4
Gestational Trophoblastic Disease

Gestational trophoblastic disease (GTD) includes disorders of placental development (hydatidiform mole) and neoplasms of the trophoblast (choriocarcinoma, placental site trophoblastic tumor [PSTT], and epithelioid trophoblastic tumor).[1;2] The recent classification of these lesions by the World Health Organization (WHO) clearly defines the different histologic forms of GTD (Table 4.1).[3] A common feature of all of these trophoblastic lesions is that they produce human chorionic gonadotropin (hCG), which serves as a marker for the presence of persistent or progressive trophoblastic disease. Because these lesions, especially postmolar trophoblastic disease, are often treated in the absence of a histologic diagnosis, they may be clinically classified as GTD without designation of the morphologic subtype. Nonetheless, identification and separation of the different pathologic forms of the disease are important, as they have different clinical presentations and behavior.

Hydatidiform mole, either partial or complete, is the most common form of GTD, and this also is the trophoblastic lesion most commonly encountered in endometrial curettings.[2] Choriocarcinoma, PSTT, and epithelioid trophoblastic tumor are infrequent. Recognition of any of these lesions can be difficult, however, because the morphologic features of all forms of GTD overlap with the features of placental and trophoblastic growth encountered in early pregnancy, abortion, and persistent placental implantation sites.

Hydatidiform Mole

General Features

Hydatidiform mole, either partial or complete, is infrequent in the United States and Europe, occurring in about one in 1000 to one in 2000 pregnancies,[4–6] although some studies have suggested that partial mole may be even more frequent, occurring in up to 1 in 700 pregnancies.[7] In other parts of the world, including Asia and Latin America, these disorders are more common, although problems in methodology often complicate studies of their frequency when deliveries take place at home.[2;8;9]

The separation of hydatidiform mole into two subtypes, complete and partial, represents a significant advance in our understanding of molar pregnancy. These two forms of hydatidiform

TABLE 4.1. Modified World Health Organization classification of gestational trophoblastic disease.

Molar lesions
Hydatidiform mole
Complete
Partial
Invasive mole
Nonmolar lesions
Choriocarcinoma
Placental site trophoblastic tumor
Epithelioid trophoblastic tumor
Miscellaneous trophoblastic lesions
Exaggerated placental site[a]
Placental site nodule[a]
Unclassified trophoblastic lesion

[a]See Chapter 3 for a description of these lesions.

mole have different cytogenetic patterns that are accompanied by different clinicopathologic profiles and different degrees of risk for the development of persistent GTD (Table 4.2).[1;2;7;10–13] Both forms of mole typically present in the first trimester, often as an abortion.

Complete mole, also known as "classic" hydatidiform mole, has been recognized and studied for many years.[4] The clinical presentation of complete mole has changed in recent years. In the past typical complete moles presented at approximately the 16th week of pregnancy, but with the widespread use of ultrasound in prenatal assessment, many moles are now detected earlier in gestation.[14;15] Currently, most cases of complete mole seen in North America and Europe present as a spontaneous or missed abortion between 6 and 18 weeks of gestation with a mean of about 11 to 12 weeks. Complete moles commonly present with uterine enlargement greater than that expected for the gestational age, and the patient may have signs or symptoms of toxemia of pregnancy. Abortion with abnormal bleeding and passage of molar tissue is a frequent presentation. Although historically many complete moles were diagnosed before curettage, in current practice complete mole may be undetected clinically and diagnosed only when the pathology is reviewed. The serum β-human chorionic gonadotropin (β-hCG) titers may be markedly elevated, but levels are often unreliable for establishing the diagnosis. However, a β-hCG titer above 82,350 mIU/ml, coupled with absence of fetal heart movement, is correlated with the presence of hydatidiform mole.[16]

Partial moles tend to present slightly later in gestation, occurring between 8 and 22 weeks of gestation with a mean of about 14 weeks. These moles also may be clinically unsuspected, presenting as a spontaneous or missed abortion (Table 4.2).[10;11] The uterus often is small for gestational age. Serum β-hCG titers are in the low or normal range for that time in pregnancy, and toxemia is less frequent than in the case of complete moles. The subtle clinical presentation of most moles, either complete or partial, underscores the need for careful pathologic evaluation of abortion specimens.[17]

Persistent GTD following a complete or partial mole is detected by serum hCG titers that fail to return to normal. The risk of persistent GTD is greater with complete mole. Up to 20% or more of patients with complete mole require further therapy, usually chemotherapy, for a plateau or increase in the serum hCG titer after evacuation.[2;18–20] About 2% to 3% of patients with complete mole will develop choriocarcinoma. Among patients with partial mole,

TABLE 4.2. Clinical and cytogenetic comparison of hydatidiform moles and hydropic abortus.

	Complete mole	Partial mole	Hydropic abortus
Presentation	Spontaneous abortion	Missed abortion	Spontaneous or missed abortion
Gestational age	8–18 weeks	8–22 weeks	6–14 weeks
hCG titer	Typically elevated	Low to normal	Low to normal
Uterine size	Often enlarged for date	Often small for date	Often small for date
Amount of tissue	Variable, may be increased	Variable, usually decreased	Usually decreased
Karyotype	46XX (all paternal)	69XXY or XXX (2:1, paternal:maternal)	Variable, often abnormal
Persistent GTD	15%–20%	0.5%–5%	None

hCG, Human chorionic gonadotropin.

the risk of persistent GTD is much lower, as it occurs in from 0.5% to 5% of cases.[2;10;11;21–25] Most cases of persistent GTD represent persistent mole in the uterine cavity or invasive mole in the myometrium. Less often a patient has invasive mole with villi and trophoblast that migrates to the lungs, vulva, or vagina, or lung metastases that are not biopsied for classification.[26] Development of choriocarcinoma following a partial mole is a very rare sequela.[25;27;28] Genotyping and chromosome in situ hybridization analysis has shown that some cases of genetically confirmed partial mole do have metastatic trophoblastic disease with lung and liver lesions.[28a]

Cytogenetics

Cytogenetic studies show that complete mole has a normal diploid DNA content, usually 46XX. The entire chromosomal complement, however, is paternal, resulting from duplication of a haploid paternal genome (23X); the complete mole lacks maternal DNA.[29] More than 90% of complete moles contain this composition of paternal chromosomes.[12;30–32] The remaining complete moles also are androgenetic but are 46XY and formed by dispermy, that is, fertilization by two spermatozoa of an ovum lacking functional maternal chromosomes.[31;33;34]

Cytogenetically, partial mole usually is triploid (69 chromosomes) with two sets of chromosomes of paternal origin (diandric) and a haploid maternal set.[12;34–36] In more than two thirds of cases, the triploid chromosomal composition is 69XXY; less often it is XXX, and rarely it is XYY.[34] Cytogenetic distinctions between complete and partial moles have not been absolute, however. There have been reports of partial moles that are diploid,[37–39] and occasional complete moles that are triploid.[37;40] Furthermore, both complete and partial moles have been reported to show marked heterogeneity in ploidy patterns. Haploid, aneuploid, and tetraploid moles, both partial and complete, have been reported.[40;41] DNA ploidy analysis can be helpful in classifying cases that lack clear-cut morphologic features to identify the mole as either complete or partial.[38;40–43] A review of apparent nontriploid partial moles found that errors in pathologic or ploidy classification were common and suggested that nontriploid partial moles may not exist.[44]

Recently, immunohistochemical analysis of the paternally imprinted gene product $p57^{KIP2}$ has been used in the differential diagnosis of moles.[45–48] The *p57KIP2* gene is expressed predominantly from the maternal allele in most tissues, and, because complete moles contain only paternal DNA, *p57KIP2* is underexpressed. As a consequence, antibodies against the $p57^{KIP2}$ protein generally show little to no expression in cytotrophoblastic cells and villous stromal cells of complete mole. In contrast, the cytotrophoblastic cells and villous mesenchyme of partial moles as well as spontaneous abortions show strong immunoreactivity for $p57^{KIP2}$.[47;48] A rare case of complete mole has shown cytotrophoblast and villous stromal cell immunoreactivity for $p57^{KIP2}$, however.[47] In addition, $p57^{KIP2}$ immunostaining can be seen in villous intermediate trophoblastic cells[48] and in intervillous trophoblast islands composed of intermediate trophoblast within complete moles.[47] Syncytiotrophoblastic cells are nonreactive for $p57^{KIP2}$ and maternal decidualized stromal cells are strongly reactive for $p57^{KIP2}$ in all types of gestations. In our experience, this antibody has not proven sufficiently specific to be useful for the subclassification of hydatidiform mole. Accordingly, the $p57^{KIP2}$ immunohistochemical findings should be interpreted with caution when using this antibody to assist in the distinction of complete versus partial moles.

To date, most studies find no consistent association between DNA ploidy and the subsequent clinical course of either partial or complete mole.[40] One report suggested that aneuploidy predicts persistence in complete moles,[49] but another study found that aneuploid complete mole is associated with less risk for progressive disease than diploid or tetraploid complete moles.[50]

Pathologic Features

Hydatidiform mole is one of the few curettage specimens that can have distinctive gross features, namely large, translucent villi.[2] Tissue recovered from molar pregnancies in these cases is voluminous, especially in complete mole. The grapelike villi typically range from several mil-

limeters to 2.0 cm or more in the largest dimension (Table 4.3). Often, however, villi are not grossly visible. This is attributable to early gestational age,[14;17] villi being passed spontaneously before curettage, or villi collapsing during the suction curettage. Besides the presence of grossly edematous villi, specimens from partial moles may contain remnants of a fetus.

Microscopically, the villi in both complete mole and partial mole show circumferential hyperplasia of trophoblast and cistern formation.[1;2] In partial mole, the villous abnormalities affect only a portion of the placenta, resulting in two populations of villi.[1;2;10;13] In complete mole, edema affects all villi, although the degree of enlargement caused by the edema is variable. Sometimes one of the two features, circumferential hyperplasia or edema, predominates, but both features should be present to establish the diagnosis. When several hydropic villi are sufficiently large to fill a microscopic field under a ×10 objective lens, the diagnosis of hydatidiform mole is probably established.

Complete Mole

The morphologic features of complete mole differ to some extent depending on the gestational age. Consequently, the diagnosis of complete mole requires recognition of both classic changes and the more subtle changes of very early complete mole. In fact, classic complete mole is now relatively uncommon, as many moles are detected earlier in pregnancy because of the routine use of ultrasound performed in early pregnancy. Whether a complete mole is detected very early in gestation or at a more advanced stage, both diffuse villous edema and irregular hyperplasia of trophoblast from the surface of some villi should be seen. The features of classic mole are considered first, followed by a description of the early complete mole, defined as a complete mole detected prior to 12 weeks of gestation. Clearly there are transitions between these patterns.

Classic features of a complete mole obtained at 16 to 18 weeks of gestation include a voluminous gross specimen showing many large, grapelike translucent villi. Microscopically, these advanced complete moles show marked villous edema with cistern formation (Figs. 4.1 and 4.2). A cistern is a completely acellular central cavity within a villus that is filled with edema fluid and surrounded by a sharply demarcated stromal border. In complete mole, many, but not all, of the villi show cistern formation, although *all* the villi are edematous (Fig. 4.3). Scattered small villi without cisterns often are admixed (Fig. 4.1). In addition to these changes, some villi may be necrotic and occasional villi can show partial calcification. Because fetal development ends very early in placentation, the villi usually do not have visible blood vessels. Although stromal vessels are indistinct, occasional vessels in the villous stroma can be found. In fact, CD34 immunostaining will show numerous blood vessels; these may contain cellular debris.[51]

Circumferential trophoblastic hyperplasia seen in complete mole is characterized by masses of trophoblast, often confluent, that

Table 4.3. Comparison of pathologic features of complete mole, partial mole, and hydropic abortus.

	Complete mole	Partial mole	Hydropic abortus
Villous hydrops (swelling)	Generalized, often grossly visible	Partial, often grossly visible	Microscopic, limited
Villous shape	Round to bulbous	Irregular, scalloped	Round, small
Cisterns	Present	Present	Usually absent
Trophoblastic inclusions	Rare	Common	Rare
Fetal tissue	Rare	Common	Rare
Trophoblast			
Distribution	Circumferential, multifocal	Circumferential, multifocal	Polar at anchoring villi only
Proliferation	Variable, may be marked	Focal, minimal, with ST sprouts	Limited to anchoring villi
Atypia	Often present	Rare	Absent
Implantation site	Exaggerated	Normal or exaggerated	Normal

ST, Syncytiotrophoblastic.

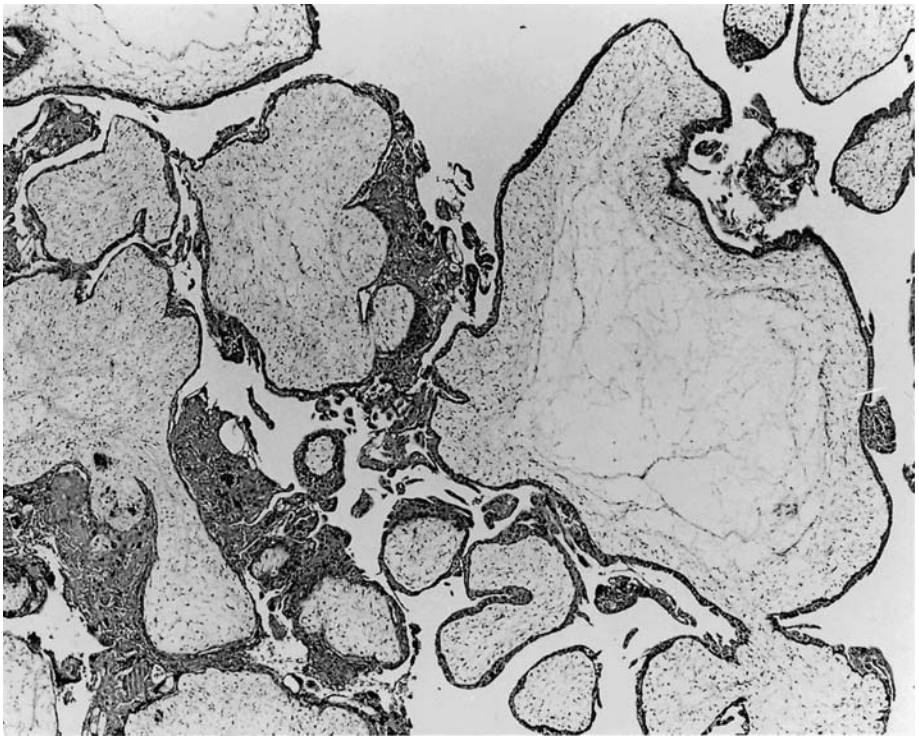

FIGURE 4.1. Complete hydatidiform mole. Low-magnification view shows generalized villous edema and marked enlargement of many villi. The massively distended villus to the right of center has a central cistern. Irregular, haphazard hyperplasia of trophoblast is present along the surface of several villi.

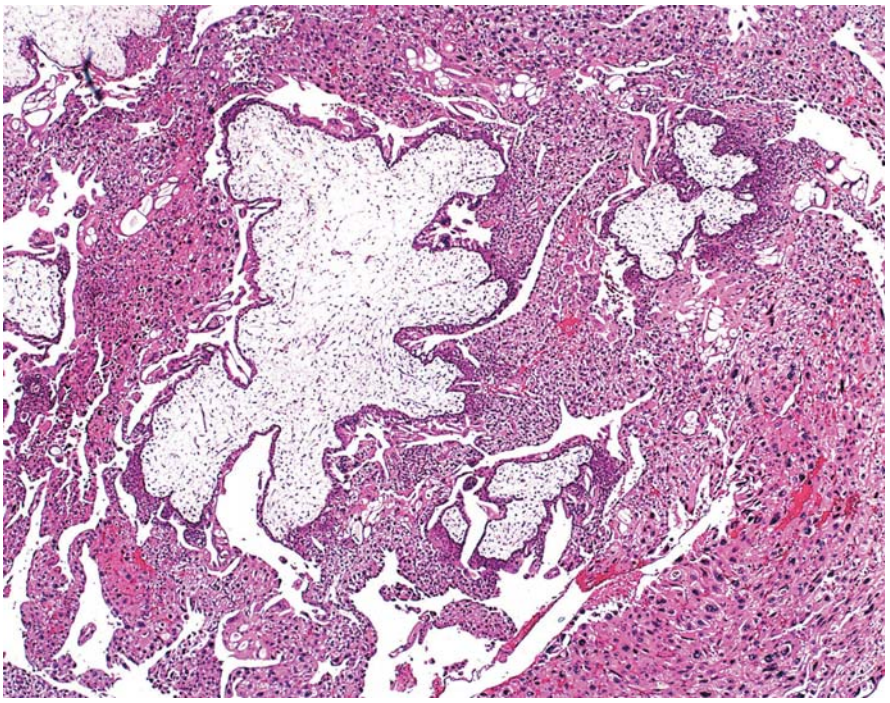

FIGURE 4.2. Complete hydatidiform mole. Marked circumferential hyperplasia of trophoblast is seen along the surface of most of the edematous villi in this field. Cisterns are ill defined but all the villi are edematous.

project randomly along the surface of edematous villi (Figs. 4.1 and 4.2).[1;2;4;52;53] The trophoblastic hyperplasia can involve smaller villi as well as the large villi with cisterns. This haphazard trophoblastic proliferation contrasts with the normal trophoblastic proliferation in an immature placenta that maintains polar orientation at the anchoring villi and is not present on other villi. The degree of trophoblastic hyperplasia in a complete mole is highly variable. Often the hyperplasia is moderate to marked with large masses of trophoblast that may be confluent, extending from the surface of the villi. Occasional cases, however, have only minimal trophoblastic hyperplasia.

In *early complete mole*, detected at a younger gestational age (<12 weeks), the villous features are subtle and well-formed cisterns may be absent.[14;15;54–56] These early complete moles demonstrate less advanced degrees of villous abnormalities at both the gross and microscopic levels. The gross specimen may not show obvious hydropic villi. Microscopically, early complete moles show bulbous, cauliflower-like terminal villi with hypercellular villous stroma and karyorrhexis (Figs. 4.4 and 4.5).[14;54;57] At this stage, villi show relatively smooth contours. Even these small villi show edema, however, with sparsely cellular stroma showing widely separated fibroblasts. In very early complete mole the trophoblastic hyperplasia tends to be focal but definite, with proliferation of both cytotrophoblastic (CT) and syncytiotrophoblastic (ST) cells from the villous surface. If present, the ST along the chorionic plate also is hyperplastic.

The trophoblast that accompanies complete moles also often shows atypia, with enlarged, pleomorphic, and hyperchromatic nuclei. Mitotic activity may be brisk. These findings contrast with those found in the trophoblast of an abortus that does not display marked nuclear atypia. In addition, "layering" of atypical implantation type trophoblast on fibrin is a

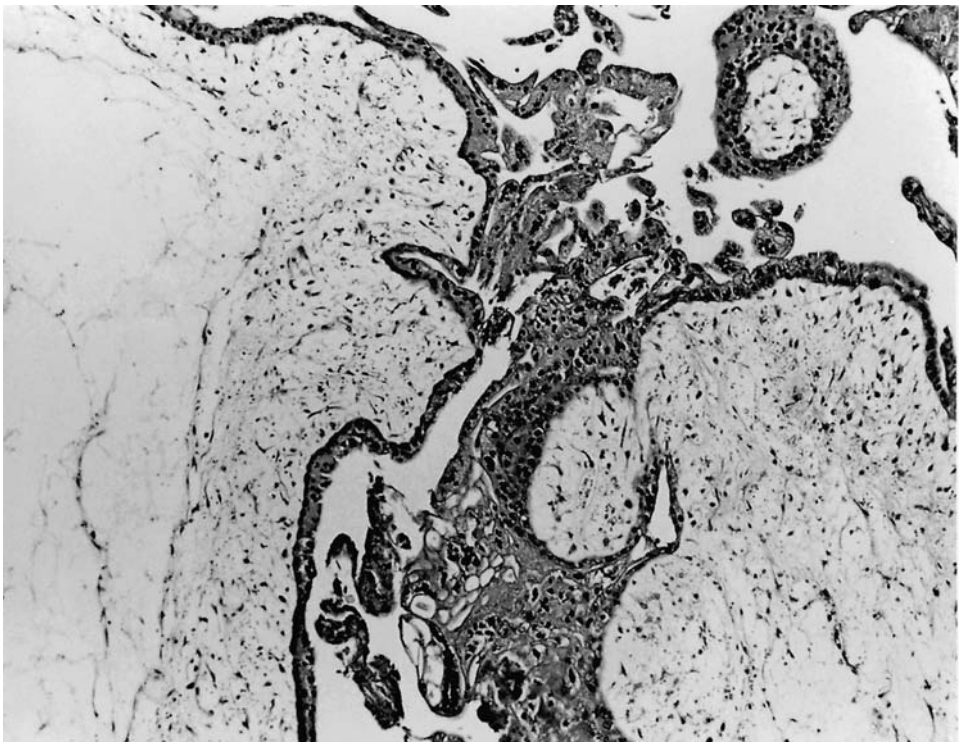

FIGURE 4.3. Complete hydatidiform mole. Portions of edematous, avascular villi in a complete mole show hyperplasia of the trophoblastic covering. A portion of a cistern is present in the villus to the left of center. Note the smaller villus with edema in the right upper corner. Occasional smaller villi such as these are commonly found in complete mole specimens.

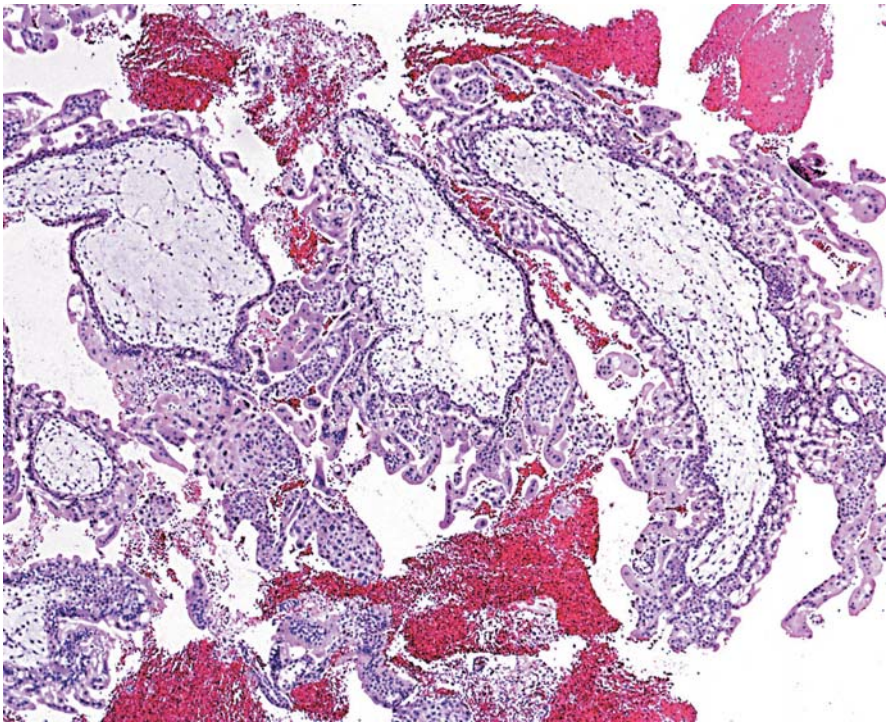

FIGURE 4.4. Early complete hydatidiform mole. The villi are bulbous with mildly hypercellular stroma that shows minimal edema with no well-formed cisterns. The trophoblast show circumferential hyperplasia, however, which distinguishes this early complete mole from a hydropic abortus.

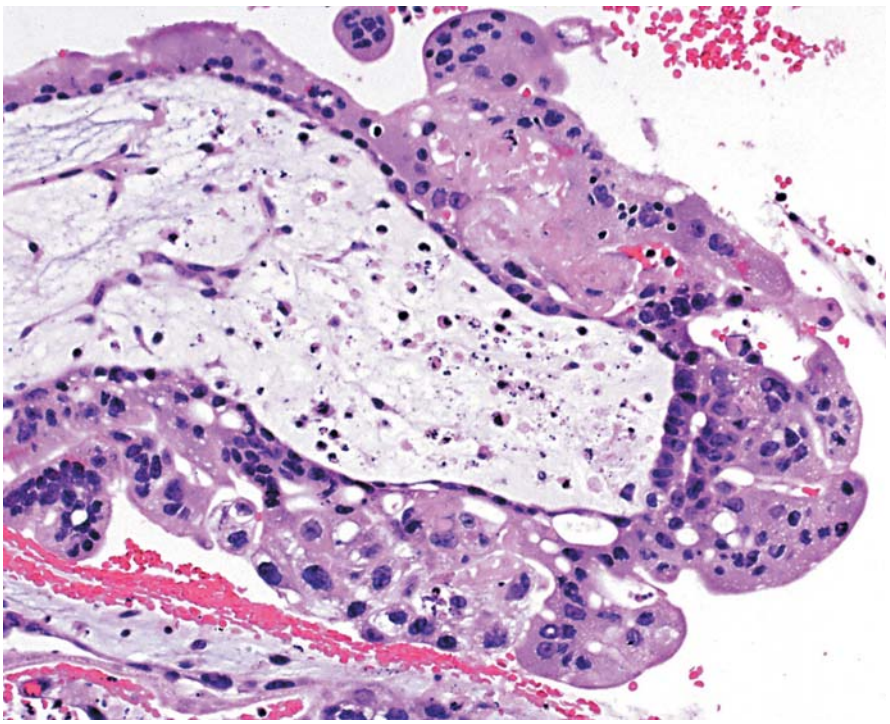

FIGURE 4.5. Early complete hydatidiform mole. Portion of a villus from early complete mole shows minimal edema and karyorrhexis of the stroma. The trophoblast demonstrates slight but definite circumferential hyperplasia with minimal atypia.

very characteristic feature of complete moles. The amount of trophoblast and the degree of atypia present in moles have no apparent bearing on the subsequent clinical course, so grading the trophoblast is not helpful.[53]

With hydatidiform mole, especially complete mole, the trophoblastic infiltration of the placental implantation site typically is exaggerated, even in early complete mole (see Chapter 3).[14;58;59] Curettage, especially sharp curettage after suction extraction, can yield abundant, atypical trophoblast including many intermediate trophoblastic cells from the implantation site (Fig. 4.6). This trophoblastic proliferation is a standard feature of hydatidiform moles, and should not be misinterpreted as a coexisting placental site trophoblastic tumor. As with the trophoblastic proliferation that covers the villi, the amount of trophoblast and the atypia in the implantation site do not influence the diagnosis or prognosis of these lesions.

Partial Mole

Partial mole, as the name implies, shows only partial involvement of villi by edema and trophoblastic hyperplasia (Table 4.3).[1;2;10;13;60] The result is two populations of villi, one composed of enlarged and hydropic and one of small, nonmolar villi that do not show edema (Figs. 4.7 to 4.9). Frequently the nonedematous villi are fibrotic, especially in partial moles that are greater than 12 weeks.[17] Typically the enlarged villi have irregular, scalloped borders with deep infoldings (Figs. 4.7 and 4.8) that contrast to the smooth or rounded contour of villi in complete mole. Transverse sectioning of the invaginations yields trophoblastic "inclusions" in the villous

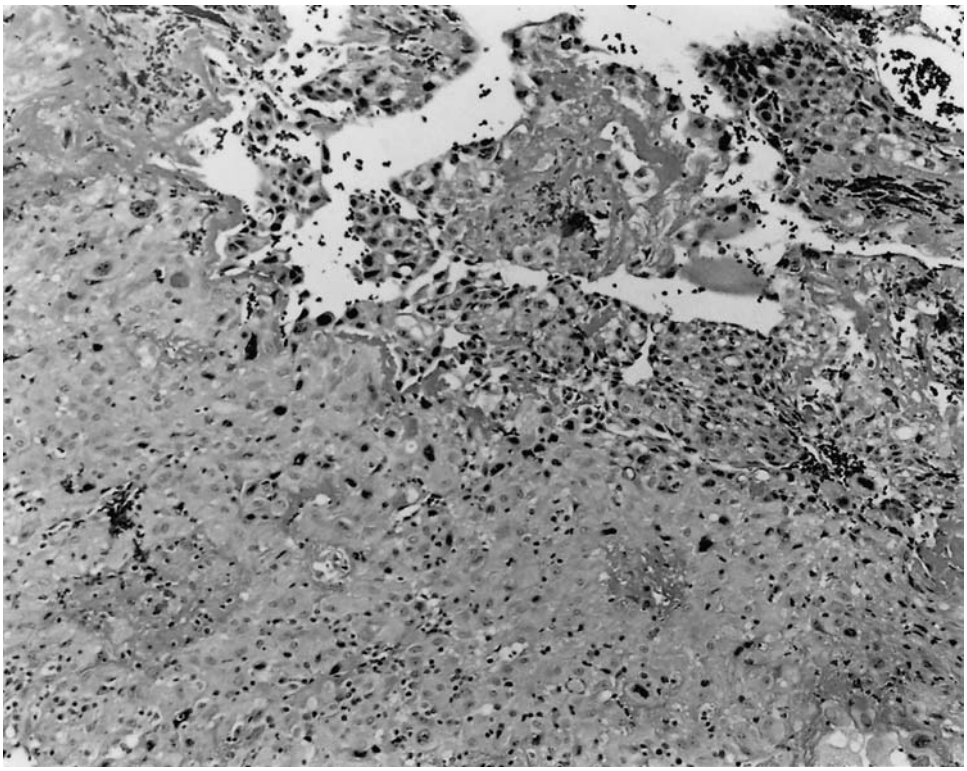

FIGURE 4.6. Exaggerated placental implantation site of complete mole. Abundant, atypical trophoblastic cells are present at the implantation site of a complete mole. The trophoblastic cells in this field are not associated with villi, but other fields showed markedly edematous villi of a complete mole. This exaggerated placental site has no significance by itself.

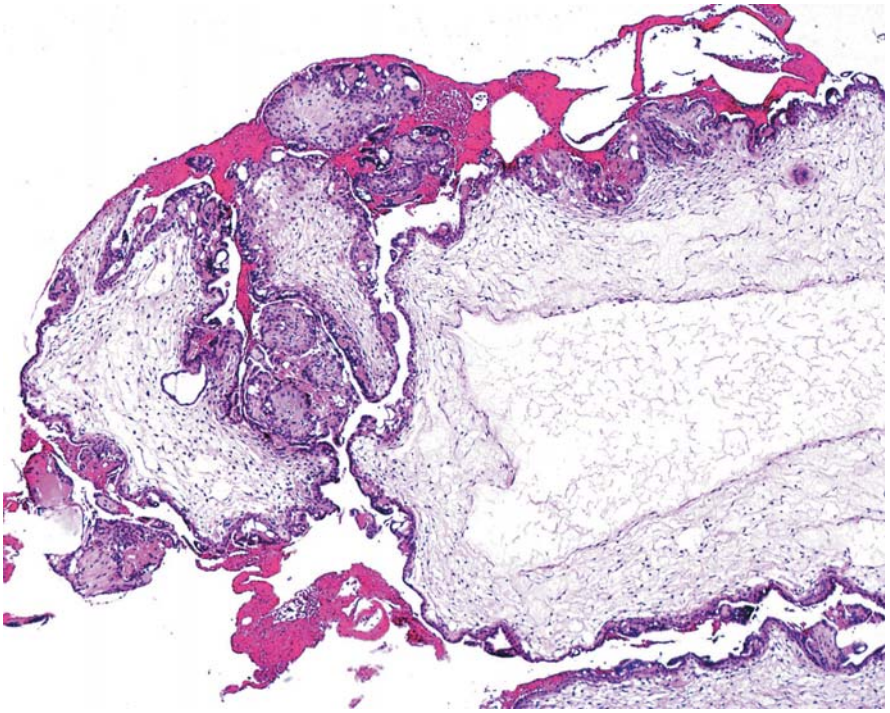

FIGURE 4.7. Partial hydatidiform mole. A mixture of large, edematous villi and small, fibrotic villi characterizes partial mole. A markedly enlarged villus to the right contains a central cistern. Irregular, patchy hyperplasia of trophoblast is present along the surface of the larger villi.

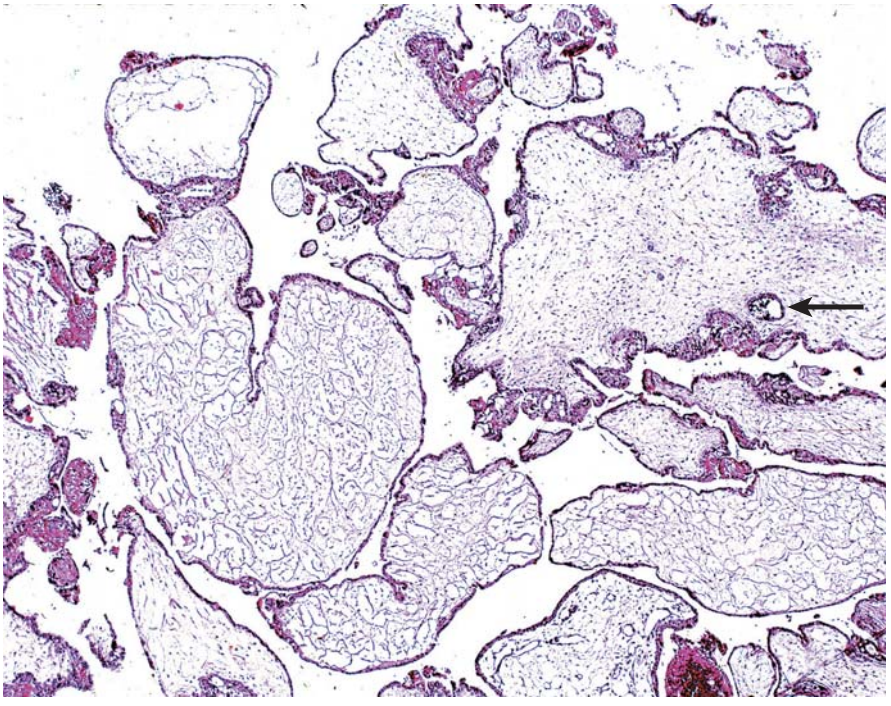

FIGURE 4.8. Partial hydatidiform mole. Many of the enlarged villi show irregular outlines. Note trophoblastic inclusion at the right of the field formed by invagination of the surface of the villi into the stroma (*arrow*).

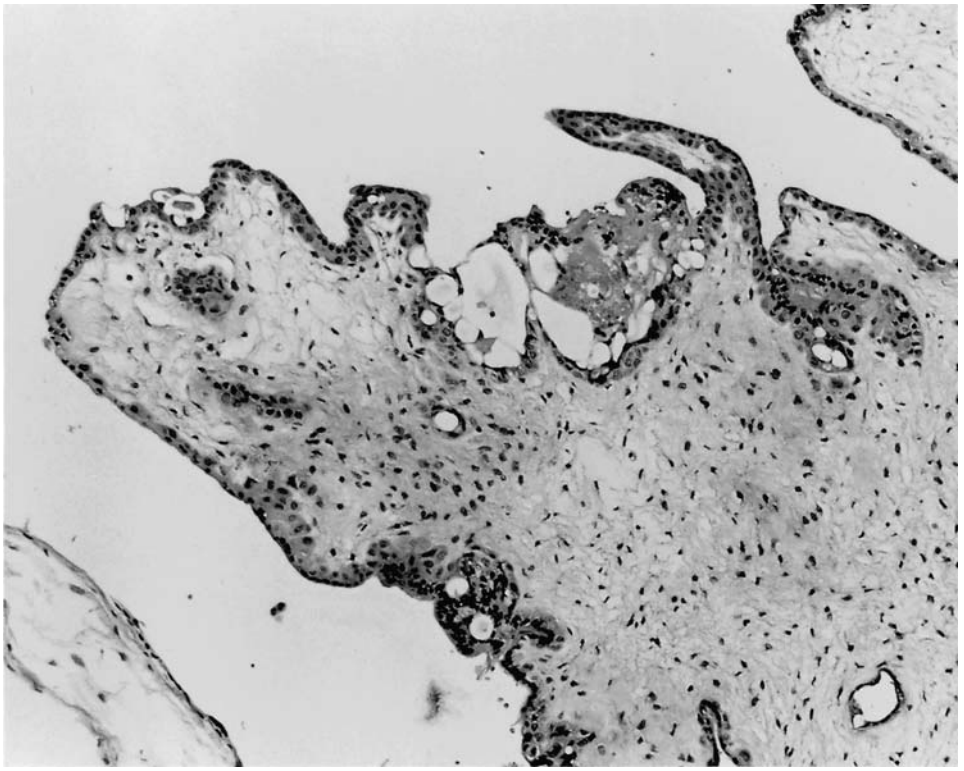

FIGURE 4.9. Partial hydatidiform mole. Portion of an edematous villus shows haphazard foci of trophoblastic hyperplasia along the surface and infoldings that form inclusions in the stroma.

stroma. Trophoblastic hyperplasia usually is limited, with only small foci of syncytiotrophoblast projecting randomly from the surface of the affected villi (Fig. 4.9). Another frequent finding in partial moles is microscopic evidence of fetal development, such as fetal tissue, erythrocytes in villous capillaries, or fetal membranes. Fetal tissue is not invariably present in partial mole, however, and in some studies this feature has been found in fewer than one half of cases.[61] The implantation site trophoblast usually shows only focal and mild atypia compared to the implantation site seen in complete mole.[59]

Differential Diagnosis

Complete Versus Partial Mole

The distinction between complete and partial mole is straightforward when the characteristic features of either entity are pronounced. Multiple edematous villi with large cisterns and diffuse trophoblastic hyperplasia of complete moles contrast with the more limited villous edema and focal trophoblastic hyperplasia of partial moles. Another feature that separates complete from partial mole is the generalized edema of the villi in the complete mole, which contrasts with the mixture of two populations of villi, with fibrosis of some of the villi in partial mole. Partial moles often show evidence of development of a fetus or embryo that generally is not seen in complete mole.

Some cases have obvious features of a mole, and the distinction between a complete mole and a partial mole is not clear cut. In these cases the morphologic features that allow separation of complete and partial mole are ambiguous, even after extensive histologic sampling. Diagnosis of a mole early in pregnancy can be particularly difficult, and more moles are now detected as early as the 7th or the 8th week of pregnancy.[14;15;17;56] In such cases the differential diagnosis is especially challenging, because the

cistern formation and trophoblastic hyperplasia are less pronounced than those found several weeks later in gestation.

Rarely a complete mole may occur as a twin gestation in conjunction with a normal placenta.[40;60;62–65] In these cases the curettage specimens contain a mixture of normal sized and molar villi, which mimics a partial mole. Thus, it may not always be possible to classify a specimen accurately as a complete or a partial mole by morphology alone. Management of either type of mole requires monitoring of serum hCG titers after evacuation. It is important to characterize the type of mole whenever possible, however, as partial mole more frequently resolves spontaneously and is only very rarely complicated by choriocarcinoma. Because of the relatively low rate of persistent GTD associated with partial mole, further management of this lesion requires shorter-term β-hCG follow-up than does complete mole.

Tissue from moles should be generously sampled (at least 4 cassettes) to ensure accurate diagnosis. The histologic features that permit the distinction of complete and partial mole as well as a hydropic abortus may not be present in all sections and therefore adequate sampling is essential. Flow cytometric analysis of paraffin blocks for ploidy is rarely used in diagnosis because of the cost and the occasional overlap in karyotypes between the two types of mole. Nonetheless, many studies suggest that ploidy is useful in difficult cases,[43;44;46;52;57;60;66] especially if the morphologic features are ambiguous and there is a pressing clinical need to determine whether the mole is complete or partial. In addition, the use of immunohistochemistry for $p57^{KIP2}$ may be useful in distinguishing the two forms of hydatidiform mole,[46–48] although this ancillary technique requires further validation.

Hydatidiform Mole Versus Hydropic Abortus

Another frequent consideration in the differential diagnosis of hydatidiform mole is the nonmolar hydropic abortion with villous edema (see Chapter 3).[7;52;67;68] Microscopically, the edema of the hydropic abortus can be striking. Gross specimens from hydropic abortions generally are smaller, however, and villous enlargement is not seen by either the clinician or the pathologist on gross examination (Table 4.3). It is important to keep microscopic observations in context with the gross findings. Most hydropic abortions yield only one or a few cassettes of tissue, whereas moles tend to be voluminous. These generalizations usually hold, but in some cases of hydatidiform mole the villi are also not grossly visible. This is especially true if part of the molar tissue was spontaneously aborted prior to curettage, if the mole is evacuated very early in gestation, if there is collapse of villi secondary to suction curettage, or if the specimen is a partial mole with limited tissue.

Several microscopic features distinguish hydropic abortus from mole.[1;2] In hydropic abortion the villi are edematous and avascular. Some also may show trophoblastic inclusions.[69] Occasional small cisterns occur in hydropic abortuses, but they are infrequent and do not cause gross villous enlargement. The most useful feature for separating a mole from a hydropic abortus is the distribution of the villous trophoblast. In a mole at least occasional villi show circumferential hyperplasia of trophoblast along their surface, whereas in the hydropic abortus the proliferating trophoblast has a polar distribution, projecting only from one surface of the anchoring villi. Because trophoblastic hyperplasia may be limited and focal, especially in a partial hydatidiform mole, thorough sampling may be needed to establish the diagnosis. In questionable cases it often is best to process multiple blocks to assess the overall edema and trophoblastic growth pattern. Nonmolar hydropic abortus specimens may be diploid, triploid, or aneuploid,[40;69] so DNA ploidy analysis is useful only for the separation of mole from hydropic abortus when it is combined with careful pathologic evaluation to identify the key morphologic features of a molar gestation.[60;70]

Villous abnormalities associated with trisomy include scalloped villous outlines and pseudoinclusion into the stroma. These features can closely simulate partial mole. The trophoblastic cells usually show a polar orientation in these cases, which can help in the diagnosis. In some cases, however, the features are not sufficiently clear to allow a definitive interpretation, and a descriptive diagnosis is appropriate.

Other placental abnormalities such as Beckwith Wiedemann syndrome or placental angiomatous malformation that can mimic partial mole are typically seen in more advanced gestations, in the second half of pregnancy, and are not a significant issue in the differential diagnosis of early abortion specimens.[60;71;72] These latter abnormalities are also referred to as "placental mesenchymal dysplasia" and may show marked hydrops of placental stem villi that can mimic a partial mole in later pregnancy. In contrast to a partial mole, however, no abnormal trophoblast proliferation or trophoblastic "inclusions" are seen in the enlarged villi.[71]

Hydatidiform Mole Versus Choriocarcinoma

The marked trophoblastic hyperplasia and cytologic atypia found in some cases of complete moles closely resemble the patterns found in choriocarcinoma. These cases can show large sheets of trophoblast with an alternating arrangement of cytotrophoblast and syncytiotrophoblast mixed with hemorrhage. Trophoblast may be prominent in the original curettage samples (Fig. 4.10) or in subsequent curettings done for abnormal elevation of hCG titers (Fig. 4.11). As long as edematous chorionic villi are present, no matter how much trophoblastic proliferation is present, the lesion is a hydatidiform mole. In addition to the absence of chorionic villi, the diagnosis of choriocarcinoma requires the presence of necrosis and destructive infiltrative growth of trophoblast into the myometrium.

Rarely, choriocarcinoma may arise in a developing placenta, and this usually is seen in a placenta from a second- or third-trimester gestation.[73] We have seen choriocarcinoma arising in association with retained intrauterine villi from either an abortion or a term preg-

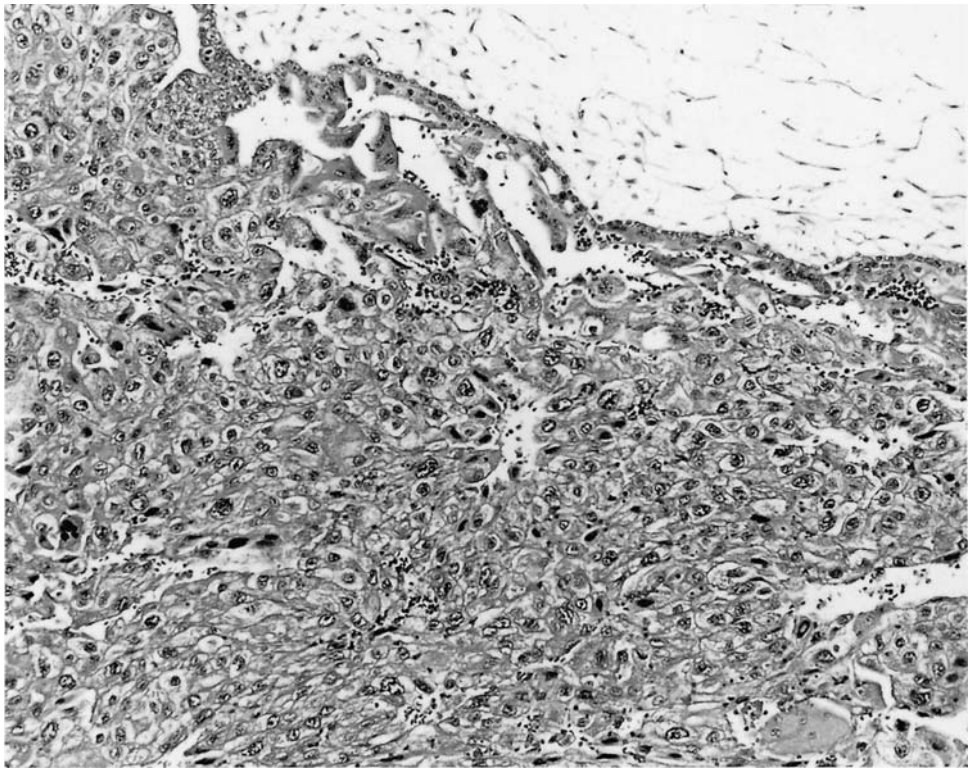

FIGURE 4.10. Hydatidiform mole. Prominent hyperplasia of the trophoblast from the surface of a villus of a complete mole.

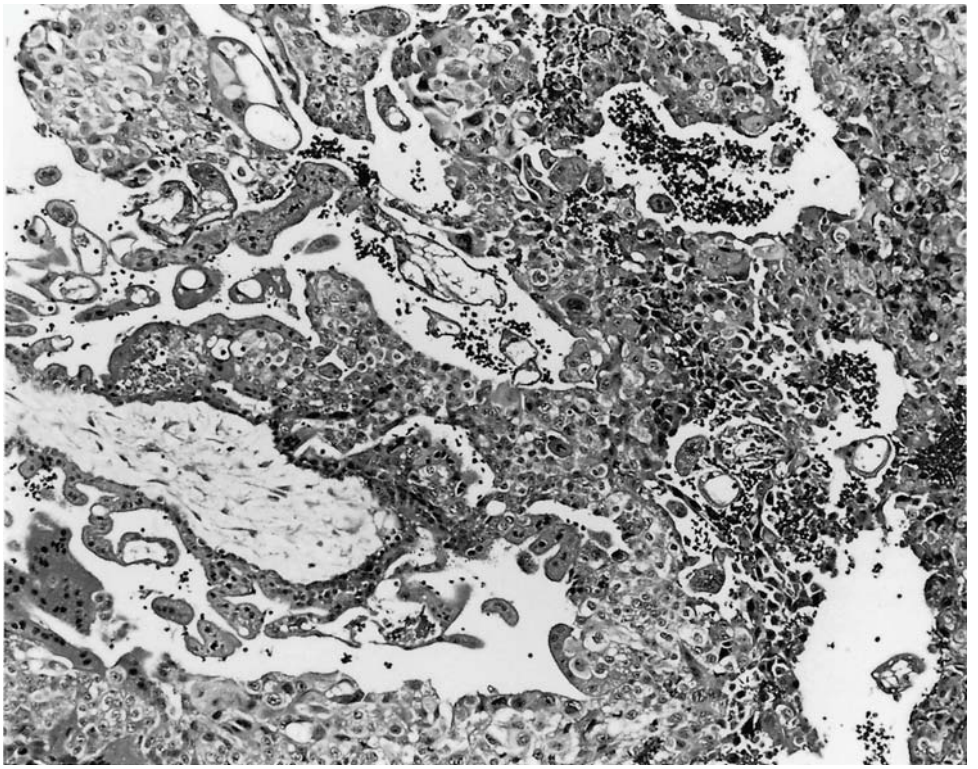

FIGURE 4.11. Persistent complete mole. Persistent mole obtained by curettage several weeks after initial evacuation of a complete hydatidiform mole. The trophoblastic proliferation is striking, but the presence of a villus to the left of center indicates that the diagnosis is persistent mole, not choriocarcinoma.

nancy. In these very unusual cases, curettage specimens show a few villi that tend to be hyalinized or fibrosed mixed with fragments of tissue showing choriocarcinoma. Presumably in these cases the neoplasm arises from the retained trophoblastic cells.

Persistent Postmolar Gestational Trophoblastic Disease and Invasive Hydatidiform Mole

After a hydatidiform mole has been evacuated, a subsequent curettage may be done for persistence or elevation of follow-up hCG titers or for significant uterine bleeding.[74–76] The repeat curettage may show persistent hydatidiform mole, choriocarcinoma, retained implantation site, no evidence of trophoblastic tissue, or, rarely, a new pregnancy.[74] If the specimen contains persistent hydatidiform mole, it will show residual molar villi mixed with trophoblast (Fig. 4.11). Usually the amount of tissue and villi are greatly reduced compared to the original curettage specimen, but as long as villi are present, the diagnosis remains that of persistent intracavitary mole. Choriocarcinoma is diagnosed when there is abundant trophoblast without villi that shows a dimorphic arrangement of syncytiotrophoblast and mononucleate trophoblast. In addition, it is necessary to see tumor necrosis or destructive infiltrative growth by trophoblast into the myometrium. Scant trophoblastic tissue without villi is not choriocarcinoma but persistent trophoblast (Fig. 4.12).[77]

With invasive hydatidiform mole, hydropic molar villi and hyperplastic trophoblast either invade myometrium or are present at other sites, usually the vulva, vagina, or lungs.[1;2;78] To establish the diagnosis, it is necessary to clearly identify molar villi beyond the endometrium. In curettings this requires find-

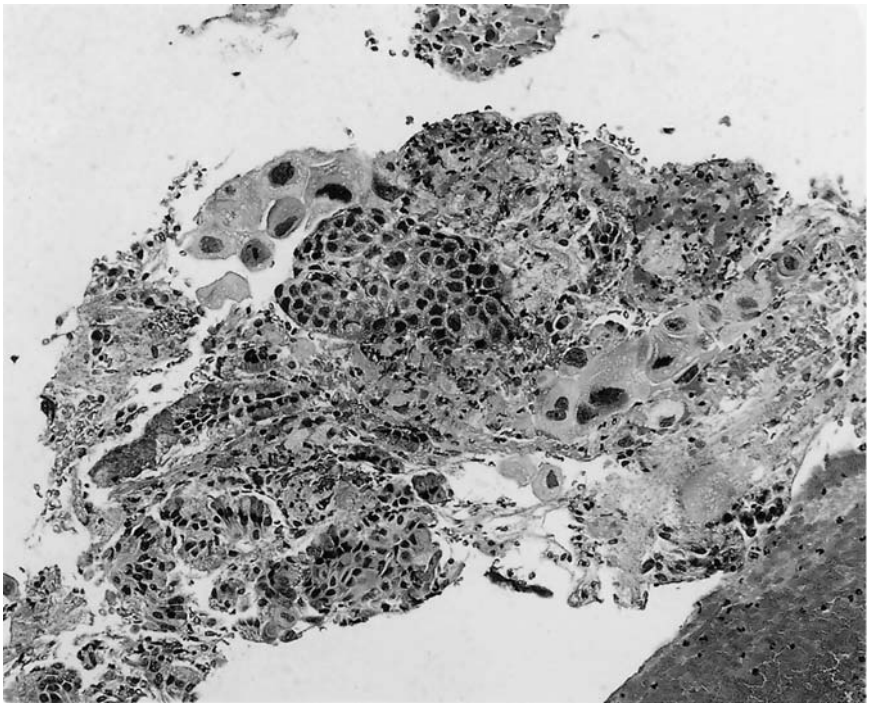

FIGURE 4.12. Persistent trophoblast following hydatidiform mole. A cluster of trophoblastic cells found in curettage specimen after evacuation of a mole. Although no villi are present, the amount of trophoblast is scant and shows no evidence of invasion. The quantity of tissue is not sufficient for a conclusive diagnosis, and this tissue should be diagnosed as "persistent trophoblast."

ing the villi within myometrial smooth muscle, an extremely rare event. Consequently, invasive mole is almost never diagnosed by endometrial biopsy or curettage. It is important to remember that the presence of residual mole in a recurettage specimen does not represent invasive mole in the absence of demonstrable myometrial invasion.

Clinical Queries and Reporting of Hydatidiform Mole

One of the most important clinical questions in the evaluation of an abortion specimen is whether gestational trophoblastic disease is present, as hydatidiform mole, choriocarcinoma, or PSTT can present as a spontaneous or missed abortion. Even a therapeutic abortion for an apparently normal gestation may reveal an unsuspected hydatidiform mole.

Often the clinician suspects a hydatidiform mole from the clinical history and from findings such as rapid uterine enlargement, abnormally high hCG titers, or toxemia in the first trimester. Ultrasound findings may support the clinical impression of a mole. At other times hydatidiform mole is clinically suspected when visibly enlarged, edematous villi are encountered at curettage. In such cases the logical questions are whether a mole is present, and, if so, whether it is a complete or partial mole. In the distinction between a complete versus a partial mole, the pathologist should err on the side of a complete mole, as the partial moles have few significant clinical consequences. With either type of mole, the grading of the trophoblast does not have clinical significance in terms of the overall risk for persistent GTD.[53] If there is any doubt about whether a specimen should be classified as an abortus with hydropic villi or as a hydatidiform mole, more tissue should be submitted if available. If a case remains equivocal, the gynecologist should be cautioned to follow the patient to be certain that hCG titers return to normal before pregnancy is attempted again.

Patients with known hydatidiform mole who are being followed may undergo repeat curettage for continued bleeding or for abnormally persistent or elevated hCG titers. If the biopsy shows trophoblastic tissue, then the presence or absence of chorionic villi is important and should be clearly reported. Molar villi generally indicate persistent intrauterine mole rather than invasive mole or development of choriocarcinoma.[77] Immature but normal villi indicate a new pregnancy unrelated to GTD.

Trophoblastic Neoplasms

Choriocarcinoma

General Features

Gestational choriocarcinoma can occur in the uterine cavity following any type of pregnancy.[1;2;4] As a rule, the risk of choriocarcinoma increases with the abnormality of the antecedent gestation. Complete hydatidiform mole is a major predisposing factor, and about half the cases of choriocarcinoma follow a complete mole. Choriocarcinoma also can arise from the trophoblast of an abortion or a term pregnancy. Consequently, this lesion may be present whenever abnormal vaginal bleeding occurs during the postpartum period in a young woman who has had a pregnancy of any type. Patients with choriocarcinoma also can present with metastatic disease without uterine signs or symptoms. Typically, the patient with choriocarcinoma has markedly elevated serum hCG titers.

Pathologic Features

Choriocarcinoma is hemorrhagic and necrotic, composed of trophoblastic cells without villi that invade normal tissues (Fig. 4.13). The two

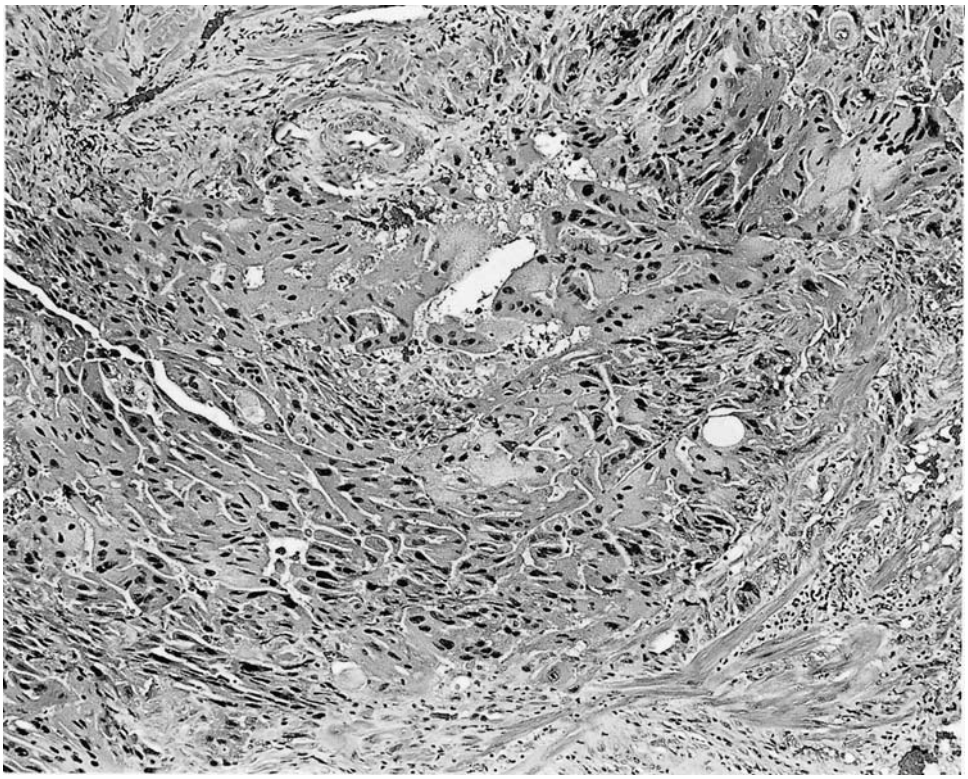

FIGURE 4.13. Choriocarcinoma. A mass of trophoblast with prominent syncytiotrophoblast in a curettage specimen of a young woman with abnormal uterine bleeding. Abundant trophoblastic tissue is present with no associated villi. The trophoblast shows invasion of the myometrium.

main diagnostic features are an absence of chorionic villi and a dimorphic population of trophoblast cells (Figs. 4.13 to 4.15). The first criterion, absence of villi, is important, as the proliferative trophoblast of hydatidiform moles or of early normal pregnancy can closely simulate the trophoblast of choriocarcinoma. The second criterion of choriocarcinoma, a dimorphic pattern of syncytiotrophoblastic (ST) cells alternating with nests or sheets of mononucleate trophoblast (cytotrophoblastic [CT] or intermediate trophoblastic [IT]) cells should be found, at least focally, to establish a histologic diagnosis of choriocarcinoma. Often, the characteristic pattern of choriocarcinoma is readily apparent, but at times the dimorphic population of trophoblast may be difficult to recognize (Fig. 4.16). The admixture of ST with CT or IT cells yields a plexiform pattern. In these cases identification of ST cells is an important diagnostic feature. These cells contain multiple nuclei, ranging from 3 to more than 20 per cell, which are variable in size. Often the nuclei are pyknotic but they can be vesicular with prominent nucleoli. ST cells have dense eosinophilic to amphophilic cytoplasm with small vacuoles or large lacunae that often contain erythrocytes (Fig. 4.14 and 4.15). In contrast to ST, CT cells are small (about the size of a decidualized stromal cell) and uniform. They have a single nucleus with a prominent nucleolus, pale to clear cytoplasm, and distinct cell borders. Large IT cells with polygonal shapes and one or two large, hyperchromatic nuclei also occur in choriocarcinoma (Figs. 4.14 and 4.15). The percentage of IT cells in choriocarcinoma is highly variable, ranging from rare cells to the large majority of mononucleate trophoblastic cells. Typically,

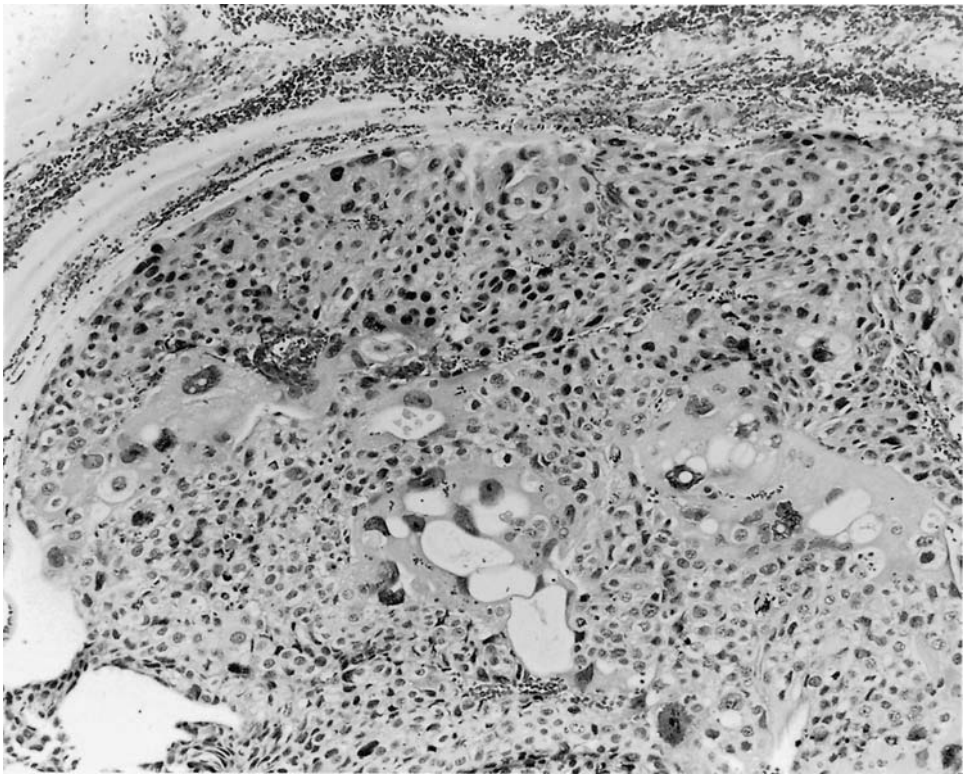

FIGURE 4.14. Choriocarcinoma. Dimorphic population of ST and CT cells in choriocarcinoma. Large ST cells with multiple nuclei and abundant, vacuolated cytoplasm are interspersed among CT and IT.

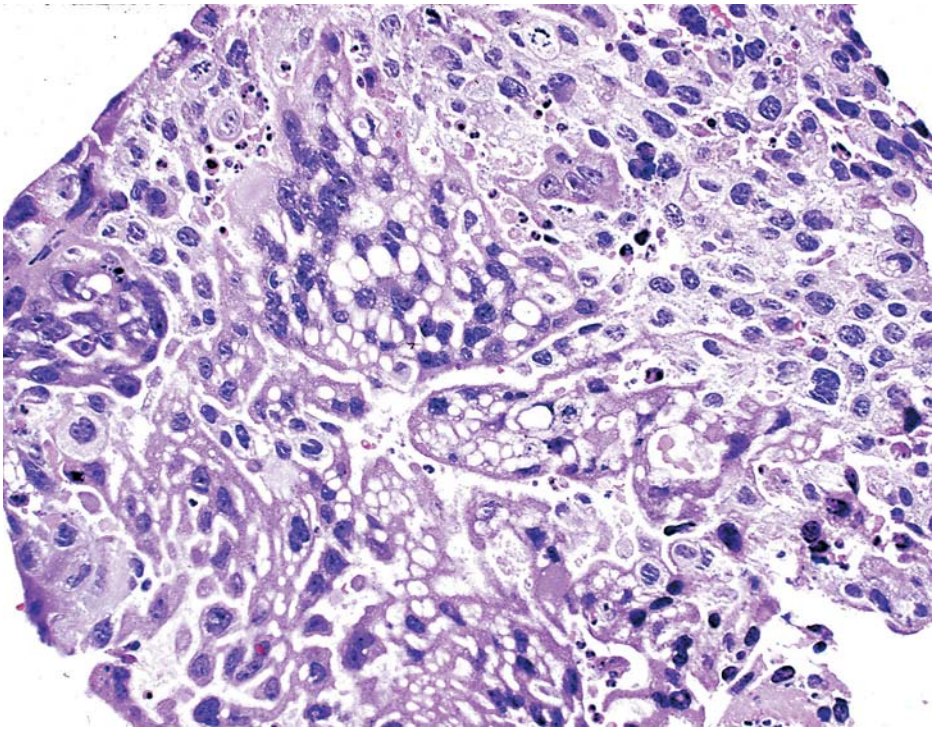

FIGURE 4.15. Choriocarcinoma. Endometrial curettings following a complete mole show ST cells containing multiple nuclei and cytoplasmic vacuoles and numerous IT interspersed. Although intermediate trophoblast is prominent, the juxtaposition of syncytiotrophoblast forming a dimorphic population establishes the diagnosis of choriocarcinoma.

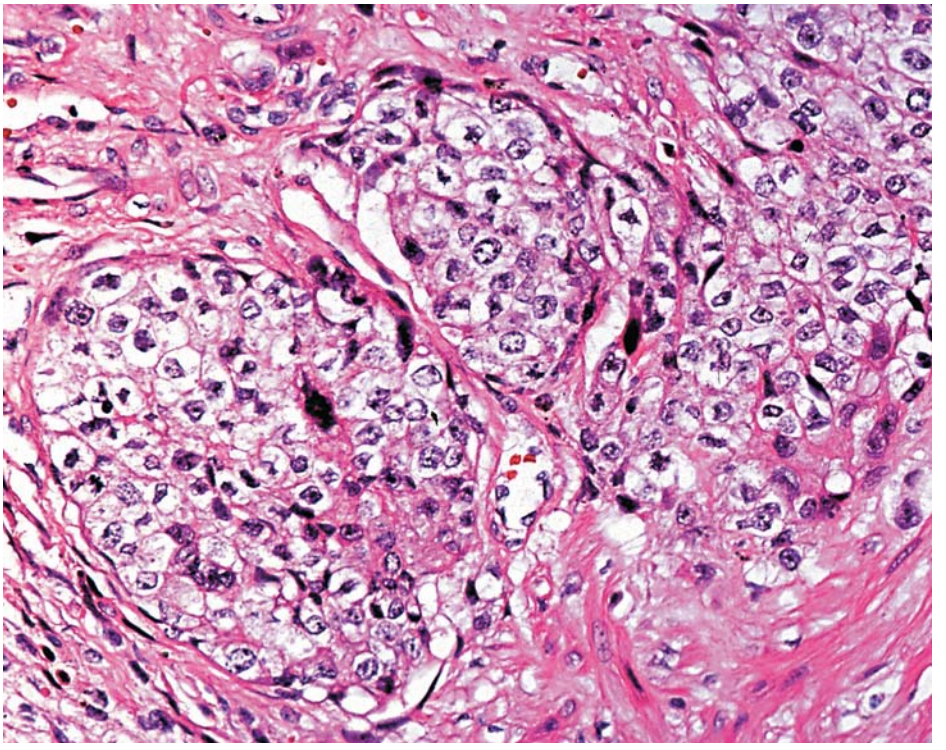

FIGURE 4.16. Choriocarcinoma. In this field ST cells are indistinct and CT cells predominate, yielding a pattern resembling poorly differentiated nontrophoblastic carcinoma.

TABLE 4.4. Immunohistochemistry of uterine trophoblastic tumors compared with nontrophoblastic tumors.

	Choriocarcinoma	PSTT	Epithelioid trophoblastic tumor	Nontrophoblastic uterine tumors
hCG	+++	+/–	+/–	+/–
Inhibin-α	++	++	++	–
hPL	+	+++	+/–	–
PLAP	+/–	–	++	+/–
Mel-CAM	++	+++	+/–	–
Keratin[a]	+++	+++	+++	+++[b]
EMA	+	++	++	++[b]
p63	+	–	+++	+

PSTT, Placental site trophoblastic tumor; hCG, human chorionic gonadotropin; hPL, human placental lactogen; PLAP, placental alkaline phosphatase; EMA, epithelial membrane antigen.

[a] Immunostaining for keratin AE1/AE3.

[b] Keratin and EMA immunostaining for carcinomas, only.

there is generalized enlargement of the trophoblastic cells with increased nuclear atypia in choriocarcinoma compared to normal trophoblastic cell populations in early pregnancy.

The amount of trophoblast in cases of choriocarcinoma is highly variable. There may be abundant neoplastic tissue, but frequently only a small amount of viable tumor associated with extensive hemorrhage is present. Small amounts of tumor may pose problems in diagnosis. While ST cells generally are prominent in uterine gestational choriocarcinoma, in occasional cases these cells are indistinct and CT and IT cells predominate. Immunohistochemical stains for hCG can be very helpful for demonstrating ST cells in such cases. The ST cells stain intensely for hCG, whereas CT and IT cells are generally nonreactive. The staining pattern will clearly demonstrate the plexiform pattern of ST cells. The ST cells of choriocarcinoma also show strong immunoreactivity for inhibin-α (Table 4.4).

Differential Diagnosis

The differential diagnosis of choriocarcinoma includes physiologic trophoblastic proliferations associated with normal pregnancies and the trophoblast associated with hydatidiform moles, as well as PSTT and nontrophoblastic tumors. Trophoblast of normal pregnancy can appear highly proliferative, especially at the implantation site of anchoring villi. In contrast to choriocarcinoma, the trophoblast in normal pregnancy usually is associated with small, immature chorionic villi and decidua. Occasionally, only trophoblast without villi is present in an abortion specimen. In such cases the trophoblast is small in quantity and lacks necrosis, significant hemorrhage, and atypical nuclear features. The finding of a significant amount of secretory endometrium, decidua, or placental implantation site favors the presence of normal trophoblast and not choriocarcinoma. The presence of atypia, including nuclear pleomorphism, macronucleoli, and abnormal mitotic figures, strongly suggests choriocarcinoma.

The marked trophoblastic proliferation that may accompany some hydatidiform moles also resembles choriocarcinoma (Figs. 4.10 and 4.11). This feature can be particularly problematic in persistent hydatidiform mole that is found in a repeat curettage, since villi often are sparse in these specimens. Nonetheless, as long as any villi are present the diagnosis is that of hydatidiform mole. Even without villi, a diagnosis of choriocarcinoma should be made only when atypical, dimorphic trophoblast without villi are present along with hemorrhage and tumor necrosis or unequivocal invasion of the myometrium by a dimorphic population of trophoblastic cells. In the absence of these features, the diagnosis should be persistent trophoblast.

Nontrophoblastic tumors may mimic choriocarcinoma when they show a large component

of giant cells. Anaplastic carcinomas and sarcomas with tumor giant cells may simulate choriocarcinoma, at least focally, and may rarely show choriocarcinomatous differentiation although this occurs in older women. Usually the clinical history helps resolve this question, as high-grade carcinomas and sarcomas generally occur in older postmenopausal patients, whereas trophoblastic tumors occur in women of reproductive age. Furthermore, many patients with choriocarcinoma have a history of a prior hydatidiform mole. In equivocal cases, immunohistochemical stains for β-hCG are useful for demonstrating syncytiotrophoblast. Inhibin-α also is very useful for demonstrating trophoblast tissue (Table 4.4). Because both choriocarcinoma and anaplastic carcinoma are epithelial tumors, immunostains for cytokeratin are less useful in establishing the diagnosis.

Rarely choriocarcinoma may be found in a postmenopausal patient. In such cases the tumor may represent gestational choriocarcinoma with a long latent period or it may represent somatic carcinoma with choriocarcinomatous transformation.[79;80] PSTT and epithelioid trophoblastic tumor are discussed and compared with choriocarcinoma in the following section.

Placental Site Trophoblastic Tumor

General Features

The placental site trophoblastic tumor (PSTT) is a rare form of trophoblastic neoplasia composed predominantly of implantation site IT.[1;2;58;81–84] Like other forms of GTD, it almost always occurs during the reproductive years. PSTT is typically diagnosed at the time a curettage is performed in a woman who is thought to be pregnant, usually with a preoperative diagnosis of a missed abortion; but in contrast to choriocarcinoma, this tumor rarely is directly associated with a recent pregnancy.[85–89] Molecular genetic analysis has established the trophoblastic origin of these tumors.[90] The hCG titer is generally low and may not be noticeably elevated if a sensitive assay method is not used. Because PSTTs extensively infiltrate the myometrium, the uterus can be perforated during curettage. These neoplasms usually are benign, despite destructive growth in the myometrium. About 15% of reported tumors have shown aggressive malignant behavior with disseminated metastases.

Pathologic Features

PSTT typically produces a mass lesion. These tumors range from focal lesions 1 to 2 cm in diameter to large masses that replace much of the corpus. As a consequence, curettings of PSTT typically yield multiple fragments of neoplastic tissue. Microscopically PSTT is composed predominantly of implantation site IT cells that invade normal tissues (Fig. 4.17).[91] These cells generally are polyhedral and grow in cohesive masses that often show areas of necrosis (Figs. 4.18 and 4.19). The curettage specimens usually include fragments of myometrium infiltrated by IT cells. The IT cell cytoplasm is generally amphophilic with occasional clear vacuoles and distinct cell borders. Some parts of the tumor, especially in areas of myometrial invasion, are composed of spindle-shaped cells. Most cells have a single irregular and hyperchromatic nucleus, but binucleate and multinucleate IT cells are also present. Marked variation in nuclear size and shape is often a feature of the tumor (Figs. 4.18 and 4.20). Some nuclei have deep folds or grooves, and others may have pseudoinclusions as a result of large cytoplasmic invaginations. Scattered ST cells with several nuclei and vacuolated cytoplasm are also present. Mitotic activity is usually low but can be brisk including occasional abnormal forms.

Besides the characteristic cytologic features of the individual cells, the growth pattern of intermediate trophoblast in PSTT is an important diagnostic feature. When myometrium is present in the biopsy, the confluent masses of cells infiltrate and dissect between smooth muscle fibers (Fig. 4.21). Furthermore, in PSTT there is a characteristic pattern of vascular invasion in which the intermediate trophoblast surrounds and replaces the vessel wall while retaining its overall structural integrity

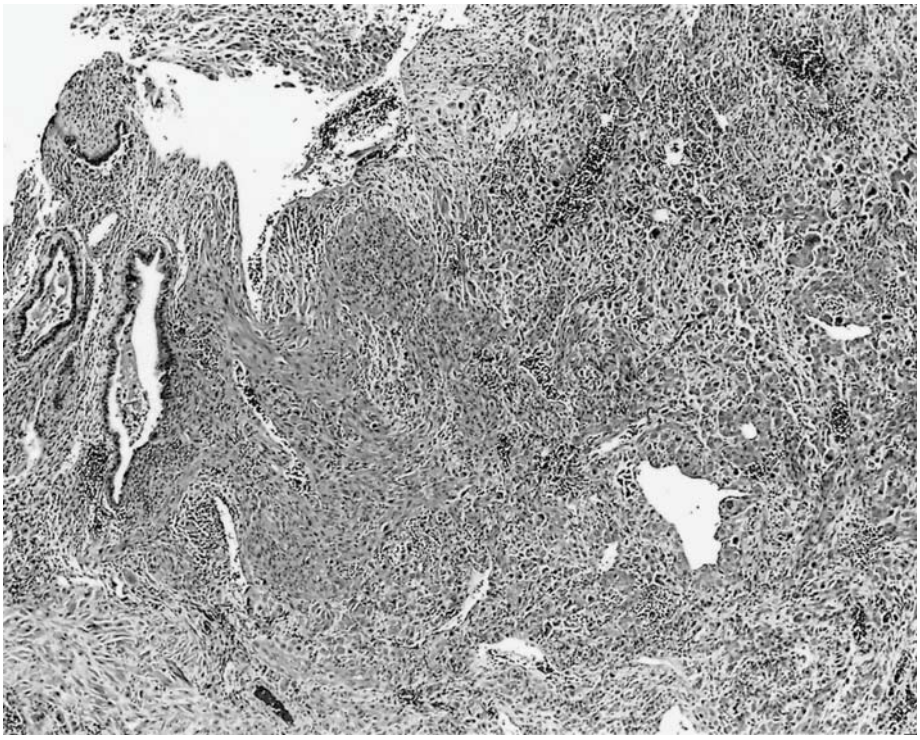

FIGURE 4.17. Placental site trophoblastic tumor. Low magnification shows PSTT invading endometrium and myometrium. Residual endometrium is present on the left side of the micrograph.

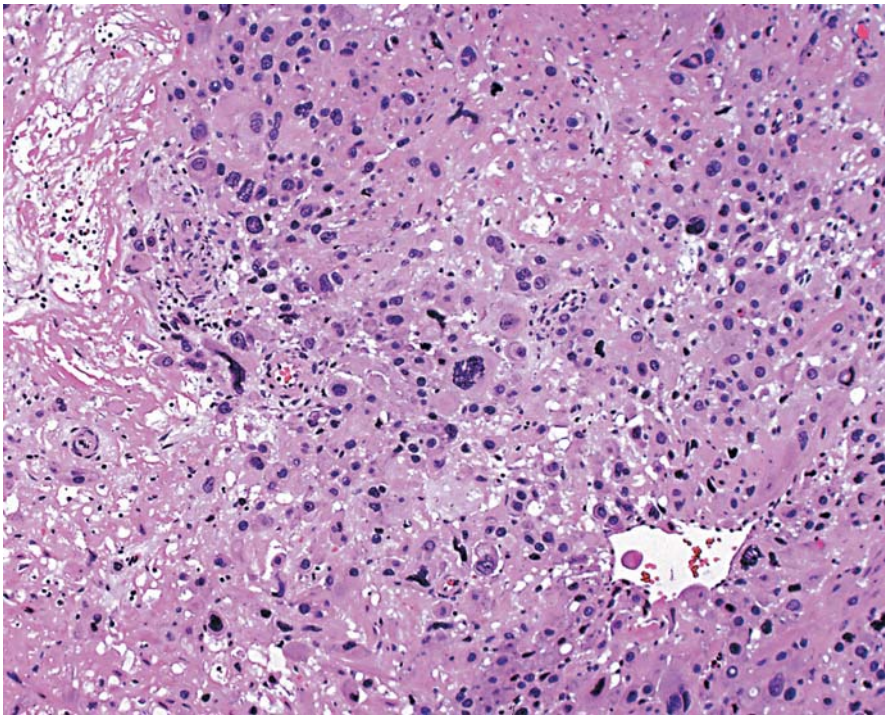

FIGURE 4.18. Placental site trophoblastic tumor. The cells are pleomorphic and generally contain a single hyperchromatic nucleus. There is moderate variation in nuclear size. In the right lower corner the IT infiltrate and replace the wall of a blood vessel while preserving the lumen. Fibrinoid material is present on the left side.

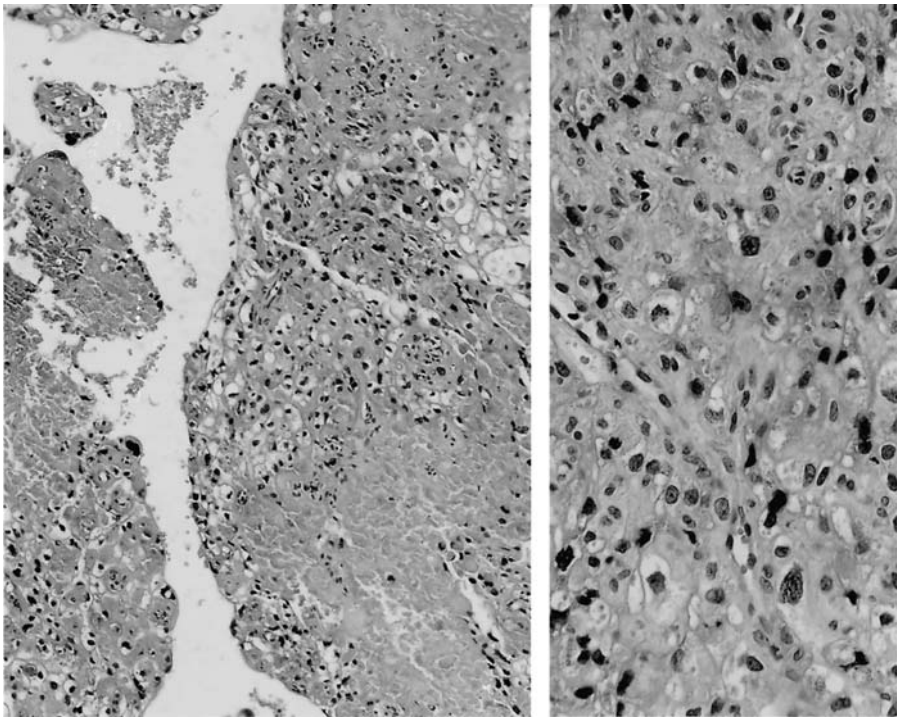

FIGURE 4.19. Placental site trophoblastic tumor. *Left:* Fragments of a PSTT in a curettage specimen show sheets of intermediate trophoblast with associated necrosis. The presence of necrosis is a helpful feature for distinguishing this tumor from an exaggerated placental site. *Right:* Higher magnification of the tumor shows characteristic IT cells.

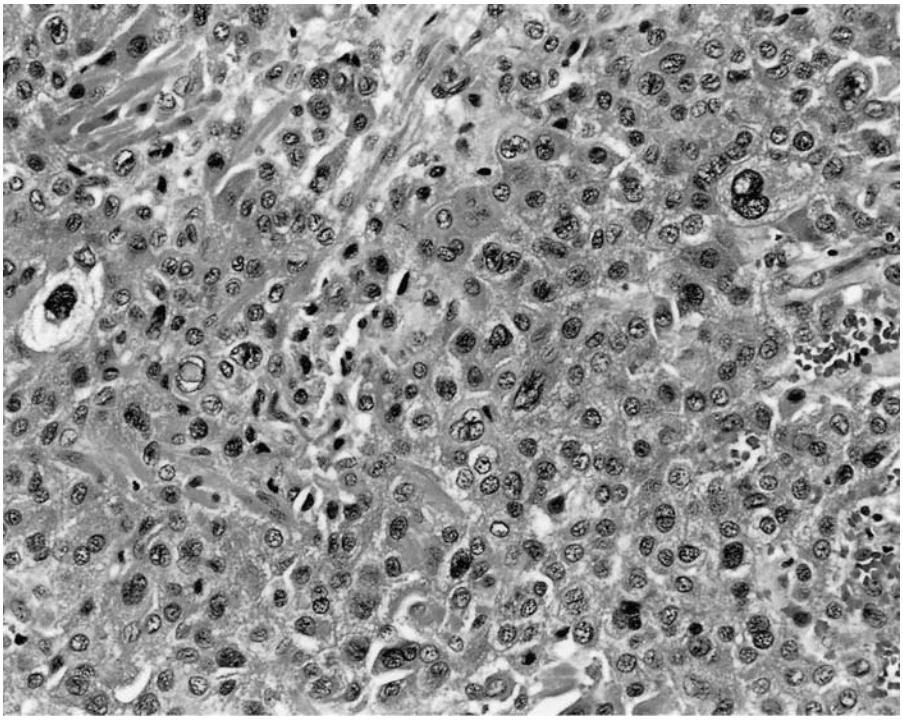

FIGURE 4.20. Placental site trophoblastic tumor. The tumor is composed of a monomorphic population of IT cells with hyperchromatic, irregular nuclei and a moderate amount of eosinophilic cytoplasm. The nuclei vary in size.

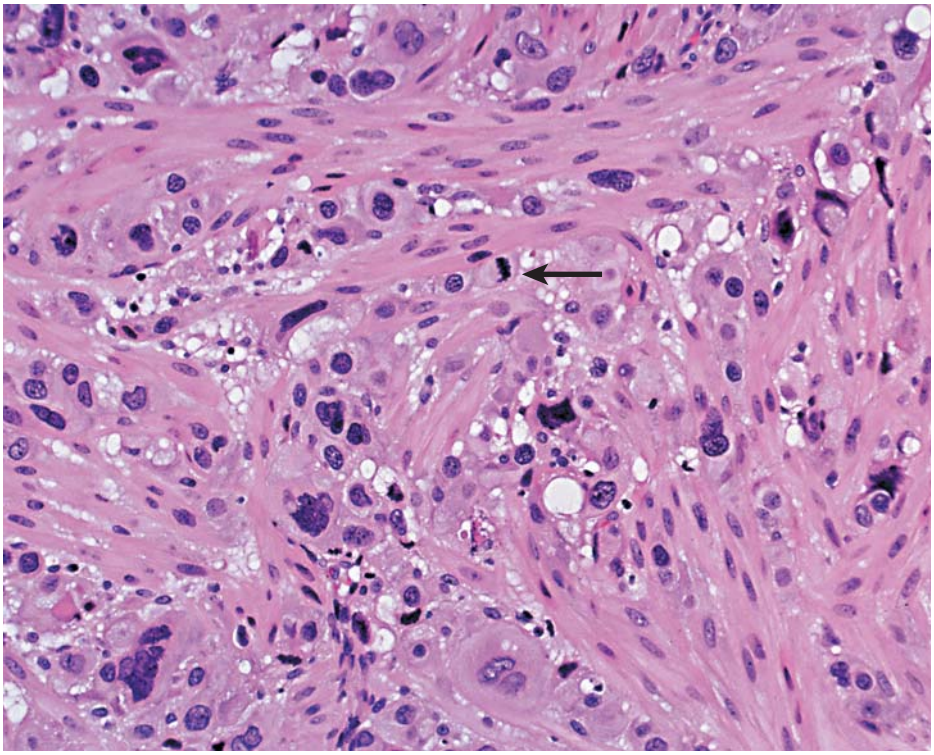

FIGURE 4.21. Placental site trophoblastic tumor. IT cells in PSTT infiltrate a fragment of myometrium. The neoplastic cells dissect between the smooth muscle fibers. A mitotic figure is present (*arrow*).

(Figs. 4.22 and 4.23). One other constant finding in this tumor is patchy deposition of eosinophilic fibrinoid material (Fig. 4.18). The hyaline, amorphous deposits of fibrinoid occur randomly throughout the tumor, often entrapping individual cells. Fibrinoid also accumulates in the walls of vessels invaded by IT (Fig. 4.22).

PSTT is diffusely immunoreactive for human placental lactogen (hPL) and Mel-CAM (CD 146), as well as inhibin-α, epithelial membrane antigen, and cytokeratins (AE1/AE3 and cytokeratin 18).[2;92] Immunohistochemical stains for these antigens can be helpful in the differential diagnosis (Table 4.4). In contrast, the other trophoblastic markers, hCG and PLAP, show limited immunostaining, with only focal reactivity.

It is difficult to reliably predict the behavior of PSTT based on the microscopic features, and therefore this neoplasm is not divided into benign and malignant categories. The reported malignant cases of PSTT generally show some features that predict aggressive behavior. These clinically malignant tumors are composed of larger sheets and masses of cells with more extensive necrosis than benign tumors.[1;2;58;83;84] In malignant PSTT the cells also tend to have clear instead of amphophilic cytoplasm. Finally, the mitotic rate usually is higher in the malignant tumors, with more than 5 mitoses per 10 high-power fields (HPFs) in most malignant cases.[2;93] In contrast, the benign tumors usually show a mitotic rate of about 2 mitoses per 10 HPFs, with the highest reported rate being 5 mitoses per 10 HPFs. In several clinically malignant PSTTs, the mitotic rate was only 2 per 10 HPFs,[94;95] so it appears that some overlap exists in the mitotic rates of malignant and benign

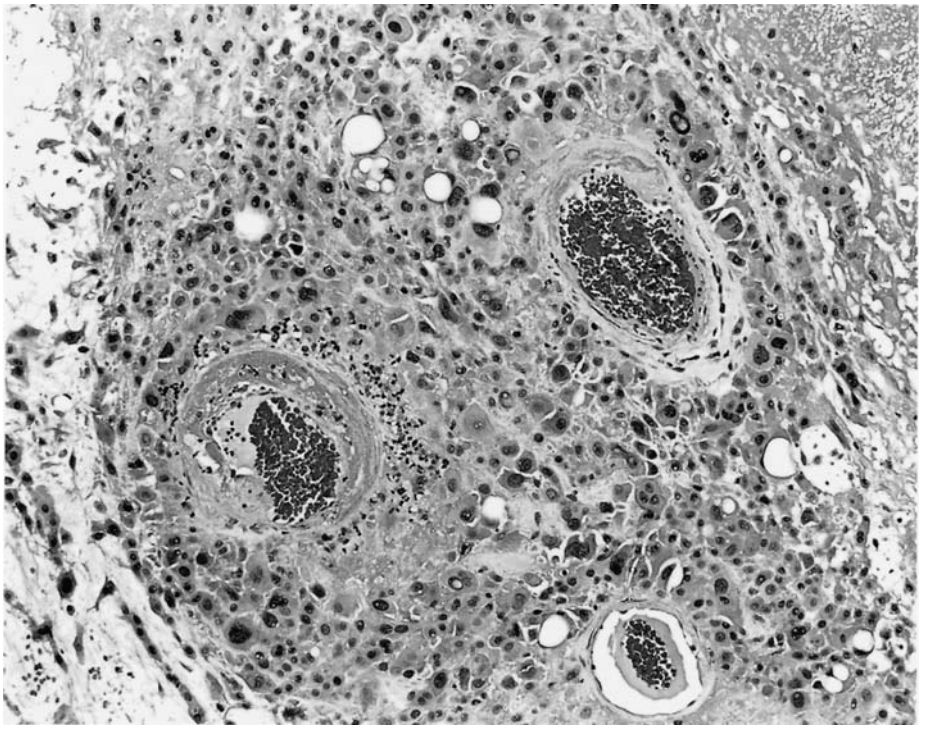

FIGURE 4.22. Placental site trophoblastic tumor. In this field the IT cells invade blood vessel walls in a characteristic fashion, preserving the lumen. In addition, amorphous fibrinoid material is deposited in the walls and in the interstitium. Several of the cells have vacuolated cytoplasm.

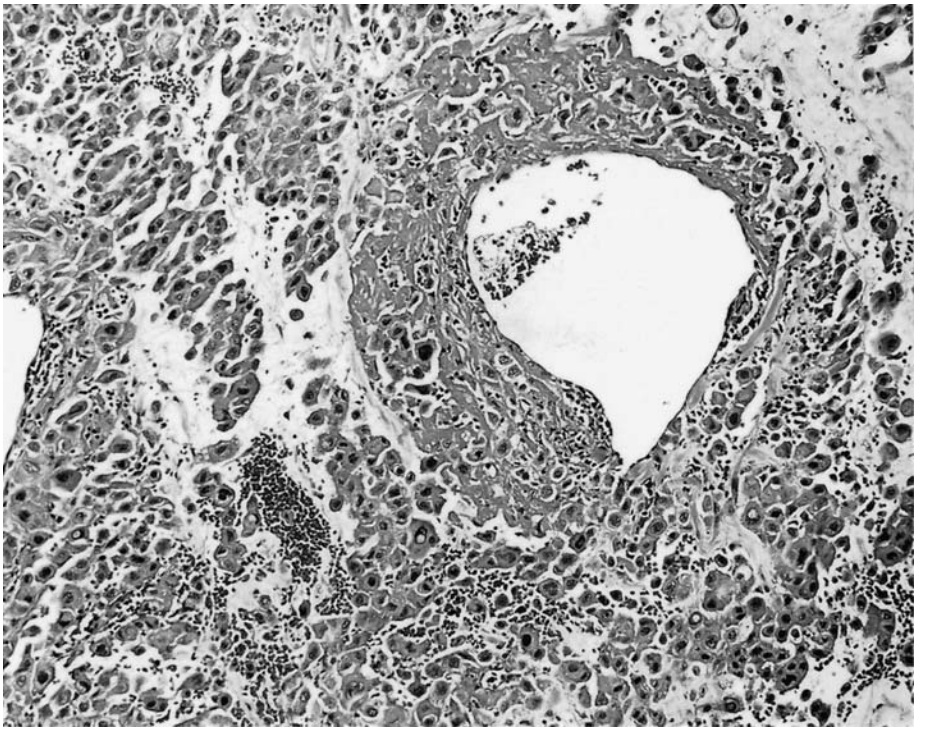

FIGURE 4.23. Placental site trophoblastic tumor. In this field the IT cells are relatively uniform with dense cytoplasm. IT cells embedded in fibrinoid material replace the wall of a large blood vessel.

PSTT. Abnormal mitotic figures occur in benign as well as malignant PSTT. Preliminary findings suggest that Ki-67 labeling index may be a significant prognostic indicator as it is usually greater than 50% in malignant tumors but only about 14% in benign PSTT.[2]

Differential Diagnosis

The differential diagnosis of PSTT includes exaggerated implantation site, choriocarcinoma, placental site nodule, and other, nontrophoblastic tumors. An exaggerated placental implantation site is one of the most important considerations in the differential diagnosis, as it can have features that are very similar to those of PSTT (see Chapter 3). The distinction is largely one of degree (Table 4.5). The exaggerated placental site usually is a focal finding, maintaining the overall architecture, and in other portions of the tissue there is decidua and/or chorionic villi. PSTT, in contrast, is composed of sheets and masses of cells typically accompanied by necrosis with little normal tissue in the sections. In addition, the exaggerated placental site tends to have more ST giant cells, the nuclei tend to have smudged (degenerative) chromatin, and mitotic activity is absent. Any evidence of unequivocal mitotic figures is suspicious for PSTT. The Ki-67 labeling index is very useful in the differential diagnosis because the index is near zero in the normal and exaggerated implantation site but 14% ± 6.9% in PSTT.[96] It may be slightly elevated (<5%) in exaggerated implantation sites associated with a complete mole.[96]

Separation of PSTT from choriocarcinoma is important, as these two tumors behave differently and are treated differently. Choriocarcinoma may have a monomorphic appearance in some areas and can have large numbers of IT. In contrast to PSTT, however, a network of syncytiotrophoblast in choriocarcinoma results in a dimorphic population, at least focally (Table 4.5). The syncytiotrophoblast in the PSTT is composed of isolated giant cells that do not show the dimorphic pattern found in choriocarcinoma. Immunohistochemical stains for β-hCG can be especially helpful in highlighting the network of syncytiotrophoblast in choriocarcinoma. Although both PSTT and choriocarcinoma show immunostaining for hPL and hCG, the ratio of the number of immunoreactive cells for each marker differs in the two tumors. In PSTT the hPL/hCG ratio is typically 3:1, whereas in choriocarcinoma it is 1:3. Occasionally, however, PSTT, especially one that behaves in a malignant fashion, shows a ratio of hPL and hCG staining that more closely resembles that of choriocarcinoma. The Ki-67 proliferative index can also assist in the differential diagnosis, as it is very high (>50%) in choriocarcinoma and significantly lower in PSTT (15% to 20%).[96]

Rarely, a trophoblastic tumor may show features of both choriocarcinoma and PSTT. This

Table 4.5. Comparison of microscopic features. Choriocarcinoma, PSTT, and exaggerated placental site.

	Choriocarcinoma	PSTT	Exaggerated placental site
Amount of lesional tissue	Variable, often abundant	Variable, often abundant	Usually limited
Villi	Absent	Absent[a]	Usually present, focal
Trophoblast growth pattern and cell types	Dimorphic: ST with CT or IT cells	Monomorphic: IT cells	Monomorphic: IT cells
Mitoses	Present, usually high rate	Present, usually low rate	Absent or rare
Nuclear atypia	Variable, may be marked	Moderate to marked	Moderate
Necrosis	Usually present	Usually present	Absent
Immunohistochemistry			
HCG	++++	+	+
HPL	+	++++	++++
Ki-67 labeling index	High	Usually about 15%	Very low to zero

PSTT, Placental site trophoblastic tumor; ST, syncytiotrophoblastic; CT, cytotrophoblastic; IT, intermediate trophoblastic, hCG, human chorionic gonadotropin; hPL, human placental lactogen.

[a] Rarely present and, if so, very focal.

is called a mixed PSTT–choriocarcinoma. There is insufficient experience with these tumors to predict their behavior accurately.

Placental site nodules also are focal abnormalities, usually associated with proliferative or secretory endometrium elsewhere in the sections (see Chapter 3).[91] In comparison to PSTT, these lesions tend to be circumscribed and small. The IT cells in placental site nodules are bland and are widely spaced in a hyalinized stroma. This distribution of IT contrasts with the sheetlike growth of IT in the PSTT. In contrast to PSTT, the placental site nodule is only focally reactive for hPL and Mel-CAM. Also, the placental site nodule is reactive for PLAP whereas the PSTT is not.

Now that the histologic features of intermediate trophoblast are better recognized, the problem of distinguishing PSTT from other forms of malignancy has decreased. PSTT is a tumor of the reproductive years, whereas many of the malignant tumors that enter into the differential diagnoses tend to occur at a more advanced age. Cytologic features of intermediate trophoblast combined with the typical patterns of vascular invasion and fibrinoid deposition usually allow differentiation of PSTT from other neoplasms. In biopsies, PSTT may be confused with keratinizing squamous cell carcinoma when the keratin has an amorphous eosinophilic appearance that superficially resembles the fibrinoid of PSTT. Squamous cell carcinoma usually arises in the cervix, however, whereas the PSTT occurs in the corpus; clinical features can help to distinguish the neoplasms (see Chapter 10). Furthermore, with squamous cell carcinoma a transition to a more obvious squamous pattern or normal endocervix often is found. Conversely, in the case of PSTT the curettage samples often contain fragments of endometrium or myometrium that have been invaded by the tumor.

On occasion PSTT can mimic leiomyosarcoma, especially in areas where intermediate trophoblast invades myometrium and becomes intimately admixed with smooth muscle cells. The trophoblastic cells of the PSTT are strongly immunoreactive for cytokeratin, inhibin-α, hPL, and Mel-CAM whereas leiomyosarcomas, except for occasional staining with keratin, are negative for these other markers. (Table 4.4). The epithelioid appearance of intermediate trophoblast can also resemble high-grade nontrophoblastic carcinomas. In questionable cases, immunohistochemical stains for inhibin-α, hPL, Mel-CAM, and hCG are very helpful in distinguishing PSTT from a nontrophoblastic neoplasm.

Epithelioid Trophoblastic Tumor

General Features

Epithelioid trophoblastic tumor is a rare form of trophoblastic tumor that has only recently become recognized.[2;90;97–100] This trophoblastic neoplasm is distinct from choriocarcinoma and PSTT with features resembling those of somatic carcinomas. This lesion was initially observed in a few patients with persistent lung metastases following intensive chemotherapy for documented choriocarcinoma.[101] Similar lesions were reported as multiple nodules of intermediate trophoblast in the uteri of patients following evacuation of hydatidiform moles.[102] These tumors have also been seen in patients without a history of antecedent GTD. We have observed similar tumors that merged imperceptibly with typical choriocarcinoma and PSTT. This lesion also has been found in the uterus adjacent to placental site nodules following hydatidiform mole.

The epithelioid trophoblastic tumor is preceded by a term gestation in two thirds of cases, with spontaneous abortions and hydatidiform moles being the antecedent gestation in the remaining cases. Usually there is a long interval following the gestation and the diagnosis of this tumor with a range of 1 to 18 years (average, 6.2 years). A case has been reported in a postmenopausal woman.[103] Serum hCG levels are usually elevated at the time of diagnosis, although the levels are generally low (<2500 mIU/ml).

Pathologic Features

Epithelioid trophoblastic tumor lacks the dimorphic pattern of classical choriocarcinoma and is composed of chorionic-type IT (Figs. 4.24 and 4.25).[2;91;97] ST cells are indistinct. The tumor

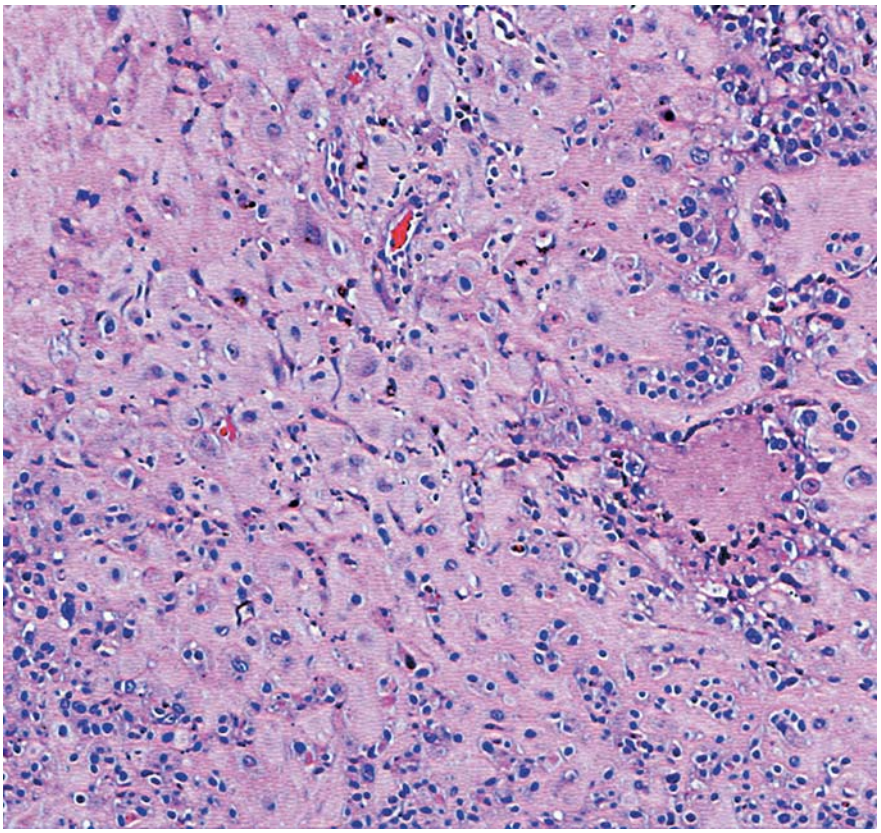

FIGURE 4.24. Epithelioid trophoblastic tumor. Cords and nests of trophoblastic cells with indistinct ST are separated by hyaline stroma. The epithelioid cells have pale to vacuolated cytoplasm.

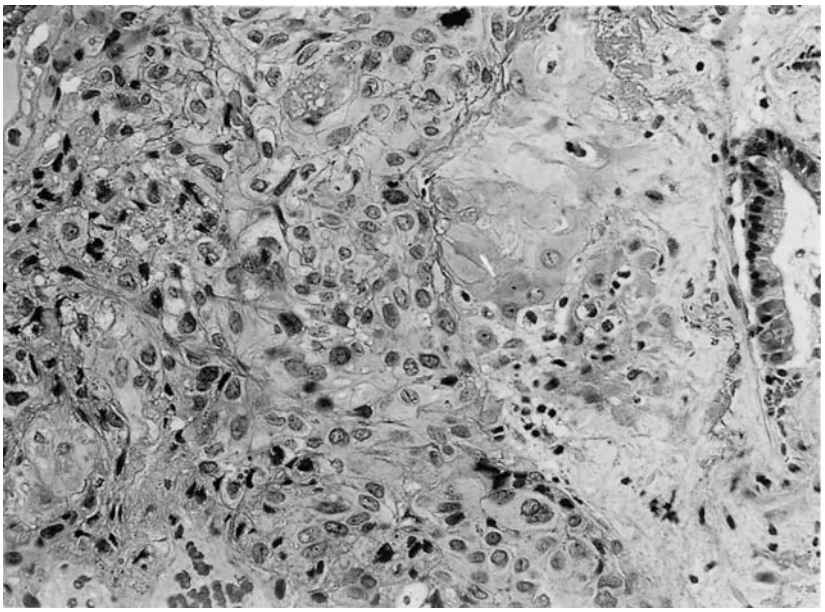

FIGURE 4.25. Epithelioid trophoblastic tumor. The tumor lacks a dimorphic pattern of CT and ST but is composed of a population of relatively uniform, polygonal, mononucleate trophoblastic cells with prominent cellular membranes. A transition to choriocarcinoma with a typical biphasic pattern was identified in other areas of the tumor.

displays a nodular growth pattern and has a striking epithelioid appearance, both in its cytologic features and in its pattern of invasion. The neoplasm is composed of small nests and cords of cells. The nests often contain dense central hyaline material and necrotic debris, and the cords are encompassed by a hyaline matrix (Fig. 4.26). The predominant cells are relatively uniform in size and are mononucleate with round, uniform nuclei and eosinophilic or clear cytoplasm. They are larger than CT cells but smaller than implantation site IT cells. Rarely, larger cells resembling implantation site IT cells are admixed or scattered within the extracellular hyaline material. Apoptotic cells and islands of necrotic debris are abundant in most tumors. The mitotic index varies from 0 to 9 per 10 HPF with an average of 2 per 10 HPF. Focal areas resembling placental site nodule, placental site trophoblastic tumor, or choriocarcinoma may be seen within these tumors.

These tumors have immunohistochemical profiles similar to that seen in normal chorionic-type IT. They are diffusely reactive for cytokeratin (AE1/AE3 and cytokeratin 18) as well as epithelial membrane antigen. In at least a portion of the cells the tumors are positive for inhibin-α.[92] Other trophoblastic markers including hCG, hPL, and Mel-CAM (CD 146) are only focally expressed (Table 4.4).[2;97] This immunophenotype contrasts with the placental site trophoblastic tumor, which is diffusely positive for hPL and Mel-CAM. The epithelioid trophoblastic tumor has a Ki-67 proliferative index of 10% to 25% with a mean of about 20%.[2]

Differential Diagnosis

The differential diagnosis includes placental site nodule, placental site trophoblastic tumor, choriocarcinoma, and keratinizing squamous cell carcinoma. The distinction from a placental site nodule is usually not difficult because the placental site nodule is typically a microscopic, well-circumscribed nodule with low cellularity, while epithelioid trophoblastic tumors are larger, cellular neoplasms that show necrosis.

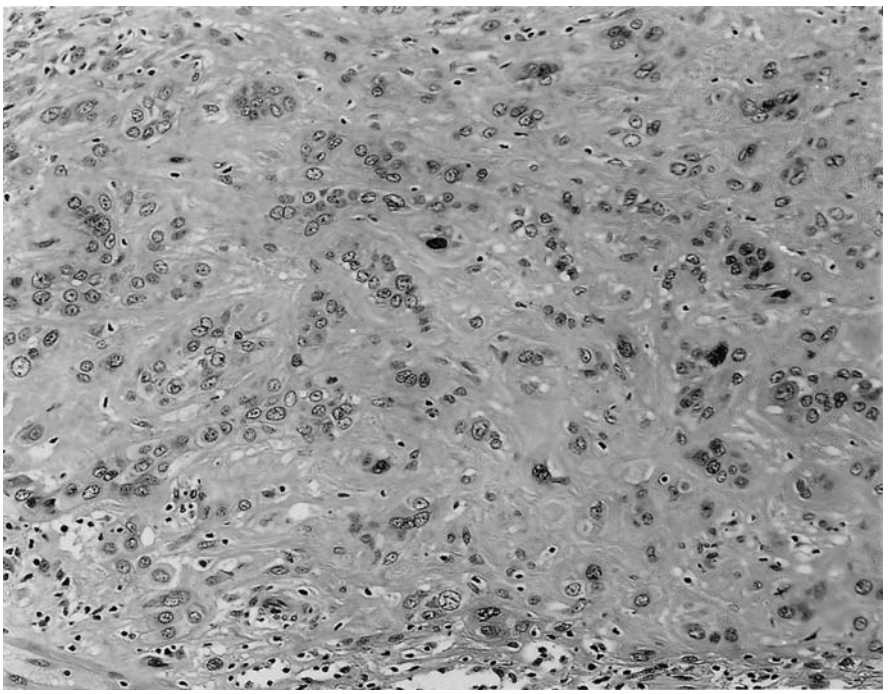

FIGURE 4.26. Epithelioid trophoblastic tumor. In this field the tumor is composed of cords and nests of monotonous cells in a hyaline matrix.

The placental site nodule has little to no mitotic activity and a Ki-67 index of less than 10% while the epithelioid trophoblastic tumor is more cellular with a Ki-67 index of greater than 10%.[2]

The nodular growth pattern with the distinctive hyaline matrix contrasts with the diffuse, infiltrative pattern of PSTT. In addition, the cells in epithelioid trophoblastic tumor are smaller than the IT cells of the PSTT and tend to grow in nests and cords. Immunohistochemistry can be very useful in distinguishing epithelioid trophoblastic tumor (ETT) from PSTT as the antibody against p63 reacts with chorionic type trophoblast that comprises ETT but not with implantation type trophoblast of PSTT.[103a] In contrast to choriocarcinoma, the epithelioid trophoblastic tumor does not have a dimorphic pattern with interspersed ST cells. Furthermore, the epithelioid trophoblastic tumor is not as hemorrhagic as choriocarcinoma. Immunohistochemical profiles are very helpful, as epithelioid trophoblastic tumor is positive for inhibin-α but shows only limited reactivity for hPL and Mel-CAM, in contrast to the PSTT, and shows only random β-hCG reactivity, in contrast to the abundant staining of ST cells in choriocarcinoma.[91]

ETT also can resemble a nontrophoblastic tumor, especially squamous cell carcinoma of the cervix, because of their epithelioid appearance, resemblance of the hyaline and necrotic debris to keratin, and propensity for the cells of ETT to grow along the surface of the cervix. In addition, about 50% of these tumors present in the cervix. Immunostains for inhibin-α and cytokeratin 18 can be very useful, as these are positive in epithelioid trophoblastic tumor but are negative in squamous cell carcinoma (Table 4.4).[97;104] Furthermore, the Ki-67 proliferative index is lower in epithelioid trophoblastic tumor (10% to 25%) compared to squamous cell carcinomas, which have Ki-67 labeling indices of greater than 50%.

Clinical Queries and Reporting of Trophoblastic Neoplasms

In curettings, choriocarcinoma is most commonly found in a repeat curettage during follow-up of a hydatidiform mole. Sometimes, however, this neoplasm is an unsuspected finding in a reproductive-age patient with abnormal uterine bleeding. PSTT, because of its rarity, often is not clinically suspected, and the patient presents with amenorrhea or an apparent missed abortion.

Obvious cases of either choriocarcinoma or PSTT do not require more than a concise diagnosis. Because of its rarity, the diagnosis of PSTT often is most useful if accompanied by an explanatory comment that describes this as a form of GTD derived from intermediate trophoblast. Furthermore, for PSTT the mitotic count should be stated, as this feature may help to predict aggressive behavior. All PSTTs should be considered potentially malignant, even those with a low mitotic index. Because of the rarity and the potential for highly aggressive growth of any trophoblastic tumor, but especially choriocarcinoma, we also recommend oral communication with the gynecologist whenever possible.

At times a specific diagnosis of a trophoblastic tumor may not be possible, yet the lesion is suspicious for neoplasia. WHO does, in fact, have a category of "unclassified" trophoblastic lesion (Table 4.1), a term reserved for those unusual cases that cannot clearly be placed in one of the defined subgroups of the disease. An example of such a case would be a small amount of proliferative trophoblast without villi, which can lead to a difficult differential diagnosis of choriocarcinoma versus trophoblast of a normal pregnancy. Also, prominent IT within decidua and myometrium may lead to a differential diagnosis of exaggerated placental site versus PSTT. When the diagnosis is not straightforward, a descriptive diagnosis of atypical trophoblast is best. With this type of diagnosis, the clinician is alerted to the possibility of trophoblastic disease. Then the patient can be followed with hCG titers or rebiopsied if symptoms persist.

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