Section 2

General medicine

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Shafiq Ahmad Joya[1,2], G. Kurmanova[1*], K. Kurmanova[3], A.D. Sadykova [1], E.N. Bosatbekov [1]

[1]Al-Farabi Kazakh National University, Almaty, Kazakhstan
[2]Herat University, Herat, Afghanistan
[3] Kazakh National Medical University, Almaty, Kazakhstan
*e-mail: gkurman@mail.ru

HCV-RELATED VASCULITIS

Up to 3% of people in the world are infected with HCV, and 75-80% of them have chronic currency of infection. In the clinical picture of HCV infection, a significant place is given to extrahepatic manifestations - more than half of patients suffer from lesions of the skin, kidneys, heart, blood vessels, autoimmune and lymphoproliferative syndromes associated with HCV. Usually, mortality from chronic hepatitis C is associated with liver cirrhosis and hepatocellular carcinoma, but in fact, more patients die from complications associated with the development of cryoglobulinemic vasculitis - chronic renal failure and cardiovascular catastrophes. 40-60% of patients with chronic HCV infection suffer from cryoglobulinemic vasculitis in a wide range of clinical manifestations: from minimal to life-threatening. The pathogenesis of mixed cryoglobulinemia syndrome is based on polyclonal activation of lymphocytes.

The systemic nature of the lesion, which is observed in HCV infection, reflects its generalized nature with the involvement of many organs and tissues in the pathological process, which complicates timely diagnosis and treatment. A variety of systemic extrahepatic pathology, which often outstrips the clinical picture of hepatitis itself, masquerading as another disease means that a specialist of any profile can meet with chronic HCV infection and its consequences.

Key words: hepatitis C, extrahepatic manifestations, cryoglobulinemic vasculitis.

Introduction

General overview.

First reported in 1989, the hepatitis C virus (HCV) is an enveloped positive-stranded RNA virus that belongs to the Flaviviridae family and to one of its three genera, hepacivirus, more specifically [1]. About 9400 nucleotides and multiple regions are found in HCV genome [2].

HCV is among the viruses with the highest diversity in the genome. One of the key characteristics of HCV, which can be categorized as genotypes, subtypes and quasi-species, is its genome heterogeneity. A lack of corrective action of virus-dependent RNA-polymerase leading to the regular introduction of nucleotide substitutions into the genome of the virus is the underlying explanation for such variability. Sequences are homologous in about 95 percent within the same genotype, although they are so in just 65 percent of cases between genotypes. Continuous HCV mutation greatly threatens immune memory as the number of memory cells capable of recognizing new varieties from the first exposure is steadily lower with each new mutation [3].

HCV is a pathogen widespread globally and a significant health concern. According to the World Health Organization (WHO) more then 71 million people had chronic HCV infection in 2015 (an approximate global prevalence of 1%). These persons have a high risk of advanced liver disease, including cirrhosis and hepatocellular cancer. HCV infection is normally asymptomatic, and just 20-40% of individuals spontaneously clear the virus, so most subjects who experience the virus become chronically

infected[4]. Compared to HCV-negative people, HCV-related all-cause mortality is twice as high and extrahepatic manifestations are a significant risk factor [5]. The most prevalent extrahepatic conditions associated with HCV infection are lymphoproliferative and autoimmune disorders, from cryoglobulinemia vasculitis to malignant B-cell lymphoma [6]. Additional extrahepatic manifestations, including cardiovascular, neurological, metabolic and renal disorders, have been revealed in large cohort studies, and multiple manifestations frequently coexist in the same patient [7]. A study recorded that up to 74% of patients infected with chronic HCV undergo at least one extrahepatic manifestation [8] .

More than 50 percent of infected patients develop recurrent, sometimes steadily progressive hepatitis, which can be associated with extrahepatic skin, renal, hematopoietic, and cardiovascular symptoms, leading to an elevated risk of atherosclerosis, cardiomyopathy, peripheral artery disease, and stroke, thus increasing mortality[9].

Around 130-170 million individuals are infected with the HCV chronically, which is 3 per cent of the world's population. It is a significant public health challenges, with an estimated 3-4 million individuals worldwide infected every year. One of the most important causes of liver-related death and the most common indication for liver transplantation in the United States of America, is chronic hepatitis C (CHC)[9]. Around 30,500 new cases of HCV in the United States have recently been identified by the Centers for Disease Control and Prevention, and the number of chronic cases has been estimated to be 2.7-3.9 million[10].

It is understood that chronic hepatitis C cancause cirrhosis and hepatocellular carcinoma. The key site of replication of HCV is in hepato- cytes, which illuminates the substantial damage it does to the liver. It is stablished, however, thatthe virus is not hepatotoxic, and that most liver injuries are caused by a cell-mediated immune response to infected liver cells. Likewise, the production of extrahepatic manifestations can include immune defects resulting in autoimmu- nity. The affected organ, system, or pathologi- cal process may be categorized by the extrahe- patic manifestations of chronic hepatitis C. The strength of available evidence that link them to CHC, however, differs [11]. The clinical appearance varies from subclinical cases to very severe immunological disorders in CHC patients. In- deed, autoimmune symptoms linked to hepatitis C virus infection often contribute to the diagno-sis of infection with this virus [12].

HCV vasculitis

Of all the extrahepatic Hepatitis C Virus (HCV) manifestations, vasculitic manifestations merit special attention. Since they include blood vessels, they have a multisystem appearance. The existence of cryoglobulins (CGs), a material with unusual physicochemical properties and substantial morbidity and mortality, is mainly due to cases [13].

The tale of revealing the association between HCV and mixed cryoglobulinemia (MC) is a noteworthy scientific success story in which an infectious agent could be traced to an autoimmune disorder. The final act of investigating the effect on patients with cryoglobulinemic vasculitis of the application of recently presented antiviral agents will provide us a vision into the management of autoimmune phenomena when they are related to microbial pathogenic factors. Centered on the ascription of vasculitis to the existence or absence of serum cryoglobulins as a pathogenic factor that involves HCV vasculitis in the existence of cryoglobulins and HCV vasculitis in the absence of cryoglobulins, HCV vasculitic syndromes will be addressed under two key topics [13].

Cryoglobulins (CGs), first termed in 1947 by Lerner and Watson, are immunoglobulins that, when exposed to temperatures below 37°C, precipitate or produce a gel and re-solubilize when re-warmed [14].

Cryoglobulinemia refers to the presence of cryoglobulins in serum (qualitative test positive findings and/or >0.05 g/L in cryocrit quantitative test concentrations). There may be no clinical symptoms of cryoglobulinemia, but it can additionally lead to a broad range of clinical presentations, including skin lesions, arthralgia, peripheral neuropathy, single or multiple organ injury. Symptomatic cryoglobulinemia is referred to as cryoglobulinemic vasculitis (Cryo Vas) or cryoglobulinemic disease[15; 16 ;17 ;18 ;19]. Three subtypes of cryoglobulinemia occur based on the immunoglobulin composition, according to Brouet's classification [20].

Single monoclonal immunoglobulins (most commonly immunoglobulin M (IgM), sometimes IgG or IgA) include type I cryoglobulinemia. Cryoglobulinemia type I accounts for 10% to 15% of cases. Mixed cryoglobulinemia is known as type II and type III since it involves two types of immunoglobulins (normally IgG and IgM) that account for 50 to 60% of cases. Form II mixed cryoglobulinemia includes a mixture of monoclonal and polyclonal immunoglobulins (usually IgM plus IgG c or IgG c), while IgM and IgG, both polyclonal, constitute type III mixed cryoglobulinemia. Oligoclonal IgM or

mixed polyclonal and monoclonal IgM along with polyclonal IgG can also be detected. An intermediate evolution from type III to type II mixed cryoglobulinemia may be this unique serological branch, referred to as type II-III mixed cryoglobulinemia. Notably, the cryoglobulins present in mixed cryoglobulinemia are autoantibodies with action of the rheumatoid factor (i.e. an antibody with the ability to bind another antibody) that allow the formation of immune complexes, which is essential for the pathogenesis of cryoglobulinemic vasculitis [17; 18]. In addition, it was occasionally reported that mixed cryoglobulins were not composed of IgM-IgG, but of other immunoglobulin combinations, like IgG-IgG, IgA-IgG, or IgM-IgG-IgA[21; 22].

Aberrant autoantibody development by B cells and B cell proliferation is the basic mechanism leading to cryoglobulinemia. By interfering with normal B cell function, many underlying diseases may promote this. A lymphoproliferative disorder of B cells is often associated with the involvement of type I cryoglobulins. By comparison, systemic autoimmune conditions, lymphoproliferative disorders and chronic infections are related with mixed type II or type III cryoglobulinemias, with hepatitis C virus (HCV) infection producing 80-90 percent of mixed cryoglobulinemia events [23; 24 ;25]

HCV-related cryoglobulinemic vasculitis

Hepatitis C virus (HCV) is noted for its hepatic and extrahepatic manifestations (25). Extrahepatic complications are mainly immunologically induced by chronic hepatitis C virus infection. Of such, the greatest correlation is cryoglobulinemia and its clinical sequelae. In 40-60 percent of HCV-infected patients, cryoglobulins are easily detectable, while cryoglobulinemia vasculitis occurs in just 5-10 percent of cases [26; 27 ;15; 28; 29]. The involvement of autoantibodies and T cells in vascular infiltrates and the discovery of the susceptibility of particular HLA alleles to cryoglobulinemic vasculitis in patients infected with hepatitis C virus support the autoimmune existence of this virus-associated pathology [30 ;31] .

Cryoglobulinemic vasculitis is a serious small vessel vasculitis mediated immune complex that mainly involves the skin, joints, kidneys, and peripheral nerves, if untreated, caused end-stage organ/tissue injury. It may be of infectious origin, with the most common cause being infection with the hepatitis C virus (HCV) [32 ;33] . cryoglobulinemia is the result of the persistent proliferation of B cells, which generates pathogenic isotypes of IgG andIgM immunoglobulin (Ig) with rheumatoid factor activity[34;35;36] .

Mixed cryoglobulinemia is one of the most serious problems in which vasculitis (mixed-cryoglobulinemic vasculitis) can be produced by deposition of cryoglobulins and cause palpable purpura, arthralgias, glomerulonephritis or neuropathy [25].

The most important etiology of mixed cryoglobulinemia type II and type III is chronichepatitis C virus infection, which accounts for 80-90% of mixed cryoglobulinemia cases [37 ;26 ;38; 39; 24 ;23 ;40]

Pathophysiology of HCV-related cryoglobulinemic vasculitis

For HCV-related mixed cryoglobulinemia, the mechanism of cryoglobulin pathogenicity is best identified (Figure 1). Due to the widespread expression of the hepatitis C virus entry receptor CD81 on the plasmamembrane of both cell types, HCV is capable of simultaneously infecting B cells and hepatocytes [24 ;40;41;42;43]. Active hepatitis C virus replication has been shown in CD19positive B cells;hepatitis C virus RNA and core and nonstructural NS3 proteins can be found in CD19 positive, but not CD19negative, peripheral blood mononuclear cells[44;45]. In monocytes, peripheral dendritic cells, and36,37 macrophages, HCV replication has also been identified [46,47].

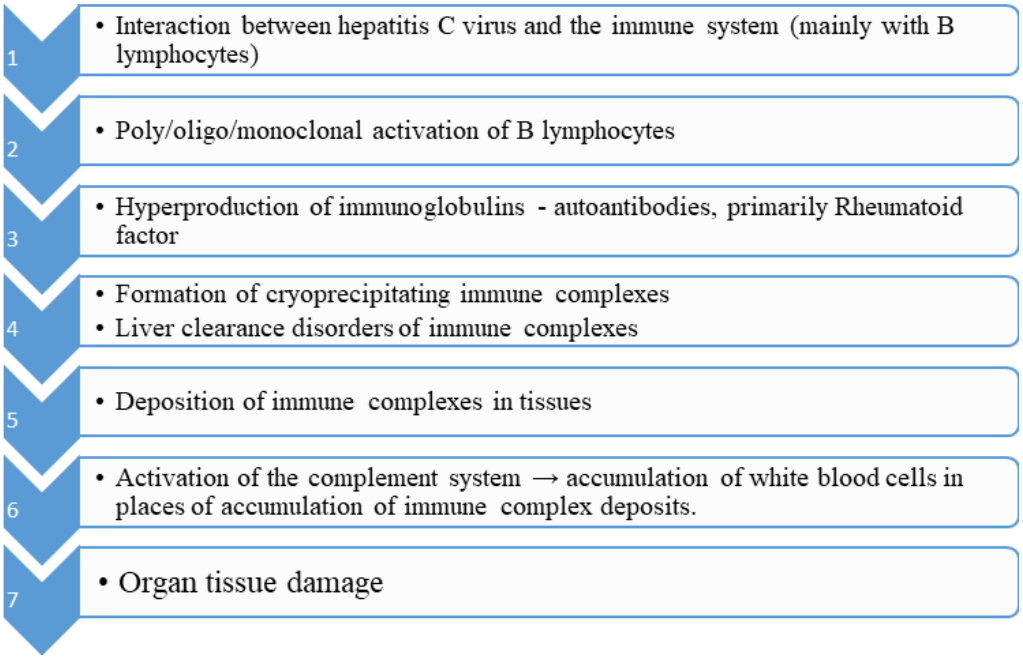


Figure 1 – Pathogenesis of clinical manifestations in mixed cryoglobulinemia

B cell proliferation and HCV infection

A significant mechanism in the pathogenesis of cryoglobulinemia and cryoglobulinemic vasculitis is the proliferation of B cells [48,49,50]. The progression from basic serological modification (cryoglobulinemia) to clinical manifestations (cryoglobulinemic vasculitis) and finally to obviousmalignant B lymphoproliferation (such as non- Hodgkin lymphoma) is accompanied by a multi- stage mechanism [51,52]. The discovery of the empathy of the hepatitis C virus envelope to a transmembrane protein, CD81, provided a foundation for understanding the lymphoproliferation-induced mechanisms of HCV [53,54]. CD81 forms amultiprotein complex with CD21 and CD19 on the surface of B cells. This multiprotein complex controls the polyclonal development of B cells when triggered by hepatitis C virus envelope binding. Furthermore, by adding an antigen to the B cell receptor (BCR) on the cell surface, B cells are activated, causing in polyclonal expansion [53;55].

While in vitro researches have indicated that specific anti-HCV antibodies are capable of stimulating BCR in B cells, it appears that HCV envelope protein activation of CD81 provokes naive B cell proliferation independently of the stimulation of BCR. In the production of lymphoproliferative disorders, CD81-mediated activation of naive (CD27-positive) B cells with subsequent differentiation to autoantibody-producing memory cells could make a contribution. Furthermore, chronic antigenic stimulation could cause the overexpression (favoring some clones) of B cells and support immune dysregulation mechanisms that give rise to the development of mixed cryoglobulinemia and finally to malignant transformation that is occasionally found in patients with chronic hepatitisC virus infection [55;56; 57; 58 ;59].

B cell transformation

Hepatitis C virus infection can lead to B cell transformation in addition to the stimulation of B cell expansion and the decrease of the B cell activation threshold [55;56; 57; 58 ;59]. HCV infection patients have clonal populations of B cells that are primarily memory B lymphocytes generating IgM, expressing modestly hypermutated immunoglobulin genes [55;56; 57; 58 ;59].In both HCV-positive non-Hodgkin lymphoma and cryoglobulinemic vasculitis, several of the same immunoglobulin idiotypes and restricted gene sequence rearrangements are observed, indicating a common pathophysiology. Furthermore, novel research on the pathogenesis of lymphomas associated with hepatitis C virus have shown evidence that this virus could have mutagenic potential. In the immunoglobulin heavy chain gene and other locations, B cells exposed to HCV in vitro had up to a tenfold increase in mutations. In addition, relative to

HCV negative lymphomas, increased mutations are seen in HCV-associated lymphomas [49]. Between genetic mutations, the most frequent chromosomal rearrangement in lymphoid cancers, mainly follicular lymphoma, a subtype of non-Hodgkin lymphoma, is the translocation [14;18] of the anti-apoptotic BCL2gene that encodes apoptosis regulator BCL2. Patients with chronic hepatitis C virus infection in 35% of cases have proof in their peripheral mononuclear cells of a widespread chromosomal rearrangement t [14;18] translocation [50].

This HCV-dependent translocation of genes blocks apoptosis of B cells, resulting in oligoclonal monotypic lymphoproliferation. The significant 'missing link' to our understanding of lymphomagenesis in the environment of chronic hepatitis C virus infection could be mutations in other oncogenes, such as MYC, and regulators of apoptosis [60].

Autoantibody production

B cells are induced to develop a variety of autoantibodies by chronic stimulation by hepatitis C virus infection [61]. This extensive production of autoantibodies promotes the creation of a variety of HCV infection-related immune manifestations that are variably assembled in what is commonly called 'HCV syndrome' [62, 63 ,64]. In addition to the characteristic image of cryoglobulinemic vasculitis, HCV syndrome could be included clinical symptoms such as autoimmune thyroiditis, sicca syndrome (dryness of the exocrine glands, especially the eyes and mouth), thrombocytopenia, hemolytic anemia, autoimmune diabetes, and pulmonary fibrosis [65 ;53; 66; 57; 54].

In patients that have chronic hepatitis C virus infection, populations of clonal B cells are found in the liver and peripheral blood. Curiously, clonally restricted B cells show biased use of the heavy1-69 and variable 3-20 immunoglobulin gene segments of the rheumatoid factor coding variable, as do B cells isolated from the lymph nodes of patients with non-Hodgkin lymphoma related with HCV [49 ;58; 50].

In patients with HCV-related mixed cryoglobulinemia, at many organs, including the portal tracts of the liver, spleen, and bone marrow, can find lymphoid infiltrates with cells expressing oligoclonal or monoclonal IgM with rheumatoid factor involvement. Mixed cryoglobulinemia thus tendsto be a crosslink between conventional autoimmune disorders and hematological (i.e. B cell lymphoma) neoplasia [66; 67 ;68; 69 ;70 ;71; 72]. Continuous stimulation of B cells thought viral antigens and increased expression of lymphomagenesis-related genes, especially activation-induced cytidine deaminase, which is critical for somatic hypermutation, leads to polyclonal and later monoclonal expansion of B cells [73]. Finally, these interactions cause a lymphoproliferative disease that can ultimately develop into non-Hodgkin lymphoma of B cells. Indeed, a significant correlation between HCV infection and large B cell lymphoma, marginal zone lymphoma and lymphoplasmacytic lymphoma has been identified among other hematologic malignancies [74].

In short, lymphoproliferation of HCV-induced B cells and the development of autoantibodies are possibly the direct result of the transformation of infected B cells, but also an indirect mechanism resulting from chronic antigenic stimulation of a small pool of autoreactive B cells.

Immune complex formation

Deposition of immune complexes in small blood vessels and subsequent endothelial damage are responsible for the clinical signs of cryoglobulinemic vasculitis. In HCV-associatedmixed cryoglobulinemia, a permanent clone of B cells induced by chronic HCV infection sustainsthe appearance of immune complexes produced by circulating HCV particles, anti-HCV polyclonal IgG and monoclonal IgM with rheumatoid factor involvement.

Because of clonically limited IgM, these cryoprecipitable immune complexes are knownto avoid the erythrocyte transport system. The existence of IgM in cryoprecipitable immunecomplexes enables them to persuade activation and consumption of complements, but not to integrate complement fragments, including complement C3b (a complementary component that promotes the binding of immune complexes to erythrocyte complement receptor 1 (CR1) [61].

In addition to escaping the erythrocyte transport system, these immune complexes stay free to circulate in the blood, since hepatic and splenicmacrophages are unable to process the immune complexes due to HCV-induced defects in lysosomal enzyme biogenesis. Furthermore, in circulating monocytes, this defect was clearly seen[74]. Excitingly, electron microscopy studies of renal tissue samples found monocytes containing engulfedcryoglobulins; however, the precise function of these cells is indistinct [75].A phagocyte influx into the glomerulus is present in cryoglobulinaemic nephritis. Phagocytes try to extract accumulated

cryoglobulins; however, they are unable to process phagocytic cryoglobulins, and cryoglobulin trapping is likely to represent ineffective clearance of cryoglobulin [75]. This mechanism is likely to perpetuate glomerular injury, as seen in a research using a mouse model of cryoglobulinaemic membrane proliferative glomerulonephritis, where macrophage ablation provided defense againstexpansion of the mesangial matrix and collection ofcollagen (nephritis markers) deprived of affecting the removal of cryoglobulin (Guo et al., 2011). In place of cleaning cryoglobulins from the glomeruli, this experimental model indicates that macrophage recruitment into the glomeruli plays a crucial role in the development of kidney damage; macrophage influx, vessel infiltration and diapedesis are linked to amplification of injury after immune complex deposition [76].

Altered lysosomal enzymes of monocytes (probably associated with hepatitis C virus infection), comprising extracellular release of procathepsin D and/or release of danger-associated molecular patterns (DAMPs) from injured resident cells, could decrease the inherent role of macrophages via immunoglobulin crystallizable fragment (Fc) gamma receptor to clear immune complexes. increase of the mesangial matrix and proliferation of glomerular cells may be maintained by extracellular activation of procathepsin D released or by proinflammatory cytokines released from macrophages triggered by DAMP [74,76].

Clonally limited IgM shares clear affinity for the constituents of the glomerular matrix, counting fibronectin, as well as the classical immune complex deposition pathway, opening the likehood for a ‘in situ’ binding mechanism of immune complexes to kidney components [77]. Consequently, the pathogenetic function of cryoglobulins in the induction of vasculitis is linked both to the enrolment of vessel leukocytes and to the deposition of immune complexes, to the activation of the complementary system and to microvascular damages [62,78].

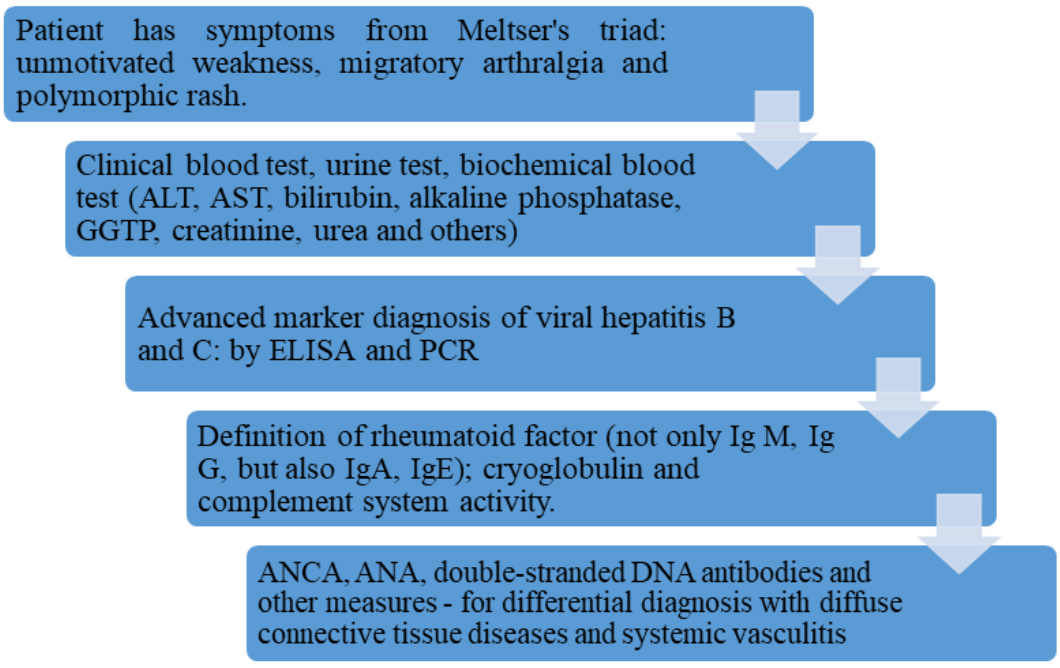


Figure 2 – Diagnostic algorithm of patients with mixed cryoglobulinemia

a. Non-HCV-related cryoglobulinemia

The major factors are other infectious disorders, B cell malignancies and autoimmune diseases in 10-20 percent of mixed cryoglobulinemia cases thatare not related with chronic HCV infection Figure 2[80].Specially, it was proposed to link cryoglobulinemia with chronic HBV infection [81]. Nevertheless, only about 2% of cryoglobulinemic vasculitis cases tend to be caused by hepatitis B virus infection [66].

Cryoglobulinemic vasculitis sometimes can be related with HIV infection, particularly in cases of hepatitis C virus coinfection [82]. Mixed cryoglobulinemia associated with non-HCV is

primarily caused by viruses, bacterial pathogens or parasites. Circulating serum cryoglobulins canbe present in patients who have active SLE and rheumatoid arthritis; mixed cryoglobulinemia has been seen in ~10% of patients with SLE or rheumatoid arthritis, but these patients generallydo not have the same clinical manifestation as patients with SLE or rheumatoid arthritis who have cryoglobulinemic vasculitis[83].

Type II cryoglobulinemia may be present in around 5-20 percent of patients who have primary Sjögren syndrome [84]. One of the main predictive factors in primary Sjögren's syndrome is currently considered to be type II mixed cryoglobulinemia as it has been correlated with extraglandularinvolvement, appearing of systemic vasculitis, B cell lymphoma and reduced survival[84].

b. HCV-related non-cryoglobulinemic vasculitis

Few studies have addressed systemic vas- culitis caused by HCV without evidence of cryoglobulinemia in the literature, most of which are HCV-related polyarthritis nodosa (PAN).

PAN is a medium sized necrotizing vasculitis classically associated with HBV but can be observed to a lesser degree in patients withHCV infection. In certain ways, HCV-related PAN patients vary from those connected to cryoglobulinemic vasculitis. Clinically, life- threatening vasculitis, severe multifocal sensorimotor mononeuropathy as opposed to distal mild sensory polyneuropathy, malignanthypertension, cerebral angiitis, ischemicabdominal pain, microaneurysms of the kidneys and liver, but lesser rates of arthralgia, purpura,and chronic hepatitis activity have been reportedto differentiate this type from cryoglobulinemic vasculitis.

Higher acute phase reactants such as ESR and CRP and more recorded renal insufficiency are shown to occur. Histopathologically HCV associated PAN affects medium-sized arteries to a greater extent with necrotizing vasculitis rather than immune complex disease indicating cell-mediated inflammation, whereas mononuclear cell infiltration is more generally recorded in cryoglobulinemic vasculitis in perivascular areas [85,86].

In the case of cryoglobulinemic vasculitis,a national-level mass campaign is to be carried out and where prioritization is to be valued, it was suggested that cases of cryoglobulinemic vasculitis and HCV-related PAN must be amongthe most important patients with hepatitis C virus infection in whom viral clearance is warranted, as stated in a latest research[87].

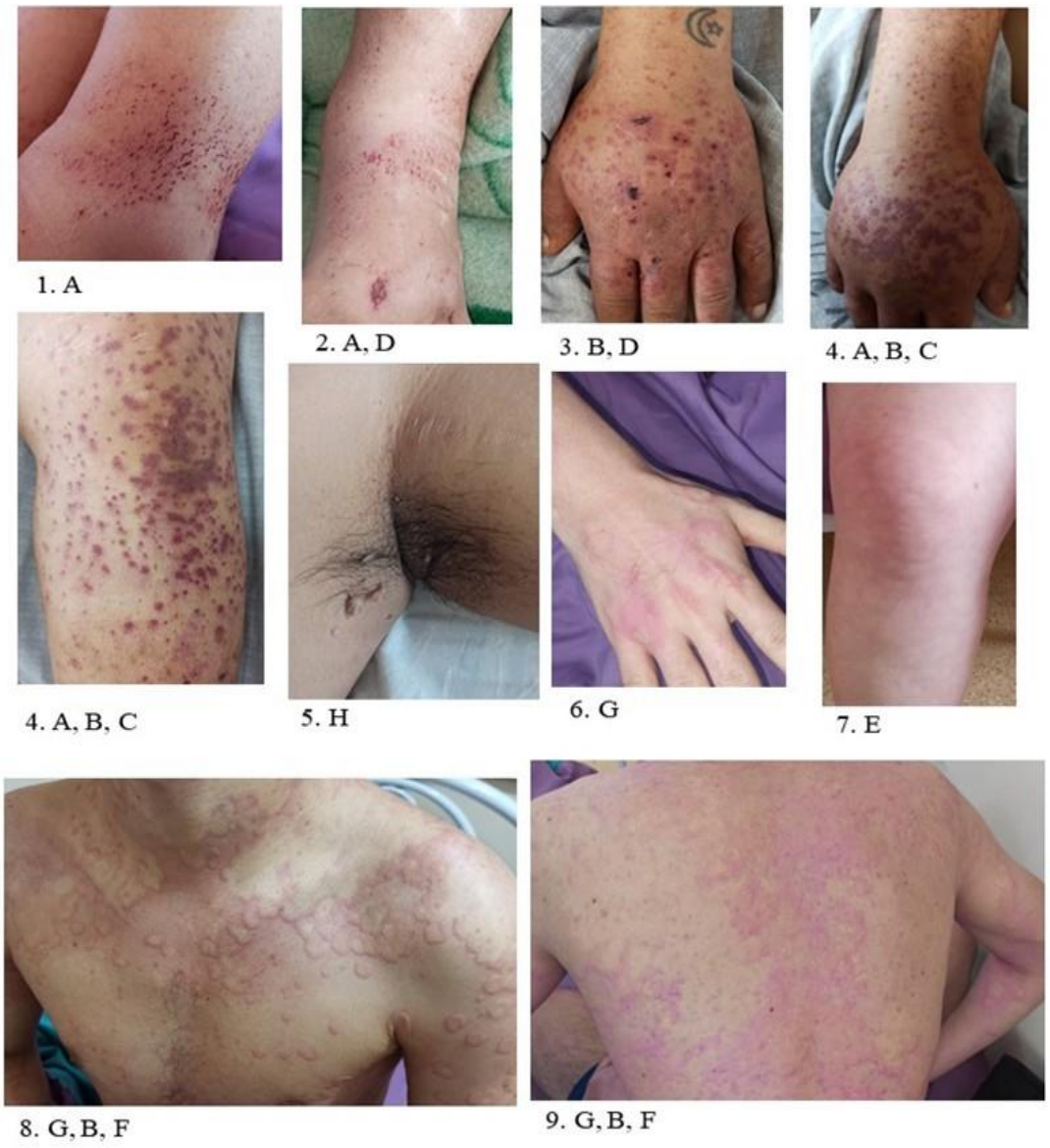
HCV-related cryoglobulinemic vasculitis manifestation

Cryoglobulinemia is an autoimmune manifestation most commonly identified among patients with hepatitis C virus infection. Purpura, arthral- gia, fatigue, myalgia, polyneuropathy, glomeru- lonephritis, ophthalmopathy, and intestinal ischemia are the major clinical symptoms [88,18].A large variety of clinical characteristics are present in patients with cryoglobulinemia and are discussed as follows:

1. Cutaneous manifestations

It is the most usual manifestation of the disease, commonly in the form of palpable purpura and less frequently maculopapular rash, mostly affecting to a lesser degree the lower limbs, the lower trunk, and the upper limbs. Typically, these purpuric lesions are transient and irregular, but leaving hyperpigmented areas will coalesce and recover.

The phenomena of Raynaud, acral cyanosis and livedo reticularis, usually seen in Type I cryoglobulinemia and seldom seen in mixed cryoglobulinemia, are other less common skin lesions. Skin ulcers usually originate on the lower extremities, particularly in the malleoli, are a more serious severe type, which can complicate confluentpurpura eruptions and cause secondary infectionand gangrene in certain patients (Pictures1)[89, 90].



Pictures1 – Skin manifestations of vasculitis: A) Petechiae. B) Macula. C) Purpura. D) Ulcer. E) Livedo reticularis. F) Urticaria. G) Erythema. H) Papillomatosis

2. Musculoskeletal manifestations

The second most frequent manifestation (60-90 percent of cases) typically involve arthralgiain the form of intermittent monooligoarthralgia that mostly affects large joints, mainly the ankles and this type, along with rheumatoid artheritis such as polyarthritis that affects small joints, which are the two most common hepatitis C virus joint manifestations. In HCV-related Cryoglobulinemic vasculitis, myalgia is also commonly stated, whereas arthritis and myositisare rarer manifestations of the disease [40].

3. Neurological manifestations

In up to 50 percent of cases, HCV mediated Cryoglobulinemic Vasculitis predominantly affects the peripheral nervous system and usually affects sensory nerves rather than motor nerves. The mixed form, however, was also noted. Distribution encompasses, to a lesser degree, polyneuropathyand mononeuritis multiplex. Patients complain of paresthesia, tingling and lower limb numbness that appears to worsen throughout the night [91].

Cryoglobulinemic Vasculitis could affect the central nervous system (CNS) less frequently,

typically in the form of cerebral vasculitis, which may present with ischemic stroke, TIA or cognitive dysfunction and may occur with high-intensity MRI lesions of white matter [92].

4. Renal manifestations

This happens in around 20-30 percent of patients and, even though treated, brings a poor prognosis. They have a high rate of deficiencies and relapses in care. Mild proteinuria and isolated hematuriaare generally present, but nephrotic and nephritic syndromes and chronic renal insufficiency have also been identified to a smaller extent [93].

In comparison to MPGN, the frequently observed histopathological pattern is membranoproliferative glomerulonephritis (MPGN) with immune complex deposition in glomeruli and IgM staining, which can also be seen in HCV without cryoglobulinemia, where staining is of the form IgG.

Excitingly, in renal biopsies of patients who have negative serum anti-HCV antibodies and PCR, several authors find hepatitis C virusantigens denoting the potential intake of theantigen and its antibody in the immune complex [34]. Mesangioproliferative and focal proliferative glomerulonephritis in up to 20 percent of renal involvement are other forms of glomerulonephritis identified in mixed cryoglobulinemia associated with HCV [94,95].

5. Sicca symptoms

As previously mentioned, HCV is a sialotropic virus with a clinical image of dry mouth and dry eyes, close to that seen in primary Sjogren's syndrome, which has a similar histopathological image, namely focal lymphocytic infiltration, but with two major variations. With the absence of glandular canal injury, infiltrates are primarily perivascular rather than pericanalicular, and also predominantly with CD8+ ve rather than CD4+ve. A point of distinction may be anti SSA and anti SSB antibodies as well. They appear to be more optimistic in patients with primary Sjogren's syndrome [96].

6. Pulmonary manifestations

In accordance with Bronchoalveolar Lavage findings, subclinical alveolitis was identified in mixed cryoglobulinemia that may progress to clinically obvious interstitial lung disease in unusual cases.

Pulmonary function tests may show evidence of minor airway disease and gas exchange dysfunction, with symptoms ranging from dyspnea to pleurisy and cough. Mixed cryoglobulinemias less frequently observed in Bronchiolitis Obliterans Organizing Pneumonia (BOOP), pulmonary hemorrhage, and pulmonary vasculitis [97].

7. Endocrine disorders

In comparison with the general population, autoimmune thyroiditis, hypothyroidism and papillary thyroid carcinoma are more prevalent in mixed cryoglobulinemia patients. Type 2 diabetes mellitus, with and without mixed cryoglobulinemia,was also statistically related to HCV more than the general population [98,99].

8. Gastrointestinal and hepatic manifestations

Hepatomegaly, abnormal liver function tests or abnormal liver biopsy, splenomegaly,lymphadenopathy and abdominal pain have been defined in up to 90 percent, 30%, 20 percent and 20 percent of cases respectively.

Nearly 3/4 of the population, liver involvement happens with almost a threefold rise in advanced liver fibrosis and steatosis, as well as a substantial association with cirrhosis after age, gender and length of infection adjustment [100].

9. Cardiovascular manifestations

Mixed cryoglobulinemia has been documented for ischemic heart disease with coronary vasculitis, valvular heart disease with mitral valve damageand incompetence, pericarditis, cardiomyopathy, in particular hypertrophic form, and congestive heart failure [101].

10. Female reproductive dysfunctions

It should be remembered that generalized vascular disease triggers reproductive function disorders in hepatitis B virus and hepatitis C virus infections. With the successive development of hormonal homeostasis dysfunction, immune complex vasculitis produces degenerative changes in the hypothalamic pituitary area [88].

Conclusion

Systemic vasculitis, which is observed in HCV infection, underlies most extrahepatic manifestations with the involvement of many organs and tissues in the pathological process,

which complicates the timely diagnosis and treatment of chronic hepatitis. A variety of systemic extrahepatic pathology, which often outstrips the clinical picture of hepatitis itself, masquerading as another disease, and for many years prevails over a moderate and mild process in the liver, means that a specialist of any profile can meet with chronic HCV infection and its outcomes.

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