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A Flu-Like Illness

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Patient Report

A 15-year-old boy whose past medical history was significant for tuberculosis exposure treated with 9 months of single-drug therapy presented to an outside hospital with a 2-day history of fever, fatigue, cough, rhinorrhea, sore throat, and nonbloody diarrhea. The patient denied any sick contacts or recent travel. The result of a rapid influenza test was negative, and the patient was found to have a white blood cell (WBC) count of 3800/mm³. The patient was discharged with a presumptive diagnosis of a viral syndrome and was prescribed a combination of antipyretics and fluids.

Five days later, he was transferred to our institution after presenting to the same outside hospital with persistent fever, increased fatigue, worsening abdominal pain, nausea, coffee-ground emesis, and a new complaint of tea-colored urine. Upon admission, a thorough review of the patient's social history was obtained using the adolescent (Home, Education, Activities, Drug use, Sexual contacts and Suicidal ideations and depression (HEADSS) format. The only pertinent positives noted were that the child lived in a mobile home located in a rural wooded area and owned a dog known to have ticks. He denied sexual contact at that time.

The patient was febrile on admission (102.0°F) but was not tachycardic. His examination was significant for bilateral tonsillar ulceration, lymphadenopathy in the posterior cervical and inguinal regions, and diffuse abdominal pain without peritoneal signs. His

laboratory values on admission were significant for elevated liver transaminases, with aspartate aminotransferase (AST) at 672 U/L and alanine aminotransferase (ALT) at 205 U/L; a platelet count of 99 000/µL, and a WBC count of 2800 cells/mm³ with 47% neutrophils, 12% bands, and 35% lymphocytes. Urinalysis was positive for 300 mg/dL protein, 10 to 20 WBC per field, 3 to 6 red blood cells (RBCs) per field, and negative leukocyte esterase and nitrates.

Urine, blood, stool, and throat cultures were obtained, and the patient was started empirically on antibiotics, antipyretics, and fluids. Results of serology for Epstein-Barr virus, HIV, hepatitis A, B, and C all returned negative. Abdominal and chest radiographs were unremarkable.

Owing to his hematuria and proteinuria in conjunction with a history of pharyngitis, an anti-streptolysin O titer, antinuclear antibody, immunoglobulin A, C3, C4, anti-neutrophil cytoplasmic antibodies, anti-myeloperoxidase, and ant basement membrane antibodies were ordered, the results of all of which were negative. Repeat transaminases remained elevated with an AST of 263 U/L and ALT of 93 U/L. His platelet count dropped to a low of 81 000/µL.

Hospital Course

During the following week, his cultures remained negative, his thrombocytopenia resolved, and his transaminases normalized, but the proteinuria and fever persisted. Owing to continued fever with pulse-dissociation, serology and cultures were sent for the more common pathogens associated with this finding. Findings included negative results for *Legionella*, *Salmonella typhi*, and *Chlamydia psittaci* but a positive result for *C trachomatis*. Subsequent reexploration of the patient's sexual history yielded his admission to having unprotected sex with 3 women since becoming sexually active 2 years earlier.

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By this time, he was clinically well enough to be discharged home. Before discharge, a polymerase-chain reaction (PCR) HIV viral load was ordered. His viral load returned at >750 000 copies/mL, confirming a diagnosis of acute HIV-1 infection. He is currently receiving treatment through the pediatric infectious disease clinic.

Commentary

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Diagnosis: Acute HIV-1 Infection

Despite 20 years of research into the presentation, pathophysiology, and treatment of HIV, acute HIV-1 infection remains difficult to diagnose. This stems from the nonspecific findings experienced by patients with acute infection—findings shared with many more common viral syndromes. The signs and symptoms identified in 50% or more of patients include fever, fatigue, rash, headache, pharyngitis, myalgias, lymphadenopathy, nausea, vomiting, and diarrhea. Less common findings include aseptic meningitis, thrombocytopenia, elevated liver enzymes, and mucocutaneous ulceration. Such ulceration may be particularly suggestive of acute HIV infection; however, case series of patients with increased risk for acute HIV infection suggest that only 50% to 90% of patients will have symptoms of seroconversion.¹⁻⁴ Furthermore, one of those studies showed that a diagnosis of acute HIV infection was considered in only 26% of patients who presented for evaluation.⁴ A high index of suspicion for acute HIV infection must be maintained in a patient with behavioral risk factors who presents with nonspecific viral symptoms.

Recent reports estimate that 10 000 of the 40 000 new cases of HIV infection yearly in the United States occur in people aged 13 to 21 years, the range defined by the American Academy of Pediatrics as adolescence. In addition, some data suggest that approximately 20% of American AIDS cases occur in adults in their 20s.⁵ Accounting for the average 10-year period between primary infection and development of clinically apparent AIDS, this would suggest that many of these patients were infected during adolescence.

One of the tenets of pediatric practice is that diseases present differently in children and adults. Further research into the signs of HIV infection in adolescents is therefore warranted, especially given the disproportionately high rates of infection in this age group.⁵ Most research on acute HIV-1 infection, however, has been focused on adults. Three cohort studies of 46, 218, and 499 patients examined the presentation of HIV-1 seroconversion. The larger 2 enrolled only patients older than age 18.^{2,3} Although the third study did not restrict the sample based on age, only 28% of patients were younger than 25.⁴ A literature search of case reports of acute HIV infection in adolescence revealed only 1 report.⁶ A clear need exists for research on adolescents with acute HIV seroconversion.

As previously noted, approximately 25% of new HIV cases occur during adolescence, and 20% of AIDS cases have their onset in the third decade of life.^{5,7,8} These trends are particularly relevant in light of the potential benefits of early detection of acute HIV infection in adolescents.

First, the period surrounding HIV seroconversion is associated with elevated viral load and therefore an increased risk of transmission to sexual partners. A cohort study of 46 patients with primary HIV-1 infection identified several transmissions from a study subject to another person in the interval between the subject's initial HIV infection and the diagnosis.⁴ In one study, 16% of high school students report having more than 4 sexual partners, and only 50% reported using a condom during their last sexual experience.⁸ This suggests that a minority of high-risk adolescents are engaging in unprotected sex with multiple partners, potentially in the period between infection and diagnosis.

Studies have also shown that early antiretroviral therapy administered near seroconversion is associated with an improved prognosis, and the International AIDS Society has called for immediate therapy in people with acute HIV-1 infection.⁹ There are findings that suggest adolescents have the potential for greater immune reconstitution than adults owing to a higher level of thymic function.⁵ Together, these reports suggest that identifying and treating adolescents during seroconversion can improve outcomes for both patients and their sexual partners.

A high level of suspicion is warranted in adolescents with behavioral risk factors—broadly defined

in 1 study as any sexual activity, drug use, or alcohol use—who present with viral symptoms.² Because anti-HIV antibodies have not had time to develop in patients presenting with acute HIV syndrome, the test of choice becomes HIV RNA viral load. At present, the expense of this test precludes its use as a screening tool, but it remains a good diagnostic test. New cost-effective methods of testing are emerging that may eventually lead to effective, affordable screening. A proposed system uses sample pooling to rapidly and efficiently screen large numbers of samples for HIV using PCR. In a low-prevalence, high-volume center, such as public health centers or commercial laboratories, the estimated cost per specimen is \$2, or \$4109 per case of acute HIV infection diagnosed.¹⁰

Conclusions

Pediatricians must have a high index of suspicion for HIV-1 seroconversion in at-risk adolescents presenting with acute viral syndrome. This case illustrates the potential delay in diagnosing HIV infection in an adolescent that results from failure to consider risk factors, particularly sexual history. Delay can result in a poor prognosis for infected patients and can lead to the spread of the HIV virus by a high-risk, unaware population. HIV PCR is the test of choice in diagnosing seroconversion, and new testing methods may lead to the emergence of cost-effective screening of larger populations.

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