Medical News

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AmFAR Launches Emergency Tuberculosis Initiative

The American Foundation for AIDS Research (AmFAR) has launched an emergency initiative against tuberculosis that will raise and distribute more than $300,000 to develop critical new tuberculosis diagnostic technologies.

AmFAR began the initiative because of the growing threat of tuberculosis and multidrug-resistant tuberculosis to the public health in general and to people living with HIV/AIDS in particular. AmFAR will provide funding for four to six research projects testing new genetic and chemical techniques to make diagnosing tuberculosis quicker, easier, and more reliable.

The emergency grants initiative will support both developing technologies and new methods currently being tested in the field that can cut the interval for diagnosing infectious tuberculosis to days, allowing people to be treated early enough to greatly increase their chance of surviving tuberculosis while also helping to prevent the spread of the disease.

AmFAR's tuberculosis initiative will be supported with the technical assistance from the American Lung Association (ALA).

From the Centers for Disease Control

UNEXPLAINED CD4 + T-LYMPHOCYTE DEPLETION IN PERSONS WITHOUT EVIDENT HIV INFECTION-UNITED STATES

Since 1989, 21 persons with unexplained CD4 + T-lymphocyte depletion, but without evident human immunodeficiency virus (HIV) infection have been described.[1-12] These reports included persons who have resided in the United States and six other countries and who sought medical care for conditions often associated with immunodeficiency. Some of these cases were also described at the VIII International Conference on AIDS/III STD World Congress in Amsterdam. In addition, the Centers for Disease Control (CDC) has received reports of five persons from three states who have had persistently low CD4 + T-cell levels but who have had no evidence of HIV infection or underlying disease processes or therapies known to be associated with T-cell depletion. In some of these five patients, opportunistic infections were diagnosed that frequently occur in persons with acquired immunodeficiency syndrome (AIDS). This report described preliminary clinical and laboratory findings from an ongoing investigation by CDC of these five patients.

Patient 1

In March 1991, a 70-year-old man developed *Pneumocystis carinii* pneumonia that was successfully treated with trimethoprim-sulfamethoxazole. Although serology for HIV antibody was negative, his CD4 count was 50 cells/μl. After this hospitalization, he developed a fungal infection of the groin that was treated with oral ketoconazole and topical antifungal medications. In April 1992, transitional cell carcinoma of the bladder, stage II, was diagnosed. As of July 1992, he was asymptomatic.

His family history and personal history were negative for immunodeficiency disease and for recurrent or unusual infections. His spouse, who has remained healthy, is HIV negative and has a normal CD4 count. He did not report sexual contact with men or intravenous drug use. In 1987, he received three units of whole blood for a bleeding duodenal ulcer; follow-up investigation in 1992 indicated that all three

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blood donors were HIV-1 and HIV-Z negative, had normal CD4 counts, and were in good health.

Patient 2

In October 1984, a 38-year-old male healthcare worker developed cryptococcal meningitis that was treated with a full course of amphotericin B and 5-fluorocytosine. In January 1985, he had an episode of localized herpes zoster. In July 1985, symptoms of meningitis recurred. A cryptococcoma was excised from his brain, and he was treated with another course of antifungal therapy. Since this hospitalization, he has been in generally good health except for a nonspecific skin rash that resolved, mild hypertension, and a grand mal seizure for which he takes phenytoin. In December 1987 and December 1988, his CD4 counts were 152 and 84 cells/μl, respectively. An enzyme immunoassay (EIA) for HIV antibody was negative in April 1989. As of July 1992, he was asymptomatic.

There was no family history or personal history of immunodeficiency or unusual infections. He did not report sexual contact with men or intravenous drug use. He had not received blood transfusions, did not perform invasive procedures, and had no known parenteral or mucous membrane exposure to blood. He reported his spouse was in good health.

Patient 3

In October 1989, a 58-year-old woman developed acute cholecystitis and underwent cholecystectomy. She had a prolonged postoperative course complicated by nosocomial pneumonia of undetermined etiology and vaginal candidiasis. She recovered with antibiotic therapy. An HIV EIA test was reported as positive during this hospitalization. In December 1989, although HIV serology by EIA was negative, a single p24 band on western blot was observed; her CD4 count was 86 cells/μl. She remained asymptomatic; when reevaluated in January 1991, HIV serology was negative on two occasions but her CD4 count remained low (103 cells/μl). As of July 1992, she was asymptomatic.

She had received multiple transfusions for hemorrhage during pregnancy during the 1950s and for menorrhagia in the late 1970s and early 1980s. There was no family history of immunodeficiency or unusual infections. She did not report intravenous drug use. She reported that her spouse was in good health.

Patient 4

In November 1986, a 45-year-old man received treatment for disseminated moluscum contagiosum. In April 1989, a lung biopsy was performed for evaluation of a mass on his chest radiograph. The lesion was consistent with a plaque secondary to asbestosis, although the man had no known history of asbestos exposure. In February and August 1989, HIV EIA serologies were negative; however, CD4 counts were 96 cells/μl and 68 cells/μl, respectively. As of July 1992, he was asymptomatic.

His family and personal history were negative for immunodeficiency or for recurrent or unusual infections. He did not report sexual contact with men or injecting-drug use; he had not received blood transfusions. His spouse was in good health and had a normal CD4 count.

Patient 5

In December 1983, a 70-year-old woman was hospitalized with disseminated cutaneous herpes zoster. In December 1988, she developed fever, cough, and pleurisy. On evaluation, mediastinal lymphadenopathy was found, and histoplasmosis was diagnosed by open lung biopsy. She was treated with amphotericin B and ketoconazole with resolution of both symptoms and lymphadenopathy. Although HIV serology was negative during this hospitalization, a CD4 count was 275 cells/μl. In February 1989, the count was 499 cells/μl.

In April 1991, she developed fever and cough, and a pulmonary infiltrate was indicated on chest radiograph; her CD4 count at that time was 199 cells/μl. Although her symptoms responded to ciprofloxacin, sputum cultures subsequently grew *Mycobacterium avium-intracellulare*. In September 1991, her pulmonary symptoms recurred, and a new pulmonary infiltrate was present on chest radiograph; *M avium-intracellulare* was again cultured from bronchial washings. Her symptoms resolved during treatment with ciprofloxacin, rifampin, and ethambutol. In January 1992, epigastric pain prompted a gastrointestinal evaluation, and an ulcerated mass lesion was detected in the stomach. Histoplasmosis was found on biopsy, and *Helicobacter pylori* was cultured from the lesion. Fluconazole therapy was initiated with good response. As of July 1992, she was asymptomatic.

She had been in excellent health with no family history or personal history of immunodeficiency or unusual infections. She did not report intravenous drug use and had not received a transfusion. Her spouse died in 1984 with atherosclerotic cardiovascular disease and carcinoma of the kidney.

Laboratory Findings

Blood samples from each of the five patients have been tested at the CDC, and low CD4 counts ((300 cells/μl) and negative HIV-1 and HIV-2 serologies (by EIA and western blot) have been confirmed. Cocultures of peripheral blood mononuclear cells from

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patients l-4 with normal peripheral blood mononuclear cells or lymphoid cell lines were negative for cytophathicity, syncytia, and the generation of reverse transcriptase activity as measured by standard methods. Human T-cell lymphotropic virus (HTLV)-I and HTLV-II serologies were negative. Neither HIV-1- nor HIV-2-related DNA sequences were detected in the blood of patients l-4 by polymerase chain reaction. Results of studies of specimens from patient 5 are pending.

Editorial Note

The clinical conditions of the patients described in this report vary considerable; however, these cases share three features: persistently low CD4 + T-cell levels; no evidence of HIV infection by serology, culture, or polymerase chain reaction analysis; and infections that prompted physicians to consider HIV infection.

Review of available data on the 26 case patients (including the five described in this report and 21 reported elsewhere)[1-12] does not indicate an epidemiologic link among the cases. Cases of unexplained CD4 + T-cell depletion have been reported in Australia,[1] Denmark,[2] England,[3,4] France,[5-7] Germany,[8] Spain,[9] and the United States.[10-12] Of the 26 case patients, five had received transfusions before onset of illness, five were homosexual men, and the remaining 16 had no known risk factors for HIV infection. In this report, followup investigation of the blood donors for patient 1 found that they were HIV seronegative, immunologically normal, and in good health. Two additional cases reported to the CDC have been excluded because CD4 + T-cell depletion may have been related to chemotherapy.

Although infections with HIV-1 or HIV-2 have been associated with immunodeficiency of the type described in these patients, no evidence for infection with either virus has been documented. The cause of CD4 + T-lymphocyte depletion in the patients described in this report and in other reports is unknown; moreover, it is unknown whether these cases represent a single syndrome. However, there are at least two possible hypotheses to explain this abnormality. Persistent CD4 + T-cell depletion may occur in some patients as a response to certain infections or other exposures. Transient CD4 + T-cell depletion has been reported following some infections; whether this persists in some patients is unknown.[13-14] Therefore, one possibility is that some or all of these case reports of unexplained CD4 + T-lymphocyte depletion are part of background occurrence that may only now be recognized because of the increased availability of T-cell phenotyping. A second possibility is that some of these cases may represent a different syndrome of immunodeficiency associated with CD4 + T-cell depletion.

Two of the recent preliminary reports of CD4 + T-cell depletion in patients who were HIV-1 and HIV-2 seronegative have suggested the presence of a retrovirus.[11,12] The relation of these reports to the immunodeficiency detected in patients described in this and other reports is not known.

The CDC and the National Institutes of Health (NIH) are collaborating with pysicians, scientists, and public health officials to identify other cases and investigate this problem. The NIH will assist in the characterization of the clinical, immunologic, and virologic features by collaborating with investigators and working through its network of grantees and contractors to collect, process, and distribute specimens and reference materials. The CDC, in collaboration with the NIH, convened a meeting of investigators and public health officials in mid-August to discuss these cases and epidemiologic and laboratory investigation in progress.

Additional CDC epidemiolgic and laboratory investigations regarding these cases are in progess. Heathcare providers are requested to report to the CDC through the AIDS surveillance section of their local or state health department patients who have CD4 + T-lymphocyte depletion (absolute CD4 + T-cell <300 cells/μl or $<20\%$ on more than one determination), no serologic evidence of HIV infection, and no defined immunodeficiency or therapy associated with T-cell depletion. Although no cases have been reported in children, HIV-negative pediatric cases with unexplained depletion of CD4 cells (as defined by age-adjusted normal CD4 counts) also should be reported.

Additional information on case reporting is available from the Surveillance Branch, Division of HIV/AIDS, National Center for Infectious Diseases, CDC, telephone (404) 639-2981. Reports of these cases will assist the CDC and other public health agencies in developing a more precise case definition to examine this problem and provide a resource for investigators who are conducting etiologic studies. General inquiries about the cases described here as well as on HIV and AIDS should be directed to the CDC National AIDS Hotline, (800) 342-2437.

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