Original Article

Liver Profile in Advanced Immunodeficiency Due to HIV Disease

Alaka Deshpande[1]

ABSTRACT

Introduction : Liver disease has emerged as the most common non-AIDS related cause of death among HIV-infected patients AIDS cases are vulnerable to various opportunistic infections (OIs). The liver involvement by OIs indicates dissemination of the OI. Non-OI markers like steatosis are also common.

Materials & Method : Seventy-five ART naïve cases of AIDS with fever and hepatomegaly were screened. Their detailed history was noted and thorough examination was done. They all were subjected to various relevant biochemical & hematological investigations. 68 of them were subjected to liver biopsy. The results are presented.

Results : Amongst the 68 patients subjected to liver biopsy, in 5 patients biopsy reveled normal histology. Macrosteatosis was found to be commonest histological finding followed by granulomas. Hepatispeliosis, Hepatitis and cryptococoma were findings seen in other patients.

Conclusion : The diagnostic yield of liver biopsy is quicker and better compared to other modalities.

Introduction :

Liver disease has emerged as the most common non-AIDS related cause of death among HIV-infected patients, accounting for 14-18% of all deaths [3, 4 Prolonged pyrexia in AIDS cases has always been a challenging problem with diagnostic dilemma. Apart from basic investigations, patients are subjected to imaging, blood cultures, bone marrow examination etc. Both infectious and non infectious complications have been reported in liver biopsies by various studies in AIDS cases suffering from prolonged febrile illness, hepatomegaly, and abnormal liver functions[1]. This study was under taken at a center in resource-limited country having a large number of HIV patients.

Material & Method :

After taking approval from Institute's Ethics Committee study was initiated. This was single center cross-sectional study undertaken in Medical College Hospital. Seventy-five HIV infected cases with prolonged fever for more than three weeks with increased alkaline phosphatase and hepatomegaly formed the study material. All the cases were ARV naïve. The patients who gave history of receiving ART from any center or who failed to give consent were excluded from the study. All the patients were clinically evaluated in detail and were subjected to various relevant investigations.

Investigations including liver function tests, prothrombin time, INR, X ray Chest, abdominal ultrasonography and CD4 counts using FACSALIBUR were done for each patient. Viral load estimation being expensive could not be estimated in these cases. The liver biopsy was performed on patients using a trucut needle after an informed consent. Seven patients with low platelet count or prolonged prothrombin time were excluded. The biopsy specimen was preserved in 10% formalin at the bedside. After processing the specimen, serial sections were stained with Haematoxylin and Eosin, Reticulin, PAS and ZN stain. The pathologist was blinded to the clinical details.

Results :

All the 75 cases were males. In the initial stages of HIV epidemic there was male preponderance, which is also reflected in AIDS cases as the epidemic matured. The patients were in the age group of 20 to 45 years. Two cases were intravenous drug users; two gave history of blood transfusion about 7-8

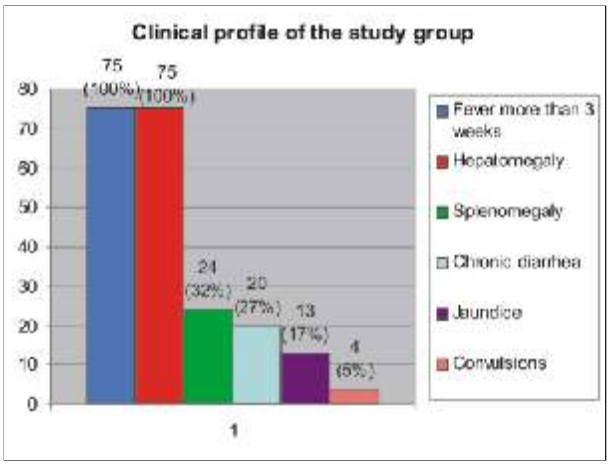
[1]Former Professor of Medicine, Grant Medical College & Sir J J Gr. of Hospitals, Mumbai

Address for Correspondence -
Dr. Alaka Deshpande
E-mail : alakadeshpande@rediffmail.com

years earlier, while the remaining seventy-one cases had multipartner, unprotected heterosexual behavior as a risk factor.

Their past history revealed events of various OIs. 22 patients had past history of TB, 13 with PTB, 6 TB Lymphadenitis, 2 each with pleural / pericardial effusion, a patient with TB Meningitis. Eighteen had completed anti TB treatment, while four were on the continuation phase of INH + Rifampicin. 6 Patients gave past history of cryptococcal meningitis adequately treated with amphotericin B and were continuing on oral fluconazole. 4 cases had past history of neuro-toxoplasmosis and were receiving sulphadoxine-pyrimethamine maintenance therapy. 6 patients had HBV and one had HCV confections. 16 patients gave history of chronic alcoholism.

Dig. 1 : **Bar diagram showing clinical profile of study population**



All the cases showed mild increase in serum transaminases, which was less than two fold of the normal value. Serum alkalinephosphatase was increased in 68 cases with mean of 42.3 KAU. The CD4 cell count ranged from 23 to 257 cell/mm^3 with mean of 93 cells mm^3.

Abdominal lymphadenopathy was noted in 15 cases while four patients had splenic micro abscesses on sonoghraphic examination. Ten patients had a hepatomegaly with coarse echo texture without any other signs of cirrhosis.

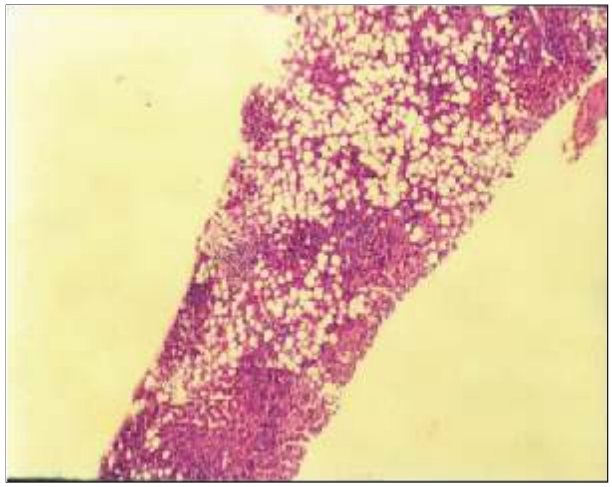
Results of liver histopathology are given in ***table 1***.

Table 1 : **Liver histopathology (N = 68)**

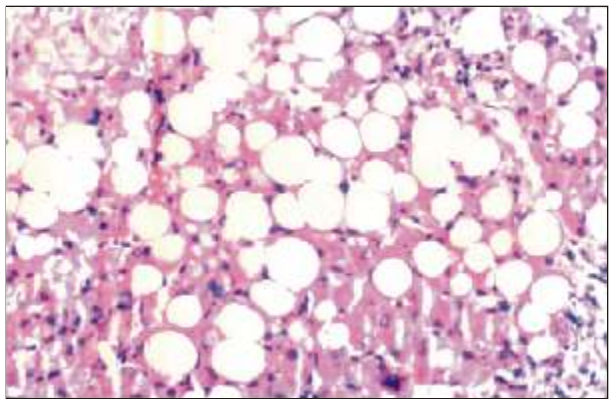
Normal	**05 (7%)**
Macrosteatosis	30 (44%)
Granulomas	28 (41%)
Hepatitis	11 (16%)
Hepatis peliosis	09 (13%)
Cryptococcoma	03 (4%)

Picture 1, 2 shows large vacuolar spaces seen in perivenular and periportal sites indicative of macrosteatosis.

Pic. 1 : **Macrosteatosis Low power, H&E stain**

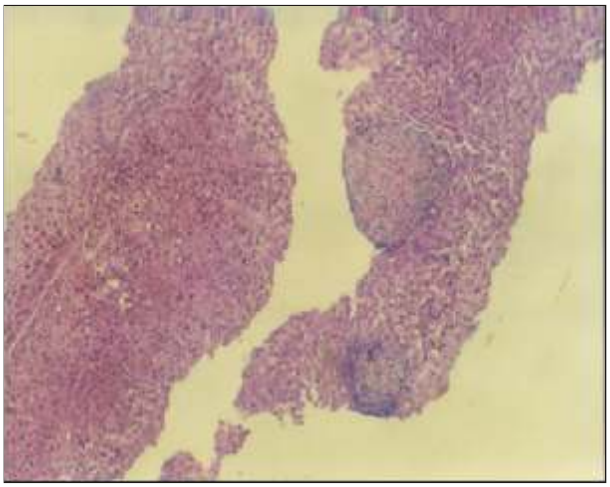


Pic. 2 : **Macrosteatosis Under HP Large vacuolar spaces, H&E stain**

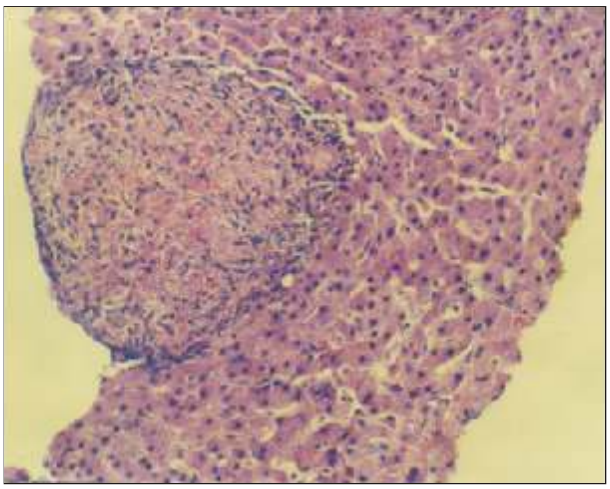


28 cases had hepatic granulomas ***(Pic. 3, 4, 5),*** acid fast bacilli were detected in eight of them. Fifteen cases of abdominal lyphadenopathy and four with splenic microabscesses gave corroborrotive evidence of the tubercular etiology of these granulomas.

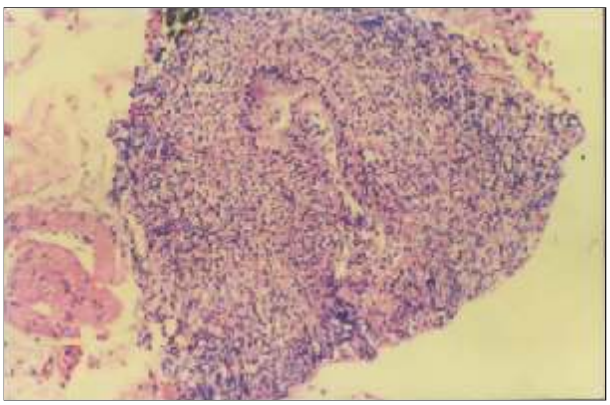
Pic. 3 : **Two Granulomas seen under LP H&E**



Pic. 4 : **Large granuloma without caseation HP, H&E stain**

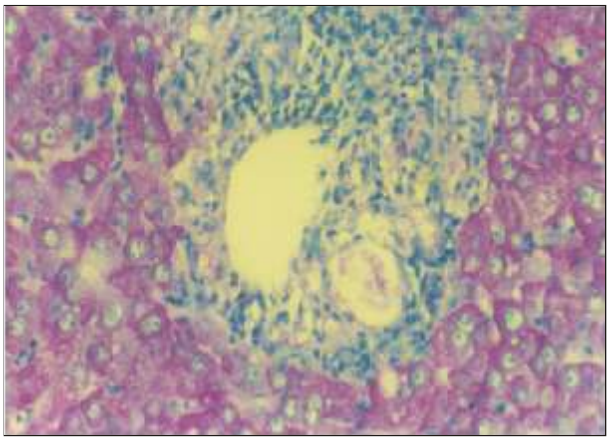


Pic. 5 : **Granuloma surrounding a bile duct H&E stain**

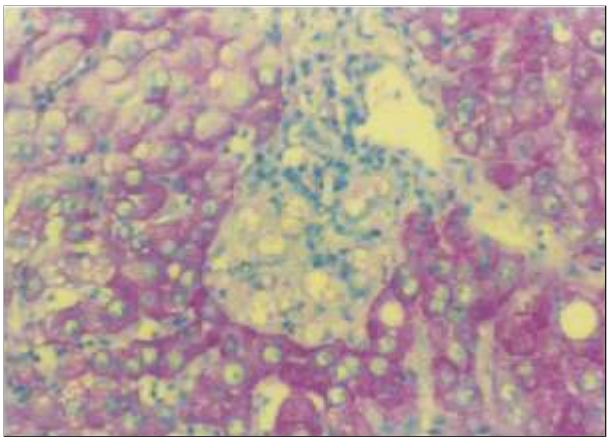


Three cases ***(Pic. 6,7,8),*** showed hepatic cryptococcomas. H&E, PAS stains revealed globular, refractile structures in the sinusoids, although six cases had been adequately treated in the immediate past for Cryptococcal meningitis, presence of hepatic cryptococcomas indicated disseminated cryptococcosis.

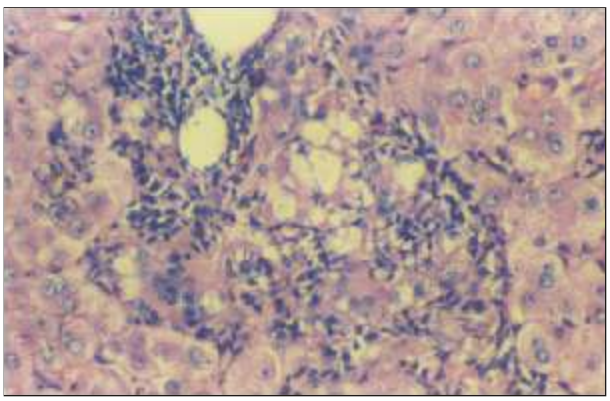
Pic. 6 : **Cryptococci seen under LP - PAS**



Pic. 7 : **Cryptococci spherical bodies seen under HP - - - PAS**



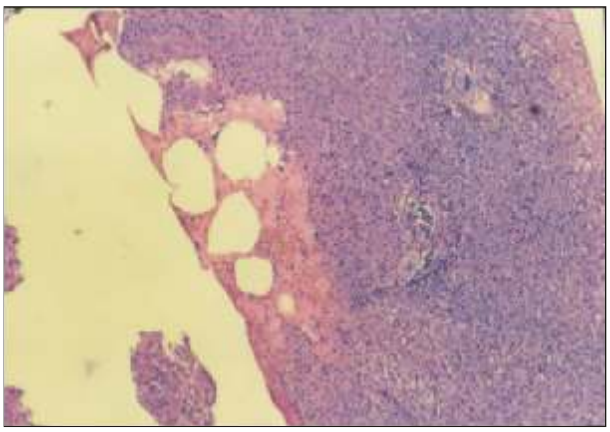
Pic. 8 : **Cryptococcal cells, H&E stain, high power**



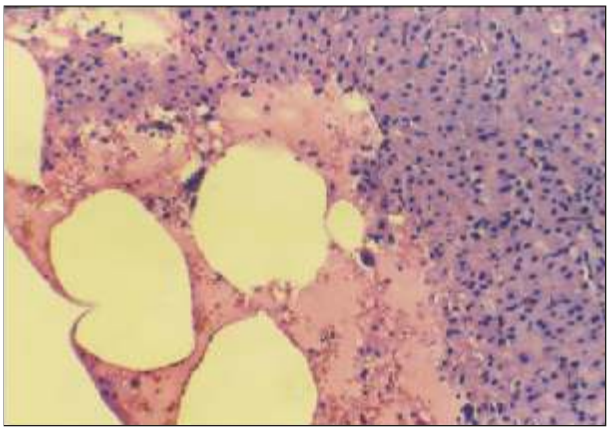
Peliosis :

Peliosis Hepatis is an uncommon vascular condition characterized by randomly distributed multiple blood-filled cavities throughout the liver. The size of the cavities usually ranges between a few millimeters to 3 cm in diameter. Microscopically, two different types of peliosis can be distinguished in the liver (1) "parenchymal peliosis" consisting of irregular cavities that are neither lined by sinusoidal cells nor by fibrous tissue, and (2) "phlebectaticpeliosis" characterized by regular, spherical cavities lined by endothelium and / or fibrosis.

Pic. 10 : **Peliosishepatis H&E stain**



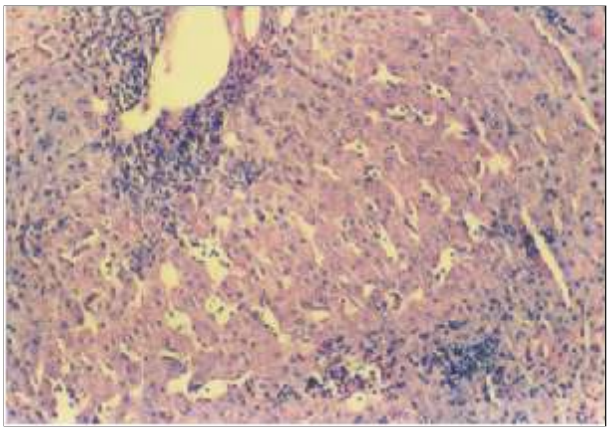
Pic. 11 : **Peliotic changes : Blood filled spaces not lined by endothelial cells**



Hepatitis

There was evidence of acute hepatitis in eleven cases ***(Pic. 11)***. Infiltration with inflammatory cells was evident. Despite the fact that four patients were on sulpha pyrimethamine suppressive therapy for neurotoxoplasomosis, eosinophilic hepatitis which is characteristic of sulpha induced hepatits was not seen.

Pic. 11 : **Acute Hepatitis, Inflammatory cell infiltrate, H&E stain**



Discussion :

Unexplained fever, hepatomegaly with abnormal biochemical parameters of liver function has been consistently used as indication for liver biopsy[2,3,4.] Poleset alhave reported the diagnostic yield of liver biopsy to be 70% in AIDS patients[5].

In this study 68 cases were subjected to biopsy out of which 63 patients have revealed various lesions. Macrosteatosis was seen in 30 cases. Chronic HIV infection, malnutrition, lack of hepatoprotective dietary substances parse can be responsible for these changes. ARV drugs particularly Stavudine have also been incriminated for these changes but all our cases were ARV naïve. Therefore chronic HIV infection, malnutrition, alcoholism could be leading to macrosteatosis in this study.

28 / 68 cases revealed hepatic granulomas- single or multiple -with eight of them showing presence of acid fast bacilli. Four were noncaseating. However corroborrative evidence of abdominal lymphadenopathy and splenic microabscesses indicated tubercular etiology. Sarcoidosis needs to be ruled out in noncaseating granulomas. However consideringTB as the commonest OI in this country and the corroborative evidence of abdominal TB, these cases were treated with ATT.

Three patients had hepatic cryptococcomas. Two of the cases were on suppressive fluconazole therapy, the third one did not have clinical evidence of Cryptococcal infection. Hepatic cryptococcomas indicate disseminated cryptococcosis. Persistence of cryptococci despite therapy also necessitates drug sensitivity testing which was not available in the institute.

Intrahepatic granulomas are identified in 48% of AIDS cases. They are generally poorly formed, hypocellular without giant cells because of the suppressive effect of the virus on T-Lymphocytes[6]. The differential diagnosis of granulomas include OIs like MTB, MAI, Cryptococcus, Histoplasma, candida etc. In addition, non infective granulomas like sarcoidosis have been described.

Prior to AIDS, peliosishepatis had been rarely reported as a consequence of chronic infectionssuch as tuberculosis, advanced malignancy or steroid/azathioprine therapy. Ultra structural studies done previously comparing HIV associated peliosis with non-HIV peliosis using Warthin-Starry stain, noted a Gram negative bacillus in the cystic spaces. DNA studies designated this bacillus as Rochalimalaehenselae which induces peliotic changes[7]. Scoazec *et al*[8] described a peculiar feature of the presence of hyperplasticsinusoidal macrophages suggesting that endothelial cell injury may precipitate these sinusoidal changes.

The involvement of liver in AIDS is usually an indicator of disseminated disease. A host of etiological agents such as mycobacteria, candida, Cryptococci, microsporidia, toxoplasma, leishmania, Peliosis, CMV as well as non-diagnostic markers of liver involvement such as macrosteatosis, granulomas etc. have been widely reported in liver biopsy studies[1,2,4,9].

Prego *et al*[3] have described that in febrile HIV infected cases blood culture or bone marrow biopsy are slow methods of diagnosis compared to the success of liver biopsy. Cavicchi et al have established microbiological diagnosis of mycobacterial, fungal, viral infection within twelve hours to three days of liver biopsy[10].

Poles *et al* have reported that the diagnostic yield of liver biopsy to be 70%.

Conclusion :

Liver disease among HIV-infected individuals is a common and important cause of non-AIDS related morbidity and mortality. The OIs and non-OI involvement of liver in HIV disease can be detected early by liver biopsy. The diagnostic yield of liver biopsy is quicker and better compared to other modalities. Hepatic involvement in HIV infected patients signifies dissemination of the disease.

Acknowledgment :

Dr. N D'souza & Dr. Dhanashree Kelkar, Resident doctors assisted in data collection of first 40 cases.

Bibliography :

1. Cappell M.S, Schwartz S.S, Biempica H: Clinical utility of liver biopsy in patients with serum antibodies to the human immune deficiency virus. *Am. J. Med.* 1990, Feb; 88 (2): 123-30.
2. Cappel M.S: hepato biliary manifestations of the acquired immunodeficiency syndrome. *Am J. Gastroenterol* 1991, Jan 06; (1): 1-15.
3. Prego V, Clatt A. C, Roy V. et al: Comparative yield of blood culture for fungi &mycrobacteria, liver biopsy, and bone marrow biopsy in the diagnosis of fever of unknown origin in human immuno- deficiency virus infected patients. *Arch. Int. Med.* 1990, Feb; 150 (2): 333-6.
4. Schneiderman D.J, M.D : Hepatobiliary abnormalities of AIDS Gastroenterol. *Clin. N. Am;* vol 17, No. 3 Sept 1988: 615-30.
5. Poles M. A, Dietrich D. T, Schwarz E. D et al: Liver biopsy findings in 501 patients infected with the human immune-deficiency virus. *J. Acquir. Immuno. Defic. Synd. Human Retrovirol.* 1996 Feb; 11[2]: 170-7.
6. Wilkins M J, Lindley R, Dourakis S P Goldil R D : Surgical Pathology of the lever in infection. *Histopathology* 1991 May; 18 (5): 459-64.
7. Schiff : Diseases of the lever. *7th edition copyright © 1993 Lippincott Ravem publishers*:1366-7.
8. Scoazec J. Y, Marche C, Giraud P.M *et al*:PeliosisHepatis and Sinusoidal Dilatation during infection by the human immune deficiency virus : *An Ultra structural Study.*
9. Argarano G, Maggy P, Rollo M P et al : diffuse necrotic lesions due to visceral leishmaniasis in AIDS. *J. Infect* 1998 March, 36 (2): 167-9.
10. Cavicchi M, Pialoux G Carnot T et al : value of liver biopsy for the rapid detection of infection in HIV infected patients who have unexplained fever & elevated serum levels of alkaline phosphatase or gamma glutamyltransferase. *Clin. Infect. Dis.* 1995, March 20 (3) : 606-10.
11. *Palella FJ Jr, Baker RK,* A Moorman AC, Chmiel JS, Wood KC, Brooks JT, Holmberg SD, HIV Outpatient Study Investigators. J Acquir Immune DeficSyndr. 2006 Sep; 43(1):27-34.[PubMed]