Histological tumour type (Core)

Gestational trophoblastic neoplasia (GTN) (World Health Organization (WHO)/International Federation of Gynecology and Obstetrics (FIGO))[1,2] is defined by post-molar evacuation serum human chorionic gonadotropin (hCG) monitoring or a tissue diagnosis of choriocarcinoma as follows:

- Three or more serum hCG values without significant changes (plateau) over four weeks.
- A rise of serum hCG of 10% or more for two values over three weeks or longer.
- Persistent elevation of serum hCG six months after evacuation of a mole.
- Tissue diagnosis of gestational choriocarcinoma.

If the diagnostic tissue specimen (biopsy, hysterectomy, etc.) is available, all GTN should be typed based on the most recent edition of the WHO Classification of Tumours of Female Genital Tumours, 5th edition, 2020 (Table 2).[3] The International Collaboration on Cancer Reporting dataset includes 5th edition Corrigenda, June 2021.[4] The most common histological diagnoses of post-molar GTN include invasive hydatidiform mole (complete or partial) and gestational choriocarcinoma. Placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT) are usually diagnosed months or years after their index gestation (term pregnancy, molar gestation or abortion), which may require ancillary studies to establish their direct relationship.

Invasive hydatidiform mole is generally diagnosed when the molar tissue (complete hydatidiform mole or less often a partial hydatidiform mole) demonstrates direct myometrial invasion without intervening decidual tissue and/or vascular invasion. Grossly the lesion typically appears as an invading hemorrhagic lesion extending from the endometrial surface into the myometrium and hydropic molar villi may be seen grossly. Transmural invasion with uterine perforation or involving the broad ligament is sometimes seen. Diagnosis of invasive hydatidiform mole generally requires a hysterectomy specimen. Metastatic mole usually involves the vagina or pelvic organs.

Based on the 2020 WHO Classification,[3] intraplacental choriocarcinoma is well recognised in term placentas, with aggregates of cytologically malignant trophoblast morphologically resembling choriocarcinoma extending from the chorionic villi into the intervillous space.[5-9] Intraplacental choriocarcinoma is mostly diagnosed in third trimester or postpartum. It may be asymptomatic until metastasis occurs in the patient or even in the infant. Sometimes hydatidiform mole, particularly invasive complete mole, may contain focal or extensive areas of trophoblastic proliferation with marked atypia, qualifying for the presence of 'emerging/ early' choriocarcinoma. Such molar-associated/intramolar choriocarcinoma — that is, choriocarcinoma coexisting with complete or invasive hydatidiform mole is increasingly recognised.[9-11]

Fully developed gestational choriocarcinoma typically presents as a bulky, destructive uterine mass with extensive hemorrhage and necrosis. While the tumour most commonly arises in the uterine corpus, it may also arise within the cervix, fallopian tube or other sites possibly involved by ectopic pregnancy. Histologically the tumour consists of diffusely infiltrative or solid destructive growth with proliferating tumour cells recapitulating chorionic villous trophoblast of various types and organised in biphasic to triphasic patterns. Sheets or cords of mononuclear tumour cells (large intermediate trophoblast with abundant amphophilic to eosinophilic cytoplasm and/or smaller cytotrophoblast) rimmed by layers of multinuclear syncytiotrophoblastic cells are typical. Marked cytological pleomorphism, nuclear enlargement and brisk mitotic activity are always present. Frequently, tumour nests display central areas of hemorrhage and necrosis with only viable tumour cells at the periphery. Lymphovascular tumour thrombi are common. Immunohistochemically, neoplastic syncytiotrophoblastic cells typically show strong and diffuse positivity for hCG and HSD3B1. The intermediate trophoblast expresses Mel-CAM, HLA-G and MUC-4. Tumour cells also stain positive for cytokeratin AE1/AE3, GATA3, inhibin and SALL4. A high Ki-67 proliferation index over 90% is typically observed.[12,13]

Placental site trophoblastic tumour (PSTT) generally grossly involves the endomyometrium as a relatively well-circumscribed solid mass with deep myometrial invasion. Perforation may occur with extension into the broad ligament and adnexa in rare cases. The cut surface of the tumour is usually solid and fleshy with white-tan to light yellow colour. Histologically, the tumour consists of relatively large, polyhedral to round, predominately mononuclear intermediate trophoblastic cells forming cords, nests or sheets. At the tumour border, the tumour cells characteristically infiltrate and separate myometrial smooth muscle fibres. Vascular involvement is common in the form of tumour cells replacing the entire vessel wall except the pre-existing endothelial cells. Cytologically, the tumour cells have abundant amphophilic, eosinophilic or clear cytoplasm and variably sized and shaped nuclei. Large convoluted nuclei with marked hyperchromasia, nuclear grooves and nuclear pseudo-inclusions are present in most cases. Scattered multinucleated cells resembling syncytiotrophoblast are common. Nucleoli are generally present and may be prominent. Mitotic count is usually between 2 to 4 per 2 mm^2, equivalent to 10 high power fields (HPF) (if field diameter is 0.55 mm; i.e., depending on the design of the microscope). PSTT typically expresses human placental lactogen (hPL), hCG, MUC-4, HSD3B1, CD10, HLA-G, GATA3, inhibin and Mel-CAM (CD146). The staining of hPL is generally strong and diffuse. In contrast, hCG and inhibin are positive only in scattered multinucleated tumour cells. Epithelial markers including cytokeratin CK AE1/AE3 and CK18 are strongly expressed. Ki-67 is expressed in 10 to 30% of tumour cells.[14] PSTT recurs or metastasizes in about 25-30% of the cases with a mortality of 6.5 -27%.[3]

Epithelioid trophoblastic tumour (ETT) generally forms a discrete nodule or a cystic hemorrhagic mass deeply invading the surrounding structures and frequently arises in the cervix or lower uterine segment. The tumour cut surface is white-tan to brown, with varying amounts of hemorrhage and necrosis. Ulceration and fistula formation may be seen. Histologically ETT shows a nodular, expansile growth with sharply circumscribed tumour border. The tumour cells form nests, cords or large sheets. They are uniform, medium sized epithelioid cells with a moderate amount of finely granular, eosinophilic to clear cytoplasm, distinct cell borders, and round nuclei with small nucleoli. Eosinophilic hyaline-like material is characteristically present in the centre of some tumour nests, simulating keratin formation. Extensive or 'geographic' necrosis is often present. Most of the tumours have a mitotic count ranging from 0-9 per 2 mm^2, equivalent to 10 HPFs (if field diameter is 0.55 mm; i.e., depending on the design of the microscope) but it may be as high as 48 per 2 mm^2. The tumour cells typically diffusely express H3D3B1, HLA-G, p63, GATA 3, p40, cyclin E, inhibin, EMA and cytokeratins (CK18, CAM5.2, AE1/3). Mel-CAM and hPL are expressed only in individual cells and the Ki-67 proliferation index is over 10%. ETT may mimic cervical squamous cell carcinoma, due to frequent eosinophilic 'keratin-like' material within the tumour nests and the ability to colonise the cervical mucosal surface or glandular epithelium, therefore, simulating high-grade squamous intraepithelial lesion. ETT metastasizes in about 25-30% of the cases with a mortality of 10-24%.[6]

Mixed trophoblastic tumours consist of discrete areas of two or more components of choriocarcinoma, PSTT, and/or ETT, with characteristic histomorphology of each type as described above. The most common mixed trophoblastic tumour is mixed choriocarcinoma and ETT; less common forms are mixed choriocarcinoma and PSTT, and mixed ETT and PSTT. The least common subtype is mixed choriocarcinoma, ETT, and PSTT.[15,16] The choriocarcinoma component often dictates the tumour recurrence.

Placental site nodule (PSN) is a non-neoplastic proliferation of chorion laeve type intermediate trophoblast and is usually an incidental finding in a curettage specimen. PSN consists of single to multiple, well-circumscribed, oval nodules or plaques of typically less than 5 mm in size. Variable numbers of intermediate trophoblastic cells are haphazardly arranged in cords or nests embedded in abundant hyalinised matrix. Zonation is usually present, with higher cellularity in the periphery and a central hyalinisated, paucicellular area. Lymphocytic infiltrate is common at the lesional periphery. Mitotic activity is very low.

Immunohistochemically, similar to ETT, the lesional cells typically express hPL, inhibin, p63, cytokeratins (CAM5.2, AE1/3) and epithelial membrane antigen (EMA). Vimentin is also strongly positive in most cases. However, Ki-67 proliferation index is less than 5%.[14] Atypical placental site nodule (APSN) is a recently reported trophoblastic lesion[17,18] which is included in the 2020 WHO Classification,[3] with morphologic features intermediate between typical PSN and ETT. Histological features of APSN include larger size of the nodule (5-10 mm), increased cellularity, marked nuclear atypia, increased mitotic activity and Ki-67 proliferation index between 5-10%. APSN has been proposed as an immediate precursor lesion to gestational trophoblastic tumours (ETT and PSTT). However, definitive diagnostic criteria have not been established. It is clinically relevant that patients with APSN should undergo imaging studies to rule out an underlying mass lesion and require clinical follow-up including serial serum hCG measurement.

'Other' may cover rarer scenarios, for example, APSN or unclassifiable trophoblastic tumour.

Table 2: World Health Organization classification of gestational trophoblastic disease.[3]

Putative Trophoblastic Cells of Origin		Gestational Trophoblastic Disease Classification		Genetic Features	ICD-0 codes[a]
Chorionic Villous Trophoblast		• **Hydatidiform Mole**	• **Complete Hydatidiform Mole**	Androgenic paternal-only genome in sporadic cases. Inherited mutations of NALP7 or KHDC3L in familial biparental complete moles	9100/0
			• **Partial Hydatidiform Mole**	Diandric-monogynic triploidy in most cases	9100/0
			• **Invasive Hydatidiform Mole**	Depending on the prior mole	9100/1
		• **Atypical Villous Lesions**		Unknown in most cases	
Intermediate Trophoblast	Villous Intermediate Trophoblast	• **Gestational Choriocarcinoma**		Androgenetic XX genome following complete moles in most cases	9100/3
	Implantation Site Intermediate Trophoblast	• **Placental Site Trophoblastic Tumour**		Preferential requirement of paternal X chromosome	9104/1
		• **Exaggerated Implantation Site Reaction**		Unknown	
	Chorionic Type Intermediate Trophoblast	• **Epithelioid Trophoblastic Tumour**		Preferential requirement of paternal X chromosome	9105/3
		• **Placental Site Nodule/Atypical Placental Site Nodule**		Unknown	
	Mixed Intermediate Trophoblast	• **Mixed Trophoblastic Tumours**		Unknown	9101/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, Third Edition, second revision (ICD-O-3.2).[19] Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Incorporates all relevant changes from the 5th Edition Corrigenda June 2021.

References

1 Ngan HYS, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekharan PK, Lurain JR and Massuger L (2018). Update on the diagnosis and management of gestational trophoblastic disease. *Int J Gynaecol Obstet* 143 Suppl 2:79-85.

2 Kohorn EI (2001). The new FIGO 2000 staging and risk factor scoring system for gestational trophoblastic disease: description and critical assessment. *Int J Gynecol Cancer* 11(1):73-77.

3 WHO Classification of Tumours Editorial Board (2020). *Female Genital Tumours, WHO Classification of Tumours, 5th Edition, Volume 4*. IARC Press, Lyon.

4 WHO Classification of Tumours Editorial Board (2021). *Female Genital Tumours, WHO Classification of Tumours, 5th Edition, Volume 4 - Corrigenda June 2021*. Available from: https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Female-Genital-Tumours-2020 (Accessed 16th June 2021).

5 Sebire NJ, Lindsay I, Fisher RA and Seckl MJ (2005). Intraplacental choriocarcinoma: experience from a tertiary referral center and relationship with infantile choriocarcinoma. *Fetal Pediatr Pathol* 24(1):21-29.

6 Black JO, Rufforny-Doudenko I and Shehata BM (2003). Pathologic quiz case: third trimester placenta exhibiting infarction. Intraplacental choriocarcinoma. *Arch Pathol Lab Med* 127(8):e340-342.

7 Ganapathi KA, Paczos T, George MD, Goodloe S, Balos LL and Chen F (2010). Incidental finding of placental choriocarcinoma after an uncomplicated term pregnancy: a case report with review of the literature. *Int J Gynecol Pathol* 29(5):476-478.

8 Jiao L, Ghorani E, Sebire NJ and Seckl MJ (2016). Intraplacental choriocarcinoma: Systematic review and management guidance. *Gynecol Oncol* 141(3):624-631.

9 Savage J, Adams E, Veras E, Murphy KM and Ronnett BM (2017). Choriocarcinoma in Women: Analysis of a Case Series With Genotyping. *Am J Surg Pathol* 41(12):1593-1606.

10 Bynum J, Murphy KM, DeScipio C, Beierl K, Adams E, Anderson D, Vang R and Ronnett BM (2016). Invasive Complete Hydatidiform Moles: Analysis of a Case Series With Genotyping. *Int J Gynecol Pathol* 35(2):134-141.

11 Hui P (2019). Gestational Trophoblastic Tumors: A Timely Review of Diagnostic Pathology. *Arch Pathol Lab Med* 143(1):65-74.

12 Kalhor N, Ramirez PT, Deavers MT, Malpica A and Silva EG (2009). Immunohistochemical studies of trophoblastic tumors. *Am J Surg Pathol* 33(4):633-638.

13 Stichelbout M, Devisme L, Franquet-Ansart H, Massardier J, Vinatier D, Renaud F and Kerdraon O (2016). SALL4 expression in gestational trophoblastic tumors: a useful tool to distinguish choriocarcinoma from placental site trophoblastic tumor and epithelioid trophoblastic tumor. *Hum Pathol* 54:121-126.

14 Shih Ie M (2007). Trophogram, an immunohistochemistry-based algorithmic approach, in the differential diagnosis of trophoblastic tumors and tumorlike lesions. *Ann Diagn Pathol* 11(3):228-234.

15 Ramondetta LM, Silva EG, Levenback CF and Burke TW (2002). Mixed choriocarcinoma in a postmenopausal patient. *Int J Gynecol Cancer* 12(3):312-316.

16 Zhang X, Zhou C, Yu M and Chen X (2015). Coexisting epithelioid trophoblastic tumor and placental site trophoblastic tumor of the uterus following a term pregnancy: report of a case and review of literature. *Int J Clin Exp Pathol* 8(6):7254-7259.

17 Kaur B, Short D, Fisher RA, Savage PM, Seckl MJ and Sebire NJ (2015). Atypical placental site nodule (APSN) and association with malignant gestational trophoblastic disease; a clinicopathologic study of 21 cases. *Int J Gynecol Pathol* 34(2):152-158.

18 Tsai HW, Lin CP, Chou CY, Li CF, Chow NH, Shih IM and Ho CL (2008). Placental site nodule transformed into a malignant epithelioid trophoblastic tumour with pelvic lymph node and lung metastasis. *Histopathology* 53(5):601-604.

19 Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM and Whelan S (eds) (2020). *International Classification of Diseases for Oncology, Third edition, Second revision ICD-O-3.2*. Available from: http://www.iacr.com.fr/index.php?option=com_content&view=category&layout=blog&id=100&Itemid=577 (Accessed 16th June 2021).