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Severe Chronic Active Epstein-Barr Virus Infection Syndrome

MOTOHIKO OKANO,[1,2]* SHUZO MATSUMOTO,[2] TOYORO OSATO,[3] YUKIO SAKIYAMA,[2] GEOFFREY M. THIELE,[4] AND DAVID T. PURTILO[1,5,6]

Department of Pathology and Microbiology,[1] Department of Internal Medicine,[4] Department of Pediatrics,[5] and Eppley Institute for Research in Cancer and Allied Diseases,[6] University of Nebraska Medical Center, 600 South 42nd Street, Omaha, Nebraska 68198-3135, and Department of Pediatrics[2] and Department of Virology, Cancer Institute,[3] Hokkaido University School of Medicine, N15 W7, Kita-ku, Sapporo 060, Japan*

INTRODUCTION

Since the discovery of Epstein-Barr virus (EBV) in 1964, EBV has been etiologically implicated in an increasing number of human diseases (20). Although primary infection with EBV during childhood is usually asymptomatic, nearly one-half to two-thirds of primary infections with this virus in older adolescents and young adults result in overt clinical disease such as infectious mononucleosis (IM) (20). EBV has also been implicated as a cause of endemic Burkitt's lymphoma and undifferentiated nasopharyngeal carcinoma because the virus genome is present in the tumors and because high levels of EBV antibody titers are found in the serum of patients with these afflictions (20). Additionally, various EBV-carrying lymphoproliferative disorders have been increasingly reported in patients with inherited or acquired immunodeficiencies (20). Recently, another category of EBV-related disease, "chronic EBV infections" or "chronic mononucleosis," has been described in persons without a clearly defined underlying disease (3, 4, 10, 26, 28, 29). There is, however, considerable debate about this disease or syndrome because of a failure to establish definitive diagnostic criteria. Nevertheless, rare patients with this syndrome have developed severe symptoms obviously associated with an active EBV infection (7, 9, 11–15, 18, 19, 21, 22, 24, 31). Therefore, we propose that this disorder be designated severe chronic active EBV infection syndrome (SCAEBV).

Patients with SCAEBV, usually children and young adults, often develop life-threatening complications over the course of months to several years. The patients show extremely high immunoglobulin G (IgG) antibody titers to Epstein-Barr viral capsid antigen (VCA) and early antigen (EA). Extensive lymphadenopathy, hepatosplenomegaly, a tendency for pancytopenia, and polyclonal gammopathy are commonly found. Although histopathological findings for affected tissues are generally benign, some patients have developed B-cell or T-cell lymphoproliferative diseases (7, 11, 14, 21).

We have reviewed the English-language literature for reports of chronic active EBV infection (CAEBV) by a computer search via MEDLINE for the years 1978 to 1990, by examining *Index Medicus* for the years 1978 to 1990, and by examining major textbooks regarding infectious diseases, virology, herpesviruses, immunodeficiency, and EBV. Indexing terms included EBV, chronic, active, and IM. We then selected the reported cases using our proposed criteria of a case definition for SCAEBV (Table 1). The criteria were based on the clinical, pathological, and virological findings for this syndrome. Here we review the historical, clinical, virological, pathological, and immunological aspects of this syndrome. Additionally, this review includes 10 patients (8 from Japan and 2 from the United States) with SCAEBV whom we have recently studied at the Hokkaido University School of Medicine, Sapporo, Japan, and the University of Nebraska Medical Center, Omaha. Further description of these patients may lead to a better understanding of this enigmatic syndrome.

HISTORICAL BACKGROUND

In 1948, Isaacs described a prolonged clinical course of IM lasting from months to years (6). During the late 1970s and early to middle 1980s, several groups described a protracted illness usually preceded by IM but with persistent fatigue, headaches, myalgia, lymphadenopathy, and intermittent or low-grade fever (3, 4, 10, 26, 29). Unexpectedly, unusual profiles of antibodies to EBV were common in this syndrome. Specifically, the titers of EBV IgG antibodies to VCA and EA were substantially higher in patients than in controls. Because of these serologic patterns and clinical symptoms, it was proposed that the syndrome arose from a chronic EBV infection. In 1978, Virelizier et al. described a case of a severe type of CAEBV (31). The affected girl had a chronic disease characterized by fever, lymphadenopathy, interstitial pneumonitis, thrombocytopenia, and polyclonal hypergammaglobulinemia. She had extremely high EBV

* Corresponding author.

TABLE 1. Diagnostic criteria of a case definition for SCAEBV[a]

Category	Criteria
Clinical	Intermittent fever, lymphadenopathy, and hepatosplenomegaly
Hematologic	Anemia, thrombocytopenia, lymphocytopenia or lymphocytosis, neutropenia, and polyclonal gammopathy
Virological	Elevated antibody titers and positivity for antibodies to EBV-related antigens (VCA IgG, ≥5,120; VCA IgA, positive; EA [D] IgG, ≥640; EA [D] IgA, positive; and EA [D] and EA [R] IgG, ≥640) and/or detection of EBV genomes in affected tissues
Other	Chronic illness which cannot be explained by other known disease processes[b]

[a] A case of SCAEBV must fulfill one criterion in each category.
[b] Some patients develop B-cell or T-cell lymphoproliferative diseases later.

antibody titers against VCA and EA (VCA IgG, ≥10,000; EA IgG, ≥5,000). Subsequently, in 1984, Joncas et al. described a similar type of CAEBV (9). The affected girl had persistent splenomegaly and extremely high EBV antibody titers against VCA and EA (VCA IgG, ≥20,480; EA IgG, 2,560).

Because of the growing interest in the possible association of EBV with a newly emerging syndrome, a broad-based workshop was held by the National Institute of Allergy and Infectious Diseases in Bethesda, Md., in April 1985 (30). Although the existence of EBV infections as an important clinical entity was controversial, those investigators who attended the workshop divided patients into three groups mainly by EBV serologic results. The first group consisted of rare persons with specific lymphoproliferative, hypoplastic, or other disorders, with some degree of demonstrable immune impairment, with extraordinarily elevated titers to EBV-related antigens (IgG antibody titers to VCA of ≥5,120 and to EA (diffuse [D] or restricted [R]) of ≥640), and with low or absent antibody titers to EBV-determined nuclear antigen (EBNA). The second group included a much larger number of patients with chronic fatigue, with no obvious immunodeficiency, and with variable but less impressive or normal EBV antibody titers. This group was further subdivided as to whether the patients had experienced an episode of acute IM. The third, small group of patients included those who could not be clinically distinguished from others with chronic fatigue but who lacked all antibodies to EBV.

During EBV infections, the precise antibody titers achieved and the time required to develop the full spectrum of antibodies vary with the individual humoral response (20). Additionally, the antibody titers obtained by different laboratories are not comparable because the interpretation of immunofluorescence tests is subjective and depends upon such factors as the fluorescence microscope used and the source of the reagents. The role of EBV antibody titers and the misuse and/or interchangeable use of similar names and acronyms for different syndromes has generated a tremendous amount of confusion. It is for these reasons that we have proposed the following criteria and terminology (Table 2) for chronic fatigue syndrome of unknown etiology (CFS), chronic EBV infection (CEBV), and SCAEBV. CFS is characterized by debilitating fatigue and is not caused by one known etiologic agent. CEBV is a form of CFS with a known etiologic agent, and patients within this group should be analyzed separately from CFS patients. The extremely high antibody titers to EBV antigens in association with the clinical and hematologic findings (Table 1) are the major characteristics separating CEBV from SCAEBV. Additionally, SCAEBV is often lethal, whereas CEBV and CFS are not. Therefore, the extraordinarily high antibody titers to EBV antigens in the group of patients described above most likely can be attributed to SCAEBV, the subject of this manuscript.

CLINICAL FEATURES AND PATIENT CASE REPORTS

The following clinical features are common in patients with SCAEBV (7, 9, 11–15, 18, 19, 21, 22, 24, 31): symptoms persisting for at least 6 months and associated with (i) either intermittent or persistent fever, lymphadenopathy, and hepatosplenomegaly, (ii) a tendency for pancytopenia and polyclonal gammopathy, and (iii) no apparent manifestation of a serious underlying disease. Pneumonitis is another clinical manifestation that has been reported in the literature (24, 31). Other symptoms, such as debilitating fatigue, sore throat, lymph node tenderness and pain, headache, myalgia, and arthralgia, are also encountered in these patients. Besides polyclonal gammopathy, in four patients with SCAEBV whom we recently studied only the IgG1 subclass was elevated (22). Additionally, only one familial case of this syndrome has been reported (9). The patient (father of the affected girl) described, however, did not have extremely high antibody titers to VCA or EA (VCA IgG, 640; EA IgG, 80).

The clinical features of patients with SCAEBV are listed in Table 3. The following are brief clinical case reports for six patients with SCAEBV whom we have recently studied and who have not been reported in detail in the literature.

Patient 8 was a 2-year-old Japanese girl with a 1-year history of fever and generalized malaise. Physical examination revealed enlarged cervical lymph nodes and hepatosplenomegaly. A cervical lymph node biopsy specimen revealed reactive lymphoid hyperplasia. Additionally, a decreased leukocyte count (2.0×10^9/liter; lymphocytes, 79%), anemia (hemoglobin, 66 g/liter), thrombocytopenia (platelets, 40×10^9/liter), and an increased serum IgG level (45.6 g/liter) were observed. Abnormal tests of liver function were noted (serum aspartate aminotransferase [AST], 2.9 μkat/liter; serum alanine aminotransferase [ALT], 1.2 μkat/liter; normal range for both, 0 to 0.6 μkat/liter). Lactate dehydrogenase (LDH) was elevated at 14.1 μkat/liter (normal range, 0.8 to 2.7 μkat/liter). The patient received acyclovir [9-(2-hydroxyethoxymethyl)guanine] without clinical improvement and died 1 year after the onset of illness, probably because of systemic lymphoid infiltration. No autopsy was performed.

Patient 9 was an 11-year-old Japanese boy who suffered from intermittent fever, cervical lymph node enlargement, and hepatosplenomegaly. Laboratory studies revealed a decreased leukocyte count (3.6×10^9/liter; lymphocytes, 38%), anemia (hemoglobin, 78 g/liter), thrombocytopenia (platelets, 24×10^9/liter), and polyclonal gammopathy (IgG, 22.7 g/liter; IgA, 3.1 g/liter; and IgM, 1.3 g/liter). Slightly elevated levels of AST (1.3 μkat/liter), ALT (1.3 μkat/liter), and LDH (10.1 μkat/liter) were seen. The patient was treated with acyclovir, recombinant gamma interferon, and cytotoxic drugs (cyclophosphamide and vincristine). An enlarged cervical lymph node biopsy specimen revealed reactive lymphoid hyperplasia. The patient died 9 months after the

TABLE 2. Differential diagnosis of SCAEBV[a]

Category	Characteristics of:				
				Immunodeficiency	
	CFS	CEBV	SCAEBV	Primary	Secondary[b] or acquired immunodeficiency syndrome
Major clinical manifestations	Often debilitating fatigue and fever	Fever, lymphadenopathy, and fatigue (onset begins with acute IM)	Fever, lymphadenopathy, hepatosplenomegaly (severe), and a tendency for pancytopenia	Variable depending on type (i.e., XLP, AT, WAS, and CVI)[c]	Secondary to the disease
Age distribution	Mostly adults	Mostly adults	Mostly children (<15 yr)	Mostly children	Mostly adults
Clinical course	Uncertain	Uncertain	Often lethal	Often lethal	Often lethal
Antibody titers to EBV	Normal, seropositive, or seronegative	Reactivation with moderately high antibody titers of VCA IgG and EA IgG and with low antibody titers to EBNA	Extremely high antibody titers of VCA IgG (≥5,120) and EA (≥640) and positivity for VCA IgA and EA IgA	Reactivation with low antibody titers to EBNA	Reactivation pattern; generally low to normal antibody titers to EBNA
Other designations or acronyms in the literature	CEBV, chronic symptomatic EBV infection, chronic mononucleosis, chronic infectious mononucleosis (CIM), chronic mononucleosis-like syndrome (CMLS), chronic active EBV infection (CAEBV), and chronic fatigue and immune dysfunction syndrome (CFIDS)	CFS, chronic symptomatic EBV infection, CMLS, and CAEBV infection, chronic mononucleosis, CIM	CAEBV	Not applicable	Not applicable

[a] Modified from reference 28.
[b] Secondary immunodeficiencies include patients on immunosuppressive therapy or patients with transplants.
[c] XLP, X-linked lymphoproliferative disease; AT, ataxia-telangiectasia; WAS, Wiskott-Aldrich syndrome; and CVI, common variable immunodeficiency.

onset of illness from severe liver dysfunction and systemic bleeding.

Patient 10 was a 2-year-old Japanese girl who suffered from persistent fever and hepatosplenomegaly. Laboratory data revealed a mildly decreased leukocyte count (4.0 × 10^9/liter; lymphocytes, 72%), severe anemia (hemoglobin, 39 g/liter), thrombocytopenia (platelets, 20 × 10^9/liter), and elevated serum IgG levels (37.6 g/liter). No abnormal liver function tests were noted. The patient has been alive for more than 6 months after the onset of illness, with only supportive treatment.

Patient 11 was a 5-year-old Japanese girl who suffered from intermittent fever and hepatosplenomegaly. Laboratory data revealed moderate anemia (hemoglobin, 89 g/liter), thrombocytopenia (platelets, 110 × 10^9/liter), and polyclonal gammopathy (IgG, 32.8 g/liter; IgA, 4.5 g/liter; and IgM, 1.0 g/liter). Elevated levels of AST (2.3 μkat/liter), ALT (1.7 μkat/liter), and LDH (6.2 μkat/liter) were seen. The patient has been alive for 4 years after the onset of illness, with only supportive treatment, but has recurrent episodes of symptoms.

Patient 12 was a 9-year-old Japanese boy who had recurrent episodes of fever, enlargement of cervical lymph nodes, and hepatosplenomegaly. An enlarged lymph node biopsy specimen revealed atypical plasmacytosis. Laboratory data revealed a decreased leukocyte count (1.7 × 10^9/liter; lymphocytes, 51%), severe anemia (hemoglobin, 55 g/liter), and thrombocytopenia (platelets, 92 × 10^9/liter). No obvious abnormalities of serum immunoglobulin levels were demonstrated. However, mildly elevated levels of AST (1.0 μkat/liter) and ALT (1.1 μkat/liter) were seen. The patient was treated with cytotoxic drugs, without clinical improvement, and died 3 years after the onset of illness, most likely because of systemic lymphoid infiltration. No autopsy was performed.

Patient 13 was a 15-year-old Japanese girl who suffered from intermittent fever and recurrent cervical lymph node enlargement since she was 5 years old. Biopsy specimens of a lymph node revealed infiltration by immunoblasts. Laboratory findings revealed mild anemia (hemoglobin, 105 g/liter) and thrombocytopenia (platelets, 71 × 10^9/liter) and polyclonal gammopathy (IgG, 18.9 g/liter; IgA, 1.5 g/liter; IgM, 6.4 g/liter). Liver function tests were within normal ranges. The patient is alive and is receiving prednisolone intermittently, without any clinical improvement.

VIROLOGICAL STUDIES

In all of these patients, EBV serologic tests revealed extremely high IgG antibody titers against EBV VCA (≥5,120) at least 50 times higher than those in seropositive healthy controls. The patients often had IgA and IgM antibodies against VCA as well. Persistently elevated IgG antibody titers to EA (D) and EA (R) (≥640), occasionally

TABLE 3. Clinical features of patients with SCAEBV

Patient	Age[a]	Sex[b]	Major clinical manifestations	Reference	Yr
1	5 (4)	F	Fever, hepatosplenomegaly, lymphadenopathy, and hyper IgG, IgM, IgA, and IgD	31	1978
2	8 (4)	F	Fever, hepatosplenomegaly, and anemia	9	1984
3	11 (1)	F	Fever, hepatosplenomegaly, lymphadenopathy, and hyper IgG	15	1985
4	5 (2)	F	Hepatosplenomegaly, lymphadenopathy, and hyper IgG and IgA	15	1985
5	15 (11)	F	Hepatosplenomegaly and hyper IgG and IgA	15	1985
6	26 (18)	F	Fever, splenomegaly, lymphadenopathy, pneumonitis, and pancytopenia	24	1986
7	23 (17)	F	Fever, pneumonitis, uveitis, leukopenia, and anemia	24	1986
8	2 (1)	F	Fever, hepatosplenomegaly, lymphadenopathy, pancytopenia, and hyper IgG	19[c]	1986
9	11 (10)	M	Fever, hepatosplenomegaly, pancytopenia, and hyper IgG and IgA	19[c]	1986
10	2 (1)	F	Fever, hepatosplenomegaly, pancytopenia, and hyper IgG	19[c]	1986
11	5 (1)	F	Fever, hepatosplenomegaly, anemia, thrombocytopenia, and hyper IgG and IgA	19[c]	1986
12	9 (6)	M	Fever, hepatosplenomegaly, lymphadenopathy, and pancytopenia	19[c]	1986
13	15 (5)	F	Fever, lymphadenopathy, anemia, thrombocytopenia, and hyper IgG, IgA, and IgM	19[c]	1986
14	4 (2)	M	Fever, lymphocytosis, anemia, thrombocytopenia, and hyper IgG	19[c]	1986
15	11 (7)	M	Fever, hepatosplenomegaly, and lymphadenopathy	12	1987
16	(5)	M	Pneumonitis and hyper IgG	18	1987
17	(10 days)	F	Fever, hepatosplenomegaly, and anemia	18	1987
18	8 (2)	M	Fever, hepatosplenomegaly, T-cell lymphoma, pneumonitis, and pancytopenia	11	1988
19	33 (31)	F	Fever, hepatosplenomegaly,T-cell lymphoblastic lymphoma, leukopenia, and hyper IgG	11	1988
20	55 (36)	M	Fever and peripheral T-cell lymphoma	11	1988
21	24 (22)	M	Fever, hepatosplenomegaly, lymphadenopathy, B-cell proliferation, pancytopenia, and hyper IgG and IgA	21	1988
22	2 (2)	M	Fever, hepatosplenomegaly, lymphadenopathy, and T-cell proliferation	14	1988
23	10 (2)	M	Fever, hepatosplenomegaly, T-cell proliferation and leukocytosis	7	1989
24	6	F	Fever, hepatosplenomegaly, and lymphadenopathy	13	1989
25	15 (11)	M	Fever, hepatosplenomegaly, lymphadenopathy, and hyper IgG and IgA	22	1990
26	22 (20)	F	Fever, mandibular swelling, lymphadenopathy, and hyper IgG and IgA	22	1990

[a] In years. Numbers in parentheses indicate the age in years, unless otherwise indicated, at the onset of symptoms.
[b] F, Female; M, male.
[c] Unpublished data included.

positive IgA antibody titers to EA (D), and nondetectable to elevated IgG antibody titers to EBNA were also seen (7, 9, 11–15, 18, 19, 21, 22, 24, 31). In general, elevated levels of IgG antibodies against EA indicate active viral replication (20); antibodies against EA (D) appear transiently during the acute phase of IM and are often observed in undifferentiated nasopharyngeal carcinoma and primary immunodeficiencies; and antibodies against EA (R) appear in pediatric primary infections, in endemic Burkitt's lymphoma, and in conjunction with some immunodeficiencies, such as acquired immunodeficiency syndrome. EBNA or EBV DNA was frequently detected in affected tissues of the patients just described (7, 9, 11–15, 18, 19, 21, 22, 24, 31). However, it was difficult to establish EBV-positive cell lines from the affected tissues and peripheral blood with or without the B95-8 EBV strain, which usually immortalizes human peripheral blood B lymphocytes in vitro (9, 14, 15, 19, 21, 22, 24; unpublished data).

Some of the patients with SCAEBV lacked an antibody response to EBNA encoded by the *Bam*HI K fragment (corresponding to EBNA 1), which is responsible for maintaining the episomal viral genome (5, 17, 18, 20). Additionally, the isolation of a defective nontransforming strain of EBV from a child with this syndrome suggests that the occurrence of EBV strains with a deleted transforming portion may explain the difficulty in establishing EBV-positive cell lines in certain patients (1, 2). Furthermore, a recent report described a homogeneous episomal population of EBV in affected tissues, including peripheral blood mononuclear cells, lymph node, lung, aorta, and spleen, in patients with SCAEBV (13). Although more cases should be studied, these findings suggest that in these patients, a single progenitor cell infected by EBV may proliferate predominantly. Moreover, we observed no differences between patients and controls with regard to the presence of antibodies to herpes simplex virus types 1 and 2, varicella-zoster virus, cytomegalovirus, human herpesvirus 6, measles virus, and rubella virus (22; unpublished data). Furthermore, no antibodies were detected to human T-lymphotropic virus type 1 or human immunodeficiency virus (22; unpublished data).

PATHOLOGICAL FINDINGS

In general, patients with SCAEBV show no malignant pathological abnormalities in affected tissues (7, 9, 11–15, 18, 19, 21, 22, 24, 31). Variable follicular lymphoid hyperplasia and atypical plasmacytosis are common findings in enlarged lymph nodes. Furthermore, no evidence of virus-associated hemophagocytic syndrome (23, 27) is observed in bone marrow specimens. However, over the course of the disease, some patients develop oligoclonal and/or monoclonal B-cell or T-cell lymphoproliferative diseases (7, 11, 14, 21). For example, the following have been described in patients

TABLE 4. Pathological findings for patients with SCAEBV

Patient	Pathological findings	Site	Reference
1	Immunoblastic lymphadenopathy	Lung	31
	Lymphoid hyperplasia	Lymph node	
2	Infiltration of abnormal cells[a]	Liver	9
4	No follicle centers, presence of T-cell-containing paracortical areas	Lymph node	15
6	Congestion and lymphoid hyperplasia	Spleen	24
7	Lymphoid hyperplasia	Liver	24
8	Lymphoid hyperplasia	Lymph node	19[b]
9	Lymphoid hyperplasia	Lymph node	19[b]
12	Infiltration of blastlike cells	Lymph node	19[b]
13	Immunoblastic lymphadenopathy	Lymph node	19[b]
18	Large T-cell lymphoma	Lung	11
19	Hyperplasia	Lymph nodes	11
	T-cell lymphoblastic lymphoma	Systemic	
20	T-cell lymphoma	Systemic	11
21	B-cell proliferation	Spleen	21
23	T-cell proliferation	Peripheral blood	7
26	Hyperplasia with lymphoplasmacytosis	Lymph node	22

[a] Malignant histiocytosis suspected.
[b] Unpublished data included.

who have SCAEBV and who have developed T-cell lymphoproliferative diseases: (i) T-cell lymphoma with clonal rearrangement of the T-cell receptor gene in three patients (11), (ii) clonal proliferation of T cells containing EBV DNA in one patient (7), and (iii) EBV-positive CD4 cells in the circulation of another patient (14). Although an interpretation of these results is difficult, the malignant or circulating T cells seem to be EBV genome positive both in Southern blot analysis and in in situ hybridization. In contrast, we have demonstrated an oligoclonal rearrangement of the heavy-chain J-region fragment of the immunoglobulin of the infiltrated cells in the spleen of a patient with SCAEBV (21). More studies are needed to establish whether the virus evokes T-cell as well as B-cell lymphomagenesis in patients with SCAEBV. No specific chromosomal abnormalities have been reported in patients with this syndrome (7, 9, 11–15, 18, 19, 21, 22, 24, 31). A summary of the pathological findings is given in Table 4.

IMMUNOLOGICAL STUDIES

Defenses against EBV infection include mucus, various interferons, natural killer (NK) cells, neutralizing antibodies, antibody-dependent cell-mediated cytotoxicity, and human leukocyte antigen-restricted or -nonrestricted EBV-specific cytotoxic T cells (20). A lack of these immunological defenses often results in EBV-induced lymphoproliferation. For example, as in patients with either inherited or acquired immunodeficiency (20), no consistent underlying immunological abnormalities have been found in patients with SCAEBV (7, 9, 11–15, 18, 19, 21, 22, 24, 31). Rather, various heterogeneous immune defects, such as defective immune interferon secretion, low NK cell activity, low mitogen stimulation of peripheral blood lymphocytes, and an inverted or increased CD4/CD8 ratio, have been reported.

TABLE 5. Immunological abnormalities in patients with SCAEBV

Patient	Immunological abnormalities	Reference(s)
1	Defective immune interferon production	31
2	Low NK cell and antibody-dependent cell-mediated cytotoxicity activities and inverted CD4/CD8 ratio	9
3	Circulating immune complexes and inverted CD4/CD8 ratio	15
4	Circulating immune complexes and no EBV cytotoxicity	15
5	Low mitogen stimulation response	15
6	Inverted CD4/CD8 ratio	24
7	Inverted CD4/CD8 ratio	24
13	Low NK cell activity	19[a]
15	Low NK cell activity	12
21	Low NK cell activity and increased CD4/CD8 ratio	21, 22
22	Increased CD4/CD8 ratio	14
23	Increased CD4/CD8 ratio	7
26	Inverted CD4/CD8 ratio	22

[a] Unpublished data included.

Because of the difficulties in establishing EBV-positive cell lines, assessing EBV-specific cytotoxic T-cell activity is difficult. However, Kuis et al. reported that one patient exhibited normal cytotoxicity, whereas a second patient exhibited no EBV-specific cytotoxicity and unusually high levels of virus-infected B cells in the peripheral blood and the affected lymph node (15). As mentioned earlier, some patients with SCAEBV fail to make antibodies to EBNA 1, suggesting some defect in the immunosurveillance of EBV infection, a cellular alteration, or a mutation elsewhere in the viral genome (5, 17, 18). Joncas et al. reported a lack of EBV antibody-dependent cell-mediated cytotoxicity, neutralizing antibodies, and NK cell activity in a patient with this syndrome (8). In contrast, we recently demonstrated the presence of normal neutralizing antibodies to EBV in four patients with SCAEBV (22). Taken together, these data indicate that a subtle heterogeneous immunodeficiency may be an underlying component in patients with this syndrome. The immunological abnormalities seen in this syndrome are listed in Table 5.

ETIOLOGY

The factors and mechanism(s) responsible for SCAEBV remain unclear. However, the magnitude of the EBV antibody response to the replicative antigens of EBV strongly indicates that unregulated replication of EBV is the main feature of the illness. Alfieri et al. isolated from the saliva of a child with SCAEBV a virus which induced EBV EA in Raji cells and in fresh EBV-negative peripheral blood lymphocytes (1, 2). The authors suggested that atypical EBV strains, such as a nontransforming lytic strain, may be the etiologic agents in certain patients. We have recently detected both adenovirus type 2 and EBV genomes in lesions in a patient with SCAEBV (21). Additionally, using monoclonal antibodies to adenoviruses, we have demonstrated that the virus isolated from throat washings of the patient induced adenovirus-related antigen expression in Raji cells (21; unpublished data). Finally, using a newly developed enzyme-linked immunosorbent assay and an immunofluores-

cence test, we have demonstrated the presence of both IgG and IgM antibodies to adenovirus type 2 in patients with SCAEBV (22). Two low-molecular-weight RNAs encoded by EBV and designated EBV-encoded RNA-1 and RNA-2 (EBER-1 and EBER-2, respectively) can functionally substitute for the adenovirus-associated RNA-1 and RNA-2 (VA-1 and VA-2) of adenovirus types 2 and 5, respectively, and are responsible for the lytic growth of the adenoviruses (21, 22). When normal B lymphocytes are infected by EBV in vitro, the cells are immortalized into continuously dividing permanent cell lines (20). On the other hand, infection of human cells by adenoviruses generally leads to a lytic event (21). Thus, we have reasoned that despite the expression of an activated EBV infection in vivo, the difficulty in establishing EBV-positive cell lines may be related to EBV activation of adenovirus-induced cell lysis. Additionally, adenoviruses may enhance the expression of EBV-related lytic antigens such as EA and VCA (21). Adenoviruses can reduce the expression of human histocompatibility class 1 antigens on infected cells (21, 22), whereas EBV induces a transient immunosuppression (21, 22) in patients during acute infections. Therefore, the combination and/or interaction of these two lymphotropic viruses may be responsible for the development of SCAEBV in some patients. Further studies, however, are needed to confirm this possibility.

The pathogenetic mechanism(s) responsible for the development of oligoclonal and/or monoclonal B-cell or T-cell lymphoproliferative diseases remains unclear. It has been postulated that malignant transformation by EBV of proliferating T cells responding to EBV-infected cells results in the development of T-cell neoplasms (11). Although the finding of monoclonality in lymphoproliferative diseases may represent extreme clonal expansion and does not necessarily indicate neoplastic transformation and although no consistent underlying immunological abnormalities have been found in patients with SCAEBV, it is well known that the transition from polyclonal to monoclonal EBV-induced lymphoproliferative lesions occurs in patients with immunodeficiencies (20). This observation may explain the development of B-cell lymphoproliferative diseases in patients with SCAEBV. More cases, however, should be studied to evaluate B-cell or T-cell lymphoproliferative diseases in patients with SCAEBV.

THERAPY

No effective treatment is available for SCAEBV. Acyclovir, a potent antiherpesvirus agent which is useful for treating some transplant recipients with life-threatening EBV-induced polyclonal lymphoproliferative disease, has no significant clinical effect in patients with SCAEBV (15, 21, 22). However, some success with recombinant interleukin-2 treatment has been reported (12). One patient was in a clinical remission for more than 6 months as a result of the restoration of NK cell activity. Several promising new approaches for treating EBV-induced lymphoproliferative diseases, including high-dose intravenous immunoglobulin and alpha interferon, are under investigation (22; unpublished data). The results of these studies may provide new approaches for the assessment and treatment of SCAEBV.

DIFFERENTIAL DIAGNOSIS

Other clinical conditions that may produce symptoms similar to those of SCAEBV must be excluded by a thorough evaluation based on history, physical examination, and appropriate laboratory findings. For example, this syndrome has to be differentiated from EBV-induced lymphoproliferative disorders in patients who have increased EBV antibody titers and who may have inherited or acquired immunodeficiencies (20). These diseases result from defective immune responses during the primary EBV infection or a reactivated EBV infection with acquired immunodeficiency. In these cases, however, the underlying immunodeficiency can be detected.

Rheumatic disease, such as systemic lupus erythematosus and rheumatoid arthritis (33), and chronic inflammatory disease or lymphoid malignancy, such as angioimmunoblastic lymphadenopathy with dysproteinemia, leukemia, and Hodgkin's disease (16, 25, 32), should be considered in the differential diagnosis. Patients with these diseases often have elevated antibody titers to EBV. However, they rarely exhibit IgG antibody titers to VCA as high as $\geq$5,120, as are seen in patients with SCAEBV. Moreover, clinical and histopathological features are distinctive in these other diseases.

CONCLUDING REMARKS

Although lymphoproliferation, such as IM arising from EBV infection, is almost always self-limiting, some patients develop uncontrolled proliferation resulting from various degrees of immunodeficiency, genetic background, or other unknown factors (20). Since the discovery of EBV, this virus has been etiologically implicated in an increasing number of human diseases (20). During the 1980s, several studies focused on patients with chronic fatigue and other nonspecific symptoms following acute IM without a clearly defined underlying disease (3, 4, 10, 26, 28, 29). Defining the etiology of such syndromes is difficult because the interpretation of EBV serology is complex and the nonspecific symptoms are varied. Although we cannot completely rule out other diseases, the SCAEBV which we have described appears to be distinctive because of its characteristic clinical features. The case definition criteria in Table 1 should help to improve the comparability and the reproducibility of clinical research and epidemiologic studies for evaluating patients. This review is intended to provide further opportunities to investigate this enigmatic syndrome. The results of these investigations may lead to new approaches for the assessment and treatment of lymphoproliferative disorders of unknown etiology.

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