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Reply

Sr:—We agree with Lo Re and Kostman [1] that hepatic steatosis may influence liver fibrosis progression in HIV–hepatitis C virus (HCV)–coinfected patients. Liver steatosis has been independently associated with both HIV infection and HCV infection (particularly infection involving HCV genotype 3). Moreover, the use of certain antiretroviral drugs—mainly protease inhibitors and some nucleoside analogues (e.g., stavudine and zidovudine)—and the metabolic abnormalities associated with their prolonged use (e.g., dyslipidemias and hyperglycemia) have been equally involved in fat accumulation in the liver [2]. However, despite its potential impact, the prevalence of steatohepatitis in HIV-HCV–coinfected patients seems to be lower than suspected. For instance, a recent analysis of 306 liver biopsy specimens obtained from HIV–HCV–coinfected individuals in the United States demonstrated that a proportion of hepatocytes with fat accumulation of >5% was seen in only 11% of patients [3]. The authors concluded that steatohepatitis was an uncommon finding in HIV-HCV–coinfected patients.

In our retrospective analysis of 914 liver biopsy specimens [4], we did not assess steatosis for several reasons. First, the aim of our study was to identify clinical predictors of liver fibrosis progression, and steatosis is a histologic feature. Second, attempts to determine the severity of steatohepatitis uniformly have been made only recently, and our liver biopsies were performed over a 10-year period, before that scale was available.

We do not believe that obesity and diabetes mellitus introduced a significant bias in our results. Although insulin resistance and hyperglycemia are common in HIV-HCV–coinfected patients [5], diabetes mellitus is less common (19%–6% of cases) [6]. Obesity is less prevalent among Europeans than among North Americans, and our findings are only derived from the former. Moreover, in a recent study, we analyzed plasma glucose and body mass index (BMI) values in a cohort of HIV-HCV–coinfected individuals, and the mean values (±SD) were only 103 ± 26 mg/dL and 22 ± 3 kg/m² for glucose plasma level and BMI, respectively. Therefore, whether there is a higher risk of steatohepatitis could not be determined using these metabolic parameters.

Liver fibrosis progression is clearly accelerated in HIV-HCV–coinfected patients, compared with HCV-monoinfected individuals [7]. Our study identified older age, alcohol abuse, and CD4 T cell count of <500 × 10⁶ cells/L as independent predictors of advanced liver fibrosis. The possible contribution of other factors, including steatohepatitis, if relevant, remains to be demonstrated.

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and is a condition that is often associated with elevated intracranial pressure (ICP) of $\geq 200$ mm H$_2$O in $\geq 50\%$ of cases [2]. Elevated ICP may result in increased mortality and morbidity. In a study by Van der Horst et al. [3], almost all of the early deaths (13 of 14) and 40% of the deaths during weeks 3–10 were associated with elevated ICP. Visual loss was also observed as a consequence of elevated ICP [4]. Frequent lumbar punctures have been advocated for the management of increased ICP [2, 5]. However, the risk of brain herniation as a result of frequent lumbar punctures for elevated ICP has been a major concern among clinicians [6, 7]. Here, we present our experience with frequent lumbar punctures and large-volume drainage of CSF in the management of extremely high ICP (>600 mm H$_2$O) in HIV-infected patients who had cryptococcal meningitis.

Between June 1994 and August 2003, a total of 35 patients were given a diagnosis of cryptococcal meningitis on the basis of a CSF culture positive for Cryptococcus neoformans or a positive result of a CSF cryptococcal antigen test or CSF India ink smear. During the study period, lumbar puncture was performed according to a standardized protocol after obtaining written informed consent from patients or their family members. CT of the brain was performed to rule out mass lesions before performing lumbar puncture for patients suspected of having cryptococcal meningitis. The frequency of the lumbar puncture was determined by previous pressure levels and the symptoms of the patients. If the patient’s initial opening pressure was $\geq 350$ mm H$_2$O, lumbar puncture was performed daily to drain 20–30 mL of CSF until the pressure was <350 mm H$_2$O. Later, we performed lumbar puncture every 2–3 days until the pressure measured <200 mm H$_2$O, followed by 1 lumbar puncture per week until the patient’s discharge from the hospital.

For each patient, a standardized case-record form was used to document the initial opening and closing pressures of lumbar punctures and the results of CSF analysis, which included fungal culture, India ink smear, WBC count, and tests for levels of glucose, protein, and cryptococcal antigen. Age, sex, risk factors, CD4/CD8 cell count, peripheral virus load when cryptococcal meningitis was diagnosed, and antiretroviral therapy received were also recorded. Amphotericin B at a daily dosage of 0.8–1 mg/kg was administered as induction therapy for 2–3 weeks, followed by maintenance therapy with oral fluconazole. The patients were followed up until death, loss to follow-up, or the end date of the study (31 December 2003).

There were 9 patients who had ever had extremely high ICP; 5 patients had extremely high ICP at presentation, and 4 developed extremely high ICP during hospitalization. They were all male patients, with a median age of 32 years (range, 23–57 years). Seven patients developed concurrent cryptococcosis, and 2 had cryptococcal pneumonia. Three patients developed diplopia, and 1 had blurred vision. Five patients had altered consciousness at presentation, and 2 other patients developed this complication during the hospital stay. The median initial WBC count in the CSF was 0 cells/µL (range, 0–5 cells/µL), and the median initial CSF cryptococcal antigen titer was 1:1024 (range, 1:512 to 1:65536). The median CD4 count at the time of diagnosis of cryptococcal meningitis was 25 cells/µL (range, 9–53 cells/µL).

The patients underwent multiple lumbar punctures and received glycerol or mannitol for increased ICP. The median number of lumbar punctures performed was 6 (range, 1–29). A lumbar drain was placed in one patient, and another patient underwent ventriculoperitoneal (VP) shunting for refractory elevated ICP. The median duration of follow-up was 360 days (range, 1–1009 days). The condition of the patient who developed visual loss because of extremely high ICP improved with external CSF drainage. The median duration from hospital admission to the initiation of treatment with amphotericin B was 1 day (range, 1–3 days). The median durations of treatment with amphotericin B and fluconazole were 22 days (range, 1–44 days) and 312 days (range, 0–900 days), respectively.

Death directly attributed to cryptococcal meningitis occurred in 2 patients. One patient presented with nausea and vomiting followed by altered consciousness and seizures, which occurred before lumbar puncture was performed. Signs of increased ICP (headache, nausea, and vomiting) resolved gradually, and the altered consciousness returned to normal after another lumbar puncture and concurrent administration of amphotericin B and fluconazole. However, later, altered consciousness and profound shock developed, and a follow-up lumbar puncture revealed an opening CSF pressure of $\geq 600$ mm H$_2$O. The second patient, who had a 1-month history of cavitary pneumonia, presented with altered consciousness and septic shock due to cryptococcal fungemia, meningitis, and pneumonia before a lumbar puncture was performed. The patient died on the third day of hospitalization, despite the initiation of treatment with amphotericin B soon after the lumbar puncture.

Except for the 2 patients who died and the patient with VP shunt placement, the patients had an ICP of <400 mm H$_2$O after a median of 3.5 lumbar punctures (range, 1–27). Only 1 patient had a relapse episode, which occurred after treatment with amphotericin B for 13 days and oral fluconazole for 15 days. Of the other 26 patients without extremely high ICP, 11 patients remained alive and 14 patients died, with 3 deaths directly caused by cryptococcal meningitis.

Elevated ICP due to cryptococcal meningitis was postulated to be the result of failed CSF reabsorption in the channels of subarachnoid villi and lymphatic vessels due to elevated CSF viscosity, the accumulation of fungal polysaccharides that form microscopic plugs, and the fungal cells themselves [4, 8]. External lumbar drainage by daily lumbar puncture, inser-
tion of a lumbar drain, or implantation of a VP shunt is recommended if neither focal neurologic signs nor obtunded consciousness with space-occupying lesions visible by radiographic imaging were observed [2, 9]. However, frequent lumbar punctures and large-volume drainage in the presence of elevated ICP have raised concerns among clinicians about the risk of brain herniation [6]. Antinori and colleagues [6] reported 2 cases of cryptococcal meningitis in patients who experienced loss of consciousness and died soon after lumbar puncture. At autopsy, brain herniation was considered by Antinori et al. [6] to be the cause of death; however, inadequate CSF drainage and the resultant brain herniation—not the lumbar puncture—was suspected by Graybill and Sobel [10] to be the cause of death.

In our patients with cryptococcal meningitis who had extremely high ICP and poor prognostic predictors of death during initial therapy (i.e., abnormal mental status, a CSF antigen titer of >1:1024, and a CSF WBC count of <20 × 10^3/µL [11]), we found that, with frequent, multiple lumbar punctures combined with antifungal therapy consisting of amphotericin B and fluconazole, 7 patients survived the disease. The condition of the patient who developed visual loss because of extremely high ICP improved with our aggressive external CSF drainage. The 2 deaths were most likely caused by delayed presentation for appropriate HIV care. In 1 of the 2 patients, signs of increased ICP resolved gradually, and altered consciousness returned to normal after multiple procedures. However, extremely high ICP recurred and resulted in death. This case should alert clinicians to the possibility of recurrent high ICP despite antifungal therapy, and careful monitoring of the ICP is indicated.

In conclusion, the findings of our study support the recommendation of aggressive use of lumbar puncture for the management of elevated ICP to reduce the risk of early mortality and late morbidity, even for patients with extremely high ICP. Multiple lumbar punctures and large-volume CSF drainage in HIV-infected patients with elevated ICP due to cryptococcal meningitis is safe after the presence of space-occupying lesions is excluded.

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Hemophagocytic Syndrome in a Patient with Acute Human Immunodeficiency Virus Infection

Sr.—In their recent case report, Sproat et al. [1] described a patient with advanced HIV infection and hemophagocytic syndrome (HPS) who did not respond to HAART, and they underlined the fact that HPS caused by HIV infection alone has not been widely reported.

Recently, we observed an acute HIV infection complicated by severe HPS that occurred in a 27-year-old Italian man. The patient was admitted to our institution (Ospedale Belcolle, Viterbo, Italy) with a 7-day history of fever (temperature, 40°C), headache, sore throat, and malaise. At admission, he had a diffuse rash, generalized lymphadenopathy, and hepatosplenomegaly. Laboratory results showed mild anemia (Hb 9.8 g/dL), leukopenia (WBC count, 3400 cells/mm³), and raised enzyme levels (alanine aminotransferase, 468 U/L; γ-glutamyl transferase, 1.974 U/L; lactate dehydrogenase, 9.404 mU/mL). The patient denied having any risk behaviors for HIV infection. His serum sample was initially negative for HIV antibody by ELISA and Western blotting. Antibodies to Epstein-Barr virus, cytomegalovirus, herpes simplex virus, parvovirus B19, hepatitis C virus, and Toxoplasma gondii were absent, as was antibody to hepatitis B surface antigen. The patient’s CD4+ lymphocyte count was 138 cells/mm³ (CD4+ percentage, 22%), with a CD4+:CD8+ ratio of 0.66. A total body CT scan showed he-