Extrahepatic Manifestations of Hepatitis C Virus: An Extending List

Amira M Soliman[1] , Soha A El hawari[1], Mohamed M Refaey[1], Nabila H Ahmed[1], Mohamed H Emara[1]

[1]*Tropical Medicine Department , Faculty of Medicine , Zagazig University, Egypt*

Corresponding Author
Nabila H Ahmed
email: nabila.hassan25@yahoo.com
Received : 1 /1 /2012
Accepted after revision: 5 / 2 /2012
Keywords : HepatitisC, Mixed cryoglobulinemia, Lymphoproliferative disorders, Porphyria cutanea tarda

Hepatitis C virus is a hepato-lymphotropic virus that was also detected in various organs of the body. Furthermore, this form of infection may be presented for the first time by an extrahepatic manifestation. Different extrahepatic manifestations for hepatitis C was described; these extend from strong associations as in mixed cryoglobulinemia to others were anecdotal finding as vitiligo was reported. The list of extrahepatic manifestations of hepatitis C is extending. In this review we tried to shade the light on this expanding list.

INTRODUCTION

Extrahepatic manifestations (EHM) of hepatitis C virus (HCV) include diseases that affect organs other than the liver, and it may be the first presentation of HCV infection. Association between them was first described in 1990 with cryoglobulinemia [1]. Subsequently, nearly all organs were reported as kidney, skin and thyroid [2]. Up to 40-74% of patients infected with HCV might develop at least one extrahepatic manifestation during the course of their disease [3].

PATHOGENESIS

HCV replicates within extrahepatic tissues with expression of viral proteins, leading to EHM. An important feature of HCV is that the virus avoids immune elimination. The consequences are chronic infection, accumulation of immune complexes and auto-immune phenomena. HCV shows lymphotropism in addition to the hepatotropism, which is responsible for many EHM [4].

I) Autoimmunity

- Auto antibodies production

The cellular components leak from the persistent destruction of the infected cells. About 20% with hepatitis C patients are ANA positive [5].

- The molecular mimicry between HCV and auto antigens [6].

- Abnormality of lymphocytic cells

HCV infection and proliferation within lymphocytes leads to functional alteration of lymphocyte and production of excessive auto antibodies and cryoglobulins [7].

II) HCV infection of cells other than hepatocytes

HCV binds several cell surface receptors. Cell tropism required for HCV genome replication are not well characterized [8].

Classification of EHM of hepatitis C virus

EHM classified into four groups according to degree of association recorded to HCV infection.

Table (1): EHM Classification [9].

Group A	Group B	Group C	Group D
Strong association	Significant association	Similar pathologic nature	Anecdotal
- Mixed cryoglobulinemia - B-cell non-Hodgkin's lymphoma	- Monoclonal gammopathies - Porphyria cutanea tarda - Lichen planus - Diabetes mellitus	- Autoimmune thyroiditis - Thyroid cancer - Sicca syndrome - Idiopathic lung fibrosis - Non cryoglobulinemic nephropathies - Erectile dysfunctions - Carotid atherosclerosis - Psychopathological disorders	- Psoriasis - Peripheral/central neuropathies - Rheumatoid arthritis - Polyarteritis nodosa - Behcet's syndrome - dermatomyositis - Fibromyalgia - Chronic pruritus - Kaposi's pseudosarcoma - Vitiligo - Cardiomyopathies - Mooren corneal ulcer -Necrolytic acral erythema

Mixed cryoglobulinemia (MC)

Is a systemic vasculitis characterized by the deposition of circulating immuno-complexes in small and medium-sized blood vessels resulting in clinical manifestations [10].

Cryoglobulins

Are serum proteins that precipitate at low temperatures and then redissolve during incubation at 37ºC. Different categories have been described that refer to their different immunologic compositions [11].

Table (2): Classification of cryoglobulins [12].

Type	Clonality of immunoglobulins	Associated diseases
I	Monoclonal immunoglobulins (IgM or IgG)	Lymphoproliferative diseases
II (mixed)	Polyclonal immunoglobulins (mainly IgG) plus monoclonal Immunoglobulins (IgM, IgG, IgA)	Mixed cryoglobulinemia
III (mixed)	Polyclonal IgG and polyclonal IgM	Mixed cryoglobulinemia

Prevalence

Although overt symptoms of cryoglobulinemic vasculitis develop in only approximately 5% of chronic HCV infection cases, circulating mixed cryoglobulin complexes are much more common in about 40–50% in chronic HCV-infected patients [10].

Significant geographic diversity appears among patients with HCV-related MC, with greater prevalence in southern Europe compared to northern Europe and North America, with high values (over 90%) in the Mediterranean area [13].

Pathogenesis

The Circulating immune complexes in HCV related MC comprises hepatitis C virions , IgG-IgM-RF antibody complexes and complement [14].

The common hypothesis regarding HCV-related cryoglobulinemia is the chronic antigenic stimulation of the humoral immune system, which facilitates clonal B-lymphocyte expansion [15].

Other hypotheses:

-Chronic HCV infection of B cells and Bcl-2 activation (protoncogene) which increase B cell survival by inhibiting apoptosis [16].

-Interaction of HCV E2 envelope protein with the cell surface glycoprotein CD81 that is present on B cells as well as on hepatocyte reduces the threshold for B-cell activation. HCV-specific proteins also demonstrate molecular mimicry with auto antigens. NS5A and NS core proteins can simulate host auto antigens, possibly resulting in B-lymphocyte activation and auto antibody production which may allow cross-

reaction between a virus-associated epitope and IgG auto antigen [17].

-Cytokine, B-cell activating factor of the tumor necrosis factor family (BAFF) also known as B-lymphocyte stimulators as zTNF4 were found in high levels in patients with MC associated HCV [18].

Correlation with Liver Disease

MC tends to correlate with duration of HCV infection and older age. However, cryoglobulinemia in the serum of HCV patients has been associated with increased risk of advanced fibrosis, the severity of hepatic steatosis on liver biopsy and cirrhosis, irrespective of age or disease duration [19].

Clinical features of MC

More common symptoms are general malaise, arthralgia and weakness. Arthralgia without arthritis is common, typically affecting the proximal interphalangeal joints of the hands, metacarpophalangeal joints, knees, and hips [20].

1- Skin

Commonly involved (95% of cases) with a cutaneous vasculitis ranging from palpable purpura (leukocytoklastic vasculitis) and petechiae in the lower extremities to large necrotic ulcerations. Raynaud's phenomenon occurs in up to 1/3 of cases and involves hands, feet, lips, ears, and the tip of the nose [20]

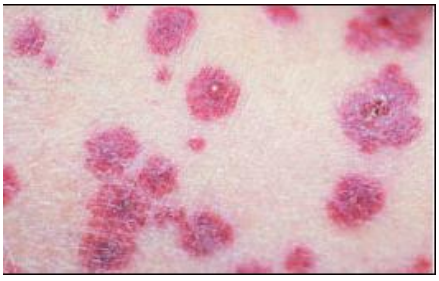

Figure (1): Leukocytoclastic vasculitis [21]

2- Kidney

Frequently involved (35-60%) and Membranous proliferative glomerulonephritis (MPGN) is the prevalent type associated with MC [22]. Anti-HCV-Ab is universal in patients with both cryoglobulinemia and MPGN. HCV-RNA is present in nearly 81% of MC related MPGN versus only 25% of cases of non-cryoglobulinemic MPGN [23].

Less often HCV causes focal segmental glomerular sclerosis or membranous or proliferative glomerulonephritis [24]. The course of renal pathology is variable. A clinical regression is observed in 10-15% of patients with nephritic syndrome. In 30% of cases, the clinical trend is slow and renal function is maintained for many years. In 20% of patients the disease is characterized by recurrent episodes of nephritic syndrome. In less than 15% of MC, dialysis is required [25].

3- Peripheral neuropathy

Mostly sensory and is characterized by numbness, burning, needles and pins sensations most often in the hands and feet [26].

4- Central nervous system (CNS)

CNS involvement in patients with HCV-positive MC is rare [27].

5-Other manifestations

Rarely other organs as lungs, GIT and heart may be involved, secondary to vasculitis has been reported [28].

Diagnosis of MC

Classification criteria for MC diagnosis include clinical and serological data. Some patients with chronic HCV infection may show complete or even incomplete forms of MC. In the latter, a strict follow up of the patient is required [29].

Table (3): Criteria for the diagnosis and classification of patients with MC [29]**.**

Criteria	Serologic	Pathologic	Clinical
Major	Mixed cryoglobulins Low C4	Leukocytoclastic vasculitis	Purpura
Minor	RF HCV+, HBV+	Clonal B-cell infiltrates (liver and/ or bone marrow)	Chronic hepatitis, MPGN, peripheral neuropathy, skin ulcers

"Definite" Mixed Cryoglobulinemia Syndrome

1) Serum mixed cryoglobulins (± low C4) + purpura + leukocytoclastic vasculitis

2) Serum mixed cryoglobulins (± low C4) + 2 minor clinical symptoms + 2 minor serological/pathologic findings [29].

Biopsy of skin lesions shows immune-complexes vasculitis of small vessels with mononuclear infiltration. HCV antigens are detected in skin lesions in 40% of cases [30].

Renal biopsy demonstrates deposits of IgG-IgM-RF activity and C3 in capillary loops. The most characteristic findings are the capillary thrombi consisting of precipitated cryoglobulins at light microscopy [31].

Nerve Biopsy shows show axonal degeneration, differential fascicular loss of axons, demyelinization signs and small-vessel vasculitis with mononuclear cell infiltrates in the perivascular area [32].

Treatment of MC

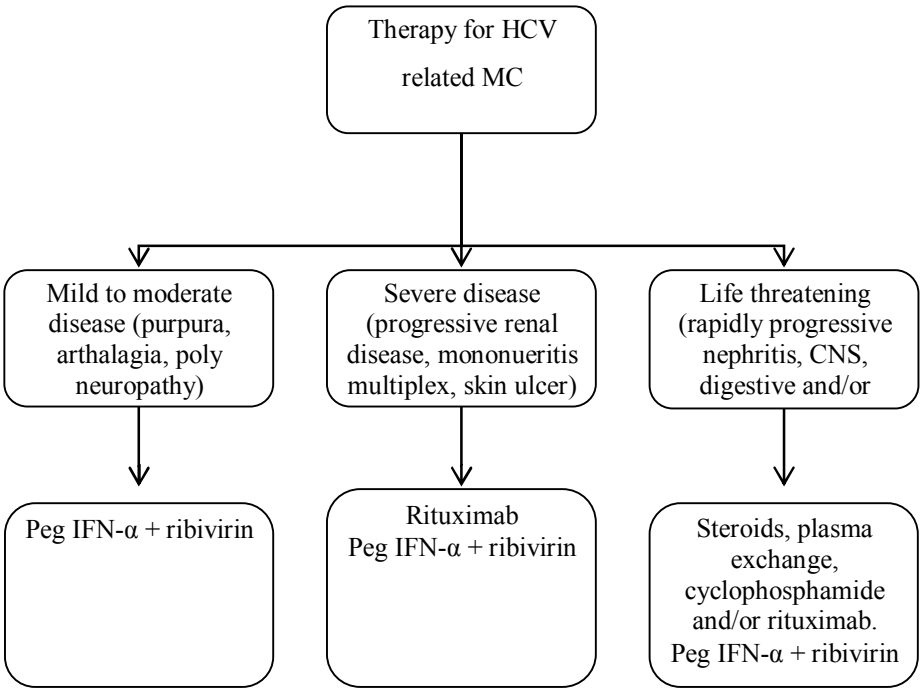

Figure (2): Therapeutic strategies in patients with HCV-associated MC [33].

Therapy should be initiated for patients with symptomatic MC, and is directed to both the virus and the immune-mediated inflammation [34].

Plasma exchange (PE)

PE is the removal of circulating immunocomplexes. Immunosuppressive therapy is usually associated with plasma exchange in order to avoid the rebound increase in cryoglobulinaemia that is commonly seen after discontinuation of exchange [35]. When used in combination with anti-HCV treatment, plasmapheresis did not modify the virological response [36].

Antiviral Therapy

Antiviral therapy is the mainstay of long-term control of both the hepatic and extrahepatic manifestations. It should be started after systemic vasculitis has come under initial control, because the disease can be exacerbated with the initiation of interferon therapy in some patients [37].

IFN alfa monotherapy:

Can reduce viral load and induce clinical improvement in MC. However, relapse within a few months of therapy withdrawal is common [38].

Pegylated IFN-a:

Results showed improving tolerability and giving good outcomes [39].

Ribavirin monotherapy:

Ribavirin may be effective in IFN-α intolerant patient with symptomatic HCV cryoglobulinaemia. Its use in patients with renal involvement should be monitored carefully and the effect is not sustained when therapy is discontinued [38].

Therapy with PEG-IFN and ribavirin:

Has significantly increased sustained virologic response to therapy [40]. Patients with HCV-MC who achieve SVR also achieve prolonged clinical remission. The current treatment duration in HCV–MC is 12 months for all genotypes [19].

Immunosuppressive drugs:

Cyclophosfamid, chlorambucil, and azathioprine

It can be used in life threatening organ involvement when there is no response to steroids. These drugs have severe side effects and can lead to liver disease progression due to their immnuosuppresive effect [41].

Rituximab

Its action includes antibody dependent cellular cytotoxicity, complement dependent cytotoxicity, and apoptosis effective in reducing IgM production [42]. Significant reductions in serum levels of IgM, cryoglobulins, and RF were demonstrated with a rise in C4 levels [43].

Treatment with rituximab at a dose of 375 mg/m2 weekly for 4 consecutive weeks, 80% of patients achieve complete response within 4 months of therapy, with their skin, joint, and neuromuscular symptoms showing strong response to treatment. Therapy with rituximab also allows most patients to discontinue maintenance therapy with corticosteroids [44]. Its combination with antiviral is necessary and duration of its use lasting from 6-12 months according to response. The continued efficacy and safety of repeated therapy in HCV-MC needs further investigations [33].

A low antigen content diets (LAC diet)

Lac-diet consists of a diet with a reduced content of alimentary macromolecules with high antigenic properties, are prescribed in order to help immunocomplexes clearance. It prescribed at the initial stage of disease, to reducing the antigen load to the reticulo–endothelial system, thus allowing a more efficient removal of cryoglobulins. This diet can improve minor manifestations of the MC [9].

The end of therapy criteria

These criteria are needed for patients with cryoglobulinemia.

-Undetectable serum HCV and cryoglobulins,

-Clearance of monoclonal RF producing cells from the blood by B cell clonal expansion analysis, and

-Clearance of HCV and lymphoid aggregates in the liver [45].

It is not clear whether Peg-IFN and ribavirin therapy can produce long-term remission of HCV-MC and whether achieving SVR means that patients are free from the risk of relapse of their HCV-MC symptoms [46]. The optimum length of treatment remains unknown, and severe cases may need long term or even life long therapy [47].

Lymphoproliferative disorders (LPD)

In HCV infected persons, LPD may be as progress of MC in up to 11% of cases (intermediary disorder) or occurred independently in patients without MC [48]. A frequent association reported between HCV infection and non-Hodgkin lymphoma [49].

Prevalence

The prevalence of HCV infection in B-cell NHL has given conflicting results. Several countries data ranges from 9% to 37% [50] and 90% of NHL patients have cryoglobulinemia [51]. Low grade lymphomas are more frequently associated with HCV [52]. The association between HCV and NHL is strongest in geographic areas with the highest prevalence of the viral infection [53].

Pathogenesis

The mechanism may be due to long term HCV infection, resulting in clonal B cell expansion of immunoglobulin (cryoglobulin) secreting lymphocytes, also a combination of a mutation agents like factors (genetic, environmental, immunological) result in activation of oncogenes and resulting in NHL. Another possibility is the inhibition of apoptosis of HCV infected lymphocytes by over-expression of the bcl2, and a second mutation (myc oncogene) may lead to the development of lymphoma [54]. This data suggest that the multi step lymphomagenetic cascade may have points of no-return, making LPD progressively independent from HCV infection [55].

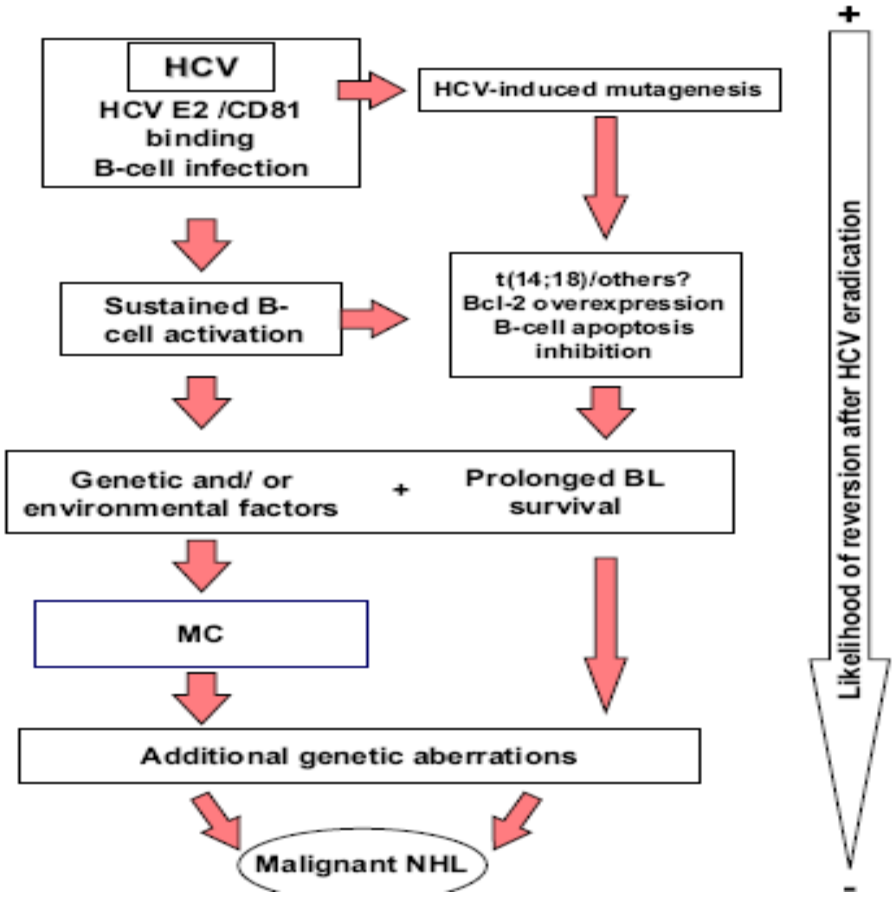

Figure (3): Pathogenesis of hepatitis C virus-related lymphoproliferative disorders [55].

Classification of LPD

All types of lymphoid malignancy can be found in patients with HCV infection but, the strongest association is noticed with B-cell derived NHL [56].

Non- Hodgkin Lymphoma (NHL)

According to the Revised European-American Lymphoma (REAL) classification/World Health Organization (WHO), the most frequent histological subtypes observed is: lympho-plasmacytic (29%), diffuse large B-cell (27%), follicular (16%), marginal zone (10%) and mantle cell (7%) lymphomas [57]. Approximately 65% of HCV-related NHL shows extra nodal involvement [58] . A strong link between HCV infection and mucosa-associated lymphoid tissue (MALT) lymphoma, HCV RNA has been isolated in the gastric mucosa of patients with MALT lymphoma [59].

Splenic marginal zone lymphoma shows a particularly high incidence (35%) of HCV infection, and is related to the hypothesis that B-cell NHL arises selectively from the marginal zone B-cell [60].

Monoclonal Gammopathies:-

Other LPDs reported in the course of HCV infection are monoclonal gammopathies (MG). Usually they are gammopathies IgM/Kappa. In most patients with HCV, MG was classified as monoclonal gammopathies of uncertain significance, which are present in up to 11% patients with HCV infection without cryoglobulins [61], Whereas a few patients who have HCV with MG can be considered as myeloma according to their clinicopathologic characteristics [62].

Soresi et al., [63] found significant relationship between abdominal lymphadenopathy and histological abnormalities of the liver, presence of HCV RNA in the serum and gamma globulin levels indicating a possible interaction between viral antigens and the immune system.

Treatment of LPD

Antiviral Therapy

It is an attractive therapy for low-grade HCV-positive NHL, but in intermediate and high-grade NHL, chemotherapy is necessary while antiviral

treatment possibly could represent a maintenance therapy [64].

Treatment with IFN +/- ribavirin is effective in HCV-associated indolent and marginal zone lymphomas which are mostly occurred with cryoglobulinemia [65]. A complete remission with IFN and ribavirin has been also reported in a patient with HCV-associated mantle cell NHL resistant to chemotherapy and rituximab [66] . In addition, regression of clonal proliferation in response to antiviral treatment was shown to be associated clearly with virological response [67]. Although of SVR, the rearrangement of the monoclonal immunoglobulin genes persistently was detected in the blood even after a complete hematological response [68].

Chemotherapy

Rituximab has become part of the standard treatment regimens used in a variety of B-cell NHL [69]. The use of rituximab in HCV-associated NHL, in monotherapy or in combination with antiviral treatment and/or chemotherapy, appears very promising, particularly in the setting of low-grade NHL, where rituximab monotherapy has been proposed as first-line treatment [70]. However Complications of NHL therapy with rituximab, manifested by increased levels of HCV RNA in blood have been reported [71].

Porphyria cutanea tarda (PCT)

Is a metabolic disease caused by the reduction of hepatic uroporphyrinogen decarboxylase activity, resulting in an over production and deposition of the protein uroporphyrinogen in the blood and urine of patients [72].

Prevalence

HCV infection in patients with porphyria is high, 40-50% depending on the country [73]. A strong association (50-90%) has been demonstrated between sporadic PCT cases and HCV infection in patients from the Mediterranean basin, Japan and the United States [74].

Pathogenesis

HCV does not appear to induce alteration of porphyrin metabolism but it may induce the disease in genetically predisposed individuals [75]. PCT might be related to HCV induced hepatic iron overload. Patients with PCT who are of northern European origin were also found to have increased prevalence of HFE gene mutation, which is responsible of hereditary hemochromatosis [76]. ***Cacoub et al.,*** [3] suggested that cirrhosis may play a role in its development, reporting that the highest rates of PCT were in patients with HCV related liver cirrhosis.

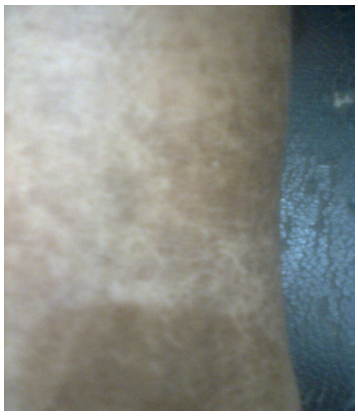

Figure (4): Lower limb pigmentation in HCV cirrhosis

Clinical features

Photosensitivity, skin fragility, bruising and vesicles and bullae that may become hemorrhagic are the main manifestations of PCT. Chronic findings include hypo or hyperpigmentation, alopecia, hirsutism and skin thickening [25].

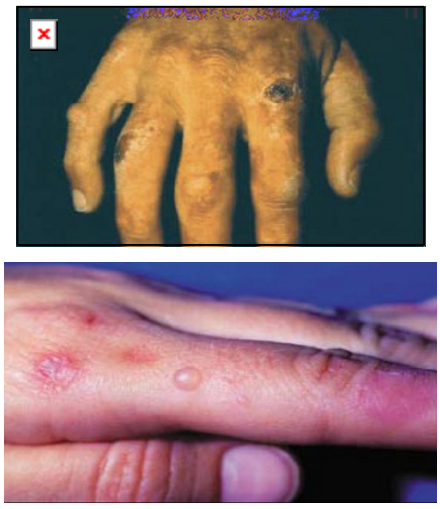

Figure (5): Porphyria Cutanea Tarda [77].

Diagnosis

Gross examination of the urine can provide a valuable clue, because urine of PCT patients is red to brown in natural light and pink to red in fluorescent light. Confirmation requires measurement of porphyrin levels in a 24-hour urine collection [78]. It is recommended that all patients with PCT should be screened for HCV infection [79].

Treatment

Vigorous iron removal by dietary restriction of foods rich in iron, avoidance of alcohol and estrogen use and phlebotomy to remove iron. The next step is the treatment of chronic hepatitis C with interferon and ribavirin. Antimalarial drugs like chloroquine have been used in the treatment of PCT [80].

Lichen planus (LP)

Is a recurrent pruritic eruption characterized by flat-topped violaceous papules that can develop on any skin site (arms, trunk, genitalia, nails and scalp), and mucosal membranes mainly oral mucosa [72]. The presence of HCV RNA in gingival crevicular fluid might have possibly reflected the viral presence in mucosal epithelial cells [81].

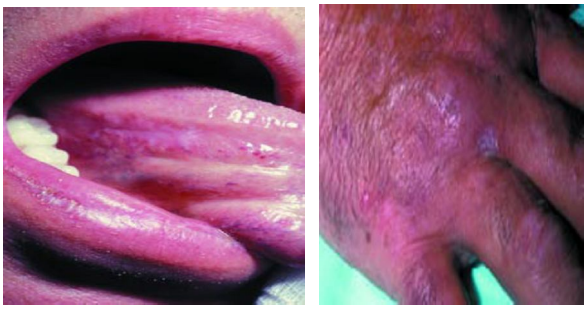

Figure (6): Oral and skin LP [82].

Pathogenesis

HCV infection may induce autoantibodies against the product of a host gene termed GOR which shares several amino acids with the core gene product of HCV [83]. HCV may play a pathogenic role by stimulating LP in genetically succeptible patients [84].

Treatment

LP responds variably to interferon treatment: both improvement and exacerbation of symptoms have been reported [85].

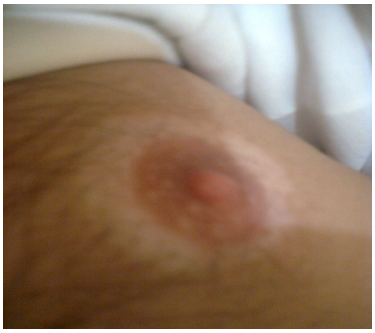

Figure (7): Circum-areola vitiligo in chronic HCV

Diabetes mellitus

DM is found more commonly in patients with chronic HCV infection than in the general population. HCV alone acts as a risk factor for DM, independent from liver disease [86].

Prevalence

DM in patients with cirrhosis due to HCV is 25%, in alcoholic liver disease is 19% and in patients with cirrhosis due to cholestatic liver disease is 13%**.** It was found that the countries which have high prevalence of HCV infection showed increased risk of type 2 diabetes, from 2 to 10 fold compared with liver disease control subjects [87]**.**

HCV positive patients having liver transplantation, reported from 4 to 8 folds increased prevalence of diabetes as compared with patients with other viral or cholestatic liver disease one year after liver transplantation[88]. HCV infection provided a more than three folds increased risk of developing diabetes in individuals aged more than 40 y and two fold for those aged less than 40 years [89].

Pathogenesis

There is evidence that HCV-positive diabetic patients have both peripheral insulin resistance and B-cell dysfunction [90]. TNF-α has been shown to inhibit insulin-stimulated tyrosine phosphorylation of insulin receptor and insulin receptor substrate 1 in adiopocytes, stimulate lipolysis, and increase serum FFA leading to insulin resistance and down regulate of genes in adipocytes encoding proteins such as insulin receptor substrate 1, glucose transporter-4, peroxisome proliferators-activated receptors, and adiponectin. In addition, TNF- α may reduce B-cell function by direct toxic effects. TNF- α receptors were found in higher levels in diabetic HCV patients than non diabetic HCV patients [91]. Also, postmortem studies expose that HCV replicates in the pancreas [92].

HCV genotypes and diabetes

In chronic HCV genotype 1 patients, insulin resistance and overt diabetes are major determinants of advanced fibrosis, regardless of the degree of steatosis [93]**.** ***Chehadeh et al.,*** [94] made two observations that support direct pathogenic role of HCV genotype 4. First, in presence of HCV infection, diabetes occurs at a significantly lower median age with less prevalence of obesity than those diabetic HCV-

negative patients. Second, follow up of HCV patients who had received antiviral drugs revealed a significant decrease of glucose level among diabetic patients who achieved SVR.

Treatment

The role of antiviral therapy is debated due to association between interferon and the induction of anti-pancreas auto anti bodies in some patients [95]. But clinical trials report improvement in measures of glucose metabolism after antiviral treatment [90].

Thyroid dysfunction

The direct link between HCV infection and thyroid diseases is unclear, but thyroid disease usually hypothyroidism is more commonly seen in people with HCV than in the general population [95]. Antiviral therapy can also induce thyroid disease or may unmask autoimmune disease as Graves disease**.** In about 50% of people who develop therapy related hypothyroidism, thyroid function will return to normal when treatment is stopped [97].

The prevalence

About 13% of HCV infected patients have hypothyroidism and up to 25% have thyroid antibodies. Papillary thyroid cancer was reported in patients with HCV infection [98].

Pathogenesis

It was suggested through molecular mimicry between viral antigens and self-antigens [99].

Treatment

The principal risk factor for developing thyroid disease in the course of antiviral therapy is the previous positivity for anti-thyroid antibodies (anti-peroxidase) especially in older women [100] and patients who may be genetically susceptible [101].

Antiviral therapy is contraindicated in patients with thyroid disease not controlled but the presence of autoantibodies against thyroid without clinical manifestations is a relative contraindication to antiviral therapy. In the case of a good therapeutical control of a preexistent thyroid disease, antiviral therapy can be continued. During treatment, frequent controlled tests for thyroid functionality should be performed [25].

Lung involvement

Idiopathic pulmonary fibrosis, diffuse alveolar damage, desquamative interstitial pneumonia, bronchiolitis obliterans organizing pneumonia, pulmonary vascuilitis and acute respiratory distress syndrome have been described in only anecdotal case reports [102].

Idiopathic pulmonary fibrosis

Is a chronic inflammatory interstitial lung disease characterized by an accumulation of alveolar macrophages and neutrophils in the lower respiratory tract, parenchymal injury, and interstitial fibrosis [103].

Pathogenesis

HCV may trigger a subclinical lymphocyte alveolitis [104]. Age, liver cirrhosis and smoking enhance the development of IPF in patients with chronic hepatitis C infection [105].

Treatment

Treatment with corticosteroid and antiviral therapy in most cases of lung involvement associated HCV mainly have no good results [103].

Noncryoglobulinemic nephropathies

HCV associated renal disease including membranous, membranoproliferative and acute proliferative glomerular disease are well documented [106]**.** HCV related glomerulonephritis, must be considered before the onset of therapy with antiviral and/or immunosuppressive agents by the histological demonstration and classification of inflammatory glomerular damage in the renal biopsy [26]. About 30% of patients have complete or partial remission of their renal disease, 30% suffer from intermittent exacerbations and remissions, 30% have an indolent course and 10% may develop chronic renal failure [107].

Erectile Dysfunction

Ferri et al., [15] diagnosed erectile dysfunction in 39% HCV-positive patients and in 14% control subjects. Erectile dysfunction was more common in patients with cryoglobulinemic vasculitis than in those with chronic HCV infection. Plasma levels of total and free testosterone were generally lower in HCV-positive patients, but they were significantly lower in patients with erectile dysfunction versus those without. However, it is also possible, that

antiviral treatment may improve erectile function in some patients.

Psychopathological disorders

Neuropsychiatric symptoms as malaise, fatigue and depressive symptoms have been reported during both acute and chronic stages of hepatitis C and IFN-α treatment [108]. Patients, have a low quality of life and decreased cognitive ability [109].

Prevalence

Depression was reported in 2%–30% of hepatitis C patients [110].

Pathogenesis

It has been supposed that the virus may cause direct cerebral dysfunction by an unknown mechanism [111]. Plasma tryptophan and kynurenine content in blood, together with indoleamine 2, 3-dioxygenase activity in macrophages, was evaluated in whom had mild HCV related chronic liver disease. Serum tryptophan concentrations were lower than those of healthy subjects or patients who had chronic HBV infection, and were associated with high levels of anxiety and depression [112,113].

Treatment

Antidepressants can help in the reduction of depression associated with hepatitis C treatment which should be under supervision [109].

Peripheral neuropathy (PN)

Up to 15.3% of the HCV population has PN. The exact cause of HCV related PN is not completely understood. Some theories suggest that HCV related PN is by HCV RNA deposits in blood vessels that supply oxygen to the nerves, HCV infection of the nerves, an inflammation process in the nerves, and/or HCV related immune disorder [114].

The best initial treatment option in patients with slight to moderate neuropathy is corticosteroids and/or IFN-α monotherapy [115]. However, treatment with interferon has produced mixed results and there is a chance that interferon could exacerbate PN. In patients who do not respond, combined antiviral therapy or intravenous immunoglobulins should be considered. The best option in severe or refractory cases is plasmapheresis [26].

Psoriasis

HCV is suggested to be one of the triggering factors of psoriasis [116]. The management of patients with psoriasis and concomitant HCV is often difficult because treatments for hepatitis C may trigger or exacerbate psoriasis. In addition, most systemic therapies for psoriasis, including immunosuppressants are relatively contraindicated in HCV infection [117]. Etanercept (TNF inhibitor) has an excellent safety profile for the treatment of severe psoriasis with psoriatic arthritis and concomitant hepatitis C virus [118].

Arthralgia

Arthralgia is common in patients with chronic HCV infection and is reported in 19% of HCV patients [3].

HCV-related Arthritis

This includes arthritis associated with or without the presence of MC [119]. Overt arthritis occurs less frequently than arthralgia, with prevalence of less than 5% in patients with chronic HCV infection [26].

Clinical Manifestations

It commonly presented as rheumatoid like symmetrical inflammatory polyarthritis involving mainly small joints or less commonly as mono or oligoarthritis of large joints [21]. In about 2/3 of the affected individuals, morning stiffness may be severe, resolving after more than an hour [120]. The presence of MC in patients with HCV infection consists of an intermittent, mono or oligoarticular, nondestructive arthritis affecting large and medium size joints [119].

Differences between true RA disease and HCV related arthritis.

Differentiation may be difficult. HCV related arthritis usually runs a relatively benign course that is typically non deforming [21]. Furthermore, unlike classic RA, ESR is elevated only in about half of the patients, articular bony erosions and subcutaneous nodules are absent [120].

Patients with HCV related arthritis are seropositive for RF. Therefore; anti keratin antibodies (AKA) are a useful marker to differentiate patients them. In a study AKA were detected in 69% of patients with RA compared to only 8% with HCV associated arthritis [121].

Positive HCV antibody and HCV RNA may be useful in distinguishing between HCV related arthritis and RA. Anti-cyclic citrullinated peptide antibodies were rarely present in HCV infected patients and were a reliable serological marker to discriminate between patients with HCV associated rheumatological manifestations and patients with rheumatoid arthritis [122].

Pathogenesis

HCV arthritis may be a part of MC or it may be directly or indirectly mediated by HCV infection. Direct invasion of synovial cells by the virus, causes local inflammatory response, cytokine induced disease or immune complex disease, particularly in genetically susceptible individuals [123]. HLA-DR4 histocompatibility antigen is significantly elevated in HCV infected patients with autoimmune diseases, including RA [124].

Fibromyalgia (FM)

Rivera et al., found that 15% of patients with FM have an HCV infection. IFN-α therapy can trigger FM symptoms in some patients [125].

Pruritus (Itching)

Pruritus is a presenting symptom in 20% of HCV infected patients and is associated with nonspecific lesions [126].

Pathogenesis

The pathogenesis is uncertain, but it may be caused by a portion of the hepatocyte cell membrane in association with a non-bile pruritogen acting as an opioid agonist [127]. However, subclinical cholestasis may also be a factor. Others causes may contribute in the pathogenesis of pruritus as accumulation of toxins as bilirubin, autoimmune conditions associated HCV, side effects of interferon and ribavirin which causing dry skin [128].

Necrolytic Acral Erythema

Necrolytic acral erythema is a rare, but pathognomonic manifestation of HCV. All cases are associated with HCV. Patients develop annular, hyperkeratotic, and violaceous plaques with raised scaly borders, although some lesions may be vesiculobullous. Lesions are acral in distribution. The pathogenesis of the disorder is unknown and the response to treatment is highly variable. Suggested treatments include amino acid and zinc, interferon-alpha, and ribavirin [129].

Mooren corneal ulcer

Chronic HCV virus infection is associated with Mooren type peripheral ulcerative keratitis. The cause appears to be due to cross reactivity between the HCV envelope protein and corneal antigen. All patients with Mooren type ulcers should be tested for HCV infection. Even when improvement is obtained with interferon alfa-2b treatment, however, continued follow up is important because relapse is common and repeated treatment may be effective [130].

Cardiomyopathy

Multiple studies have recorded relationship between HCV infection and the development of hypertrophic and dilated cardiomyopathy [131].

Prevalence

In a research project for the Study of Idiopathic Cardiomyopathy, HCV antibody was found in 10.6% with hypertrophic cardiomyopathy and 6.3% with dilated cardiomyopathy patients [131]. The association between chronic hepatitis C in various types of cardiomyopathy was originally reported in Japan up to 15%. A study was done in Italy reported a prevalence of hepatitis C antibodies in patients with cardiomyopathy to be 3.9%, [132]. A study from Brazil reported a prevalence of hepatitis C carrier state of 2.9% [133].

Pathogenesis

HCV induced cardiomyopathy is still controversial. The mechanisms by which this virus damages the myocardium have not been known. The development of HCV associated cardiomyopathy may take place in genetically susceptible individuals in whom viral, immunologic, and apoptotic mechanisms may act to produce myocardial damage. However, HCV may promote the development of cardiomyopathy by inducing continuous myocarditis, similar to other virus infections [134]. Some studies have proposed that hepatitis C virus (HCV) generates a tissue lesion mechanism similar to that caused by enterovirus and Coxsackie-B-virus, which are common in cases of myocarditis [135].

The physiopathology involves complex processes characterized by three phases:

- Infection of myocytes, and immunologically mediated cytotoxicity [136].

- Changing the entire heart anatomical and functional structure.

- Activation of an adaptive mechanism known as heart remodeling, which involves heart dilation and ventricular dysfunction in patients with CHF [137].

Okabe et al., [138] have reported strands of HCV RNA in cardiac tissue from patients with chronic active myocarditis.

Treatment

The understanding of cardiomyopathy as an extrahepatic manifestation of HCV infection is of great importance because the treatments available for chronic hepatitis C at present are considered relative contraindicated in patients with myocardial dysfunction. However, if the cause is HCV associated cardiomyopathy may benefit from therapeutic managment that may result in eradication of the virus and reversal of myocardial dysfunction [139].

HCV related Thrombocytopenia

HCV antibodies were identified in 30% of patients with chronic idiopathic thrombocytopenia purpura [140].

Pathogenesis

Thrombocytopenia associated HCV may be present even in the absence of clinically evident liver disease or splenomegaly and may be wrongly diagnosed as ITP [140]. The detection of HCV in platelet and megakaryocytes make HCV related thrombocytopenia is probable cause. High affinity binding of HCV to platelet membrane with subsequent binding of anti-HCV antibody might lead to phagocytosis of platelets [141]**.** High rate of HCV RNA in HCV related thrombocytopenia than non thrombocytopenic patients was detected. Furthermore, HCV may be causative factor for the production of platelate associated immunoglobulin G inducing thrombocytopenia in mechanism similar to idiopathic thrombocytopenia purpura (ITP) [142].

Treatment

Classical therapeutic approaches such as corticosteroid, antiviral therapy and intravenous immunoglobulin and splenectomy can be used. Disappearance of HCV RNA after IFN α associated with improvement of thrombocytopenia. Caution is recommended in thrombocytopenic patients treated with PEG-IFN α and ribavirin when platelet count less than 50,000/µl as significant aggravation of thrombocytopenia may occur [143]**.** Platelet count can be decrease from 30-50% in patient who administrates interferon or peginterferon, so reduction of the dose must be if the platelet counts reach 50.000/mm and discontinuation of the antiviral therapy if the counts reach 25.000/mm. Peg interferon alpha 2a can reduce the weekly dose from 180µg to 135 or even to 90µg, and peg interferon alpha 2b can reduce from 1.5µg/kg to 1µg/kg or even to 0.5µg/kg [40].

Human Recombinant Interleukin (IL)-II (Oprelvekin)

Oprelvekin promoting proliferation and maturation of megakerocytes which can be used to stimulate increasing number of platelet count at dose of 5 µg/kg/day S.C for 7 days initially and if necessary during antiviral therapy maintainance by taking 1-3 doses per week [144].

Elthrombopag

Active thrombopoietin receptor agonist (Elthrombopag) may be applied before and during antiviral therapy in HCV related thrombocytopenia at dose 30, 50 and 75mg lead to sustained increase of platelate count and it allows initiation and/or continuation of antiviral therapy [145].

Rituximib has promising therapeutic approach, especially in refractory cases or aggravating thrombocytopenia during the course of antiviral therapy [146].

Funding: Non.

Conflicts of Interest: Non.

Ethical Approval: Not needed.

REFERENCES

1. Pascual M, Perrin L, Giostra E, Schifferli J. Hepatitis C virus in patients with cryoglobulinemia type II. *J Infect Dis.*1990; 162: 569-70.
2. Zignego A, Brechot C. Extrahepatic manifestations of HCV infection: facts and controversies. *J Hepatol.* 1999; 31: 369-76.
3. Cacoub P, Renou C, Rosenthal E, Cohen P, Loury I, Loustaud-Ratti V, et al. Extrahepatic manifestations associated with hepatitis C virus infection. A prospective multicenter study of 321 patients. *Medicine* 2000; 79: 47-56.

4. Agnello V, De Rosa FG. Extrahepatic disease manifestations of HCV infection: some current issues. *J Hepatol* 2004; 40: 341-52.
5. Manns M, Obermayer-Straub P. Viral induction of autoimmunity: mechanisms and examples in hepatology. *J Viral Hepatol* 1997; 4: 42-47.
6. Moore P, Belvedere O, Orr A, Pieri K, LaFleur D, Feng P. Bly S: member of the tumor necrosis factor family and B lymphocyte stimulator. *Science* 1999; 285: 260-3.
7. Sansonno D, Cornacchiulo V, Iacobelli AR, Gatti P, Distasi M, Dammacco F. Hepatitis C virus infection and clonal B-cell expansion. *Clin Exp Rheumatol* 1996; 14: 45-50.
8. Favre D, Muellhaupt B. Potential cellular receptors involved in hepatitis C virus entry into cells. *Lipids Health Dis* 2005; 4: 9-14.
9. Zignego A, Ferri C, Pileri S, Caini P, Bianchi F. Extrahepatic manifestations of Hepatitis C Virus infection: a general overview and guidelines for a clinical approach. *Dig Liver Dis* 2007; 39: 2-17.
10. Lunel F, Musset L, Cacoub P, Frangeul L, Cresta P, Perrin M, et al. Cryoglobulinemia in chronic liver diseases: role of hepatitis C virus and liver damage. *Gastroenterol* 1994; 106: 1291-300.
11. Ferri C, Zignego A, Pileri S. Cryoglobulins. In: (Clinical hematology) by Young N, Gerson S, and High K. Mosby (MO): *Elsevier* 2005; 625-36.
12. Brouet J, Clauvel J, Danon F, Klein M, Seligmann M. Biologic and clinical significance of cryoglobulins. A report of 86 cases. *Am J Med* 1974; 57: 775-88.
13. Sansonno D, Dammacco F. Hepatitis C virus, cryoglobulinemia, and vasculitis: immune complex relations. *Lancet Infect Dis* 2005; 5: 227-36.
14. Wang A, Wells J, Fudenberg H. Chemical analyses of cryoglobulins. *Immunochemistry* 1974; 11: 341-5.
15. Ferri C, Zignego A, Pileri S. Cryoglobulins. *J Clin Pathol* 2002; 55: 4-13.
16. Zignego A, Ferri C, Giannelli F, Giannini C, Caini P, Monti M, et al. Prevalence of bcl-2 rearrangement in patients with hepatitis C virus-related mixed cryoglobulinemia with or without B-cell lymphomas. *Ann Intern Med* 2002; 137: 571-80.
17. De Re V, Sansonno D, Simula M, Caggiari L, Gasparotto D, Fabris M, et al. HCV-NS3 and IgG-Fc crossreactive IgM in patients with type II mixed cryoglobulinemia and B-cell clonal proliferations. *Leukemia* 2006; 20: 1145-54.
18. Fabris M, Quartuccio L, Sacco S, De Marchi G, Pozzato G, Mazzaro C, et al. B-lymphocyte stimulator (BLyS) up-regulation in mixed cryoglobulinaemia syndrome and hepatitis-C virus infection. *Rheumatol* 2007; 46: 37-43.
19. Saadoun D, Asselah T, Resche-Rigon M, Charlotte F, Bedossa P, Valla D, et al. Cryoglobulinemia is associated with steatosis and fibrosis in chronic hepatitis C. *Hepatol* 2006; 43: 1337-45.
20. Dammacco F, Sansonno D, Piccoli C, Tucci F, Racanelli V. The cryoglobulins: an overview. *Eur J Clin Invest* 2001; 31: 628-38.
21. Remoroza R, Bonkovsky H. Extrahepatic manifestations of chronic hepatitis C. August 2003,available at http//: www.hcvadvocate.org
22. Johnson R, Gretch D, Yamabe H, Johnson R, Gretch D, Yamabe H, et al. Membranoproliferative glomerulonephritis associated with hepatitis C virus infection. *N Engl J Med* 1993; 328: 465-70.
23. Misiani R, Bellavita P, Fenili D, Borelli G, Marchesi D, Massazza M. Hepatitis C infection in patients with essential mixed cryoglobulinemia. *Ann Intern Med* 1992; 117: 573-77.
24. Tarantino A, Campise M, Banfi G, Confalonieri R, Bucci A, Montoli A. Long-term predictors of survival in essential mixed cryoglobulinemic glomerulonephritis. *Kidney Int* 1995; 47: 618-23.
25. Galossi Al, Guarisco R, Bellis L, Puoti C. Extrahepatic manifestations of chronic HCV infection. *J Gastrointestin Liver Dis* 2007; 16: 65-73.
26. Ramos-Casals M, Trejo O, Garcia-Carrasco M, Font J. Therapeutic management of extrahepatic manifestations in patients with chronic hepatitis C virus infection. *Rheumatol* 2003; 42: 818-28.
27. Casato M, Saadun D, Marchetti A, Limal N, Pic, C, Pantano P, et al. Central nervous system involvement in hepatitis C virus cryoglobulinemia vasculitis: a multicenter case-control study using magnetic resonance imaging and neuropsychological tests. *J Rheumatol* 2005; 32: 484-8.
28. Moschella C, Palmieri I, Bartolucci P, Assenza M, Maiuolo A, Modini, C. Spontaneous rectus sheath haematoma in HCV mixed cryoglobulinemia requiring emergency treatment (case report). *G Chir* 2002; 23: 331-33.
29. Ferri C, Sebastiani M, Giuggioli D, Cazzato M, Longombardo G, Antonelli A, et al. Mixed cryoglobulinemia: demographic, clinical, and serological features and survival in 231 patients. *Semin Arthritis Rheum* 2004; 33: 355-74.
30. Sansonno D, Cornacchiuolo V, Iacobelli A, Di Stefano R, Lospalluti M, Dammacco F. Localization of hepatitis C virus antigens in liver and skin tissues of chronic hepatitis C virus infected patients with mixed cryoglobulinemia. *Hepatol* 1995; 21: 305-12.
31. Sabry A, El-Agroudy A, Sheashaa H, El-Hussein, A, Mohamed N, Elbaz M, et al. HCV associated glomerulopathy in Egyptian patients: clinicopathological analysis. *Virol* 2005; 334: 10-6.

32. Cacoub P, Saadoun D, Limal N, Leger J, Maisonobe T. Hepatitis C virus infection and mixed cryoglobulinaemia vasculitis: a review of neurological complications. *AIDS* 2005; 19: 128-34.
33. Saadoun, D.; Landau, D..; Calabrese, L. and Cacoub, P. (2007): Hepatitis C-associated mixed cryoglobulinaemia: a cross road between autoimmunity and lymphoproliferation. *Rheumatol* 2007; 46: 1234-42.
34. Gertz MA. Cold agglutinin disease and cryoglobulinemia. *Clinical Lymphoma* 2005; 5: 290-93.
35. D'Amico G. Renal involvement in hepatitis C infection: cryoglobulinemic glomerulonephritis. *Kidney Int* 1998; 54: 650-71.
36. Hausfater P, Cacoub P, Assogba U, Lebon P, Piette J. Plasma exchange and interferon-alpha pharmacokinetics in patients with hepatitis C virus-associated systemic vasculitis. *Nephron* 2002; 91: 627-30.
37. Boonyapisit K, Katirji B. Severe exacerbation of hepatitis C-associated vasculitic neuropathy following treatment with interferon alpha: a case report and literature review. *Muscle Nerve* 2002; 25: 909-13.
38. Misiani R, Bellavita P, Baio P, Caldara R, Ferruzzi S, Rossi P, et al. Successful treatment of HCV-associated cryoglobulinaemic glomerulonephritis with a combination of interferon-alpha and ribavirin. *Nephrol Dial Transplant* 1999; 14: 1558-60.
39. Heathcote E, Shiffman M, Cooksley W, Dusheiko G, Lee S, Balart L, et al. Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. *N Engl J Med* 2000; 343: 1673-80.
40. Fried M, Shiffman M, Reddy K, Smith C, Marinos G, Gonçales F, et al. (2002): Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; 347: 975-82.
41. Ballare M, Bobbio F, Poggi S, Bordin G, Bertoncelli M, Catania E, et al. A pilot study on the effectiveness of cyclosporine in type II mixed cryoglobulinemia. *Clin Exp Rheumatol* 1995; 13: 201-3.
42. De Vita S, Quartuccio L. Treatment of rheumatoid arthritis with rituximab: an update and possible indications. *Autoimmun Rev* 2006; 5: 443-8.
43. Cheung MC, Haynes AE, Meyer RM, Stevens A, Imrie KR. Rituximab in lymphoma: a systematic review and consensus practice guideline from Cancer Care Ontario. *Cancer Treat Rev* 2007; 33: 161-76.
44. Sansonno D, De Re V, Lauletta G, Tucci F, Boiocchi M, Dammacco F. Monoclonal antibody treatment of mixed cryoglobulinemia resistant to interferon alpha with an anti-CD20. *Blood* 2003; 101: 3818-26.
45. Agnello, V. Therapy for cryoglobulinemia secondary to hepatitis C virus: the need for tailored protocols and multiclinic studies. J Rheumatol 2000; 27(9): 2065-7.
46. Neal J, Gerond V. Hepatitis C virus-related mixed cryoglobulinemia: pathogenesis, clinical manifestations, and new therapies. *Gastroenterol & Hepatol* 2007; 3: 697-8.
47. Ramos-Casals M, Trejo O, Garcia-Carrasco M, Font J. Therapeutic management of extrahepatic manifestations in patients with chronic hepatitis C virus infection. *Rheumatol* 2003; 42: 818-28.
48. Luppi M, Longo G, Ferrari MG, Barozzi P, Marasca R, Morselli M, et al. Clinico-pathological characterization of hepatitis C virus-related B-cell non-Hodgkin's lymphomas without symptomatic cryoglobulinemia. *Ann Oncol* 1998; 9: 495-8.
49. Mele A, Pulsioni A, Bianco E, Musto P, Szklo A, Sanpaolo M, et al. Hepatitis C virus and B-cell non-Hodgkin lymphomas: an Italian multicenter case-control study. *Blood* 2003; 102: 996-9.
50. Duberg A, Nordstrom M, Torner A, Reichard O, Strauss R, Janzon R, et al. Non-Hodgkin's lymphoma and other nonhepatic malignancies in Swedish patients with hepatitis C virus infection. *Hepatol* 2005; 41: 652-9.
51. Dammacco F, Sansonno D, Piccoli C, Racanelli V, D'Amore FP, Lauletta G. The lymphoid system in hepatitis C virus infection: autoimmunity, mixed cryoglobulinemia, and overt B-cell malignancy. *Semin Liver Dis* 2000; 20: 143-57.
52. Zuckerman E, Zuckerman T. Hepatitis C and B-cell lymphoma: the hematohepatologist linkage. *Blood Rev* 2000; 16: 119-25.
53. Gisbert J, Garcia-Buey L, Pajares J, Moreno-Otero R. Prevalence of hepatitis C virus infection in B-cell non-Hodgkin's lymphoma: systematic review and meta-analysis. *Gastroenterol* 2003; 125: 1723-32.
54. Zignego A, Giannelli F, Marocchi M, Mazzocca A, Ferri C, Giannini C, et al. T (14;18) translocation in chronic hepatitis C virus infection. *Hepatol* 2000; 31: 474-9.
55. Zignego A, Craxi A. Extrahepatic manifestations of hepatitis C virus infection. Clin Liver Dis 2008; 12: 611-36.
56. Ferri C, Pileri S, Zignego A. Hepatitis C virus infection and non-Hodgkin's lymphoma. In: Geodert JJ, editor. Infectious causes of cancer. Targets for intervention. Totowa (NJ): The Human Press Inc 2000; 349-68.
57. Trejo O, Ramos-Casals M, Lopez-Guillermo A, García-Carrasco M, Yagüe J, Cervera R, et al. Hematologic malignancies in patients with cryoglobulinemia: association with autoimmune and chronic viral diseases. *Semin Arthritis Rheum* 2003; 33: 19-28.

58. Ascoli V, Lo Coco F, Artini M, Levrero M, Martelli M, Negro F. Extranodal lymphomas associated with hepatitis C virus infection. *Am J Clin Pathol* 1998; 109: 600-9.
59. Tursi A, Brandimante G, Chiarelli F, Spagnoli A, Torello M. Detection of HCV RNA in gastric mucosa-associated lymphoid tissue by in situ hybridization: evidence of a new extrahepatic localization of HCV with increased risk of gastric MALT lymphoma. *Am J Gastroenterol* 2002; 97: 1802-6.
60. Arcaini L, Paulli M, Boveri E, Vallisa D, Bernuzzi P, Orlandi E, et al. Splenic and nodal marginal zone lymphomas are indolent disorders at high hepatitis C virus seroprevalence with distinct presenting features but similar morphologic and phenotypic profiles. *Cancer* 2004; 100: 107-15.
61. Andreone P, Zignego AL, Cursaro C, Gramenzi A, Gherlinzoni F, Fiorino S, et al. Prevalence of monoclonal gammopathies in patients with hepatitis C virus infection. *Ann Intern Med* 1998; 129: 294-8.
62. Jaffe ES, Harris NL, Stein H, Vardiman JW. Tumours of haematopoietic and lymphoid tissues. World Health Organization classification of tumours. Lyon (France): IARC Press 2001; 75–107.
63. Soresi M, Carroccio A, Bonfissuto G, Agate V, Magliarisi C, Aragona F, et al. Ultrasound detection of abdominal lymphadenomegaly in subjects with hepatitis C virus infection and persistently normal transaminases: a predictive index of liver histology severity. *J Hepatol* 1998; 28: 544-9.
64. Gisbert J, Garcia-Buey L, Pajares J, Moreno-Otero R. Systematic review: regression of lymphoproliferative disorders after treatment for hepatitis C infection. *Aliment Pharmacol Ther* 2005; 21: 653-62.
65. Vallisa D, Bernuzzi P, Arcaini L, Sacchi S, Callea V, Marasca R, et al. Role of anti-hepatitis C virus (HCV) treatment in HCV-related, low-grade, non-Hodgkin's lymphoma: a multicenter Italian experience. *J Clin Oncol* 2005; 23: 468-73.
66. Levine A, Shimodaira S, Lai M. Treatment of HCV-related mantle-cell lymphoma with ribavirin and pegylated Interferon alfa. *N Engl J Med* 2003; 349: 2078-9.
67. Giannelli F, Moscarella S, Giannini C, Caini P, Monti M, Gragnani L, et al. Effect of antiviral treatment in patients with chronic HCV infection and t (14; 18) translocation. *Blood* 2003; 102: 1196-201.
68. Saadoun D, Suarez F, Lefrere F, Valensi F, Mariette X, Aouba A, et al. Splenic lymphoma with villous lymphocytes, associated with type II cryoglobulinemia and HCV infection: a new entity? *Blood* 2005; 105: 74-6.
69. Cheung MC, Haynes AE, Meyer RM, Stevens A, Imrie KR. Rituximab in lymphoma: a systematic review and consensus practice guideline from Cancer Care Ontario. *Cancer Treat Rev* 2007; 33: 161-76.
70. Dundar Y, Bagust A, Hounsome J, McLeod C, Boland A, Davis H, et al. Rituximab for the first-line treatment of stage III/IV follicular non-Hodgkin's lymphoma. *Health Technol Assess* 2009; 13: 23-8.
71. Aksoy S, Abali H, Kilickap S, Erman M, Kars A. Accelerated hepatitis C virus replication with rituximab treatment in a non-Hodgkin's lymphoma patient. *Clin Lab Haematol* 2006; 28: 211-4.
72. Galossi Al, Guarisco R, Bellis L, Puoti C. Extrahepatic manifestations of chronic HCV infection. *J Gastrointestin Liver Dis* 2007; 16: 65-73.
73. Fargion S, Piperno A, Cappellini M, Sampietro M, Fracanzani AL, Romano R, et al. Hepatitis C virus and porphyria cutanea tarda: evidence of a strong association. *Hepatol* 1992; 16: 1322-6.
74. Kondo M, Horie Y, Okano J, Kitamura A, Maeda N, Kawasaki H, et al. High prevalence of hepatitis C virus infection in Japanese patients with porphyria cutanea tarda. *Hepatol* 1997; 26: 246.
75. O'Reilly F, Darby C, Fogarty J, O'Moore R, Courtney M, O'Connor J, et al. Porphyrin metabolism in hepatitis C infection. *Photodermatol Photoimmunol Photomed* 1996; 12: 31-3.
76. Bonkovsky H, Poh-Fitzpatrick M, pimstone N, Obando J, Di Bisceglie A, Tattrie C, et al. Porphyria cutanea tarda, hepatitis C, and HFE gene mutations in North America. *Hepatol* 1998; 27: 1661-9.
77. Phillips J, Bergonia H, Reilly C, Franklin M, Kushner J. A porphomethene inhibitor of uroporphyrinogen decarboxylase causes porphyria cutanea tarda. *Proc Natl Acad Sci USA* 2007; 104: 5079-84.
78. Rich, MW. Porphyria cutanea tarda. Don't forget to look at the urine. *Postgrad Med* 1999; 105: 208-10, 213-4.
79. Maticic M. Hepatitis C virus infection: the dermatological perspective. *Acta Dermatoven APA* 2003; 12: 19-27.
80. Bonkovsky H, Mehta S. Hepatitis C: a review and update. *Journal of the American Academy of Dermatol* 2001; 44: 159-79.
81. Matii M, Poljak M, Kramar B, Seme K, Brinovec V, Megli- Volkar J. Detection of hepatitis C virus RNA from gingival crevicular fluid and its relation to virus presence in saliva. *J Periodontol* 2001; 72:11-16.
82. Ali L, Zein N. Hepatitis C infection: a systemic disease with extrahepatic manifestations. *Cleve Clin J Med* 2005; 72: 1005-8, 1010-4, 1016.

83. Divano M, Prodi A, Rebora A. Anti-GOR antibodies in lichen planus. *Dermatol* 1994; 188: 205-6.
84. Erkek E, Bozdogan O, Olut A. Hepatitis C virus infection prevalence in lichen planus: examination of lesional and normal skin of hepatitis C virus-infected patients with lichen planus for the presence of hepatitis C virus RNA. *Clin Exper Dermatol* 2001; 26: 540-4.
85. Areias J, Velho GC, Cerqueira R, Barbêdo C, Amaral B, Sanches M, et al. Lichen planus and chronic hepatitis C: exacerbation of the lichen under interferon-alpha-2a therapy. *Eur J Gastroenterol Hepatol* 1996; 8: 825-8.
86. Knobler H, Schihmanter R, Zifroni A, Fenakel G, Schattner A. Increased risk of type 2 diabetes in noncirrhotic patients with chronic hepatitis C virus infection. *Mayo Clin Proc* 2000; 75: 355-9.
87. Zein N, Abdulkarim A, Wiesner R, Egan K, Persing D. Prevalence of diabetes mellitus in patients with end-stage liver cirrhosis due to hepatitis C, alcohol, or cholestatic disease. *J Hepatol* 2000; 32: 209-17.
88. Bigam D, Pennington J, Carpentier A, Wanless I, Hemming A, Croxford R, et al. Hepatitis C-related cirrhosis: a predictor of diabetes after liver transplantation. *Hepatol* 2000; 32: 87-90.
89. Mehta S, Brancati F, Sulkowski M, Strathdee S, Szklo M, Thomas D. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. *Ann Intern Med* 2000; 133: 592-9.
90. Konrad T, Zeuzem S, Vicini P, Toffolo G, Briem D, Lormann J, et al. Evaluation of factors controlling glucose tolerance in patients with HCV infection before and after 4 months therapy with interferon-α. *Eur J Clin Invest* 2000; 30: 111-21.
91. Knobler H, Schattner T. TNF- α, chronic hepatitis C and diabetes: a novel triad. *QJM* 2005; 98: 1-6.
92. Laskus T, Radkowski M, Wang L, Vargas H, Rakela J. Search for hepatitis C virus extrahepatic replication sites in patients with acquired immunodeficiency syndrome: Specific detection of negative-strand viral RNA in various tissues. *Hepatol* 1998; 28: 1398-401.
93. Petta S, Camma C, Marco V, Alessi N, Cabibi D, Caldarella R, et al. Insulin resistance and diabetes increase fibrosis in the liver of patients with genotype 1 HCV infection. *Am J Gastroenterol* 2008; 103: 1136–44.
94. Chehadeh W, Abdella N, Ben-Nakhi A, Al-Arouj M, Al-Nakib W. Risk factors for the development of diabetes mellitus in chronic hepatitis C virus genotype 4 infection. *J Gastroenterol Hepatol* 2009; 24: 42-8.
95. Fabris P, Betterle C, Greggio N, Zanchetta R, Bosi E, Biasin M, et al. Insulin-dependent diabetes mellitus during alpha-interferon therapy for chronic viral hepatitis. *J Hepatol* 1998; 28: 514-7.
96. Huang M,Tsai S, Huang B, Sheen I, Yeh C, Liaw Y. Prevalence and significance of thyroid autoantibodies in patients with chronic hepatitis C virus infection: a prospective controlled study. *Clin Endocrinol* 1999; 50: 503-9.
97. Fernandez-Soto L, Gonzales A, Escobar-Jimenez F, Vazquez R, Ocete E, Olea N, et al. Increased risk of autoimmune thyroid disease in hepatitis C vs. hepatitis B before, during and after discontinuing interferon therapy. *Arch Intern Med* 1998; 158: 1445-8.
98. Antonelli A, Ferri C, Pampana A, Fallahi P, Nesti C, Pasquini M, et al. Thyroid disorders in chronic hepatitis C. *Am J Med* 2004; 117: 10-3.
99. Muratori L, Bogdanos D, Muratori P, Lenzi M, Granito A, Ma Y, et al. Susceptibility to thyroid disorders in hepatitis C. *Clin Gastroenterol Hepatol* 2005; 3: 595-603.
100. Deutsch M, Dourakis S, Manesis E, Gioustozi A, Hess G, Horsch A, et al. Thyroid abnormalities in chronic viral hepatitis and their relationship to interferon alpha therapy. *Hepatol* 1997; 26: 206-10.
101. Prummel M, Laurberg P. Interferon-alpha and autoimmune thyroid disease. *Thyroid* 2003; 13: 547-51.
102. Ferri C, La Civita L, Fazzi P, Pasero G, Zignego A. Polymyositis, lung fibrosis, and cranial neuropathy in a patient with hepatitis C virus infection. *Arthritis Rheum* 1996; 39: 1074-5.
103. Ferri C, La Civita L, Fazzi P, Solfanelli S, Lombardini F, Begliomini E, et al. Interstitial lung fibrosis and rheumatic disorders in patients with hepatitis C virus infection. *Br J Rheumatol* 1997; 36: 360-5.
104. Weidensaul D, Imam T, Holyst M, King P, McMurray R. Polymyositis, pulmonary fibrosis and hepatitis C. *Arthritis Rheum* 1995; 38: 437-9.
105. Arase Y, Suzuki F, Suzuki Y, Akuta N, Kobayashi M, Kawamura Y, et al. Hepatitis C virus enhances incidence of idiopathic pulmonary fibrosis. *World J Gastroenterol* 2008; 14: 5880-6.
106. Yamabe H, Johnson R, Gretch D, Osawa H, Inuma H, Sasaki, T. Membranoproliferative glomerulonephritis associated with hepatitis C virus infection responsive to interferon-alpha. *Am J Kidney Dis* 1995; 25: 67-9.
107. Kaupke C, Vaziri N. Renal complications of hepatitis C virus infection. *West J Med* 1996; 164: 442-3.
108. Johnson M, Fisher D, Fenaughty A, Theno S. Hepatitis C virus and depression in drug users. *Am J Gastroenterol* 1998; 93: 785-9.
109. Hilsabeck R, Perry W, Hassanein T. Neuropsychological impairment in patients with chronic hepatitis C. *Hepatol* 2002; 35: 440-6.

110. Pariante C, Orru M, Baita A, Farci M, Carpiniello B. Treatment with interferon-α in patient with chronic hepatitis and mood or anxiety disorders. *Lancet* 1999; 354:131-2.
111. Forton D, Thomas H, Murphy C, Allsop J, Foster G, Main J, et al. Hepatitis C and cognitive impairment in a cohort of patients with mild liver disease. *Hepatol* 2002; 35: 433-9.
112. Cozzi A, Zignego AL, Carpendo R, Biagiotti T, Aldinucci A, Monti M, et al. (2006): low serum tryptophan levels, reduced macrophage IDO activity and high frequency of psychopathology in HCV patients. *J viral Hepat* 2006; 13: 402-8.
113. Porter L. HCV and mental health: Overview of depression. Hepatitis C Support Project (HCSP); Available at http//:www.hcvadvocate.org. Last modified at April 2009. Last cited at 11/10/2009.
114. Franciscus A. HCV – Extrahepatic Manifestations: Peripheral Neuropathy (PN). Hepatitis C Support Project (HCSP); Available at http//: www.hcvadvocate.org. Last modified at February 2009. Last cited at 21/8/2009.
115. Apartis E, Le´ger J, Musset L, Gugenheim M, Cacoub P, Lyon-Caen O, et al. Peripheral neuropathy associated with essential mixed cryoglobulinemia: a role for hepatitis C virus infection? *J Neurol Neurosurg Psychiatry* 1996; 60: 661-6.
116. Yamamoto T, Katayama I, Nishioka K. Psoriasis and hepatitis C virus. *Acta Derm Venereol* 1995; 75: 482-3.
117. Cecchi R, Bartoli L. Psoriasis and hepatitis C treated with anti-TNF alpha therapy (etanercept). *Dermatol Online J* 2006; 12: 4.
118. Magliocco M, Gottlieb A. Etanercept therapy for patients with psoriatic arthritis and concurrent hepatitis C virus infection: report of 3 cases. *J Am Acad Dermatol* 2004; 51: 580-4.
119. Buskila D. (2000): Hepatitis C-associated arthritis. *Curr Opin Rheumatol* 2000; 12: 295-9.
120. Zuckerman E, Zuckerman T, Sahar D, Streichman S, Attias D, Sabo E, et al. The effect of antiviral therapy on t (14; 18) translocation and immunoglobulin gene rearrangement in patients with chronic hepatitis C virus infection. *Blood* 2001; 97: 1555-9.
121. Kessel A, Rosner I, Zuckerman E, Golan T, Toubi E. Use of antikeratin antibodies to distinguish between rheumatoid arthritis and polyarthritis associated with hepatitis C infection. *J Rheumatol* 2000; 27: 610-2.
122. Sene D, Ghillani-Dalbin P, Limal N, Thibault V, van Boekel T, Piette J-C, et al. Anti-cyclic citrullinated peptide antibodies in hepatitis C virus associated rheumatological manifestations and Sjögren's syndrome. *Ann Rheum Dis* 2006; 65: 394-7.
123. Gordon S. Extrahepatic manifestations of hepatitis C. *Dig Dis* 1996; 14: 157-68.
124. Rivera J, De Diego A, Trinchest M, Garcia A. Fibromyalgia-associated hepatitis C virus infection, *Br J Rheumatol* 1997; 36: 981-5.
125. Middleton G, McFarlin J, Lipsky P. The prevalence and clinical impact of fibromyalgia in systemic lupus erythematosus. *Arthritis Rheum* 1994; 37: 1181-8.
126. Kanazawa K, Yaoita H, Murata K, Tsuda F, Okamoto H. Association of prurigo with hepatitis C virus infection. *Dermatol* 1995; 131: 825-53.
127. Fisher D, Wright T. Pruritus as a symptom of hepatitis C. J *Am Acad Dermatol* 1994; 30: 629-32.
128. Cordel N, Chosidow O, Frances C. Cutaneous disorders associated with hepatitis C virus infection. *Ann Med Intern* (Paris) 2000; 151: 46-52.
129. Khanna V, Shieh S, Benjamin J, Somach S, TarifZaim M, Dorner J, et al. Necrolytic acral erythema associated with hepatitis C. *Dermatol* 2000; 136: 755-7.
130. Wilson S, Lee W, Murakami C, Weng J, Moninger G. Mooren- type hepatitis C virus-associated corneal ulceration. *Ophthalmol* 1994; 101: 736-45.
131. Matsumori A, Ohashi N, Hasegawa K, Sasayama S, Eto T, Imaizumi T, et al. Hepatitis C virus infection and heart diseases: A multicenter study in Japan. *Jpn Circ J* 1998; 62: 389-91.
132. Prati D, Poli F, Farma E, Picone A, Porta E, De Mattei C, et al. Multicenter study on hepatitis C virus infection in patients with dilated cardiomyopathy. North Italy Transplant Program (NITP). *J Med Virol* 1999; 58: 116-20.
133. Reis F, Viana M, Oliveira M, Sousa T, Parana R. Prevalence of hepatitis C and B virus infection in patients with idiopathic dilated cardiomyopathy in Brazil: a pilot study. *Braz J Infect Dis* 2007; 11: 318-21.
134. Takashi O, Minoru Y, Tetsuya H, Shuhei N, Masahiko K, Shinichiro H, et al. Core protein of hepatitis C virus induces cardiomyopathy. *Circ Res* 2005; 96: 148-50.
135. Matsumori A, Matoba Y, Sasayama S. Dilated cardiomyopathy associated with hepatitis C virus infection. *Circ* 1995; 92: 2519-25.
136. Liu P, Mason J. Advances in the understanding of myocarditis. *Circulation* 2001; 104: 1076-82.
137. Ono K, Matsumori A, Shioi T, Furukawa Y, Sasayama S. Cytokine gene expression after myocardial infarction in rat heart: possible implication in left ventricular remodeling. *Circ* 1998; 98: 149-56.
138. Okabe M, Fukuda K, Arakawa K, Kikuchi M. Chronic variant of myocarditis associated with hepatitis C virus infection. *Circ* 1997; 96: 22-4.
139. Sanchez M, Bergasa N. Hepatitis C associated cardiomyopathy: potential pathogenic mechanisms and clinical implications. *Med Sci Monit* 2008; 14: 55-63.

140. Rajan S, Espina B, Liebman H. Hepatitis C virus related thrombocytopenia: clinical and laboratory characteristics compared with chronic immune thrombocytopenic purpura. *Br J Haematol* 2005; 129: 818-4.
141. Hamaia S, Li C, Allain J. The dynamics of hepatitis C virus binding to platelets and 2 mononuclear cell lines. *Blood* 2001; 98: 2293-300.
142. De Almeida A, Campos-de-Magalhaes M, De Melo Marçal O, Brandão-Mello C, Okawa M, Vieira de Oliveira R, et al. Hepatitis C virus-associated thrombocytopenia: a condition prospective, virological study. *Ann Hematol* 2004; 83: 434-40.
143. Iga D, Tomimatsu M, Endo H, Ohkawa S, Yamada O. Improvement of thrombocytopenia with disappearance of HCV RNA in patients treated by interferon- α therapy: possible etiology of HCV associated immune thrombocytopenia. *Eur J Hematol* 2005; 75: 417-23.
144. Hennepin County Medical Center. Management of HCV and treatment side effects. HCMC Co-infection Clinic. Last modified at April 10, 2005. Last cited at 30/10/2009.
145. McHutchison J, Dusheiko G, Shiffman M, Rodriguez-Torres M, Sigal S, Bourliere M, et al. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. *N Engl J Med* 2007; 357: 2227-36.
146. Weitz IC. Treatment of immune thrombocytopenia associated with interferon therapy of hepatitis C with the anti-CD20 monoclonal antibody, rituximab. *Am J Hematol* 2005; 78: 138-41.