IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 23, Issue 1 Ser. 10 (January. 2024), PP 08-14
www.iosrjournals.org

Hepatitis B Virus-Related Cryoglobulinemic Vasculitis: A Comprehensive Review And Case Report

Francisco Andres Tama Sánchez [1], José Enrique Paredes Romero[2], Javier Orlando Benavides Camacho[3], Alisson Vanessa Orellana Nieto[4], Irene Camila Cherrez Paredes[5], Vanessa Jarelly Rodríguez Huerta[6]

[1](Universidad Católica De Santiago De Guayaquil, Ecuador)
[2](Physician, Hospital General Del Norte De Guayaquil Iess Los Ceibo, Ecuador)
[3,4](Universidad De Guayaquil, Ecuador)
[5](Obstetrician, Master´S Degree In Management Of Health Institutions, Ecuador)
[6](Physician, Instituto Mexicano Del Seguro Social, México)

Abstract:
This review comprehensively explores the multifaceted aspects of Hepatitis B Virus (HBV)-related cryoglobulinemic vasculitis. The clinical manifestations, diagnostic challenges, and diverse treatment modalities are discussed, emphasizing the need for a multidisciplinary approach.
Much of the review dives into emerging perspectives, including advancements in therapeutic strategies, immunogenetics, and personalized treatment approaches. The interplay between genetic predispositions and environmental factors is explored, shedding light on the complexities of disease development. The economic burden of HBV-related cryoglobulinemic vasculitis, encompassing healthcare costs, productivity losses, and burdens on healthcare systems, is thoroughly examined.
Furthermore, the review addresses the associations with comorbid conditions, complications, and the disease's impact on the pediatric population. The role of immunogenetics, including B-cell dysregulation, cytokine pathways, HLA alleles, and epigenetic modifications, is highlighted, offering insights into potential breakthroughs in personalized medicine. This case report presents a patient with clinical and laboratory diagnosis of Hepatitis B Virus (HBV)-related cryoglobulinemic vasculitis and its extrahepatic manifestations.
This comprehensive overview contributes to a deeper understanding of the disease, informing clinicians, researchers, and policymakers alike.

Key Word*: Vasculitis; Cryoglobulinemic; Hepatitis B Virus (HBV)*

Date of Submission: 20-01-2024 Date of Acceptance: 30-01-2024

I. Introduction

Cryoglobulinemic vasculitis (CV) associated with the hepatitis B virus (HBV) is an uncommon extrahepatic symptom of persistent HBV infection. Clinical signs and symptoms of HBV-related CV can range widely, from minor to severe. Purpura, asthenia, and arthralgias are common symptoms; dermatitis, polyarthralgias, arthritis, respiratory disorders, aplastic anaemia, leg ulcers, peripheral neuropathy, and nephropathy might appear in severe instances. HBV-related CV can manifest clinically in a wide range of ways, affecting different body areas, and the severity can vary from person to person [1],[2].

Small to medium-sized blood vessels are primarily affected by the condition, and immune complexes containing cryoglobulin are the cause of vasculitis. A systemic inflammatory condition that manifests as arthralgia, purpura, neuropathy, tiredness, and glomerulonephritis may result from it. Cryoglobulins must be shown in a laboratory setting to be diagnosed with cryoglobulinemic syndrome, either with or without accompanying distinctive clinical signs and symptoms [3].

Immunoglobulins precipitate when the temperature falls below 37°C and dissolve again when the body warms up, a condition known as cryoglobulinemia [1].

IgM, IgG, or IgA monoclonal antibodies are included in type I cryoglobulinemia. It is linked to NHL, Waldenstrom's disease, and multiple myeloma. Referred to as mixed cryoglobulinemia (MC) in kinds II and III [4].

Immunocomplexes made up of polyclonal IgG with monoclonal or polyclonal IgM with rheumatoid factor activity make up cryoglobulins. Up until the 1990s, almost 90% of occurrences of MC were linked to HCV infection [5].

Levo et al. first proposed the possibility that HBV is the etiologic agent of mixed cryoglobulinemia more than 40 years ago. In a groundbreaking investigation involving thirty patients with essential mixed cryoglobulinemia, the authors made the case that viral infection may be a primary cause of immunocomplex vasculitis. A cohort of 717 individuals with essential cryoglobulinemia was retrospectively analyzed by Monti et al., and the Italian Group for the Study of Cryoglobulinemia (GISC) reported a 5.5% prevalence of HBsAg positivity. Following this, Ferri et al. assessed 231 MC patients and found that 1.8% of them had HBsAg. Cacoub et al. recently examined all these data. HBV-related CV is associated with elevated levels of HBsAg or anti-HBc antibodies as well as HBV-DNA. Over the past 20 years, multiple case series in Europe (mostly in Italy and France) have now shown the prevalence of chronic HBV infections in CV, with estimates ranging from 0.5% to 5.5% of cases [6].

This type of vasculitis has a great polymorphism and can range from mild to severe forms that compromise the patient's life. The classic triad consists of asthenia, joint involvement in the form of arthralgias or arthritis and palpable cutaneous purpura. The cutaneous manifestations are due to leukocytoclastic vasculitis of the small vessels of the skin and include palpable purpura, Raynaud's phenomenon, ulcers, livedo reticularis and ischemic lesions in acral regions. Joint involvement as arthralgias or non-erosive arthritis. Xerostomia and xerophthalmia occur in approximately 50% of patients with HCV due to its sialotropic, hepatotropic, and lymphotropic nature. Additionally, there is an overlap between patients with cryoglobulinemic vasculitis and Sjögren's syndrome, making it challenging to distinguish between the two conditions.

The severity of symptoms associated with cryoglobulinemic vasculitis (CV) caused by the Hepatitis B virus (HBV) might vary. They could consist of:

1. **Moderate to mild symptoms:**
- Purpura, or purple-colored skin lesions brought on by subcutaneous hemorrhage,
- Asthenia, or weakening.
- arthritis discomfort in the joints

2. **Extensive symptoms:**
- ulcers on the legs
- peripheral neuropathy
- Skin irritation
- arthritis and polyarthralgia's
- respiratory conditions
- Anemia aplastic
- Kidney illness, or nephropathy [2], [7].

Skin symptoms to more serious cerebral, renal, and infrequent pulmonary involvement might be seen in the clinical presentation of HBV-related CV [2]. It is crucial to remember that different bodily areas may be affected by the symptoms, and that each person may experience the disease to a different degree. Estimates of the frequency of HBV-related cryoglobulinemic vasculitis (CV) in people infected with HBV range from 1.2% to 4%. About 350 million people worldwide are infected with HBV. People with mixed cryoglobulinemia (MC), a rare occurrence in people with HBV infection, may develop cryoglobulinemic vasculitis. According to a cohort study by Ramos-Casals et al., out of 209 individuals with cryoglobulinemic vasculitis, 14% had a condition that was potentially fatal. Four patients with pulmonary hemorrhage out of the 29 patients with life-threatening cryoglobulinemic vasculitis also experienced fever, hemoptysis, dyspnea, and pulmonary infiltrates on the chest radiography

Chronic HBV infection is one of the risk factors for developing HBV-related cryoglobulinemic vasculitis (CV), which affects around 350 million individuals worldwide and can cause CV in 1.2–4% of HBV-infected patients [1]. Furthermore, it has been found that a poor prognostic factor for cryoglobulinemic vasculitis associated with hepatitis C virus infection is the existence of significant liver fibrosis at the time of diagnosis [1]. Better results have been linked to the use of antiviral therapy; in around 60% of cases, cryoglobulinemia has been shown to vanish [10]. Therefore, it is crucial to consider the severity of liver fibrosis and the existence of a chronic HBV infection when managing HBV-related cryoglobulinemic vasculitis.

The most common neurologic manifestation is peripheral neuropathy with mild sensory involvement; some patients may have sudden motor involvement such as mononeuritis multiplex. Central nervous system involvement is exceptional.

Renal involvement occurs in 20% of patients at the time of diagnosis and in 35-60% during the disease. Typically, it is asymptomatic and presents as proteinuria or pathological sediment. Progression to nephrotic syndrome and renal failure is less common. Membrane proliferative glomerulonephritis, characterized by thickening of the glomerular basement membrane and cellular proliferation, especially of macrophages, is often

seen on renal biopsy. In cases of mixed cryoglobulinemia, intraluminal thrombi are observed in the vascular loops, corresponding to cryoprecipitate. In some studies, HCV particles have been identified.

Diagnosis

Diagnosis of cryoglobulinemia vasculitis (CV) due to HBV is made by combining laboratory testing and clinical assessment. Usually, the diagnosis entails the following actions:

1. Clinical evaluation:

Through a patient's medical history and do a comprehensive physical examination to identify symptoms and signs of vasculitis, such as purpura, arthralgia, weakness, and organ-specific manifestations like renal or neurological involvement.

2. Laboratory tests:

Hepatitis B serology: To confirm HBV infection, tests are performed for the hepatitis B surface antigen (HBsAg), hepatitis B e-antigen (HBeAg), and hepatitis B core antibody (anti-HBc).

Cryoglobulin testing: It is the process of finding out whether the blood contains cryoglobulins, which are immunoglobulins that precipitate in cold environments. Usually, to accomplish this, blood samples are obtained and processed following particular guidelines.

Tests for the HBV Viral Load and Liver Function: These tests measure the HBV infection's severity and the liver's reaction to it [11].

3. Imaging Studies:

When certain symptoms, such as pulmonary or renal signs, are present, imaging studies, such as ultrasound, CT scan, or MRI, may be carried out to evaluate organ involvement.

4. Biopsy:

In some circumstances, especially when there is cutaneous or renal involvement, a tissue biopsy may be required to confirm the diagnosis and assess the degree of organ damage [2].

Indirect immunofluorescence shows diffuse IgM deposits in the capillary loops, while electron microscopy shows parallel subendothelial deposits arranged in a rectilinear pattern (fingerprints). No subepithelial deposits are present due to the size of the cryoglobulins, which are too large to cross the glomerular basement membrane. In these patients, a benign lymphoproliferative disorder characterized by the infiltration of lymphocytes with rheumatoid factor on their surface can be observed in the liver, spleen, and bone marrow. In rare cases, this disorder may progress to non-Hodgkin B-cell lymphoma.

A thorough approach is necessary for the diagnosis of HBV-related CV, combining laboratory, clinical, and, if necessary, histological results to confirm the existence of both cryoglobulinemic vasculitis and HBV infection. Depending on how severe the condition is, there are many therapy options for HBV-related cryoglobulinemic vasculitis (CV).

Treatment

Managing HBV-related cryoglobulinemic vasculitis necessitates a multidisciplinary approach, addressing both the viral infection and the associated vasculitis. Antiviral therapy, aimed at suppressing HBV replication, forms the cornerstone of treatment. Nucleotide analogs, such as entecavir or tenofovir, are commonly employed to achieve sustained viral suppression.

1. Antiviral treatment:

For HBV-related CV, antiviral medication combined with NAs need to be regarded as the optimal treatment. NAs often have little trouble establishing efficient HBV-DNA suppression and, in rare instances, HBs/anti-HBs seroconversion. In relation to HCV infection, it is noteworthy to emphasize that cryoglobulin persistence can also be observed in cases of virological response, and that the persistence of B-cell clones that produce cryoglobulinemic agents might cause vasculitis to recur in patients who are not infected with the virus. Patients who test positive for HBV may find that the same idea applies to them. The primary distinction between HCV and HBV in terms of antiviral therapy is that NA medication is lifelong. Antiviral medication may only be discontinued in patients who achieve seroconversion. More generally, it should be emphasized that, unlike HCV, viral clearance is not possible in cases of HBV infection; nevertheless, replication control (if seroconversion is not attained) or a state of latent infection (if seroconversion is acquired) can be preserved.

Enomoto et al. used entecavir 0.5 mg day−1 for 20 weeks to treat a patient with cryoglobulinemic vasculitis associated with HBV. By the time therapy ended, they saw the purpura on the leg go away, the HBV-DNA turned negative, the serum cryoglobulin levels regress, and the Alanine Transaminase (ALT) level return to normal [1].

2. Corticosteroid-oriented therapy:

For mild-to-moderate cases of HBV-related CV, corticosteroids are helpful. They aid in symptom relief and inflammation reduction.

As first-line treatment, twelve (52.2%) patients were given corticosteroid (0.5–1 mg/kg) and NAs (0.5 mg/d for patient 11; ETV, 0.5 mg/d). These regimens included corticosteroids and NAs (n = 6); corticosteroids and cyclophosphamide (CTX) and NAs (n = 2); corticosteroids and mycophenolate mofetil and NAs (n = 2); corticosteroids and plasma exchange (PE) and NAs (n = 1), and corticosteroids and NAs, corticosteroids, and CTX in combination with PE (n = 1). Patients on corticosteroid-based regimens experienced the following symptoms: hematuria (n = 7), purpura (n = 7), livedo reticularis (n = 2), peripheral neuropathy (n = 2), arthralgia (n = 1), proteinuria (n = 11) and renal function impairment (n = 8), including RPGN (n = 1); Two patients (patients 11 and 12) died from infection, and one patient (patient 7) was lost to follow-up. Three patients attained CR and six patients achieved PR out of the remaining nine patients evaluated for clinical remission. Two patients had CR and three had PR out of the five who were evaluated for laboratory reaction. Moreover, none of the five patients (n = 5) who had HBV-DNA replication at baseline had any detectable HBV-DNA replication following treatment [8]. Healthcare professionals should utilize the lowest effective dose of corticosteroids and regularly monitor patients for signs of infection, glucose intolerance, hypertension, and weight gain to minimize side effects. In certain situations, corticosteroids can be used in smaller doses overall by combining them with other immunosuppressive medications, such as mycophenolate mofetil.

3. Rituximab-oriented therapy:

In severe cases of HBV-related CV, rituximab, a chimeric antibody, is employed. It binds to the B-cell surface antigen CD20. It is effective in refractory instances and interferes with the generation of monoclonal IgM and cryoglobulins. Healthcare professionals should actively monitor patients for evidence of infection, infusion reactions, and hypogammaglobulinemia to treat the adverse effects of rituximab. In many instances, rituximab can be taken in smaller doses overall by combining it with other immunosuppressive medications, including cyclophosphamide. Furthermore, to avoid a potentially fatal HBV flare-up, rituximab must always be used in conjunction with nucleotide analogues (NAs) therapy [10].

The literature that is currently accessible reports that there is variability in the success rate of rituximab while treating cryoglobulinemic vasculitis (CV) due to HBV. Rituximab is helpful in individuals with hepatitis C virus (HCV)-related cryoglobulinemic vasculitis that persists despite virological clearance by antivirals, according to a randomized controlled trial conducted after antiviral therapy failed. In a patient with HBV-associated type II cryoglobulinemia and severe multisystem disease, another investigation found that rituximab reduced cryoglobulin levels and improved disease control. But there is not much data on the best way to take rituximab for CV caused by HBV, therefore customized therapy regimens would be required. There are conflicting reports regarding rituximab's effectiveness in non-HCV-cryoglobulinemic vasculitis. Infusion reactions, infections, and hypogammaglobulinemia are among the side effects of rituximab that require close observation for infectious complications. In conclusion, rituximab may be useful in the treatment of CV associated with HBV; however, the response rate may differ based on the specific circumstances of each patient [10-12].

Plasma exchange:

To treat severe CV flare-ups in cases with HBV-related CV, high-dose corticosteroids mixed with plasma exchange can be used in conjunction with NAs therapy [12].

II. Case Report

A 63-year-old patient was admitted with complaints of large erythematous maculopapular lesions scattered across the back and lower limbs, displaying a vasculitis pattern. The patient also reported diffuse arthralgias. Diagnostic studies revealed post necrotic liver cirrhosis, indicating chronic postnecrotic hepatitis. Furthermore, the presence of anti-HBV antigenemia was detected.

Upon further investigation, direct immunofluorescence studies of the skin exhibited intense dermal deposition of immunoglobulins, supporting the suspicion of cryoglobulinemic vasculitis. Microscopic analysis revealed cryoglobulins and vasculitis due to hypersensitivity, confirming the extrahepatic manifestations of the hepatitis B virus.

This case exemplifies the complex nature of extrahepatic manifestations associated with hepatitis B virus infection. The clinical presentation, characterized by vasculitis skin lesions, arthralgias, and evidence of cryoglobulinemic vasculitis, highlights the importance of considering systemic involvement in patients with chronic HBV infection.

The findings underscore the need for a comprehensive approach to managing hepatitis B-related cryoglobulinemic vasculitis, incorporating antiviral therapy, immunosuppression, and tailored interventions based on the specific clinical manifestations observed in individual.

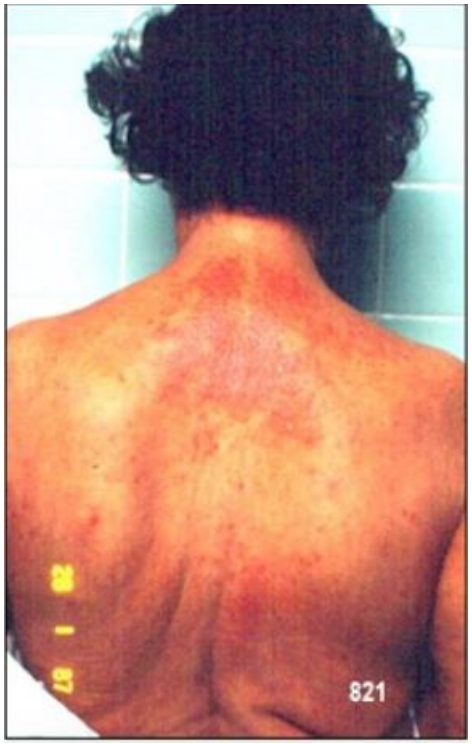

Fig 1.- Extrahepatic manifestations of hepatitis B virus. Vasculitis due to hypersensitivity.

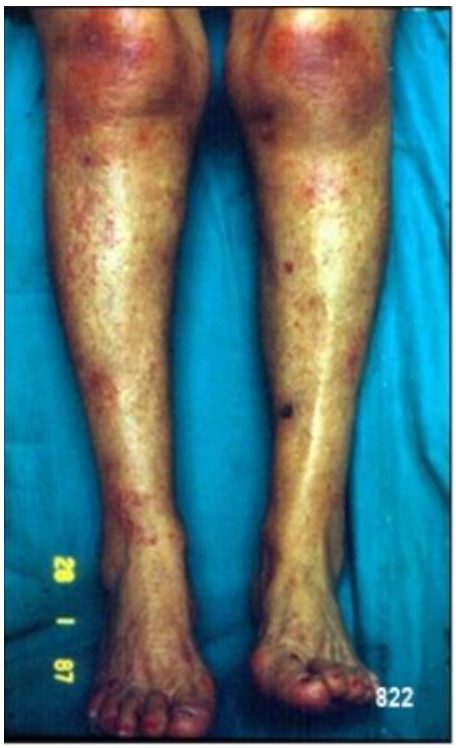

Fig 2.- Extrahepatic manifestations of hepatitis B virus. Vasculitis due to hypersensitivity. Large erythematous macules are located on both lower limbs and knees. Notice that one of them has a necrotic ulcer.

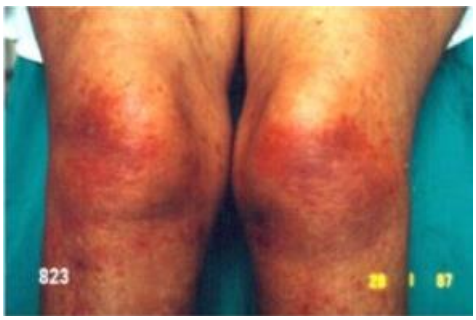

Fig 3.- Extrahepatic manifestations of hepatitis B virus. Vasculitis due to hypersensitivity. Vasculitis and phlogosis of both knees.

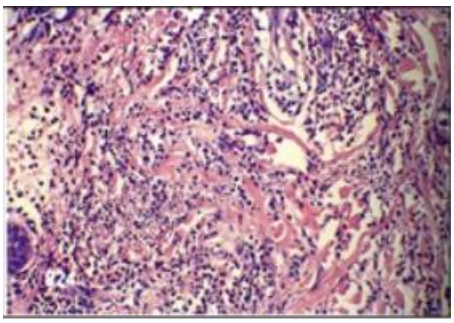

Figure 4.- Extrahepatic manifestations of hepatitis B virus. Vasculitis due to hypersensitivity. Skin biopsy. Histopathology. Major infiltration of neutrophils and nuclear material or dust (leukocytoclastic vasculitis).

III. Discussion.

The present case highlights the complex relationship between hepatitis B virus (HBV) infection and the development of vasculitis, providing valuable insights into the less explored area of extrahepatic manifestations. The underlying pathogenesis involves a complex interplay of viral antigens and host immune responses, resulting in a series of hypersensitivity reactions.

A noteworthy aspect of this case is the varied clinical presentations observed in HBV-associated vasculitis. The variability in symptoms poses a diagnostic challenge, likely due to the heterogeneity of immune responses influenced by viral genotypes, host factors, and genetic predispositions. Further investigation is warranted to find potential therapeutic targets for immune-mediated pathogenesis. This pathogenesis is characterized by immune complex deposition and inflammatory cascades.

Diagnosing HBV-associated vasculitis remains challenging due to the absence of specific criteria. In this case, a comprehensive diagnosis was achieved through a combination of serological markers, imaging studies, and biopsy findings. Valuable insights were gained from the detection of immune complexes and viral antigens in affected tissues. Timely therapeutic intervention is based on the improvement of diagnostic accuracy.

Therapeutic management involves a dual strategy that targets both viral replication and the aberrant immune response. Antiviral therapy with drugs such as entecavir or tenofovir aims to suppress viral replication. Immunosuppressive agents, such as corticosteroids or immunomodulatory drugs, modulate the immune response. Balancing viral control and immunosuppression is crucial for achieving remission while avoiding viral reactivation.

The review of existing literature emphasizes the importance of understanding extrahepatic manifestations, particularly vasculitis, in individuals infected with HBV. The variable prevalence reported in epidemiological studies underscores the need for increased clinical awareness. The wide range of treatment outcomes reported in different studies underscores the ongoing quest for the refinement of therapeutic strategies and the identification of novel intervention targets.

Understanding the extrahepatic manifestations of HBV, particularly vasculitis, is significant. Vasculitis has a variable prevalence in HBV-infected individuals and clinical awareness needs to be increased. Ongoing research is refining therapeutic strategies and uncovering novel targets for intervention to improve diverse treatment outcomes.

IV. Conclusion.

Our review of Hepatitis B Virus (HBV)-related cryoglobulinemic vasculitis has uncovered a complex scenario. The disease varies globally. Understanding and diagnosing its symptoms can be challenging, but recent advances have improved accuracy.

Treatment combining antiviral drugs and immunosuppression has transformed patient care, but a personalized approach is crucial due to the uniqueness of each case. Exciting new perspectives, such as targeted therapies and precision medicine, offer hope for more effective treatments.

The economic impact is significant, affecting individuals and healthcare systems. Managing associated health issues adds another layer of complexity. Dealing with this condition presents unique challenges requiring special attention for children. In the bigger picture, genetic factors and environmental influences play key roles, giving us clues for potential breakthroughs. It brings a fuller understanding of HBV-related cryoglobulinemic vasculitis, offering insights that can guide future research and improve the lives of those affected.

Continued research is necessary to understand the immune-mediated pathogenesis of hypersensitivity reactions in HBV-associated vasculitis. Enhancing patient outcomes and preventing complications associated with vasculitis manifestations requires improved diagnostic precision and refined therapeutic strategies.

This case report adds to the increasing knowledge about extrahepatic complications of HBV. It highlights the importance of considering vasculitis in the differential diagnosis of patients with unexplained systemic symptoms. Ongoing research will further clarify the pathophysiological mechanisms, leading to more targeted and effective therapeutic interventions for HBV-associated vasculitis.

References:

[1]. Mazzaro C, Dal Maso L, Urraro T, Mauro E, Castelnovo L, Casarin P, Et Al. Hepatitis B Virus Related Cryoglobulinemic Vasculitis: A Multicentre Open Label Study From The Gruppo Italiano Di Studio Delle Crioglobulinemie - Gisc. Dig Liver Dis. 2016;48(7).

[2]. Alfraji N, Upadhyaya Vd, Bekampis C, Kuzyshyn H. Mixed Cryoglobulinemia Syndrome (Mcs) Due To Untreated Hepatitis B With Uncommon Presentation: Case Report And Literature Review. Bmc Rheumatol. 2020;4(1).

[3]. Takada S, Shimizu T, Hadano Y, Matsumoto K, Kataoka Y, Arima Y, Et Al. Cryoglobulinemia (Review). Mol Med Rep. 2012;6(1):3–8.

[4]. Mazzaro C, Bomben R, Visentini M, Gragnani L, Quartuccio L, Saccardo F, Et Al. Hepatitis B Virus-Infection Related Cryoglobulinemic Vasculitis. Clinical Manifestations And The Effect Of Antiviral Therapy: A Review Of The Literature. Vol. 13, Frontiers In Oncology. 2023.

[5]. Galossi A, Guarisco R, Bellis L, Puoti C. Extrahepatic Manifestations Of Chronic Hcv Infection. Vol. 16, Journal Of Gastrointestinal And Liver Diseases. 2007.

[6]. Mazzaro C, Dal Maso L, Visentini M, Gitto S, Andreone P, Toffolutti F, Et Al. Hepatitis B Virus-Related Cryogobulinemic Vasculitis. The Role Of Antiviral Nucleot(S)Ide Analogues: A Review. Vol. 286, Journal Of Internal Medicine. 2019.

[7]. Viganò M, Martin P, Cappelletti M, Fabrizi F. Hbv-Associated Cryoglobulinemic Vasculitis: Remission After Antiviral Therapy With Entecavir. Kidney Blood Press Res. 2014;39(1).

[8]. Han H Xiao, Su W, Zhou D Bin, Li J, Cao X Xin. Hepatitis B Virus-Related Cryoglobulinemia: Clinical Characteristics, Virological Features, And Treatment. Virus Res. 2023;336.

[9]. Garcia R. Situación Epidemiológica Del Cáncer Cérvicouterino En El Ecuador. 2020. Rev Venez Oncol. 2021;33(2).

[10]. Quartuccio L, Bortoluzzi A, Scirè Ca, Marangoni A, Del Frate G, Treppo E, Et Al. Management Of Mixed Cryoglobulinemia With Rituximab: Evidence And Consensus-Based Recommendations From The Italian Study Group Of Cryoglobulinemia (Gisc). Vol. 42, Clinical Rheumatology. 2023.

[11]. Terrier B, Cacoub P. Cryoglobulinemia Vasculitis: An Update. Vol. 25, Current Opinion In Rheumatology. 2013.

[12]. Goglin S, Chung Sa. Current Treatment Of Cryoglobulinemic Vasculitis. Curr Treat Options Rheumatol. 2016;2(2).