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HCV Induced Cryoglobulinemic Vasculitis - Diagnostic Difficulties in Suburban India - A Case Based Review

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Abstract: ***While HCV vasculitis with mild symptoms is a fairly common presentation, cryoglobulinemia with renal impairment causing the death of a patient is not a very commonly encountered scenario in everyday clinical practice. Here we present an engrossing case of an elderly woman who was referred with bilateral lower limb swelling, acute renal impairment secondary to suspicious sepsis with no response to multiple antibiotics. There were also complaints of arthralgias and severe neuropathic pain. Routine screening for viral markers came out positive for HCV. Examination findings of purpura and Raynaud's phenomenon lead to clinical suspicion of cryoglobulinemic vasculitis. Serum complement levels were decreased, Anti- Nuclear Antibodies came back positive along with Rheumatoid factor. While awaiting the biochemical confirmation of cryoglobulins, the patient deteriorated even after starting on high dose steroids. We lost the patient during the course of treatment due to renal failure, poor general condition, and late presentation to the hospital.***

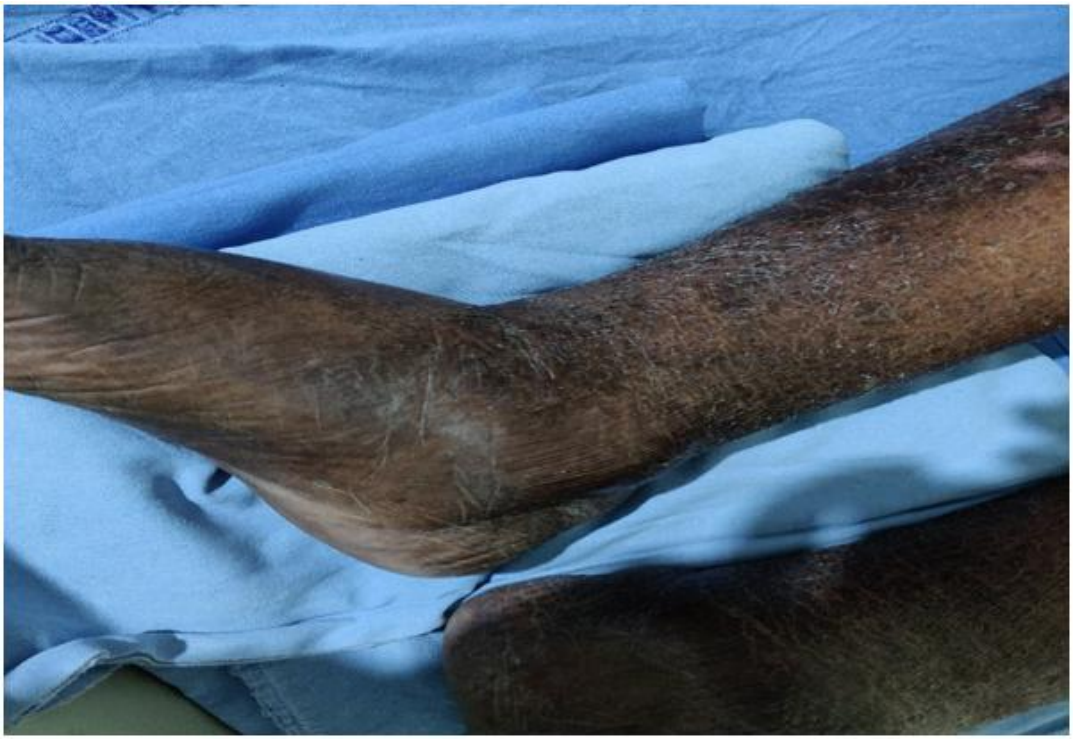
Keywords: HCV vasculitis, Cryoglobulinemia, Purpura, Raynaud's phenomenon, Anti-nuclear antibodies, Rheumatoid factor, Renal failure

1. Introduction

Hepatitis C virus globally infects over 170 million people annually and is a leading indicator of liver transplantation. One of the under-reported extrahepatic manifestations is mixed cryoglobulinemic vasculitis. It is characterized by deposition of immune complexes containing RF, IgG, HCV RNA, and complement on the endothelium of small and medium-sized vessels eliciting an inflammatory response. Here we present a case of MC with a grave presentation.

2. Case Report

A 77-year-old female was referred to our center after multiple hospitalizations with bilateral lower limb swellings, fever diagnosed as sepsis with renal impairment. Routine screenings for viral markers came back positive for HCV with cirrhotic changes in ultrasound and Acute Renal impairment. The patient had a history of arthralgias, neuropathic pain, and generalized weakness. On evaluation- purpuric rash onboth lower limbs was noted.



Bluish discoloration of upper limb digits was noted with cold exposure. This lead to suspicion of CTD- likely HCV induced cryoglobulinemic vasculitis. HCV belonged to genotype-1a and viral load was very high (14795112). Rheumatoid factor was strongly positive. So, ANA, C3, C4 was sent, and pulse doses of Methylprednisone were started as there was no diagnostic facility for cryoglobulins testing. ANA was weak positive along with a disproportionate decrease of C4 than C3. Skin biopsy was suggestive of leukocytoclastic vasculitis. Nevertheless, the patient's

general condition deteriorated further given declining renal functions, so Rituximab was avoided, and plasma exchange was planned. We lost the patient during the treatment course.

3. Discussion

Definition

Cryoglobulins are monoclonal or polyclonal Immunoglobulins that undergo reversible precipitation at low temperatures. Cryoglobulinemia is the presence of cryoglobulins in blood.

According to Brouet, cryoglobulinemia is classified as follows:

Type	Composition	Common disease association
Type 1	Monoclonal IGs	Lymphoproliferative disorders like MM, Waldenstorm Macroglobulinemia, MGUS.
Type 2	Monoclonal IG- usually IgM RF and Polyclonal IgG	Most commonly seen in HCV.
Type 3	Polyclonal IG that is usually IgM and Polyclonal IgG.	HCV and other connective tissue disorders like SLE, Sjogren syndrome.

Type 2 and 3 are classified under Mixed Cryoglobulinemias (MC).Agne

Chronic HCV is the most common cause of mixed cryoglobulinemia (80-90%) cases. Prevalence of MC was higher with increasing apparent duration of the disease and the presence of cirrhosis. The female gender may predispose towards Mixed Cryoglobulinemia, although this association is not strong. Studies proved that only 2-15% of patients with cryoglobulins would develop symptoms. Our patient was amongst this unfortunate category and developed severe systemic consequences.

Pathology

The exact mechanism is unknown, but it is hypothesized that chronic HCV infection triggers B-cell activation, resulting in the expansion of peculiar B-cell clones. Furthermore, the resultant Igs, particularly polyclonal IgG along with HCV RNA and complement, precipitates and deposits on the vascular endothelium and triggers vasculitis. HCV MC vasculitis primarily affects small and medium-sized vessels of the skin, kidneys, and peripheral nerves. Histology reveals leukocytoclastic vasculitis and fibrinoid necrosis of the vessel wall intima, which was evidenced in this patient.

Clinical Manifestations

In 1966, Meltzer described the clinical triad of palpable purpura, arthralgias, and weakness in Mixed Cryoglobulinemia, which is seen in almost 80% of patients. The above-discussed patient also classically exhibited this triad and strengthened our clinical suspicion. Other manifestations include peripheral neuropathy, most commonly as mononeuritis (58%), renal involvement (20%), and Reynaud's phenomenon (36%). Renal involvement is usually Type 1 Membranoproliferative Glomerulonephritis, and it frequently incurs a poor prognosis. Manifestations can range from isolated proteinuria to nephrotic syndrome and chronic renal insufficiency. This female patient's renal insufficiency progressed very quickly.

Diagnosis

Typically, diagnosis is made from the history, typical clinical manifestations, and lab detection of serum cryoglobulins. Laboratory tests that suggest the presence of cryoglobulins in the blood are a positive Rheumatoid factor seen in two-thirds of patients, along with hypocomplementemia with low C4 levels and normal or mildly decreased C3 levels.

Treatment

As two-thirds of HCV cryoglobulinemic vasculitis patients present with a benign course, removing the antigenic stimuli with newer antivirals will suffice. A flare-up or renal involvement as in the above-discussed patient indicates severe disease and poses challenges as antivirals in this condition may further exacerbate the underlying condition.

Severe Cryoglobulinemic vasculitis should be treated with pulse doses of steroids and Rituximab at 375mg weekly for four weeks or one gram every two weeks. We initiated this patient on Methylprednisone, which she initially tolerated very well. However, she developed steroid-induced psychosis within four days.

In life-threatening conditions where high levels of cryoglobulins with a proportionate decrease in C4, plasma exchange on alternate days to decrease cryoglobulin load coupled with Rituximab is being tried in a few tertiary care centers. That being said, we tried to start our patient on plasma exchange, but she could not tolerate it well and landed into hypovolemic shock, and we could not retrieve her and lost her.

Diagnostic Difficulties

Though cryoglobulins can cause devastating clinical consequences, they are present in only minor quantities in serum (100- 300 mg/dl) compared to normal serum proteins (60,000- 80000), posing a multitude of difficulties in isolation.

Large sample volume is needed.

Analysis is slow (3-7 days).

There are no standards and controls.

Laboratory personnel lack experience in interpreting the electrophoretic patterns and quantitative results as they do not frequently encounter testing for cryoglobulins.

Above all, lack of facilities that can handle the sample and analyze at various temperatures, and financial implications of patient limited testing in this case.

4. Conclusion

1) Early initiation of antivirals decreases the frequency of Cryoglobulinemia which is not routinely practiced in Suburban India.

2) High clinical suspicion in seropositive HCV patients regarding cryoglobulinemia helps in early initiation of required management.
3) Strengthening of diagnostic facilities and training of healthcare personnel will help in early intervention.

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