DIAGNOSING MULTIPLE OPPORTUNISTIC INFECTIONS: THE VALUE OF A LIVER BIOPSY

Jonathan G Peter, *MB ChB*

Mark W Sonderup, *FCP (SA)*

Division of Hepatology, Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town

Liver function test abnormalities are prevalent in patients with HIV, and in particular advanced HIV.[1] Opportunistic infections, drug hepatotoxicity and viral hepatitis co-infections are frequently encountered.[2-4] We present a patient with advanced HIV and abnormal liver function tests in whom the definitive diagnosis of multiple opportunistic infections was made by liver biopsy. This case illustrates the diagnostic value of liver biopsy in our local patient population, where diagnostic uncertainty is common and empiric therapy is often the standard of care.

A 33-year-old man was noted to be HIV positive in 2005 after a diagnosis of sputum-positive pulmonary tuberculosis (TB). He responded well to 6 months of standard TB therapy. The initial HIV diagnosis was made in Durban and he was lost to follow-up after moving to Cape Town.

In August 2007 he presented to a regional hospital in the Cape Town metropole with cryptococcal meningitis (cerebrospinal fluid culture positive for *Cryptococcus neoformans*, CLAT titre 1:2 048). At this stage his CD4 count was 116 cells/µl. He was initially treated with intravenous amphotericin B for 10 days followed by oral fluconazole 400 mg daily for 8 weeks. This was then reduced to a maintenance dose of 200 mg daily. He was also commenced on co-trimoxazole prophylaxis. He was referred to a regional antiretroviral (ARV) roll-out clinic but did not immediately attend for follow-up. Instead, in late November 2007 he again presented to the regional hospital emergency service with meningeal symptoms. Lumbar puncture again demonstrated a lymphocyte-predominant CSF that was CLAT positive (titre 1:296). The repeat CSF culture was negative.

A preliminary pre-ARV assessment was performed during this admission and abnormal liver function test (LFT) results were noted. He was not jaundiced and the liver profile abnormality was a mixed pattern with elevated transaminases and canalicular enzymes, both approximately 2 - 5 times above the normal range (Table I). Synthetic liver function was preserved. Despite withdrawal of co-trimoxazole, the patient's liver enzymes remained deranged and he was referred to our service for evaluation.

At evaluation, no history of alcohol, other drugs or toxin use was obtained. Clinically he was thin with no obvious lymphadenopathy or typical features of chronic liver disease. He had a modest hepatomegaly but no splenomegaly. He was pyrexial with a temperature of 38⁰C. An abdominal ultrasound scan demonstrated increased liver echogenicity, no biliary dilation, normal portal and hepatic vessels and no intra-abdominal lymph nodes or ascites. A viral hepatitis screen was negative. A repeat CD4 count was now 1 cell/µl. The pattern of liver enzyme abnormalities was unchanged. Of note on the chest radiograph were right upper lobe alveolar infiltrates.

An early morning sputum specimen was sent for TB assessment and all samples were negative for acid-fast bacilli. The initial sputum culture was positive for *Streptococcus pneumoniae* and he was treated appropriately.

A liver biopsy specimen demonstrated an unanticipated and uncommon finding of numerous intraparenchymal collections of histiocytes associated with numerous fungi in yeast forms. These were confirmed to be *C. neoformans* (Fig. 1). Additionally there was modest macrovesicular fatty change with no associated inflammation. A piece of the core of liver tissue was submitted for TB and fungal culture. The fungal culture was negative for cryptococcus, suggesting that the organisms were non-viable after the previous treatment.

After the biopsy findings, a diagnosis of sub-optimally treated disseminated cryptcococosis was made. The patient received 2 weeks of intravenous amphotericin B followed by oral fluconazole. He improved both clinically and in terms of LFT results. He was discharged in late January 2008 and an appointment for counselling and commencement of ARV therapy was made. Three weeks
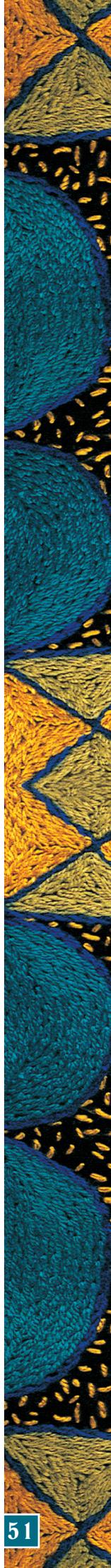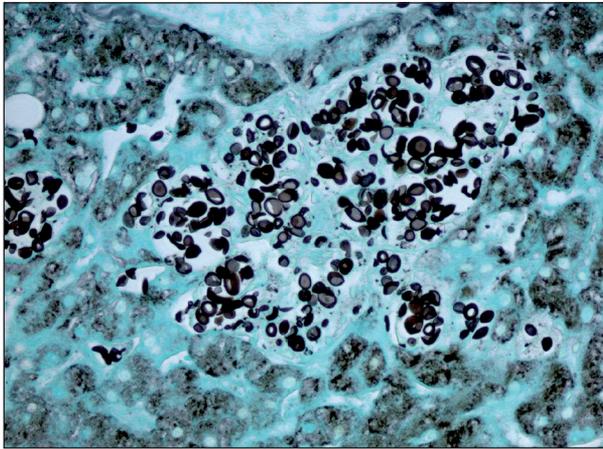
Fig. 1. Grocott stain of liver biopsy core demonstrating Cryptococcus neoformans.

later, before attending the ARV clinic, he was readmitted with a febrile illness. A chest radiograph demonstrated segmental right lower lobe consolidation with cavitation and right hilar lymphadenopathy. Sputum samples were now positive for acid-fast bacilli. *Mycobacterium tuberculosis* (MTB) was suspected.

All previous cultures were reviewed. Notably, the liver tissue as well as sputum previously submitted had cultured *M. intracellulare*. Retrospectively a modified Ziehl-Neelsen stain of the liver biopsy specimen was performed and was negative. The patient was commenced on rifabutin, clarithromycin and ethambutol and steadily improved. ARV therapy was commenced as an inpatient.

Notably, the patient's liver function progressively improved and he was discharged to a regional ARV clinic. He continues to do well, and recent LFT results are set out in Table I.

DISCUSSION

The investigation and management of patients with advanced HIV in South Africa often poses a multitude of diagnostic and therapeutic challenges. LFT abnormalities are a frequent finding in HIV-positive patients, with previous studies reporting a prevalence ranging between 30% and 75%.[1] Liver biopsy-based studies

have demonstrated the benefit of liver biopsy as a useful diagnostic tool in the setting of advanced HIV with pyrexia of uncertain origin and/or hepatomegaly and LFT changes.[4]

The patient described demonstrates the above together with several other issues. Firstly the liver biopsy provided a clear histopathological diagnosis. The finding of a prevalent opportunistic infection (OI) such as *C. neoformans* in the liver has not commonly been reported in the literature despite the pathophysiological tendency for widespread dissemination of cryptococcus following entry via the pulmonary route. In our own local experience this is the first case in which we have demonstrated it in the liver.

The second issue was the unexpected culture of *M. intracellulare*, or MAC (*M. avium* complex) as it is more commonly referred to, from the liver tissue. The presence of multiple OIs is not unusual in patients with advanced HIV/AIDS. What is unusual is finding MAC in our setting. In the pre-ARV era MAC was a frequent finding on liver biopsy in patients with advanced HIV in the developed world; however, as has been demonstrated previously, MAC appears to be uncommon in our local setting.[5] The reasons for this are not clear, but may relate to the overwhelming presence of *M. tuberculosis* in our HIV population. The culture of MAC in this patient demonstrates the additional value of liver biopsy in that it provided tissue for culture. As many OIs involve disseminated infection, liver tissue is a potential source of tissue for culture.

In summary, this case highlights the potential value of liver biopsy in patients with advanced HIV and abnormal LFTs where there is a wide range of differential diagnoses. Provided the procedure can be performed safely, liver biopsy both enables demonstration of the histological pattern of injury accounting for the LFT abnormalities and provides tissue for culture to diagnose opportunistic infections. In this case, an accurate diagnosis could be made following readmission and enabled appropriate treatment to be initiated.

TABLE I. LIVER FUNCTION TEST RESULTS

Parameter (normal range)	Dec 07	Jan 08	Feb 08	June 08
TBil (0 - 17)	3	6	87	17
ALT (0 - 40)	111	80	122	40
AST (0 - 40)	126	60	268	48
ALP (40 - 120)	277	190	332	100
GGT (0 - 35)	295	196	507	96

TBil = total bilirubin (μmol/l); ALT = alanine transaminase (IU/l); AST = aspartate transaminase (IU/l); ALP = alkaline phosphatase (IU/l); GGT = gamma-glutamyltranspeptidase (IU/l).

REFERENCES

1. Freedberg KA, Malabanan A, Samet JH, *et al.* Initial assessment of patients infected with HIV: the yield and cost of laboratory testing. *J Acquir Immune Defic Syndr* 1994; 7(11): 1134-1140.
2. Poles MA, Dieterich DT, Schwarz ED, *et al.* Liver biopsy findings in 501 patients infected with human immunodeficiency virus. *J Acquir Immune Defic Syndr* 1996; 11(2): 170-185.
3. Lanjewar DN, Rao RJ, Kulkarni SB, *et al.* Hepatic pathology in AIDS: a pathological study from Mumbai, India. *HIV Med* 2004; 5: 253-257.
4. Piratvisuth T, Siripaitoon P, Sriplug H, *et al.* Findings and benefit of liver biopsies in 46 patients infected with human immunodeficiency virus. *J Gastroenterol Hepatol* 1999; 14: 146-149.
5. Holmes CB, Wood R, Badri M, *et al.* CD4 decline and Incidence of opportunistic infections in Cape Town, South Africa: Implications for prophylaxis and treatment. *J Acquir Immune Defic Syndr* 2006; 42(4): 464-469.