Disseminated Mycobacterial Infection in a Hemophilia B Patient with Acquired Immunodeficiency Syndrome

Hideo WADA, Michiaki OHIWA, Yoshitaka MORI, Motoaki TANIGAWA, Shigehisa TAMAKI, Thoru KOBAYASHI, Nobuyuki MINAMI*, Katsumi DEGUCHI, Shigeru SHIRAKAWA, Itsuo KUSANO**, Ryuichi YATANI**

Disseminated mycobacterial infection was found at autopsy in a male patient with hemophilia B and acquired immunodeficiency syndrome (AIDS). In May 1986, 23 months before death, the patient had encephalitis for one month and in July he developed a fever, malaise and generalized lymphadenopathy. Human immunosuppressive virus (HIV) was positive and the CD 4/8 ratio of lymphocyte surface markers was 0.1, but mycobacterium was not detected. In September 1986, he had severe dyspnea due to interstitial pneumonia and he was treated with high-dose methylprednisolone. He died after a 23-month course of fever, severe weight loss and terminal progressive deterioration, although he was treated with antibiotics, antifungal agents, \( \gamma \)-globulin, steroid and Azidothymidine.

Key words: HIV, AIDS encephalitis, Opportunistic infections

Acquired immune deficiency syndrome (AIDS), caused by human immunodeficiency virus (HIV) infection (1–3), has become a major disease characterized by opportunistic infections and high grade malignancies since it was first described in 1981 in homosexual men (4). There is no radical cure for HIV infection itself; immunopotentiation and symptomatic therapies against opportunistic infections are the only treatments available. Therefore, early detection and therapy of opportunistic infections is important for the treatment of patients with AIDS. This report describes an AIDS patient with hemophilia B in whom unexplained fever and marked hepatosplenomegaly persisted, and mycobacterial infection was first demonstrated at autopsy.

CASE REPORT

A 21-year-old male initially presented fever and loss of body weight. His mother was a carrier of hemophilia B, and the patient was diagnosed to be a hemophiliac at 5 years of age. He had since been administered about 120,000 units of concentrated factor IX preparations.

The patient developed fever, malaise, and a decrease in the level of consciousness on May 21, 1986 and was admitted to our hospital. A diagnosis of encephalitis was made, the fever was resolved, and the level of consciousness was nearly normalized temporarily by the administration of antibiotics, \( \gamma \)-globulin, and antifungal agents. However, abnormal brain waves and epileptic attacks persisted, and fever recurred with marked lymph node enlargement in July of the same year. These symptoms were alleviated by the administration of Phenobarbital®, antibiotics, and \( \gamma \)-globulin. Candidiasis of the oral cavity was noted around this time, requiring rinsing of the mouth with Fungizone®. In September of the same year, dyspnea appeared, and a diagnosis of interstitial pneumonia was made on the basis of radiography and blood gas analysis.
Mycobacterial Infection in AIDS

High-dose methylprednisolone therapy was performed immediately, and the subjective symptoms subsided temporarily. However, episodes of loss of consciousness, fever, oral candidiasis, and interstitial pneumonia recurred, the loss of body weight progressed. The patient was re-admitted due to persistent of high fever in November 1987 (Fig. 1).

**Physical findings on admission**

The patient was 170 cm tall and weighed 52 kg. His body temperature was 38.5°C, and marked oral candidiasis, generalized lymph node enlargement of several millimeters in diameter, and hepatosplenomegaly were noted.

**Laboratory findings on admission**

Laboratory results on admission were: lymphocytopenia, particularly a reduction in CD4 lymphocytes with a marked reduction in the CD4/8 ratio to 0.1; thrombocytopenia of 85,000/μl; negative conversion of tuberculin reaction; an increase in the erythrocyte sedimentation rate; positive CRP(3+); a high cold agglutinin level; prolongation of APTT; a reduction in coagulation factor IX activity; positive for HIV antigen and antibody (Table 1).

**Clinical course after admission**

The administration of antibiotics, antifungal agents, and γ-globulin or massive glycyrrhizin therapy produced little effect, and the hepatosplenomegaly was aggravated, becoming larger in dimension (Fig. 2). No pathogenic bacteria including acid-fast bacteria were detected by sputum, blood, feces, or urine cultures. High-dose methylprednisolone therapy resulted in a temporary reduction of fever but eventually was ineffective. Retardation of neuro-motor responses was noted from about November 1987, and impairment of
retention, enhancement of tendon reflex, and incontinence of urine developed in February 1988 (Fig. 3). Consciousness was further disturbed from February 1988, and the patient died without responding to administration of azidothymidine (AZT) (Fig. 1).

**Examinations for HIV**

Western blot for HIV antibody was negative through July 1985 and was positive in May 1986. The band at 24 K was obscured from May 1986 and was obliterated from about October the same year, when an increase in the HIV antigen level was observed. Lymphocyte cultures were performed 6 times throughout the entire course but the virus could not be identified (Fig. 4).

**Autopsy findings**

The most characteristic findings were observed in the reticuloendothelial system. All thoracic and abdominal lymph nodes were swollen without adhesion to each other. Microscopically, the lymph nodes were completely filled with infiltrating, large, foamy macrophages, the cytoplasm of which had a semitransparent, granular appearance. In the involved lymph nodes, lymphocytes were severely depleted but the number of plasma cells was increased. Small foci of necrosis consisting of neutrophils, giant cells and nuclear debris without caseation nor epithelioid proliferation were occasionally present in the center of some lymph nodes. The spleen was massively enlarged, weighing 1,915 g. There were numerous poorly defined white granulomatous nodules of less than 5 mm in diameter disseminated throughout the whole organ (Fig. 5-A). Microscopically, these nodules were foci of nodular infiltration of rounded foamy macrophages localized mostly in the white pulp (Fig. 5-B). Feit stain and electromicroscopic examination showed abundant acid-fast and rod-shaped bacilli within the cytoplasm of the macrophages (Fig. 5-C, D). But, cultures of the lymph nodes and spleen were not performed at autopsy.
Mycobacterial Infection in AIDS

a) Macroscopic view. The spleen was massively enlarged. There were numerous poorly defined white granulomatous nodules, in the range of less than 5 mm in diameter, disseminated throughout the whole organ.

c) Acid-fast staining. Acid-fast bacteria stain showed abundant acid-fast bacilli within the cytoplasm of the macrophages.

b) Histological profile. Microscopically, these nodules were the foci of nodular infiltration of rounded foamy macrophages localized primarily in the white pulp. The spleen showed severe lymphocyte depletion.

d) Electron microscopic profile. The atypical acid-fast bacteria incorporated in macrophages measured 1.3–2.0 μm in the longitudinal cross-section and 0.3–0.5 μm in the transverse cross-section. The spleen showed severe lymphocyte depletion with a relative increase of plasma cells. The liver was twice as large as normal (2,665 g). Histological examination revealed microscopic nodular macrophage accumulation scattered in the portal areas and lobules. There was no evidence of interstitial fibrosis, fungal infection or Pneumocystis carinii infection in either lung at autopsy. Bone marrow showed moderate to severe hypocellularity with nodular infiltration of foamy macrophages. The brain showed mild swelling (1,395 g) and an otherwise normal appearance, but the microscopic findings suggested AIDS encephalopathy. There were three distinct histological features: perivascular cuffing of foamy macrophages, microglial nodules and the appearance of multinucleated giant cells. The foamy macrophages were localized only in the perivascular zone of the white matter, resulting in collapse of the vessels. Randomly scattered throughout the white matter and brain stem were glial nodules composed of microglia and a few hypertrophic astrocytes. A few multinucleated giant cells were scattered throughout the areas of perivascular macrophage infiltration and in some glial nodules in the deep white matter (Fig. 6).

Fig. 5. Autopsy findings in the spleen.
Fig. 6. Histological profile of the cerebrum. In microscopic findings, macrophage infiltration, microglial nodules and a large number of multinucleated giant cells were noted primarily in the white matter.

DISCUSSION

AIDS was first reported in 1981 in 4 homosexual males who developed Pneumocytosis carinii, candidiasis, and Kaposi sarcoma associated with unexplained immunodeficiency (4). The number of AIDS patients has been increasing exponentially. In Japan, the first AIDS patient was discovered in 1985, and approximately 100 patients have been reported to date. Opportunistic infections are the most frequent cause of death in AIDS patients, and their control is the most important problem in the treatment of AIDS in the absence of a radical cure against HIV.

Fauci et al. (5) studied pathogenic bacteria and opportunistic infections associated with AIDS and demonstrated Cytomegalovirus in 58%, Candida albicans in 55%, Pneumocystis carinii in 49%, Mycobacterium avium in 28%, Cryptococcus neoformans in 15%, herpes simplex in 13%, varicella zoster in 8%, and toxoplasmosis in 9% of 53 AIDS patients. Blaser and Cohn (6) also detected Mycobacterium avium in 9 of 446 patients. An atypical mycobacterial disease has often been shown to complicate AIDS, and this has also been noted in 5 out of 30 patients in Japan (7). These Mycobacterium avium complex infections cannot be distinguished from Mycobacterium tuberculosis either clinically or morphologically. In the present case, the bacilli were acid-fast stained and rod shaped in electromicroscopic specimens, but the bacilli were not cultured. Central necrosis was observed in the involved lymph nodes and spleen histologically, however, there was no caseous necrosis or epithelioid cell proliferation in the lesions. Due to the above findings, we strongly suspected that the bacilli in the foamy macrophages were M. avium complex. Unfortunately, cultures were not performed, and the species of mycobacteria could not be identified. Mycobacterial infection produces lung lesions in 90% of the patients; a premortal diagnosis is difficult in patients showing no lung lesions such as in the present case. The presence of the disease has also often been unknown until autopsy in Europe and America (8). Careful examination for the disease is considered necessary in AIDS patients exhibiting lymph node enlargement, hepatosplenomegaly, and unexplained fever.

HIV infection is considered to have occurred in this patient between July 1985, when HIV antibody was negative, and May 1986, when encephalitis was seen and the patient was positive for HIV antibody. However, the p24 band in Western blots representing HIV antibody was already obscured in May 1986, suggesting the possibility that the seroconversion had occurred much earlier. Moreover, concerning the time of the onset of AIDS, the p24 band disappeared in November 1986 with an elevation in the HIV antigen level, but it was not until December 1987 that clinical symptoms of HIV encephalitis became noticeable. Mycobacterial disease was diagnosed only by autopsy but the clinical symptoms developed at sometime around October 1987. The diagnosis of AIDS was made in December 1987. Retrospectively, however, mycobacterial disease is considered to have been apparent from October 1987, and the changes in the HIV antigen and antibody levels suggest that the transition to AIDS occurred in November 1986. The failure of HIV identification by repeated mononuclear cell cultures in this patient even after the onset of AIDS suggests several problems concerning the diagnosis of AIDS. This patient was treated with low-dose glycyrrhizin administration from 1986, and with massive glycyrrhizin and AZT therapies after re-admission with the onset of AIDS, but no marked response was obtained. Since, at present, no substantial therapeutic effects can be expected, treatments such as the administration of AZT should be started as early as possible according...
to the monitor of HIV antigen and antibody levels.

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