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CASE REPORT

Post-Molar Gestational Trophoblastic Neoplasia In a 25-Year-Old Woman

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Abstract

Introduction*: Hydatidiform mole is the most common gestational trophoblastic disease in regions such as Asia, Africa, and Latin America, with a lower incidence in European countries. In Indonesia, the incidence ranges from 1 in 100 to 141 pregnancies, particularly affecting women under 20 and over 45 years old, often in those with low socio-economic status and nutritional deficiencies (such as protein, folic acid, and carotene).*
Case Presentation: *A 25-year-old female presented to Malang City General Hospital with complaints of recurring brownish-black foamy vaginal discharge, nausea-vomiting for two months. She had regular menstrual cycles and no contraception use. On examination, the uterine fundal height was one finger above the symphysis pubis with no fetal heart sounds or uterine contractions. Vaginal examination revealed a closed cervix and foamy black blood. Ultrasound showed a retroverted uterus, a 6.4 mm gestational sac without a fetal pole, 37.0×31.6mm residual tissue, a honeycomb pattern, and no myometrial invasion. Blunt curettage removed 30 grams of bubble-like tissue. Histopathology confirmed a complete hydatidiform mole. β-hCG levels and uterine size continued rising post-curettage.*
Discussion*: A significant number of low-risk PGTN patients with a FIGO score of 0-6 show a complete response to first-line methotrexate/folinic acid therapy. However, those with a score of 6 or β-hCG levels >100,000 IU/l have a higher resistance rate. Despite this, the survival rate remains very high.*
Conclusion*: PGTN is a malignant uterine tumor linked to molar pregnancies. Single-agent chemotherapy remains the standard treatment and has a generally favorable prognosis.*

Keywords: *Hydatidiform mole; post-molar gestational trophoblastic neoplasia; β-hCG levels*

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INTRODUCTION

Hydatidiform mole is the most common gestational trophoblastic disease in Asia, Africa, and Latin America, with a lower incidence in European countries. [1,2] Gestational trophoblastic disease is defined as a group of neoplastic processes originating from trophoblastic cells, which play a role in placental development during pregnancy. The World Health Organization (WHO) has classified gestational trophoblastic disease into two pre-malignant conditions (complete hydatidiform mole (CHM) and partial hydatidiform mole (PHM)), and three malignant conditions (Invasive Mole, Choriocarcinoma, and Placental Site Trophoblastic Tumor (PSTT)/ Epitheloid Trophoblastic Tumor (ETT)).[3,4] In Indonesia, the incidence is 1:100-141 pregnancies, with higher rates in women under 20 and over 45 years old, particularly among those with low socio-economic status and nutritional deficiencies (protein, folic acid, and carotene). Women over the age of 40 are 5-10 times more likely to experience a complete hydatidiform mole, and approximately one-third of pregnancies in women over 50 years old result in a molar pregnancy. Partial hydatidiform mole is often found in women with a history of irregular menstruation and those who have used oral contraceptives for more than 4 years. In Bandung and surrounding areas, the incidence of hydatidiform mole is 1:427 pregnancies, while at Sanglah General Hospital in Denpasar, the incidence in 2013 was 2.9 cases per 1000 pregnancies, rising to 3.2 cases per 1000 pregnancies in 2014.[7,8]

The diagnosis of hydatidiform mole must be established based on anamnesis, clinical examination, ultrasound examination, serum β-hCG levels, and histopathological examination.[9] Patients with complete hydatidiform mole must undergo monitoring of β-hCG levels every two weeks for 12 weeks until the levels return to normal. If normalization occurs within 8 weeks, monitoring continues monthly for 6 months post-evacuation. If normalization takes longer than 8 weeks, monitoring continues monthly for 6 months after normalization. Patients with partial hydatidiform mole must undergo β-hCG monitoring every two weeks until the levels normalize, followed by one additional β-hCG test 4 weeks later for confirmation. If the additional β-hCG test is normal, monitoring is considered complete.[5 9 10 11 12]

Studies have shown that the incidence of developing post-molar gestational trophoblastic neoplasia (PGTN) is approximately 15-20% in complete hydatidiform moles (CHMs) and less than 1-5% in partial hydatidiform moles. The prognosis for more than 98% of women diagnosed with gestational trophoblastic neoplasia is very good; however, a small number of women may die due to late diagnosis or drug resistance. In another study of 618 patients treated, 97% achieved remission after initial therapy, and only 3% experienced relapse and required further treatment.[5 13 14]

Patients with molar pregnancies can have normal reproductive function after the management of the mole, although they are at risk of experiencing recurrent molar pregnancies. Similarly, patients diagnosed with gestational trophoblastic neoplasia can regain normal reproductive function after completing comprehensive treatment.[15]

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CASE PRESENTATION

This study used a prospective case study method on a 25-year-old female patient at Malang City General Hospital. She complained of recurring brownish-black foamy vaginal discharge, nausea, and vomiting for 2 months. Initially, the patient only complained of brown vaginal spotting, but after a month, she experienced the passage of dark brown, foamy blood clots from the vagina, accompanied by lower abdominal pain. The patient had regular menstruation, no contraception use, and was unmarried.

The patient underwent a Plano test, which returned positive. On physical examination, the patient was conscious with a blood pressure of 114/71 mmHg, pulse rate of 86 beats per minute, respiratory rate of 20 breaths per minute, and axillary temperature of 36.2°C. The patient weighed 68 kg, had a height of 168 cm, and a BMI of 24.09 kg/m². Abdominal examination revealed a uterine fundal height 1 finger above the symphysis pubis, absence of fetal heart sounds, and no uterine contractions. Vaginal examination showed no cervical dilation, a smooth cervix, and black foamy blood.



Figure 1. Obstetric and Ginecologic Utrasound: , a gestational sac (GS) of 6.4mm, residual tissue of 37.0x31.6mm, honeycomb appearance, no fetus, no fetal pole

Ultrasound revealed a retroverted uterus, a gestational sac (GS) measuring 6.4 mm, no fetal pole, residual tissue measuring 37.0 x 31.6 mm with a honeycomb appearance, no fetus, no myometrial invasion, and thinned myometrium on the anterior wall. Laboratory results showed a hemoglobin level of 11.1 g/dL, hematocrit 33.3%, erythrocytes 3.54 x 10^6/µL, leukocytes 9,700/µL, platelets 315,000/µL, bleeding time 1 minute 30 seconds, and clotting time 10 minutes.

Ultrasound can accurately detect molar pregnancies in only 34% of patients out of a total of 155 molar pregnancies confirmed by pathology. However, 84% of cases suspected to be molar pregnancies based on ultrasound findings were indeed confirmed as molar pregnancies (53 out of

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63 patients) based on histopathological examination, indicating that ultrasound examination has a high positive predictive value.[5]

The patient was diagnosed with a complete hydatidiform mole, with a differential diagnosis of gestational trophoblastic neoplasia and incomplete abortion. The patient and her family were educated regarding the condition and the planned treatment. The patient underwent blunt curettage, with surgical findings showing bubble-like tissue weighing 30 grams. The bubble-like tissue was sent for pathological examination, confirming a complete hydatidiform mole.

If histopathological examination cannot be performed due to the unavailability of tissue for testing, the diagnosis of Gestational Trophoblastic Neoplasia can be established when the beta hCG levels continue to show persistent elevation, even after the molar pregnancy has been evacuated.[15]

Post-curettage on day 1, the patient was allowed to go home with instructions to return for follow-up visits on days 7, 14, and 21 to monitor her general condition, perform obstetric ultrasound, and evaluate β-hCG levels.

According to The International Federation of Gynecology and Obstetrics (FIGO), post-evacuation β-hCG monitoring for suspected Gestational Trophoblastic Neoplasia (GTT) should follow these criteria: [5 15]

a. A plateau in β-hCG levels lasting more than 4 weeks (days 1, 7, 14, and 21).
b. A rise in β-hCG levels in three consecutive tests (days 1, 7, and 14).
c. β-hCG levels remain elevated or exceed normal levels for 6 months or more.
d. Histopathological evidence of choriocarcinoma.

Choriocarcinoma is a malignancy characterized by abnormal trophoblastic hyperplasia and anaplasia, without the presence of chorionic villi, accompanied by bleeding, necrosis, and invasion into the myometrium and blood vessels, which can lead to metastasis.[15]

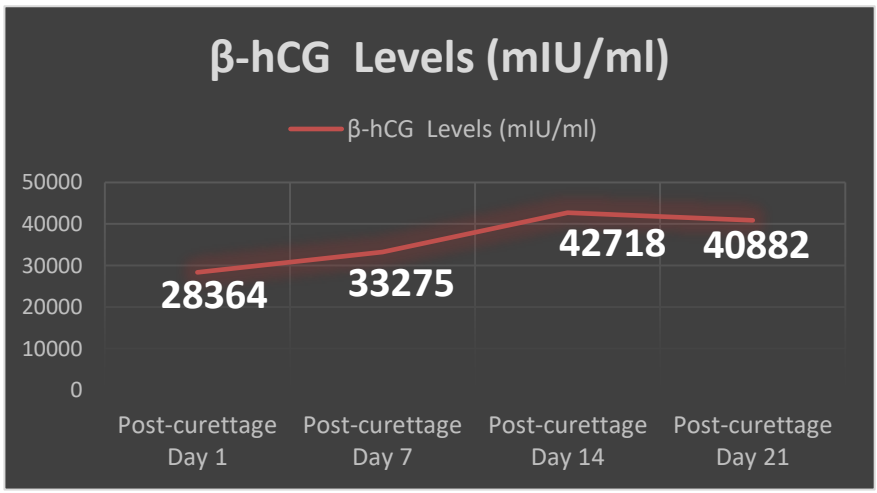
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Table 1. Post-curettage Follow up

Follow Up	Post-curettage Day 1	Post-curettage Day 7	Post-curettage Day 14	Post-curettage Day 21
Subjective	Stomach pain Nausea decreased Few red spots from the vagina	Nausea decreased Few brownish spots from the vagina	A little nausea spots no longer come out of the vagina	Nausea sometimes spots no longer come out of the vagina
Ultrasound	-	Uterine size 77,7x36,4x41,2 mm Honeycomb appearance (-) Myometrium invasion (-) Lutein cyst (-) Residual tissue (-)	Uterine size 97,98x49,1 mm Honeycomb appearance (-) Myometrium invasion (-) Lutein cyst (-) Residual tissue (-)	Uterine size 93,4x52,5x78,2 mm Honeycomb appearance (-) Myometrium invasion (-) Lutein cyst (-) Residual tissue (-)

On day 1 post-curettage, the patient reported reduced abdominal pain and nausea, with minimal red vaginal spotting remaining. The β-hCG level was 28,364.00 mIU/mL. On day 7 post-curettage, the patient no longer experienced abdominal pain, though mild nausea persisted, and light brown vaginal spotting remained. The uterine size was 77.7 x 36.4 x 41.2 mm, and the β-hCG level was 33,275.00 mIU/mL. On day 14 post-curettage, mild nausea persisted, but no vaginal spotting was present. The uterine size was 97.98 x 49.1 mm, and the β-hCG level was 42,718.00 mIU/mL. On day 21 post-curettage, nausea occasionally recurred, but no vaginal spotting was noted. The uterine size was 93.4 x 52.5 x 78.2 mm, and the β-hCG level was 40,882.00 mIU/mL.

Table 2. β-hCG level Post Currettage



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DISCUSSION

Gestational trophoblastic neoplasia in patients who have experienced hydatidiform mole (HM) can be detected early by monitoring beta hCG levels. Treatment can be determined based on information obtained from anamnesis, clinical examination, serum beta hCG measurements, and Doppler ultrasound examination of the pelvis to confirm the absence of pregnancy, assess the size/volume of the uterus, and determine the spread of the disease within the pelvis and pelvic blood vessels.[15 19]

Metastasis in the lungs should be assessed using a chest X-ray and not a chest CT scan, as the staging classification criteria by the International Federation of Gynecology and Obstetrics (FIGO) use chest X-rays. If the chest X-ray reveals lesions, additional examinations, such as magnetic resonance imaging (MRI) of the brain and CT scans of the body, should be performed to detect widespread metastasis to other organs.[10 15 19]

Since 2002, the anatomical staging system and prognosis assessment system for gestational trophoblastic neoplasia have been based on the system of the International Federation of Gynecology and Obstetrics (FIGO). A score of 0-6 indicates a low risk of resistance, while a score of ≥7 indicates a high risk of resistance.[10 15 19]

Based on The International Federation of Gynecology and Obstetrics (FIGO), post-molar gestational trophoblastic neoplasia in this patient is classified as Stage I because the gestational trophoblastic neoplasia are strictly confined to the uterine corpus. According to the prognosis assessment by the World Health Organization (WHO), modified and adapted by FIGO, the patient is categorized as low risk with a prognosis score of 2, due to being under 40 years old, having a history of previous molar pregnancies, β-hCG levels before therapy <103, the largest tumor size including the uterus being <3 cm, no evidence of metastasis, and no history of chemotherapy failure.[12 16]

The indications for chemotherapy as defined by FIGO are an increase or plateau in β-hCG levels after evacuation, the presence of choriocarcinoma, metastasis to other organs, massive vaginal bleeding, gastrointestinal bleeding, or intraperitoneal hemorrhage.[12 17]

The standard therapy for almost all patients with low-risk gestational trophoblastic neoplasia is chemotherapy using a single-agent regimen, such as methotrexate alone, actinomycin D alone, or etoposide alone. High-intensity therapy (administered daily for 5-8 days every 2 weeks) is more beneficial compared to low-intensity therapy (administered once every 2 weeks). Some studies suggest that actinomycin D has a greater likelihood of inducing remission compared to methotrexate. Currently, a large-scale randomized clinical trial has been conducted to compare the commonly used methotrexate regimen in Europe and other gestational trophoblastic neoplasia management centers (methotrexate 0.4 mg/kg (maximum 25 mg) IV on days 1 to 5 every 2 weeks) with an etoposide regimen of 200 mg/m² per day orally for 5 days every 2 weeks. Meanwhile, the administration of actinomycin D for low-risk gestational trophoblastic neoplasia is 9-13 mcg/kg body weight per day intravenously, with a maximum dose of 500 mcg per day for 5 days every 2 weeks, or it can be administered as 1.25 mg/m² as an intravenous bolus every 2 weeks.[15 17]

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In another study, more than half of the patients with low risk and a FIGO/WHO score of 0-6 showed a complete response to first-line therapy using methotrexate/folinic acid (60%). Regimen kombinasi ini bersifat efektif, dapat ditoleransi dengan baik dan tidak menyebabkan kerontokan rambut (berbeda halnya dengan actinomycin-D). However, patients with a score of 6 or β-hCG levels >100,000 IU/l had a significantly higher resistance rate. Despite this, the survival rate for these patients remains very high, approximately ~100%. Therefore, chemotherapy should begin with the least toxic regimen first.[19 20]

In gestational trophoblastic neoplasia, both vaginal and intraperitoneal bleeding can occur. If the bleeding is moderate, it can usually be managed with bed rest and chemotherapy. However, if the bleeding is massive, therapies such as vaginal tamponade, hemostatic radiation, blood transfusion, anti-fibrinolytic agents, emergency embolization, or hysterectomy may be necessary. A total hysterectomy is indicated for massive bleeding or chemotherapy resistance in gestational trophoblastic neoplasia.[21 22]

β-hCG levels must be continuously monitored during chemotherapy. Chemotherapy should continue until β-hCG levels return to normal and remain so for 2-3 additional cycles. Once the patient achieves remission, β-hCG levels should be checked every 2 weeks until monitoring indicates that the levels remain within the normal range for 1 year. Some centers around the world continue to monitor β-hCG levels every 6 months for life in individuals at high risk. Individuals considered at high risk include women with very high resistance who require multiple chemotherapy combination regimens, women with advanced-stage choriocarcinoma, and women who experience recurrence later on. Follow-up for at least 5 years may be considered for patients with such very high risk.[19]

The regimen should be changed if the therapeutic response is inadequate (e.g., if β-hCG levels show no change (plateau) or even increase (rising) in two consecutive tests, or if toxicity occurs (such as mucositis, pleuritic chest pain, or abdominal pain).[10 15 19]

Resistance to first-line chemotherapy and recurrence of disease is more commonly found in high-risk gestational trophoblastic neoplasia without metastasis , occurring in approximately 5% of cases dan sekitar 10-15% dengan metastasis.[12 20]

In women with low-risk gestational trophoblastic neoplasia, if subsequent chemotherapy with a single agent fails, multi-agent chemotherapy should be administered to achieve remission; this approach is needed in about 6-15% of cases. The most commonly used multi-agent chemotherapy regimens are etoposide, methotrexate, actinomycin D (EMA) / cyclophosphamide, vincristine (CO). However, the New England Trophoblastic Disease Centre (NETDC, USA) prefers to try the MAC chemotherapy regimen (methotrexate, dactinomycin, cyclophosphamide) before administering the EMA/CO regimen, citing that etoposide is associated with an increased risk of secondary tumors. The choice of subsequent therapy depends on the patient's β-hCG levels. If the patient has β-hCG levels of 300 IU/l, EMA-CO can be given.[10 15 19]

In 250 patients with low-risk gestational trophoblastic neoplasia treated with EMA/CO (as second-line therapy after relapse or resistance to single-agent chemotherapy), the overall survival rate was 99.6%. Only 4 patients (1.5%) experienced resistance and/or relapse after EMA/CO.[10 15 19]

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Patients with gestational trophoblastic neoplasia (GTN) with metastasis to the liver showed a complete response in 82% of cases with the EMA/CO regimen, while only 17% of patients showed a complete response to the MAC regimen. For patients with GTN and brain metastasis, high-dose EMA/CO therapy is administered, which includes high-dose methotrexate (1 g/m²) combined with an extended duration of folinic acid rescue (FA). The EMA/CO chemotherapy regimen for the central nervous system is continued for 8 weeks after β-hCG levels return to normal. Intrathecal methotrexate is also administered at a dose of 12.5 mg, along with 15 mg of folinic acid during the CO therapy cycle, until β-hCG levels normalize, after which the treatment can be stopped. In patients with GTN and pulmonary metastasis, they often present with severe dyspnea or respiratory failure due to tumors in the pulmonary vasculature, requiring immediate treatment with high-dose oxygen via a mask. Ventilator support is not feasible for these patients due to the risk of traumatic hemorrhage from the tumor vasculature. [243 24 25]

CONCLUSION

Post-molar gestational trophoblastic neoplasia (PGTN) is a malignant uterine tumor closely associated with molar pregnancies.. Generally, a diagnosis of pGTN is made by monitoring β-hCG levels post-evacuation of the uterine molar tissue.

In cases of complete hydatidiform mole, β-hCG levels are monitored every week until normal levels are achieved for 3 consecutive weeks, in accordance with WHO criteria.

Chemotherapy is administered based on indications. The selection of chemotherapy regimens is determined by the FIGO score. Single-agent chemotherapy is recommended for low-risk post-molar gestational trophoblastic neoplasia, which generally has a good prognosis. Once β-hCG levels return to normal, chemotherapy for low-risk patients is continued with 2-3 additional cycles as consolidation therapy. After remission is achieved, β-hCG levels should be checked every 2 weeks until monitoring shows that β-hCG levels remain within the normal range for 1 year.

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