International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Severe Cholestatic Hepatitis in Retroviral Infection

Ravi Shankar Bagepally[1], B Karthik Rao[2], Monalisa Sahu[3], Milap Shah[4], Vamsi Krishna Bodireddy[5], Devasree C. Srinivasulu[6]

[1, 5, 6]Department of Medical Gastroenterology, Yashoda Hospitals, Secunderabad

[2]Department of General Medicine, Yashoda Hospitals, Secunderabad

[3]Department of Infectious Disease, Yashoda Hospitals, Secunderabad

[4]Department of Pathology, Yashoda Hospitals, Secunderabad

Corresponding Author: Ravi Shankar Bagepally
Email Id: *b_ravishankar[at]yahoo.com*
Contact No: +91 - 9391075600

Abstract: ***Cytomegalovirus (CMV) related hepatitis is usually characterized by cytopathic effects on hepatocytes, enlargement of infected cells with cytoplasmic and nuclear inclusions. Intranuclear inclusion have an owl eye morphology. Additional features include mild lobular hepatitis, portal infiltration and micro abscesses. Immunohistochemistry (DDG9 and CCH$_2$ positivity) is used when CMV inclusion are not seen in H and E stain. We present the case of a HIV infected patient with severe cholestatic hepatitis and negative lab evaluation. Liver biopsy was not characteristic of CMV infection but viral load was elevated. Treatment with sequential course of ganciclovir - valganciclovir resulted in a successful outcome.***

Keywords: Cholestatic Hepatitis, CMV infection, Ganciclovir, Plasmapheresis, ART.

1. Introduction

Retroviral infection is a worldwide disease with higher prevalence in certain geographic areas. Till a definite cure could be achieved for this disease, it is likely to cause considerable morbidity and mortality [(1).] The present regimens like Highly Active Anti - Retroviral Therapy can considerably suppress the infection but not to the extent of curing the disease [(2).] In view of immunocompromised status, several infections and diseases are likely to occur in patients with HIV infection [(3).] Hepatitis is a common condition caused by hepatotropic viruses and also by several other causes which are uncommon and rare [(4).] Non hepatotropic viruses and drugs also take a share in the etiology of hepatitis [(5).] Hepatitis is usually a self limited disease but may cause severe manifestations and can lead to fulminant hepatic failure. Despite the present knowledge and available laboratory modalities, some causes of acute hepatitis are difficult to diagnose and the etiology may be multifactorial. Lower sensitivity of diagnostic tests could also be a reason for not being able to pinpoint the exact cause, in a few cases. Herein we present a case of acute cholestatic hepatitis with protracted course in a HIV infected patient responding to treatment for CMV infection.

2. Case Report

A 34 year old male patient with retroviral infection was admitted for severe jaundice. He was evaluated elsewhere before presenting to us and had a negative workup. At presentation he had jaundice with severe cholestatic symptoms. Lab evaluation revealed bilirubin 32.2 mg%; direct 21 mg%, SGOT 53 U/L, SGPT 47 U/L, albumin 3.9 g/dL, serum creatinine 1.30 mg/dL, hemoglobin 14.4 g/dL, WBC 9550, platelets 3.5 lakhs/cumm, prothrombin time INR 1.52; ultrasound abdomen excluded biliary obstruction and viral screen HBV, HCV, IgM HAV, IgM for HEV and herpes simplex I IgM were negative. HIV serology was positive, HIV1viral load was < 72 IU/ml and absolute CD4 count was 328 cells/cumm. Additional tests like AMA, EBV IgM, CMV IgM were negative. His treatment with anti - retroviral drugs constituted of Bictegravir 50 mg, emtricitabine 200 mg and tenofovir alafenamide 25 mg, all of which may be considered as drugs with minimal or no potential for hepatotoxicity. He was on this regimen of drugs for about two years before this presentation.

In view of severe jaundice, ARV medication was stopped and he was given 3 sessions of plasmapheresis (PLEX) for severe cholestatic symptoms. Post PLEX, there was minimal reduction of bilirubin (23 mg %). He was given symptomatic treatment for cholestasis and discharged from hospital.

He was readmitted after 10 days with severe generalized pruritus, weight loss, alopecia, intermittent abdominal pain and deep jaundice. Lab evaluation revealed bilirubin 35 mg%; direct fraction 23 mg%, SGOT 72, SGPT 52, alkaline phosphatase 226, albumin 3.9 g/dL, hemoglobin 12.7 g/dL, white cell count 10, 880 cumm, platelets 4.4 lakh cells/cumm, prothrombin time INR 0.94, absolute CD4 count 212 cells/cumm and HIV viral load 8928 IU/mL; PCR of HSV, VZV, EBV were negative, PCR CMV qualitative was positive and CMV viral load was 470 copies per mL (Table no.1). AMA was negative; MRCP and triphasic CT abdomen did not reveal any abnormality. Liver biopsy was done, and microscopic examination revealed: expanded portal tracts, mixed inflammation, ductular reaction with neutrophilic infiltration, ductular injury and lobules showed extensive canalicular and hepatocellular cholestatis (Fig 1). Viral inclusions and steatosis was not seen; IHC was negative for CMV. As the HIV load increased and the only positive lab evaluation was CMV PCR positivity, he was

reinitiated on ARV (Dolutegravir, Emtricitabine and Tenofovir alafenamide) and intravenous ganciclovir 5mg/kg/IV infusion 12th hourly for 5 days followed by valganciclovir 900mg twice daily for 21 days. He was followed up on regular basis. Symptomatic treatment was provided with Ursodeoxycholic acid, antihistamines and Naltrexone 50mg twice daily. Hyperbilirubinaemia gradually subsided over a month and LFT normalized (Table no.2). Recheck CMV DNA PCR was done and valganciclovir was withdrawn 15 days of negative CMV PCR quantitative reports. There was good improvement in weight, complete symptomatic recovery and pruritus subsided. Treatment with ART was continued and he was followed up.

3. Discussion

Acute hepatitis (AH) is a common condition and usually diagnosed easily. But in a proportion of patients etiology is unclear and even an exhaustive diagnostic work up may not be helpful (Table no.3). The usual work up includes routine hepatotropic viral markers and autoimmune work up; an extended evaluation includes the other viruses, detailed drug history and if needed liver biopsy. Some patients of AH present as cholestatic hepatitis and they tend to have a prolonged clinical course with significant morbidity [6].

Acute hepatitis in Human Immunodeficiency Viral (HIV) infection may be caused by the same etiology as in normal subjects, but there could be some causes particularly specific to HIV infection [6]. Drug induced liver injury (DILI) caused by antiretroviral drugs may be an important if not the only cause of hepatitis in HIV infected patients. Antiretroviral drug related liver injury (ARLI) is a common cause of significant morbidity in HIV infected patients (Table no.4). Any HIV infected patient developing hepatitis should be evaluated in detail for etiology and the most important could be viral infections affecting liver or various drugs used in the treatment. The ARLI may be due to different mechanism (Table no.5) and also may vary in the presentation based on the duration of drug exposure: early onset (1 - 8 weeks) and late onset (2 - 12 months) [7].

The uncommon viruses that may cause hepatitis are HSV, VZV, EBV and CMV. Our patient lab results revealed a low titer of CMV DNA in the absence of CMV antibody and the histological evidence of inclusion bodies was absent. We treated our patient with ganciclovir and later with valganciclovir and documented loss of viraemia at the time of stopping valganciclovir. The recovery of the patient in terms of general well being and biochemical improvement started after antiviral treatment for CMV. Though the definite evidence of CMV hepatitis could not be documented, there seems to be a definitive response to ganciclovir. In a study by Zhao et al, CMV DNA by PCR was highly valuable in screening CMV infection in HIV/AIDS patients, while detection of blood CMV IgM and CMV IgG level had limited value [9] (Table no.6).

Unfortunately, in our case, liver biopsy did not show any classical intranuclear or intracytoplasmic inclusions. IHC for CMV was also negative. Differential diagnosis for cholestatic hepatic pattern of injury in the present case could be due to systemic infection, cholangitis or drug induced liver injury (DILI). As the clinical situation was worsening ganciclovir was initiated and the response to treatment was good with improvement in liver function. Though the obvious cause for hepatic dysfunction in this patient was not clear, probability of ARLI and CMV hepatitis were considered as the cause of liver dysfunction and was managed with supportive care, antiviral therapy for CMV and modification of HAART regimen ([10]). Presence of lobular inflammation, neutrophil rich infiltration favour systemic infective etiology; and absence of significant eosinophils in the biopsy makes the probability of ARLI less likely (Fig 2).

4. Conclusions

Hepatitis in HIV infected patient needs to be evaluated in detail, but in some situations etiology is unclear and the course protracted with considerable morbidity. In the present case, etiology has been attributed to CMV infection. Absence of other causes, detection of CMV DNA in blood, response to antivirals against CMV gives a considerable support in favour CMV hepatitis. Not finding CMV inclusions by microscopy or IHC positivity may not exclude the possibility of CMV hepatitis.

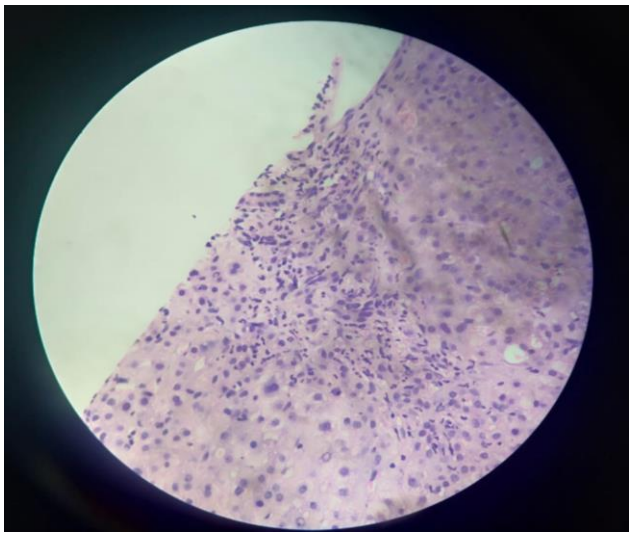

Figure 1: Expanded portal tracts with mixed inflammation and ductular reaction

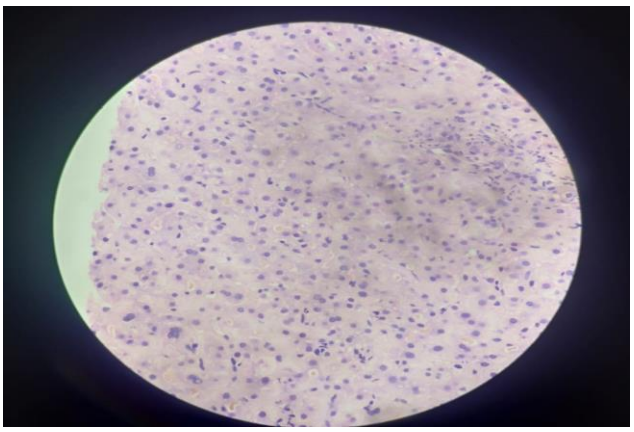

Figure 2: Lobular Inflammation with scattered neutrophils.

No CMV viral inclusions seen

Table 1: Etiological work up

July 2023	August 2023
HBsAg negative Anti HCV negative HIV 1 positive CD4 count 328/cumm IgM HAV negative IgM HEV negative CMV IgM negative HSV IgM negative AMA negative Ultrasound abdomen - Normal MRCP - No biliary disease	HBsAg negative HBV core antibody - negative Anti HCV negative HIV 1 positive CD4 count 214/cumm HIV Quant 8928 IU/ml CMV Qualitative PCR positive CMV Quantitative PCR 470 copies/ml HSV 1 Qualitative PCR negative HSV 2 Qualitative PCR negative EBV Qualitative PCR negative VZV Qualitative PCR negative Liver Biopsy and IHC

Table 2: Liver Function Test

Parameter	July 2023	PLEX 07.08. 2023	17.08 2023	Ganciclovir (D3) 22.08. 2023	26.08.2023	11.09.2023	25.09.2023	10.10.2023
Bilirubin	32	26	35	28	19	9.3	3.10	1.7
Direct	21	20	23	17	17	2.0	0.00	0.0
Indirect	2	1.5	3	3	2	1.27	0.82	0.39
SGPT	47	41	52	57	77	94	52	32
SGOT	53	52	72	89	111	110	49	32
ALP	196	114	226	256	234	214	150	117
Albumin	3.9	3.8	3.9	3.4	3.7	4.1	4.1	4.1
Globulin	3.8	2.6	3.8	4.0	3.6	4.1	3.7	3.4

Table 3: Causes of Acute Hepatitis

Infectious	Non - infecticious
Viral: HAV, HBV, HCV, HDV, HEV, CMV, EBV, HSV, Varicella, Coxsackievirus, Adenovirus, Yellow fever virus, Dengue virus **Parasitic:** Amoebiasis, Toxoplasmosis **Fungal:** Actinomycetes **Granulomatous:** Tuberculosis, Brucellosis	Drug induced AIH Wilsons disease Budd chiari syndrome Alfa 1 antitrypsin deficiency Hepatorenal tyrosinemia Mitrochondrial hepatopathy FA oxidation disorder Alcoholic hepatitis Ischemic hepatitis

Table 4: Classification of Anti retroviral Drugs

Drugs	Hepatotoxic potential
1. Nucleoside reverse transcriptase inhibitors (NRTIs) Zidovudine, Stavudine, Lamivudine, Abacavir, Zalcitabine, Emtricitabine, Didanosine	Zidovudine, Stavudine, Didanosine
2. Non - nucleoside reverse transcriptase inhibitors (NNRTIs) Efavirenz, Nevirapine, Delavirdine, Etravirine, Rilpivirine, Doravirine.	Efavirenz, Nevirapine
3. Nucleotide reverse transcriptase inhibitors (NTRTIs) Tenofovir	—
4. Protease Inhibitors (PIs) Saquinavir, Indinavir, Nelfinavir, Amprenavir, Fosamprenavir, Ritonavir, Lopinavir, Atazanavir, Tipranavir, Darunavir	Ritonavir, tipranavir
5. Entry fusion inhibitors (CCR5 Receptor Antagonists) (PAI) Enfuvirtide, Maraviroc, Vicriviroc, Alpaviroc.	Low
6. Integrase Strand Transfer Inhibitors (INSTIS) Dolutegravir, Raltegravir, Bictegravir, Cabotegravir, Elvitegravir/Cobicistat	—

Table 5: Mechanism of ARLI

- Metabolic post mediated injury.
- Hypersensitivity reactions
- Mitochondrial toxicity
- Immune reconstitution phenomenon
- Drug related hepatic steatosis

Table 6: Diagnosis of CMV hepatitis

Test	Sensitivity	Specificity
IgM CMV	70.7 - 84.4 %	99.3 - 100 %
IgG CMV	-	-
CMV antigen	64 %	81 %
CMV DNA PCR Quantitative (Blood)	61 - 92 %	75 - 99 %
CMV DNA PCR Quantitative (Tissue)	More sensitive than blood PCR	-
Histopathology	Less sensitive than IHC	High
IHC	93 %	91%

References

[1] Fauci AS, Lane HC. Four decades of HIV/AIDS—much accomplished, much to do. New England Journal of Medicine.2020 Jul 2; 383 (1): 1 - 4.
[2] Nishijima T, Inaba Y, Kawasaki Y, Tsukada K, Teruya K, Kikuchi Y, Gatanaga H, Oka S. Mortality and causes of death in people living with HIV in the era of combination antiretroviral therapy compared with the general population in Japan. AIDS (London, England).2020 May 5; 34 (6): 913.
[3] Fleming AF. Opportunistic infections in AIDS in developed and developing countries. Transactions of the Royal Society of Tropical Medicine and Hygiene.1990 Jan 1; 84: 1 - 6.
[4] Jain P, Prakash S, Gupta S, Singh KP, Shrivastava S, Singh DD, Singh J, Jain A. Prevalence of hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis D virus and hepatitis E virus as causes of acute viral hepatitis in North India: A hospital based study. Indian journal of medical microbiology.2013 Jul 1; 31 (3): 261 - 5.
[5] Dancygier H, Dancygier H. Viral infections by nonhepatotropic viruses. Clinical Hepatology: Principles and Practice of Hepatobiliary Diseases.2010: 823 - 30.
[6] Coppola N, Genovese D, Pisaturo M, Taffon S, Argentini C, Pasquale G, Sagnelli C, Piccinino F, Rapicetta M, Sagnelli E. Acute hepatitis with severe cholestasis and prolonged clinical course due to hepatitis A virus Ia and Ib coinfection. Clinical infectious diseases.2007 May 1; 44 (9): e73 - 7.
[7] Soriano V, Puoti M, Garcia - Gascó P, Rockstroh JK, Benhamou Y, Barreiro P, McGovern B. Antiretroviral drugs and liver injury. Aids.2008 Jan 2; 22 (1): 1 - 3.
[8] Otto AO, Rivera CG, Zeuli JD, Temesgen Z. Hepatotoxicity of contemporary antiretroviral drugs: a review and evaluation of published clinical data. Cells.2021 May 20; 10 (5): 1263.
[9] Núñez M. Hepatotoxicity of antiretrovirals: incidence, mechanisms and management. Journal of hepatology.2006 Jan 1; 44: S132 - 9.
[10] APM Annals of Palliative Medicine: Vol 9, No 5 Sep 2020
[11] Da Cunha T, Wu GY. Cytomegalovirus hepatitis in immunocompetent and immunocompromised hosts. Journal of Clinical and Translational Hepatology.2021 Feb 2; 9 (1): 106.