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Original Article

Histological spectrum of liver in HIV – Autopsy study

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Abstract

Introduction: **Liver abnormalities are common in HIV positive patients. They are usually part of generalized process and rarely produce significant liver failure.** ***Aim:*** **To evaluate histological spectrum of liver disease in HIV positive patients and to ascertain if any pathologic features are widespread among HIV infection.** ***Material & methods:*** **Autopsy data from year 1991 to 2003 consisting of 60 HIV positive patients were evaluated. Demographic profile, clinical and laboratory data were obtained from hospital records. Macroscopic findings of all organs at autopsy were noted. Histological features of liver were studied in detail using routine H & E., Ziehl-Neelson stain for acid fast bacilli and other special stains such as PAS and GMS for fungal infection were done whenever indicated.** ***Results:*** **Patients were in age group 19 to 55 years with mean age of 32.1 year; male to female ratio was 4:1. Evidence of tuberculosis either pulmonary or extrapulmonary was found in 35 (58.3%) cases. On histological examination of liver, tubercular granulomas were seen in 19 (31.6%) cases of disseminated tuberculosis. Granulomas were typical caseating epitheloid cell type in 14 (73.6%) and in 5 cases granulomas were not typical. Acid fast bacilli were demonstrated in 4 (6.6%) cases, all of which showed presence of granulomas. Other histological findings were sinusoidal and centrivenular congestion in 14 (23.3%), extensive fatty change 6 (10%), portal inflammation resembling chronic hepatitis 5 (8.3%), focal necrosis 2 (3.3%), Kupffer cell hyperplasia 1 (1.6%) and metastasis from known case of adenocarcinoma of pancreas 1 (1.6%). Associated hepatitis C and B infections were seen in 4 (6.6%) and 1 (1.6%) respectively. Opportunistic infection was seen in only 1 (1.6%) case with disseminated cryptococcosis involving liver. In remaining 6 (10%) liver histology was normal. Considering cause of death, 58.3% patients died due to disseminated tuberculosis. Patients with associated hepatitis B & C infection died due to liver cirrhosis and the remaining died of miscellaneous conditions, which were not related to HIV infection.** ***Conclusion:*** **Histopathological findings of the liver in HIV positive patients were mainly non specific. Tuberculosis was the commonest infection noted. There was no significant mortality observed specifically related to liver involvement in these patients.**

Key words: Liver, HIV, pathology, AIDS.

Introduction

The human immunodeficiency virus (HIV) was unknown until the 1980's but since that time it has infected millions of persons resulting in a worldwide pandemic. The primary target of HIV is the immune system, which leads to progressive destruction of CD4 lymphocytes. A decrease in the total CD4 lymphocyte count below 500/ micro liter presages the development of clinical AIDS, and a drop below 200/ micro liter not only defines AIDS, but also indicates a high probability for the development of AIDS related opportunistic infections and or neoplasms.[1-3] Liver abnormalities are common in HIV positive patients. But these are usually part of generalized process and rarely produce significant liver failure.[4] Factors such as chronic alcoholism, frequent histories of hepatitis, intravenous drug abuse, disseminated infections and treatment with multiple chemotherapeutic agents for infections and neoplasms, predispose patients with AIDS for significant liver disease.[5-8] Abnormalities in liver function tests have been documented upto 60 to 90% in HIV positive patients.[4] Hepatic changes range from simple steatosis, viral hepatitis, opportunistic infection, to development of Kaposis sarcoma or lymphoma.[9-12] Tuberculosis is the commonest infection found in HIV positive patients in our country.[13-15] Hence the aim of this study was to evaluate histological spectrum of liver disease in HIV positive patients and to ascertain if any pathological features are widespread among HIV patients from Western India.

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Material and methods

A total 60 adult HIV positive autopsies from year 1991 to 2003 were included in the study. All the patients were seropositive by ELISA and confirmed by Western blot tests. Complete history, clinical presentation and laboratory data were obtained from hospital records. Gross examination of each organ was done meticulously at autopsy as a routine procedure with special emphasis on liver. Minimum two representative sections of liver were submitted for histopathology. Sections were processed routinely with paraffin embedding and stained with hematoxylin and eosin stain. All slides were also stained with Ziehl Neelson's stain for acid fast bacilli, Periodic – acid Schiff (PAS) and Gomorri's methenamine silver (GMS) stain for fungal infections whenever necessary. Liver histology was reviewed by experienced liver pathologist.

Results

The demographic profile of the 60 HIV positive patients consists of 48 (80%) males and 12 (20%) females with male to female ratio of 4: 1. The age range was 19 to 55 years with mean age of 32.1 years. The youngest patient was a 19 year old male and eldest was a 55 year old female. The clinical presentation of these patients were pulmonary tuberculosis 17 (28.3%), disseminated tuberculosis 18 (30%). Eight (13.3%) patients presented with pneumonia, 8(13.3%) with meningitis and encephalitis, 2(3.3%) had gastroenteritis and 2(3.3%) were cases of HCV infection who presented with liver cirrhosis. Remaining cases were one case each of pancreatitis, septicemia, DIC, intestinal obstruction and pancreatic carcinoma *(Table I)*. Evidence of tuberculosis on gross examination at autopsy was found in 35 (58.3%) out of 60 HIV positive cases, of which 16 (45.7%) patients had evidence of only pulmonary tuberculosis (TB), 18 (51.4%) had disseminated TB and 01 (2.8%) had miliary tuberculosis. Out of these 35 cases, on histological examination of liver, epitheloid cell granulomas were seen in 19 (31.6%) of which 18 were cases of disseminated tuberculosis and 1 miliary tuberculosis. Granulomas were typical caseating epitheloid cell type in 14 (73.6%) and in 05 (26.4%) they were not typical. These atypical granulomas were composed of foamy macrophages, nuclear debris with absence of lymphocytic cuffing. One of them showed granuloma made up of only foamy histiocytes. Acid fast bacilli were demonstrated in only 4 (6.6%) cases, of which 3 showed typical caseating granulomas and the remaining case consisted of only foamy histiocytes. None of the cases of pulmonary tuberculosis showed granulomas in the liver on gross as well as histopathological examination.

Histopathology in remaining cases was sinusoidal and centrivenular congestion in 14 (23.3%) and macrovesicular steatosis in 6(10%) cases. Chronic hepatitis in the form of mild to moderate portal inflammation was present in 3 (5%) cases. All these cases were negative for hepatitis B virus (HBV) or hepatitis C virus (HCV) serology. No other etiology could be attributed as cause for chronic hepatitis in these cases. Focal necrosis was seen in 2(3.3%) and Kupffer cell hyperplasia in 1(1.6%) cases. Liver showed evidence of metastasis from adenocarcinoma of pancreas in one case who was found to be HIV positive. A case of HBV infection on histopathology showed characteristic ground glass hepatocytes. Six (10%) patients who were HCV positive showed lymphoid aggregates in portal tracts and fatty change suggestive of HCV infection. One case of disseminated cryptococcal infection on histopathological examination revealed yeast forms of cryptococci, which was confirmed on mucicarmine staining. Liver histology was normal in 6 (10%) patients on histopathological examination *(Table II)*.

Out of 35 patients who presented with tuberculosis, 5 (14.3%) had completed course of anti – tubercular therapy (AKT), 2 (5.8%) were on AKT, 5 (14.2%) were defaulters and 23(65.7%) patients had never taken AKT. Of the seven patients who were taking AKT, only two showed tubercular granulomas in the liver. Two out of the 5 defaulters showed granulomas in the liver and amongst

Table I. Clinical presentation of patients.

Mode of clinical presentation	No. of cases	Percentage (%)
Pulmonary tuberculosis	17	28.3
Disseminated tuberculosis	18	30
Pneumonia	8	13.3
Meningitis / encephalitis	8	13.3
Gastroenteritis	2	3.3
Liver cirrhosis	2	3.3
Pancreatitis	1	1.7
Septicemia	1	1.7
Disseminated intravascular coagulation (DIC)	1	1.7
Intestinal obstruction	1	1.7
Pancreatic carcinoma	1	1.7
Total	60	100

Table II. Histopathological spectrum of liver in HIV.

Histology	No. of cases	Percentage (%)
Tuberculosis	19	31.6
Congestion	14	23.3
Fatty change	6	10
Chronic hepatitis	3	5
Focal necrosis	2	3.3
Kupffer cell hyperplasia	1	1.6
Metastasis of adenocarcinoma pancreas	1	1.6
HBV infection	1	1.6
HCV infection	6	10
Cryptococcosis	1	1.6
Normal histology	6	10
Total	60	100

23, who had never taken AKT, granulomas in the liver were seen in 15 patients. None of them received antiretroviral therapy. Considering cause of death, 35 (58.3%) patients died due to tuberculosis (pulmonary / disseminated). Patients of associated hepatitis B 1 (1.6%) and C 4 (6.6%) infection died due to liver cirrhosis and remaining patients 20 (33.4%) died of miscellaneous conditions such as meningitis, septicemia, pneumonia, which were not related to liver disease.

Discussion

Tuberculosis was the most common clinical presentation in our HIV positive patients. They presented with fever, cough, dyspnoea, hemoptysis and weight loss. Other presenting features were those of pneumonia, meningitis, septicemia, gastroenteritis, liver cirrhosis and intestinal obstruction. Two patients presented with features of liver cirrhosis were known hepatitis C virus (HCV) positive. These clinical presentations are similar to other reports from India in which tuberculosis was the commonest secondary infection.[13-15] Though liver involvement in HIV patients is very common, presentation of the patient with liver failure is very rare.[4,5] In this study none of our patients presented with liver failure. Tuberculosis (TB) was noted at autopsy in 35 (58.3%) out of 60 HIV positive patients. However, 16 (45.7%) out of these 35 patients had evidence of only pulmonary tuberculosis, 18 (51.4%) had disseminated tuberculosis and 1 (2.8%) had miliary tuberculosis. Such high incidence (41%) of tuberculosis has also been reported in another study from Mumbai by Lanjewar et al.[17] Tubercular granulomas were noted in liver in 19 (31.6%) of them who were cases of disseminated tuberculosis. None of our patients with pulmonary tuberculosis had evidence of tuberculous focus in the liver. Typical granulomas of mycobacterium tuberculosis, composed of central caseation, epitheloid cells, Langhans type giant cells, lymphocyte cuffing were seen in 14 (73.6%) out of 19 cases of tuberculosis. Remaining 26.4% showed granulomas with atypical features such as foamy macrophages and necrosis with nuclear debris. Reaction to granulomas in the form of lymphocytic cuffing was minimal or absent. One out of these 5 cases, showed granulomas made up entirely of foamy macrophages suggestive of mycobacterium avium intracellulare (MAI) infection. However culture was not performed in this case to confirm MAI infection. Acid fast bacilli (AFB) were demonstrated in 4 (21%) out of the above 19 cases. Of these 4 cases, 3 showed typical caseating granulomas and in 1 granuloma consisted of only foamy macrophages which were packed with acid fast bacilli. It is well known fact that the acid- fast bacilli (AFB) positivity for mycobacterium tuberculosis varies widely ranging from 19 – 40%.[18] In Western studies, MAI infection has been reported to be common in HIV infected patients.[4,5,9,16] Levobics E et al demonstrated atypical granulomas in 3 (12%) out of 25 AIDS cases. The granulomas were composed of histiocytes, epitheloid cells, without lymphocytic cuffing, caseation necrosis and multinucleated giant cells. These were cases of mycoobacterium avium intracellulare confirmed on culture.[9] Schneiderman DJ et al have also noted, mycobacterium avium intracellulare (MAI) as the most common (16.5%) opportunistic pathogen involving the liver of AIDS patients.[4]

Other histological changes of liver in HIV patients include sinusoidal and centrivenular congestion.[4,5,9] Comer GM et al and Glasgow BJ et al have noted 2% incidence of congestion in AIDS patients.[19,5] As against this, Schneiderman DJ et al have shown high incidence (22.4%) of hepatic congestion which is similar to this study.[4] Fatty change in liver has been reported in 3-57% HIV positive patients in various studies.[4,5,9,10,16,19] Schneiderman DJ et al and Levobics E etal have reported macrovesicular steatosis in 42% and 56% respectively in AIDS patients, which was the most common histological finding.[4,9] Glasgow BJ et al have reported steatosis in 24 (57%) out of 42 AIDS patients, which in most cases were not related to alcohol.[5] The major likely etiology for steatosis has been attributed to poor nutrition following chronic debilitating systemic disease.[4,5,9] We found significantly predominant macrovesicular steatosis in 6 (10%) cases. Steatosis was noted in a range of 40 – 90% within the hepatocytes. Three patients were alcoholics and one patient was malnourished. Of these 6 cases; four showed mild to moderate portal inflammation and one with portal fibrosis on histology.

Various studies have reported histopatholgical changes resembling chronic hepatitis ranging from 3-35% HIV infected patients.[4,5,9,10,16,19] Schneiderman DJ et al noted chronic hepatitis in 30 (35.3%) out of 85 AIDS cases.[4] Chronic hepatitis was found in 10 (10%) out of 101 HIV infected patients by Wilkins AJ et al.[10] None of these were HBV or HCV positive. Levobics E et al and Comer GM et al have reported 4% and 22.9% cases showing features of chronic hepatitis respectively.[9,19] In our study population, chronic hepatitis on histology was present in 5% patients. None of these cases showed positivity for serological markers of hepatitis viruses and also histopathology was not suggestive of HBV or HCV infection. No specific etiology could be attributed to as the cause for chronic hepatitis in these patients. Focal necrosis in the liver has been reported in 2-11% cases in HIV patients.[4,5] We found 2 cases with focal necrosis in the liver. These areas showed coagulative type of necrosis leaving only outline of hepatocytes without inflammatory response. Special stains in these cases did not reveal any organisms. The exact etiology of focal necrosis in our cases could not be determined.

Studies have found an incidence of 4 to 17% of Kupffer cell hyperplasia in the liver of HIV infected patients.[4,5] Schneiderman DJ et al and Comer GM et al have found incidence of Kupffer cell hyperplasia in 7.1% and 16.7% respectively.[4,19] We have come across only one (1.6%) case

showing Kupffer cell hyperplasia. This Kupffer cell hyperplasia can be seen probably due to stimulation of reticule – endothelial system. There was a single case of metastasis of adenocarcinoma to the liver. This was a known case of carcinoma head of pancreas found to be HIV positive, which was an incidental finding.

Hepatitis B virus (HBV) infection has been reported to be ranging between 16-89% in HIV positive cases.[4,5,9,10,15,16,20] Schneiderman DJ et al have reported high incidence (89%) of HBV coinfection. None of their patients showed evidence of cirrhosis on histopathology. They have attributed the low incidence of cirrhosis in patients with HIV-HBV coinfection to immune suppression caused by HIV virus which in turn attenuates the inflammation of chronic hepatitis. Glasgow BJ et al, Dworkin BM et al and Levobics E et al found HBV infection in 30 (71.4%), 88% and 95% respectively.[5,16,9] Lanjewar DN et al have noted hepatitis B infection in five (3%) out of 171 AIDS cases.[17] In our study, HIV-HBV coinfection was seen in only 1(1.6%) out of 60 cases. This does not reflect a true prevalence since it is an autopsy data. Histopathology showed typical ground glass hepatocytes without inflammation and fibrosis. Liver biopsy studies have shown that HIV positive patients have less active chronic hepatitis B virus (HBV) disease and scarring as compared to HIV negative patients. Also HBV associated liver cirrhosis is less frequent in HIV positive patients.[19] Hepatitis C virus (HCV) infection in HIV infected has been reported to be 2-10% cases in autopsy series.[5,7,16,21] Glasgow BJ et al have found only one (2.3%) out of 42 cases to be HCV positive.[5] Wilkins MJ et al found HCV infection in 10 (10%) out of 101 HIV cases studied.[10] Six (10%) out of 60 patients in our study population had evidence of HCV infection. Features of HCV infection such as lymphoid aggregates in portal areas and steatosis were noted in these patients. Of these, four patients showed presence of liver cirrhosis. Remaining two cases showed features of only chronic hepatitis. It is known that patients with HIV – HCV coinfection have an increased risk of development of liver cirrhosis.[5,7,21-23]

Opportunistic infections are more common in AIDS patients as compared to HIV positive patients. We have come across only one case of disseminated cryptococcosis involving the liver. Histopathological sections of liver showed budding yeasts of cryptococci on HE stain within liver parenchyma, which was confirmed as capsulated yeast forms of cryptococci on mucicarmine stain. Normal histology of liver has been reported in 4-12% HIV / AIDS patients.[4,9,16] We found normal liver on histopathological examination in 6(10%) out of 60 cases. These patients died due to other causes such as meningitis, pneumonia and septicemia.

Liver failure is not believed to contribute to the death of HIV patients. Glasgow BJ et al have demonstrated a spectrum of infections and neoplasms affecting the liver in AIDS patients, however this did not appear to significantly affect morbidity and mortality of these patients.[5] Dworkin BM et al believe that liver disease does not contribute significantly to the death of AIDS patients.[16] Chalasani N et al have documented various causes for death of HIV positive patients like drug induced liver disease, Kaposi's sarcoma, multifactorial etiologies, AIDS related cholangiopathy and extrahepatic lymhoma.[24] We found tuberculosis (pulmonary + disseminated) as the commonest cause leading to death of HIV positive patients (58.3%). In five patients death could be attributed to liver cirrhosis as a result of HBV / HCV infection. Remaining 20 (33.4%) out of 60 cases had miscellaneous conditions leading to death which were not related to liver disease. Thus cause of death was not attributed to liver failure in any of our cases. In conclusion histopathological findings of the liver in HIV positive patients were mainly non specific. Tuberculosis was the commonest infection noted. There was no significant mortality observed specifically related to liver involvement in these patients.

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