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

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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...
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 motor and sensory function loss in the peripheral nerves.

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 52.4% (22/42) patients, IS, including CYC, mycophenolic acid, and rituximab (RTX), were prescribed to 52.4% (22/42) patients. 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 one had their anti-HBV drugs adjusted, and two added RTX to their therapy. One had their anti-HBV drugs adjusted, and two added RTX to their therapy. One had their anti-HBV drugs adjusted, and two added RTX to their therapy.
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. 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. 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. 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. 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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