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CASE REPORT

GESTATIONAL TROPHOBLASTIC NEOPLASIA (INVASIVE MOLE) FOLLOWING INCOMPLETE ABORTION- A RARE CASE PRESENTING WITH UTERINE PERFORATION WITH GROSS HEMOPERITONEUM: A CASE REPORT

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ABSTRACT

Invasive mole is gestational trophoblastic neoplasia, characterized by aggressive invasion of the wall of the uterus by the trophoblastic cells. Here, we report a rare case of 17 years primigravida who presented with per vaginal bleeding and uterine perforation with gross hemoperitoneum about 1 month of manual vacuum aspiration of incomplete abortion. Resuscitation followed by emergency laparotomy with subsequent repair of uterine perforation was done. The patient received a total of 5 cycles of single agent chemotherapy (Methotrexate with leukovorin rescue). The beta hCG level became normal after 3 cycles of chemotherapy and further 2 cycles chemotherapy was administered. She was followed up for another 1 year in which her beta hCG levels were within normal limits.

***Key words:** Gestational trophoblastic neoplasia, Invasive mole, Uterine perforation.*

INTRODUCTION

Gestational trophoblastic disease (GTD) comprises a spectrum of interrelated conditions originating from the placenta.[1] Histologically distinct disease entities encompassed by this general terminology include complete and partial hydatidiform moles, invasive moles, gestational choriocarcinomas, and placental site trophoblastic tumors.[1] Gestational trophoblastic neoplasia (GTN) are characterized by aggressive invasion of the endometrium and myometrium of the uterus by trophoblastic cells.[2] Persistent gestational trophoblastic neoplasia is evidenced by the persistence of trophoblastic activity following evacuation of molar pregnancy or following previous abortion or ectopic pregnancy or even normal pregnancy. Gestational trophoblastic neoplasia follows hydatidiform mole (60%), previous spontaneous abortion/abortion (30%), and normal pregnancy or ectopic gestation (10%).[3,4]

GTN usually presents with continued vaginal bleeding, persistently soft and enlarged uterus and persistently raised beta hCG (human chorionic gonadotrophin) level following initial evacuation of a molar pregnancy.[2]

We report a rare case of GTN (invasive mole) following manual vacuum aspiration of a non-molar incomplete abortion presenting with uterine perforation with gross hemoperitoneum after 27 days following manual vacuum aspiration.

CASE REPORT

A 17 years primigravida at 9 weeks 5 days of gestation arrived to the Emergency Department (ED) with complaints of abdominal pain for 2 days and per vaginal bleeding for 2 days. The pain was localized to the lower abdomen. It was dull in nature, continuous and non-radiating. She also complaint of per vaginal (PV) bleeding, which started two hours after pain abdomen. Bleeding was bright red in color with passage of few clots. She used 2 pads

each day for two days and they were fully soaked. The patient was not on any medications. Her initial vitals were as follows: blood pressure 110/70 mmHg, pulse rate 68 beats/min, respiratory rate 18 breaths/min and body temperature 98.2° F in right axilla. Urine pregnancy test (UPT) was positive. Laboratory investigations revealed hemoglobin of 10.7 g/dl. Other laboratory results, including blood chemistry and urinalysis, were within normal limits. Ultrasonography (USG) revealed a heterogenous area of approximately 1.8 x 1.69 centimeters (cm) in the uterine cavity suggestive of retained product of conception (RPOC) with uterine size of 8.7 x 5.6 x 3.9 cm and unremarkable adnexae.

Under the impression of incomplete abortion, Misoprostol 800 micrograms (mcg) was administered per vaginally and Manual Vacuum Aspiration (MVA) was done under intravenous anesthesia, with the intra-operative findings of about 25 milligrams of tissues and/or clots. The patient was discharged the following day with oral antibiotic (Doxycycline) for 5 days and was advised to follow up in the Out Patient Department (OPD) after 1 week. The follow-up USG after one week showed thin unformed endometrium of 5 millimeters (mm) without the evidence of RPOC.

After 27 days following MVA, she again presented to the ED with complaints of diffuse abdominal pain for 1 day, 3 episodes of non-bilious, non-blood stained vomiting with no history of PV bleeding. Her initial vitals were as follows: blood pressure 90/60 mmHg, Pulse rate 104 beats/min, respiratory rate 24 breaths/min and body temperature 98.4° F in right axilla. Physical examination revealed pallor and generalized tenderness and rebound tenderness with guarding all over the abdomen. Initial fluid resuscitation was done and all relevant investigations including USG was done. The USG revealed a heterogenous mass measuring approximately 5.3 x 4.2 cm in the right adnexa with massive hemoperitoneum. The investigations were as follows: UPT positive, hemoglobin of 6.8 g/dl, total leukocyte count of 11,300/mm^3 with 80% neutrophils. Other blood chemistry and urinalysis were within normal limits. And, serology was non-reactive. She was taken to Operating Room for laparotomy. Intraoperative findings were as follows:

1) Gross hemoperitoneum with clots (approximately 1.5 liters of blood and clots)
2) Perforation rent of about 5 millimeters in uterine corpus 2 cm below and medial to the right cornua in the posterior aspect. Uterus enlarged to 6-8 weeks size.
3) Blood clot (of approximately 5cm x 4 cm size) adherent to right adnexa (this was shown by USG stating a heterogenous mass measuring approximately 5.3 cm x 4.2 cm in the right adnexa).
4) Bilateral healthy adnexae

Subsequent repairing of the rent in the uterine corpus was done; peritoneal washing was done with 2 liters of warm normal saline; hemostasis was secured and the abdomen was closed in layers.

Serum beta hCG was done on the next day and after 48 hours which respectively showed 1840 mIU/mL and 2050 mIU/mL. Subsequently, four pints of whole blood transfusion was done over 2 days and her hemoglobin increased to 10.7 g/dL. She was discharged after 6 days and was advised for follow-up after 1 week with beta hCG report. The serum beta hCG level after 1 week was 3350 mIU/mL. Thereby, she was admitted for chemotherapy with the impression of persistent gestational trophoblastic disease (invasive mole) Stage I (WHO Prognostic score 2).

A diagnosis of invasive mole was made on the basis of following evidences:

1) Evidence of uterine perforation that was subsequently repaired via laparotomy (although definite tissue was not available for histopathology)
2) Persistently high serum beta hCG levels:
    1) On Day 1 following uterine perforation = 1840 mIU/mL (28 days following MVA)
    2) On Day 3 following uterine perforation = 2050 mIU/mL (30 days following MVA)
    3) On Day 12 following uterine perforation =

3350 mIU/mL (39 days following MVA)

4) On Day 19 following uterine perforation = 1350 mIU/mL (49 days following MVA; after 1 cycle of chemotherapy)

Before starting chemotherapy, complete blood count (CBC), liver function test and renal function tests and chest x-ray were performed. Hemoglobin was 10.2 g/dl and all the other investigations were within normal limits. And, chest X-ray was normal. WHO Prognostic scoring was 2 (Antecedent pregnancy: Abortion-Score of 1 and pre-treatment beta hCG level in the range of 1,000-10,000-Score of 1). So, single agent chemotherapy with Methotrexate (with Leukovorin rescue) was started. She was discharged after 8 day course of Methotrexate 50 mg IM and Folinic acid 5 mg IM on alternate days.

And she was advised for follow up after 1 week with beta hCG report. The beta hCG level after 1 week of first cycle of chemotherapy was 1350 mIU/mL.

Then, second cycle of chemotherapy was completed in OPD basis. Serum beta hCG level following completion of second cycle of chemotherapy was 15.2 mIU/mL. The third cycle of chemotherapy was also completed in OPD basis. Serum beta hCG level after third cycle of chemotherapy was 2.0 mIU/mL (within normal range). Further two courses of chemotherapy was administered with subsequent undetectable beta hCG level. She was under close follow-up.

DISCUSSION

Gestational trophoblastic neoplasia (GTN) are rare tumours that constitute less than 1% of all gynecological malignancies.[5] The diagnosis of GTN is made on the basis of elevated hCG levels supported, if possible, by histologic or radiologic evidence. Although distinct histologic types have been characterized and described, in most of the cases there is no tissue available for pathologic study.[2] The agreed criteria to diagnose GTN include:[3]

1) At least 4 values of persistently elevated beta hCG (human chorionic gonadotrophin) plateau (days 1, 7, 14, and 21) or longer, or sequential rise of beta hCG for 2 weeks (days 1, 7, 14) or longer. The actual values of hCG are left to the discretion of individual physicians. (In this case we have reported, the values of beta hCG levels were persistently high though the beta hCG level was not done precisely on the days mentioned in the diagnostic criteria)

2) Lung metastases are diagnosed by chest X-ray (in case of gestational choriocarcinoma)

3) Beta hCG remains elevated for 6 months or more

4) Histologic diagnosis of choriocarcinoma

Invasive mole is a distinct subgroup of GTN, which if not diagnosed and treated early, can result in serious complications like uterine perforation and haemoperitoneum.[5] Invasive mole is characterized by the presence of whole chorionic villi that accompany excessive trophoblastic overgrowth and invasion.[2] These tissues penetrate deep into the myometrium, sometimes involving the peritoneum, adjacent parametrium or vaginal vault.[2] Such moles are locally invasive but generally lack the pronounced tendency to develop widespread metastasis typical of choriocarcinoma.[2]

In 2000, FIGO recommended a clinical staging of gestational trophoblastic tumors and requested that such cases be reported in the Annual Report on the Results of Treatment of Gynecological

Cancers. The definitions of the clinical stages of gestational trophoblastic tumors[3] are shown in Table 1.

Table 1: FIGO STAGING OF TROPHOBLASTIC TUMORS[3]

Stage	Description
I	Gestational trophoblastic tumors strictly confined to the uterine corpus
II	Gestational trophoblastic tumors extending to the adnexae or to the vagina, but limited to the genital structures
III	Gestational trophoblastic tumors extending to the lungs, with or without genital tract involvement
IV	All other metastatic sites

This case of 17 years primigravida was labeled Stage I Trophoblastic Tumor as the tumor was confined to

the uterine corpus without extension to the adnexa or vagina (although definitive tumor/tissue was not found to be sent for histopathology analysis) and there was no evidence of lung metastasis.

In 2000, FIGO accepted the WHO scoring system based on prognostic factors that were first devised by Bagshawe[6] (Table 2). The score values for the risk factors are 1, 2, and 4.[3,6] Blood groups are not used in the scoring system. Liver metastases are given a score of 4.[3] The cut-off scores for low-risk and high-risk neoplasia were ratified by the FIGO Committee on Gynecologic Oncology in June 2002.[3] A score of 6 or less is low-risk disease treatable by single agent chemotherapy. A score of 7 or greater is high-risk disease that requires combination chemotherapy. Medium-risk disease has been eliminated.[3]

Table 2: FIGO/WHO Prognostic Scoring

Risk factors	Score of 0	Score of 1	Score of 2	Score of 4
Age	< 40y	≥40y	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval months from index pregnancy	< 4	4-6	7-12	>12
Pretreatment serum hCG* level	< 10^3	10^3 -10^4	10^4 -10^5	>10^5
Largest tumor size (including uterus)	< 3 cm	3-4 cm	≥5 cm	–
Site of metastases	Lung	Spleen, kidney	Gastrointestinal system	Liver, brain
Number of metastases	–	1-4	5-8	>8
Previous failed chemotherapy	–	–	Single drug	≥2 drugs
*hCG = human chorionic gonadotropin				

In this case we have reported, the WHO Prognostic score was 2. Antecedent pregnancy: abortion (Score of 1) and Pretreatment serum beta hCG level in the range of 1,000-10,000 (Score of 1) adding to a total score of 2 (i.e, low risk).

Low-risk GTN includes non-metastatic neoplasia (except lung metastasis) where the WHO Prognostic Score is 6 or less in FIGO Stage I–III[3,7,8]

1) Drug schedules: Single agent chemotherapy[3,7,8]

   a) Methotrexate with leucovorin rescue

      Methotrexate 50mg intramuscularly or 1 mg/kg every other day for 4 doses with leucovorin 15mg or 0.1 mg/kg 24–30 hours after each dose of methotrexate. This is a widely used protocol in the UK and the USA, but has a 20%–25% primary failure rate [8]. Methotrexate is a folic acid antagonist that inhibits DNA synthesis by causing an acute intracellular deficiency of folate co-enzymes.[2] Mild stomatitis is the most common side effect, but other serosal symptoms, especially pleurisy, develop in upto one quarter of patients treated with low dose methotrexate.[2] In this case, single agent chemotherapy with this regimen was done.

   b) Methotrexate 0.4 mg/kg intramuscularly for 5 days, repeated every 2 weeks. This is one of the original protocols used in GTD and is still used at Yale University. It is the standard protocol at the Brewer Trophoblast Center in Chicago, where it is used intravenously. The primary failure rate is 11%–15% for non-metastatic disease and 27%–33% for metastatic disease.[7]

   c) Methotrexate 50mg/m^2 intramuscularly given weekly

      This regimen is associated with a 30% primary failure rate. If this occurs, methotrexate 0.4 mg/kg intramuscularly for 5 days may be administered or the medication may be changed to actinomycin D 12 mg/kg for 5 days.[9]

   d) Actinomycin D 1.25mg/m^2 intravenously given every 2 weeks. This protocol carries a

20% primary failure rate. It is an alternative to the pulsed weekly methotrexate protocol.[10,11]

Repeat complete blood count, platelets, creatinine, BUN, and SGOT (serum glutamic oxaloacetic transaminase) are obtained on the first day of each course.[3] These investigations were done on every first day of chemotherapy cycle in this case and they were within normal limits.

At least 1 course, and usually 2–3 courses of chemotherapy should be given beyond the first negative beta hCG titer, particularly if the decrease in hCG is slow or there has been extensive disease.[3] In this case, 2 further courses of chemotherapy were given beyond the first normal beta hCG titer.

In conclusion, in a patient with hemorrhage in early pregnancy, abortion, ectopic pregnancy and molar pregnancy should be kept in mind by each and every practitioner. And, in every case of incomplete abortion, molar pregnancy has to be excluded. From this case study, we strongly recommend the use of histopathology examination of products of conception in every case after performing manual vacuum aspiration or electric vacuum aspiration to rule out molar pregnancy changes that may not be detected with naked eye observation. Furthermore, even if the definitive tissue is not available for histopathology study, the diagnosis of invasive mole is almost certain with persistently high serum beta hCG levels and evidence of uterine perforation.

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