Unusual Extrahepatic Manifestations of Hepatitis C Infection

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How to cite this article:
Mohindra R, Ghai S, Negi NS et al. Unusual Extrahepatic Manifestations of Hepatitis C Infection. *J Adv Res Med* 2016; 3(1): 31-34.

ISSN: 2349-7181

Introduction

Hepatitis C infection is a global health problem affecting 3% of the world's population.[1] In addition to causing liver diseases like cirrhosis and carcinoma, hepatitis C infection has been associated with wide variety of extrahepatic manifestations with multitude of disease processes affecting the small vessels, skin, kidneys, salivary glands, eyes, thyroid gland and immunologic system. The majority of these conditions are thought to be immune-mediated. Other HCV-associated entities include porphyria cutanea tarda, lichen planus, necrolytic acral erythema, membranous glomerulonephritis, diabetic nephropathy, B-cell non-Hodgkin lymphomas, insulin resistance, sialadenitis, sicca syndrome and autoimmune thyroiditis. However, multiple extrahepatic manifestation of hepatitis C in a single patient have never been reported till now. Here we are reporting one such case of Hepatitis C with multiple rare extrahepatic manifestations.

Case Report

A 17-year-old male presented to us with history of swelling of body, beginning from the face and progressing to generalized anasarca over one month associated with decreased urine output. He had similar complaints off and on for the last 4 years.

There was no history of fever, burning micturition, hematuria, dysuria, joint pains, rashes, allergy or atopic reaction, loose motions, hematemesis, malena, alcohol addiction, smoking, etc.

In the past, he had a history of fall from height about 6 years back for which he was hospitalized, was given IV injections and also received a blood transfusion but no records were available with the patient. There was also history of one episode of jaundice which lasted for 15 days about 6 months following that hospitalization. At that time, the patient did not take any treatment. He is a non-vegetarian by diet and belongs to lower socioeconomic class as per the modified Kuppuswamy scale.

On examination, facial puffiness and pedal edema were present. No pallor, icterus, cyanosis, clubbing, significant peripheral lymphadenopathy was seen. JVP was not raised. His blood pressure was normal. Chest examination revealed diffuse bilateral crepitations and occasional ronchi. On abdominal examination, shifting dullness was present but no dilated veins, scar marks, tenderness or organomegaly were clinically appreciable. Examination of the other systems was essentially normal.

Investigations showed Hb-14.6 gm%, TLC-13,600, DLC-$P_{40}L_{32}E_{27}M_1B_0$, Absolute Eosinophil Count-1632, ESR-78.5mm in 1st hour, platelet count-3.24 lac/mm^3, peripheral smear showed eosinophilia with no abnormal cells. However, other secondary causes of eosinophilia were ruled out by history, examination and a negative stool examination for ova and parasitic cysts.

Blood urea-18 mg%, serum creatinine-0.6mg%, serum sodium-140 mmol/L, serum potassium-5.2 mmol/L, serum calcium-5.8 mg/dL, serum phosphate-3.5 mg/dL. Routine urine examination showed albumin 4+ with no RBCs or pus cells or casts. Urine culture was sterile after 48 hours of incubation. 24-hour urine protein was high

(3.8 gm/24 hour). Lipid profile was deranged with total cholesterol-220 mg%, HDL-34.6 mg%, LDL-161.8 mg%. Serum bilirubin-0.6 mg/dL, SGOT-19 IU/mL, SGPT-12 IU/mL, serum proteins-3.2 gm% with low albumin-1.4 gm%. Ascitic fluid analysis showed 30 cells (predominantly mononuclear) and protein was 0.6 mg/dL suggesting transudative nature.

His serological markers revealed a positive anti-HCV while HIV, HbsAg, ANA, pANCA, c ANCA were all negative. Mantoux was also negative. USG abdomen/ KUB showed mildly enlarged kidneys with mild ascites.

Chest X-ray showed minimal infiltrates in upper lobe of right lung. CECT chest/ abdomen was done which showed opacity in the right upper lung with 'tree in bud' appearance, multiple-mediastinal and mesenteric-lymphadenopathy with renal parenchymal disease with ascites.

Mediastinal lymph node biopsy showed non-specific changes. There was no evidence of any granulomas. AFB staining was negative. Renal biopsy was also done which showed sclerosed glomeruli with mild glomerulomegaly in some glomeruli with focal mild increase in mesangial cellularity suggestive of focal segmental glomerulosclerosis (FSGS). Immunofluroscence studies of the biopsy specimen showed weak positivity for IgM and C3 which was negative for IgA, IgG, C1q and fibrinogen which also suggest focal segmental glomerulosclerosis.

The patient was treated with diuretics, ACE inhibitors, Diethylcarbazine and statins. The edema reduced and the urine output improved. The absolute eosinophil count was still raised (1042) despite treatment. Further investigations like HCV genotyping and RNA levels were advised.

Discussion

Multiple extra-hepatic manifestations of HCV have been reported like cryoglobulinemia, cutaneous vasculitis, MPGN, EMC, etc. Chronic HCV infection can potentially cause chronic kidney diseases. Both glomerular and tubulointerstitial diseases associated with HCV have been described.[2-6] The most common renal manifestations of HCV infection are essential mixed cryoglobulinemia (EMC) leading to membranoproliferative glomerulonephritis (MPGN),[7] MPGN without cryoglobulinemia and membranous glomerulonephritis. Although MPGN is most commonly associated with HCV infection, other glomerulonephritides are also reportedly associated with HCV, including membranous nephropathy, focal segmental glomerulosclerosis, postinfectious glomerulonephritis, thrombotic micro-angiopathies, IgA nephropathy and fibrillary or immuno-tactoid glomerulopathy.[8] The pathogenesis is still unclear. It is postulated that cryoglobulins are circulating immunoglobulins that precipitate with cold temperature and resolubilize when warmed. In type-II cryoglobulinemia, the cryoglobulins are composed of two or more classes of different immunoglobulins; of which one is a monoclonal IgM component with rheumatoid factor-like activity.[9] Expansion of rheumatoid factor synthetizing B cells represents the biological hallmark of MC.[10] Many organs including the skin, gastrointestinal tract and kidney may be involved. Our patient was diagnosed as focal segmental glomerulosclerosis (FSGS). Only few case reports for FSGS in hepatitis C patients are available.[11-12.] Our patient had developed nephrotic syndrome with proteinuria of 3.8 gm/24 hrs. Renal biopsy showed sclerosed glomeruli with increased mesangial cellularity and immunofluroscence studies were positive for IgM and C3, both suggestive of FSGS. The mechanism of FSGS in hepatitis C patients is also not clear. Whether this is due to increased viral damage in areas of underlying glomerular damage or due to immunomodulation in hepatitis C that augments underlying glomerular injury, is not known.

Early after its discovery, it was shown that HCV is also a lymphotropic virus [(13).] As a consequence of the lymphatic infection, several lymphoproliferative disorders (LPDs) have been associated with this virus,[14] including B-cell non-Hodgkin's lymphoma (NHL)[15-22] and monoclonal gammopathies. Sustained HCV-driven antigenic stimulation has been suggested to play a key role in inducing B-cell clonal expansion characterizing these disorders.

There is a possible role of proteins of the HCV envelope and mainly on HCV E2 protein. It has been shown that E2 interacts with the tetraspanin CD81, present also on the B-cell surface. This binding has been suggested to be responsible for sustained polyclonal B-cell activation essentially by lowering the B-cell activation threshold.[23-24] The association between viral infection of peripheral blood mononuclear cells (PBMCs) and the presence of LPDs was initially shown in patients with MC, where more evident infection of PBMCs in comparison with HCV-positive patients without MC was observed. HCV infection was then observed by Galli et al. in bone marrow cells from all patients with MC versus 43% of patients without MC.[25] Other mechanisms include chromosomal aberrations, recruitment of cytokines and chemokines Th1 cytokine profile IFNγ and TNFα, MIP-

1α, MIP-1β, CXCL10, and CXCR3.[26] Our patient had mediastinal and mesentric lymphadenopathy that has been rarely reported in hepatitis C patients.[27] It is postulated that recruitment of HCV infected lymphocytes and macrophages into draining lymph nodes may be the contributing cause. HCV is the stimulus for the apparent benign lymphoproliferative process underlying a wide spectrum of clinical features to frank lymphoid malignancy in patients. Theoretically, B cells and other lymphocytes or monocytes may become infected while circulating in blood or perhaps during passage through liver and then establish local infections within lymph nodes. Another possibility is that HCV infection may spread locally through the lymphatics to lymph nodes, at which time peripheral immune cells might become productively infected prior to recirculation.

Eosinophilic infiltrates in hepatitis C have been previously described in the live.[28] The possible mechanism may be expansion of Th2 type T helper cells → Cytokine secretion → eosinophilia. A dermatology case report with eosinophilic pustular folliculitis[29] and angiolymphoid hyperplasia[30] with eosinophilia have been reported in hepatitis C patients, but this is a first report on a hepatitis C patient with peripheral eosinophilia. A detailed search of literature did not show any case of peripheral eosinophilia due to HCV infection.

Conflict of Interest: None

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Date of Submission: 01st Feb. 2016

Date of Acceptance: 03rd Feb. 2016