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CASE REPORT

Uterine Arteriovenous Malformation after First Trimester Termination of Pregnancy in a Patient with Hereditary Haemorrhagic Telangiectasia

Nicola Strobelt, MD[1*], Elena Osella, MD[2] and Vittorio Aguggia, MD[3]

Obstetrics and Gynaecology Ward, SS Antonio e Biagio e Cesare Arrigo General Hospital, Alessandria, Italy

***Corresponding author:** *Nicola Strobelt, MD, c/o Centro Wocare, Rotonda dei Mille 4, 24122, Bergamo, Italy*

Abstract

Hereditary haemorrhagic teleangiectasia (HHT) is a rare autosomic dominant genetic disorder, characterised by epistaxis, cutaneous teleangiectasias, and arteriovenous malformations (AVMs) located mainly in lungs, gastrointestinal tract, liver, and central nervous system. We report a case of uterine arteriovenous malformation acquired after medical pregnancy interruption in a patient with HHT, discussing the atypical genetic setting and the strategy for the case management.

Keywords

Arteriovenous malformation, Hereditary haemorrhagic telangiectasia, Rendu-osler, First trimester abortion, Triptorelin, Arterial embolization

Abbreviations

HHT: Hereditary haemorrhagic teleangiectasia; AVM(s): Arteriovenous malformation(s); UAVM(s): Uterine arteriovenous malformation(s); HCG: Human chorionic gonadotropin; CT: Computerised tomography; MR: Magnetic resonance

Introduction

Uterine arteriovenous malformations (UAVMs) are rare but potentially life-threatening conditions. They consist in vascular lesions formed by the abnormal connection between artery and vein. They are usually classified into two types: Congenital and acquired. Acquired UAVMs are generally traumatic and follow delivery, abortion, curettage, or uterine surgery.

Hereditary Haemorrhagic Telangiectasia (HHT), also known as Rendu-Osler syndrome, is a rare dominantly inherited vascular disorder characterized by recurrent epistaxis, cutaneous telangiectasias, and visceral AVMs, mainly with pulmonary, hepatic or cerebral, but also gastroenteric and spinal localization. Complications during pregnancy are rare but can be severe. They are usually related to the impact of pregnancy on maternal vascular bed in terms of vasodilation and increased cardiac output, leading to increased risk of bleeding, desaturation, and cardiac failure.

To our knowledge, this is the first described case of acquired UAVM after a medically induced first trimester abortion in a patient with HHT. It represents an interesting model for speculating on pathogenesis of acquired UAMs and on their prevention and treatment in particular clinical settings.

Presentation of the Case

A 30-year-old woman was admitted on the obstetrics and gynecological ward on July 9th, 2019. She was 6 weeks and 4 days pregnant according to her last menstrual period.

She had no past medical history except a cesarean section performed for obstetric indication in 2017. Her family history was also not relevant except for her mother and sister who were both affected by HHT.

She was admitted to hospital because she wanted to undergo a pharmacological termination of pregnancy. On July 9th, 2019 she was administered one tablet of Mifepristone 600 mg. Two days later, 11th July 2019, she was administered Gemeprost 1 mg vaginally. On that

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same day the abortion was completed as she successfully expelled the gestational sack.

She was dismissed after being injected one vial of methylergoamine maleate, as she was bleeding slightly more than expected. A transvaginal ultrasound at discharge showed a uterine cavity containing only non structured material, interpreted as blood clots.

She had no menstrual period for 3 months until she went for a transvaginal ultrasound scan on October 2nd 2019, about three months after pregnancy termination. Beta-HCG assays showed values of 49.9 IU/L on September 6th, and of 30.7 IU/L on September 13th. Transvaginal sonography found a disomogeneous intrauterine mass with color score 3, suggestive of an intrauterine arteriovenous malformation. She was thus admitted to hospital on the day after. A second ultrasound scan was performed and the initial hypothesis was confirmed: A hypervascularized formation of about 30 mm was found inside the uterus. Its main feature was the presence of a low resistance arterial flow associated with large vessels with arterial pulsation (Figure 1). At admission the level of serum beta-HCG was of 8 IU/L, this excluded the hypothesis of a trophoblastic disease. On the days 5th and 6th of October she reported having some dark discharge which resulted in scarce vaginal bleeding.

A pelvic MR was performed which confirmed the presence of an intrauterine mass of uncertain origin: Differential diagnosis was proposed again by the radiologist between post abortive molar tissue and arteriovenous malformation. On 8th October an X-Ray of the thorax was performed and no pathological finding was detected.

The patient was thereafter managed considering the diagnosis of UAVM. D&C was not performed for two main reasons: High risk of bleeding secondary to the hypervascularization of the uterine formation, high risk of developing further vascular anomalies in the hypothesis the patient were affected by HHT as her mother and her sister. On the 9th October the patient underwent embolization of the right uterine artery since the blood supply was found at angiography coming mainly from that artery (Figure 2). On the same day serum betaHCG were dosed on blood and the levels were undetectable.

On 11th October a post-procedural scan was performed and there was a scarcely vascularized disomogeneous intrauterine formation of 49 × 36 × 49 mm.

As the patient had been complaining of pain at her right popliteal fossa she also underwent an echocolor-doppler of her lower limbs. This along with a clinical evaluation, in order to rule out any form of thrombosis which was, indeed, excluded. On that day her haemoglobin levels were 11.3 gr/dl.

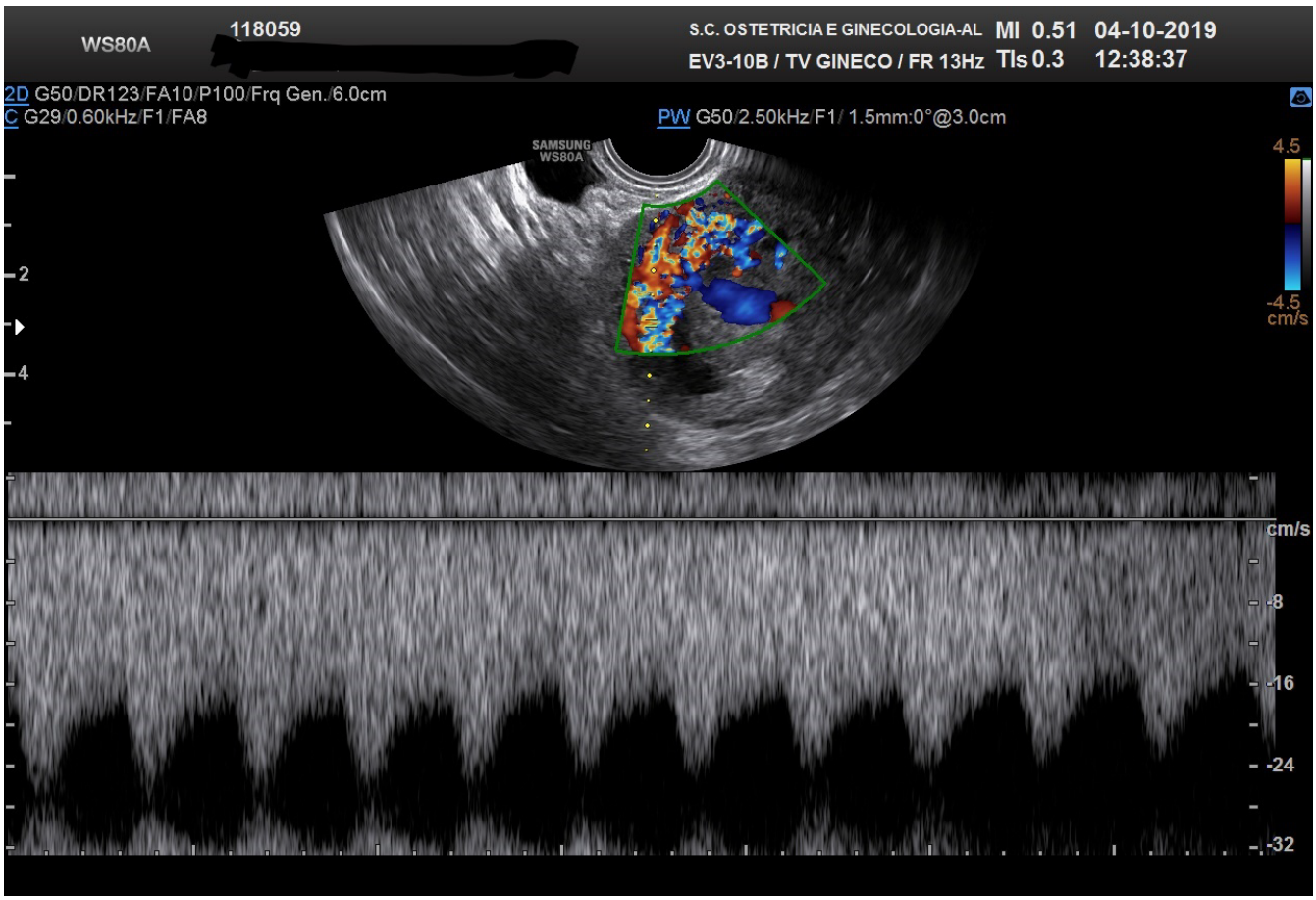

Figure 1: Uterine arteriovenous malformation with high flow and arterial pulse at color doppler.

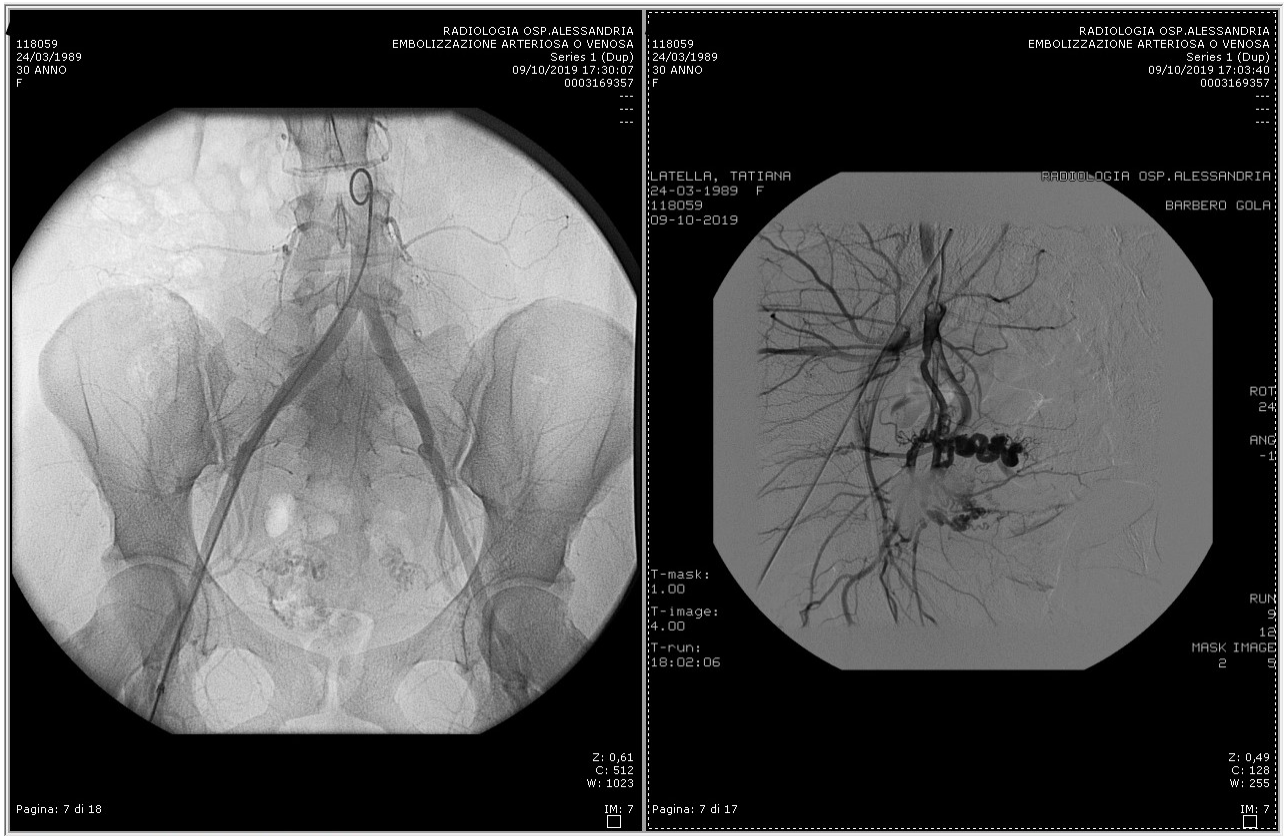

Figure 2: Selective uterine angiography before embolization.

Decision of inhibiting ovarian function by administering Gn/RH analogue was taken, in order to prevent any menstrual bleeding during the next months and to enhance the chance of resolution with no further procedure. She was thus administered the first of three vials of Triptorelin 3.75 mg.

On 14th October she was dismissed and a last scan was performed with a finding of almost complete regression of any vascularised area inside the endometrial cavity.

Evaluation by a medical geneticist on November 26, 2019 led to the clinical diagnosis of HHT.

On 5th December she was injected the last vial of Gonapeptyl (she completed a cycle of three vials, one a month). On 10th December she performed a CT scan of the thorax to identify any pulmonary vascular malformation.

On 12th December 2019 she underwent a final sonographic scan: There was no evidence of intrauterine mass, and therefore no further therapy was required.

Discussions

Our patient underwent medically induced first trimester abortion, and presented after three months for post-abortion bleeding. Sonography revealed an intrauterine pattern suggestive of UAVM. She was managed conservatively and later found to be affected by HHT, a dominantly inherited disease, as well as her mother and her sister.

Clinical diagnosis of HHT is based on the Curaçao Criteria defined in year 2000 by the Scientific Advisory Board of the HHT Foundation. These consist of the following 4 signs: 1. Epistaxis that occurs spontaneously on more than one occasion; 2. Telangiectasias at typical sites like nose, fingers, and oral cavity; 3. Pulmonary, hepatic, cerebral, gastroenteric or spinal arteriovenous malformations (AVMs); 4. A family history of HHT (first-degree relative affected). To be diagnosed with HHT, a patient must meet at least 3 of the 4 criteria [1,2]. AVMs are the main clinical determinant of HHT, since most of the complications arise from two pathogenetic mechanisms both envolving these vascular anomalies: ruptures, leading to bleeding in various sites, and high flow arteriovenous shunting, leading to desaturation and/or high flow cardiac failure.

HHT is caused by mutations in different genes: ENG (encoding endoglin) [3], ACVRL1 (encoding activin receptor like kinase 1) [4], or MADH4 (encoding SMAD4), which are responsible for an imbalanced state between anti- and pro-angiogenic factors [5]. More than 90% of all cases of HHT are due to mutations in either ENG or ACVRL1. These mutations lead to altered responses to vascular endothelial growth factors (VEGFs) in terms of neo-angiogenesis. VEGFs are a family of proteins, which includes VEGFA, VEGFB, VEGFC, VEGFD and placental growth factor (PLGF). VEGFs receptors (VEGFR) are usually classified in three different types: VEGFR1, VEGFR2 and VEGFR3. VEGFRs consist of seven immunoglobulin (Ig) homology domains that contain the ligand-binding

part and a split tyrosine kinase domain, which transduces the growth factor signals. VEGFA signaling in blood vascular endothelial cells is mediated predominantly via activation of VEGFR2. VEGFR1 and its soluble form of VEGFR1 (sVEGFR1) act as endogenous inhibitors of VEGFA/VEGFR2 signaling, thus VEGFR1 mis-regulation can also participate in pathological processes. It has also been shown that the placenta produces high levels of sVEGFR1 during pregnancy, and the pathogenesis of pre-eclampsia during the last trimester has been linked to sVEGFR1 neutralization of VEGFA and PLGF [6]. Pregnancy could thus theoretically be considered a possible con-cause for the imbalance of pro- and anti-angiogenetic factors in patients with HHT.

Based on the vascular anomaly classification proposed by Mulliken and Glowaki, AVMs can be defined as a vascular anomaly involving abnormal communication between arteries and veins, since the capillary system is by-passed [7]. In some cases the abnormal communication is represented by one or more dilated vascular structures called “nidus” with high flow, presenting sometimes with a Ying-Yang color-doppler appearance, in other cases the high pressure gradient flow is caused by a direct fistula between artery and vein. Color Doppler ultrasonography has become the preferred diagnostic method in the last two decades, even if diagnoses done by CT and RM have been reported. However, angiography remains the gold-standard modality for diagnosing uterine AVMs, as it is required for both definitive diagnosis and treatment [8].

Uterine AVMs are divided into congenital and acquired forms.

Congenital UAVMs result from a defect in the differentiation of the primitive capillary plexus during fetal angiogenesis [9]. Congenital cases of UAVM have been previously published, although very rare, even in association of pregnancy. Of note, we found a single published case of congenital UAVM in a pregnant woman with HHT, that ended with an uneventful term pregnancy and delivery by planned cesarean section [10].

Acquired UAVMs are also called “traumatic” since their pathogenesis is almost always secondary to uterine D&C after miscarriage, abortion, post-partum bleeding treated with D&C, or located in scars after cesarean sections or myomectomies [11-13]. In our case, the persistence of low levels of beta-HCG, even in the absence of any form of trophoblastic disease, may have been a local hormonal stimulation for neo-angiogenesis in a genetic setting of predisposition to AVMs development

Our case is indeed peculiar for at least two reasons:

1. It’s a case of acquired UAVM after medically induced abortion that never underwent any D&C procedure.
2. It’s an acquired UAVM case that developed in a particular clinical setting, represented by HHT.

The combination of the two aforementioned conditions led us to approach the case with a non-invasive treatment, represented by uterine artery embolization, with the purpose of avoiding the uterine tissues trauma of a D&C, a possible further stimulation of neo-angiogenesis in a setting of genetic predisposition as well as high risk of haemorrhage as the blood vessels were rather large. Embolization led to a prompt and dramatic reduction in vascularization of the intrauterine mass, as expected. The subsequent administration of GnRH analogue allowed us to prevent further bleeding episodes by inhibiting menstrual flows for the following three months. The absence of further bleeding episodes, even after monthly menstruation recovery, prompts us to evaluate as efficient our non invasive approach.

On the other hand, because of the clinical history of the present case and after reading published data on the pathogenesis of UAVMs, we wonder if first trimester interruption of pregnancy should be managed, in patients with a diagnosis or a familiar history of HHT, with careful clinical monitoring represented by sonographic serial examinations and serial betaHCG assays, in order to early identify cases of throfoblastic tissue persistence and/or neo-vascularization masses. These cases should presumably undergo early embolization rather than D&C, to prevent subsequent development of recurence of UAVMs and to protect the fertility potential of the patient.

Furthermore, literature reading and the history of this case, with its family background, prompt us to recommend genetic diagnosis in all the cases of women with first degree relatives affected by HHT before planning a pregnancy, in order to carry out a complete screening of the typical target organs, and to perform risk and treatment counseling before pregnancy.

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