

Histologic diagnosis of gestational trophoblastic diseases (GTD)

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Hydatidiform moles

With the increased use of ultrasound hydatidiform mole (HM) is being diagnosed at increasingly early stages of gestation. As villous edema is not fully developed, we cannot make a diagnosis of HM by macroscopic observation. Furthermore, microscopically the classic features of complete mole (CM) may be lacking and CM can be easily misdiagnosed as partial mole (PM) or hydropic abortion (HA).

The incidence of cases of PM have been increasing lately, however, it may be partly due to underdiagnosis of early CM as PM. Many PMs have been still misdiagnosed as HA. In our previous study, significant interobserver and intraobserver variability in the diagnosis of molar pregnancy was observed even among placental pathologists (1). Since the risk of persistent disease is 10 to 15% in CMs and 1 to 2% in PMs, and no serious consequences are observed in the majority of patients with PM, practically, a correct diagnosis of early CM is most important. Following are histologic features of early CM; diffuse or focal hydropic change of villi, bulbous or polypoid villi, focal or circumference trophoblastic hyperplasia, cellular villous stroma, network of capillaries, karyorrhexis in villous stroma, prominent placental site intermediate trophoblasts, and absence of embryo. Criteria of PM are; two populations of villi, normal sized villi and edematous villi, irregular villous outlines, focal mild syncytiotrophoblastic hyperplasia, central cistern, trophoblastic inclusion, and the presence of an embryo or fetus. p57 immunostaining is useful for differential diagnosis between CM and PM (2, 3). Villous cytotrophoblasts and stromal cells are negative for p57 in CM.

Gestational choriocarcinoma (CC)

Currently 50% of CCs are diagnosed after a term pregnancy and 25% are after a recognized CM (4). Although the latency varies from weeks to many years, the histological diagnosis is made at an average of 13 months after a CM, and 1 to 3 months after a term pregnancy. Marked elevation of serum

hCG is invariably found (5).

Macroscopically, the tumor is generally bulky and destructive with single to multiple dark red, shaggy masses with extensive hemorrhage and variable amounts of necrosis. The tumor may arise from extrauterine sites involved by an ectopic pregnancy (fallopian tube, ovary, etc.).

Histologically, CC presents either as diffusely infiltrative or solid masses consisting of cohesive sheets of malignant trophoblasts, including mononuclear intermediate trophoblast, cytotrophoblast and syncytiotrophoblast. Hemorrhage and necrosis are invariably present. Cytological atypia is generally striking and mitotic figures are numerous. The tumor does not have intrinsic stromal and vascular elements. All tumor cells express cytokeratin AE1/AE3 and a high Ki-67 labeling index is typically observed. Differential diagnoses include other trophoblastic tumors (placental site trophoblastic tumor and epithelioid trophoblastic), non-gestational CC and poorly differentiated carcinoma with trophoblastic differentiation. Florid trophoblastic proliferation in CC, early gestational villous trophoblast and exaggerated placental site reaction can also simulate CC in a curettage specimen. Rare intraplacental or in-situ CC has been encountered in full term placentas (6) and the patient and the new born baby may present with concurrent metastatic disease. Macroscopically intraplacental CC shows infarction-like changes and is histologically characterized by a sheet of atypical cells in non-hydropic normal villi (6).

CC metastasizes frequently to the vagina, lung, liver, brain and kidney. Over 90% of patients can be cured by various combined or sequential chemotherapy regimens.

Placental site trophoblastic tumor (PSTT)

PSTT is trophoblastic tumor consisting of neoplastic implantation site type intermediate trophoblast (7). Two-third of the cases follows a full-term pregnancy with a median latency of 12 to 18 months (8). Vaginal bleeding is the most common presentation. Mild to moderate elevation of serum hCG of < 1,000 mIU/ml (average 680 mIU/ml) is detectable in 80% of the cases (9, 10). At presentation, 84% of the cases are FIGO stage I tumors (9). FIGO stage II diseases commonly involve adnexa, pelvic lymph nodes and parametrium.

Macroscopically, PSTT generally involves the endo-myometrium as solid

masses. The cut-surface of the tumor is usually solid and fleshy with a white-tan to light yellow color. Focal hemorrhage and necrosis are seen in nearly half of the cases (10).

Histologically, the tumor has an infiltrative growth of aggregates to sheets of large, polyhedral to round, predominately mononuclear intermediate trophoblast. Scattered multinucleated cells are common. At the periphery, the tumor cells typically infiltrate and split myometrial smooth muscle fibers. Perivascular or intravascular proliferations with fibrin deposits are often observed. Cytologically, the cells have abundant amphophilic, eosinophilic or clear cytoplasm, and nuclear atypia is generally pronounced with frequent large convoluted nuclei and marked hyperchromasia. Most tumors have a mitotic count between 2 to 4/10 HPF (10). Immunohistochemically, tumor cells diffusely express CAM5.2, hPL and Mel-CAM (CD146). Expression of hCG and inhibin may be limited to the multinucleated tumor cells. The differential diagnoses include other trophoblastic tumors (ETT and CC), poorly differentiated carcinoma, epithelioid leiomyoma or leiomyosarcoma, and most commonly exaggerated placental site reaction.

Most patients are cured by simple hysterectomy. However, 25 to 30% of patients may develop recurrent disease, and about a half of those may die of the tumor (11, 12). Histological parameters that correlate with prognosis include tumor cells with clear cytoplasm, depth of invasion, tumor size, necrosis and high mitotic count (>5/10 HPFs). However, only advanced FIGO stage and the presence of tumor cells with clear cytoplasm are independent predictors of worse prognosis (9).

Epithelioid trophoblastic tumor (ETT)

Clinically, antecedent gestations include term pregnancy in 67%, spontaneous abortion in 16% and hydatidiform moles in 16% of cases (13). The latency ranges from 1 to 15 years with an average of 6.2 years (14). Mild to moderate elevation of serum hCG of less than 2,500 mIU/ml is detectable in 80% of the cases (14).

Macroscopically, the tumor generally forms discrete nodules or cystic hemorrhagic masses deeply invading the surrounding structures. Near half of the cases arise in the cervix or lower uterine segment. The cut surface of the tumor is white-tan to brown, with varying amounts of hemorrhage and necrosis.

Histologically, ETT is characterized by nodular growth of medium sized tumor cells arranged in nests or cords to large masses. The cells are relatively uniform with a moderate amount of finely granular, eosinophilic to clear cytoplasm, distinct cell membranes and round nuclei with distinct small nucleoli. Nuclear atypia is generally moderate and the mitotic count ranges from 0-9/10 HPFs. Deposition of eosinophilic hyaline-like material is characteristically present in the center of tumor nests or between tumor cells (13, 14). Extensive or “geographic” necrosis is often present. Decidualized stromal cells may be found at the tumor periphery (14). When involving the cervix, tumor cells may colonize the mucosal epithelium simulating high-grade squamous intraepithelial lesion (14). The tumor cells diffusely express CA5.2 and inhibin-alpha. Mel-CAM and hPL are expressed only in individual cells and the Ki-67 labeling index is over 10 % (15).

ETT arises from chorionic-type intermediate trophoblast (13, 14). Possible malignant transformation from PSN to ETT has been reported (16). ETT may coexist with other trophoblastic neoplasms (17).

The prognosis of ETT is similar to that of PSTT with 25% metastatic rate and 10% mortality (13). The survival is near 100% for non-metastatic cases but decreases to 50-60% in those with metastasis. Among the histological features, only high mitotic count (>6/10 HPFs) has been indicated as an unfavorable factor (18).

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