Severe Hepatic Failure Related to Nevirapine Treatment

Nevirapine, a nonnucleoside reverse transcriptase inhibitor, has recently been introduced in combination antiretroviral therapy for HIV type 1–positive patients. Major adverse effects associated with nevirapine are rash (occurring in 32–48% of patients) [1, 2], transient sedation, headache, nausea and/or vomiting [3], and other severe mucocutaneous reactions [4]. Herein, we report the case of an HIV-positive patient who developed severe hepatic failure related to nevirapine.

A 61-year-old man who had been HIV-positive since 1992 and did not have any specific HIV-related infections was admitted to our hospital with fever, arthralgia, abdominal pain, vomiting, and dark urine. In 1996, he began receiving antiretroviral therapy with di-
danosine and zidovudine, but later in July 1997, this treatment was switched to stavudine and lamivudine because of high levels of HIV RNA (46,500 copies/mL; Amplicor Monitor, Roche Molecular Systems, Perkin-Elmer, Branchburg, NJ). His CD4+ cell count was always >500/μL. Two weeks before admission, nevirapine (at a 15-day lead-in dosage of 200 mg/d) was added to previous antiretroviral therapy with stavudine (40 mg twice daily) and lamivudine (150 mg twice daily). He was not taking any other medications and had no history of drug allergies or chronic hepatitis.

At the time of admission, physical examination revealed a temperature of 39.2°C, marked scleral jaundice, distended abdomen, and moderate hepatomegaly. Initial laboratory studies disclosed the following values: leukocytes, 14.4 × 10^9/L (80% neutrophils, 10% lymphocytes, and 3% eosinophils); aspartate aminotransferase, 255 U/L (normal, <55 U/L); alanine aminotransferase, 337 U/L (normal, <55 U/L); γ-glutamyltransferase, 443 U/L (normal, <65 U/L); alkaline phosphatase, 237 U/L (normal, <128 U/L); lactate dehydrogenase, 713 U/L (normal, <380 U/L); prothrombin time, 35%; total bilirubin, 62.2 µmol/L (conjugated bilirubin, 55.4 µmol/L); and hypoalbuminemia (serum albumin, 29 g/L). The C-reactive protein level was 153 mg/L (normal value, <6 mg/L), and the erythrocyte sedimentation rate was 35 mm/h (normal range, 0–20 mm/h). Other findings of biochemistry and hematologic studies were normal. Abdominal ultrasonography disclosed enlargement of the liver with a nonhomogeneous echotexture and abundant ascites, but no focal lesions and splenomegaly were found. No thrombosis of the hepatic veins was revealed.

After a 3-day hospital stay, an itching skin reaction appeared on his face and trunk. Therapy with nevirapine, stavudine, and lamivudine was discontinued, and supportive care with administration of intravenous fluids and antihistamines was started.

Laboratory evaluation showed a further increase in the leukocyte count (18.33 × 10^9/L) with 46% eosinophils (eosinophil count, 8.33 × 10^9/L) and an abrupt rise in the IgE value to 1,735 kU/L (normal value, <200 kU/L). Multiple blood and urine cultures were negative, as were examinations for infections and neoplastic cells in the ascitic fluid. Serologies for herpes simplex virus types 1 and 2, cytomegalovirus, and hepatitis A, B, and C viruses were negative. Cytomegalovirus viremia and hepatitis B virus DNA were also not found. No autoantibodies (antinuclear, anti-smooth muscle, antimitochondrial, or antireticulium) were found.

Because the patient had worked for >20 years in Malawi, additional specific diagnostic tests for parasitic infections were performed to complete the evaluation. Both urine and stool examinations as well as sigmoidoscopy with biopsy were negative for Schistosoma haematobium and Entamoeba histolytica; microscopy and culture of bone marrow smears were negative for Leishmania. All serological tests for parasitic infections were negative. Furthermore, the diagnoses of malaria and filariasis were ruled out by several microscopic examinations of thick and thin blood smears.

Within 2 weeks, the patient’s symptoms abated with subsequent, although slow, complete resolution of ascites and rash. Liver enzyme levels, eosinophilia, C-reactive protein level, and prothrombin time returned to normal. The patient was discharged 30 days later. Triple combination therapy with stavudine and lamivudine at the same dosages and saquinavir, which replaced nevirapine, was reintroduced. After 1 month of follow-up, no new adverse events were reported.

We believe that in this case, the connection between liver failure and nevirapine is evident even if the patient did not receive nevirapine therapy again. Until now, no data have been reported about the mechanism of nevirapine-induced liver disease; nevertheless, nevirapine could be considered both an intrinsic hepatotoxin and an idiosyncratic drug. Clinicians need to be aware of this potential liver injury and consider performing liver function tests during the first weeks of antiretroviral combination therapy including nevirapine.

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References

A 9-week-old female infant was admitted to the hospital in November 1996 because of several weeks’ history of failure to thrive, irritability, intermittent vomiting, and pallor. Physical examination revealed massive hepatosplenomegaly, and laboratory investigation showed leukocytosis (leukocyte count, 670 × 10^9/L with >95% blast cells). Examination of a bone marrow aspirate showed a gross infiltration with lymphoblasts displaying early pre-B phenotype (CD10+, CD19+, CD33+, CD34+, TdT+), and cytogenetic analysis revealed chromosomal translocation t(4;11)(q21;q23) typical of infantile acute lymphoblastic leukemia. Multigent phase II chemotherapy (Childrens’ Cancer Group study no. 1,953) was started, and despite numerous interruptions because of severe mucositis, sepsis, and systemic candidiasis, the induction and consolidation phases of her chemotherapy were delivered successfully. Since then, she has remained in remission, has continued...