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PERSISTENT HEPATITIS C VIRUS-ASSOCIATED CRYOGLOBULINEMIC VASCULITIS IN A PATIENT SUCCESSFULLY TREATED WITH DIRECT-ACTING ANTIVIRAL THERAPY

Abhishek Kumar	MD, Assistant Professor, Department of General Medicine, Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India
Md Fahim Ahmad	MS, MCh, Assistant Professor, Department of Pediatric Surgery, Maulana Azad Medical College, New Delhi, India
Priyanka Gupta	MD, Senior Resident, Department of Pathology, Uttar Pradesh Institute of Medical Sciences, Saifai, Etawah- 206130
Eram Nahid*	MD, DM, Department of Endocrinology and Metabolism, All India Institute of Medical Sciences Jodhpur, Rajasthan- 342005, India *Corresponding Author

ABSTRACT The development of hepatitis C virus associated cryoglobulinemic vasculitis (HCV-CryoVas) is driven by expansion of memory B-cell clones induced by HCV, leading to the production of pathogenic monoclonal IgM with rheumatoid factor (RF) activity. However, patients who attain sustained virologic response (SVR) through direct-acting antiviral (DAA) therapy experience a decrease in the proportions of these autoreactive memory B-cell clones. In a subset of patients, HCV-CryoVas may persist despite achieving SVR. This persistence is likely attributed to residual RF-producing B-cell clones. Clinical evidence of ongoing immunological activity, marked by persistent circulating cryoglobulins, RF seropositivity, and/or low levels of C4, can aid in identifying patients at risk for persistent CryoVas despite achieving SVR. In these cases where antiviral therapies alone fail to induce clinical remission, B-cell depletion with rituximab may offer additional benefits for patients with HCV-CryoVas. Herein we described 55 year female with persistent Cryo-Vas despite achieving SVR with DAA therapy.

KEYWORDS : Hepatitis C, Cryoglobulinemic vasculitis, Rituximab

INTRODUCTION:

Approximately 25% to 30% of individuals with chronic Hepatitis C Virus (HCV) exhibit mixed (type II) cryoglobulinemia, with a minority (10%-15%) experiencing symptomatic cryoglobulinemic vasculitis (CryoVas)[1]. The primary approach for HCV-associated cryoglobulinemic vasculitis (HCV-CryoVas) involves antiviral therapy, as viral eradication is generally linked to clinical improvement in the majority of patients with CryoVas[2]. However, CryoVas may persist or relapse over variable length of time in small subset of patients despite sustained virological response (SVR), posing a risk of significant organ damage and mortality[3] .The enduring presence of circulating cryoglobulins, complement activation, rheumatoid factor (RF) activity, and clonal B-cell proliferation is linked to the recurrence of CryoVas[4].

Reports of HCV-CryoVas despite SVR after DAA therapy are rare. We report herein biopsy proven case of CryoVas in 53 year old female presenting with non-healing bilateral lower limb ulcer who previously had achieved SVR with Direct-acting antiviral (DAA) therapy.

Case Study:

A 53-year-old female previously treated with a 12-week course of Sofosbuvir and Daclatasvir combination therapy five years ago, achieved sustained virological response (SVR), presented with a nonhealing ulcer on both lower limbs for last two years, accompanied by a reddish-colored rash. Additional complaints included abdominal distention, exertional dyspnea over the last six months, and yellowish discoloration of eyes and urine for the past 20 days. Upon examination, the patient had pallor, icterus, ascites, and splenomegaly (palpable 5 cm below the left costal margin). A well-defined ulcer measuring 5 x 7 cm, exhibiting active granulation tissue without any active discharge, was present on both lower limbs, situated just above the ankles on the lateral aspect (**Fig.1**).

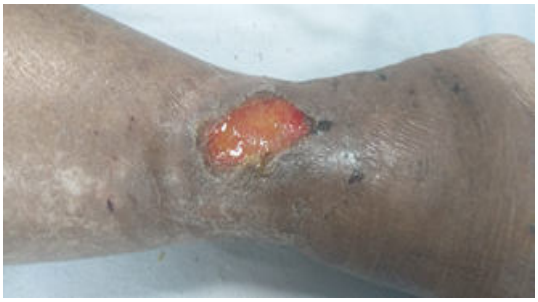

Figure 1: A 5x7 cm ulcer present on lateral aspect of ankle joint with well-defined margin and granulation tissue

Routine investigations showed pancytopenia, raised PT-INR, direct hyperbilirubinemia and low serum albumin. Antibody against HCV was positive and HCV RNA was undetectable. Color Doppler of Hepato-portal venous system revealed dilated portal vein, splenomegaly and coarsened liver echotexture. Serum complements levels C3 and C4 were low, RA factor was positive and serum cryoglobulins positive for IgM and IgG. Skin biopsy was taken from nonhealing ulcer and it revealed feature of vasculitis (**Fig.2**).

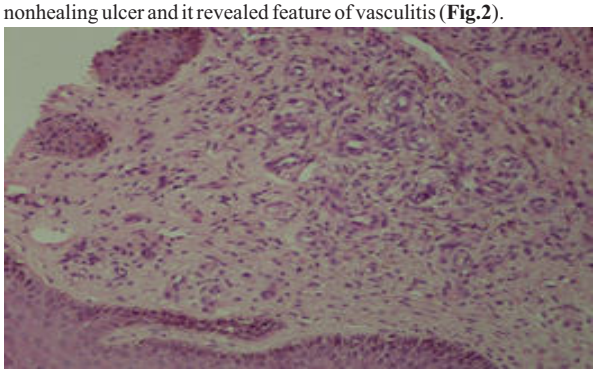

Figure 2: A low power view (20X) showing infiltration of neutrophils, leukocytes, fibrin deposition with nuclear dust suggestive of pericapillary inflammation and vasculitis

She was managed as a case of chronic liver disease and scheduled for Rituximab and glucocorticoid therapy for cryoglobulinemic vasculitis (CryoVas). Unfortunately, despite our best efforts, the patient succumbed to the illness.

DISCUSSION:

DAAs demonstrate remarkable efficacy in treating HCV infection, achieving SVR in the majority of patients. However, their efficacy in treating CryoVas is less consistent, with clinical response rates ranging from 64% to 96% while Immunological response rates (defined by the disappearance or marked reduction of circulating cryoglobulins and normalization of rheumatoid factor (RF) and C4 levels) vary from 48% to 89%[2, 5,6]. Herein we report a case of CryoVas diagnosed on biopsy after successful completion of DAA therapy and achieving SVR.

The pathogenesis of HCV-CryoVas involves disruptions in immune homeostasis, particularly the HCV-induced proliferation of memory

B-cell clones responsible for the production of pathogenic IgM with RF activity. The restoration of peripheral B-cell and T-cell homeostasis is an important factor in achieving clinical remission of HCV-CryoVas[7]. Some studies have indicated that immunological improvement may lag behind the achievement of SVR during the initial 12 weeks following DAA therapy especially in patients of advanced fibrosis and cirrhosis due to impaired clearance of cryoglobulin-containing immune complexes[8,9].

The persistence of immunological and clinical activity is presumably due to the continued presence of RF-producing memory B-cell clones. These clones have been demonstrated to persist for at least 24 weeks in certain patients who have been successfully treated with DAAs[10]. In case of persistent or relapsed CryoVas after achieving SVR, treatment with Rituximab (RTX) should be considered especially those with severe vasculitis and/or skin ulcers, peripheral neuropathy or glomerulonephritis. High-dose pulsed glucocorticoid (GC) therapy is useful in severe conditions and can be considered in combination with RTX. For severe life-threatening hyperviscosity syndrome, apheresis remains the last treatment option[11].

In our case, the patient had cirrhosis and developed biopsy-proven CryoVas three years after treatment with DAAs despite achieving SVR. She had low complement levels and was positive for cryoglobulins. The patient was planned for treatment with RTX and glucocorticoids. Unfortunately, despite our best efforts, the patient ultimately succumbed to end-stage liver disease.

The course of chronic HCV infection is marked by its unpredictable nature, with potential pathways including the development of CryoVas. While CryoVas typically progresses slowly, it can occasionally present with acute and life-threatening manifestations. Therefore, clinical practitioners must conduct thorough evaluations of each patient and promptly initiate appropriate therapy while their overall health status is favorable. Considering its efficacy, the early use of RTX in the early stages of the disease represents a reasonable treatment option.

CONCLUSION:

In conclusion, clinicians should be aware that CryoVas can occur even in the absence of ongoing viral replication, attributed to the persistence of memory B cell clones. The presence of CryoVas alongside persistent immunological activity (evidenced by detectable circulating cryoglobulins, elevated RF levels, and/or depressed C4 level) warrants consideration for biopsy to evaluate the necessity of immuno suppressive therapy, even in cases associated with SVR.

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