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Triplet Pregnancy with a Complete Hydatidiform Mole and Two Live Fetuses: A Case Report

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ABSTRACT

Background: *A complete hydatidiform mole (CHM) coexistent with a live fetus is rare; however, in a triplet pregnancy it is even rarer. In such cases, diagnosis is complex and often delayed, since unlike cases of a hydatidiform mole alone, the coexisting CHM often fails to bedetected at ultrasound, while B-hCG, a marker of the disease, is already elevated because of the multiple pregnancy. The risk of maternal complications and of progression to malignant gestational trophoblastic disease is significantly greater in cases of a complete mole.*

Case: *Thecase reported here refers to a triplet pregnancy consisting of two viable fetuses and a CHM.*

Conclusion: *Outcome was favorable for the two live fetuses; however, the hydatidiform moleprogressed to an invasive mole, requiring chemotherapy. Remission was achieved successfully.*

Keywords

Hydatidiform mole, Invasive hydatidiform mole, Triplet pregnancy.

Introduction

A complete hydatidiform mole (CHM) results from the fertilization of an egg with no active nucleus, meaning that all the genes are from the father (uniparental disomy) [1,2]. Overall, 90% of CHM have the 46, XX karyotype, while the remaining 10% have 46, XY. These chromosomal abnormalities lead to early miscarriage and excessive proliferation of trophoblastic cells [1,3,4]. A CHM associated with a live fetus is a rare event; however, in a triplet pregnancy it is even more unusual [1]. Risk factors for this type of pathology include advanced or early maternal age, late menarche, prior use of oral contraceptives, and a prior history of gestational trophoblastic disease [4,5].

Diagnosing a hydatidiform mole associated with a viable fetus is complex [3,4]. In up to 40% of cases, high-resolution ultrasound may fail to identify placental abnormalities indicative of a molar pregnancy, hence diagnosis is often made at later gestational ages compared to cases of a hydatidiform mole alone when characteristic ultrasound images of cystic trophoblast tissue, generally known as the classic snowflake-like pattern, are found [4,6].

The risks of maternal complications and of progression to malignant trophoblastic disease are significantly higher in cases of CHM [4,7]. The risk of malignization of a complete mole

co- existing with a normal fetus is 56-62%, while in cases of a partial mole with a viable fetus the risk is 4%. The birth of a viable neonate is rare, since the most common outcome is miscarriage or an extremely premature birth [3,4,7].

The present paper describes a triplet pregnancy consisting of two normal conceptuses and a complete hydatidiform mole. Outcome was favorable for the two live fetuses. The paper also discusses the patient's clinical condition during care, the progression to an invasive mole, and the particularities involved in the clinical management, diagnosis, treatment, follow-up and outcome of this rare association.

Case

A 29-year old primigravida with a multiple pregnancy was receiving prenatal care at a primary health clinic with no apparent complications. At 33 weeks of pregnancy, however, she was admitted to a maternity hospital complaining of pelvic pain and a watery vaginal discharge. Physical examination revealed that she was in the second stage of labor. She proceeded to deliver two live baby girls. The amniotic fluid was meconium-stained and foul-smelling. Delivery was uneventful and examination of the placenta confirmed a monochorionic diamniotic twin pregnancy (Figure 1A). After placental delivery, a large quantity of vesicular material was eliminated (Figure 1B). In the immediate postpartum, the patient developed abdominal pain and uterine atony, eliminating a large number of blood clots and vesicular material from the vagina. She was taken to the operating room for uterine evacuation. Material adhered to the cul-de-sac proved difficult to remove and the procedure was interrupted due to the possibility of myometrial invasion and perforation. Uterotonics (4 ampoules of intravenous oxytocin and 800 mcg of rectal misoprostol) and antifibrinolytics (tranexamic acid) were administered for uterine atony. Antimicrobial therapy was initiated for suspected chorioamnionitis while a full blood count revealed hemoglobin of 9.8 g/dl, hematocrit 29.1%, leucocytes 6,280/mm³ (with no left shift) and platelets of 98,000/mm³. The placenta and vesicular material were sent to anatomopathology.
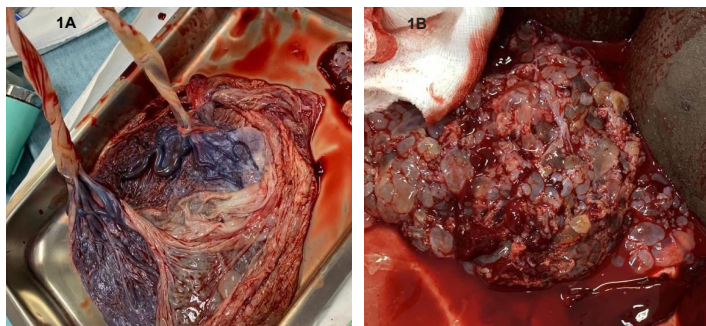

Figure 1 (A): Placenta from the monochorionic diamniotic twin pregnancy. **(B):** Vesicular material seen during delivery of the placenta.

The patient was transferred to the Gynecology Department of the Santa Casa de Misericórdia, a tertiary hospital in Vitoria, where greater clinical support was available and where she could be evaluated regarding the possible need for vacuum aspiration of the uterine contents. At admission, she was in a good general state of health and asymptomatic. B-hCG levels were 80,765.79 mIU/ml.

Vacuum aspiration of the uterine contents was performed, resulting in the elimination of a large quantity of amorphous material containing clots. This material was also sent for anatomopathology. The patient made a complete recovery following the procedure, with no complications. She was discharged from hospital and follow-up for gestational trophoblastic disease was scheduled, initially on a weekly basis.

Anatomopathology showed a monochorionic diamniotic twin placenta with foci of placental infarction (fibrinoid necrosis) and mild fibrin deposition (Figure 2). The placenta measured 13 x 11 x 5 cm and weighed 415 grams. The fetal surface of the placenta was covered with transparent amniotic membrane. Of the two umbilical cords, one measured 23 x 0.6 cm and the other 28 x 0.8 cm. When sectioned, each cord presented three vessels. Additionally, there were many fluid-filled vesicles, measuring 18 x 12 x 2 cm in total and compatible with gestational trophoblastic disease (hydatidiform mole).

Immunohistochemistry confirmed a complete hydatidiform mole. The full immunohistochemical profile is described in Table 1.

Table 1: Immunohistochemical profile of the trophoblastic material.

Target antigens	Expression
p53 protein (clone DO-7)	Positive
Chorionic gonadotropin beta-subunit (beta-hCG)	Positive
Placental alkaline phosphatase - PLAP (clone 8A9)	Positive
Cytokeratin 8/18 (clone EP17/30)	Positive
p57 KIP2 (clone KP10)	Negative
Cell proliferation antigen Ki-67 (clone MIB-11)	Positive (around 10% of the cells of interest)

B-hCG levels decreased slowly from 80,765.79 mIU/ml at the first measurement performed before aspiration to 2,857.58 on the 21st day of follow-up. Nevertheless, on the 28th day, levels were 3,401.00 mIU/ml, an increase of almost 16% compared to the preceding week. Levels continued to rise over the two subsequent weeks, with values of 4,338,31 and 4,830.07 mIU/ml, respectively. The clinical oncology team opted for in-patient chemotherapy with methotrexate and folinic acid rescue.

B-hCG levels fell to 2,165.69 mIU/ml on the 7th day after the first chemotherapy cycle and in the subsequent weeks to 321.22 and 317.54 mIU/ml (as confirmed in a repeat sample). Following the other scheduled cycles of chemotherapy, B-hCG continued to drop weekly until reaching measurements <5 mIU/ml.

Disease remission, defined as three consecutive B-hCG measurements <5 mIU/ml, was achieved around 12 weeks after
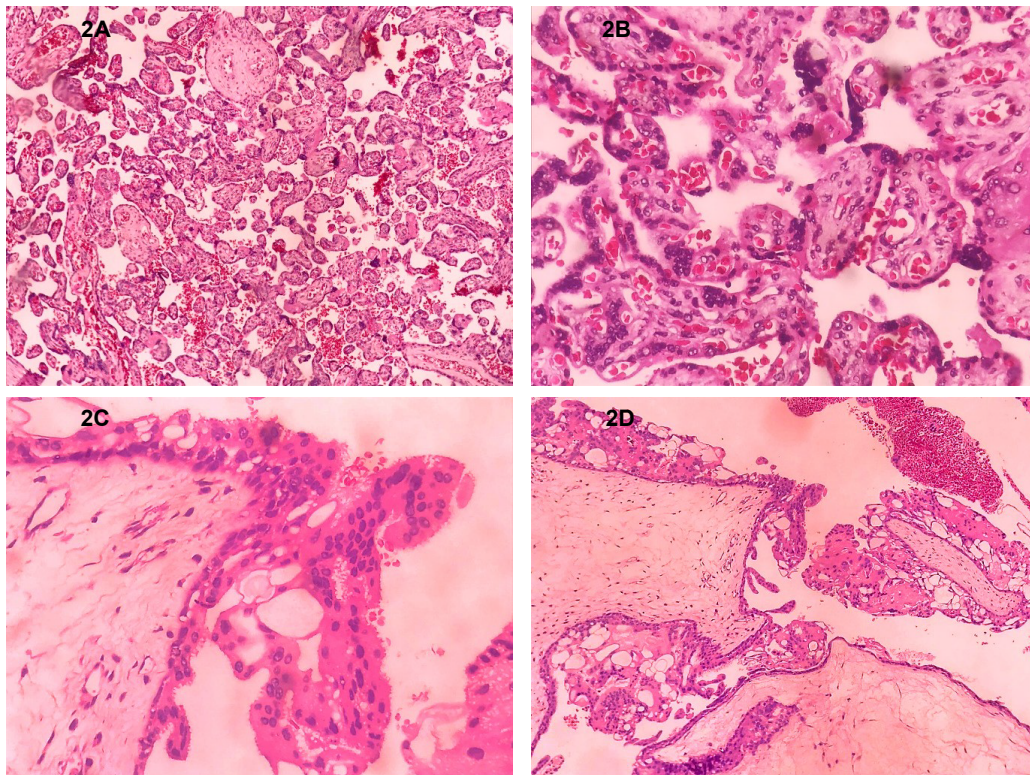
Figure 2 (A-D): Microscopic evaluation of the placenta and vesicular material (hematoxylin- eosin staining). Note the presence of chorionic villi of increased size and irregular contours, as well as the formation of vesicles. Edematous stroma, papillary and syncytial proliferation with hyperplasia of the cytotrophoblast and syncytiotrophoblast and architectural atypia.

chemotherapy. Two cycles of consolidation chemotherapy were then administered. In gestational trophoblastic disease, this refers to chemotherapy given after serum B-hCG levels have normalized (remission). No metastases were found on the chest, abdomen or head according to computed tomography performed following diagnosis.

Discussion

Multiple pregnancy with more than one normal fetus and a complete hydatidiform mole is a rare event, with the possibility of clinical complications and an increased risk of malignancy [4,7,8]. Diagnosis, often delayed due to laboratory and imaging limitations [6,9], may not be reached until delivery, as in the present case.

In general, gestational trophoblastic diseases are characterized by high serum B-hCG levels due to abnormal trophoblast proliferation [1]. This finding should raise suspicion regarding diagnosis, bearing in mind that only around 50% of molar pregnancies are detected at first trimester ultrasonography [1]. The classic ultrasound appearance is of multiple cysts/vesicles of varying sizes resulting from the extensive villous edema and is more commonly seen in second trimester scans [1,5]. The presence of one or more fetuses together with a molar pregnancy hampers diagnosis, both at ultrasonography (due to obstacles to visualization) and in laboratory tests (because of increased B-hCG levels resulting from the actual viable pregnancy) [1,2,5,7].

When not diagnosed during pregnancy, a postpartum finding of a placenta with molar degeneration associated with one or more live fetuses should trigger suspicion of a hydatidiform mole with a viable pregnancy. Anatomopathology, immunohistochemistry and karyotyping, whenever available, should be the next step as results will determine treatment and follow-up [5,9].

A multiple pregnancy with gestational trophoblastic disease was first suspected in the present case during delivery of the two infants when a substantial amount of vesicular material was seen. In addition, uterine volume was increased during delivery of the placenta. Diagnosis was confirmed by the persistently high B-hCG levels following delivery and from anatomopathology and immunohistochemistry of the placenta, umbilical cord and membranes. Outcome for the twin pregnancy was positive, with two live, apparently normal neonates.

No consensus has yet been reached on the ideal prenatal management for cases of a molar pregnancy associated with a multiple pregnancy. Some authors favor expectant management, with pregnancy interruption dependent on clinical complications associated with trophoblastic growth [2,8,9]. Hyperemesis, hyperthyroidism, preeclampsia, vaginal bleeding, theca lutein cysts and progression to invasive disease are the most common complications associated with CHM [1,2,6]. In this particular case, no maternal complications were reported during prenatal care or preceding delivery, which may also explain the late diagnosis.

Since B-hCG levels remained high following aspiration, increasing even further at a certain moment, the multidisciplinary team raised the possibility of invasive disease and chemotherapy was recommended.

An invasive mole is a malignant form of gestational trophoblastic disease and may develop after any pregnancy, normal or abnormal; however, 50% appear following a hydatidiform mole [10,11]. A complete mole is associated with a 20% risk of progression to an invasive mole compared to around 5% in cases of an incomplete mole [2,6]. The incidence of invasive moles in Europe and the United States is low [10,12]; however, data on the epidemiology of the condition in Brazil are sparse.

Since an invasive mole may present in different ways, diagnosis is even more difficult when it is not preceded by a hydatidiform mole. Classically, uterine volume is increased, vaginal bleeding continues and B-hCG levels fail to decrease satisfactorily [1,10,12]. Signs suggestive of metastasis include intra-abdominal bleeding, cough, hemoptysis, pleuritic chest pain, dyspnea and respiratory failure when the lungs are affected, and gastrointestinal symptoms such as hematemesis and melena, as well as vaginal lesions and signs of brain involvement [1,10,12]. Although symptomless, this patient was screened strictly according to the established protocol. No secondary implants were found, with the neoplasm being confined to the organ of origin, hence stage I according to the FIGO staging system [13].

Treatment ranges from uterine evacuation to hysterectomy and chemotherapy [10,12]. The rate of cure or disease remission with chemotherapy can be as high as 100% except when prognosis is poor due to the patient's clinical characteristics or advanced disease. Studies show that in cured patients the long-term risk of maternal or fetal complications in subsequent pregnancies is no higher than in the general population [10,12].

The chemotherapy regimens used are those recommended by FIGO, based on a score calculated from risk factors for malignant gestational trophoblastic disease in accordance with the patient's clinical history and exam results. The sum of these factors determines the optimal regimen: monotherapy (methotrexate and folinic acid rescue) for low-risk cases or polytherapy (etoposide + methotrexate + actinomycin D - cyclophosphamide + vincristine) for high-risk cases.[13] Since this patient was under 39 years of age, primigravida, with B-hCG levels between 100,000 and 1,000,000 at diagnosis, and since the disease was confined to the organ of origin, her risk score was low.

Single-agent chemotherapy with methotrexate and folinic acid rescue was given over a total of six cycles (4 rescue cycles and 2 consolidation cycles). The regimen of choice adopted by international institutes involved in the research and treatment of gestational trophoblastic diseases consists of 0.3-0.5 mg/kg of methotrexate (intramuscularly or intravenously) for five consecutive days every two weeks [14]. Here, this regimen resulted in good clinical response, meeting the laboratory criteria for remission 12 weeks after the beginning of chemotherapy. In addition, after B-hCG measurements return to normal, another 2-3 cycles of consolidation chemotherapy are recommended to prevent recurrences [5,15].

Monitoring such cases is complex and requires technical skills from the attending team. The patient and her family must be aware of the importance of complying with the proposed treatment, understand the need for the interventions recommended and comply with the outpatient follow-up.

The role of contraception following diagnosis is important, since a further pregnancy will affect

B-hCG levels, the tumor marker of gestational trophoblastic diseases [2,12]. Patients should be monitored clinically, with weekly B-hCG measurements until levels are normal for three consecutive weeks (considered a sign of complete remission) after which levels should be measured monthly for a year [10,12]. The risk of recurrence is greater in the first year after diagnosis; nonetheless, it is believed to be below 3% [12].

This case report provides valid data on the progression of a triplet pregnancy consisting of a complete hydatidiform mole and two live fetuses. In view of the late, unexpected diagnosis and because of its progression to one of the complications of this pathology, an invasive mole, we consider this case a clinical challenge.

Acknowledgments

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