An Adult Case of Severe Chronic Active Epstein-Barr Virus Infection Syndrome

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A 23-year-old man with persisting high fever developed hepatosplenomegaly, lymphadenopathy and massive pericardial effusion. Immunological examination revealed a marked elevation of anti-Epstein-Barr virus antibodies (anti-viral capsid antigens IgG-antibody 1:10,240, anti-early antigens-DR IgG-antibody 1:5,120), decreased activities of Epstein-Barr virus specific cytotoxic T lymphocytes, natural killer cells and lymphokine activated killer cells. A liver biopsy showed moderate sinusoidal lymphocytosis with punched-out lesions. These findings suggested severe chronic active Epstein-Barr virus infection syndrome. The patient was treated with recombinant human interleukin-2, but it was discontinued because of an adverse reaction. Twelve months later, he died of suspected pulmonary infection. (Internal Medicine 31: 1381–1386, 1992)

Key words: anti-Epstein-Barr virus antibodies, cytotoxic T lymphocyte, recombinant interleukin-2, steroid

Introduction

Epstein-Barr virus (EBV) infection generally causes a self-limiting lymphoproliferative disease, and after the primary infection EBV establishes a life-long latent infection of B lymphocytes (1). In most cases, the prognosis is good. However, in the immunocompromised host as in Duncan's disease (2), ataxia-teleangiectasia (3), Wiscott-Aldrich syndrome (4) or the acquired immunodeficiency syndrome (5), and also in the immunocompetent host with no hereditary background (6), EBV infection may show a chronic and active manifestation. This syndrome has been named severe chronic active EBV infection syndrome, and is characterized by markedly high titers of EBV-associated antibodies, and serious symptoms and signs such as persistent high fever, hepatosplenomegaly, lymphadenitis and liver dysfunction. The syndrome has been predominantly reported in children, and it is rare in adults.

Case Report

A 23-year-old man with no particular past history developed a productive cough in June, and edema of

the face and legs in September 1989. He was admitted to a hospital, where left axillary and right inguinal lymphadenopathy, tonsillar hypertrophy, pericardial effusion and hepatosplenomegaly accompanied by leukocytopenia and atypical lymphocytes were noted. There were no arthralgias or skin eruptions. Computed tomography of the abdomen revealed swelling of both kidneys. Serological examination demonstrated extremely high titers of anti-EBV antibodies. The edema and pericardial effusion disappeared after the administration of diuretics and the limitation of water intake, but persistent high fever and liver dysfunction continued. Oral administration of prednisolone (40 mg/day) made the symptoms subside temporarily, but tapering induced recurrence. On November 9, 1989, he was referred to Nagasaki University Hospital for further examination and therapy.

Physical examination showed a low grade fever of 37.4°C, aphtha in the oral mucosa, bilateral tonsillar hypertrophy and marked hepatosplenomegaly. There were no particular findings for the superficial lymph nodes, skin, joints or neurological system.

Laboratory data on admission showed anemia, acute inflammation, liver dysfunction, hypergammaglobulinemia and a high concentration of β_2 -microglobulin in

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the serum and urine (Table 1). The serum creatinine level was normal and there was no azotemia. Negative results were obtained in tests for hepatitis-A antibody (HA-Ab), hepatitis-B surface antigen (HBs-Ag) and human T-cell leukemia virus type-I antibody. Auto-antibodies, including rheumatoid arthritis test (RA), rheumatoid arthritis hemagglutination test (RAHA), antinuclear antibodies (ANA), SS-A, SS-B, thyroid test and microsome test, were negative throughout his stay in our hospital. Routine examination of urine and stool revealed no abnormalities. ^{67}Ga scintigraphy showed no accumulation in any organ.

Immunological examination demonstrated high titers of anti-EB-viral capsid antigens (VCA) IgG (1:10,240), anti-EB-VCA IgA (1:160), anti-EB-VCA IgM (1:10), anti-early antigens (EA)-DR IgG (1:5,120), and anti-Epstein-Barr nuclear antigens (EBNA) (1:20). These

high titers continued even after admission to our hospital (Fig. 1). There was no significant elevation in the antibody titers of other viruses such as Coxsackie, mumps, polio, echo, parainfluenza or adenoviruses. In the lymphocyte function tests (Table 2), activities of EBV-specific cytotoxic T lymphocytes (EBV-CTL), natural killer cells (NK) and lymphokine activated killer cells (LAK) were significantly depressed. Addition of interferon- α normalized the activity of natural killer cells. Interleukin-2 production of mononuclear cells was accelerated, after stimulation with mitogens, in comparison with that of healthy individuals. Serum circulating immune complex was slightly elevated. The ratio of CD4 to CD8 was not inverted (Table 1).

A chest X-ray on October 3, 1989, showed the cardiomegaly, and the echocardiography revealed pericardial effusion (Fig. 1). The aspirated pericardial fluid was an exudate. A chest X-ray on February 5, 1990, showed

Table 1. Laboratory Data on Admission

Hematological examinations	RAHA (-)
RBC $364 \times 10^4/\text{mm}^3$	ANA (-)
Hb 9.7 g/dl	SS-A (-)
Ht 29.2%	SS-B (-)
WBC $6,400/\text{mm}^3$	Thyroid test (-)
Baso. 0%	Microsome test (-)
Eosino. 2%	HTLV-1 Ab (-)
St. 5%	HIV Ab (-)
Seg. 64%	HBs Ag (-)
Lym. 20%	Cytomegalovirus Ab-IgG <10
Atyp. Lym 0%	Adenovirus type-2 Ab $\times 4$
Mono. 9%	Immunoglobulins
Plt. $25.0 \times 10^4/\text{mm}^3$	IgG 2,516 mg/dl
ESR 53 mm/h	IgA 560 mg/dl
	IgM 389 mg/dl
	IgE 495 U/ml
Biochemical examinations	Lymphocyte surface markers
T.B. 0.5 mg/dl	CD3 77.2%
D.B. 0.3 mg/dl	CD4 47.6%
T.P. 7.3 mg/dl	CD8 21.2%
Alb. 51.7%	CD4/CD8 2.24
α_1 -glb. 3.7%	M1 8.0%
α_2 -glb. 6.4%	Leu11 2.8%
β -glb. 10.6%	Leu7 1.4%
γ -glb. 27.6%	
TTT 11.7 KU	Lymphocyte blastoid formation test
ZTT 17.8 KU	PHA 3.48 S.I. (norm. 2.0-4.9)
ALP 304 mu/dl	ConA 3.40 S.I. (2.5-5.0)
GOT 70 mu/dl	PWM 2.03 S.I. (1.2-2.9)
GPT 141 mu/dl	
LDH 613 mu/dl	Urine: n.p.
LAP 216 mu/dl	Stool: n.p.
γ -GTP 127 mu/dl	
ChE 0.79 $\Delta\text{pH/h}$	Others
Sialic acid 82 mg/dl	β_2 -microglobulin
Muco-P 131 mg/dl	Serum 5.1 mg/l
BUN 14 mg/dl	Urine >8,000 mg/l
Cr 0.8 mg/dl	NAG 8.1 U/l
FBS 87 mg/dl	Circulating immune complex
	3.7 mg AHG Eq/l
Serological examinations	
CRP 2+	
RA (-)

Fig. 1. Chest X-ray on October 3, 1989 showing cardiomegaly suggesting pericardial effusion.

Table 2. Lymphocyte Function Tests

	Patient	Control
EBV-CTL(Reg50)*	$>40 \times 10^4/\text{well}$	$5.47-21.59 \times 10^4/\text{well}$
NK	14.2%	$40.4 \pm 15.9\%$
NK-INF- α	23.0%	$17.5 \pm 7.4\%$
LAK	7.3%	$29.2 \pm 15.9\%$

* EBV-CTL(Reg 50): EBV specific cytotoxic T cell activity by 50% incidence of regression assay.

NK: natural killer, NK-INF- α : natural killer activity stimulated by interferon- α , LAK: lymphocyte activated killer.

mild bilateral pleural effusion, which was noted to have increased in size in the photograph of February 20 (Fig. 2). This was also an exudate, and large immature lymphoid cells were observed in the smear specimen (Fig. 3). No microorganism was seen and the culture for bacteria, fungi and acid-fast bacilli were all negative. Abnormal findings were not observed in the lung field.

Abdominal computed tomography revealed marked hepatosplenomegaly and swelling of the kidneys (Fig. 4). The liver was observed laparoscopically to be hypertrophied with lymphatic follicles on its surface. Histologically, diffuse and moderate sinusoidal lymphocytosis

presenting "single file" appearance (7), and some scattered punched-out lesions (7) which were made up of nodular accumulations of lymphocytes and histiocytes, were noted (Fig. 5). Hepatocytic changes, such as swelling, cytolysis or multinuclearization, were absent. No mitosis of the hepatocytes was observed.

Clinical course (Fig. 6): Oral prednisolone made the patient afebrile temporarily, but high fever reappeared when it was tapered. IL-2 was then administered subcutaneously at a dose of 5 U/kg/day from January 29, 1990. High fever and liver dysfunction developed three days after the commencement of the therapy. IL-2 administration was suspended on the fourth day of the therapy and he gradually became afebrile. IL-2

Fig. 2. Chest X-ray on February 20, 1990 showing bilateral pleural effusion after interleukin-2 treatment.

Fig. 3. Cytology of pleural effusion revealing large immature lymphoid cells (May-Giemsa stain, $\times 200$).

Fig. 4. Abdominal computed tomography showing marked hepatosplenomegaly and swelling of the kidneys.

Fig. 5. (a) Moderate lymphocyte infiltration and a punched-out lesion (arrows) (HE stain, $\times 200$). (b) Sinusoidal lymphocytosis presenting "single file" appearance (arrowheads) (HE stain, $\times 400$).

was readministered at a lower dose of 2.5 U/kg/day. Although no adverse reaction was seen for the first seven days, as soon as the dose of IL-2 was increased to 5 U/kg/day, the high fever returned and liver function deteriorated. IL-2 therapy was discontinued. In February 1991, he complained of a sore throat and productive cough with low grade fever, and his chest X-ray revealed an infiltrative shadow on the left lower lung field. On suspicion of an opportunistic pulmonary infection, he was treated with a combination of antibiotics, antifungals and antiviral agents. But he died of progressive respiratory failure on March 13, 1991. An autopsy was not conducted.

Discussion

Severe chronic infection syndrome caused by EBV is occasionally seen in children, but an adult case is rare. This virus affects multiple organs including eyes (8), joints (9), kidneys (10) and brain (11). In this patient, computed tomography revealed marked hypertrophy of the kidneys; however, the relationship between this manifestation and EBV infection was not clear, because

further examinations such as renal biopsy were not performed due to the patient's poor general condition.

The diagnosis of severe chronic active EBV infection syndrome was made from the following: 1) continuous high fever and fatigue for more than six months which could not be explained by other causative diseases, 2) lymphadenopathy, 3) hepatosplenomegaly, 4) persistent liver dysfunction with histologically proven mononuclear inflammatory cell infiltration, 5) extremely and continuously elevated titers of antibodies to viral production-related antigens, and 6) decreased activity of EBV-specific cytotoxic T lymphocytes (12). Criteria for diagnosis of this syndrome have not yet been established. Although Straus (13) proposed tentative criteria, including clinical, serological and virological characteristics, they have not been generally accepted. Therefore, ruling out other causative diseases is important for making the diagnosis.

In the present patient, excluding other disease entities, such as autoimmune diseases, immunodeficiency syndrome and viral infections other than EBV, was required. Adult onset Still disease was incompatible because of the absence of arthralgia, skin eruption, leukocytosis, marked elevation of CRP or thrombocytosis. Yamaoka et al (14) reported that 29 patients with Sjögren's syndrome revealed the significantly elevated anti-EB-VCA antibodies of both the IgG and the IgM class and impaired activity of EBV-specific cytotoxic T lymphocytes. Depressed NK and LAK cell function can also be observed in other autoimmune diseases. In this patient, however, neither sicca syndrome nor joint and skin manifestation was seen; moreover autoantibodies such as rheumatoid factor, ANA including antibodies to SS-A or SS-B, were negative. Hereditary immunodeficiency syndromes were unlikely because he had been well until the onset of the disease, and the clinical findings and his hereditary background were not compatible. Acquired immunodeficiency syndrome and adult T cell leukemia were ruled out from negative serology. Paired sera examination did not reveal any involvement with other viruses but EBV. We, therefore, concluded that chronic active EBV infection was the most likely diagnosis of this patient.

Extremely high titers of both anti-EB-VCA IgG (1:10,240) and anti-EA-DR IgG (1:5,120) antibodies and a disproportionately low titer of anti-EBNA antibody (1:20) were characteristically observed in this case. Rickinson (15) attributed these abnormal immune responses, indicating a disturbance of the virus-host relationship, to be a consequence of infection, rather than a cause. In this patient, impaired cellular immunity against EBV, demonstrated by significantly decreased activity of specific cytotoxic T cells, natural killer cells and lymphokine activated killer cells, might explain the difficulty in destruction of EBV integrated host cells. Therefore, anti-EBNA antibody response remains low,

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Fig. 6. Clinical course 23 y.o. male.

and the virus is allowed to infect persistently, chronically stimulating humoral immune system of the host. As a result, high titers of anti-VCA and anti-EA antibodies are maintained. Moreover, Olson et al reported that patients with this syndrome had significantly increased responses toward greater numbers of allergens, compared to those who suffer from allergies in the absence of this syndrome (16). These immunological disorders might play an important role in perpetuating the fatigue, fever and other symptoms.

Histological examination of a liver specimen showed findings of lymphoid hyperplasia, sinusoidal lymphocytosis and punched-out lesions, which were consistent with mononucleosis of the liver. Based on histological and serological findings, viral or drug-induced hepatitis was ruled out. In the literature, in an infant case of chronic active EBV infection, marked mononuclear cell infiltration and moderate fibrosis in the portal and peribulbar areas has been reported (17).

Standard and specific therapy for this syndrome has not been established. There have been reports of cases successfully treated with transfer factor (18), a combination of high-dose gammaglobulin and interferon

alpha (19). Additionally, in child cases in particular, several authors have administered IL-2, which is expected to improve the defective activities of EBV-CTL (12) and NK, and reported the relatively high efficacy of this agent (20). However, the occurrence of fever, with or without eosinophilia or abnormality of liver function is considerably high. Further studies with larger number of patients are needed to substantiate the efficacy of this promising agent.

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References

- 1) Andiman WA. The Epstein-Barr virus and EB virus infection in childhood. *J Pediatr* 132: 78, 1979.
- 2) Purtilo DT, Cassel CK, Yang JPS, et al. X-linked recessive progressive combined variable immunodeficiency (Duncan's

- disease). *Lancet* **1**: 935, 1975.
- 3) Joncas JH, Lapointe N, Gervais F, Leyritz M. Unusual prevalence of Epstein-Barr virus early antigen (EBV-EA) antibodies in ataxia-teleangiectasia. *J Immunol* **119**: 1857, 1977.
 - 4) Okano M, Mizuno F, Osato T, Takahashi Y, Sakiyama Y, Matsumoto S. Wiscott-Aldrich syndrome and Epstein-Barr virus-induced lymphoproliferation. *Lancet* **2**: 933, 1984.
 - 5) Petersen JM, Tubbs RR, Savage RA, et al. Small noncleaved B cell Burkitt-like lymphoma with chromosome t(8; 14) translocation and Epstein-Barr virus nuclear-associated antigen in a homosexual man with acquired immunodeficiency syndrome. *Am J Med* **78**: 141, 1985.
 - 6) Straus SE, Tosato G, Armstrong G, et al. Persisting illness and fatigue in adults with evidence of Epstein-Barr virus infection. *Ann Intern Med* **102**: 7, 1985.
 - 7) Peters RL. Viral inflammatory diseases. in: *Liver Pathology*, Peters RL, Craig JR, Eds. Churchill Livingstone, New York, 1986, p73.
 - 8) Wong KW, D'Amico DJ, Hedges TR, Soong HK, Schooley RT, Kenyon KR. Ocular involvement associated with chronic Epstein-Barr virus disease. *Arch Ophthalmol* **105**: 788, 1987.
 - 9) Dlesk A, Panush RS. Viral disease and arthritis. *Compr Ther* **13**: 13, 1987.
 - 10) Peters JH. Heterophile reactive antigen in infectious mononucleosis. *Science* **157**: 1200, 1967.
 - 11) Neumann B, Ritter k, Prange HW. Encephalitis in association with chronic active Epstein-Barr virus infection. *J Neuroimmunol* **20**: 169, 1988.
 - 12) Wakiguchi H, Fujieda M, Matsumoto K, et al. Defective immune response to Epstein-Barr virus in patients with acute lymphocytic leukemia. *Acta Paediatr Jpn* **31**: 144, 1989.
 - 13) Straus SE. The chronic mononucleosis syndrome. *J Infect Dis* **157**: 405, 1988.
 - 14) Yamaoka K, Miyasaka N, Yamamoto K. Possible involvement of Epstein-Barr virus in polyclonal B cell activation in Sjögren's syndrome. *Arthritis Rheum* **31**: 1014, 1988.
 - 15) Rickinson AB. Chronic symptomatic Epstein-Barr virus infection. *Immunol Today* **7**: 13, 1986.
 - 16) Olson GB, Kanaan MN, Gersuk GM, et al. Correlation between allergy and persistent Epstein-Barr virus infections in chronic active Epstein-Barr virus-infected patients. *J Allergy Clin Immunol* **78**: 308, 1986.
 - 17) Tanaka K, Shimada M, Sasahara A, Yamamoto H, Naruto T, Tomida Y. Chronic hepatitis associated with Epstein-Barr virus infection in an infant. *J Pediatr Gastroenterol Nutr* **5**: 467, 1986.
 - 18) Levin AS, Spitler LF, Fudenberg HH. Transfer factor therapy in immune deficiency states. *Annu Rev Med* **24**: 175, 1973.
 - 19) Shapiro RS, Chauvenet A, McGuire W, et al. Treatment of B-cell lymphoproliferative disorders with interferon alpha and intravenous gamma globulin. *N Engl J Med* **318**: 1334, 1988.
 - 20) Kawa-Ha K, Franco E, Doi S, et al. Successful treatment of chronic active Epstein-Barr virus infection with recombinant interleukin-2. *Lancet* **1**: 154, 1987.
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