

## Case Report

# Fulminant EBV-driven CD8 T-cell Lymphoproliferative Disorder Following Primary Acute EBV Infection: A Unique Spectrum of T-Cell Malignancy

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**Abstract:** Fulminant Epstein-Barr virus (EBV)-driven clonal T-cell lymphoproliferative disorder (T-LPD) is rare and most patients are of Asian origin. The disease usually develops shortly after primary acute EBV infection and the mechanism remains poorly understood. Here we report such a rare case in a 28-year-old Caucasian female with systemic lupus erythematosus (SLE). Immunophenotypic and molecular studies revealed that the proliferating lymphoid cells displayed a CD8<sup>+</sup> T-cell phenotype with clonal rearrangement of the T-cell receptor gamma gene. Epstein-Barr virus-encoded RNA was also observed in the clonal lymphoid cells by in situ hybridization. The patient subsequently developed fatal virus-associated hemophagocytic syndrome one month after the primary acute EBV infection. The case represents the first report of fulminant EBV-driven CD8<sup>+</sup> T-LPD occurring in an immunocompromised Caucasian SLE patient. This study, along with studies of similar Asian cases reported in the literature, suggests that dysregulated immunity due to either acquired or genetically determined susceptibility may result in an abnormal response to primary EBV infection and contribute to the pathogenesis of EBV-mediated fatal T-LPD.

**Key Words:** Fatal infectious mononucleosis, Epstein-Barr virus, T-cell lymphoproliferative disorder, virus-associated hemophagocytic syndrome, hemophagocytosis, systemic lupus erythematosus

## Introduction

Epstein-Barr virus (EBV) is a member of the herpes virus family that infects B-cells in the majority of individuals during their early childhood in developing countries. Infants and young children with primary EBV infection are generally asymptomatic, but adolescents and adults usually develop infectious mononucleosis (IM), a self-limited lymphoid proliferation with a benign clinical course. This is due to regulated immune surveillance by the polyclonal proliferation of CD8<sup>+</sup> cytotoxic T-cells which themselves are free of EBV [1, 2].

Fatal infectious mononucleosis (FIM) is an uncommon disease and is characterized by fever, rash, generalized lymphadenopathy, hepatosplenomegaly and blood cytopenia. FIM occurs sporadically in immunocompetent patients, but develops with high incidence in patients with X-linked lymphoproliferative disease (XLP, Duncan's disease) due to

mutations in the SH2 domain-containing 1A gene (SH2D1A) [1-4]. Most FIM develops shortly after primary acute EBV infection and is almost always of T-cell lineage. Biologically, a defect in T-cell mediated immune regulation results in uncontrolled immune responses with extensive infiltration of lymphoid cells in marrow, lymph nodes, liver and spleen [5-9]. The lesion is often associated with cellular necrosis, histiocytic hyperplasia and virus-associated hemophagocytic syndrome (VAHS), which has been attributed to the defective or imbalanced cytotoxic T-cell response, as well as the vascular damage mediated by chemokines [10-11]. EBV is the virus most frequently found in VAHS, which occurs primarily in immunosuppressed patients and has a fatal outcome with a median survival of six weeks [5-8, 10, 12].

Fulminant EBV-driven clonal T-LPD in immunocompetent patients is very rare. Almost all reported cases were of Asian origin

and some patients lacked serologic responses to infected virus, suggesting that geographic location and ethnicity associated with a specific vulnerability to EBV infection may play an important role [13-22]. The clinical presentation of this fulminant EBV<sup>+</sup> clonal T-LPD significantly overlaps with the classical form of FIM, resulting in difficulties in differential diagnosis. The biological relationship of fulminant EBV<sup>+</sup> clonal T-LPD to classical FIM remains undefined. In classical FIM, an antigen-specific CD8<sup>+</sup> cytotoxic T-cell response is crucial to control EBV-infected B-lymphocyte proliferation [7]. However, the role and mechanism of EBV infection in the pathogenesis of fulminant EBV<sup>+</sup> clonal T-LPD are poorly understood.

In addition to FIM, EBV infection has also been etiologically implicated in the development of a variety of human cancers, including Burkitt lymphoma [1], certain forms of natural killer (NK)-cell lymphomas [23], Hodgkin lymphoma [24-26], nasopharyngeal carcinoma [27], smooth muscle tumors and gastric cancers [28-30]. It has been particularly implicated as the causative agent in a wide range of B-cell lymphomas in immunocompromised patients, including post-transplant recipients and those with inherited or acquired immunodeficiencies [29, 31]. The clonal EBV infection has been confirmed in the tumor cells of these malignancies, supporting a causative role of EBV in tumorigenesis.

Here we report an EBV<sup>+</sup> CD8<sup>+</sup> clonal T-LPD in a 28-year-old Caucasian female with systemic lupus erythematosus (SLE) after primary acute EBV infection. The abnormal proliferation of T-cells was evaluated by immunohistochemistry, in situ hybridization, flow cytometry, cytogenetics and molecular analysis. To the best of our knowledge, this case represents the first report of a fulminant EBV<sup>+</sup> clonal CD8<sup>+</sup> T-LPD in a Caucasian SLE patient, and the results suggest that dysregulated immunity may contribute to the pathogenesis of EBV-mediated fatal T-LPD.

## Materials and Methods

### *Histological and Immunohistochemical Studies*

Tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, and 4 µm sections were cut and stained with

hematoxylin and eosin (H&E) for histological evaluation. Immunohistochemical stains were also performed on formalin-fixed, paraffin-embedded tissue sections. Briefly, after deparaffinization in xylene and rehydration in graded alcohols, endogenous peroxidase was blocked with 3% hydrogen peroxide. Antigen retrieval was performed in citrate buffer, pH 6.0, as appropriate for the antibodies. After rinsing in phosphate-buffered saline, antibodies against CD2 (DAKO), CD3 (Ventana Biotek), CD5 (Biocare), CD7 (DAKO), terminal deoxynucleotidyl transferase (Biocare), CD30 (Ventana Biotek), ALK-1 (Biocare) were employed for immunohistochemical stains. These stains were performed on a Ventana ES automated immunostainer (Ventana Biotek, Tucson, AZ) using an avidin-biotin-peroxidase complex method.

### *In Situ Hybridization for EBV-encoded Nuclear RNA*

In situ hybridization for EBV-encoded RNA (EBER) was performed according to the manufacturer's instructions on a Ventana ES automated immunostainer using a streptavidin-biotin peroxidase detection system [32]. The optimum probe concentration was titrated to eliminate background staining while retaining good signal strength and contrast. Negative controls consisted of stains with omission of the EBV probes in the hybridization protocol. The quality of mRNA was estimated in tissue sections using poly A probes.

### *Flow Cytometric Immunophenotyping*

Bone marrow and lymph node specimens were processed using previously described methods [33]. At least 30,000 events were routinely acquired using a FACSCalibur (4-color) flow cytometer (Becton Dickinson [BD] Immunocytometry Systems, San Jose, CA) with CellQuest software (BD). All antibodies were purchased from BD Biosciences (except kappa and lambda light chains from DAKO) and were used according to manufacturer's recommendations. Monoclonal antibodies and fluorescent labels were specified as follows: fluorescein isothiocyanate-conjugated antibodies: CD5, CD7, CD8, CD103, TdT and kappa light chain; phycoerythrin-conjugated antibodies: CD19, CD22, CD23, lambda light chain and CD56; allophycocyanin-conjugated antibodies: CD2, CD4, CD10, CD11c, and

CD38; peridinin chlorophyll protein-conjugated antibodies: CD3, CD20 and CD45. Fluorochrome-conjugated surface IgG1 monoclonal antibody was used as an isotypic control. Data were collected on FACSCalibur flow cytometer and cluster analysis was performed using Paint-a-Gate software (BD).

#### PCR and Cytogenetic Analysis

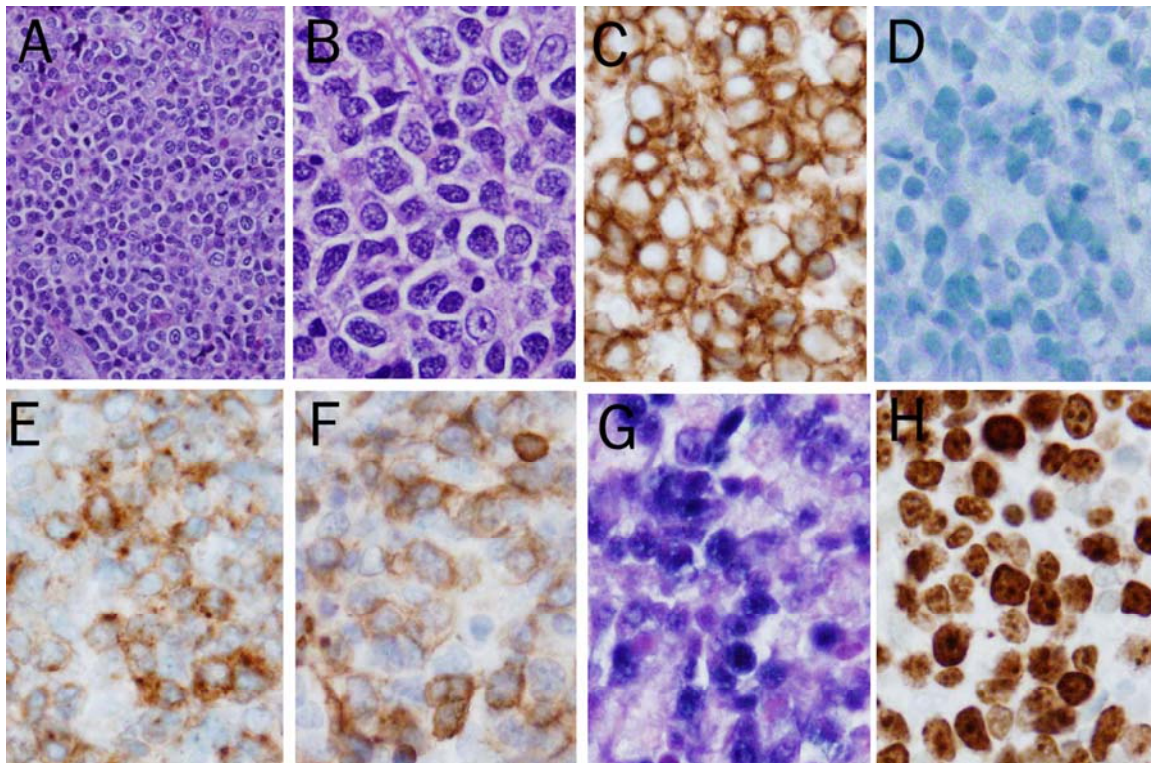
Genomic DNA was extracted from paraffin-embedded tissue sections using the QIAamp DNA Mini kit (QIAGEN, Valencia, CA). PCR for T-cell receptor (TCR) gamma gene and immunoglobulin heavy chain gene rearrangements was performed at the Mayo Medical Laboratories (Rochester, MN). Conventional cytogenetic analysis was performed on direct bone marrow cultures using standard techniques. Twenty metaphase cells from overnight and short-term cultures were analyzed using procedures described in The AGT Cytogenetics Laboratory Manual with

modifications [34]. The karyotype was expressed according to the International System for Human Cytogenetic Nomenclature [35].

#### Results

##### *Premortem Findings*

A 28-year-old woman with a history of SLE for nine years presented with fever, headache, splenomegaly and cervical lymphadenopathy. An acute IM was diagnosed and her medications for SLE (hydroxychloroquine, methotrexate and folic acid) were discontinued. She experienced partial improvement for one week, and then developed high fever and upper abdominal pain. A computerized tomographic scan revealed cholecystitis and diffuse lymphadenopathy. The patient underwent cholecystectomy. However, her fever and malaise persisted with decline of her



**Figure 1** Histological and immunohistochemical features of fulminant EBV-driven CD8<sup>+</sup> T-LPD in the peri-cystic duct lymph node. **A.** H&E section shows complete effacement of the nodal architecture by atypical lymphoid cells (400x). **B.** The atypical lymphoid cells demonstrate slightly irregular hyperchromatic nuclei and some with prominent nucleoli (1000x). The atypical lymphoid cells show strong CD3, but not CD20 immunoreactivity (**C, D**). **E** and **F.** The atypical lymphoid cells show partial loss of immunoreactivity to CD5 and CD7, respectively. **G.** The atypical lymphoid cells show strong reactivity with EBV-encoded RNA by in situ hybridization. **H.** The atypical lymphoid cells show a high proliferative index (immunostain with Ki-67).

hemoglobin and platelet count over the following days. The gall bladder was found to exhibit chronic cholecystitis, whereas the pericystic duct lymph node was initially diagnosed as “diffuse large cell lymphoma” at an outside hospital. A diagnosis of fulminant EBV<sup>+</sup> clonal CD8<sup>+</sup> T-LPD was made 7 days later at the University of Wisconsin Hospital and Clinics, where she was treated with allopurinol and two doses of Rituximab. Bone marrow biopsy at that time showed extensive involvement by fulminant EBV<sup>+</sup> clonal CD8<sup>+</sup> T-LPD. Treatment with antibiotics, fentanyl, hydrocortisone and supportive care was given. Her subsequent course was complicated by extensive disease progression, renal failure, coagulopathy, and respiratory distress symptoms. She expired two months after her initial presentation.

Laboratory findings on admission revealed a white blood cell count of  $4.8 \times 10^9/L$  (81% polymorphonuclear cells, 15% lymphocytes, 3% immature myeloid cells and 1% monocytes), hemoglobin 7.4 g/dL, hematocrit 22% and a platelet count of  $88 \times 10^9/L$ . Reticulocyte count was  $10 \times 10^9/L$ . Serum lactate dehydrogenase (LDH) was markedly elevated (5760 IU/L; normal reference range 105-230 IU/L). Liver function test was also abnormal with following results: total bilirubin, 8.4 mg/dL (normal: 0.0-0.4 mg/dL); direct bilirubin, 6.7 mg/dL (normal: 0.0-0.3 mg/dL); alkaline phosphatase (AP), 386 U/L (normal: 35-130 U/L); gamma glutamyl transferase (GGT) 245 U/L (normal: 0-40 U/L); aspartate transaminase (AST), 3618 U/L (normal: 0-40 U/L); and alanine aminotransferase (ALT), 849 U/L (normal: 0-65 U/L). Triglycerides were elevated at 385 mg/dL (normal: 3-149 mg/dL). Serum ferritin was >10,000 (normal: 20-300 ng/mL). Antibodies to EBV capsid (VCA), early (EA) and nuclear (EBNA) antigens showed IgG (+) for anti-VCA, anti-EA (-) and anti-EBNA (-), consistent with a primary acute infection. Antibody and quantitative PCR for CMV were negative. Antibodies for SLE, including anti-SSA, anti-SSB, anti-SM/RNP, anti-Smith, anti-cardiolipin and anti-ds DNA antibodies, were all negative.

The peri-cystic duct lymph node showed a complete effacement of the normal nodal architecture by small to intermediate-sized lymphoid cells. These lymphoid cells had round to slight irregular hyperchromatic nuclei and small prominent nucleoli. Scattered large cells with prominent nucleolus were also seen.

Occasional mitosis and apoptotic bodies were noted. Micro-foci of necrosis were also present (**Figures 1A and 1B**). The concurrent bone marrow biopsy was hypercellular with erythroid hypoplasia, left-shifted myeloid and dysmegakaryocytic hyperplasia. The atypical lymphoid cells constituted 30% of the cellular components and they were intermediate in size with higher nuclear to cytoplasmic ratio and dense chromatin (**Figures 2A and 2B**).

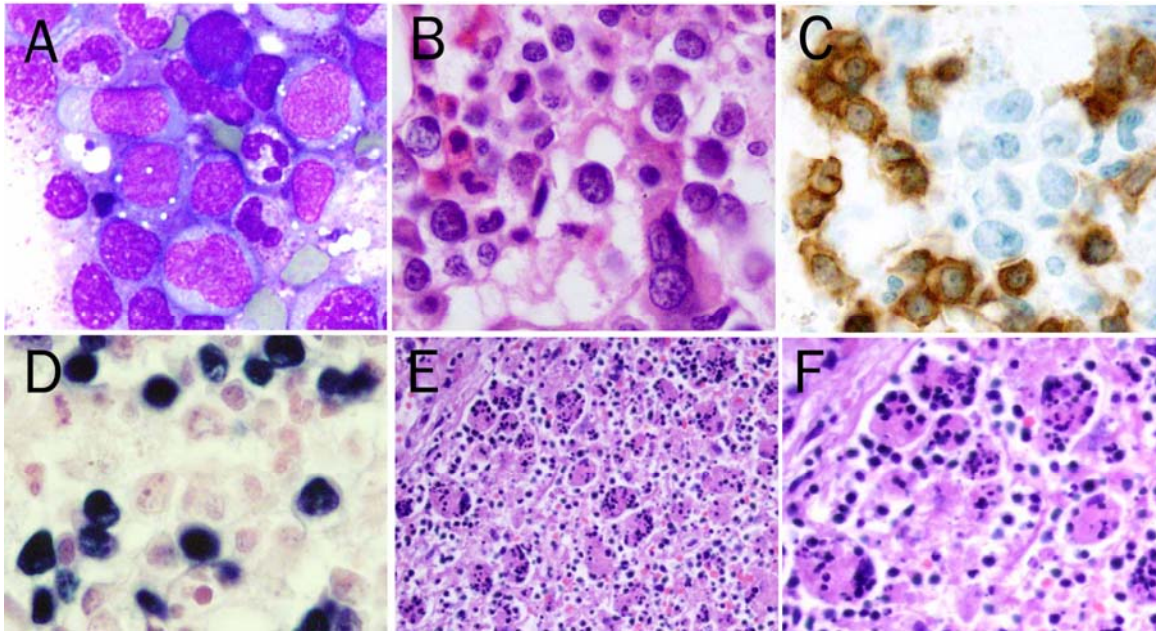
Immunohistochemistry showed these lymphoid cells were positive for CD2, CD3, CD5, CD7 and CD8; but were negative for CD4, CD20, BCL-2, BCL-6, cyclin D1, CD30, ALK-1, and TdT (**Figures 1C-1F; Figure 2C**). Partial loss of antigen expression was noted for CD5 and CD7 in the lymphoid cells. In situ hybridization confirmed that these T-cells were positive for EBV RNA (**Figures 1G and 2D**), and showed a nearly 100% proliferation index by Ki-67 immunostain (**Figure 1H**).

Flow cytometric immunophenotyping demonstrated a predominant population of mature CD8<sup>+</sup> T-cells that express CD2, CD5 and CD7 with lower density CD3 expression compared to normal CD4<sup>+</sup> T-lymphocytes (**Figure 3A**). Normal B-cells were nearly absent. Molecular studies performed at the Mayo Medical Laboratories showed a clonal T-cell receptor gamma gene rearrangement (**Figure 3B**). Immunoglobulin heavy chain gene rearrangement was polyclonal. Conventional cytogenetic analysis on the marrow aspirate revealed a normal female karyotype.

#### *Autopsy Findings*

The liver was markedly enlarged (2,400 g) with infiltrates of mostly small lymphoid cells in the periportal and centrilobular areas. There were interspersed foci of hepatocyte necrosis with ghosted nuclei, cholestasis, macrovesicular steatosis and vascular congestion. Spleen was mildly enlarged (420 g) due to chronic congestion and prominent infiltration of atypical lymphoid cells in the parenchyma. Diffuse karyorrhexis was observed in the white pulp, mainly in the follicular areas. In contrast, the periarterial lymphoid sheath corresponding to the T-cell regions appeared to be hypocellular. The follicles of the spleen were essentially normal, some of which showed diminished germinal centers. No karyorrhexis was observed in the red pulp.





**Figure 2** Histological and immunohistochemical features of EBV-driven CD8<sup>+</sup> fulminant T-cell lymphoproliferative disorder and hemophagocytosis in the bone marrow and lymph node. **A.** The bone marrow aspirate smear shows a small cluster of neoplastic cells with basophilic cytoplasm and conspicuous nucleoli (Wright stain, 1000x). **B.** The bone marrow biopsy demonstrates interstitial distribution of neoplastic cells that are difficult to differentiate from immature myeloid cells (H&E stain, 1000x). **C.** CD3 immunostain highlights neoplastic T-cells. **D.** The tumor cells show strong reactivity with EBV-encoded RNA by in situ hybridization. **E** and **F.** The lymph node is effaced by proliferation of histiocytes with extensive hemaphagocytosis (H&E, 400x and 1000x, respectively).

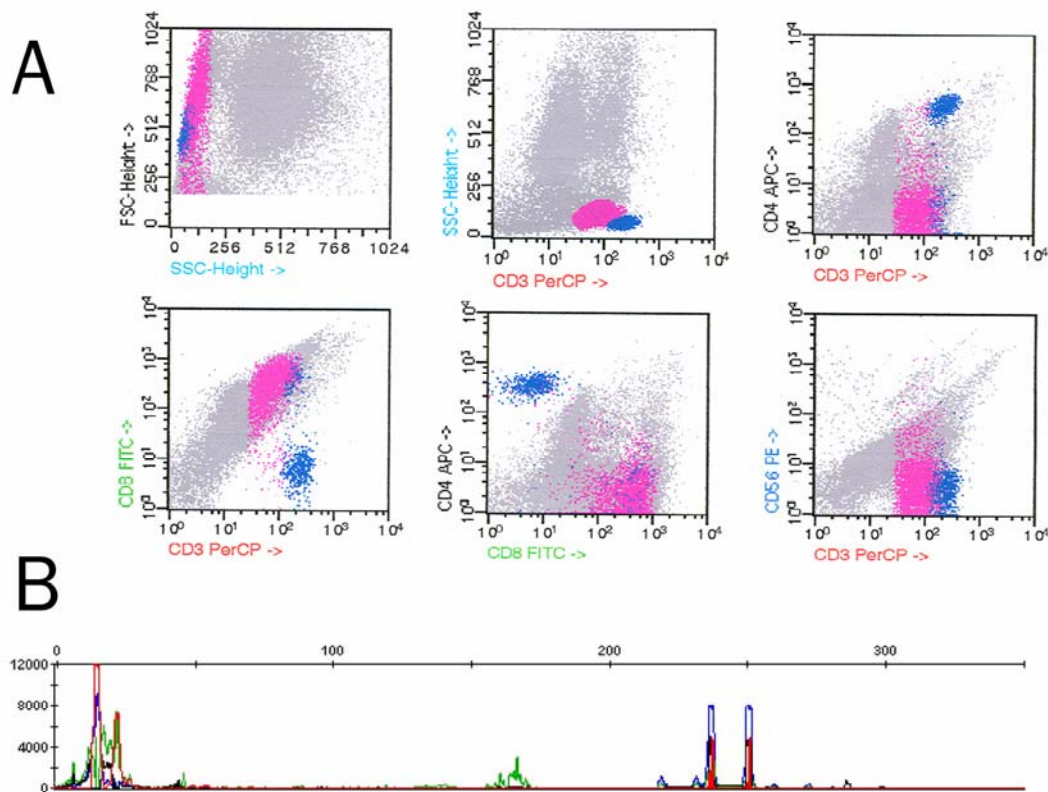
The bone marrow was hypercellular with extensive involvement by atypical lymphoid infiltrates. There was an increased mitotic index, and geographic foci of necrosis with much apoptotic debris. Generalized lymphadenopathy with atypical lymphoid proliferation was observed in all lymph nodes. Kidneys demonstrated acute tubular injury, necrosis and focal glomerulosclerosis with atypical lymphoid infiltrates. Strikingly increased histiocytes filled with apoptotic debris were observed in lymph nodes (**Figure 2E** and **2F**) with similar changes present in the bone marrow, spleen and kidneys.

The gastric, intestinal, and colonic mucosae were diffusely hemorrhagic with bloody peritoneal fluid. Pulmonary parenchyma was severely edematous and hemorrhagic with bilateral pleural effusion. Brain dissection revealed atypical lymphoid infiltrates with a perivascular arrangement in the subarachnoid, bilateral temporal, basal cistern, and spinal nerve roots. Hemorrhagic lesions were also seen within the subarachnoid space of the left hippocampus, cerebellar vermis, and nerve

roots of the spinal cord and cauda equine.

## Discussion

Healthy young children are typically asymptomatic following primary EBV infection, but adolescents and adults usually develop IM. This is characterized by an integrated proliferation of cytotoxic T- and polyclonal B-cells through controlled immune responses including interferon production and neutralizing antibodies [1, 2]. FIM is associated with a defect in T-cell mediated immune regulation, resulting in aberrant cytotoxic T-cell activity, uncontrolled B-cell proliferation, and tissue damage [5-9]. A majority of the T-cell lymphomas associated with EBV appear to develop as a direct complication of EBV infection, usually in the setting of severe chronic active EBV infection (SCAEBV) [10, 36-44]. This type of T-LPD usually exhibits a CD4<sup>+</sup> T-cell phenotype. In contrast, fulminant T-LPD is a less well-characterized and unique in that it usually develops shortly after primary acute EBV infection in immunocompetent individuals and



**Figure 3** Phenotypic and molecular features of EBV-driven CD8<sup>+</sup> fulminant T-cell lymphoproliferative disorder by flow cytometry and molecular studies. **A.** The CD8<sup>+</sup> neoplastic lymphocytes (red) are larger than normal CD4<sup>+</sup> T-cells (blue) and express low intensity CD3 and high intensity CD8 expression. **B.** Clonal rearrangement of the TCR gamma gene is confirmed by PCR followed by capillary electrophoresis on the peri-cystic duct lymph node.

typically presents with CD8<sup>+</sup> T-cell phenotype. Almost all cases have been reported in Asian or Mexican population. Some patients lacked serologic responses to the viral infection, suggesting that ethnicity may be an important for predisposition to EBV infection. However, detailed evaluation of the phenotype and clonality of the lymphoid cells has only been performed in few cases [13-21]. The clinical presentation of fulminant EBV<sup>+</sup> clonal CD8<sup>+</sup> T-LPD shows significant overlap with the classical form of FIM, and its relationship to classic FIM remains elusive. Molecular, phenotypic and viral studies are often required to confirm the diagnosis. It should also be distinguished from dissemination of nasal type extranodal NK/T cell lymphoma.

We report here a rare case of fulminant EBV<sup>+</sup> clonal CD8<sup>+</sup> T-LPD arising in an immunocompromised Caucasian female with a history

of SLE. The patient developed clonal CD8<sup>+</sup> T-LPD one month after initial diagnosis of IM. To our knowledge, only 13 similar cases have been reported in the literature as summarized in **Table 1** [13-21, 45, 46]. Nearly all reported cases were of Asian or Mexican origin and showed a diffuse growth pattern of atypical lymphoid cells in the bone marrow, lymph nodes and solid organs. The cytologic features in these cases are heterogeneous, possibly resulting from the combined effects of lymphokines released by transformed or activated T cells and genetic defects. Two characteristic histological features are recognized. One is the presence of atypical small or intermediate-sized lymphoid cells exhibiting coarsely stippled chromatin and inconspicuous nucleoli, which was present in four cases. The second feature is the presence of immunoblasts or immunoblast-like cells, found in nine cases. This type of cell has been

**Table 1** Summary of fulminant EBV-driven CD8<sup>+</sup> clonal T-cell lymphoproliferative disorder

| Case | Age (yrs)/Sex | Ethnicity/Country | Pathology | EBV/Genome | Clinical History  | Anti-EBV antibody |    |      | HPS | Molecular/Genetics  | Outcome/Death after diagnosis | References                        |
|------|---------------|-------------------|-----------|------------|---|-------------------|----|------|-----|---------------------|-------------------------------|-----------------------------------|
|      |               |                   |           |            |   | VCA               | EA | EBNA |     |                     |                               |                                   |
| 1    | 31/F          | Asian/Taiwan      | IBL       | +/clonal   | Fever, hepatomegaly, LAD  | IgM-IgG+          | +  | +    | -   | TCR-β               | 19 M                          | Su IJ et al [61]                  |
| 2    | 7/M           | Asian/Taiwan      | IBL       | +/clonal   | Hepatosplenomegaly, LAD   | IgG+              | +  | +    | -   | TCR-β               | 13 M                          | Su IJ et al [61]                  |
| 3    | 13/M          | Asian/Taiwan      | IBL       | +/clonal   | Hepatosplenomegaly, LAD, pleural effusion                       | IgG+              | +  | +    | -   | TCR-β               | 3 M                           | Su IJ et al [61]                  |
| 4    | 62/M          | Asian/Taiwan      | IBL       | +/clonal   | Fever, hepatomegaly, LAD  | IgM-IgG+          | -  | +    | -   | TCR-β               | 9 M                           | Su IJ et al [61]                  |
| 5    | 3/F           | Asian/Taiwan      | LGL       | +/clonal   | Fever, pleural effusion, LAD, hepatosplenomegaly                | IgG+              | -  | +    | +   | TCR-β AND 6q        | 11 D                          | Chan LC et al [9]                 |
| 6    | 16/F          | Caucasian/France  | LBL       | +/-ND      | IM followed by splenomegaly, VAHS and LAD                       | IgM+ IgG-         | -  | -    | +   | TCR-β/γ             | 1 M                           | Mori M et al [45]                 |
| 7    | 2/M           | Asian/Japan       | ALP       | +/-ND      | IM followed by liver failure, sepsis and pancytopenia           | IgG+              | +  | -    | +   | ND                  | 37 D                          | Gaillard F et al [20]             |
| 8    | 13/M          | Asian/Taiwan      | IBL       | +/-clonal  | Fever, pleural effusion, LAD, hepatosplenomegaly                | ND                | ND | ND   | N/A | Clonal hyperdiploid | 3 M                           | Tien HF et al [67]                |
| 9    | 31/F          | Asian/Taiwan      | IBL       | +/-clonal  | Fever, hepatomegaly, LAD  | ND                | ND | ND   | N/A | Clonal hyperdiploid | 19 D                          | Tien HF et al [67]                |
| 10   | 1/M           | Asian/Japan       | ALP       | +/-clonal  | Fever, hepatomegaly, LAD, DIC                                   | IgM-IgG+          | -  | -    | +   | ND                  | 3 D                           | Tazawa Y et al [65]               |
| 11   | 17/M          | Mexican           | ALP       | +/-clonal  | Fever, hepatomegaly, LAD, pancytopenia                          | ND                | ND | ND   | +   | ND                  | 2 M                           | Quintanilla-Martinez L et al [55] |
| 12   | 2/M           | Mexican           | IBL       | +/-clonal  | Fever, hepatomegaly, LAD, rash, pancytopenia and liver failure  | IgG+              | -  | -    | +   | TCR-γ/β             | 5 D                           | Quintanilla-Martinez L et al [55] |
| 13   | 37/M          | Asian/Japan       | IBL       | +/-ND      | Fever, hepatomegaly, LAD and DIC                                | IgM+ IgG+         | -  | -    | +   | TCR-γ               | 43 D                          | Satoh N et al [57]                |
| 14   | 28/F          | Caucasian/US      | ALP       | +/-ND      | Fever, DIC, LAD, liver failure, effusion and hepatosplenomegaly | IgG+              | -  | -    | +   |                     | 2 M                           | Current report                    |

IBL: immunoblastic lymphoma; LGL: large granular lymphocytic; ALP: atypical small/intermediate lymphoid infiltrate; DIC: disseminated intravascular coagulation; VCA, viral capsid antigen; EA; early antigen; EBNA; early Epstein-Barr nuclear antigen; VAHS; virus-associated hemophagocytic syndrome; TCR: T-cell receptor; LAD: lymphadenopathy; M: month; D: days; N/A; data not available; ND; not done.

**Table 2** Summary of EBV-driven CD4<sup>+</sup> clonal T-cell lymphoproliferative disorder

| Case | Age (yrs)/ Sex | Ethnicity/ Country | Pathology                | EBV/ Genome | Clinical History  | Anti-EBV antibody |    |      | HPS | Molecular/ Genetics | Outcome/ Death after diagnosis | References            |
|------|----------------|--------------------|--------------------------|-------------|---|-------------------|----|------|-----|---------------------|--------------------------------|-----------------------|
|      |                |                    |                          |             |   | VCA               | EA | EBNA |     |                     |                                |                       |
| 1    | 2/M            | NA/USA             | Large cell               | +/-clonal   | Fever, dyspnea, pulmonary infiltrates                               | IgM-IgG+          | +  | +/-  | -   | TCR-β               | 6 years                        | Jones JF et al [32]   |
| 2    | 31/F           | NA/USA             | Large cell               | +/-clonal   | Diarrhea, abdominal pain and generalized LAD                        | IgM-IgG+          | +  | +/-  | -   | TCR-β/γ             | 1 year                         | Jones JF et al [32]   |
| 3    | 55/M           | NA/USA             | PTCL-NOS                 | +/-clonal   | Gluten enteropathy for 19 yrs; nodular skin lesion                  | IgM-IgG+          | +  | +/-  | -   | ND                  | 1 year                         | Jones JF et al [32]   |
| 4    | 2/M            | Asian/Japan        | Peripheral lymphocytosis | +/-clonal   | Fever, generalized LAD, hepatosplenomegaly, and pneumonitis         | IgM-IgG+          | +  | +    | -   | ND                  | 1 year                         | Kijuta H et al [36]   |
| 5    | 10/M           | Asian/Japan        | Peripheral lymphocytosis | +/-clonal   | Fever, hepatosplenomegaly, progressive liver failure                | IgM-IgG+          | +  | +    | -   | TCR-β               | 8 years                        | Ishihara S et al [28] |
| 6    | 10/F           | NA/USA             | PTCL-NOS                 | +/-clonal   | Generalized LAD, ascites, sinus infiltrates and frontal lobe lesion | IgM-IgG+          | +  | +    | -   | TCR-β               | 6 years                        | Bonagura VR et al [8] |
| 7    | 11/M           | Asian/Japan        | Large cell               | +/-clonal   | Multiple pulmonary nodules and hemoptysis                           | IgM-IgG+          | +  | +    | -   | TCR-β               | 9 years                        | Tanaka Y et al [63]   |
| 8    | 2/F            | Asian/Japan        | PTCL-NOS                 | +/-clonal   | Generalized LAD   | IgM-IgG+          | +  | +    | -   | TCR-β/γ             | 2 years                        | Kanegane H et al [33] |
| 9    | 11/M           | Asian/Japan        | PTCL-NOS                 | +/-clonal   | High fever, hepatosplenomegaly and parotid swelling                 | IgM-IgG+          | +  | +    | -   | TCR-β/γ             | 0.4 years                      | Kanegane H et al [33] |
| 10   | 29/M           | Caucasian/ France  | PTCL-NOS                 | +/-clonal   | Ear, nasal and hepatic lymphoma                                     | ND                | ND | ND   | +   | TCR-β               | 10 years                       | Gallot G et al [21]   |

PTCL-NOS; peripheral T-cell lymphoma, not otherwise specified; VCA, viral capsid antigen; EA; early antigen; EBNA; early Epstein-Barr nuclear antigen; VAHS; virus-associated hemophagocytic syndrome; TCR: T-cell receptor; LAD: lymphadenopathy; M: month; D: days; N/A; data not available; ND; not done.



shown in various types of EBV-associated lymphoproliferative disorders, such as IM and Hodgkin lymphoma. One case developed a large granular lymphocyte-type proliferation. The clinical behavior of fulminant EBV<sup>+</sup> clonal CD8<sup>+</sup> T-LPD was aggressive in all patients, and did not respond to intensive chemotherapy and supportive care. There were prominent systemic symptoms and signs in most patients. A characteristic finding was prolonged fever of unknown origin preceding the diagnosis. The interval from initial diagnosis of IM to fulminant clonal CD8<sup>+</sup> T-LPD was variable, and ranged from 3 days to 19 months with a median survival of 1.7 months. The prognosis is significantly worse than that of EBV-negative peripheral T-cell lymphoma (18 months), and closely approaches that of human T-cell leukemia virus (HTLV-1)-positive adult T-cell lymphoma/leukemia (7 months) [47, 48]. In nine cases, T cell clonality was confirmed by Southern blot or PCR-based molecular analysis, whereas the remaining five cases were evaluated by conventional cytogenetics for hypertriploid abnormalities, or immunoblastic morphologic features only. All fourteen cases (including the current case) showed the presence of EBV, and ten of these cases revealed clonality of EBV genome, all with type A. Of fourteen fulminant CD8<sup>+</sup> T-LPD cases, eleven cases had a complete analysis of EBV serology and the findings support primary acute infection in six cases, and possible chronic EBV infection in 3 cases (**Table 1**). Eight patients developed VAHS in the late stage of their clinical course. The current case demonstrated an extensive involvement of atypical lymphoid cells in the bone marrow, lymph nodes and solid organs. The lymphoid cells exhibited a CD8 T-cell phenotype and, most importantly, had clonal TCR gamma gene rearrangement. These observations support the contention that a fulminant EBV<sup>+</sup> clonal CD8<sup>+</sup> T-LPD can occur in an immunocompromised Caucasian patient, and suggest that dysregulated immunity resulted from an acquired immunologic disorder may result in an abnormal response to EBV infection and contribute to the pathogenesis [49-51].

Rare EBV<sup>+</sup> clonal T-LPDs with a CD4<sup>+</sup> phenotype developing as a direct complication of EBV infection have been reported; these diseases commonly occur in the setting of severe chronic active EBV infection (SCAEBV) (**Table 2**) [37, 38, 40-44]. Virtually all cases

reported in the literature have occurred in Japanese children, and EBV infection had been present for several years before the development of the CD4<sup>+</sup> clonal T-LPD. In comparison, the clinicopathologic features and outcome of the EBV<sup>+</sup> CD4<sup>+</sup> clonal T-LPD are significantly different from those seen in the fulminant EBV<sup>+</sup> CD8<sup>+</sup> T-LPD summarized in **Table 1**. It has been hypothesized that the high prevalence of EBV<sup>+</sup>T-LPDs in the Asian and Mexican populations may be due to a genetically determined susceptibility, possibly based on certain HLA types that result in an abnormal response to EBV infection [52, 53]. These observations suggest that EBV may infect precursor T-cells and that unique genetic defects may exist in different types of EBV<sup>+</sup>T-LPDs. The mechanisms that lead some patients to preferentially develop one type over the other have yet to be determined.

In situ and Southern blot hybridization have confirmed the clonotypic proliferation of EBV genomes in the neoplastic T cells of fulminant T-LPD, therefore, supporting an etiologic role of EBV in malignant transformation, as was previously demonstrated in B-cell and Hodgkin lymphomas [54, 55]. Molecular and serologic studies for anti-VCA and anti-EBNA of EBV show that fulminant EBV<sup>+</sup> T-LPD occurs primarily in the setting of primary acute EBV infections and is rarely associated with chronic active EBV infection. The EBV-associated fulminant T-LPD develops mostly in healthy or immunocompetent individuals and exhibits a CD8 T-cell phenotype [46, 56-58]. The biological mechanism of EBV infection on primary T-cells, however, remains a point of contention. The EBV receptor (CD21) has been found to express primarily on immature precursor T-cells, and its expression declines markedly as the cells differentiate [59-61]. CD21 has also been shown to be expressed in a low percentage of neoplastic T-cells in CD4<sup>+</sup> T-LPD [38]. Infection of thymocytes by EBV and the binding of EBV to CD8<sup>+</sup> T-cells have also been reported [62, 63]. However, T cells infected with EBV have yet to be identified in the blood or tonsils of healthy individuals. It is possible that the expression of CD21 on the precursor T-cells or the neoplastic CD8<sup>+</sup> T-cells may be transient, or cell-cycle specific, as was demonstrated in epithelial cells of nasopharyngeal carcinoma. Alternatively, infection of T-cells by EBV may be mediated through a receptor distinct from CD21 that has yet to be identified.

SLE is an idiopathic autoimmune disease characterized by basic defects in T- and B-lymphocytes, which result in immune dysregulation and production of autoantibodies, ultimately leading to organ damage. The risk of non-Hodgkin lymphoma was 3-4 fold higher compared with the risk in the general population, and B-cell lymphomas are the most common types [64-66]. Rare cases of anaplastic and peripheral T-cell lymphomas have also been reported [67, 68]. It has been postulated that this association is mediated by both genetic and exogenous factors by which uncontrolled lymphocyte activity leads to chromosomal translocations and malignant transformation. The immunological response to EBV has been found to be abnormal in individuals with SLE [49, 69]. Common findings in SLE patients include the presence of over 15-fold EBV viral burden, significantly elevated EBV antibodies and impaired EBV-specific cytotoxic cell function. Abnormal expression or function of CD21 is also found both in human and murine models of SLE [70, 71]. One can speculate that if patients with SLE release T cells from the thymus at a relatively immature state, these cells would be infected with increased frequency in the periphery. As a result, it might increase the risk for T-cell infection and the subsequent monoclonal expansion. It is possible that in compromised patients, the expanded T-cell populations become infected with EBV, and progress to fulminant T-LPD. This phenomenon appears similar to that seen in EBV-related B-LPD, in which there is progression from classical polyclonal B-cell expansion into an atypical oligoclonal phase and subsequent clonal malignant B-cell lymphoma. However, such a case has never been reported, and this may be partly due to the rarity of this disease.

In conclusion, we describe a fulminant EBV<sup>+</sup> CD8<sup>+</sup> clonal T-LPD in an immunocompromised Caucasian SLE patient following acute primary EBV infection. Biologically, the disorder represents a malignant proliferation of T cells that acquires the EBV genome as a crucial pathologic event. Patients with this type of lymphoid proliferation have very poor clinical outcomes with extensive lymphoid infiltration in the hematologic system, and often exhibit VAHS. Clinical, morphologic and immunophenotypic evaluation, along with molecular studies, are necessary to fully characterize such cases.

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