses of intravenous cyclophosphamide, 3 received ciclosporin and 2 received only corticosteroids. Three patients went in complete remission (proteinuria ≤ 0.3g/day, stable serum creatinine and serum albumin >3.5g/dl), 5 didn't respond to the treatment (nephrotic range proteinuria and or high serum creatinine at the end of follow up). In case of relapse (proteinuria >3.5g/day), all patients received corticosteroids (1mg/kg/day) and ciclosporin (3-5mg/kg/day).

One FSGS patient and one with membranous nephropathy had a stable creatinine, despite having proteinuria >3.5g/day during the entire follow up. Most cryoglobulinemic patients (10 patients) had a deterioration of renal function, with doubling creatinine or even evolving towards ESRD and 6 patients had a stable creatinine. Intravenous cyclophosphamide pulses were used (500-750mg/m^2) in combination with intravenous methylprednisolone (500mg-1g/day), followed by oral prednisone (1mg/kg/day, with lowering doses towards 15-20mg/day). Patients with nephrotic range proteinuria and/or high serum creatinine without cryoglobulinemia evolved towards ESRD at the end of follow-up and one had doubled his serum creatinine.

As for lupus nephritis, 6 patients had complete remission (defined as proteinuria <500mg/g creatinine and stabilization or improvement in kidney function) and were on maintenance treatment with hydroxychloroquine and low dose prednisone. Meanwhile, the other 5 had partial remission (defined as reduction in proteinuria ≤ 50% and to <3g/g and stabilization or improvement in kidney function). Three patients had at least one relapse (defined as an increase in proteinuria by more than 2g/day, an active urine sediment or an increase in creatinine >30%) and they received intravenous cyclophosphamide, rituximab and methylprednisolone. Anti dsDNA had variable levels during relapses with values between 143.8-730 IU/ml and patients with complete remission had a median value of anti dsDNA 356 IU/ml (Table 2).

Table 2: Renal response to therapy in 59 patients with glomerulonephritis.

GN type	Total Number of Relapses	Complete Remission	Partial Remission	No Response
MCD	0	3	0	0
Membranous nephropathy	6	3	5	1
FSGS	10	2	3	5
Ig A nephropathy	0	2	4	0
Membranoproliferatie GN	1	0	0	4
Cryoglobulinemic GN	6	0	6	10
Lupus nephritis	4	5	5	1

***Note:** *MCD- Minimal Change Disease; FSGS- Focal Segmental Glomerulosclerosis; GN- Glomerulonephritis.

Immunosuppression and Hepatitis Virus C - Viral Disease and Hepatotoxicity

Regardless of their viral status, the patients in our study received immunosuppression according to protocols and they were supervised by a gastroenterologist. A raise in viral replication was observed during induction immunosuppression therapy, but not during maintenance therapy, with a medium level of HCV RNA during follow up of 139.809 IU/ml ± 267. On the other hand, renal relapse wasn't linked to viral status. Pearson correlation test suggested no significant correlations between viremia and eGFR during follow-up ($p>0.05$).

All patients had controlled hepatic disease when included in the study and the evolution of virus C infection and hepatic disease wasn't influenced by immunosuppressive regimens. Nonetheless, immunosuppression was delayed or stopped in 3 patients. Two of them were SLE patients (lupus nephritis class IV) who received induction treatment consisting of cyclophosphamide (total dose 1g, total dose 2.2g respectively) and had a significant raise in viral copies – HCV RNA 42 million IU/ml, respectively 4.5million IU/ml. The other one was a patient with cryoglobulinemic glomerulonephritis who received 600mg of intravenous cyclophosphamide and viral load after immunosuppression was 5 million IU/ml.

Detectable viral load was found in 55 patients during immunosuppressive treatment (induction/maintenance) and antiviral therapy was started during or right after induction treatment. Regardless of the immunosuppressive regimen, 70% of the patients had undetectable viremia at the end of follow-up. From the subgroup of patients with ESRD, eleven patients (representing 55%) had detectable viremia at the end of monitoring. Pearson correlation coefficient suggested no significant correlations between viremia and baseline proteinuria nor proteinuria recorded at follow-ups ($p>0.05$).

As for liver function tests, GOT and GPT had maximum values either during induction treatment or maintenance treatment, regardless of the immunosuppression levels. Pearson correlation coefficient showed that there was a negligible and not statistically significant, but positive correlation between maximum GOT and GPT values and HCV RNA levels ($r=0.057$, $p>0.05$, $r=0.02$, $p>0.05$ respectively). Furthermore, 22% of patients had undetectable viremia when reaching maximum levels of aminotransferases.

Antiviral Treatment and Renal and Overall Prognosis

All patients received the classic regimen consisting in interferon plus ribavirin and they were treated between 1997-2013. Hemolytic anemia and pancytopenia were reported in 10% of patients who received ribavirin and they were given erythropoietin (maximum dose 40.000 IU) or a lower dose of ribavirin.

Only 20% of patients received DAAs (direct acting antivirals), consisting of Dasabuvir and Ombitasvir/Paritaprevir/Ritonavir and they had SVR (sustained viral response) during follow-up and no adverse effect was recorded.

Complications

In the event of infectious complications (most frequent low UTI and herpes zoster) due to immunosuppressive treatment, therapy was delayed, doses were reduced or maintained and antibiotics or antimycotics were added to the therapy. No septic patient was recorded. As for other important complications, immunosuppression was stopped due to neoplastic disease occurrence (ovary cancer and Hodgkin lymphoma). In both cases the therapeutic scheme implied cyclophosphamide (total dose 6.4g and 4.8g, respectively).

Study Limitations

Small number of patients

Our study focused on patients with a glomerular disease that could be secondary to hepatitis C virus infection. We therefore excluded patients with diabetic nephropathy, ischemic nephropathy or nephroangiosclerosis. After we applied all exclusion criteria, only 59 patients were left.

Only a few patients received DAAS

All our patients were treated with the classic regimen (interferon and ribavirin) and just 20% of them received later DAAs.

A technique to detect occult hepatitis C virus infection wasn't available (the detection of HCV RNA in lymphocytes and monocytes from peripheral blood) in the case of patients with undetected viremia who developed glomerular disease.

Viral particles on renal biopsy fragments couldn't be identified due to technical issues.

Discussion

Fabrizi's meta-analysis reported an increased incidence for CKD in pacients with positive HCV serologic status [8] and Park's study showed a 27% increased risk of CKD in HCV patients when compared with patients without hepatitis C virus infection [9]. In our study, median period between hepatitis C infection diagnosis and renal disease diagnosis was 11.76 years ± 8.05, suggesting the fact that a longer evolution of virus C infection is needed in order to induce renal disease by several mechanisms (cryoglobulins, deposits of HVC antigens in the endothelial cell or in the mesangium, viral attachment to cell receptors) [10].

Logistic regression analysis showed that a high baseline creatinine increased by 9 times the risk of ESRD ($Chi2(1) = 14.99$, $p <.001$), as well as proteinuria, but the influence wasn't statistically significant ($p>0.05$). Fifty percent of patients with extracapillary proliferation responded to therapy, probably because the therapy was initiated correctly and early in the diagnosis of the patients. A favorable response was defined by a decrease in serum creatinine/stabilization of serum creatinine, a decrease in proteinuria, inactive urinary sediment. As for patients with more than 20% of interstitial fibrosis and tubular atrophy on renal biopsy fragments, only 20% of them had ESRD at the end of the study. Hommos et al found that even though severe fibrosis is a very strong predictor of ESRD, some patients will not progress to kidney failure and not require dialysis within 5 years from the moment of renal biopsy [11].

In patients with cryoglobulinemic glomerulonephritis, most of the patients (9 of 16 patients) had no response to treatment, evolving towards ESRD (all of them had nephrotic syndrome). Also, all of them had at least one associated complication (peripheral neuropathy, skin involvement, myalgia, arthralgia) and one had intra-alveolar hemorrhage treated with cyclophosphamide and methylprednisolone. As for laboratory abnormalities, all cryoglobulinemic patients had a high rheumatoid factor and a positive cryoglobulinemic test at the end of the follow up. This can be the effect of an incomplete clearance of cryoglobulin deposits despite antiviral and/or immunosuppressive therapy. Furthermore, all patients had persistent low c4 (persistent immunologic activity during the entire follow up).

Active renal disease can persist even when patients achieve SVR after antiviral treatment, most likely because of residual B cell clones that produce rheumatoid factor [12]. Regarding lupus and hepatitis C virus, the infection is associated with autoimmune processes and has been postulated as a potential etiologic agent or triggering agent of systemic lupus erythematosus. In our study, lupus nephritis was the most frequent type of glomerulonephritis after cryoglobulinemic glomerulonephritis. Ongoing immunologic activity, suggested by persistent high levels of anti dsDNA antibodies, could be a risk factor for a subsequent relapse in the future. The study of Ramos-Casals et al. showed a higher prevalence of HCV infection in 134 SLE (systemic lupus erythematosus) patients compared to 200 controls [13]. The late onset of SLE (defined as onset

after the age of 50) is generally associated with milder evolution of the disease, with less serious major organ manifestations and less frequent [14]. In our study, the youngest patient was 45 years old and we found that 8 of 11 patients had a stable creatinine and proteinuria <1g/day at the end of follow-up.

The clinical severity of the glomerulonephritis associated with virus C infection does not correlate with the severity of liver damage. Pearson correlation test found no correlation between GOT, GPT values and serum creatinine ($r<0.1$, $p>0.05$). Furthermore, viral status doesn't correlate with renal relapse. The same correlation test suggested no significant correlations between viremia and eGFR during follow-up ($p>0.05$) and no significant correlations between viremia and baseline proteinuria nor proteinuria at successive follow-ups ($r=0.16$, $p>0.05$).

Viral load increased during immunosuppressive treatment, but immunosuppression was delayed or stopped in only 3 patients. All patients had a controlled hepatic disease when included in the study, and the evolution of virus C infection and hepatic disease wasn't influenced by immunosuppressive therapy regimens. Even if viral replication increases, the cases of severe hepatitis or hepatic decompensation of a preexistent hepatic disease are rare, maybe because of a less vigorous immune response to viral antigens – which finally induces a higher chronicity rate [15]. Pearson correlation coefficient showed that there was a negligible and not statistically significant, positive correlation between maximum GOT and GPT values and HCV RNA levels ($r=0.057$, $p>0.05$, $r=0.02$, $p>0.05$ respectively). Furthermore, 22% of patients had undetectable viremia when reaching maximum levels of aminotransferases.

The reason for undetectable viremia in patients who received immunosuppressive therapy or supportive treatment could be the association between occult virus C infection and renal disease (the literature describes cases of patients with HCV-NS3 found in renal cells in patients with undetectable HCV RNA [16]), but due to technical issues we couldn't identify viral antigens in renal fragments in our study. Immunosuppressants can be directly hepatotoxic, or they can amplify a preexistent hepatic disease, especially in the situation of a viral hepatitis [17-19]. When hepatic metabolism is altered due to a preexistent hepatic disease, it can lead to higher and more persistent levels of a drug, causing a raise in systemic toxicity and exacerbating hepatic dysfunction. Higher doses of immunosuppressive therapy (chemotherapeutic doses) are associated with impaired liver functional tests in patients with hepatitis C virus, but it can cause problems only in the situation of a decompensated hepatic disease. The actual recommendation is to continue with immunosuppression if there are no severe alterations of liver functional tests [20,21]. The clinical and renal outcome of most of the patients was due to a combination between immunosuppressive drugs, nephroprotective measures and patients' compliance.

Conclusions

Predicting the outcome of glomerulonephritis associated with hepatitis C virus is not easy, due to a heterogenous nature of the association between these two entities. Furthermore, a huge number of factors (some of them time dependent) influence this outcome, so the clinician will have to decide the most appropriate therapy for each patient. As we have seen in our study too, an early diagnosis and treatment start are important for the prognosis of these patients. The new antiviral and immunosuppressive therapy (especially biological therapy) bring hope of a more efficacious and less toxic treatment, even in the case of a life-threatening event. What remains still unclear is the duration of both antiviral and immunosuppression therapy so more studies are necessary to clarify this issue.

Acknowledgement

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Conflict of Interest

None.

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