Documentation of Epstein-Barr Virus Infection in Immunodeficient Patients with Life-threatening Lymphoproliferative Diseases by Clinical, Virological, and Immunopathological Studies

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Abstract

Multiple methods, pedigree analysis, clinical evaluation, and Epstein-Barr virus (EBV)-specific serology, EBV DNA hybridization of tissues to probe for viral genome, staining of touch imprints for EBV nuclear-associated antigen, establishment of spontaneous infected B-cell lines from peripheral blood or tissues, examination of peripheral blood smears, and hematopathology studies, were used to study seven patients with the X-linked lymphoproliferative syndrome and seven additional patients with life-threatening EBV-associated diseases. These studies demonstrated EBV in the tissues of all 14 patients and immunodeficient antibody responses to EBV were documented. This virus can produce various life-threatening lymphoproliferative diseases in a variety of immunodeficient patients.

Recently, Purtilo (18) postulated that EBV3 could be oncogenic in individuals with inherited or acquired immunodeficiency disorders. This postulation was based on observations that following EBV infection of males with XLP various diseases develop including aplastic anemia, acquired agammaglobulinemia, chronic or fatal IM, pseudolymphoma, and B-cell malignant lymphomas such as Burkitt’s lymphoma or immunoblastic sarcoma (17–25, 29, 31).

During the 5-year interval since Purtilo et al. (23) described Duncan’s disease (XLP preferred), evidence that EBV is the etiological agent of the lymphoproliferative diseases of the syndrome has accumulated (17–25, 29, 31). Owing to the deaths of 6 males in the Duncan kindred with fatal IM, acquired agammaglobulinemia after IM, and chronic IM progressing to malignant lymphoma and the marked T-cell depletion of thymus glands, lymph nodes, and splenic T-cell sheaths, we postulated in 1975, that immunodeficiency had predisposed the boys to fatal EBV infection (17, 23). The following year, we began studying a second unrelated kindred with 18 affected maternally related males (24). Among the many families investigated for XLP are 2 brothers reported in 1969 (5) who had developed malignant lymphoma following IM, a large Mexican-American kindred wherein 17 preschool-aged boys had died of a lymphoproliferative disease by 1972 (3), and 4 maternally related males reported in 1974 by Bar et al. (1) who had succumbed to IM. Our registry of XLP has enrolled 26 kindreds and 105 males and has comprehensively investigated the families, obligate carrier females, 20 affected surviving males, siblings, and other relatives at risk (6, 20) for immunodeficiency and EBV.

Briefly, immunopathology studies of XLP have revealed T-cell depletion of thymus gland and lymphoid compartments (17–25), and in vitro immune studies have quantitated and elaborated various subtle T-cell and B-cell defects (15, 33). EBV-specific antibody studies of sera of males with XLP have demonstrated severe immunodeficiency; especially lacking is an anti-EBNA (31) response.

Renal transplant recipients develop opportunistic malignant lymphomas at a frequency far above normal (reviewed in Ref. 7). The etiology of these lymphomas has been undetermined; however, recently EBV has been documented within these unusual polyclonal B-cell lymphomas. Elsewhere in this issue, other accounts of clinical (7) and EBV DNA hybridization studies (26) of such patients are presented. The immune defects of patients with XLP and renal transplant recipients allow EBV to provoke an explosive polyclonal B-cell proliferation (18, 20).

Until 1970, only 20 documented cases of fatal IM had been published (reviewed in Ref. 19). Owing to results of recent investigations, immunodeficient patients who fail to exhibit the usual clinical heterophil and EBV-specific serological responses to EBV infections can be diagnosed to have EBV-associated diseases (1, 2, 7, 15, 17–26, 28, 30, 34). Here, we present clinical, serological, and pathological aspects of cases illustrating EBV-induced lymphoproliferative diseases in various immunodeficiency disorders. Concepts regarding immunopathogenesis of EBV-induced diseases and methods of documentation of the infection are discussed.

Materials and Methods

EBV-specific antibodies were measured using well-defined techniques (8–11). When sufficient tissues were available, both cRNA/DNA and vDNA/DNA hybridization techniques were used to probe for
the EBV genome (2, 10, 11, 14, 26, 31). The technology and results are discussed in detail elsewhere in this issue (29).

Spontaneous outgrowth of peripheral-blood lymphocytes and lymphoid cells from tissues was tested for after cutting tissues with scissors and passing them through a fine stainless steel mesh, separating them further by Ficoll-Hypaque sedimentation, and placing them in long-term culture in Roswell Park Memorial Institute Tissue Culture Medium 1640 enriched with 20% fetal calf serum at 37°C in 5% CO2. The cultures were examined weekly for outgrowth of colonies of lymphoblasts.

EBNA staining of air-dried touch imprints of lymphoid organs and 6-μm-thick frozen sections were cut in a cryostat, fixed in (−20°C) acetone:methanol, and stained by the Reedman-Klein technique (27) using anti-EBNA-positive and -negative sera diluted 1:10.

Case Reports

Two groups of patients are presented including 7 with XLP and 7 with diverse immunodeficiency-lymphoproliferative diseases.

XLP

Seven patients referred to our XLP registry were studied. The patients were members of 5 separate unrelated kindreds with XLP. Details of their clinical and immunopathological studies have been (17–20, 22–24) or will be reported elsewhere. A clinical and pathological summary of each is provided focusing on studies documenting EBV infections. Specific comments are made for each case. An overall discussion follows the case presentations.

Case A. M. A 16-year-old boy began to have increasingly severe infections at 4 (22). Measles pneumonia had occurred in 1969, and he had bronchopneumonia 4 times since 1975. In 1977, he developed recurrent fever. Six weeks after consulting Dr. Purtilo, he developed pharyngitis which, despite penicillin, persisted for several days. Wheezing developed, and on the ninth day of illness a chest X-ray revealed bronchopneumonia. A ‘‘Monospot’’ test for IM (Ortho Diagnostics, Raritan, N. J.) was positive. At the University of Massachusetts Hospital, his temperature was 38°C, pulse 120/min, respirations 40/min, blood pressure 110/60 mm Hg, and weight 40.5 kg. He was small (tenth percentile), prepubertal, dyspneic, and tender, and the spleen tip could be felt. Tables 1 and 2 summarize laboratory studies. Peripheral-blood smear showed many plasmacytoid cells (Fig. 1). Two Monospot tests were positive. Liver function tests were very abnormal. Prothrombin time was 37 sec (control, 12.5 sec), partial thromboplastin time was 110 sec (control, 35.5 sec), fibrin split products were 1:80, and fibrinogen was 98 mg/dl.

Immunological and EBV studies (see Table 1). Serum IgM was increased markedly to 810 mg/dl. C3 was <35 mg/dl, and factor D was increased markedly to 810 mg/dl. C3 was <35 mg/dl, and fibrinogen was 98 mg/dl. PHA were much depressed. He failed to mount an effective antibody response to EBV (Table 2). His fulminating IM ended in severe hepatitis with hemorrhagic, respiratory, and cardiac arrest. Necropsy revealed IM complicated by extensive hepatic necrosis and thrombocytopenia associated with pronounced hemorrhagic gastroenteritis. Atrophy of the thymus gland (14 g weight; normal, 28 g), splenomegaly (370 g; normal, 120 g) with extensive necrosis of the T-cell periarterial sheath of the spleen, and infiltration by plasma cells were observed. The maculopapular rash resembled graft-versus-host reaction. Dyskeratosis, vacuolation and focal necrosis of basal layer, perivascular lymphoid infiltrate, and edema of the papillary dermis were seen. Bone marrow was depleted of erythroid and myeloid precursors, but plasmacytosis and extensive histiocytoisis with erythropagocytosis and nucleophagocytosis were found. Proliferating plasma cells expanded all lymph nodes (Fig. 2). An immunoblastic sarcoma of B-cells replaced 3 left cervical lymph nodes. Lymphoblastoid cells grew spontaneously in tissue culture from lymph nodes and bone marrow. The cell lines contained EBNA and electron microscopy of cultured cells revealed moderate numbers of herpesvirus particles, consistent with EBV. EBNA-positive cells were also detected in a few (<1%) lymphoid cells in touch imprints of the spleen. Results of other studies are summarized in Tables 1 and 2.

Comment. The polyclonal increase of serum immunoglobulins following EBV infection within a few weeks (Table 1) illustrates the potency of EBV as a polyclonal activator of B-cells, even in immunodeficient persons. The cervical lymph nodes showed features of immunoblastic sarcoma; however, the proliferation was probably polyclonal. Time was probably insufficient to select out a genetically altered clone (12, 18). Neither cell surface nor karyotype studies were done.

Case R. M. The 15-year-old brother of A. M. had also been evaluated by Dr. Purtilo in 1977 and had hypogammaglobulinemia (Table 1). During his brother’s fatal IM, R. M. developed pharyngitis and elevated anti-EA and -VCA antibodies (Table 2). A cervical lymph node was biopsied, divided, and frozen at −70°C for hybridization, and the remainder was used for histopathology studies. T-Cell areas were expanded and germinal centers were not active (Fig. 2), and hybridization studies revealed EBV DNA (Table 2). The patient continues to experience intermittent pharyngitis, his lymphocytes grow spontaneously in vitro from peripheral blood, and his anti-VCA has remained elevated. Anti-EBNA has been lacking persistently for over 3 years (31).

Comment. Not reported here is the 19-year-old brother who had malignant lymphoma of the ileum in 1972 and who has selective IgA deficiency. The 3 brothers illustrate the variable phenotypes of XLP (24). R. M. has a variety of cellular immune defects, some of which are reported elsewhere (15, 33).

Case L. G. A 30-month-old male member of the second kindred was described by Purtilo et al. (24) with XLP. His brother had died of XLP at 2 years of age with fatal IM and immunoblastic sarcoma phenotypes. Therefore, we had carefully monitored the child for EBV infection and immunological function. Three weeks prior to hospitalization for fatal IM, he was seen by Dr. Sullivan and was asymptomatic.

In brief, he presented with marked lymphadenomegaly, a fine generalized rash, a temperature of 38.2°C, and moderate hepatosplenomegaly. Tables 1 and 2 summarize laboratory stud-
### Table 1

**Clinical and pathological diagnoses, WBC’s, serum immunoglobulin concentrations in immunodeficient patients with life-threatening EBV-induced lymphoproliferative diseases**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Clinical diagnoses</th>
<th>Pathological diagnoses</th>
<th>Monospot</th>
<th>WBC/µl</th>
<th>% of neutrophils</th>
<th>% of stabs</th>
<th>% of lymphocytes and other cells</th>
<th>Dates</th>
<th>IgG</th>
<th>IgM</th>
<th>IgA</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. M.</td>
<td>16</td>
<td>M</td>
<td>XLP, hypogammaglobulinemia</td>
<td>Fatal IM, IBS, XLP</td>
<td>+</td>
<td>9,100</td>
<td>12</td>
<td>8</td>
<td>48</td>
<td>5/29/77, 7/12/77</td>
<td>745</td>
<td>183</td>
<td>60</td>
<td>More severe illnesses pre-EBV infection than brother R. M.</td>
</tr>
<tr>
<td>R. M.</td>
<td>15</td>
<td>M</td>
<td>XLP, hypogammaglobulinemia</td>
<td>Chronic EBV, hypogammaglobulinemia, XLP</td>
<td>–</td>
<td>9,100</td>
<td>40</td>
<td>0</td>
<td>40</td>
<td>5/29/77, 7/12/77</td>
<td>1300</td>
<td>87</td>
<td>52</td>
<td>Has never mounted anti-EBNA response</td>
</tr>
<tr>
<td>L. G.</td>
<td>2½</td>
<td>M</td>
<td>XLP at risk</td>
<td>Fatal IM, XLP</td>
<td>+</td>
<td>10,200</td>
<td>15</td>
<td>10</td>
<td>75</td>
<td>2/19/80, 3/5/80</td>
<td>640</td>
<td>310</td>
<td>192</td>
<td>Brother died of IM and IBS</td>
</tr>
<tr>
<td>K. W.</td>
<td>6</td>
<td>M</td>
<td>Acute leukemia</td>
<td>Hypogammaglobulinemia, pseudolymphoma</td>
<td>–</td>
<td>13,300</td>
<td>25</td>
<td>10</td>
<td>50</td>
<td>5/20/72, 6/10/75</td>
<td>1150</td>
<td>145</td>
<td>260</td>
<td>17 maternally related males died of IM; Age 10 pseudolymphoma Two brothers died, cousin has hypogammaglobulinemia</td>
</tr>
<tr>
<td>V. G.</td>
<td>4</td>
<td>M</td>
<td>Neutropenia</td>
<td>Neutropenia, hypogammaglobulinemia, malignant lymphoma, aplastic anemia, and XLP</td>
<td>–</td>
<td>2,900</td>
<td>45</td>
<td>8</td>
<td>47</td>
<td>9/8/78, 8/2/79</td>
<td>190</td>
<td>16</td>
<td>10</td>
<td>Trace</td>
</tr>
<tr>
<td>B. P.</td>
<td>7</td>
<td>M</td>
<td>Stevens-Johnson and inappropriate antiuremic hormone secretion</td>
<td>Fatal IM, XLP</td>
<td>ND</td>
<td>8,400</td>
<td>65</td>
<td>3</td>
<td>28</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td></td>
<td>Maternal cousins died of IM</td>
</tr>
<tr>
<td>J. C.</td>
<td>4½</td>
<td>M</td>
<td>Fatal IM</td>
<td>Fatal IM, XLP</td>
<td>+</td>
<td>8,400</td>
<td>45</td>
<td>8</td>
<td>47</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td></td>
<td>Maternal uncle died of ‘Hand-Schüller-Christian syndrome’. Chronic IM possibly to lymphoproliferative malignancy</td>
</tr>
<tr>
<td>D. S.</td>
<td>2½</td>
<td>M</td>
<td>Malignant histiocytosis</td>
<td>Fatal EBV infection</td>
<td>ND</td>
<td>7,000</td>
<td>21</td>
<td>5</td>
<td>60</td>
<td>4/9/80</td>
<td>980</td>
<td>89</td>
<td>32</td>
<td>No siblings</td>
</tr>
<tr>
<td>R. T.</td>
<td>2½</td>
<td>M</td>
<td>Lymphohistiocytosis</td>
<td>Fatal IM, aplastic anemia, XLP</td>
<td>–</td>
<td>7,800</td>
<td>3</td>
<td>2</td>
<td>95</td>
<td>4/4/77</td>
<td>328</td>
<td>660</td>
<td>168</td>
<td>IU/ml anemic</td>
</tr>
<tr>
<td>H. W.</td>
<td>10</td>
<td>M</td>
<td>Chronic IM</td>
<td>Fatal IM</td>
<td>PBT</td>
<td>4,800</td>
<td>39</td>
<td>0</td>
<td>58</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td>Sister also died of IM (see Ref. 2)</td>
</tr>
<tr>
<td>C. F.</td>
<td>4</td>
<td>M</td>
<td>Chronic neurological degeneration</td>
<td>Fatal IM</td>
<td>ND</td>
<td>7,600</td>
<td>30</td>
<td>5.5</td>
<td>61.5</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T. T.</td>
<td>8½</td>
<td>M</td>
<td>Immune hemolytic anemia</td>
<td>Hyperplastic lymph node, hypogammaglobulinemia</td>
<td>–</td>
<td>2,900</td>
<td>60</td>
<td>7</td>
<td>17</td>
<td>5/9/79, 7/6/79, 7/31/79</td>
<td>440</td>
<td>66</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>J. W.</td>
<td>18</td>
<td>M</td>
<td>Recurrent IM</td>
<td>Recurrent IM</td>
<td>+</td>
<td>9,500</td>
<td>14</td>
<td>10</td>
<td>16</td>
<td>7/9/79, 9/10/79</td>
<td>1625</td>
<td>77</td>
<td>110</td>
<td>Sister has hypogammaglobulinemia, chronic IM</td>
</tr>
<tr>
<td>B. N.</td>
<td>1½</td>
<td>F</td>
<td>Congenital EBV infection</td>
<td>Chronic IM syndrome</td>
<td>–</td>
<td>3,200</td>
<td>50</td>
<td>8</td>
<td>38</td>
<td>12/11/78, 11/13/79</td>
<td>995</td>
<td>792</td>
<td>106</td>
<td>Regression of pancytopenia with splenectomy</td>
</tr>
</tbody>
</table>

a hypogammaglobulinemia; IBS, immunoblastic sarcoma; ND, not done; PBT, Paul-Bunnell positive.

b Note added in press. Brother recently succumbed to IM and hence XLP was eventually the diagnosis.
ies. He developed progressive hepatic failure and died in the third week of illness. Autopsy revealed a small thymus gland, lymph nodes, and spleen with immunoblasts and plasma cells in great numbers. Similar cells infiltrated liver, heart, and other vital organs. Numerous polyclonal spontaneous cell lines were established from thymus, spleen, lymph nodes, and bone marrow. Other studies are summarized in Tables 1 and 2.

Comment. This patient with XLP, studied prospectively, showed apparently normal immune competence prior to infection by EBV. Documentation that EBV was the agent responsible for his demise included: prospective negative preinfection serology with seroconversion; positive EBNA-positive touch imprints of tissues; spontaneous lymphoblastoid lines; and DNA hybridization studies of EBV genome in tissues following infection by EBV.

Case K. W. An 11-year-old Mexican-American boy is a member of a kindred wherein 17 males had died of XLP, chiefly with the fatal IM phenotype, before 6 years of age (1, 6). At 6, he developed grand mal seizures which had responded to phenobarbitol and ritalin treatment. Two months later, gas troenteritis appeared followed 2 weeks later by fever, pharyngitis, malaise, vomiting, and a rash. He was rehospitalized a week later with fever, lymphadenomegaly, anemia, (Hgb, 5.4 g/dl), and a WBC of 8200/jul, and 85% lymphocytes including atypical plasmacytoid forms, 14% monocytes, and 1% eosinophils were detected. Serum immunoglobulins were markedly reduced (Table 1), and he was lacking EBV antibodies (Table 2), whereas his mother's titers were elevated as is found in most carriers of XLP (31). Blood contained 44% erythrocyte rosettes, 33% complement receptor rosettes, 9% IgM, and 11% IgD-bearing lymphocytes. Response of lymphocytes to PHA was normal but depressed for pokeweed and concanavalin A mitogens. His natural killer activity to K562 targets was very low. Details are published elsewhere (33). Bactrim and plasma therapy were provided. Pseudolymphoma of the lung developed 3 months later (Fig. 3). EBV DNA hybridization studies revealed the EBV genome (Table 2). He received no further treatment and his condition rapidly deteriorated. On April 13, 2017. © 1981 American Association for Cancer Research. cancerres.aacrjournals.org Downloaded from cancerres.aacrjournals.org on April 13, 2017. © 1981 American Association for Cancer Research.
treatment for the pulmonary lesion and has remained well for 2 years.

Comment. He has been relatively free of infections during the 2-year interval since initiating therapy with plasma-containing EBV-specific antibodies. No further therapy was provided for the lesion in the lung.

Case V. G. A 4-year-old Mexican-American boy (unrelated to K. W.) had neutropenia in July 1978. Male siblings had died at 1 and 4 of infections and thrombocytopenia. A surviving brother and sister were healthy, but a maternally related male cousin was misdiagnosed as having Bruton’s agammaglobulinemia.

Severe bronchitis occurred in September 1978, and hypogammaglobulinemia was detected with IgG 190, IgA 10, and IgM 16 mg/dl. Bone marrow cells were megaloblastic. His bronchitis remitted following antibiotics. In June 1979, fever, abdominal pain, and diarrhea occurred. Physical examination disclosed gingival hypertrophy, decreased tonsillar mass, and hepatosplenomegaly. Serum IgM had increased 8-fold to 100 mg/dl (Table 1). Total hemolytic complement decreased to 3.3%, and antinuclear antibody and rheumatoid factor were not detected. A normal response to PHA was determined. Stool examination revealed *Giardia lamblia*. He was treated with quinacrine for 10 days, intramuscular vitamin B12, and γ-globulin.

He was well for 2 weeks, and then rectal hemorrhage appeared. Blood platelets were 24,000/μl, and prothrombin and partial thromboplastin times were prolonged. Fresh frozen plasma and albumin blood transfusion produced cessation of bleeding. A gingival biopsy specimen revealed infiltration by lymphocytes, and X-ray studies revealed an ileocecal mass which was resected. The malignant lymphoma was diffuse and well differentiated (Rappaport). The malignant lymphoma was diffuse and well differentiated (Rappaport). Regrettably, karyotype, cell surface marker, and EBV DNA hybridization studies were not done.

The postoperative course was marked by persistent pancytopenia, progressive visual loss, and septicemia. He was well for 2 weeks, and then rectal hemorrhage appeared. Blood platelets were 24,000/μl, and prothrombin and partial thromboplastin times were prolonged. Fresh frozen plasma and albumin blood transfusion produced cessation of bleeding. A gingival biopsy specimen revealed infiltration by lymphocytes, and X-ray studies revealed an ileocecal mass which was resected. The malignant lymphoma was diffuse and well differentiated (Rappaport). Regrettably, karyotype, cell surface marker, and EBV DNA hybridization studies were not done.

Comment. Fortunately, tissues from autopsy had been frozen. EBV DNA hybridization revealed that the lymphoproliferation which had caused diabetes insipidus had been due to EBV infection.

Case J. C. A 4½-year-old male developed otitis, fever, and irritability in May 1979. He was given ampicillin, and one week later a generalized rash appeared. Persistent fever, nausea, and vomiting prompted further evaluation.

Physical examination revealed a small thymus gland, moderate splenomegaly with depletion of T-dependent regions, and hyperplastic lymph nodes with immunoblastic proliferation and showing plasma cell differentiation. Lymphoid cells infiltrated into the neurohypophysis producing necrosis and diabetes insipidus. EBV DNA hybridization studies revealed the EBV genome (Table 2). Serological studies on his mother revealed the characteristic elevated anti-VCA levels of carriers of XLP (31).

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Case B. P. A 7-year-old boy was seen in consultation for perioral edema, hemorrhagic gingivae, nocturia, and thirst.

Physical examination revealed a pale intelligent boy complaining of headache and mild photophobia. Temperature was 38.3°C, heart rate 116, and respiratory rates 20/min. No lymphadenomegaly or organomegaly was detected. Marked chorioidal effusion was found. No papillodema was seen.

Pneumonia had occurred the previous year. Several maternal uncles had died in infancy, and a 4-year-old male maternally related cousin had died of IM. No untoward reactions to usual infections of childhood or vaccines were noted. His sister had symptoms of the “flu” the previous week.

A lumbar puncture revealed CSF pressure was 130 mm of H2O, protein was elevated to 650 mg/dl, and 21 WBC’s with 84% lymphocytes were found. Urine analysis showed specific gravity of only 1.003. He was diagnosed as having diabetes insipidus and mild meningitis. *Mycoplasma* titers were elevated from 1:128 to 1:256, and hence he was treated with erythromycin. Later, CSF protein had increased to 1040 mg/dl (very elevated). Other laboratory studies are summarized in Tables 1 and 2. He became progressively dyspeptic and obtunded, and retinal detachment had occurred.

During his hospitalization, an open-lung biopsy specimen was obtained and diagnosed as histiocytosis X. Serum γ-globulin was 6.2 g/dl and elevated in a polyclonal pattern. No EBV-specific serology was done. He died approximately 10 months following the onset of his illness.

Autopsy studies revealed a small thymus gland, moderate splenomegaly with depletion of T-dependent regions, and hyperplastic lymph nodes with immunoblastic proliferation and showing plasma cell differentiation. Lymphoid cells infiltrated into the neurohypophysis producing necrosis and diabetes insipidus. EBV DNA hybridization studies revealed the EBV genome (Table 2). Serological studies on his mother revealed the characteristic elevated anti-VCA levels of carriers of XLP (31).

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Physical examination revealed a generalized maculopapular rash, heart rate 160/min, respirations 28/min, and 39°C temperature. Cervical lymphadenomegaly and hepatomegaly were present. Hgb was 8.2 g/dl and WBC was 8400/μl with atypical lymphocytosis. Both Monospot and heterophil determinations were reactive, indicative of IM. Bone marrow showed atypical lymphocytes admixed with normal elements. Chest X-ray revealed interstitial pneumonitis. On the fourth day, the indirect Coombs’ test was positive. Anti-VCA was 1:40 and anti-EA 1:10, consistent with acute IM. Hepatic enzymes became progressively elevated. On Day 6, papillodema occurred. Lumbar puncture revealed 18 atypical lymphocytes in CSF, and his WBC increased to 51,000/μl. Hepatic biopsy showed pericellular infiltration, and the direct Coombs’ test was positive. Pancreatitis ensued. Prednisolone was given, he improved for several weeks, and his WBC had become nearly normal. He died suddenly with hantemesis while convalescing at home 6.
months after illness began.

Autopsy revealed a Cushinoid child. A thymus gland was not detected; however, parathyroid glands were found. The stomach was filled with clotted blood, and multiple petechial hemorrhages were present in the esophagus. Staphylococcal pneumonia was present. Marked hepatic necrosis associated with a lymphocytic and plasma cell infiltrate was found. The meninges and heart showed lymphocytic infiltration. Lymph nodes were depleted of lymphocytes, and macrophages were activated. Staphylococcal organisms were cultured from blood, spleen, and other organs. The EBV genome was detected (Table 1).

Comment. A maternally related uncle had died with a diagnosis of 'Hand-Schüller-Christian disease' at 9. Review of the autopsy slides also demonstrated an IM phenotype. The uncle and J. C. probably had XLP.

Other Life-threatening EBV-associated Diseases

A second group of 7 patients were studied. They illustrate diagnostic problems and the diversity of EBV-associated diseases in immunodeficient patients.

Case D. S. A 2 1/2-year-old boy at 5 months experienced bronchiolitis due to respiratory syncytial virus. He was pale had scattered purpuric lesions, and hepatosplenomegaly. Laboratory values are summarized in Table 1. A serum rubella hemagglutination inhibition titer of 1:32 was noted. Initially, titers to EBV and CMV were negative. On X-ray examination, symmetrical sclerotic lesions were present in the diaphyses of both femora and humeri. A bone marrow trephine biopsy specimen showed fibrosis interspersed with sheets of cells with large pale nuclei and abundant foamy cytoplasm. Malignant histiocytosis was diagnosed tentatively.

During the next 3 months, spontaneous resolution of the hepatosplenomegaly developed. Lymphocyte surface marker studies showed normal numbers of T- and B-cells. For 16 months, he maintained a normal WBC, although frequent respiratory tract infections had occurred.

At 26 months, otitis media, slight pancycopenia, and an elevated erythrocyte sedimentation rate were noted. The infection resolved on antibiotics, but he developed malaise, fever, and bone pain. Hgb was 6.8 g/dl with platelets 23,000/μl and WBC was 5600/μl with neutrophils 40%, lymphocytes 51%, and monocytes 9%. The spleen became palpable and firm, and enlarged nodes appeared in the supraclavicular fossa. Bone marrow showed dense infiltration with "histiocytic" cells, and hence the diagnosis of malignant histiocytosis was retained. Treatment with vincristine and prednisolone provided no relief. Laboratory studies are summarized in Tables 1 and 2. A Monospot test was unreactive. Six days later, his face became swollen on the left side. Cellulitis had developed in his scalp. His WBC had decreased to 3300/μl with 100% lymphocytes. Urine analysis showed specific gravity of 1.021, 2+ protein, pH 5, 2 to 5 WBC's/high-power field, and numerous bacteria. Methicillin and gentamicin were provided.

This only child had no relevant family history. Physical examination revealed a stuporous febrile boy with a resolving rash and marked cervical and facial edema. Hepatomegaly but no splenomegaly was evident. Bone marrow contained numerous atypical lymphocytes, plasma cells, and histiocytes. Serum uric acid was elevated to 13.1 mg/dl, calcium was 6.6, and phosphate at 2.2 mg/dl was decreased. Hgb was 5.6 g/dl, WBC 550/μl, and platelets 7800/μl. Hepatic and respiratory functions worsened with time. Marked polyclonal increase of IgM and IgA with decreased IgG and anti-EBV antibodies were detected (Table 1). He became hypotensive and expired on Day 14 of his illness. Anti-VCA was barely detectable (Table 1).

Autopsy examination revealed 600 ml ascites. Acute bronchopneumonia, due to Aspergillus and Pseudomonas, was present. The thymus gland was replaced by adipose tissue. The liver and spleen were enlarged 3-fold, and splenic periaortic T-cell zones were necrotic. A rim of plasma cells and immature lymphoid cells surrounded the necrotic shafts. Thoracic and abdominal lymph nodes were enlarged by lymphoid cells. Rare cells resembling Reed-Sternberg cells were found. A 125-cm segment of ileum and colon contained 5- to 10-mm diameter ulcers infiltrated by plasmacytoid lymphocytes. Hepatic periportal infiltration by lymphoid cells associated with parenchymal necrosis was seen. The heart, kidneys, and me-
nages were mildly infiltrated by such cells. Bone marrow was depleted of myeloid and erythroid elements and replaced by plasmacytoid lymphoid cells, and abundant macrophages were present. The EBV genome was detected in the spleen (Table 2).

**Comment.** The clinical and pathological findings which show a lack of EBV antibodies and the EBV genome in tissues suggest that the patient had XLP (21); however, no maternal family history of phenotypes of XLP was obtained. Perhaps, the illness resulted from a new germlinal mutation of the XLP locus.

**Case H. W.** A 10-year-old boy from Sri Lanka was admitted to Hospital for Sick Children in mid-December with a 2-month history of malaise, pharyngitis, anorexia, headache, and tonsillitis. He had a Paul-Bunnell titer consistent with IM. He was the only child; however, his mother had 4 spontaneous abortions. He was treated with penicillin and ampicillin.

Physical examination revealed a slim boy at the tenth percentile for height and weight. Posterior cervical enlargement of lymph nodes bilaterally and tonsillitis were observed. His tender liver extended to the umbilicus, and splenomegaly was moderate.

Laboratory studies are summarized in Tables 1 and 2. A bone marrow aspirate was done, and histiocytic medullary reticulosis was diagnosed. The direct Coombs test was negative. Total protein had increased to 7.8 and globulin to 5.8 g/dl. Polyclonal elevation of serum immunoglobulin was found. A lymph node biopsy specimen showed extensive activation of macrophages with erythrophagocytosis, immunoblasts, and plasmacytosis. Neovascularization had occurred. Lymphoid follicles were obliterated. CMV titer was 1:4, anti-VCA 1:512, and IgG and IgM <1:10. The lymph node biopsy site became infected with *Staphylococcus aureus*, and cloxacillin was given. He became afebrile and was discharged.

In January, a generalized erythematous puritic rash appeared. His temperature was 39°C, and tender, firm lymph nodes were palpable over the right mandible and left cervical region. There was moderate hepatosplenomegaly. Penicillin and cloxacillin led to resolution of fever. During the remaining 4 months of his life, he was plagued by recurrent fever, lymphadenomegaly, hepatosplenomegaly, pancytopenia, atypical lymphocytosis, and weight loss. Serum immunoglobulin was persistently elevated. Erythrocyte rosettes numbered 74%, IgM and IgD was detected on 11% of cells, and response of lymphocytes to PHA was low.

In April, an open liver biopsy specimen revealed a periportal infiltrate of plasma cells, lymphocytes, and macrophages. To a lesser extent, lymphoid cells were in sinuses, and focal necrosis was present. The findings were consistent with hepatitis of IM. Hybridization studies revealed the EBV genome (Table 2).

He was treated with prednisolone, but he frequently experienced pyoderma, otitis media, and pneumonia. He died 18 months after the onset of the illness. No autopsy was performed.

**Comment.** This boy had the chronic EBV infectious syndrome characterized by relapsing fever, lymphadenomegaly, hepatosplenomegaly, pancytopenia, atypical lymphocytosis, polyclonal hypergammaglobulinemia, and pyogenic infections. Documentation of EBV infection was made serologically, pathologically, and by hybridization studies.

**Case C. F.** A 3-year-old Swedish boy was normal until 'asthmatic bronchitis' developed at 10 months. His 3-year-old sister had succumbed to IM in 1976 (2), and his other sibling and parents were healthy. C. F. had experienced recurrent ataxia in 1978. X-Ray revealed destruction of the left middle ear. The tympanic membrane was incised, and penicillin was given. Residual ataxia was attributed to encephalitis.

Hgb was 11.6 g/dl, erythrocyte sedimentation was 22 mm/hr, and CSF contained 8 lymphoid cells and 26 erythrocytes/µl. Results of other laboratory studies are summarized in Tables 1 and 2.

Progressive spasticity, attacks of drowsiness, and status epilepticus began in the autumn of 1978. No hepatosplenomegaly or lymphadenomegaly was evident. Papilledema was not seen. Hgb was 11.6 g/dl, WBC 10,500/gml, neutrophils 65 bands 23.5, lymphocytes 7.5, monocytes 4, and platelets 264,000/µl. Antibody titers to CMV, Coxsackie B, herpes simplex, rubella, and *Toxoplasma* were negative. EBV antibodies were not tested. Numbers of T- and B-cells in blood and response to PHA were normal. Slightly increased γ-globulin was detected in CSF. During the winter of 1980, he lapsed into a coma, was febrile, developed pancytopenia, and died.

At necropsy, the body was cachectic and slightly icteric. The thymus gland was markedly depleted of thymocytes, and Hassall's corpuscles were calcified. The lymph nodes showed immunoblastic proliferation with plasma cell differentiation. Splenomegaly was marked (270 g; normal, 100 g). Necrosis of T-cell zones in the lymph nodes and splenic lymphoid periarterial sheaths was found. Invasion of blood vessel walls and splenic capsules by atypical lymphoid cells was seen. The bone marrow contained numerous plasma cells and was hypoplastic. Hepatomegaly (775 g; 670 g, normal) due to a periportal and intrasinusoidal infiltration by lymphoid cells including plasma cells was seen. A moderate peribronchiolar infiltrate was present in lungs. The brain weighed 1380 g (normal, 1140 g) and was soft, and the paraventricular white matter was infiltrated by lymphoid cells. The leptomeninges, brain (Fig. 5), spinal cord, nerve trunks (Fig. 6), and skeletal muscle contained a prominent lymphoid infiltrate. The EBV genome was present in spleen (Table 2).

**Comment.** EBV DNA hybridization studies and the autopsy findings of lymphoproliferation implied that both C. F. and his sister (2) had succumbed to EBV infections.

**Case T. T.** An 8½-year-old white boy had recurrent pyoderma. His father had neutropenia of unknown etiology. Physical examination revealed enlarged axillary and right inguinal lymph nodes, and hepatosplenomegaly was not noted.

Laboratory studies are summarized in Tables 1 and 2. He had slight hypogammaglobulinemia, and isohemagglutinins were 1:64. Delayed cutaneous hypersensitivity testing to purified protein derivative was negative but positive for streptokinase-streptodornase, diphertheria, and tetanus. Platelet count was 129,000/µl, reticulocytes numbers 12%, and the direct Coombs test was reactive. X-Ray examination revealed an enlarged hilar lymph node, and a biopsy specimen showed reactive hyperplasia. A thickened capsule, arborized blood vessels, expanded paracortex and numerous activated ger-
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Minal centers, and erythrophagocytosis were evident, consistent with immune hemolytic anemia. Lymphocyte surface marker studies of the lymph nodes showed surface IgM 15%, IgD 9%, total membrane immunoglobulin-bearing cells 23% [(anti-Fab')2]. Sheep erythrocyte-rosetting cells numbered 62% and complement receptor rosettes 8%. Hybridization studies revealed the EBV genome (Table 2), and spontaneous cell lines grew from the lymph node.

Cytoscan (12.5 mg daily) and prednisone (40 mg daily), iron, and folate therapy were given. His WBC returned to the range of 4,000 to 10,000/uL with neutrophils predominating, and lymphopenia in the range of 9 to 18% lymphocytes was noted. Reticulocyte count was from 2.1 to 18.9%. Erythrocyte survival time was 13.2 days (normal, 25 to 30 days). Radionucleotide studies revealed no splenic sequestration. Erythrocyte-bound IgG revealed 25% agglutination versus 10% normal for IgG G. Attempts at decreasing prednisone therapy have resulted in increased hemolysis. Autoantibody was regarded as having anti-ε specificities. Gradually, the hemolytic anemia has subsided.

Comment. Often autoantibody against anti-l antigen appears in blood of patients with acute IM (reviewed in Ref. 19). The presence of mild hypogammaglobulinemia suggests that immunodeficiency had allowed EBV to induce the immune hemolytic anemia.

Case J. W. An 18-year-old white male was seen by Dr. Purtilo in consultation for recurrent IM in 1979. Ten days previously, a lymph node had “popped out” on the back of his posterior cervical region. One week later, he developed severe pharyngitis and generalized cervical lymphadenomegaly. A Monospot test was positive. In addition, he was fatigued and had headaches.

IM had been diagnosed clinically, hematologically, and by Monospot tests in 1976. The disease had persisted for 2 months. During the past 6 years, sinuses and allergies to numerous antigens persisted. His 21-year-old sister has had chronic IM for the past 2 years.

Physical examination revealed moderate cervical lymphadenomegaly and pharyngitis. Laboratory studies are summarized in Tables 1 and 2.

A lymph node biopsy specimen revealed marked immunoblastic transformation with plasma cell differentiation, and a spontaneous lymphoblastoid cell line was obtained from peripheral blood. The lymph node contained the EBV genome (Table 2).

Comment. His persistent lack of anti-EBNA indicates an immunodeficiency. His sister with chronic EBV infection had anti-VCA of 1:80, EA 1:40, and EBNA 1:10 and partial selective IgM deficiency. Both siblings had active EBV infection.

Case B. N. An 18-month-old girl at 10 weeks developed an erythematous rash, persistent fever with hepatosplenomegaly, lymphadenomegaly, and pancytopenia. There was no relevant family history, except her father and brother have heart murmurs.

Her temperature was 37.8°, heart rate 146/min, respirations 24/min, and weight 7.8 kg (< third percentile). A large right anterior cervical lymph node, several smaller left anterior cervical nodes, and shotty firm nodes in inguinal regions were palpated. The liver extended 12 cm below the right costal margin, and the spleen extended to the umbilicus.

Laboratory studies are summarized in Tables 1 and 2. Platelets numbered 70,000/uL, and EBV-specific antibodies were elevated (Table 2). Antibodies for CMV, adenovirus, herpes simplex, respiratory syncytial virus, and parainfluenza were all <1:4. Erythrocyte-rosetting T-cells numbered 32%; however, lymphocyte response to PHA was normal and decreased to pokeweed. Proliferative response in an allogeneic mixed leukocyte response was decreased. Serum IgG and IgM became progressively elevated during a 1-year period (Table 1). A bone marrow aspirate revealed prominent lymphocytosis, normal maturation of erythroid and myeloid elements, and an increased number of megakaryocytes.

Owing to the persistent chronic EBV infection, a splenectomy was performed in May 1980. Hybridization studies revealed one EBV genome equivalent/cell (Table 2). She has improved following splenectomy.

Comment. Onset of chronic EBV infection apparently began at 16 weeks of age. Seldom does EBV infect prior to 5 months because maternal antibodies protect against primary infection (9). We do not know the EBV antibody profile of the mother at parturition.

Discussion

Immunocompetence and the age of the individual at time of infection by EBV determine clinical expressions of EBV infections (reviewed in Ref. 19). Infection of children usually produces silent infection, whereas infection in early adolescence or adulthood often leads to IM. When normal immunocompetent persons become infected by EBV, predictable antibody and cellular immune responses can be measured (10). In contrast, patients with inherited or acquired immunodeficiency disorders possess varying capabilities to defend themselves immunologically against EBV. For example, primary infection of males with XLP results in chronic or fatal IM, acquired agammaglobulinemia or aplastic anemia after IM, or malignant lymphoma in maternally related males within families (1, 3, 5, 6, 15, 17–25). These diseases in males with XLP have prompted Purtilo (17) to postulate that EBV triggers B-cell proliferation which persists due to deficient T- and B-cell responses to the virus. Children may succumb to EBV-induced lymphoproliferative diseases due to various inherited immunodeficiency disorders (2, 15, 26, 28, 34).

Prior to the present study, our evidence supporting the immunodeficiency hypothesis to explain EBV-induced lymphoproliferation in XLP was circumstantial (17, 23–25). Direct proof of EBV infection was lacking, except for one patient (22). Circumstantial evidence of EBV induction of the phenotypes of XLP include the polyclonal elevation of serum immunoglobulin concurrent with IM, heterophil reactions, histopathology, and EBV-specific serological responses. Sakamoto et al. (31) recently demonstrated that 14 affected male survivors of XLP had deficient antibody responses to infection with EBV. Noteworthy is the lack of anti-EBNA in the males. Cellular immune studies of patients with XLP have revealed defective natural killer cell activity (33) and combined variable immunodeficiency (15).

The present study documents that all 7 males with XLP were infected by EBV. Serological profiles of the patients indicated acute or long-term infection by EBV. Spontaneous establishment of lymphoblastoid cell lines from blood and lymphoid tissues in 4 of 5 of the patients who were tested corroborated...
infection by EBV. Demonstration of EBNA in touch imprints and frozen sections of organs from all patients so tested indicated infection, and the presence of the EBV genome by 2 independent molecular probes cRNA/DNA and vDNA/DNA was established (reported in detail in Ref. 29). The magnitude (1 to 33 EBV genome equivalents/cell) has not been found in lymphoproliferative diseases other than Burkitt lymphoma (14, 35). However, recently, lymphoproliferative diseases in immunodeficient patients have been associated with the EBV genome in lymphoid tissues (2, 7, 26, 28, 29, 34). In summary, proof of infection by EBV was demonstrated by multiple independent analyses.

Lymphoblastoid cells transformed by EBV from patients with IM are polyclonal and diploid, whereas EBV-carrying Burkitt lymphoma cells are monoclonal and almost always show a specific 14q+ cytogenetic change (reviewed in Ref. 12). None of the 7 patients with XLP reported had developed unequivocal malignant lymphoma. K. W. had developed a pseudolymphoma of lung, and A. M. had a florid immunoblastic proliferation in cervical lymph glands resembling immunoblastic sarcoma. We must emphasize that other cases of XLP, not reported here, have been true malignant lymphomas (reviewed in Ref. 20). Purtilo (17) has postulated that males with profound immunodeficiency to EBV die from a polyclonal B-cell proliferation which infiltrates vital organs and kills within a few weeks of infection. These patients exhibit classical clinical features of IM; however, they may not exhibit a heterophil antibody response, and only low titer EBV-specific antibodies can be detected. The peripheral blood may show predominantly plasmacytoid lymphocytes (Fig. 1) rather than classical Downey lymphocytes (19).

Owing to these atypical features, IM may not be recognized. D. S., B. N., and H. W. did not show classical features of IM but had the chronic IM syndrome. In such patients, establishing spontaneous lymphoblastoid cell lines from blood and tissues, staining of lymphoid cells for EBNA, and using EBV DNA and RNA hybridization probes for the virus genome are indicated. Documentation of EBV infection by hybridization was of great value in all the patients reported here, especially in V. G. and R. T. who had lacked the capacity to mount EBNA responses.

Opportunity for documentation of the EBV genome in malignant lymphomas of patients with XLP has not yet been possible. The probability that EBV is responsible for most of the lymphomas in patients with XLP is very high. Our collaborative studies with Hanto et al. (7, 29) have demonstrated significant quantities of the EBV genome in immunoblastic sarcomas in immunosuppressed renal transplant recipients. Children with ataxia telangiectasia (28) and the combined immunodeficiency syndrome (26) have developed EBV-carrying lymphoproliferative diseases.

In summary, the results of this study of 7 boys with XLP and 7 other cases of life-threatening lymphoproliferative diseases in immunodeficient patients support the hypothesis that EBV can prove fatal in immunodeficient patients (18, 20). Moreover, typical antibody responses to EBV may not be found. Depending on whether immunodeficiency antedates primary infection by EBV or follows infection, the antibody titers to the virus will often be unusually low or high, respectively (reviewed in Ref. 30). Clinicians ought to resist the urge to diagnose malignant histiocytosis or atypical leukemia before they have excluded underlying immunodeficiency and herpesviral infections.

We urge that, when immunodeficient persons develop life-threatening lymphoproliferative diseases, comprehensive studies be undertaken including: (a) family pedigree analysis, immunological profile including quantitation of serum immunoglobulins, and EBV-specific antibody studies of the patient and family members; (b) deep-throat gargle to test for transformation of cord B-cells by EBV; (c) spontaneous lymphoblastoid transformation in vitro of peripheral blood and lymphoid cells derived from lymphoma, lymphoid, and other tissues; (d) cell surface marker studies of lymphoid cells to demonstrate clonality; (e) EBNA staining of touch imprints and frozen sections using appropriate controls; (f) direct karyotype of lymphoma, lymphocytes in blood, and other tissues; and (g) hybridization studies of fresh tissues (frozen at −70°) to demonstrate the EBV genome. If sufficient tissue is available, cRNA/DNA, vDNA/DNA, and in situ hybridization studies ought to be performed.

Optimal information can be derived when these determinations are done simultaneously. Eventually, data should become available to test the hypothesis that polyclonal proliferation converts to a monoclonal lymphoma when a specific cytogenetic error occurs (12, 18, 20).

Accumulating evidence suggests that EBV can induce fatal or life-threatening lymphoproliferative diseases in immunodeficient patients (1-3, 6, 7, 15, 17–26, 28, 29, 34). We must learn to prevent, diagnose, and treat the various EBV-induced diseases with immunotherapy, antiviral therapy, genetic counseling, and genetic or immunological reconstitution.

Acknowledgments

We thank Linda Dickman and Word Processing at the University of Massachusetts Medical Center for typing the manuscript and Peter Healey for photography. Thanks are owed to Dr. Mark Ballow for contributing Case J. W. and Dr. David Gang for Case B. P. Especially, we thank the families and their physicians for their continuing assistance.

References

R. M. mounted an effective immune response to Epstein-Barr virus, whereas A. M. did not and succumbed to IM (see Tables 1 and 2).

Fig. 2. A cervical lymph node from R. M. x 3 (bottom). Photomicrograph (inset at left) shows rather uniform small lymphocytes, H & E, x 450. In contrast, an enlarged pulmonary hilar lymph node from A. M. is shown, x 3 (top). Photomicrograph (inset at right) shows plasma cells. H & E, x 450. The brothers both had XLP.
Documentation of Epstein-Barr Virus Infection in Immunodeficient Patients with Life-threatening Lymphoproliferative Diseases by Clinical, Virological, and Immunopathological Studies


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