Mixed Cryoglobulinemia and HCV: An Overview

Mahmoud El-Bendary¹*, Hatem Elalfy¹, Hala Sobh¹ and Mustafa Neamatallah²

1Department of Hepatology, Mansoura University, Egypt
2Department of Medical Biochemistry, Mansoura University, Egypt

Abstract

Chronic Hepatitis C Virus (HCV) is a worldwide public health problem affecting over 170 million people, or about 3% of the world’s population. In Egypt, the situation is quite worse, with the overall prevalence (percentage) of positive for antibody to HCV being 14.7% [1].

HCV predominantly affects the liver but it can also produce a number of extra hepatic manifestations. It has been reported that 74% of patients with hepatitis C have at least one extrahepatic manifestation, the most common condition being essential mixed cryoglobulinemia (40%). The syndrome of mixed cryoglobulinemia represents the consequence of an immune complex type vasculitis. It is characterized by the clinical triad of purpura, arthralgia, and asthenia, and may involve numerous organs, particularly the peripheral nervous system and kidneys. Understanding the immunopathogenesis of mixed cryoglobulinemia is important for the development of diagnostic tools and appropriate therapy for such a condition.

Immunopathogenesis of HCV-Related Cryoglobulinemia

Global B-cell stimulation may be fundamental to HCV-related cryoglobulinemia, which is a consequence of chronic antigenic stimulation of the humeral immune system. It is believed that the hepatitis C virus attaches itself to B lymphocyte cells, which causes the immune system to produce auto-antibodies [6].

It is suggested that a proto-oncogene named Bcl-2, when activated, increases B-cell survival by inhibiting apoptosis. This could lead to increased B-cell quantities which may lead to the increased production of auto-antibodies and cryoglobulins [7]. Another possibility suggested is that the HCV E2 envelope protein binds to the cell surface glycoprotein CD81 that is present on B cells as well as on hepatocytes, thus reducing the threshold for B-cell activation. A molecular mimicry with NS5A and E2 envelope protein binds to the cell surface glycoprotein CD81 that is present on B cells as well as on hepatocytes, thus reducing the threshold for B-cell activation. A molecular mimicry with NS5A and E2 envelope protein binds to the cell surface glycoprotein CD81 that is present on B cells as well as on hepatocytes, thus reducing the threshold for B-cell activation.

A cytokine named BAFF (B-cell activating factor), of the tumor necrosis factor family, is another
important player not only in the development in HCV-related cryoglobulinemia but also in the pathogenesis of several systemic autoimmune diseases, including Rheumatoid Arthritis (RA), Primary Sjogren's Syndrome (pSS), and Systemic Lupus Erythematosus (SLE) [8,9]. BAFF binds to specific receptors selectively expressed by B cells which play a critical role in B-cell maturation, long-lived bone marrow plasma cell survival, promotion of humoral immune response, and CD40-independent immunoglobulin class-switch recombination [10]. Furthermore, the fact that auto reactive B cells, which are associated with the development of autoimmune disorders, are more dependent on BAFF for survival than alloreactive B cells strongly suggests that BAFF plays a role in HCV-related cryoglobulinemia. Interestingly, serum BAFF levels were found to be even higher in patients with chronic HCV and mixed cryoglobulinemia [11].

In addition, hypocomplementemia has also been described in association with hepatitis C viremia in healthy blood donors. Complement solubilization of immune complexes could provide an explanation for the observation that symptomatic HCV-MC correlates with advanced liver disease when synthesis by hepatocytes might be expected to be low [12].

Mannan-Binding Lectin (MBL) is a liver derived plupotent serum lectin that plays a role in the innate immune response of the host [13]. It is an acute phase protein that is involved in the activation of the complement pathway, which results in destruction of pathogens by the membrane attack complex or by complement mediated phagocytosis [14]. HCV encodes two highly glycosylated envelope proteins, E1 and E2, which are potential targets for interaction with MBL. Mutant MBL2 haplotypes have been linked to disease progression and response to therapy in HCV infection [15]. In addition, MBL concentration tended to increase with the grades of fibrosis and hepatic inflammation [16].

Circumstances predisposing HCV infected patients to develop mixed cryoglobulinemia vaucities remain unclear. Studies have failed to demonstrate a clear role of either viral or host factors, including viral load and host lymphocytes or immunoglobulin subsets. In a prospective analysis of human leukocyte antigen (HLA) class II alleles performed in a large cohort of patients with HCV with and without HCV mixed cryoglobulinemia associated vasculitis [17,18], univariate and multivariate analysis showed that HLA-DR1 was the only positive predictive factor for the presence of mixed cryoglobulinemia and HCV-mixed cryoglobulinemia associated vasculitis [18], while HLA-DR7 appears to be protective against the production of type II mixed cryoglobulins. These results suggest that the host's immune response genes may play a role in the pathogenesis of HCV-Mixed Cryoglobulinemia [17].

**Diagnosis of Cryoglobulinemia**

There are no standardized criteria for the diagnosis of Mixed Cryoglobulinemia Syndrome (MCS) [19,20]. Diagnosis is based on clinic-pathological and laboratory findings. Cryoglobulinemia may be suspected if the patient has positive rheumatoid factors. Clinically, asymptomatic serum MC can be found in some individuals chronically infected with HCV, a condition that may precede the clinical onset of the disease by years or even decades. Palpable purpura is the most common clinical finding, occurring in 90% of cases [22], while glomerulonephritis, peripheral neuropathy, and generalized vasculitis are the most common complications of cryoglobulinemia [21]. The association between MC and severe liver damage or steatosis has been discussed widely [22], with several studies showing an epidemiological association between MC and severe liver damage. However, the pathogenesis' mechanisms of such an association have not been clearly identified [20,23].

The laboratory work-up of cryoglobulinemia vasculitis includes cryoglobulins testing, quantification of total serum protein and immunoglobulins, complement levels, evaluation of serum for monoclonal gammopathy, RF activity, virological markers (anti-HCV antibodies, HCV RNA, hepatitis B virus serology, hepatitis B virus DNA, and others), blood chemistry, and urine analysis [24]. Diagnosis of cryoglobulinemia commonly requires repetition of these tests in different laboratories, reflecting the high frequency of laboratory errors in the detection of cryoglobulins due to the failure of proper separation of serum from whole blood, loss of cryoprecipitate due to refrigeration before centrifugation, and an inadequate volume of serum for testing cryoglobulins at low levels [25].

**Common Signs and Symptoms Associated with Cryoglobulinemia**

**Weakness**

Approximately 2/3 of patients with cryoglobulinemia experience this symptom [26-28].

**Kidney disease**

Several kidney disorders can be seen with cryoglobulinemia, although the clinical symptoms and signs of MC can precede the onset of renal involvement for years. The most common is Membranoproliferative Glomerulonephritis (MPGN), usually type I, less commonly type III. In some cases, patients initially diagnosed with (MPGN) are unsuspected of chronic hepatitis C, which is diagnosed in the process of trying to uncover the cause for this disorder. Approximately 1/4th of patients with cryoglobulinemia have acute kidney involvement marked by a sudden rise in creatinine with severe proteinuria. Oliguria and dialysis requirement occur in a small minority of patients [29-30].

---

**Citation:** El-Bendary M, Elalfy H, Sobh H and Neamataallah M. Mixed Cryoglobulinemia and HCV: An Overview. SM J Hepat Res Treat. 2015; 1(1): 1005
Neuropathy

Neuropathy is numbness, tingling, or other abnormal sensation in the hands and feet, which may work their way up the arms or legs over time. Neuropathy is experienced by approximately 1/4th of people with cryoglobulinemia [31-32]. The pathogenic mechanism of peripheral nerve damage has been postulated to be vasculitis of the vasa nervorum, as well as autoimmune nerve damage, with cases of demonstrated demyelization [32]. Abnormalities on electrophysiological studies can be readily detected and can often be progressive with involvement of new areas over time, even if overall cryoglobulin levels decline with therapy. There is no clear central nervous system involvement [32].

Reynaud's phenomenon

Reynaud’s phenomenon describes intermittent episodes where the arteries of the fingers or toes suddenly go into spasm causing the skin to become very pale, cold, and numb. Attacks are usually brought on by exposure to cold or emotional stress. This phenomenon is experienced by approximately 1/4th of people with cryoglobulinemia [24].

Skin disorders

Purpura (dark red to purple lesions on the skin) is the most common skin manifestation of cryoglobulinemia (Figure 1). These lesions usually appear on the lower legs, but can be present elsewhere, and may progress to deep ulcers in approximately 10% of patients. Around 20% of patients with cryoglobulinemia have associated skin disorders [33]. Skin eruptions can be intermittent, with repeated episodes leading to hyper pigmentation of the involved skin, whereas ulcers usually appear above the malleoli. Frank skin necrosis and gangrene can also occur, but are less common.

Leukocytoclastic vasculitis, involving medium and, more often, small sized blood vessels (arterioles, capillaries, and venules) is the typical pathological finding of involved tissues. Leukocytoclastic vasculitis is easily detectable by means of skin biopsy of recent vasculitis lesions (within the first 24 to 48 hours) [34].

Sjogren’s syndrome

Sjogren’s syndrome is the drying of normally moist membranes of the eyes, mouth, and upper airway. This syndrome affects approximately 20% of patients with cryoglobulinemia [35].

Joint disease

Approximately 15% of patients with cryoglobulinemia experience joint pain that may be confused with rheumatoid arthritis [30-36].

Endocrinial manifestations

Type II diabetes, hypothyroidism with positive ant thyroid antibodies, and gonadal dysfunction are the most common manifestations [21].

Treatment Options

Therapy should be initiated for patients with symptomatic MC, and is directed both at the virus as well as the immune-mediated inflammation (Figure 1). According to disease severity, treatment options may include the following: (A) Patients with mild to moderate cryoglobulimic symptoms (purpura, arthralgias, peripheral sensory neuropathy) are typically managed with low doses of steroids. (B) Severe disease, including skin ulcers, motor neuropathy, glomerulonephritis, and disseminated vasculitis, require rapid and aggressive therapy to control the widespread immune devastation. (C) Life threatening conditions (rapidly progressive renal disease with CNS manifestations) warrant Plasmapheresis, steroids and rituximab [37]. Treatment may either eradicate HCV infection (etiologic therapy), suppress B-cell clonal expansion and cryoglobulins production (pathogenesis’ therapy), or ameliorate symptoms (symptomatic therapy).

Etiologic therapy

Under ideal circumstances, the treatment of MC aims to eradicate the HCV infection. Interferon therapy should not be started except after systemic vasculitis has come under initial control with immunosuppressant and/or plasma exchange, as the Initiation of Interferon (IFN) therapy can exacerbate the disease. Treatment of MC with interferon (IFN) therapy is associated with a relatively poor response [37], although PEG-IFN plus Ribavirin (RBV) have shown better results [38]. The goal of therapy in these patients is not limited to a sustained virological response; rather, patients might see an improvement in their renal manifestations with prolonged treatment courses. However, clinical improvements are often transient and restricted to patients with mild to moderate disease activity [39, 40]. While IFN therapy can induce an exacerbation of various vasculitis manifestations (i.e. glomerulonephritis, neuropathy) RBV, due to its renal elimination, may be contraindicated in patients with severe renal impairment [41]. The role of new Direct Acting Antiviral (DAA) is not yet established.Urraro et al 2015 reported a complete remission of a case of MC after sustained virological response following the addition of boceprevir (DAAs) to the combined RTX/Peg-IFN+RBV [42]. Stine et al 2014 found variable response of 3 cases of chronic HCV associated with MC when the Sofosbuvir is combined with Peg-INF +RBV ( 2 cases clear cryoglobulinaemia while the 3rd case did not clear MC) [43]. In another study by Cornella et al 2015 found persistence of MC in 5 cases despite completion of triple therapy with
oral antiviral agents (boceprevir, telaprevir or sofosbuvir) especially in cirrhotic cases which may need longer duration[44].

Pathogenetic therapy

This therapy is used when antiviral therapy is not recommended. Treatment should be limited to the time (weeks or months) required for symptom remission. Several alternative therapies may be adopted, which include corticosteroids due to their anti-inflammatory and immunosuppressive actions (at high doses of 1 mg/kg or 0.5–1 g daily). However, the disadvantage of favoring this agent is that it can lead to increased viral replication [45].

Immunosuppressive drugs (e.g. cyclophosphamide, chlorambucil, and azathioprine) are used to suppress antibody and cryoglobulins production. The most effective and commonly used cytotoxic drug is cyclophosphamide, given orally at doses of 2 mg/kg per day. Mycophenolate mofetil (1 g twice a day) can be used as a less toxic alternative to cyclophosphamide for the induction of remission in MC vasculitis. Mycophenolic acid is more selective than cyclophosphamide in inhibiting lymphocyte proliferation and functions [46]. Interestingly, mycophenolic acid seems to reduce viremia in HCV infected renal or heart-transplant recipients due to its ability to inhibit inosine monophosphate dehydrogenases, the same target enzyme inhibited by RBV [47]. However, data supporting this approach are limited and almost exclusively derived from anecdotal reports [48].

In patients unresponsive to treatment with steroids or other immunosuppressant, the administration of the immunosuppressant rituximab, a chimerical monoclonal antibody directed against CD20 antigen on B cells, has been proposed for the pathogenic treatment of HCV-related MC. By depleting B cells, rituximab has the potential to reduce the development of plasma cells, thereby limiting cryoglobulins production [49–50]. Rituximab, at the standard dose of 375 mg/m² weekly for 4 weeks proved to be a safe and effective treatment for most patients with HCV-MC, leading to significant clinical improvement as a consequence of both B cell depletion and decreases in serum cryoglobulins levels [51–52].

Although fever, chills, nausea, vomiting, urticaria, orthostatic hypotension, and bronchospasm occur in more than 80% of patients, these side effects are generally mild and limited to the infusion period. An increase in viral load, without significant variations in liver function tests, has been detected after rituximab treatment, so to reduce HCV replication a combination of rituximab with antiviral agents has been suggested [49,53].

Because the median duration of the response to rituximab therapy is about 1 year, a relapse of cryoglobulinemia vasculitis may develop following treatment. Relapses are preceded by peripheral B-cell repletion. It is unknown whether maintenance therapy with rituximab is better than retreatment after relapse [49].

Plasmapheresis can be used as an effective adjuvant therapy to treat severe exacerbations of cryoglobulinemia vasculitis, particularly active cryoglobulinemia glomerulonephritis. Both traditional plasma exchange and double-filtration plasma exchange are able to markedly reduce the levels of circulating immune complex, especially the cryoglobulins [54].

Oral cyclophosphamide (50 to 100 mg/day for 2 to 6 weeks) during the tapering of aphaeresic sessions can reinforce the beneficial effect of plasma exchange; moreover, it can prevent the rebound phenomenon that may be observed after the discontinuation of aphaeresis [19,55].

Symptomatic therapy

The hypo-antigenic diet, LAC diet, consists of a diet with reduced content of alimentary macromolecules with high antigenic properties, allowing for more efficient removal of cryoglobulins by the reticuloendothelial system. This diet can improve minor manifestations of the disease (purpura, arthralgias, and paresthesias) and is generally prescribed at the initial stage of the disease [24].

Colchicine, an anti-inflammatory agent with a relatively selective effect for gouty arthritides, has been proposed for MC patients with mild to moderate levels of the disease. In an uncontrolled trial, colchicine (1 mg/day for 6 to 48 months) improved clinical and laboratory variables, but its toxicity and the availability of alternative less toxic agents have substantially lessened its use [19].

References
