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CASE REPORT

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Cold feet and rare vasculitis: a case report.

Nishant Agrawal [1] - A,B,G,L,M,N,O. ORCID www.orcid.org/0000-0003-4071-5142
Sandeep Sadashivrao Kansurkar [2] - A,B,L,M,N,O. ORCID www.orcid.org/0000-0002-1231-7983
Kiran Vadapalli [3] - M,N,O. ORCID www.orcid.org/0000-0002-4075-5817
Jignesh Navinchandra Shah [3] - H,J,O. ORCID www.orcid.org/0000-0002-8812-8791
Prashant Jedge [3] - H,J,O. ORCID www.orcid.org/0000-0002-9655-159X

[1] *Department of Critical Care Medicine, Bharati Vidyapeeth (DTU) Medical College and Hospital, Pune, India.*
[2] *Department of Clinical Immunology and Rheumatology, Bharati Vidyapeeth (DTU) Medical College and Hospital, Pune, India.*
[3] *Department of Critical Care Medicine, Bharati Vidyapeeth (DTU) Medical College and Hospital, Pune, India.*

Address for correspondence:
Dr. Nishant Agrawal 1 - MD, Senior Resident. Department of Critical Care Medicine, Bharati Vidyapeeth (DTU) Medical College and Hospital, Medical College Road, Pune - Satara Rd, Dhankawadi, Pune, Maharashtra 411043, Indie. e-mail: nishanta1992@gmail.com; phone: +91 96779 88026

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ABSTRACT

Cryoglobulinemic vasculitis is a systemic inflammatory response syndrome which affects multiple systems. The distinct presentations are due to the different pathophysiological mechanisms involved in the disease process that tends to create an inflammatory response in various organs.Here, we present a rare and a challenging case of Cryoglobulinemic Vasculitis in a patient who had both cutaneous and renal involvement despite of no underlying Hepatitis-C virus (HCV) infection and responded well to the immunosuppressive agents.Cryoglobulinemic Vasculitis is a complex immunological condition which can result in a life-threatening devastating complications such as loss of limb. It is very important that an Emergency Medicine specialist is aware of this complex immunological condition called as Cryoglobulinemic Vasculitis and picks up the clues which help in its early diagnosis and management.

KEY WORDS: Cryoglobulin, arthritis, immunosuppression, hepatitis-C virus infection.

INTRODUCTION

Cryoglobulins are immunoglobulins that precipitate in vitro at temperatures less than 37°C and dissolve when rewarmed (unlike normal serum proteins which remain dissolved even at low temperatures) [1]. They produce organ damage through two important pathways: vascular sludging (type I cryoglobulinaemia characterised by hyperviscosity syndrome) and immune-mediated mechanisms (mixed cryoglobulinaemia which is typically characterised by vasculitis) [2]. It was first described in 1933 when Wintrobe and Buell, delineated cryoprecipitation as a laboratory phenomenon [1]. In 1966, Meltzer and Franklin described the characteristic clinical triad associated with cryoglobulinemia. The triad includes purpura, arthralgia, and weakness but only a third of the patients present with all these classical features [3].

In 1974, Brouet et al. classified cryoglobulins into 3 different types [4]. Type I cryoglobulinaemia which is composed of single monoclonal immunoglobulins mostly IgM. Types II and III cryoglobulinemias are due to monoclonal (type II) or polyclonal (type III) IgM with rheumatoid factor activity along with the corresponding antigen which is usually polyclonal IgG. Due to this type II and III are also referred to as mixed cryoglobulinemia. When there is no obvious underlying disease, the condition is called essential cryoglobulinemia and in most of the cases, it is associated with HCV infection. Cryoglobulins have also been observed in other disease conditions like infections, malignancies, and systemic autoimmune diseases [2].

CASE REPORT

PATIENT INFORMATION: A young lady aged thirty five years who was on treatment for hypertension for the last 6 months presented with bilateral lower limb swelling for 4 weeks, burning micturition, decreased appetite and malaise for 3 weeks. There was on and off fever with facial puffiness for 2 weeks. She also complained of an episode of dark coloured sticky stools during that time. She started experiencing shortness of breath, dry cough and purpuric rashes over feet extending just above the ankles a week before presentation. She was also experiencing severe pain in her both feet a couple of days before presentation.

On enquiring about her previous medical history, she complained that she had pain in multiple joints without any obvious swelling for the last 2 years for which she received intermittent treatment with hydroxychloroquine and low dose prednisolone. In her work up for polyarthralgia there was absence of rheumatoid factor, however it was noticed that she had unexplained anaemia and leukopenia. She underwent upper gastrointestinal tract endoscopy and sigmoidoscopy a couple of weeks before presentation when she had melena which was unremarkable. She was treated conservatively with parenteral iron supplementation at that time. Her investigations done in Emergency Medicine Department were suggestive of Acute Kidney Injury (AKI) [Urea: 58 mg/dl (reference range: 20-40 mg/dl, Serum Creatinine: 2.7 mg/dl (reference range: 0.5-1.5 mg/dl] though her urine output was adequate.

She was admitted to our centre with the provisional diagnosis of undifferentiated medium vessel vasculitis with rapidly progressive renal failure. She was treated with intravenous methylprednisolone, 7.5 mg/kg for 3 days followed by prednisolone 1mg/kg. Along with this she also received oral diltiazem, cilostazol and alprostadil. Two days after admission she developed new onset respiratory distress with hypoxaemia and oliguria and hence was shifted to the Intensive Care Unit.

CLINICAL FINDINGS: On arrival to Intensive Care Unit, she was conscious and hemodynamically stable. She was febrile, had tachycardia & tachypnoea while maintaining oxygen saturation of 96% on venturi face mask with FiO2 of 60%. Physical examination showed purpuric papules over the lower extremities with blisters on feet and bilateral leg discolouration. Her repeat renal function test was suggestive of AKI stage 3 as per Kidney Disease Improving Global Outcomes (KDIGO) classification Chest x-ray revealed bilateral diffuse haziness suggestive of pulmonary edema. Arterial blood gas analysis showed high anion gap metabolic acidosis with lactic acidosis (lactates= 3mmol/L). Ultrasonography of thorax screening was suggestive of multiple bilateral B-lines in both lungs in basal areas. Electrocardiogram was suggestive of sinus tachycardia. Echocardiography did not reveal any dilatation of cardiac chambers or regional wall motion abnormality. Thin rim of pericardial effusion was noted with an ejection fraction of 55-60%. Nephrology team advised haemodialysis as a part of initial stabilisation. There was a significant improvement post dialysis, her respiratory distress reduced and oxygenation had improved.

INITIAL DIAGNOSTIC TESTING: She was investigated with viral markers for HIV, Hepatitis B and Hepatitis C which were all negative. Rheumatological work up with Antinuclear antibodies, Antineutrophil cytoplasmic antibodies, anti-double stranded deoxyribonucleic acid antibody and rheumatoid factor were negative. Her complement C3 was within normal range, however C4 was low with a value of 3.3 mg/dl (reference range : 16-45 mg/dl). Her blood cultures showed no bacterial growth, but urine culture revealed Klebsiella (non- extended spectrum beta lactamase). Arterial and venous doppler of both lower limbs was also done which was normal. As patient was requiring supplemental oxygen, High resolution computed tomography of thorax was also done to look for any evidence of diffuse alveolar haemorrhage secondary to vasculitis. HRCT thorax revealed features of pulmonary edema and bilateral minimal pleural effusion. Her plasma and serum both tested positive for cryoglobulins (Figure: 1) which dissolved when exposed to room temperature (Figure: 2). Quantification of cryoglobulins indicated high titres around 20%.

Plasmapheresis was initiated in view of high cryocrit. CT-Angiogram of the abdomen could not be done in the initial stages to rule out any intra-abdominal aneurysms in view of her deranged serum creatinine. Renal biopsy could not be performed without the preliminary angiogram reports and overall poor physical status of the patient. Serum Protein Electrophoresis revealed M- band in the Gamma region (Figure: 3). Immunofixation electrophoresis was done which was suggestive of monoclonal gammopathy seen in IgG and lambda region.

INITIAL THERAPEUTIC INTERVENTION: She underwent regular hemodialysis sessions during her stay at the intensive care unit. Unfortunately she had to undergo bilateral below knee amputation after couple of days as wet gangrene of feet had already set in. She was then shifted back to the ward and initiated on Rituximab.

FOLLOW UP AND OUTCOMES: Her renal function gradually normalised. She underwent rehabilitation and is on regular follow up and interdepartmental care. She was prescribed prosthesis and is receiving regular physiotherapy, rehabilitation and counselling.

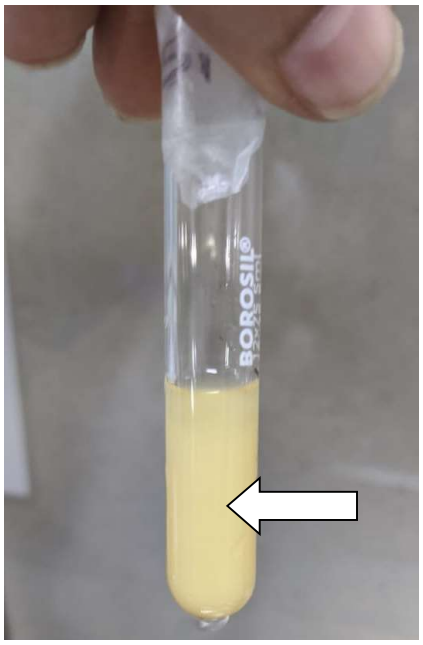

Figure 1. Cryoglobulin precipitation on exposure to cold temperature.

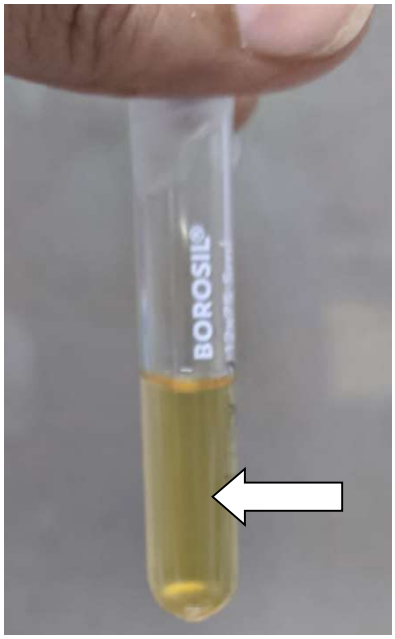

Figure 1. Dissolved cryoglobulins on rewarming

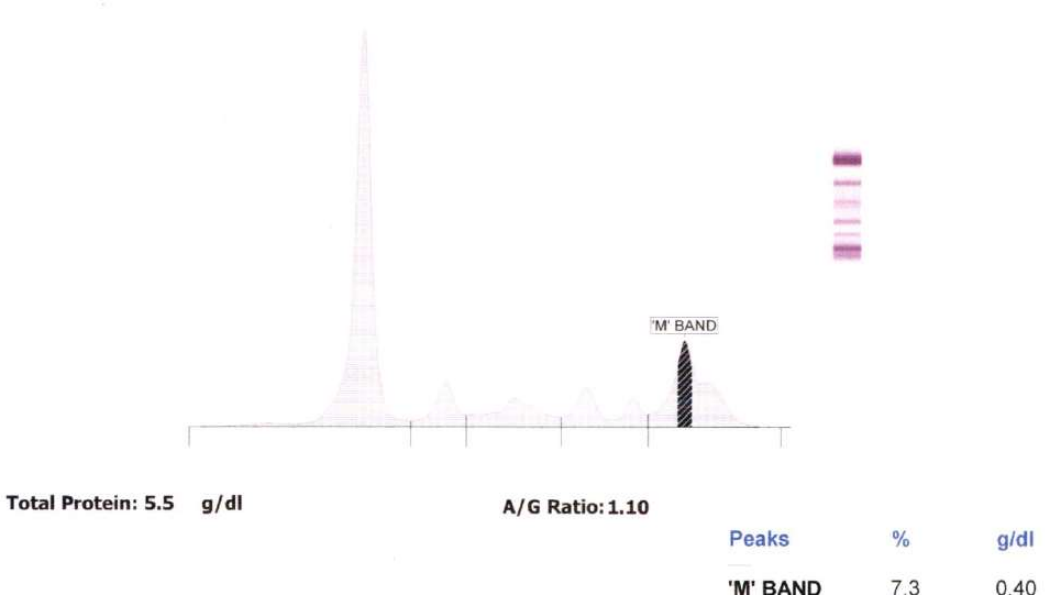

Figure 3. Serum Protein Electrophoresis.

DISCUSSION

The present case is an example of devastating presentation of cryoglobulinaemic vasculitis. Medium vessel vasculitis, glomerulonephritis and low C4 were the key pointers for the diagnosis. The presence of IgG lambda monoclonal gammopathy on electrophoresis was suggestive of type I cryoglobulinemia. Cryoglobulin detection is a simple laboratory test without requirement of any specific reagents which can be carried out with basic laboratory set up. This helped us in early diagnosis and prompted us to start plasmapheresis resulting in a swift recovery. The disease left behind significant morbidity to the patient as she lost both her feet due to gangrene. Early recognition of this rare entity by the treating clinician is crucial to prevent permanent major disability.

Cryoglobulins are immunoglobulins in serum that tend to precipitate with cooling (with tempertures less than 370 C and dissolve on rewarming [1]. They are unlike the normal serum proteins which remain in solution even at cooler temperatures. Cryoglobulemic syndrome is a form of immune mediated systemic vasculitis [3]. It involves small and medium sized arteries and veins. Cryoglobulenemias are categorised into three types. Type I cryoglobulins comprise of monoclonal immunoglobulin (Ig), mostly IgM and less frequently IgG or IgA usually seen in Waldenstrom's macroglobulinemia and Multiple myeloma. Type II cryoglobulins consist of monoclonal IgM rheumatoid factor (RF) against IgG, or polyclonal IgG which is most commonly associated with HCV infection but can also occur with Hepatitis B or Epstein-Barr virus infection. Type III cryoglobulins are polyclonal IgM and polyclonal IgG, commonly seen in autoimmune disorders like Systemic Lupus Erythematosus (SLE), Systemic Sclerosis and Lymphoproliferative diseases. Mixed cryoglobulinemia denotes the presence of type II or type III cryoglobulins in the blood sample [4]. Essential cryoglobulinemia denotes no identifiable etiological disease for the cryoglobulins.

It usually presents with weakness and fatigue (80-90%), purpura (70-90%), arthralgia (40-60%), and frank arthritis in less than 10%. In 20% of affected individuals fulminant presentation in the form of glomerulonephritis and systemic vasculitis can also occur. Neurological manifestations include distal sensory or sensory motor polyneuropathy. Central nervous system involvement occurs in 20 % of the patients in the form of epilepsy, stroke or cognitive involvement [5].

In a French study of 36 cases of Type I cryoglobulinemia, skin or vasomotor symptoms were seen in 75% cases and nephropathy was seen in 30% cases [6]. In another study of 153 cases of cryoglobulinemia, renal involvement was seen in 29% cases. Majority of them (65%) had type II cryoglobulinemia [7]. A recent study from Hong Kong studied the clinical profile and renal outcome was studied in patients with diagnosed cryoglobulinemia. It was found that patients who had cryoglobulenemia secondary to hepatitis B had worse renal outcome compared to Hepatitis C and paraproteinemias [8]. The detailed work-up and treatment should be tailored based on the clinical presentation. HCV infection is commonly associated with the presence of either type II or type III cryoglobulins without any obvious

vasculitis symptoms. Strong clinical suspicion should be raised for those patients who present with purpura or arthralgia with an evidence of hypocomplementemia.

Cryocrit levels do not have a consensus reference range. Normal level of cryoglobulin is 2–5 mg/dL. The normal cryocrit level should be near to zero and level >1% is said to be clinically significant. The cryocrit level in Type III is between 1-3% and in Type II mixed cryoglobulinemia its around 2–7%. Failure to maintain warm temperature can result in cryoglobulin precipitation at the bottom of the collection tube and the supernatant serum would not yield any cryoglobulins resulting in false negative results [9].

Therapeutic management is thus based on the severity the underlying disease. Presence of cryoglobulins in the absence of any clinical symptom warrants close watch. Addition of low to moderate doses of glucocorticoids will help in relieving mild symptoms like arthralgia and purpura. Cold exposure should be avoided in order to prevent cryoglobulin precipitation. Angiotensin converting enzyme inhibitors are used to reduce intraglomerular filtration pressure and proteinuria, if at all present.

Early initiation of treatment with immunosuppressive therapy viz., Rituximab or Cyclophosphamide and pulsed high dose corticosteroids is required in order to prevent production of new cryoglobulins. It is essential in life threatening and rapidly progressive disease which includes pulmonary haemorrhage, nervous system vasculitis, gastrointestinal haemorrhage, and skin necrosis so that the disease can be stabilised [1]. Plasmapheresis is a very promising strategy in preventing impending renal failure [10]. Replacement fluid for plasmapheresis should be warmed.

CONCLUSIONS

Even though cryoglobulinemic vasculitis is a rare cause of systemic vasculitis, it is very important that clinicians are aware of overall disease process, diagnostic options and treatment modalities available in order to avoid the mortality and morbidity associated with it. A high index of suspicion and a simple bed side test could help us in arriving at a diagnosis for early initiation of effective therapy. Since immunosuppressive agents remain the main stay of treatment, it is very important to consider the reactivation of latent infections such as hepatitis B.

SUPPLEMENTARY INFORMATION

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Conflicts of Interest: *The authors declare no conflicts of interest.*

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