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CASE REPORT

A Case of Hepatitis C Related Mixed Cryoglobulinemia Syndrome

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Abstract

Hepatitis C virus (HCV) is an RNA virus that preferentially infects hepatocytes and is transmitted through infected blood contact. Chronic hepatitis C can result in serious life-threatening conditions like fibrosis, cirrhosis, and liver cancer. Additionally, it can result in extrahepatic conditions including lymphoproliferative disease and mixed cryoglobulinemic vasculitis.

Mixed cryoglobulinemic vasculitis occurs as a result of immune system dysfunction leading to immunoglobulin deposits into different blood vessels in the body. The main manifestations commonly seen are purpura, weakness, arthralgias. Other symptoms include peripheral neuropathy, arthritis, vasculitic skin ulcers, liver, and renal involvement.

This case highlights a 57-year-old male with a medical history of substance use disorder, bilateral lower extremity ulcers, and chronic hepatitis C infection who presented with complaints of bilateral lower extremity wounds, abdominal distension, and scrotal swelling.

Our patient was confirmed to have new-onset cirrhotic liver secondary to intravenous drug use, with worsening renal function. Further investigations confirmed the diagnosis of mixed cryoglobulinemia secondary to hepatitis C virus.

Keywords: Mixed cryoglobulinemia, Cirrhosis, Hepatitis C, Substance use disorder

1. Introduction

Chronic Hepatitis C infection has been strongly linked and associated with glomerular diseases. Some of these diseases include mixed cryoglobulinemia, membranoproliferative glomerulonephritis (MPGN), membranous nephropathy, and polyarteritis nodosa (PAN). One of the major diseases associated with HCV infection is mixed cryoglobulinemia. Most patients with mixed cryoglobulinemia tend to have HCV infection, with evidence suggesting that HCV-containing immune complexes are responsible for the pathogenesis of this disease. Our case report highlights a patient with a chronic history of HCV and developed mixed cryoglobulinemia.

2. Case presentation

A 57-year-old male with a past medical history of substance use disorder, bilateral lower extremity ulcers, chronic hepatitis C infection for 6 years, and poor compliance with medical care presented to the ED with complaints of abdominal distention and scrotal swelling. The patient reported that symptoms started two weeks before his presentation and had progressively worsened. Patient also complained of bilateral non-healing lower extremity wounds which he had for a year. In terms of the hepatitis C, it was diagnosed six years prior to this presentation. Patient denied being on any treatment plan, with no adequate follow up with any physician. On examination, the abdomen was grossly distended with positive fluid wave, suggesting ascites. There was a 3+ pitting edema extending from the scrotum to the bilateral lower extremity ulcers with draining a foul-smelling purulent discharge. The lower extremity ulcers had sparce open lesions each noted to be superficial with fibro-granular wound beds, with mild odor, and serous discharge noted.

Initial vital signs revealed a temperature of 98.7 F, BP 129/70 mmHg, Pulse 71 bpm, RR 18 breaths per

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minute with oxygen saturation of 100%. Labs revealed hemoglobin of 12.1 g/dl (Normal: 12–16 g/dl) with platelet count of 78 K (Normal: 130–400 K). Urinalysis revealed large blood with 0–2 RBCs, negative nitrite, trace leukocyte esterase with 0–2 WBCs, and 100 mg/dl protein. A repeat urinalysis revealed large blood with 2–4 RBCs, positive nitrite, trace leukocyte esterase with 0–2 WBCs, and >300 mg/dl protein. CMP showed creatinine of 4.3 mg/dl with a baseline creatinine of 0.8 mg/dl a year prior, and BUN 55 mg/dl. A CT abdomen and pelvis confirmed a new-onset cirrhotic liver with abdominal ascites (See Fig. 1). A hepatitis panel was ordered, and it was negative for hepatitis A, and B, but positive for Hepatitis C virus. HIV was also negative. The patient was started on Furosemide, Octreotide, and Nadolol. He also received antibiotics and his wounds were managed.

The next day, the patient developed leukopenia with WBC of 4.5, with worsening hemoglobin and platelet count of 11.1 g/dl and 47 $\times$ 10^9/L respectively. His renal function continued to worsen with creatinine 4.76 mg/dl, and BUN 63 mg/dl. Patient underwent ultrasound-guided paracentesis, with 1.5 L of fluid removed. A renal ultrasound was performed which showed nonspecific increased echogenicity. His ascites and lower extremity ulcers improved significantly on the treatment regimen however, renal function continued to decline precipitously.

Given worsening renal function and cirrhosis, a possible diagnosis of the hepatorenal syndrome was made. Patient was started on Albumin infusion with no significant improvement in renal function. Hence, the nephrology team was consulted, and a renal biopsy was recommended. Patient was started on dialysis and the renal biopsy was subsequently performed.

Renal biopsy results showed mild focal mesangial proliferative glomerulonephritis with co-dominant deposits of IgA and C3. Serum complement levels were also low with C3 of 66 (normal: 82–185), C4 count of 11 (normal: 15–53), and low total complement levels <10 (normal: 31–60). Patient had HCV viral load count of 156,000 IU/mL and HCV genotype of 1a. Serum cryoglobulin levels were ordered, but due to a lab error it was not resulted. These findings, together with the patient's clinical presentation, suggested a picture of mixed cryoglobulinemia secondary to HCV over hepatorenal syndrome as the cause of the patient's presenting symptoms. Patient was managed with Methylprednisone 1 g IV for 3 days and discharged with a plan for outpatient hemodialysis three times per week, as well as outpatient gastroenterology follow up to initiate Hepatitis C virus treatment. Patient was also encouraged to follow up outpatient to start treatment with Rituximab.

After being discharged from the hospital, patient was noted to have followed up with his dialysis appointments. We also scheduled the patient with our medicine clinic for a visit. Prior to the scheduled time of his clinic visit, the patient was called to confirm his appointment by a clinic staff. A family member responded to the call and confirmed that the patient passed away due to suspicions of drug overdose.

3. Discussion

Cryoglobulinemia refers to the presence of proteins or cryoglobulins in the blood. They are immunoglobulins that are known to precipitate at low temperatures (below 37C) and redissolve on rewarming. They are usually classified into 3 types; Type 1 which causes hyper viscosity from levels of single monoclonal cryoglobulin due to

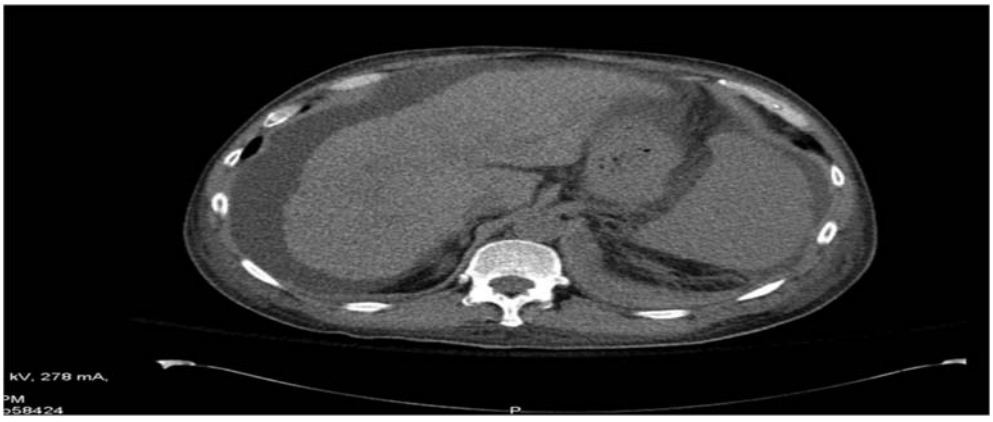

Fig. 1. CT Abdomen: Showing cirrhotic liver with abdominal ascites.

Table 1. Classification of Mixed Cryoglobulinemia.

Criteria	Major	Minor
Serologic	Mixed cryoglobulins	Rheumatoid factor
	Low C4	HCV+
		HBV+
Pathologic	Leukocytoclastic vasculitis	Clonal B-cell infiltrates (liver or bone marrow)
Clinical	Purpura	Chronic hepatitis
		Membranoproliferative glomerulonephritis
		Peripheral neuropathy
		Skin ulcers

lymphoproliferative disorders, and type II and III, which are referred to as mixed cryoglobulins, and can be as a result from chronic hepatitis C or connective tissue disorders.[1]

Mixed cryoglobulinemia refers to cryoglobulins in the serum that contain more than one immunological component.[2] The main symptoms seen in mixed cryoglobulinemia includes purpura, weakness, arthralgias, also known as the Meltzer's triad. Other features could include peripheral neuropathy, Raynaud's phenomenon, arthritis, vasculitic skin ulcers, liver and renal involvement.[2] In terms of diagnosing this, light microscopy will show a membranoproliferative pattern of injury which is secondary to the deposition of immune complexes. Electron microscopy highlights endocapillary proliferation with subendothelial deposits, and immunofluorescence will show depositions of immunoglobulins such as IgM, IgG, and C3.[3] Our patient was seen to have weakness, purpura, skin ulcers, with both pathological liver and renal involvement.

Several studies have shown a possible relationship between HCV and mixed cryoglobulinemia, yet the potential role and pathogenesis on how these conditions are associated has not been fully studied. Thus, concluding information are yet to be made on this topic.[4] According to a study done by Lunel et al., they reported a higher prevalence of mixed cryoglobulinemia in France in HCV positive patients, which was associated with a long history of hepatitis and the presence of liver cirrhosis.[5] Just as in this case presented, our patient was diagnosed with Hepatitis C at least 10 years before presenting with mixed cryoglobulinemia.

Diagnosing mixed cryoglobulinemia depends on both clinical and laboratory findings. Laboratory findings should include cryoglobulin testing, total serum protein and immunoglobulins, complement levels, virologic markers such as hepatitis panel, blood chemistry and urinalysis. The Italian Group for the Study of Cryoglobulinemia proposed a set of criteria necessary for diagnosing and classifying mixed cryoglobulinemia[6] (see Table 1).

Mixed cryoglobulinemia (MC) can be managed with immunosuppressive drugs, steroids, and plasmapheresis, but these therapies are ineffective in allowing for long-term remission. Interferon a (INF-a) is the choice drug for managing MC, and this shows an indirect proof between the association of mixed cryoglobulinemia with hepatis C virus infection, and the results of IFN treatment in MC patients represent an indirect proof for the pathogenetic link between MC and HCV infection.[7]

In addition to treating the associated underlying disease (when present), patients who have one or more of these manifestations should be treated with immunosuppressive therapy to rapidly improve or resolve target-organ damage, rather than therapy directed at the underlying etiology alone. Immunosuppressive therapy usually combines a short course of glucocorticoids with rituximab and, in selected patients, plasmapheresis.[1] Our goal with our patient is to have him follow up with the required specialist outpatient to start him on the right therapy to improve his health. While a relationship can be seen between hepatitis C, membranous glomerulonephritis and mixed cryoglobulinemia, more studies need to be done to prove a causal relationship.

4. Conclusion

This case illustrates a rare cause of systemic organ damage and particularly, renal function loss in patients with chronic hepatitis C infection. A high degree of suspicion and early treatment could prevent permanent kidney damage and lifelong hemodialysis.

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