Human immunodeficiency virus testing pitfalls and clinical suspicion

Abstract

Universal human immunodeficiency virus (HIV) screening was recommended in 2012, and major improvements in HIV testing have occurred in the past decade, but identification of HIV-infected individuals remains inadequate in the United States. We report the case of a seronegative HIV-infected man who despite clinical and laboratory findings of acquired immunodeficiency syndrome, repeatedly tested nonreactive to third-generation HIV enzyme immunoassays (EIAs) and Western blot testing. Serologic diagnosis in this case required fourth-generation EIA testing due to the seronegativity of standard testing. The fourth-generation HIV EIA was positive presumably because it detects p24 HIV antigen as well as antibodies, unlike rapid HIV tests and third-generation HIV EIAs. This case highlights not only the importance of frontline providers to understand the different testing methodologies for HIV screening and their limitations but the importance of clinical suspicion as well.

A 43-year-old previously healthy man presented to the emergency department with a 2-month history of fatigue, dyspnea, cough, and weight loss. He immigrated to the United States from India in the late 1990s. His only sexual encounters were all with males, and within 3 years, with inconsistent barrier precautions. He denied history of previous HIV testing, history of transfusion, use of recreational drugs, and was unaware of any recent sick contacts. On presentation, he was afebrile and normotensive but tachypneic and tachycardic with an oxygen saturation of 91% with 4-L nasal cannula oxygen supplementation. He was cachectic with body mass index of 15 kg/m². Lung examination revealed bibasilar crackles. His physical examination was otherwise normal. His laboratory results revealed white blood cell count of 1.8/mm³ with 43% neutrophils and 18% lymphocytes and otherwise normal. His laboratory results revealed white blood cell examination revealed bibasilar crackles. His physical examination was otherwise normal. His laboratory results revealed white blood cell count of 1.8/mm³ with 43% neutrophils and 18% lymphocytes and normal serum chemistry measurements. Rapid HIV testing (Clearview HIV1/2 STAT-PAK; Alere, Waltham, MA) obtained in our emergency department was nonreactive. Ground-glass opacities were seen in chest computed tomographic imaging. Bronchoscopy with bronchoalveolar lavage revealed Pneumocystis jiroveci pneumonia (PJP), although testing for other pathogens was negative.

Despite clinical and laboratory evidence of acquired immunodeficiency syndrome, third-generation HIV enzyme immunoassay (EIA) (ADVIA Centaur XP, Washington D.C.) and Western blot (Cambridge Biotech, Rockville, MD) were negative. His presentation CD4 count was quantitated at 2/mm³, and HIV viral load was 3 million copy/mL. His fourth-generation HIV EIA (ARCHITECT HIV Ag/Ab Combo; Abbott, Abbott Park, IL), performed at the Wisconsin State Laboratory of Hygiene, was 12-fold above the cut-off positive result. Systemic glucocorticoids and high-dose trimethoprim/sulfamethoxazole for PJP were initiated in addition to highly active antiretroviral therapy (HAART) with emtricitabine, tenofovir, darunavir, and ritonavir. His clinical course gradually improved, and he was discharged to a long-term acute care facility after 6 weeks of hospitalization. Upon discharge, his HIV RNA decreased to 575000 copy/mL, and CD4 count increased to 28/mm³, in spite of persistent negative third-generation HIV EIA and Western blot. Phenotypic analysis of his HIV strain revealed subtype B virus common in North America with multiple resistance mutations. Of note, serum immunoglobulin (Ig) IgG, IgM, IgE, and IgA were obtained with levels all within the reference ranges.

Identification of HIV-infected individuals in the United States remains inadequate, despite policy recommendations for universal HIV screening [1]. There is ongoing effort to increase HIV testing in emergency departments without slowing visits [2-4]. Although every opportunity to test should be capitalized on, no test is perfect including rapid HIV antibody test [5,6]. There remains a false-negative rate due to several factors including the inability of the assay to recognize all antibody responses especially not detecting nonclade B virus, very early infection within the window period, and lack of antibody production [7,8]. This case likely represents a rarely reported case of seronegative HIV-1 infection despite chronic infection [8]. Some patients do not develop humoral immunity to HIV-1 despite evidence of HIV-1 infection. Surprisingly, only 25 cases have been published despite 35 million HIV patients identified worldwide [9]. Most of these patients featured severe immunodeficiency, high-level viremia, rapid disease progression, possible association with certain human leukocyte antigen type, and frequent seroconversion after HAART initiation. A more common problem is acute HIV in which HIV antibody has not yet developed [10]. Here, the fourth-generation HIV EIA was positive presumably because it detects p24 HIV antigen as well as antibodies, unlike rapid and third-generation HIV EIAs [11]. This case highlights the importance of frontline providers to put all test results in the proper clinical context and understand the limitations of all testing methods. Clinical suspicion is a crucial aspect to interpreting either a negative rapid HIV test or even laboratory-based EIAs and supplemental tests with fourth-generation HIV EIA or nucleic acid test may be necessary for accurate diagnosis. Settings that use the rapid test must remain aware of the caveats to negative HIV tests and be able to offer further testing if appropriate.

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