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CASE IMAGE

X-linked lymphoproliferative syndrome associated with Epstein–Barr virus encephalitis and lymphoproliferative disorder

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Key Clinical Message

When treating patients with EBV encephalitis, the possibility of XLP should be considered. Once the diagnosis of XLP is made, aggressive treatment such as rituximab, and other immunosuppressive agents are desired for rapid transition to HSCT.

KEYWORDS

Epstein–Barr virus, hemophagocytic Lymphohistiocytosis, lymphoproliferative disorders, rituximab, X-linked lymphoproliferative syndrome

1 | CASE PRESENTATION

The patient was a 3-year-old boy. He had had a fever of approximately 38°C for 1 month before admission, and he was suspected by a local doctor of having otitis media, for which antibiotics were prescribed. The fever continued, and the patient visited our outpatient clinic 1 week before admission, at which time acute Epstein–Barr virus (EBV) infection (infectious mononucleosis) was suspected with the observation of anemia, thrombocytopenia, elevated liver enzymes, splenohepatomegaly, and generalized lymphadenopathy. The day before admission, he had developed lethargy. His decreased response to stimuli and tachypnea/retractive breathing resulted in emergency admission. Serum EBV-PCR levels were high at 140,000 (copies/μg DNA). EBV-PCR in the cerebrospinal fluid was also high at 88,000, and an electroencephalogram (EEG) showed high-amplitude slow waves (Figure 1A). Cerebrospinal fluid test findings showed sugar 47 mg/dL (blood sugar 72 mg/dL), protein 98 mg/dL, cell count 100/3/μL (mononuclear cells 91%, polynuclear cells % 9%). He showed a depressed level of consciousness, including lethargy lasting ≥24 h, fever (≥38.0°C), cerebrospinal fluid pleocytosis, and EEG findings compatible with encephalitis, which led to a diagnosis of EBV encephalitis.[1] After admission, treatment with γ-globulin and steroid pulse therapy was initiated.

Due to the subsequent increase in serum EBV-PCR to 470,000, immunochemotherapy with oral cyclosporine and etoposide infusion was initiated. Epstein–Barr encoded RNA (EBER)-1 in situ hybridization (ISH), performed 2 months after admission, detected EBV infection only in B cells, leading to the suspicion of X-linked lymphoproliferative syndrome (XLP). Genetic testing revealed mutations in the SH2D1A gene (c.239_240insA, p.80LysfsX22), and the patient was diagnosed with XLP. As the gene mutations were absent in the mother, this was considered a sporadic case.

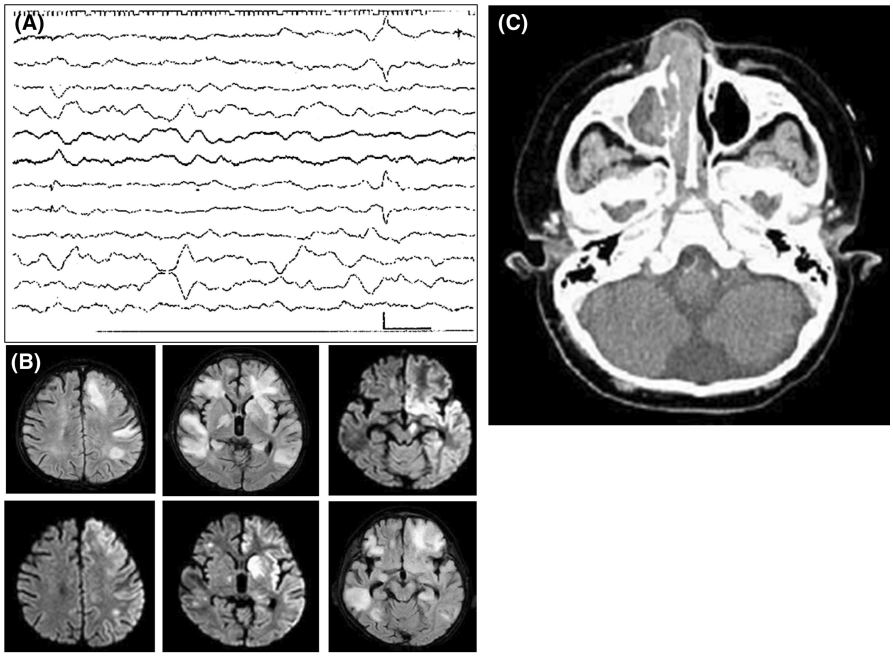

FIGURE 1 (A) Diffuse 50-150 μV, 1-3 Hz slow waves predominate in the occiput in EEG. (B) Newly sporadic T2 and FLAIR-high signal areas are observed in the cerebral cortex, white matter, basal ganglia, and midbrain. (C) CT revealed a filling mass with bone destruction in the right nasal cavity, which extended to the right maxillary sinus and nasopharynx.

With the diagnosis of XLP, the patient was prepared for hematopoietic stem cell transplantation (HSCT). However, he developed a fever of 39°C and tonic–clonic convulsions 3 months after admission, and following tracheal intubation, he was admitted to the intensive care unit where he received artificial respiration management. Head magnetic resonance imaging showed exacerbation of encephalitis (Figure 1B), and γ-globulin and steroid pulse therapy were added. Starting at around 4 months after admission, a tumor with bone destruction was observed in the right nasal cavity (Figure 1C). Histological results from the biopsy revealed a lymphoproliferative lesion associated with XLP. Immunohistochemical staining was positive for CD20, and treatment with an anti-CD20 monoclonal antibody (rituximab) was initiated. With no improvement in consciousness disturbance, his respiratory condition gradually worsened, and pleural effusion was also observed. The patient died on the 150th day after admission. Parents decided not to perform tissue autopsy.

2 | DISCUSSION

Lymphoproliferative disorders comprise a heterogeneous group of diseases such as XLP, ALPS (Autoimmune Lymphoproliferative Syndrome), HLH (Hemophagocytic Lymphohistiocytosis), LCH (Langerhans Cell Histiocytosis), leukemia and so on, which are characterized by uncontrolled production of lymphocytes that cause monoclonal lymphocytosis. XLP may follow EBV infection and is characterized by severe immunodeficiency. Its prevalence is estimated to be 1–3 per 1,000,000 boys, and it usually develops during childhood or adolescence. XLP is thought to be caused by mutations in two different genes: SH2D1A (XLP1) and XIAP/BIRC4 (XLP2). The SH2D1A gene, causative for XLP1, encodes the SAP protein, which regulates the immune functions of T, NK, NKT, and other cells, and patients with XLP exhibit severe immunodeficiency, likely owing to the failure of the immune functions of these cells.[2] Currently, the only definitive treatment available for XLP1 patients is allogeneic HSCT, however, depending on clinical features, treatment of XLP1 is tailored to particular clinical symptoms and supportive care.[2] If there is evidence of disease due to EBV, treatment with a monoclonal anti-CD20 antibody (rituximab) can be used to deplete virus-bearing B cell populations. Although this approach is effective in reducing viremia, it carries the risk of B-cell depletion effects, including exacerbation of long-term hypogammaglobulinemia.[3] Antiviral drugs are not very effective against EBV, but acyclovir has been used in some situations. Hemophagocytic lymphohistiocytosis is treated according to standardized protocols (HLH 94 and 2004) based on the use of dexamethasone, etoposide, and cyclosporin. In addition, other immunosuppressive agents such as Toculizumab (anti-IL6R antibody) or Ruxolitinib (JAK1/2 inhibitor) might be considered as therapeutics.[4] These more targeted therapies may lead to rapid transition to HSCT.

Weeks et al. reported a case of XLP complicated with EBV encephalitis, which developed EBER-positive lymphoma in the frontal lobe, as in our case.[5] This patient was administered the anti-CD52 monoclonal antibody alemtuzumab, in addition to cyclosporine and rituximab, and eventually underwent a half-HLA-matched transplant from the mother, but the patient died of liver failure 1 month later. XLP complicated with EBV

encephalitis is rare, and the patients in both the previous report and our case had a poor general condition from the time of admission, showing that it is considerably difficult to maintain the patient in a good condition until transplantation.

In our case, the patient was complicated with encephalitis from the time of admission, and his poor general condition due to the subsequent worsening of encephalitis with convulsions and artificial respiration management is thought to have made it difficult to survive until transplantation. Therefore, when treating patients with EBV encephalitis, the possibility of XLP should be considered, and once the diagnosis of XLP is made, aggressive treatment, including the administration of rituximab, is considered desirable with early hematopoietic stem cell transplantation in mind.

AUTHOR CONTRIBUTIONS

Takeo Mukai: Conceptualization; formal analysis; funding acquisition; project administration; supervision; writing – original draft; writing – review and editing. **Kenji Waki:** Conceptualization; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

CONSENT

Written informed consent was obtained from parents to publish this report in accordance with the journal's patient consent policy.

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