



## Therapeutic approach to the iatrogenic invasive mole – A report of two cases

### Terapijski pristup jatrogeno nastaloj invazivnoj moli – prikaz dva slučaja

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#### Abstract

**Introduction.** Invasive mole, a form of gestational trophoblastic neoplasia (GTN), is defined as penetration of molar tissue into the myometrium and/or presence of extra-uterine metastases. An invasive mole arising from a complete hydatidiform mole is more common than an invasive mole arising from the partial hydatidiform mole. Dilatation and uterine evacuation and/or curettage (D&E/C) is the first step in managing molar pregnancy. Uterine perforation is the most serious complication of this procedure. A less common one is the false passage. **Case report.** The first case report describes a 47-year-old woman who was referred to our Clinic under the suspicion of GTN, with elevated serum beta human chorionic gonadotropin (beta hCG) levels. Intraoperatively, devitalized ovular tissue arising from the uterine perforation was observed. Histopathological exam (HPE) of tissue obtained from hysterectomy confirmed an invasive mole as a result of uterine perforation made during D&E/C. The second patient, a 32-year-old woman with vaginal bleeding, nausea, and high levels of serum beta hCG levels was admitted to our Clinic. After four D&E/C, and persistently high levels of serum beta hCG levels, explorative laparotomy has been performed. A false passage created during D&E/C with necrotic and molar tissue was observed. The partial hydatidiform mole was confirmed by the HPE. **Conclusion.** This is the second reported case in the literature of postmolar GTN as a result of iatrogenic perforation of the uterus, and also the first described case of postmolar GTN arising from a false passage, created as an iatrogenic complication of D&E/C. A national survey of iatrogenic events during the treatment of gestational trophoblastic diseases is needed since these events could completely change the therapeutic strategies in managing these diseases.

#### Key words:

diagnosis; gynecologic surgical procedures; histological techniques; iatrogenic disease; postoperative complications; trophoblastic neoplasms; uterine perforation.

#### Apstrakt

**Uvod.** Invazivnu molu, oblik gestacijskih trofoblastnih neoplazmi (GTN), karakteriše penetracija molarnog tkiva u miometrijum i/ili prisustvo udaljenih metastaza. Invazivna mola nastala nakon kompletne mole je češća od invazivne mole nastale od parcijalne hidatiformne mole. Kiretaža materične šupljine sa evakuacijom sadržaja sukcijom je prvi korak u tretmanu molarne trudnoće. Perforacija uterusa je najopasnija komplikacija te procedure, dok je „lažni put“ (*false passage*) dosta ređa komplikacija. **Prikaz bolesnika.** Prvi prikaz opisuje bolesnicu staru 47 godina koja je primljena u našu Kliniku sa povišenim vrednostima serumskog beta humanog horionskog gonadotropina (beta hCG)-a pod sumnjom na GTN. Intraoperativno je uočena perforacija u predelu levog roga uterusa kroz koju je prominiralo ovularno tkivo. Histopatološkom analizom (HPA) nakon histerektomije potvrđena je invazivna mola nastala kao posledica jatrogene perforacije uterusa uzrokovane kiretažom. Drugi slučaj predstavlja bolesnicu staru 32 godine koja je primljena u Kliniku zbog krvarenja *ex utero*, sa mučninom i povišenim vrednostima beta hCG. S obzirom na perzistirajuće povišene vrednosti beta hCG-a i nakon četiri kiretaže, odlučeno je da se izvrši eksplorativna laparotomija. Intraoperativno je uočen „lažni put“ nastao kao komplikacija kiretaže, sa nekrotičnim i molarnim tkivom. HPA tkiva potvrdila je invazivnu molu nastalu od parcijalne mole, kao posledica pomenute jatrogene komplikacije. **Zaključak.** Prvi slučaj prikazan u ovom radu predstavlja drugi u literaturi opisani slučaj postmolarne GTN nastale kao rezultat jatrogene perforacije uterusa načinjene tokom kiretaže. Drugi slučaj opisan u ovom radu je prvi u literaturi opisan slučaj postmolarne GTN nastale stvaranjem „lažnog puta“ kao jatrogene komplikacije kiretaže materične šupljine. Smatramo da je nacionalni registar jatrogenih komplikacija nastalih tokom lečenja gestacijskih trofoblastnih bolesti neophodan, budući da te komplikacije mogu značajno uticati na terapijske protokole u lečenju ovih bolesti.

#### Ključne reči:

dijagnoza; hirurgija, ginekološka, procedure; histološke tehnike; jatrogena bolest; postoperativne komplikacije; neoplazme, trofoblastne; materica, perforacija.

## Introduction

Invasive mole, a form of gestational trophoblastic neoplasia (GTN), is defined as penetration of molar tissue into the myometrium and/or presence of extrauterine metastases. The myometrial invasion occurs via direct tissue extension or through venous channels<sup>1, 2</sup>. Malignant alterations occur in 15%–20% of complete hydatidiform mole, while transformation into postmolar GTN from partial hydatidiform mole happens in less than 5% of cases<sup>1</sup>.

Diagnosis of the invasive mole is almost exclusively based on clinical findings, while the histopathological exam usually shows the existence of edematous villi and proliferative trophoblasts in the myometrial tissue<sup>1, 3</sup>. Distant metastases are found rarely, mostly in the lungs, vagina, and brain<sup>2</sup>.

Numerous reports recommend dilatation and uterine evacuation and/or curettage to be performed as the first step in managing molar pregnancy. Dilatation and evacuation and/or curettage are regarded as safe procedures but not without potential complications, the most serious of them being uterine perforation. Other complications include false passage, cervical or vaginal lacerations, and endometritis<sup>4</sup>.

We presented two cases of invasive mole with signs of the destruction of uterine tissue possibly arising after iatrogenic dilatation and evacuation/curettage complications.

## Case report

### Case 1

A 47-year-old woman was referred to Gynecology and Obstetrics Clinic “Narodni Front” under the suspicion of invasive mole, with elevated serum beta human chorionic gonadotropin (beta hCG) levels, without

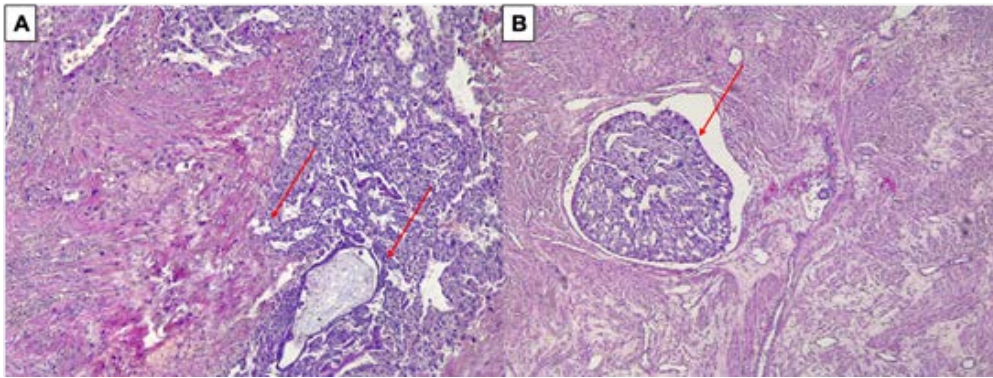
symptoms of vaginal bleeding or abdominal pain.

The patient had one failed assisted reproduction attempt five months before hospitalization. Two months prior to admission to the Clinic, the patient was diagnosed with pregnancy with a visualized gestational sac on ultrasound exam with mean sac diameter estimated for 5 gestational weeks, levels of serum beta hCG > 10,000 mIU/mL, and a suspicious change in the uterine fundus projection. After two weeks, the ultrasonographic exam raised suspicion for molar pregnancy, and the serum beta hCG level was 72,889 mIU/mL. Instrumental revision of the uterine cavity was performed, which showed chorionic villi with the elements of the hydatidiform transformation on the histopathological exam (HPE). Since the levels of serum beta hCG failed to drop, the second uterine curettage was performed. Histopathological exam of the obtained tissue samples showed decidual fragments along with atypical cytotrophoblasts and syncytiotrophoblasts. The last serum beta hCG level before admission was 80,500 mIU/mL. Ultrasonographic exam performed at the Clinic showed the large field of the destruction of the corpus of the uterus, without residual tissue at the uterine cavity, and without theca-lutein ovarian cysts. The decision was to perform laparoscopic hysterectomy with conservation of the adnexa.

Intraoperatively, a softened uterus with devitalized ovular tissue arising from the uterine perforation was observed (Figure 1A). To avoid dissemination of the neoplastic tissue, a conversion into the transversal laparotomy and subsequent hysterectomy with conservation of both ovaries were performed. Results from the histopathological analysis (HPA) of the uterus (Figure 1B) revealed chorionic villi with hydrops degeneration in the superficial myometrium with a myometrial invasion of atypical cytotrophoblasts, syncytiotrophoblasts, and intermedial trophoblasts (Figure 2A), along with the extensive vascular myometrial invasion of atypical trophoblasts (Figure 2B).



**Fig. 1 – A) Devitalized ovular tissue arising from the uterine perforation (laparoscopic view); B) Myometrial destruction in the region of the left uterine cornu and the left uterine wall (sample gained after hysterectomy).**



**Fig. 2 – A) Chorionic villus (left arrow) with hydrops degeneration in the superficial myometrium and myometrial invasion of atypical cytotrophoblasts, syncytiotrophoblasts, and intermedial trophoblasts (right arrow) [hematoxylin and eosin staining (HE),  $\times 5$ ]; B) Vascular myometrial invasion of atypical trophoblasts (arrow) (HE,  $\times 5$ ).**

### Case II

A 32-year-old woman was admitted to Gynecology and Obstetrics Clinic “Narodni Front” with signs of vaginal bleeding and nausea after uterus dilatation and evacuation and two curettages.

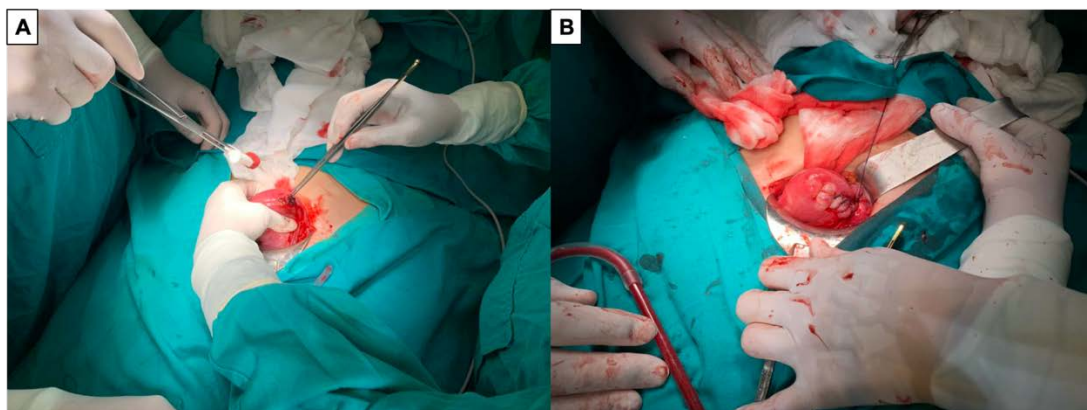
The patient was diagnosed with pregnancy two months before admission to the Clinic. After presenting with vaginal bleeding and ultrasonographic signs of missed abortion, a dilatation and suction curettage was performed. In the following two weeks, serum levels of beta hCG remained high. After another episode of vaginal bleeding, the first recurettage was performed. The HPA of the obtained tissue showed chorionic villi and circumferent proliferation of atypical trophoblasts. A week after the first recurettage, the beta hCG serum level was 10,880 mIU/mL. The second recurettage was performed and the HPA of the tissue revealed irregular secretory endometrium and decidual tissue with intermediate trophoblasts of the placental site. Immediate serum beta hCG levels after the intervention were 90,000 mIU/mL and 131,100 mIU/mL. The patient underwent the third recurettage and was administrated with one cycle of chemotherapy [methotrexate (MTX) and folinic acid (FA) – MTX+FA]. The radiographic exam of the chest and head showed the absence of metastatic changes. Since

the levels of serum beta hCG failed to drop after one cycle of chemotherapy (73,361 mIU/mL), and the ultrasound exam revealed the field of the tissue destruction in the region of the left uterine cornu a decision for the hysterectomy has been made.

The procedure revealed a lividly colored surface in the regions of the fundus, left cornu, and anterior wall. After incision, necrotic and molar tissue was evacuated from the left cornu. A false passage, going through the left lateral uterine wall to the vesicouterine fold was revealed. Evacuation of necrotic and molar tissue from the false passage was also performed (Figure 3A). The obtained samples were sent to the HPA, and the uterine incision was managed by simple interrupted stitches (Figure 3B). Another hemostatic suture was placed in the posterior uterine wall.

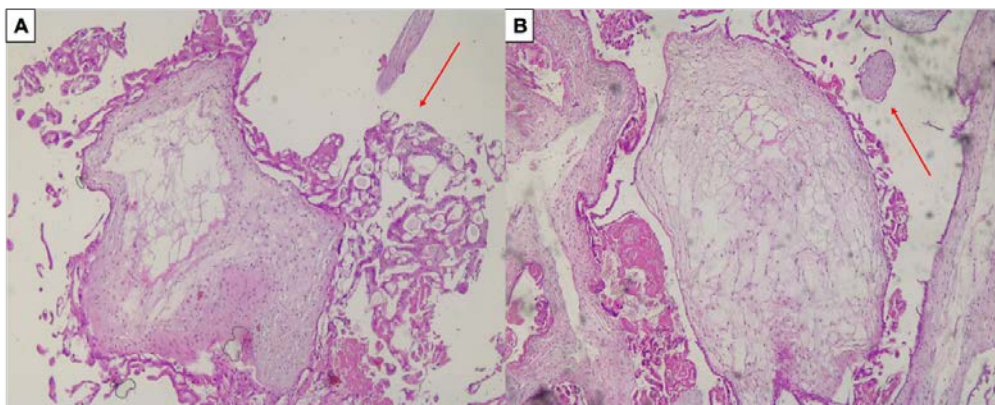
The HPA of the sample obtained from the left uterine cornu revealed partial hydatidiform mole (Figures 4A and 4B), and the analysis of the sample from false passage confirmed the presence of chorionic villi and mildly atypical cytotrophoblasts, syncytiotrophoblasts, and intermedial trophoblasts in the myometrial layer without vascular invasion.

Levels of serum beta hCG saw a significant decline in the days following the procedure.



**Fig. 3 – A) Evacuation of necrotic and molar tissue from the false passage; B) Uterine incision managed by simple interrupted stitches.**





**Fig. 4 – A) Chorionic villus surrounded by circumferential mildly atypical trophoblasts (arrow) [hematoxylin and eosin staining (HE), ×10]; B) Chorionic villus with circumferential mildly atypical trophoblasts and normal chorionic villi (arrow), confirming the diagnosis of partial hydatidiform mole (HE, ×10).**

### Discussion

To the best of our knowledge, this is only the second reported case in the literature of postmolar GTN as a result of iatrogenic perforation of the uterus, and also the first described case of postmolar GTN arising from a false passage, created as an iatrogenic complication of uterine curettage.

Gestational trophoblastic diseases (GTD) are a group of diseases that originate from abnormal placental tissue and include complete and partial hydatidiform mole, along with malignant forms, named gestational trophoblastic neoplasia: invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor<sup>5</sup>. The newest guidelines have expanded the GTN group with atypical placental site nodule because of its possible coexistence and/or progression into the placental site trophoblastic tumor, and epithelioid trophoblastic tumor<sup>6</sup>.

The exact incidence of GTD varies mostly from geographical location, race, socioeconomic factors, and nutritional factors<sup>6, 7</sup>. Reports from the literature acknowledge choriocarcinoma and invasive mole as the most frequent forms of GTN, while the incidence of placental site trophoblastic tumor and the epithelioid trophoblastic tumor is around 0.2–2% of the GTN cases<sup>1, 6</sup>.

An invasive mole arising from a complete hydatidiform mole is more common than an invasive mole arising from the partial hydatidiform mole. As far as we are aware, our case of invasive mole originating from the created false passage is the first reported case of invasive mole arising from the iatrogenic event in the management of partial hydatidiform mole.

According to the literature, serum beta hCG levels before evacuation >100,000 mIU/mL are one of the prognostic markers for the risk of development of postmolar GTN<sup>1</sup>. Along with serum beta hCG levels, other prognostic markers include uterine enlargement and theca lutein cyst with > 6 cm in their diameter<sup>1</sup>. Both of our patients had pre-evacuation serum beta hCG levels <100,000 mIU/mL,

which could favor the iatrogenic nature of GTN. Moreover, theca lutein cysts were not present in both patients.

Regardless of the size of the uterus, suction evacuation of molar tissue followed by a sharp curettage is the preferred first step in the management of patients with suspected GTD who wish to preserve their fertility. This should be done immediately after the hydatidiform mole is diagnosed<sup>6</sup>.

On the other hand, every patient with suspected or diagnosed GTN should be evaluated and assessed through the International Federation of Gynecology and Obstetrics (FIGO) and modified World Health Organization (WHO) scoring system<sup>3, 6</sup>. In the majority of the cases, patients with GTN develop a low-risk disease<sup>3</sup>. The favorable treatment method for these patients is usually monotherapy. An invasive mole is an almost completely curable disease due to its high sensitivity to chemotherapy.

There is still an ongoing debate in the scientific community whether hysterectomy could prevent the progression from hydatidiform mole to GTN since reports are suggesting the potential dissemination of molar tissue intraoperatively<sup>8</sup>. Nevertheless, a hysterectomy is still the treatment of choice in most of the medical centers worldwide for older patients (aged 40 or more) with GTD who no longer require fertility<sup>8</sup>.

A second curettage approximately seven days after the first curettage was introduced as a therapeutic approach for patients with GTD almost four decades ago<sup>9, 10</sup>. A recent study found that the routine second curettage might increase the risk for the development of GTN<sup>9</sup>. Moreover, some researchers advocate that the usage of oxytocin during or after the curettage might lead to trophoblastic embolism in the lungs<sup>9</sup>. On the other hand, some studies suggest that the second curettage could be seen as an alternative to the initial chemotherapy for patients with low-risk disease<sup>11</sup>.

There are insufficient data regarding the incidence of uterine perforation after dilatation and curettage in patients with GTD. Furthermore, reviews from the literature impose caution when performing this procedure because, in these cases, the uterus is often softened and the perforation is possible<sup>2</sup>.

We have presented a case of invasive mole caused by uterine perforation. In our opinion, the uterine evacuation was performed inadequately on the already softened and morphologically transformed uterus. This provided a path for the trophoblasts into the myometrium. A conversion from laparoscopy to laparotomy was done to avoid possible dissemination of trophoblastic tissue. A hysterectomy was done primarily because two-thirds of the uterine wall was destructed by an invasive mole.

Even though the patient from our second case underwent four curettages, serum levels of beta hCG were still elevated. Only diagnostic laparoscopy revealed performed false passage, which caused the penetration of trophoblasts into the myometrium. Even though the false passage is one of the possible complications of uterine curettage, its incidence is relatively low and its consequences are not life-threatening. The false passage is usually formed during the initial dilatation of the cervix. This is why numerous guidelines suggest that the dilatation should be performed by an expert, as gently as possible and with caution.

### Conclusion

Dilatation and evacuation are still the treatment of choice in patients with GTD who wish to preserve their

fertility. Uterine perforation, arguably the most serious complication of this procedure, besides life-threatening consequences, could be the base of the iatrogenic cause of GTN.

We also presented the first case of an invasive mole arising from the false passage, a rare yet another possible complication of dilatation and curettage. This underlines the importance of uterine evacuation in these patients to be done cautiously and performed by an expert. Lastly, we think that a national survey of iatrogenic events during the treatment of GTD is needed since these complications could easily be overlooked. Moreover, these events could completely change the therapeutic strategies, and, instead of the simple procedure, the patient could require chemotherapy treatment or even hysterectomy.

### Disclosure statement

The authors declare no conflicts of interest.

### Acknowledgement

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