Reversible Posterior Leukoencephalopathy Syndrome Sometimes Could be Irreversible: A Case Following Tumor Lysis Syndrome in Childhood Burkitt's Lymphoma

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Reversible posterior leukoencephalopathy syndrome (RPLS) was first described by Hinchey *et al*.[1] in 1996 as a clinical radiologic syndrome consisting of reversible cortical neurologic dysfunction and brain imaging findings involving the posterior circulation, especially the occipital lobes.

RPLS is caused by various heterogeneous factors. However, there are only a few reports that have paid attention to the relationship between tumor lysis syndrome (TLS) and RPLS.[2] A child with Burkitt's lymphoma (BL) who developed RPLS following TLS during the first cycle of combined chemotherapy is reported here.

A 9-year-old girl was admitted for intermittent vomiting and mass in the bilateral cheeks for 25 days. Physical examination revealed cervical lymphadenopathy, masses in both cheeks, and large intraabdominal masses. Imaging studies including ultrasonic and computed tomography (CT) scan showed extensive involvement of liver, kidneys, gastrointestinal walls, pancreas, omentum minus, bilateral ovaries, right parotid, maxillofacial region, and cervical lymph nodes. The volume of the largest mass in the abdomen was 7.4 cm × 5.3 cm × 6.2 cm. Cerebral CT scan was normal before treatment. Tumor cells were negative in bone marrow biopsy. Cerebrospinal fluid (CSF) test was normal. Immunochemistry stain of biopsies from stomach mucosa and cervical lymph node showed CD20 (+), CD10 (+), PAX-5 (+), CD3 (−), CD7 (−), TDT (−), CD99 (−), mum-1 (−), BCL-2 (−), BCL-6 (minor+), and Ki-67 99% (+). Chromosomal translocation between IgH and c-myc was positive by florescence *in situ* hybridization. Stage III BL was diagnosed.

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Her blood tests showed elevated lactate dehydrogenase (1267 U/L) level and hypomagnesemia (0.68 mmol/L) on admission. For fear of severe TLS development, only prednisone (7.5–20 $mg \cdot m^{-2} \cdot d^{-1}$) instead of cyclophosphamide, vincristine (VCR), and prednisone (COP) was given from the 1st to 6th day. Hydration, alkalinization, and allopurinol were given at the same time. On the 4th day, she became anuric with elevated blood urea nitrogen (8.51 μmol/L) and serum creatinine (235 μmol/L). TLS with renal function failure developed. Her blood pressure elevated from 90/60 mmHg to 110–125/70–85 mmHg. Hemodialysis was performed daily for twice. On day 7, VCR, 1.5 mg/m^2 was given. In addition, cyclophosphamide (CTX, 300 mg/m^2) was given on day 8. Her blood pressure increased to 145/95 mmHg and captopril and nifedipine were used. Her blood pressure fluctuated between 135/100 and 110/50 mmHg. On day 13, she developed abrupt headache and then generalized tonic-clonic seizure when her blood pressure was 135/95 mmHg. Seizure continued for about 5 min. It was controlled after the usage of diazepam (0.3 mg/kg, intravenous) and phenobarbitone (8 mg/kg, im). Then, she went to coma. She stayed in coma for the following 10 d.

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CSF test was performed on day 5 of the episode and the results were normal. Her serum magnesium was between 0.44 mmol/L and 0.50 mmol/L from day 9 to day 14 of chemotherapy.

Brain magnetic resonance imaging (MRI) was conducted after 8 h in coma. Slightly, high T2-weighted and fluid-attenuated inversion recovery (FLAIR) signals were found in bilateral parietal, occipital lobes, and right frontal lobe. Punctate and linear contrast T1-weighted enhancements were identified in cortical and subcortical regions [Figure 1]. After awake, her visual acuity decreased below 0.1 for around 2 weeks and recovered spontaneously. Then, she received combined chemotherapy according to the LMB 96 B-NHL protocol and it went smoothly. She has been in complete remission for 70 months till now. The follow-up brain magnetic resonance (MR) examinations were obtained at 2, 4, 8, 12, and 24 months after the first MR examination [Figure 2].

Several RPLS-associated clinical conditions have been well established. Preeclampsia (or eclampsia), infection, autoimmune disease, cancer chemotherapy, and transplantation are all identified to be associated with RPLS.[3] In pediatric oncologic area, there is an increasing awareness of RPLS as a complication of cancer treatment. Since Emiko first reported on a child with B-cell lymphoma who developed RPLS after chemotherapy conducted during recovery from TLS in 2005, only a few reports have paid attention to the relationship between TLS and RPLS in pediatric patients [Table 1].[2,4]

In our patient, it is unlikely that the COP chemotherapy alone induced RPLS because RPLS did not recur upon continuation of combination chemotherapy that included more drugs and increased doses. Hence, we consider that chemotherapy might have indirectly induced RPLS by exacerbating TLS, and thereby systemic hypertension.

The clinical symptoms of RPLS include headache, decreased alertness, mental abnormalities, such as confusion, diminished spontaneity of speech, and changed behavior ranging from drowsiness to stupor, seizures, vomiting, and abnormalities of visual perception such as cortical blindness.[4] The onset of symptoms can occur as early as 6 h and as late as 3 months after exposure to the precipitating factor.[1] The episode in this case occurred on day 8 of COP (the 2nd day of VCR and CTX) and day 5 of TLS. Clinical findings in this case fit well to the diagnosis of RPLS.

MRI diffusion weighted imaging (DWI) and FLAIR imaging best identify the bilateral, symmetrical, and posterior cerebral cortical and subcortical white matter edema typical of the disorder. The lesion also could be found in the anterior portions, basal ganglia, brainstem, and cerebellum.[5] In our case, slightly, high signals were found in bilateral, parietal, occipital lobes, and right frontal lobe on T2-weighted and FLAIR images. But, all the lesions appeared as high signal on DWI, indicating cytotoxic edema. The lesions could evolve from an early reversible vasogenic edema to a later irreversible ischemic damage, if not properly treated.[4] Punctate and linear enhancement lesions were identified in cortical and subcortical regions on contrast T1-weighted images [Figure 1], which meant transient breakdown of the blood-brain barrier. Although initially termed RPLS, the lesions in some cases are irreversible and can progress to permanent tissue injury,[5] as evidenced by volume loss, hemorrhage, and increased signal on follow-up T1-,

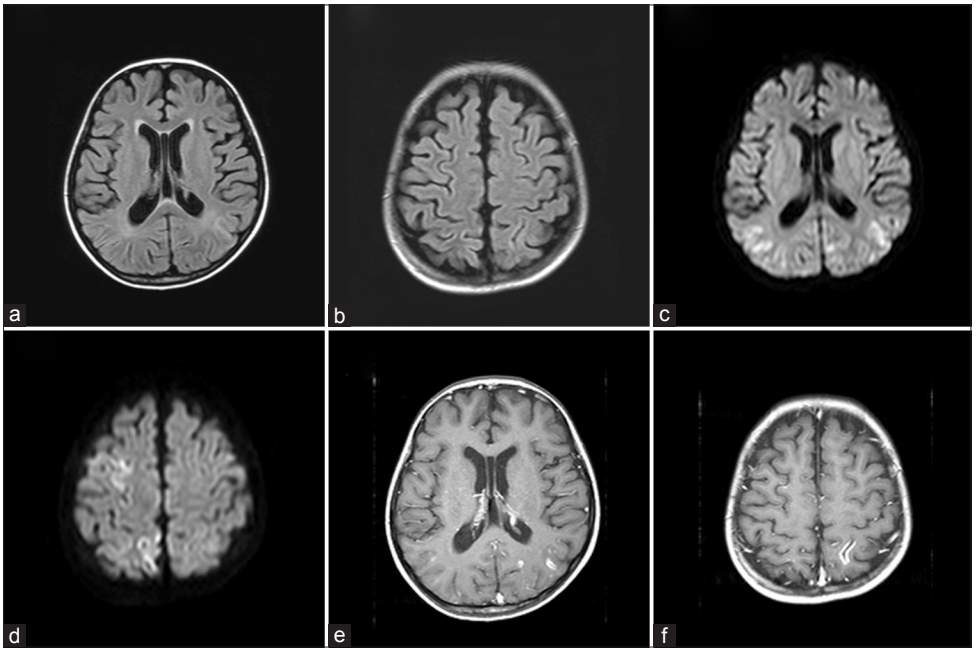

Figure 1: Initial brain magnetic resonance images. Slightly hyperintense areas were found in bilateral parietal, occipital lobes and right frontal lobe, predominantly in the subcortical white matter and cortex, on fluid-attenuated inversion recovery images (a and b). Hyperintense areas also appeared high signal on diffusion weighted imaging (c and d). Linear and punctate intense enhancements in cortical and subcortical areas were found on gadolinium-enhanced T1-weighted images (e and f).

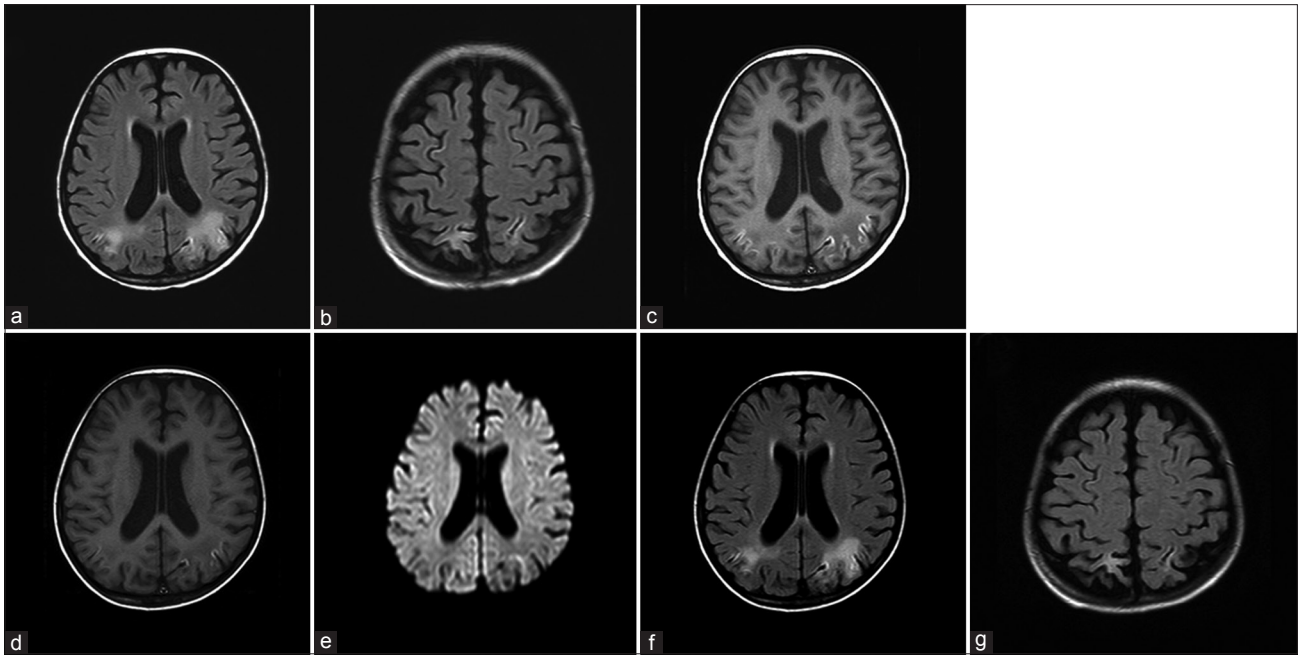

Figure 2: Two months later, the lesions deteriorated, patchy high-signal lesions were seen in bilateral parietal, occipital lobes and right frontal lobe on fluid-attenuated inversion recovery images (a and b). Linear hyperintense lesions along the gyri were found on T1-weighted images (c). Four months later, most of the hemorrhage resolved on T1-weighted images (d). Diffusion weighted imaging (e) was normal. Fluid-attenuated inversion recovery images (f) showed patchy hyperintense lesions in the parietal and occipital lobes, cystic encephalomalacia foci were identified in subcortical area symmetrically. The hyperintense lesions in frontal lobe dissolved 8 months later (g).

Table 1: Clinical characteristics and radiological findings of RPLS in association with TLS in pediatric patient

Reference	Age (year)	Gender	Disease	Chemo-therapy	Clinical features	Radiological findings	Outcome
[2]	6	Male	B-cell lymphoma	Pred, VCR, CTX, PIR	Hypertension, visual disturbances	Increased FLAIR and ADC bilateral parietal, occipital, and frontal lobes	Complete recovery
[4]	17	Female	Burkitt's lymphoma	CTX, ADR, Pred	Headache, hypertension, seizures	Increased FLAIR bilateral occipital, parietal, and temporal lobes, increased DWI frontal loci	Complete recovery
Our patient	9	Female	Burkitt's lymphoma	Pred, VCR, CTX	Headache, hypertension, seizures, hypomagnesemia	Increased FLAIR bilateral parietal, occipital lobes and right frontal lobe, punctate and linear T1-weighted enhancement in cortical and subcortical regions	Partial recovery

Pred: Prednisolone; VCR: Vincristine; CTX: Cyclophosphamide; ADR: Adriamycin; PIR: Pirarubicin; RPLS: Reversible posterior leukoencephalopathy syndrome; TLS: Tumor lysis syndrome; FLAIR: Fluid-attenuated inversion recovery; ADC: Apparent diffusion coefficient; DWI: Diffusion weighted imaging.

T2-weighted and/or FLAIR images as observed in our patient [Figure 2].

The mechanism responsible for RPLS remains unclear and controversial. Hypertension with failed autoregulation and hyperperfusion remains a popular consideration for the developing brain edema.[3]

It was speculated that TLS causes damage to the vascular endothelium through severe metabolic abnormalities. However, this damage alone will not cause RPLS. If chemotherapeutic drugs are administered before recovery from the endothelial damage, the drugs will further damage the vascular endothelium to such an extent as to cause RPLS.[2] In addition, fluid overload caused by hydration therapy for TLS and hypertension might also be the predisposing factors for RPLS. This patient developed TLS after the treatment of prednisone, but without RPLS. After the use of CTX and VCR on day 7, RPLS occurred within 24 h. Hypertension was also a risk factor in this patient.

Hypomagnesemia is also associated with RPLS.[3] In the patient described here, the magnesium level was always low. It dropped to 0.47 mmol/L the day before the episode and remained below 0.50 mmol/L during the following days.

Early recognition of RPLS is vital. Once the condition is recognized, offending agents such as antineoplastic drugs should be identified and withheld, and abnormalities such as high blood pressure, renal dysfunction, and hypomagnesemia should be corrected. After recognition of RPLS in the current patient, chemotherapy was withheld except corticosteroid,

considering it could help alleviate encephaledema. There are some evidences supporting that steroid administration might have beneficial effects.[2] Renal dysfunction was corrected by hemodialysis. $MgSO_4$ was not used to improve the serum level of magnesium in this patient. The blood pressure was controlled only after managing the high intracranial pressure with mannitol, indicating that hypertension may in fact be a secondary effect of RPLS.

There is another issue to which we should pay extra attention during the management of RPLS. Status epilepticus (SE) can be the initial presenting symptom of RPLS. However, more patients just have nonconvulsive SE (NCSE).[6] Clinical abnormalities such as eye fluttering, prolonged confusion, and coma can be indicators of underlying seizures. Electroencephalogram (EEG) recordings are crucial to diagnose NCSE. Prompt recognition of SE and initiation of treatment are essential because delays can cause irreversible neurologic sequelae or death. After seizures, the current patient went to coma during the following 10 d. Unfortunately, we did not have EEG recordings so that there was no evidence to diagnose NCSE. According to the prolonged coma and irreversible MRI imaging, we speculate probably she had NCSE and should get proper treatment.

RPLS is usually reversible if the underlying causative condition is promptly addressed. The majority of patients previously reported have complete or near-complete resolution of clinical and radiological changes within days to weeks.[1] Although initially termed RPLS, still there have been reports of irreversible change and consequent disability.[7] The lesions in our case are irreversible, as evidenced on follow-up images [Figure 2]. We emphasize the importance of early recognition of RPLS and institution of appropriate management in reducing the risk of development to permanent neurological disability.

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Conflicts of interest

There are no conflicts of interest.

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