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Authors Jokanović Predrag*, Rakić Aleksandar*, Vojnosanitetski pregled (2021); Online First August, 2021.

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LAPAROSCOPIC HYSTERECTOMY AS A TREATMENT MODALITY FOR GESTATIONAL TROPHOBLASTIC NEOPLASIA – REPORT OF TWO CASES

LAPAROSKOPSKA HISTEREKTOMIJA U LEČENJU GESTACIJSKIH TROFOBLASTNIH NEOPLAZMI – PRIKAZ DVA SLUČAJA

Jokanović Predrag*, Rakić Aleksandar*
* - Gynecology and Obstetrics Clinic „Narodni front“, Belgrade, Serbia

Correspondence to:
Dr Predrag Jokanović
Department of Conservative Gynecology, Gynecology and Obstetrics Clinic „Narodni front“, 11000 Belgrade, Serbia
Email: drpredragjokanovic@gmail.com
Telephone number: +381 11 2068 351
Abstract

Introduction. Measurement of the serum levels of human chorionic gonadotropin’s beta isoform (βhCG) remains a crucial marker for diagnosing the GTN. Choriocarcinoma is commonly diagnosed due to extremely high levels of βhCG, but the presence of distant metastasis is not uncommon. Placental site trophoblastic tumor and epithelioid trophoblastic tumor remain some sort of an enigma because the levels of βhCG are usually low.

Case report. A 44-year old patient, P2G3, was admitted to the Clinic under the suspicion of molar pregnancy, vaginal bleeding with variable intensity, and levels of βhCG of 1,837,787 mIU/mL. After two explorative curetages, βhCG saw a decline and a partial hydatidiform mole was diagnosed histopathologically. The patient was admitted to the Clinic on two occasions due to the increasing values of βhCG. Since βhCG failed to drop after two explorative curetages, hysteroscopic biopsy, one chemotherapy cycle, along with the suspicious ultrasonographic feature of metastatic GTN and the fact that the patient has refused further chemotherapy, a total laparoscopic hysterectomy was performed. Histopathological exam made the diagnosis of choriocarcinoma.

A 50-year old patient, P2G4, was admitted to the Clinic under the ultrasonographic suspicion of molar pregnancy. She was complaining of pelvic discomfort and frequent urination. Initial levels of βhCG were 128,351 mIU/mL. Instrumental revision of the uterine cavity was performed and partial hydatidiform mole was diagnosed histopathologically. Because of the increasing levels of βhCG, ultrasonographical suspicion of the development of GTN in the uterine corpus, in accordance with patient’s age and the fact that she has regular menstrual cycles, total laparoscopic hysterectomy was performed, and a histopathological exam made the diagnosis of the placental site trophoblastic tumor.

Conclusion. Laparoscopic hysterectomy could be a treatment of choice for the chemotherapy resistant GTNs but also for the chorionicarcoma in patient’s who have finished their reproductive activity and refuse to be treated with chemotherapeutics.

Key words: gestational trophoblastic neoplasia, choriocarcinoma, placental site trophoblastic tumor, laparoscopic hysterectomy.
Apstrakt

Uvod Značajan marker gestacijskih trofoblastnih bolesti predstavlja određivanje serumskih koncentracija beta izoforme humanog horionskog gonadotropina (βhCG). Horiokarcinom se najčešće dijagnostikuje usled izrazito visokih vrednosti βhCG-a, uz neretko prisustvo metastaza. Sa druge strane, trofoblastni tumor placentnog ležišta i epitelioidni trofoblastni tumor ostaju velika enigma, s obzirom da su koncentracije βhCG-a kod ovih tumora često niske. Prikaz bolesnika. 44 godine stara pacijentkinja, P2G3, primljena je na Kliniku zbog sumnje na molarnu trudnoću. Žalila se na vaginalno krvarenje varijabilnog intenziteta. Inicijalna vrednost serumskog βhCG-a iznosila je 1 837 787 mIU/mL. Nakon dve eksplorativne kiretaže došlo je pada βhCG-a, a histopatološki je dijagnostikovana parcijalna mola. Pacijentkinja je u dva navrata hospitalizovana zbog ponovnog rasta βhCG-a. S obzirom da nije došlo do pada vrednosti βhCG-a nakon dve instrumentalne revizije materične duplje, histeroskopije sa ciljanom biopsijom, jednog ciklusa hemoterapije, uz ultrazvučni nalaz visoko suspektan na metastatsku GTN u zidu uterusa i činjenice da je pacijentkinja odbila dalju hemoterapiju, urađena je totalna laparoskopska histerektomija sa konzervacijom adneksa. Histopatološkom analizom dijagnostikovano je horiokarcinom. 50 godina stara pacijentkinja, P2G4, upućena je na Kliniku zbog ultrazvučno postavljene sumnje na molarnu trudnoću. Žalila se na nelagodu u maloj karlici i često mokrenje. Inicijalna vrednost βhCG-a iznosila je 128 351 mIU/mL. Urađena je instrumentalna revizija materične duplje, a histopatološki je dijagnostikovana parcijalna mola. Zbog rastućih vrednosti βhCG-a, ultrazvučno postavljene sumnje na perzistirajuću GTN, a shodno godinama pacijentkinje i činjenicu da ima redovne cikluse, urađena je totalna laparoskopska histerektomija sa konzervacijom jajnika. Histopatološkom analizom dijagnostikovan je trofoblastni tumor placentnog ležišta. Zakujučak. Laparoskopska histerektomija bi mogla biti tretman izbora u lečenju GTN-a rezistentnih na hemoterapiju kao i pacijentkinja sa horiokarcinomom, koje su završile svoju reproduktivnu aktivnost i koje odbijaju lečenje hemoterapijom.

Ključne reči gestacijske trofoblastne neoplazme, horiokarcinom, trofoblastni tumor placentnog ležišta, laparoskopska histerektomija.
Introduction

Gestational trophoblastic diseases (GTD) represent a spectrum of abnormal proliferation of trophoblast cells. They include complete and partial hydatidiform mole, sometimes marked as „premalignant GTD“, and gestational trophoblastic neoplasia (GTN), which include: choriocarcinoma, placental site trophoblastic tumor, epithelioid trophoblastic tumor, and invasive mole\textsuperscript{1}.

Measurement of the serum levels of human chorionic gonadotropin’s beta isoform (\(\beta\)hCG) remains a crucial marker for diagnosing the GTN, but also a valuable indicator of (un)successful therapy\textsuperscript{1,2}. The diagnosis of postmolar GTN is usually made by observing the persistent or increasing levels of\(\beta\)hCG following the evacuation of the hydatidiform mole. Choriocarcinoma is commonly diagnosed due to extremely high levels of \(\beta\)hCG, but the presence of distant metastasis is not uncommon\textsuperscript{1-3}. At the same time, choriocarcinoma is highly chemotherapy-sensitive, therefore nowadays, a complete recovery is possible in 90\% of the cases\textsuperscript{3}. On the other hand, placental site trophoblastic tumor and epithelioid trophoblastic tumor remain some sort of an enigma, because the levels of \(\beta\)hCG are usually low, or even normal, and in most cases, these tumors are resistant to chemotherapy\textsuperscript{1-3}.

Even though modern chemotherapy protocols provide almost complete remission of the disease, cases of chemotherapy-resistant GTNs require surgical treatment\textsuperscript{4}. A particular challenge in surgical treatment represents patients who wish to preserve their fertility, along with those where the ovarian function must be conserved\textsuperscript{4}. On the other hand, another challenge represent the group of patients who refuse chemotherapy treatment method.

We will present two cases of GTN with unusual clinical features in which total laparoscopic hysterectomy provided a complete recovery for the patients.

Case report

Case I

A 44-year old patient, P2G3, was admitted to the Clinic under the suspicion of molar pregnancy. Vaginal bleeding of variable intensity was the only symptom she was complaining about. Levels of \(\beta\)hCG were 1 837 787 mIU/mL (Figure 1). On the first and the fourth hospital day, explorative curettages were performed. From the obtained samples,
a histopathological diagnosis of the partial hydatidiform mole was made. After the procedures, the levels of βhCG were in decline (Figure 1). After one month, she was once again admitted to the Clinic. The levels of βhCG were increasing (from 630 to 1263 mIU/mL). A suspicious mass in the right uterine cornu, intimately besides the uterine cavity, was seen on the ultrasonographic exam (Figure 2A). A diagnostic hysteroscopy was performed. Hysteroscopically, no residual tissue nor trophoblastic protrusion was seen, and the histopathological exam of the tissue obtained from endometrial biopsy revealed a secretory endometrium. After diagnostic hysteroscopy and one chemotherapy cycle, the serum levels of βhCG dropped (from 1694 to 1314 mIU/mL) (Figure 1). After more than one month, she has been admitted again to the Clinic given that βhCG levels were persisting (296 and 329 mIU/mL) (Figure 1). The patient refused further chemotherapy treatment and it was decided to perform a total laparoscopic hysterectomy with preservation of the ovaries (Figure 2B). Histopathological exam of the obtained tissue revealed choriocarcinoma. The levels of βhCG significantly dropped, and the patient was discharged.

**Figure 1.** Levels of serum βhCG (mIU/mL) in Case I; interventions are marked with an arrow.
Case II
A 50-year old woman, P2G4, was admitted to the Clinic under the ultrasonographic suspicion of molar pregnancy. She was complaining of pelvic discomfort and frequent urination. Serum levels of $\beta$hCG were 128 351 mIU/mL (Figure 3). Since the ultrasonographic exam confirmed the suspicion of molar pregnancy, explorative curettage of the uterine cavity was performed. Histopathological diagnosis from the obtained sample of the partial hydatidiform mole was made. Levels of serum $\beta$hCG were in decline after the intervention (31 611 mIU/mL) (Figure 3). Since the concentration of $\beta$hCG saw a trend of increase (from 430 to 598 mIU/mL) (Figure 3), the patient was once again admitted to the Clinic. When the patient's age, the fact that she had regular menstrual cycles, and serum levels of $\beta$hCG were taken into concern, along with the suspicion of the development of GTN in the uterine corpus (Figure 4A), it was decided to perform a total laparoscopic hysterectomy with the conservation of the one ovary (Figure 4B). Histopathologically, the decidual remains, along with the several intermediate trophoblastic cells of the placental site in the endometrium were seen. Chorionic villi were not present. The diagnosis of the
placental site trophoblastic tumor was made. A few days after the surgery, serum βhCG was negative, and the patient was discharged.

**Figure 3.** Levels of serum βhCG (mIU/mL) in Case II; interventions are marked with an arrow.

**Figure 4.** A. Ultrasonographic feature in the second patient before the operation. B. Uterus after the hysterectomy.
Discussion

Complete hydatidiform moles are usually presented with high levels of serum hCG. It was shown that in more than 50% of the patients with the complete hydatidiform mole, the levels of βhCG before evacuation exceeded 100 000 mIU/mL. On the other hand, only 10% of the patients with the partial hydatidiform mole had such high serum βhCG levels. Our patient, in which the final diagnosis was choriocarcinoma, was initially diagnosed with partial hydatidiform mole, along with the βhCG levels of 1 837 787 mIU/mL, a concentration unusually high for this type of GTD. Moreover, it has been reported that 15-20% of the complete hydatidiform moles progress into an invasive mole or other forms of GTN. However, only 0.5-2% of the partial hydatidiform moles transform into some form of GTN. In both of our patients with GTN, the initial diagnosis was the partial hydatidiform mole.

About 50% of the choriocarcinomas arise on the basis of the complete hydatidiform mole, 25% after the normal pregnancy, and about 25% after the miscarriage or ectopic pregnancy. There are only a few reports in the literature regarding choriocarcinomas that occurred on the basis of the partial hydatidiform moles. One of the main features of choriocarcinoma is extremely high βhCG levels. In our first case, the levels of βhCG persisted in the range from 329 to 1694 mIU/mL, which is unusual for this type of GTN. Choriocarcinomas are chemotherapy-sensitive, which can explain the significant drop in hCG levels after one chemotherapy cycle. When there is no distant metastasis, an individualized chemotherapy protocol for each patient is made, and the chemotherapy itself is usually the treatment of choice.

Placental site trophoblastic tumor is an extremely rare tumor, and, along with the epithelioid trophoblastic tumor, accounts for about 0.2-3% of GTN. A special challenge for the correct diagnosis and proper treatment of these tumors are relatively low levels of βhCG, often non-specific clinical features, and chemotherapy resistance. Even though the data is limited, it has been reported that placental site trophoblastic tumor occurs in 61% after a normal pregnancy, in 12% after the molar pregnancy, in 9% after the spontaneous miscarriage, in 8% after the induced abortions, and in 3% after ectopic pregnancy. The remaining 7% does not have a clear etiology. This tumor arises exclusively from the proliferation of the intermediate trophoblasts. The absence of the syncytiotrophoblasts is
exactly the reason why the levels of \( \beta \)hCG in these tumors are usually low, or even normal. Therefore, the measurement of human placental lactogen (hPL) has shown to be a good marker for the diagnosis of these tumors\(^8\,^9\). These tumors usually present with irregular bleeding and an invasion of the myometrium and endometrium\(^9\). In our case, the invasion of the tumor into the uterine walls was not present. In almost all of the cases of this tumor, the treatment of choice was total hysterectomy with the preservation of the adnexa, besides in cases with a family history of ovarian cancer and postmenopausal women\(^10\). To the best of our knowledge, there are no reports of laparoscopic hysterectomy as a treatment method for the placental site trophoblastic tumor.

**Conclusion**

Even though gestational trophoblastic diseases are known for a long time, they can still be a mystery for the modern gynecological practice. Thanks to everyday progress in chemotherapy, they are often marked as completely curable diseases. Although chemotherapy is usually the treatment of choice, there are types of GTN which are resistant to chemotherapy and require surgical treatment. Laparoscopy, on the other hand, brings many advantages for the patients, from less intraoperative bleeding to shorter postoperative recovery. With these two cases, we have shown that laparoscopic hysterectomy could become a treatment of choice for chemotherapy resistant GTNs, but also for the treatment of choriocarcinomas in patients who have finished their reproductive activity and refuse the treatment with chemotherapeutics.

**Disclosure statement**

The authors declare no conflict of interest
References

1. Ning F, Hou H, Morse AN, Lash GE. Understanding and management of gestational trophoblastic disease. F1000Res. 2019;8:F1000 Faculty Rev-428.
2. Shaaban AM, Rezvani M, Haroun RR, et al. Gestational Trophoblastic Disease: Clinical and Imaging Features. Radiographics. 2017;37(2):681–700.
3. Hui P. Gestational Trophoblastic Tumors: A Timely Review of Diagnostic Pathology. Arch Pathol Lab Med. 2019;143(1):65-74.
4. Lima LLA, Padron L, Câmara R et al. The role of surgery in the management of women with gestational trophoblastic disease. Rev Col Bras Cir. 2017;44(1):94–101.
5. Froeling FE, Seckl MJ. Gestational trophoblastic tumours: an update for 2014. Curr Oncol Rep. 2014;16(11):408.
6. Ranade M, Aguilera-Barrantes I, Quiroz FA. Gestational Trophoblastic Disease and Choriocarcinoma. Ultrasound Q. 2015;31(3):221-3.
7. Strohl AE, Lurain JR. Nonmetastatic Excised Gestational Choriocarcinoma: To Treat or Not to Treat. Gynecol Oncol. 2018;148(2):237-238.
8. Horowitz NS, Goldstein DP, Berkowitz RS. Placental site trophoblastic tumors and epithelioid trophoblastic tumors: Biology, natural history, and treatment modalities. Gynecol Oncol. 2017;144(1):208–214.
9. Feng X, Wei Z, Zhang S, Du Y, Zhao H. A Review on the Pathogenesis and Clinical Management of Placental Site Trophoblastic Tumors. Front Oncol. 2019;9:937.
10. Chiofalo B, Palmara V, Laganà AS et al. Fertility Sparing Strategies in Patients Affected by Placental Site Trophoblastic Tumor. Curr Treat Options Oncol. 2017;18(10):58.

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