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Case Report

False positive fourth generation HIV test in a patient with severe malaria

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ABSTRACT

Severe malaria is an uncommon diagnosis in the United States. However, awareness of signs, symptoms, and treatment options is imperative in order to promptly initiate optimal therapy. False positive human immunodeficiency virus (HIV) results are rare in the setting of acute malaria infection and with the introduction of newer fourth-generation immunoassays. The Centers for Disease Control algorithms assist in confirming true HIV infection (Branson et al. 2014).

Case presentation

We present a case of a 63-year old female without significant past medical history who presented 3 weeks after returning from a 3-month trip to West Africa having not taken antimicrobial prophylaxis for malaria. She reported 2 weeks of flu-like symptoms and altered mental status. She denied high-risk sexual activities or receiving blood transfusions while abroad. Initial laboratory workup revealed hemolysis and acute kidney injury. On peripheral smear, several erythrocytes contained ring-shaped trophozoites, with an estimated parasitemia of 3%. BinaxNOW® Malarial Antigen testing (BinaxNOW® malaria test kit [Global], product code 665-000, Abbott Laboratories, Abbott Park, IL) identified two Plasmodial species: *Plasmodium falciparum* and *Plasmodium ovale*. Admitted to the intensive care unit for severe malaria, she was treated with intravenous quinidine (0.02 mg/kg/min) and doxycycline (100 mg twice daily). Parasitemia was monitored every twelve hours until the level was <1%, then daily thereafter for 2 days. The 4th generation HIV test (ARCHITECT® HIV Ag/Ab Combo Assay, Abbott Laboratories, Abbott Park, IL) was repeatedly reactive with negative differentiation tests for HIV-1/-2 antibodies (Bio-Rad Geenius™ HIV 1/2 confirmatory assay, product code 72460, Marnes-la-Coquette, France). Subsequent HIV-1 RNA real-time PCR was also negative (APTIMA® HIV-RNA Qualitative Assay [Gen-Probe, Inc., San Diego, CA]). She clinically improved and completed a 14-day course of oral atovaquone/proguanil and primaquine. Approximately eighteen months following treatment completion, a repeat ARCHITECT® HIV Ag/Ab Combo Assay reverted to negative. This subsequent test was sent to the same laboratory and different lots were used. Differentiation tests and RNA real-time PCR were not repeated.

Discussion

HIV infection has evolved from a highly lethal disease to a chronic illness commonly managed in the primary care setting. Despite awareness efforts, over 38,000 new cases of HIV were diagnosed in 2015 (CDC, 2018). A caveat of older generation assays is the risk of false negative results due to the lengthy window period between HIV infection and positive test results (Alexander, 2016). The current fourth generation HIV-1/2 antibody/antigen (Ab/Ag) Combo assay narrows the window period by identifying HIV-1/-2 antibodies as well as the early-appearing HIV p24 antigen with a sensitivity and specificity of over 99% (Chavez et al., 2011). With this assay, the CDC diagnostic algorithm is as follows (Branson et al., 2014): a reactive combination test triggers a differentiation immunoassay for HIV-1 and -2 antibodies. If negative or indeterminate, HIV-1 nucleic acid amplification testing (NAT) is performed. Serial testing reduces laboratory errors created by incorrect labeling and cross-reactivity with secondary antigens.

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False positive HIV results have been reported in a myriad of different settings—schistosomiasis, systemic lupus erythematosus, influenza vaccination (Erickson et al., 2006; Gasasira et al., 2006; Everett et al., 2010)—leading to significant patient distress and mistrust of providers. Although the majority of false positive testing has been reported with earlier generation assays and rapid diagnostic tests, false positive 4th generation assays have been reported (Klarkowski et al., 2014; Liu et al., 2016). Anti- *P. falciparum* antibody cross reactivity with HIV-1/-2 antibodies on second and third generation assays is well documented (Fonseca et al., 2000; Gasasira et al., 2006). To our knowledge, this is the first case of a false positive 4th generation HIV assay due to severe acute malaria. Acute malarial infection is hypothesized to lead to marked immunological activation and hypergammaglobulinemia resulting in false positive serological results (Fonseca et al., 2000; Gasasira et al., 2006; Klarkowski et al., 2014). Given the geographic overlap of malaria and HIV endemicity, health care providers must remain aware that even with the more sensitive and specific immunoassays, false positive results and cross-reactivity may be more frequent in the setting of certain immunological stimuli such as malaria. Our finding underlines the importance of continued standardized confirmatory HIV testing despite the use and implementation of higher generation HIV screening assays.

Indeterminate test results may also arise in the setting of HIV-2 infection. Over 200 cases of HIV-2 have been reported in the United States from 2000 to 2009, of which 132 patients were born in or traveled to West Africa (CDC, 2011). HIV-2 has lower rates of transmission, produces lower viral loads, and demonstrates a slower progression to acquired immunodeficiency syndrome than does HIV-1 (Reeves and Doms, 2002). The patient did not have additional risk factors for HIV-2 and her HIV test reverted to negative, thus HIV-2 NAT testing was not clinically indicated.

Although the sensitivity and specificity of HIV tests have significantly improved with the fourth-generation immunoassays, discordant results remain a diagnostic challenge (Liu et al., 2016). The reversion of our patient's HIV test to negative definitively confirmed the initial assay as a false positive. Severe malaria should be highlighted as a cause of false positive ARCHITECT HIV Ag/Ab Combo assay and healthcare providers should be aware of the potential cross-reactivity in this scenario. Misdiagnosis can be avoided by adhering to the CDC algorithm for diagnosing HIV infection.

Conflict of interest

The authors do not have any conflicts of interest to declare.

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Ethical approval

Written informed consent was obtained from the patient for the publication of this case report.

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