Conservative therapy with a gonadotropin-releasing hormone agonist for a uterine arteriovenous malformation in a patient with congenital heart disease

Kinue Katano, Yutaka Takeda & Mayumi Sugiura-Ogasawara

1Department of Obstetrics & Gynecology, Nagoya City University, Graduate School of Medical Sciences, Nagoya, Japan
2Department of Cardiology, Nagoya City University, Graduate School of Medical Sciences, Nagoya, Japan

Correspondence
Kinue Katano, Department of Obstetrics and Gynecology, Nagoya City University, Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan. Tel: +81 52 853 8241; Fax: +81 52 842 2269; E-mail: og.kktn@med.nagoya-cu.ac

Funding Information
No sources of funding were declared for this study.

Received: 3 September 2014; Revised: 30 December 2014; Accepted: 20 January 2015

Clinical Case Reports 2015; 3(6): 479-482
doi: 10.1002/ccr3.233

Introduction

Uterine arteriovenous malformation (AVM) is rare, but it can cause life-threatening heavy genital bleeding in reproductive-age women. Uterine artery embolization (UAE) for an AVM is the gold standard, to avoid hysterectomy [1]. Some authors reported that a gonadotropin-releasing hormone agonist (GnRHa) was effective for treating uterine AVM patients in a nonemergency state [2]. Only two cases of uterine AVM in patients with congenital heart disease have been reported, to the best of our knowledge [3]. Here we report the case of a young woman with a uterine AVM and congenital heart disease diagnosed just after miscarriage, treated successfully with conservative GnRHa therapy.

Case

The patient was a 20-year-old, married, and non-gravida Japanese woman. Her written consent for publication of this case report was obtained. Her menarche was at 13 years old. Her menstrual period was regular. Her height was 152 cm, body weight was 37 kg. At the age of 10, she underwent an intracardiac repair for a left atrial isomerism and an incomplete endocardial cushion defect (ostium primum atrial septal defect). She thereafter dropped out from the pediatrician’s follow-up. She had no history of uterine surgery nor gastro-intestinal bleeding. She and her family had no history of hereditary hemorrhagic telangiectases. She got pregnant naturally at 20 years old, and at her 11th gestational week she was admitted for 2 weeks at another hospital for a subchorionic hematoma. Echocardiography (ECG) revealed an unrestricted reopening of the atrial septal defect (ASD), a left-to-right shunt, and pulmonary hypertension. A ventricular septal defect was not detected. The patient reported that she had no trouble with physical exertion in her daily life. She was referred to our hospital for perinatal care at 14w6d gestational age. The subchorionic hematoma was followed by placental abruption, resulting in a miscarriage on 16w3d gestational age. Bleeding during labor was 600 mL. Immediately after this...
miscarriage, the patient’s hemoglobin was 10.1 g/dL. Uterine color Doppler ultrasonography was not performed before the pregnancy or just after the miscarriage. Despite oxygenation, her SaO₂ gradually dropped to 89%.

Two days later, the patient was transferred to the CCU for heart failure. Her chest X-ray showed the cardiothoracic ratio (CTR) 63%, and ECG revealed an ASD (I; nonrestrictive) and an almost single-atrium state, indicating no vestige of the repair operation, and pulmonary arterial hypertension. Her estimated pulmonary-systemic flow ratio (Qp/Qs) was 5.23, and the estimated maximum pulmonary arterial pressure was 72 mmHg. After 1 week of heart failure treatment with tadalafil 40 mg, ambrisentan 2.5 mg and sildenafil citrate 30 mg per day, the patient’s general status became stable and she was discharged with home oxygen therapy.

After a 1-month-long improvement in her physical status, the patient experienced heavy genital bleeding and discontinuous atypical genital bleeding. At 66 days after the miscarriage, she was admitted again for anemia (hemoglobin 7.8 g/dL). A transvaginal ultrasound with color Doppler (Logic S6, GE-Yokokawa Medical Systems, Hino, Japan) scan revealed a 2-cm diameter mass of abnormal vascularity with mixed arterial and venous flow in the uterine posterior wall, suggesting a uterine AVM (Fig. 1). Magnetic resonance imaging (MRI; Achieva 1.5T; Philips, Best, The Netherlands) confirmed a uterine AVM, and digital subtraction angiography showed a bending and winding flow void and early venous image as drainage vessels (Fig. 2). Computed tomography (CT) showed findings of polysplenia, abdominal heterotaxy, a subhepatic defect of the inferior vena cava, and an azygos vein connection (Mx8000 IDT 16; Philips) (Fig. 3). At the time of diagnosis of the uterine AVM, the urine HCG was negative. We considered intracardiac repair surgery risky because the powerful heparinization during the use of an artificial heart-lung machine could cause uncontrollable genital bleeding. Moreover, the patient’s slowed recovery from heart failure and elevated pulmonary arterial pressure also suggested an increased mortality risk from surgery. The patient did not want to take such a risk, and she also refused a UAE due to fear of a paradoxical embolism with the embolization materials [4]. She also declined a hysterectomy.

At 13 days after the patient’s re-admission, the long-term administration of a GnRHa (1.88 mg leuprolelin

Figure 1. Transvaginal ultrasonography with color Doppler scan before GnRHa therapy in a 20-year-old non-gravida woman, showing a 2-cm diameter lesion suggesting a uterine AVM (on which a 1-cm scale is indicated).

Figure 2. Magnetic resonance imaging before GnRHa therapy. The arrows point to the bending and winding flow void and early venous image as drainage vessels in the uterine posterior wall, which indicates a uterine AVM.
acetate by subcutaneous injection, monthly) was begun as a way to improve her cardiac function by controlling the heavy genital bleeding and reduce the uterine AVM. At 111 days after the initiation of the GnRHa regimen, CT showed the finding of alveolar hemorrhage in S6 of the lower lobe of the right lung and no brain AVM. CT scintigraphy revealed a right-to-left shunt, providing indirect proof of a pulmonary arteriovenous fistula, but a left-to-right shunt of the ASD was shown by ECG. After the 1-year administration of the GnRHa (11 times), transvaginal ultrasound and MRI showed the disappearance of the uterine AVM lesion. She had no vasomotor symptoms while on leuprorelin therapy. However, she had transient unexplained chest pain, which might be a side effect due to the 11 leuprorelin injections.

The patient’s menstrual periods were regular again after 2 months without hypermenorrhea, and she felt that they were lighter than before the pregnancy. Her hemoglobin was recovered to 14.3 g/dL and her body weight had risen to 44 kg. No uterine AVM lesion has been detected in her uterus in the 2 years since the discontinuation of the GnRHa (Fig. 4). The home oxygen therapy was stopped, with the patient’s SaO₂ of 94%. Her estimated Qp/Qs was 2.4, and her estimated maximum pulmonary arterial pressure was 50 mmHg. Her chest X-ray showed the CTR 62%.

A cardiac catheter test using heparin can now be safely administered to the patient, because she no longer experiences heavy genital bleeding. Her cardiac function has improved, and a radical cardiac operation could now be considered.

Comment

Uterine AVM, a rare but life-threatening disease in women of child-bearing age, can be congenital due to embryonic angiodysplasia and acquired due to uterine...
surgeries such as myomectomy, caesarian section, and curettage. Differential diagnoses are uterine pseudoaneurysm, retained product of conception, gestational trophoblastic disease, and hemangioma [1]. A possible etiological mechanism in AVM may involve neovascularization caused by vascular endothelial growth factor (VEGF), which is associated with uterine angiogenesis and vascular remodeling during pregnancy [3, 5]. It has been pointed out that a history of pregnancy is frequently associated with a typically single occurrence in case of acquired uterine AVM [1].

The hormonal changes that occur during pregnancy and menstruation may be key points in the pathogenesis of uterine AVM [1]. Notch signaling in the endothelium mediated by estrogen plays an important role in the development of arteriovenous malformation [6]. The downregulation of estrogen secretion with GnRHa induces an increase in uterine arterial resistance and a decrease in uterine blood flow and histological changes such as vasculitis and atherosclerosis in the blood vessels [7]. We speculated that the manifested symptoms of uterine AVM were due to increased estrogen secretion with the pregnancy, in a probable case of congenital latent uterine AVM, rather than a possible uterine AVM as a result of miscarriage curettage.

Our patient, who suffered from worse cardiac function after the pregnancy load, originally had pulmonary arterial hypertension with an almost single atrium of reopen ASD. Her cardiac function became worse still due to the heavy genital bleeding derived from the uterine AVM. Peitsidis et al. [8] reported the natural regression of a uterine AVM. In our patient, however, we started the administration of GnRHα (instead of the refused UAE and hysterectomy) as soon as possible to stop her uterine bleeding for a fast recovery from anemia and for the restoration of her cardiac function.

We conclude that the cessation of this patient’s heavy genital bleeding from a uterine AVM was achieved with GnRHa therapy, which was also effective for the recovery of her cardiac function. Conservative therapy with GnRHα can be a useful option for treating a uterine AVM presenting with a congenital heart disease shunt in hemodynamically stable patients.

Acknowledgments
We thank Dr. Osamu Yamada of the Department of Pediatric Cardiology, National Cerebral and Cardiovascular Center and Dr. Tatsuya Kawai and Dr. Masashi Shimohira of the Department of Radiology, Nagoya City University, Graduate School of Medical Sciences.

Conflict of Interest
None declared.

References
1. Grivell, R., K. Reid, and A. Mellor. 2005. Uterine arteriovenous malformations: a review of the current literature. Obstet. Gynecol. Surv. 60:761–767.
2. Nonaka, T., T. Yahata, K. Kashima, and K. Tanaka. 2011. Resolution of uterine arteriovenous malformation and successful pregnancy after treatment with a gonadotropin-releasing hormone agonist. Obstet. Gynecol. 117:452–455.
3. Wijesekera, N. T., S. P. Padley, F. Kazmi, C. L. Davies, and J. M. McCall. 2009. Embolization of uterine arteriovenous malformations associated with cyanotic congenital heart disease. Cardiovasc. Intervent. Radiol. 32:1075–1079.
4. Bilbao, J. I., A. Martinez-Cuesta, F. Urtasun, and O. Cosín. 2006. Complications of embolization. Semin. Intervent. Radiol. 23:126–142.
5. Kim, M., H. J. Park, J. W. Seol, J.Y. Jang, Y.S. Cho, K.R. Kim et al. 2013. VEGF-A regulated by progesterone governs uterine angiogenesis and vascular remodeling during pregnancy. EMBO Mol. Med. 5:1415–1430.
6. Carlson, T. R., Y. Yan, X. Wu, M. T. Lam, G. L. Tang, L. J. Beverly, et al. 2005. Endothelial expression of constitutively active Notch4 elicits reversible arteriovenous malformations in adult mice. Proc. Natl. Acad. Sci. USA 102:9884–9889.
7. Mesia, A. F., D. Gahr, M. Wild, K. Mittal, and R. I. Demopoulos. 1997. Immunohistochemistry of vascular changes in leuprolide acetate-treated leiomyomas. Am. J. Obstet. Gynecol. 176:1026–1029.
8. Peitsidis, P., E. Manolakos, V. Tsekoura, R. Kreienberg, and L. Schwentner. 2011. Uterine arteriovenous malformations induced after diagnostic curettage: a systemic review. Arch. Gynecol. Obstet. 284:1137–1151.