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AIDS in Japanese Hemophiliacs

Takeshi ABE

Department of Medicine, Teikyo University School of Medicine, Tokyo 173, Japan

AIDS is now a serious problem in Japan as has been so in the United States and European countries. The disease shows a marked trend to spread rapidly over the world. Japanese virologists, immunologists, clinicians and participants in public health have a great concern for the problem. To date, 14 cases of AIDS have been officially acknowledged in Japan; 7 of them were hemophiliacs. Since the first report of AIDS in hemophiliacs in 1981 (2), they have been recognized as being at high risk for AIDS, which is presumably due to frequent opportunities of exposure to AIDS virus, LAV/HTLV-III (1,4,5), transmitted by blood products. Blood products used in Japanese hemophiliacs are mostly imported from the United States, therfore, Japanese hemohpiliacs are similarly at high risk for AIDS.

We had two patients with AIDS developed in hemophiliacs. Both had preceding ARC symptoms with impaired cellular immunity and LAV/HTLV-III seropositivity, and then developed fatal opportunistic infections. We present the cases in some details here.

Patient 1 was a 48-year-old man with hemophilia B. He had no other risk factor of AIDS. He had received factor IX concentrates once or twice a month since 1973 when it became available. Since the summer of 1981 he experienced repeated fever of unknown origin and occasionally had abdominal pain and diarrhea. Appetite loss and general malaise persisted. He was admitted to our hospital in January and March 1982, and was discharged both times in fairly improved conditions. The similar symptoms recurred thereafter, and in May 1982, he was hospitalized because of high fever with development of generalized lymphadenopathy and erythematous skin eruptions (Fig 1, left half). Since I had chances to see and treat some AIDS patients in abroad beforehand, I suspected AIDS. Although the symptoms met the criteria for AIDS proposed by American CDC, it was difficult to make the convincing diagnosis. At that time HTLV-III was not yet known as the causative agent of AIDS.

Episodes of fever recurred thereafter and his general conditions grew worse progressively; he was hospitalized again in May 1983 (Fig 1, left half). Infection with Candida albicans occurred in the mouth and esophagus. Then he fell into cachexia and died in June 1983, two years after the initial fever episode.

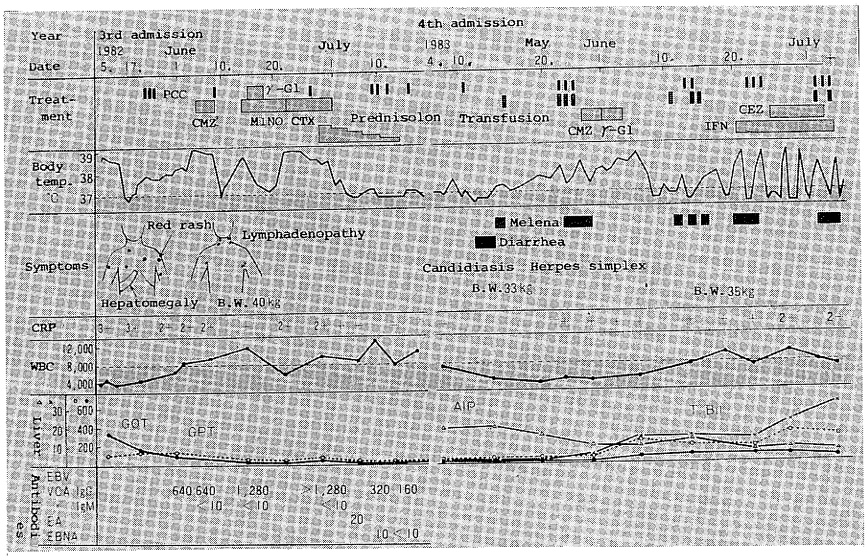

Fig. 1 Clinical course of Patient 1. The left half illustrates the course of the third hospitalization and the right half the fourth hospitalization.

The results of immunologic study of this patient is shown in Table 1. The T4/T8 ratio, which was 0.9 in March 1983, became reduced to 0.2 in April of the same year and remained low thereafter. The NK cell activity was extremely depressed and PPD skin test was negative in March 1983. In addition, the lymphocyte response to PHA and PWM was weak. These data indicated marked impairment of cellular immunity of the patient.

The autopsy revealed extensive candidiasis involving various organs and outstanding atrophy of lymph nodes. Candida invasion was observed even in the myocardium, which reflected profound impairment of the patient's immunologic function.

Later, antibody to HTLV-III was detected in the serum, leading to the final diagnosis of AIDS for the patient.

Patient 2 was a 62-year-old man with hemophilia A. He had received cryoprecipitates before 1978 and factor VIII concentrate since then when it was available for use. He had a history of lung tuberculosis seven years before. It was completely healed clinically and bacteriologically. Since the summer of 1983, he gradually developed ARC symptoms: consisting of recurrent fever, diarrhea, malaise, and body weight loss. He was admitted to our hospital in September 1983. The course of his hospitalization is shown in Fig. 2. During the hospitalization he developed lymphadenopathy in addition to the continuation of recurrence of fever, and diarrhea. Later, infection with Mycobacterium fortuitum occurred, which caused troublesome cough and hemoptysis. In spite of antimycobacterial treatment the symptoms and general

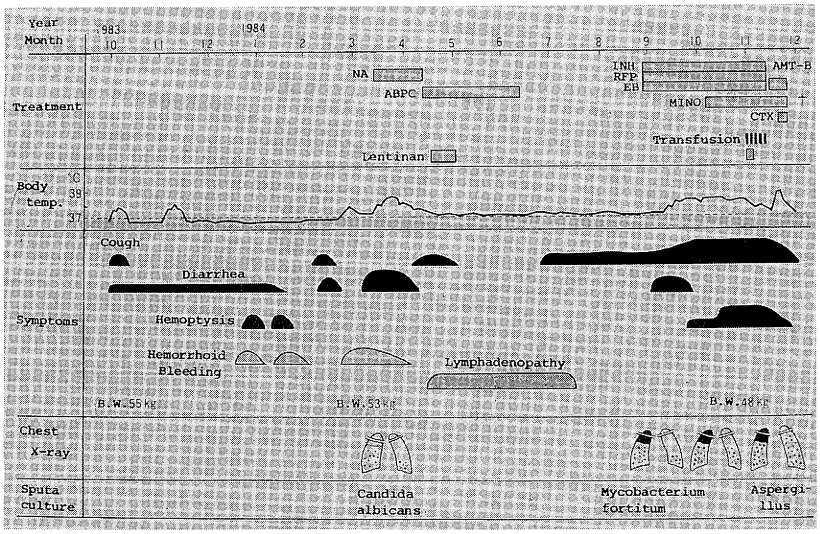

Fig. 2 Clinical course of Patient 2

in the lung. He died of respiratory insufficiency in November 1984, one and a half years after the onset of the ARC symptoms.

Immunologic study showed that the T4/T8 ratio and NK cell activity became lowered with the lapse of time since March 1983 and PPD skin test also turned to negative (Table 2). Antibody to LAV/HTLV-III, tested in April 1983, was positive in the serum.

The autopsy demonstrated mixed infection with atypical mycobacteria and Aspergillus in the lung, and markedly atrophied lymph nodes.

Table 1 Immunologic studies of Patient 1 and 2

	Patient 1					Patient 2				
Date	1982 Oct	1983 Mar	Apr	Jun	Jul	1983 Mar	Dec	1984 Mar	Apr	Oct
Lymphocyte counts (/ul)	3150	970	1850	1620	1540	620	710	390	530	780
T4 (%)		34	15	11	23	24	16	12	14	11
T8 (%)		36	64	50	53	31	55	58	58	49
T4/T8 ratio		0.9	0.2	0.2	0.4	0.8	0.3	0.2	0.2	0.2
NK activity (%)			1.8		20.8	68.8		6.9		15.8
PPD skin reaction	(+)	(-)	(-)			(+)	(+)	(-)		

By electron microscopy of the postmortem specimens, retroviruses were observed to be present in various organs including the lymph nodes, spleen and liver. The electron micrographs in Fig. 3 show various stages representing the formation of retrovirus: budding, release of virus particles, and nucleoid maturation. This manner of virus formation is characteristic of the retrovirus, and the mature virus, assuming D type retrovirus morphology, was identical with the reported LAV/HTLV-III.

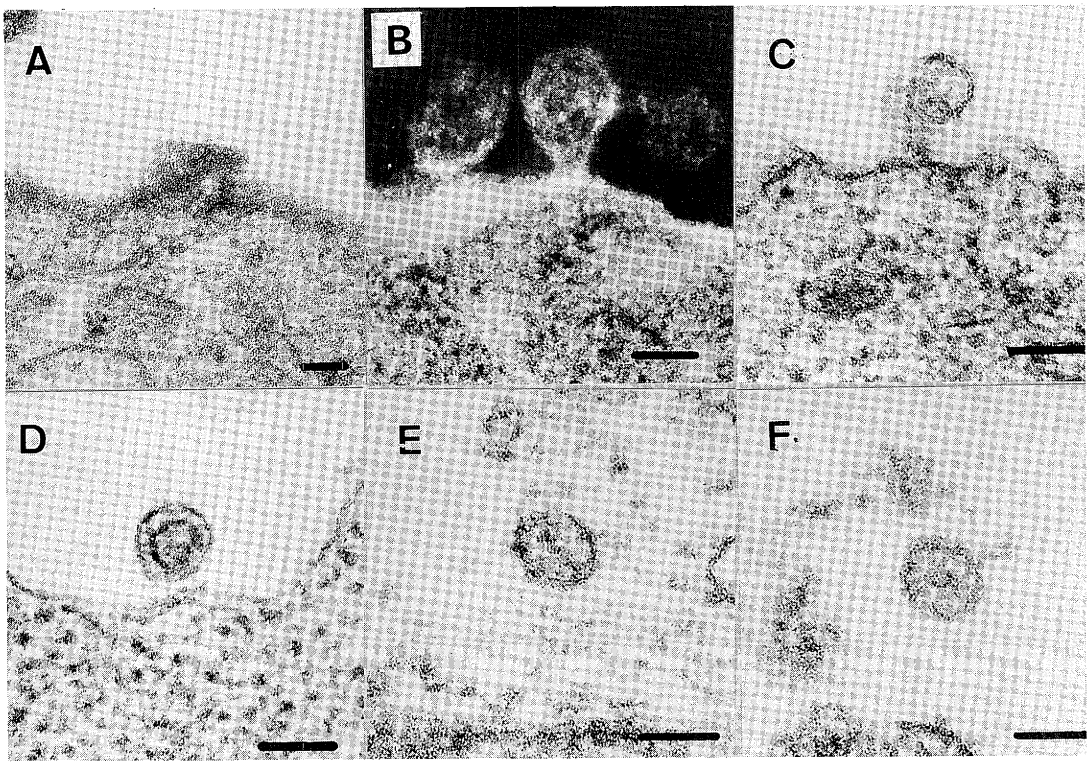

Fig. 3 Electron micrographs of retrovirus in the lymphnode obtained on the necropsy of Patient 2. A-F represent various stages of the sequence of virus formation. The bars indicate 100 nm.

To assess the blood product-associated infections of LAV/HTLV-III and other viruses in hemophiliacs, we assayed the sera of our patients with hemophilia for the antibodies. Table 3 shows the results. The prevalence of seropositivity for hepatitis B virus (HBV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and parvovirus (SPLV) antibodies, was higher in hemophiliacs than in general Japanese population. Anti-HTLV-I was positive in 16 % of hemophiliacs tested. This rate is also high, considering that they live in non-endemic area of adult T cell leukemia. Antibody to LAV/HTLV-III was positive in 52% of 66 hemophiliacs.

We further examined immunologic states of our hemophiliacs. Fig. 4 shows the result of T cell subset analysis.

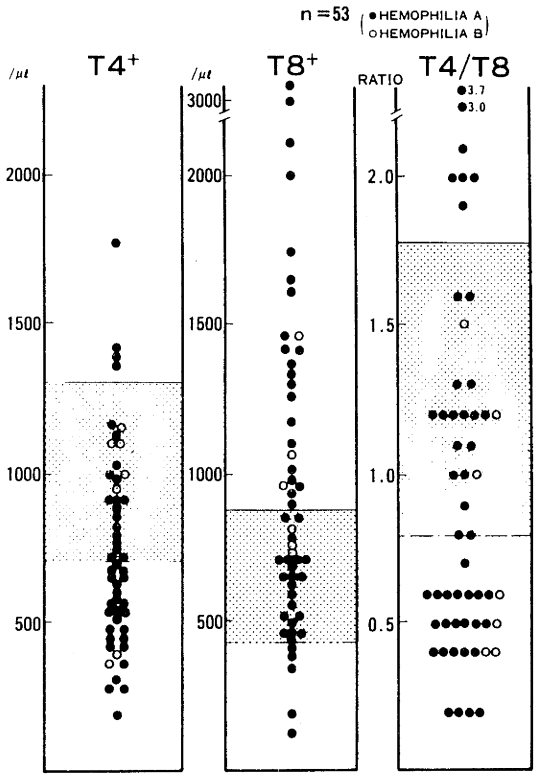

Fig. 4 T4 and T8 lymphocyte counts and T4/T8 ratios in patients with hemophilia

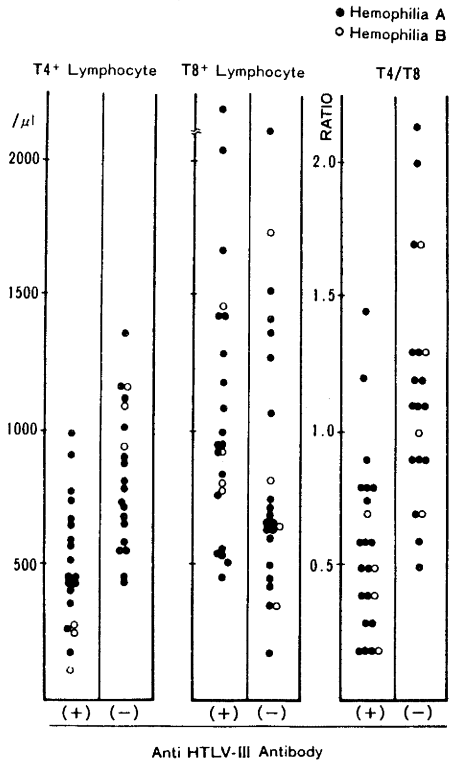

Fig. 5 Comparison of T4 and T8 lymphocyte counts and T4/T8 ratio between LAV/HTLV-III seropositive and seronegative patient with hemophilia

Table 2 Prevalence of seropositivity for antibodies of various viruses in patients with hemophilia

Antibodies	No. of patient tested	No. of seropositive patients (%)
Anti-HBs	66	56 (85)
Anti-EBV	21	20 (95)
Anti-CMV	17	14 (82)
Anti-SPLV	27	24 (89)
Anti-HTLV-I	50	8 (16)
Anti-HTLV-III	66	34 (52)

about a half of the patients had subnormal T4 lymphocyte

generally increased. The T4/T8 ratios were lowered: about a half of the patients showed the values lower than the normal range. Other immunologic features we observed in hemophiliacs were that NK cell activity, lymphocyte response to mitogens, T cell colony formation, interleukin 2 production of T cell and delayed hypersensitivity of the skin were suppressed; phagocytic activity of neutrophils and monocytes was also reduced. Regarding humoral immunity, serum opsonic activity, ASO titer and isohemagglutinin titer were lowered, while immunoglobulin concentrations, serum immunosuppressive acid protein (IAP) and $_2$-microglobulin concentrations were elevated.

When the T lymphocyte subset data were compared between the LAV/HTLV-III seropositive and seronegative groups, the mean T4 lymphocyte count was lower, the mean T8 lymphocyte count was higher, and the mean T4/T8 ratio was considerably lower in the seropositive group than in the seronegative group, as shown in Fig. 5. However, it was noticed that there were patients with lowered T4 cell counts and T4/T8 ratios in the seronegative group.

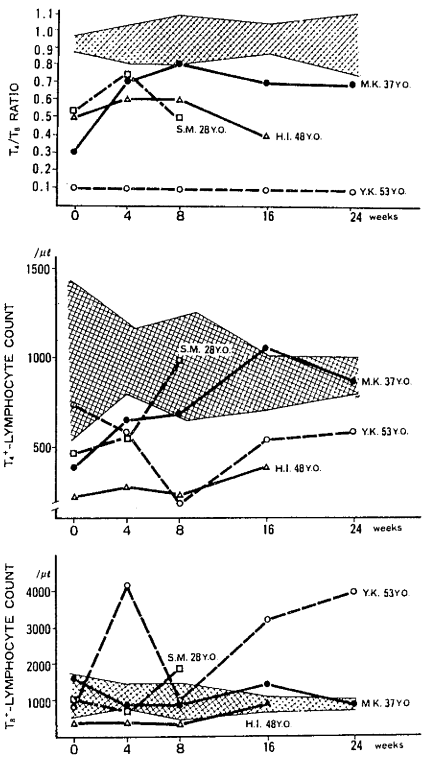

Fig. 6 Effects of Lentinan on T4/T8 ratios and T4 and T8 lymphocyte counts in four patients with hemophilia

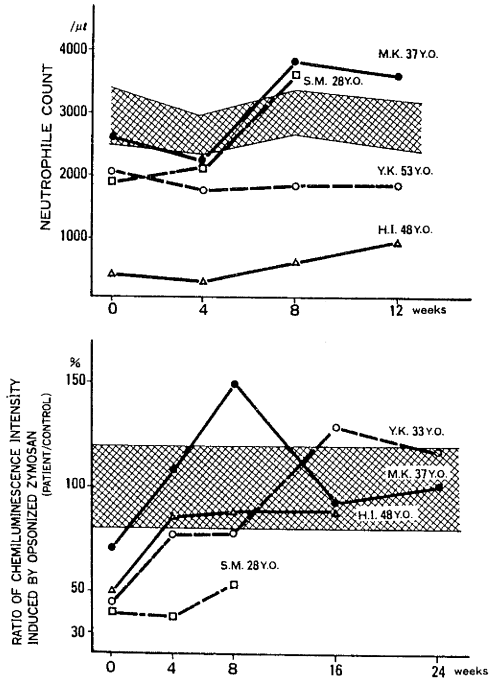

Fig. 7 Effects of Lentinan on neutrophils counts and phagocytic activity in four patients with hemophilia. Neutrophil phagocytic activity was measured by chemiluminescence response to stimulation with opsonized zymosan

Treatment of AIDS is a much more dificult problem at present. In spite of great efforts, definitely effective means of therapy have not been established yet. Approaches to this problem should be made in three directtions: 1. killing of the causative virus, LAV/HTLV-III, 2. augmentation of immunologic functions, 3. therapy for opportunistic infections. A number of agents have thus far been proposed and tried for possible effect to improve immunologic dysfunctions of AIDS and ARC patients. We are trying a few drugs to hemophilic patients with LAV/HTLV-III seropositivity and lowered T4/T8 ratio. Here we report a trial of Lentinan, a polysaccharide immuno-modulating agent (3), in four hemophiliacs. Lentinan was given at a dose of 10 mg once every week, and the changes in T4 and T8 lymphocyte counts, T4/T8 ratio, and neutrophil phagocytic activity were followed. As shown in Fig. 6, the T4 counts increased in three patients and the T4/T8 ratio rose in one patient. Noticeably, phagocytic activity of neutrophils, as measured by chemiluminescence, increased to almost normal range in all the four patients treated. These effects may contribute favorably to host defence in the patients with defect of cellular immunity and hopefully prevent development of AIDS. Of course, much more clinical studies on this and other drugs are required for evaluation.

Finally, I express my annoying but sincere questions in dealing with hemophiliacs at risk for AIDS in consideration from not only medical but also social and psycological aspects. Firstly, how to promote the survey of LAV/HTLV-III infection in the hemophilacs? Secondly, how to deal with the results of the tests? Particularly, whether the results should be informed to the patients or not? Can we do it to seropositive patients without getting up a panic among them at the present time we have no definite therapeutic means against AIDS? Thirdly, how to guide the patients to behave themselves at home and society to avoid further spread of LAV/HTLV-III virus from them.

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