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Case Report

Misdiagnosis of intramural ectopic pregnancy and invasive gestational trophoblastic disease on ultrasound: A challenging case at Tu Du Hospital in Vietnam in COVID-19 pandemic peak and mini-review of literature ☆,☆☆

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ABSTRACT

Differentiation between intramural ectopic pregnancy and molar ectopic pregnancy is very difficult because of their exceptional rarity. Herein, we present a misdiagnosed case of intramural pregnancy and invasive trophoblastic disease on ultrasound. A 45-year-old female patient was admitted to our tertiary referral hospital due to abdominal pain and unusual ultrasonography findings. Initially, a diagnosis of intramural ectopic pregnancy was identified based on transvaginal color Doppler ultrasonography, 3-dimensional ultrasound, and serial serum beta-human chorionic gonadotropin, thus the patient underwent laparotomy with hysterectomy. However, the histopathological endpoint showed an invasive trophoblastic disease. Clinically, this pathology should be included in the differential diagnosis of intramural ectopic pregnancy since an imaging scan remains quite unclear.

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Abbreviations: β -hCG, beta-human chorionic gonadotrophin; COVID-19, coronavirus disease of 2019; IEP, intramural ectopic pregnancy; GTD, gestational trophoblastic disease; GS, gestational sac; TV-CDU, transvaginal color Doppler ultrasound.

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Introduction

Gestational trophoblastic disease (GTD) refers to the pathology of an abnormal placenta that is associated with pregnancy [1]. The overall incidence of GTD varies from 0.57 to 2/1000 pregnancies, with higher frequencies reported in Asia, the Middle East, and Africa than in Europe and America [1,2]. Classically, the 2 main types and some subtypes are molar pregnancy (complete and partial mole) and gestational trophoblastic neoplasia (invasive mole, choriocarcinoma, placental site trophoblastic tumor, epithelioid trophoblastic tumor) [3]. The last 3 malignant subtypes can arise from any type of pregnancy despite their rare condition. Inappropriate treatment of complete mole can lead to gestational trophoblastic neoplasia (GTN) which is related to poor prognosis due to its invasion and metastasis [4]. Age, race, and past abortion history are risk factors for GTD, and the prognosis depends on early treatment. The initial diagnosis was established by histology as the "gold standard" and was based on ultrasonic results. Chemotherapy and surgical procedures are used to treat GTD. Occasionally, several writers also describe an ectopic molar pregnancy, which is connected to GTD and is generally found in the fallopian tube or at the layer of the uterine wall known as the myometrium [5–7].

In the literature, intramural ectopic pregnancy (IEP) is an extremely rare subtype of ectopic pregnancy with an unclear etiology [8]. It is defined as the gestational sac (GS) completely encircled by the myometrium isolated from the endometrial cavity, fallopian tubes, and broad ligament, which is unsustainable and potentially life-threatening [9]. Several reports have also mentioned the partial location of GS within the myometrium of the uterine wall [10]. Very rarely, intramural pregnancies are located in the uterine myometrium without communication with the endometrial cavity [11]. Pathological examination showed villous and trophoblastic cells in blood clots and smooth muscle [12]. This uncommon pathology is estimated as less than 1% of ectopic pregnancies. The first case of IEP was reported by Doederlien in 1913 [13]. Before 2013, the literature documented approximately 53 cases around the world [14]. To our knowledge, from 2013 to the present, we summarized roughly 18 cases that were found in PubMed Library searches for "intramural ectopic pregnancy." Since the anatomical nature of the myometrium differs from the endometrial cavity for fetal development, fetal survival is undoubtedly very unlikely. However, a few incredibly uncommon examples up to 30 weeks or even 37 weeks of gestation have been documented in the literature [15,16]. Myomectomy, cesarean section, intrauterine operation, uterine resection, as well as the implantation of intrauterine devices, pelvic inflammatory illness, and following fertility treatment are all potential risk factors for IEP [10,11,17]. Recently, the incidence of intramural ectopic pregnancy in assisted reproductive technology such as *in vitro* fertilization is higher than that in natural pregnancy [13,18]. Particularly, adenomyosis pathology, an aberrant uterine disease, also contributes to the development of IEP via the micro-fistulous tube connecting the endometrial cavity to the myometrium layer [14].

Similar to well-known manifestations of ectopic pregnancy, signs of IEP are revealed including amenorrhea, lower

abdominal pain, vaginal bleeding, nausea, vomiting, or also being asymptomatic [18]. Progressive serum β -human chorionic gonadotrophin (β -hCG) concentration was similar to ectopic pregnancy, increased lightly or equally after 48 hours. Accordingly, transvaginal Doppler color ultrasound (TV-CDU) plays a pivotal role in diagnosing IEP [12,19]. There were 3 types of ultrasound characteristics including gestational cyst type, mass type, and uterine rupture type. The gestational cyst type or mass type presented with an empty uterus and a gestational sac or mixed mass was found in the myometrium, which was separated from the endometrium. The sac mass was unconnected with the uterine cavity, and an abundant blood flow supply was observed in the mass [20]. Additionally, 3-dimensional sonography has also a high value in this entity [21]. In some difficult cases, the diagnosis was identified intraoperatively [13]. This abnormal form is usually considered after excluding all other diagnoses. On imaging scans, this pathology can also be mimicked with an intramural myoma or choriocarcinoma [8,22].

IEP implant locations that are uncommon cause uterine rupture and serious bleeding. Pregnancy above 10 weeks is more likely to result in uterine rupture. After diagnosis, this pathology may require prompt surgical therapy, possibly with minimally invasive techniques such laparoscopy and laparotomy [21]. However, several writers also noted that methotrexate (MTX) and expectant management in response to GS size and β -hCG levels were effective medicinal treatments [14]. Because there is a dearth of data from study, the IEP management strategy is still debatable. The location of GS, the gestational age, and the intention to preserve fertility all affect management tactics [18,19]. The research claims that due to its rarity, it can be challenging to distinguish between intramural ectopic pregnancy and molar ectopic pregnancy. However, since the prognosis of these pathologies is different, thus, early recognition plays an important role in appropriate management and saving the patient's life [23]. We hereby report a rare case with a diagnostic challenge between intramural ectopic pregnancy and invasive trophoblastic disease.

Case description

A 45-year-old patient (Gravida 2 Parity 1) was admitted for 3 days to a local hospital due to abdominal pain and menstrual cycle that was being delayed. The patient's last menstrual date was forgettable. The patient underwent laparoscopic surgery for an ectopic pregnancy. Nevertheless, despite serum β -HCG levels ranging from 25,503 to 24,969 mUI/mL, no gestational mass was seen in the abdominal cavity. Additionally, serum progesterone was also low. The patient was then transferred to our hospital since invasive trophoblastic disease was thought to be present. Her medical history was unremarkable and the patient received a laparoscopic appendectomy. Her obstetrical history included spontaneous vaginal birth and miscarriage that did not require uterine curettage throughout the first trimester. The patient's last menstrual cycle was irregular.

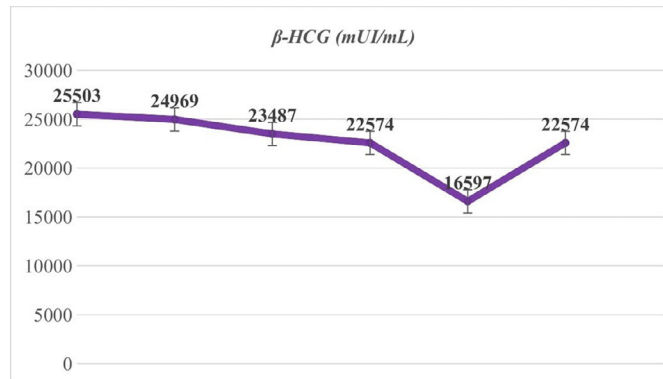


Fig. 1 – Progressive serum β -hCG every 48 hours before surgical intervention.

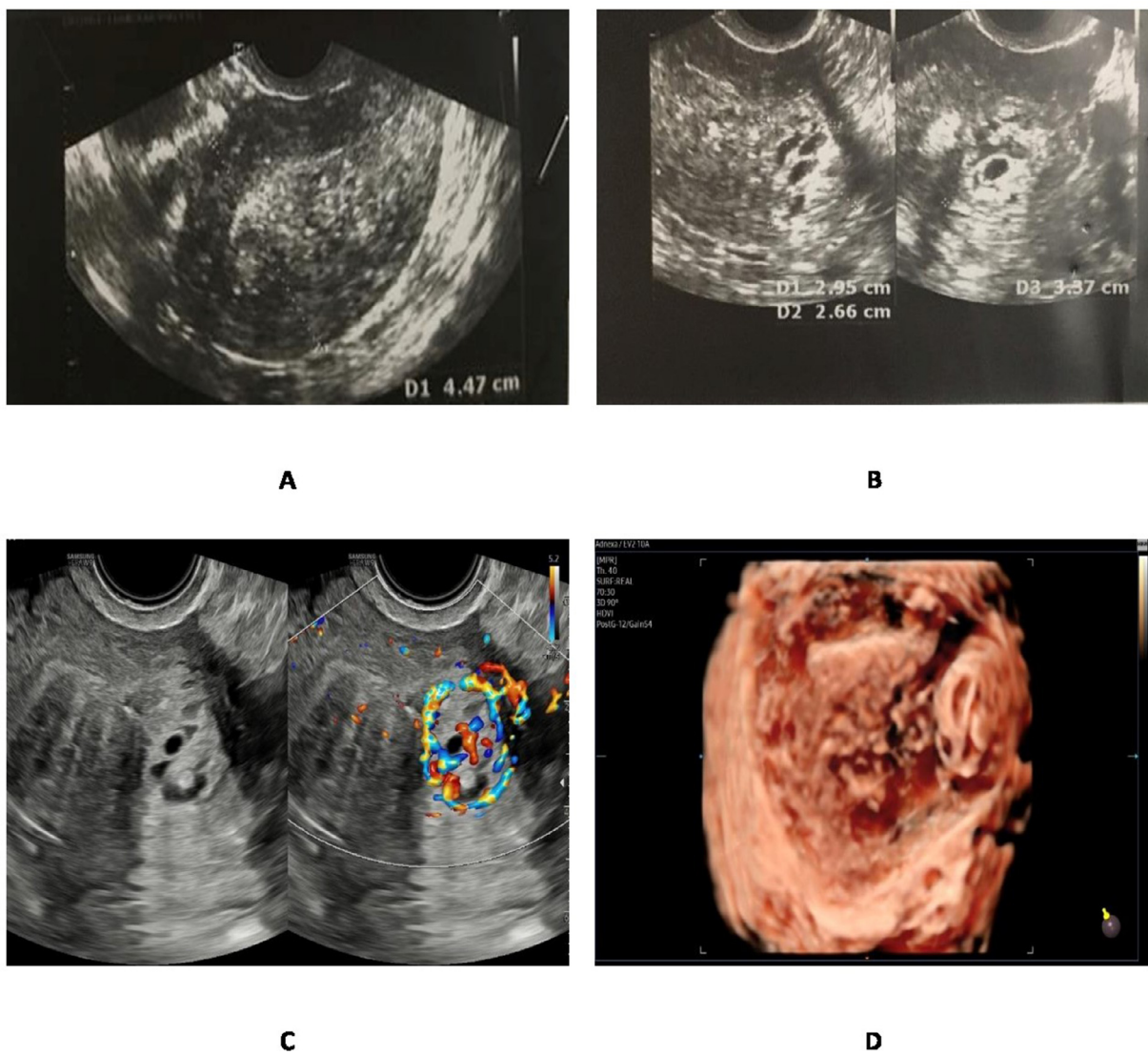


Fig. 2 – Transvaginal ultrasound findings were performed in the present case. (A) Adenomyosis on a transvaginal sonographic scan in grayscale. (B) The size of the bilateral ovaries was normal. (C) A heterogeneously echogenic mass was visible on grayscale ultrasonography (left side), and Doppler color ultrasound findings showed convoluted arteries surrounding the aberrant mass (right side). (D) A myometrial ringed mass protruding from the uterine fundus was visible on a 3-dimensional transvaginal ultrasound.

Clinical findings

The patient's vital signs were unremarkable upon admission and her hemodynamic condition was normal. She had a body mass index (BMI) of 23.3 kg/m². Despite having a COVID-19 (coronavirus disease of 2019) test was positive, the patient showed no sign of respiratory illness. In a few days, the COVID-19 test had returned as negative. Her oxygen saturation peripheral capillary (SpO₂) was 99%. The results of the physical examination were a slightly enlarged uterus that was not tender, a closed external os, bilateral ovaries that were in normal form, and no palpable abnormal pelvic masses.

Diagnostic assessment

Overall, laboratory testing such as blood counts, liver tests, kidney tests, and urine tests were within normal ranges. Chest X-ray was also in the normal image. Over the course of 10 days, the variance in serum-hCG content declined progressively from 25,503 mUI/mL to 16,597 mUI/mL, then unexpectedly climbed to 22,574 mUI/mL (Fig. 1).

According to ultrasound sonography results, the uterus was 54×87×64 mm, with an endometrial thickness of 3–6 mm and a normal border. Both ovaries had normal sizes of 9×25 mm and 13×30 mm. The right ovary contained a 10×7×9 mm hypoechoic mass. According to some images from the ultrasonic scan, which included asymmetrical myometrium thickening, linear striations, and parallel myometrium cysts measuring 2–3 mm in size, adenomyosis was diagnosed. A heterogeneous mass that was implanted in the myometrium layer close to the uterine fundus, extending to the left side relative to the uterine axis, separated from the endometrial cavity, and measuring roughly 30 × 26 × 29 mm in size was also discovered. The myometrium-endometrial barrier was not seen, the mass reached the serosa layer, and the thinnest myometrium layer was measured to be 1.9 mm thick. A Doppler scan revealed numerous vascular growth with a peak systolic velocity of 161 cm/s, in particular. Furthermore, a heterogeneous echogenic region emerging from the uterine fundus and encircled by the myometrium was confirmed by 3-dimensional transvaginal ultrasound. After several rounds of ultrasonic scanning, the mass size remained constant and grew marginally. An expert in gynecologic sonography at our facility with more than 20 years of experience made a differential diagnosis of invasive trophoblastic disease in light of imaging findings that suggested an intramural ectopic pregnancy (Fig. 2).

Therapeutic interventions

A tentative diagnosis of intramural ectopic pregnancy was made based on the ultrasound scan and serum-hCG level, although the invasive trophoblastic condition was not completely ruled out. The patient underwent a laparotomy to diagnose and treat an intramural ectopic pregnancy twelve days after being admitted, along with strict monitoring. After a laparotomy, the uterus was found to be normal and free of any aberrant masses or purplish-blue coloring, which are characteristics of IEP as reported in the literature. Following preoperative indication, a hysterectomy without oophorectomy

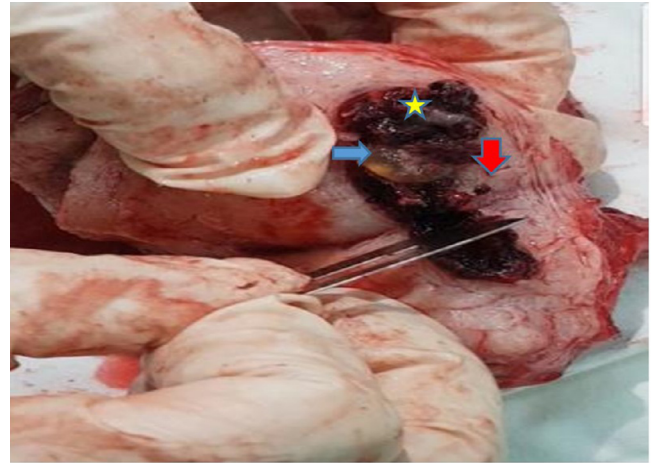


Fig. 3 – A longitudinal dissected uterine specimen with a dark brown material (yellow star) in the posterior wall of the uterine fundus that was entirely and visibly encircled by myometrium (red arrow). Blue arrow indicates where a yellow liquid-filled sac was discovered inside the retained degenerative conception products.

was carried out. The total amount of blood lost was under 100 ml. An aberrant mass was visible in the uterine myometrium when a macroscopic specimen of the uterus was cut (Fig. 3).

Endometrial cysts in the myometrium layer and adenomyosis pathology were also verified by the histological findings. Additionally, the placental villi swelled, the trophoblastic cells were enlarged, cytotrophoblasts and syncytiotrophoblasts encircled them, and hemorrhagic necrosis tissue was present. These alterations demonstrated an invasion of the uterine smooth muscle by a trophoblastic tumor (Fig. 4).

Outcome and follow-up

The postoperative course was uneventful. Following the procedure, the serum β -hCG levels were carefully tracked every 2 days and fell to 202 mUI/mL before discharge. Following discharge, a 2-week follow-up revealed that the serum-hCG levels had returned to the negative value. The patient was nevertheless required to continually monitor both her general health and the serum β -hCG levels regression for a period of 6 months. As at the time this case study was being written, her serum β -hCG level has been still at a baseline value. The patient is in excellent physical and mental health, free of anxiety or depression. We proceeded to check serum β -hCG levels in accordance with our hospital's medical protocol, initially every 3 months in the first year and then every 6 months in the second.

Discussion

In this uncommon case, adenomyosis was identified preoperatively and then ultrasonic features were used to confirm the diagnosis [24]. The patient did not get fertility treatment

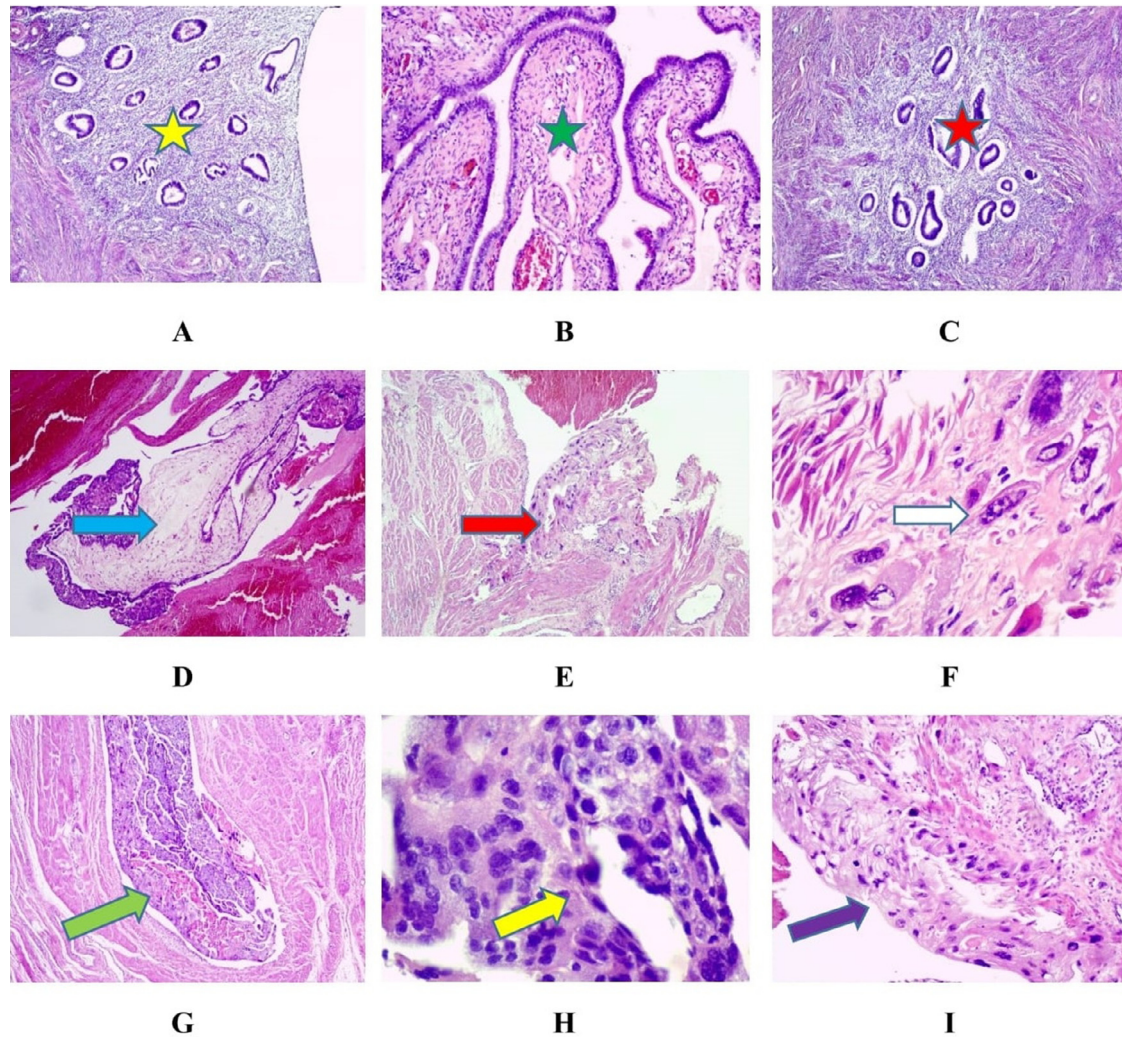


Fig. 4 – A histopathological examination with hematoxylin and eosin stained section showed: (A) Normal endometrial layer (4x) (yellow star). (B) Normal-shaped fallopian tube (10x) (green star). (C) An adenomyosis with an imbedded endometrial gland and stroma (4x) (red star). (D) Exaggerated hydropic villi (4x) (blue arrow). (E) The wall of the uterine myometrium was penetrated by villous trophoblast (4x) (red arrow). (F) The myometrial layer was invaded by villous cytotrophoblast and syncytiotrophoblast (40x) (white arrow). (G) The vascular structure was infiltrated by trophoblast (4x) (green arrow). (H) Trophoblastic hyperplasia that is abnormal (40x) (yellow arrow). (I) The myometrial layer was abnormally infiltrated by trophoblastic hyperplasia (10x) (violet arrow).

or uterine surgery. Fertilized eggs or embryos may implant into the myometrium in cases of adenomyosis through the dilated sinus of the ectopic endometrium [8,14]. As above-described, a typical ultrasonography image of an IEP reveals a GS implant inside the myometrium, spaced apart from the uterine cavity and surrounded by strong blood flow Doppler signals. However, IEP can also present as a heterogeneous mass that is very difficult to distinguish from intramural fibroids type 2-5 following the Leiomyoma Subclassification System by the International Federation of Gynecology and Obstetrics (FIGO) [25]. It can be challenging to distinguish an intramural pregnancy from gestational trophoblastic pathology and intramural pregnancy, and the presence of uterine leiomyoma and adenomyosis may also alter the diagnosis of intramural pregnancy [18,26]. In our case, despite a high serum

β -hCG increased, GS was not detected by ultrasound in the endometrial cavity, and traditional laparoscopy revealed no aberrant mass in the pelvis. Monitoring revealed a suspicion of intramural ectopic pregnancy, gestational trophoblastic pathology, or an aberrant tumor in the myometrium near the uterine fundus. A choriocarcinoma or invasive molar pregnancy is the cause of the numerous vascularity surrounding the abnormal mass, according to transvaginal color Doppler ultrasonography (TV-CDU) findings.

In GTD pathology, almost all cases have an extremely high level of β -hCG, and this concentration exceeds more than 100,000 mUI/mL resulting in a risk of therapeutic persistence [1]. Because the serum β -hCG rise in our situation was not typical for GTD, we suspected IEP and underwent a laparotomy to facilitate an early diagnosis and course of therapy. Computed

tomography (CT) and magnetic resonance imaging (MRI) have been shown to be useful in assessing intrauterine bulk, invaded tissue, and metastasis in numerous investigations. Prior to surgical intervention, hysteroscopy was also carried out to rule out the chance that the mass was inside the uterine cavity [8,26–28]. However, these modalities remain expensive methods for clinical assessment. Based on the sonographic findings, combined with 3-dimensional technics, we can repeat this available imaging tool for clinical surveillance.

We conducted a hysterectomy after taking into account her gravidity, age, and getting her consent. After surgery, the uterus was dissected and the uterine myometrium revealed an aberrant tumor (Fig. 3). Adenomyosis and invasive trophoblastic pathology were discovered through histopathological analysis. Unfortunately, postoperative tissue was not examined for immunohistochemical examination. An intramural ectopic pregnancy that was mistakenly identified as gestational trophoblastic tumor in 2021 by Zang et al. was attributed to exceptionally high serum levels of β -hCG which rose from 39,576 to 225,000 mIU/ml—and strong blood flow signals. Immunohistochemical analysis revealed intramural ectopic pregnancy even though the patient's pathology findings from uterine curettage tissue supported a hydatiform mole [29].

In the present case, based on the clinical process, abortion was not recorded recently and no intrauterine GS was observed prior to admission. However, because of an empty uterine cavity and the tendency of serum β -hCG levels, we suspected a degenerative IEP resulting in gestational trophoblastic disease in our case [30].

Accordingly, some publications mentioned chemotherapy based on methotrexate as the first line of therapy. The size of the mass may not always be lowered by this care, despite the fact that serum β -hCG levels are reduced [11]. For instance, Song et al. reported that while the uterine mass was not reduced after 3 sessions of treatment with Etoposide + Methotrexate + Actinomycin D + Cyclophosphamide (EMA-CO), serum β -hCG levels were significantly lowered [26]. In the present case, because the initial diagnosis was IEP, thus the uterine rupture was risky. Moreover, the patient did not desire to maintain fertility. In addition, the present side effects of chemotherapy treatment such as mouth ulcers and decreased blood cell count could be present [8]. Expectant management (a wait-and-see approach) was also not prioritized in this case; therefore, we decided to interfere with the surgical procedure.

Conclusion

Briefly, it is always required to make a distinction between an intramural ectopic pregnancy and an invasive trophoblastic disease. Serum β -hCG levels and TV-CDU are required for a strict monitoring. Ultimately, an appropriate selection of prompt treatment is depended on clinical evaluation and should be individualized following the patient's fertility desire. Further data are needed to elucidate this critical issue.

Author contributions

D.P.T. was involved in patient care, organized to collect pictures and contributed to editing the manuscript. T.H.P. was responsible for providing the pictures, supervision and administrative procedures. N.P.N. contributed to receiving information, writing the draft, reviewing and to editing the manuscript. Q.N.H. contributed to review the manuscript. All authors read and approved the final manuscript.

Data availability

Data including reports, patient details, and consent is stored on a secure drive accessible to the corresponding author.

Ethical approval

Not applicable.

Patient consent

Written informed consent was obtained from the patients for publication of this case report and the use of accompanying images.

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