Letter to the editor: additional evidence to support a cross-reactivity of SARS-CoV-2 with HIV chemiluminescent assay

During the COVID-19 pandemic, a 43-year-old male patient with no clinically relevant changes, underwent routine examinations at the Brazilian Army Institute of Biology on 25 May 2021. The fourth-generation chemiluminescence assay, Vitros HIV Combo (Ortho Clinical Diagnostics, New Jersey, USA), for HIV-1 and HIV-2 was performed. The Vitros HIV Combo test detects both HIV-1 and HIV-2 antibodies and the p24 antigen in acute cases of HIV infection. The result obtained was 2.54 s/CO (sample relative light unit/cut-off relative light unit). Specimens with s/CO values of ≥1 are considered reactive for HIV. Following the flowchart established by the Technical Manual for the Diagnosis of HIV Infection in Adults and Children, prepared by the Brazilian Health Ministry, a new sample was obtained on 4 June 2021, for confirmation and additional quantification of HIV-1 viral load using real-time reverse transcription PCR (M2000sp and M2000rt; Laboratories, Abbott Park, Illinois, USA) and an antibody specific search for viral HIV-1 antibodies (p17, p24, p31, gp41, p51, p55, p66 and gp120/160) using western blotting. The new chemiluminescent HIV-1/HIV2 test showed reactivity at 2.67 s/CO, similar to the first sample. Conversely, undetectable viral load and negative western blotting results excluded the possibility of HIV infection. Recently, in June, two more HIV-negative results from other laboratories have confirmed the diagnosis. Autoimmune disease, severe liver diseases and infectious conditions have been previously reported as false-positive HIV result sources. Therefore, new tests were performed concurrently with the chemiluminescence tests for HIV-1 and HIV-2. No hepatic disorders were observed using the markers for alanine aminotransferase (ALT) (48 U/L and reference value (RV): <50 U/L), aspartate aminotransferase (AST) (35 U/L and RV: <59 U/L), alkaline phosphatase (ALP) (62 U/L and RV: 62–203 U/L), and gamma-glutamyl transferase (GGT) (28 U/L and RV: 15–73 U/L). For the evaluation of possible autoimmune diseases such as lupus, insignificant results for antinuclear antibodies (1:80 dilution) were obtained. These antibodies can be found in normal individuals and those with viral infections and chronic inflammatory diseases and therefore should be correlated with clinical data. Similarly, negative results for anti-dsDNA (non-reactive) were obtained. Furthermore, immune thyroid disorders, such as Hashimoto’s thyroiditis, were ruled out based on normal thyroid-stimulating hormone (TSH) (1.230 mIU/mL and RV: 0.46–4.68 mIU/mL), T3 (1.23 ng/mL and RV: 0.97–1.69 ng/mL) and T4 (7.6 µg/dL and RV: 5.53–11.00 µg/dL) results. Regarding additional possible infections that could affect the patient results, new assays were performed: test to detect Trypanosoma cruzi antibodies (Chagas’ disease), Venereal disease research laboratory (VDRL) test for syphilis, stool examination test for parasites, quantitative polymerase chain reaction (qPCR) for hepatitis C virus/hepatitis B virus and a multiplex qPCR panel for 26 respiratory pathogens, including influenza viruses A/B, A-SUB H1, H1N1, SUB-H3; rhinovirus A/B/C; coronavirus 229E/NL63 and OC43; parainfluenza viruses 1–4; metapneumovirus A/B; bacovirus; Chlamydia pneumoniae; Mycoplasma pneumoniae; respiratory syncytial virus A/B; enterovirus; adenovirus; Legionella pneumophila; Bordetella pertussis and Bordetella parapertussis; Streptococcus pneumoniae; and Haemophilus influenzae. All the test results were negative. In addition to the laboratory tests performed, the subject did not report any recent vaccinations (including H1N1) or risk behaviour for HIV infection, such as drug abuse, frequent blood transfusion or large numbers of sexual partners. The patient was positive for SARS-CoV-2 on 4 January 2021, and HIV-1/HIV-2 chemiluminescence tests performed before that period did not show any reactivity. Because of this, total unspecific IgG (1143 mg/dL and RV: 650–1600 mg/dL) and IgM (152.17 mg/dL and RV: 40.00–230.00 mg/dL) were performed without relevant altered results. In addition, SARS-CoV-2 total receptor-binding domain IgG test was performed, and SARS-CoV-2 neutralising antibodies, specific to the Spike region, were quantified; the results showed expressive levels of 310.17 AU/mL (RV: 0.00–0.10 AU/mL) and 10.17 µg/mL (RV: 0.00–0.30 µg/mL), respectively. Our data corroborate our hypothesis about the cross-reactivity of HIV immunoassay and SARS-CoV-2 infection, as has been previously described. However, for the first time, we have shown a possible persistent cross-reactivity related to COVID-19 infection. It is important to highlight that Kliger and Levanon have shown protein similarities between HIV and SARS-CoV. Sequence analysis revealed shared motifs in the N-terminal leucine/isoleucine zipper-like sequence and a C-terminal heptad repeat located upstream of an aromatic residue-rich region. These similarities and the presence of COVID-19 antibodies may explain the reactivity observed in this case. Moreover, the fourth-generation chemiluminescence assay has the limitation of false-positive events described for several pathogens, such as the H1N1 virus, Epstein-Barr virus and some types of cancers, besides other factors, such as autoimmune diseases, liver damage and patient risk factors (drug abuse, blood transfusions and some types of vaccines). These limitations were investigated and not found in this case. Finally, recent or not so recent individual exposure to SARS-CoV-2 could be an additional factor for evaluating possible false-positive cases in HIV chemiluminescence assays.

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REFERENCES