

[CASE REPORT]

High-dose-infliximab-associated Cerebral Venous Sinus Thrombosis: A Case Report and Review of the Literature

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Abstract:

A 28-year-old woman experienced severe headache and right homonymous hemianopia after receiving high-dose infliximab for Crohn's disease. Computed tomography showed hemorrhagic infarction in the left temporal and parietal lobes. An angiogram revealed left transverse to sigmoid sinus occlusion and a stagnated Labbe vein. The patient was treated surgically and achieved a good outcome. Inflammatory bowel diseases are known to accompany venous and arterial thrombosis in 1-2% of cases. Recently, infliximab has been suggested to increase this possibility. A case of Crohn's disease presenting with cerebral sinus thrombosis in the remission period during long-term/high-dose use of infliximab is presented. In addition, infliximab-associated thrombosis cases were reviewed.

Key words: cerebral infarct, inflammatory bowel disease, infliximab, sinus thrombosis

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Introduction

Inflammatory bowel disease (IBD) refers mainly to ulcerative colitis (UC) and Crohn's disease (CD). Often affecting women in their 20s and 30s, its prevalence is increasing year by year. Thrombosis is a major adverse event in patients with IBD because of its severe symptoms (1, 2).

In a cohort study of 13,756 IBD patients, IBD revealed an overall hazard ratio of 3.4 in venous thromboembolism patients compared to controls (3). This ratio was high in the flare [8.4] and chronic activity phase [6.5] but low in the remission period [2.1]. It was also reported to be more likely to occur in UC than in CD patients (4). Cerebral infarction is also known to give rise to complications in IBD patients (5). A literature review in 2014 by Katsanos et al. reported cases with arterial cerebral thromboembolic complications among 33 IBD patients (6). Concerning cerebral venous thrombosis in IBD patient, it has also been found that seven out of nine cases of cerebral infarction were due to sinus thrombosis in one series (8).

Infliximab (IFX) is a potent anti-tumor necrosis factor (TNF) antibody, highly effective in IBD patients (8, 9). It is

also widely used to treat chronic inflammatory diseases, such as rheumatoid arthritis, Behcet's disease, ankylosing spondylitis, psoriasis vulgaris, and Kawasaki disease, in their acute phases (10-14). IFX is effective even in steroid-resistant IBD patients (15). Infection (16, 17) and the development of malignancy, especially systemic lymphoma (18), are well-known adverse events of IFX. Furthermore, it seems likely that the administration of IFX to IBD patients further increases the risk of venous or arterial thrombotic complications. At present, nine cases of thromboembolic complications have been reported in patients with IBD treated using IFX (Table). Puli et al. reported the first case in 2003, wherein retinal vein thrombosis occurred after the third administration of IFX in a CD patient (19). The location and timing of the thromboembolic complications have been widely inconsistent among these patients.

To our knowledge, this is the first case report of cerebral venous sinus thrombosis after high-dose IFX administration in an endoscopic remission phase. In addition, we summarize cases of thromboembolic complication occurring after IFX administration in IBD in an attempt to characterize the thromboembolic complications. The present case report highlights the importance of a sinus thrombosis diagnosis in

Table. Thromboembolic Complications in Patients with IBD after IFX Administration.

No.	Age (y)	Sex	Disease	Stage of IBD	IFX dosage (mg/kg)	Cycle of IFX	Onset after IFX administration	Location of thrombosis	Reference
1	45	F	CD	flare	5	3	UNK	Retinal vein thrombosis	19
2	73	M	UC	UNK	UNK	1	2 weeks	Pulmonary embolism	23
3	31	F	CD	active	5	3	30 minutes	Forearm vein thrombosis	21
4	40	M	CD	active	5	3	3 days	Acute coronary syndrome	25
5	67	M	UC	remission	5	6	2 weeks	Retinal vein thrombosis	20
6	33	F	UC	remission	UNK	3	4 weeks	Inferior vena cava and renal vein thrombosis	24
7	48	M	CD	active	5	2	3 days	Femoral artery occlusion	26
8	44	M	UC	flare	5	1	3 days	Acute renal artery occlusion	27
9	27	F	CD	active	5	2	5 hours	Radial cutaneous vein thrombosis	22
10	28	F	CD	remission	10	11 (5 mg/kg) 22 (10 mg/kg)	5 days	Cerebral sinus thrombosis	Current case

CD: Crohn's disease, F: female, IBD: inflammatory bowel disease, IFX: infliximab, M: male, UC: ulcerative colitis, UNK: unknown

patients undergoing long-term high-dose IFX therapy and assesses the optimal treatment options for achieving a favorable outcome in such patients.

Case Report

A 28-year-old woman was sent to our center because of severe headache and right homonymous hemianopia. She had been diagnosed with CD at another hospital five years earlier and was receiving treatment there. Initially, her disease had been controlled using mesalazine but later had required the additional use of oral steroid due to deterioration. Despite four weeks of high-dose steroid administration, her CD remained active and refractory to conventional medical therapy. Therefore, steroids were discontinued, and IFX was started.

IFX had been introduced at a regular dose (5 mg/kg) with an 8-week interval starting 4 years earlier. Despite 11 cycles of IFX (5 mg/kg), her CD remained active indicating that she was refractory to conventional medical therapy. The patient was therefore treated using high-dose IFX at 10 mg/kg followed by a total of 22 cycles with a 6-week interval. She had recently maintained disease remission with mercaptopurine hydrate 30 mg and high-dose IFX.

At 5 days after the last high-dose IFX administration, she experienced rapidly worsening headache and visual disturbance. Her blood examination results were as follows: white blood cell count, 5,800/mL; hemoglobin, 9.5 g/dL; and platelet count, 222,000/mL. Major blood biochemistry data were within normal values. The coagulation/fibrinolysis parameters were as follows: activated partial thromboplastin time (APTT), 26.4 seconds (normal 27 to 45), prothrombin time (PT), 13.8 seconds (normal 10 to 13); international normalized ratio (INR), 1.16; fibrinogen, 299 mg/dL (normal 150 to 400); D-dimer, 3.0 µg/mL (normal <1.0); thrombin-antithrombin (TAT) complex, 5.8 ng/mL (normal

<3.0); homocysteine, 13.4 nmol/mL (normal 3.7 to 13.5); protein C activity, 83% (normal 64% to 146%); and protein S activity, 54% (normal 56% to 126%). The factors involved in the congealing fibrinogenolysis system (D-dimer, TAT complex) were slightly elevated temporarily. Anti-nuclear antibody was strongly positive (1:640 dilutions, above 1:160 as positive), anti-cardiolipin antibody was within the normal range (8 U/mL, normal <10), and the anti-double stranded DNA antibody level was 12 IU/mL, which was at the upper limit of normal. The erythrocyte sedimentation rate was elevated at 47 mm/h (normal <15). An IFX screening test was positive. Vasculitis and sepsis screening results were normal.

Brain computed tomography revealed hemorrhagic infarction in the left parietal and temporal lobes. Magnetic resonance imaging (MRI) and three-dimensional computed angiography demonstrated left transverse to sigmoid sinus thrombosis and Labbe vein congestion (Fig. 1). Cerebral angiography revealed a left transverse to sigmoid sinus thrombus extending into the Labbe vein. In addition, a distant thrombus was found in the anterior segment of the superior sagittal sinus. Her consciousness level gradually worsened along with increasing intracranial pressure. MRI before emergency surgery (Fig. 2A-D) revealed vasogenic edema in the left temporal lobe with a high signal intensity on apparent diffusion coefficient map.

She underwent emergency external decompression surgery to decrease the intracranial pressure. After surgery, her consciousness completely recovered, and treatment was continued with low-molecular-weight heparin (LMWH) and osmotic diuretics. The patient was treated with anticoagulation measures comprising LMWH 75 IU/kg/day for 10 days. Anticoagulation was initiated with warfarin 2-3 mg orally once daily after bridging with LMWH. The dose was adjusted to maintain the patient's INR at 2 to 3. She had only maintained disease remission with a mesalazine 3,000 mg and mercaptopurine hydrate 30 mg during treatment of cerebral

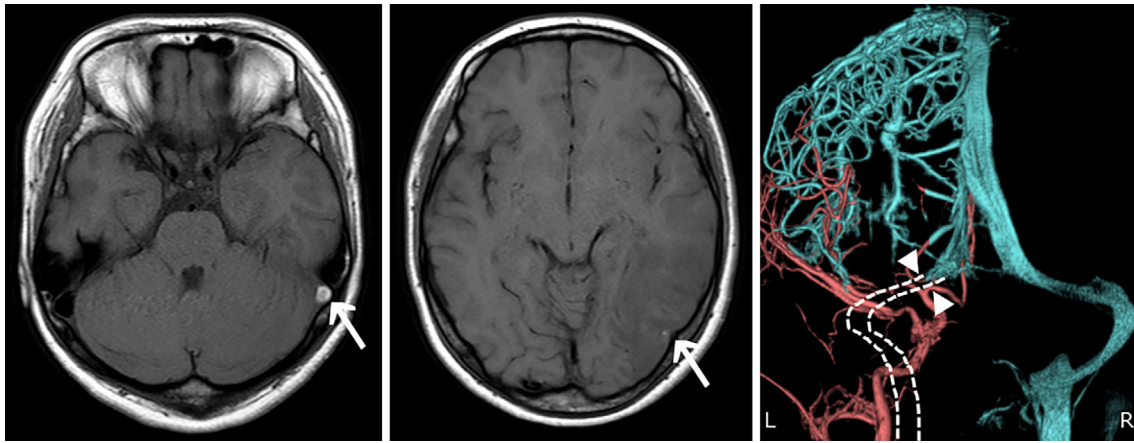


Figure 1. Brain magnetic resonance imaging T1 image on admission. A high-intensity signal is observed in the transverse to sigmoid sinus (left panel) and Labbe vein (central panel) suggesting the presence of thrombosis (arrow). 3D computed angiography shows sinus occlusion (arrowheads) in the transverse to sigmoid sinus (right panel).

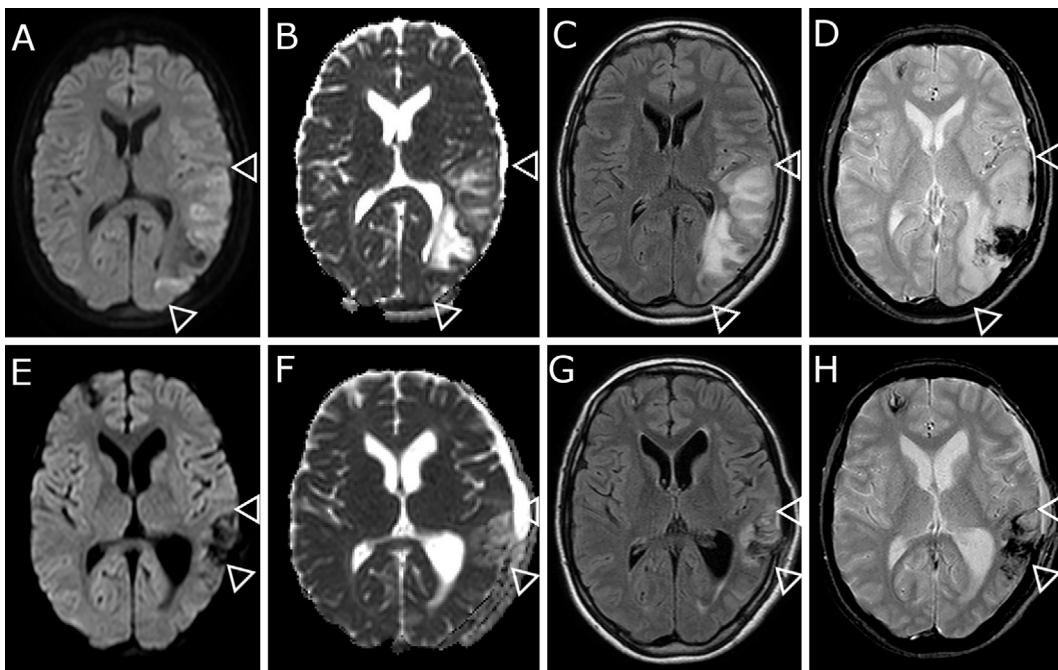


Figure 2. Brain magnetic resonance imaging on admission (A: DWI, B: ADC map, C: FLAIR, D: T2*). Brain magnetic resonance imaging at one month after onset (E: DWI, F: ADC map, G: FLAIR, H: T2*). The high-intensity signal (arrowheads) was reduced, and no new lesions were observed.

venous thrombosis. At one month after surgery, remarkable improvement in the MRI findings was observed (Fig. 2E-H). She returned to her own life without any neurological deficit after undergoing cranioplasty surgery.

A blood examination was repeated at six months after surgery. The coagulation/fibrinolysis parameters were as follows: APTT, 29.2 seconds, PT, 16.4 seconds; INR, 1.28; fibrinogen, 218 mg/dL; D-dimer, 1.0 μ g/mL; TAT complex, 1.0 ng/mL; protein C activity, 124%; and protein S activity, 96%. Anti-nuclear antibody became negative (1:80 dilutions), and the double stranded DNA antibody level was 2.9 IU/mL (normal <12) in the interval periods of IFX treat-

ment. The erythrocyte sedimentation rate was normalized at 7 mm/h. Anti-coagulation therapy was discontinued at six months after surgery because of a negative test for anti-nuclear antibodies. No further treatment was required, except for a reduction in the IFX dosage. Follow-up brain MRI demonstrated a small old infarction in the left inferior temporal gyrus at 10 months after the onset.

Discussion

To our knowledge, there have been nine cases of venous thrombosis/arterial occlusion associated with IFX admini-

stration. Among these patients, two developed retinal vein thrombosis (19, 20), two developed forearm vein thrombosis (21, 22), one developed pulmonary embolism (23), one developed inferior vena cava thrombosis (24), and three developed artery occlusion (25-27). Panteris et al. noted that thrombosis is frequently observed at three to seven days after IFX administration (25). Ljung et al. emphasized that the use of IFX in IBD patients increases the possibility of adverse events and mortality (23). Among 217 patients who received IFX in that study, 6 fatal adverse events were found, including 2 cases with lymphoma, 3 cases with severe infection (sepsis), and 1 with pulmonary embolism. Several adverse events related or unrelated to embolism may occur following IFX administration (28, 29).

The relative risk of a thromboembolic event increases above 3-fold in IBD patients and exceeds 16-fold during non-hospitalized flare phase periods (3). Cerebral venous thrombosis is rarely associated with IBD. An estimated 1.3-6.4% of patients with IBD experience cerebral venous thrombosis at some point during the course of the disease (30). Cerebral venous thrombosis is more common in UC than in CD (4); indeed, cerebral venous thrombosis has only rarely been reported in patients with CD. What makes patients with IBD susceptible to venous thrombosis has been investigated but is still poorly understood, but there has been some speculation. Immobilization, surgery, intra-venous catheters, using steroid, and coagulation/fibrinolysis disorders may be a cause in some patients. However, the present patient had not been exposed to such additional risks or underlying coagulation/fibrinolysis disorders. Systemic factors appear to be the major reason that activated coagulation/fibrinolysis cascade occurred in the present case.

The expression of TNF- α receptors has been proposed as a possible reason for thrombosis occurring in IBD patients after IFX administration (25). The TNF- α driven procoagulant loop increases the incidence of thrombosis after TNF- α administration, and conversely, TNF- α inhibition reduces the incidence of venous thrombosis (31). A counter-regulation mechanism might upregulate the expression of TNF- α receptors on the inflammatory cell membrane when IFX administration leads to a reduction in serum TNF- α levels, resulting in thrombus formation (25). This so-called "paradoxical thrombus formation" is one reason for thrombosis being caused by IFX administration. In addition, it was suggested that IFX can also lead paradoxical thrombus formation if administered at a dose of 10 mg/kg.

Molecular-targeted drugs may induce various autoantibodies, including anti-nuclear, anti-double stranded DNA, anti-cardiolipin and anti-phospholipid antibodies. Autoantibodies are the most prominent factor in thrombophilia and may contribute to the development of systemic lupus erythematosus-like syndrome (drug-induced lupus erythematosus) secondary to molecular-targeted drug administration. In addition, some authors have suggested that the emergence of autoantibodies after IFX administration may be related to a transient increase in TNF- α (32). The sinus thrombosis in

our case appears to have resulted from temporarily elevated autoantibodies and coagulation/fibrinolysis disorder, since these factors became normalized after the dose of IFX was reduced. The expression of autoantibodies seems to be another reason for "paradoxical thrombus formation."

Infusion reactions (IRs) are another possible mechanism responsible for thrombosis. Molecular-targeted drugs are known to increase the risk of thrombosis by causing severe IRs. Ryan et al. indicated that IFX can cause thrombus formation via IRs (21). In their report, IRs developed in 10-20% of cases after IFX administration (17, 33), commonly occurring at a mild to moderate level, although approximately 2% presented with severe IRs. Repeated use of IFX is a risk factor for severe IRs. Severe IRs are characterized by anaphylactoid symptoms that occur within 24 hours of administration (17). The mechanism underlying IFX-induced IRs has not yet been elucidated but is considered to be related to the temporary release of cytokines. Cytokine release can lead to the activation of the platelet agglutinin ability and thrombus formation, similar to disseminated intravascular coagulation (DIC) syndrome (21, 22).

In the present case, sinus thrombosis occurred during the remission phase, shortly after high-dose IFX administration. Since autoantibodies had already formed when the sinus thrombosis became symptomatic and cerebral angiography demonstrated thrombosis in the superior sagittal sinus, it seems likely that asymptomatic thrombosis was occurring repeatedly before becoming symptomatic in this case. Care must be taken to administer IFX therapy at an appropriate dosage and interval in order to prevent thromboembolic complications. On this point, blood examinations including autoantibody measurements might be useful for indicating the presence of asymptomatic thrombosis. In addition, the timing of thromboembolic complications varied from the first administration to 33rd cycle in our case. Furthermore, the time lag between the thrombosis onset and the final IFX administration varied from 30 minutes to 4 weeks. It is worth noting that thromboembolic complications might occur with any timing, probably because several mechanisms exist for thrombus formation.

The present case demonstrated full clinical recovery after treatment with external decompression and low-molecular-weight heparin. No further treatment was required, except for a reduction in the IFX dosage. The prognosis of sinus thrombosis is usually favorable, with more than 80% of patients achieving a good clinical outcome (34). In fact, follow-up brain MRI and magnetic resonance venography did not reveal the recurrence of venous thrombosis in our case. Nevertheless, because long-term use of IFX is necessary in some IBD cases, strict observation is needed to detect variable complications.

In conclusion, there is a possible risk of cerebral sinus thrombosis with IFX treatment. This case report highlights the need to clarify the details and incidence of adverse events occurring during long-term/high-dose use of IFX.

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

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