Hepatitis C Virus-related Heat-insoluble Cryoglobulinemia and Thrombotic Microangiopathy

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Abstract: Heat-insoluble cryoglobulinemia is rare, and its pathogenesis and comorbidities remain poorly understood. Here, the authors report a case of hepatitis C virus (HCV)-related heat-insoluble cryoglobulinemia associated with thrombotic microangiopathy and cryoglobulin-occlusive membranoproliferative glomerulonephritis. The patient, a 57-year-old woman, presented with acute kidney injury, thrombocytopenia, anemia with schistocytes, high levels of serum HCV RNA of HCV genotype 2a, rheumatoid factor positivity and high levels of serum immunoglobulin (Ig) M and Igκ. The patient's serum was positive for cryoglobulin at 4°C, and the precipitate required heating to 47°C for dissolution. Cryoglobulin immunofixation was positive for monoclonal IgM and Igκ and polyclonal IgG. However, immunofixation of the cryoglobulin supernatant was negative. Histological examination of renal biopsy revealed a membranoproliferative type I glomerulonephritis. The patient was treated with plasmapheresis, corticosteroids and antiviral therapy of peginterferon plus ribavirin, but symptoms only partially resolved.

Key Indexing Terms: Heat-insoluble cryoglobulinemia; Thrombotic microangiopathy; Membranoproliferative glomerulonephritis; Hepatitis C virus; Immunoglobulins. **[Am J Med Sci 2013;346(4):345–348.]**

Cryoglobulinemia is diagnosed by the presence of insoluble immunoglobulins (Igs) in the serum, which precipitate at low temperatures and redissolve when heated at 37ºC.[1] Three types of cryoglobulinemia have been described: types I, characterized by insoluble monoclonal Igs, usually IgM and less frequently IgG; type II, characterized by a mix of insoluble monoclonal and polyclonal Igs, specifically monoclonal IgM that has rheumatoid factor (RF) activity and polyclonal IgG; and type III, characterized by insoluble polyclonal Igs.[2,3] Such inappropriate precipitation leads to accumulation of Igs in the vasculature, which may disrupt normal blood flow and/or exert a wide range of systemic effects.[4]

Many cryoglobulinemia associated with different diseases have been reported. Yet, another type of so-called heat-insoluble cryoglobulinemia is rarely reported and the related pathogenesis remains poorly understood. There have only been 5 case reports of heat-insoluble cryoglobulins.[2,5–8] Among the heat-insoluble cases reported are type I associated with glomerulonephritis,[6] type II associated with Sjögren syndrome and glomerulonephritis,[7] type I associated with gangrene in multiple myeloma 8 and type II associated with membranoproliferative glomerulonephritis.[2] We recently encountered a unique case of type II heat-insoluble cryoglobulinemia associated with hepatitis C virus (HCV) infection and membranoproliferative glomerulonephritis. This patient also presented with thrombotic microangiopathy (TMA) secondary to cryoglobulinemia and was only partially responsive to therapy.

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CASE REPORT

Clinical Presentation

A 57-year-old woman was admitted to our hospital with a 3-week history of edema and proteinuria and a 9-day history of acute kidney injury. Medical history review revealed that the patient had been evaluated 4 years previously for purpura on her limbs. There was no history of fever, chills, Raynaud's phenomenon, weight loss or dyspnea. At admission, the patient suffered from fatigue, arthralgia, dizziness and edema. Physical examination revealed a blood pressure of 200/90 mm Hg. In addition, mild anemia and pretibial edema were observed, along with a purpuric rash and brownish pigmentation on the lower extremities (Figure S1, **Supplemental Digital Content 1**, http://links.lww.com/MAJ/A49).

Laboratory Findings

The laboratory findings (shown in Table 1) indicated that the patient had anemia, thrombocytopenia, acute kidney injury, proteinuria, microscopic hematuria, urinary siderosis, low serum albumin, high serum IgM and kappa (κ), RF positivity and low serum C3 and C4. In addition, positive reactivity with HCV antibody and high levels of HCV RNA (of HCV genotype 2a) were detected. Serum protein electrophoresis demonstrated a polyclonal spike in the gamma region, which was characterized as monoclonal IgM-κ and polyclonal IgG by serum immunofixation electrophoresis (Figure S2a, **Supplemental Digital Content 2**, http://links.lww.com/MAJ/A50).

Cryoglobulin investigation, by the standard protocol,[8] revealed a moderate amount of white, jelly-like precipitate at 4°C. After 72 hours of heating at 37°C, the precipitate had not fully dissolved, and only after heating at 47°C for 30 minutes did complete dissolution occur (Figure S3, **Supplemental Digital Content 3**, http://links.lww.com/MAJ/A51). Immunofixation electrophoresis of the 4°C cryoglobulin precipitate indicated the presence of monoclonal IgM-κ and polyclonal IgG (Figure S2b, **Supplemental Digital Content 2**, http://links.lww.com/MAJ/A50), suggesting type II cryoglobulinemia. However, immunofixation of the cryoglobulin supernatant showed no positive bands (Figure S2c, **Supplemental Digital Content 2**, http://links.lww.com/MAJ/A50).

A renal biopsy was taken from the patient for histological examination. Membranoproliferative type I glomerulonephritis was indicated by the diffuse proliferation of mesangial cells, lobulation of glomeruli (Figure 1), diffuse thickening of the basement membrane, double contours along with mesangial proliferation (Figure S4a, **Supplemental Digital Content 4**, http://links.lww.com/MAJ/A52) and deposition of the kappa chain along the granular capillary wall (Figure S4b, **Supplemental Digital Content 4**, http://links.lww.com/MAJ/A52). In addition,

TABLE 1. Laboratory parameters and response to treatment

		At admission		Post-treatment	
Laboratory parameter	Normal range	Value	Finding	Value	Finding
Abnormal and responsive to treatment					
HCV-RNA, IU/mL	<1,000	547,000	High	207	Normal
Indirect bilirubin, μmol/L	5.1–21.4	26	High	10.4	Normal
LDH, U/L	135–226	316	High	208	Normal
Serum free κ light chains, g/L	1.70–3.70	4.67	High	3.35	Normal
Abnormal and unresponsive to treatment					
BUN, mmol/L	3.20–7.00	13.02	High	18.31	High
Creatinine, μmol/L	44.0–115.0	359.6	High	286.6	High
Cryoglobulin immunofixation	NA	Monoclonal IgM-κ and polyclonal IgG	High	Monoclonal IgM-κ and polyclonal IgG	High
Serum immunofixation	NA	Monoclonal IgM-κ and polyclonal IgG	High	Monoclonal IgM-κ and polyclonal IgG	High
Hb, g/L	110–150	56	Low	68	Low
Hematocrit, L/L	0.370–0.480	0.184	Low	0.205	Low
PLT, 10^9/L	100–300	40	Low	493	High
RBC, 10^{12}/L	3.50–5.00	1.82	Low	2.18	Low
RF, IU/mL	0.00–15.00	35.70	High	30.60	High
Serum albumin, g/L	35.0–55.0	21.9	Low	28.9	Low
Serum C3, g/L	0.90–1.80	0.77	Low	0.78	Low
Serum C4, g/L	0.10–1.40	0.05	Low	0.05	Low
Serum IgM, g/L	0.40–2.30	4.06	High	3.87	High
Urinary protein excretion, g/d	<0.20	4.98	High	7.47	High
Urinary proteinuria	NA	3+	High	ND	NA
Urinary sediments RBC per high-power field	0.0–5.0	87.0	High	65.3	High
Urinary siderosis	NA	+	High	+	High
Urine free κ light chains, mg/24 hr	<14.2	750.0	High	126.0	High
Urine free λ light chains, mg/24 hr	<7.80	84.75	High	40.10	High
Urine IgG, mg/24 hr	0.0–17.0	808.5	High	235.0	High
Urine α1 microglobulin, mg/24 hr	<24.0	186.0	High	64.6	High
Urine β2 microglobulin, mg/24 hr	<0.40	9.63	High	21.30	High
Abnormal and unknown treatment response					
Ferritin, μg/L	20–200	776	High	ND	NA
HCV genotype	NA	2a	High	NA	NA
Peripheral blood smear	NA	2% schistocytes	High	ND	NA
Reactivity of HCV antibody	NA	+	High	ND	NA
Reticulocytes, 10^{12}/L	0.0224–0.0829	0. 100	High	ND	NA
Urinary occult blood	NA	3+	High	ND	NA
Urine immunofixation	NA	Monoclonal IgM-κ and polyclonal IgG	High	ND	NA
Normal					
Serum free λ light chains, g/L	0.90–2.10	1.42	Normal	1.42	Normal
Serum IgA, g/L	0.70–4.00	1.20	Normal	1.69	Normal
Serum IgG, g/L	7.00–16.00	15.84	Normal	13.00	Normal
Cryoglobulin supernatant immunofixation	NA	No positive band	Normal	ND	NA
Serum iron, μmol/L	9.0–27.0	16.8	Normal	ND	NA
Serum total protein, g/L	60.0–83.0	41.4	Normal	57.9	Normal
TIBC, μmol/L	50.0–70.0	44.1	Normal	ND	NA
Transferrin saturation, %	14.0–51.0	38.1	Normal	ND	Normal

BUN, blood urea nitrogen; C, complement; Hb, hemoglobin; Ig, immunoglobulin; LDH, serum lactic dehydrogenase; PLT, platelet; RBC, red blood cell; RF, rheumatoid factor; TIBC, total iron binding capacity; −, negative; +, positive.