Chinese Journal of Cancer

Case Research

Lymphoma and cerebral vasculitis in association with X-linked lymphoproliferative disease

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Abstract

Lymphoma is seen in up to 30% of patients with X-linked lymphoproliferative disease (XLP), but cerebral vasculitis related with XLP after cure of Burkitt lymphoma is rarely reported. We describe a case of a 5-year-old boy with XLP who developed cerebral vasculitis two years after cure of Burkitt lymphoma. He had Burkitt lymphoma at the age of 3 years and received chemotherapy (non-Hodgkin's lymphoma-Berlin-Frankfurt-Milan-90 protocol plus rituximab), which induced complete remission over the following two years. At the age of 5 years, the patient first developed headache, vomiting, and then intellectual and motorial retrogression. His condition was not improved after anti-infection, dehydration, or dexamethasone therapy. No tumor cells were found in his cerebrospinal fluid. Magnetic resonance imaging showed multiple non-homogeneous, hypodense masses along the bilateral cortex. Pathology after biopsy revealed hyperplasia of neurogliocytes and vessels, accompanied by lymphocyte infiltration but no tumor cell infiltration. Despite aggressive treatment, his cognition and motor functions deteriorated in response to progressive cerebral changes. The patient is presently in a vegetative state. We present this case to inform clinicians of association between lymphoma and immunodeficiency and explore an optimal treatment for lymphoma patients with compromised immune system.

Key words Burkitt lymphoma, cerebral vasculitis, X-linked lymphoproliferative disease, Epstein-Barr virus

X-linked lymphoproliferative disease (XLP) is a rare immuno-deficiency disease characterized by severe immune dysregulation and caused by mutations in the *SH2D1A/SAP* gene. Clinical types include fulminant infectious mononucleosis (FIM), lymphoma, hemophagocytic lymphohistiocytosis (HLH), and dysgammaglobulinemia. Lymphoma is recognized worldwide as a common clinical type of X-linked lymphoproliferative disease in children and early adolescents. For patients with XLP, the incidence of lymphoma has been estimated at 30%[1], but cerebral vasculitis is rare. Here, we report one pediatric case of cerebral vasculitis associated with XLP to inform clinicians of the clinical features and explore optimal treatment for Burkitt lymphoma with XLP.

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doi: 10.5732/cjc.012.10238

Case Report

A 5-year-old boy who presented with a one-month history of headache and vomiting two years after being cured of Burkitt lymphoma was admitted to our cancer center on March 7, 2011. Prior to being admitted to our center, he was initially treated at a local hospital with mannitol-induced dehydration and dexamethasone for suspected relapse of lymphoma involving the brain. His symptoms were partially controlled with mannitol and dexamethasone but worsened with regular exacerbation of mental and movement retrogression. He manifested with abnormal gait and declined ability to play games without fever. During each exacerbation, his symptoms were controlled with dehydration. During one episode on the day after admission, he developed transient headache, vomiting, and obnubilation. He developed seizures involving both hands and legs. He was treated with mannitol and dexamethasone intravenously. Anti-infection therapy including meropenem, itraconazole, voriconazole, and aciclovir was initiated; he recovered consciousness and headache disappeared on the following day.

At the age of 3 years, the patient was diagnosed with stage IV Burkitt lymphoma in our cancer center. Fluorescence *in situ* hybridization (FISH) examination showed positive for MYC/IgH translocation. Epstein-Barr virus (EBV)–encoded early RNA (EBER) was negative. Treatment consisted of non-Hodgkin's lymphoma-Berlin-Frankfurt-Milan-90 (NHL-BFM-90) protocol and rituximab. The patient completed chemotherapy on July 14, 2009. He continued to have persistent complete remission and was well on follow-up. There was a family history of fulminant infectious mononucleosis (FIM); his older brother and maternal male cousin died of this condition at the age of 10 months and 2 years, respectively. The patient was diagnosed with confirmed mutation in *SH2D1A*, a C >T nonsense substitution mutation. There was no family history of other cerebral vascular accidents or cerebral tumors.

Magnetic resonance imaging (MRI) revealed multiple non-homogeneous, hypodense masses along the bilateral cortex, diffusing edema of the cerebral white matter, and demyelination (**Figure 1**). The bone marrow showed normal presentation. Cerebrospinal fluid (CSF) was grey yellow, and laboratory examinations showed a slight decrease in glu (1.13 mmol/L, normal 2.5–4.5 mmol/L) and Cl (110.4 mmol/L, normal 120–130 mmol/L). In the CSF, protein levels were elevated (1,950 mg/L, normal 80–430 mg/L), and cell concentration was 6×10^6/L. Pandy test was positive. CSF pressure was normal. Evidence of tumor cells was absent on repeated examinations. CSF culture showed gram-positive bacteria; there was no evidence of the pathogens cryptococcosis, mycete, or mycobacterium. EBV-DNA copy number was 0. C-reactive protein (CRP) and procalcitonin (PCT) were normal.

Lumbar puncture was carried out in two weeks again after anti-infection therapy. CSF remained grey yellow. CSF smears showed many mature lymphocytes. CSF culture was negative. Glu and Cl levels in CSF were lower than normal (0.79 mmol/L and 117.2 mmol/L, respectively), whereas protein levels were high (1,910 mg/L). The patient's worsening mental and motor conditions were not resolved by two-week anti-infection therapy. He could not speak clearly or recognize his parents. The patient remained seizure-free. MRI scans of his brain showed multiple non-homogeneous, hypodense masses along the bilateral cortex, diffuse abnormal signals in the bilateral cerebral cortex, and extensive edema in the bilateral white matter. These brain lesions were more severe than those revealed by prior MRI. His mental condition had not improved after 3 weeks of anti-infection therapy. Biopsy was performed on masses in the right cerebral front lobe to exclude Burkitt lymphoma relapse involving the central nervous system. Cerebral pathology revealed local pallium and white matter with a yellow appearance. Light microscopy revealed neurogliocyte and vessel hyperplasia accompanied by lymphocyte infiltration. Immunohistochemistry revealed moderate CD68, CD3, CD2, CD5, CD8, cytotoxic granule-associated RNA binding protein (TIA1), and glial fibrillary acidic protein (GFAP) staining and mild Ki-67 staining (1%). T-cell receptor (TCR) rearrangment, CD4, and EBER were negative (**Figure 2**). Special staining for Ag, periodic acid-schiff (PAS), and anti-acid was negative. There was no tumor in the brain. The biopsy tissue was cultured and no pathogen was found. Pathologic presentation coincided with chronic inflammatory changes, and pathologic diagnosis was cerebral vasculitis in the brain. On follow-up, the patient remains in a vegetative state.

Discussion

X-linked lymphoproliferative disease (XLP), also known as Duncan disease, is a rare immunodeficiency disease characterized by severe immune dysregulation. Since XLP was initially described in 1975[2], more than 270 boys with the condition have been identified in 80 kindreds[3] (**Table 1**). XLP affects 1 to 3 million boys[3], with disease onset occurring in childhood or early adolescence.

XLP is caused by mutations in the *SH2D1A/SAP* gene on the

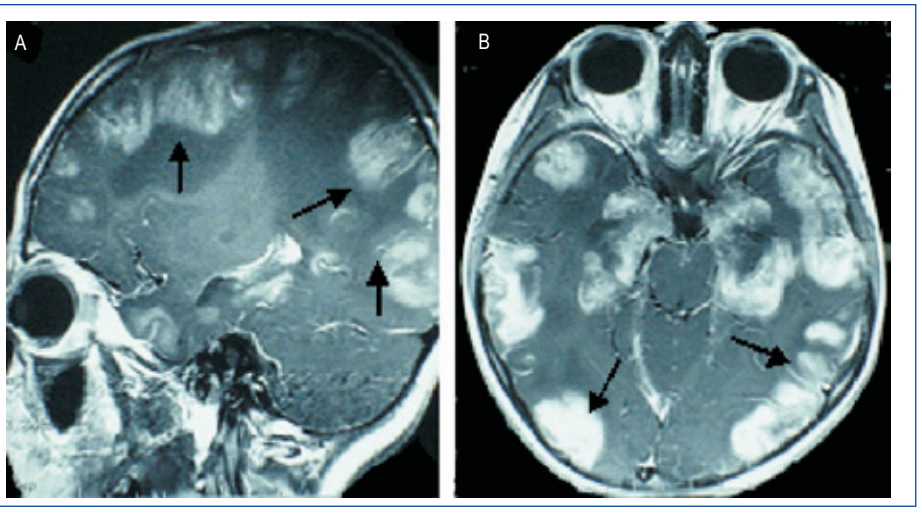

Figure 1. **Magnetic resonance imaging (MRI) of the brain. MRI scans of the brain with contrast-T1 sagittal (A) and axial (B) views show multiple non-homogeneous, hypodense masses along the bilateral cortex as indicated by arrows.**

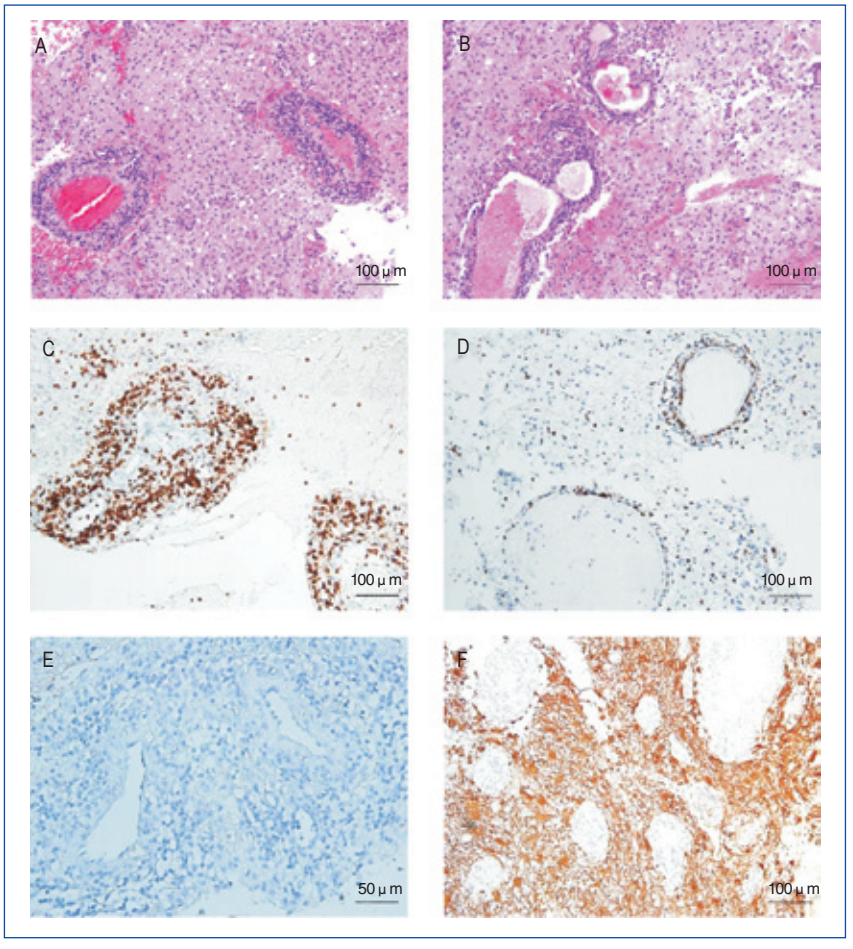

Figure 2. **Histologic changes in the right cerebral frontal lobe. A and B, histologic examination of the cerebral tissue showing lymphocyte infiltration and hyperplasia with neurogliocytes and vessels (HE, 100×). Immunochemistry stains positive for CD3 (C, 100×) and CD8 (D, 100×), negative for Epstein-Barr virus–encoded early RNA (EBER) (E, 200×), and positive for glial fibrillary acidic protein (GFAP) (F, 100×). Pathologic diagnosis for this case is cerebral vasculitis.**

Table 1. Demographic and clinical characteristics of evaluable patients with XLP

Authors	FIM	HLH	Dysgammaglobulinemia	Lymphoma	Others
Booth *et al*.[3] [a]	7 (7.7)	29 (31.9)	20 (22.0)	13 (14.3)	22 (24.1)
Seemayer *et al*.[17] [b]	157 (57.7)	Not mentioned	84 (30.9)	3 (1.1)	Not mentioned

XLP, X-linked lymphoproliferative disease; FIM, fulminant infectious mononucleosis; HLH, hemophagocytic lymphohistiocytosis. All values are presented as numbers of cases, with percentage in parentheses. [a]Retrospective analysis was performed on data collected for 91 patients from 32 centers worldwide. The patients were born between 1941 and 2005; 63 were born in or after 1990. [b]Characteristics of 272 boys with XLP from the XLP registry were summarized. Some patients had two or more clinical types. The other types included lymphoproliferative disorders (82 cases, 30%), aplastic anemia (8 cases, 3%), and vasculitis and lymphomatoid granulomatosis (7 cases, 3%).

X chromosome at position Xq25. The *SH2D1A* gene encodes the adaptor molecule SAP that binds to cell surface receptors from the signaling lymphocyte activation molecule (SLAM) family[4]. SAP is an important regulator of normal immune function in T cells[5-7], natural killer cells[8-11], natural killer T (NKT) cells, and possibly B cells[12,13]. Defects in this gene result in SAP protein deficiency, limiting SAP's ability to compete with other SH2 domain-containing proteins to bind SLAM. Other inhibitory signals via binding SLAM competitively lead to immune defects. Patients with XLP have increased susceptibility to EBV. Furthermore, humoral defects arise from the interaction between impaired mature B lymphocytes and $CD4^+$ T cells[14], resulting in the expansion of lymphocytes that are primarily reactive $CD8^+$ T cells[1,4]. In the case reported here, cerebral pathology showed infiltration of lymphocytes positive for CD8 and negative for CD4. Lymphocyte

expansion can lead to infiltration of several organs, including the liver and bone marrow.

A diagnosis of confirmed XLP1 is established on clinical features of XLP1 and mutation in *SH2D1A* in a male patient. Clinical diagnosis is based on clinical manifestations and family history in absence of genetic status. Suspected diagnosis is established on clinical features only. In the case reported here, the patient had confirmed XLP.

Clinical manifestations of XLP vary, ranging from lymphoma, HLH, dysgammaglobulinemia, and FIM to aplastic anemia[1]. Patients often manifest more than one clinical type, or the clinical type may change from one type to another. This patient presented with stage IV Burkitt lymphoma at the age of 3 years and progressed to cerebral vasculitis. Although EBV was initially identified as a catalyst for XLP[3], there was no evidence of EBV infection in either disease, suggesting that some clinical features of XLP are independent of EBV[15]. Rezaei *et al*.[1] reported that 30% of patients with XLP can develop lymphoma and dysgammaglobulinemia, which occur in both EBV-positive and EBV-negative patients. Moreover, 10% of patients with XLP are reported to have immunological abnormality before EBV exposure[16]. SAP-deficient patients, like the patient in this case, can also be diagnosed with a lymphoproliferative disorder defined as cerebral vasculitis after infection and cerebral tumor are excluded. This presentation is rarely seen in XLP patients and should be distinguished from Burkitt lymphoma relapse involving the central nervous system. The pathogenesis of XLP with central nervous system vasculitis is poorly understood. One proposition is that cerebral vessels may be attacked upon activation of $CD8^+$ cells, which can be caused by antigens independent of EBV or altered clearance of viruses such as EBV. Although EBV was not detected in the patient's blood in this case, EBV infection cannot be fully excluded without evidence that EBV is absent in the brain, lung, or skin tissue by PCR. Based on this case presentation, we infer that cerebral vasculitis associated with XLP can be characterized by retrogression in mentality, movement, and cognition. Lymphocytes may infiltrate the cortex and cause demyelination.

Prognosis for Burkitt lymphoma treated with standard chemotherapy is better than that for XLP1. In a clinical study, the overall mortality for patients with XLP after undergoing chemotherapy or anti-virus or steroid therapy was 75%[3]. In contrast, the cure rate exceeds 80% for Burkitt lymphoma treated with NHL-95 protocol. Historically, 70% of patients died before 10 years of age. The prognosis for XLP1 has greatly improved since 1995, when Seemayer *et al*.[17] reported an overall survival of 25%. Indeed, 71.4% of patients in the European Registry for XLP were alive at the time of data analysis. Because the prognosis for HLH in XLP1 without hematopoietic stem cell transplantation (HSCT) is extremely poor, mortality in the untransplanted group of XLP1 secondary to HLH remains as high as 81.3%[3]. HSCT is recommended for all patients with HLH. Although more than 60% of patients survive without HSCT[3], it will be important to follow patients carefully, as this group manifested as lymphoma or dysgammaglobulinemia may progress to HLH or FIM in clinical course. The outcome of HSCT for manifestations of XLP1 other than HLH is very good[1]. For this case, wherein the patient consistently showed no evidence of EBV infection, HSCT should have been a better strategy. However, before onset of cerebral vasculitis, when the patient is stable and relatively well, it is challenging to make the decision to perform a transplant. Notably, the survival rate for XLP patients without transplant was 84.4%, and these patients did not manifest HLH[3]. An allogenic transplant procedure, on the other hand, will be associated with mortality[3]. HSCT is still controversial for XLP patients with conditions other than HLH or FIM[1]. Central nervous system vasculitis can be seen in autoimmune diseases such as rheumatoid arthritis and systemic lupus erythmatosis. Remission is achievable with methylprednisone and cyclophosphamide or agents targeting B cells or tumor necrosis factor-α. Myeloabative or reduced intensity allogeneic HSCT targets activated $CD8^+$ T cells and corrects the underlying immune defect, thereby curing XLP-associated central nervous system vasculitis[18].

The pathogenesis of lymphoma has not been fully understood. Individuals with compromised immune system are subject to develop B-cell lymphoproliferative malignancies[17]. Clinicians should inquire family history when facing a lymphoma patient with a family history of unexplained death in male cousins. A further gene test should be performed for these patients. If primary diagnosis of lymphoma with XLP is made, HSCT is considered in options of treatment after thorough evaluation. Total cure rate is highly achievable for Burkitt lymphoma. Lymphoma relapse in the brain after several years for a patient in complete remission is rare. After being cured for several years, any patient with lymphoma who has signs associated with the brain should undergo brain biopsy if possible. The prognosis of XLP-cerebral vasculitis may improve if methylprednisone and cyclophosphamide treatments are started as soon as possible.

Received: 2012-09-21; revised: 2013-03-14;
accepted: 2013-05-07.

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