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CASE REPORT | LIVER

Resolution of Hepatitis Delta Virus-Related Cryoglobulinemic Vasculitis With the Use of Bulevirtide

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ABSTRACT

The global prevalence of hepatitis B virus (HBV) infection is around 257 million people, and about 5% are coinfected with hepatitis delta virus (HDV). HDV infection can progress from acute fulminant hepatitis to chronic hepatitis, cirrhosis, or hepatocellular carcinoma. About 20% of HBV patients develop extrahepatic manifestations; among them, cryoglobulinemic vasculitis (CV) occurs in less than 5% of cases and can lead to heterogeneous clinical manifestations. We present the case of a woman with HBV-HDV coinfection who was referred to our clinic with suspected virus-related CV. One-year treatment with bulevirtide led to complete and durable resolution of CV.

KEYWORDS: purpura; mixed cryoglobulinemic; hepatitis D virus; bulevirtide

ABBREVIATIONS: ALT, alanine aminotransferase; HBV, hepatitis B virus; HDV, hepatitis D virus; BLV, bulevirtide; CV, cryoglobulinemic vasculitis; MC, mixed cryoglobulinemia

INTRODUCTION

The global prevalence of hepatitis B virus (HBV) infection is estimated at 257.5 million people, and chronic infection can progress to cirrhosis, end-stage liver disease, and hepatocellular carcinoma.[1–3] HBV infection may be associated with extrahepatic manifestations in approximately 20% of cases, mainly represented by polyarthritis nodosa, glomerulonephritis, dermatitis, arthritis, and aplastic anemia, while cryoglobulinemic vasculitis (CV) occurs in less than 5% of cases.[4] Cryoglobulinemias are characterized by serum immunoglobulins that can precipitate with low temperature and are classified as types I, II and III; types II-III, also called mixed cryoglobulinemia (MC), are associated with chronic HBV infection.[4] Clinical manifestations of MC include leg purpura, arthralgias, asthenia, ulcers, neurologic, and renal involvement, and a potential risk of lymphoproliferative disorders.[4]

Approximately 5% of patients with HBV are coinfected with hepatitis D virus (HDV), and these patients often have more severe liver disease.[5] Following positive registration study, bulevirtide (BLV) has been recently approved for the management of chronic HDV infection.[6,7] To date, the association between chronic hepatitis C virus infection and cryoglobulins is well known (90%–95% of MC is secondary to chronic hepatitis C virus infection), although HBV infection may also lead to chronic lymphocytes B stimulation, inducing cryoglobulin production in about 1.2%–4% of cases.[5] However, despite the immunogenic role of HDV, there are no published data describing an association between cryoglobulinemia and HDV infection.[8]

CASE REPORT

In December 2021, a 54-year-old woman was referred to our outpatient clinic for suspected vasculitis related to HBV infection (previously investigated and diagnosed elsewhere). She presented with erythema on the trunk and palmas; purplish papules on the calves, ankles, and feet; and livedo reticularis of the lower limbs (Figure 1). She also reported pain and difficulty walking. The abdominal examination was unremarkable. Blood tests showed elevated aminotransferases (aspartate aminotransferase/alanine aminotransferase [ALT] 182/188 U/L, platelets 128 $\times$ 10^9/L, bilirubin 0.88 mg/dL, albumin 38.2 g/L, international normalized ratio

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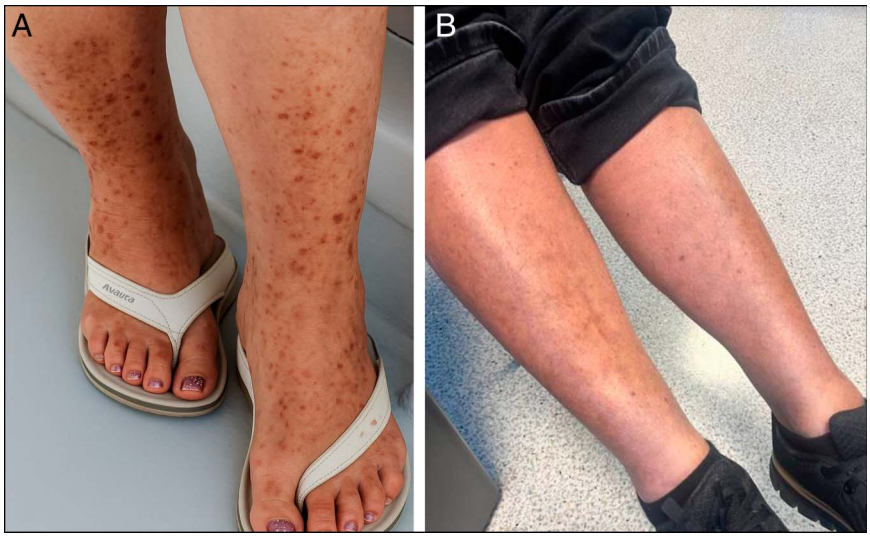

Figure 1. (A) Purplish papules and livedo reticularis on the patient's lower limbs at diagnosis, before bulevirtide therapy. (B) Complete resolution of the lower limbs cutaneous manifestations after 1 year of bulevirtide therapy. BLV, bulevirtide.

1.14, creatinine 0.9 mg/dL, and Model for End-Stage Liver Disease score 8).[9] She was hepatitis B virus surface antigen positive, HBeAg negative/HBeAb positive, with HBV DNA 2.53×10^5 IU/mL, anti-HDV positive with HDV RNA 1.3×10^5 IU/mL, and anti-HCV negative. Cryoglobulins were positive. Abdominal ultrasound showed hepatomegaly with fine heterogeneous echotexture, no focal liver lesions, no biliary dilatation, an alithiasic gallbladder, a normal caliber portal vein, unremarkable hepatic veins, and splenomegaly (18 cm). She underwent liver biopsy, and the histological examination showed cirrhosis with moderate chronic hepatitis consistent with HBV infection in a patient with HDV coinfection (Ishak stage 6, Ishak grade 9, and METAVIR fibrosis score F4). Esophagogastroduodenoscopy showed mild congestive gastropathy. We started treatment with entecavir 0.5 mg/d and proposed pegylated-interferon-α therapy for 48 months; although after 2 months of treatment with entecavir alone, the patient refused any further pharmacological treatment and missed subsequent visits, and was therefore considered lost to follow-up without any antiviral therapy.

In September 2023, she returned to our outpatient clinic with recent laboratory assessment (aspartate aminotransferase/ALT 89/89 U/L, platelets 110×10^9 L, bilirubin 0.73 mg/dL, international normalized ratio 1.11, creatinine 1.0 mg/dL, Model for End-Stage Liver Disease score 8, HBsAb 1 mlU/mL, HBeAg negative, HBeAb positive, hepatitis B virus surface antigen 1,573 mlU/mL, HBV DNA <10 IU/mL, and HDV RNA 1.2×10^5 IU/mL). Cutaneous manifestations were still present, and cryoglobulins were positive (10%). Abdominal ultrasound showed no focal liver lesions and persistent splenomegaly, with hepatic elastometry measured stiffness at 40.2 kPa. Esophagogastroduodenoscopy confirmed absence of esophageal varices and presence of mild congestive gastropathy. At this visit, due to the recent approval, we proposed treatment with BLV 2 mg/d, and despite negative HBV DNA, entecavir was (re) started as standard of care treatment in the presence of underlying cirrhosis. On monthly follow-up, aminotransferases normalized, HBV DNA was consistently negative and HDV RNA became undetectable after approximately 4 months of BLV treatment (Table 1). One year after starting BLV, hepatic stiffness decreased to 18.9 kPa. Noteworthy, dermatologic lesions disappeared (Figure 1), gait difficulties resolved, and cryoglobulins decreased to approximately 2%.

DISCUSSION

HDV infection may cause a severe form of viral hepatitis and evolves into chronic infection in the majority of cases.[8] Until 2020, the only available treatment for chronic HDV infection was off-label use of pegylated interferon-α for 48 weeks, with limited off-therapy response and an unfavorable safety profile. More recently, BLV has been shown to improve ALT, significantly reduce serum HDV RNA, and be associated with favorable outcomes even in patients with advanced disease.[6,7] CV can be found in about 1.2%–4% of patients with chronic HBV infection, but the association between CV and HDV is poorly studied.[5] Published studies have shown that nucleos(t)ide analog therapy in HBV-related CV yields high virologic and satisfactory clinical responses in patients with mild and moderate disease but lower response in patients with severe CV. Early suppression of HBV viral load should be a primary goal to prevent organ complication and lymphoproliferative disorders.[5]

We document how both the initial monotherapy with entecavir, although just for a few months, and the apparent spontaneous clearance of HBV-DNA—a finding often encountered in patients with HDV-dominant infections—did not lead to any clinical improvement in CV manifestations.[10] In fact, when the patient re-presented to our clinic, she still had cutaneous

Table 1. Monthly laboratory follow-up from treatment initiation with bulevirtide

	September 2023	October 2023	November 2023	December 2023	January 2024	April 2024	July 2024	September 2024
AST (U/L)	89	53	35	36	28	27	24	25
ALT (U/L)	89	58	26	24	18	16	14	11
Platelet count ($\times 10^9$/L)	110	124	106	102	112	123	100	96
Gamma globulin (%)	21.7	25.9	24.4	21.3	23.8	21.2	19	
MC1	2.6	4.1	3.3	2.6	2.5	2.9	1.9	
MC2	3.8	4.5	3.7	3.4	4.5	3.6	2.7	20.1
HbsAg (IU/mL)	1,573	-	1,454	1,582	1,330	1,342	1,342	1,293
HBV-DNA (IU/mL)	<10	-	<10	-	<10	<10	<10	<10
HDV-RNA (IU/mL)	1.2×10^5	1.5×10^4	1.3×10^4	1.1×10^3	630	<10	<10	<10
Cryoglobulin (%)	10							2

AST, aspartate aminotransaminase; ALT, alanine aminotransferase; HBV, hepatitis B virus; HDV, hepatitis D virus; MC1, MC2, monoclonal components 1 and 2 within the gamma globulin fraction; HBsAg, hepatitis B virus surface antigen.

manifestations and impaired ambulation, despite being HBV DNA negative. After initiating BLV in 2023, she experienced progressive improvement with complete resolution of CV manifestations alongside progressive HDV RNA decrease and clearance after approximately 4 months of treatment up to 1 year of follow-up. Therefore, we inferred that CV resolution was driven primarily by BLV with consequent viral HDV suppression, rather than by HBV DNA negativity, although spontaneous HBV DNA clearance CV manifestations were still presented and resolved only with HDV treatment.

To the best of our knowledge, this is the first reported case of HBV-HDV coinfection presenting with CV in which BLV induced complete and durable clinical and virologic response.

In conclusion, BLV may improve not only the hepatic disease course but also the extrahepatic complications associated with chronic HDV infection. Further studies in larger cohorts are needed to gain a deeper understanding of the relationship between CV, HDV, and response to treatment of this systemic manifestation of disease.

DISCLOSURES

Author contributions: G. Geremicca and S. Labanca collected the clinical data and drafted the initial manuscript; A. Pasta contributed to data analysis and critical revision of the text; S. Marenco, Sara Cariati, A. Grossi, and G. Pieri oversaw the patient's clinical management and provided supporting materials; EG Giannini supervised the work, serves as the guarantor of the article, and approved the final version.

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