The Acquired Immunodeficiency Syndrome in the Wife of a Hemophiliac

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A 71-year-old previously healthy woman developed unexplained thrush, onychomycosis, *Pneumocystis carinii* pneumonia, and a T-cell defect consistent with the acquired immunodeficiency syndrome. Her only apparent risk factor was infrequent, monogamous sexual contact with her husband, a 74-year-old hemophiliac who had received factor VIII concentrate and subsequently died due to *P. carinii* pneumonia. She first developed probable signs of the syndrome (recurrent thrush and onychomycosis) 1 year before her husband became ill. These findings suggest that the syndrome can be transmitted heterosexually by an asymptomatic person, and that the female sexual partners of hemophiliacs treated with factor VIII concentrate may be at risk of acquiring the syndrome; frequent sexual contact or several sexual partners are not necessary for transmission to occur; and the syndrome can occur in elderly people if exposed to risk factors. This case further supports the theory that the syndrome in hemophiliacs is due to an infectious agent that can be transmitted heterosexually as well as parenterally.

THE ACQUIRED IMMUNODEFICIENCY SYNDROME has been reported in homosexual men, intravenous drug abusers, Haitians, hemophiliacs, infants born to mothers in high-risk groups for this syndrome, and female sexual contacts of male intravenous drug abusers or bisexual men (1-19). Over 90% of these patients have been less than 50 years old and almost all have been less than 70 (4; CENTERS FOR DISEASE CONTROL. Unpublished data). We report a case of the acquired immunodeficiency syndrome in the 71-year-old wife of a 74-year-old hemophiliac who had received factor VIII concentrate and subsequently died due to *Pneumocystis carinii* pneumonia and probable acquired immunodeficiency syndrome. Her only apparent risk factor for acquiring the syndrome was infrequent monogamous sexual contact with her husband when he was asymptomatic.

Methods

The patient, her husband, and other family members were extensively interviewed. Historical data from the patient were confirmed by a personal interview done by a member of the Centers for Disease Control (CDC) Task Force on the acquired immunodeficiency syndrome. Several interviews were done in the patient's house in order to better evaluate her home environment. The patient and her husband were also examined and followed over a period of 8 years.

Immunologic and serologic testing was done as previously described (6). Antibody to human T-cell leukemia virus membrane antigens was measured using indirect living cell immunoflourescence of human T-cell leukemia virus infected HUT-102 cells (20).

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Case Report

A 71-year-old white woman, the wife of a patient with hemophilia A, was in good health until January 1982, when she developed slowly progressive fatigue, recurrent crusting blisters on her lips diagnosed clinically as herpes simplex, onychomycosis, and extensive thrush. The thrush responded to treatment with nystatin or ketoconazole but repeatedly recurred when these medications were discontinued. At the start of 1983 she developed watery, non-bloody diarrhea that recurred intermittently. In June 1983 she developed fever, a nonproductive cough, and dyspnea requiring hospitalization.

On admission, the patient appeared chronically ill and had a temperature of 38.9 °C. There were crusted herpetic lesions on her lower lip, onychomycosis of her fingers and toes, thrush, and fine rales throughout both lung fields. Other findings on physical examination were normal. The hematocrit was 39.9%, the peripheral leukocyte count was 5900/mm^3 with 58% neutrophils, 2% band forms, 34% lymphocytes, 3% monocytes, and 3% eosinophils. The sedimentation rate was 73 mm/h. The platelet count, blood urea nitrogen, blood glucose levels, and the results of a urinalysis were normal. Quantitative immunoglobulin studies showed an elevated IgG at 1690 mg/dL (normal, 617 to 1325 mg/dL), an elevated IgA at 669 mg/dL (normal, 65 to 301 mg/dL), and a normal IgM. Skin tests read at 24, 48, and 72 hours showed no reactivity to trichophytin, 1:500 strength (Iatric Corporation, Tempe, Arizona), mumps (Eli Lilly and Company, Indianapolis, Indiana), intermediate strength tuberculin purified protein derivative (Connaught Laboratories, Willowdale, Ontario, Canada), and candida, 1:500 strength (Iatric Corporation). Arterial blood gas tests done with the patient breathing room air showed a partial pressure of oxygen of 49 mm Hg, a partial pressure of carbon dioxide of 31 mm Hg, and pH 7.46. Initial chest roentgenogram showed a left upper lobe infiltrate and a right perihilar infiltrate, later developed. Routine sputum and blood cultures were negative. Transbronchial lung biopsy samples stained with methenamine silver showed numerous *P. carinii* cysts and intra-alveolar exudate. Cultures of bronchial washings were negative for mycobacteria and fungi. Her pulmonary symptoms resolved, and her chest roentgenogram showed significant clearance after 2 weeks of treatment with trimethoprim-sulfamethoxazole. The thrush cleared after a course of ketoconazole. The patient was discharged from the hospital on 20 June 1983 and was examined bimonthly through mid-October 1983. During this time, the patient's temperature reached 38.9 °C on several occasions, the onychomycosis persisted, herpetic lesions recurred several times on her lips, and severe thrush recurred repeatedly requiring several courses of ketoconazole. (The thrush recurred each time ketoconazole therapy was discontinued.) No underlying immunosuppressive illness has been found to explain the patient's opportunistic infections. Immunologic blood tests done 29 June 1983 and 17 July 1983 (after discharge from the hospital and after recovery from *P. carinii* pneumonia) showed a decreased T-helper cell: T-suppressor/cytotoxic cell ratio and decreased to absent in-vitro blastogenic responses to mitogens and antigens (Table 1). Serologic tests showed antibody evidence of previous infection with hepatitis A virus, cytomegalovirus, Epstein-Barr virus, and human T-cell leukemia virus (Table 2).

The patient is of Irish descent, was born in Philadelphia, and lived there until 1970, when she moved to Florida with her

Table 1. Patient's Peripheral-Blood Lymphocyte Phenotypes and Blastogenic Responses to Mitogens and Antigens*

	Date of Testing		Normal Range†
	6/29/83	7/17/83	
Lymphocyte count, /mm^3	1760	1551	1046-3085
B cells, %	6	11	4-23
B cells, /mm^3	106	171	54-419
T cells, %	46	55	46-82
T cells, /mm^3	810	853	671-2073
T-helper/inducer cells (Th), %	17	19	30-60
T-helper/inducer cells, mm^3	299	295	401-1588
T-suppressor/cytotoxic cells (Ts), %	33	38	12-35
T-suppressor/cytotoxic cells, /mm^3	581	589	188-831
Th/Ts ratio	0.51	0.5	1-3.9
Mitogens (normalized %)‡			
Phytohemagglutinin	86	0	86-370
Concanavalin A	27	1	61-691
Pokeweed	68	0	41-309
Antigens (stimulation ratio)			
Candida	0.6	0.5	> 3
Tetanus	0.8	1.2	> 3
Streptolysin O	2.1	0.8	> 3
Herpes simplex virus	1.6	2.2	> 3
Cytomegalovirus	1.0	0.7	> 3

* Lymphocyte subpopulations presented as a percent of peripheral-blood lymphocyte count. T cells = OKT3, T-helper/inducer cells = OKT4, T-suppressor/cytotoxic cells = OKT8.
† 95% confidence limits. Although normal ranges were not obtained for an elderly population, the number of T-helper cells and the blastogenic responses to mitogens were still low compared to reported normal values in elderly patients (21, 22).
‡ This formula was used to determine the normalized mitogen response with stimulated and unstimulated values expressed in counts per minute: stimulated − unstimulated (patient)/stimulated − unstimulated (control) × 100.

husband. There was no other history of travel. The patient had worked as a cook in restaurants until 1974 when she retired. She had sex only with her husband, to whom she had been married for the past 50 years. For the past 10 years they slept in separate beds and had genital intercourse approximately once every 2 to 3 months until mid 1981 (approximately 6 months before she first became ill and 18 months before her husband first became ill). There was no bleeding or trauma during sexual intercourse. She denied any other sexual practices and denied the use of alcohol, tobacco, or illicit drugs by any route. Before this illness she had always been in good health and took no medication. She had never administered factor VIII concentrate to her husband or had contact with instruments for drug use. (The factor VIII was always administered by a nurse.) She had never had a blood transfusion or shared a common razor, tooth brush, or scissors with her husband. Except for bleeding hemorrhoids on several occasions in 1981 and 1982, her husband had had no external bleeding or open wounds since 1970. The husband had a left knee arthroplasty done in 1978 but there was no postoperative external bleeding and his wife had no contact with the operative site or with the bandages. A few times in 1981 the patient hand-washed her husband's shorts, which were stained with small amounts of dried blood from his bleeding hemorrhoids; however, the shorts were always first soaked in household bleach (an effective antiviral agent recommended empirically for use as a disinfectant in acquired immunodeficiency syndrome precautions) (23) before she washed them in fresh water. Further, she had no skin abrasions, skin punctures, or open wounds of any kind. The patient and her husband had no children and lived alone. They had few outside social or community activities and never had social contact with persons in a high-risk group for the acquired immunodeficiency syndrome.

The patient's husband was a 74-year-old white man of Italian descent who had clinically mild hemophilia A. Although he had a traumatic below-the-knee amputation of his right leg with excessive bleeding, occasional nosebleeds, and spontaneous bruising of his skin in childhood, hemophilia was not diagnosed nor did he receive factor VIII until 1970, when he hemorrhaged after a tooth extraction. He subsequently received factor VIII concentrate in November 1976, May 1977, and October 1977 for recurrent hemarthrosis of the left knee, January through June 1978 for a left knee arthroplasty that was complicated by recurrent hemarthrosis, March 1981 for bleeding hemorrhoids, and January 1982 for bleeding hemorrhoids and hemarthrosis of the left knee. He did not receive factor VIII after this time. Factor VIII coagulant activity measured in January 1978 was less than 1% of normal, and the factor VIII antigen was 182% of normal. Circulating anticoagulant against antihemophilic factor was not found. The husband's only other medications were ibuprofen for joint pains and propranolol for occasional cardiac palpitations. He had sexual contact only with his wife, and there was no history of illicit drug use. Except for his bleeding diathesis, he was in good health until January 1983 when h(developed a mild non-productive cough, low-grade fever, and

Table 2. Virologic Data

Test*	Results
Hepatitis A antibody	Positive
HBsAg	Negative
HBsAg antibody	Negative
HBcAg antibody	Negative
CMV	1:32
CMV (IHA)	1:16000
EBV IgG	> 1:10
EBV IgM	Negative
HSV I	1:2048
HSV II	1:16
HTLV (%)	48

* *HBsAg* = hepatitis B surface antigen; *HBcAg* = hepatitis B core antigen; CMV = cytomegalovirus measured by complement fixation; CMV (IHA) = cytomegalovirus measured by indirect hemagglutination assay; HSV I = herpes simplex virus type I measured by indirect hemagglutination assay; HSV II = herpes simplex virus type II measured by indirect hemagglutination assay; EBV = Epstein-Barr virus (viral capsid antigens) measured by immunofluorescent assay; HTLV (%) = percent of T-cells infected with human T-cell leukemia virus that fluoresced using patient serum (6.1% of uninfected control cells fluoresced using patient serum; a negative test was less than 20%).

progressive weakness, malaise, and weight loss for which he was hospitalized on 15 April 1983. These symptoms started about 1 year after his wife first developed recurrent herpetic oral lesions, onychomycosis, and thrush.

On admission he appeared chronically ill and had a temperature of 38.4 °C. There was a healed amputation below the right knee, deformed knee joints secondary to previous hemarthroses, and the healed scar of his previous left knee surgery. The rest of the physical examination was normal. The hematocrit was 32.3%, the peripheral blood leukocyte count was 4100/mm^3 with 25% lymphocytes, and the sedimentation rate was 119 mm/h. Partial thromboplastin time was 104 s. Prothrombin time and platelet count were normal. Several blood cultures and initial chest roentgenogram were negative. Serum levels of IgG and IgM were normal, but IgA was elevated to 1030 mg/dL. Cytomegalovirus titer by complement fixation was 1:16. Serologic tests for syphilis and hepatitis B surface antigen were negative. The patient was treated with a 2-week course of ampicillin because an oral cholecystogram showed nonvisualization of the gallbladder and an abdominal sonogram revealed gallstones; however, the fever, malaise, and weakness persisted. A repeat peripheral blood leukocyte count on 26 April was 3700/mm^3 with 27% lymphocytes. On 7 May, he had dysphagia and rapid respirations. A repeat chest roentgenogram showed an interstitial infiltrate in both upper lung fields, and tests for arterial blood gases with the patient breathing room air showed a partial pressure of oxygen of 44 mm Hg, a partial pressure of carbon dioxide of 25 mm Hg, and pH 7.5. Therapy with high-dose corticosteroids and penicillin was started. The patient subsequently developed thrush, diffuse interstitial infiltrates as shown on chest roentgenogram, and worsening respiratory distress. He died on 19 May 1983. An autopsy showed extensive *P. carinii* pneumonia, acute and chronic ulcerative esophagitis with epithelial cell intranuclear inclusions typical of herpes viral infection, chronic cholecystitis, cholelithiasis, and mild nonspecific hepatitis. There was no malignancy or evidence for other underlying immunosuppressive diseases.

Discussion

The patient, a 71-year-old woman, had a significant T-cell defect (Table 1) and unexplained opportunistic infections meeting the CDC criteria for the acquired immunodeficiency syndrome (24). After extensive interviews with the patient, her husband, and other family members, and after investigation of her home environment, we determined that her only apparent risk factor was sexual intercourse approximately once every 2 to 3 months with her husband, a 74-year-old hemophiliac who had received factor VIII concentrate and who subsequently died due to *P. carinii* pneumonia. Further, she first developed probable signs of the acquired immunodeficiency syndrome (recurrent thrush and onychomycosis) 1 year before her husband became ill. This suggests that the syndrome can be transmitted heterosexually by an asymptomatic person and the female sexual partners of hemophiliacs treated with factor VIII concentrate may be at risk for acquiring the syndrome; frequent sexual contact or several sexual partners are not necessary for transmission to occur; and the syndrome can occur in elderly people (given the proper risk factors) and need not be restricted to the younger population as previously described (4).

Although the patient's husband received high-dose steroids for 13 days before the histologic diagnosis of *P. carinii* pneumonia, the clinical evidence suggests that this infection preceded the steroids and that he had the acquired immunodeficiency syndrome. The onset of illness in the patient approximately 6 months after her last sexual contact with her husband and the onset of symptoms in her husband 1 year after last receiving factor VIII concentrate suggest a long incubation period for the acquired immunodeficiency syndrome.

The patient had antibody evidence of current or past infection with herpes simplex virus, Epstein-Barr virus, and cytomegalovirus (Table 2); however, antibodies to these viruses are prevalent in control groups for the syndrome and the general population (6, 25, 26). Of possible greater significance is antibody evidence in the patient for infection with human T-cell leukemia virus. Human T-cell leukemia virus is a lymphotrophic virus that preferentially infects T-helper cells and has recently been hypothesized to be of etiologic importance in the acquired immunodeficiency syndrome (20, 27-30). In a study, 25% to 40% of cases of the syndrome (mostly homosexual men) had antibodies to this virus compared to only 1% or less of controls (20). Further, there is evidence that human T-cell leukemia virus can be transmitted by heterosexual contact (31), and it is possible that our patient acquired human T-cell leukemia virus infection from her husband in this way.

The wives of patients with factor VIII deficiencies who had abnormal OKT4/OKT8 ratios were reported to show decreased percentages of OKT4 cells (32). Although it is possible that these immunologic abnormalities were related to the acquired immunodeficiency syndrome, these women and their hemophiliac husbands did not have the syndrome, and the meaning of their T-cell defects was therefore uncertain. The probable transmission of the syndrome in the present case from a hemophiliac husband to his wife further supports the theory that the occurrence of the syndrome among hemophiliacs who are treated with factor VIII concentrate is due to an infectious agent that can be transmitted heterosexually as well as parenterally through blood products. Monogamous and infrequent sexual contact as well as the absence of other risk factors in the patient (who led a remarkably secluded life with her husband) is evidence against the theory that frequently repeated stimulation with multiple antigens (as occurs among promiscuous male homosexuals) is necessary for the acquired immunodeficiency syndrome to occur (33).

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