Mixed Cryoglobulinemia Syndrome Associated with Non-HCV B-Cell Lymphoproliferative Disorder Presenting with Gangrene and Peripheral Neuropathy

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ABSTRACT

Mixed cryoglobulinemia is a rare disorder characterized by gangrene, weakness, and arthralgias with variable organ involvement. It is often associated with hepatitis C, HIV, and immunological disorders. Diagnosis is based on clinical features and laboratory testing with serology detecting cryoglobulins. Our patient, a 64-year-old female, presented with weakness, fatigue, and discoloration of her fingers and toes. Physical examination showed upper- and lower-extremity skin changes with dry gangrene. Serology showed a non-hepatitis C status, positive cryoglobulin test with a positive rheumatoid factor, and monoclonal IgM-kappa, confirming the diagnosis of mixed cryoglobulinemia. She was treated with intravenous immunoglobulins, glucocorticoids, multiple cycles of rituximab, cyclophosphamide, and plasma exchange. Following a significant event of exacerbation and relapse requiring a below-knee amputation, this case report aims to raise awareness among clinicians to consider this as a rare cause of gangrene and peripheral neuropathy in an elderly adult.

KEYWORDS: Mixed cryoglobulinemia, relapse, below-knee amputation, internal medicine

CASE PRESENTATION

A 64-year-old female presented to the Emergency Department (ED) for blisters over her feet, discoloration over several digits of her hands and feet, and generalized weakness, more pronounced in her lower extremities. The weakness was accompanied by severe dull pain over the left lower leg with numbness over the left foot. She reported worsening symptoms over the last month and pain up the left leg with loss of fine touch sensation. The patient reported the symptoms began four years ago and have been conservatively managed. The left leg pain had gradually become worse despite treatment. The patient was a non-smoker, did not drink alcohol, and denied any history of substance use.

Physical examination showed an anxious female with a blood pressure of 151/89, heart rate of 86 beats/min, respiratory rate of 20 breaths/min, and a temperature of 38°C. Local examination of the upper extremities showed discoloration of the digits over the middle and ring finger of the right

Figure 1. Physical examination findings of the hands. Top to bottom: [**A**] Raynaud's phenomenon involving three digits of the left hand. [**B**] Dry gangrene of the tips of the middle digit of the right hand and ring finger (marked). [**C**] Dry gangrene of the tip of the middle finger of the right hand (dorsal view).

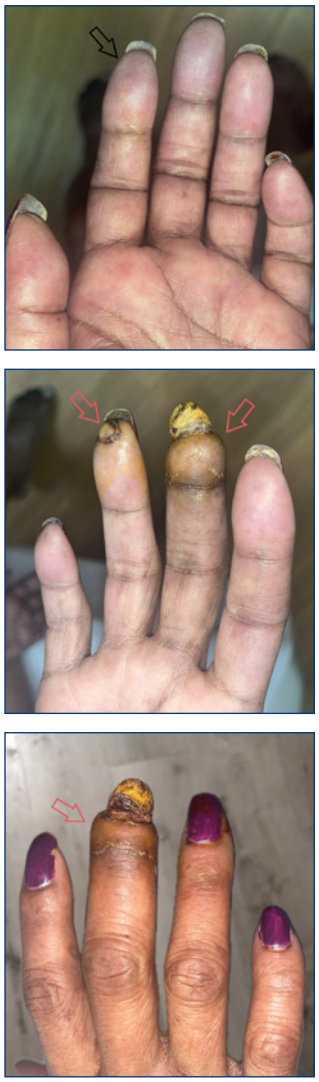
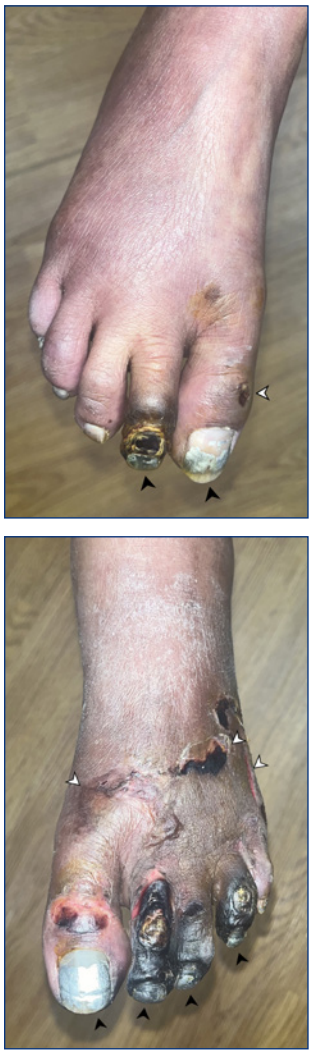


Figure 2. Physical examination of the lower extremities showing dry gangrene (black) and ulceration (white). Top to bottom: [**A**] Right foot with dry gangrene of the second digit, with noticeable blisters of the skin. [**B**] Left foot with dry gangrene involving 4 digits with blisters and erosion.



hand, with noted nail bed necrosis of the left middle and ring finger with cyanotic appearance of the tips of the middle three digits of the left hand (**Figure 1A,B,C**). Lower extremities showed marked discoloration of several digits over both feet, with extensive blistering and demarcation between the devitalized and vital tissues (**Figure 2A,B**).

Sensory examination showed a marked reduction in sensation over the left lower extremity. Pulses were palpable over bilateral feet. Examination of lymph nodes revealed no abnormal palpable nodes in the neck, axilla, abdomen, and pelvis.

Following the initial results, further investigations were performed to elucidate the cause of these findings [**Table 1,** Rheumatological profile]. Low C4 levels, normal C3 levels, and increased rheumatoid factor (RF) levels were noted. Serum protein electrophoresis with immunofixation showed a kappa IgM monoclonal protein with polyclonal IgG titer.

A seven-day cryoprecipitate test showed a positive study with a cryocrit ratio of 3%. Infectious workup including blood cultures, HIV, hepatitis B surface antigen and antibody, and serologic testing for hepatitis C were negative. Bone marrow biopsy and flow cytometry [**Table 1**] showed a small CD5 and CD10-negative monoclonal B-cell population indicative of monoclonal lymphoproliferation of uncertain significance (MLUS). Cytogenetic studies and myeloid NGS panel showed no pathogenic mutations. Evaluation for non-Hodgkin's lymphoma via peripheral smear studies and multiple node biopsies from several groups (USG-guided) were normal. Full-body CT was negative for lymphadenopathy. Peripheral nerve biopsies showed large arteriole necrotizing vasculitis. Electromyographic studies were positive for acute severe length-dependent axonal sensorimotor polyneuropathy. There was no evidence of arterial or venous thrombosis in the bilateral lower extremities on venous ultrasound.

Based on the patient's initial presentation due to suspected autoimmune or rheumatological causation, the patient was started on a high dose of prednisone (100mg/day). In light of the rheumatological profile and negative autoimmune workup in conjunction with physical findings, the working diagnosis shifted towards mixed cryoglobulinemia type 2 (MC). She was started on intravenous

Table 1. Complete hematological investigations and rheumatological profile

Investigations	Results	Reference Range
White Blood Cells	23.1 (H)	4–11 (10^9/L)
Red Blood Cells	4.06	4.40–6 (10^12/L)
Hemoglobin	10.2 (L)	13.5–17.5 (g/dL)
Hematocrit	29.6 (L)	41–51 (%)
Mean corpuscular volume	72.8 (L)	80–99 (fL)
Mean corpuscular hemoglobin	31.2 (L)	25–35 (pg/cell)
Platelet count	731 (H)	140–440 (10^9/L)
Erythrocyte sedimentation rate	118 (H)	<15 (mm/hr)
Creatinine	0.45 (L)	0.7–1.3 (mg/dL)
eGFR	>90	>60 (ml/min)
Alkaline Phosphatase	153 (H)	40–129 (U/L)
Albumin	3.1 (L)	3.5–5 (g/dL)
AST	20	0–37 (U/L)
ALT	11	6–45 (U/L)
Total protein	5.4 (L)	6–8 (g/dL)
Globulin	3.3	1.7–3.7 (g/dL)
Total bilirubin	0.2	0–1.2 (mg/dL)
Rheumatological profile		
CMV PCR	Not detected	Negative or positive
Thyroid cascade panel	Within normal limits	—
CPK	70 mcg/L	10–120 mcg/L
Folate	12.2 ng/mL	>=5.9ng/mL
Rheumatoid factor (RF)	128 (H)	0–15 U/mL
ANA titer	<1:40	<1:40 neg, 1:40–1:80 low, >1:80 high
Extractable nuclear antibody panel	Negative	Negative or positive
p-ANCA, C-ANCA screen	Negative	Negative or positive
C3, C4 complement factor	99, 6 (L)	83–240 mg/dL, 13–60 mg/dL
Hepatitis panel (PCR)	Negative for HCV and HepB	Negative or positive
HIV	Negative	Negative or positive
Bone marrow biopsy with flow cytometry	Hypercellular bone marrow with left sided granulocytic hyperplasia without significant lymphoid infiltrate or blasts. Small population of monoclonal B-cell population, CD5-negative and CD10- negative.	
Urine analysis with electrophoresis	Albuminuria and Bence-Jones proteinuria.	
Kappa lambda ratio	1.23, indicative of a non-plasma cell disorder	
Quantitative immunoglobulins	IgA: 108 mg/dL (N), IgM: 58 mg/dL (N), IgG:182 mg/dL (N)	
Myeloid NGS cytogenetics	No pathogenic mutations	
Peripheral smear	No evidence of lymphocytosis or circulating blasts	
EMG studies	Acute severe length-dependent axonal sensorimotor polyneuropathy	
Lumbar puncture	Normal cell count with no albuminocytologic dissociation	
7-day cryoprecipitate test	Positive, with noted cryoprecipitate with 3% cryocrit ratio.	

Legend: H – high, L– low. eGFR- estimated glomerular filtration rate, BUN – blood urea nitrogen, AST – aspartate aminotransferase, ALT – alanine aminotransferase. CMV – cytomegalovirus, CPK – creatine phosphokinase, ANA – antinuclear antibody, HCV – hepatitis C, HepB – hepatitis B, NGS – next generation sequencing, Ig – immunoglobulin, EMG – electromyography study.

immunoglobulins (IVIG, 1 g/kg/day) with four cycles of rituximab (375 mg/m^2/week) and a prolonged prednisone taper. The patient reported symptomatic improvement in terms of strength; however, she was unable to walk without assistance due to continued pain of the left lower limb. Due to worsening pain, she was started on plasmapheresis every other day for a total of 14 treatments in addition to glucocorticoids. The regimen of rituximab was discontinued as there was no symptomatic response, leading to a change to cyclophosphamide (750 mg/m^2/month), which was started inpatient. On discharge, the patient was to continue receiving cyclophosphamide infusions until the patient achieved complete remission of symptoms. Reevaluation of the patient's disease state showed RF reduced to 17 U/mL prior to discharge. Due to the condition requiring prolonged immunosuppression, the patient was continued on a low dose of oral prednisone (30mg/day).

Following continued wound care, there was a natural progression of her dry gangrene, leading to auto-amputation of the affected toes. Despite outpatient continuation of prednisone and cyclophosphamide, due to worsening disease, she was readmitted in three months. Labs were then significant for lactic acidosis, leukocytosis, and thrombocytosis. Radiological investigations were negative for arterial and venous thrombosis. RF was noted to be elevated to 458 U/mL at the time of readmission. Her presentation was attributed to fulminant relapsing cryoglobulinemic vasculitis. The patient was started on a pulse-high dose of methylprednisolone (1000 mg/day) for three days, considering her previous response to glucocorticoids, with a transition to oral prednisone at 100mg/day. Broad-spectrum IV antibiotics (vancomycin, ceftriaxone, and levofloxacin) were started.

The patient's symptom profile did not improve, and hence, she underwent three sessions of plasma exchange. The antibiotics were escalated to imipenem/cilastatin and levofloxacin due to non-improvement on day four of hospital care. She developed a foul-smelling discharge, increased swelling, warmth, and redness over the left foot, and X-rays showed marked gas formation in the soft tissues of the left foot. Due to fulminant cryoglobulinemic vasculitis and length-dependent axonal neuropathy, the limb was deemed unsalvageable. Additionally, the growth of gas-forming bacteria not responding to continued antibiotics and plasmapheresis, as well as ongoing immunosuppression and glucocorticoids, made surgical intervention necessary.

The patient agreed to undergo a left below-knee amputation (BKA). Following the procedure, there was rapid improvement and normalization of the pain and infectious picture. After rehabilitative planning, she was later discharged on oral prednisone with a taper to 30mg/day.

She also continued to receive cyclophosphamide infusions (750 mg/m^2/month) under the care of her rheumatologist and hematologist. At the six-month follow-up, the patient did not report any further occurrences of blisters or Raynaud's phenomenon in the hands or foot. The pain over the hands and foot did improve to manageable levels with flare-ups on exposure to cold weather. Serum protein electrophoresis with immunofixation showed no evidence of multiple myeloma, supported by a normal kappa/lambda ratio of 1.12. Labs also showed a return to a normal RF level of 15 U/mL, and repeat cryoglobulin and cryofibrinogen testing was negative, indicating remission. Following continued immunosuppression and surveillance, the patient is still under follow-up at our academic center.

DISCUSSION

Mixed cryoglobulinemia (MC) syndrome refers to the presence of cryoglobulins in a person's sera, which has been known to precipitate at a low temperature of 4°C (39.2°F).[1,2] Type 2 cryoglobulinemia is a subtype in which immune complexes of polyclonal IgGs and monoclonal IgM cryoprecipitate due to their reduced solubility. The monoclonal IgM almost always contains kappa light chains and represents autoantibodies with the rheumatoid factor (RF).[3]

Characteristically, the syndrome presents with multisystemic features, but initial suspicion of the syndrome relies primarily on the dermatological appearance of purpura associated with weakness and polyarthralgia.[1-4] The prevalence of the disease is estimated to be one in 100,000 individuals, with a greater preponderance in individuals from North America and Southern Europe.[4] Of the cumulative pool of MC patients, 50–60% are of type 2.[3] Its etiopathogenesis is multivariate with several hypotheses for its origin with a documented correlation between hepatitis C virus (HCV), hepatitis B (HepB), auto-immune conditions, and infections with HIV.[1,2] Other correlating contributing factors, although rarely seen, may include lymphoproliferative disorders involving B-cell clonal proliferation.[5-7]

Clinical presentations of the disease include purpura, arthralgias, and generalized weakness (Meltzer's triad). The co-appearance of these three findings is noted in roughly one-third of patients. Other findings may include a wide list of abnormalities, such as MC-related vasculitic findings, organ dysfunction, lymphoid disorders, and malignancies.[1,4,5,8,10] Cutaneous involvement, as seen in 25% of cases may present as leukocytoclastic vasculitis.[1,4] Digital ischemia and gangrene, as reported in our case, are only seen in 2% of cases.[4]

Systemic involvement may include chronic hepatitis, membranoproliferative glomerulonephritis, interstitial lung disease, endocrinopathies, peripheral neuropathy, neoplastic manifestations of B-cell lymphoma, hepatocellular carcinoma, and papillary thyroid cancer.[1,2,11] These presenting features may vary and may depend on the subtype of cryoglobulinemia. The absence of carcinoma may not preclude a negative state on a long-term basis as MC syndromes can be regarded as a pre-neoplastic disorder, increasing the future risk of organ and lymphatic malignancy.[1]

MLUS has the potential to transform to B-cell lymphocytic leukemia and hence can be regarded as a precursor condition that will require monitoring efforts to assess its evolution.[1,2] Other such common triggers of MC in the absence of HCV, HepB, or HIV may relate to an underlying autoimmune condition. However, due to a heterogeneous causation, the role of further workup, once the diagnosis of MC is made, is to form a holistic approach for its management. The noted role of HCV causing lymphoproliferative disorders has been extensively studied and has been noted to be the inciting factor for MLUS leading to MC.[12,13] However, the standalone cause of MLUS leading to MC type II, not associated with an HCV infection, has been documented to a lesser extent in literature.[2] In our case, the patient's lymphoproliferative disorder was considered to be a non-CLL B-cell lymphoproliferative disorder, and here, MLUS was considered the driving factor behind the presentation. Moreover, as seen in our case, in patients whose clonal hematologic disorders do not meet the requirements for chemotherapy, relapses of cryoglobulinemia can be observed and can be hard to mitigate.[2,14]

Due to the varied heterogeneity of the clinical features and associated coexisting causation, treatment is aimed at reducing immune mediated systemic involvement. In patients with HCV and HepB, eradicating the viral state via pegylated interferons and ribavirin administration may help with resolution of symptoms. In mild to moderate symptom profiles, treatment with low-dose glucocorticoids is indicated.[1,2] Treatment is usually escalated from rituximab to cyclophosphamide to plasma exchange with continued immunosuppression with low to high-dose glucocorticoids throughout the entire treatment process.[1,2,9] In life-threatening conditions, as in our case of fulminant relapsing cryoglobulinemic vasculitis, high doses of pulse glucocorticoids (1000mg/day prednisolone) for three days can be used.[2] Further management of the condition may include monitoring via RF titers to assess disease activity.[2]

A rapid response and alleviation of symptoms are usually noted following plasma exchange in 70–80% of patients. Failure to manage symptoms or progression of disease using multiple modalities of treatment can result in surgical intervention, as seen in our case. Moreover, despite remission, cases of MC can relapse with time due to a quiescent process, as noted previously. Catastrophic presentations due to cryoglobulinemic vasculitis have been noted in literature wherein limbs were deemed unsalvageable or has resulted in the demise of the patient.[14] As noted here, due to associated poor long-term prognosis, regular follow-ups are imperative to prevent future disease progression and disability due to arthralgias, amputations, and end-organ damage.

CONCLUSIONS

Mixed cryoglobulinemia (MC) syndrome refers to a complex disorder with a diversity of clinical manifestations related to the presence of cryoglobulins in a person's sera, which has been known to precipitate at a low temperature of 4°. Type 2 MC can rarely precipitate with underlying MLUS without the presence of preceding viral infections. Findings may include a wide list of abnormalities, including vasculitis. Management strategies aim to mitigate immune-mediated system involvement by eradicating the causative source, such as hepatitis C or the underlying lymphoproliferative cause. In patients with life-threatening complications like cryoglobulinemic vasculitis, aggressive intervention via pulse glucocorticoids and plasma exchange may be necessary. A rapid response and alleviation in symptoms are usually noted following plasma exchange in 70–80% of patients. Non-resolution of features resistant to multiple treatment modalities can lead to surgical intervention. Patients with MC can relapse with time due to a quiescent underlying process. Due to the associated poor long-term prognosis, regular follow-ups are needed to prevent future burden of care and disability due to arthralgias, amputations, and end-organ damage.

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