CASE REPORT

False positivity of fourth generation human immunodeficiency virus rapid diagnostic tests in a malaria patient: a case report

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SUMMARY

Early diagnosis and initiation of treatment is a cornerstone of managing human immunodeficiency virus (HIV) infections and rapid diagnostic tests which provide same-day results are instrumental in bolstering this approach. Fourth-generation (4G) enzyme-linked immunosorbent assays boast near-perfect accuracies; nevertheless, false positives are still possible. We report one such occurrence in a patient with severe *Plasmodium knowlesi* malarial infection. This case report highlights the importance of good history-taking coupled with pre- and post-test counselling when performing HIV screening tests with the 4G HIV rapid diagnostic kits. Clinicians should keep in mind the possibility of false positives and adhere strictly to the WHO standardised testing algorithm to avoid misdiagnosing patients as HIV positive based on a reactive 4G HIV test.

INTRODUCTION

The human immunodeficiency virus (HIV) epidemic continues to be a major public health issue globally, having claimed an estimated 36.3 million lives thus far. Early diagnosis and initiation of treatment remains a cornerstone of managing HIV infections, and rapid diagnostic tests which provide same-day results are instrumental in bolstering this approach.[1] The advent of fourth-generation (4G) enzyme-linked immunosorbent assays has been a huge boon to the establishment of comprehensive HIV testing strategies by the World Health Organization (WHO).[2] These assays test for the p24 antigen in addition to anti-HIV antibodies and boast the ability to identify acute infections earlier and more rapidly than the third-generation assays that only test for antibodies. While 4G assays promise near-perfect accuracies,[3] false-positive 4G HIV test results are nevertheless still possible. Here, we report one such occurrence in a patient with severe *Plasmodium knowlesi* malarial infection.

CASE REPORT

Our patient is a healthy 35-year-old Malay man who works as a hawker by the fringe of a forest. He presented to us with a 4-day history of fever, chills and rigors, headache, abdominal pain, and reduced oral intake. Physical examination revealed that he was febrile (temperature 39.8℃) and slightly hypotensive (111/70mmHg); his other vital signs were otherwise not deranged (heart rate 91 beats/min, SpO_2 98% at room air). Remaining physical findings were likewise unremarkable. Laboratory investigations demonstrated bicytopaenia (haemoglobin 13.1g/dL, platelets 20×10^9/L) with raised creatinine levels (156µmol/L). An urgent peripheral blood film revealed features consistent with malarial infection, and this was confirmed with blood film for malarial parasite identification of *Plasmodium knowlesi* (parasite count 36,320 asexual/0 sexual per µL). Dengue serology was negative.

The patient's condition deteriorated in the emergency department while awaiting laboratory results. He went into septic shock, necessitating inotropic support briefly with a 1-day stay in our intensive care unit for close monitoring. Artesunate and arthemeter/lumefantrine therapy was quickly initiated with good response, and the patient was discharged uneventfully after another 4 days in the general ward.

Due to the initial severity of clinical presentation, inpatient HIV screening was done to assess for HIV co-infection. His 4G HIV test (ARCHITECT HIV Ag/Ab Combo assay; Abbott Laboratories; Wiesbaden, Germany) and particle agglutination test returned weakly positive thrice; however, subsequent HIV polymerase chain reaction (PCR) did not produce any detectable viral load. Further history taking regarding high-risk behaviours were strongly denied by the patient. A second HIV PCR test repeated at three months follow-up after discharge was also negative. The patient was counselled accordingly regarding the false-positive HIV results and subsequently discharged from our care.

DISCUSSION

Fourth-generation (4G) HIV tests differ from third-generation tests in their ability to detect the p24 antigen, on top of anti-HIV antibodies. Detection of the p24 antigen allows for improved diagnostic accuracy, especially in the acute phase

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where antibodies have yet to develop. The assay used in this case study, ARCHITECT HIV Ag/Ab Combo assay, has a reported sensitivity of 100%, specificity 99.77%, positive predictive value 81.25%, and negative predictive value 100%.[3]

The phenomenon of false-positive HIV results has been implicated in several conditions, including African trypanosomiasis, schistosomiasis, systemic lupus erythematosus, and influenza vaccinations; the assays used in these reports were often of the earlier generations.[4-6] Nevertheless, false positives may still occur with 4G HIV tests despite their improved accuracies.[7,8] Such an incidence in malaria specifically has been recorded in the literature previously,[9] though ours is the first case involving *P. knowlesi* to the best of our knowledge.

Malarial infections, along with other parasitic infections, are hypothesised to cause false-positive HIV results via activation of a marked immunological response in the host. The introduction of *P. knowlesi* antigens into our patient triggered his CD5+ B-lymphocytes to produce broad-spectrum antibodies. These non-specific polyclonal antibodies then cross-reacted with the p24 antigens in the ARCHITECT 4G HIV test, producing chemiluminescence which was consequently interpreted by the system as "reactive". Other probable risk factors for such a false-positive result in our patient include his younger age, poor socioeconomic status, and dietary limitations.[7]

There are a number of lessons to be drawn from our reported case of a false-positive HIV 4G test result. It serves as a reminder that 'reactive HIV test' does not necessarily equate to 'HIV positive'. It also underscores the importance of following up initially reactive samples with a confirmatory nucleic acid amplification test as prescribed in WHO's standardised testing algorithm.[2] Had the algorithm not been followed, our patient would have been misdiagnosed as HIV positive.

With regards to the bedside approach, such a possibility of false positives illustrates the significance of pre- and post-test counselling for HIV, especially given the persisting societal stigma associated with this viral infection. Targeted and concise history taking in relation to high-risk behaviours is also crucial as part of the consultation prior to pre-test counselling. In this case, the initial positive rapid test results caused a considerable amount of marital discord between the patient and his newly wed wife. Notwithstanding that, we managed to elicit that the patient had no risk factors, and so we are able to somewhat reassure the patient and his wife of the probable false results during the post-test counselling prior to hospital discharge.

CONCLUSION

We report a false-positive HIV 4G test result in a patient with severe *Plasmodium knowlesi* malarial infection. Clinicians should keep in mind such a possibility when managing a patient who had a reactive test result but lacked apparent risk factors. Good history-taking and strict adherence to the WHO standardised testing algorithm are essential to ensure that such patients are not misdiagnosed with an HIV infection. Pre- and post-test counselling sessions are necessary to ameliorate the patient's (and spousal) anxiety and distress upon learning of their initial results.

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