Original Article

Ectopic Gestational Trophoblastic Disease: A 20-Year Histopathological Review in a Tertiary Center

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Abstract

Background: Gestational trophoblastic disease (GTD) is a group of proliferative disorders of the placental trophoblast. While the etiopathogenesis is not fully understood, this spectrum of diseases has varied histological appearances, with clinical behaviors ranging from benign to malignant. The burden of this group of lesions seems to be more in the developing countries. A high index of clinical suspicion, early laboratory confirmation of the diagnosis, and prompt treatment ensure total cures, even of malignant disease. These diseases, just like gestation itself, are known to occur in both intrauterine and extrauterine (ectopic) sites. **Aim and Objectives:** This study sought to determine the morphological pattern as well as the age and site distribution of the various forms of ectopic GTD histologically diagnosed in the University of Benin Teaching Hospital (UBTH), Benin City, Nigeria, between January 1993 and December 2012. It is a hospital-based, retrospective review utilizing materials from the archives of the Department of Pathology, UBTH. The parameters studied include the specific histological diagnoses and the age and site distribution. **Results:** A total of 28 cases of ectopic GTDs were encountered. There were 17 cases (60.7%) and 8 cases (28.6%) of GTD found in the right and left fallopian tubes, respectively. Other sites of ectopic GTD were the left ovary (2 cases; 7.1%) and the right ovary (1 case; 3.5%). Partial mole was the most common (75.0%), followed by complete mole and invasive mole (10.7% each), and then choriocarcinoma (3.6%). The malignant: benign ratio was 1:27. **Conclusion:** Ectopic GTD, though still a relatively uncommon occurrence, should not be overlooked as a possibility in women with ectopic gestation, hence the need for histopathological and other ancillary evaluation of all ectopic conceptuses.

Keywords: Benin City, ectopic, gestational trophoblastic disease, histopathological pattern

Introduction

Gestational trophoblastic disease (GTD) is a spectrum of proliferative lesions of placental trophoblastic tissue, with a range of histological appearances and clinical profiles.[1] The World Health Organization (WHO) classification of GTD[2] includes hydatidiform mole (partial, complete, and invasive), tumors (gestational choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor), and tumor-like conditions, including exaggerated placental site, placental site nodule, or plaque.[3-6]

The etiopathogenesis is not well elucidated; however, GTD has been epidemiologically linked with ethnicity, extremes of reproductive age, prior molar pregnancy, lower socioeconomic class, and diet.[7] GTD can occur wherever pregnancy can occur, meaning that sites other than the uterine cavity are also possible primarily sites for the disease,[8] with the presentation of ectopic GTD mimicking that of conventional ectopic pregnancy.[9,10] The malignant potential is similar to that of intrauterine GTD. The prognosis is however excellent with early diagnosis and prompt treatment.[9,11]

GTD appears to be more common in Africa and Asia than in Europe and North America.[8] It is fairly common among Nigerian women of reproductive age, and the following figures have been published: 1 in 172 deliveries in Ibadan, 1 in 184 in Lagos, 1 in 357 in Jos,[9] 1 in 166 in Gombe,[10] and 1 in 252 from a study carried out a few decades ago in Benin.[11] Notably, however, there seems to be a dearth of research

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focusing specifically on the histopathological pattern of ectopic GTD, and it would appear from the existing literature on histopathological patterns of GTD that occurrence in ectopic sites is a rarity.[9,12,13] This article is intended to draw attention to its prevalence and histological pattern as seen in Benin City and environments.

Materials And Methods

This study retrospectively analyzed the histopathological pattern of ectopic GTD from January 1993 to December 2012, at the University of Benin Teaching Hospital (UBTH), Benin City, Edo state, Nigeria. The records of all specimens from ectopic sites diagnosed as GTD during this period were reviewed. These were specimens received from the Department of Obstetrics and Gynaecology, UBTH, other hospitals within Benin City and Edo State, as well as from neighboring states. Histopathological data were retrieved from departmental records. Patients' tissue biopsies were fixed in 10% formalin and processed with paraffin wax. Histology slides stained with hematoxylin and eosin were studied.

Study area and design

This was a descriptive cross-sectional study done in the Department of Morbid Anatomy, UBTH. This hospital is the major tertiary care hospital and referral centre in the Benin metropolis, having well-established Obstetrics and Gynaecology and Histopathology Departments, and serving as catchment center to neighboring states.

Diagnosis and classification

Strict histological diagnostic criteria were applied in diagnosing the specimens as GTD. The nomenclatures of the diagnostic entities were stated according to the 2003 WHO histological classification [Appendix 1]. Partial mole is optimally diagnosed histopathologically mainly by the coexistence of the following microscopic features: two populations of villi, one normal, and the other hydropic; enlarged villi (≥3–4 mm) with central cavitation; irregular villi with geographic, scalloped borders with trophoblast inclusions and trophoblast hyperplasia (usually focal and involving syncytiotrophoblast).[14] Blood vessels containing fetal red cells are often found together with other evidence of the fetal presence. Complete moles show pronounced hydropic change of all villi with central cistern formation. There is gross haphazard, circumferential hyperplasia of both cytotrophoblast and syncytiotrophoblast with the complete absence of fetal blood vessels and other features of the fetal presence.[15]

Data analysis

The data were analyzed using the Statistical Package for Social Sciences, version 16 (SPSS16, SPSS Inc. Chicago, Illinois, United States of America), with representative tables. Descriptive statistics were used in view of the small number of cases.

Results

General findings

Over the 20-year study period, histopathological diagnoses of GTD were made in 168 cases; of these, 28 (16.67%) occurred in ectopic sites. A look at the ectopic gestation specimens received during the study period revealed that ectopic GTD was diagnosed in 4.59% of all ectopic pregnancies. The clinical presentation of ectopic GTD was similar to that of other ectopic pregnancies with patients reporting a history of complaints including amenorrhea, pelvic pain, and bleeding per vaginam. The rupture of the ectopic gestational sacs, usually in early gestation, resulted in surgical emergencies following which surgical specimens were sent to the histopathology laboratory. In none of the cases was there a clinical suspicion that the ectopic pregnancy specimen sent was of GTD.

The partial mole was the most common form of ectopic GTD encountered (21 cases, 75.0%), followed by complete mole and invasive mole (10.7% each), and then choriocarcinoma (3.6%). Nearly all the cases of ectopic GTD were benign, the only malignancy being a case of choriocarcinoma of the left fallopian tube.

Age distribution

The ages of the patients ranged between 20 and 49 years. The mean age was 29.5 years, the median 28.5 years, and the modal age 24 years. An overwhelming majority of the cases (26, 92.9%) were diagnosed in women of reproductive age under 40 years (20–39 years) as depicted in Table 1. More than half of the cases (53.6%) occurred in the age group of 20–29 years.

Site distribution

The right fallopian tube was found to be the most common site with over half the number of cases of ectopic GTD occurring here (17 cases, 60.71%). The left fallopian tube was next with 8 cases (28.57%).

Of all the lesions seen in the right fallopian tube, partial mole was the most frequent (14 cases, 82.3%). In the left fallopian tube, partial mole was also the most frequent (5 cases, 62.5%). The left ovary had one case of partial mole and one case of invasive mole (which was an extension from an adjacent invasive uterine complete mole), while the right ovary had one case of partial mole. Site distribution of ectopic GTD is as shown in Table 2. Table 3 depicts the site distribution as it relates to the age groups. The frequency distribution of benign

Table 1: Age group distribution of ectopic gestational trophoblastic disease

Diagnosis	Age group			
	20-29	30-39	40-49	Total
Partial mole	10	9	2	21
Complete mole	1	2	0	3
Invasive mole	3	0	0	3
Choriocarcinoma	1	0	0	1
Total	15	11	2	28

Table 2: Site distribution of ectopic gestational trophoblastic disease

Site	Diagnosis				
	Partial mole	Complete mole	Invasive mole	Choriocarcinoma	Frequency (%)
Right fallopian tube	14	2	1	0	17 (60.71)
Left fallopian tube	5	1	1	1	8 (28.57)
Right ovary	1	0	0	0	1 (3.57)
Left ovary	1	0	1	0	2 (7.14)
Total	21	3	3	1	28 (100)

Table 3: Site and age group distribution of forms of ectopic gestational trophoblastic disease

Site	Age group			
	20-29	30-39	40-49	Total
Right fallopian tube	6	10	1	17
Left fallopian tube	6	1	1	8
Right ovary	1	0	0	1
Left ovary	2	0	0	2
Total	15	11	2	28

Table 4: Frequency distribution of benign and malignant ectopic gestational trophoblastic disease

	Frequency (%)
Benign GTD (*n*=27; 96.4%)	
Partial mole	21 (75.0)
Complete mole	3 (10.7)
Invasive mole	3 (10.7)
Malignant GTD (*n*=1; 3.6%)	
Choriocarcinoma	1 (3.6)
Total	28 (100.0)

GTD: Gestational trophoblastic disease

and malignant ectopic GTD (with a malignant: benign ratio of 1:27) is as shown in Table 4.

Discussion

The WHO classification of GTDs[2] includes hydatidiform mole (partial, complete, and invasive), tumors (gestational choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor), tumor-like conditions, including exaggerated placental site, placental site nodule or plaque, and mixed or unclassified trophoblastic lesions.

Ectopic GTD is reported to be a rare occurrence in many of the available literature,[8,9,11] many of which are case reports or case series describing only a few cases. Many studies on GTD report no cases of its occurrence in ectopic sites.

This retrospective histopathological review of ectopic GTD revealed that 28 cases were diagnosed using strict histological criteria over a 20-year period from specimens received from Benin City, Edo State, and neighboring cities and states in South-South Nigeria. Studies from another tertiary hospital elsewhere in Nigeria revealed five cases over a 9-year period,[8] while a report from the United Kingdom revealed 12 cases over 13 years.[9] A review in Venezuela revealed 6 cases over a 9-year period.[10] There was, however, a report of a high prevalence of ectopic GTD in an Albanian study,[16] in which 18 cases were seen over a 3-year period.

The mean age of occurrence of ectopic GTD in this study was 29.5 years, which is similar to those reported by Cortés-Charry *et al*.[10] (29.0 years) and Samaila *et al*.[8] (30.6 years). Tasha *et al*.[16] however reported a mean age of 23.0 years.

The partial mole was the most common form of GTD diagnosed in ectopic sites in this study, which recorded 21 cases (75%). It was also reported as the most common form of ectopic GTD by Tasha *et al*.[16] and Hassadia *et al*.,[9] who reported 11 cases (61%) and 5 cases (42%), respectively. Cortés-Charry *et al*.[10] reported partial mole to be as high as 83% of ectopic GTD in their series. Extrauterine gestational choriocarcinoma is very seldom reported in the literature. Hassadia *et al*.[9] reported four cases in 13 years, while Chan and Wong[17] published a case report of two instances. Only one case of ectopic gestational choriocarcinoma was found here in the 20-year period, just as in a 9-year review in South America.[10]

The possibility of overdiagnosis of ectopic GTD is well recognized, especially where histological criteria are not strictly followed.[9,16,18] For instance, trophoblastic hyperplasia, beyond hydropic distention, is an essential morphologic feature for differentiating partial moles from simple hydropic abortions. Partial mole is optimally diagnosed histopathologically mainly by the coexistence of the following four microscopic features: (1) two populations of villi, one normal, and the other hydropic; (2) enlarged villi (≥3–4 mm) with central captivation; (3) irregular villi with geographic, scalloped borders with trophoblast inclusions; and (4) trophoblast hyperplasia (usually focal and involving syncytiotrophoblast).[14] Blood vessels containing fetal red cells are often found together with other evidence of the fetal presence. Complete moles show a pronounced hydropic change of all villi with central cistern formation. There is gross haphazard hyperplasia of both cytotrophoblast and syncytiotrophoblast with the complete absence of fetal blood vessels and other features of the fetal presence.[15]

Studies have shown that overdiagnosis of ectopic GTD is also more likely to occur where there is no access to ancillary

investigations such as flow cytometry for DNA ploidy analysis,[13] and it has been argued that completely reliable morphological diagnostic criteria do not exist, especially in early gestational age specimens.[18] There is also the possibility of intra- and interobserver variation that may favor overdiagnosis.[19] Where there are no facilities for confirmation beyond histopathological examination, it is recommended that to avoid overdiagnosis of ectopic GTD, strict morphologic criteria are applied alongside proper serial human chorionic gonadotropin (HCG) monitoring.

Conclusion

Ectopic GTD is uncommon in this environment as in most other climes, with the fallopian tubes being the most frequent site.[8,9] The relative rarity should not, however, result in clinicians and pathologists ignoring its certain existence. Histopathological examination of all ectopic conceptuses remains the standard practice if cases of ectopic GTD are to be picked. Serial HCG monitoring, immunohistochemistry (p57), and flow cytometry for DNA ploidy analysis, among other ancillary techniques, are useful once GTD is detected using strict morphological criteria.

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Conflicts of interest

There are no conflicts of interest.

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Appendix

Appendix 1: The World Health Organization (WHO) Classification of Gestational Trophoblastic Disease (2003)

CHM
PHM
IHM
CC
PSN
EPS
PSTT
ETT
Mixed or unclassified trophoblastic lesions

CHM: Complete hydatidiform mole, PHM: Partial hydatidiform mole, IHM: Invasive hydatidiform mole, GC: Gestational choriocarcinoma, PSN: Placental site trophoblastic nodule, EPS: Exaggerated placental site, PSTT: Placental site trophoblastic tumor, ETT: Epithelioid trophoblastic tumor