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AUTOIMMUNE HEPATITIS IN HIV: CASE REPORT
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AUTOIMMUNE HEPATITIS IN HIV: CASE REPORT

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SUMMARY

We present a middle aged lady positive HIV who developed liver disease one year after initiation of anti-retroviral therapy (ART). Laboratory and histo-pathology finding supported a diagnosis of autoimmune hepatitis (AIH). She responded well to immuno-suppressive therapy and is currently doing well on maintenance therapy for AIH and the initial ART regimen.

INTRODUCTION

Liver disease is a cause of significant morbidity and mortality amongpersons living with HIV (PLHIV) accounting for about 14-18% of all non-AIDs related deaths (1). Prior to ART, the most common causes of liver dysfunction in HIV-infected patients were opportunistic infections, including cytomegalovirus (CMV), mycobacterium infections, and AIDS-related neoplasms such as lymphoma and Kaposi's sarcoma. However, since the ART-era, the spectrum of liver disease among PLHIV has shifted to concomitant infection with chronic hepatitis C virus (HCV), chronic hepatitis B virus (HBV), medication-related hepatotoxicity, alcohol abuse, and nonalcoholic fatty liver disease (NAFLD) (1).We present a rare cause of liver disease in an HIV infected patient.

CASE REPORT

A 59 year old female was diagnosed with HIV infection at a rural facility in Eastern Kenya in 2008. In September 2014, she was commenced on Tenofovir (TDF), Lamuvidine (3TC) and Efavirenz (EFV). She did not know her baseline CD4 count (at ART initiation) but her CD4 count one year later in September 2015 was 454 cells per mm^3.

In October 2015, she presented to her general practitioner (GP) with a four month history of yellow eyes, nausea and epigastric pain. She was a non-smoker and did not abuse alcohol or other substances. She had not used any new medication (including herbal) in the preceding six months.

Physical Examination: The general examination was remarkable foricteric sclera. The patient did not have edema, enlarged lymph nodes or any stigmata of liver disease such as spider angiomata.
On abdominal examination, the liver span was 10 cm in the mid-clavicular line, with mild tenderness along the entire palpable liver edge. Shifting dullness was absent and the spleen was not palpable.There were no signs of hepatic encephalopathy.

Laboratory Findings: Liver function tests (LFTs) were not done at ART initiation in 2014. LFTs done at the GP's visit on 7/10/15 showed: ALT 437 u/l, AST 2193 U/L, ALP 214 U/L, GGT 508 U/L, Bilirubin total 243 μmol/l, Direct Bilirubin 218 μmol/l. Other findings were: INR 1.63 and albumin 3.76 g/dL.An abdominal ultrasound was normal. The GP made a decision to stop ART on the suspicion of drug induced liver injury (DILI) and referred the patientto our clinic for further management. Table 1 below shows liver function tests done at our clinic at baseline and after five days.

The patient was worked up to assess her immune status, viral suppression and to investigate the liver dysfunction. Her CD4 count was 493 cells per mm^3 and her viral load (HIV) was undetectable. Completeblood count (CBC) and renal function tests (Urea, Creatinine and Electrolytes) were normal. Eyrthrocyte sedimentation rate (ESR) was elevated at 58mm per hour.

Test results were negative for hepatitis A, B and C viruses. The abdominal CT scan was normal.

To further elucidate etiology of liver disease in this patient with HIV infection, serologic tests for Cytomegalovirus, Herpes simplex virus and Epstein barr virus were done and found to be negative. Serum iron studies and ceruloplasmin levels were normal.Other pertinent laboratory findings were: antinuclear antibody (ANA) ,negative; anti–smooth muscle antibody (ASMA) titer, positive 1:40 and IgG level elevated at 2640 mg/dL; Liver kidney microsomal antibody (Anti-LKM), negative; alpha fetoprotein levels (αFP), normal. Magnetic Resonance Cholangiopancreatography(MRCP) was normal. A liver biopsy was done and histology

demonstrated diffuse lobular and sinusoidal active chronic inflammatory cell infiltrate of predominantly neutrophils and lymphocytes. Bile ducts were intact. No fibrosis was noted.

Given the liver histology, laboratory values of markedly elevated transaminases, positive anti–smooth muscle antibody and elevated IgG level, a diagnosis of autoimmune hepatitis was made. The patient had an autoimmune hepatitis score of 14; a score 15 indicates definite autoimmune hepatitis and 10-15 indicates probable diagnosis (2).

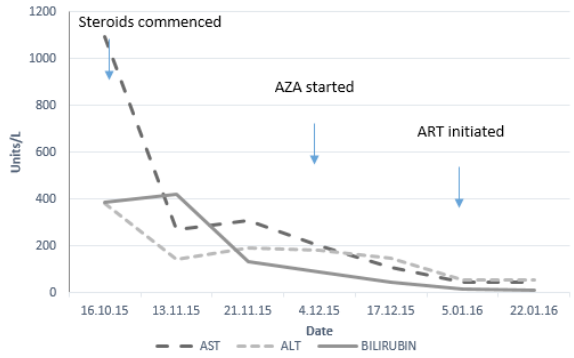
Table 2
Revised Original Scoring System of the International Hepatitis Group

Sex	Female	+2	HLA	HLA DR3, DR4	+1
AP/AST (or ALT) Ratio	>3	2	Immune diseases	thyroiditis, colitis,	+2
	<1.5	+2	others		
ɤ globulin or IgG above normal	>2	+3	Other markers	AntiSLA, Anti	+2
	1.5-2	+2		actin, Anti LC1,	
	1-1.5	+1		pANCA	
	<1				
	0				
ANA, SMA or antiLKM					
titers	>1:80	+3	Histological	Interface hepatitis	+3
	1:80	+2	markers	Plasmacytic	
	1:40	+1		Rosettes	+2
	<1:40	0		None of the above	+1
				Biliary changes	-5
				Other features	
					-3
					-3
AMA	Positive	-4	Treatment	Complete	+2
			Response	Relapse	+3
Viral Markers	Positive	-3			
	Negative	+3	Pretreatment		
			Aggregate score		
Drugs	Yes	-4	Definite diagnosis >15		
	No	+1	Probable diagnosis 10-15		
Alcohol	<25g/day	+2	Post treatment aggregate		
	60g/day	-2	Definite diagnosis >17		
			Probable diagnosis 15-17		

ANA-Antinuclear antibody,AMA-antimitochondrail, AntiLKM-liverkidney microsomal, ratio of alkaline phosphatase to alanine transaminase or aspartate transaminase, IgG-immunoglobulin G, HLA-human leucocyte antigen, pANCA- Perinuclearantineutrophilic cytoplasmic antibodies, SMA-smooth muscle antibody

The patient's condition responded to prednisone initiated at 50mg per day, with a prompt decrease in her ALT and AST as shown in figure 1 below. The improvement in bilirubin level lagged behind the improvement in the ALT and AST level.

Figure 1
Response of ALT/AST to corticosteroid therapy



After five weeks of prednisone therapy, the patient was then initiated on azathioprine at a dose of 1mg/kg/day which was gradually tapered. ART was restartedon 5th January 2016. Liver function tests repeated two weeks later demonstrated continued improvement of liver function. The patient is currently on daily maintenance therapy of Azathioprine 100mg (2mg/kg/day) and prednisone 10mg.

DISCUSSION

In PLHIV who develop liver dysfunction while receiving ART, it is important to exclude drug-induced liver disease (DILI). In our patient, the findings on the liver biopsy and the fact that she had been taking these medications long before she developed symptoms indicate that a drug reaction was unlikely. Tenofovir and Lamuvidine have not been convincingly associated with clinically apparent hepatotoxicity. There are case reports of Efavirenz associated hepatotoxicity but this is also rare.[1]HIV co-infectionwith viral hepatitis B (HBV) and C (HCV) is common in developing countries. In Kenya, the prevalence of HIV/HBV and HIV/HCV co-infection are 4.6% and 6% respectively (3). Viral hepatitis was excluded in this patient.

The relationship between autoimmune diseases and HIV is intriguing. Autoimmune diseases occur in the absence of immune suppression such as during acute infection (Stage I), when the CD4 count is above 200 per mm^3(Stage II), or following successful ART therapy (Stage IV). Autoimmune disease is yet to be reported in the context of profound immune-suppression (Stage I). Reported autoimmune diseases in the setting of HIV infection include SLE, anti-phospholipid syndrome, autoimmune thrombocytopenia, vasculitis, polymyositis, Grave's disease, autoimmune hepatitis and primary biliary cirrhosis (4).

Autoimmune hepatitis is a rare cause of liver disease in PLHIV globally. In literature, only fifteen cases of autoimmune hepatitis in HIV disease have been described to date (5,6,7). Of these cases, three were receiving interferon therapy for HIV/HCV co-infection,six patients had AIH before starting ART and sixdeveloped AIH after startingART, as did our patient. All patients who received ART prior to developing AIH had a significant rise in CD4 count and undetectable HIV RNA. Two patients had other concomitant autoimmune diseases: One hadGrave's disease and the other, diffuse infiltrative lymphocytic syndrome. AIH has been encountered in women with significant elevations in CD4 count, suggesting the emergence during immune restoration. It presents insidiously with non-specific manifestations. The diagnosis is usually based on AIH score, the absence of other conditions and characteristic histopathological findings (5, 6).

`The two phases of standard therapy for autoimmune hepatitis are: high-dose of corticosteroids for induction of remission and low-dose corticosteroids and azathioprine for maintenance. On prednisolone and azathioprine, more than 80% of the patients achieve remission (2).

There are no guidelines for the treatment of autoimmune hepatitis in PLHIV. As such we used standard guidelines and the patient responded well. If left untreated, the prognosis of AIH is poor with 5 and 10-year survival rates of 50% and 10% respectively (7). In PLHIV this prognosis appears to be variable. In a review of 12 cases (AIH/HIV) two patients died while receiving interferon therapy for concomitant HCV, and one died as a result of severe Pneumocystis jiroveci pneumonia (PCP) while receiving high-dose steroids for AIH (5).

In conclusion, we have presented a case report of autoimmune hepatitis in a HIV-infected person on ART with good immunological response and viral suppression. Clinicians, who care for HIV-infected persons, should consider autoimmune hepatitis (AIH) in the differential diagnosis of liver dysfunction in patients on antiretroviral therapy.

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