MAK HILL Publications International Journal of Tropical Medicine

Research Article
doi: 10.36478/makijtm.2024.3.110.115

Hepatitis C Causing Membranous Nephropathy

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Abstract
Hepatitis C virus (HCV) is a persistent infective condition that mostly affects the liver. While HCV primarily causes hepatitis, many chronic HCV patients experience extra hepatic involvement during their disease. Chronic HCV infection can lead to many forms of renal disorders. HCV infection has been associated to a range of histopathological types of kidney diseases, including membra no proliferative glomerulonephritis (MPGN), membranous nephropathy, fibrillary/immunotactoid glomerulopathy, focal segmental glomerulosclerosis, IgA nephropathy, renal thrombotic micro an giopathy, interstitial nephritis and vasculitic renal involvement. The most common kind of HCV-related glomerulonephritis is membrane proliferative glomerulonephritis (MPGN), which is linked to type II cryoglobulinemia. Direct-acting antiviral treatments have significantly improved the treatment of HCV infection, leading to faster viral clearance. Patients with HCV with kidney dysfunction can be managed using a combination of antiviral medications, immunosuppressant, plasm apheresis and monoclonal antibodies. If antiviral therapy alone does not result in renal disease remission, adding B-cell depleting drugs can help prevent pathogenic antibodies from forming. Immunosuppressive treatments, including steroids, alkylating drugs and plasma exchanges, can effectively decrease immune-complex-driven inflammation. However, their propensity to promote HCV replication and aggravate liver disease is a significant drawback.

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Key Words
Hepatitis C virus (HCV), nephropathy, membranous nephropathy

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Received: 20 May 2024
Accepted: 15 July 2024
Published: 19 July 2024

Citation: Rahul Ade, Hema Manvi Koneru and Avula Surya Teja, 2024. Hepatitis C Causing Membranous Nephropathy. Int. J. Trop. Med., 19: 110-115, doi: 10.36478/makijtm. 2024.3.110.115

INTRODUCTION

Hepatitis C virus (HCV) infections are the most common contributing factors liver damage[1]. Infection with the Hepatitis C virus (HCV) encompasses organ involvement both hepatic and extra hepatic[2]. HCV is a lipid-enveloped tiny RNA virus measuring 30-38 nm. from the Flaviviridae family. This virus may induce kidney problems. Renal illness patients are more susceptible to HCV infection due to increased exposure to other patients' blood through transfusions, haemodialysis, or transplants[3]. The most prevalent category of hepatitis C virus-associated glomerul one phritisis membrane proliferative glomerulonephritis (MPGN), which is linked to type II cryoglobulinemia. Immunoglobulins (Igs) that precipitate at low temperatures are known as cryoglobulins[4]. HCV-associated glomerulonephritis is induced by immune complexes including HCV antigens, anti-HCV antibodies and rheumatoid factors (anti-IgG antibodies) being accumulated in the glomerulus[5]. Patients with proteinuria and renal failure may not have clinical manifestations of cryoglobulinemia or liver damage. Nonetheless, a large number of patients do exhibit cryoglobulinemia, rheumatoid factors, and hypocom plementemia in their lab tests[6]. More focused, hypothesis-driven strategies have become possible as our knowledge of the aetiology of HCV-related nephropathies has increased[7]. Regular screening for cryoglobulinemia, complement factors, rheumatoid factor, hypertension, microscopic hematuria, micro albuminuria and renal function should be performed on HCV-infected patients. In situations of proteinuria, abnormal kidney process, or cryoglobulinemia, a renal biopsy ought to be conducted. With this approach, we will be able to identify HCV-related silent glomerular illness early on. Patients who have membrane glomerulonephritis (MGN) or MPGN should also be checked for HCV infection. This covers the following: liver enzyme levels, HCV serology using a 3D-generation enzyme-linked immuno sorbent test, and, if available, HCV RNA in the serum and cryoprecipitate. A normal level of liver enzymes does not rule out an HCV infection[8]. Treatment options for viruses include: (a) antiviral drugs to prevent the generation of immune complexes, cryoglobulins and prompt kidney damage., (b) B-cell exhaustion to lessen the development of cryoglobulins and (c) immunosuppressive medications to reduce glomerular inflammatory process[7]. In summary, the severity of the clinical condition and response to therapy should be taken into account while managing MPGN associated with HCV. Following the viral response, there may be a delay in the renal reaction. Hence, it is imperative to initiate immuno suppression concurrently with or prior to antiviral therapy in severe instances and to sustain immuno suppression even in the event of a negative HCV viral load[9]. Recommendations for the treatment of HCV-related cryoglobulinemic glomerulonephritis are based on case reports, limited uncontrolled trials, and the views of specialists because there is no standardised categorization of severity for this condition[10]. Understanding the renal involvement of HCV infection and associated sequelae is crucial. Testing of antiviral medications with improved efficacy and lower toxicity are required to enhance the outcomes of chronic renal disease patients with HCV infection. There is a shortage of randomized controlled studies to evaluate therapeutic alternatives[11].

Pathogenesis of HCV Associated Nephropathy: Each year, around 3-4 million people globally get infected with HCV. HCV infection causes around 350,000 deaths annually[11]. Hepatitis C virus (HCV) infection is a serious medical condition that is often preceded by extra hepatic symptoms such as glomerulo pathies. End-stage renal disease was depicted to be more prevalent in HCV-infected individuals[10]. HCV infection can cause renal symptoms such as essential mixed cryoglobulinemia, MPGN without cryoglobulinemia, and membranous glomerulonephritis[11]. Patients with HCV with kidney dysfunction can frequently be treated with a particular combination of antiviral medications, immune-suppressive drugs, plasm apheresis and modern monoclonal antibodies[12,13].

HCV Associated Nephropathy: In glomerulonephritis due to the hepatitis C virus (HCV), the most common kind is membrane-proliferative glomerulonephritis (MPGN), which is linked to type II cryoglobulinemia. For individuals suffering from HCV-related glomerulonephritis, blocking the renin-angiotensin system and administering ribavirin in combination with conventional or pegylated a-interferon anti-HCV treatment are essential. Immunosuppressive medication is required for individuals with nephrotic-range proteinuria and/or worsening renal failure[4].

There is not much research on the pathophysiology of kidney damage linked to HCV. Cryoglobulin synthesis is excessive when HCV is present. Because of cryoglobulin deposits, immune complex-mediated vasculitis may be triggered by the cryoglobulin, resulting in vascular thrombosis and inflammation[2].

Cryoglobulinemic Glomerulo Nephritis/ cryoglobulinemic nephropathy: Type 1 cryoglobulinemia accounts for 10-15% of case cenarios. Type 2 cryoglobulinemia is caused by immunological

complexes that include both monoclonal IgM and polyclonal IgG antibodies. It occurs in viral infections such HCV, HBV (hepatitis b) and cytomegalovirus, as well as persistent inflammatory disorders as systemic lupus erythematosus, Sjogren syndrome and rheumatoid arthritis[11]. The deposition of immunological complexes in the glomerulus composed of the HCV antigen, anti-HCV Ig G antibodies and an IgM kappa rheumatoid factor appears to be linked with HCV-associated cryoglobulinemic glomerul one phritis. Extra-renal symptoms are frequently linked to renal illness caused by HCV-related cryoglobulinemic renal disease[4]. Hypertension, microscopic hematuria, proteinuria, acute nephritis, or nephrotic syndrome are among the clinical manifestations, which are frequently linked to the ingestion of C3 and C4 complement[7]. Under light microscopy, the histological appearance reveals widespread and universal endocapillary hypercellularity together with mesangial proliferation. Additionally, cryoglobulins can form eosinophilic thrombi in glomerular capillaries, which are often linked to fibrinoid necrosis of the glomeruli and vasculitis[7]. C3, IgG and IgM depositions on the mesangium and the capillary wall may be seen using immunofluorescence microscopy[10].

HCV infection in B cells produces IgM with RF activity, which binds to HCV-IgG immune complexes. Cold-precipitable immune complexes accumulate in the subendothelial region and mesangium, activating the classical complement pathway. This results in the production of C5a and C3 anaphylatoxins, which attract and activate inflammatory cells. Additionally, membrane attack complex (MAC) is deposited on the endothelium, activating proinflammatory activities[7].

Membrano Proliferative Glomerulonephritis (MPGN): The glomerulonephritis most closely linked to long-term HCV infection is type I MPGN[10]. Immunoglobulins known as kinds I, II and III cryoglobulins precipitate at low temperatures. The deposition of immunological complexes consisting of the HCV antigen, anti-HCV immunoglobulin (Ig) G antibodies and a rheumatoid factor-most commonly IgM kappa-in the glomerulus is linked to HCV-associated cryoglobulinemic glomerulonephritis, which is frequently associated with type II cryoglobulinemia. Patients typically show up clinically with microscopic hematuria and proteinuria[8]. Kidney samples that undergo histological investigation typically show evidence of glomerular infiltration by activated macrophages. Because monocytes are positioned between the endothelium and the basement membrane, the glomerular basement membrane has two shapes. IgM, IgG and complement components are seen as subendothelial deposits in immunofluorescence[8].

Immunofluorescence reveals the presence of 1gM, IgG, and C3. Electron imaging reveals immunological deposits in the subendothelial and paramesangial regions (arrows)[5]. Hepatitis B virus-related membranous nephropathy coupled with mesangioca pillaryglo merul one phritis, displaying capillary wall duplication with a "tram-track" look[13].

Membranous Glomerulonephritis (MGN): Membrane glomerulonephritis is caused by the deposition of HCV-containing IC in the subepithelial glomerulus[7]. Both the histology results and the clinical appearance resemble idiopathic MGN. Their biological characteristics include normal complement levels, no serum rheumatoid factors and no cryoglobulins[8].

Focal Segmental Glomerular Sclerosis (FSGN): FSGN is a rare glomerul one phropathy in HCV-infected individuals. Diagnosing primary FSGS can be tough, however HCV infection test and clinic characteristics can assist distinguish between the two forms[2]. HCV infection causes glomerular lesions that are primarily supported by cryoglobulins and immune complex deposits. In HCV-positive individuals, antibody-independent glomerul one phritides may mimic FSGS[7]. Pegylated interferon-a (PEG-IFN-a) monotherapy led to clinical remission of nephrotic syndrome, sustained virological response (SVR) and stability of renal function. Patients stayed in remission for up to five years following therapy[10].

IgA Nephropathy: Reduced IgA clearance with IgA-containing IC is the mechanism of kidney damage in this type of nephropathy[7].

Fibrillary/Immunotactoid Glomerulopathy: The majority of patients presented with hypertension, edema, nephrotic proteinuria and microscopic hematuria in fibrillary glomerulopathy. Every patient exhibited detectable HCV antibody levels[10]. Microfibrils are extracellular deposits seen in the glomerular capillary walls and mesangium. The deposits exhibit IgG4 high prevalence, similar to typical fibrillar GN[7].

Diagnosis: Patients infected with HCV typically show no symptoms at all or very little. Thus, it's crucial to routinely check for anti-HCV antibodies in order to detect HCV infection, particularly in patients with chronic kidney disease (CKD), those on dialysis and those who have had kidney transplants[2].

HCV patients need to be frequently examined for microscopic hematuria, micro albuminuria, renal function, hypertension, cryoglobulinemia, rheumatoid factor and complement factors. A kidney biopsy is recommended for those with impaired renal function,

cryoglobulinemia or proteinuria. This method can detect HCV-related silent glomerular disease in its early stages[8].

Patients with MGN or MPGN must be tested for HCV infection. This comprises HCV serology using a 3D-generation enzyme-linked immunosorbent test, liver enzyme values and HCV RNA in blood and cryoprecipitate (if available). Having normal liver enzyme levels does not always rule out HCV infection[8].

Light microscopy may reveal glomerular hypercellularity due to leukocyte infiltration of glomerular capillaries (mononuclear and polymorphonuclear)[12]. Immunofluorescence typically shows the presence of IgG, IgM and C3 in the capillary walls and mesangium[12].

Treatment: A greater knowledge of the etiopathologenesis of HCV-linked nephropathies has gradually led to more focused, hypothesis-driven approaches: (a) antiviral treatment to prevent the generation of immune complexes, cryoglobulins, and prompt viral harm to the kidney., (b) B-cell reduction to lessen synthesis of cryoglobulin and (c) immunosuppressive treatment that target inflammation of the glomerulus[7].

Specific therapy is needed for HCV-related renal dysfunction. This treatment consists of either anti-HCV medication alone for mild renal disease or a combination of antiviral and immunosuppressive medicines for severe renal illness, including progressive renal failure, nephrotic syndrome and disorders that are resistant to sole anti-HCV therapy[8]. For HCV-related cryoglobulinemic glomerulonephritis, there is no conventional categorization of severity, hence suggestions on case reports, small uncontrolled research and specialist's opinions form the basis for the care of this condition[10].

Anti-HCV Treatment: Anti-viral therapy have been utilized to remove HCV from the serum and reduce renal damage in HCV-positive patients with glomerulonephritis, as a relationship between cryoglobulinemic MPGN and HCV infection has been identified[8]. Sustained virologic response (SVR) is the most reliable long-term prognostic factor. Combination treatment (ribavirin+IFN (interferon)α) leads to improved SVR and reduced proteinuria[10]. HCV-specific antiviral medications including direct acting antivirals (DAAs) have changed the therapy of chronic HCV infection, but interferon and ribavirin remain the mainstay of care for newer cases[7]. Side effects of IFN-α include malaise, flu-like symptoms, asthenia, myalgia, weight loss, hematological abnormalities, cardiovascular problems and neurological diseases. Patients with impaired kidney function experience more adverse effects from IFN-α than those patients with normal kidney function, which might be due to varying IFN-α pharmacokinetics[8].

Non-specific Immunosuppressive Therapy/Cytotoxic Agents: Cytotoxic medicines reduce B-lymphocyte proliferation, which reduces cryoglobulin synthesis[11]. Cyclophosphamide is used to treat HCV-associated glomerulopathies because it effectively inhibits the formation of cryoglobulin by B cells. Mycophenolate mofetil (MMF) inhibits lymphocyte proliferation and function with more selectivity than cyclophosphamide. Corticosteroids may be administered in severe mixed cryoglobulinemia presentations at high oral dosages (e.g., prednisone 0.5-1.5 mg/kg per day) or intravenous pulses (methylprednisolone 0.5-1.0 g/d for 3 days followed by oral prednisone). However, corticosteroids may induce HCV replication and aggravate hepatic disorders[10]. Previous uncontrolled investigations on a minimal number of patients of found that these medications effectively managed the acute stage of the condition, but were typically less tolerated[8].

B-Cell Depletion Therapy-Rituximab: Rituximab is a monoclonal antibody that depletes B cells and targets CD-20. It inhibits the formation of monoclonal IgM and cryoglobulins[10]. Rituximab is a human-mouse chimeric monoclonal antibody that attacks B cells through the CD20 antigen, has been shown to be efficacious and well-tolerated in B-cell non-Hodgkin lymphomas patients. Therefore, it is utilized for therapy of both HCV-related cryoglobulinemic MPGN and mixed cryoglobulinemia[8]. The most effective treatment for MC-GN is to eliminate the viral cause of HCV-associated glomerular disorders. B-cell depleting medications, either alone or in conjunction with antiviral treatments, are commonly used to prevent immunological complex development and manage disease progression[7]. Common adverse effects include vomiting, fever, nausea, fever, broncho spasm and chills, which are typically confined to the time of infusion and generally tolerated[11].

Plasmapheresis: It is claimed that eliminating immune-complexes from the blood may also slow their buildup in the kidney. To prevent immune complexes and cryoglobulins from re-accumulating, it should be used in conjunction with immunosuppressive therapy[10].

Drawbacks of Current Therapies: Limitations include a scarcity of studies with small sample sizes, a focus on individuals with significant hematuria, proteinuria or impaired renal function, a lack of information in

patients with prior signs of renal illness and inconsistent outcome assessments across research, making comparisons challenging[12].

Possible Future Treatments: Further exploration are needed to provide evidence-based guidelines for treating HCV-related glomerulopathies[4]. It is theorized that IL-2 promotes the survival and function of regulatory T cells. A prospective open-label, phase 1-phase 2a research, conducted on ten patients diagnosed with HCV-induced vasculitis who were resistant to conventional therapy received low-dose IL-2. In the majority of the patients, cryoglobulinemia decreased and vasculitis improved. Furthermore, it significantly reduced oxidative stress mediators and inflammation. These beneficial effects of IL-2 were thought to be linked to regulatory T cells (Treg) recovery[10].

RESULTS AND DISCUSSION

Hepatitis C virus (HCV) is a chronic infection that predominantly damages the liver[11]. HCV is primarily responsible for chronic liver disease, but it can also induce extra hepatic symptoms such as mixed cryoglobulinemia and glomerulonephritis[5]. Small trials suggest potential for innovative antiviral treatments in HCV-associated glomerulopathies[7]. Patients with HCV should be examined once a year for micro albuminuria, microscopic hematuria, cryoglobulinemia, micro albuminuria, renal function, hypertension and complement factors. To diagnose cryoglobulinemia, serum is kept warm and assays at 37 °C are done. Patients with proteinuria, decreased renal function, or cryoglobulinemia should have a kidney biopsy. Similarly, individuals with MGN or MPGN should be examined for HCV infection[10]. This comprises HCV serology using a 3D enzyme-linked immunosorbent test, liver enzyme values and HCV RNA in serum and cryoprecipitate (if available). A normal liver enzyme level does not exclude the possibility of HCV infection[8].

Three techniques might be proposed for treating HCV-associated glomerulopathies and cryoglobulinemic renal disease[1]: Antiviral therapy to prevent HCV-induced renal damage and immune-complex production[2] B-cell reduction therapy to prevent immune-complex and cryoglobulin synthesis and[3] nonspecific immunosuppressive treatment aiming inflammatory cells to halt immune-complex production and treat cryoglobulin-associated vasculitis[10].

Combining these therapies with B-cell depleting medications may lead to better results for afflicted individuals. Limited research in this field make it difficult to determine the safety and efficacy of these medicines[7].

The development of direct-acting antiviral medicines in recent decades has transformed the treatment of HCV infection, drastically boosting viral clearance rates. When antiviral medication solely fails to promote kidney disease remission, add-on B-cell reducing drugs can be used to prevent the manufacture of harmful antibodies[7].

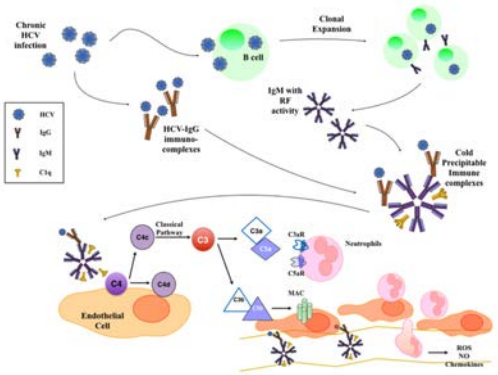

Fig 1: Etiogenesis of HCV-induced Cryoglobulinemic Nephropathy

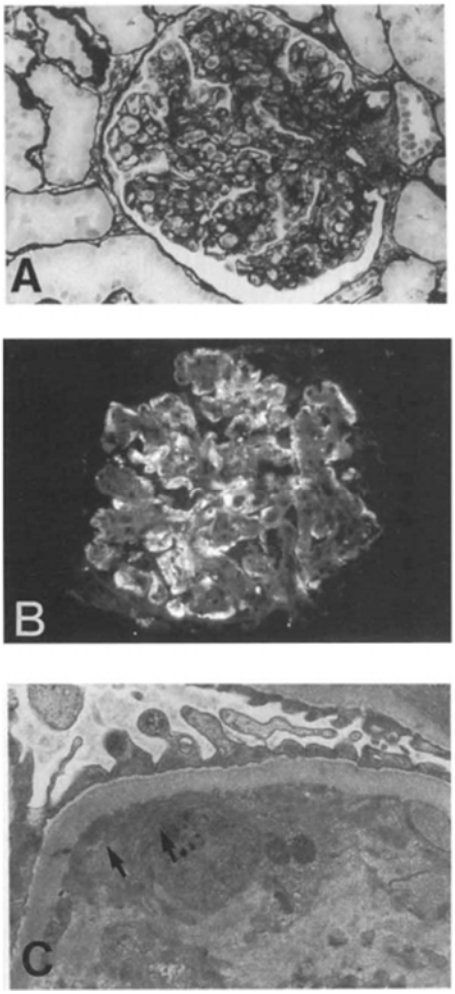

Fig 2: HCV-associated MPGN is characterized by glomerular hypercellularity in a lobular pattern

Treatment with α-interferon may help by suppressing viremia, lowering proteinuria, and maintaining renal function. However, long-term and controlled trials are needed to establish this and evaluate the risk of recurrence[5].

CONCLUSION

HCV causes a variety of renal diseases and complications in both natural and transplanted kidneys. HCV can cause a variety of kidney diseases, including cryoglobulinemia, membranous, IgA and fibrillary nephropathy[7].

To effectively manage HCV-related MPGN, it's important to consider the severity of the condition and therapy response. The renal reaction might occur following the virological reaction. In severe circumstances, it is crucial to initiate immunosuppression prior to antiviral therapy and maintain it even after a negative HCV viral load[9]. Emerging evidence from modest studies indicate that innovative antiviral treatments have potential in HCV-associated glomerulopathies. These medications, together with B-cell reducing medications, may refine the results of afflicted individuals. However, the minute number of research in this field prohibits a definitive evaluation of the safety/efficacy profile of these medicines[7].

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