Case Report

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An Unusual Case of HCV Negative Cryoglobulinemia Presenting as Symmetrical Peripheral Gangrene

Internal Medicine Section

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ABSTRACT

Cryoglobulins are monoclonal or polyclonal immunoglobulins that undergo reversible precipitation at low temperatures. Cryoglobulinemia is associated with HCV infection in more than 90% cases, the remaining 10% being called as Essential Cryoglobulinemia which is generally associated with a severe course and suboptimal response to conventional therapies. As the digital vessels are more prone to colder temperatures, hyperviscosity in those vessels can initiate local thrombosis and may manifest as ischemic ulceration and gangrene. We report here a very unusual case of HCV negative cryoglobulinemic vasculitis presenting as symmetrical peripheral gangrene of fingers and toes.

Keywords: Acronecrosis, Essential mixed cryoglobulinemia, Symmetrical digital gangrene, Vasculitis.

CASE REPORT

A 60-year-old male presented to the Department of Medicine of MKCG Medical College with complaints of sudden onset, severe localized pain over the distal part of fingers and toes of both the hands, feet and tip of the nose. The hands were affected more than the feet, right hand more than the left, 2nd and 3rd digits more than the rest of the fingers [Table/Fig-1]. The pain gradually increased in intensity over the last two days, did not subside by analgesics and was associated with sensation of pins and needles over the affected parts. He also complained of joint pain over bilateral knee, ankle, distal interphalangeal and metacarpophalangeal joints of hand.

There was no history of fever, intake of ergotamine drugs or beta blockers, any insect bite, or living at high altitude at any point of time. There was no history of diabetes, hypertension, peripheral vascular diseases, respiratory ailment, rheumatoid arthritis, Raynaud's phenomenon or any other connective tissue disorders. He was not a smoker.

General physical examination was unremarkable. Pulse was 84/minute, regular and all peripheral pulses were well felt. Blood pressure was 130/80 mm Hg. Systemic examination was also normal except for decreased touch, pain and temperature sensation over the tips of fingers and toes. The affected parts revealed a cold, cyanosed distal phalanx of both hands and feet. Allen's and Adson's tests were negative.A provisional diagnosis of symmetrical peripheral gangrene was made.

Complete haemogram along with peripheral smear revealed dimorphic anemia [Table/Fig-2]. Coagulation studies as well as liver and kidney function were within normal limits except for a raised alkaline phosphatase level (545 IU/L) (Reference range: 110-310 IU/L) [Table/Fig-3]. Urine routine and microscopy was normal. Serum antibodies against malarial parasite, HIV, Hepatitis B and Hepatitis C virus were absent. C- Reactive Protein (CRP) and Rheumatoid factor were positive.

[Table/Fig-1]: Symmetrical peripheral gangrene affecting fingers and toes.

Antinuclear antibody (ANA) came out to be positive (47.2)(Positive = >23 IU/ml). Anti ds- DNA, anti Smooth muscle Ab, anti Scl-70 were negative. Complement studies revealed a normal C3 levels (110 mg/dL) (Reference range: 88-252 mg/dl) and low C4 levels (8 mg/dL) (Reference range: 12-72 mg/dl). Bone marrow aspiration study revealed hypercellular marrow with no evidence of metastatic deposits or leukemia. Reactive plasma cells were increased in number.

Serum was then evaluated for the presence of cryoglobulins (qualitative) which revealed presence of cryoglobulins in the sample. Serum electrophoresis showed diffuse increase in gamma globulin and a normal albumin, alpha and beta bands which was suggestive of Type III Cryoglobulinemia. Bone marrow biopsy and skin biopsy were normal.

Serological studies for cytomegalovirus, Brucella and Epstein-Barr as well as Mantoux and serial blood cultures were negative. The

Parameter Tested	Test Values	Reference Range
Haemoglobin (Hb)	7.8 g/dl	11.0-15.5 g/dl
Red Blood Count	2.95 lacs/ µL	3.5-5.5 lacs/ µL
Mean Corpuscular Volume (MCV)	70.8 fL	60-90 fL
Mean Corpuscular Haemoglobin (MCH)	22.4 pg	27-32 pg
Mean Corpuscular Haemoglobin Concentration (MCHC)	31.6 g/dl	30-35 g/dl
Total Leuckocyte Count (TLC)	10,500/ µL	4000-11,000/ µL
Total Platelet Count (TPC)	0.9 lacs	1.6-4.0 lacs/ µL
Erythrocyte Sedimentation Rate (ESR)	150 mm in 1st hour	0-22 (M) 0-29 (F)
Differential count		
Neutrophil	78	40-75
Lymphocyte	21	20-45
Eosinophil	01	01-06
Monocyte	00	02-10
Basophil	00	00-01

[Table/Fig-2]: CBC reports.
Comment on peripheral smear (CPS) Dimorphic anemia with neutrophilia

Parameter Tested	Test Values	Reference Range
BLEEDING TIME	5 minutes 10 seconds	3-9 minutes
CLOTTING TIME	4 minutes 30 seconds	2-6 minutes
PROTHROMBIN TIME	12 seconds	11-13.5 seconds
PT-INR	1.2	0.8-1.2
Sr UREA	39 mg/dl	10-50 mg/dl
Sr CREATININE	0.9 mg/dl	0.6-1.4 mg/dl
Sr SODIUM (Na+)	133 meq/L	135-145 meq/L
Sr POTTASSIUM (K+)	4.3 meq/L	3.5-5.5 meq/L
Sr BILIRUBIN (TOTAL)	1.5mg/dl	Upto 1 mg/dl
Sr BILIRUBIN (DIRECT)	0.7 mg/dl	Upto 0.2 mg/dl
Sr SGOT	51 IU/L	Upto 40 IU/L
Sr SGPT	45 IU/L	Upto 40 IU/L
Sr ALKALINE PHOSPHATE	545 IU/L	110-310 IU/L
Sr PROTEIN	6.6 mg/dl	6.6-8.0 mg/dl
Sr ALBUMIN	2.8 mg/dl	3.5-4.0 mg/dl

[Table/Fig-3]: Investigation reports.

remaining studies such as abdominal ultrasound, echocardiogram, chest radiography and ECG showed no abnormality.

A provisional diagnosis of HCV negative Mixed Cryoglobulinemia (MC) (TYPE III) was made and patient was put on oral steroids prednisone 40 mg once daily and underwent plasmapheresis. The symptoms slightly improved with this treatment. Although he was planned for Anti CD-20 monoclonal antibody Rituximab therapy, the patient was subsequently lost to follow up.

DISCUSSION

Mixed Cryoglobulinemia (MC) is a relatively rare entity with an etiology not yet adequately explained. It is known that Hepatitis C virus (HCV) infection plays an important causal role, but the contribution of genetic factors and/or environmental factors is controversial [1,2]. HCV infection has been recognized as the cause of about 90% of cases of Mixed Cryoglobulinemia [3]. There is no evidence of HCV infection in approximately 10% of the population with Mixed Cryoglobulinemia (MC). Several diseases have also been shown to play an etiologic role in some cases of HCV-negative MC e.g., connective tissue diseases (mainly systemic lupus erythematosus, Sjögren's syndrome, and systemic sclerosis) and lymphoproliferative disorders (in most cases B-cell non-Hodgkin lymphoma). Fewer than 5% patients with cryoglobulinemia show no identifiable underlying diseases and they are therefore considered as having "essential" MC [4].

In terms of clinical manifestations, these can range from a relatively benign course, to dramatic complications that might endanger the life of the patient. The common presentations include palpable purpura, systemic symptoms, arthralgias, lymphadenopathy, hepatosplenomegaly, peripheral neuropathy, hypocomplementemia, bronchiolitis obliterans, glomerulonephritis, Raynaud's phenomenon, lividoreticularis and acrocyanosis, as well as ulcers and necrosis of the skin [1,2]. The severe skin involvement seen in our patient occurs in only about 2% of cases and is due to vasculitis with fibrinoid necrosis and inflammation of the vessel wall and perivascular space which can evolve into a chronic ulcer and gangrene [5,6].

The highlight of this case is the presentation of one of the few cases of MC [7] associated with no underlying disease (non-HCV), being therefore essential. Such cases generally have an abrupt clinical presentation and poor response to conventional therapy including plasmapheresis, immunosuppressive medications like steroids, azathioprine and cyclophosphamide. There has been only a handful of cases that have responded favourably to Anti CD-20 monoclonal antibody Rituximab and Anti TNF antibody Infliximab [8,9].

CONCLUSION

In conclusion, cases presenting with symmetrical peripheral gangrene can have a varied etiology ranging from infections both bacterial and viral; connective tissue disorders like systemic lupus erythematosus, polymyalgia rheumatica, antiphospolipid antibodies, cryoglobulinemia; malignancies like Hodgkin's lymphoma, acute lymphatic leukemia, small cell carcinoma of lung; cardiovascular diseases like myocardial infarction, hypovolemic shock, heart failure, pulmonary embolism; drugs such as adrenaline, noradrenaline, dopamine and many others. Prompt clinical suspicion and judicious investigations are warranted to avoid mistakes in the diagnosis. Currently there is absence of a clear consensus about appropriate management of cases presenting with HCV negative Cryoglobulinemia and further studies are warranted in this direction.

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