

Recurrent Mixed Cryoglobulinemia (MCS): A Case Report and Literature Review

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ABSTRACT

We report a case of recurrent mixed type II cryoglobulinemia with difficult diagnosis and treatment dilemma and uncertain prognosis in view of limited studies. A 60-year-old male with history of essential mixed cryoglobulinemia 12 years ago treated successfully with six months of cyclophosphamide and prednisone presented with bilateral lower extremity purpuric rash and swelling. He was found to have proteinuria, hematuria, RBC casts, low serum complement levels, and acute kidney injury (AKI). Initial therapy with methylprednisone and oral cyclophosphamide was ineffective (patient developed respiratory failure due to alveolar hemorrhage). Additional labs revealed positive type II cryoglobulins, high free Kappa/Lambda, UPEP with minimal urine protein, SPEP with marked hypogammaglobulinemia, and negative tests for HIV, HCV, ANA, and ANCA. More aggressive therapy with daily plasmapheresis and rituximab was instituted with very good clinical response. He achieved clinical remission but developed another flare 8 months later. Kidney biopsy showed membranoproliferative glomerulonephritis with cryoglobulin deposits. Flow cytometry and biopsy of bone marrow was consistent with lymphoplasmacytic lymphoma. His diagnosis was eventually confirmed and responded clinically to another course of rituximab and plasmapheresis, but prognosis is yet to be seen.

KEYWORDS: Cryoglobulinemia, Lymphoplasmacytic Lymphoma, Hepatitis C, Rituximab, Cyclophosphamide, Plasmapheresis

BACKGROUND

The paucity of available data and lack of clear clinical guidelines pose diagnostic and therapeutic dilemma in patients with recurrent noninfectious MCS. In this report, we present a patient who was diagnosed with essential MCS 12 years ago, treated successfully with cyclophosphamide and prednisone. After more than a decade of complete remission he had recurrence of disease when he presented with skin purpura and acute kidney injury complicated by life-threatening pulmonary hemorrhage that was effectively treated with rituximab and plasmapheresis and a tapering course of oral prednisone. A month later after discontinuation of oral prednisone and following a dental procedure (removal of six teeth)

he experienced another recurrence with skin and AKI. At that time a bone marrow and flow cytometry was performed. This case represents a rare cause of cryoglobulinemia, and the diagnostic and treatment dilemma associated with it.

CASE PRESENTATION

A 60-year-old male originally from Argentina with history of essential MCS diagnosed 12 years ago and successfully treated with six months of cyclophosphamide and prednisone presented with bilateral lower extremity purpuric skin rash and ankle swelling. Exam findings were significant for elevated BP, 169/89 mmHg, bilateral lower extremity purpura, and trace edema. Laboratory tests revealed serum creatinine at 2 mg/dL (baseline 1 mg/dL); C3 at 35 mg/dL (reference range 79-152 mg/dL) and C4 at <10 mg/dL (reference range 16-38 mg/dL). The urinalysis revealed proteinuria (spot protein/creatinine: 1.5 mcg/gr creatinine), hematuria, and RBC casts. Haptoglobin was <5.8 mg/dL (reference range 36-195 mg/dL), LDH 449 IU/L (reference range <171 IU/L), hemoglobin 11.2 gm/dL, and peripheral blood smear showed no evidence of schistocytes. He was initially treated with intravenous solumedrol 1 gm daily for 3 days. However, he developed respiratory distress, decreased pulse oxygenation (83% on room air) on day 3 of admission. Chest X-ray showed diffuse bilateral airspace consolidation along with drop in hemoglobin level, concerning for diffuse alveolar hemorrhage. His therapy was switched to combination oral cyclophosphamide 100 mg/day and daily plasmapheresis. Additional laboratory findings showed presence of type II cryoglobulins, rheumatoid factor (RF) at 115 IU/mL (reference range <20 IU/mL), free Kappa/Lambda at 3.53, urine protein electrophoresis (UPEP) with minimal urine protein, serum protein electrophoresis (SPEP) with marked hypogammaglobulinemia; and serological tests negative for HIV, HCV PCR, antinuclear antibody (ANA), and anti-neutrophil cytoplasmic antibody (ANCA). On Day 7 of hospitalization, patient required intubation for progressive respiratory failure although creatinine had improved from 2.2 to 1.3 mg/dL. Because of recurrent disease involving lungs, kidneys, and skin with light chain abnormalities and rapidly deteriorating course, his treatment regimen was switched to daily plasmapheresis and rituximab 375 mg/m²/week. There was remarkable improvement in clinical course with discontinuation of ventilatory support eight days later. Subsequent

three additional doses of rituximab administered one week apart (total of 4 doses) were completed as outpatient. Follow-up laboratory studies five months post-hospital discharge revealed creatinine at 1 mg/dL, urinalysis with trace proteinuria (urine protein/creatinine: 0.15 gm/day), non-dysmorphic RBCs and absent casts, C3 at 121 mg/dL, C4 at 14 mg/dL, free Kappa/Lambda at 0.83 and absent cryoglobulins. Monoclonal protein was absent on serum immunofixation. The prednisone therapy had been tapered to 10 mg/day with excellent clinical and biochemical remission.

He represented 8 months later with similar complaints consistent with mixed cryoglobulinemia flare. By that time, he was off oral prednisone for a month. Following a dental procedure (removal of six teeth) he experienced another flare-up with purpuric skin rash and AKI. A repeat kidney biopsy

showed recurrent type II membranoproliferative glomerulonephritis with cryoglobulinemia deposits (Figures 1–5). Bone marrow biopsy showed hypocellular (25%) marrow with kappa-positive mild plasmacytosis (4%). Flow cytometric immunophenotypic analysis of bone marrow demonstrated less than 1% of CD19+, CD20-, kappa-restricted B cells consistent with low level B-cell lymphoplasmacytic lymphoma. Bone marrow chromosomal analysis did not reveal any numerical or structural abnormalities. CT scan of chest, abdomen, and pelvis excluded occult lymphadenopathy. Treatment with Rituximab and plasmapheresis, due to previous life-threatening presentation was instituted. His clinical condition improved and was subsequently discharged from the hospital. His last serum creatinine has normalized and he is now on oral cyclophosphamide at 50 mg/day.

Figure 1. Mesangiocapillary proliferation and cryoglobulin thrombi (H&E stain at 400x)

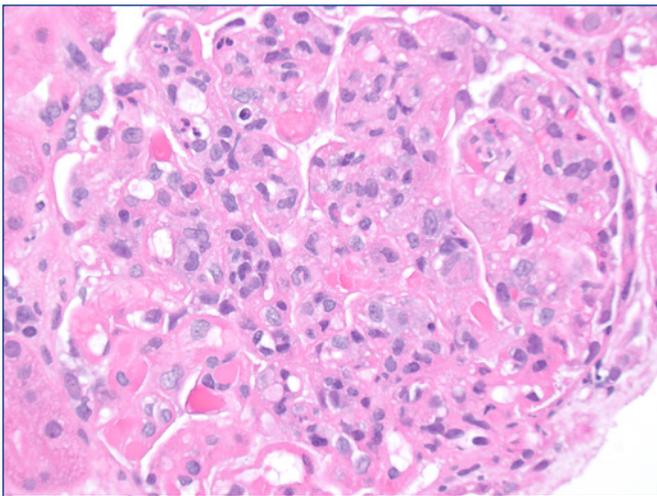


Figure 2. Cryoglobulin thrombi is present in upper right (PAS stain at 400x)

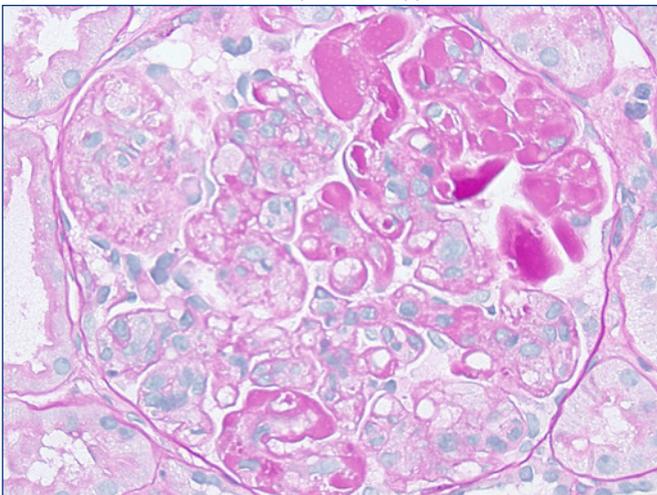


Figure 3. Cryoglobulin thrombi is seen in lower right and glomerular basement membrane deposits are stained throughout the glomerulus (IgM immunoperoxidase stain at 400x)

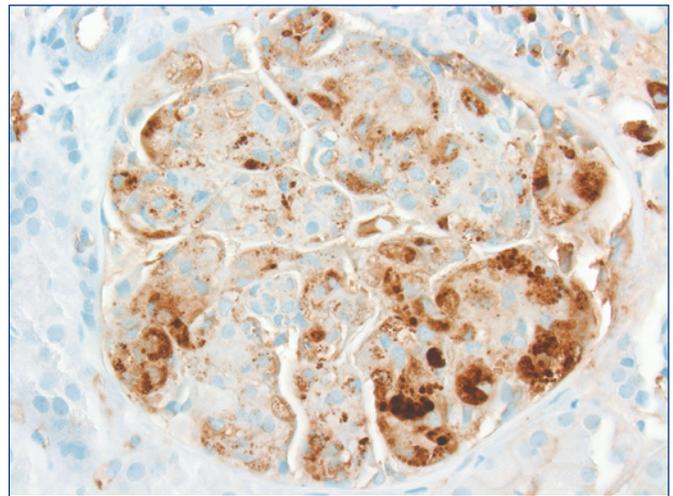


Figure 4. Cryoglobulin thrombus is seen in the capillary loop with double contoured glomerular basement membrane. There are proximal tubule protein resorption droplets seen in left upper quadrant (Jones silver stain at 400x)

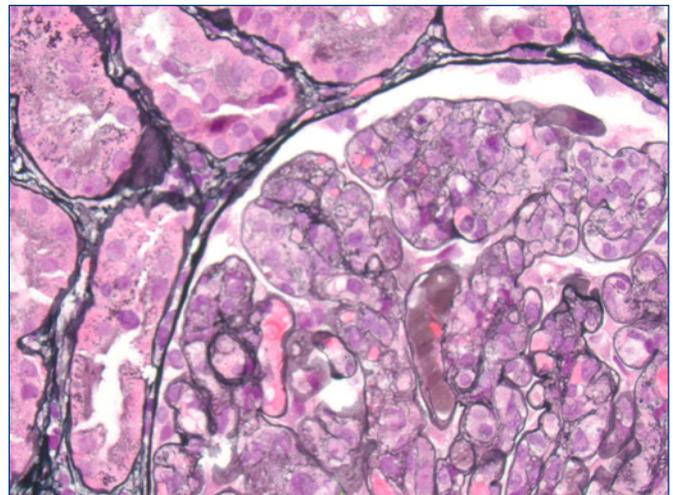
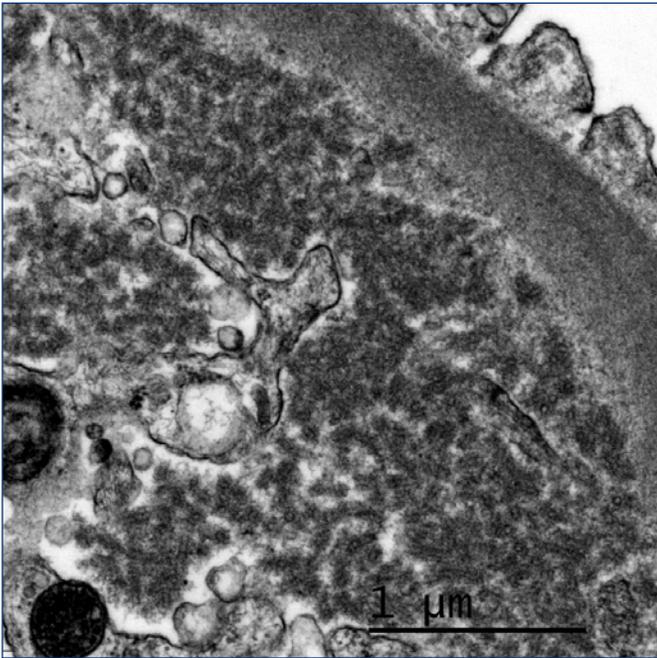


Figure 5. Cryoglobulin deposits are seen in the endothelium (EM at 30kx)



DISCUSSION

Cryoglobulins are serum immunoglobulins that precipitate with cooling (<37°C) and redissolve upon rewarming. Meltzer et al identified mixed cryoglobulins in 1966¹, then Brouet et al, in 1974, classified cryoglobulins into three different biochemical types.² Type I cryoglobulin consists of monoclonal immunoglobulin (Ig), either IgG or IgM, usually seen in Multiple Myeloma (MM) and Waldenstrom's Macroglobulinemia (WM). Type II cryoglobulins imply monoclonal IgM RF against polyclonal IgG, more commonly associated with HCV infection, and less commonly with hepatitis B (HBV) and Epstein-Barr virus (EBV). Type III cryoglobulins are polyclonal IgM RF against IgG, seen in autoimmune diseases (systemic lupus nephritis (SLE) and Systemic Sclerosis (SS)) and Lymphoproliferative diseases (LPD). Reported incidence of type I, II, and III cryoglobulins are 6%, 62%, and 32%, respectively.³ Mixed cryoglobulinemia connotes the presence of type II or type III cryoglobulins in the blood sample and 'essential' means obscure cause, therefore eMCS indicates absence of identifiable cause of type II or III cryoglobulinemia.

Recurrence risk of eMCS after complete remission is unpredictable. Our patient presented with skin purpura which constitutes 81% of presenting feature in MCS.⁴ It may present with weakness and fatigue (80%), arthralgia (72%), and frank arthritis (8%). Renal involvement in the form of glomerulonephritis (GN) is evident on presentation in 20% of MCS patients. The most frequent renal presentation is microscopic hematuria and proteinuria. Beddhu et al reported type I MPGN as the predominant histologic pattern, followed by focal and mesangioproliferative GN in a series

of 17 patients with cryoglobulinemia and renal disease.⁵ In the same report, HCV positive, as compared to HCV negative, cryoglobulinemia was more commonly associated with progression to end stage renal disease (ESRD) attributable to less immunosuppressive usage in the former group. Rapidly progressive course is infrequent but when present signals poor prognosis.

The detailed work-up and treatment should be tailored to the clinical presentation. HCV infection is frequently associated with the presence of type II or type III cryoglobulins without obvious vasculitis symptoms, thus the utility of checking cryoglobulin level in the absence of vasculitis symptoms is unhelpful as it would not alter the treatment plan. Conversely, strong clinical suspicion should be raised and pertinent work-up pursued if patients present with purpura or arthralgia with the evidence of positive RF titer and hypocomplementemia. It was necessary to investigate deeply in our patient in view of multi-organ involvement. Approximately 30–40% of type II and some type III MCS have undetectable cryoglobulins on presentation. In such scenario, improper handling of specimen (specimen collection at temperature below 37°C) has to be ruled out by carefully reviewing the entire procedure and cryoglobulin level be repeated if clinical suspicion is very high. Failure to maintain warm temperature results in precipitation of cryoglobulin to the bottom of the collection tube and the supernatant serum would not yield any cryoglobulins leading to false negative result. The cryocrit is percentage of packed cryoglobulins and it is frequently used measure to report cryoglobulins by the most laboratories. The normal cryocrit level should be close to zero in the absence of MCS and level >1% is clinically significant. The cryocrit level between 1-3% is seen in Type III and 2–7% is seen in Type II MCS. Normal cryoglobulin level is 2–5 mg/dL. Approximately, 95% of MCS are associated with HCV infection^{6,9}; this clinical correlation was unknown before the early 1990s, prior to discovery of HCV. Detailed work-up to delineate the cause of cryoglobulinemia must include HCV, HBV, HIV, MM, WM, LPD, SLE, SS, and Sjogren's syndrome as the primary goal is to treat the underlying cause of cryoglobulinemia. Presence of severe hypogammaglobulinemia, abnormal kappa/lambda ratio, IgM kappa monoclonal protein in our case during recurrence, responding to rituximab, initially suggested underlying chronic low-grade lymphoproliferative disorder precipitating the recurrent events which was eventually proven by bone marrow biopsy and flow cytometry.

Therapeutic management of MCS is based on the severity of disease and the underlying disorder. Presence of cryoglobulins in the absence of clinical symptoms warrants close monitoring. Addition of low to moderate doses of steroids relieves mild symptoms like purpura and arthralgia. Cold exposure should be avoided to prevent cryoglobulin precipitation. Angiotensin converting enzyme inhibitor is prescribed to reduce intraglomerular filtration pressure and proteinuria, if present. Limited data is available on colchicine

and low antigen diet to restore saturated mononuclear phagocytic system and spare steroid use.¹⁰ Prompt therapeutic intervention with combined immunosuppressive therapy (Rituximab or, if unavailable, Cyclophosphamide) and pulse steroid, to prevent new cryoglobulins production, is mandated in life threatening or rapidly progressive disease including pulmonary hemorrhage, CNS vasculitis, GI hemorrhage, and skin necrosis to stabilize disease. This patient's renal function improved after 3 doses, total of 3 grams, of methylprednisolone but clinical course deteriorated, despite upgraded therapy with cyclophosphamide, until rituximab was added. Modest dose of rituximab can deplete CD20+ B cells in the peripheral blood at 24–72 hours with the effect lasting at least 2–3 months.¹¹ Plasmapheresis, although controversial, may be added in such a situation.¹² Replacement fluid for plasmapheresis should be warmed to prevent precipitation of cryoglobulins.¹³ Once the disease is stabilized the underlying cause must be identified and treated. The exception to this rule is HIV and HBV infection which must be treated before or at the same time of aggressive therapy with immunosuppressants and plasmapheresis in order to prevent enhanced viral replication. In MCS related to viral etiology presenting with mild symptoms, the goal should be focused on the eradication of the virus. HCV infection, with the exception of decompensated cirrhosis, is treated with pegylated IF and Rituximab.¹⁴ Rituximab is an effective therapy in severe cryoglobulinemic vasculitis.¹⁵ It has steroid sparing effect as well. In HCV-related MCS it inhibits auto-reactive antibodies produced by oligoclonal or polyclonal B lymphocyte expansion related to chronic HCV infection. Complete remission in MCS secondary to non-infectious etiology is higher with rituximab plus glucocorticoids compared to glucocorticoids alone but associated with increased risk of infection, especially when a higher steroid dose is used.¹⁶ In the same study combined cyclophosphamide and glucocorticoid therapy was not associated with better outcome compared to glucocorticoid alone. One small study on low-dose rituximab 250 mg/m² in the treatment of MCS was less effective in achieving one-year remission.¹⁷ Clinical response is determined based on improvement of clinical picture (improvement of ulcers, respiratory failure), serum creatinine and proteinuria. Serum concentration of cryoglobulin (cryocrit) is not a marker of severity of disease or a response to the therapy.¹⁸ The tapering of steroids and total duration of course depends on the disease response. The duration of antiviral therapy is the same for HCV infection with or without cryoglobulinemia. Treatment of lymphoplasmacytic lymphoma is challenging in the absence of strong data. For the treatment of recurrent disease like in our case, combination therapy with rituximab and bendamustine or fludarabine can be administered in patients older than 70 years; however, there is no comparison data between these two regimens. In patients younger than 70 years, combination therapy with cyclophosphamide, fludarabine, and rituximab has been suggested by the Italian Society of

Hematology to minimize the toxicity of fludarabine in the absence of comorbidities.

Prognosis in MCS does not rely on presence or absence of viral infection; absence of infection in fact may have a worse prognosis. In a cohort of HCV-infected patients treated with appropriate anti-HCV therapy, overall survival was more than 80% at a median of 15 years regardless of presence or absence of MCS.¹⁹ Patient survival in non-infectious MCS at 1, 2, 5, and 10 years are 91, 89, 79, and 65%, respectively.²⁰ Lymphoplasmacytic lymphoma usually has an indolent clinical course and some have an aggressive course with median survival of 5 to 7 years. This case had an indolent course for a decade followed by an aggressive course. Overall one-year survival with the manifestation of acute pulmonary hemorrhage, CNS vasculitis, intestinal vasculitis with gastrointestinal bleeding/ischemia, rapidly progressive glomerulonephritis, and cardiac vasculitis are 22%, 66%, 67%, 79%, and 100%, respectively.^{21, 22} Recurrence rate of MCS after renal transplantation has been reported between 50–70% even with clinical and serologic remission during transplantation but most patients do not lose graft from recurrent disease.²³

SUMMARY

In summary, 12 years ago our patient presented with eMCS and completely responded to Cyclophosphamide and prednisone. He was admitted with an identical cryoglobulin profile with a rapid deterioration failing high-dose steroids, plasmapheresis and cyclophosphamide. After a single dose of rituximab his clinical condition dramatically improved allowing him to be extubated and have his therapy completed as an outpatient. Patients with low-grade NHL commonly go into a complete remission with an alkylating agent and corticosteroid therapy and commonly recur years later. As our patient had a monoclonal protein detected in the serum separate from the cryoglobulin, we postulated that he had all along suffered from a low-grade LPD which secretes an IgM Kappa monoclonal protein with the biophysical properties to instigate the development of the aforementioned type II mixed cryoglobulinemia. This diagnosis was confirmed on his second recurrence with flow cytometry and biopsy of bone marrow. His recurrent flares have been controlled with rituximab therapy and plasmapheresis. He subsequently has been started on oral cyclophosphamide with fair tolerance. His future treatment will be challenging due to his recurrence while on rituximab therapy.

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