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【 CASE REPORT 】

Recurrent Cerebral Infarcts Associated with Uterine Adenomyosis: Successful Prevention by Surgical Removal

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Abstract:

Hypercoagulability associated with malignant tumors causes thrombosis, termed Trousseau's syndrome, but is rarely associated with benign gynecological tumors, such as myoma and adenomyosis. We herein report a 47-year-old Japanese woman with uterine adenomyosis who developed multiple cerebral infarcts during menstruation. Edoxaban was initially used for prevention but failed to prevent recurrence of thrombosis. However, hysterectomy and bilateral salpingo-oophorectomy resulted in the successful prevention of recurrence of cerebral infarct for five years without antiplatelet or anticoagulant agents. In our patient, the surgical removal of adenomyosis was highly effective for preventing thrombosis in a patient with adenomyosis.

Key words: adenomyosis, hypercoagulability, multiple cerebral infarcts, hysterectomy

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Introduction

Hypercoagulability associated with malignant tumors sometimes causes thrombosis, such as cerebral infarct. Adenomyosis is a benign gynecological tumor; however, there are some reports referring to cerebral infarction that can be caused by adenomyosis (1-9).

We herein report a Japanese woman with adenomyosis and recurrent cerebral infarcts that were successfully prevented for five years by surgical resection of adenomyosis without using antiplatelet or anticoagulant therapy.

Case Report

A 47-year-old woman had a 7-year history of uterine adenomyosis and heavy menstrual bleeding. She took carbazochrome and tranexamic acid during her menstrual periods and had no history of using oral contraceptives. She developed acute numbness of the right hand three days after the start of a menstrual period, and over the next two days, she showed right-hand weakness and aphasia.

On admission, the patient's blood pressure was 144/90 mmHg, her pulse was 100 bpm and regular, and her National Institutes of Health Stroke Scale score was 3. Brain magnetic resonance imaging (MRI) revealed multiple infarcts in the right cerebellum and bilateral cerebral hemispheres (Fig. 1A). MR angiography showed poor visualization of the left M2 branch of the middle cerebral artery. Laboratory tests revealed a low hemoglobin level (11.3 g/dL) and elevated concentrations of D-dimer (3.8 μg/mL, normal <0.5 μg/mL) and fibrin/fibrinogen degradation products (11.1 μg/mL, normal <5 μg/mL), while the prothrombin time, activated partial thromboplastin time and antithrombin III values were normal. There was no reduction in platelet counts. The serum levels of protein C and protein S were normal. Antineutrophil cytoplasmic and antiphospholipid antibodies were negative. Carcinoembryonic antigen was normal; however, the serum levels of cancer antigen 125 (CA 125) (90.3 U/mL, normal <24.5 U/mL) and carbohydrate antigen 19-9 (CA19-9) (52.3 U/mL, normal <36.8 U/ml) were increased. Plasma brain natriuretic peptide was slightly elevated (72.1 U/mL, normal <18.4 U/mL).

Cardiogenic embolism was suspected because of the presence of multiple simultaneous infarcts and elevated concentrations of D-dimer, but her electrocardiogram was unre-

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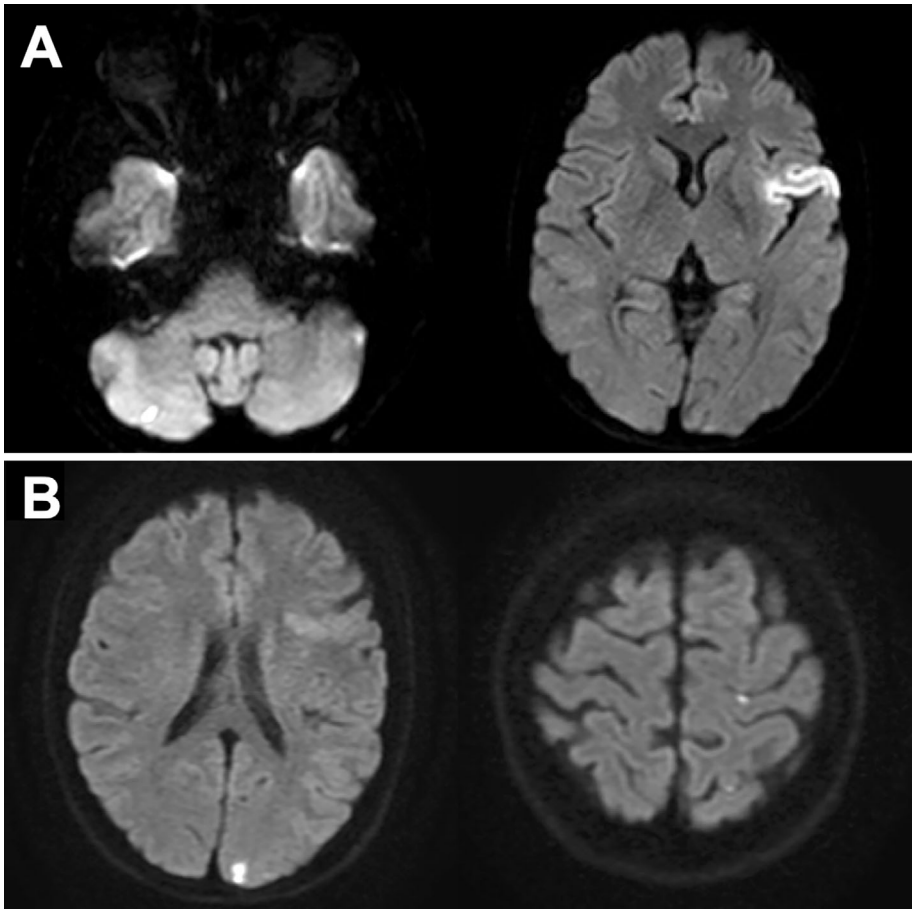

Figure 1. **A: Diffusion-weighted magnetic resonance imaging (DWI) revealed multiple infarctions on admission at the initial onset. B: DWI revealed recurrent cerebral infarctions.**

markable, and continuous bedside electrocardiographic monitoring did not detect paroxysmal atrial fibrillation. Transesophageal echocardiography (TEE) with agitated saline injection found no vegetations, left atrial thrombus, left atrial enlargement, aortic atherosclerotic plaques or patent foramen ovale. Contrast-enhanced computed tomography (CT) revealed no evidence of deep venous thrombosis or malignant tumors, such as lung cancer or lymphoma. Pelvic MRI showed uterine adenomyosis (Fig. 2A), a right ovarian teratoma, and a left ovarian cyst.

Carbazochrome and tranexamic acid were stopped, and unfractionated heparin and edaravone were started. The neurological symptoms/signs disappeared within a few days. On day 8 of admission, the D-dimer level decreased to 0.5 μg/mL. The mechanism underlying her cerebral infarctions was likely cardiogenic embolism, as multiple cerebral infarcts occurred in different vascular territories, with no evidence of a malignant tumor; therefore, we decided to switch the prevention therapy to an oral anticoagulant. Since she had heavy menstrual bleeding, we choose edoxaban, a direct oral anticoagulant considered safer than warfarin (10, 11). On day 11, unfractionated heparin was changed to edoxaban. She was discharged on day 19.

Twenty-four days later, she presented with weakness of her left hand and visual disturbance during her next menstrual period and was readmitted. Brain MRI revealed new multiple infarcts (Fig. 1B), and abdominal CT showed a left renal infarction. Laboratory investigations revealed elevated D-dimer levels (4.2 μg/mL). Edoxaban was stopped, and unfractionated heparin was started. On day 5 of the second hospitalization, the concentration of D-dimer returned to normal (0.4 μg/mL). Because both cerebral infarction events occurred during her menstruation periods, we suspected that the cause was hypercoagulability associated with her uterine adenomyosis.

Adenomyosis treatment with gonadotropin-releasing hormone (GnRH) agonists or surgery was proposed. The patient chose surgery because of the risk of an initial flare-up of gonadotropin levels leading to a thrombophilic state (12). After discontinuing unfractionated heparin, hysterectomy with bilateral salpingo-oophorectomy was performed. A histopathological examination revealed the presence of a right ovarian mature teratoma, left ovarian serous cystadenoma, endocervical and endometrial polyps, and uterine adenomyosis (Fig. 2B). In addition, Alcian blue-periodic acid-Schiff staining showed mucus in some of the endometrial glands of adenomyosis, but the findings did not indicate clear overproduction of mucus. Unfractionated heparin was restarted 24 hours after surgery, but anticoagulant therapy was stopped after 7 days because of the development of in-

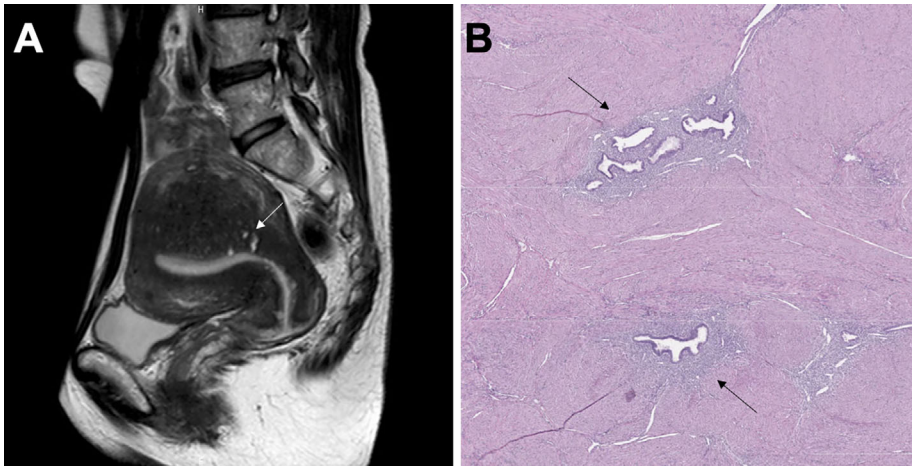

Figure 2. **A: Sagittal T2-weighted image showed thickening of the posterior myometrium and multiple hypertense foci in the lesion (white arrow). B: A photomicrograph (original magnification, ×20; Hematoxylin and Eosin staining) showed islands of ectopic endometrial glands in the myometrium (black arrows).**

traperitoneal hemorrhaging. Seven months after the surgery, the levels of CA125 and CA19-9 returned to normal (CA 125: 5.6 U/mL, CA19-9: 30.8 U/mL). At 5 years after surgery, there has been no recurrence of infarction despite no antiplatelet or anticoagulant therapy.

Discussion

We encountered a 47-year-old woman with adenomyosis for 7 years who had multiple cerebral infarctions during her menstrual phase. At the time of stroke, D-dimer, CA125 and CA19-9 levels were elevated, possibly leading to a gradually progressive hypercoagulability state. Hysterectomy with bilateral salpingo-oophorectomy resulted in no recurrence of thrombosis despite no administration of antiplatelet or anticoagulant agents.

The occurrence of cerebral infarction in adenomyosis patients has been previously reported (1-9). Yamashiro et al. reported cerebral infarction and adenomyosis in four patients (1). Three developed multiple cerebral infarctions, three had histories of heavy menstrual bleeding, and two developed cerebral infarctions during menstrual phases. Three had elevated levels of CA125, and two had elevated D-dimer levels. All of them were treated with GnRH agonists and antiplatelet agents or anticoagulants.

In our patient, recurrent cerebral infarction was prevented by only surgery for adenomyosis without using antiplatelet or anticoagulant therapy. Aso et al. also reported one case of recurrent cerebral infarction in a middle-aged female patient with adenomyosis, and the patient outcome is similar to our case (3). Rivaroxaban which is one of the direct oral anticoagulants, could not prevent a recurrence of cerebral infarction, and total hysterectomy could prevent the onset of cerebral infarction for 2 years without anticoagulation therapy. These outcomes more strongly support the hypothesis that cerebral infarction is associated with adenomyosis, and hysterectomy is an effective prevention for cerebral infarction.

Compared with the endometrium of healthy women and adenomyosis patients, elevated tissue factor, which is considered to play an important role in coagulation, has been reported in both eutopic and ectopic endometrium of adenomyosis patients, and the elevated tissue factor immunoreactivity is related to heavy menses and dysmenorrhea (13).

Carcinoma mucins, including CA125 and CA19-9, promote thrombosis in Trousseau's syndrome by adhesion-dependent, bidirectional signaling in neutrophils and platelets (14). In previous reports, most adenomyosis patients with cerebral infarctions had high CA125 levels (1-9). In addition, several studies reported that CA19-9 levels were elevated in patients with adenomyosis who developed cerebral infarction (3, 4, 6, 7, 9). In our case, CA125 and CA 19-9 levels were slightly elevated, and pathological examination did not prove the overproduction of mucus. However, after surgery, the CA125 and CA19-9 levels returned to normal without recurrence of infarction, suggesting that upregulated CA125 and CA19-9, though only slightly, might contribute to the development of cerebral infarction in patients with uterine adenomyosis. Furthermore, our patient had not only adenomyosis but also ovarian mature teratoma, ovarian serous cystadenoma, and uterine polyps, and these tumors were also removed. CA125 and CA19-9 are sometimes elevated in ovarian mature teratoma (15). Our literature search failed to find an association between cerebral infarction and ovarian teratoma; however, the possibility that teratoma contributed to the onset of cerebral infarctions in our case could not be excluded.

Edoxaban did not prevent the recurrence of cerebral infarction in our case. A large, randomized trial showed that edoxaban was noninferior to low-molecular-weight heparin in managing cancer-associated venous thromboembolism (16). However, the preventive effect of edoxaban against cancer-associated arterial thromboembolism is un-

known. In patients with cancer, especially adenocarcinoma, a common source of arterial thromboembolism is nonbacterial thrombotic endocarditis (NBTE) (17). There have been several reported cases of NBTE associated with adenomyosis (2, 4, 6). Although vegetations were not detected by TEE in our case, thromboembolic events may have been caused by NBTE as cerebral infarcts were located in multiple cerebral circulations and complicated by renal infarction.

In conclusion, it should be noted that adenomyosis patients, particularly those with heavy menstrual bleeding with anemia or elevated concentrations of CA125 and CA19-9, will have thrombosis. Surgical resection of adenomyosis is an effective treatment option for patients with adenomyosis and thrombotic events.

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

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