Chapter 22

Neoplasms

General Considerations

There are only a few primary neoplasms of the placenta, but there is a wide variety of maternal malignancies that metastasize to the placenta. This reflects the diversity of neoplasms seen in the maternal population. Fetal tumors may also metastasize to the placenta, but these tumors are derived from a smaller group of congenital neoplasms.

Primary Placental Neoplasms

Chorangioma (Angioma)

Pathogenesis

Chorangiomas are basically angiomas that develop within a chorionic villus, most likely a stem villus. They are the most common benign tumor of the placenta. Tumors that have been designated **chorioangiomas, chorangiomas, angiomyxomas, fibroangiomyxomas,** and **fibromas** are essentially the same lesion, usually designated simply, **chorangioma.** The incidence of these tumors is reported to be one in 9,000 to one in 50,000 placentas. When careful study and sectioning of

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placentas are undertaken, the prevalence may be as high as 1 in 100, as many lesions are small and not grossly identifiable but rather are discovered incidentally on microscopic examination. Chorangiomas occur more frequently in Caucasian mothers than in those of other races. They are seen more often with *multiple gestations* and more often with *neonates who have congenital anomalies*, particularly infants with hemangiomas. This suggests that this tumor may be a congenital malformation or hamartoma, rather than a true neoplasm. Indeed, clonal studies, which would differentiate these lesions, have not been done at this point in time. Interestingly, the incidence of chorangiomas in high-altitude populations such as in Nepal is reported to be from 2.5% to 7.6%, which is much higher than the incidence at lower elevations. This suggests that chorangiomas may have a similar etiology to chorangiosis, which occurs with increased frequency at higher altitudes and in association with chronic hypoxia (see Chap. 19). Furthermore, like chorangiosis, chorangiomas may be associated with *elevated nucleated red blood cells (NRBCs)* in the fetal circulation, suggesting that a hypoxic stimulus leads to the excessive villous capillary proliferation. While still speculative, such angiogenesis may well be regulated by vascular growth factors.

Pathologic Features

Grossly, chorangiomas are sharply circumscribed from the surrounding parenchyma and often *bulge from the fetal surface of the placenta* (Fig. 22.1). When they are embedded deeper in the villous tissue, they are almost always located closer to the fetal surface. They are also more common in a peripheral rather than a central location within the placenta. The color and consistency of the cut surface is variable, from a *dark red, soft appearance similar to a blood clot to a firm, white lesion similar*

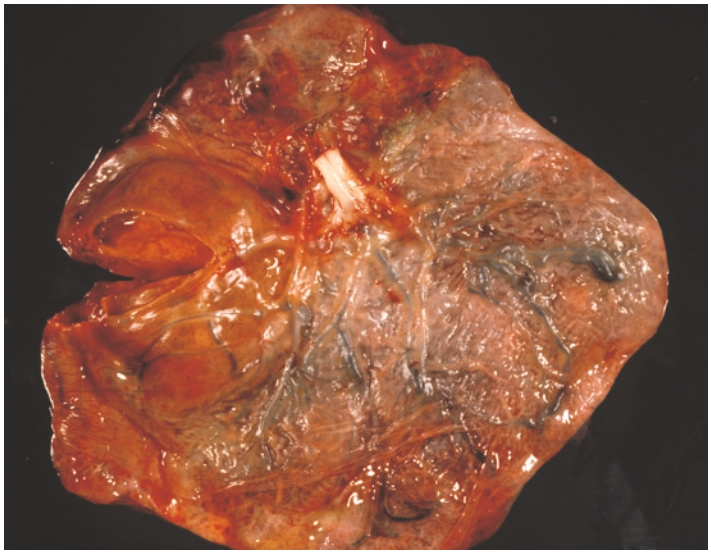

Figure 22.1. Typical chorangioma (*left*) bulging from the fetal surface. The cut surface is hemorrhagic.

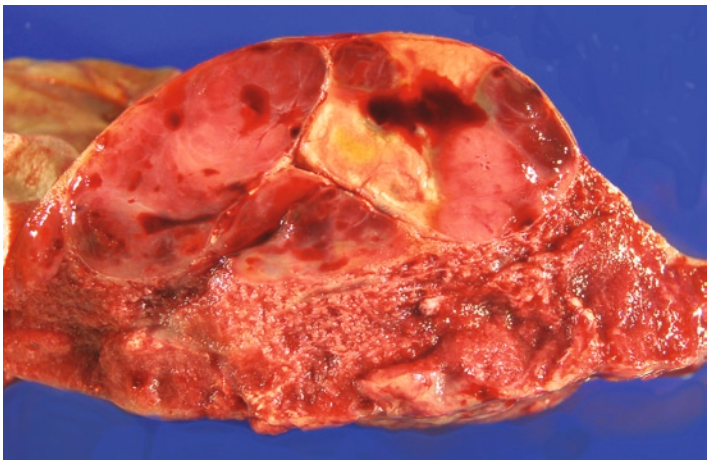

Figure 22.2. Chorangioma. The cut surface is heterogeneous with some areas having the appearance of blood clot, while others appear more fibrous. Normal placental tissue is seen underlying the tumor.

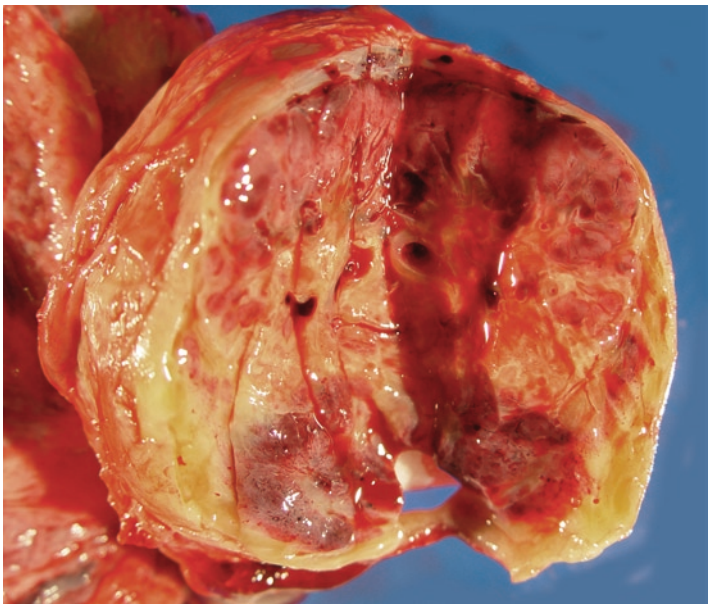

Figure 22.3. A chorangioma with some myxoid change. The lesion was large (10 cm) and was associated with mild neonatal cardiac failure.

to an infarct (Figs. 22.2 and 22.3). If there is associated fetal hydrops (see below), the entire placenta may be enlarged and edematous. Extremely large tumors may occur (Fig. 22.4). The record is probably held by a 1,500-g tumor measuring 30 by 20 by 5 cm, which was associated with placenta previa, hydramnios, preeclampsia, and abruptio placentae. The 32-week gestation fetus weighed 1,000 g and died from anemia and asphyxia.

Microscopically, the typical chorangioma is *composed of a proliferation of fetal blood vessels, usually supported by scant connective tissue* (Figs. 22.5 and 22.6). The vessels comprising the tumor may be capillary or sinusoidal. The *stromal component is variable but is frequently abundant*, and the lesion may then resemble a fibroma (Fig. 22.7). When

Figure 22.4. Exceptionally large (400 g) chorangioma shelled out from its placenta. The infant was stillborn and had cardiomegaly. The surface in this case had a fibromyxoid appearance.

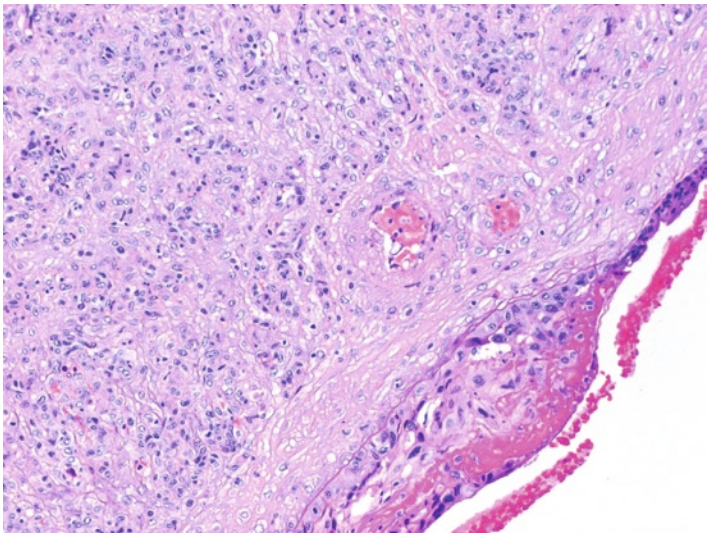

Figure 22.5. Typical microscopic appearance of a chorangioma with numerous small capillaries. The convexity of the tumor is covered by syncytiotrophoblast. H&E ×160.

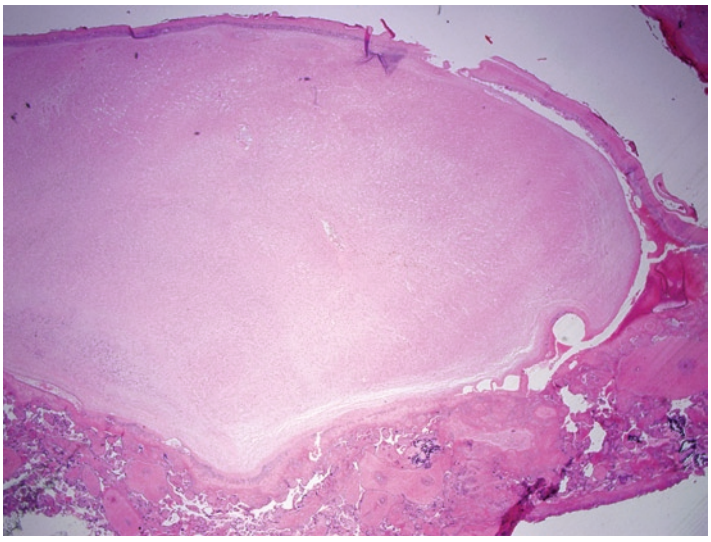

Figure 22.6. This chorangioma is completely infarcted and appears as a well-circumscribed nodule under the chorionic plate. H&E ×40.

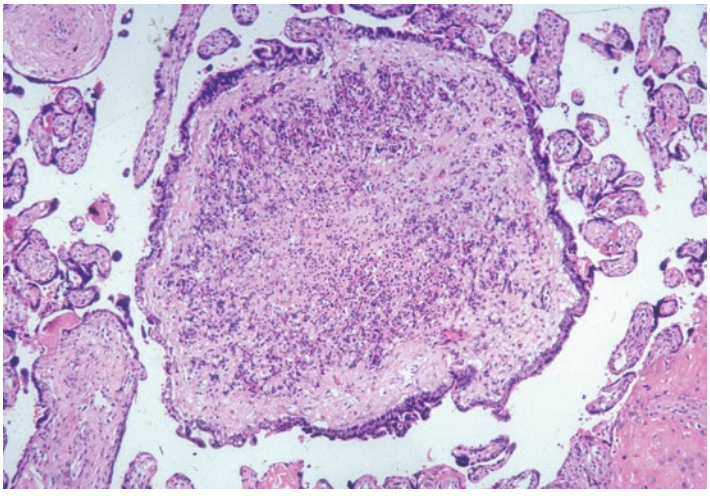

Figure 22.7. Small, incidental chorangioma identified only on microscopic examination. It has a primarily fibromatous appearance. Cellularity of these lesions may sometimes suggest a sarcoma. H&E ×170.

Wharton's jelly-like material participates in formation of the tumor, the appearance is that of a *myxomatous neoplasm*. The latter is particularly frequent when a chorangioma arises near the base of the umbilical cord. In such cases, a mucicarmine stain reveals the presence of mucin. *Capillary, cavernous, endotheliomatous, fibrosing*, and *fibromatous* tumors have been differentiated, but such precision is unwarranted as the clinical outcome depends more on the size of the mass than on its composition. The variable components of the lesions give rise to the

difference in appearance grossly. Chorangiomas are invariably *covered by trophoblast*, and one may envisage them to be the proliferation of vessels within a villus whose surface thus expands. Recent studies have suggested that chorangiomas arise from stem villi rather than terminal villi, as previously thought. These tumors often have *degenerative changes, calcification, infarction, and thrombosis* (Fig. 22.7). This may lead to problems in identification. They may also be multiple and in some cases have been recurrent. As they are characterized by an increase in villous vessels, chorangiomas have features in common with chorangiomatosis and chorangiosis, both of which are discussed in Chap. 19. Uncommonly, chorangiomas have marked cellularity, cytologic atypia, and prominent mitoses; however, despite this appearance, the tumors are invariably benign. Metastases and true invasion have never been described. At times, these variants have been called cellular chorangioma or atypical chorangioma.

Clinical Features and Implications

The relation of chorangioma to *hydramnios* and *fetal hydrops*, particularly in large tumors, is well known. Other complications include *stillbirth, fetal growth restriction, anemia, cardiomegaly, heart failure, disseminated intravascular coagulation, transplacental hemorrhage, premature delivery, abruptio, and preeclampsia*. Many complications are secondary to transplacental hemorrhage or sequestration of blood. Most tumors are not associated with sequelae, and the large tumors are more likely to be associated with severe complications. *Thrombocytopenia*, which is often observed in these newborns, is secondary to sequestration of platelets within the tumor. Repetitive multiple chorangiomas have been described in several families, sometimes associated with recurrent fetal demise. Whether isolated chorangiomas can occur repetitively is unknown.

Chorangiocarcinoma

Chorangiocarcinoma is a lesion with features similar to both chorangioma and choriocarcinoma and has been variably reported in the literature. Reported cases have depicted a *solitary lesion typical of a chorangioma whose surface, however, was covered by proliferating trophoblastic cells*. No untoward sequelae have been noted, and there is no chemical or cytochemical evidence of choriocarcinoma. Certainly, in most cases the tumors are truly variants of a benign chorangioma. However, a recent report describes a case of chorangioma associated with areas of marked syncytiotrophoblastic and cytotrophoblastic proliferation histologically consistent with choriocarcinoma. The authors opined that this was a true case of chorangiocarcinoma; however, again no malignant sequelae were noted. It appears that there may be cases in which a chorangioma was in close proximity to choriocarcinoma, representing a type of "collision" tumor. Therefore, the issue is not completely resolved and caution should be taken when presented with a chorangioma with trophoblastic proliferation.

Suggestions for Examination and Report
(Chorangioma)

Gross Examination: Note size, location and gross appearance of the tumor or tumors. Representative sections of the tumor should be submitted.

Comment: Large chorangiomas may be associated with anemia, thrombocytopenia, hydrops, growth restriction and stillbirth. In the case of "chorangiocarcinoma", it is preferable to refer to the lesion as "chorangioma with trophoblastic proliferation" with a description and notation that no malignant sequelae have been reported but that the lesion is not well studied. In some cases it may be prudent to suggest that the clinicians check and/or follow maternal serum beta-hCG levels.

Leiomyoma

There have been several reported cases of tumors morphologically and immunohistochemically compatible with **leiomyomas**, located within the placental tissue and covered by decidua at the maternal surface. Easy separation of the tumors from the uterus suggests these may not be uterine primaries. However, molecular studies on one reported case confirmed its maternal origin. Furthermore, no intrinsic structures in the placenta contain smooth muscle. For these reasons, it is likely these are *primary uterine leiomyomas that have become parasitic*, losing their vascular connection to the uterus and stealing a new blood supply from the placenta. These tumors have not been associated with adverse outcome.

Endometrial Stromal Lesions

Rarely, **endometrial stromal sarcomas** and **endometrial stromal nodules** have been identified. They are found either within the membranes or within the basal plate of the placenta. Like leiomyomas, their derivation from uterus, specifically endometrial stroma, has been documented by immunohistochemistry. They likely arise by the same mechanism that leiomyomas do, becoming parasitic and stealing the blood supply from the placenta. Metastasis has been reported in cases associated with endometrial stromal sarcoma.

Teratomas Versus Acardiac Twinning

Masses of tissue composed of *ectodermal, mesodermal, and endodermal elements* have been noted in the fetal membranes, umbilical cord, and chorionic plate of the placenta (see also Chap. 14). In cases where either umbilical cord structures or axial skeleton is present, they are usually considered a component of an acardiac twin. There is, however, disagreement over those cases that do not contain either of these elements. Since proof of neoplastic origin has not been presented, we believe that

true teratomas of the placenta likely do not exist and that all these cases represent variants of acardiac twining.

Hepatocellular Adenoma

Several cases of **hepatocellular adenoma** in the placenta have been reported. Grossly they have been *tan-white, sharply delimited* lesions present in intervillous or subchorionic locations. Microscopically, they *are composed of polyhedral cells with the appearance of hepatocytes*. The cells contain glycogen, and some show reactivity with antibodies to α-fetoprotein, α_1-antitrypsin, and carcinoembryonic antigen; convincing evidence of hepatic differentiation. No portal areas or central veins are seen, but study by electron microscopy has shown structures that resemble bile canaliculi. These lesions likely originate from displaced yolk sac structures. The clinical course for both fetus and mother is benign.

Heterotopia

Heterotopic tissues, such as **adrenal gland**, and **liver** occasionally occur in the placenta. Suggested mechanisms for the origin of these tissues have included embolic spread via the fetal vasculature, monodermal teratoma, and abnormal mesodermal differentiation. No sequelae have been reported.

Suggestions for Examination and Report
(Miscellaneous neoplasms and heterotopia)

Gross Examination: Grossly, neoplasms usually present as a mass, which should be described and liberally sampled for microscopic examination.

Comment: The diagnosis of the lesion should be given and a comment may be included indicating the lack of clinical sequelae (if it is known).

Maternal Neoplasms Metastatic to the Placenta

Clinical Features and Implications

Maternal malignancy occurs in approximately one in 1,000 pregnancies. Metastasis to the placenta, however, is rare, with less than 100 reported cases in the literature. The most common tumor to metastasize to the placenta is *melanoma*. Carcinomas of the *breast, cervix, gastrointestinal tract, and lung* occur less frequently, and there are rare reports of metastases from the *pancreas, ovary, endometrium, rectum, eye*, and *skin*, as well metastases from *medulloblastoma* and *rhabdomyosarcoma*. *Hematopoietic neoplasms* of various types have also been described. It is interesting to note that melanoma metastasizes so commonly, since it is not frequent in the pregnant population. This phenomenon is probably due

to the hematogenous dissemination in melanoma and to the fact that melanoma patients are more likely to have advanced disease. Many placental metastases occur in patients with end-stage disease who presumably had a significant tumor burden, facilitating vascular spread to the placenta.

Transplacental metastasis to the fetus is much rarer than placental metastasis. Here again, *melanoma is most common*, but cases of *lymphoma, leukemia, and pulmonary adenocarcinoma* have been reported. Many cases have resulted in neonatal death, but there are also reports of spontaneous regression. The immunologic ramifications of these cases remain to be studied. *Due to the occurrence of fetal metastasis, although rare, it is recommended that all placentas from patients with a diagnosis of malignancy be examined histologically*.

Pathologic Features

Placental metastases often go unnoticed. In many cases, the lesions are not visible grossly, while in other cases they are overlooked, as they may appear *similar to infarcts*. Microscopically, metastases usually consist of clusters of *malignant cells in the intervillous space* (Fig. 22.8). In some cases, *invasion of the villous structures and even the fetal vasculature may occur*. However, the latter feature does not correlate well with the presence of metastasis to the infant. Often these intervillous collections do not show vascularization, leading some authors to call them "pseudometastases." In the case of maternal **leukemia**, metastasis cannot be documented merely by the presence of leukemic cells in the intervillous space, but must be made by the presence of leukemic cells in the villous tissue and/or fetal vessels.

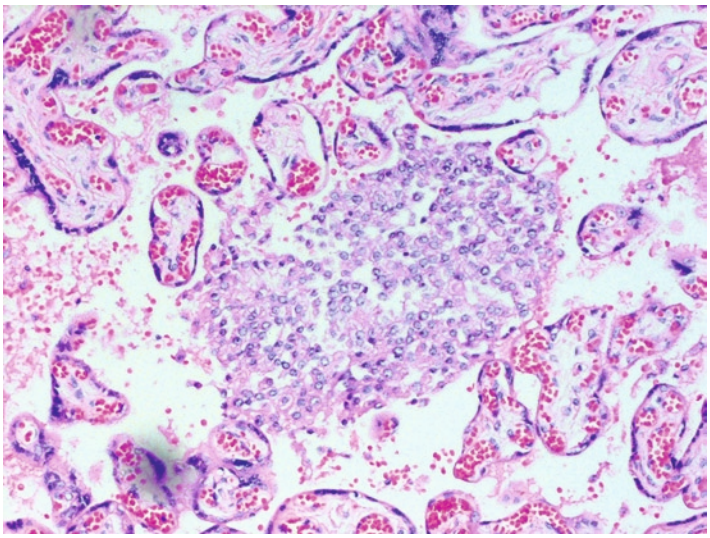

Figure 22.8. Metastatic melanoma to the placenta. Note the large, atypical cells present in the intervillous space. The mother had widespread metastases at the time of delivery and died 1 month later. H&E ×200.

Suggestions for Examination and Report
(Maternal metastasis to the placenta)

Gross Examination: Metastatic lesions are usually not grossly visible, but, if large, may appear similar to an infarct. In the context of a maternal malignancy, any parenchymal lesion should be sampled. If no gross lesions are present, additional random sections should be submitted.

Comment: If metastases are present, characterization of the type of metastasis and comparison with the maternal primary is optimal. Immunohistochemistry may be necessary to fully evaluate the malignant cells. In addition, involvement of the villous stroma or fetal vessels should also be noted. The fact that fetal metastasis is a possible, although rare complication, may also be stated. Follow up in the infant may be suggested if placental lesions are present.

Fetal Neoplasms Metastatic to the Placenta

Malignant Fetal Tumors

Congenital malignancies include **neuroblastoma, lymphoma, leukemia, sarcomas, brain tumors, hepatoblastoma,** and **teratomas.** Metastases from these neoplasms to the placenta are rare but do occur. Congenital **neuroblastoma** has repeatedly been shown to cause fetal heart failure, hydrops and death, but the pathogenesis of hydrops remains to be identified. Grossly, the *placenta is markedly enlarged*. On histologic examination, the villi are *enlarged and edematous, and have increased numbers of Hofbauer cells with persistent villous cytotrophoblast*. *Cords of neuroblastoma cells may be found in fetal capillaries* sometimes accompanied by erythroblasts (Fig. 22.9). Neuroblastoma cells may also infiltrate the villous tissue. Fetal hydrops and placentomegaly may also be seen in association with fetal **hepatoblastoma**. Similar to neuroblastoma, the placental metastases consist of *malignant, immature-appearing cells filling the villous capillaries*. Due to the lack of differentiation, immunohistochemistry may be necessary to identify the true nature of these cells. **Sacrococcygeal teratomas** may produce *placentomegaly, fetal edema, hydramnios, and elevated human chorionic gonadotropin (hCG) levels*. On histologic examination, one sees only large numbers of *NRBCs in the villous capillaries*. There is one reported case of a teratoma with placental metastasis within villous vessels. Lastly, fetal **leukemia** occurs rarely and placental involvement is even rarer. When it does occur, it is also associated with placentomegaly. On microscopic examination, villous capillaries are packed with leukemic cells, which may extend into the villous stroma (Fig. 22.10). Diagnosis can be quite difficult on placental tissue alone.

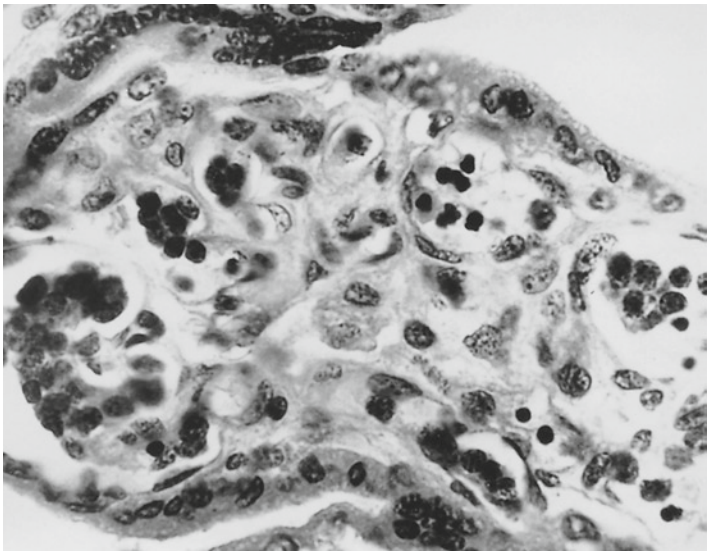

Figure 22.9. Villus from a case of congenital neuroblastoma. The enlarged villus has numerous neuroblastoma cells within the villous capillaries, some of which show rosetting. H&E ×400.

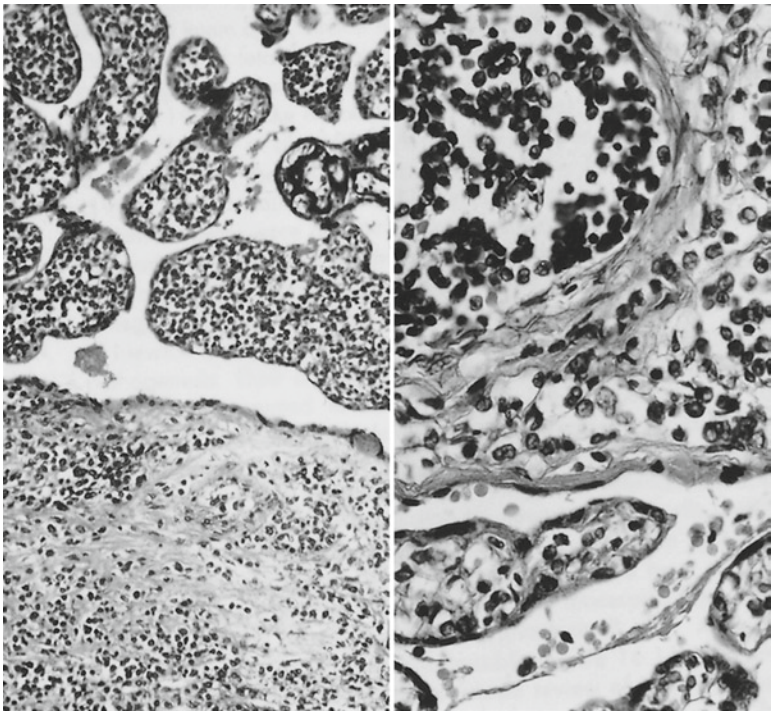

Figure 22.10 Placenta from a macerated stillborn with presumed leukemia. The villous capillaries are packed with leukemic cells, and some stromal infiltration is seen. H&E: *left* ×60, *right* ×160.

Benign "Metastatic" Lesions

Fetal giant pigmented nevi have been described in the placenta, usually as *multiple foci of pigmented nevus cells in the villi*. Occasionally, there is extensive placental involvement, but the lesions are considered benign. The cells may derive from early neural crest cell migration.

Suggestions for Examination and Report
(Fetal neoplasms metastatic to the placenta)

Gross Examination: When a fetal malignancy is known, additional sections of placenta should be submitted for identification of metastases.

Comment: Diagnosis of the neoplasm is essential and may require immunohistochemistry. As with maternal malignancy, the location and extent of involvement should also be mentioned.

Selected References

PHP5, pages 863–870 (Chorangiomas), pages 870–871 (Other Benign Tumors), pages 600–604 (Maternal Neoplasms), pages 530–532 (Fetal Tumors).

Baergen RN, Johnson D, Moore T, et al. Maternal melanoma metastatic to the placenta. Arch Pathol Lab Med 1997;121:508–511.

Benirschke K. Recent trends in chorangiomas, especially those of multiple and recurrent chorangiomas. Pediatr Dev Pathol 1999;2:264–269.

Doss BJ, Vicari J, Jacques SM, et al. Placental involvement in congenital hepatoblastoma. Pediatr Dev Pathol 1998;1:538–542.

Ernst LM, Hui P, Parkash V. Intraplacental smooth muscle tumor: a case report. Int J Gynecol Pathol 2001;29:284–288.

Guschman M, Vogel M, Urban M. Adrenal tissue in the placenta. A heterotopia caused by migration and embolism? Placenta 2000;21:427–431.

Khalifa MA, Gersell DJ, Hansen CH, et al. Hepatic (hepatocellular) adenoma of the placenta: a study of four cases. Int J Gynecol Pathol 1998;17:241–244.

Lentz SE, Coulson CC, Gocke CD, et al. Placental pathology in maternal and neonatal myeloproliferative disorders. Obstet Gynecol 1998;91:863–864.

Leung JC, Mann S, Salafia CM, et al. Sacrococcygeal teratoma with vascular placental dissemination. Obstet Gynecol 1999;93:856.

Lynn AA, Parry SI, Morgan M, et al. Disseminated congenital neuroblastoma involving the placenta. Arch Pathol Lab Med 1997;121:741–744.

Majlessi HF, Wagner KM, Brooks JJ. Atypical cellular chorangioma of the placenta. Int J Gynecol Pathol 1983;1:403–408.

Qureshi F, Jacques SM. Adrenocortical heterotopia in the placenta. Pediatr Pathol Lab Med 1995;15:51–56.