Acute HIV Infection in a Critically Ill 15-Year-Old Male

A 15-year-old previously healthy male presented with fever, vomiting, diarrhea, malaise, and altered mental status. In the emergency department, the patient appeared acutely ill, was febrile, tachycardic, hypotensive, and slow to respond to commands. He was quickly transferred to the ICU where initial evaluation revealed elevated white blood cell count and inflammatory markers, coagulopathy, abnormal liver function, and renal failure. Head computed tomography, cerebrospinal fluid studies, and blood cultures were negative. He was quickly stabilized with intravenous fluids and broad-spectrum antibiotics. When his mental status improved, the patient consented to HIV testing and was found to be negative using laboratory-based and rapid third-generation HIV type 1 (HIV-1)/HIV type 2 antibody assays. The specimen was subsequently shown to be positive for HIV by a newly licensed fourth-generation antigen/antibody test. HIV-1 Western blot performed on this sample was negative, but molecular testing for HIV-1 RNA 4 days later was positive and confirmed the screening result. The patient was later determined to have a viral load of 5,624,053 copies/mL and subsequently admitted to unprotected receptive anal intercourse 2 weeks before admission. This case demonstrates an atypically severe presentation of acute HIV infection with important lessons for pediatricians. It highlights the need to consider acute HIV infection in the differential diagnosis of the critically ill adolescent and for appropriate testing if acute infection is suspected. This case also illustrates the shortcomings of testing adolescents based only on reported risk and supports Centers for Disease Control and Prevention and American Academy of Pediatrics recommendations for routine testing. Pediatrics 2013;131:e959–e963
Currently, there are more than 1 million people living in the United States with AIDS caused by HIV infection. Although the incidence of HIV in the United States has stabilized at ~50 000 new infections each year, nearly one-third of new infections occur among adolescents and young adults aged 13 to 24, with rates increasing among young men who have sex with men and youth of color. It is essential to rapidly identify youth who recently have been infected with HIV to improve individual health outcomes and to prevent secondary transmission. Clinicians must maintain a high suspicion for acute or primary HIV infection, as appropriate testing and treatment strategies may differ during this period and because, from a public health perspective, patients are more likely to transmit HIV during this stage of active viral replication. Here we describe an atypical presentation of acute HIV infection (AHI) in a 15-year-old critically ill male.

PATIENT PRESENTATION

A 15-year-old previously healthy African American male presented with 3 days of fever to 39.4°C; progressively nonbloody, nonbilious vomiting; and watery, nonbloody diarrhea to the point where he became incontinent of stool. The patient was also noted to be extremely fatigued with slow mentation. His review of systems was significant for diffuse abdominal pain, chest pain, shortness of breath, headache, and photophobia. He denied any rash, visual changes, sore throat, recent travel, or sick contacts. His past medical history was significant for glucose-6-phosphate dehydrogenase deficiency and behavioral problems that required inpatient psychiatric treatment 4 months before admission. He had been prescribed aripiprazole, sertraline, trazodone, and dextroamphetamine and amphetamine, but had not taken any of these medications for more than 1 month before admission.

At the time of admission, he reported sexual activity with 2 lifetime partners, both female, and reported intermittent condom use. He denied any alcohol or drug use.

On arrival to the emergency department, the patient appeared acutely ill, with febrile to 39.2°C, tachycardic to 120 beats per minute, hypotensive to 80s/50s, with a normal respiratory rate of 20 and oxygen saturation of 100% on room air. He was oriented, although extremely slow to respond to questioning. His head, eyes, ears, nose, and throat; and cardiac, respiratory, and musculoskeletal examinations were normal. His abdominal examination was significant for minor diffuse tenderness, but no guarding or rebound, and no hepatosplenomegaly. He had inguinal adenopathy consisting of multiple small (<1.0 cm), contiguous lymph nodes, and no skin rash or petechiae. On neurologic examination, the patient was difficult to arouse and slow, but appropriate to respond to questions. He was oriented ×3. Pupils were equal, round, reactive to light and accommodation. Funduscopic examination was within normal limits. Initial laboratory evaluation revealed a white blood cell (WBC) count of 21.3 \times 10^3/\mu L with a left shift (62% segmented neutrophils, 16% bands, and 16% lymphocytes); hemoglobin of 14.2 g/dL; hematocrit of 42.9%; and a platelet count of 164 \times 10^3/\mu L. Serum chemistry showed evidence of mild acute renal failure with a serum urea nitrogen of 32 mg/dL (normal 7–20 mg/dL), creatinine of 1.5 mg/dL (normal 0.7–1.2 mg/dL), and a calcium of 8.5 mg/dL (normal 8.8–10.1 mg/dL). Sodium, potassium, bicarbonate, glucose, and chloride were all within normal limits. The patient also had abnormal liver function tests with an elevated total bilirubin of 1.9 mg/dL (normal 0.6–1.4 mg/dL), mostly unconjugated at 1.4 mg/dL (normal 0.2–1 mg/dL) and an aspartate aminotransferase that was slightly elevated at 94 (normal 15–40 U/L). Tests for γ-glutamyl transpeptidase, alanine aminotransferase, lactate, and total protein were all normal. A C-reactive protein was elevated at 7 mg/dL (normal 0–0.9 mg/dL). The patient was also found to have a coagulopathy with a prothrombin ratio/international normalized ratio of 18.5 seconds (normal 11.0–13.5 seconds) and 1.71 respectively. His lactate dehydrogenase was elevated at 1468 U/L (normal 105–333 U/L), with a uric acid of 4.1 mg/dL (normal 2.4–7.8 mg/dL). His urinalysis was significant for 1+ protein (30 mg/dL), moderate ketones, 0 to 2 red blood cells, and 5 to 10 WBCs with negative leukocytes and nitrites. His urine drug screen was negative. Because of concern for sepsis and his altered mental status, blood, urine, and cerebrospinal fluid (CSF) were obtained for culture. CSF studies revealed a WBC count of 2 and a red blood cell count of 10, with a total protein of 25 (normal 15–40 mg/dL) and a glucose of 73 (normal 32–82 mg/dL). Rare WBCs with no organisms were seen on the CSF Gram stain. A head computed tomography (CT) scan was also performed and was normal.

On arrival to the emergency department, the patient was aggressively treated with 4 L of crystalloid solution to improve his blood pressure and tachycardia. He was empirically started on vancomycin and cefotaxime and admitted to the ICU for concern of sepsis and impending circulatory failure. He was continued on vancomycin and cefotaxime for 48 hours after admission, and given vitamin K for his coagulopathy. While in the ICU, further evaluations included a chest x-ray, an electrocardiogram, and tests for cardiac enzymes because of his chest pain;
all were normal. His cell counts and chemistries showed an improvement of bandemia, lowered WBC count, and thrombocytopenia over time. Other tests performed included real-time polymerase chain reaction assays for adenovirus; respiratory syncytial virus types A and B; influenza virus types A and B; parainfluenza virus types 1, 2, and 3; metapneumovirus; and rhinovirus from respiratory secretions and for herpes simplex virus types 1 and 2, enteroviruses, and parechoviruses from CSF; all were found to be negative. Stool was sent for cultures of enteric bacterial pathogens; rapid antigen tests for rotavirus, adenovirus types 40 and 41, Giardia, and Cryptosporidium; real-time polymerase chain reaction for norovirus genogroups I and II; and ova and parasite examination and negative results were obtained. Because of his reported sexual activity, blood specimens were submitted for rapid plasma reagin and diagnosis of HIV using laboratory-based and rapid third-generation HIV type 1 (HIV-1)/HIV type 2 (HIV-1/2) antibody tests. Results of this testing were negative as well. The patient was taken off vancomycin and cefotaxime after 48 hours of negative blood, urine, and CSF cultures, but repeat blood and urine cultures were sent on day 3 because of continued fevers.

By the third day of admission, the patient’s clinical condition had improved and he was transferred to the floor for further management, at which time he continued to be febrile and complained of abdominal pain and right hip pain. A 7-day course of cefotaxime was started because of concern for culture-negative sepsis or toxic shock syndrome. An enzyme immunoassay for Clostridium difficile toxins A and B was positive at this time and the patient was also started on a 10-day course of metronidazole. A CT scan of his abdomen and pelvis was obtained to evaluate for persistent abdominal and right hip pain and continued fever. The CT scan was significant for the presence of free fluid in his pelvis and scattered subcentimeter lymph nodes, but no bowel wall thickening and no sign of acute intraabdominal process, organomegaly, abscesses, or osteomyelitis. His symptoms of watery diarrhea began to resolve before starting metronidazole. The description of voluminous, watery diarrhea, a lack of evidence of colitis on radiography, the limitations of C. difficile testing to distinguish colonization from active disease, and the spontaneous resolution of symptoms before appropriate treatment suggest that C. difficile infection was an unlikely cause of his diarrhea or overall illness. 7–9 His transaminitis worsened over time with a peak alanine aminotransferase test of 240 U/L (normal 10–45 U/L) and aspartate aminotransferase test of 432 U/L (normal 15–40 U/L) on day 8 of admission.

There were also several hematologic abnormalities throughout the hospitalization. Atypical lymphocytes ranging from 2% to 13% (normal 0%–0%) and elevated monocytes of 1% to 13% (normal 3%–8%) were consistently noted in the differential of his complete blood count. The patient had worsening thrombocytopenia to a nadir of 74 000/μL (normal 150–400) on day 5 of admission with a low absolute neutrophil count to a nadir of 612/μL. Findings consistent with hemolysis included a significantly elevated lactate dehydrogenase, undetectable haptoglobin, large amounts of blood on urinalysis with absence of microscopic hematuria, elevated indirect bilirubin, schistocytes on an early smear, and a mild normocytic, normochromic anemia. These findings are possibly explained by severe hemolytic crisis resulting from acute illness that has been previously reported in a patient with glucose-6-phosphate dehydrogenase deficiency and primary HIV infection. 10

Despite clinical improvement, the primary team caring for the patient was concerned that AHI was the cause of the patient’s illness and requested that additional HIV-related testing be performed on the blood specimens submitted to the laboratory. The patient’s initial specimen was subsequently shown to be positive for HIV by a newly licensed fourth-generation antigen/antibody test (Architect HIV Ag/Ab Combo Assay; Abbott Diagnostics, Abbott Park, IL) that, at the time, had been recently validated and implemented in the hospital’s Clinical Virology Laboratory. An HIV-1 Western blot done on this sample was negative, but a nucleic acid amplification test (NAAT) for HIV-1 RNA (Gen-Probe APTIMA HIV-1 RNA Qualitative Assay; Gen-Probe, Inc., San Diego, CA) performed on a specimen collected 4 days later was positive and confirmed the screening test result. The patient was later determined to have a viral load of 5 624 053 copies/mL. See Table 1 and Fig 1 for a summary of results obtained for the HIV-related testing performed. The patient later admitted to having unprotected receptive anal intercourse ~2 weeks before admission, which was his first sexual encounter with another male whom he had met on the Internet.

By day 9 of admission, the patient’s fevers and diarrhea had resolved and coagulopathy, thrombocytopenia, and transaminitis had all improved. He was discharged on day 9 of admission with follow-up at the hospital’s adolescent HIV clinic. Results of the third-generation rapid HIV-1/2 antibody-only assay and HIV-1 Western blot were positive at the first clinic follow-up visit 2 weeks after discharge following negative results during the patient’s hospital course.

**DISCUSSION**

This case represents an atypically severe, yet instructive presentation of AHI in a critically ill adolescent. AHI, also
known as primary HIV infection, is defined as the time from HIV acquisition until seroconversion. AHI can be difficult to diagnose because symptoms are usually nonspecific, as was observed with our patient. Symptoms typically include fever, fatigue/malaise, headache, rash, myalgias or arthralgias, vomiting or diarrhea, anorexia or weight loss, pharyngitis, lymphadenopathy, and mucocutaneous ulcers, which are easily confused with infectious mononucleosis or influenza-like illnesses. More than half of patients will experience at least some symptoms of AHI. Symptoms typically develop within 1 to 4 weeks after transmission and usually last for 2 to 4 weeks. The case presented here was atypical in its severity, but the patient’s symptoms were consistent with AHI and many of his laboratory findings, including transaminitis, thrombocytopenia, and atypical lymphocytosis, are representative of acute infection. Clinicians must maintain a high suspicion and be aware of appropriate testing to make the diagnosis of AHI. The diagnosis of AHI in our case would have been missed if clinicians caring for this patient had relied solely on the results of the third-generation HIV-1/2 antibody tests. As evidenced by the initial negative test results on multiple specimens examined in this case, laboratory-based third-generation antibody assays or the more rapid, point-of-care antibody screening tests will often fail to detect patients with AHI who have not yet seroconverted and it can take more than 3 weeks to develop and detect the presence of antibodies to HIV. If acute infection is suspected, an NAAT or fourth-generation antigen/antibody combination test should be used and are more likely to detect early infection. Depending on the assay selected, NAATs can detect proviral DNA or viral RNA in the blood of a patient as soon as 7 to 10 days after exposure and the fourth-generation antigen/antibody test can

TABLE 1 Summary of Case Patient’s HIV-related Test Results

<table>
<thead>
<tr>
<th>Test Performed</th>
<th>Specimen Collection Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>02/15/11</td>
</tr>
<tr>
<td>Abbott Diagnostics 3rd Gen HIV-1/2 EIA</td>
<td>NR</td>
</tr>
<tr>
<td>Orasure OraQuick Advance Rapid HIV-1/2 IA</td>
<td>NR</td>
</tr>
<tr>
<td>Maxim Biomedical HIV-1 Western blot</td>
<td>NR</td>
</tr>
<tr>
<td>Abbott Diagnostics fourth Gen HIV Ag/Ab CMIA</td>
<td>RR (S/CO: 5.47)</td>
</tr>
<tr>
<td>Gen-Probe APTIMA Qualitative HIV-1 RNA</td>
<td>ND</td>
</tr>
<tr>
<td>Abbott Molecular Quantitative RealTime HIV-1 RNA copies/mL</td>
<td>ND</td>
</tr>
</tbody>
</table>

CD4+ cells/µL | ND | ND | ND | 655 | 590 | 500

Ab, antibody; Ag, antigen; CMIA, chemiluminescent microparticle immunoassay; EIA, enzyme immunoassay; Gen, generation; IA, immunoassay; ND, not done; NR, nonreactive; POS, positive; R, reactive; RR, repeatedly reactive; S/CO, signal-to-cutoff ratio. OraQuick Advance Rapid HIV-1/2 is manufactured by OraSure Technologies based in Bethlehem, Pennsylvania. HIV-1 Western blot is Maxim Biomedical, Inc, Rockville, MD.
detect p24 antigen within 10 to 14 days of exposure. Based on the availability of multiple consecutive specimens that were collected and the history provided for this patient, Fig 1 and Table 1 detail the appearance and magnitude of the various markers of HIV infection during the time course from acute infection to seroconversion in this patient.

Once an adolescent patient has been diagnosed with AHI, an infectious disease or other pediatric/adolescent HIV specialist should be consulted to determine further management. Individuals diagnosed with AHI should be counseled on the need for safer sex practices, including using condoms for oral, anal, and vaginal sex. Additionally, providers may consider starting antiretroviral therapy during acute infection, which may theoretically lead to preservation of immune function and decrease the likelihood of onward transmission by suppressing viral load. However, in addition to concerns related to treatment immediately after diagnosis, a time of psychological distress and development of resistance if the highest levels of adherence are not achieved, studies thus far have failed to show long-term benefit of initiating antiretroviral therapy during acute infection. Given the various options and challenges to consider, diagnosis during AHI represents a key time to link a young person to a pediatric or adolescent HIV care team that will assume long-term care of the patient and work with the youth to make difficult decisions and develop the best treatment plan.

In conclusion, it is important that providers obtain a sexual history and test for acute infection when they have a suspicion, because early identification of infection and linkage to care can improve health outcomes and provide opportunities for prevention of transmission. Identifying patients with AHI is particularly important because viral replication is high during this period and patients are more likely to transmit HIV through unprotected sex if they are unaware of their diagnosis. As nicely illustrated in this case, other studies have shown that patients often do not report their specific HIV-risk factors to providers, underscoring the importance of routine screening for adolescents in primary care settings and testing adolescents who present with symptoms consistent with acute infection regardless of reported risk.

REFERENCES

8. Torre D. Is Clostridium difficile the leading pathogen in bacterial diarrhea in HIV type 1-infected patients? Clin Infect Dis. 2006;42(8):1215–1216, author reply 1216
15. Perlata L, Deeds BG, Hipszer S, Ghaliib K. Barriers and facilitators to adolescent HIV testing. AIDS Patient Care STDS. 2007;21(6):400–408
Acute HIV Infection in a Critically Ill 15-Year-Old Male
Nadia Dowshen, Virginia M. Pierce, Allison Zanno, Nicole Salazar-Austin, Carol Ford and Richard L. Hodinka
Pediatrics 2013;131;e959
DOI: 10.1542/peds.2012-1533 originally published online February 18, 2013;
Acute HIV Infection in a Critically Ill 15-Year-Old Male
Nadia Dowshen, Virginia M. Pierce, Allison Zanno, Nicole Salazar-Austin, Carol Ford and Richard L. Hodinka
*Pediatrics* 2013;131;e959
DOI: 10.1542/peds.2012-1533 originally published online February 18, 2013;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/131/3/e959