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 EBV 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, B-cell 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 deaths of 6 males in the Duncan kindred with fatal IM, acquired agammaglobulinemia, chronic or fatal IM, pseudolymphoma, and B-cell malignant lymphomas such as Burkitt’s lymphoma or immunoblastic sarcoma (17-25, 29, 31).

...
EBV Infections in Immunodeficient Patients

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° in 5% CO₂. The cultures were examined weekly for outgrowth of colonies of lymphoblasts.

EBV staining of air-dried touch imprints of lymphoid organs and 6-μm-thick frozen sections were cut in a cryostat, fixed in (-20°) 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. Purtill, 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°, pulse 120/min, respirations 40/min, blood pressure 110/60 mm Hg, and weight 40.5 kg. 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. Bone marrow was depleted of erythroid and myeloid precursors, but plasmacytosis and extensive histiocytosis 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. Purtill in 1977 and had hypogammaglobulinemia (Table 1). During his brother’s fatal IM, R. M. developed pharyngitis and elevated anti-EA and -CVA antibodies (Table 2). A cervical lymph node was biopsied, divided, and frozen at −70° 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 Purtill 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°, and moderate hepatosplenomegaly. Tables 1 and 2 summarize laboratory stud-

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### 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>mg/dl</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. M.</td>
<td>16</td>
<td>M</td>
<td>XLP, hypoy⁸</td>
<td>Fatal IM, IBS, XLP</td>
<td>+</td>
<td>9,100</td>
<td>12</td>
<td>8</td>
<td>48 Atypical</td>
<td>5/29/77</td>
<td>745</td>
<td>183</td>
</tr>
<tr>
<td>R. M.</td>
<td>15</td>
<td>M</td>
<td>XLP, hypoy</td>
<td>Chronic EBV, hypoy, XLP</td>
<td>–</td>
<td>9,100</td>
<td>40</td>
<td>0</td>
<td>40 Atypical</td>
<td>5/29/77</td>
<td>1300</td>
<td>87</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 Many plasmacytoid</td>
<td>2/19/80</td>
<td>640</td>
<td>310</td>
</tr>
<tr>
<td>K. W.</td>
<td>6</td>
<td>M</td>
<td>Acute leukemia</td>
<td>Hypoy, pseudolymphoma</td>
<td>–</td>
<td>13,300</td>
<td>25</td>
<td>10</td>
<td>70 Basophil</td>
<td>6/10/75</td>
<td>1150</td>
<td>145</td>
</tr>
<tr>
<td>V. G.</td>
<td>4</td>
<td>M</td>
<td>Neutropenia</td>
<td>Neutropenia, hypoy, malignant lymphoma, aplastic anemia, and XLP</td>
<td>–</td>
<td>2,900</td>
<td>45</td>
<td>8</td>
<td>50 Monocytes</td>
<td>9/8/78</td>
<td>190</td>
<td>16</td>
</tr>
<tr>
<td>B. P.</td>
<td>7</td>
<td>M</td>
<td>Stevens-Johnson syndrome</td>
<td>Fatal IM, XLP</td>
<td>ND</td>
<td>8,400</td>
<td>65</td>
<td>3</td>
<td>28 Monocytes</td>
<td>ND</td>
<td>ND</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>60</td>
<td>2</td>
<td>4/9/80 Atypical lymphocytosis</td>
<td>ND</td>
<td>ND</td>
<td>Maternal uncle died of 'Hand-Schüllter-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 Monocytes</td>
<td>4/4/77</td>
<td>328</td>
<td>660</td>
</tr>
<tr>
<td>R. T.⁹</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 Many plasmacytoid</td>
<td>ND</td>
<td>440</td>
<td>732</td>
</tr>
<tr>
<td>H. W.</td>
<td>10</td>
<td>M</td>
<td>Chronic IM</td>
<td>Fatal IM</td>
<td>PBI</td>
<td>4,800</td>
<td>39</td>
<td>0</td>
<td>59 6 Atypical</td>
<td>4/4/77</td>
<td>328</td>
<td>660</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 Monocytes</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>T. T.</td>
<td>8½</td>
<td>M</td>
<td>Immune hemolytic anemia</td>
<td>Hyperplastic lymph node, hypoy</td>
<td>–</td>
<td>2,900</td>
<td>60</td>
<td>7</td>
<td>17</td>
<td>5/9/79</td>
<td>440</td>
<td>66</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>20 Monocytes</td>
<td>7/6/79</td>
<td>220</td>
<td>20</td>
</tr>
<tr>
<td>B. N.</td>
<td>1.5</td>
<td>F</td>
<td>Congenital EBV infection</td>
<td>Chronic IM syndrome</td>
<td>–</td>
<td>3,200</td>
<td>50</td>
<td>10</td>
<td>50 Monocytes</td>
<td>9/10/79</td>
<td>320</td>
<td>48</td>
</tr>
</tbody>
</table>

⁸ hypoy, hypogammaglobulinemia; IBS, immunoblastic sarcoma; ND, not done; PBI, Paul-Bunnell positive.

⁹ 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.

Documentation of EBV infections in patients with life-threatening EBV-induced diseases with EBV-specific serology, cell line formation, EBNA staining, and DNA hybridization

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnoses</th>
<th>EBV antibodies</th>
<th>Tissues</th>
<th>Spontaneous cell lines</th>
<th>EBNA touch imprints</th>
<th>Renaturation vDNA/DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. M.</td>
<td>Hypop, fatal IM, XLP</td>
<td>EA:1:10 VCA:1:10 EBNA:&lt;1:2</td>
<td>Spleen</td>
<td>ND + 1.1</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Parotid</td>
<td>ND 33</td>
<td>ND</td>
</tr>
<tr>
<td>R. M.</td>
<td>Hypop, chronic IM, XLP</td>
<td>EA:1:40 VCA:1:320 EBNA:1:2</td>
<td>Lymph node</td>
<td>ND</td>
<td>+ 6</td>
<td>2</td>
</tr>
<tr>
<td>V. G.</td>
<td>Neutropenia, hypop, malignant lymphoma, aplastic anemia, XLP</td>
<td>EA:&lt;1:5 VCA:&lt;1:5 EBNA:&lt;1:2</td>
<td>Lymph node</td>
<td>ND</td>
<td>- 1</td>
<td>3</td>
</tr>
<tr>
<td>K. W.</td>
<td>Acquired hypop after IM and then pseudolymphoma of lung, XLP</td>
<td>EA:&lt;1:2 VCA:&lt;1:2 EBNA:&lt;1:2</td>
<td>Pulmonary lymphoma</td>
<td>ND</td>
<td>ND 9</td>
<td>ND</td>
</tr>
<tr>
<td>L. G.</td>
<td>Fatal IM, XLP</td>
<td>EA:1:20 VCA:1:160 (IgM) EBNA:&lt;1:2</td>
<td>Spleen</td>
<td>ND + 40-50%</td>
<td>4 ND</td>
<td></td>
</tr>
<tr>
<td>B. P.</td>
<td>Fatal IM, XLP</td>
<td>ND ND ND</td>
<td>Liver</td>
<td>ND ND 8</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>J. C.</td>
<td>Fatal IM, XLP</td>
<td>ND ND ND</td>
<td>Skin</td>
<td>ND ND 1</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>R. T.</td>
<td>Fatal IM, XLP</td>
<td>EA:&lt;1:5 VCA:1:10 EBNA:&lt;1:2</td>
<td>Lymph node</td>
<td>ND ND 3</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>J. W.</td>
<td>Recurrent IM</td>
<td>EA:1:40 VCA:1:80 EBNA:&lt;1:2</td>
<td>Lymph node</td>
<td>ND ND 14</td>
<td>ND</td>
<td></td>
</tr>
</tbody>
</table>

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 demonstration of the 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, gastroenteritis appeared followed 2 weeks later by fever, pharyngitis, malaise, vomiting, and a rash.

On hospitalization, he was listless, had a maculopapular rash on his arms, and no organomegaly. Results of studies are summarized in Tables 1 and 2. The heterophil test was negative. Total protein was 5.2 g/dl with albumin 2.9 and globulin 2.3 g/dl. A skin biopsy specimen revealed numerous lymphocytes in the epidermis and dermis, especially around the blood vessels. The Coombs test was negative. The bone marrow showed marked erythroid hypoplasia and Hgb decreased to 4.9 g/dl. He was transfused with 2 units of whole blood and discharged.

He was rehospitalized a week later with fever, lymphadenomegaly, anemia, (Hgb, 5.4 g/dl), and a WBC of 8200/µl, and 85% lymphocytes including atypical plasmacytoid forms, 14% monocytes, and 1% eosinophils were detected. Serum immunoglobulins were elevated slightly (Table 1). A celluilitis of the hand was treated with methicillin and Keflex. A bone marrow aspiration sample was interpreted as containing numerous immature forms, and thus a diagnosis of acute leukemia was made and was treated with multiple courses of vincristine, 1-β-arabinofuranosylcytosine, Cytoxan, prednisolone, and Thioguan. He developed pneumonia and a generalized rash during the third month of treatment. He responded to antibiotics, and the dose of prednisolone was increased.

Dr. Purtilo saw him in consultation in 1979, and a hacking cough was noted. 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 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 tonsilar 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 y-globulin.

He was well for 2 weeks, and then rectal hemorrhage appeared. Blood platelets were 24,000/μl, and prothrombin 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.

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 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.

The postoperative course was marked by persistent pancytopenia, progressive visual loss, and septicemia. He was treated with appropriate antibiotics, blood transfusions, and y-globulin. Two weeks postoperatively, a slightly purpuric rash was noted on his trunk and proximal extremities. A biopsy specimen of skin revealed features compatible with a mild graft-versus-host disease. Progressive hepatosplenomegaly and elevated hepatic enzymes were noted. He expired 13 months after onset of illness.

Autopsy revealed a very depleted thymus gland with calcified Hassall’s corpuscles. T-Cell zones in lymph nodes and spleen were depleted. Slight plasmacytosis was noted in hematopoietic organs. Bone marrow was hypoplastic and macrophages with erythrophagocytosis were prominent. A mild lymphocyte infiltration was present in various visceral organs. The lungs contained multinucleated giant cells with uniformly distributed chromatin within the nuclei. No viral inclusions were seen. Serum samples tested at various times of his illness all lacked detectable EBV-specific antibodies (Table 2); however, numerous EBV genomes were detected in many tissues by EBV DNA hybridization techniques (Table 2).

Comment. The patient’s cousin has acquired agammaglobulinemia of XLP rather than Bruton’s type. The spectrum of phenotypes seen in V. G. ranged nearly the full range of XLP expressions. Diagnosis would not have been possible without the EBV DNA hybridization studies.

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°, heart rate 116, and respiratory rates 20/min. No lymphadenomegaly or organomegaly was detected. Marked choroidal effusion was found. No papilledema 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 insipidis 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 y-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).

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 4 1/2-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 generalized maculopapular rash, heart rate 160/min, respirations 28/min, and 39° 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, papilledema occurred. Lumbar puncture revealed 18 atypical lymphocytes in CSF, and his WBC increased to 51,000/μl. Hepatic biopsy showed periporal infiltration, and the direct Coombs’ test was positive. Pancytopenia ensued. Prednisolone was given, he improved for several weeks, and his WBC had become nearly normal. He died suddenly with hematemesis while convalescing at home 6
months after illness began.

Autopsy revealed a Cushingoid 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 scurvy 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 pancytopenia, 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 biopsy specimen showed fibrosis interspersed with sheets of cells with large pale nuclei and abundant foamy cytoplasm. Malignant histiocytosis was diagnosed tentatively.

The liver and spleen were enlarged 3-fold, and splenic periar-

ticular T-cell zones were necrotic. A rim of plasma cells and immature lymphoid cells surrounded the necrotic sheaths. The spleen became palpable and firm, and enlarged nodes appeared in the supraventricular fossa. Bone marrow showed dense infiltration with ‘‘histiocytic’’ cells, and hence the diagnosis of malignant histiocytosis was retained. Treatment with vincristine and prednisolone relieved bone pain. He remained anemic and thrombocytopenic, and thus he experienced recurrent hemorrhage. His EBV IgG VCA titer was 1:160 and CMV was 1:128. The possibility of EBV-associated disease was therefore pursued. Later, his IgG anti-VCA titer increased to 1:1280, and IgM VCA titer was 1:20, anti-EA 1:80, and EBNA 1:20 (Table 2). Circulating sheep erythrocyte-rosetting T-cells numbered 18%, erythrocyte + antibody + complement-rosetting cells 17%, surface IgM 10%, and IgD 22%. Response to concanavalin A was reduced. Natural killing against target K562 at a target:cell ratio of 50:1 was 19%, and no evidence of killing against the EBV-infected target 8392 was found. Serum IgA was borderline low. Erythrocyte adenose deaminase and nucleoside phosphorylase levels were also normal. Before the immunology and virology results became available, cyclophosphamide and Adriamycin were provided. Lymphadenomegaly and splenomegaly resolved, but he developed intractable hemorrhagic cystitis and died.

Autopsy revealed widespread petechial hemorrhages. The thymus gland was involuted and contained calcified Hassall’s corpuscles. Enlarged lymph nodes were infiltrated by uniform immature lymphoid cells with enlarged nuclei, 2 to 3 nucleoli, and scanty cytoplasm. The nodal architecture remained intact, and lymphatic sinuses contained erythrophagocytosis and hemosiderin. Lymphoid cells infiltrated splenic red (Fig. 4) and white pulp and were present in a patchy distribution in bone marrow. The marrow was hypoplastic. Activated macrophages and increased numbers of plasma cells were evident. The liver showed moderate lymphoid infiltration of periportal regions and activated Kupffer cells. EBV hybridization studies of spleen revealed the EBV genome (Table 2).

Comment. Among misdiagnoses of severe EBV infections in immunodeficient persons were leukemias (Case K. W.) and malignant histiocytosis (Case D. S.). The latter patient had severe chronic EBV infection characterized by recurrent generalized malaise, fever, hepatosplenomegaly, and pancytopenia. However, the uniformity of the lymphoid cells suggests that a disease had occurred. Cell surface studies and karyotype for clonality had not been done. Hence, a final diagnosis is not possible.

Case R. T. A 2 1/2-year-old white boy was in good health until he had developed a generalized ‘‘welt-like’’ rash, irritability, and a temperature of 38.7°. Amoxicillin and aspirin 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 no 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 periar
terior T-cell zones were necrotic. A rim of plasma cells and immature lymphoid cells surrounded the necrotic sheaths. 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-
niges 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 germinal 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°, 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, atypical lymphocytosis, and weight loss. Serum immunoglobulin was persistently elevated. Erythrocyte rosettes numbered 74%, lgM and lgD 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 sinususes, 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, rubeola, 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, diphtheria, and tetanus. Platelet count was 129,000/µl, reticulocytes numbered 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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4 This unfortunately proved to be correct. The 10-month-old brother born of a different father recently succumbed to IM. This and other studies indicate that the family had XLP.
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.

Cytoxan (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/μl 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). Radiouclide 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-e 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/μl, 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 10 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).

Purtillo (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°C) 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.

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References


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


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