

## The Rare Association of Ectopic Pregnancy and Hydatidiform Mole: A Case Report

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### ABSTRACT

*An ectopic molar pregnancy is a rare event, occurring in 1 in every 20,000–100,000 pregnancies. The condition may present as a complete or partial molar pregnancy and the ectopic site can vary as in a non-molar ectopic pregnancy. When a molar pregnancy presents as a tubal ectopic pregnancy, the risks related to both conditions, including tubal rupture and progress to malignancy, are compounded. The definitive diagnosis is normally reached by histopathology of the surgical specimen, since imaging tests are usually unable to differentiate between a molar and a non-molar ectopic pregnancy. While the specific histological findings may confirm the diagnosis of hydatidiform mole, immunohistochemistry is essential to differentiate between a complete and a partial molar pregnancy. Although in the majority of cases surgical resection is considered the definitive treatment, it is estimated that 20% of patients with a molar pregnancy may develop gestational trophoblastic neoplasia, hence requiring a risk-specific follow-up. This report describes a case of a tubal molar pregnancy and includes a review of clinical, diagnostic and therapeutic aspects, as well as a discussion on the particularities of this rare association.*

### Keywords

Ectopic pregnancy, Gestational trophoblastic disease, Hydatidiform mole.

### Introduction

Between 6% and 16% of all pregnancies are ectopic [1]. In Brazil, molar pregnancies account for 1 in every 200-400 pregnancies, with this rate being up to ten times higher than those reported in the United States and in European countries [2]. An ectopic molar pregnancy is considered a rare event, with an estimated incidence of 1 in 20,000 to 100,000 pregnancies [2].

A molar pregnancy may present as complete (androgenetic diploidy) or partial (diandric triploidy). The type of presentation affects cell behavior and the potential to progress to gestational

trophoblastic neoplasia [2]. Some risk factors are associated with the development of a molar pregnancy, including a prior personal history of molar pregnancy, a diet lacking in vitamin A and animal fat, maternal age < 20 or > 40 years, recurrent miscarriages, and blood groups A and AB [3]. In the case of ectopic pregnancy, known risk factors include pelvic inflammatory disease, a history of tubal surgery, and pregnancies achieved using assisted reproduction technology [3].

The definitive diagnosis of an ectopic molar pregnancy depends largely on histopathology; however, histological differentiation with two other clinical conditions, non-molar hydropic abortion and early placental maturation, can be difficult [4]. Immunohistochemical evaluation, particularly with respect to the cyclin-dependent kinase inhibitor P57<sup>KIP2</sup> (clone KP10), helps

differentiate between a complete molar pregnancy, a partial molar pregnancy and non-molar conditions [2,5,6].

An ectopic molar pregnancy is usually resolved surgically; however, subsequent chemotherapy may be required depending on the clinical presentation and histological/molecular type [2,3]. Rigorous monitoring is recommended due to the possibility of progression to gestational trophoblastic neoplasia, although this risk is much lower compared to cases of gestational trophoblastic disease in the uterus [4,6].

The objective of this article is to describe a rare case of molar tubal ectopic pregnancy, including a review of the clinical and diagnostic features and treatment, focusing on the particularities of this unusual association.

### Case Report

The patient was a 37-year old woman in her second pregnancy, who had had a previous natural birth and no miscarriages or abortions. She complained of mild cramping/abdominal pain and vaginal bleeding over the preceding week. Ultrasonography performed at admission to hospital showed an adnexal mass on the right side measuring 29 x 55 mm, containing a yolk sac suggestive of an ectopic tubal pregnancy. Qualitative beta-hCG measurement was >10,000 mIU/ml. Physical examination revealed no sign of hemodynamic instability and no abdominal pain on palpation. Bleeding at speculum examination was slight. The patient complained of pain in the region of the pouch of Douglas during vaginal examination but there was no sign of bulging. Culdocentesis was negative.

Laboratory tests performed at admission revealed: hemoglobin of 11.0 g/dl, hematocrit 32.8%, leukocytes 7,340/mm<sup>3</sup> (with no left shift), platelets 189,000/mm<sup>3</sup>, and prothrombin activity 73%. Quantitative beta-hCG measurement was 32,610.76 mIU/ml at admission, reaching 36,883.05 mIU/ml on the second day of hospitalization and 42,384.71 on the fourth day. In view of the increasingly elevated beta-hCG levels, exploratory laparotomy

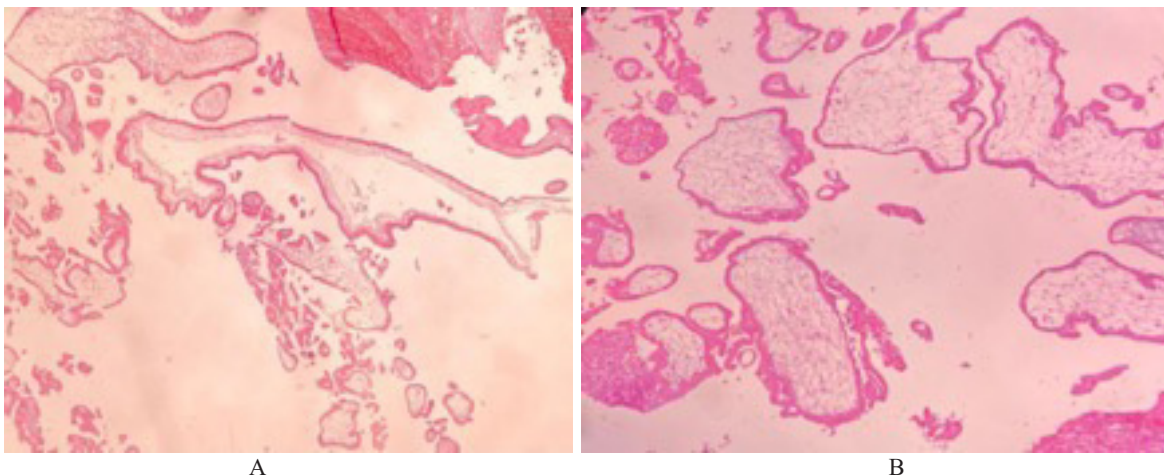
was performed, revealing an ectopic pregnancy in the right fallopian tube, measuring around 5.0 x 4.0 cm. The fallopian tube was unruptured and there was no blood in the abdominal cavity. Right salpingectomy was performed, while preserving the ovaries on both sides as well as the left fallopian tube. The material removed was sent for histopathological evaluation. The patient made good progress following surgery, with no complications. She was discharged the following day and instructed to return for postoperative follow-up.

The histopathological findings confirmed the presence of an ectopic pregnancy. The features described included fibroelastic tissue with chorionic villi, some of which were large and edematous, some with central cistern formation, with varying degrees of trophoblastic proliferation, in general mild and focal (Figure 1). Immunohistochemistry was performed to complete the evaluation in an attempt to define the precise diagnosis, aiming to differentiate hydropic trophoblastic tissue from gestational trophoblastic disease. P57<sup>KIP2</sup> (clone KP10) immunostaining was positive, revealing first trimester hydropic abortion with mild trophoblastic proliferation, corresponding to a partial hydatidiform mole.

The patient was referred for monitoring to a specialist center in gestational trophoblastic disease at the Santa Casa de Misericórdia in Vitória.

### Discussion

An ectopic pregnancy is the result of the implantation of a fertilized egg outside the uterine cavity, while a hydatidiform mole is the consequence of a chromosomal abnormality that occurs during gametogenesis and fertilization [7]. The chromosomal profile of a complete molar pregnancy is 46, XX and originates in the paternal genome. It occurs due to the fertilization of an oocyte with no active nucleus by a haploid spermatozoid that then undergoes processes of cell division. Partial molar pregnancies, on the other hand, generally result from the dispermic fertilization of a haploid oocyte, resulting in a triploid genome (46, XXY) [8].



**Figure 1:** Histological section (right fallopian tube): hyperplastic trophoblastic proliferation and cystic, avascular and hydropic villi.

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A major epidemiological study conducted in Brazil estimated the rate of progression from a molar pregnancy to gestational trophoblastic neoplasia at around 24.6% for patients with a complete molar pregnancy and 7.6% for patients with a partial molar pregnancy [2]. Therefore, identifying these categories will directly impact on the specialist care required when monitoring patients with a complete molar pregnancy.

The rare association of an ectopic pregnancy with a molar pregnancy combines the risks associated with both, including intra-abdominal rupture and progression to malignancy. Nevertheless, the differential diagnosis in cases of an ectopic molar pregnancy is difficult from a clinical viewpoint, since clinically, it resembles a non-molar ectopic pregnancy, usually presenting with abdominal pain and vaginal bleeding [7,9].

Imaging tests are crucial in defining the ectopic site of the gestational sac; nonetheless, they may not yield a definitive diagnosis. Although the snowstorm sign on ultrasound is a finding that is strongly characteristic of a molar pregnancy, this feature is not always seen; therefore, this sign consists of a very objective and largely non-specific element [9].

Serum beta-hCG levels tend to be high in cases of intrauterine molar pregnancy due to the disorganized proliferation of trophoblastic tissue [10]. In contrast, in cases of tubal molar pregnancy, the lack of adequate vascularization in the fallopian tube hampers the availability of the substrates required for the trophoblast to develop. As a consequence, beta-hCG serum levels are not as high as predicted in cases of intrauterine molar pregnancy [11]. Therefore, major differences in beta-hCG levels between molar and non-molar ectopic pregnancies should not be expected, making it even more difficult to distinguish them clinically.

One peculiarity of a molar ectopic pregnancy in relation to a non-molar ectopic pregnancy is that tubal rupture tends to occur earlier in the former compared to the latter due to a greater tendency of invasion and proliferation of the molar trophoblast tissue in relation to the trophoblast of a normal pregnancy [12].

The major diagnostic tool is histopathology. Since this exam can only be performed following surgical removal of the ectopic mass, an ectopic molar pregnancy tends to be suspected and diagnosed at a late stage and the condition is often managed as a conventional ectopic pregnancy until the histopathological results are available, which will make a significant difference in the patient's clinical follow-up.

The histological features of an ectopic molar pregnancy are: circumferential proliferation of the trophoblast associated with hydropic changes in some or all of the chorionic villi and karyorrhexis [8,9,13]. Although strongly suggestive, this analysis can be confused with some other conditions such as early placental maturation (presence of circumferential trophoblastic proliferation, albeit with mild hydropic changes or none at all)

and hydropic abortion (mild to moderate hydropic changes in the villi, with no circumferential trophoblastic proliferation) [13]. Therefore, interpretation is highly dependent on the quality of the slide preparation and the skill of the evaluator.

When differentiating between a complete and a partial molar pregnancy, immunohistochemistry is one of the tools used. Absence of the P57<sup>kip2</sup> protein (clone KP10) at molecular examination is suggestive of a complete molar pregnancy, while positivity for this protein is suggestive of a partial molar pregnancy [13].

Notwithstanding, immunohistochemistry is only effective for differentiating between the diploid and triploid forms of molar pregnancy in the cases in which molar pregnancy has been confirmed histologically, since molecular analysis is unable to distinguish a complete molar pregnancy from hydropic abortion [11]. On the other hand, whenever histological diagnosis proves difficult, flow cytometry techniques for evaluating DNA can be used to classify the type of molar pregnancy [7,9]. Therefore, the combination of some or all of these steps is believed to be vital in order to reach a final diagnosis of an ectopic molar pregnancy.

Regarding treatment, there is a consensus that complete surgical removal of the entire ectopic molar pregnancy is necessary. When available, laparoscopy is the preferred surgical technique.

The risk of malignancy following an ectopic molar pregnancy is considered rare (1:5,033) [11]; however, in general, molar pregnancies progress to the malignant gestational trophoblastic disease in around 20% of cases, even after appropriate surgical treatment [9]. For this reason, monitoring of these patients is crucial and should consist of periodic follow-up with measurement of serum beta-hCG until levels return to normal, chest x-ray, and use of effective contraception for at least one year after the event [7,9].

Although few cases of ectopic molar pregnancy progressing to gestational trophoblastic neoplasia have been reported, prognosis is believed to be better than in cases of intrauterine molar pregnancies. In a large proportion of cases, treatment for ectopic molar pregnancy is surgical, with little chance of preserving the fallopian tube if the ectopic molar tissue is completely excised [11,13]. In the few cases described in the literature of gestational trophoblastic neoplasia in ectopic pregnancies following salpingectomy, complete remission was achieved after treatment with methotrexate or the second-line treatment: etoposide, methotrexate, actinomycin D, cyclophosphamide and vincristine (EMA/CO) [13].

## Conclusion

The association of an ectopic pregnancy with a molar pregnancy is a rare event. Diagnosis tends to be made at a late stage, generally following surgery, with the great majority of cases being managed as a conventional ectopic pregnancy due to the absence of highly differentiating clinical characteristics. The association between

these two conditions emphasizes the importance of performing routine histology on surgical specimens, since the follow-up required for a patient with an ectopic molar pregnancy is very different from that required in cases of a non-molar ectopic pregnancy, particularly in view of the risk of malignancy associated with molar tissue, demanding specific monitoring. Positive outcomes in cases of ectopic molar pregnancy are believed to be associated with complete removal of the ectopic molar tissue by salpingectomy, whereas in cases of non-ectopic intrauterine molar pregnancies, uterine evacuation is performed, and residues may be left, increasing the potential for recurrence.

### Ethics

The present report was submitted to the internal review board of the *Escola Superior de Ciências of the Santa Casa de Misericórdia de Vitória (EMESCAM)* and approved under reference number 5.370.382 (CAAE: 56328622.4.0000.5065). Written informed consent for publication was obtained from the patient.

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