

Seronegative Acute Hepatitis C Mimicking HAART-Induced Hepatotoxicity

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Introduction

A 63 y/o HM with HIV infection presented for a routine follow-up appointment on 01/30/07. The patient reported nausea for 3-4 days and had scleral icterus on exam. He denied vomiting, abdominal pain, pruritus, fever, or chills. A serum chemistry panel obtained on 01/22/07 revealed an increase in AST/ALT levels to 313 and 359 IU/L, respectively. Total bilirubin level was 2.5 mg/dL. Previous transaminase levels in the last year had been within normal limits. A serum chemistry panel was drawn on 01/30/07 to verify results and AST/ALT/bilirubin levels were 1104 IU/L, 684 IU/L, and 2.7 mg/dL, respectively.

PMH: HIV diagnosed 1987; no history of opportunistic infections; mild facial lipodystrophy; sicca syndrome; GERD; secondary syphilis - treated 04/06 RPR trending downward 1:620 ---> 1:32; hyperlipidemia; hypertension.

Past Surgical History: None

Medications on initial presentation: abacavir, atazanavir, tenofovir/emtricitabine, ritonavir, trimethoprim/sulfamethoxazole, vardenafil, atenolol, gemfibrozil, hydrochlorothiazide, multivitamins

Social History: minimal alcohol use; no history of street drug use, transfusion, or tattoos; no recent travel

Sexual History: The patient reports that he is a homosexual male in a monogamous relationship for many years; however, recent syphilis infection suggests other sexual contacts or that patient's partner had other contacts.

Employment: Waiter

Physical Exam: vital signs and physical exam were unremarkable except for scleral icterus and jaundice.

Initial Labs: CBC wnl; RPR = 1:32; CD4 163 (13%); HIV PCR 671 copies/mL; Hep A IgM -; Hep A IgG +; HBSAg -; HBSAb +; HBcAb +; HCV Ab -; HCV PCR and HBV DNA pending.

Date	AST	ALT	Total Bilirubin
10/16/06	35	39	2.2
01/22/07	313	359	2.5
01/30/07	1104	684	2.7
01/31/07	1747	940	5.1
02/01/07	1504	800	5.3
02/02/07	1696	996	7.2
02/03/07	1834	779	6.7
02/06/07	1319	577	12.7
02/13/07	336	272	17.3
02/20/07	315	195	20.4
02/27/07	312	169	12.7
03/09/07	514	303	19.2
04/24/07	428	216	12.0
05/16/07	291	150	5.5

Course of Illness

- ❖ Transaminases levels continued to increase (AST/ALT = 1747/940 IU/L on 01/31/07).
- ❖ With negative hepatitis BSAg and hepatitis C antibody determinations, the initial assessment was drug-induced hepatitis, probably due to HAART.
- ❖ All medications were discontinued.
- ❖ Transaminase levels continued to increase, although at a slower rate.
- ❖ A liver ultrasound performed 02/01/07 showed: normal morphology and echotexture without intrahepatic biliary duct dilation or focal lesions; no ascites; gall bladder normal with several calculi; common duct within normal limits.
- ❖ At a subsequent appointment the following labs returned: HBV DNA < 100 copies/mL, HCV PCR 43 million copies/mL.
- ❖ Thus, the patient had seronegative acute hepatitis C.
- ❖ Although his transaminase levels had decreased, his total bilirubin level continued to rise, peaking at 20 IU/L.
- ❖ A CT of the abdomen done on 02/14/07 revealed a cirrhotic liver with splenomegaly.
- ❖ Liver biopsy performed on 04/10/07 noted grade 2-3/4 and stage 2-3/4 cirrhosis.
- ❖ Apparently, the patient had an underlying asymptomatic cirrhosis of unknown etiology prior to the acute hepatitis C.
- ❖ The total bilirubin level decreased to 12 mg/dL and on 02/27/07 he was restarted on HAART (lopinavir/ ritonavir and tenofovir/emtricitabine).
- ❖ Total bilirubin again spiked to 19 mg/dL.
- ❖ The continued rise in the total bilirubin level was thought to be due to the use of ritonavir, so the lopinavir/ritonavir was switched to fosamprenavir.
- ❖ Urosodiol was initiated in an effort to accelerate bilirubin clearance.
- ❖ The bilirubin level plateaued at 12 mg/dL and the transaminases continue to be approximately 10 x ULN three months after the initial patient presentation.



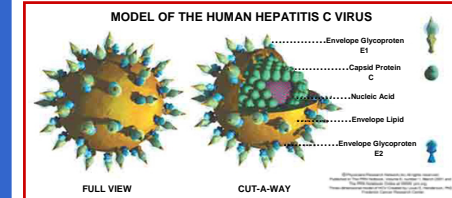
Figure 1. Photograph showing scleral icterus when patient's total bilirubin was 19 mg/dL.

Discussion

HCV infection's primary target is the liver, causing cirrhosis in 20% of those infected. In the US there are approximately 4 million people infected with HCV. Risk factors for HCV infection are: injecting drugs, receiving clotting factors before 1987, hemodialysis, blood transfusion before 1992, accidental needle stick injury and multiple sexual partners. Some individuals have no identifiable risk factors. Eighty percent of persons infected with HCV have no signs or symptoms; however, patients who become symptomatic may develop jaundice, fatigue, dark urine, abdominal discomfort, nausea, and loss of appetite. Symptomatic patients are more likely to have a spontaneous clearance of the virus. However, chronic infection develops in 85% of the cases. All HIV infected individuals should be screened for HCV antibodies and considered for HCV treatment, if viremic.

This patient was diagnosed with hepatitis C in the pre-seroconversion window phase, the time between infection and the detectability of specific anti-hepatitis C antibodies; thus, the patient may manifest signs and symptoms of hepatitis C and have detectable viremia, but has undetectable hepatitis C antibodies.

After infection with HCV, there is a huge inter-individual variation in the time before HCV antibodies become detectable. This diagnostic window phase may last several months, with 82 days as a mean value. The anti-HCV-negative window phase is characterized by a very high HCV replication rate (doubling time for HCV RNA, 10.8 hr) resulting in high viremia.



HCV is now the leading cause of morbidity and mortality in HIV infected patients in the antiretroviral era. Today HCV is the leading indication for a liver transplant. Co-infection with HCV is seen in 15-30% of the HIV infected population in the US. HCV antibody negative, but HCV RNA positive cases exist and are due to the severe cellular immune deficiency, which may result from HIV infection. The response to HCV therapy is dependent on CD4 count. Ideally, treatment should be prescribed only when the CD4 is above 350. Anti-HCV therapy should be deferred in individuals with a CD 4 count < 200 because the response rate is low, and the risk of an OI is high. Co-infected patients tend to have higher HCV viral loads, lower rates of spontaneous HCV clearance, and accelerated liver disease. Patients with decompensated cirrhosis should not be treated for HCV but should be considered for liver transplant.

Patients with hepatitis C treated early in the course of their disease may have a better response to therapy. However, in this patient, treatment has been deferred because of the underlying cirrhosis of unknown etiology, incomplete resolution of elevated transaminases, and CD4 count below 200.

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