

## Pathology of gestational trophoblastic neoplasia: a review with recent insights

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### Abstract

Gestational trophoblastic neoplasia (GTN) refers to a unique and heterogeneous group of conditions demonstrating differentiation towards various components of gestational trophoblast. Variants of hydatidiform mole (HM) are considered benign, whilst choriocarcinoma (CC), placental site trophoblastic tumour (PSTT) and the more recently described epithelioid trophoblastic tumour (ETT), a variant of PSTT, are malignant gestational trophoblastic tumours (GTT). The early and reproducible pathologic diagnosis of the various forms of GTN has been aided by recent developments in tumour markers, laboratory technology and new insights into our understanding of these different gestational diseases. Whilst CC is usually exquisitely chemosensitive, the much rarer PSTT and ETT require primary surgical management for optimal outcome. This dichotomous approach to the management of malignant GTT, determined by FIGO stage and differing tumour biology based on histology, has ensured an overall cure rate in excess of 90% for this group of tumours.

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### Introduction

Gestational trophoblastic neoplasia (GTN) encompasses a unique and heterogeneous group of entities, which range from benign to overtly malignant tumours. According to current WHO classification, the benign end of the spectrum includes variants of hydatidiform mole (HM), whilst choriocarcinoma (CC), placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT) make up the malignant gestational trophoblastic tumours (GTTs).<sup>1</sup> Related trophoblastic proliferations include placental site nodule (PSN) and exaggerated placental site trophoblastic reaction (EPSR), best classified as tumour-like lesions and included in the broader category of gestational trophoblastic disease (GTD). The past three decades have seen great progress in the field of GTN, with the advent of various new technologies leading to a progressive understanding and earlier, more reproducible, diagnosis of this group of conditions. This has ensured an overall cure rate in excess of 90% for all GTTs.<sup>2</sup>

GTTs are unique, as they are derived from gestational (rather than host) tissue, thus actually representing malignant foetal allografts.<sup>3</sup> Early in normal gestation, the external blastocyst layer (trophectoderm) develops into villous trophoblast, which then quickly differentiates into villous and extravillous components based on location in the conceptus. At a morphologic level, three types

of trophoblastic cells are recognised: cytotrophoblast, syncytiotrophoblast and intermediate trophoblast. All trophoblast types mark strongly with immunohistochemical stains for cytokeratin (including CK 7, 8, 18 and 19) and, with the exception of cytotrophoblast, are also variably positive for placental lactogen alkaline phosphatase (PLAP) and alpha-inhibin. Villous trophoblast comprises predominantly cytotrophoblast and syncytiotrophoblast, with a minimal amount of intermediate trophoblast present. Syncytiotrophoblast additionally demonstrates variable positivity for beta-human chorionic gonadotropin ( $\beta$ -HCG) and hPL (human placental lactogen), depending on the gestational age.  $\beta$ -HCG staining intensity decreases, and hPL intensity increases, with gestational duration. Extravillous trophoblast comprises intermediate trophoblast, is divided into implantation site and chorion laeve types based on location, and demonstrates moderate to strong positivity for hPL. The phenotype of different GTT (malignant GTN) mirrors this physiological trophoblast differentiation and can be confirmed utilising these immunohistochemical markers. Whilst most GTTs have a pure phenotype, mixed trophoblastic differentiation is occasionally seen.

Persistent GTN (pGTN) is a clinical diagnosis and is usually made on the basis of plateauing, increasing or persistent  $\beta$ -HCG levels postgestation. The lack of histology in the majority of these cases means that the exact nature of the

persistent trophoblastic proliferation is usually unknown.

### Hydatidiform mole

HM represents genetically abnormal, non-viable gestation associated with a trophoblast proliferation which may demonstrate neoplastic potential. The highest incidence is seen in women from Asia, Latin America and the Middle East.<sup>1</sup>

Advances in laboratory technology over the last three decades have resulted in continued refinement in the diagnosis of molar gestations (Figure 1), which are now divided into two main types: complete and partial (incomplete). HM always results from abnormal fertilisation, which most often gives rise to an aberrant diploid or triploid genotype (Figure 2). It is now recognised that the associated pathologic changes and trophoblastic proliferation are due to the resulting absolute or relative selective overexpression of paternal/androgenetic genes (so-called genomic imprinting). The pathology is more pronounced in a complete mole, as it does not have the attenuating influence of a maternal genome, and the subsequent risk of pGTN and CC is also greater.

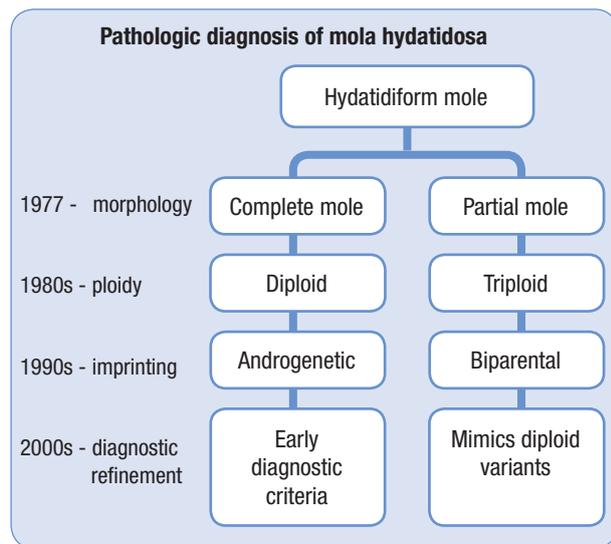


Figure 1: Chronology of the pathologic diagnosis of hydatidiform mole

Hydatidiform mole: genetic differences				
	M P	M P1 P2	P1 P1	P1 P2
<b>Gestation type</b>	Normal	Partial mole	Complete mole (90%)	Complete mole (10%)
<b>Ploidy</b>	2n	3n	2n (Duplic. 1n x 2)	2n
<b>Genome</b>	Biparental	Biparental	Paternal	Paternal
<b>pGTN/CC risk</b>	Low	Low	High	High

Figure 2: Genetic differences between partial and complete mole (M: maternal allele, P: paternal/androgenetic allele)

Complete mole (about 75% of all molar gestations) is commonest at both ends of the reproductive spectrum, when abnormal gametogenesis and oocyte fertilisation are most likely. Ninety percent arise from fertilisation of an ovum devoid of maternal chromosomes by a single sperm, which then duplicates its allele. Some of these moles may also be tetraploid. The remaining cases are usually due to dispermic fertilisation of an “empty” ovum.<sup>4</sup> Partial moles result from dispermic fertilisation of a normal ovum, but rare cases may indeed also be diploid.

The classic clinical presentation of a complete mole (in the late first to early second trimester) includes per vaginam (PV) bleeding, absent foetal heartbeat, “large for dates” uterus, severely raised β-HCG, typical ultrasound appearance and even passing of molar vesicles. The widespread use of early gestational sonar examination and β-HCG monitoring over the last three decades has, however, significantly decreased the dates at which molar gestations are presently diagnosed (mean gestational age down from 17 to 8.5 weeks).<sup>5</sup> The macroscopic features of bulky masses of oedematous villi typically seen in second trimester moles (Figure 3) are becoming increasingly uncommon. Early pregnancy failure has now become one of the commonest clinical manifestations of HM, with many cases not suspected on clinical grounds. Pre-eclampsia may occasionally be associated with an early/first trimester mole. The histopathology of an early (< 10 week) molar gestation also differs considerably from a second trimester mole, with more subtle histologic changes distinguishing a complete from a partial mole. The latter is typically characterised by the presence of embryonic/foetal tissue and less pronounced pathologic abnormalities/trophoblast proliferation than a complete mole. The pathologic features of early complete and partial mole are contrasted in Table I.



Figure 3: Macroscopic appearance of complete mole demonstrating grape-like clusters of vesicular, oedematous villi (courtesy of Dr M Louw, Department of Anatomical Pathology, University of Pretoria)

Less common variants of HM include invasive mole (myometrial invasion by molar villi, also known as chorioadenoma destruens) and metastatic mole (haematogenous dissemination of molar villi).

**Table I:** Contrasting features of early complete and partial mole

Histology of early/first trimester hydatidiform mole		
	Complete mole	Partial mole
<b>Villous morphology</b>	Smooth, contoured, with toe-like budding, pseudoinclusions irregular, large and ovoid	Irregular, "dentate" with scalloped outline, pseudoinclusions regular, small and round
<b>Villous stroma</b>	Hypercellular with karyorrhectic debris, mucoid, mild oedema	Scattered villi with mild oedema, fibrosis
<b>Villous blood vessels</b>	Absent to severely attenuated, collapsed and empty	Numerous, with many nucleated RBC, "pseudoangiomatoid"
<b>Trophoblast hyperplasia</b>	Prominent and multifocal/circumferential, extravillous pleomorphic trophoblast sheets	Mild and patchy, lace-like/vacuolated with "dripping-off" appearance

Histologic examination supplemented by genetic studies remains the gold standard in the diagnosis and typing of a molar gestation. Recent studies have, however, identified immunohistochemically detectable products from imprinted genes which allow reliable subclassification of HM. The most studied is p57<sup>KIP2</sup>, a cell cycle inhibitor and tumour suppressor gene on chromosome 11p15.<sup>6</sup> This immunohistochemical stain, although not widely available, demonstrates positivity in cytotrophoblast containing the maternal allele, thus allowing accurate distinction of complete mole from partial mole and some of its mimics (particularly non-molar hydropic abortion).<sup>7</sup> The practical use of p57<sup>KIP2</sup> staining is limited, however, as the former can usually be distinguished on morphology, and the marker is not useful in the problematic microscopic distinction between partial mole and non-molar hydropic abortion.

The outcome of complete and partial moles, as well as the associated risk of choriocarcinoma, are summarised in Table II.<sup>8,9</sup> Approximately 15% of complete molar pregnancies progress to an invasive mole. Interestingly, the risk of developing a subsequent mole is increased almost 20-fold in patients with a previous molar gestation.<sup>10</sup> Primary therapy remains suction curettage (or sometimes hysterectomy), supplemented by careful follow-up.

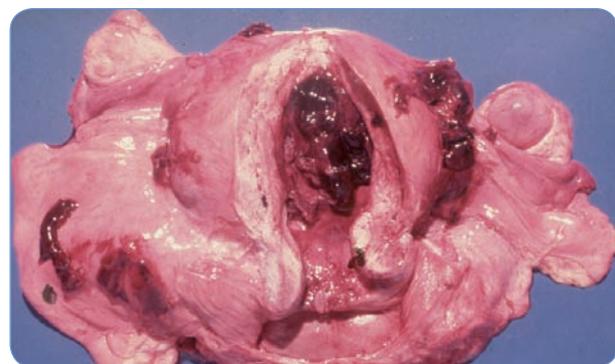
### Choriocarcinoma

Gestational CC is by far the commonest form of malignant GTT and demonstrates differentiation towards villous trophoblast (mainly cyto- and syncytiotrophoblast). In the West, it occurs in about 1:35 000 pregnancies and is preceded by HM in 40–80% of patients.<sup>11,12</sup> Without screening, the average time to presentation is about three to six months, but this interval is usually shorter in patients who develop CC post-term gestation.<sup>3</sup>

**Table II:** Outcome of complete and partial mole

Hydatidiform mole: follow-up <sup>8,9</sup>		
	Complete mole	Partial mole
Spontaneous remission	75%	95%
β-HCG persistence (pGTN)	15 – 30%	0.5 - 5 %
Choriocarcinoma	2%	Rare

CC usually presents with PV bleeding but metastatic disease may be the first manifestation, especially after a non-molar gestation. The tumour typically has a friable haemorrhagic macroscopic appearance, with single or multiple nodules (Figure 4). Extensive necrosis and haemorrhage are due to the tumour's lack of an inherent blood supply. Histologically, the tumour typically has a biphasic appearance with both mononuclear cyto- and multinucleated syncytiotrophoblast present and viable tumour, often only identifiable peripherally. These histological features may be altered postchemotherapy, however, with only bizarre mononuclear cells present. Immunohistochemistry characteristically demonstrates positivity for PLAP and b-HCG, with weak to negative staining for hPL.



**Figure 4:** Macroscopic features of gestational choriocarcinoma: opened uterus with haemorrhagic, friable luminal tumour and numerous serosal metastases (courtesy of Dr M Louw, Department of Anatomical Pathology, University of Pretoria)

Rare variants include intraplacental CC, which arises within an intact placenta ("insitu CC") and usually appears as a red to tan, granular nodule macroscopically suggestive of a recent placental infarct. Many cases are asymptomatic, almost all have a normal foetus/foetal outcome but maternal metastases are present in close to 60% of cases.<sup>13</sup> Ectopic CC has been documented in the Fallopian tube,<sup>14</sup> but always needs to be differentiated from carcinoma with trophoblastic elements/metaplasia (especially in the ovary and endometrium).<sup>15</sup> Infantile/neonatal CC is most often due to foetal involvement by metastatic spread from an intraplacental CC and carries an extremely poor foetal outcome (approximately 20%) despite intensive chemotherapy.<sup>13</sup>

CC is an extremely aggressive tumour if untreated, with haematogenous metastases most often seen in the lung, vagina, pelvis, brain and liver.<sup>12</sup> It is also not uncommon to have widespread metastatic disease with only a small or totally necrotic primary. Fortunately gestational (unlike primary ovarian) CC is highly chemoresponsive and usually managed successfully with single or combination chemotherapy, dependant on FIGO risk group. Tumour resection may be a consideration in resistant disease.<sup>16</sup>

### Placental site trophoblastic tumour

PSTT is a rare form of GTT, with differentiation towards implantation site/placental bed extravillous intermediate trophoblast. In contradistinction to CC, about 60% develop after a term pregnancy and presentation includes PV bleeding, amenorrhoea and paraneoplastic features. Serum  $\beta$ -HCG levels show mild to moderate elevation and a significantly higher free-HCG fraction than CC.<sup>17</sup> The interval from the preceding gestation to diagnosis is longer than for CC (average 18–36 months). The tumours can be polypoid or extensively infiltrative and are not as haemorrhagic or necrotic as CC. Histologically, they show an infiltrative, primarily mononuclear, cell population with prominent hPL and only weak scattered  $\beta$ -HCG positivity on immunohistochemistry. PSTT also stains strongly with the recently described melanoma marker, CD146 (Mel-CAM).<sup>18</sup>

Approximately 20% of cases develop recurrence or metastases. Adverse prognostic factors include a long interval (> 2 years) since the previous gestation, advanced stage, large tumour size, deep myometrial invasion, high mitotic activity and vascular invasion.<sup>3</sup> Hysterectomy with lymph node dissection is the recommended treatment. The latter is indicated due to the tumour's potential for lymphatic spread. Chemotherapy is reserved for patients with metastatic disease, as well as those with adverse prognostic factors.<sup>2</sup> Cases limited to the uterus are generally curable, but extrauterine disease has a much poorer outcome than CC with similar spread.<sup>19</sup>

### Epithelioid trophoblastic tumour

ETT is an extremely rare type of malignant GTT, demonstrates some differentiation towards chorionic-type extravillous (intermediate) trophoblast and is currently considered a variant of PSTT. It possibly represents the malignant counterpart of placental site trophoblastic nodule (PSN), as PSN, atypical PSN and ETT have been documented adjacent to each other.<sup>20</sup> Patients typically present with PV bleeding and mildly elevated serum  $\beta$ -HCG, although the interval between preceding gestation and diagnosis is considerably longer than for other GTT (average > 6 years). The tumour is usually well circumscribed and comprises smaller mononuclear cells in a prominent hyaline stroma with areas of necrosis and a prominent nodular growth pattern. Immunohistochemistry is similar to PSTT, except for stronger PLAP and weaker hPL and CD 146 staining,

as well as positivity for e-cadherin and epidermal growth factor receptor (EGFR).

Biologic behaviour appears comparable to PSTT, based on the limited information available.<sup>3</sup> Hysterectomy is the mainstay of treatment, due to the tumour's chemoresistance, but chemotherapy combined with tumour resection is utilised in the metastatic setting.<sup>2</sup>

Table III: Key points

- Gestational trophoblastic neoplasia (GTN) refers to a heterogenous group of diseases, ranging from benign conditions to malignant trophoblastic tumours.
- Persistent gestational trophoblastic neoplasia (pGTN) is a clinical diagnosis, usually confirmed by plateauing, rising or persistent  $\beta$ -HCG levels post-gestation.
- Overexpression of paternal (androgenetic) genes is responsible for the trophoblastic proliferation and pathology associated with hydatidiform mole.
- Histology, aided by genetic studies, remains the gold standard in the distinction between complete and partial mole.
- Immunohistochemistry for p57<sup>KIP2</sup>, a recently described maternal allele marker, may be helpful in typing a mole.
- Complete mole is associated with a 15–30% risk of subsequent pGTN, and approximately 2% risk of choriocarcinoma (CC).
- Partial mole is associated with a 0.5–5% risk of pGTN, and negligible risk of CC.
- CC is by far the commonest malignant gestational trophoblastic tumour (GTT) and demonstrates differentiation towards villous trophoblast.
- Placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT) are rare and demonstrate differentiation towards extravillous intermediate trophoblast.
- ETT is considered a variant of PSTT.
- Various routine immunohistochemical markers can assist in the distinction between different types of GTT.
- CC must be distinguished from PSTT/ETT, as this has definite therapeutic and prognostic implications.
- Early diagnosis and improvements in therapy have led to an overall cure rate of more than 90% for GTT.

### Conclusion

Our understanding of GTN has evolved considerably over the last three decades and is largely due to various technological

advances. This has led to new insights into the pathogenesis and pathology of the various forms of GTN. More intensive biochemical screening, frequent and earlier use of gestational sonar examination and more accurate histologic classification (aided by immunohistochemical markers) have resulted in a more timeous and reproducible diagnosis of GTN. Coupled with ongoing developments in the field of medical oncology, these factors have ensured an excellent outcome in the overwhelming majority of patients with malignant GTT.

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