Case Report

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Mixed Cryoglobulinaemic Glomerulonephritis Type II in the Setting of Rheumatoid Arthritis and Chronic Hepatitis B: A Case Report

Internal Medicine Section

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ABSTRACT

Mixed (Type II) cryoglobulinaemia is a systemic immune-complex vasculitis often linked to chronic infections especially Hepatitis C Virus (HCV) or autoimmune disease. Chronic Hepatitis B Virus (HBV) associated cryoglobulinaemic is rare, and its coexistence with Rheumatoid Arthritis (RA) is especially unusual. The authors report a 45-year-old female with long-standing seropositive RA on methotrexate and chronic HBV presented with fatigue, arthralgias, palpable purpura on her legs, and new-onset oedema. Laboratory workup showed elevated serum creatinine, nephrotic-range proteinuria, hypoalbuminaemia, haematuria, and a positive Rheumatoid Factor (RF). Antinuclear Antibody (ANA) and Anti-double-stranded deoxyribonucleic acid (anti-dsDNA) were negative. Complement levels i.e., Component 3 (C3) moderately reduced, Component 4 (C4) severely low, and positive mixed cryoglobulins with a high Immunoglobulin M (IgM) cryocrit. HCV and Human Immunodeficiency Virus (HIV) serologies were negative. Renal biopsy showed a diffuse endocapillary proliferative, Membranoproliferative Glomerulonephritis (MPGN) with hyaline "pseudothrombi." Immunofluorescence disclosed granular capillary wall deposits of IgM, Immunoglobulin G (IgG) (both kappa and lambda), C3, and C1q, consistent with Type II cryoglobulinaemic GN. Treatment included high-dose corticosteroids and HBV antiviral drugs. Despite antiviral therapy and plasmapheresis, renal failure progressed requiring haemodialysis, and the patient died within three weeks due to disease-related complications and nosocomial infection. The present case highlights that RA and HBV can together underlie cryoglobulinaemic GN. Early recognition using RF, complement, and cryocrit testing and biopsy-guided therapy are critical. Purpura, positive RF, and low C4/C3 should prompt consideration of mixed cryoglobulinaemic vasculitis.

Keywords: Autoimmune disease, Immune complex diseases, Membranoproliferative glomerulonephritis, Vasculitis

CASE REPORT

A 45-year-old female presented with complaints of gradually worsening fatigue, arthralgia, and new-onset lower extremity oedema for the past few weeks. The patient also noted the appearance of multiple non blanching purpuric lesions over both legs during this period. There was no history of fever, weight loss, or haematuria. She had a past medical history of seropositive RA for 10 years, for which she had been receiving low-dose methotrexate (15 mg/week orally for the past 8 years), with moderately active disease (RF positive and Anti-Cyclic Citrullinated Peptide (anti-CCP) negative). She was also a known case of chronic hepatitis B infection, which had remained untreated with normal Alanine Aminotransferase (ALT) levels and low-level HBV Deoxyribonucleic Acid (DNA). On admission due to superadded immunosuppression related sepsis, her viral loads (HBV DNA copy no. 21,000 IU/mL) became so high suggestive of active infection. The constellation of purpura, arthralgia, and RF positivity raised suspicion for mixed, cryoglobulinaemic vasculitis. Neurological examination was normal, with intact higher mental functions, cranial nerves, motor and sensory systems, and no focal neurological deficits.

Investigations

Laboratory investigations [Table/Fig-1] revealed elevated serum creatinine (2.3 mg/dL from a baseline of ~0.9 mg/dL) with reduced estimated Glomerular Filtration Rate (eGFR) (30 mL/min) and nephrotic-range proteinuria (UPCR 3.5 g/g), along with hypoalbuminaemia (2.5 g/dL). Complement levels were decreased (C3-60 mg/dL, C4-4 mg/dL). Autoimmune evaluation showed markedly positive RF with negative ANA, anti-dsDNA, and Antineutrophil Cytoplasmic Antibodies (ANCA). Cryoglobulin testing was positive, demonstrating mixed cryoglobulins (monoclonal IgMκ with polyclonal IgG; cryocrit-4%). Viral serology confirmed Hepatitis B Surface Antigen (HBsAg) positivity with Antibody to the Hepatitis B core antigen (Anti-HBc) IgG and detectable HBV DNA, while hepatitis-C and HIV were negative. Serum protein electrophoresis showed polyclonal gammopathy, and Urine Protein Electrophoresis (UPEP) revealed no monoclonal protein. These findings were consistent with immune complex-mediated GN, specifically Type II cryoglobulinaemic GN.

Biopsy

A percutaneous renal biopsy was performed. Light microscopy revealed diffuse endocapillary proliferative GN with lobular

Category	Test	Result	Reference range	Significance
Blood pressure	Brachial	108/78 mmHg	120/80 mmHg	Immediate compromise in circulatory stability
Renal function	Serum creatinine	2.3 mg/dL	0.6-1.2 mg/dL	Acute Kidney Injury (AKI)
	eGFR	~30 mL/min/1.73 m^2	>90 mL/min	Moderate severe renal impairment
Urine studies	UPCR	~3.5 g/g	<0.15 g/g	Nephrotic-range proteinuria
	Urinalysis	Haematuria, Proteinuria	-	Active glomerular sediment
Haematology	Albumin	2.5 g/dL	3.5-5.0 g/dL	Hypoalbuminaemia
	Haemoglobin	9.9 g/dL	11-14 g/dL	Anaemia
	Platelet count	1,70,000	1,50000-3,00,000 cells/mm^3	No consumptive coagulopathy

Liver Function Test	ALT(SGPT)	17 U/L	28-40 U/L	Normal Liver Function
	AST(SGOT)	23U/L	15-44 U/L	
	Alkaline Phosphatase (ALP)	29 U/L	38-126 U/L	
	Total Bilirubin	0.9 mg/dL	0.2-1.3 mg/dL	
Autoimmune	Rheumatoid Factor (RF)	Markedly positive	Negative	Supports immune-complex GN
	Anti-CCP	Negative	Negative	Supports limited extra articular manifestations
	ANA	Negative	Negative	Exclude Lupus Nephritis
	Anti dsDNA	Negative	Negative	Exclude SLE
	ANCA	Negative	Negative	Exclude ANCA-associated vasculitis
Complement	C3	60 mg/dL	90-180 mg/dL	Reduced
	C4	4 mg/dL	10-40 mg/dL	Severely reduced
Cryoglobulin	Cryoglobulins	Positive (mixed Type II: monoclonal IgMκ+polyclonal IgG; cryocrit ~4%)	Negative	Diagnostic of Type II cryoglobulinaemic
Viral serology	HBsAg	Positive	Negative	Chronic HBV
	Anti-HBc IgG	Positive	Negative	Past/chronic HBV exposure
	HBV DNA	Highly detectable	Undetectable	Active viral replication
	Anti-HCV	Negative	Negative	Excluded
	HIV serology	Negative	Negative	Excluded
Protein studies	SPEP	Polyclonal γ-globulin increase	---	Immune activation
	UPEP	No monoclonal protein	---	Excludes myeloma
Renal biopsy	Light microscopy	MPGN pattern, endocapillary proliferation, hyaline pseudothrombi	---	Typical of cryoglobulinaemic GN
	Immunofluorescence	IgM, IgG (κ & λ), C3, C1q	---	Immune-complex GN (Type II)
Renal imaging	Ultrasound kidneys	Normal size, ↑ cortical echogenicity	---	Medical renal disease

[Table/Fig-1]: Summary of investigations.
Abbreviation: ANA: Antinuclear antibody; ANCA: Antineutrophil cytoplasmic antibody; Anti-CCP: Anti–cyclic citrullinated peptide antibody; Anti-HBc IgG: Hepatitis B core antibody; IgG: Immunoglobulin G; C3: Complement component 3; C4: Complement component 4; eGFR: Estimated glomerular filtration rate; HBsAg: Hepatitis B surface antigen; SLE: Systemic lupus erythematosus, UPCR: Urine protein creatinine ratio; SPEP: Serum protein electrophoresis

accentuation (MPGN pattern). Glomeruli were hypercellular with prominent neutrophilic infiltration and mesangial expansion. Notably, numerous Periodic Acid-Schiff (PAS)-positive eosinophilic "hyaline thrombi" (immune complex aggregates) occluded capillary lumina. Basement membranes showed irregular duplication (double contours) and focal intracapillary pseudothrombi. There was no significant necrosis or crescent formation. Vessels and tubule interstitium showed mild inflammatory infiltrates without crescents or fibrinoid necrosis [Table/Fig-2].

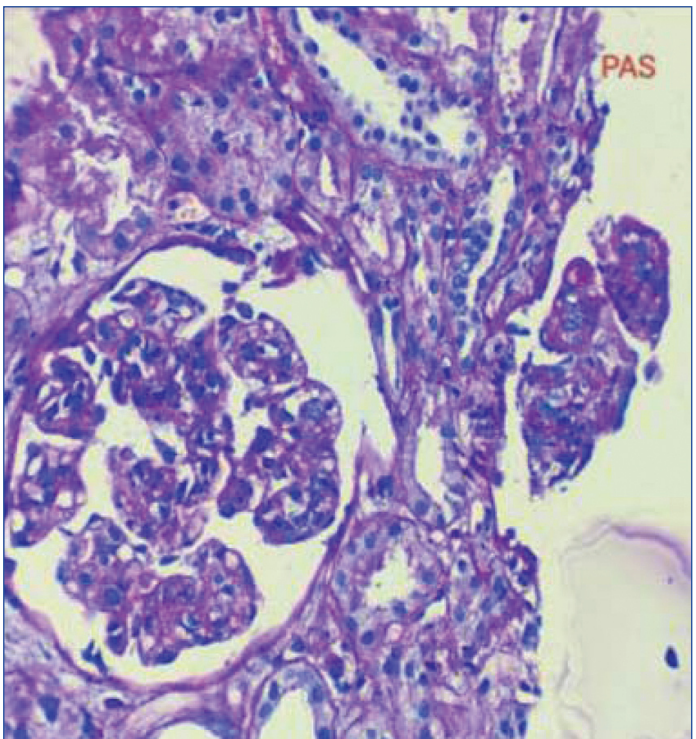
Immunofluorescence microscopy showed a diffuse and granular staining along capillary walls: IgM and IgG (with kappa and lambda light chain staining) were present in the immune complexes, along with complement C3 and C1q. IgA was negative. Focally small vessels show deposits of IgG, IgM, C3, C1q, kappa and lambda in the lumen of vessel wall. The dominant pattern (monoclonal IgMκ combined with IgG) matched Type II cryoglobulin deposition. Electron microscopy would reveal mesangial and subendothelial electron-dense deposits, often with rhomboid structures (typical cryoglobulin microtubules). These findings confirmed cryoglobulinaemic GN (a membranoproliferative, immune-complex GN) with associated immune complex mediated extra glomerular small vessel vasculitis.

Radiology

No specific renal imaging (e.g., computed Tomography/Magnetic Resonance Imaging (CT/MRI) of kidneys) was obtained, as the clinical and laboratory picture already indicated glomerular disease. Renal ultrasound showed normal-sized kidneys with mild increased cortical echogenicity. No vasculitic organ involvement required imaging at presentation.

Management

Severe cryoglobulinaemic GN requires combined antiviral and supportive therapy when hepatitis B is present. Given the biopsy-proven cryoglobulinaemic GN, management was directed at both the underlying etiologic triggers and the immune-mediated



[Table/Fig-2]: Renal biopsy sections (H&E, PAS, JMS, MT; ×400) sections showing MPGN pattern with mesangial hypercellularity, endocapillary proliferation neutrophils, intracapillary hyaline thrombi, acute tubular injury, and extraglomerular small-vessel vasculitis, (H&E, PAS, JMS, MT; ×400).
JMS: Jones methenamine silver; MT: Masson's trichrome

renal injury. High-dose corticosteroid therapy was initiated with prednisone 1 mg/kg/day to achieve rapid control of active vasculitis and glomerular inflammation. Because chronic hepatitis B infection can act as a persistent driver of immune-complex formation, antiviral therapy with entecavir (0.25 mg once daily, dose adjusted for renal impairment) was commenced to suppress viral replication and prevent reactivation during immunosuppression.

Plasmapheresis was reserved as a contingency strategy for life-threatening complications such as hyperviscosity syndrome, rapidly progressive renal failure, or refractory proteinuria. Supportive management included diuretics for volume control and oedema, and initiation of an angiotensin-converting enzyme inhibitor to reduce intraglomerular pressure and proteinuria. Potent immunosuppressive therapies, including cyclophosphamide, mycophenolate mofetil, cyclosporine, and anti-Cluster of Differentiation 20 (CD20) monoclonal antibodies such as rituximab, were deferred due to the substantial risk of hepatitis B reactivation and hepatic flare despite antiviral prophylaxis. Despite HBV suppressive treatment and plasmapheresis, she developed progressive renal failure necessitating haemodialysis. She worsened due to disease related complications in addition to nosocomial infections and expired within three weeks of treatment.

DISCUSSION

Cryoglobulinaemia refers to circulating immunoglobulins that precipitate at low temperature and dissolve on rewarming. HCV infection is the dominant cause (~80-90% of mixed cryo) [1-3]. In non-HCV cases, cryoglobulinaemia is associated with other chronic infections (HBV, HIV) or autoimmune diseases (Systemic Lupus Erythematosus (SLE), Sjögren's, and RA) [2,4]. Mixed cryoglobulinaemia (types II and III) is an immune complex mediated vasculitis of IgM with RF activity bound to IgG characterised by circulating immunoglobulin that precipitate at low temperatures [1]. Type II (monoclonal IgMκ+polyclonal IgG) accounts for ~50-65% of cryo cases and account for the most common subtype [2]. Typically presents with Meltzer's triad and variable renal involvement, as described by Ferri C et al., (2004) [3]. Hepatitis B–associated cryoglobulinaemic is rare but reported. Li C et al., (2020) and Han HX et al., (2023) described cases with purpura, arthralgia, and renal involvement showing an MPGN pattern, similar to the present case. Autoimmune diseases such as RA also contribute to cryoglobulin formation [2,4]. Dammacco F et al., (2023) reported systemic vasculitis with renal involvement, supporting a dual pathogenic mechanism [5]. Histologically, an MPGN pattern with immune deposits is characteristic, as noted in recent studies including Duggal S et al., (2025) [6]. Despite therapy, outcomes remain variable. The present case showed rapid progression, highlighting the severity of overlapping aetiologies. The patient's long-standing RA and chronic hepatitis B likely both contributed to immune complex generation. RA itself can trigger cryoglobulin production, as RF forms part of the cryoglobulin complex, and hepatitis B virus, although rare, is a recognised aetiological factor [3,4]. Clinically, mixed cryoglobulinaemic often presents with Meltzer's triad (purpura, arthralgias, weakness) plus renal and nerve involvement. Hypocomplementemia (especially low C4) and positive RF are hallmark laboratory clues [5,6]. In fact, severe C4 consumption is highly suggestive of cryoglobulinaemic-related vasculitis [6]. Our patient's purpura, low C4, and high RF prompted testing for cryoglobulins, confirming the diagnosis. Biopsy patterns in cryoGN are typically membranoproliferative (lobular capillary hypercellularity with double-contour basement membranes) [7]. Prominent PAS-positive thrombi ("pseudothrombi") of immune complexes are characteristic [7]. Immunofluorescence classically shows both IgM and IgG with complement (C3, often C1q) deposition along capillaries [8]. These findings differentiate cryoGN from, say, idiopathic MPGN or lupus nephritis; in our case the dual Ig deposition and clinical context clinched the diagnosis [7,8]. Differential diagnoses included other causes of MPGN (e.g., HBV immune complex GN without cryoglobulins, C3 glomerulopathy, SLE), but the serology and biopsy were most consistent with cryoglobulin. Notably, HBV can cause membranous or proliferative GN by subepithelial immune deposits, but those usually show granular IgG/HBsAg deposits without hyaline thrombi. RA-related renal disease (e.g., amyloid or Nonsteroidal Anti-Inflammatory Drug (NSAID) toxicity) was unlikely. Given the confirmatory biopsy, treatment was aligned with cryoglobulinaemic vasculitis management principles [5,9]. Therapeutically, mixed cryoglobulinaemic demands both aetiological and immunosuppressive approaches. Eradicating or suppressing the source of immune complexes is key: for HCV, Direct-Acting Antiviral agents (DAAs) revolutionised outcomes, and analogously we treat HBV aggressively in HBV-associated cases [10]. Immunosuppression (corticosteroids, cyclophosphamide, and rituximab) is reserved for severe or refractory vasculitis. Rituximab (anti-CD20) is particularly effective in cryoGN [6], often resulting in improved renal function. However, in HBV carriers, B-cell–depleting therapy poses reactivation risk; prophylactic antivirals are mandatory [11]. The patient of the present case, suffering from Type II cryoglobulinaemia GN with HBV-positive status, warranted anti-HBV treatment (renal dose-adjusted) and plasmapheresis, another adjunct for very high cryocrit or hyperviscosity, though used infrequently [12]. Unfortunately, in our patient, these combined measures did not lead to the remission of vasculitis and had progressive renal failure. The patient expired due to disease related complications. Cryoglobulinaemic GN often portends a guarded renal prognosis: up to 30-35% of mixed cryo patients develop proteinuria or renal impairment [13]. Early diagnosis by recognising cryoglobulinaemic's clinical clues (purpura, low C4, RF, and HBV) and confirming with biopsy is therefore critical to improve outcomes. This case underscores that clinicians should consider cryoglobulinaemic in RA patients who develop GN, especially if any infection (e.g., HBV) is present. Comparison of previously reported cases of cryoglobulinaemic GN with the present case, highlighting aetiology, clinical features, renal involvement, histopathological patterns, treatment strategies, and outcomes in [Table/Fig-3] [2-6,12].

Author/ Year	Aetiology	Clinical features	Renal findings	Biopsy pattern	Treatment	Outcome
Ferri C et al., 2004 [3]	Mixed cryoglobulinaemic	Meltzer's triad	Variable renal involvement	MPGN	Steroids/ immunotherapy	Variable
Li C et al., 2020 [2]	HBV	Purpura, arthralgia	Proteinuria, renal dysfunction	MPGN	Antivirals±steroids	Partial/complete remission
Han HX et al., 2023 [4]	HBV	Vasculitis, systemic features	Haematuria, proteinuria	MPGN	Antivirals+immunosuppression	Variable
Dammacco F et al., 2023 [5]	Mixed cryoglobulinaemic	Systemic vasculitis	Glomerulonephritis (GN) in subset	MPGN	Immunotherapy	Improved outcomes
Quartuccio L et al., 2023 [12]	Mixed cryoglobulinaemic	Severe vasculitis	Renal involvement	MPGN	Rituximab-based therapy	Better renal outcomes
Duggal S et al., 2025 [6]	Mixed cryoglobulinaemic	Multisystem involvement	Renal+systemic	MPGN	Immunotherapy	Variable
Present case	RA+HBV	Purpura, arthralgia, oedema	Nephrotic proteinuria, AKI	MPGN with pseudothrombi	Steroids+antivirals+plasmapheresis	Rapid progression, mortality

[Table/Fig-3]: Reported cases of HBV-associated cryoglobulinaemic Glomerulonephritis (GN) [2-6,12].

CONCLUSION(S)

Type II cryoglobulinaemic GN is a rare but serious immune-complex nephritis that can complicate chronic HBV infection and autoimmune disease. The classic triad of purpura, positive RF, and low complement levels should alert clinicians to order cryoglobulin testing. Kidney biopsy (showing an MPGN pattern with IgM/IgG deposits) confirms the diagnosis. Dual etiologies may be associated with a more aggressive clinical course and poorer outcomes. Management combines treatment of the underlying trigger (e.g., antiviral therapy for HBV) with immunosuppression (steroids, rituximab). The present case illustrates the necessity of a multidisciplinary approach coordinating rheumatology, nephrology, and hepatology to recognise and treat mixed cryoglobulinaemic. Early intervention can stabilise renal function and prevent life-threatening complications. Vigilance for cryoglobulinaemia in atypical GN presentations remains a key learning point.

REFERENCES

[1] Muchtar E, Magen H, Gertz MA. How I treat cryoglobulinemia. Blood. 2017;129(3):289-98.
[2] Li C, Li H, Su W, Bing WY, Ye W, Ling YW, et al. Clinicopathological study of mixed cryoglobulinemic glomerulonephritis secondary to hepatitis B virus infection. BMC Nephrol. 2020;21(1):395.
[3] Ferri C, Sebastiani M, Giuggioli D, Cazzato M, Longombardo G, Antonelli A, et al. Mixed cryoglobulinemia: Demographic, clinical, and serologic features and survival in 231 patients. Semin Arthritis Rheum. 2004;33(6):355-74.
[4] Han HX, Su W, Zhou DB, Li J, Cao XX. Hepatitis B virus-related cryoglobulinemia: Clinical characteristics, virological features, and treatment. Virus Res. 2023;336:199212.
[5] Dammacco F, Lauletta G, Vacca A. The wide spectrum of cryoglobulinemic vasculitis and an overview of therapeutic advancements. Clin Exp Med. 2023;23(2):255-72.
[6] Duggal S, Kattamuri LVP, Toutoungy M, Ceron EL, Rondla M, Lehker A. Exploring Cryoglobulinemia's clinical odyssey: A case series. EJHaem. 2025;6(2):e70029.
[7] Menter T, Hopfer H. Renal disease in cryoglobulinemia. Glomerular Dis. 2021;1(2):92-104.
[8] Chen YP, Cheng H, Rui HL, Dong HR. Cryoglobulinemic vasculitis and glomerulonephritis: Concerns in clinical practice. Chin Med J (Engl). 2019;132(14):1723-32.
[9] Cacoub P, Vieira M, Saadoun D. Cryoglobulinemia - one name for two diseases. N Engl J Med. 2024;391(15):1426-39.
[10] Desbois AC, Cacoub P, Saadoun D. Cryoglobulinemia: An update in 2019. Joint Bone Spine. 2019;86(6):707-13.
[11] Leleux C, Zerbib Y, Pommerolle P, Da Rocha A, Serpier M, Caillard P. Rare manifestations of cryoglobulinemic vasculitis: A case report. Front Immunol. 2023;14:1271584.
[12] Quartuccio L, Bortoluzzi A, Scirè CA, Marangoni A, Del Frate G, Treppo E, et al. Management of mixed cryoglobulinemia with rituximab: Evidence and consensus-based recommendations from the Italian Study Group of Cryoglobulinemia (GISC). Clin Rheumatol. 2023;42(2):359-70.
[13] Won A, Hanna P, Hassanein M, Shaikh A. Cryoglobulinemic glomerulonephritis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2026 Jan 10]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK613279/.

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