CASE REPORT

Small Vessel Vasculitis: A Rare Presentation

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Abstract:

Mixed Cryoglobulinemia (MC) is a rare disorder and often causes diagnostic dilemma. Cryoglobulinemia is of 3 types according to Brouet Classification. Types 2 and 3 are known as MC as type 2 is a mixture of polyclonal IgG and monoclonal IgM associated with viral infection and type 3 consists of polyclonal IgG, associated with systemic lupus erythematosus. Cryoglobulins must be differentiated from cryofibrinogen which precipitates only in plasma and not in serum. Immune complex deposition leads to cryoglobulinemic vasculitis. Females are more commonly affected that males. The case presented here, had recurrent episodes of anemia, painful rashes, pedal swelling with subsequent renal dysfunction which ultimately responded to intravenous steroids and rituximab. Hepatitis C Virus (HCV) infection was ruled out twice during the hospital visits. Skin biopsy and bone marrow biopsy and detection of cryoglobulins clinched the diagnosis. The importance of the case lies in the fact that MC, though a rare disorder, should not be missed in the diagnosis and it should be remembered that HCV negative cryoglobulinemic vasculitis has poor prognosis and may be refractory to treatment.

Keywords: Mixed Cryoglobulinemia, vasculitis, Hepatitis C Virus

Introduction:

Cryoglobulins are proteins that are not soluble and they usually precipitate at temperatures which are below the normal body temperature and dissolve back after rewarming, in the serum. They are immunoglobulins or a combination of complements and immunoglobulins [1]. They must be differentiated from cryofibrinogen which consists of fibrinogen, fibrin, fibrin split products and fibronectin. When plasma and serum of the patient are refrigerated at 4^0C for a period of 72 hours, the proteins forming the precipitate are called the cryoglobulins. Precipitation of cryofibrinogen occurs only in plasma and not in serum.

Cryoglobulinemia may be of 3 types according to immunological composition:

1. Type 1 - Monoclonal immunoglobulin (IgM>IgG, IgA, light chains) associated with lymphoma, Waldenstrom's macroglobulinemia and multiple myeloma
2. Type 2 - Monoclonal immunoglobulins with Rheumatoid Factor (RF) activity
3. Type 3 - Polyclonal RF

Types 2 and 3 are MC associated with infections such as hepatitis C, autoimmune diseases, lymphoproliferative disorders or is idiopathic (rare) which is also called essential cryoglobulinemia. Chronic Hepatitis C Virus (HCV) infection was the commonest association with mixed cryoglobulinemia.

The small vessel eukocytoclastic vasculitis is the hallmark of Cryoglobulinemic Vasculitis (CV) [2]. Cryoprecipitation and increased blood viscosity are also important apart from immune complex activation [3]. We present an interesting

case of type 2 CV presenting with recurrent episodes of painful rashes and dyspnea.

Case Report:

A 66 year old female presented with reddish rashes with swelling in both lower limbs for 10 days with breathlessness for 5 days. There was past history of similar lesions, 6 months earlier, which were self-resolving. C-reactive Protein (CRP) was 114 mg/L, Erythrocyte Sedimentation Rate (ESR) was 100. Hemoglobin was 8.8 g/dl, creatinine and urine examination were normal. Echocardiography revealed moderate Mitral Regurgitation (MR), Tricuspid Regurgitation (TR) and severe Pulmonary Arterial Hypertension (PAH) with grade 2 diastolic dysfunction. Diuretics, nitro-glycerine infusion, intermittent Bilevel Positive Airway Pressure (BiPAP) was used for treatment, after which patient improved and was discharged with nitroglycerine, trimetazidine and diuretic. Ten days after discharge, patient presented with breathlessness and bilateral lower limb swelling. Rashes were painful, generalized, but more in the lower limbs. Hemoglobin dropped to 5.3 g/dL. There was proteinuria, occasional Red Blood Cell (RBC) in urine, creatinine was raised (2.2 mg/dl) and Antinuclear Antibody (ANA) Indirect Fluorescent Antibody (IFA) and Antineutrophil Cytoplasmic Antibodies (ANCA) were negative. Two units of packed RBCs were transfused and patient was discharged 6 days after admission with 15mg steroid which was tapered over next 15 days. She again attended hospital 15 days later with the same symptoms and decrease in urine output (oliguria for the last 3 days prior to admission) without any cough, hemoptysis or orthopnoea. Patient was tachypnoeic with pulse 98/min and BP-150/100 mm Hg. There was severe pallor and bilateral pitting edema. Macular erythematous painful rashes were present more in the lower limbs with blackish discoloration without ulceration. Examination of the chest revealed bilateral vesicular breath sounds, diminished in intensity with diffuse crepitation. Cardiology examination revealed pan systolic murmur at apex with P2 loud. ESR 138 mm (1st hour), CRP- 113 mg/dl. Urine revealed protein + puscells- 8-10/hpf, RBC- 6-8/hpf, WBC- 5-7/ hpf, LDH- 274 mg/dl, Ferritin-652 ng/ml later 998 ng/ml, LFT normal, Calcium-9.2 mg/dl, Hepatitis B, C, ANA and ANCA were negative. No M band was detected on SPEP, very thin IgM band with lambda component was detected on immunofixation. IgM scrub typhus and dengue IgM antibody were positive, while leptospira antibody was negative. A diagnostic skin biopsy and bone marrow biopsy was done. Skin biopsy revealed focal hyper keratosis and follicular plugging in epidermis, lymphoplasmacytic infiltrates around blood vessels in the dermis, no staining for IgM, IgG, IgA and C3. Bone marrow revealed hyper cellular marrow with mild erythroid hyperplasia with nonspecific reactive changes. Cryoglobulin and cryofibrinogen test was done among which cryoglobulin was positive, RF- 900 IU/ML, C3-41 gm/l, C4- 12 gm/l. HCV was negative once again. Unlike, type1 cryoglobu-linemia, the cryoglobulins in types 2 and 3 contains rheumatoid factor which is an auto antibody. The key test for mixed cryoglobulinemia is blood test. When a blood sample is taken, its temperature is 37^0C. The sample is stored in a water bath to mimic body temperature. After 3 days, the sample is spun in the centrifuge, to separate out the cells. If cryoglobulinemia is present, it forms a white precipitate that re-dissolves on warming. Type 2 is associated with polyclonal IgG and monoclonal IgM in 40-60% of cases and is associated with viral

infections. IgM dengue was positive in this patient. Diagnosis was CV type 2 (Table 1). Treatment was done with IV steroids and Rituximab therapy after which the patient was lost to followup.

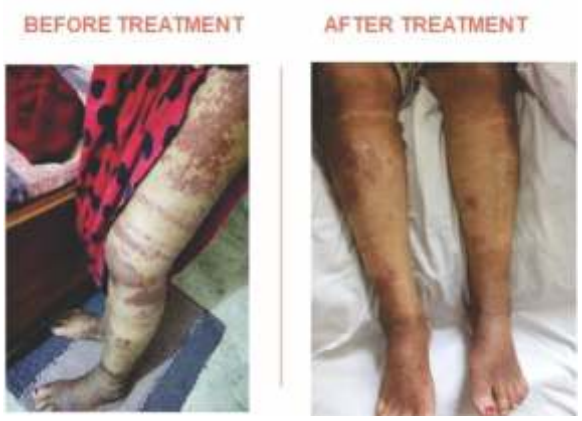

Fig. 1: Showing Before Treatment and After Treatment

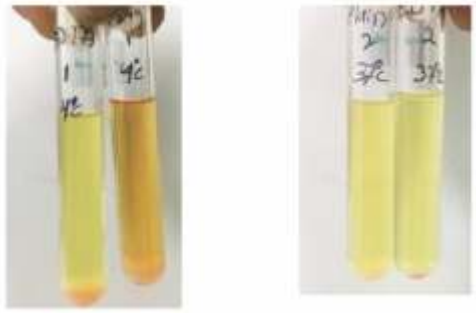

Fig. 2: Showing Tests after 3 Days of Incubation

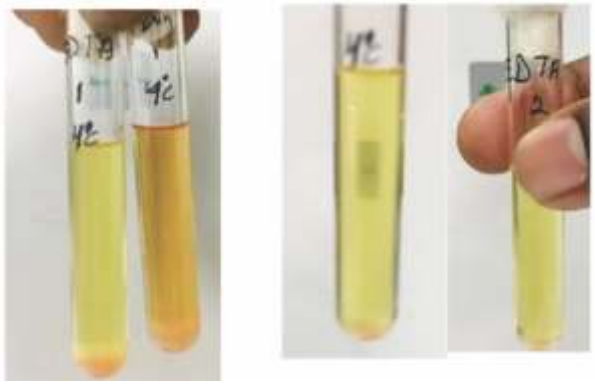

Fig. 3: Showing Tests after Rewarming

Table 1: Clinical Features of Cryoglobulinemia

Signs and Symptoms	Type 1	Type 2	Type 3
Purpura	+	+++	+++
Gangrene / Acrocyanosis	+++	+/++	+/-
Arthralgia > Arthritis	+	++	+++
Renal	+	++	+
Neurologic	+	++	++
Liver	+/-	++	+++

Discussion:

MC is a rare disorder posing challenges in diagnosis and treatment. The case presented here had recurrent symptoms of painful rashes, breathlessness with subsequent development of renal dysfunction and worsening of anemia. After extensive investigation and multiple episodes of treatment, patient improved and was referred to the rheumatology clinic. MC prevalence is approximately 1:100000 with a female to male ratio of 3:1 [4]. Prognosis and survival depend on kidney involvement. Prognosis depends on underlying disease with better prognosis in chronic HCV infection with antiviral therapy than in patients with lymphoproliferative disease, renal disease or plasma cell disorders [5]. Treatment should be done according to treatment of small vessel vasculitis. In severe disease, glucocorticoids, pulse cyclophosphamide with or without plasmapheresis is recommended. Methotrexate may be used in mild cases [6]. To define remission, Birmingham Vasculitis Activity Score (BVAS) may be used [7-

9]. Rituximab use was also documented in a case report of cryoglobulinemic vasculitis [10]. Other examples of small vessel vasculitis with ANCA positivity are Wegener's Granulomatosis [11] which is confused with tuberculosis due to overlapping clinical features [12]. It is a rare and severe form of systemic vasculitis.

Conclusion:

MC is a rare disorder. The patient discussed here presented with recurrent symptoms of rashes, limb swelling and breathlessness with renal involvement and a diagnosis of type 2 CV was made after exclusion of other causes of vasculitis and cryoglobulins. The importance of the case lies in the fact that being a rare disorder, prompt diagnosis and treatment is required for the survival of the patient and to also remember that prognosis is worse in non HCV related cryoglobulinemic vasculitis which may also be refractory to the treatment.

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How to cite this article:

Maiti J, Maitra S, Sarkar S. Small Vessel Vasculitis: A Rare Presentation. *J Krishna Inst Med Sci Univ* 2021; 10(2):161-164

Submitted: *01-Feb-2021* ***Accepted:*** *20-Mar-2021* ***Published:*** *01-Apr-2021*