Chapter 24

Choriocarcinoma

General Considerations

Choriocarcinoma is a rare tumor with an incidence of one in 25,000–40,000 pregnancies. It may develop after an abortion, a term or preterm pregnancy, an ectopic pregnancy, or a hydatidiform mole. In their oft-depicted diagram (Fig. 24.1), Hertig and Mansell estimated that the lesion was preceded by a *complete hydatidiform mole in 50%, an abortion in 25%, a normal pregnancy in 22.5%, and an ectopic pregnancy in 2.5%*. Choriocarcinoma is more common in young women and in those 40 years of age or older. There is as wide a geographic variation in its incidence as there is for hydatidiform moles.

Clinical Features and Implications

The most common presenting symptom is *abnormal vaginal bleeding*, usually developing several months following a pregnancy. Long latency periods of up to 14 years or more have been reported. Some patients present with *elevated serum β-human chorionic gonadotropin (β-hCG), a radiographically detectable lesion or metastatic disease* with symptoms reflecting the site of the metastasis.

Before the advent of chemotherapy, the prognosis of choriocarcinoma was dismal, with a 5-year survival of 32%, which dropped to 19% if metastatic disease was present. Survival has improved dramatically since the introduction of efficacious chemotherapeutic agents, and the *overall survival for all gestational trophoblastic disease (GTD) is greater than 90%*. Some women successfully treated for choriocarcinoma have gone on to have normal pregnancies. Prognosis is primarily

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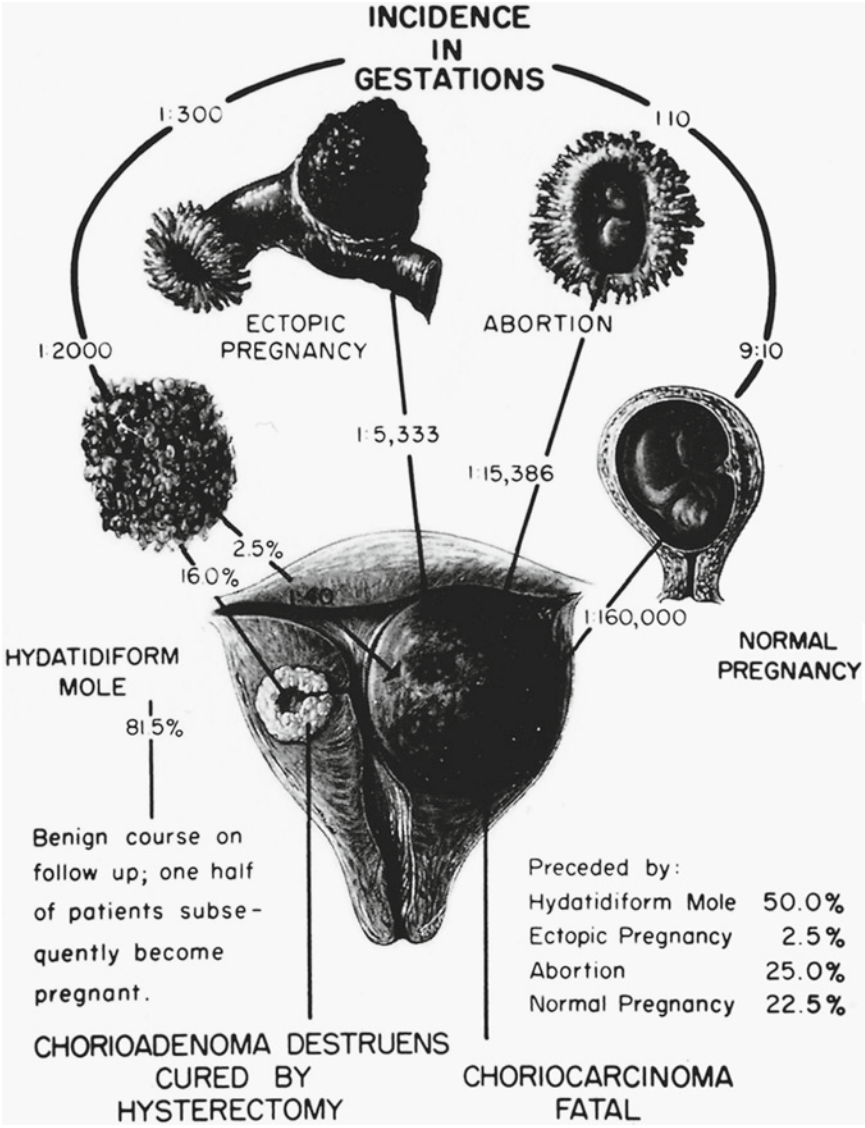

Figure 24.1. Frequency of choriocarcinoma relative to its various precursors (from Hertig and Mansell 1956, with permission).

based on the stage (Table 24.1). A staging system for GTD devised by the International Federation of Gynecology and Obstetrics has been recently revised to include the modified World Health Organization risk factor scoring system (Table 24.2). *Older age, longer interval from preceding pregnancy, antecedent term pregnancy, high serum β-hCG levels, location and number of metastases, and history of failed treatment are all poor prognostic indicators*. This scoring system along with staging forms the basis for treatment. In general, patients with a score of 7 or more are considered high risk and treated with more aggressive multiagent chemotherapy.

Pathologic Features

Grossly, choriocarcinoma may vary from an inconspicuous tumor only a few millimeters in diameter to large, bulky tumors. It presents as a *friable, hemorrhagic, and often necrotic mass* with an infiltrating border (Fig. 24.2). The tumors may be so large as to completely fill the uterine cavity (Fig. 24.3). On microscopic examination, choriocarcinoma consists of *solid sheets of cytotrophoblast and multinucleated syncytium without stroma* (Fig. 24.4). As the tumor has no intrinsic vascular stroma, it takes its blood supply from invasion of host vessels. This great propensity for *vascular invasion* leads to the prominent *hemorrhage and necrosis* characteristic of choriocarcinoma (Fig. 24.5). So much blood may be present in some tumors that one may have to search long for the tumor cells, which are often at the periphery of the lesion. Classically, *broad sheets or smaller nests of cytotrophoblast form the central portions of the tumor, the periphery being syncytium*, recapitulating the normal relationship of trophoblast in the early embryo (Fig. 24.6). Commonly, there is a completely haphazard mixture of trophoblastic cells that irregularly infiltrate the surrounding tissue. The **syncytiotrophoblast** contains *multiple irregular, hyperchromatic nuclei with dense, eosinophilic cytoplasm*. Nuclear pleomorphism is common. Because of its dilated cytoplasmic cisternae, the *syncytium is frequently vacuolated*

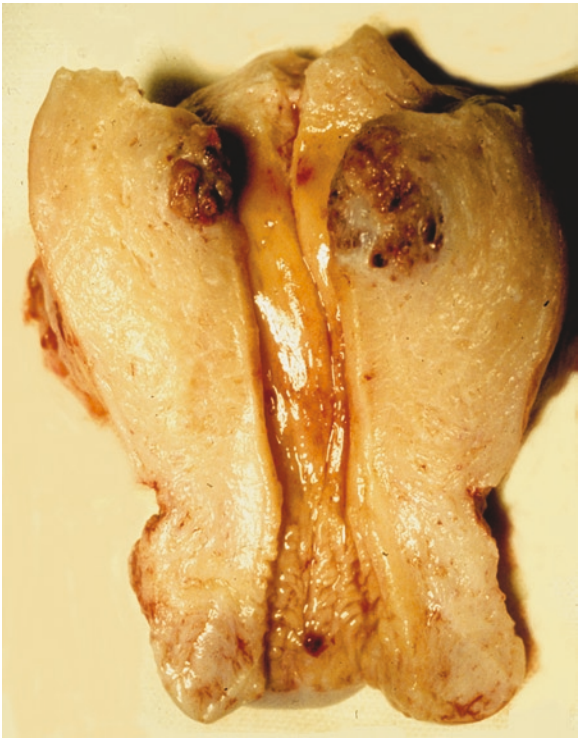

Figure 24.2. Opened uterus showing an irregular, necrotic and hemorrhagic tumor involving the endomyometrium (Baergen and Rutgers 1997, with permission).

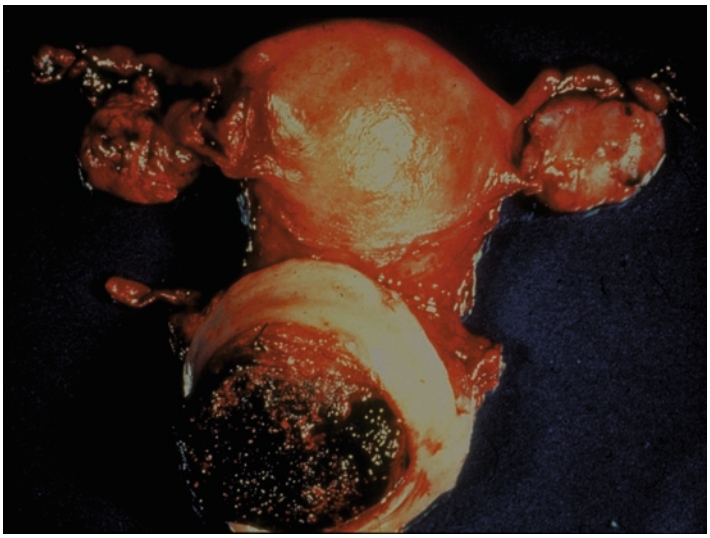

Figure 24.3. Hemorrhagic choriocarcinoma completely filling the uterine cavity.

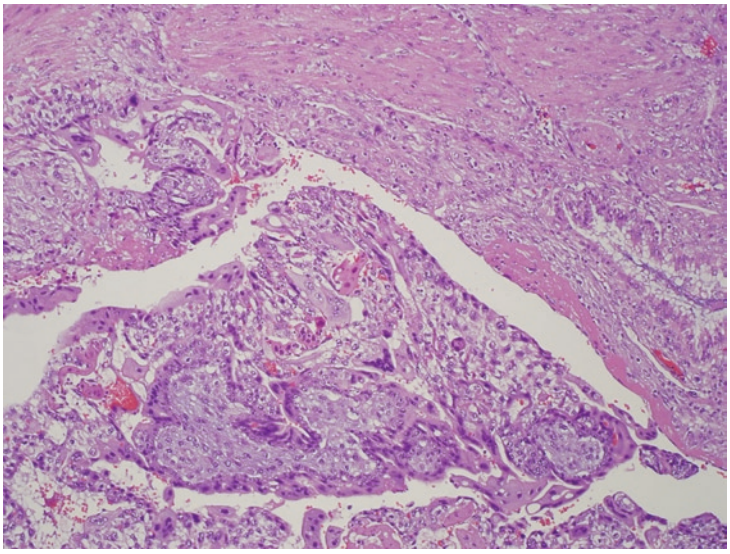

Figure 24.4. Choriocarcinoma of the uterus. Solid sheets of neoplastic cytotrophoblast and syncytiotrophoblast with marked nuclear pleomorphism. H&E ×160.

(Fig. 24.7). The **cytotrophoblastic cells** are *large, with moderate clear to lightly eosinophilic cytoplasm, large round nuclei, clumped chromatin, and one or more nucleoli*. A few **transitional trophoblastic cells** may be present in choriocarcinoma, even though they are not the hallmark of the lesion. Those cells are truly intermediate between cytotrophoblast and syncytium but are **not** the "intermediate trophoblast" of the implantation site (extravillous trophoblast). Differentiation of

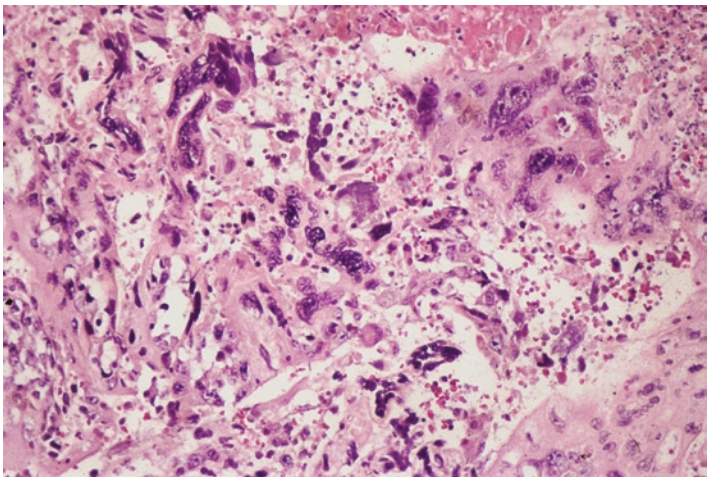

Figure 24.5. Choriocarcinoma demonstrating marked nuclear atypia. Characteristic associated necrosis is present in the upper portion of the figure. H&E ×200.

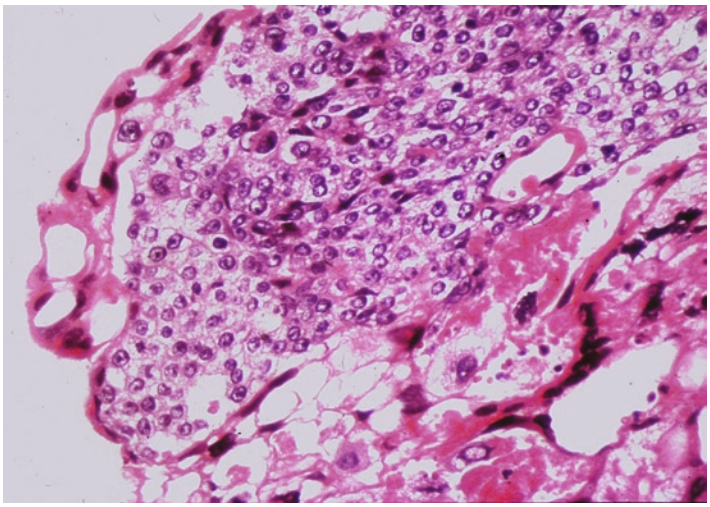

Figure 24.6. Choriocarcinoma, recapitulating the normal arrangement seen in chorionic villi, with syncytial cells surrounding groups of cytotrophoblast. H&E ×200.

choriocarcinoma from lesions of extravillous trophoblast is discussed in Chapter 25 and summarized in Tables 25.1–25.3.

Occasionally confusion with early abortion specimens may occur as the latter will contain sheets of proliferating trophoblastic cells with mitotic activity. Choriocarcinoma has no villous stroma or blood vessels, and these can easily be found in the early abortus. One does not usually make the diagnosis of a choriocarcinoma in the presence

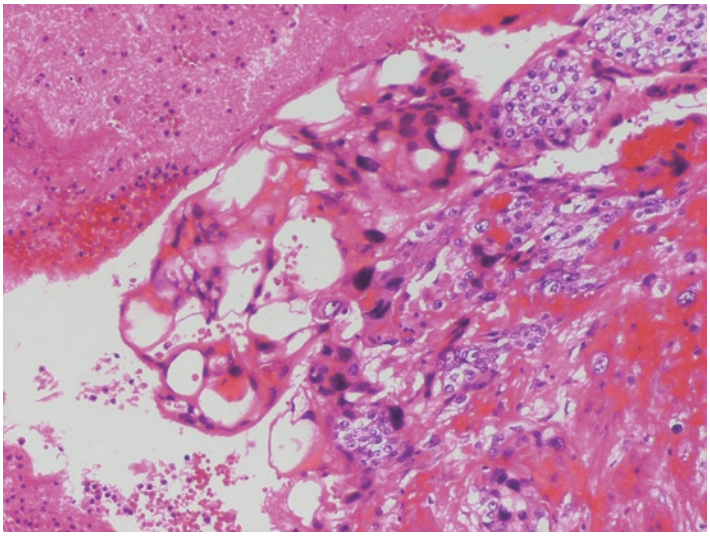

Figure 24.7. Vacuolated syncytiotrophoblast with marked atypia, characteristic for choriocarcinoma. Hemorrhage and necrosis is also present. H&E ×200.

of chorionic villi, although clearly they must develop in this context. The exception is choriocarcinoma in a term or near term placenta (see below).

Metastasis

Metastases occur largely from *hematogenous dissemination through the venous system to the lungs*, and in some cases into the systemic circulation. Therefore, metastatic lung lesions are present in 94% of patients with metastases. The *vagina* is also often involved. Other, less common, metastatic sites include *brain, liver, kidney, spleen, intestines, broad ligament, ovary, pelvis, and cervix*. Rarely metastases have occurred in the *oral gingival, subungual region, gastrocnemius muscle, coronary artery, aorta, and choroid of the eye*. Histologically, metastatic lesions tend to be *better circumscribed* but are otherwise histologically similar to the primary (Figs. 24.8 and 24.9). Occasionally, a metastasis is identified without an identifiable primary. Spontaneous resolution of the primary lesion can occur as well as spontaneous remission of metastasis, although these have been reported only infrequently.

Choriocarcinoma-In Situ: Placental Choriocarcinoma

Pathogenesis

When choriocarcinoma develops during a term or near-term pregnancy, an intraplacental lesion is likely present and may be identified in some cases. This lesion has been referred to as a **choriocarcinoma-in situ**. The lesion clearly arises in the placenta (Fig. 24.10), but these intraplacental lesions are usually invasive within the placenta and often metastatic at the time they are discovered. Therefore, the

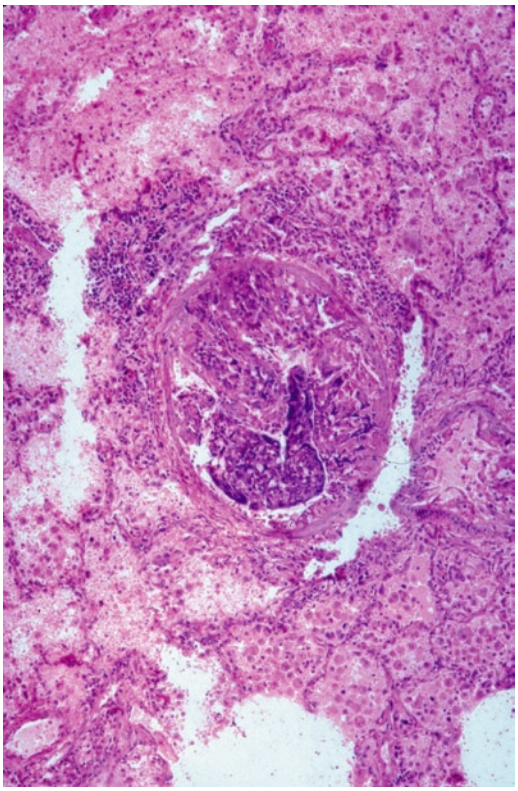

Figure 24.8. Choriocarcinoma metastatic to the lungs. This vessel is filled with solid nodules of choriocarcinoma. Some inflammatory reaction is also present in the vascular wall. H&E ×40.

term **choriocarcinoma-in situ** is not appropriate and the preferred designation is **placental choriocarcinoma**. These lesions are the probable origin of many of the choriocarcinomas that develop after a term pregnancy. However, one must keep in mind that some choriocarcinomas that develop after a term pregnancy may actually have arisen from a prior pregnancy. Since routine placental examination is not performed on every placenta, it is quite likely that many of these lesions are missed. Furthermore, the subtlety of the gross appearance of these lesions may result in them being overlooked when the placenta is examined.

Pathologic Features

Placental choriocarcinomas are usually *inconspicuous grossly and are often mistaken for an infarct as they will have a similar appearance*. Some are quite small and thus only identified by microscopic examination. Microscopically, they show proliferation of both cytotrophoblast and syncytiotrophoblast in the intervillous space (Figs. 24.11 and 24.12), which is typical for this lesion. Usually there is focal involvement of the adjacent chorionic villi. Invasion of the villous stroma or fetal vessels may also be present.

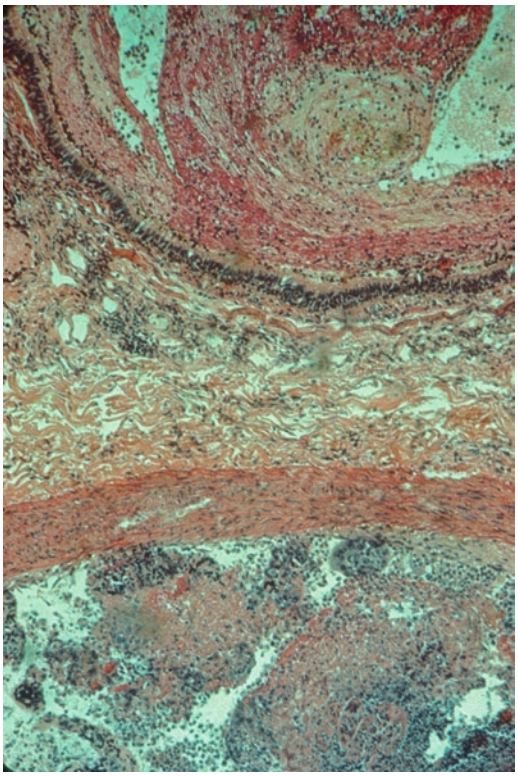

Figure 24.9. Metastatic choriocarcinoma to the lungs. Tumor is present within the lumen of a large vessel (*bottom*) and exudate is present with a bronchus (*top*) Trichrome ×40.

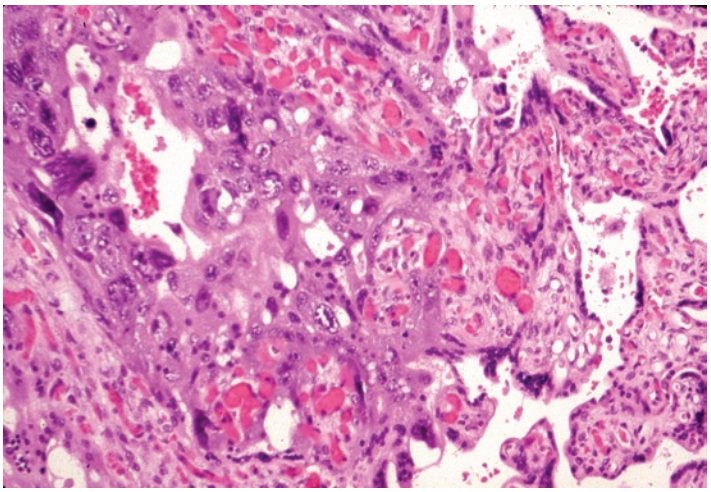

Figure 24.10. Term placenta with proliferation of trophoblast, consistent with intraplacental choriocarcinoma. H&E ×200.

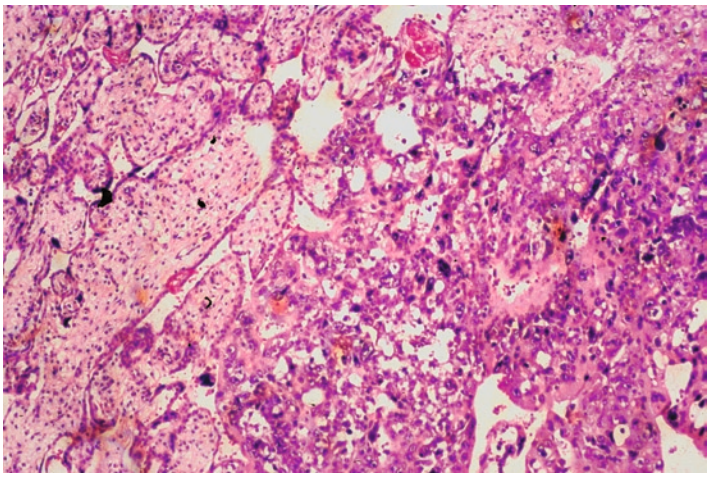

Figure 24.11. Mature placenta with placental choriocarcinoma ("choriocarcinoma-in situ"). Sheets of atypical trophoblast proliferate between the chorionic villi within the intervillous space. H&E ×80.

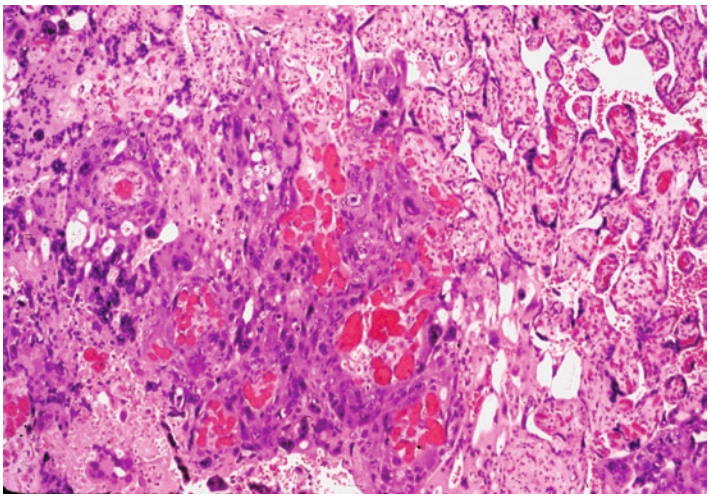

Figure 24.12. Placental choriocarcinoma demonstrating the cytologic atypia pleomorphism. H&E ×200.

Clinical Features and Implications

The reported cases of placental choriocarcinoma have had a varied outcome. In some cases, mother and infant showed no ill effect, while in other cases metastatic lesions, particularly to the lungs, required treatment. Placental choriocarcinoma can *metastasize to both the mother and the fetus*, and may be fatal to both. *Massive transplacental fetal hemorrhage* has also been reported. Occasionally, tumor in the placenta is not identified despite metastasis in the neonate. In some of these cases, this was certainly due to lack of placental examination. Due to the subtle nature of the gross appearance of these lesions, it is likely that many cases go undiagnosed.

Suggestions for Examination and Report
(Choriocarcinoma)

Gross Examination: Uterine choriocarcinomas are hemorrhagic and necrotic and may require many sections for identification of viable tumor cells. Often, the primary lesion is not resected or even noted and it is the metastatic lesions that find its way to the pathology laboratory. Generous sampling is advised. Placental choriocarcinomas are not usually visible grossly or have an inconspicuous appearance.

Comment: If placental choriocarcinoma is present, a comment may be made about the possibility of maternal or fetal metastases. In the rare case of a resection of a primary uterine choriocarcinoma or a metastasis, information about the extent of disease spread is necessary in order that proper staging be performed (see Table 24.1).

Table 24.1. Staging of gestational trophoblastic disease.

Stage	Definition
I	Disease confined to the uterus
II	Disease outside the uterus but limited to the genital structures (i.e., pelvis, vagina)
III	Metastatic disease to the lungs
IV	Metastatic disease to sites other than the lungs

Modified from Kohorn EI. The new FIGO 2000 staging and risk factor scoring system for gestational trophoblastic disease: description and critical assessment. Int J Gynecol Cancer 2001;11:73–77

Table 24.2. FIGO 2000 scoring system for gestational trophoblastic disease.

FIGO score	0	1	2	3
Age at diagnosis	≤39 years	>39 years		
Type of antecedent pregnancy	Hydatidiform mole	Abortion	Term pregnancy	
Interval from antecedent pregnancy	<4 months	4–6 months	7 to 12 months	>12 months
Serum β-hCG mIU/mL	<1,000	1,000–10,000	10,000–100,000	>100,000
Tumor size	≤4 cm	>4 cm		
Sites of metastases	None	Spleen or kidney	Gastrointestinal tract	Brain or liver
Number of metastases	0	1–3	4–8	>8
Response to chemotherapy	Full response	Full response	Failure with single drug chemotherapy	Failure with multiagent chemotherapy

Risk is assessed by adding factors according to the above system. Scores of seven or greater constitute a high-risk group that is treated more aggressively
Modified from Kohorn EI. The new FIGO 2000 staging and risk factor scoring system for gestational trophoblastic disease: description and critical assessment. Int J Gynecol Cancer 2001;11:73–77

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