Recurrent Cerebral Hemorrhage Associated with Ulcerative Colitis

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Abstract

Ulcerative colitis (UC) is a rare cause of stroke. Most such cases result from cerebral venous thrombosis, and cerebral vasculitis is one cause of venous thrombus formation. Here, we report a patient with UC who experienced recurrent cerebral hemorrhage. A 53-year-old Japanese woman with UC presented with sudden onset of disorientation and sensory aphasia. Brain computed tomography revealed cerebral hemorrhage in the left temporal lobe. She had a history of UC for two decades but had discontinued her medication. On the fifth hospital day, another cerebral hemorrhage occurred in the right occipital lobe. After steroid therapy, these abnormal findings on MRI improved within a short time, and she was discharged from hospital with no sequelae. Physicians should be alert to cerebral hemorrhage in patients with UC, consider cerebral vasculitis as an etiology, and treat with steroid therapy for a good outcome.

Key words

Cerebral hemorrhage, ulcerative colitis, neurologic complication

Introduction

Ulcerative colitis (UC) is a diffuse non-specific inflammatory bowel disease that mostly affects the mucosa of the large intestine. Neurologic disease is one of the extra-intestinal complications of UC. Although there are some case reports of cerebral sinus thrombosis associated with UC, cerebral hemorrhage is extremely rare. We report a case of UC with recurrent cerebral hemorrhage that was treated by intravenous corticosteroids, which resulted in a good outcome.

Case Presentation

A 53-year-old woman developed sudden onset of disorientation and sensory aphasia. She had a medical history of UC diagnosed by intestinal biopsy 20 years ago and also iron deficiency anemia and osteoporosis. She had no risk factors for cerebrovascular disease and was a non-smoker. There was no family history of cerebrovascular disease or autoimmune disease. She was treated with steroids for a while and after that, she took only mesalazine but had discontinued her medication several years earlier. Colonoscopy was performed at another hospital three months before admission which revealed findings of inflammation throughout the large intestine, as grade 2 in Mayo endoscopic sub-score. The patient reported that she often had a lower abdominal pain and repeated diarrhea at night. She had up to six bloody bowel movements per day on admission. When she was talking on the phone with her mother on the night of hospital admission, the conversation had not made sense to her mother, who then called the patient’s husband. When he came home, they could not communicate with each other, and she was taken to hospital by ambulance.

On physical examination in the emergency department, she appeared ill and was febrile with a temperature of 38.1°C. Her blood pressure was 194/105 mm Hg, pulse 101/min, with a respiratory rate 30/min and O2 saturation of 99% on room air. She showed conjunctival pallor. Her cardiovascular examination was normal, lungs were clear to auscultation, and abdominal examination revealed tenderness in the lower abdomen, and she had bloody stool.
A neurological examination revealed disorientation with inability to tell date, person, and location. A higher cerebral function test revealed naming difficulty, fluent spontaneous speech, and normal repetition, but her verbal comprehension was impaired. There were no abnormal findings in the cranial nerves, motor system, reflex system, sensory system, coordination system, extrapyramidal system and autonomic nervous system. Her neurological findings were summarized as sensory aphasia, and her NIHSS score was 3 points.

Initial laboratory values on admission revealed microcytic anemia (white blood cell count 7400/µL, hemoglobin 6.9 g/dL, hematocrit 23.5%, mean cell volume 66.4 fl and platelet count 41.1×10^3/µL). Her anemia was considered to derive from apparent or inapparent continuous bleeding from colonic mucosa. Her C-reactive protein level was 0.81 mg/dL, and her erythrocyte sedimentation rate (ESR) was 45 mm/h. The coagulation screen showed a prothrombin time of 100% (normal 75–125%), INR 1.00, activated partial thromboplastin time 23.7 sec (normal 25–35 sec), fibrinogen 483 mg/dL and D-dimer 2.5 µg/mL (normal <0.5 µg/mL). Blood biochemistry tests were normal.

Brain computed tomographic (CT) scan revealed a high-density area surrounded by an area of low-density in the left temporal lobe (Figure 1A). On brain magnetic resonance imaging (MRI), this lesion showed high-intensity on fluid-attenuated inversion recovery (FLAIR) imaging (Figure 1B) and low-intensity on T2-weighted fast-field echo (FFE) imaging (Figure 1C), which was diagnosed as cerebral hemorrhage surrounded by edema.

The patient underwent CT angiography (CTA) and digital subtraction angiography (DSA), which revealed no obvious vascular abnormalities suggestive of vasculitis, thrombus, infectious aneurysm, arteriovenous malformation (AVM) or arteriovenous fistula (AVF) (Figure 2).

Concentrated glycerin was administered as an anti-edema therapy. She received oral mesalazine at a dose of 2,250 mg/day simultaneously as her frequent diarrhea, bloody stool, high fever, tachycardia, anemia and elevated ESR indicated the severity of her UC. Her neurological symptoms improved within a short time, and she could communicate almost normally on the 3rd hospital day (HD).

A brain MRI repeated on the 5th HD revealed another cerebral hemorrhage in the right occipital lobe (Figure 3, red circle). Magnetic resonance spectroscopy (MRS) performed on the 13th HD showed no pattern of demyelination or tumor (Figure 3), but the high-intensity area suggesting brain edema from the initial hemorrhage had expanded (Figure 3, red square). Magnetic resonance venography showed no findings of venous thrombosis.

Further laboratory evaluation showed negative antinuclear, anticardiolipin, other immunological examinations and tumor markers. Both myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) and proteinase3 ANCA (PR3-ANCA) were negative.

**Figure 1.** Initial radiographic studies.

Brain CT (A) on the 1st hospital day shows a high-density area surrounded by a low-density area in the left temporal lobe. This lesion appeared as a high-intensity area on the brain MRI FLAIR image (B) and as a low-intensity area on the FFE image (C) and was diagnosed as cerebral hemorrhage surrounded by edema.
Figure 2. Evaluation of vascular abnormalities.
CTA and DSA revealed no obvious vascular abnormalities suggestive of vasculitis, thrombus, infectious aneurysm, AVM or AVF.

Figure 3. Follow-up MRI studies.
Brain MRI on the 5th hospital day revealed another high-intensity area at the right occipital lobe (A). This lesion showed as low intensity on the FFE image (B) and was diagnosed as cerebral hemorrhage (red circle). MRS was performed on the 13th hospital day. A region-of-interest voxel was placed at the initial high-intensity area (red square in C). Acquisition parameters showed no pattern of demyelination or tumor (D). The high-intensity area suggestive of brain edema from the initial hemorrhage has expanded.

negative, but perinuclear ANCA (P-ANCA) measured by the indirect fluorescent antibody method was positive. Cerebrospinal fluid (CSF) examination showed a normal cell count and normal protein but elevation of myelin basic protein to 619 pg/mL. CSF cytology and blood culture were also negative. We discussed a brain biopsy but did not perform it because of the potential risk of neurological deficit. She had painless skin nodules without rash or redness on her right lower extremities, skin biopsy was performed from two nodules to search for vasculitis but no specific findings were observed. We considered
her to have cerebral hemorrhage caused by an autoimmune mechanism due to UC and administered intravenous corticosteroids 1000 mg per day from the 22nd to 25th HD, followed by oral prednisolone at 1 mg/kg/day. After steroid therapy, her brain MRI findings improved over time, and her neurological symptoms did not worsen. She was discharged on the 47th HD with no sequelae.

Oral steroids were gradually reduced, and brain MRI performed on the 61st day from disease onset revealed almost no high-intensity findings on FLAIR imaging (Figure 4).

Discussion

Guidelines for inflammatory bowel disease (IBD) define IBD as diseases of chronic or remitting/relapsing intestinal inflammation and include primary UC and Crohn’s disease. The number of patients with UC in Japan in 2013 (approximately 100 per 100,000 population) was quite low compared to that in Western countries. UC is a diffuse non-specific inflammatory disease of unknown cause that chronically affects the colonic mucosa proximally from the rectum and often forms erosions and/or ulcers. It frequently repeats cycles of relapse and remission during its course and may be accompanied by extraintestinal complications affecting the joints, skin, eyes and other areas.

In terms of neurological complications, Lossos et al. reported that 19 of 638 IBD patients (3%) and 9 of 261 UC patients (3.4%) had evidence of neurological involvement. Among these 9 UC patients, 6 had peripheral neuropathy, 2 had a stroke including sinus vein thrombosis, of which many cases are reported in Japan, and one had myelopathy. In a systematic search of the literature in the MEDLINE database, Scheid and Teich reported that there are three major pathogenic entities causing neurologic manifestations in patients with UC: first, cerebrovascular disease as a consequence of thrombosis and thromboembolism; second, systemic and cerebral vasculitis; and third, probable immune-mediated neuropathy and cerebral demyelination. Among neurologic disorders of undefined cause reported in patients with IBD, cerebrovascular disorders are documented in 0.12% to 4% of IBD patients. They can occur at any age in both sexes and tend to correlate with disease activity.

The severity of UC can be classified as mild, moderate or severe, based on clinical symptoms and signs and blood tests. Our patient was considered to have severe UC based on her frequent diarrhea,
bloody stool, pyrexia, tachycardia, anemia and elevated ESR. In Japan, most case reports of cerebrovascular complications of UC are of cerebral sinus thrombosis. A hypercoagulable state and cerebral vasculitis have been hypothesized as the etiologies.

Published case reports of UC patients with cerebral hemorrhage are listed in Table 1. Most of the complications were cerebral sinus/venous thrombosis that caused hemorrhagic infarction. The volume of hemorrhage tended to be massive with high mortality in those cases. In comparison with most of the other cases associated with cerebral hemorrhage, which resulted in fatal clinical outcomes, our patient experienced a good outcome.

Our patient had no predisposing factors for stroke and especially for cerebral hemorrhage. However, she suffered a second cerebral hemorrhage within a 5-day interval, and the high-intensity area suggesting brain edema at the initial hemorrhage expanded chronologically on MRI. The differential diagnosis during this period included malignancy, demyelination and vasculitis.

She also had an elevated level of myelin basic protein, which is a cause of demyelination, of 619 pg/mL on CSF examination. Abnormal values are observed in diseases such as multiple sclerosis and Beh-

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chet’s disease. Because our patient had no clinical symptoms or other laboratory or MRS findings suggesting such conditions, we considered the high level to be a secondary elevation due to myelin sheath destruction by cerebral hemorrhage.

Because her workup for malignancy was unrevealing, we considered a brain biopsy. We consulted with Neurosurgery, but at this point she was free of neurological symptoms. Therefore, because of the risk of biopsy causing a neurological deficit, especially a repeat of her sensory aphasia, we decided against brain biopsy.

Our patient had a positive P-ANCA but her levels of C-ANCA, MPO-ANCA and PR3-ANCA were within normal range. We performed skin biopsies of two nodules on her lower extremities to evaluate the evidence for systemic vasculitis, but no specific findings were observed. Unnikrishnan et al.14 reviewed 15 case reports of possible cerebral vasculitis in UC. Among them, 11 patients had definite vasculitis based on histopathology, angiography or serology. Necrotizing vasculitis was confirmed by brain biopsy in 3 patients and autopsy in one patient. Skin biopsy performed in 2 patients suggested possible systemic disease in one patient, but necrotizing vasculitis was not found. Most of these patients were treated with steroids alone or in combination with immunosuppressive therapy. One patient died, in whom autopsy had revealed necrotizing angiitis of the brain, but the other patients experienced a good outcome with steroid therapy.

Raj et al.15 reported a patient who showed large areas of multiple enhanced masses on brain MRI. With steroid therapy, the patient’s neurological symptoms improved rapidly, and at one-month follow-up, MRI showed resolution of the lesions, with no masses or mass effect and no abnormal enhancement. This chronological change on brain MRI was similar to that in our patient. Their patient underwent a brain biopsy that showed small-sized vessels with endothelial cell edema, infiltration by lymphocytes, neutrophils and possibly macrophages, and necrosis and hemorrhage, which were diagnosed as central nervous system vasculitis. They concluded that a brain biopsy may ultimately be necessary to diagnose this type of vasculitis. Although a brain biopsy was not performed and skin biopsies did not show any evidence of vasculitis in our patient, resolution of the brain lesions on MRI by steroid therapy suggested vasculitis as a possible etiology.

In conclusion, we experienced a patient with UC who suffered recurrent cerebral hemorrhages that were treated by intravenous corticosteroids, which resulted in a good outcome. Physicians should be alert to cerebral hemorrhage in patients with UC, consider cerebral vasculitis as an etiology, and treat with steroid therapy for a good outcome.

Conflicts of Interest

The authors have nothing to disclose.

References

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