Clinico-biological characteristics and treatment of hepatitis B virus-related mixed cryoglobulinemia

Xiufen Wang[1], Xiangcheng Xiao[1], Huipeng Ge[1], Tianci Deng[1], Qiaoling Zhou[1], Jianping Ning[1], Xiaoying Wu[2], Hongling Yin[2], Wei Lin[2], Wenbin Tang[1,3]

[1]Department of Nephrology, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China;
[2]Department of Pathology, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China;
[3]Health Management Center, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China.

To the Editor: Cryoglobulinemia is a disease characterized by cryoglobulins in serum that precipitate under *in vitro* conditions <37°C and redissolve on rewarming. It is divided into three types: Type I, where the cryoglobulin is composed of monoclonal IgG or IgM, and rarely IgA or free immunoglobulin (Ig) light chains; Type II, where the cryoglobulin is made of monoclonal IgM with rheumatoid factor (RF) activity and polyclonal IgG; and Type III, where the cryoglobulin is composed of polyclonal IgM with RF activity and polyclonal IgG.[1] Types II and III are mixed cryoglobulinemia (MC). MC could be related to several infectious diseases, like hepatitis C and B. It mainly presents as cryoglobulinemic vasculitis,[2] including fatigue, purpura, arthralgia, myalgia, peripheral neuropathy, and even severe organ damage, like glomerulonephritis. However, cryoglobulinemic vasculitis involving the gastrointestinal tract and heart is rare. Besides, neurological, ocular, and rhino-otological symptoms of hyperviscosity syndrome are also hardly seen in MC. Here, we report one hepatitis B virus (HBV)-related MC case and analyze 41 cases in literature. We have analyzed these 42 HBV-related MC cases to clarify their clinico-biological characteristics and treatment.

A 62-year-old man was presented with edema and purpura over the lower extremities together with impaired renal function. Laboratory test results indicated the following values: albumin 34 g/L, creatinine 199.0 μmol/L, complement C3 35.60 mg/dL, complement C4 3.27 mg/dL, RF 128 IU/mL; also, 24-h urine protein was 0.56 g while urine volume was 200 mL. Serological studies showed that he was positive for HBV surface antigen (HBsAg), HBV envelope antibody, and HBV core antibody and negative for HBsAg antibody and HBV envelope antigen; and no serum HBV DNA was detected. Immunofixation electrophoresis of serum and urine indicated a monoclonal IgM-kappa component. IgG, IgA, and IgM as well as a bone marrow biopsy were all normal. Serological tests were negative for hepatitis C virus (HCV) and human immunodeficiency viruses. Besides, antinuclear antibodies, antineutrophil cytoplasmic antibodies, anti-double-stranded DNA, and tumor markers were normal. Ultrasonography revealed kidneys measuring 127 × 56 mm (left) and 112 × 41 mm (right). Renal biopsy results showed membranous proliferative glomerulonephritis. The capillary lumen disclosed Periodic Acid-Schiff stain+ hyaline thrombi. Immunofluorescence microscopy showed IgA (2+), IgG (2+), IgM (3+), C3 (2+), and C4 (3+) deposition on the capillary walls and positive staining for HBsAg (2+). Electron microscopy found basement membrane reduplication and organized subendothelial microtubular substructure deposits, indicating HBV-related cryoglobulinemic glomerulonephritis likelihood [Supplementary Figure 1, http://links.lww.com/CM9/A731]. We then assessed serum cryoglobulin, whose qualitative test and cryoglobulin content were positive and 2609 μg/mL, respectively. By immunofixation electrophoresis, the cryoglobulin was characterized as monoclonal IgM kappa-polyclonal IgG. The final diagnosis was type II cryoglobulinemia, HBV-related cryoglobulinemic glomerulonephritis, and rapidly progressive glomerulonephritis.

The patient received treatment with prednisone, entecavir after successful diagnosis, fresh plasma transfusion (750 mL), plasma exchange (PE) (thrice), and intravenous cyclophosphamide (CYC) (0.8 g) were added. After 10 days, purpura had regressed, and creatinine levels decreased. The patient did not receive further CYC therapy and PE because of economic reasons. Nevertheless, he was treated with

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Correspondence to: Wenbin Tang, Department of Nephrology, Xiangya Hospital, Central South University, No. 87, Xiangya Road, Changsha, Hunan 410008, China; Health Management Center, Xiangya Hospital, Central South University, No. 87, Xiangya Road, Changsha, Hunan 410008, China
E-Mail: twb-candy@163.com

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prednisone, entecavir, and hemo-dialysis twice a week at a local hospital, but died 6 months later.

HBV-related MC cases review was conducted in English using PubMed, Embase, and Web of Science, and in Chinese by cnki.net and the Wanfang Database. We used keywords or Medical Subject Headings for searching, including 41 cases from 19 references as of September 10th, 2020 [Supplementary Figure 2, http://links.lww.com/CM9/A731]. Demographic information, extrahepatic clinical manifestation, laboratory test data, treatment, and outcome were collected. Cutaneous manifestations included purpura, ulcers, and necrosis. Articular involvement referred to arthritis or arthralgia, and peripheral neuropathy involved motor and sensory function loss in the peripheral nerves. The central nervous system involvement was presented as stroke. Kidney involvement included proteinuria, hematuria, and renal insufficiency, whereas gastrointestinal manifestations included abdominal pain (gastrointestinal ischemia or intestinal perforation). Cardiac involvement is associated with myocardial infarction (myocardial vasculitis). Eye involvement manifested as peripheral ulcerative keratitis. Laboratory results were recorded using a standardized form. The first therapy stage referred to the treatment used after disease diagnosis, including antiviral drugs, corticosteroids (CS), immunosuppressive agents (IS), and PE. The second therapy stage was the adjusted treatment following response assessment to the first stage. Turning negative for cryoglobulin was defined as cryoglobulin being undetectable after therapy. Treatment response was based on clinical presentation and serum cryoglobulin detection. Disease remission referred to regression of more than half of clinical symptoms combined with serum cryoglobulin disappearance (duplicate detection). Disease relapse was classified by reappearance or new-onset manifestations during follow-up, while refractory disease was ascertained by absence of improvement in clinical manifestations or serum cryoglobulin persistence. We recorded the above information of 42 HBV-related MC cases in detail [Supplementary Tables 1–3, http://links.lww.com/CM9/A731].

Data were analyzed using SPSS 22.0. Descriptive statistics included mean ± standard deviation for normally distributed data, median and interquartile range for skewed distribution data, and frequency for categorical variables.

Of the 42 HBV-related MC cases, 16 patients (38.1%) were from China, ten (23.8%) from Italy, five (11.9%) from France, three from Japan, two each from Turkey and Greece [Supplementary Figure 3, http://links.lww.com/CM9/A731]. Mean age was 53 ± 14 years; 47.6% were male and 52.4% female [Table 1]. Extrahepatic clinical manifestations mainly included cutaneous lesions, kidney involvement, and peripheral neuropathy, accounting for 78.6%, 54.8%, and 35.7%, respectively [Table 1]. Thirty-four patients were tested for the cryoglobulin type; 61.8% (21/34) were Type II, and 38.2% (13/34) were Type III. 60.7% (17/28) had low C3 (<80 mg/dL), while 87.1% (27/31) had low C4 (<10 mg/dL). 92.6% (25/27) patients' RF was positive. Serum HBV DNA was 5.0×10^4 (8.2×10^3–5.2×10^5) U/mL; however, 13.9% (5/36) were negative for serum HBV DNA [Table 1].

Table 1: The characteristics of the 42 HBV-related MC cases.

Characteristics	Values
Socio-demographic features	
Age (years)	53 ± 14
Sex/male	20 (47.6)
Extrahepatic clinical manifestations	
Cutaneous	33 (78.6)
Purpura	25 (59.5)
Necrosis	5 (11.9)
Ulcers	3 (7.1)
Peripheral neuropathy	15 (35.7)
Central nervous system involvement	1 (2.4)
Articular	8 (19.0)
Kidney	23 (54.8)
Gastrointestinal	3 (7.1)
Cardiac	1 (2.4)
Eyes	1 (2.4)
Laboratory testing	
Type of cryoglobulin	
Type II	21/34 (61.8)
Type III	13/34 (38.2)
Albumin (g/L)	27 ± 5 (n = 21)
Alanine aminotransferase (U/L)	71 (30–107) (n = 29)
Creatinine* (μmmol/L)	244 (164–380) (n = 22)
Complement	
Low C3	17/28 (60.7)
Low C4	27/31 (87.1)
Positive of RF	25/27 (92.6)
HBV DNA (U/mL)	5.0×10^4 (8.2×10^3–5.2×10^5) (n = 28)
Negative of HBV DNA	5/36 (13.9)
Treatment†	
Anti-HBV	36 (85.7)
Entecavir	17 (40.5)
Lamivudine	11 (26.2)
Telbivudine	7 (16.7)
Interferon	2 (4.8)
Adefovir	2 (4.8)
Tenofovir	2 (4.8)
CS	22 (52.4)
IS	13 (31.0)
CYC	7 (16.7)
MMF	5 (11.9)
RTX	4 (9.5)
PE	9 (21.4)
Outcome	
Remission	22 (52.4)
Refractory	20 (47.6)
Death	5 (11.9)

Data are presented as n (%) or mean ± standard deviation or median (interquartile range). *Median creatinine of patients with kidney involvement. †The first stage of therapy and the second stage of therapy are calculated as a whole. CS: Corticosteroids; CYC: Cyclophosphamide; HBV: Hepatitis B virus; IS: Immunosuppressive agent; MC: Mixed cryoglobulinemia; MMF: Mycophenolate mofetil; PE: Plasma exchange; RF: Rheumatoid factor; RTX: Rituximab.

Overall, 85.7% (36/42) patients received antiviral therapy [Table 1]. Entecavir and lamivudine were frequently used, accounting for 40.5% and 26.2%, respectively. CS were given to 52.4% (22/42) patients, IS, including CYC, mycophenolic acid, and rituximab (RTX), were prescribed to 31.0% (13/42) patients, and 21.4% (9/42) received PE therapy. After the first stage of therapy, 35.7% (15/42) of patients reached disease remission. However, 64.3% (27/42) had the refractory or relapsing disease after the first therapeutic stage, and seven patients entered remission after the second stage. Among them, four patients added or had their anti-HBV drugs adjusted, and two added RTX to their therapy. One had their anti-HBV drugs changed and had four RTX infusions, followed by mycophenolic acid

for maintenance therapy [Supplementary Table 3, http://links.lww.com/CM9/A731]. Generally, 28.6% (12/42) patients entered remission with only anti-HBV drugs. A total of 19.0% (8/42) patients in remission were treated with anti-HBV drugs together with different combinations of CS, IS, and PE [Supplementary Table 3, http://links.lww.com/CM9/A731]. At the end of the follow-up, 52.4% (22/42) patients were in remission; 47.6% (20/42) had refractory disease, among which five patients had died [Table 1].

The HBV-related MC prevalence is unclear, and geographical differences could exist between the cryoglobulinemia and HBV association. After the viral infection, chronic antigen stimulation decreases B-lymphocyte threshold for activation and proliferation, and reduces apoptosis. A B-cell clone expands and produces antibodies directed against the IgG fragment crystallizable portion (RF activity), forming immune complexes and activating complements that induce vasculitis.[3] Herein, purpura, kidney involvement, and peripheral neuropathy are the most common symptoms. Research has reported that cutaneous ulcers, progressive motor neuropathy, kidney involvement with rapid renal failure and/or nephrotic syndrome, recurrent severe abdominal pain, acute cerebrovascular, and cardiovascular events are considered to be severe or life-threatening manifestations of MC.[4]

Like treating HCV-related MC, HBV replication suppression and specific B-cell clonalities deletion are critical. Anti-HBV drugs form the basis of treatment, and mild to moderate cases could be cured with nucleot(s)ide analogues. High-dose pulsed glucocorticoid with PE could be the first-line treatment for severe MC, and RTX-based treatments should be included in patients with persistent life-threatening manifestations.[4] Here, some of the cases also show the effectiveness of these approaches. RTX is a chimeric monoclonal antibody that binds to the B-cell surface antigen CD20 and has been widely studied and proven effective in treating HCV-related MC.[5] Besides, it could be a potential treatment for relapsing or refractory HBV-related MC patients. Overall, this study had 20 patients with refractory disease, including five deaths, indicating that HBV-related MC patients could have a poor prognosis. However, it should be noted that most patients were admitted with severe symptoms. Therefore, several multicenter studies are needed to investigate the outcome of HBV-related MC comprehensively.

Declaration of patient consent

The patient and his family consent to publication of this manuscript.

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Conflicts of interest

None.

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