

*Full Length Research paper*

## **HIV/TB co-infection: Liver biopsy findings**

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Human immunodeficiency virus (HIV) and tuberculosis co-infection in an individual constitutes a serious diagnostic and therapeutic challenge. The diagnosis of tuberculosis using hypersensitivity skin reaction such as the Mantoux test could turn out to be a poor predictor in an immunocompromised individual, and the yield of mycobacterium tuberculosis from sputum or gastric washings is also poor. We undertook this study to determine liver involvement in HIV and tuberculosis co-infection. Prospective liver biopsies were done on 67 patients who died of complications of HIV/TB co-infections. Liver tissue cores were obtained using the blind percutaneous approach. The tissues were fixed in 10% buffered formal saline and then subjected to routine tissue processing. The slides were read independently by the pathologists. The results of a total of 67 biopsies, comprising of 33 males and 34 females were analysed. Thirty nine (58.2%) had pulmonary tuberculosis (PTB) while 26 (38.8%) had disseminated tuberculosis (DTB). Two (3%) had tuberculous meningitis (TBM). Fourteen (36%) patients with PTB, 10 (38%) with DTB and one (50%) with TBM had hepatic granuloma with caseation. Histologically granuloma 25 (37.4%), chronic hepatitis 13 (19.4%), non-specific reactive hepatitis 11 (16.4%), steatosis nine (13.4%), and cirrhosis seven (10.4%) were found. The age of the patients ranged from 18 - 55 years (mean  $35.5 \pm 8.4$  years). This study shows that liver is frequently involved by TB and other opportunistic infections in HIV/TB co-infection irrespective of whether it's PTB, DTB or TBM.

**Key words:** HIV, tuberculosis, liver biopsy, opportunistic infection.

### **INTRODUCTION**

Globally, tuberculosis (TB) is a major opportunistic infection in HIV-infected patients, often representing their AIDS-defining illness and the first indication of immunodeficiency. Epidemiology, clinical manifestation and management of TB are altered in HIV-infected patients (Barnes et al. 1991). The incidence of TB in HIV-infected persons is more than 100 times that of the general population. Escalating TB rates over the past decade in many countries in sub-Saharan Africa and in parts of south East Asia are mainly due to the HIV epidemic. There is evidence that the immune response in patients with TB might enhance HIV viral replication and accelerate the natural progression of HIV infection (Moreno et al. 1997). In patients with advanced HIV disease, TB may present atypically and extra pulmonary TB is more common than in isolated tuberculosis

infection. Disseminated disease with involvement of bone marrow, bone, urinary and gastrointestinal tracts, liver, regional lymph nodes and the central nervous system is common (Chaisson et al. 1987, Selwyn et al. 1989).

The world Health Organization (WHO) estimates that TB accounts for up to a third of AIDS deaths worldwide (World Health Organization strategic framework to decrease the burden of TB/HIV). The HIV/AIDS epidemic is reviving an old problem in well resourced countries and greatly worsening an existing problem in resource poor countries. There are several important associations between epidemics of HIV and TB.

TB is harder to diagnose in HIV positive people, it progresses faster, is more likely to be fatal if undiagnosed or left untreated and occurs earlier in the course of HIV-infection than other opportunistic infections. It is the only major AIDS-related opportunistic infection that poses a risk to HIV-negative people (Rob 2005). Several studies from different parts of the world have shown that liver is commonly affected by tuberculosis in HIV/AIDS (Kawashima et al. 2000, Roger et al. 1996, Escartin

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Munoz-Ortiz et al., 1991, Martinez et al., 1994).

We therefore, undertook this study to determine liver involvement in HIV/TB co-infected patients in Jos, North central Nigeria

## MATERIALS AND METHODS

### Study area

Jos city is the capital of plateau state with a population of about 1.5 million people. It is on an altitude of about 1250metres (4100 ft) above sea level with temperature of 21<sup>0</sup> to 25<sup>0</sup>C. Jos University Teaching Hospital (JUTH), located in the centre of Jos town, has over 500 beds with 20 wards in addition to intensive care unit (ICU) and special care baby unit (SCBU). It has a well functioning histopathology laboratory that receives and processes about 2000 tissue samples and 1000 cytology specimens annually. It receives specimens from north central region of Nigeria comprising of 6 states with a population of over 20 million people.

### Methods

Ethical clearance was obtained from the ethical committee of Jos University Teaching Hospital for the use of the patients.

The following data were extracted from the patients' case notes; age, sex, clinical presentations/ provisional diagnosis and other laboratory tests results. Liver biopsy was done using 'Bard-biopty' Tru cut needle on every patient who died of TB and HIV/AIDS confirmed by western blot from September 2003 to July 2004. Three to five biopsies (cores) were taken from different lobes of the liver using the blind percutaneous approach (BPLB). The tissues were immediately fixed in labeled bottles containing 10% buffered formal saline. The samples were transported to the histopathology laboratory of Jos University Teaching Hospital where they underwent routine tissue processing. Six sections (3-5 $\mu$  each) were obtained from the paraffin wax embedded tissues. They were deparaffinized and each of the six sections was stained with one of the following stains: haematoxylin and eosin, Orcein, periodic acid Schiff (PAS), Perls, Masson trichrome and Grocott. A few sections (10) were selected for Ziehl Neelson stain. All the slides were then read independently by four pathologists (authors), and results compared. Where there were serious inter-observer variations, group review was done until consensus diagnosis was reached.

### Statistical Analysis

Epi-info 2000, version 3.2.2 computer soft-ware was used for data analysis. Comparison of categorical variables was by chi-squared test. For the test of significance,  $p < 0.05$  was considered significant.

## RESULTS

The age of the patients ranged from 18 years to 55 years with a mean of  $35.5 \pm 8.4$  years. Fifty three percent of the males with the age range of 22 years to 55 years (mean SD  $36.8 \pm 9.3$ ), were within age group 31-40 years while 50% of the females with the age range of 18 years to 54 years (mean SD  $33.4 \pm 8.9$ ) were within age group 21-30 years. The females were relatively younger than the males ( $\chi^2 = 4.73$ ;  $df = 1$ ;  $p = 0.03$ ; Kruskal Wallis test for two groups).

The results of a total of 67 biopsies were analysed comprising of 33 males and 34 females. Thirty nine (58.2%) had PTB while 26 (38.8%) had DTB. Two (3%) had TBM. Fourteen (36%) patients with PTB, 10 (38%) of those with DTB and one (50%) of TBM had hepatic granuloma with caseation. Other associated clinical diagnoses were diarrhea disease seven cases, septicemia six, anaemia four, chronic liver disease three, Kaposi sarcoma three, and ten others including peptic ulcer disease, dementia, diabetes mellitus, pyelonephritis, cardiomyopathy, renal failure and hypertensive heart disease, (Table 1). Majority of the patients (50 cases) and (40 cases), presented with pain and cough respectively. Thirteen had hepatomegaly/or splenomegaly. Five patients had positive HBsAg serological test out of the 8 tested (Table 1). The only two patients that were tested for CD<sub>4</sub> count had very low values of 7/mL and 14/mL respectively.

The spectrum of histological diagnosis was granuloma 25 (37.4%), chronic hepatitis 13 (19.4%), non-specific reactive hepatitis (NSRH) 11 (16.4%), steatosis nine (13.4%), cirrhosis seven (10.4%) and sclerosing cholangitis one (1.5%) while one (1.5%) had normal histological picture. Table 2 shows the age and sex distribution of the patients. Figures 1, 2 and 3 show the photomicrograph of caseation granuloma, diffuse macro-vesicular steatosis and chronic hepatitis respectively. Nine patients out of 17 that had liver function test (LFT) done, had deranged results with 8 (47.1%) of the seventeen having increased alkaline phosphatase. Seven (41.2%) surprisingly had normal LFT result. (Table 1).

## DISCUSSION

In these patients with HIV/TB co-infection, the liver was involved in various pathologies in 98.5% of cases. The most common histological diagnosis was caseating granuloma which accounted for 37.3%. This was expected since all the patients had clinical and laboratory evidence of pulmonary TB, disseminated TB or tuberculous meningitis. However, the frequency of occurrence of liver involvement was rather high, and was present in all the various types of TB. Tuberculosis of the liver in HIV infection was reported in several studies in other parts of the world ((Kawashima et al. 2000, Roger et al. 1996, Escartin Munoz-Ortiz et al. 1991, Martinez et al. 1994). Co-infection of HIV/TB is common in African subcontinent. Edamisan et al (2006), in Lagos Nigeria and Zumla et al (2000) in Zambia reported co-infection rates of 25.8% and 67% respectively from their studies. It is well known that progressive TB and death are more common in HIV infected individuals than isolated TB infection (Kawashima et al. 2000, Roger et al. 1996, Escartin Munoz-Ortiz et al. 1991, Martinez et al. 1994, Madhi et al. 2000).

The challenge in diagnosing tuberculosis in patients with HIV/AIDS is that the yield in conventional method of

**Table 1:** Clinical features of HIV/Tb infected patients.

| <b>Variables (Sign or symptom)</b>                | <b>Number (%) of patients</b>              |
|---|--|
| *pain   | 53(79%)                                    |
| Cough   | 40(60%)                                    |
| Hepatomegaly                                      | 9(13.4%)                                   |
| Splenomegaly                                      | 4(6%)                                      |
| Ascites   | 3(4.5%)                                    |
| Skin rashes                                       | 1(1.5%)                                    |
| Drugs- Anti Koch's                                |  |
| Isoniazide, rifampicin, ethambutol, pyrazinamide. | 60(90%)                                    |
| Anti retrovirals:                                 |  |
| Zidovudine, lamivudine                            | 9(13.4%)                                   |
| Analgesic/haematinics:                            |  |
| Paracetamol, haematinics, multivitamins           | 65(97%)                                    |
| Laboratory test results                           |  |
| Liver function test (LFT)                         |  |
| Normal  | 7  |
| Increased alkaline phosphatase                    | 8(range:95iu/L-636iu/L;Mean SD=284.8±20.9) |
| Increased alanine aminotransferase                | 2 (22iu/L, 35 iu/L)                        |
| Increased aspartate aminotransferase              | 2 (23iu/L, 25 iu/L)                        |
| Decreased Albumin                                 | 2 (17g/L, 31g/L)                           |
| Increased Total bilirubin                         | 1 (17 µm/L)                                |
| HBsAg   |  |
| Positive  | 5  |
| Negative  | 3  |

\*chest or abdominal pain, some with general body pains

**Table 2:** Distribution of subjects by age group and sex

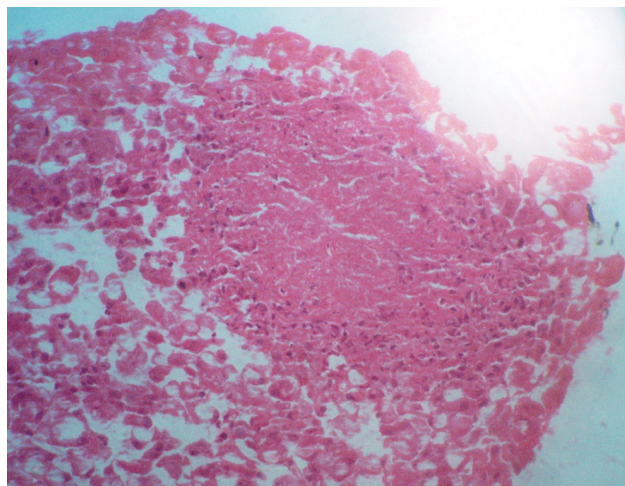
| <b>Age group (years)</b> | <b>Frequency N (%)</b> |             | <b>Total</b> |
|--------------------------|------------------------|-------------|--------------|
|                          | <b>Female</b>          | <b>Male</b> |              |
| 11-20                    | 1(1.5%)                | 0(0%)       | 1(1.5%)      |
| 21-30                    | 17(25.3%)              | 4(6%)       | 21(31.3%)    |
| 31-40                    | 8(12%)                 | 18(27%)     | 26(38.8%)    |
| 41-50                    | 7(10.4%)               | 9(13.3%)    | 16(23.9%)    |
| 51-60                    | 1(1.5%)                | 2(3%)       | 3(4.5%)      |
| Total                    | 34(50.7%)              | 33(49.3%)   | 67(100%)     |

sputum AFB, Mantoux test and gastric washings (in children) is poor ([Eamranond et al.2001]). And the non invasive fibrosis and other tests hardly specify if granulomas are present.

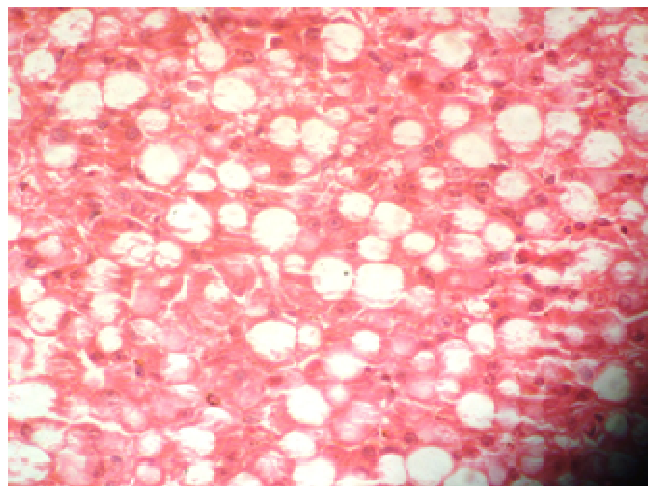
Some biochemical parameters may be deranged in TB of the liver. Kawashima et al (2000) recorded a persistent increased alkaline phosphatase in one study in Japan. In

our study, we discovered that 50% of those that had complete liver function test had increased alkaline phosphatase.

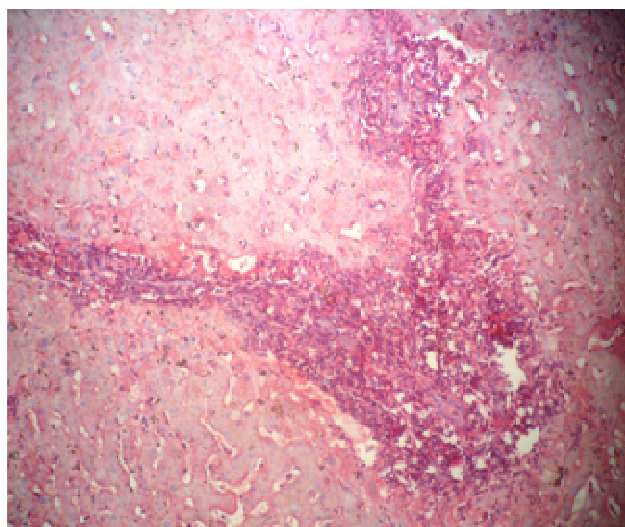
The second most common histological diagnosis was chronic hepatitis accounting for 19.4%. Sixty five percent of this had chronic active hepatitis. However, only 8 cases had serological test for hepatitis viruses with 5



**Figure 1.** Liver with a caseation granuloma. H&E stains. (X20 objective)



**Figure 2.** Liver with diffuse steatosis. H&E stains. (x20 objective)



**Figure 3.** Liver showing chronic hepatitis with moderate chronic inflammatory cells infiltrate and bridging necrosis connecting portal tracts from lower right to the left and top of the micrograph. H&E stains. (x20 objective)

being positive for hepatitis B virus infection (HBsAg +ve). Categorization of the chronic hepatitis by aetiology was not done due to dearth of facilities for assessment of various aetiological agents of chronic hepatitis in our centre. HIV and HBV/or HCV co-infection was a common finding in many studies in other parts of the world (Roger et al. 1996, Escartin Munoz-Ortiz et al. 1991, Martinez et al. 1994 ). Martinez et al (1994) reported that chronic hepatitis especially by HCV was the most common finding in their study. Co-infection of HIV and HBV or HCV is believed to be due to the common route of infection shared by these viruses. And co-infection of these viruses portends worse clinical outcome for the patients Goldin (1998).

The liver is known to react in a non specific way to debilitating diseases like cancers, HIV/AIDS, and tuberculosis (Scheuer 1980). In this study, 16.4% of the patients had nonspecific reactive hepatitis (NSRH) a finding similar to that reported by Wilkins et al (1991). However, Garcia-Ordonez et al (1993) reported a finding of as high as 34.5% in their study. Diffuse micro or macro vesicular steatosis accounted for 13.4% of the diagnosis although there was some degree of non specific fatty change associated with other diagnoses.

Liver cirrhosis was seen in 10.4% of the study population. Four of them had positive serological test for HBsAg. There was associated ongoing chronic inflammatory process. Only one out of the studied population had relatively normal histological picture although there were some dilated sinusoids and erythrophagocytosis.

## CONCLUSION

This study showed that the liver is frequently involved by TB and other opportunistic infections in HIV/TB co-infection irrespective of whether it's PTB, DTB or TBM. And the degree of involvement is sometimes not detected by most of the non invasive diagnostic techniques. This may worsen morbidity in these patients.

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