**CASE REPORT**

Diffuse Leukoencephalopathy Associated with Dialysis Disequilibrium Syndrome

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**Abstract**

A 52-year-old woman, previously treated for gastric cancer, began hemodialysis (HD) to treat the onset of severe acidemia. After her initial HD sessions, she suffered from a prolonged coma for approximately ten days. Magnetic resonance imaging revealed diffuse leucoencephalopathy, with increased apparent diffusion coefficient. Magnetic resonance spectroscopy showed a reduction of the N-acetylaspartate/creatine ratio. Her neuroimaging findings gradually resolved. Her transient cerebral white matter lesions were thought to be interstitial edema derived from dialysis disequilibrium syndrome (DDS), which might have been amplified by subclinical brain injury due to past chemotherapy. Her history of cancer chemotherapy may be a risk factor for an exacerbation of DDS.

**Key words:** cancer chemotherapy, interstitial edema, apparent diffusion coefficient map, magnetic resonance spectroscopy

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**Introduction**

Dialysis disequilibrium syndrome (DDS) is an acute neurological complication of hemodialysis (HD) (1), especially in patients undergoing rapid dialysis during their initial treatment (2). Clinical features include headache, nausea, hypertension, seizures, and coma, leading to death in some severely affected patients (3, 4). Since DDS is a clinical diagnosis, a radiological study is mainly used to exclude other central nervous system (CNS) diseases. However, since the pathogenesis of DDS is thought to be cerebral edema, diffusion-weighted magnetic resonance imaging (MRI) may be helpful for revealing the presence of cerebral edema and diagnosing DDS (1). We herein report a case of diffuse leucoencephalopathy associated with DDS after the initial sessions of HD. Based on the findings on MRI and magnetic resonance spectroscopy (MRS) of the patient’s brain, we discuss the pathogenesis of her white matter lesions.

**Case Report**

A 52-year-old woman, who had diabetic nephropathy and a past history of gastric cancer, developed a coma approximately ten days after HD for metabolic acidosis. The patient had suffered from diabetic nephropathy and nephrotic syndrome for three years, and her creatinine level had been approximately 3 mg/dL. Two years prior to this presentation, she had undergone partial gastrectomy for gastric cancer and received oral chemotherapy with TS-1 (an anticancer drug consisting of tegafur, gimeracil, and oteracil) and lentinan intravenous infusion. However, she also went to another clinic, where she had received “cancer immunotherapy” [infusion of natural killer (NK) cells, bevacizumab, and cancer-associated genes including p53, fused in sarcoma-1 (FUS-1), tumor necrosis factor-related apoptosis inducing ligand (TRAIL), and interleukin 24 (IL-24)], which was not covered by health insurance. She received these chemotherapy regimens from both clinics for several months; then she had continued only infusion of cancer-associated genes, which

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had often been associated with reactive fever. She did not receive radiation therapy. Eighteen days before admission, she received gene infusion therapy and suffered fever, epigastralgia, and diarrhea. After a partial resolution, her epigastralgia and general fatigue continued. She received a red cell transfusion for anemia, but her symptoms continued. Then she came to our hospital and was admitted.

She did not smoke, drink alcohol, or use illicit drugs. She had no food or drug allergy. Although she had diabetic retinopathy, her hemoglobin A1c had been normal after gastrectomy without any antidiabetic therapy.

On examination, the patient was alert and oriented. Her temperature was 36.2°C, blood pressure 115/51 mmHg, pulse 105 beats per minute, and oxygen saturation 96% while breathing ambient air. Her respiratory and heart sounds were normal, and there was no ankle edema. The remainder of the examination was normal. Laboratory studies revealed a mild elevation of liver enzymes, anemia (hemoglobin 7.7 g/dL and hematocrit 23.3%), uremia (serum blood urea nitrogen 75.8 mg/dL and creatinine 6.46 mg/dL), and hyperkalemia (5.7 mEq/L). Creatine kinase, C-reactive protein, blood counts, and coagulation test results were almost within normal limits. The findings of an electrocardiogram and chest X-rays were normal.

Since an infusion of 8.4% sodium bicarbonate was not effective, she underwent a three-hour session of emergent HD on the second hospital day and another three-hour session of HD on the third hospital day. The dialysis blood flow rate was 150 mL/min. The PS-1 dialyzer was manufactured by Kawasumi Laboratories, Inc., Tokyo, Japan (polysulfone membrane, effective surface area: 1.3 m²). Bicarbonate dialysate was used, and the dialysate flow rate was 500 mL/min. Red blood cells were also transfused on the second hospital day. During the second HD session, the patient’s systolic/diastolic blood pressure ranged between 166/80 and 188/86 mmHg. Laboratory data before the first HD session and data after the second HD session are shown in Table.

|                      | Before hemodialysis / first admission | After hemodialysis / first admission (with DDS) | Before hemodialysis / second admission | After hemodialysis / second admission (without DDS) |
|----------------------|--------------------------------------|-----------------------------------------------|----------------------------------------|---------------------------------------------------|
| pH                   | 7.22                                 | 7.352                                         | 7.26                                   | 7.332                                             |
| PCO₂ (mmHg)          | 25.8                                 | 44                                            | 34.8                                   | 41.8                                              |
| HCO₃⁻ (mmol/L)       | 10.3                                 | 23.9                                          | 15.3                                   | 21.6                                              |
| Base excess (mmol/L) | -15.9                                | -1.7                                          | -10.8                                  | -4                                                |
| Hemoglobin (g/dL)    | 6.8                                  | 9.3                                           | 8.3                                    | None                                              |
| Hematocrit (%)       | 19.9                                 | 27.1                                          | 25.4                                   | None                                              |
| Serum albumin (g/dL) | 2.4                                  | None                                          | 2.1                                    | None                                              |
| BUN (mg/dL)          | 76.9                                 | 27.1                                          | 101                                    | 64.7                                              |
| Creatinine (mg/dL)   | 6.56                                 | 2.91                                          | 9.21                                   | 6.07                                               |
| Sodium (mEq/L)       | 146                                  | 138                                           | 137                                    | 137                                               |

Note that the data after hemodialysis at the first admission were obtained after the first two daily hemodialysis sessions. The blood gas analysis data were acquired from venous blood except for the data after hemodialysis at the first admission, which were from arterial blood.

Abbreviations: DDS: Dialysis disequilibrium syndrome, PCO₂: partial pressure of carbon dioxide, HCO₃⁻: bicarbonate, BUN: blood urea nitrogen.

After the second HD on the third hospital day, the patient complained of nausea and headache. Five hours later she became confused for several hours. Her blood pressure was 195/90 and computed tomography of her brain revealed white matter low density. Early morning on the next (fourth) hospital day, she became comatose and general convulsions occurred. At this time, T₂-weighted and fluid-attenuated inversion recovery (FLAIR) MRI of the patient’s brain revealed diffuse hyperintensity signal regions in the cerebral white matter (Fig. 1). These lesions were slightly hypointense on diffusion-weighted imaging (DWI) and hyperintense on the apparent diffusion coefficient (ADC) map (Fig. 1). In the lower part of the cerebrum the abnormalities were less prominent, and the brainstem and cerebellum were almost normal.

Since her acidemia and uremia did not become exacerbated, the dialysis was stopped, and conservative therapy with an antibiotic and anticonvulsant was started. Blood tests showed that the liver enzymes, creatine kinase, electrolytes, C-reactive protein, blood counts, and coagulation test results were within normal limits. The anti-human immunodeficiency virus antibody and autoantibodies were negative. A cerebrospinal fluid (CSF) study showed a normal protein concentration, cell count, and IgG-albumin index. Her myelin basic protein was not elevated. Her electroencephalogram (EEG) revealed triphasic waves without any epileptic activity.

On the ninth hospital day, spontaneous swallowing and slight reaction to stimuli appeared. On the next day, her serum albumin concentration was low at 1.6 g/dL. She received a 25% human serum albumin infusion for two days; thereafter, her serum albumin level rose to 2.1 g/dL. On the eleventh hospital day, she began to respond verbally; then her level of consciousness rapidly improved. On the 15th hospital day, her brain MRI findings were improving (Fig. 1), and MR angiography and venography were normal. An MRS scan with the region of interest in the frontal subcortical area was acquired (Fig. 2), and the metabolite ratios...
of N-acetylaspartate (NAA)/creatine (Cr) and choline (Cho)/Cr ratios were calculated from the relative peak height measurement of the acquired spectra. At this time the NAA/Cr and Cho/Cr ratios were 1.23 and 1.43 on the right side and 1.25 and 1.53 on the left side, respectively. Since there was no epileptic discharge on the second EEG, the anticonvulsant was discontinued. On the 42nd hospital day, her MRI was unremarkable (Fig. 1); the NAA/Cr and Cho/Cr ratios were 1.66 and 1.49 in the right side and 1.44 and 1.31 in the left side, respectively. After she underwent a rehabilitation program for disuse weakness, she was discharged.

About three months later, the patient became uremic, and was admitted again to this hospital (Table). She underwent HD again, with dialysis blood flow rate 80 mL/min. The BK-1.0 dialyzer was manufactured by Toray Medical Co., Ltd., Tokyo, Japan (polymethylmethacrylate membrane, effective surface area: 1.0 m²). Bicarbonate dialysate was
used, and the dialysate flow rate was 300 mL/min. At the beginning of the two sessions, the duration of hemodialysis was two hours, and thereafter it was prolonged to three hours. The patient did not show any complications and her MRI at this time did not show any changes. She was then introduced to chronic HD (PS-1.3 dialyzer, Kawasumi Laboratories, Inc., dialysis blood flow rate 150 mL/min for three hours, three times per week) without any recurrent symptoms.

**Discussion**

An acute neurological complication associated with hemodialysis without any other diseases is clinically diagnosed as DDS (1, 2, 5). As reversible cerebral white matter diseases associated with DDS, osmotic demyelination syndrome (ODS) (6, 7) and posterior reversible encephalopathy syndrome (PRES) (2, 8) have been known. ODS is a demyelinating disorder caused by the rapid increase of sodium in hyponatremia, chronic alcoholism, malnutrition, and chronic liver disease (6). White matter lesions have been thought to represent a combination of edema and demyelination (7). PRES is a reversible encephalopathy (especially in the posterior white matter) caused by the breakdown of the blood-brain barrier (BBB) due to acute hypertension or vascular endothelial dysfunction (9, 10). Typical lesions of both ODS and PRES are hyperintense on T2-weighted and FLAIR images on MRI, but DWI can discriminate them (11). In ODS lesions, decreased ADC values suggest cytotoxic edema (7); these lesions are hyperintense on DWI and hypointense on the ADC map. Meanwhile, increased ADC values suggest vasogenic edema in the lesions of PRES. These lesions are hypo- or isointense on DWI, although some lesions are hyperintense on DWI depending on its severity (9). Moreover, a reversible reduction of NAA has also been reported in regions with vasogenic edema of PRES (12). In the present case, the white matter lesions were hyperintense on the ADC map, and MRS showed a transient decrease of the NAA peak in the white matter, suggesting a mechanism of vasogenic edema, as in PRES.

Since the distribution of the lesions of PRES is usually not homogeneous, even in the broad distribution of the “holohemispheric watershed pattern” (13), diffuse leukoencephalopathy is atypical for PRES. Cases of diffuse leukoencephalopathy associated with DDS, similar to our case, have also been reported (5, 14, 15). Although Chang et al. thought demyelination due to DDS was the cause in their case, they described that apparent diffusion images on MRI demonstrated increased signals in bilateral cerebral white matter (5). Based on studies of renal disease in rats (16) and in patients with end-stage renal disease (17), the cerebral edema of DDS is considered to be from diffuse interstitial edema and an ADC increase in white and gray matter. Therefore, it is possible that the diffuse white matter changes with an increased ADC seen in the present case showed broad interstitial edema due to the severe DDS rather than from demyelination.

As a cause of an unusual exacerbation of DDS, Chang et al. suggested pre-existing CNS disease, i.e., an underlying age-related cerebral degenerative process and old ischemic

**Figure 2.** MRS images with region of interest in the frontal subcortical area. Serial proton MRS from the second MRI scan was acquired using a spin-echo spectroscopy sequence with parameters of 2,000/136 (repetition time/echo time) using 128 scans and single voxel volume 20 × 20 × 20 mm. Spectra obtained in the right (A) and the left (B) hemisphere on the 15th hospital day showed that the NAA peak was lower than the Cho peak. On the 42nd hospital day, spectra obtained in the right (C) and the left (D) hemisphere revealed that the NAA peak was higher than the Cho peak. Although the first MRS revealed an equivocal lactate peak in the left frontal lobe (B), there were no lactate peaks in the other MRS studies. MRS: magnetic resonance spectroscopy, NAA: N-acetylaspartate, Cho: choline.
infarcts (5). In reports of critical DDS cases, the complication of sepsis was thought to be the amplifier of cerebral edema through altered BBB permeability, which then led to brain herniation and death (3, 4). In our patient, although brain imaging before the development of DDS was not performed, there was no past history of CNS disease. However, our patient had received “cancer immunotherapy” (infusion of NK cells and cancer-associated genes) and chemotherapy (tegafur and bevacizumab). The cancer-associated gene infusions, performed regularly until the first admission in the present patient, might have caused fever, gastrointestinal symptoms, and dehydration, which might thus have led to the exacerbation of chronic kidney dysfunction and metabolic acidosis in the first admission. However, to our knowledge, no reports have so far been published that describe any association of NK cell infusion and cancer-associated gene therapy with DDS and leukoencephalopathy. Tegafur, a 5-fluorouracil derivative, might cause diffuse injury to the cerebral white matter, but not to the vessel wall (18). Bevacizumab, a recombinant humanized monoclonal anti-vascular endothelial growth factor (VEGF) antibody, decreases the permeability of the BBB through the inhibition of VEGF, which causes vasodilation and increased capillary permeability of the vascular endothelium (19). In spite of this BBB “stabilizing” effect (20), bevacizumab, often accompanied with other chemotherapeutic agents, especially 5-fluorouracil (21), might cause PRES (21, 22). An increase in blood pressure (21) and VEGF signaling pathway downregulation (22) in the vascular endothelium have all been speculated as possible mechanisms of developing PRES due to bevacizumab. We also speculate that, in our patient, subclinical BBB dysfunction might have been caused by the chemotherapeutic agents she had received, and then exacerbated the DDS after her initial hemodialysis, thus leading to diffuse leukoencephalopathy.

Since treatment of DDS is difficult after onset, prevention is the ideal management strategy (4). Slow initial hemodialysis was one of the preventive measures performed in our case during our patient’s second admission. Meanwhile, it has been reported that blood transfusion (23) and decreased serum albumin levels (9) might be risk factors for the vasogenic edema of PRES, and serum albumin infusion might be therapeutic (9). In the present case, although blood transfusions were administered before and during the initial HD sessions and albumin transfusion was given for hypalbuminemia, the influence of these treatments on the patient’s clinical course was unclear. These factors therefore need to be investigated in future similar cases.

In conclusion, we herein described a case of diffuse leukoencephalopathy associated with DDS that developed after undergoing initial hemodialysis. Considering the patient’s past history of gastric cancer chemotherapy and her MRI findings, a past history of cancer chemotherapy may therefore be a risk factor for an exacerbation of DDS.

This case was presented at the 42nd Eastern Regional Meeting of the Japanese Society of Nephrology by Kozo Kitazawa (second author). We herein report this case with additional MRI and MRS findings.

The authors state that they have no Conflict of Interest (COI).

References

1. Patel N, Dalal P, Panesar M. Dialysis disequilibrium syndrome: a narrative review. Semin Dial 21: 493-498, 2008.
2. Sheth KN, Wu GF, Messer SR, Wolf RL, Kasner SE. Dialysis disequilibrium syndrome: another reversible posterior leukoencephalopathy syndrome? Clin Neurol Neurosurg 105: 249-252, 2003.
3. Bagshaw SM, Peets AD, Hameed M, Boitue PJ, Laupland KB, Doig CJ. Dialysis Disequilibrium Syndrome: brain death following hemodialysis for metabolic acidosis and acute renal failure - a case report. BMC Nephrol 5: 9, 2004.
4. Shaikh N, Louon A, Hanssens Y. Fatal dialysis disequilibrium syndrome: A tale of two patients. J Emerg Trauma Shock 3: 300, 2010.
5. Chang CH, Hsu KT, Lee CH, et al. Leukoencephalopathy associated with dialysis disequilibrium syndrome. Ren Fail 29: 631-634, 2007.
6. Ağildere AM, Benli S, Ertan Y, Coşkun M, Boyvat F, Ozdemir N. Osmotic demyelination syndrome with a dysequilibrium syndrome: reversible MRI findings. Neuroradiology 40: 228-232, 1998.
7. Tarhan NC, Ağildere AM, Benli US, Ozdemir FN, Aytekin C, Can U. Osmotic demyelination syndrome in end-stage renal disease after recent hemodialysis: MRI of the brain. Am J Roentgenol 182: 809-816, 2004.
8. Soomro A, Al Bahri R, Alkhassan N, Hejaili FF, Al Sayyari AA. Posterior reversible encephalopathy syndrome with tactile hallucinations secondary to dialysis disequilibrium syndrome. Saudi J Kidney Dis Transpl 25: 625-629, 2014.
9. Pirker A, Kramer L, Voller B, Loadar B, Auff E, Prayer D. Type of edema in posterior reversible encephalopathy syndrome depends on serum albumin levels: an MR imaging study in 28 patients. Am J Neuroradiol 32: 527-531, 2011.
10. Graham BR, Pylypchuk GB. Posterior reversible encephalopathy syndrome in an adult patient undergoing peritoneal dialysis: a case report and literature review. BMC Nephrol 15: 10, 2014.
11. Casey SO, Truwit CL. Pontine reversible edema: A newly recognized imaging variant of hypertensive encephalopathy? Am J Neuroradiol 21: 243-245, 2000.
12. Eichler FS, Wang P, Wityk RJ, Beauchamp NJ Jr, Barker PB. Diffuse metabolic abnormalities in reversible posterior leukoencephalopathy syndrome. Am J Neuroradiol 23: 833-837, 2002.
13. Bartsynski WS, Boardman JF. Distinct imaging patterns and lesion distribution in posterior reversible encephalopathy syndrome. Am J Neuroradiol 28: 1320-1327, 2007.
14. Attur RP, Kandavare R, Kadavigere R, Baig WW. Dialysis disequilibrium syndrome presenting as a focal neurological deficit: a preliminary report of brain edema in patients with uremia at first hemodialysis: another reversible posterior leukoencephalopathy syndrome. Am J Neuroradiol 28: 1320-1327, 2007.
15. Yetim E, Gocmen R, Topcuoglu MA, Arsava EM. Reversible white matter edema in dialysis disequilibrium syndrome. J Neuroradiol 42: 247-249, 2015.
16. Galons JP, Trouard T, Gmitro AF, Lien YH. Hemodialysis increases apparent diffusion coefficient of brain water in nephrectomized rats measured by isotropic diffusion-weighted magnetic resonance imaging. J Clin Invest 98: 750-755, 1996.
17. Chen CL, Lai PH, Chou KJ, Lee PT, Chung HM, Fang HC. A preliminary report of brain edema in patients with uremia at first hemodialysis: evaluation by diffusion-weighted MR imaging. Am J Neuroradiol 28: 68-71, 2007.
18. Ohara S, Hayashi R, Hata S, Itoh N, Hanyu N, Yamamoto K.
Leukoencephalopathy induced by chemotherapy with tegafur, a 5-fluorouracil derivative. Acta Neuropathol 96: 527-531, 1998.

19. Stewart MW. The expanding role of vascular endothelial growth factor inhibitors in ophthalmology. Mayo Clin Proc 87: 77-88, 2012.

20. Thompson EM, Frenkel EP, Neuwelt EA. The paradoxical effect of bevacizumab in the therapy of malignant gliomas. Neurology 76: 87-93, 2011.

21. Seet RC, Rabinstein AA. Clinical features and outcomes of posterior reversible encephalopathy syndrome following bevacizumab treatment. QJM 105: 69-75, 2012.

22. Abbas O, Shamseedin A, Temraz S, Haydar A. Posterior reversible encephalopathy syndrome after bevacizumab therapy in a normotensive patient. BMJ Case Rep 2013: 2013.

23. Sato Y, Hirose M, Inoue Y, et al. Reversible posterior leukoencephalopathy syndrome after blood transfusion in a patient with end-stage renal disease. Clin Exp Nephrol 15: 942-947, 2011.