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Partial Hydatidiform Mole Complicated by Multinodular Goiter: A Case from Bulgaria

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Abstract

Partial mole occurs when an egg is fertilized by two spermatozoids or by one spermatozoid which reduplicates itself yielding most commonly triploid genotype of 69,XXY. We present a case of a partial hydatidiform mole associated with multinodular goiter. The patient is a 27-year-old primigravida who presented for termination of non-viable pregnancy at 11 weeks gestation. Her ultrasound examination showed lack of growth and presence of degenerative changes. Thyroid gland ultrasound scan revealed multinodular goiter. Flow cytometry analysis showed triploid pick index of 1.46 which confirmed the triploid karyotype (69, XXY) detected by genetic studies. Partial hydatidiform mole could be a risk factor for the occurrence of nodular goiter and even hyperthyroidism as the underlying hormonal imbalance triggers pathogenetic mechanisms of the thyroid dysfunction**.**

Keywords: partial hydatidiform mole; nodular goiter; triploidy.

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1. Introduction

Hydatidiform mole is a form of gestational trophoblastic disease which affects the ovum and the developing trophoblast. The importance of correct diagnosis stems from its association with an increased risk of persistent trophoblastic disease (invasive mole) or choriocarcinoma. The incidence varies considerably in different regions of the world. Two types of moles—complete and partial—can be identified by cytogenetic and histologic studies. Majority of complete moles result from fertilization of an ovum that has lost its chromosomes, and the genetic material is completely paternally derived. Most complete moles have a 46,XX diploid complement derived from duplication of the genetic material of one sperm (a phenomenon called androgenesis). The embryo usually dies very early in development. Patients have 2.5% risk of subsequent choriocarcinoma. Partial mole occurs when an ovum is fertilized by two sperms or by one sperm which reduplicates itself resulting most commonly in triploid genotype of 69,XXY. Fetal/embryonic tissue and/or embryonic red blood cells are usually identified on histologic examination and the risk of choriocarcinoma is considerably less compared to complete mole.

2. Case report

We present a case of partial hydatidiform mole with triploidy 69 XXY associated with multinodular goiter. The patient is a healthy-appearing 27-year-old primigravida who presented for termination of non-viable pregnancy at 11 weeks gestation.

On early prenatal ultrasound examination an yolk sac and gestational sac were visualized and fetal heart rate was detected. Subsequent scan revealed a lack of growth, no fetal heart activity and presence of degenerative changes.

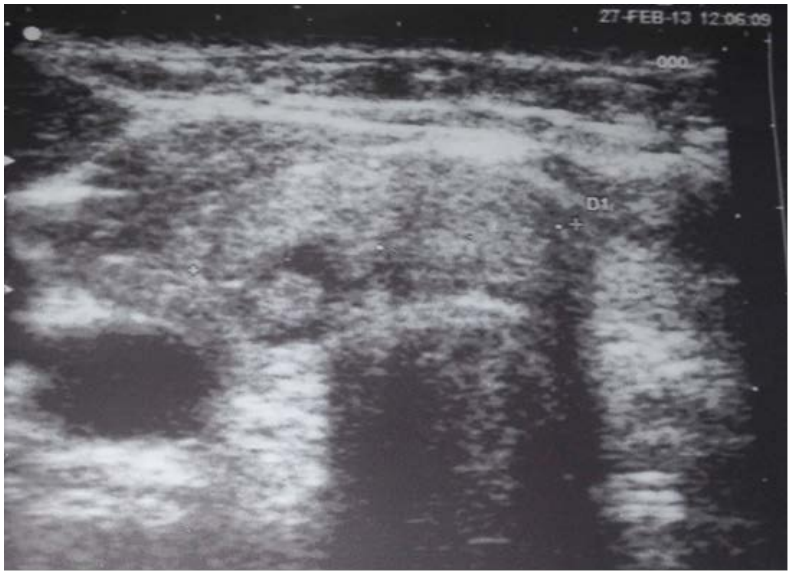

Figure 1: Ultrasound of thyroid gland. Multinodular goiter.

At the same time a prophylactic ultrasound scan of the thyroid gland revealed multinodular goiter with no

palpable lesions on physical examination. (Figure 1)

Biochemical analysis showed a TSH of 1,23 mIU/L (0.4 - 4.0) and a β- hCG of 1832 mIU/mL corresponding to 5 weeks gestational age.

Patient reported using topical Retinoic acid solutio - Locacid lot. 0,1%, 1mg/1ml for several months prior to and during pregnancy.

Family history is significant for maternal great-grandmother with recurrent miscarriages and a history of congenital anomalies of paternal siblings, including a Down syndrome.

Following appropriate consent, pathology examination of miscarriage material was performed with subsequent genetic and immunohistochemical analysis on placental tissue.

Macroscopic pathology examination of the products of conception revealed multiple 1 to 2 mm in diameter translucent vesicles. (Figure 2).

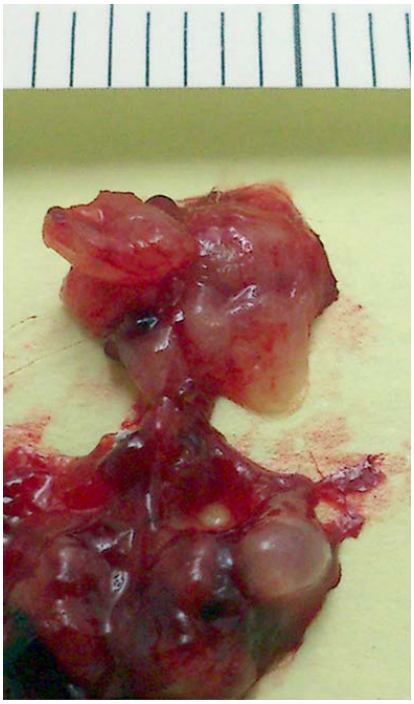

Figure 2: Uterine contents after curettage showing multiple 1-2 mm translucent vesicles.

Microscopic examination revealed the presence of two populations of chorionic villi, one of which showed enlarged hydropic villi with irregualr contour and trophoblastic pseudoinclusions. Embryonic red blood cells were noted within villous capillaries which is an evidence of embryonic development. (Figure 3)

Immunohistochemistry analysis with antibodies to p57,kip2, a cyclin-dependent kinase inhibitor 1C, showed positive expression of villous cytotrophoblast, villous stromal cells, and extravillous trophoblast.

Flow cytometry analysis performed on paraffin embedded villous tissue showed triploid pick of 1.46 for 91.31% of the cells, which confirmed the triploid karyotype (69, XXY) detected by genetic studies.

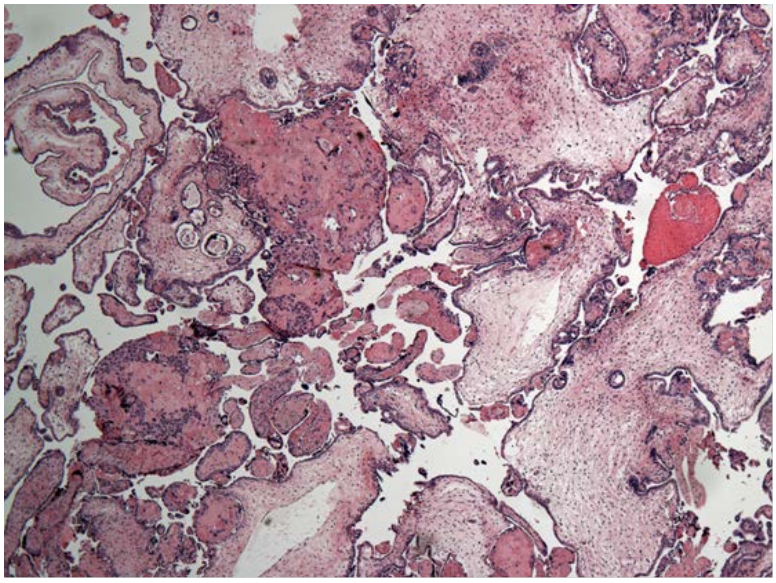

Figure 3: Photomicrograph of histology section showing a hydropic chorionic villus with irregular contours and trophoblast pseudoinclusions. H&E 10X magnification.

3. Discussion

3.1. Differential diagnosis

Complete hydatidiform mole - in 90% of cases, the zygote is the result of fusion of the ovum with a single sperm cell and only in 10% - with two sperms.

Unlike partial mole, genetic analysis shows diploid set of chromosomes – 46XY or 46XX. Histologically, the chorionic villi are large, distended with cistern formation and exuberant circumferential proliferation of the villous trophoblast. Immunohistochemical analysis with kip 2 p 57 antibody shows lack of expression of the villous cytotrophoblast and villous stromal cells. There is a 2-3% risk of complete moles developing into choriocarcinoma, and approximately 20% developing into invasive mole. Risk of choriocarcinoma arising from partial mole is negligible. Therefore, it is imperative to rule-out complete hydatidiform mole.

Choriocarcinoma. Gestational choriocarcinoma is an epithelial malignant neoplasm of trophoblastic cells derived from any form of previously normal or abnormal pregnancy. Choriocarcinoma is a rapidly invasive, widely metastasizing malignant neoplasm, but once it is identified, it responds well to chemotherapy.

Placental site trophoblastic tumor (PSTT) is a tumor arising from the intermediate trophoblast. PSTTs comprise less than 2% of gestational trophoblastic neoplasms and present as neoplastic polygonal cells infiltrating the endomyometrium of the uterus. Overall, about 10% result in disseminated metastases and death. Distinction of PSTTs from normal exaggerated placental implantation site trophoblast may be difficult and can be achieved by

using biomarkers (Mel-Cam and Ki-67) that detect increased proliferation in the trophoblastic cells.

The histopathologic findings in this case are highly suspicious for a partial hydatidiform mole. Immunohistochemical analysis revealed normal expression of p57, Kip2 of the villous cytotrohoblast, villous stromal cells and extravillous trophoblast. This pattern of staining practically excludes complete mole, which is an important differential diagnostic consideration due to its association with increased risk for choriocarcinoma. Complete moles show negative staining for p57, Kip2 of the villous cytotrohoblast and villous stromal cells. Flow cytometry results revealed triploid genetic complement of the villous tissue analyzed, which is in agreement with the genetic results and supports the diagnosis of a partial hydatidiform mole since most partial moles are triploid. Complete moles, on the other hand, are diploid with all the genetic material derived paternally. The final diagnosis is partial hydatidiform mole.

3.2. Endocrine aspects

There are reasons to believe that hyperthyroidism is due to cross-reactivity of the TSH receptor and molecular mimicry between human chorionic gonadotropin (HCG) and thyroid stimulating hormone (TSH) [1]. Human chorionic gonadotropin is a glycoprotein composed of α and β subunits, in which the α subunit is almost identical to that of TSH [2]. Thyroid stimulation is proportional to the concentration of HCG and depends on the deglycosylation, and/or desialylation in the metabolism of HCG and can lead to increased thyrotropic effects [3]. Cross-reactivity between the two hormones has also been confirmed by in vitro experiments [4].

The patient in our case had a multinodular goiter without increased TSH associated with a partial hydatidiform mole. The combination of these findings is highly suggestive of cross-reactivity between the two hormones.

3.3. Genetic aspects

We identified the genotype of our case as triploid (69 XXY), which proves the paternal origin of the extra haplotype, a phenomenon known as diandric triploidy. Duplication of the haploid chromosomal set in the sperm may be the result of an error in meiosis [5].

Triploidy is a type of aneuploidy, which on the other hand is the most common cause of miscarriage in the first trimester of pregnancy [6]. It should be noted that partial hydatidiform mole is not synonymous with triploidy syndrome. Triploidy refers to a complete extra set of haploid chromosomes derived from the mother (digynic) or the father (diandric). When the triploid is diandric, the placenta is enlarged and the histology is consistent with a partial hydatidiform mole. The fetus is mildly growth restricted. By comparison, a digynic triploid is associated with severe fetal growth restriction, relative macrocephaly, and a small, noncystic placenta.

Advanced maternal age appears to be a risk factor for non-disjunction of the maternal meiotic division [7]. Extremes of maternal reproductive age, younger than 16 years and older than 50 years, is associated with significantly increased risk for molar gestation. Potential risk factors for the development of partial hydatidiform mole could be related to nutritional deficiencies and toxic effects of diets low in protein, folic acid, and carotene [8]. Recent research confirms the pulse effects of retinoic acid on meiosis and differentiation of sperms. The

clinical history of the presented case reveals evidence of retinoic acid use; however the significance of that exposure is difficult to interpret.

4. Conclusion

Partial hydatidiform mole could be a risk factor for the occurrence of nodular goiter and even hyperthyroidism as the underlying hormonal imbalance triggers pathogenetic mechanisms of the thyroid dysfunction**.** Therefore, the importance of follow-up and close monitoring of TSH and thyroid hormones for planning and managing affected pregnancies cannot be overstated.

On the other hand, the current advanced methods for diagnosis of triploidy and hydatidiform mole, including histopathologic, genetic and immunohistochemical analysis, should become routine practice for better patient care.

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