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Case Report
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Seronegative HIV-1 Infection, a Difficult Clinical Entity; a Case Report

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Abstract

Patients infected with HIV typically seroconvert within weeks of primary HIV infection. In rare cases, patient do not develops antibodies despite demonstrable HIV infection by p24 antigen or viral load assays; a seronegative HIV. Very few such cases been reported so far in the literature [1-11]. Seronegative HIV is many times difficult to differentiate from acute seroconversion illness due to HIV in clinical practice. Here we are describing such case with clinical dilemma.

Case History

A 68 years old male patient was admitted with febrile illness in February 2010. His routine work up was inconclusive for diagnosis of common infectious cause of acute febrile illness. He responded to antibiotic treatment. His HIV ELISA (4th generation of ELISA for HIV 1 and 2; result 0.0 by Enzyme linked fluorescent assay [ELFA]) and Western blot test were negative (27/2/2010). His P24 Antigen assay with ELFA was positive.

His HIV ELISA repeated after 1 week was also negative with p24 antigen positive. Patient was subjected for HIV Viral load showed 18,84,644 copies/ml and CD4 count: 122/cmm (10.51%), CD8: 719/cmm.

With this reports patient was referred for further evaluation at our clinic. He was asymptomatic with history of Tobacco chewing > 40 years and stopped since 10 years. No history of sore throat, myalgia, skin rashes, gastrointestinal or genitourinary complaints. He gave history of unprotected sexual exposure before 20 years with recurrent genital ulcers since then. No past history of jaundice/tuberculosis (TB)/operation/Blood transfusion/Major medical illness Physical examination was normal except oral candidiasis. His X-ray chest/ Ultrasound examination and other relevant tests carried out during his febrile illness were within normal limits. We repeated his HIV ELISA, HBsAg and hepatitis C virus (HCV) antibodies and all were non-reactive. His syphilis antibody by ELISA was reactive and VDRL titer was 1:8. His complete blood count, renal and liver functions tests including serum proteins (total protein: 6.93 gm%, albumin: 3.77gm%, globulin: 3.16gm %) were normal. Diagnosis arrived at our clinic was Latent Syphilis with possible seronegative HIV infection versus acute seroconversion illness.

Antiretroviral treatment was considered for the patient in view of high viral load, low CD4 count and elderly patient. Antiretroviral treatment was discussed and started with fixed drug combination of Tenofovir + Emtricitabine + Efavirenz along with Injection Benzathine Penicillin 24 lacs Intra Muscular after negative test dose per week X 3 weeks, Bactrim DS 1 qd and multivitamin tablet.

Patient tolerated drug well. His western blot test was repeated after one month and two and half months of antiretroviral therapy is showed in (Figure 1). At one-month post treatment two bands appeared in the region of p24 and gp 160 and at the end of two and half months western-blot fully evolved to positive. Patient had immunological and virological response to ART. At three & six months following treatment his CD4 increases to 428 and 368 /cmm and viral load were 3820 copies/ml and < 400 copies/ml.

Discussion

Diagnostic algorithm for HIV includes screening with ELISA or rapid tests and then confirmation using alternative screening tests, western blot test or a test to detect HIV RNA [12]. The diagnosis of HIV infection by the detection of HIV- specific antibody is not possible if infected individuals do not produces HIV specific antibodies.

The sensitivity and specificity of this testing strategy is greater than 99% and it has proven to be one of the most reliable and accurate diagnostic tests in clinical medicine [13-15]. False negative results are mostly attributed to window period, immunoglobulin deficiency and infection with HIV-2 or non-clad B virus. Diagnosis of HIV during acute seroconversion illness rests on negative or indeterminate antibody based tests and demonstratable HIV RNA in the blood. Diagnosis during acute phase is very difficult as signs and

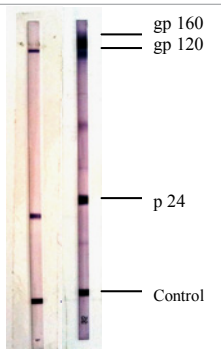

Figure 1: Showing evolving western blot after starting HAART. **a**: repeat Westernblot after 1 month of antiretroviral treatment **b**: Westernblot after 2½ months of antiretroviral treatment.

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symptoms of illness mimic other common viral illness. Most of the patients demonstrate antibody response within weeks of infection, however in some patients antibody response may be delayed (e.g. pregnancy, HCV co-infection) and rarely antibodies may not develop for prolonged period. Serologic Testing Algorithms for Recent HIV Seroconversion (STARHS) assays, also termed Recent Infection Testing Algorithms (RITAs), are used to distinguish recent from long-standing HIV infections. High titer and avidity HIV-1 IgG immune responses to the STAHRS/RITA assays are usually complete by one year following HIV infection; dynamic period is from two to eleven months following infection. In our patient had negative HIV antibody to begin with and it only appeared after initiation of HAART. This test can't use to differentiate recent seroconversion illness from seronegative HIV infection. Our patient had febrile illness of unknown etiology responded to antibiotics, oral candidiasis in absence of any other immunosuppressive condition, diabetes mellitus or steroid use and had persistently negative antibody based tests including western blot with positive P24 antigen and high HIV RNA in blood.

We looked for possibility of acute Seroconversion illness in our patient. No information about the prior serological status of our patient was available. Therefore, we cannot differentiate clearly whether the seronegativity of our patient represents a prolonged window period of acute seroconversion illness or seroreversion in the context of waning immunological function in far advanced AIDS. Point against this possibility is history of sexual exposure before 20 years, followed by recurrent genital ulcer and he denies history of sexual exposure, high-risk behavior or blood transfusion in recent past and latent syphilis. Combined antigen/antibody HIV assays used for screening for HIV infection in our case guide us to get further testing to confirm HIV.

Diagnosis of HIV infection was made on the basis of clinical symptoms of candidiasis, positive P24 antigen and detectable HIV RNA in the blood. Patient had positive syphilis antibodies and positive VDRL tests without symptoms suggestive of primary or secondary syphilis, suggesting that patient probably had acquired syphilis in the past and not recently. The points, which are against acute seroconversion illness, are persistently negative HIV antibodies two months after the symptoms of febrile illness, absence of sexual exposure, absence of high risk behaviors and blood transfusion in recent past and a very low CD4 count. This made us to think of seronegative HIV infection in this patient. Similar few cases had been reported in literature [1-10]. In the review by Spivak et al. [11] most of the patient (n=25) were in 3rd or 4th decade of life, presented with severe symptoms (12 had pneumocystic carinii pneumonia (PCP), others had TB, oropharyngeal candidiasis, bacillary angiomatosis and cryptococcosis), low CD4 cell count (<200/cmm, n=21), high HIV RNA (16 had >10 lacs copies/ml), rapid disease progression, high mortality, lack of other immune deficiency disease and normal quantitative IgM and IgG response to other pathogens [11]. Our patient was 68 years old and had mild symptoms in form short febrile illness and oral candidiasis in contrast to the reported cases, while his CD4 count and HIV RNA were consistent with that reported in the literature. As seronegative HIV infection is associated with rapid progression to AIDS within months and high mortality, we started combination antiretroviral therapy (tenofovir + emtricitabine +efavirenz). Repeat western blot after one month showed 2 bands (p24 and gp160), while it evolved to positive after two and half months. Like our patient seronegative HIV patients seroconverted only after starting highly active antiretroviral treatment (HAART), while those not on HAART either died or lost to follow-up [1-4]. Evolving western blot after HAART could be a natural evolution after acute seroconversion illness in our patient. This can be differentiated well by use of avidity test. Early institutions of HAART in our patient had prevented severe symptoms due to opportunistic infections and associated with better outcome in contrast to severe symptoms and high mortality reported in the literature [11]. Reason for persistent seronegativity in this group of patient is absence of HIV-1 specific humoral response. Ineffective cellular immunity led to unimpeded viral replication and further rapid CD4 loss after primary HIV infection. As B cells require CD4 T-cell signaling to become activated and produce antibodies in the setting of acute infection, profound and sudden CD4 lymphopenia may lead to a lack of detectable antibody production. This inference is supported by the observation that in several of the patients described in the literature, antibody production to HIV-1 antigens develops with restoration of CD4 T cells after initiation of HAART. Case reports from Chin BS et al [10], Bartolo I et al [9] performed genotyping and phylogenetic analysis to further characterize viral subtypes. [9,10] In private practice settings we have not performed HIV genotyping and phylogenetic analysis to characterize HIV type responsible for clinical dilemma.

This case represents one of the most difficult situations in clinical practice and strong clinical suspicion is required for diagnosis of such case.

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