CASE REPORT

Acute Hepatitis in an Immunosuppressed Patient: A Dilemma

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Abstract

Acute hepatitis in patients on chemotherapy has always been challenging. Demystifying the truth becomes essential to continue chemotherapy. We present a case of carcinoma buccal mucosa who developed acute hepatitis following a single dose of cisplatin and radiotherapy. In the background of a history of chronic alcoholism, and alcohol abstinence of more than 3 months, acute alcoholic hepatitis was unlikely. Though he had occult hepatitis B with HBsAg negative and positive IgG anti-HBc antibody status, however, with undetectable HBV DNA PCR quantitative, hepatitis B was unlikely to be the cause of acute hepatitis. With all viral markers including atypical viruses and autoimmune work-up being negative, it was a real-time challenge to find the exact cause.

Keywords: Acute hepatitis, Carcinoma buccal mucosa, Cisplatin, Occult hepatitis B, Occult hepatitis C.

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Background

Acute hepatitis is a condition that presents with gastrointestinal symptoms as well as deranged liver functions suggestive of liver injury. Etiological causes of acute hepatitis include viral hepatitis, toxins, drugs, autoimmune liver diseases, infiltrative and metabolic disorders. With rising prevalence of malignancies and need of chemotherapy, acute hepatitis is a major concern in these patients. Liver dysfunction is one of the important causes for drug discontinuation. It is imperative to establish the cause of acute hepatitis for targeted management and resuming the chemotherapy.

Case Report

The index case was a 54-year-old male with a history of smoking, alcohol intake of ~20 g/day for 20 years with his last alcohol intake in July 2021. He had diabetes mellitus and ischemic heart disease for 2 years with coronary angioplasty done in past. The patient was taking oral metformin, linagliptin, aspirin, atorvastatin, metoprolol, and ramipril. Subsequently, in September 2021, he developed a buccal mucosal lesion and a biopsy revealed a well-differentiated squamous cell carcinoma. His baseline hemogram, liver and renal function tests, viral markers including hepatitis B and C were unremarkable. Patient was started on injection cisplatin followed by radiotherapy in September 2021. After 15 days, patient developed jaundice and nonspecific diffuse abdominal pain. He had nausea with decreased appetite. On general physical examination, he had mild icterus with no signs of chronic liver disease. His abdominal examination was unremarkable with no hepatosplenomegaly. On blood investigations, his hemoglobin was 17 g/dL, leukocyte counts 7000/mm^3, and platelet count 315 × 10^3/mm^3. Liver function tests (LFTs) were suggestive of raised liver enzymes AST 245 IU/L, ALT 119 IU/L with normal ALP 130 U/L and GGTP levels. Total serum bilirubin was 1.5 mg/dL, with direct fraction 1.0 mg/dL. Serum albumin was 4 g/dL with normal globulins and albumin-to-globulin ratio. Prothrombin time was within normal limits. Ultrasound abdomen revealed normal liver echogenicity and size with no evidence of chronic liver disease or portal hypertension. All viral markers HBsAg, Anti-HCV, IgM Anti-HAV, IgM Anti-HEV antibodies were negative. Autoimmune workup including ANA by immunofluorescence, smooth muscle antibody (SMA), antimitochondrial antibody (AMA), and anti-LKM1 antibodies was negative. Total IgGs were within normal limits. Patient was screened for occult hepatitis B; his IgG anti-HBc antibodies were positive with undetectable hepatitis B virus DNA on quantitative PCR. Patient was started on tenofovir alafenamide considering immunosuppressive therapy and occult hepatitis B status. However, on follow-up, LFTs were still deranged and on a rising trend (Table 1). All viral screens including atypical viruses such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), and herpes simplex virus (HSV) were found to be negative. Subsequently, in the occult hepatitis C virus screen, hepatitis C viral load was high at 1.63 × 10^6 IU/mL. The corresponding bilirubin was 4.6 mg/dL with a direct fraction of 2.4 mg/dL with AST >15 upper limit of normal (ULN) and ALT >10 ULN. He was immediately started on antiviral therapy with tablet sofosbuvir 400 mg and velpatasvir 100 mg once daily. Interestingly, LFTs normalized within 15 days of starting antiviral therapy (Table 1). The transient elastography showed a liver stiffness measurement (LSM) of 19.4 kPa with an interquartile range (IQR) of 1.6 kPa. His upper gastrointestinal endoscopy was unremarkable with no evidence of portal hypertension. Patient completed 12 weeks of

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Table 1: Laboratory parameters of the patient to time

Variable	*28/8/21 (baseline)*	*1st day*	*8th day*	*21st day*	*Postantiviral therapy*
Hb (g%)	17.2	17.1	16.4	16.2	17
TLC ($\times10^3$/mm^3)	6	6.2	7	6.8	5
Platelets ($\times10^3$/mm^3)	1.3	1.5	1.1	2.2	2.5
Total bilirubin (mg/dL)	1.0	1.0	1.5	4.6	1.4
SGOT (U/L)	50	245	326	694	31
SGPT (U/L)	40	119	283	414	17
ALP (/L)	121	93	118	130	124
Proteins (g/dL)	7.4	7.5	7.3	7.7	7.2
Albumin (g/dL)	4.4	4.8	4.3	4.6	4.2
PT prolongation (seconds)	14.6	17.5	—	17.1	13.3
INR	1.08	1.2	—	1.23	0.9

ALP, alkaline phosphatase; Hb, hemoglobin; INR, international normalized ratio; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; TLC, total leukocyte count

antiviral therapy uneventfully. His LFTs were completely normalized with undetectable HCV RNA on quantitative PCR. His repeat anti-HCV antibodies were still negative at the end of therapy.

Discussion

The current practice for screening hepatitis C infection is done by anti-HCV antibodies in immunocompetent individuals and by serum HCV RNA level detection in immunocompromised persons/patients on chemotherapy/hemodialysis.[1] Anti-HCV antibodies are taken as a marker of present or past infection (resolved spontaneously or on antiviral therapy).[2] Occult hepatitis C virus infection (OCI) has been defined considering exposure and clearance of the virus from the host body. The occult hepatitis C infection means undetectable HCV RNA from serum with virus detected in either/both peripheral blood mononuclear cells (PBMC) and liver. Two types of occult infections have been described in HCV infection: seropositive OCI and seronegative OCI. The seropositive OCI refers to patients with positive anti-HCV antibodies and undetectable HCV RNA levels in serum who had HCV infection in the past resolved with antiviral therapy. The seronegative OCI refers to patients with negative anti-HCV antibodies with undetectable HCV RNA levels in serum who possibly had asymptomatic HCV infection in past with spontaneous clearance of HCV RNA and disappearance of antibodies from serum. In a prospective study over 8 years in patients on multiple transfusions for hemoglobinopathies, Lefrère et al.[3] documented partial or full seroreversion to an anti-HCV negative state in 5 out of 178 patients. They described full or partial seroreversion due to possible three reasons; spontaneous, patients with human immunodeficiency virus (HIV) infection, and induced by antiviral therapy (interferons in their study). In yet another study, Takaki et al.[4] documented decreasing humoral response with persistent cellular immune responses for hepatitis C infection in a cohort of women over 18–20 years. These patients had spontaneous resolution of infection with undetectable antibodies. They also postulated that the incidence of HCV infections that are self-limited and recovered may be underestimated in a general population due to waning or disappearing humoral responses.

Our patient had been screened for HCV in past also. Every time, anti-HCV antibodies ELISA (enzyme-linked immunoassay) was negative. Though the patient was an alcoholic in past, he was abstinent for 3 months. Additionally, his ALT > AST, ALT >15 ULN, 3 months of alcohol abstinence do not support the possibility of alcoholic hepatitis. We had also screened the patient for atypical viruses including HSV, CMV, and EBV. In extended workup, his autoimmune profile was also unremarkable. There are a few reports of mild elevation of serum transaminases with continued cisplatin use which normalizes after drug discontinuation.[5,6] No case related to cisplatin-induced acute hepatitis was found in the literature. Finally, HCV RNA PCR was found to be positive. The corresponding LFTs were deranged suggestive of acute hepatitis. The patient responded well to antiviral therapy with complete normalization of LFTs. We kept a possibility of acute HCV infection or reactivation of occult hepatitis C infection. The patient's history was revisited; however, there was no clue regarding any blood transfusion or IV drug use for HCV transmission in the recent past. Considering acute HCV infection, where HCV RNA appears at a mean of 2 weeks after acquiring infection instead of anti-HCV antibodies which may take 4–6 weeks for appearance; the patient was re-tested for anti-HCV antibodies at the end of antiviral therapy; however, this was still negative. Therefore, a diagnosis of occult HCV infection with reactivation was kept which responded well to antivirals.

Clinical Significance

Diagnosing acute viral hepatitis in the background of alcohol intake and drugs is challenging. The occult hepatitis C and its reactivation on chemotherapy is a forgotten entity that may become relevant in future as we move toward the goal of HCV eradication and we shall have more individuals with disappearing humoral responses.

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