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UNRAVELING GESTATIONAL TROPHOBLASTIC DISEASE: A CASE SERIES HIGHLIGHTING DIAGNOSTIC CHALLENGES AND THERAPEUTIC OUTCOMES

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Abstract:

Gestational trophoblastic disease (GTD) refers to a group of pregnancy-related tumors that are recognized as the most curable gynecologic malignancies. Diagnosing GTD can be challenging, particularly after a non-molar pregnancy, due to its various presentations, which may mimic retained products with hypervascularity or arteriovenous malformation. Human chorionic gonadotropin (HCG) serves as an excellent biomarker for monitoring disease progression, response to treatment, and post-treatment surveillance. A plateaued or rising HCG level can facilitate the early detection of progression from complete or partial hydatidiform mole to GTD.

Here, we present a case series involving six patients with GTD who initially presented with elevated beta-HCG levels and abnormal bleeding. Of these six patients, five were initially diagnosed with hypervascular retained products following a first-trimester abortion and underwent surgical evacuation. However, due to persistently elevated beta-HCG levels and evidence of myometrial invasion, the diagnosis was later revised to GTD. All patients were successfully

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managed with chemotherapy. Methotrexate, as a first-line treatment, is effective in achieving complete remission in most non-metastatic and low-risk cases. It has minimal severe toxicity, excellent cure rates, and does not appear to affect fertility. In summary, gestational trophoblastic diseases represent a diagnostic conundrum for clinicians due to their diverse presentations and potential for mimicking other conditions. Nevertheless, when these diseases are identified and managed in a timely manner, the prognosis is highly favorable, underscoring the importance of vigilant monitoring and early intervention.

Keywords: Gestational trophoblastic disease, Invasive mole, Retained Products of Conception, Evacuation, Chemotherapy.

INTRODUCTION:

ß-Human chorionic gonadotropin (beta-HCG) is a hormone detectable in pregnancy as early as ten days post-conception and persists for several weeks following normal delivery or abortion. Persistently elevated low levels of beta-HCG, in the absence of a viable pregnancy, can occur in various contexts, including the post-abortal period, post-delivery, ectopic pregnancies, trophoblastic disease, retained products of conception, and arteriovenous malformations (AVMs).

The term gestational trophoblastic disease (GTD) encompasses a spectrum of benign and malignant clinical entities, including hydatidiform mole, chorioadenoma destruens, persistent mole, choriocarcinoma, and placental site and epithelioid trophoblastic tumors. More specifically, the malignant forms of GTD should be classified as gestational trophoblastic neoplasia (GTN) due to their potential for independent growth and metastasis. A low but rising level of HCG may indicate the presence of GTN, which includes invasive moles, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). Quiescent gestational trophoblastic disease can present in two distinct scenarios: either with a prior diagnosis of hydatidiform mole or GTN, which is typically managed through surgical evacuation or chemotherapy, or in cases with no history of these conditions. In the latter, patients may exhibit persistently low HCG levels over months or years or present with an unexpected positive pregnancy test, showing no response to treatment, whether surgical or medical. Approximately 7-

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25% of these patients may develop overt disease, which can be effectively treated with chemotherapy. [1,2]

The term retained products of conception (RPOC) refers to residual placental tissue remaining in the uterine cavity following abortion or full-term delivery. Retained placental fragments are a notable source of abnormal uterine bleeding (AUB) in women of reproductive age. The preferred diagnostic modality is ultrasonography, with Doppler studies used to assess vascularization. While invasive moles and RPOC may present with overlapping imaging findings, the clinical context usually facilitates differentiation; notably, a history of molar pregnancy with persistently elevated and increasing HCG levels is crucial for diagnosis. Risk factors for invasive placenta include a history of cesarean sections, uterine evacuation, advanced maternal age, and multiparity. Risk factors for gestational trophoblastic disease include a prior molar pregnancy, miscarriage, age, and family history. Early detection of these conditions is essential to prevent complications such as recurrent bleeding and infection, and to guide appropriate treatment.[3]

We report a case series involving six patients with GTD who presented to our emergency department over a two-year period. Each patient underwent thorough evaluation for metastasis. Following successful induction of remission, two courses of the remission regimen were administered. Post-chemotherapy, patients were monitored with serial measurements of beta-HCG.

Case reports:

Case 1:

A 27-year-old female, gravida 0, para 0, abortus 1, presented with two months of amenorrhea and a history of a missed abortion managed by dilatation and curettage two months prior. She presented to the labor room with intermittent spotting. The histopathology from her previous procedure showed markedly vesicular villi with focal trophoblastic hyperplasia but normal-sized villi. Serum beta-HCG levels were initially 1494 mIU/ml and increased to 2389 mIU/ml one week later. She received two doses of methotrexate before being referred to our institute.

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Upon presentation, the patient was conscious, oriented, and hemodynamically stable. A vaginal examination revealed a closed external os, a uterus consistent with a 6-8 week gestational size, and free bilateral fornices. Ultrasound imaging identified retained products of conception with associated myometrial thinning. MRI further characterized a heterogeneous T2 hyperintense mass in the fundus and anterior myometrium, with focal thinning of the myometrium and disruption of the junctional zone, measuring 6 x 3.8 x 5 cm, suggestive of adherent retained products (Figure 1).

Suction and evacuation were performed, but the histopathology report indicated only blood clots and mucus. Despite this, beta-HCG levels remained elevated at 1772 mIU/ml. Given the clinical suspicion of an invasive mole, the patient was treated with six cycles of methotrexate and folinic acid. However, her beta-HCG levels plateaued. Consequently, second-line chemotherapy was initiated with three cycles of EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine). Following this regimen, her beta-HCG levels decreased to <0.5 mIU/ml, and she was placed under regular follow-up.

Case 2:

A 21-year-old female, gravida 1, para 1, abortus 1, presented to the emergency department with vaginal bleeding and passage of a fleshy mass following 3 months of amenorrhea. She had previously undergone suction and evacuation for an incomplete abortion. Histopathological examination of the tissue revealed findings consistent with a hydatidiform mole. Her initial beta-HCG level was 21,908 mIU/ml. Thyroid function tests and chest X-ray were within normal limits. Following the evacuation, the patient's bleeding ceased; however, she presented again with renewed vaginal bleeding 15-20 days later. At this visit, she was conscious, oriented, and hemodynamically stable. Her beta-HCG level had decreased to 42.97 mIU/ml. Vaginal examination revealed a normal cervix and vagina, with a uterine size consistent with a 6-week pregnancy and free bilateral fornices. Ultrasound imaging identified an echogenic mass measuring 2 x 2 cm with evidence of myometrial invasion.

Based on these findings, a diagnosis of gestational trophoblastic disease (GTD) was established. The patient was subsequently treated with six cycles of methotrexate and folinic acid, which

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successfully reduced her beta-HCG level to <0.01 mIU/ml. The patient was then placed on regular follow-up to monitor her condition.

Case 3:

A 31-year-old female, gravida 4, para 2, living 2, abortus 1, with a history of two previous cesarean sections, presented to the emergency department. She reported having taken a medical termination of pregnancy (MTP) pill for a 3-month pregnancy and had been experiencing vaginal bleeding for one month. Upon examination, the patient was conscious, oriented, and hemodynamically stable. A vaginal examination revealed a closed external os with slight bleeding. The uterus was of a size consistent with a 6-8 week pregnancy, and bilateral fornices were free.

MRI imaging demonstrated a heterogeneous cystic lesion with minimal vascularity located at the cesarean scar site, measuring 6.2 x 4.5 x 5 cm. The lesion involved the myometrium and extended to the cervix. The provisional diagnosis was either invasive retained products of conception or gestational trophoblastic disease (GTD).

Suction and evacuation were performed, and histopathological examination of the tissue revealed placental tissue consistent with an invasive mole. The initial beta-HCG level was 250,000 mIU/ml. Consequently, a diagnosis of GTD was confirmed.

The patient was treated with seven cycles of methotrexate and folinic acid, resulting in a decrease of her beta-HCG levels to within normal limits (<0.5 mIU/ml). She continues to be monitored with regular follow-up and beta-HCG testing.

Case 4:

A 31-year-old female, gravida 2, para 1, living 1, presented to the emergency department with 3 months of amenorrhea and intermittent spotting over the past month. Ultrasound initially revealed retained products of conception, leading to a dilatation and curettage (D&C). Despite the procedure, bleeding persisted, necessitating evacuation four times at a private hospital. However,

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the patient experienced another episode of bleeding 15 days post-D&C, prompting referral to our institute.

On examination, the patient was hemodynamically stable but continued to experience spotting. Vaginal examination revealed a uterus consistent with a 6-8 weeks gestational size. Her beta-HCG level was 61,820 mIU/ml. Ultrasound imaging showed heterogeneous content with intense flow on color Doppler, indicating a peak systolic velocity (PSV) of 20 cm/sec. This content extended into the anterior myometrium with thinning of the overlying muscle, suggesting possible adherent retained placenta or invasive mole (Figure 2).

MRI imaging demonstrated a bulky uterus with heterogeneous content and loss of endo-myometrial differentiation, accompanied by multiple flow voids. These findings raised differential diagnoses of highly vascular retained products of conception (RPOC), arteriovenous malformation, or gestational trophoblastic disease (GTD).

The patient was treated with one cycle of methotrexate and folinic acid, leading to symptomatic improvement with no further active bleeding. Her beta-HCG level decreased to 19,387 mIU/ml following the first cycle. She was discharged in stable condition with instructions for close follow-up. Subsequently, she received three additional cycles of methotrexate and folinic acid

Case 5:

A 29-year-old female, gravida 2, para 1, living 1, with a history of a previous cesarean section, presented with 3 months of amenorrhea and intermittent vaginal bleeding for the past 7 days. She had undergone evacuation twice at a primary healthcare center but continued to experience bleeding, prompting her referral to our tertiary center. Histopathological analysis of the products of conception had not been performed.

Upon arrival, the patient was hemodynamically stable. Vaginal examination revealed slight bleeding, with a uterine size consistent with 8 weeks of gestation and free bilateral fornices. Initial beta-HCG levels were 961 mIU/ml at the time of evacuation, but repeat testing revealed a significant increase to 46,083 mIU/ml.

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Ultrasound examination showed multiple tortuous vessels within the myometrium, indicative of an arteriovenous malformation (AVM). MRI further characterized a bulky uterus with heterogeneous content measuring 3.9 x 3.2 x 4.2 cm, extending into the parametrium. The MRI also showed multiple low-resistance, high-velocity flow voids, consistent with a uterine AVM.

The patient was treated with one cycle of methotrexate and folinic acid. Following chemotherapy, her bleeding ceased, and she was discharged with instructions for close follow-up and ongoing beta-HCG monitoring.

Case 6:

A 29-year-old female, gravida 0, para 0, abortus 2, presented with 3 months of amenorrhea and a history of missed abortion. She had undergone medical termination of pregnancy but subsequently reported vaginal bleeding persisting for the past month. On examination, her vital signs were stable, and her uterus was of a size consistent with a 6-week gestation.

Ultrasound examination revealed an irregularly thickened myometrium with loss of the endo-myometrial plane anteriorly, accompanied by increased vascularity. MRI imaging showed a bulky uterus with an endometrial cavity containing an enhancing lesion extending into the myometrium, with loss of the junctional zone. The serosa remained intact, supporting a diagnosis of retained products of conception (RPOC) with myometrial invasion.

The patient underwent suction and evacuation twice for RPOC, but bleeding continued. Her initial beta-HCG level was 4,496 mIU/ml. Although the beta-HCG levels began to decrease following the evacuations, they later plateaued, complicating the diagnosis.

Given the persistent elevated beta-HCG levels and clinical findings, the patient was treated with methotrexate and folinic acid for three cycles. Post-treatment, her beta-HCG level decreased to <0.1 mIU/ml. She received two additional cycles of methotrexate and folinic acid. The patient was discharged with instructions for follow-up in the outpatient department with regular beta-HCG monitoring.

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Discussion

Gestational trophoblastic disease (GTD) poses significant diagnostic challenges following a non-molar pregnancy due to its diverse presentations. Human chorionic gonadotropin (HCG) is a highly effective biomarker for tracking disease progression, evaluating therapeutic response, and conducting post-treatment surveillance. Persistent or rising HCG levels are critical for the early detection of disease progression from complete or partial hydatidiform mole to GTD, which occurs in approximately 15%-20% and 0.5%-5% of cases, respectively.[4]

Patients with GTD typically present with abnormal vaginal bleeding or symptoms indicative of metastatic spread to other organs. Ultrasound imaging may reveal hyperechoic or hypoechoic focal masses within the myometrium, along with anechoic cystic regions suggestive of bleeding or necrosis. Color Doppler studies further elucidate the diagnosis by demonstrating increased vascularity, with trophoblastic vessels displaying a high-velocity, low-resistance waveform. [5,6]

In the present case series of six patients, five were initially diagnosed with hypervascular retained products of conception following first-trimester abortions and subsequently underwent surgical evacuation. However, persistent elevated beta-HCG levels and evidence of myometrial invasion led to a revised diagnosis of gestational trophoblastic disease (GTD). These patients were successfully managed with chemotherapy. The remaining patient had a histopathological diagnosis indicative of an invasive mole and was also treated with chemotherapy. All patients demonstrated favorable responses to the treatment.

Retained products of conception complicate around 1-5% of all pregnancies. The term RPOC refers to intrauterine tissue of trophoblastic origin that develops after conception and persists after delivery or termination of pregnancy. Various causes of increased vascularity of RPOCs include arteriovenous malformations, placental polyps, and excessive myometrial invasion by trophoblasts. Due to excessive trophoblastic invasion of the myometrium, the physiological myometrial arteriovenous shunting in the placental bed persists, leading to prominent vascularity and a broad spectrum of differential diagnoses. Among the several therapeutic options available today for refractory patients, cautious therapy helps to protect future fertility in younger women. Methotrexate has proven excellent results in the treatment of persistent retained placental tissue.

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Its impact on the proliferating trophoblastic cells of the placental tissue decreases neovascularization, and the retained placental tissue resorbs over time. Conservative treatment should be supplemented with serial beta-HCG monitoring. The failure of the blood beta-HCG level to become undetectable in retained conception products is most likely due to a small quantity of viable trophoblastic tissue, which may be associated with the presence of an endomyometrial mass and high vascularity.[7]

In a study by Betel C et al., five sonographic features were observed significantly more often in women with confirmed gestational trophoblastic disease (GTD). These features included a myometrial epicenter, a depth of myometrial invasion greater than one-third, placental venous lakes, a maximum mass dimension greater than 3.45 cm, and a maximum endometrial thickness of less than 12 mm. Delays in diagnosing GTD can lead to increased morbidity and adversely affect the World Health Organization risk score, thereby raising the likelihood that the patient will require multiagent chemotherapy. A high (or rising) β-hCG titer helps differentiate retained products of conception (RPOC) from GTD. However, low β-hCG titers may still occur in patients with persistent trophoblastic illness. [8]

Pathological diagnosis of an invasive mole is relatively uncommon, as most cases are managed conservatively without the need for hysterectomy. While invasive mole is rarely metastatic, if metastasis does occur, it typically spreads to the lungs. In contrast, choriocarcinoma is known for its propensity to metastasize, with common sites including the lower vaginal tract, brain, liver, lung, kidney, and gastrointestinal system. The absence of metastases can help differentiate an invasive mole from choriocarcinoma.[9] In our series, all cases underwent thorough evaluation for metastasis, and only one out of six patients had histopathological confirmation of invasive mole.

Management of an invasive mole involves chemotherapy and continuous monitoring of β-HCG levels. Ultrasound and Color Doppler imaging are effective for assessing the resolution or persistence of gestational trophoblastic neoplasia (GTN) post-treatment. Dilatation and curettage are contraindicated due to the risk of uterine perforation. Criteria for initiating chemotherapy in persistent trophoblastic disease include: β-HCG levels exceeding 20,000 IU/L after one or two uterine evacuations; static or rising β-HCG levels after one or two evacuations; persistent β-HCG elevation six months after evacuation; ongoing uterine hemorrhage with elevated β-HCG levels;

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pulmonary metastasis with static or rising β-HCG levels; metastasis to the liver, brain, or gastrointestinal tract; and histological diagnosis of choriocarcinoma. Methotrexate is typically used as a first-line treatment and can achieve complete remission in most non-metastatic and low-risk cases. It is well-tolerated, with minimal severe toxicity, excellent cure rates, and does not significantly impact fertility. [10,11] Gestational trophoblastic neoplasia that does not respond to first-line treatment is considered resistant or refractory. Resistance to a specific chemotherapeutic regimen is indicated by a plateau or rise in β-HCG levels. Despite the challenges of refractory disease, the overall prognosis for GTN remains excellent.

Conclusion

The gestational trophoblastic disease is a contemporary oncology success story with excellent response to medical (chemotherapy) and surgical (suction evacuation) treatments, with beta hCG as a key prognostic marker during pre-treatment evaluation and follow-up.

This case series underscores the diagnostic intricacies and therapeutic successes associated with gestational trophoblastic disease (GTD). Our findings reveal the diagnostic challenges posed by GTD's varied presentations, which can often be mistaken for retained products of conception or other conditions. The critical role of serial beta-hCG measurements in both diagnosing and monitoring GTD is evident, highlighting its value as a key prognostic marker.

The effective use of chemotherapy, supported by timely and precise treatment strategies, highlights the robustness of current management protocols. Despite the diagnostic complexities, the favorable outcomes achieved in this series affirm the potential for excellent prognosis with appropriate intervention.

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Figures:

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Figure 1: MRI image revealing heterogenous mass of size 6*3.8*5 cm in fundus and anterior myometrium with focal thinning of myometrium and interruption of junctional zone.

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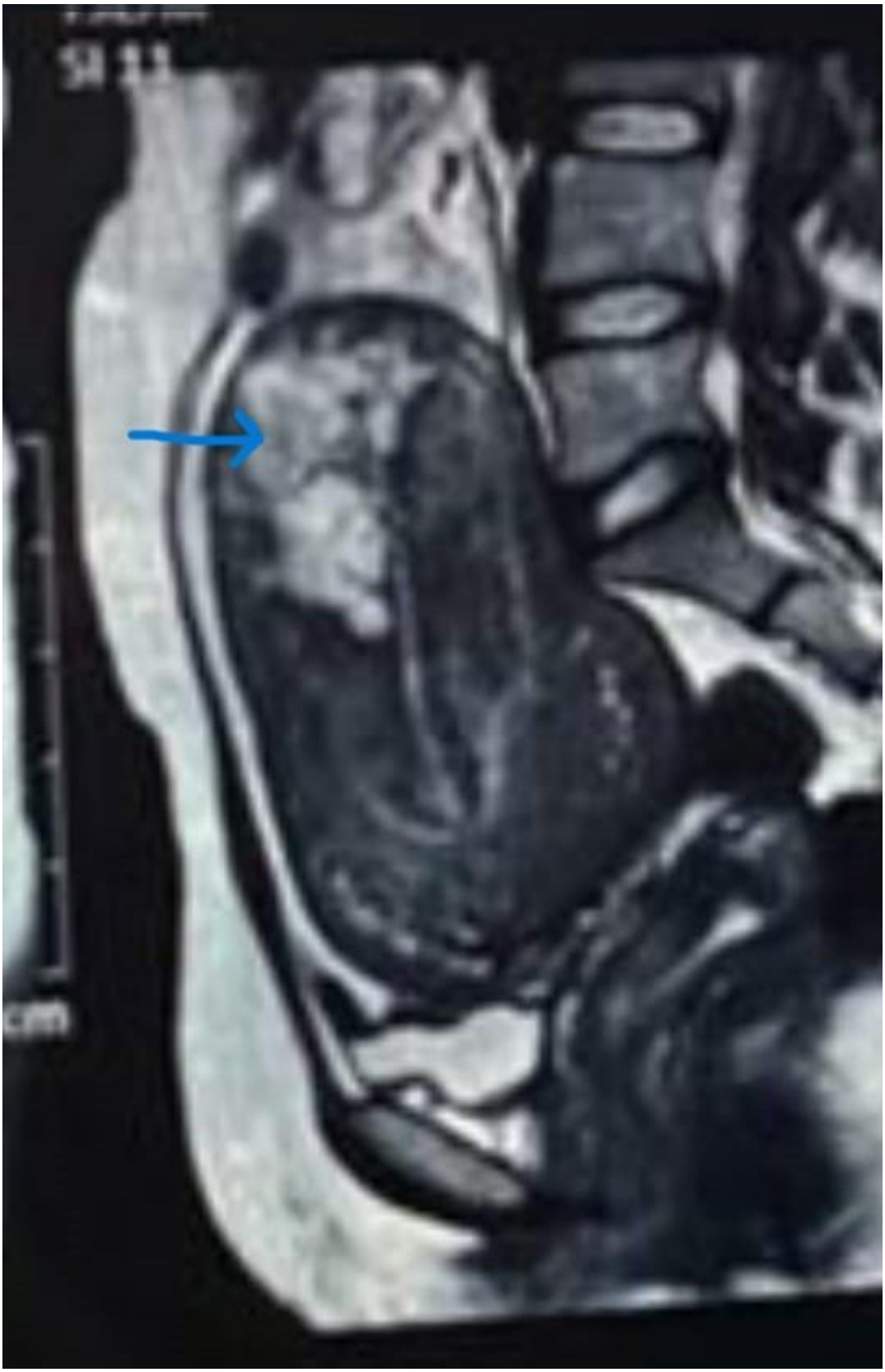

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Figure 2: Ultrasound image showing heterogenous content in uterus with intense flow on color Doppler extending to anterior myometrium with thinning of overlying muscle.