Review Article

HISTOLOGICAL ASPECTS OF THE CHORIONIC VILLI AND THE ROLE OF IMMUNOHISTOCHEMISTRY MARKERS IN THE DIFFERNTIAL DIAGNOSIS OF HYDATIFORM MOLE

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Abstract

The hydatiform mole is a gestational trophoblastic disease caused by abnormal gametogenesis and fertilization. The incidence is rare in our country. It seems to be encourage by poor nutrition in beta carotene, consanguinity, to early or to old maternal age, abortion history, endocrine problems, dysfunctions of genital organs, genital disorders. It is frequent between the 11th and 25th week of pregnancy.

The aim of this study is to show the histological changes of the chorionic villi in hydatiform mole and the role of immunohistochemistry markers used for the differential diagnosis of it.

Keywords: *hydatiform mole, trophoblastic disease, chorionic villi, placenta;*

Rezumat

Mola hidatiforma este o afecţiune trofoblastică gestaţională, cauzată de o gametogeneză şi fertilizare anormală. Incidența molei hidatiforme este rară la noi în țară. Factori favorizanți: antecedente de sarcina molară, vârsta prea tânără sau prea în vârstă a mamei (>30 ani, <20 ani), antecedente de avort spontan, dieta săracă în beta caroten, consanguinitatea, disfuncţii endocrine, disfuncţii ale organelor genitale, afecţiuni genitale. Mola hidatiforma este frecventă în special între a 9-a şi a 25-a săptămână de sarcină.

Scopul acestui studiu este de a prezenta modificările histologice ale vilozităților coriale afectate de mola hidatiforma şi rolul markerilor imunohistochimici folosiți pentru diagnosticul diferențial al acesteia de alte afecţiuni.

Cuvinte cheie: *mola hidatiforma, boala trofoblastică, vilozități coriale, placenta, sarcina.*

Introduction

The hydatiform mole is a gestational trophoblastic disease caused by abnormal gametogenesis and fertilization with an abnormal placentation.

It may be partial or complete and almost always occur in the reproductive age group, although rare cases have occurred in postmenopausal women. Many studies have shown that increased maternal age correlates with an increased incidence of hydatiform mole. The relative risk clearly becomes greater after age 40 and much greater after age 45. Conversely, there appears to be a somewhat greater risk for molar pregnancy in women under age 20 in some studies.

In general, the incidence of hydatiform mole is more frequently in parts of Asia, Latin America and the Middle East than it does in North America or Europe. In Europe and the United States it occurs in 1:2000 deliveries, whereas in Singapore, Japan or Malaysia the incidence is 1 in 500 to 800 pregnancies.

The hydatiform mole seems to be encouraged by personal or family history of gestational trophoblastic disease, poor nutrition in beta carotene, consanguinity, increased maternal age, two or more previous spontaneous abortions, endocrine problems, dysfunctions of genital organs, genital disorders, infertility, smoking.

The aim of this study is to show the histological changes of the chorionic villi in hydatiform mole and the role of the immunohistochemistry markers in the differential diagnosis of it.

Material and methods

For this clinical-morphological study, we used a retrospective lot of 634 cases which was analyzed at The University Emergency Hospital, Bucharest between January 2008 and December 2010.

The biological fragments used by us were represented by the fragments of placenta from the Obstetrics-Gynecology and Pathology Departments of The University Emergency Hospital Bucharest.

First, the placental fragments were macroscopic examined and after that, they were fixed in formaldehyde 10%, embedded in paraffin, cut and stained with Hematoxylin-Eosin.

Although, in general, the diagnosis of hydatiform mole is established microscopically sometimes, the immunohistochemistry markers are necessary too, for the differential diagnosis.

In our study, we used: p57, Ki67, CD34, p53, inhibin, hCG.

p57 Protein is a marker used in the gestational disease with proliferative disorders of the placental trophoblast too. It used for the nuclear proliferation. The reaction location: nucleus of cytotrophoblast and villous stromal cells.

Ki67Antigen is used to identify the proliferative rate of cell growth in normal and neoplastic tissues. Reaction location: nucleus and perinucleus of cytotrophoblast.

CD34 is used for identification of vascular and lymphatic vessels. Reaction location: membrane. The endothelial cells of all vessels should show a distinct predominantly membranous reaction. Especially, the endothelial cells of the small submucosal vessels should be demonstrated.

p53 Protein is a monoclonal antibody which recognizes both wild type and mutant forms of human p53 protein under denaturing and non denaturing conditions. It used for the nuclear proliferation. The reaction location: nucleus. The majority of the neoplastic cells should show a moderate to strong distinct nuclear staining reaction.

Inhibin is used for identification of complete hydatiforme mole, especially the extravillous trophoblast. Reaction location is cytoplasm. The trophoblast and syncytiotrophoblasts should show a moderate to strong heterogeneous and granular cytoplasmic staining reaction.

hCG: human chorionic gonadotrophin is a glycoprotein hormone produced by trophoblastic cells of the placenta beginning 10 to 12 days after conception. Reaction location: cytoplasms of syncytiotrophoblast.

Results and discussion

In our study, from all 634 cases analyzed between 2008 to 2010, we found only 19 cases of hydatiform mole: 6 cases in 2008, 10 cases in 2009 and 3 cases in 2010. So, we noticed that the incidence of hydatiforme mole is rare in our country (Table no.1)

Table no. 1: Cases in study

Year	Nr Hydatiform mole	Nr total cases
2008	6	245
2009	10	207
2010	3	182
Total	19	634

Also, we noticed from all 19 cases of hydatiform mole the most common histological type was the complete hydatiforme mole (13 cases), the rest of them were partial hydatiforme mole (only 6 cases) (table 2, *figure* 1).

Table no 2: Aspects of mole of patients

Year	Hydatiforme Mole	Complete Mole	Partial Mole
2008	6	4	2
2009	10	7	3
2010	3	2	1

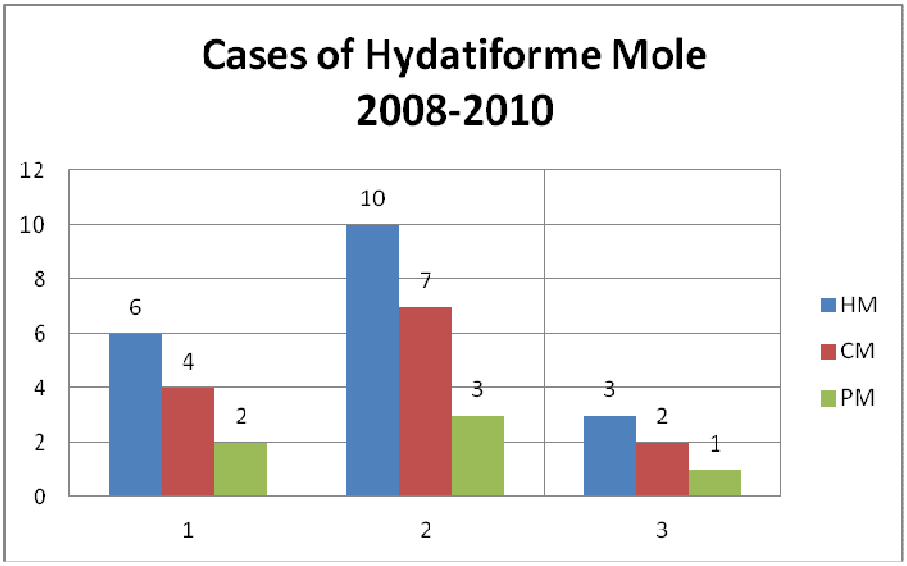

Figure 1: cases representation graphic.

In our study, the hydatiforme mole was frequent between the 11th and 25th week of pregnancy.

There are some distinct features between complete and partial hydatiforme mole both macroscopically and microscopically.

Macroscopically, the placenta with complete hydatiforme mole is bulky with edema and numerous evident transparent vesicles as a “bunch of grapes”, 1-20 mm in diameter, without any fetal tissue.

The placental fragments with partial hydatiforme mole are less than that found in complete mole and are form both large hydropic villi like those seen in

complete mole and nonmolar, normal–appearing immature placental tissue sometimes, a gestational sac or evidence of an embryo or fetus may be present.

In our study we found placental fragments with these features:

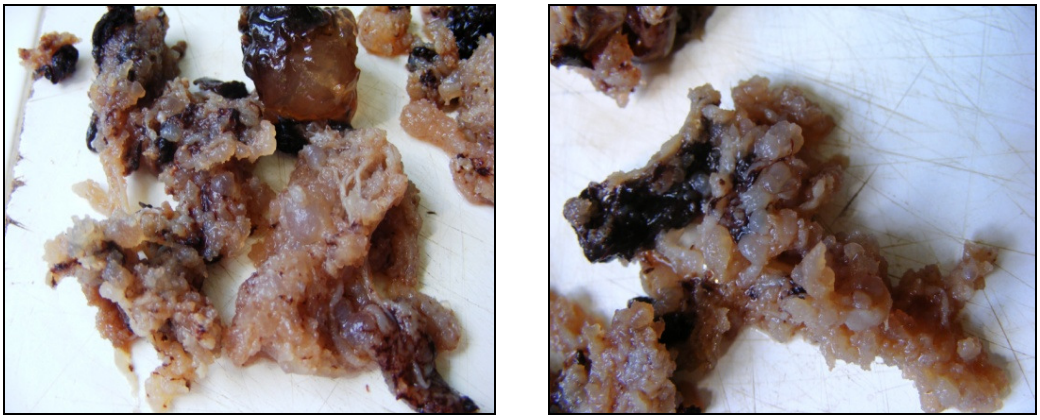

Figure 2: Gross – complete mole

Figure 3: Gross-partial mole

Microscopically, we noticed the different features between complete and partial hydatiforme mole.

The placental fragments with complete hydatiform mole show generalized villous swelling with edematous stroma. The hydropic villi are irregular in shape and may have different sizes. In the stroma of the larger villi, there are cisterns (cavities), with an acellular central core. The villi appear avascular.

Also there is an important proliferation of villous trophoblast. We noticed that this proliferation is irregular. Some villi have a marked overgrowth of trophoblast, whereas others including some huge villi, show little trophoblastic hyperplasia. The proliferating trophoblast, composed of syncitiotrpphoblast, cytotrophoblast and intermediate trophoblast shows a circumferential growth from the villous surface.

The cytotrophoblast has an important nuclear pleomorfism and the syncytiotrophoblast cells may contain cytoplasmic vacuoles. The trophoblastic inclusions appear intravillous too. In the intervilous spaces is present the intermediate trophoblast with severe nuclear atypia [1, 2, 3, 4, 5].

We noticed there are not any fetal tissue, no fibrosis and not scalloped vilous contours in complete mole.

In contrast, the placental fragments with partial hydatiforme mole have both large edematous villi and small, normal sized villi, which are often with fibrosis. Only some of the hydropic villi show the central acellular cisterns, which are less common than in complete mole. The villi are irregular with infoldings of the trophoblast into the villous stroma (pseudoinclusions). The trophoblast hyperplasia is limited and focal, (polar growth), not circumferential, with rare atypia. The fetal tissue is present and includes stromal blood vessels with nucleated erythrocytes (chorionic plate, amnion, or umbilical cord) [*Figures* 4÷7];

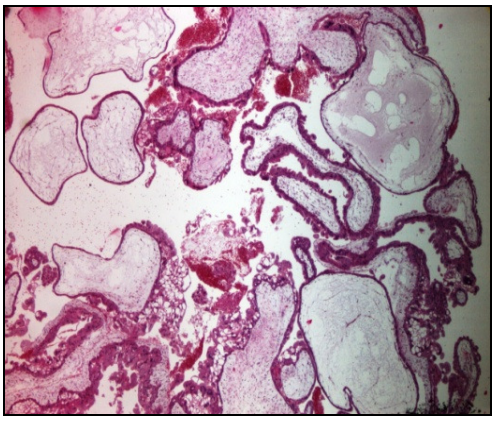

Figure 4: complet mole; HEx20

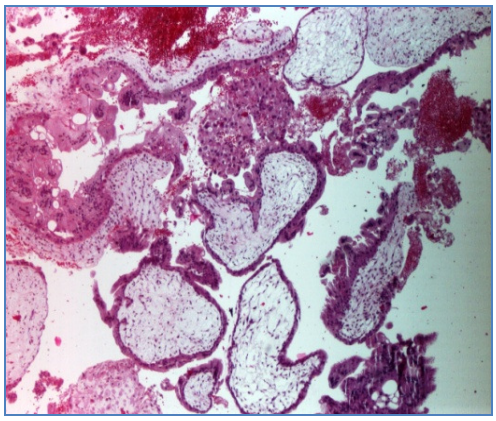

Figure 5: complete mole: HEx40

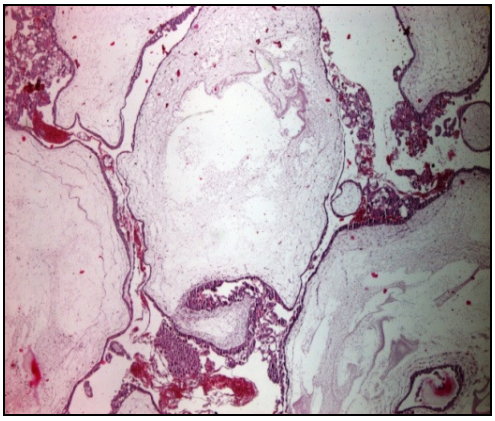

Figure 6: partial mole; HEx20

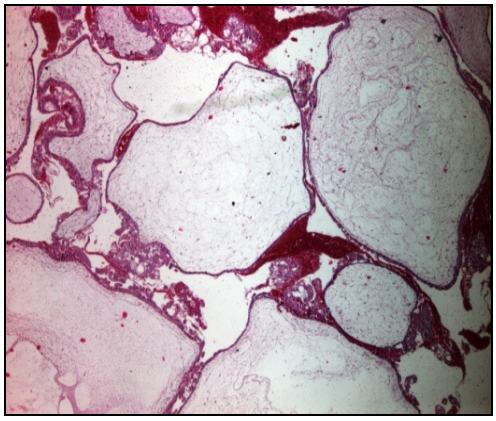

Figure 7: partial mole; HEx20

The complete hydatiforme mole has to be differentiated by partial hydatiforme mole and hydropic abortus.

In the hydropic abortus, the villi are variable sizes but not so large as in complete mole, to be macroscopically visible. The microscopically the small villi are often fibrotic. The hydropic villi tend to have an uniform balloon-like shape. Stroma is edematous, hypocellular, hypovascular with some of vessels empty and collapsed or with fetal erythrocytes. The trophoblast is usually diffusely attenuated, without atypia. There is invaginated trophoblast or rounded trophoblastic inclusions but no trophoblast proliferation, or mononuclear trophoblast cells [5÷10].

For the differential diagnosis are very helpfully the immunohistochemistry markers.

The hydatiforme mole must be differentiated by partial mole and also by hydropic abortus. In our study we used: p57, Ki67, CD34, p53, inhibin, hCG.

1. For the differential diagnosis between complete and partial hydatiforme mole, p57 protein is very helpfully. It stains the nucleus of syncytiotrophoblast. So, it is absent or less 10% in complete mole and more proeminent in partial mole. Also, the inhibin is absent in complete mole and positive in partial mole. Complete mole is characterized by proliferating cytotrophoblast, and partial mole by syncytiotrophoblast only. Inhibin helps to distinguish the cytotrophoblast from the more peripheral extravillous trophoblast. It stains the cytoplasms.

The hCG levels are higher in complete mole, than in partial mole, where, the hCG levels is usually low to normal.

2. For the differential diagnosis between complete or partial hydatiforme mole and hydropic abortus, the CD34 is very helpfully, which is used to identification of vascular and lymphatic vessels. It stains the membranes of the endothelial cells of all vessels. So, CD34 is negative in hydatiform mole and positive in hydropic abortus.

P57 protein is absent in complete mole, but proeminent in partial mole and also more positive in hydropic abortus.

Ki67 is intens positive in hydatiforme mole, but negative or very low positive in hydropic abortus. It is a marker for the nuclear proliferation.

- Complete hydatiforme mole: CD34(-), p57(-), inhibin(-), p53(-), Ki67(+++, >70%), hCG (+++);
- Partial hydatiforme mole: CD34(-), p57(+++), inhibin(+), p53(+), Ki67(+++,>70%), hCG(+/++).
- Hidropic abortus: CD34(+), p57(+++), Ki67(-/<25%).

[*figures* no 8, 9, 10, 11].

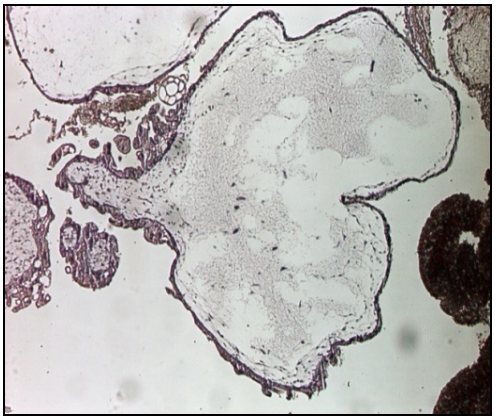

Figure 8: CD34(-) x40

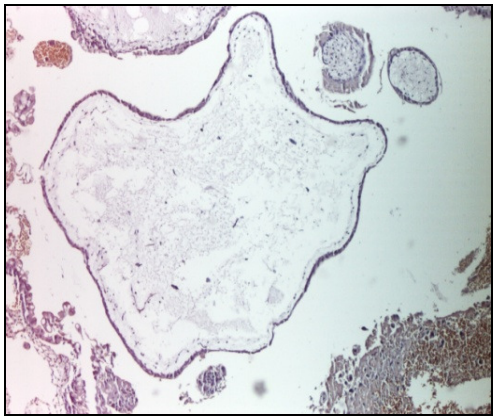

Figure 9: CD34(-); x40

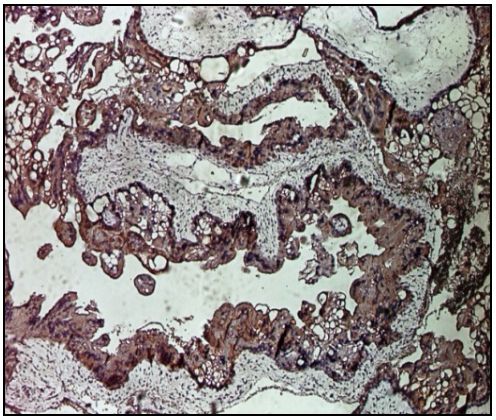

Figure 10: Inhibin (+); x40

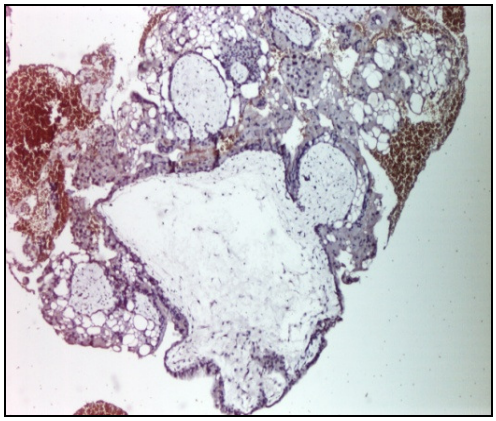

Figure 11: p53(-); x4

Conclusions

Although, the hydatiform mole is rare in our country, it should be recognized and treated with more attention.

The differential diagnosis must be made.

Complete mole has a greater risk for persistent gestational trophoblastic disease. It has long been recognized that hydatiforme mole may be followed by persistent molar disease, invasive hydatiforme mole or choriocarcinoma. Choriocarcinoma occurs in about 2% to 3% of women with complete mole.

Partial mole has a less risk for persistent gestational trophoblastic disease.

For this, is always necessary to control the serum beta-hCG levels after any form of hydatiforme mole, till the hCG levels fall too and remain in the normal range.

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