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The diagnosis of symptomatic acute antiretroviral syndrome during the window period with antigen/antibody testing and HIV viral load

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A B S T R A C T

Despite much focus on moving toward a cure to end the epidemic human immunodeficiency virus (HIV) epidemic there are still thousands of new infections occurring every year in the United States. Although there is ongoing transmission of HIV in the United States and a growing population of people living with HIV, the acute presentation of HIV infection can be challenging to diagnose and is often not considered when patients present to healthcare providers. Although in certain states there are HIV testing laws that require that all persons between the ages of 13 and 64 be offered HIV testing in an opt-out approach, many patient presenting with an acute illness, that would warrant diagnostic testing for HIV, leave without having an HIV test performed for either diagnostic or screening purposes.

We describe the case of a woman who presented to medical attention with symptoms later confirmed to be due to acute HIV infection. She was initially discharged from the hospital and only underwent HIV testing with confirmation of her diagnosis after readmission. We describe the algorithm where fourth generation testing combined with HIV viral load testing allowed for the diagnosis of acute HIV prior to the development of a specific immunoglobulin response. Consideration of this diagnosis, improved HIV screening, and understanding of the use of antigen/antibody screening tests, combined with Multispot and HIV viral RNA detection, when appropriate, can allow for early diagnosis of HIV before progression of disease and before undiagnosed patient spread the infection to new contacts.

Introduction

Human immunodeficiency virus (HIV) is the established pathogen responsible for the AIDS epidemic [1]. Despite tremendous advances in the treatment and management of HIV infection, there are over one million individuals in the United States living with HIV infection and an estimated 40 million people infected with HIV worldwide [2]. Models using CD4 counts suggest even higher estimates [3]. Ongoing transmission of the virus to individuals lacking any obvious high risk factors continues to occur throughout the world with women accounting for about 25% of all new AIDS diagnoses in the United States and the majority of new cases worldwide [4–6].

Identifying acute HIV infection can decrease transmission events that might occur during this period and can provide both immediate symptomatic and long-term benefit for patients [7,8]. The introduction of newer generation antigen/antibody screening tests reflexed to immunoblot and qualitative HIV RNA detection assays is closing the window between acquisition of HIV and the ability of our tests to accurately diagnosis HIV infection [9]. We present a case of a patient with acute HIV infection presenting as an acute mononucleosis-like illness with rash that was not immediately recognized despite multiple interactions with the healthcare system.

Case presentation

A 47-year-old female elementary school teacher (1st grade) was initially seen in an emergency room on Long Island, New York with a report of sore throat and fever and discharged with a diagnosis of pharyngitis and a prescription for clindamycin. She returned to the hospital three days later reporting that her symptoms were getting worse and was admitted with complaints of fatigue, fever, continued sore throat, and myalgia. She was admitted to the general medicine service under the care of a hospitalist and seen by an Infectious Disease physician. After 48 h with negative blood cultures the patient was felt to have probable viral pharyngitis and discharged to home with the recommendation that further diagnostic investigations could be

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performed in the outpatient setting. The patient returned to the emergency room the next day reporting that fevers were continuing and was readmitted.

The patient reported a past medical history significant for anxiety, fibromyalgia, morbid obesity (BMI > 45), sleep apnea (on CPAP), and sarcoidosis. No prior surgeries were reported. She reported no remarkable medical illnesses in her family other than diabetes in a sibling. The patient reported living with a long-term boyfriend that she had recently had a falling out and no recent sexual activity. She reports no alcohol or tobacco use, no pets, and no known sick contact exposure.

On exam, when she was admitted the second time, she was afebrile with a normal respiratory rate, heart rate and blood pressure but reported subjective fevers were continuing at home. Exam was remarkable for the patient being morbidly obese with enlarged erythematous tonsils with white patches. Prominent tender anterior and posterior cervical adenopathy and axillary adenopathy was present. On abdominal exam the spleen tip was palpable, firm, slightly tender, but not significantly enlarged. A light erythematous maculo papular rash was noted on the back, chest and arms that the patient reported was very pruritic.

Initially laboratory investigations on readmission were significant for a WBC count of 4.1 K/uL with 50% neutrophils, 25% lymphocytes, 9% bands and 4% reactive lymphocytes. The percentage of bands ultimately rose to 20%. Chest x-ray was unremarkable and additional testing was ordered by a second infectious disease consultant who saw the patient on this readmission.

The patient underwent serological testing for Epstein Barr Virus (EBV) that showed EBV IgM-negative, EBV capsid antigen IgG-positive, EBV early antigen negative, and EBV nuclear antigen positive. Toxoplasmosis studies demonstrated IgM and IgG negativity. Cytomegalovirus (CMV) testing revealed IgM-positive, IgG-negative, and CMV virus detection by polymerase chain reaction (PCR) was reported as positive but below the level of quantification. Quantiferon Gold Testing (QFG), syphilis and Hepatitis tests were negative. The patient had a positive 4th generation test for HIV with a negative Multispot HIV-1/HIV-2 test.

The patient had a chest computed tomography (CT) radiological test performed demonstrating mediastinal and bilateral hilar adenopathy with scattered parenchymal lung nodules.

An HIV viral load was sent which was positive with an HIV-1 viral load of 8,708,069 copies/mL (log 6.94). Analysis of T cell subsets revealed CD4%-14%, CD4 count 505, CD8%-65%, CD8 count 2427 and CD4/CD8 ratio of 0.21. A repeat HIV test 10 days after the initial negative was positive again and this time serological evidence of antibodies to HIV-1 was noted with a positive Multispot test.

Following the diagnosis of acute antiretroviral infection the patient reported that her initial history was not entirely accurate and that after the falling out with her long-term boyfriend she had a one time unprotected vaginal sexual exposure with a different person of unknown HIV status 1–2 weeks prior to the onset of symptoms. The patient reported that this was only her second lifetime sexual partner. The patient proceeded to contact this individual as well as her long-term partner advising them both of her new diagnosis and recommended they get tested for HIV.

The patient was started on triple combination integrase inhibitor therapy with elvitegravir/colbicistat/t-alafenamide/emtricitabine fixed combination (Genvoya) and underwent testing for additional sexually transmitted infections, testing for HLA-B5701 status, G6PD levels, and other baseline testing. At discharge the patient was scheduled to be seen our group for discussion of the results of her pending HIV genotype test and continued out patient monitoring and care. Her genotype result returned with no resistance mutations.

Discussion

There are a number of features of this case that make it both interesting and challenging for the clinician. The fact that this patient had multiple interactions with the healthcare system in a part of the country with a prevalence of HIV infections suggests that despite the description of acute HIV presenting as a mononucleosis-like illness and the mandatory opt out testing approaches there can still be a failure to diagnose acute HIV infection [10]. Current New York State law mandates opt-out HIV testing in all emergency departments with evidence that this approach increases testing and diagnosis in all risk groups [11]. In some screening programs, up to a quarter of the patients newly diagnosed through ER screening have acute HIV infection and more than a quarter have advanced disease with a CD4 count of less than 200 cells/μL [12].

Despite the awareness of the high prevalence of HIV in and around New York City a large number of the newly diagnosed patients referred to the largest HIV clinic in the immediate area of this hospital are late diagnoses with CD4 counts less than 200 cells/μL [13,14].

The initial challenge noted in this case was the failure to include acute HIV in the differential of an acute mononucleosis-like illness when testing revealed this was not due to acute EBV infection. This early diagnosis during the period of high viremia and potential transmission is one of the critical challenges of the treatment as prevention strategies [10]. Although the differential for and acute EBV-negative mononucleosis-like illness includes acute CMV, acute toxoplasmosis, human herpesvirus-6 or -7, and acute HIV, the incidence of HIV in many areas may represent less than one percent of these presentations thus dropping this diagnosis from consideration on many experienced clinicians' differential [15].

Once HIV was under consideration a failure to fully understand the fourth generation assay represented a second challenge. The legacy of the original ELISA screening test for HIV followed by the confirmatory Western blot may have been responsible for the view among the treating physicians that the negative immunoblot was evidence that the fourth generation antigen/antibody test was a false positive. Reflex to a qualitative HIV RNA PCR approved for diagnosis of HIV is one effective strategy to decrease the chances of an acute HIV diagnosis being missed. It is also critical for healthcare providers, who are in a position to see and potentially diagnose acute HIV, that they have an understanding of the timing of HIV infection to symptom onset, viremia, antigenemia, and a detectible serological response (Fig. 1) [16].

It is also essential that healthcare providers understand the

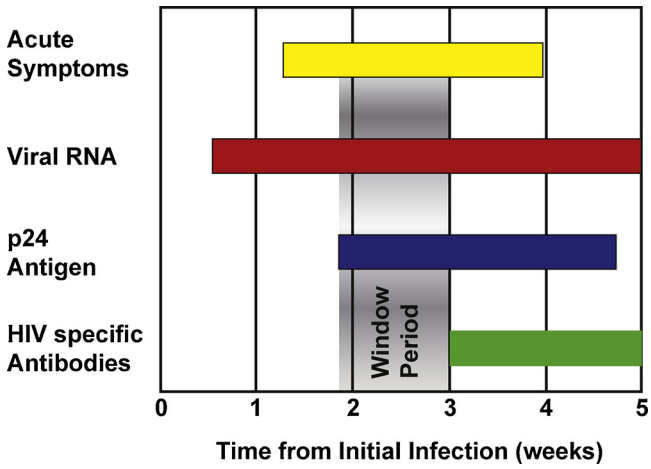

Fig. 1. The Association Between Time of Exposure, Symptoms, and Detection of Viremia, Antigenemia, and Detectible Antibodies Specific for HIV. Onset of symptoms of acute HIV infection start within a few days to weeks of infection with HIV viral RNA detectable less than one week after infection and preceding the onset of symptoms. Detectable serum levels of p24 are present approximately 2 weeks after initial infection and after the onset of symptoms while HIV specific antibodies do not generally become detectable until approximately 3 weeks after infection.

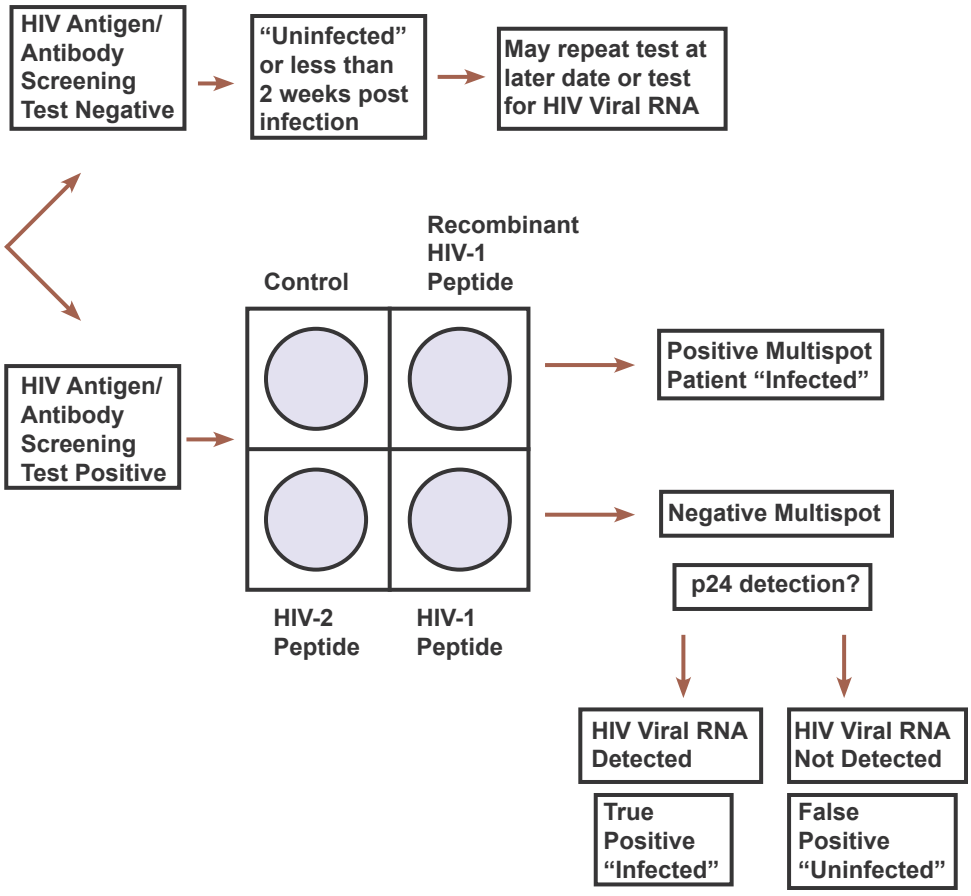

Fig. 2. An Algorithm of Negative Immunoblot after Positive Antigen/Antibody Screen Undergoing Viral RNA Testing Can Allow for the Diagnosis of Acute HIV During the Window after p24 Antigen Presence but Before the Development of HIV specific Antibodies. Positive antigen/antibody screens can be due to antigen detection, antibody detection or truly false. Reflex to immunoblot and HIV viral RNA testing can determine if a screening assay is detecting early disease during the period prior to serological conversion or is falsely positive.

available tests and what next steps to take in the evaluation when screening patients for HIV infection or for making the diagnosis of acute HIV. Positive results with current 4th generation testing with negative Multispot testing can be due to detection of viral p24 antigen or be false positive. These different situations can be determined with testing for viral RNA (Fig. 2) [17].

It is known from studying the time course of the replicative cycle of HIV that there is an initial period of time from exposure of a cell to HIV and before there is integration of provirus and production of new detectable HIV virions [18,19]. While initial serological testing left us with a 3 week window from exposure to detection, p24 antigen testing reduced this window and fortunately, the window between exposure and our ability to make the diagnosis is narrowed further through testing for HIV viral RNA and now is possible as soon as and prior to the onset of symptoms of acute disease [20]. With current ultrasensitive assays we may be reaching our limits in closing the window between exposure and detection.

Conflict-of-interest disclosure

The author/s declare no competing financial interests.

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