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ACUTE HIV INFECTION IN A PATIENT WITH REPEAT HIV ANTIBODY/ANTIGEN NEGATIVE RESULTS PRESENTING AT AN URBAN EMERGENCY DEPARTMENT: A CASE REPORT

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Abstract—Background: It is not uncommon for patients with human immunodeficiency virus (HIV) infections to visit the emergency department (ED) during seroconversion. However, patients with newly acquired HIV may not have a reactive screening result. We report a case of a patient who initially screened reactive on a fourth generation HIV test and subsequently nonreactive twice, but ultimately had positive viral load tests. **Case Report:** A 41-year-old woman experiencing symptoms of a sore throat,odynophagia, and back and flank pain for 5 days presented to the ED. The patient had a reactive HIV screen but negative confirmatory antibody test. The ED provider ordered a HIV viral load, informed the patient, and discharged with oral antibacterial agent. The patient returned the next day and after review of Visit 1 results, the ED provider ordered a second HIV screen, which had a nonreactive result. Another HIV viral load order was placed. The patient was discharged and returned a third time, 4 days after initial presentation. On this visit she was admitted, and the initial HIV viral load result returned positive. **Why Should an Emergency Physician Be Aware of This?:** We report a case of a patient who initially screened reactive on a fourth generation HIV

screening and then twice nonreactive on the same screening test, ultimately having positive viral loads. The most probable explanation for her series of atypical HIV results is that the patient presented during the p24 seroconversion window, which is graphically conveyed in Figure 1. If her first screening had been performed during the window, no further test would have been performed to rule out HIV, contributing to misdiagnosis. ED providers need to be aware that, at some time points during seroconversion from “negative” to “positive”, patients recently infected with HIV and manifesting prodromal symptoms may nonetheless have a negative screening result. © 2019 Elsevier Inc. All rights reserved.

Keywords—HIV seroconversion; negative HIV Ab/Ag screen; second p24 window

INTRODUCTION

The 2006 Centers for Disease Control and Prevention (CDC) recommendation for routine human immunodeficiency virus (HIV) screening had been implemented by only 19% of emergency departments (EDs) surveyed in 2011 (1). However, high-risk patients’ first point of entry into the health care system for assessment during the

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clinically symptomatic phase of acute seroconversion may be via an ED visit for care of their acute illness symptoms. Screening of patients for HIV upon presentation to an ED can facilitate awareness of one's HIV status, toward a potentially decreased likelihood of that patient transmitting HIV to others. It is known that patients with confirmed HIV reactivity are less likely to contribute to the transmission rate of the virus (2). The diagnosis of HIV is determined by a reactive antibody/antigen (Ab/Ag) screening test followed by a positive confirmatory test (3). The currently approved "fourth generation" screening test has a low false positive rate and a low false negative rate compared with the "third generation" screening test (4). We report a case of seroconversion HIV test in a patient with an initial reactive test, followed by repeatedly negative screening results and repeatedly positive quantitative polymerase chain reaction (PCR) tests.

The current CDC guidelines recommend a once-in-a-lifetime screening for patients aged 13–64 years at any point of entry into the health care system (5). Patients presenting to the ED may have a higher pretest probability than an asymptomatic population. In addition, patients seeking care due to prodromal or other symptoms that are attributable to being newly infected with the HIV virus can nonetheless have a negative HIV screening test result during acute seroconversion, if they are tested at certain times during the seroconversion process. Via review of the natural history of an acute HIV seroconversion laboratory test profile, the fact that some infected patients will screen "negative" despite harboring a new or recently acquired HIV infection can be understood. This understanding can facilitate

optimum implementation of the current CDC algorithm for initial detection and treatment of HIV in the ED setting.

CASE REPORT

A 41-year-old woman with no known history of HIV or "reactive" HIV screening tests presented to the ED complaining of a sore throat, odynophagia, back pain, and left flank pain. The patient was screened for HIV due to implementation by our ED of a universal HIV screening program implemented in May 2016. Inclusion criteria for screening included age 13–64 years and no documentation within the electronic medical record of having had a fourth generation HIV screen within the past year. At the first visit in the ED, she tested reactive on a fourth generation HIV Ab/p24 Ag test on the Abbott ARCHITECT (Abbott Diagnostics, Lake Forest, IL). However, a follow-up "confirmatory" HIV-1 and HIV-2 antibody test was negative on the Bio-Rad Geenius (Hercules, CA). An order was placed for a viral load via RNA PCR on the Hologic Aptima (Marlborough, MA), and a presumptive HIV diagnosis was made. Her complete blood count and Comprehensive Metabolic Panel were unremarkable except for the white blood cell count, as shown in Table 1. Urinalysis was significant for leukocytes. The patient was ultimately discharged with a diagnosis of pyelonephritic and a prescription for oral cefpodoxime 100 mg by mouth every 12 hours for seven days.

She returned to the ED on visit 2 (day 2) due to persistent complaints and the inability to fill the antibiotic prescription despite going to multiple pharmacies. At that time, the patient continued to have worsened left flank

Table 1. Laboratory Values Visits 1–3 Over the Course of 4 Days

Test Results	Reference Range & Units	Visit 1 (Day 1)	Visit 2 (Day 2)	Visit 3 (Day 4)
HIV fourth generation screen	–	Reactive*	Nonreactive	Non reactive
HIV antibody confirmation/antigen	–	Negative	–	–
HIV viral load	30–10 million copies/mL	4,150,104*	340,173*	110,782*
Other relevant lab results				
Influenza A Ag, POC	–	Negative	–	–
Influenza B Ag, POC	–	Negative	–	–
Streptococcus group A culture	–	Negative	–	–
Respiratory viral PCR panel	–	Negative	–	–
White blood cell (WBC) count	4.6–10.2 10 ³ /uL	3.14*	–	3.29*
% Lymphocytes	15–47%	–	37	56*
Atypical lymphocytes	0%	–	4	–
Absolute lymph count	/uL	–	–	1491
% CD4 (T cells)	33–66%	–	–	52
Absolute CD4	500–2600/uL	–	–	775
Leukocytes	Negative Leu/uL	Small*	–	–
Protein	Negative mg/dL	30*	–	–
Ascorbic acid	Negative mg/dL	40*	–	–
Urine ketones	Negative mg/dL	20*	–	–
Urine WBCs	0–5/HPF	10–20*	–	–

POC = point of care; PCR = polymerase chain reaction.

* Values that were outside of reference range.

pain and sore throat that was then radiating up her back. The patient was unable to lie down or sleep due to the severity of the pain. The patient was subsequently worked-up for other etiologies of sore throat and flank pain. Streptococcal swab and respiratory viral PCR panel were performed to evaluate for concomitant pneumonia; both tests were negative. She was screened for HIV because the results of the initial viral load test remained pending. Her screening test was negative on the second visit and a new order was placed for a viral load PCR by another provider prior to being discharged with a filled prescription for oral cefpodoxime that the patient found difficult to obtain. The patient presented again to the ED on visit 3 (day 4) secondary to unresolved left flank pain, sore throat, and odynophagia. The patient was also noted at this time to have erythematous sub-centimeter lesions on the hard palate and right tongue.

Given the inconsistent HIV results identified in the electronic medical record, the patient was screened a third time for HIV because the viral load was still in process. Her screening result was negative on both the second and third visits. At the third visit, she was admitted for fluconazole therapy for thrush and diagnosed with gingivostomatitis. White blood cell count upon admission was $3.29 \times 10^3/\mu\text{L}$, and the percentage CD4 count was 52% (reference interval 33–66). The viral load test obtained at the time of the first ED visit (Visit 1) finally became available and indicated a viral load of 4,150,104 copies. Subsequent viral loads at the time of the other visits included 340,173 copies during Visit 2 and 110,782 copies during Visit 3. Her CD4 count on admission was 775%. Our patient was then evaluated by Infectious Disease providers and was diagnosed with acute HIV infection (AHI) despite the two nonreactive HIV p24 Ab/Ag screening tests.

DISCUSSION

We present a case of an acute HIV-infected, previously seronegative patient who had variably reactive serial HIV antibody/antigen screens at various times of presentation to our ED for diagnosis and care. The most likely explanation for these variable HIV test results is that she probably presented during the p24 “window period” of acute HIV infection. Our patient initially tested reactive in the ED for HIV with a fourth generation Abbott ARCHITECT, a p24 Ab/Ag screening test. We believe that upon initial screening, the p24 antigen was still detectable on HIV Ab/p24 Ag testing. At our center, HIV viral testing takes a minimum of 48 h to return results. Therefore, during the course of her repeat ED visits, we hypothesize that the p24 antigen levels decreased to an undetectable level, suggesting she was not mounting an antibody response to the virus. This could explain why her second and third Ab/Ag screening tests resulted

as nonreactive, whereas the viral load tests, which at that time were still “in process,” eventually resulted as “positive.” The occurrence of a false negative result after an initial reactive screen highlights the correlation between timing of visit and screening results. If this patient had presented a few days after the initial visit, her nonreactive screen would have been presumed a “true negative” screening test result. Therefore, no confirmatory test would have been performed, and the diagnosis of HIV would likely have been missed. Thus, this case underscores a potential means by which proper deployment of the current CDC HIV Ab/Ag screening algorithm may nonetheless miss detection of a newly HIV positive patient. A reasonable estimate of the period of seroconversion may help a clinician interpret screen results and take a more detailed sexual or risk-based history from a patient. In this case, the viral load was detectable each time the patient was tested. However, the patient’s viral load decreased significantly, from 4,150,104 (Visit 1) to 340,173 (Visit 2), to 110,782 copies (Visit 3). Concurrently, the p24 antigen was not detectable on the Ab/Ag combo assay on Visit 2 and Visit 3. Based on Figure 1, we hypothesize that this patient may not be following the typical timeline of an HIV seroconversion (6). This case also suggests that the timeline might benefit from further investigation.

In a study conducted by Chavez et al. of 10,995 specimens sent for HIV screen using the Abbott ARCHITECT, two specimens were false negative and 48 of 58 AHI specimens (83%) were correctly identified on initial screen (7). One of the false negative samples was reactive on repeat testing on a Bio-Rad ½ Plus O, HIV-1/HIV-2 differentiation assay. Chavez et al. discuss that ARCHITECT’s high sensitivity means that few truly infected individuals would receive the potentially harmful

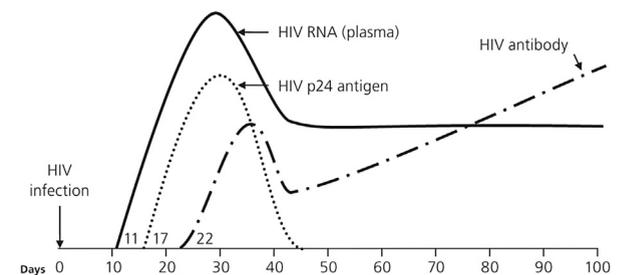


Figure 1. Typical timeline for human immunodeficiency virus (HIV) infection: Most patients will mount a detectable antibody response before p24 Ag levels have decreased. This patient did not develop antibodies by the time the viral load and p24 levels had decreased, rendering the HIV Ab/Ag test negative on repeat testing. Reprinted from Patel P, Bennett B, Sullivan T, Parker MM, Heffelfinger JD, Sullivan PS; CDC AHI Study Group. Rapid HIV screening: missed opportunities for HIV diagnosis and prevention. *J Clin Virol* 2012;54:43, with permission from Elsevier (6). <http://www.sciencedirect.com/science/journal/13866532>.

information that they were not infected (7). This would be true unless patients presented in the p24 window, which may be why 17.2% of AHI specimens were not reactive on the ARCHITECT. The second diagnostic window has been previously documented, and similar cases have also been seen, but in an acute care setting such as an ED, the opportunity to test and diagnose are within a span of a few hours (8–12). To diagnose a patient accurately with HIV, a clinical provider must consider presenting symptoms, screen and confirmatory test results, and sociobehavioral history.

This case demonstrates a rare occurrence of seronegative HIV infection, likely due to the patient presenting during the p24 antigen window period of early infection while not yet developing antibodies to the virus. Seven months post diagnosis, the patient that presented to our ED is in care of an Infectious Disease specialist, adherent to medication, and had an HIV RNA of 130 copies and CD4 of 922%.

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

This case report illustrates the importance of understanding AHI, the HIV seroconversion timeline, and the currently available HIV tests' specificity and sensitivity. EDs are considered first points of entry to the health system, and ED patients with AHI undergoing seroconversion need to be accurately identified. During the seroconversion stage, variable screening results may occur, where the majority may screen reactive and some may screen negative. It is important to have a screening test that has both a high sensitivity and specificity. First, detecting AHI accurately is important due to high viremia in acute infection, which increases the chance of transmission to partners. Second, failing to detect AHI in an ED patient could result in missed opportunities to result, counsel, link, and retain in care. Our case presents an example of this unique window in time when a patient could have been missed. As more EDs implement routine HIV screening, point-of-care viral load testing may be an answer to the need for rapid

confirmatory testing among patients presenting to the ED with AHI symptoms.

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