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Mixed Cryoglobulinemia as a Potential Indicator of Clinically Silent Hepatitis C Infection

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Abstract

Hepatitis C virus (HCV) is one of the major causes of chronic liver disease and its prevalence is increasing worldwide. There are many extra hepatic manifestations of Hepatitis C infection including B –cell lymphoproliferative disorders. Mixed cryoglobulinemia (MC) is the most common prototype of B-cell lymphoproliferative disorders. Cryoglobulinemia is an immune complex mediated disease causing multi organ damage with vasculitis being the primary manifestation. We report a case of 50-year-old female having clinically silent chronic liver disease secondary to hepatitis C who presented to us with a purpuric skin rash, joint pains and fatigue. She was confirmed to be a case of mixed cryoglobulinemia. The patient was prescribed direct antiviral agents and prednisolone which improved her condition to a great extent. Heightened awareness of cutaneous manifestations of MC associated with HCV might improve the detection rate of clinically silent HCV infection.

Keywords: Cryoglobulinemia, Hepatitis C, vasculitis, chronic liver disease

1. Introduction:

Mixed Cryoglobulinemia (MC) can be defined as the presence of large amounts of circulating antibodies called cryoglobulins in blood which can clump together with cold temperature and re-solubilize when heated (1). The generation of these antibody titers by B-lymphocytes indicates an underlying lymphoproliferative disorder, which can be attributed to various causes, including an infection with hepatitis B virus (HBV), hepatitis C virus (HCV), or HIV, a hematological malignancy like multiple myeloma, or an autoimmune disease such as systemic lupus erythematosus (SLE) or Sjögren's syndrome (1-4). Immune complexes are formed and deposit in systemic blood vessels which triggers a vasculitic process that ultimately leads to damage to organs. Patients with mixed cryoglobulinemia frequently present with lethargy, joint and muscle pains, and a skin rash but many patients can be asymptomatic (7). Mixed cryoglobulinemia is a clinicopathological diagnosis that requires the presence of both characteristic clinical features (skin purpura,

symptoms of organ damage from leukocytoclastic vasculitis) and serological evidence (raised cryoglobulins, low complement C4 levels) on laboratory investigation (8). Workup involves evaluating for an underlying etiology. It frequently includes viral serology for HCV and HBV and an autoimmune screen with Anti-nuclear antibody (ANA), anti-double stranded DNA antibody (Anti-dsDNA), anti-smooth muscle antibody (ASMA), serum complement and rheumatoid factor (RF) levels. A CBC, urinalysis and bone marrow biopsy (if indicated) might also be ordered to rule out hematological malignancy as a potential cause (9). Early diagnosis and prompt treatment can improve the prognosis of MC and prevent the development of severe complications. For cryoglobulinemia associated with an identifiable etiology, management largely focuses on treating or controlling the underlying cause, such as anti-virals for hepatitis C, steroids for SLE and chemotherapy or stem cell transplant for multiple myeloma. MC is associated with morbidity and mortality if left untreated. There is a spectrum of complications and organ dysfunction that can result from vasculitic damage to the skin, kidneys, liver, lungs, heart and brain. Some complications that have been reported include skin ulcers, nephritic and nephrotic syndromes, pneumonitis and pulmonary hemorrhage and a variety of CNS disorders, such as peripheral neuropathy (12-15). We report a case of a 50 year-old woman presenting to us with arthralgias and a skin rash. Workup revealed mixed cryoglobulinemia and moderate cirrhosis.

2. Objectives for case reporting:

To enhance the clinical knowledge and diagnostic approach of physicians regarding clinically silent hepatitis C, particularly in rare cases where it may present only as a skin rash. To review the latest guidelines in the management of mixed cryoglobulinemia due to hepatitis C.

3. Case report:

A female of Asian descent presented to the outpatient department of our hospital with complaints of a skin rash that had been progressing gradually over the last four months. The patient reported feeling increasingly fatigued during this duration and felt like she couldn't do her household chores as easily as before. A review of systems revealed mild abdominal discomfort and occasional pins and needles sensation in the feet. The patient was diagnosed with diabetes 10 years ago and taking metformin daily but had not seen a physician for the last couple of years. On general physical examination, palmar erythema was noted. There was purpura on the hands and forearms as shown and described in figures 1-2. Pedal edema was also present bilaterally. On respiratory examination, patient had normal vesicular breathing bilaterally. Heart sounds were normal with no added sounds. Abdominal examination was unremarkable with no visceromegaly. Neurological examination revealed decreased pin prick sensation in the feet.

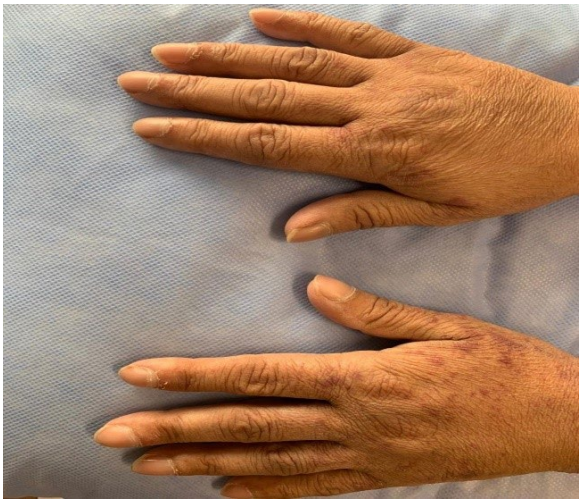

Figure 1

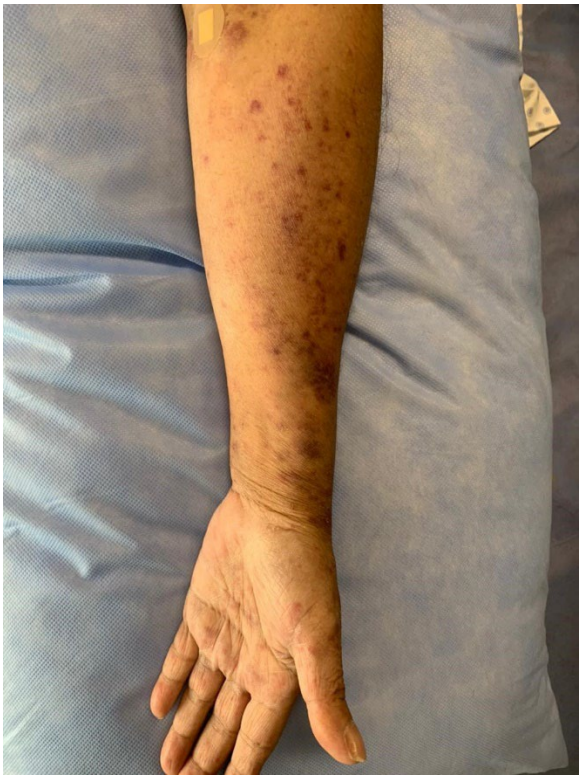

Figure 2

Figure 1-2. Violaceous and erythematous macules can be noted on dorsum of right hand and the right forearm

Table 1. Laboratory Values		
Investigation	**Result**	**Normal Range**
TLC	8500	4000-1000 cells/ µL
Hb	11.5	12.0 - 15.5 g/dL
PLT	175000	150000 - 450000 /µL
Cr	1.0	0.6 - 1.2 mg/dL
Urea	25	7 - 20 mg/dL
Na	141	135 - 145 mmol/L
K	3.5	3.5 - 5.1 mmol/L
ALT	301	7 - 56 U/L
AST	284	13 - 39 U/L
ALP	135	44 - 147 U/L
HbA1C	8.5	4.0 - 5.6 %
Blood counts, renal profile and serum electrolytes are within normal range. HbA1C indicates poor glycemic control. Transaminases are elevated indicating liver injury. Total leukocyte count (TLC), hemoglobin (Hb), platelets (PLT), creatinine (Cr), sodium (Na), potassium (K), alkaline phosphatase (ALK), transaminases (ALT and AST).		

CBC, LFTS, RFTs and HbA1c were ordered. The results are shown in table 1. A hepatocellular pattern of injury was noted on LFTs and further workup was planned to ascertain the cause. Viral serology and autoimmune profile with Antinuclear (ANA) and Anti smooth muscle (ASMA) antibodies were obtained. Autoimmune profile was normal, but ELISA was positive for HCV infection with PCR showing a very high viral load of 896,321 IU/mL in high thousands. A detailed history was undertaken to trace the source of infection. The patient had not received any blood transfusions. She had a history of visits to a local vendor for dental procedures that might have been a source of acquiring the infection.

Table 1. Blood counts, renal profile and serum electrolytes are within normal range. HbA1C indicates poor glycemic control. Transaminases are elevated indicating liver injury.

An abdominal ultrasound showed early liver parenchymal changes with coarse echotexture indicating early cirrhosis. Mild ascites was also present. Cryoglobulin levels were raised two to three- fold. A primary diagnosis of chronic hepatitis C infection and a secondary diagnosis of mixed cryoglobulinemia was made. After obtaining informed consent, the patient was admitted to the hospital for three days of pulse therapy with intravenous methylprednisolone, administered at a dose of 1 gram once daily. She

was discharged on oral prednisolone 1mg/kg with oral steroids and direct acting antiviral therapy with sofosbuvir 400mg once daily, daclatasvir 60mg once daily and ribavirin 600mg once daily. Her symptoms improved in a few months with clearing of the rash and steroids were tapered off gradually.

4. Discussion:

Pakistan has one of the highest frequencies of hepatitis C in the world with an estimated overall prevalence of 8.64% (16). Most cases of hepatitis C result in a chronic infection with an insidious course for many years, until the liver has been damaged significantly (cirrhosis) to produce signs and symptoms. Hence, it is appropriately named as a silent disease. Hepatitis C is associated with considerable morbidity and mortality. Timely diagnosis not only allows for treatment of patients before the development of chronic liver disease, but can also help to prevent transmission and decrease the overall disease burden in the population.

While mixed cryoglobulinemia (MC) can be a manifestation of various conditions, hepatitis C virus (HCV) infection is the most common underlying cause. MC is present in over 50% patients with chronic hepatitis C (17). In our patient, a normal autoimmune profile and a normal complete blood picture ruled out autoimmune disease or hematological malignancy as a cause of cryoglobulinemia, so it was most likely a manifestation of her chronic hepatitis C infection. Even though she did not have severe manifestations of cryoglobulinemia, a targeted workup led to the timely diagnosis of a much more serious infection with hepatitis C in early stages of liver cirrhosis.

The presentation of mixed cryoglobulinemia MC can vary widely from mild and asymptomatic to severe and life threatening. Meltzer and Franklin's triad comprising of (arthralgias, purpura and weakness) was first described in 1966 to highlight the common symptoms with which patients present with cryoglobulinemia. However, Meltzer's triad has limited clinical sensitivity, occurring in only 33% of patients (18). In contrast, the most frequent manifestation of cryoglobulinemia is a skin rash (7). Dermatological disorders associated with mixed cryoglobulinemia range from purpuric macules and erythematous papules to crusts and ulcers, which most commonly appear on the legs (19). Purpuric lesions, when present in MC, can range from small pinpoint petechiae (less than 3 mm in diameter) to larger ecchymotic areas, which may be several centimeters in diameter. It's important to note that the size of purpuric lesions is a variable characteristic, and individual cases may exhibit different patterns. The clinical appearance and distribution of purpuric lesions can depend on factors such as the severity of the underlying condition, the presence of associated complications, and the specific characteristics of the patient. In our patient, the most prevailing symptom was diffuse purpura on the hands and forearms. While repeated episodes of purpura often lead to stable confluent discoloration in many patients, our case exhibited non-coalescing purpuric lesions. To sum up, our case underscores the significance of recognizing diverse dermatological presentations, particularly purpura, as valuable indicators for initiating more sensitive testing in suspected cases of cryoglobulinemia. As stated already, peripheral neuropathy can be one of the complications of cryoglobulinemia. Our patient exhibited signs and symptoms of peripheral neuropathy; however, she was diabetic, so it is debatable whether it was due to prolonged diabetes or cryoglobulinemia.

Treatment of MC is patient specific and depends on the severity of symptoms and extent of organ damage in patients. Treatment, where required, is associated with improved survival rates (20). While patients with mild symptoms do not require intervention, those with moderate to severe disease manifestations can benefit from immunosuppressive therapy with cyclophosphamide and corticosteroids (7). The main goal of treatment, however, is to treat the

cause. For patients with MC associated with HCV, treatment of HCV with direct acting anti-viral therapy is the main objective, which results in simultaneous improvement of MC in most cases. In severe and refractory cases, Rituximab has been reported to induce remission (21). Our patient showed a good response to direct-acting antiviral therapy, incorporating sofosbuvir, daclatasvir, and ribavirin for hepatitis C. The PCR results after 6 months revealed a significant reduction in viral load, decreasing from a value in high-thousands before treatment to an undetectable level (SVR <15 IU/mL) at the 6-month follow-up. For MC, she was treated with pulse therapy during a short hospital stay and then continued on oral prednisone which was tapered off after her symptoms improved in a couple of months. We believe that both the treatment of her chronic hepatitis C infection and concurrent steroid therapy lead to the resolution of her symptoms of MC. The patient was advised to maintain regular follow-up appointments at the outpatient clinic to monitor for HCV reinfection and possible recurrence of MC.

5. Conclusion:

Heightened awareness of the cutaneous manifestations of mixed cryoglobulinemia might significantly improve the detection rate of clinically silent hepatitis C infection.

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