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Low-dose gonadotropin-releasing hormone agonist therapy (draw-back therapy) for successful long-term management of adenomyosis associated with cerebral venous and sinus thrombosis from low-dose oral contraceptive use

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Summary

The authors report a case of cerebral venous and sinus thrombosis (CVST) in a patient receiving a low-dose estrogen-progestin combination (oral contraceptives, OCs) for uterine adenomyosis. She was switched to gonadotropin-releasing hormone agonist (GnRHa) draw-back therapy, which was successfully administered long-term. *Case:* The patient was a 38-year-old nulligravida with a history of smoking. She presented to this hospital with dysmenorrhea and postmenstrual lower abdominal pain. Adenomyosis was diagnosed using ultrasound and magnetic resonance imaging. She was instructed to stop smoking and was administered low-dose OCs. CVST occurred 18 months later. OC therapy was halted, and only antiplatelet therapy was administered. After six months, her chief complaint symptoms intensified, therefore GnRHa draw-back therapy was administered after obtaining informed consent. No uterine enlargement was observed, and the abdominal pain resolved. During 2.5 years of therapy, her bone density levels remained within normal limits. CVST did not recur and no other thromboses were observed.

Key words: Adenomyosis; Cerebral venous and sinus thrombosis; Low-dose gonadotropin-releasing hormone agonist therapy; Low-dose oral contraceptive.

Introduction

Recently, more patients desire to preserve the uterus when treating uterine adenomyosis. Gonadotropin-releasing hormone agonist (GnRHa) therapy is highly effective for adenomyosis, but it can only be administered for a limited duration and is associated with high recurrence rates [1]. Draw-back therapy, in which side effects are suppressed and the effect is extended by lowering the GnRHa dose, has been proposed and reported to be effective for adenomyosis [2-4]. Previously, the authors reported on the effectiveness of draw-back therapy for a patient with deep thrombosis of the lower limb associated with adenomyosis [5]. However, the safety and efficacy of draw-back therapy for adenomyosis with thrombosis caused by low-dose oral contraceptives (OCs) have not been reported. Here, they describe their experience with a case of cerebral venous and sinus thrombosis (CVST) that occurred during low-dose OC therapy for adenomyosis for which long-term GnRHa draw-back therapy was possible.

Case Report

The patient was a 38-year-old married nulligravida with a body mass index of 22.5 and a history of smoking. Her history was also significant for adenomyosis, which was diagnosed at age 34 years at another hospital and which receded after six months on low-dose OCs. She presented to this hospital with menstrual pain and postmenstrual lower abdominal pain. Adenomyosis was diagnosed using ultrasound examination and magnetic resonance imaging (MRI). After diagnosis at this hospital, regular GnRHa therapy (leuprorelin acetate 1.88 mg, six months) was administered twice in two years. The patient's adenomyosis receded after administration, but both times it worsened again and the symptoms reappeared, so she was instructed to stop smoking and was administered low-dose OCs.

The patient complained of headaches after 18 months on low-dose OCs and was examined by the neurosurgery department at another general hospital. CVST was diagnosed using imaging studies (Figures 1a, b). Laboratory tests revealed a high D-dimer level at 3.0 μg/ml, but no other abnormalities were observed, including thrombotic factors such as antithrombin, protein C, protein S, and antiphospholipid antibodies. Low-dose OC therapy was halted, and antiplatelet therapy was administered for the CVST. The patient's dysmenorrhea and postmenstrual lower abdominal pain from adenomyosis were treated only symptomatically.

After six months, the adenomyosis symptoms reappeared and intensified, therefore GnRHa draw-back therapy was initiated after obtaining sufficiently informed consent and the approval of

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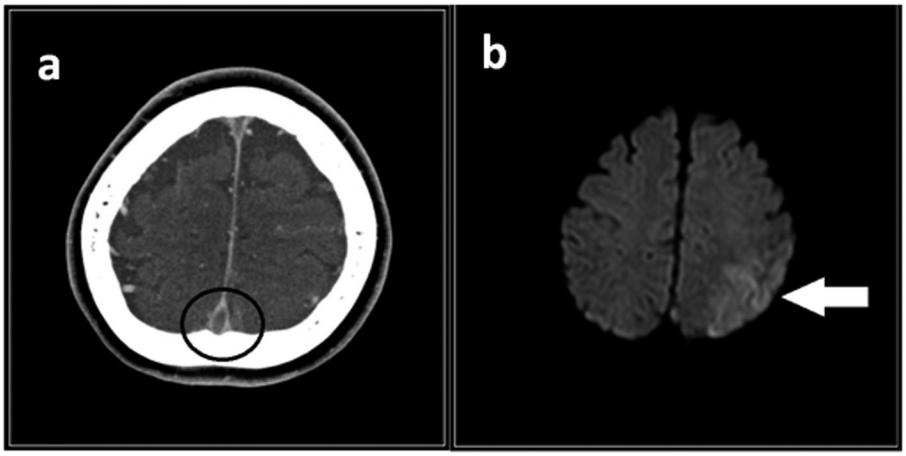

Figure 1. — a: Loss of contrast (empty delta sign) is observed on contrast CT (delay) (inside the circle). b: MRI FLAIR image: High signal findings are observed in the left parietal lobe, indicating edematous changes and cortical infarct (arrow).

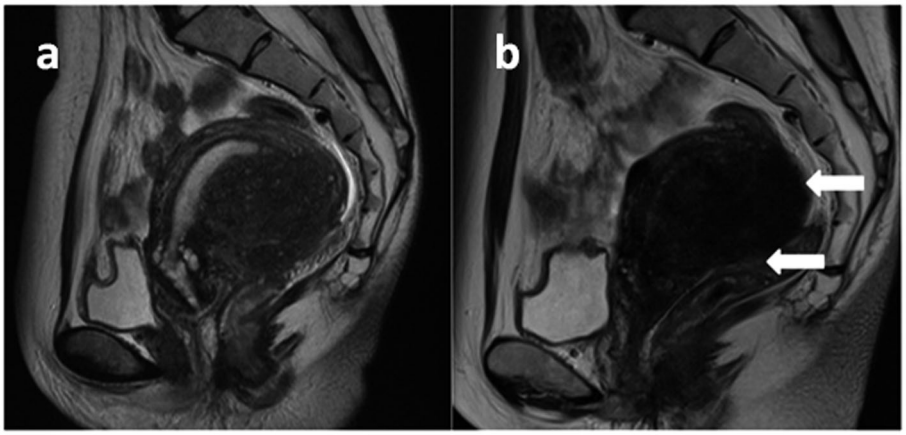

Figure 2. — a: before draw-back therapy, b: during draw-back therapy. Atrophy of adenomyosis tissue is observed (arrows).

the neurosurgeon in charge of treating the CVST. In addition, the present hospital's ethics committee approved the use of GnRHa draw-back therapy for this patient.

The procedure for this therapy first involves four subcutaneous injections of leuprorelin acetate 1.88 mg (once every four weeks) to decrease the uterine volume. After this was confirmed, buserelin acetate nasal spray at the normal dose (900 μg/day: six sprays/day) was administered for four weeks. The dose was then reduced to 2/3 (600 μg/day) and adjusted on a monthly basis (number of sprays) to maintain blood estradiol levels between 20 and 50 pg/ml. During GnRHa draw-back therapy, this patient's estradiol levels temporarily increased, and she menstruated once, but otherwise amenorrhea was continuous. There was no unusual vaginal bleeding, and the uterus did not enlarge during therapy (Figures 2a, b). Blood cancer antigen 125 (CA 125) levels normalized, and the patient's lower abdominal pain resolved. No abnormalities were observed in yearly cervical and endometrial cytology exams. Bone density remained above the age-appropriate lower limit (0.630 g/cm^2 radial dual-energy x-ray absorptiometry). The patient temporarily experienced mild hot flashes, but no other side effects were observed. At present, the patient has been undergoing therapy for 2.5 years. D-dimer levels have remained at 0.5 μg/ml or lower, and there has been no recurrence of CVST or other thrombosis.

Discussion

This case was notable for two successes. First, the authors successfully administered GnRHa draw-back therapy in a case of thrombosis caused by low-dose OCs. Second, GnRHa draw-back therapy was successfully administered, even in the presence of CVST.

GnRHa is the most effective treatment for alleviating dysmenorrhea, chronic lower abdominal pain, and uterine hypertrophy from adenomyosis. However, it can only be used for at most six months due to the low-estrogen state it causes. Symptoms of low estrogen from long-term GnRHa administration can be addressed with hormone supplementation (add-back therapy) [6, 7] or draw-back therapy [2-4], both of which have been shown to be effective for endometriosis. Unlike add-back therapy, draw-back therapy is not contraindicated for breast cancer or deep vein thrombosis. The present authors previously reported a case of a patient with deep thrombosis of the lower limb and endometriosis, for whom draw-back therapy was effective [5]. However, the use of draw-back therapy has not been reported for thrombosis or CVST caused by low-dose OC ad-

ministration. The present authors' experience suggests that draw-back therapy could serve as a conservative therapy for thrombosis or CVST that occurs from low-dose OCs. Further, draw-back therapy could be an alternative to low-dose OCs in cases of menorrhagia or dysmenorrhea.

Low-dose OCs are used to treat dysmenorrhea and endometriosis, as well as to lighten menorrhagia, so they are also used to treat uterine fibroids and adenomyosis. However, OCs have long been known to be associated with venous thromboembolism (VTE) [8]. Moreover, cerebral infarction [9] and cerebral venous thrombosis [10] have been reported to occur with adenomyosis. Because D-dimer and CA 125 levels are elevated in adenomyosis [9, 10], more obstetricians need to be educated about the association between adenomyosis and thrombosis. That is, they need to understand that administering low-dose OCs for adenomyosis doubles the risk of thrombosis, so other internal therapies should be selected first.

Cerebral sinus thrombosis involves thromboses in the cerebral veins and venous sinuses. The resulting blood flow impairment causes cranial pressure to rise. It is a rare form of VTE [11] and is known to be more common in women and relatively young stroke patients [12]. Its onset is associated with a variety of pathologies, including infection, malignant tumor, blood disease, diabetes, and trauma [13]. Pregnancy, childbirth, and OC use are also risk factors [11]. Headache is the most common symptom [14], but nausea, vomiting, local paralysis, spasms, and consciousness disorders also occur. Contrast CT is useful for diagnosis and might exhibit the cord sign (thrombosed cortical or deep vein), the dense triangle sign (visualization of the clot inside the sinus), or the empty delta sign. However, a combination of MRI and magnetic resonance venography is currently the preferred form of diagnosis [12]. Approximately 85% of patients recover without aftereffects, whereas 15% experience aftereffects or die [15]. In this case, the patient experienced no after effects and is living a normal life with no recurrence. This suggests that draw-back therapy can be performed even in cases with a history of CVST.

Currently, internal therapies for adenomyosis include GnRHa, low-dose OCs progestin therapy (dienogest, the levonorgestrel-releasing intrauterine system) and antigonadotropin danazol. However, each has its disadvantages. The present authors believe that GnRHa draw-back therapy should be the first choice for patients who wish to preserve the uterus.

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