Case Report

A case report of chronic hepatitis-C genotype 4c infection: Non-specific symptoms can become contextually relevant in clinical diagnosis

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ABSTRACT

Chronic hepatitis C (CHC) infection is one of the leading causes of liver disease worldwide and its early diagnosis is often considered a challenge because of its non-symptomatic presentation until late disease progression stages. We report the case of a 52-year-old, South-Indian male with CHC genotype 4c infection. We start with the patient's initial presentation 12 weeks before the diagnosis with seemingly non-specific symptoms of pedal edema, purpura, peripheral neuropathy, arthralgia, and recent onset of diabetes mellitus (DM). We then present the employed direct-acting antiviral (DAA) management regimen and the patient's response over the span of 48 weeks. Correlating with observations from recent literature highlighting CHC's extra-hepatic role in inducing cryoglobulinemic vasculitis (CV) and pancreatic dysfunction, we discuss some educational perspectives on how CV and DM-related symptoms may sometimes become contextually specific in clinically suspecting, assessing risk, and warranting CHC screening and diagnostic confirmation.

Key words: Chronic hepatitis C, Cryoglobulinemic vasculitis, DAA therapy

Chronic hepatitis C (CHC) infection is one of the major causes of non-alcoholic cirrhosis, decompensated liver disease, and hepatocellular carcinoma (HCC) worldwide [1]. It has often been termed a "silent killer" owing to the highly asymptomatic and under-diagnosed nature of the disease during its progressive phase [2]. It is caused by an acute hepatitis C virus (HCV) infection progressing (~80% of the time) into a chronic phase [3,4], and through complex viral replication and immune system-mediated pathogenesis causes gradual hepatocellular damage and cirrhosis. Six major HCV genotypes (G 1-6) have been identified so far with different country-specific incidence rates [5], some of which have been associated with an increased risk of HCC (G1) and steatohepatitis (G3). G4 HCV infections constitute ~13% of worldwide HCV infections and its high prevalence has been demographically associated with Africa, the Middle East, and Egyptian territories [6]. In India, CHC infections are predominantly from G1 and G3, while G4 has also been reported [7]. While Interferon-based therapies with or without nucleoside analogs (such as Ribavirin) have historically been first used for the treatment of CHC, recent therapeutic revolutions have enabled the use of direct-acting antivirals (DAAs) to be highly effective in achieving a sustained virological response (SVR) post 12–24-week regimen across different genotypes [8].

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CASE REPORT

A 52-year-old, non-smoker and non-alcohol-consuming male patient of south-Indian origin, presented with complaints of pedal edema, peripheral neuropathy, arthralgia, and hyper-pigmented spots on both feet (Fig. 1) for about 6 months of duration. He first noticed the symptoms while on an antifungal therapy (2 months; Itraconazole 100 mg/day) for recurrent ringworm infection. After noticing mildly elevated serum glutamic-pyruvic and glutamic-oxaloacetic transaminases (SGOT and SGPT: 52/60 U/L) within a liver function test (LFT), the Itraconazole therapy was stopped by the concerned dermatologist, after which he reported that the pedal edema to be initially resolved, but with intermittent flare-ups over the following 6-month duration leading up to his latest visit. Furthermore, during this time, the patient reports noticing hyper-pigmented spots on both feet with frequent "pins-and-needles" sensations and joint pain, at which point he consulted his primary care provider (PCP).

In view of the patient's pedal edema along with a positive previous history of hypertension, the patient's cardiac function was assessed with an electrocardiogram and 2D echocardiography, which were unremarkable.

However, a diabetic-panel investigation revealed an elevated glycosylated hemoglobin (Hb1Ac) of 7.3% and thus was started on metformin therapy (500 mg/day), and pregabalin (75 mg/day) was prescribed for neuropathic symptoms. During a subsequent

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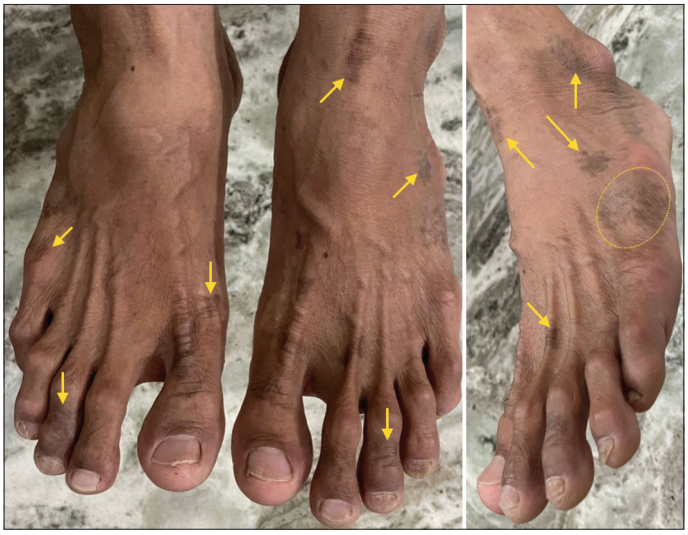

Figure 1: Images of the patient's feet with the highlight of the patchy purpura (yellow markers)

follow-up with PCP after 2 weeks, the patient offered a family history, expressing concern that the patient's mother developed similar hyper-pigmented spots decades ago, which progressed into necrotizing ulcers during her later stages of life. He added about his mother's death in 2017 due to esophageal varices rupture related hematemesis and cardiac arrest due to undiagnosed chronic liver disease. In view of the reported family history, concerned about the possibility of chronic viral hepatitis, the patient was tested for HCV and hepatitis B virus antibodies which came out to be positive and negative, respectively, and the patient was referred for expert intervention.

Upon examination, the patient had mild bilateral pitting pedal edema with variable-sized, patchy hyper-pigmented purpura on both feet. All other system examinations were unremarkable. An LFT was performed, which indicated mildly elevated SGOT (72 U/L) and SGPT (65 U/L). An HCV viral load using real-time polymerase chain reaction (RT-PCR; Taqman probe) revealed a log (viral load [IU/mL]) ~ 6.03 and sequencing using 3500 DX genetic analyzer identified a Genotype 4c infection. In addition, retroviral disease testing was done to assess for any coinfections and the patient tested negative. Furthermore, an abdominal ultrasound revealed normal hepatic and portal-vein morphologies. To assess for any liver fibrosis, liver elastography (LE) was performed, and the stiffness score was ~17.4 Kpa indicating substantial scarring and potential cirrhosis. The patient was started on a 12-week DAA regimen of Sofosbuvir/Velpatasvir (400/100 mg/day) and was recommended PCP follow-up for diabetic management with metformin.

12 weeks post an uneventful DAA regimen, a repeat HCV viral load with adjunct LFT was performed, which revealed a factor of 2 increase over the previous viral load value to log (viral load [IU/mL]) ~ 6.34 and marginally elevated SGOT (48 U/L), SGPT (46 U/L), highlighting the failure of the initial DAA therapy to achieve a 12-week SVR. In view of this, the patient was started on a second round of DAA therapy with sofosbuvir/ledipasvir (400/90 mg/day) and ribavirin (1000 mg/day) for 24 weeks, during which the patient's Hb and serum creatine (Sc) were monitored, where the baselines (i.e., before the Ribavirin introduction) were noted at Hemoglobin (Hb) ~14.5 g/dL and Sc ~ 1 mg/dL. At 4 weeks of the DAA+Ribavirin regimen, the patient's Hb and Sc were 11.4 g/dL and 1.25 mg/dL, respectively. In addition, a viral load was acquired which revealed non-detectable amounts (sensitivity <21 IU/mL), indicating a rapid virological response (RVR). Over the next 20 weeks, the patient's Hb and Sc stabilized to be 12.3–12.5 g/dL and 1.1–1.2 mg/dL, respectively. A repeat LE yielded a stiffness score of 13.3 Kpa. The patient's only new-onset complaint during this treatment was constipation and trace amounts of rectal bleeding induced by difficulty in passing stools, for which he was prescribed fiber supplementation and corticosteroid rectal ointment. After the 24-week DAA+Ribavirin regimen, a repeat investigation yielded a non-detectable viral load, indicating a successful complete virological response (CVR) to the treatment. An LFT was also done at this stage, which showed near-normal SGOT (32 U/L) and SGPT (42 U/L). Furthermore, the patient's Hb1Ac was 5.8 % (~12 weeks into the DAA+Ribavirin treatment) at which the PCP prescribed a lower-dose metformin (250 mg/day). Then, the Hb1Ac became 5% at the end of 24 weeks and the PCP recommended to stop the metformin. The patient also reported a subsiding of pedal edema, arthralgia, and peripheral neuropathy at this time. The patient was recommended to follow-up every 12 weeks, where a post-DAA+Ribavirin therapy SVR will be assessed along with regular Alpha Fetoprotein monitoring.

DISCUSSION

Over the past decade, research has uncovered and confirmed the unexpected correlation between HCV and the reversible precipitation (at <37°C) of immune complexes called cryoglobulins, causing cryoglobulinemic vasculitis (CV) in small- to medium-sized blood vessels [9]. As such, CV has been considered one of the most notable extra-hepatic manifestations of CHC/HCV infection, causing anywhere from mild symptoms to sometimes fatal complications (e.g., glomerulonephritis, and systemic vasculitis) [9]. Clinically, purpura (such as in Fig. 1), arthralgia, and peripheral neuropathy are seen in HCV-induced CV as much as 55–90% of the time [9,10]. In the present case, the patient's initial presentation of these seemingly non-specific symptoms, which in retrospect could have been triggered by an underlying CHC-induced CV, played a critical role in directing toward diagnosis and confirmation of CHC. As such, in a clinical setting, it may be worth being cognizant of and up-weighting CV-related symptomatic presentations along with any standard relevant risk factors and family history toward suspecting and warranting further HCV screening and confirmatory testing.

Simultaneously, research studies into the correlation between increased incidence of type-2 diabetes mellitus (DM) in CHC patients have lent support to different HCV-induced pathways of pancreatic beta-cell dysfunction and impairment of insulin secretion/sensitivity [11,12]. In the presented case, the patient had

persistently elevated Hb1Ac (~7%) before responsive therapy with DAA+Ribavirin, after which the Hb1Ac reduced substantially to 5%. While some of this reduction could be attributed to the introduction of metformin therapy itself, it is worth highlighting the RVR and CVR achieved with a 6-log fold reduction in viral load with a simultaneous reduction in the metformin dosage during this overlapping period associated with Hb1Ac reduction. As such, this case aligns with research studies that hypothesize that HCV does not actively lead to beta-cell destruction, and thus a reduction in HCV load leads to an improvement in DM control [12].

Finally, DAA regimens have been shown to yield high pan-genotypic efficiencies (>95%) in achieving SVR, however, globally less-dominant genotypes (such as G4) and especially their related subtypes such as the one reported in this case (4c) have sometimes been associated with lower response rates and DAA failures [6,13]. Our case report indeed reflects on these challenges, as an initial DAA regimen failed and a follow-up DAA+Ribavirin regimen resulted in a RVR and CVR. While G1 and G3 are predominant throughout India, G4 has been reported at a notable level (~14%) in south India [7]. As such, it is worth being cognizant of potential low response or failures among G4 infections (with less common subtypes) from DAA regimens that are successful with dominant genotypes.

CONCLUSION

This case presents educational talking points on how the extra-hepatic symptomatic manifestations of HCV in the form of CV can potentially be an informative risk factor for CHC clinical diagnosis. This report also highlights some resonant points with recent literature on the observed cooccurrence and resolution of DM during the management of CHC.

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