False-Positive Human Immunodeficiency Virus Antibody Test and Autoimmune Hemolytic Anemia in a Patient with Angioimmunoblastic T-Cell Lymphoma

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Abstract

A 44-year-old woman was admitted with generalized lymphadenopathy, which was diagnosed as angioimmunoblastic T-cell lymphoma (AITL). The patient showed autoimmune hemolytic anemia (AIHA), polyclonal hypergammaglobulinemia and a high antinuclear antibody titer. Moreover, a human immunodeficiency virus (HIV)-1/2 screening test using the particle agglutination method was reactive. After chemotherapy for AITL, the AIHA was eliminated, and the false-positive HIV results were no longer detected. Autoimmunity associated with AITL is the likely cause of the cross-reaction with HIV and the AIHA. It is important to recognize that the cross-reaction with HIV can be a potential complication in AITL as well as AIHA.

Key words: angioimmunoblastic T-cell lymphoma, autoimmune hemolytic anemia, human immunodeficiency virus

(Intern Med 50: 2383-2387, 2011)
(DOI: 10.2169/internalmedicine.50.5764)

Introduction

Patients suspected of having malignant lymphoma must be tested for human immunodeficiency virus (HIV), because some lymphomas are associated with HIV infection and patients sometimes show immunodeficiency. This is generally accomplished by screening serum from the patient using an enzyme immunoassay (EIA) or particle agglutination assay for HIV-1/2. However, it has been estimated that up to 0.5% of patients found to be seropositive for HIV are false positives (1, 2). Individuals likely to have a false-positive HIV screening test include pregnant women (1), patients with autoimmune disease (3, 4) and patients with hypergammaglobulinemia related to another condition, such as hematological malignancy, liver cirrhosis or hepatitis.

Angioimmunoblastic T-cell lymphoma (AITL) presents with generalized lymphadenopathy, hepatosplenomegaly, fever, skin rash, polyclonal hypergammaglobulinemia, pleural effusion and arthritis (2). Laboratory findings include autoimmune phenomena such as autoimmune hemolytic anemia, a positive Coombs test, cold agglutinins, circulating complexes, rheumatoid factors, cryoglobulins and antinuclear antibodies (3). The clinical course is aggressive, with a median survival of less than three years, largely owing to associated immune dysregulation with opportunistic infection (2). The characteristic clinical features of AITL are widely believed to be related to an abnormal pattern of cytokine expression by neoplastic T cells and various non-neoplastic cells (7, 8).

Although AITL accompanies autoimmune disease or hypergammaglobulinemia, there are a few reports on the complication of false-positive HIV antibody test in AITL.

Here we report on a patient with AITL and autoimmune hemolytic anemia (AIHA) whose HIV screening test was positive, and discuss this phenomenon in the context of the clinical features of AITL.

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Received for publication May 5, 2011; Accepted for publication July 8, 2011
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**Case Report**

A 44-year-old woman was admitted to our hospital in April 2007 because of generalized lymphadenopathy. As a teenager, the patient had suffered from chronic glomerulonephritis, but there was no other serious illness or injury. On admission, the patient’s body temperature was 38.8°C, her pulse rate was 102 beats/min and her blood pressure was 122/61 mmHg. Physical examination revealed moderate anemia and jaundice in the conjunctivas, systemic lymphadenopathy and hepatosplenomegaly. There was no manifestation suggestive of systemic lupus erythematosus (SLE). The results of routine laboratory tests done at the time of admission are shown in Table 1. Complete blood counts revealed normocytic anemia with reticulocytosis. Blood chemistry showed elevated serum levels of indirect bilirubin and lactate dehydrogenase (LDH). Both direct and indirect Coombs tests were positive (direct Coombs test for IgG: ++, direct Coombs test for C3d: -, indirect Coombs test: ++++). Antibody identification showed anti-E (IgG) and warm panreactive IgM. The cold agglutinin titer was not detected. Antinuclear antibodies (ANA) were strongly positive (homogeneous plus speckled pattern) (Table 2). The specific autoantibodies, including anti-dsDNA IgM, anti-Sm IgG, anti-ribonucleoprotein (RNP) IgG, anti-SS-A/Ro IgG, anti-SS-B/La IgG, anti-topoisomerase-I (Scl-70) IgG, anti-centromere IgG and anti-cardiolipin IgM were negative, however, anti-dsDNA IgG (16 IU/mL, normal range <12 IU/mL) and anti-cardiolipin IgM (25 U/mL, normal range <8 U/mL) were weakly positive. Soluble interleukin (IL)-2 receptor was elevated in the serum, and polyclonal hypergammopathy was detected. HIV screening using a particle agglutination assay revealed an elevated titer of HIV1/2 antibody (×512), but the HIV Western blot was negative and HIV RNA was not detected in a reverse transcriptase-polymerase chain reaction assay (RT-PCR), indicating the patient was not an HIV carrier.

Biopsy of an axillary lymph node revealed the normal architecture of the node to be completely effaced by a mixed population of inflammatory cells, including reactive lymphocytes, immunoblasts, plasma cells, eosinophils and epithelioid cells, as well as arborizing blood vessels (Fig. 1a). In addition, there were frequent foci of diffuse proliferations of medium-to-large atypical lymphoid cells with occasional pale cells (Fig. 1b). Both of these cell types were considered to be neoplastic, based on morphological examination (Fig. 1c and 1d). The cells were positive for the T-cell anti-
gens CD2, CD3, CD5, CD4, CD7 and CD10 (Fig. 2a). Also found were foci containing an irregular meshwork of follicular dendritic cells, defined based on their CD21 positivity (Fig. 2b), and occasional Epstein-Barr virus-positive cells. Moreover, atypical cells with clear cytoplasm were also observed in the patient’s bone marrow. Real-time polymerase chain reaction documented evidence of the Epstein-Barr virus genome in her blood. From these clinical data, the patient was diagnosed as having angioimmunoblastic T-cell lymphoma (AITL), and her disease was staged as IVB according to the Ann Arbor classification. The patient was treated with CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisone), and after 6 cycles of CHOP she had achieved complete remission. Interestingly, not only did the CHOP chemotherapy eliminate the AITL, it also resolved AIHA and the cross-reaction with HIV (Table 2).

The patient relapsed with generalized lymphadenopathy in April 2008. Biopsy specimens collected at that time revealed the same histopathological findings as the lymph node biopsy performed when she was first admitted. However, there was no finding of overt AIHA in laboratory data, even though slightly elevated titer on Coombs tests was observed. On the other hand, cross-reaction of HIV1/2 antibody in a particle
agglutination assay was again detected. The patient was placed on CHASE salvage therapy (cyclophosphamide, high dose cytarabine, methylprednisolone and etoposide); however, her lymphoma continued to progress. In July 2008, she underwent allogeneic transplantation using peripheral blood stem cells from an HLA-identical sibling donor which resolved the autoimmune phenomena as well as AITL (Table 2). The patient is currently well, without serious complications (e.g., graft-versus-host disease or viral infections).

Discussion

Although SLE patients may have a positive Coombs test even without overt hemolysis, overt AIHA has been reported in 10% of patients with SLE (4). As the present patient was strongly positive for ANA, the mechanism underlying the antibody reaction to AIHA may also be the same as in SLE patients. Recently, Wong et al reported that the elevated production of CXCL13 and IL-21 may be associated with the function of follicular helper T (T_{fh}) cells for the immunopathogenesis in SLE (5). T_{fh} was identified as the cell of origin of AITL and the T_{fh} cytokines CXCL13 and IL-21 play key roles in B-cell activation, B-cell expansion, plasmacytic differentiation and hypergammaglobulinemia (6). The common immunological aberrations might make the same autoimmune phenomenon in the present case with AITL as in patients with SLE.

Moreover, HIV-1/2 screening test using the particle agglutination method was reactive on admission and relapse in the present case. The test used, the GENEDIA® HIV-1/2 test (Fujirebio, Inc., Tokyo, Japan), is a simple-to-perform agglutination assay capable of detecting antibodies to HIV1/gp41, HIV-1/p24 and HIV-2/gp36. The false-positive rate for this test is believed to be much lower than the previous test, SERODIA® HIV-1/2 (Fujirebio, Inc.), the specificity of which was reported to be 99.97% (7). In cases with lymphoma or autoimmune disorders, if HIV-1/2 screening test is positive, the result had to be confirmed by Western blotting or RT-PCR assay, even keeping in mind the potential for false positive HIV serology in an autoimmune disorder (false-positive rate: one-third) (8, 9), or non-Hodgkin lymphoma (8%) (10).

To our knowledge, the present patient is the third reported case of cross-reaction with HIV associated with AITL (11, 12). The other two cases showed cross-reaction with HIV gag protein p24 on Western blots. In our case, by contrast, cross-reaction with HIV was detected using a particle agglutination assay; Western blotting showed no such cross-reaction. In one study, antibodies reactive with HIV p24 were detected in 22 of 66 patients with SLE (8). The investigators speculated that the mechanism of the reactivity with HIV p24 was antigenic mimicry between self-epitopes, such as small ribonucleoproteins (so-called Sm) or retroviral antigens. On the other hand, Muta and Yamano speculated that in their case with AITL some of the numerous subtypes of polyclonal gamma globulin had coincidentally cross-
reacted with HIV p24 (11). Although the mechanism underlying the antibody reaction to HIV in the present case is unclear, HIV gag protein p24 might be related to the cross-reaction as same as in the other cases with AITL or patients with SLE, and HIV cross-reaction might be independently coincident with AIHA.

Conclusion

We have reported on a patient with AITL who exhibited AIHA and had a false-positive HIV test. The autoimmune-associated phenomenon was resolved as remission of AITL was achieved with combination chemotherapy or allogeneic transplantation. Although false-positive HIV antibody test appear to be rarely reported in AITL patients, it is important to appreciate that the cross-reaction with HIV can be a potential complication as well as AIHA.

The authors state that they have no Conflict of Interest (COI).

References