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Case Report

Concurrent gestational trophoblastic neoplasia and large uterine fibroid in a nullipara – Case report☆

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ABSTRACT

Introduction: The management of a large uterine fibroid concurrent with gestational trophoblastic disease (GTD) in a nullipara is complicated, challenging yet should focus on conserving fertility. We would like to share our experience.

Case description: A 28-year-old G1P0A0 of 10–11 weeks' gestation presented with a profuse vaginal bleeding with a history of passing swollen, grape-like tissues from the vagina. Since 7 months prior, a large uterine fibroid >10 cm had been diagnosed on ultrasound. Patient was diagnosed with GTD with β-human chorionic gonadotropin (hCG) levels exceeding 1,000,000 mIU/mL. No pulmonary metastases were detected. She underwent a vacuum curettage for her complete hydatidiform mole.Six days later, she underwent an elective myomectomy. Her nulliparity precluded hysterectomy. Post-discharge, her β-hCG levels plateaued and were consistently high over 3 consecutive measurements. A diagnosis of gestational trophoblastic neoplasia (GTN) was established. Patient is currently undergoing a methotrexate-folinic acid rescue chemotherapy regimen due to her having a low risk, stage 1 GTN.

Discussion: Uterine fibroid may reach exceptional sizes. There is so far no link between GTD and uterine fibroids but their concurrent presence is extremely rare. The definitive management for a large fibroid is hysterectomy but considering the patient's nulliparity, a myomectomy was appropriate. GTD's definitive management is vacuum curettage.Periodical β-hCG measurement should follow discharge. Plateauing β-hCG levels indicated GTN and due to her low-risk GTN, she required a single-agent methotrexate chemotherapy. Most patients with low-risk GTN make a complete recovery.

Conclusion: Fertility after myomectomy and GTN generally has an excellent prognosis.

1. Introduction

Uterine fibroids are a common gynaecologic disorder during the female reproductive age with prevalence up to 30% [1]. Uterine fibroids proliferate from a single cell and may grow exponentially in size [1]. Large fibroids distort the normal uterine anatomy and may contribute to poor reproductive function [2]. Definitive management of exceptionally large fibroids is hysterectomy, but such approach is inappropriate in nulliparas [1].

Gestational trophoblastic disease (GTD) is a complication of pregnancy infrequently occurring in nulliparas [3]. It requires a definitive evacuation and a long follow-up to monitor its possible development towards gestational trophoblastic neoplasia (GTN) [3].

Very rarely, the two pathologies coexist in a nullipara. The nulliparous patient's reproductive status, history and eventual future dictate an individualised approach that may not be readily available in all hospitals. Above all, such case would be particularly complex given its rarity. This case report will hopefully offer a clinical insight that will prioritise the reproductive potential in patient management.

☆ During her recovery at the hospital, she was also prepared to undergo an elective myomectomy with possible conversion to hysterectomy. She underwent an elective myomectomy 7 days later by the attending gynaecology consultant (RA), during which a fibroid of 18x18 × 10 cm was removed (Fig. 1). The patient made an uneventful recovery, and she was discharged 2 days later.

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2. Case description

We report a single case of concurrent GTN with an excessively large uterine fibroid in a nullipara. This case description is in line with the SCARE 2020 criteria [4].

A 28-year-old G1P0A0 of 10–11 weeks' gestation complained of profuse vaginal bleeding since 2 days prior which increased since 12 hours prior. The patient admitted passing swollen, grape-like tissues accompanied by cramps and fatigue. There was no history of fever, consumption of traditional drugs or medicines. She also denied history of palpitations, exophthalmos and profuse sweating.

7 months prior, she had initially complained of heavy and prolonged menstrual bleeding reaching 8–14 days in duration, accompanied by clots. There were also increasingly severe menstrual cramps. She consulted a local obstetrician and an enlarging uterine fibroid >10 cm in diameter was discovered on ultrasound. The patient denied history of complaints regarding urinary function and bowel movement. There was neither history of chronic diseases nor allergies. The patient also denied any history of smoking, alcohol and recreational drug use.

At presentation, her vital signs were within normal limits. Her abdominal examination revealed an abnormally enlarged uterus with the fundus palpated 2 finger-breadths below the umbilicus. Neither uterine contraction nor foetal heartbeat was detected. Speculum examination revealed blood passing from the uterine cavity. Ultrasound revealed an intrauterine mass with vesicular appearance with no foetal parts. There was also a separate hyperechoic mass in the uterine fundus measuring 18x18 × 10 cm. Her blood examination revealed slight anaemia at 9.6 gr/dL. Her chest X-ray revealed no pulmonary metastases. An internal medicine consult confirmed the absence of thyrotoxicosis in our patient.

She was then diagnosed as G1P0A0 of 10–11 weeks of gestation with hydatidiform mole, uterine fibroid, and anaemia. She then underwent an urgent evacuation of her molar pregnancy by the attending gynaecology consultant (RA). During the vacuum curettage, a 300-g molar tissue was removed.

The histology report confirmed her pregnancy being a molar pregnancy. She was also confirmed to suffer from a giant uterine fibroid with no signs of malignancy.

She was then followed up every 2 weeks to monitor her beta-hCG level. Unfortunately, upon 3 consecutive tests, her beta-hCG level was consistently above 8000 mIU/mL and she was then diagnosed with GTN. She was treated with a single agent chemotherapy of Methotrexate 50 mg given every other day through intramuscular (IM) injections, alternating with 10 mg folinic acid rescue once daily administered through IM injections. She has so far completed her first chemotherapy regimen and waiting for her second regimen. She has been responding well to her chemotherapy thus far and been under our care for more than 4 months.

3. Discussion

Encountering uterine fibroid complicated by gestational trophoblastic disease and/or neoplasia in a nullipara is very rare, requires a subspecialist and multidisciplinary approach. The rarity also means there is no specific consensus on this matter, yet. Each pathology will be discussed separately below.

Uterine fibroid is a common gynaecologic disorder with varying number, size, and location [1]. The wide-ranging effects lead to various signs and symptoms, including menometrorrhagia, dysmenorrhea, dyspareunia, and dysuria [1]. Uterine fibroid may also be located at various locations inside the uterus. A classification by the European Society of Gynecological Endoscopy (ESGE) divides uterine fibroids into 3 groups:

- G0: pedunculated intrauterine myoma.
- G1: uterine fibroid with the majority (>50%) within the uterine cavity.
- G2: uterine fibroid with the majority (>50%) within the myometrium [5].

There is also a separate classification from Federation International d'Obstetrique et Gynecologie (FIGO) as depicted below (Fig. 2) [6]:

Uterine fibroids may have various effects on pregnancy and fertility [7]. Generally, the effects depend on the location of the fibroid relative to the uterine cavity [7]. Subserosal uterine fibroids do not distort the uterine cavity, so they generally do not affect fertility [7]. Intramural uterine fibroids, especially large ones, increase the risks of miscarriage [7]. They exert the following effects which hamper pregnancy success: increasing uterine contractility, increased local production of cytokines and changes to the endo-myometrial junction [8,9].

Managing uterine fibroids involve pharmacological and non-pharmacological means [1]. Pharmacological therapy involves levonorgestrel intrauterine system, gonadotropin-releasing hormone analogues, and selective progesterone-receptor modulators [1]. Non-pharmacological therapies entail uterine artery embolization and magnetic resonance imaging-guided focused ultrasonography [1]. The definitive management, though, involves surgery and it may involve either myomectomy or hysterectomy [1]. The excessively large size of the fibroid in our patient effectively excludes attempts per hysteroscopy and laparoscopy [1].

Gestational trophoblastic disease includes complete and partial hydatidiform moles [3]. Epidemiologically speaking, molar pregnancies develop in 1–3 per 1000 pregnancies and they are more common in Asian than Caucasian populations [10]. Nulliparity and extreme reproductive ages are their risk factors [10]. In their pathogenesis, complete and partial hydatidiform moles differ [11]. Complete moles are produced when an empty oocyte is fertilised by either two sperms (dispermic theory) or one sperm that replicates its genetic material once inside the oocyte [11]. Partial moles are produced when a normal oocyte is fertilised by two sperms producing a triploid embryo [11].

Patients with molar pregnancy often present with early pregnancy vaginal bleeding, usually in the first trimester [12]. On ultrasound, molar pregnancies appear like a honeycomb structure with no foetal parts [12]. Beta-hCG level measurement is a prerequisite with very high levels (often >100,000 mIU/mL) often detected [12].

The definitive management of molar pregnancies is evacuation through vacuum curettage followed by sharp curettage [12]. This should be ultrasound-guided with most of the molar tissue being removed by vacuum curettage [12]. Sharp curettage should be performed at the very end of the procedure to scrape the remaining molar tissue that adheres to the endometrium [13]. Post-curettage, there should be a continuous monitoring and follow-up of the beta-hCG level every 2 weeks to exclude the development of GTN [3]. Successful monitoring is when the beta-hCG becomes undetectable and remains so for 3 consecutive tests [13]. Monitoring is continued for 6 months post-evacuation to ensure no development of GTN [13]. However, there are times when the beta-hCG does not decline as quickly or it rises to persistently high levels over consecutive tests. In such cases, GTN is diagnosed [14].

Once GTN is established, a FIGO scoring system is used to stage GTN (Figs. 3 and 4) [14]. In our patient, she had developed a low risk, stage I GTN. Her subsequent management was tailored according to the risk stratification and staging [14]. Due to her low risk and stage 1 GTN, she was assigned to have a single-agent chemotherapy. The most popular drug choice is either methotrexate or actinomycin D [14]. Methotrexate is a folic acid antagonist with little to almost no risk of incurring amenorrhea in reproductive-aged women [15,16]. Lertkhachonsuk et al. have reported that actinomycin D have a higher cure rate than methotrexate [16]. This was further confirmed by a Cochrane review by Lawrie et al. [17] Methotrexate was chosen on this patient as currently under the national health insurance framework, actinomycin D was not yet available. Furthermore, methotrexate was appropriate due to its well-known protective effects on the female reproductive function with very low risks of inducing long-term amenorrhea among patients [15].

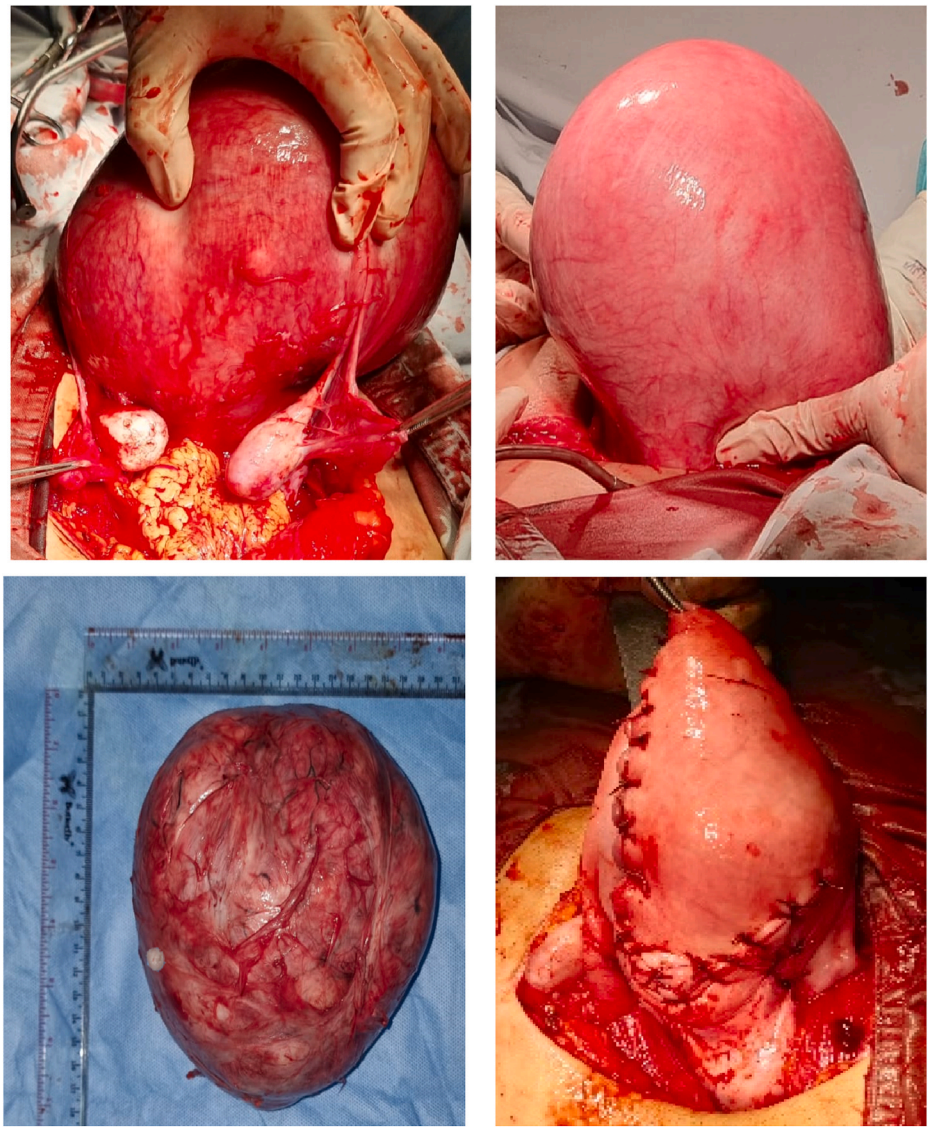

Fig. 1. Intraoperative findings during myomectomy.

Chemotherapy needs to be administered until the beta-hCG level becomes normal and for at least 1 regimen after the normalisation of the beta-hCG level [18]. If there is inadequate response from the first-line regimen, then a switch to a multi-agent chemotherapy and/or hysterectomy may be required to eliminate the persistent disease [18]. So far, the patient has been showing adequate response to the prescribed chemotherapy regimens.

With this complicated medical history, the patient will be concerned about her future fertility. Future fertility is discussed separately according to the patient's pathologies. It is common to be concerned about fertility after a myomectomy [2]. Desai and Patel (2011) reviewed the evidence and reported that myomectomy restores fertility with pregnancy rates ranging from 44% to 62% [2]. Around 80% of such pregnancies also occur within 1 year of post-myomectomy [2]. Thus, it appears that our patient may be optimistic about her chances of spontaneous conception after myomectomy procedure.

Fertility after gestational trophoblastic disease is also another reasonable concern. However, the reproductive prognosis after treatment for GTN is generally excellent [15]. Joneborg et al. in their review reported that after a chemotherapy with methotrexate, there is no increased risk of premature or early menopause among patients with GTN [15]. It was also discovered that more than 97% of women with low-risk GTN resumed regular menstrual cycles [15]. Even if the patient had been treated with actinomycin-D, it is likely that the prognosis would have remained excellent [15]. However, it was notable that 6 months after the completion of chemotherapy, there was a significantly higher number of miscarriages compared to 12 months post-chemotherapy [15].

Fertility-wise, it is observed that the uterine cavity, both Fallopian tubes and the ovaries are normal and there is not much concern for our patient. As fertility post-myomectomy and post-single agent chemotherapy for GTN is generally excellent, the patient should expect to be able to conceive once the 12-month follow-up post-chemotherapy is concluded [15].

To conclude, the prognosis of fertility after both myomectomy and single-agent chemotherapy for GTN is excellent and patients should expect to spontaneously conceive within the first year after the conclusion of chemotherapy follow-up.

Sources of funding

This study does not receive any external funding

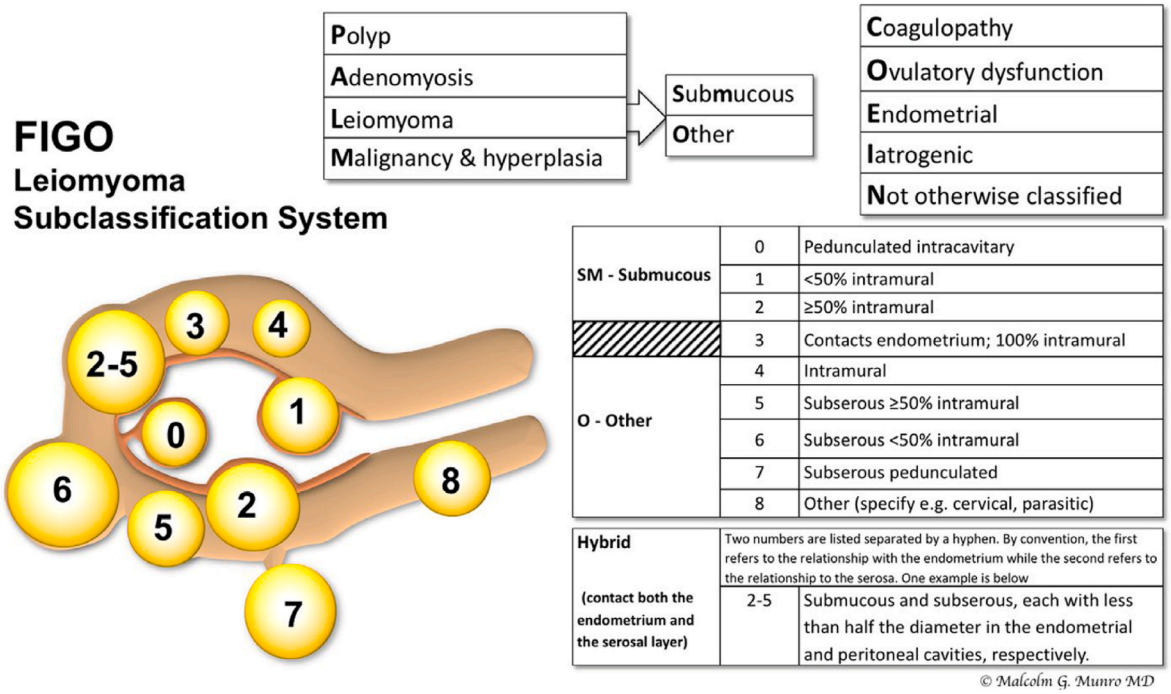

Fig. 2. FIGO Classification of uterine Fibroids(6).

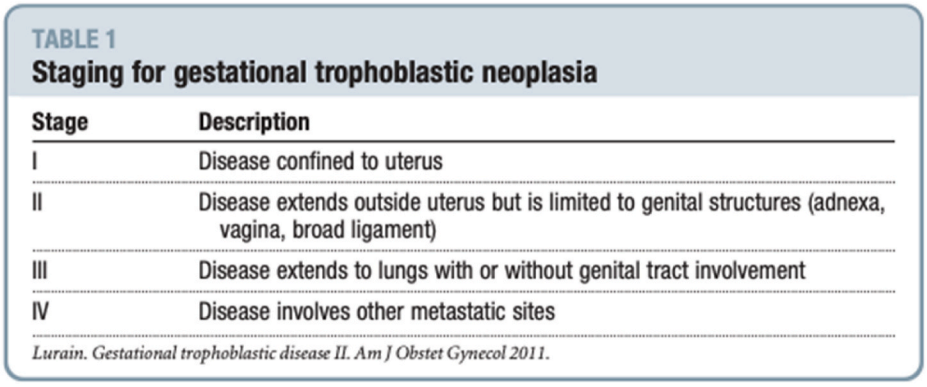

TABLE 1
Staging for gestational trophoblastic neoplasia

Stage	Description
I	Disease confined to uterus
II	Disease extends outside uterus but is limited to genital structures (adnexa, vagina, broad ligament)
III	Disease extends to lungs with or without genital tract involvement
IV	Disease involves other metastatic sites

Lurain. Gestational trophoblastic disease II. Am J Obstet Gynecol 2011.

Fig. 3. FIGO staging for gestational trophoblastic neoplasia(14).

Ethical approval

This study has been exempted from ethical clearance as outlined by the institutional review board.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

RA, KDT and BI conceived this study. RA and KDT collected patient data. RA, KDT and BI drafted the manuscript. RA, KDT and BI reviewed this version of the manuscript and agreed for its publication in its current form.

Research Registration

Not applicable as this is a case report.

Guarantor

The guarantor for this case report is Ruswana Anwar, M.D., Ph.D as the first author and Kevin Dominique Tjandraprawira, M.D., M.Sc. as the corresponding author.

Provenance and peer review

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Declaration of competing interest

The authors declare that we do not have any conflicts of interests.

TABLE 2
Scoring system for gestational trophoblastic neoplasia

Risk factor	Score			
	0	1	2	4
Age, y	≤39	>39	–	–
Antecedent pregnancy	Mole	Abortion	Term	
Pregnancy event to treatment interval, mo	<4	4-6	7-12	>12
Pretreatment hCG, mIU/mL	$<10^3$	10^3-10^4	10^4-10^5	$>10^5$
Largest tumor mass, including uterus, cm	<3	3-4	≥5	–
Site of metastases	–	Spleen, kidney	GI tract	Brain, liver
No. of metastases	–	1-4	5-8	>8
Previous failed chemotherapy	–	–	Single drug	≥2 drugs

GI, gastrointestinal; *hCG*, human chorionic gonadotropin.
Total score for patient is obtained by adding individual scores for each prognostic factor: low risk <7; high risk ≥7.

Lurain. Gestational trophoblastic disease II. Am J Obstet Gynecol 2011.

Fig. 4. FIGO scoring system for gestational trophoblastic neoplasia(14).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103659.

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