Diagnostic Problems With Trophoblastic Lesions

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● The purpose of this review is to address some common problems involving the diagnosis of trophoblastic lesions. (Arch Pathol Lab Med. 2008;132:168–174)

ENDOMETRIAL CURETTAGE WITH ABUNDANT DECIDUA BUT WITHOUT CHORIONIC VILLI

A very common problem is the absence of chorionic villi in endometrial curettage from a patient with a clinical history of a possible abortion.1–3 To identify the presence of products of conception, the first step is to submit the entire specimen, if this has not already been done. The presence of abundant decidua and hypersecretory glands is highly suggestive of pregnancy; however, frequently chorionic villi are not seen because most of them are lost at the beginning of a spontaneous abortion. In this situation, it is important to examine the areas of decidual reaction. If these areas are void of inflammatory cells, there is a possibility that the patient has an ectopic pregnancy. If the areas of abundant decidua contain moderate numbers of inflammatory cells, there is a greater likelihood of an intrauterine pregnancy (Figure 1). Because the area of implantation is likely one of the last to be expelled, it can be useful to look for this area, which contains decidual cells, abundant fibrin, large vessels, inflammatory cells, and also enlarged cells that represent intermediate trophoblastic cells (Figures 2 and 3). The presence of intermediate trophoblastic cells should be confirmed by immunohistochemistry with a keratin stain.3 Decidual cells are negative for keratin cocktail and trophoblastic cells are positive for keratin cocktail (Figures 4 and 5). Intermediate trophoblastic cells are probably one of the few cells that are always strongly positive for keratin (Figure 6). It is recommended that keratin staining be performed on a section of decidua without glands because tangential sections of the glands might contain small groups of cells positive for keratin; in contrast, trophoblastic cells are represented by individual large cells with a strong keratin reaction. If there is doubt about the nature of the positive cells, additional stains can be performed (to be described later in this review); however, usually the diffuse strong positive keratin expression by individual cells is enough to render a diagnosis of products of conception.

HIGHLY ATYPICAL VILLOUS TROPHOBLASTS

The histologic appearance of the villous trophoblast changes during different periods of the pregnancy. Trophoblasts are most active at the beginning of the pregnancy when trophoblastic cells form groups with abundant mitotic figures; however, even during this period of pregnancy, marked atypia is not seen. Later during the mid and last trimesters of pregnancy, the villous trophoblast becomes smaller, significant atypia is not seen, and mitotic figures are not very frequent. Normally, villous trophoblasts have a polar distribution, with cytotrophoblastic cells at the center of the group and syncytiotrophoblastic cells at the periphery. The presence of highly atypical villous trophoblasts is diagnostic of trophoblastic disease. They can represent either hydatidiform mole or choriocarcinoma depending on the presence or absence of hydropic villi.4,5 Even in the presence of normal chorionic villi, highly atypical trophoblasts are diagnostic of trophoblastic disease; these cases are designated as choriocarcinoma in situ. Some pathologists are reluctant to make a diagnosis of trophoblastic disease when highly atypical trophoblastic cells are associated with a normal placenta; as there are no hydropic villi the diagnosis of hydatidiform mole cannot be rendered, and a common belief is that choriocarcinoma cannot be diagnosed in the presence of chorionic villi. However, this applies only to the differential diagnosis of choriocarcinoma versus hydatidiform mole. Today we know that it is possible for choriocarcinoma to arise in an otherwise normal placenta and that in this case there are foci of highly atypical trophoblasts adjacent to normal chorionic villi (Figures 7 through 9).6,7

DIAGNOSIS OF EARLY HYDATIDIFORM MOLE

Hydatidiform mole has always been recognized as an entity characterized by dilated hydropic chorionic villi with abundant trophoblastic cells around them (Figure 10). However, clinicians now can detect hydatidiform moles at a very early stage, and, therefore, the classic histologic features of a hydatidiform mole are not always seen.8 As it can be difficult to diagnose hydatidiform moles, the relative frequency of the different types is unclear; however, it appears that partial moles are more frequent than complete moles. This is significant because of the lower risk of persistent trophoblastic disease and progression to choriocarcinoma associated with partial moles.
Figure 1. Decidual cells with abundant inflammatory cells (hematoxylin-eosin).
Figure 2. Decidual cells mixed with larger, hyperchromatic intermediate trophoblastic cells (hematoxylin-eosin).
Figure 3. Decidual cells mixed with intermediate trophoblastic cells. Some of the latter are multinucleated (hematoxylin-eosin).
Figure 4. Keratin stain is positive in the endometrial glandular epithelial cells. Decidual cells are negative.
Figure 5. Keratin stain is positive in the endometrial glandular epithelial cells and also in the intermediate trophoblastic cells (lower left).
Figure 6. Strong positive reaction for keratin cocktail in the intermediate trophoblastic cells.
Figure 7. Choriocarcinoma arising in a normal placenta (choriocarcinoma in situ) (hematoxylin-eosin).
Figure 8. Choriocarcinoma arising in a normal placenta (choriocarcinoma in situ) (hematoxylin-eosin).
Figure 9.  Choriocarcinoma arising in a normal placenta (choriocarcinoma in situ) (hematoxylin-eosin).

Figure 10.  Classic complete hydatidiform mole. Hydropic avascular chorionic villi with abundant trophoblasts around them.

Figure 11.  Partial mole. Chorionic villi of different sizes and mild trophoblastic proliferation around the villi (hematoxylin-eosin).

Figure 12.  Partial mole. The trophoblastic proliferation forms small papillary projections and there are clusters of trophoblastic cells between the villi (hematoxylin-eosin).

Figure 13.  Partial mole. Fluorescence in situ hybridization showing 3 signals in several nuclei.

Figure 14.  Early complete mole containing thin vessels within a hydropic villus (hematoxylin-eosin).

Figure 15.  p57 stain with positive nuclei in the trophoblastic cells and the chorionic villi cells of a mature placenta.

Figure 16.  p57 stain is negative in hydropic chorionic villi of a complete mole (left). Decidual reaction (right) is a positive internal control.
Figure 17. Placental site trophoblastic tumor. Groups of intermediate trophoblastic cells infiltrating myometrium.

Figure 18. Epithelioid trophoblastic tumor. Intermediate trophoblastic cells forming well-demarcated nodules with abundant hyalin.

Figure 19. Intermediate trophoblastic tumor that had an area of placental site trophoblastic tumor.

Figure 20. The same intermediate trophoblastic tumor shown in Figure 19 that also had an area of epithelioid trophoblastic tumor.

Figure 21. Metastatic intermediate trophoblastic tumor in lung simulating a primary carcinoma (hematoxylin-eosin).

Figure 22. Metastatic intermediate trophoblastic tumor in lung simulating a primary carcinoma (hematoxylin-eosin).

Figure 23. Same case as Figures 21 and 22. Diffuse positivity for keratin.

Figure 24. Metastatic intermediate trophoblastic tumor in lung positive for CD10.
Figure 25. Metastatic intermediate trophoblastic tumor in lung. Mononuclear cells positive for human chorionic gonadotropin (hCG).

Figure 26. Placental site nodule. Sparse intermediate trophoblastic cells mixed with decidual cells (hematoxylin-eosin).

Figure 27. Placental site nodule. Keratin stain strongly positive in the intermediate trophoblastic cells.

Figure 28. Placental site nodule. Positive CD10 stain in intermediate trophoblastic cells.

Figure 29. Placental site nodule. Low proliferative activity demonstrated by rare cells positive for Ki-67.

Figure 30. Intermediate trophoblastic tumor with a uniform cell population (hematoxylin-eosin).

Figure 31. Intermediate trophoblastic tumor with some cells having large nuclei, but a biphasic cell population is not seen (hematoxylin-eosin).

Figure 32. Choriocarcinoma with a biphasic cell population. Cytotrophoblasts are seen at the bottom and syncytiotrophoblasts at the top (hematoxylin-eosin).
Partial Mole

A partial mole should always be suspected when some chorionic villi are dilated and others are not, and the dilated villi have irregular outlines because of trophoblastic proliferation that produces small papilla on the border of the villous structures (Figures 11 and 12). Another important histologic feature of partial moles is that tangential sections of the small papillary proliferations of trophoblastic cells leave clusters of these cells between villi creating small, detached groups of cells, which are not seen in normal pregnancies (Figure 12). The diagnosis of a partial mole can be difficult with hematoxylin-eosin slides alone, so confirmation is advisable through special studies that demonstrate the triploid population present in 99% of partial moles—1% of partial moles are tetraploid. The triploid population can be confirmed by flow cytometry or by fluorescence in situ hybridization. For both studies, it is important to select a paraffin block with abundant chorionic villi rather than abundant decidua. If the diagnosis is to be confirmed by fluorescence in situ hybridization, it is important to read the number of positive signals in cells of the chorionic villi (Figure 13).

Early Complete Mole

A complete mole evacuated at an early stage is characterized by mild hydropic changes and mild trophoblastic proliferation. The trophoblasts around the villi in an early complete mole usually do not form the small papillary projections, so the background between the villi is cleaner than in a partial mole. Early complete moles also have vessels within the villi, which is a feature that is not seen in well-developed or late complete moles (Figure 14). The diagnosis of an early complete mole is difficult with hematoxylin-eosin slides alone; therefore, immunostaining for p57 is recommended.9–11 This stain is positive when a maternal allele is present. Complete moles do not have maternal chromosomes; therefore, they are negative for p57. When requesting this stain, it is important to select a slide having both decidua and chorionic villi. The cells of the decidual reaction are the positive control. Complete mole is the only entity in which the cells are negative for p57; p57 is positive in nonmolar pregnancies and in partial moles. Two important points about this stain are that even in the positive cases only a few cells express p57 and that there is an unexplained cross reactivity for p57 with intermediate trophoblasts, even in cases of complete mole. Therefore, it is very important to interpret the p57 stain in chorionic villi, avoiding areas of intermediate trophoblasts such as the implantation site and in the placental cell islands (Figures 15 and 16).

TYPES OF INTERMEDIATE TROPHOBLASTIC TUMORS

Recently, 2 different types of intermediate trophoblastic tumors have been recognized, the placental site trophoblastic tumor and the epithelioid trophoblastic tumor.12 Both have similar intermediate trophoblastic cells, but in placental site trophoblastic tumors the cells form diffuse masses without significant necrosis that infiltrate the myometrium, and in epithelioid trophoblastic tumors the cells form nodules with abundant hyalin material (Figures 17 and 18). There are some cases in which this distinction is difficult because the tumor has both components or does not have features typical of either one (Figures 19 and 20). In addition, when an intermediate trophoblastic tumor appears after treatment for choriocarcinoma it can be impossible to classify the tumor as one of these 2 types. We believe that distinction between the 2 types of intermediate trophoblastic tumors is not strictly necessary because both are treated in a similar fashion.

INTERMEDIATE TROPHOBLASTIC TUMOR VERSUS CARCINOMA

The diagnosis of choriocarcinoma is not difficult because of the presence of cytotrophoblasts and syncytiotrophoblasts, in addition to intermediate trophoblasts. However, the diagnosis of an intermediate trophoblastic tumor can be difficult because, although it is a trophoblastic lesion, it is composed of a single cell population. If the lesion follows pregnancy and involves the endometrial cavity and the myometrium, the diagnosis is not difficult; however, often intermediate trophoblastic tumors appear in the cervix or the lung or at other sites. In these situations, it can be difficult to distinguish an intermediate trophoblastic tumor from a poorly differentiated carcinoma. Immunostains are almost always necessary. The Table contains the stains that we prefer to use for differentiating trophoblastic tumors from poorly differentiated carcinomas (Figures 21 and 22).13,14 We believe that keratin can be useful in this differential, because even though both tumors are positive for this marker, most of the cells in intermediate trophoblastic tumors are strongly positive, whereas frequently the expression is not very strong or diffuse in poorly dedifferentiated carcinomas (Figure 23). In addition to keratin, human leukocyte antigen and CD10 are probably the most useful stains to separate intermediate trophoblastic tumor and carcinoma (Figure 24). Human chorionic gonadotropin can also be helpful because intermediate trophoblastic tumors are positive in 87% of the cases (Figure 25). In our experience, human placental lactogen is positive in only 60% of the intermediate trophoblastic tumors, and it is only focally positive.

In cases involving the uterine cervix, it is important to obtain a p16 stain. The majority of cervical carcinomas are associated with high-risk human papillomavirus and have diffuse positive staining for p16, whereas intermediate trophoblastic tumors are only focally positive.

INTERMEDIATE TROPHOBLASTIC TUMOR VERSUS PLACENTAL SITE NODULE

When a proliferation of intermediate trophoblastic cells is discovered in an endometrial curetting, the main diagnostic considerations are an intermediate trophoblastic tumor and a large placental site nodule (Figure 26). Both lesions have similar cells and these cells have identical immunohistochemical characteristics (Figures 27 and 28). The presence of abundant inflammatory cells and decidual cells mixed with the intermediate trophoblastic cells favors the diagnosis of a placental site nodule. This diagnosis is also favored when chorionic villi are present in the spec-

<table>
<thead>
<tr>
<th>Trophoblastic Tumors Versus Carcinoma (Ca)*</th>
<th>HLA</th>
<th>CD10</th>
<th>hCG</th>
<th>HPL</th>
<th>p16</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT, %</td>
<td>93</td>
<td>100</td>
<td>87</td>
<td>60</td>
<td>Focal</td>
</tr>
<tr>
<td>Ca, %</td>
<td>10</td>
<td>20</td>
<td>10</td>
<td>0</td>
<td>Diffuse in cervical lesions</td>
</tr>
</tbody>
</table>

* HLA indicates human leukocyte antigen; hCG, human chorionic gonadotropin; HPL, human placental lactogen; and ITT, intermediate trophoblastic tumor.
imen. The most important feature that separates a small intermediate trophoblastic tumor from a placental site nodule is proliferative activity, which can be identified by the presence of mitoses or with a Ki-67 stain or other proliferation markers. Most intermediate trophoblastic tumors have low proliferative activity, whereas there is essentially no proliferation in placental site nodules. Staining of Ki-67 in 5% or more of the trophoblastic cells favors a trophoblastic tumor; it should be noted that Ki-67 expression in inflammatory cells could make accurate determination of the proliferation index difficult at times (Figure 29). The distinction between an intermediate trophoblastic tumor and a placental site nodule is not always possible, and in cases in which there is still uncertainty about the diagnosis, follow-up of the patient with human chorionic gonadotropin titers should be recommended.

INTERMEDIATE TROPHOBLASTIC TUMOR VERSUS CHORIOCARCINOMA

Intermediate trophoblastic tumors can contain large atypical cells and even multinucleated cells. In these instances, a diagnosis of choriocarcinoma may be considered. In our experience, thorough examination of the hematoxylin-eosin slides is more important than immunohistochemistry in this situation because choriocarcinomas are positive for the same markers that are used to identify intermediate trophoblastic tumors (Figures 30 through 32). This differential diagnosis is extremely important because intermediate trophoblastic tumors do not respond well to chemotherapy, as compared with the extremely good response of choriocarcinoma to chemotherapy.

References