Reversible Posterior Leukoencephalopathy Syndrome Associated with Treatment for Acute Exacerbation of Ulcerative Colitis

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Abstract

Reversible posterior leukoencephalopathy syndrome (RPLS) is a clinical syndrome of varying etiologies with similar neuroimaging findings. This is a case report of a 25-year-old woman who developed typical, neurological symptoms and magnetic resonance imaging abnormalities after treatment for the acute exacerbation of ulcerative colitis (UC), which included blood transfusion, the systemic administration of prednisolone, and the administration of metronidazole. It has been reported that these treatments may contribute to the development of RPLS. RPLS should therefore be considered in the differential diagnosis of UC patients who exhibit impaired consciousness, seizures or visual deficits during treatment. We report a rare case of RPLS in a patient with UC.

Key words: reversible posterior leukoencephalopathy syndrome, ulcerative colitis

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Introduction

Reversible posterior leukoencephalopathy syndrome (RPLS) was first clinically and radiologically described by Hinchey in 1996 (1). It is characterized by the following features: 1) various neurological symptoms, such as headache, mental disorder, tetanus and visual abnormality; 2) cranial computed tomography (CT) and magnetic resonance imaging (MRI) findings of cerebral edema in the white matter of the occipital to the parietal lobes; and 3) the reversible resolution of the symptoms and imaging findings through the control of blood pressure, treatment of the underlying disease, or discontinuing the use of the causative medication. With the development of imaging diagnostics, RPLS has been reported with increasing frequency in many diseases; however, reports of RPLS associated with inflammatory bowel disease (IBD) are rare. The underlying diseases in patients with RPLS range from simple infections to diseases treated with anti-cancer drugs or immunosuppressive agents. There are some reports on the potential contribution

of treatments, such as cyclosporine (1), steroids (2-4) and blood transfusion (5, 6), which are frequently employed in the treatment of the severe manifestations of IBD. RPLS should be considered in the differential diagnosis of IBD patients who exhibit impaired consciousness, seizures or visual deficits during treatment. We herein present a rare case of a patient who experienced and recovered from RPLS during treatment for the acute exacerbation of ulcerative colitis (UC).

Case Report

A 25-year-old woman presented to an emergency room complaining of profuse bloody diarrhea with more than 20 bowel movements per day and fever (<38.0°C). She had been diagnosed with UC 4 years previously, and had declined regular treatment in the 2 years prior to her emergency room presentation. With the exception of UC, she had no medical history. Her blood pressure was 100/60 mmHg at presentation. A physical examination was normal, with the exception of conjunctival pallor. A cardiac examination

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Figure 1. Contrast enhanced abdominal CT images at admission. The images showed enhancement-positive and sequential wall thickness with loss of haustra in the entire colon (arrowheads).

was normal and her lungs were clear. An abdominal examination showed a flat abdomen that was soft and had no tenderness to palpation. A blood analysis at presentation showed a white blood cell count of $10,800/\text{mm}^3$, hemoglobin 7.9 g/dL, blood urea nitrogen (BUN) 44.6 mg/dL, creatinine 3.22 mg/dL, C-reactive protein (CRP) 12.27 mg/dL, and an erythrocyte sedimentation rate of 39 mm/hr. A stool test for *Clostridium difficile* toxin was negative. Urgent colonoscopy was avoided because the patient's UC activity was determined to be severe according to the criteria of the Truelove and Witts' classification (7). The distribution and intensity of the colonic inflammation was confirmed by contrast enhanced CT. Total colonic inflammation was detected, which showed the loss of haustral marking, positive enhancement and sequential wall thickening from the rectum to the ascending colon (Fig. 1). Rehydration and a blood transfusion (total blood volume: 960 mL) were performed for severe dehydration and anemia. She was also treated, starting at admission, with cefazolin [2.0 g/day, intravenous (i.v.)], vancomycin [2,000 mg/day, per oral (p.o.)], and 5-aminosalicylate acid (5-ASA 2,250 mg/day, p.o.). Prednisolone treatment (60 mg/day i.v.) was also started on the 5th hospital day. The dose was subsequently decreased (50 mg/day from 10th to 14th; 40 mg/day from 15th to 18th hospital day) and stopped on the 19th hospital day. In addition to these treatments, metronidazole was administered on the 10th hospital day, following the administration of vancomycin. At night, her blood pressure increased to 140/90 mmHg, which was obviously higher than usual and she complained of a headache of sufficient severity to warrant the administration of analgesic medication. She presented a sudden disturbance of consciousness with tetanus the next morning. A blood test revealed a WBC of $14,300/\text{mm}^3$, hemoglobin 10.0 g/dL, BUN 27.5 mg/dL, creatinine 0.99 mg/dL, and CRP

0.99 mg/dL. The blood sample was negative for herpes simplex virus (HSV) antibodies, IgG and IgM. A cerebrospinal fluid (CSF) test showed clear, colorless and acellular fluid with a total protein level of 18 mg/dL and a glucose level of 83 mg/dL. The patient's CSF sample was negative for anti-HSV antibodies (IgG and IgM) and HSV-DNA. Cranial CT showed brain edema. Although a stroke was excluded by MRI, T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI of the brain revealed an increased signal intensity in the occipital and parietal lobes (Fig. 2A). An electroencephalogram showed slow waves in all parts of the brain (Fig. 3). RPLS was considered for the diagnosis based on the MRI findings, which were typical for RPLS.

Phenytoin and glyceol were administered to prevent the recurrence of tetanus and treat the brain edema, respectively. Metronidazole was discontinued because it was a potential cause of the patient's RPLS. Prednisolone and 5-ASA were continued because she had been taking those treatments for a long time before the onset of symptoms. Additionally, aciclovir (1,500 mg/day, i.v.) was administered because we also considered the possibility of herpes simplex encephalitis (HSE) and hypothesized that the absence of HSV antibodies might have been the result of false negatives because the condition was in the early phase of onset. The next day, she recovered from her consciousness disturbance without neurological complications. MRI on the 8th day after the onset showed that the high signal intensity in the occipital and parietal lobes had disappeared (Fig. 2B). No recurrence of the patient's neurological symptoms was observed until she was discharged. Colonoscopy performed on the 23rd hospital day showed improvement of the colonic mucosa (Fig. 4).

Figure 2. Fluid-attenuated inversion recovery of MRI of the brain. The images at development of RPLS showed high signal intensity (arrows) in the occipital and parietal lobes (A). The abnormality completely disappeared 8 days after the development (B).

Figure 3. Electroencephalogram during loss of consciousness after the tetanus. Slow waves are detected over entire areas.

Discussion

We reported the case of a 25-year-old woman who suffered from RPLS during treatment for UC. There have been only two previously published reports on RPLS associated with IBD that focus specifically on patients with UC (8, 9). In the treatment of IBD, many different medications, such as

corticosteroids, immunosuppressive agents, and biological agents, are routinely used simultaneously and administered for extended periods of time. Physicians should be aware of these medications can potentially contribute to the development of RPLS.

RPLS was first described in 1996 (1). It is characterized by the following features: clinical signs, such as headache, mental disorder, seizure and visual deficits with hypertension, as well as neuroimaging findings on MRI or CT, indicating the presence of edematous lesions in the occipital and parietal lobes that are reversible with the successful treatment of the cause of the symptoms (10). Vasogenic edema in the central nervous system, leading to neurological symptoms is reported to be the main cause of RPLS; (11) however, the change is non-specific. RPLS is gaining attention because it develops as a side effect of medication in addition to developing from internal diseases such as hypertensive encephalopathy and puerperal eclampsia (which are known to be forms of reversible encephalopathy). Among the causative medications, the administration of immunosuppressants (2, 12-14), especially cyclosporine and tacrolimus, is most frequently reported before the manifestation of RPLS. Treatment for RPLS usually involves the reduction or discontinuation of the causative medication(s) and blood pressure control as soon after the onset of symptoms as possible in order to prevent the reversible symptoms from developing into irreversible dysfunctions of the central nervous system (15, 16). Stroke and central venous thrombosis

Figure 4. Distal colonoscopy showed irregular mucosa with high-grade neoplasia (A) and polypoid mucosal tag in a contrast image by indigo carmine spraying (B).

(CVT) should also be considered as possibilities in the differential diagnoses for RPLS (9). CVT is a rare but devastating complication for IBD patients who are prone to thrombosis (17-19). The most common symptom of CVT is headache (80%), followed by seizure (35%), and altered conscious (21%), which are similar to the neurological symptoms of RPLS (18). CT or MRI venography is essential to the diagnosis, and anticoagulant therapy is a necessary component of the treatment. In the patient of the present case, we did not exclude the diagnosis of CVT because her clinical symptoms were observed to have completely recovered on the day after the occurrence.

Dou et al. reviewed a few cases of RPLS after blood transfusion (20), in which the patients received multiple blood transfusions, for a total volume of 800-3,000 mL, over a period of 5-7 days. The onset of symptoms occurred 2-10 days after the last blood transfusion. The authors concluded that RPLS was likely for patients with severe anemia resulting in a >5 g/dL increase in hemoglobin. Cerebral vasoconstriction was demonstrated by MRI in cases of RPLS after blood transfusion (20, 21). In our case, blood transfusions (total volume: 960 mL) were performed for 5 days after admission. The blood transfusions resulted in a hemoglobin increase from 7.9 g/dL to 9.9 g/dL by the time of the onset of the patient's symptoms, which was 5 days after the last blood transfusion. Therefore, blood transfusion was considered to be a possible cause of the patient's RPLS.

The association between steroid use and the development of RPLS is elusive since steroids are frequently used concomitantly with other medications, including cyclosporine (1, 4, 22-24) to treat underlying diseases, such as renal failure or connective tissue diseases, which may also lead to RPLS (22, 25). Thus, the contribution of steroid therapy to RPLS remains unclear. In our case, the serum creatinine concentration increased to more than 3 mg/dL on admission and rapidly decreased to 2.0 mg/dL after rehydration. This rapid reduction in dehydration may also contribute to the development of RPLS. Although it is unclear whether

steroid therapy is involved in the development of RPLS, the possibility was considered to be unlikely (as noted above) in our patient because her symptoms improved without the discontinuation of steroid therapy.

In the present case, metronidazole-induced encephalopathy (MIE) was one of the more likely causes of RPLS because the patient developed a headache that coincided with the initiation of the metronidazole treatment, and because her neurological symptoms were observed the following day. Reports in relation to MIE (12, 26, 27) have indicated that it can be reversed in all patients, and that the onset of symptoms was delayed after the administration of metronidazole. The total dose of metronidazole and the duration of treatment that resulted in the development of MIE were reported to be 45-120 g and 1-12 weeks, respectively (28), suggesting that the development of MIE depends on the dosage and duration. In the present case, the total dose was only 500 mg for one day. The time to clinical improvement after the discontinuation of metronidazole has been reported to be approximately one week; (26, 27) however, our case improved after only one day. Although metronidazole was the likely cause of RPLS, the case seems to be an atypical presentation of MIE.

We focused on HSE as a possible differential diagnosis. The most common area of HSE involvement on MRI is the medial-temporal cortex (85% sensitivity). This finding, however, can mimic atypical RPLS with frontal distribution (29). The polymerase chain reaction (PCR) detection of viral DNA from the CSF is considered to be the standard test for the diagnosis of HSE, with sensitivity and specificity of over 95% (30). However, false-negative PCR results of may be possible when a CSF sample is taken in the very early phase of HSE (1-4 days after onset). In our case, aciclovir was continued until the diagnosis of RPLS was confirmed because we were not able to rule out the possibility of HSE. However, we subsequently learned that encephalopathy is an infrequent but well-recognized adverse effect of aciclovir (31). We should have considered the possibility

that the administration of aciclovir could have led to the deterioration of the patient's RPLS symptoms, because it had the potential to further complicate the patient's condition. Electroencephalogram (EEG) is also useful for diagnosing RPLS, which is demonstrated by a periodic lateralized epileptiform (30) or a generalized slow wave pattern (32), as was observed in our present case.

In conclusion, medications that may cause RPLS are often used in the treatment of UC. RPLS should be considered in the differential diagnosis when UC patients develop neurological symptoms, including consciousness disturbance, tetanus and visual disorders, and the possible causative medications should be stopped. Furthermore, immediate intervention is important to prevent the patient's reversible pathological condition from becoming irreversible.

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

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