Seronegative acquired immunodeficiency syndrome (AIDS)

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The case reported here fulfilled the Centers for Disease Control surveillance case definition for acquired immunodeficiency syndrome without laboratory evidence of human immunodeficiency virus. The patient, a 63-year-old man, had received transfusions of several units of packed red blood cells after a coronary bypass graft. He had recurrent fever and lymphopenia. He had a depressed helper T-cell count, esophageal and tracheobronchial candidiasis, and *Pneumocystis carinii* pneumonia. Results of all tests for human immunodeficiency virus were negative or inconclusive. However, the patient may have been seroconverting at the time of his death.

(Key words: Acquired immunodeficiency syndrome, human immunodeficiency virus, *Pneumocystis carinii* pneumonia, seronegative HIV antibody)

The revised Centers for Disease Control (CDC) (Atlanta, Ga) surveillance case definition for the acquired immunodeficiency syndrome (AIDS) provided criteria for diagnosing AIDS in the absence of laboratory evidence of

human immunodeficiency virus (HIV) infection.¹ These guidelines included exclusion of other causes of immunodeficiency (Table 1), evidence of an indicator opportunistic infection or neoplasm (Table 2), and a depressed T-helper (CD4-positive) lymphocyte count of less than 400/mm³.

We describe an HIV-seronegative person with recurrent fever and lymphopenia whose eventual death was due to *Pneumocystis carinii* pneumonia. This case exemplifies an unusual presentation of AIDS, and illustrates the capability of HIV to produce life-threatening disease in the absence of conclusive serologic findings.

Report of case

A 63-year-old man was admitted to Kennedy Memorial Hospitals—University Medical Center, Stratford (NJ) Division, Aug 11, 1987, with complaints of nausea, anorexia, and a 10- to 15-pound weight loss over the previous 14 days.

The patient had a history of coronary artery disease, and a coronary artery bypass graft had been performed at another institution in June 1985. Several units of packed red blood cells were transfused postoperatively. His current medications included diltiazem hydrochloride (30 mg four times a day), dipyridamole (75 mg three times a day), and aspirin (5 grains daily). He had no known drug allergies. He had a 36-pack-year cigarette smoking history. He had consumed one fifth of whiskey per week prior to 1985. There was no history of illicit drug use. The patient was married with no history of extramarital or homosexual contacts. He had

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References: 1. Pharmaceutical Data Services, Alpha Data Services, December, 1989.
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Brief Summary

VERELAN[®] Verapamil HCl
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For complete Prescribing Information, consult package insert.

CLINICAL PHARMACOLOGY: Food does not affect the extent or rate of the controlled absorption of verapamil from the VERELAN capsule.

Atrioventricular block can occur in patients without preexisting condition defects (see **WARNINGS**).

Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see **WARNINGS**).

In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14 to 16 hours (see **PRECAUTIONS**), the volume of distribution is increased, and plasma clearance reduced to about 30% of normal.

CONTRAINDICATIONS: Severe LV dysfunction (see **WARNINGS**), hypotension (systolic pressure <90 mmHg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), second- or third-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes). (see **WARNINGS**), hypersensitivity to verapamil.

WARNINGS: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction <30%) or moderate-to-severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker. Control mild heart failure with optimum digitalization and/or diuretics before VERELAN is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported.

Several cases of hepatocellular injury have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving IV verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (second- and third-degree, 0.8%). Development of marked first-degree block or progression to second- or third-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, second-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

PRECAUTIONS: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the

first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect on patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Verapamil has been given concomitantly with short- and long-acting nitroglycerin without any undesirable drug interactions. Interaction between cimetidine and chronically administered verapamil has not been studied. In healthy volunteers, clearance of verapamil was reduced or unchanged. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully.

Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest tumorigenic potential, and verapamil was not mutagenic in the Ames test. **Pregnancy Category C.** There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use. Safety and efficacy of verapamil in children below the age of 18 years have not been established.

ADVERSE REACTIONS: In clinical trials with 285 hypertensive patients on VERELAN verapamil sustained-release pellet-filled capsules for more than 1 week, the following adverse reactions were reported: constipation (74%); headache (5.3%); dizziness (4.2%); lethargy (3.2%); dyspepsia (2.5%); rash (14%); ankle edema (14%); sleep disturbance (14%); myalgia (11%). In clinical trials of other formulations of verapamil HCl (N = 4,954), the following reactions have occurred at rates greater than 10%: constipation (73%); dizziness (3.3%); nausea (2.7%); hypotension (2.5%); edema (1.9%); headache (2.2%); rash (1.2%); CHF/pulmonary edema (1.8%); fatigue (1.7%); bradycardia (HR <50/min) (1.4%); AV block-total 1°, 2°, 3° (1.2%); 2° and 3° (0.8%); flushing (0.6%); elevated liver enzymes (see **WARNINGS**).

The following reactions, reported in 10% or less of patients, occurred under conditions (open trial, marketing experience) where a causal relationship is uncertain.

Cardiovascular: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope. **Digestive System:** diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia. **Hemic and Lymphatic:** ecchymosis or bruising. **Nervous System:** cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence. **Respiratory:** dyspnea. **Skin:** arthralgia, rash, exanthema, hair loss, hyperkeratosis, maculae, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme. **Special Senses:** blurred vision. **Urogenital:** gynecomastia, impotence, increased urination, spotty menstruation.

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been employed as a barber for 40 years. He owned no pets, and he had never traveled outside the United States.

At the time of admission, his blood pressure was 128/70 mm Hg; pulse, 92 beats per minute; respiratory rate, 20 per minute; and temperature, 38.6°C. Results of a physical examination of the head and neck were normal. The heart was regular and without murmurs or gallops. Bibasilar rales were present in both lungs. The abdomen was soft, without hepatosplenomegaly. Results of a rectal examination were normal, and the stool was Hemocult negative. No lymphadenopathy was present. No clubbing, cyanosis, edema, or rashes were present. Results of a neurological examination were normal.

Result of laboratory studies on admission disclosed the following values: white blood cell count, 4600/mm³, with a normal differential cell count; hemoglobin, 13.8 g/dL; hematocrit, 42.2%; and platelet count, 264,000/mm³. Results of serum chemistry studies were normal, with the exception of a mildly depressed albumin concentration of 3.3 g/dL. The erythrocyte sedimentation rate was 72 mm/h. Serologic tests for hepatitis A and B were nonreactive. A chest roentgenogram revealed evidence of a previous sternotomy. An electrocardiogram revealed a sinus rhythm, poor R-wave progression, and inverted T-waves in leads III and VI, which were stable.

The patient experienced multiple temperature elevations associated with negative blood, urine, and sputum cultures, and no changes in his chest roentgenograms. Initially, treatment with mezlocillin (3.0 g every 6 hours intravenously) was begun empirically on the second hospital day and was subsequently discontinued because of lack of defervescence and negative cultures.

Results of a lymphocyte profile revealed an absolute lymphocyte count of 500/mm³ (normal, 960 to 4320/mm³); total T-cells, 360/mm³ (normal 633 to 3170/mm³); helper T-cells, 20/mm³ (normal 240 to 1200/mm³); and a helper/suppressor ratio, 0.04 (normal 0.8 to 3.0). Results of an HIV antibody test were negative by enzyme immunoassay (EIA) and Western blot.

An echocardiogram revealed no evidence of vegetations. A computed tomographic scan of the abdomen and pelvis was normal. Results of an upper endoscopy examination revealed the presence of esophageal candidiasis. Results of endoscopic retrograde cholangiopancreatography revealed the presence of cholelithiasis. Results of cerebrospinal fluid analyses were normal, and cultures were negative for routine bacteria, acid-fast bacilli, and fungi. A bone marrow biopsy specimen was 35% cellular,

with a myeloid-to-erythroid ratio of 2.5:1 and normal maturation of myeloid and erythroid cell lines. There was no evidence of neoplastic or granulomatous disease, and cultures were negative for acid-fast bacilli and fungi.

Delayed hypersensitivity skin testing failed to reveal any reaction to purified protein derivative, mumps, *Candida*, or saline control. A gallium scan showed diffuse bilateral uptake in the lungs.

A reticulonodular pattern developed on chest roentgenogram, and a fiberoptic bronchoscopy was performed on the 15th hospital day. Transbronchial biopsy specimens, endobronchial brushings, and bronchoalveolar lavage revealed mild fibrosis and hemorrhage, the presence of *Candida albicans*, and negative reactions to silver and Giemsa stains. Treatment with intravenously administered sulfamethoxazole-trimethoprim was started empirically; however, temperature elevations persisted and the chest roentgenogram progressed to a bilateral consolidative process.

An open-lung biopsy was performed on the 28th hospital day and revealed an interstitial pneumonia with focal areas of atelectasis. Silver stains were positive for *P. carinii*. A repeated HIV antibody test was positive by EIA, but the Western blot was nonconfirmatory.

The patient had adult respiratory distress syndrome postoperatively and subsequently died on the 35th hospital day. At the time of his death, blood was drawn for HIV antigen tests, which were negative. However, HIV antibody testing revealed antibody to p41 (envelope protein) to be persistently positive and antibody to p24 (core protein) to be negative (Michael Sogona, MD, Abbott Laboratories, North Chicago, Ill, telephone conversation, September 1987).

Discussion

Seronegative HIV infections have been reported previously. Salahuddin and associates² isolated HIV from the blood or body fluids in 96 patients, four of whom were HIV-antibody-negative. All four were sexual partners of patients with AIDS or the AIDS-related complex (ARC); two were homosexual men and two were heterosexual women. All four were asymptomatic.

Groopman and colleagues³ described two patients who had been diagnosed with AIDS or ARC, both of whom were HIV-antibody-negative by EIA, Western blot, indirect membrane immunofluorescent assay, and radioimmunoprecipitation techniques. Human immunodeficiency

Table 1
Other Causes of Immunodeficiency^{1(p48)}

- Use of high-dose or long-term systemic corticosteroid therapy or other immunosuppressive agents within 3 months prior to the diagnosis of the indicator disease
- Diagnosis of Hodgkin's disease, non-Hodgkin's lymphoma (other than primary brain lymphoma), lymphocytic leukemia, multiple myeloma, or any other cancer of the lymphoreticular or histiocytic tissues, or angioimmunoblastic lymphadenopathy within 3 months after diagnosis of the indicator disease
- Diagnosis of a congenital immunodeficiency syndrome, an acquired immunodeficiency syndrome atypical of human immunodeficiency virus infection, such as one involving hypogammaglobulinemia

ciency virus was recovered from the peripheral blood from both patients. The first patient was a 55-year-old homosexual man with biopsy-proved Kaposi's sarcoma who was otherwise asymptomatic. The other patient was a 24-year-old bisexual man with generalized lymphadenopathy who was also asymptomatic. Both patients remained seronegative and asymptomatic at 6-month follow-up.

Mayer and coworkers⁴ described a cohort of 215 asymptomatic, high-risk, HIV-antibody-negative homosexual men, 33 of whom consented to HIV cultures. Two of the 33 had HIV recovered from lymphocyte cultures. One patient, a 29-year-old man remained seronegative and asymptomatic at 6-month follow-up. The other patient, a 33-year-old man remained seronegative, but generalized lymphadenopathy developed.

Seronegative asymptomatic homosexual men

Evidence of HIV infection has recently been demonstrated in a cohort of seronegative asymptomatic homosexual men who continued to engage in high-risk sexual activity.⁵ Mitogen stimulation of cultured peripheral blood lymphocytes was used to increase the expression of the integrated HIV genome. Human immunodeficiency virus was isolated in 31 (23%) of 133 men in this cohort. Twenty-seven of the 31 subjects remained seronegative for up to 36 months following the positive culture.

Four of the 31 subjects became positive for HIV antibody 11 to 17 months after recovery of HIV from the peripheral blood. In three of these four patients, evidence of HIV provirus infection 23 to 35 months prior to seroconversion was demonstrated by enzymatically amplifying small amounts of viral DNA in cryopreserved lymphocytes using the polymerase chain reaction (PCR). In a separate analysis of the PCR, Imagawa and colleagues⁵ found 310 (99%) of 313 HIV-antibody-positive blood samples that were positive by PCR, and 433 of (97.7%) of 443 HIV-antibody-negative samples that were negative by PCR.

Seronegative HIV infections in children

Seronegative HIV infections have also been reported in children. Pahwa and colleagues⁶ described 36 children with HIV infection. Two of these patients, aged 1.5 and 8 years, respectively, were HIV-antibody-negative but had HIV cultured from their peripheral blood specimens. Both subjects were asymptomatic at 10-month follow-up. Marshall and associates⁴ described the case of an infant, born to parents who were both HIV-antibody-positive, who had esophageal candidiasis at the age of 10 months, followed by *P carinii* pneumonia with concurrent cytomegalovirus infection at age 14 months, and who subsequently died of respiratory failure 2 weeks later.

The patient was repeatedly HIV-antibody-negative by EIA and Western blot techniques. Attempts to culture HIV from the peripheral blood prior to death were unsuccessful. However, the case was atypical of AIDS in that the patient was hypogammaglobulinemic.

Seronegative HIV infections in acute viral syndromes

Seronegative HIV infections have also been documented in acute viral syndromes. Ho and associates⁸ described the cases of three homosexual men who were HIV-antibody-negative and who had fevers, rigors, arthralgias, and myalgias. Human immunodeficiency virus was cultured from the blood or spinal fluid in all three patients during their acute illness. Subsequent production of antibody to HIV occurred 8 to 12 weeks later.

Kessler and coauthors⁹ described the cases

of four homosexual men who had fever, rash, myalgias, and pharyngitis. All four were HIV-antibody-negative and HIV-antigen-positive at presentation. All four subsequently seroconverted to HIV-antibody-positive, and three of the four have become HIV-antigen-negative.

In addition to acute HIV infections, other reasons for seronegative HIV infection include sampling the patient's serum during the window period in early HIV infection not associated with an acute viral syndrome¹⁰⁻¹²; loss of HIV antibody in terminal AIDS¹²; errors in interpretation of EIA^{12,13} and Western blot¹⁴; low levels of HIV antibodies present in the serum (ie, borderline results of EIA tests)¹⁵; true false-negative results of EIA or Western blot (or both) tests (specificities of screening and confirmatory tests range from 94.1% to 100%); HIV-antibody-positive patients treated with immunosuppressive agents possibly resulting in loss of EIA reactivity (unpublished data)¹⁰; and the presence of HIV-2 infection (which is associated with AIDS in West Africa and has recently been described in a few case reports in the United States),^{17,18} antibodies to which may not cross-react with antibodies to HIV-1.

Seroreversion in asymptomatic patients

Seroreversion from HIV-antibody-positive to HIV-antibody-negative has also been described in asymptomatic patients. Burger and colleagues¹⁹ described a case of a hemophiliac with AIDS whose wife became HIV-antibody-positive. During 10 months of follow-up, she remained asymptomatic, discontinued exposure to semen, and became HIV-antibody-negative.

Farzadegan and coworkers²⁰ described four asymptomatic homosexual men who seroreverted, and who were negative for HIV antigen and for HIV culture. However, PCR revealed HIV provirus in all four patients 6 to 18 months after the last positive antibody test. It is possible that evidence of persistent HIV infection could have been documented in the case described by Burger¹⁹ if PCR had been available and used in the analysis of the HIV-antibody-negative samples.

Comment

In summary, our patient represents a case of

Table 2
Indicator Diseases^{1(p48)}

- Candidiasis of the esophagus, trachea, bronchi, or lungs
- Extrapulmonary cryptococcosis
- Cryptosporidiosis with diarrhea lasting 1 month or longer
- Cytomegalovirus disease of an organ other than liver, spleen, or lymph nodes in a patient older than 1 month
- Herpes simplex virus infection with mucocutaneous ulcer persisting for 1 month or longer, or bronchitis, pneumonitis, or esophagitis for any duration in a patient older than 1 month
- Kaposi's sarcoma affecting a patient younger than 60 years
- Lymphoma of the brain (primary) affecting a patient younger than 60 years
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia (or both) affecting a child younger than 13 years
- *Mycobacterium avium* complex or *Mycobacterium kansasii* disease disseminated to a site other than, or in addition to, the lungs, skin, or cervical or hilar lymph nodes
- *Pneumocystis carinii* pneumonia
- Progressive multifocal leukoencephalopathy
- Toxoplasmosis of the brain affecting a patient older than 1 month

AIDS by virtue of the depressed helper T-cell count and the presence of esophageal and tracheobronchial candidiasis as well as *P carinii* pneumonia. Human immunodeficiency virus antibody testing was negative or inconclusive. However, it may be speculated that the patient was seroconverting at the time of his death. Other tests for HIV infection, such as HIV antigenemia, PCR, or mitogen stimulation of CD4 cells, were not performed or were not available at the time the patient was seen. It is possible that any of these tests could have been positive if performed at the time of the initial HIV-antibody testing, results of which were negative. Tissue culture for HIV (eg, endoscopic biopsy of the duodenal mucosa or transbronchial lung biopsy) may have been rewarding if performed. However, the current techniques for HIV cultures are of low sensitivity.²¹

Our patient's only risk factor for HIV infection was the red blood cell transfusions that he received during coronary artery bypass surgery, which occurred shortly after HIV-antibody testing of the nation's blood supply was implemented.

The association of blood transfusions and the development of AIDS was first described in 1984 by Curran and associates.²² Screening of all donated units of blood for the HIV antibody has decreased, but not eliminated, the risk of acquiring transfusion-associated HIV infection. Ward and colleagues²³ described 13 patients positive for HIV antibody who had received blood from seven donors who were negative for HIV antibody at the time of donation. All seven were subsequently found to be infected with HIV. Initial estimates of the risk of a unit of blood being falsely HIV-antibody-negative were as low as 1 in 10,000.²⁴ However, the current risk is estimated to be 1 in 153,000.²⁵

The natural history of transfusion-associated HIV infection was recently reviewed by Ward and coworkers.²⁶ They found that most recipients of HIV-infected blood become seropositive, and that AIDS develops in approximately half of these patients within 7 years. The risk of developing AIDS following transfusion of HIV-infected blood appears to be higher with an increasing number of transfusions and when AIDS develops in the donor soon after donation.

With the revision of the CDC surveillance case definition for AIDS¹ and the use of more specific diagnostic tests to document HIV infection, more cases of AIDS will surely be diagnosed with inconclusive or negative HIV-antibody test results.

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