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Case Report

Rheumatoid Arthritis Complicated with Mixed Cryoglobulinemia and Thrombotic Microangiopathy, Presenting as Extensive Cutaneous Thrombosis: A Rare Clinical Phenotype

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Abstract

Rheumatoid arthritis–associated mixed cryoglobulinemia is rare and may occasionally trigger severe thrombotic microangiopathy. We report a patient who developed acute hemolysis, thrombocytopenia, acute renal dysfunction, and extensive cutaneous thrombosis, creating a challenging diagnostic scenario of cryoglobulinemia-induced thrombotic microangiopathy (TMA). This unusual phenotype underscores the difficulty of differentiating overlapping TMA syndromes and highlights the importance of early immunosuppression and supportive therapy to prevent organ injury. The structured approach, from confirming systemic and dermatological involvement to identifying cryoglobulinemia and excluding infectious and prothrombotic causes, supported the diagnosis of TMA secondary to cryoglobulinemia.

Keywords: cryoglobulinemia, rheumatoid arthritis, thrombotic microangiopathy, cutaneous thrombosis

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Introduction

Cryoglobulinemia refers to the presence of cryoglobulins, immunoglobulins that reversibly precipitate at low temperatures between 0°C and 4°C and dissolve when rewarmed to 37°C [1]. These proteins can precipitate in various settings, including infectious diseases, autoimmune disorders, and haematological malignancies [1].

Cryoglobulins are classified into three types based on their immunoglobulin composition [2]. Type I cryoglobulins are monoclonal and often associated with lymphoproliferative disorders [2]. Types II and III are mixed cryoglobulins, with type II containing monoclonal IgM with rheumatoid factor activity and polyclonal IgG, while type III cryoglobulins contain only polyclonal immunoglobulins [1].

Mixed cryoglobulinemia is associated with autoimmune disorders, chronic infections such as hepatitis C, and B-cell lymphoproliferative diseases [3]. Its clinical spectrum varies widely, ranging from mild purpura to life-threatening organ damage [4]. Mixed cryoglobulinemia (types II/III) may produce severe small-vessel injury, including necrotising vasculitis and microthrombosis [4]. Although classical digital ischemia and purpura are well described, thrombotic microangiopathy (TMA) in the context of

cryoglobulinemia remains rare [5]. This case illustrates the diagnostic complexity of secondary TMA.

Case Presentation

A 70-year-old woman with a history of hypertension and type 2 diabetes mellitus for eight years presented with acute gastroenteritis, fever for three days and progressive shortness of breath for one day. The fever was low grade and subsided on the day of admission to the district general hospital (DGH), Trincomalee. She denied weight loss, anorexia, or constitutional symptoms. She reported chronic intermittent pain and swelling of the proximal interphalangeal joints (PIP) of both hands, involving the second to fifth digits, with associated morning stiffness for more than an hour for three months before this admission.

On admission, she was febrile, dyspneic, and required admission to the medical intensive care unit due to respiratory distress. Following non-invasive ventilation, she was stabilised and transferred to the general medical ward after 3 days. She developed widespread purpuric and thrombotic skin lesions affecting both upper and lower limbs, the periumbilical region, and the areolar area of the breast bilaterally on the fourth day in the hospital (Figure 1). Subsequently, dry gangrene developed in the first three toes bilaterally and progressed to involve all toes. She was started on intravenous methylprednisolone pulse therapy and transferred to the Teaching Hospital, Anuradhapura, from Trincomalee on the fifth day of admission for therapeutic plasma exchange on the suspicion of thrombotic thrombocytopenic purpura (TTP).

On admission to Teaching Hospital, Anuradhapura, physical examination revealed generalised oedema, bilateral lower-limb swelling, and sharply demarcated areas of dry gangrene of toes. All lower limb peripheral pulses were present. Her respiratory examination revealed bilateral basal fine crepitations, which improved with treatment. On cardiovascular examination, her blood pressure was 150/80 mmHg, and her pulse rate was 80 beats per minute, with normal heart sounds. She had no organomegaly, lymphadenopathy, or neurological deficits.

Her laboratory investigations are summarised below (Table1). A peripheral blood smear showed schistocytes, consistent with low-grade microangiopathic haemolytic anaemia (MAHA). The presence of evidence for acute hemolysis (high LDH and indirect bilirubin levels), thrombocytopenia, purpuric lesions progressing to gangrene, and positive cryoglobulins on two occasions with preserved peripheral pulses in the feet indicated a microvascular thrombotic process affecting small vessels. The absence of monoclonal bands suggested that either type II or III mixed cryoglobulinemia is the likely type. The patient's chronic symmetrical PIP joints involvement for 3 months and elevated rheumatoid factor and ESR were compatible with the diagnosis of rheumatoid arthritis (7/10 EULAR criteria), a known but rare cause of mixed cryoglobulinemia.

The absence of severe acute renal impairment made typical haemolytic uraemic syndrome (HUS) less likely, and the lack of neurological deficits made classical TTP unlikely. The findings favoured secondary TMA due to cryoglobulinemic vasculitis. Her APTT was normal, and APLS screening was negative for lupus anticoagulant, anti-cardiolipin antibodies, and beta-2 glycoprotein all were normal. A normal clotting profile made disseminated intravascular coagulation (DIC) an unlikely cause for her presentation. Positive blood and urine cultures (micrococci and coliforms, respectively) obtained on the fourth day at DGH Trincomalee, along with elevated inflammatory markers, suggest a hospital-acquired infection likely following initiation of immunosuppressive therapy and intensive care support. This was supported by negative blood, urine, and stool cultures obtained on admission to DGH Trincomalee. Her virology tests for hepatitis B, hepatitis C, Epstein-Barr virus, cytomegalovirus, and influenza A and B were all negative.

Tumour markers, including carcinoembryonic antigen, cancer antigen 125, and alpha-fetoprotein, were negative. The contrast-enhanced computed tomography scan of the chest, abdomen and pelvis was normal, excluding the possibility of underlying malignancies. However, serum protein electrophoresis did not rule out light-chain myeloma, but, given the absence of urinary casts or severe renal impairment and a normal serum calcium level, this possibility is unlikely.

She was treated with three days of methylprednisolone pulse therapy followed by three cycles of therapeutic plasma exchange from the 3rd day of admission to the Teaching Hospital, Anuradhapura. After the first therapeutic plasma exchange, the patient's breathlessness improved markedly. Following the subsequent two therapeutic plasma exchanges, her biochemical parameters improved, with reduced LDH levels, a normal coagulation profile, and increased Hb and platelet counts. She was on a therapeutic dose of low-molecular-weight heparin after her platelet count increased above 80 $x10^3$/L. Her bilateral dorsalis pedis vascular flow was preserved, and she did not lose any toes, even though her distal phalanges showed dry gangrene with undetectable perfusion. She was treated with intravenous meropenem and metronidazole for 10 days based on positive culture and sensitivity patterns. The infection resolved with antibiotic treatment, as evidenced by negative cultures after treatment and by C-

reactive protein levels returning to baseline. She was discharged home at this point.

She was started on methotrexate and warfarin on discharge. After two months of treatment, she showed improvement in the thrombotic rash, with the necrotic skin peeling off, revealing healthy skin. The distal phalanges of all toes with dry gangrene were atrophied. The patient demonstrated a marked response to therapy during clinic visits. She was back to her routine after six months of treatment.

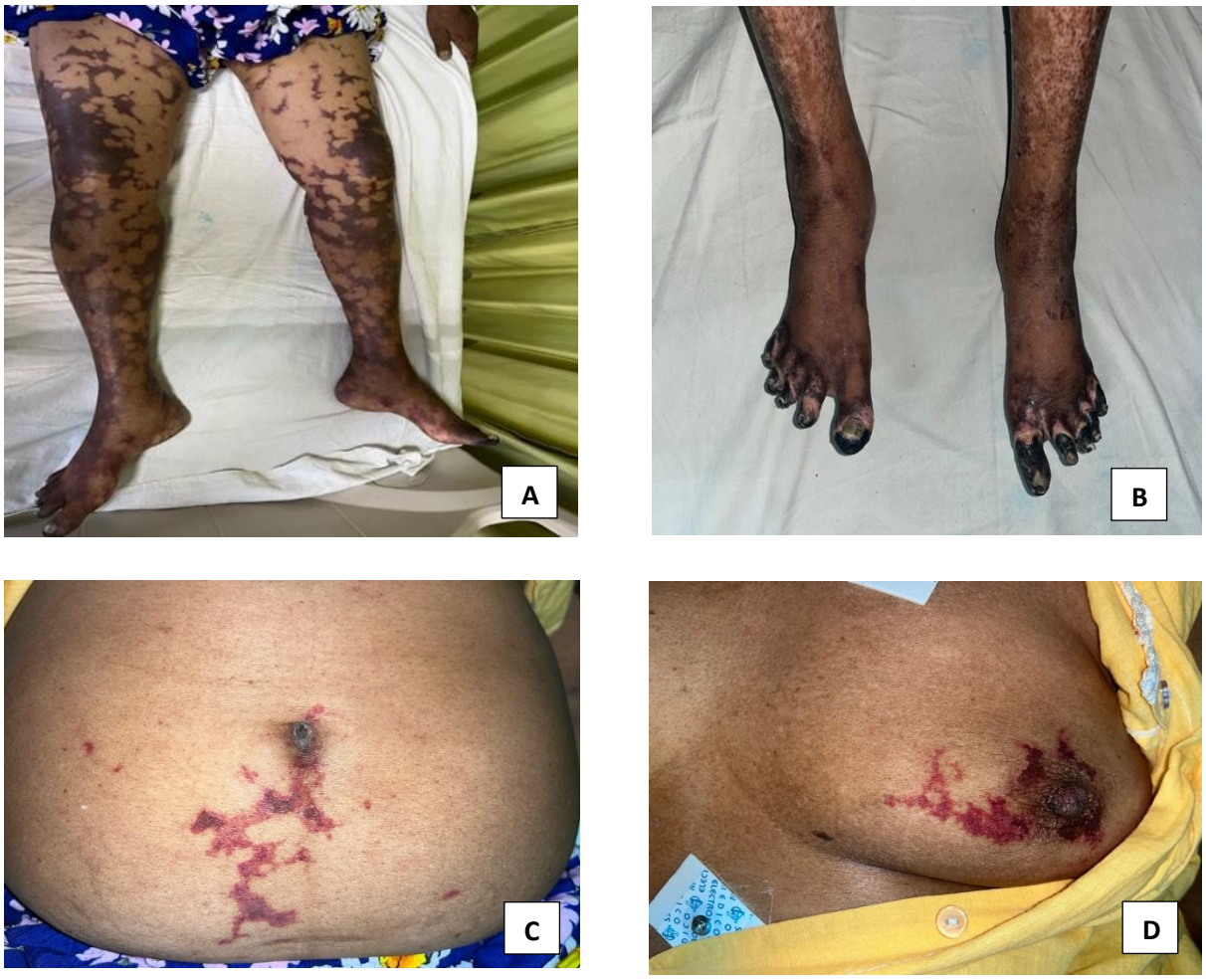

Figure: 1

Image A: Thrombotic rashes over the lower limbs

Image B: Bilateral digital dry gangrene

Image C: Thrombotic rashes around the umbilicus

Image D: Thrombotic rashes around the left areola

Discussion

This case highlights an unusual presentation of rheumatoid arthritis associated with mixed cryoglobulinemia and TMA. When a patient presents with thrombotic and coagulation dysregulation features, the likelihood of cryoglobulinemia is increased. Early identification and initiation of management will lead to a favourable outcome and are crucial for preventing irreversible multisystem damage.

Cryoglobulinemia presents a unique diagnostic challenge due to its variable clinical manifestations and diverse underlying etiologies [4,5]. In this patient, the absence of monoclonal gammopathy and the positive rheumatoid factor, combined with longstanding inflammatory small-joint disease, suggest an autoimmune-driven mixed cryoglobulinemia, most likely type II or III. Rheumatoid arthritis is a recognised but less common trigger for mixed cryoglobulinemia [1,6].

Table 1: Summary of investigations

Investigation	Result	Normal range
White blood cells	12 x 10^9 /L	4.5-10
Hemoglobin	9.8 g/dL	12 -15
Platelets	110 x 10^9/L	150 - 450
Erythrocyte sedimentation rate	70 mm/1st hour	<20
C-reactive protein	225 mg/dL	0-5
Serum sodium	137 mmol/L	135 -145
Serum potassium	4.12 mmol/L	3.5 -5.5
Procalcitonin	0.091 ng/ml	<0.05
Cancer antigen 125	11 IU/ml	< 35
Carcinoembryonic antigen	4.63 ug/L	<5
Alpha fetoprotein	20 ng/ml	10-40
Aspartate aminotransferase	50 U/L	10-35
Alanine aminotransferase	20 U/L	5-21
Albumin	24 g/L	35-52
Globulin	35 g/L	20-35
Alkaline phosphatase	45 IU/L	35-130
International normalized ratio	1.2	0.8-1.2
Total bilirubin	8.29 µmol/L	5-21
Direct bilirubin	3.71 µmol/L	<5.1
Indirect bilirubin	4.6 µmol/L	3.4-12
Prothrombin time	10.74 seconds	10-13.5
Activated partial thromboplastin time	30 seconds	25-35
Serum creatinine	240 µmol	60-120
Blood urea	7.8mmol/L	2.8-7.7
Unsaturated iron binding capacity	29.8 µmol/L	22-70
Iron	12.3 µmol/L	10.7-30.4
Total iron binding capacity	42.1 µmol/L	40-90
Saturation of transferrin	29.22 %	20-50
Serum ferritin	1696 ug/L	11- 307
Urine for Benz's Jones proteins	negative	
Urine dysmorphic RBC	not seen	
Total calcium	2.54 µmol/L	2.1-2.6
Lactate dehydrogenase	864 to 150 U/L	140-280
Rheumatoid factor	8.71 IU/ml	<8
Urine albumin to creatinine ratio	50 mg/g	<30
Anti-nuclear antibody	negative	
Complement-C3 level	100 mg/dL	88-201
Complement-C4 level	20 mg/dL	15-45
Serum cryoglobulins	positive on two occasions	

Cutaneous involvement is present in over 90% of cryoglobulinemia cases and often includes purpura, ulcers, livedo, and acral ischemia [3]. The patient's widespread thrombotic lesions and dry gangrene with intact distal arterial pulses indicated a small-vessel occlusive process. Cryo-fibrinogenemia was considered, given its association with fibrin-mediated vascular thrombosis, but cryoglobulinemia remained the predominant explanation [5].

The presence of MAHA, thrombocytopenia, and organ damage characterises TMA. Secondary TMAs may arise in autoimmune diseases, infections, and malignancies. Cryoglobulinemia is a rare cause of secondary TMA and has been reported in severe systemic inflammation characterised by immune complex deposition and complement activation. Typically, mixed cryoglobulinemia is associated with normal C3 and low C4 levels. In this patient, normal C4 levels could be due to a strong concurrent inflammatory response from bacterial sepsis; the liver may be

producing large amounts of C4, which masks the low levels caused by consumption.

Leukocytoclastic vasculitis, a histologic pattern of small-vessel vasculitis, may also occur in association with cryoglobulinemia, autoimmune connective tissue diseases, infections, and malignancy [7]. While cryoglobulinemia classically presents with the triad of purpura, weakness, and arthralgias (Meltzer's triad), this case illustrates an overlap with TMA in a patient with underlying rheumatoid arthritis [6]. This patient's laboratory findings, including elevated LDH, anaemia, thrombocytopenia, purpuric lesions, and digital gangrene, are compatible with secondary TMA.

In tropical and subtropical regions such as Sri Lanka and India, cryoglobulinemia is often underdiagnosed due to infrequent cold exposure and minimal temperature-triggered symptoms [1]. Nonetheless, systemic inflammation, infections, or autoimmune activation can precipitate symptomatic disease. Therefore, patients may present late, often with advanced vasculitis manifestations, as in this case.

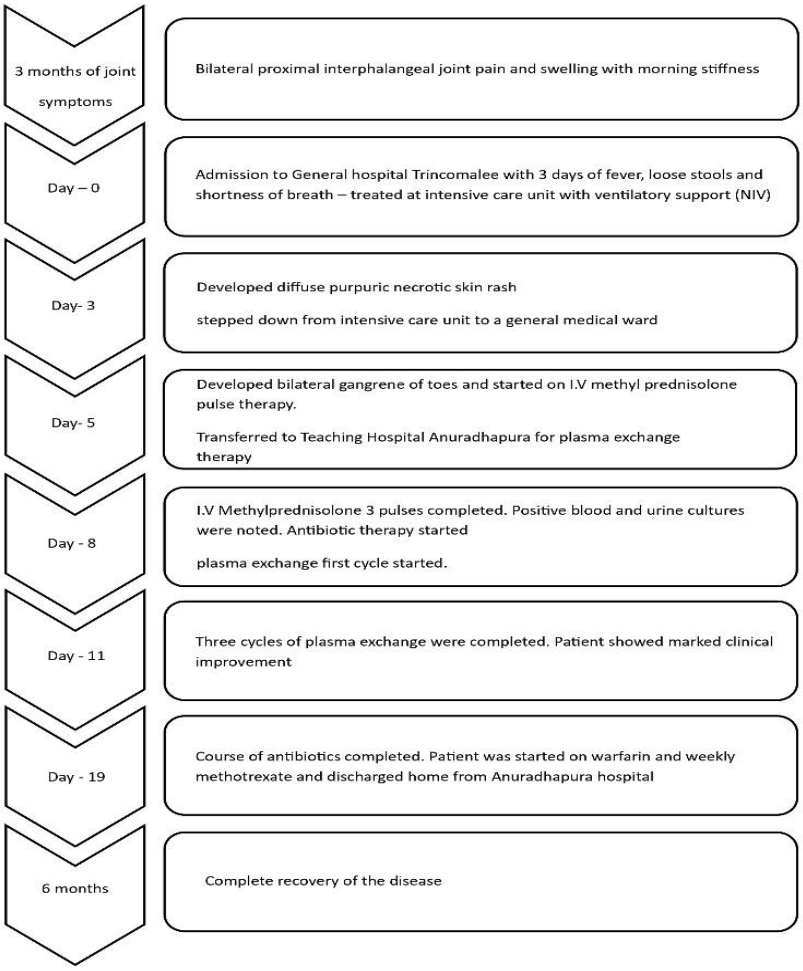

Figure 2: Timeline of events

Conclusion

This case demonstrates a rare and severe presentation of mixed cryoglobulinemia associated with underlying rheumatoid arthritis, complicated by secondary thrombotic microangiopathy. The rapid progression from purpura to gangrene highlights the aggressive nature of cryoglobulin-mediated small-vessel injury. Early identification and treatment are essential to prevent irreversible tissue damage. Clinicians should maintain a high index of suspicion for cryoglobulinemia in vasculitis or ischemic presentations, even in tropical climates where cold exposure is minimal. This case highlights the importance of recognising cryoglobulinemia as a potential cause of TMA, especially in patients with underlying autoimmune disease.

Patient's perspective

"I suddenly developed painful skin patches and severe weakness, learning it was a rare, life-threatening blood-

clotting complication was terrifying, yet timely diagnosis and treatment by doctors saved my life".

Informed consent

Informed written consent was obtained from the patient for publication of this case report and images.

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