

Case of Moyamoya Disease Aggravated during the Treatment of Behçet's Disease

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Behçet's disease (BD) is a multi-organ involved inflammatory disorder described by recurrent oral ulcers and other systemic manifestations. Almost all the clinical manifestations of BD are believed to be due to vasculitis. On the other hand, the cerebral arteries are rarely involved. Moyamoya disease (MMD) is an unusual chronic cerebrovascular disorder that is described by bilateral progressive stenosis or occlusion of the internal carotid artery and an abnormal collateral vascular network. A 32-year-old woman with MMD was referred for fever, oral pain, and diarrhea, and was diagnosed with BD. Her MMD was aggravated during treatment with high dose steroids to control the intestinal BD and a reduction in the MMD medication due to gastrointestinal bleeding. This is the first reported case of intestinal BD in a patient previously diagnosed with MMD, who experienced aggravation of her MMD after the cessation of MMD medication due to aggravated intestinal BD. (*J Rheum Dis* 2016;23:386-391)

Key Words. Behcet syndrom, Intestinal Behçet's disease, Moyamoya disease, Aggravated

INTRODUCTION

Behçet's disease (BD) is a multi-organ involved inflammatory disorder described by recurrent oral aphthae ulcers, genital ulcers, skin lesions, and systemic manifestations including vascular, gastrointestinal involvement, neurologic involvement, ocular disease, or arthritis. Almost the whole clinical manifestations of BD are thought to be due to vasculitis [1]. It involves all sizes of blood vessels, and both artery and vein. However, the cerebral arteries are rarely involved.

Moyamoya disease (MMD) is a cerebrovascular disorder that is characterized by progressive stenosis or occlusion of bilateral internal carotid arteries and the formation of an abnormal vascular collaterals called "moyamoya vessels". Moyamoya syndrome (MMS) is a term used to explain moyamoya-like vessels related with other diseases [2]. Although the etiology of MMD related to auto-

immune conditions is unclear, an immunologic basis has been suggested, and recent studies have noted an association between MMD and autoimmune diseases, including Graves' disease, diabetes mellitus, and systemic lupus erythematosus (SLE) [3].

Although there is a similarity between BD and MMD, which is characterized by vasculopathy, reports of cases of MMD accompanied by BD are very rare [4-6], and little is known about the association between the two diseases.

In this report, we present a rare case of a patient who was diagnosed with intestinal BD 5 years after MMD onset. She developed intracerebral hemorrhage (ICH), which indicated MMD progression after cessation of MMD medication due to aggravated intestinal BD, and we controlled both diseases with medical treatment.

Received : July 6, 2016, **Revised :** (1st) July 25, 2016, (2nd) July 27, 2016, **Accepted :** July 29, 2016

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pISSN: 2093-940X, eISSN: 2233-4718

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CASE REPORT

In June 2012, a 32-year-old Korean woman was visited to the hospital with fever (up to 39.4°C), oral pain, and diarrhea for 7 days. At age 27, in November 2007, she was diagnosed with MMD with manifestations of right arm weakness, left hemiparesis, and transient ischemic attacks (TIA) lasting for 2 months. At that time, brain magnetic resonance angiography (MRA) and cerebral angiography revealed bilateral stenosis of the distal internal carotid arteries (ICA) and A1 segment, and occlusion of the bilateral M1 segments with profound basal and pial collaterals (Figure 1A and 1B). Brain single positron emission computed tomography (CT) revealed decreased vascular reserve of the left cerebral hemisphere. She was diagnosed with MMD and was given medical treatment (acetyl-L-carnitine and choline alfoscerate).

In May 2012, although she was recommended to undergo bypass surgery because of recurrent right arm weakness, which was thought to be associated with MMD progression. However, she refused surgery and main-

tained only medical treatment (aspirin, clopidogrel, choline alfoscerate). Other medical history, drug history, and family history were unremarkable.

Upon admittance in June 2012, her mental status was normal but she had an acute ill-looking appearance. On admission, her body temperature was 38.0°C, systolic blood pressure was 132 mmHg, and pulse rate was 102 beats per minute. Physical examination revealed oral ulcers, perianal ulcers (two 0.5×1.0 cm ulcers filled with yellowish granulation tissue on the right and caudal side), a genital ulcer (2×1 cm ulcer filled with yellowish granulation tissue on the left labia major) and no other skin lesions. She complained of abdominal pain but there was no abdominal direct or rebound tenderness. The results of a neurological examination were unremarkable. Because of the bilateral ocular discomfort, an ophthalmic examination was performed and revealed anterior uveitis in both eyes.

Laboratory examination revealed the following data: leukocytosis (16,000/ μ L total white blood cell count), hemoglobin 12.4 g/dL, platelet 177,000/ μ L, erythrocyte

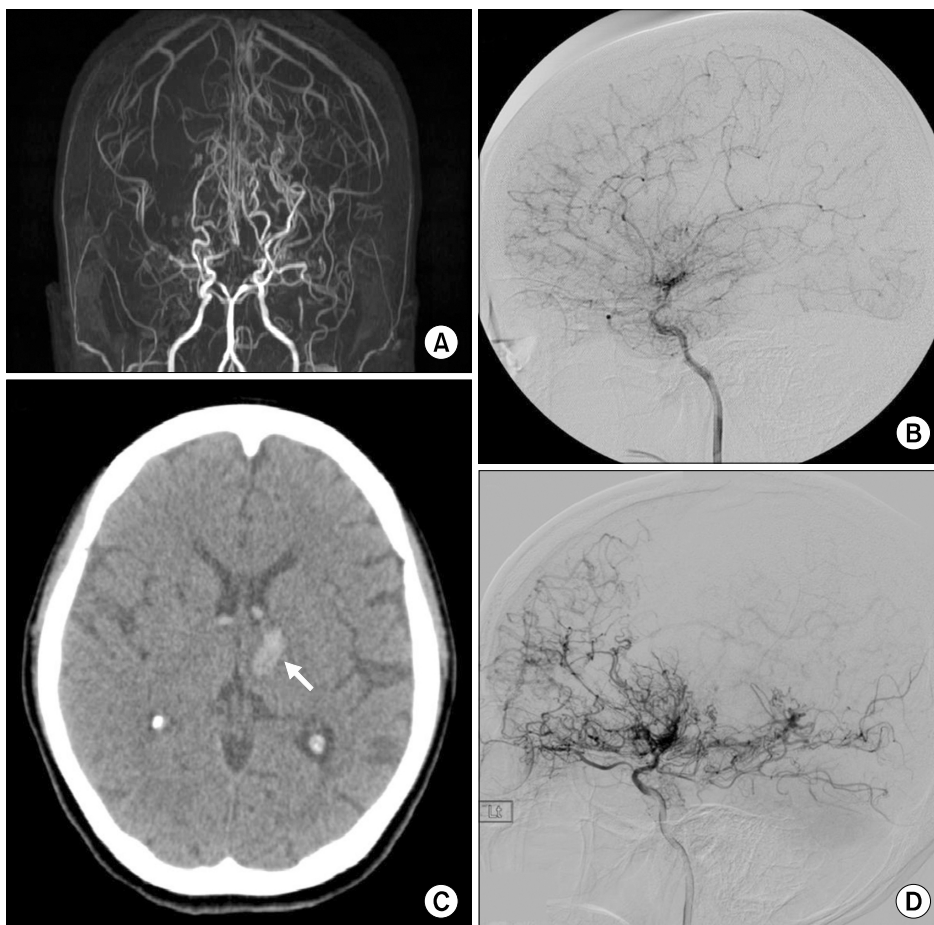


Figure 1. (A) Initial brain magnetic resonance angiography shows stenosis of bilateral distal internal carotid arteries with well-developed basal and pial collaterals. (B) Initial left internal carotid angiography shows stenosis of the left distal internal carotid artery. Well-developed basal collaterals and pial collaterals to the left hemisphere through the left posterior cerebral artery are also seen. (C) Follow up brain computed tomography shows a newly appearing acute intracerebral hemorrhage in the left thalamus with extension to the ventricles (arrow). (D) On follow up cerebral angiography, aggravated stenosis of the left distal internal carotid artery is seen.

sedimentation rate 36 mm/h, and C-reactive protein (CRP) 18.72 mg/dL. Chemical analyses of serum were within normal limits. An infectious workup was negative for bacteria. Cultures of blood, urine, and sputum showed no growth of bacteria. Results of immunological analyses were as follows: immunoglobulin (Ig) G 1,284 mg/dL, IgA 188 mg/dL, IgM 166 mg/dL, C3 105 mg/dL, C4 48 mg/dL, human leukocyte antigen 51 negative, anti-nuclear antibody negative, rheumatoid factor negative, anti-neutrophil cytoplasmic antibody negative. Chest X-ray, electrocardiogram, and echocardiogram findings were all nonspecific.

Because of her abdominal pain and diarrhea, an abdominal CT was performed and it showed mild wall thickening of the terminal ileum, suggesting terminal ileitis (Figure 2A). A colonoscopy showed a large well-demarcated ulcer

at the terminal ileum and several small ulcers in the colon (Figure 2B), which suggested intestinal BD. The pathology of terminal ileum revealed erosion and chronic inflammation with lymphoid follicles and regenerative change. She was diagnosed with BD after meeting the criteria of recurrent oral ulcers, genital ulcers, and uveitis. Because she had a fever and laboratory data showed CRP elevation, empirical antibiotics (flomoxef/clindamycin/gentamycin for 8 days) were started because of the probability of infection. She was also administered oral prednisolone 20 mg/day. Since her fever continued and hematochezia developed, we stepped up the antibiotics (piperacillin-sulbactam/metronidazole for 8 days) and prednisolone (50 mg/day, 1 mg/kg) and stopped the aspirin and clopidogrel. Her hematochezia improved over the follow-up, and she was discharged on steroid therapy

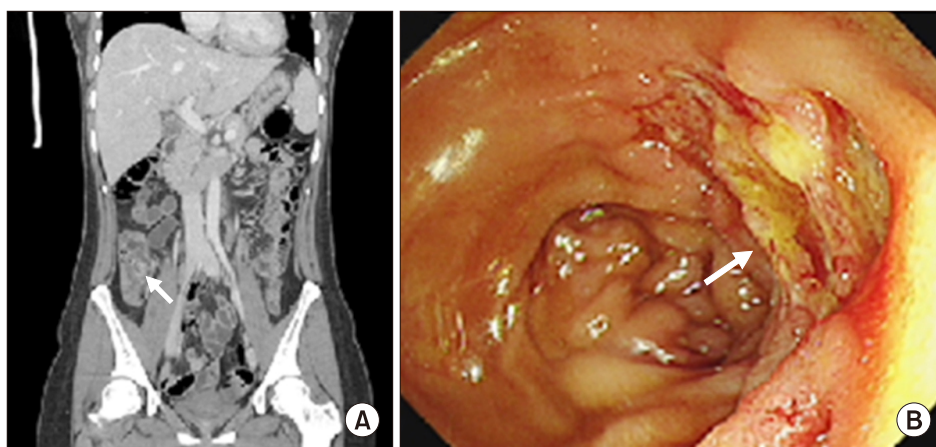


Figure 2. (A) Abdominal computed tomography shows mild wall thickening of the terminal ileum (arrow) suggesting terminal ileitis. (B) Colonoscopy shows a large ulcerative lesion at the terminal ileum (arrow).

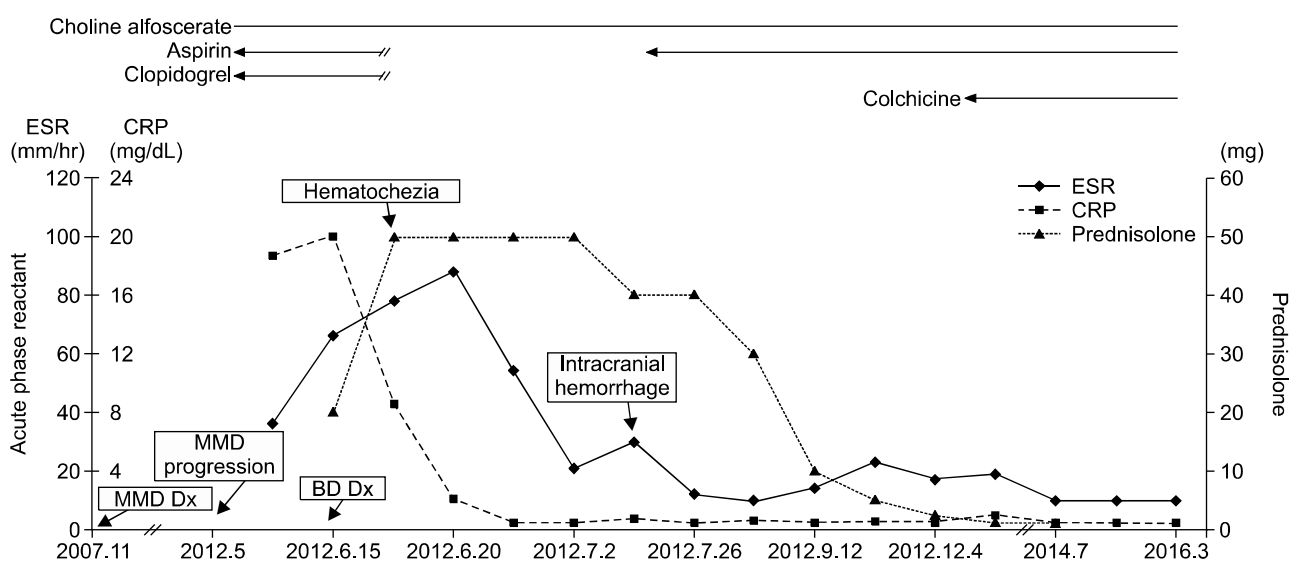


Figure 3. Acute phase reactant level and medication according to the clinical course. ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, MMD: Moyamoya disease, BD: Behçet's disease, Dx: diagnosed.

at a dose of 1 mg/kg.

One week after discharge, the patient was readmitted with right side weakness and dysarthria that was aggravated after psychiatric stress. CT angiography showed newly appearing acute ICH in the left thalamus with extension to the ventricles (Figure 1C) and cerebral angiography revealed bilateral occlusion of the distal M1 and A1 with profound basal collaterals, aggravated stenosis of the left middle cerebral artery (MCA), and bilateral anterior cerebral arteries (Figure 1D). This was thought to be because of progression of MMD. Steroid treatment was maintained and she was given conservative care for 2 weeks with aspirin and choline alfoscerate and was discharged without any evidence of BD or MMD progression.

Her symptoms had improved on her next follow-up and the steroids were tapered down over the next 6 months and colchicine was started (Figure 3). Currently (after 48 months of follow-up), she does not have any symptoms and is under observation on colchicine, aspirin, and choline alfoscerate.

DISCUSSION

BD is a multi-organ involved inflammatory disorder and many clinical manifestations of BD are thought to be due to vasculitis [1]. Among the systemic vasculitides, BD is notable for its property to involve all sizes of blood vessels on both sides of the artery and vein of the circulation. Arterial lesions are usually pseudoaneurysm or true aneurysms, which are the major causes of mortality in BD

patients [7]. However, cerebral arteries are rarely involved. BD is more common (and often more severe) along the ancient silk road, which extends from eastern Asia to the Mediterranean [1].

MMD is an unusual chronic cerebrovascular disorder that is described by progressive stenosis or occlusion of bilateral internal carotid arteries and branches of the Circle of Willis and is accompanied by the formation of a smoky angiographic appearance (fine and rich, but fragile and easy to rupture) of the collateral vascular network called “moyamoya vessels.” Its incidence is higher in East Asian countries such as Japan and Korea [2].

Both MMD and BD are common in Asia, especially eastern Asia, and are related to genetic factors such as human leukocyte antigen genes. Along with an environmental similarity, these two diseases have a similar pathogenesis, which is supported by the association of infection and autoantibodies [8-10]. However, a claim of similar pathology or an incidental coexistence would be speculative.

MMS or quasi-MMD is a term applied to describe the development of Moyamoya vessels secondary to other pathologies such as SLE, Down syndrome, atherosclerosis, neurofibromatosis, sickle cell disease, or others [3].

There have been several reported cases of MMD related with autoimmune diseases such as SLE. Only three MMD cases associated with BD have been reported (two from Korea, one from Turkey). These three cases and this case are detailed in Table 1.

Park et al. [4] made the first case report of BD associated

Table 1. Clinical characteristics of Moyamoya disease (MMD)/Behçet's disease (BD) coexistence cases

Variable	Park et al. [4]	Joo et al. [5]	Degirmenci et al. [6]	This patient
Country	Korea	Korea	Turkey	Korea
Sex	Female	Female	Female	Female
Dx age of BD/MMD (yr)	27/32	32/36	28/28	32/27
HLA-B51	Positive	Not mentioned	Positive	Negative
Other medical history	None	Tuberculosis	none	None
Clinical manifestation of BD	OU, GU, EN	OU, GU, EN, arthritis, uveitis	OU, GU, EN	OU, GU, uveitis, GI
Onset symptom of MMD	Rt. hemiparesis, dizziness	TIA, dizziness	Involuntary movement of Rt. arm, leg	Rt. arm weakness, Lt. hemiparesis, TIA
ICA involvement	Bilateral	Bilateral	Bilateral	Bilateral
Treatment of MMD	Surgery	Surgery	Medical treatment	Medical treatment
Prognosis	Well controlled MMD and BD	Well controlled MMD and BD	Well controlled MMD and BD	Aggravated MMS after BD Dx

Dx: diagnosis, HLA: human leukocyte antigen, ICA: internal carotid artery, OU: oral ulcer, GU: genital ulcer, EN: erythema nodosum, GI: gastrointestinal, Rt.: right, TIA: transient ischemic attack, Lt.: left.

with MMD. The patient was a Korean woman who was diagnosed with BD on the basis of oral ulcers, genital ulcers, erythema nodosum, and pathergy test positive 5 years ago, and admitted with right hemiplegia and dizziness at the age of 32. MRA revealed stenosis and occlusion of bilateral distal ICAs and MCAs (M1 segment) with basal rich collaterals, which suggests Moyamoya vessels. Right extracranial/intracranial arterial bypass surgery with encephalo-muscular synangiosis (EMS) was performed, and symptoms improved [4].

Joo et al. [5] reported a 32-year-old Korean woman who was diagnosed with BD on the basis of oral ulcers, recurrent genital ulcers, erythema nodules, vasculitis, and arthritis 4 years ago, and was admitted with TIA and dizziness. MRA showed occlusion of both MCAs, and cerebral angiography showed occlusion of the supraclinoid portion of the internal carotid arteries with large basal vascular collaterals, suggesting MMD. The patient has had no further TIAs after a superficial temporal artery-middle cerebral artery bypass with EMS [5].

Degirmenci et al. [6], described a case of a woman presenting with involuntary movement of her right arm and leg at the age of 28 and who had a medical history of BD as indicated by on recurrent oral ulcers, genital ulcers, and skin lesions. MRA revealed bilateral occlusion of the distal carotid arteries and basilar artery and rich vascular collateral circulation bringing out a smoky angiographic appearance was suggestive of MMD. Her symptoms fully resolved after intravenous hydration and bed rest [6].

All four cases including this case were young Asian women. Although the diagnosis of intestinal BD was made 5 years after the appearance of MMD in our case, other three cases were diagnosed with BD before the occurrence of MMD or simultaneously.

In other cases, MMD was well controlled after bypass surgery or conservative care. However, this patient was readmitted due to MMD progression with newly developed ICH during treatment with high dose steroids for the control of BD activity and a reduction in MMD medication because of gastrointestinal bleeding.

This is the first reported case of MMD diagnosed before the appearance of BD and that showed progression of MMD despite ongoing BD treatment. Based on this patient, we have two hypotheses about MMD progression.

First, it is possible that inappropriate treatment aggravates MMD. Although MMD treatment is controversial, a recent study demonstrated surgical intervention could prevent recurrent hemorrhage [11]. Our patient was rec-

ommended to undergo surgical treatment due to disease progression despite medical treatment, but she refused surgery. Also, stopping aspirin and clopidogrel due to recurrent hematochezia could be associated with MMD progression.

Second, MMD may progress with increased BD disease activity. In cases associated with SLE and MMD, many hypotheses and analyses indicate that MMD aggravation is correlated with disease activity; one case suggests that cessation of immunosuppressive therapy may result in the development of MMD [12]. If BD has a disease pattern similar to SLE, increased disease activity related to stressful events such as psychiatric stress could aggravate MMD. However, this is just speculation, and needs further study.

In this case, uncontrolled BD activity induces medication cessation of MMD and affects MMD aggravation consequentially. Therefore, in a patient with these two diseases, proper disease control of BD and continuous treatment maintenance of MMD are important. Also, it is important to distinguish MMD aggravation and newly developed neurologic involvement of BD in a patient with BD and MMD who is complaining neurologic symptom such as dysarthria, unilateral side weakness.

SUMMARY

We report a case of intestinal BD patient with MMD and describe an uncommon association of BD and MMD. We suggest there is a possibility of a similar pathogenesis of BD and MMD and formulated hypotheses about MMD aggravation. In a patient with BD and MMD, it is thought that proper and continuous treatment of these two diseases is important. Rare cases of association with MMD and BD have been reported and little is known regarding the relationship between the two diseases. Further studies are necessitated to elucidate the relation between BD and MMD.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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