CASE REPORT

Multiple Cerebral Infarction Associated with Cerebral Vasculitis in a Patient with Ulcerative Colitis

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Abstract:
A 40-year-old man was admitted to the hospital due to both a worsening of symptoms associated with ulcerative colitis (UC), which had been diagnosed 3 years previously, and limb paralysis. Colonoscopy revealed severe pancolitis-type UC. He was diagnosed with cerebral vasculitis with multiple white matter infarctions associated with the disease activity of UC by contrast-enhanced head magnetic resonance imaging. Mesalazine at 4,000 mg/day and prednisolone at 60 mg/day were started, and the prednisolone dosage was thereafter gradually reduced and switched to golimumab. He achieved a long-term remission from UC, and thereafter his neurological abnormalities improved significantly. He had no recurrence of cerebral infarction.

Key words: ulcerative colitis, cerebral infarction, cerebral vasculitis

Introduction
Ulcerative colitis (UC) is an inflammatory bowel disease that causes chronic inflammation of the large intestine, extending from the rectum to the ascending colon (1). In Asian countries, such as in Japan, as well as in western countries, the number of patients with UC has been increasing (2, 3). The chief complaints are bloody diarrhea and abdominal pain, although approximately 10-25% of UC patients are reported to be complicated by extraintestinal manifestations (4). Vasculitis syndromes, such as Takayasu arteritis or antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, are among the rare extraintestinal manifestations associated with UC (5, 6). Terao et al. demonstrated the genetic overlap between Takayasu arteritis and UC (7). Furthermore, Mahler et al. reported that proteinase 3-ANCA (PR3-ANCA), a well-known diagnostic marker of granulomatosis with polyangiitis, might be a biomarker for the severity of UC (8). In contrast, cerebral vasculitis as an extraintestinal manifestation of UC is quite rare. We herein report a rare case of cerebral vasculitis with multiple white matter infarctions associated with an active UC in a patient who successfully achieved remission with prednisolone and mesalazine treatment and thereafter has remained in remission from UC while receiving anti-tumor necrosis factor-alpha (anti-TNFα) therapy.

Case Report
A 40-year-old man was admitted to our hospital with a worsening the symptoms of bloody diarrhea and abdominal pain accompanied by right arm paralysis, left-sided hemiplegia, and a swallowing disorder that had started several days prior to his admission. He has a 30-month history of pancolitis-type UC that had been well-controlled with 5-aminosalicylic acid (5-ASA) treatment. However, he had stopped taking the medication based on his own judgement from 16 months prior to this presentation. He did not have any other medical history associated with arteriosclerosis and cerebral infarction, such as diabetes mellitus, hypertension, or dyslipidemia. He had no known allergic reactions to

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medications and foods.

Upon admission, his vital signs were as follows: blood pressure, 123/83 mmHg; heart rate, 63 beats/min; respiratory rate, 16 counts/min; oxygen saturation, 98%; and temperature, 36.2°C. His palpebral conjunctiva was not pale, his abdomen was flat and soft upon palpation, and his intestinal peristalsis was hyper-active. He had mild lower abdominal tenderness, although he did not have any rebound tenderness or abdominal guarding at any site of his abdomen. Additionally, he had left facial paralysis, slurred speech, right arm paralysis, left-sided hemiplegia, and a swallowing disorder. The patient’s National Institutes of Health Stroke Scale (NIHSS) score was 7 points (facial palsy, 1 point; left arm, 3 points; right arm, 1 point; left leg, 1 point; best language, 1 point).

The blood chemistry test results showed an obvious inflammatory status with a white blood cell count of 12,300/\mu \text{L} and a C-reactive protein level of 1.41 \text{mg/dL} (Table 1). The patient had no anemia or liver dysfunction, and no signs of dehydration due to the UC flare up occurring prior to reaching the hospital. The D-dimer level was slightly raised. Stool culture tests confirmed the absence of any pathologic bacteria.

Abdominal contrast-enhanced computed tomography (CT) revealed thickening of the mucosa from the transverse colon to the rectum due to UC (Fig. 1a, b). No marked colon expansion indicating a toxic megacolon was identified. Eight days after the development of symptoms, colonoscopy was performed to rule out infectious colitis and to make a definite diagnosis, which is necessary for treatment. Given that performing endoscopy within the acute phase of cerebral infarction might be highly risky, we performed colonoscopy after confirming that the patient’s neurological symptoms had not deteriorated. Colonoscopy revealed a rough intestinal mucosa with the disappearance of any visible submucosal vascular pattern and deep ulcerations from the transverse colon to the rectum. Deep ulcerations were also identified in the sigmoid colon (Fig. 2a-d). The patient’s Lichtiger index, which is widely used for evaluating UC severity, was 13 points, with the following details: frequency of diarrhea per day, 10 (4 points); nocturnal diarrhea, yes (1 point); visible blood in stool ≥50% (2 points); fecal incontinence, yes (1 point); abdominal pain, mild (1 point); general wellbeing, average (3 points); abdominal tenderness, mild and localized (1 point), and need for antidiarrheal drugs, no (0 points).

Table 1. Laboratory Data on Admission.

| WBC  | 12,300 /mm³ | Na   | 140 mEq/L |
|------|-------------|------|-----------|
| Hb   | 14.8 g/dL   | K    | 4.1 mEq/L |
| Plt  | 34.4×10⁴ /μL| Cl   | 104 mEq/L |
| BUN  | 8.2 mg/dL   | ANA  | <40 times |
| Cre  | 0.91 mg/dL  | Anti-CL-Ab | negative |
| CRP  | 1.41 mg/dL  | Anti-SS-A | <1.0 mg/dL |
| TP   | 7.1 g/dL    | PR3-ANCA | 1.3 |
| Alb  | 3.8 g/dL    | MPO-ANCA | <1.0 |
| T-Bil| 0.71 mg/dL  | PT activity | 89 % |
| AST  | 11 IUL/L    | INR  | 1.05 |
| ALT  | 10 IUL/L    | APTT | 30.2 sec |
| LDH  | 105 IUL/L   | D-dimer | 2.4 μg/mL |

WBC: white blood cells, Hb: hemoglobin, Plt: platelets, BUN: blood urea nitrogen, Cre: serum creatinine, TP: total protein, Alb: albumin, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, Na: serum sodium, K: serum potassium, Cl: serum chloride, ANA: anti nuclear antibody, Anti-CLβ2GP1: anti-cardiolipin-beta2-glycoprotein 1 complex antibody, Anti-CL-AbG: anti-cardiolipin antibody, Anti-SS-A-Ab: anti Sjögren’s syndrome A antibody, PR3-ANCA: proteinase 3-antineutrophil cytoplasmic antibody, MPO-ANCA: myeloperoxidase-antineutrophil cytoplasmic antibody, PT activity: prothrombin percentage activity, INR: international normalized ratio, APTT: activated partial thromboplastin time.

Figure 1. Abdominal computed tomography (CT) was performed upon admission. A CT scan revealed thickening of the mucosa from the transverse (a) colon to the sigmoid colon (b) due to ulcerative colitis (UC).
Regarding the neurological abnormalities, further examinations were performed. A magnetic resonance imaging (MRI) examination of the brain revealed acute cerebral infarctions scattered in the left semioval center (Fig. 3a), bilateral corona radiata (Fig. 3b), and right midbrain. MR angiography (MRA) did not show any occlusion or stenosis of the major cerebral arteries (Fig. 3c). Holter electrocardiography and carotid, cardiac, and lower extremity venous ultrasonography were performed and showed the absence of paroxysmal atrial fibrillation, carotid plaque, left atrial ventricle thrombus, and venous thromboembolism (data not shown). From these examinations, an embolic mechanism was excluded from the diagnosis. In a further close investigation, the contrast-enhanced MRI of the brain revealed multiple small round contrast effects in the bilateral deep white matter (Fig. 3d) and linear-enhanced effects in the meninges of the left temporal lobe (Fig. 3e). MRI susceptibility-weighted imaging, which is useful for the detection of small cerebral hemorrhages, revealed microbleeds in the bilateral deep white matter (Fig. 3f). Generally, cerebral curvilinear gadolinium enhancement and cerebral punctate reflected blood-brain barrier disruption caused by the inflammation of small cerebral vessels (9). Based on these findings, he was diagnosed with cerebral vasculitis with multiple white matter infarctions associated with the disease activity of UC.

For treating the cerebral infarction, the continuous administration of heparin was started. Initially, on the 35th day from admission, 200 mg/day of cilostazol, instead of heparin, was started. However, he complained of a drug-induced headache; thus, cilostazol was stopped and switched to 75 mg/day of clopidogrel.

For treating UC and cerebral vasculitis, 4,000 mg/day of mesalazine and 60 mg/day of intravenous drip prednisolone were started. His abdominal symptoms due to UC slowly improved. The dosage of prednisolone was gradually reduced to 20 mg/day of oral prednisolone. He was discharged on the 48th day from admission without any abdominal symptoms. The neurological abnormalities improved dramatically, with only minor facial and left arm paralysis (National Institutes of Health Stroke Scale (NIHSS), 2 points) remaining prior to being discharged. Follow-up colonoscopy on day 56 revealed improvement of the inflamed mucosa of the colon. Subsequently, we tapered the prednisolone dose and switched to anti-TNFα therapy with golimumab (Fig. 4). He remained in remission from ulcerative colitis without paralysis for 10 months after the attack. In fact, follow-up MRI performed at 9 months after admission showed the disappearance of high-intensity areas in the white matter that had been present at the time of admission (Fig. 5).
Discussion

We herein describe a case of cerebral vasculitis with multiple white matter infarctions associated with the disease activity of UC. White matter infarctions associated with cerebral vasculitis in active UC patients are a rare occurrence (10), although there have been several reports on obvious arterial infarctions in UC patients (11-13). In addition, the patient’s severe active UC and cerebral vasculitis were successfully treated with the induction therapy by prednisolone and the maintenance therapy by anti-TNFα therapy with golimumab.

UC patients occasionally have extraintestinal manifestations, which usually include systemic disorders (4). The incidence of extraintestinal manifestation is reportedly to range from 10-25%; however, complications of the central nervous system (CNS) are relatively rare and are estimated to only be 0.12-4% (14, 15). Regarding CNS complications in UC patients, some pathogenesis of cerebral infarction associated with the disease activity of UC, such as (i) arterial and venous thrombosis, (ii) vasculitis, and (iii) anemia or malnutrition, have been considered in past reports (13, 16). Regarding the etiology of arterial and venous thromboses, Bargen et al. first reported the relationship between inflammatory bowel disease (IBD) and venous thromboembolism in 1936 (17). The systematic inflammation caused by IBD is considered to lead to a hypercoagulable state owing to the hemostatic alterations of the coagulation cascade (18, 19). However, the details of this mechanism are not well understood. In our case, arterial and venous thromboembolisms were not found in the MRA or carotid, cardiac, and lower limb venous ultrasonography. There was no sign of thrombosis in the patient’s body. Although our case showed no other extraintestinal manifestations, except for the cerebral infarction, cerebral vasculitis and UC are considered included in such systemic events (20, 21). Hence, we cannot deny the possibility that undetectable and asymptomatic systemic inflammation may have occurred.

CNS vasculitis is considered to be caused by immune-mediated mechanisms, such as genetic susceptibility, immune complex deposition, human leukocyte antigen status, and T lymphocyte-mediated cytotoxicity (22, 23). Cerebral complications probably occur in combination with these factors, which affected the vulnerable site of the brain due to ischemia. Contrast-enhanced MRI revealed cerebral punctate and curvilinear gadolinium enhancements, which suggested the disruption of the blood-brain barrier caused by small
vessel inflammation. Although the diagnosis of cerebral vasculitis is often confirmed by either a brain biopsy or cerebral angiography, these examinations do not necessarily lead to a definite diagnosis, because the biopsy specimen often displays non-specific inflammation, and the characteristic findings in cerebral vasculitis detected by angiography are not limited to vasculitis and can also be found in many other differential diagnoses (9). Furthermore, these examinations have cerebral complication risks. Hence, after ruling out other causes of cerebral infarction, we diagnosed this

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Figure 4. The patient’s clinical course from recurrence of UC to remission.

Figure 5. Head magnetic resonance imaging (MRI) of the left semioval center (a) and bilateral corona radiata (b), which was performed at 9 months after the onset of cerebral infarction. The high-intensity areas disappeared, and no new lesions were observed.
mainly used as a general treatment for CNS vasculitis (36), although the effect of anti-TNFα agents has been studied to avoid the long-term use of prednisolone. Al-though the effect of anti-TNFα agents for treating CNS vasculitis is uncertain because of its limited evidence, no adverse events by treatment with anti-TNFα agents has been reported in patients with cerebral infarction or cerebral vasculitis (42). Indeed, this patient’s UC, cerebral vasculitis, and cerebral infarction have not occurred so far.

In summary, we described a case of CNS vasculitis with cerebral infarction associated with UC. We administered prednisolone as a remission induction therapy for UC, which showed a satisfactory effect on the patient’s cerebral vasculitis. Subsequently, we successfully treated the patient with golimumab as a remission maintenance therapy without any relapse of UC and CNS complications. There is no evidence regarding the remission induction and maintenance therapy of UC with CNS manifestations thus far. Hence, further studies will be required to support our findings.

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

1. Nikolaus S, Schreiber S. Diagnostics of inflammatory bowel disease. Gastroenterology 133: 1670-1689, 2007.

2. Thia KT, Loftus EV Jr, Sandborn WJ, Yang SK. An update on the epidemiology of inflammatory bowel disease in Asia. Am J Gastroenterol 103: 3167-3182, 2008.

3. Hou JK, El-Serag H, Thirumurthi S. Distribution and manifestations of inflammatory bowel disease in Asians, Hispanics, and African Americans: a systematic review. Am J Gastroenterol 104: 2100-2109, 2009.

4. Monsen U, Sorstad J, Hellers G, Johansson C. Extracolonic diagnoses in ulcerative colitis: an epidemiological study. Am J Gastroenterol 85: 711-716, 1990.

5. Watanabe R, Ishii T, Nakamura K, et al. Ulcerative colitis is not a rare complication of Takayasu arteritis. Mod Rheumatol 24: 372-373, 2014.

6. Unnikrishnan A, Azodi S, Ansari N, Brown M, Kamnetz J, Uchiyama RC. PR3-ANCA related cerebral vasculitis in ulcerative colitis presenting with orbital involvement: a case report with review of literature. Case Rep Rheumatol 2014: 582094, 2014.

7. Terao C, Matsumura T, Yoshifuji H, et al. Takayasu arteritis and ulcerative colitis: high rate of co-occurrence and genetic overlap. Anthritis Rheum 67: 2226-2232, 2015.

8. Mahler M, Bogdanos DP, Pavlidis P, et al. PR3-ANCA: a promising biomarker for ulcerative colitis with extensive disease. Clin Chim Acta 424: 267-273, 2013.

9. Taeib G, Dura-Pena A, de Chamfleur NM, et al. Punctate and curvilinear gadolinium enhancing lesions in the brain: a practical approach. Neuroradiology 58: 221-235, 2016.

10. Druschky A, Heckmann JG, Druschky K, Huk WJ, Erbguth F, Neundorfer B. Severe neurological complications of ulcerative colitis. J Clin Neorosci 9: 84-86, 2002.

11. Schneiderman JH, Sharpe JA, Sutton DM. Cerebral and retinal vascular complications of inflammatory bowel disease. Ann Neur 5: 331-337, 1979.

12. Houissa F, Salem M, Bouzaidi S, et al. Cerebral thrombosis in inflammatory bowel disease: a report of four cases. J Crohns Colitis 5: 249-252, 2011.

13. Katsanos AH, Kosmidou M, Giannopoulos S, et al. Cerebral arterial infarction in inflammatory bowel diseases. Eur J Intern Med 25: 37-44, 2014.

14. Baumgart DC, Carding SR. Inflammatory bowel disease: cause and immunobiology. Lancet 369: 1627-1640, 2007.

15. Lossos A, River Y, Eliakim A, Steiner I. Neurologic aspects of inflammatory bowel disease. Neurology 35: 416-421, 1995.

16. Dolapcioglu C, Dolapcioglu H. Structural brain lesions in inflammatory bowel disease. World J Gastrointest Pathophysiol 6: 124-130, 2015.

17. Bargen JA, Barker NW. Extensive arterial and venous thrombosis complicating chronic ulcerative colitis. Arch Intern Med 58: 17-31, 1936.

18. Lake AM, Stauffer JQ, Stuart MJ. Hemostatic alterations in inflammatory bowel disease: response to therapy. Am J Dig Dis 23: 897-902, 1978.

19. Kume K, Yamasaki M, Tashiro M, Yoshikawa I, Otsuki M. Activations of coagulation and fibrinolysis secondary to bowel inflammation in patients with ulcerative colitis. Intern Med 46: 1323-1329, 2007.

20. Scheid R, Teich N. Neurologic manifestations of ulcerative colitis. Eur J Neurol 14: 483-493, 2007.

21. Panani AD, Grigoriadou M, Magira E, Roussos C, Raptis SA. Perineural antineutrophil cytoplasmic antibody myeloperoxidase-positive vasculitis in association with ulcerative colitis. Clin Rheumatol 25: 35-37, 2006.

22. Snook JA, de Silva HJ, Jewell DP. The association of autoimmune disorders with inflammatory bowel disease. Q J Med 72: 835-840, 1989.

23. Danese S, Semeraro S, Papa A, et al. Extraintestinal manifestations in inflammatory bowel disease. World J Gastroenterol 11: 7227-7236, 2005.

24. Glotzer DJ, Yuan RH, Patterson JF. Ulcerative colitis complicated by toxic megacolon, polyserositis and hemorrhagic leukoencephalitis with recovery. Ann Surg 159: 445-450, 1964.

25. Edwards KR. Hemorrhagic complications of cerebral arteritis. Arch Neurol 34: 549-552, 1977.

26. Nelson J, Barron MM, Riggs JE, Guttmann L, Schochet SS Jr. Cerebral vasculitis and ulcerative colitis. Neurology 36: 719-721, 1986.

27. Karacostas D, Mavromatis J, Artemis K, Milonas I. Hemorrhagic cerebral infarct and ulcerative colitis. A case report. Funct Neurol 6: 181-184, 1991.

28. Dejaco C, Ferti E, Prager D, et al. Symptomatic cerebral microangiopathy preceding initial manifestation of ulcerative colitis. Dig Dis Sci 41: 1807-1810, 1996.

29. Masaki T, Muto T, Shinozaki M, Kuroda T. Unusual cerebral complication associated with ulcerative colitis. J Gastroenterol 32: 251-254, 1997.

30. Carmona MA, Jaume Anselmi F, Ramirez RJ. Cerebral thrombosis and vasculitis: an uncommon complication of ulcerative colitis. Bol Asoc Med P R 92: 9-11, 2000.

31. Nomoto T, Nagao T, Hirabayashi K, et al. Cerebral arteriopathy with extracranial artery involvement in a patient with ulcerative colitis. J Neurol Sci 243: 87-89, 2006.

32. Pandian JD, Henderson RD, O’Sullivan JD, Rajah T. Cerebral vasculitis in ulcerative colitis. Arch Neurol 63: 780, 2006.

33. Raj N, Arkebauer M, Waters B, Dickinson B. A case of cerebral vasculitis associated with ulcerative colitis. Case Rep Rheumatol 2015: 598273, 2015.

34. Park MR, Min MK, Ryu HH, Lee DS, Lee KH. Multiple cerebral infarct with cerebral vasculitis in a young patient with ulcerative colitis. Am J Emerg Med 36: 733.e3-733.e5, 2018.

35. Parks PT, Easton AS. Cerebral vasculitis in ulcerative colitis: predominantly venular: case report and review of the literature. Case Rep Rheumatol 2019: 9563874, 2019.

36. Salvarani C, Brown RD Jr, Calamia KT, et al. Primary CNS vasculitis with spinal cord involvement. Neurology 70: 2394-2400, 2008.

37. Bollen L, Vande Casteele N, Ballet V, et al. Thromboembolism as an important complication of inflammatory bowel disease. Eur J Gastroenterol Hepatol 28: 1-7, 2016.

38. Vegh Z, Golovics PA, Lovasz BD, et al. Low incidence of venous thromboembolism in inflammatory bowel diseases: prevalence and predictors from a population-based inception cohort. Scand J Gastroenterol 50: 306-311, 2015.

39. Gu J, Stocchi L, Gorgun E, Remzi FH. Risk factors associated with portomesenteric venous thrombosis in patients undergoing restorative proctocolectomy for medically refractory ulcerative colitis. Colorectal Dis 18: 399-390, 2016.

40. Magro F, Soares JB, Fernandes D. Venous thrombosis and prothrombotic factors in inflammatory bowel disease. World J Gastroenterol 20: 4857-4872, 2014.

41. Adrish M, Rios R. Intracranial hemorrhage and extensive cerebral venous thrombosis associated with ulcerative colitis. Can J Gastroenterol Hepatol 28: 299-300, 2014.
42. Koster MJ, Matteson EL, Warrington KJ. Recent advances in the clinical management of giant cell arteritis and Takayasu arteritis. Curr Opin Rheumatol 28: 211-217, 2016.

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