Chorangiotic Lesions, Benign Tumors, and Heterotopias

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Chorangiotic lesions and benign tumors are commonly encountered lesions in the practice of perinatal pathology. By far, the most common benign tumors of the placenta are vascular in nature. They have historically gone by a variety of names including chorangiomas, myxomas, fibroangiomyxomas, and fibromas, among others. They were first described by Clark in 1798 and officially reported by Fox in 1967, with several large reviews bringing together most of the literature [39, 49, 130] (Marchetti 1939). Initially, it was thought that these neoplasms may be rare, with an incidence of approximately one in 9000 to one in 50,000 (Fox). However, according to some authors, when comprehensive study of the placenta is undertaken, the true prevalence may be as high as one in 100 pregnancies. For example, in 1965, Wentworth found one in 77, Wallenburg [145] identified one in 117, and Soma et al. [134] found one in 500. They have been reported as more frequent in populations at high altitudes such as Nepal (1), Soma Lesson from nepalese placenta. Based on 20 years' pathological studies. Industrial Publ. & Consulting, Inc., Tokyo http://www.ipij.com, 2001, [121].

Non-tumoral chorangiotic lesions of the placenta include chorangiosis and chorangiomatosis, the distinction of which is based upon the location of the affected vessels. Chorangiomatosis is defined as a focus of excessive capillary growth within and permeating stem villi and immature intermediate villi. These foci are not as clearly circumscribed as chorangiomas, and though not considered neoplasms, they may have a similar etiology to the chorangioma. Conversely, chorangiosis is a diffuse process in which there is proliferation of villous capillaries within the terminal villi and is thought to be associated with chronic hypoxia.

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Rare reports of other tumors or proliferations within the placenta have a varied histology and are discussed in greater detail below. These include hepatocellular adenomas (Chen et al. Am J Surg Pathol 10:436, 1986), smooth muscle tumors (Harirah et al. J Reprod Med 46:937, 2001), and teratomas (Fox Pathology of the placenta. London: Saunders; 1978). In addition, heterotopic tissues such as adrenal cortical tissue have also been described, albeit less commonly.

Chorangiomas: Pathogenesis

With rare exceptions, vascular tumors are the only benign tumors of the placenta. These tumors have been known by many names including chorioangiomas, chorangiomas, placental hemangiomas, fibroangiomyxomas, and fibromas, among many others [12]. As the pathogenesis has not been completely resolved, they currently may be regarded as either hemangiomas or hamartomas. For instance, the trophoblastic cover does not appear to participate in the composition of these lesions [20] and likely does not have the capacity to produce blood vessels. This might be expected if the designation hamartoma were to apply, a point amply discussed by Marchetti (1939). Fox [48] also believed them to be hamartomas as he considered their derivation to be from villous mesenchyme. However, Barry et al's. [12] discussion of angiomas of cord and placenta supported a neoplastic etiology, and some suggest that the disproportionate growth of these lesions relative to the background placenta supports a neoplastic origin (Fox 2007, Jaiman 2019). Interestingly, a recent study of 8 chorangiomas using array comparative genomic hybridization (array-CGH) analysis revealed no rare or novel copy number variants in the tumor compared with control unaffected placental DNA, findings which indicate a nongenetic, nontumorous origin [132]. Of note, the authors concede that although their study failed to demonstrate large pathogenic genetic changes, additional studies are necessary to fully explore possible smaller genomic

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alterations. Others have opined that chorangiomas form as a result of low oxygen tension (much like chorangiosis, vide infra) [112] in areas with abundant mesenchyme and endothelial progenitor cells such as stem villi and the margins of the chorionic plate, locations where they do indeed form.

The association with and resemblance to infantile hemangiomas is an additional etiologic consideration. Infantile hemangiomas are thought to form from deportation of placental mesenchymal or endothelial stem cells into the fetal circulation [109]. Chorangiomas have been shown to be associated with fetal and neonatal angiomas by multiple authors [9, 53, 90, 127]. This supports the notion that this tumor, as with fetal angiomas, may actually represent some form of congenital malformation rather than a true neoplasm, an idea which has been considered by a number of authors. Bakaris et al. [9] and Cvetanovska et al. [34] presented cases associated with neonatal hemangiomatosis and infantile angioma of the liver. Drut et al. (1992) reported the presence of hemangioendotheliomas and multiple chorangiomas in the Beckwith-Wiedemann syndrome and referred to a few case descriptions of similar combinations.

Examination by cytogenetics has demonstrated varying results. For example, a case was reported of a severely intellectually disabled fraternal twin with a chromosomal abnormality [46,XX t (2q−; 15q+)] that had angiomatous masses in the placenta [150]. A later case of a single chorangioma showed a normal chromosome complement [83] while an additional case of a placental chorangioma and liver hemangioma showed deletions at 2q13 and 7p21.1, present at both sites [101]. Electron microscopic studies of chorangiomas performed by Cash and Powell [24] revealed normal endothelial cells and capillaries, a finding later confirmed by Soma et al. [134]. Finally, SNPs of cDNA of mother/child pairs failed to disclose mother-to-child transmission or "microchimerism" [115]. The transcriptomes of placental and neonatal hemangiomas were similar [10, 11], suggesting a possible placental origin of fetal angiomas. On the other hand, Walter et al. [146] found that juvenile hemangiomas resulted from nonrandom (X-inactivation) and monoclonal lesional mutations, suggestive of a target within the VEGF signaling pathway.

Guschmann and his colleagues in Berlin [60, 63, 64] have described various angiogenesis factors in chorangiomas. It was their experience that high expression of angiopoietin-1 and -2 and their receptors was demonstrated in chorangiomas, while VEGF was uniform with the normal villi, but variability existed. Further remarkable findings in their series were that 72% of accompanying babies were of female gender and tumors occurred much more commonly in the first pregnancy. North et al. [109] studied immunoreactivity for a variety of antigens in chorangiomas and juvenile angiomas. Thus, FcgammaRII, Lewis Y antigen, merosin, and GLUT1 were found to be highly expressed in the small placental vessels and angiomas, but not in control blood vessels or those of granulomas, etc.

Chorangiomas have been associated with chronic vascular thrombi and elevated NRBCs in the fetal circulation. Thus, a hypoxic stimulus may be inferred to lead to induction of excessive villous capillary proliferation. While still speculative, such angiogenesis may well be regulated by such vascular growth factors as demonstrated by [74, 131]. Additionally, chorangiomas have been frequently noted at the placental margin or immediately below the chorionic plate, regions known to be hypoxemic relative to the remaining placenta. In summary, based on the data presently available, the issue of whether these represent tumors or hamartomas is as yet unresolved.

Chorangioma: Gross and Microscopic Pathology

The typical chorangioma often bulges from the fetal surface of the placenta (Fig. 30.1). When they are embedded in the villous tissue, they are located closer to the fetal surface and are often peripheral (Fig. 30.2). Macroscopically, chorangiomas may be small and multiple; alternatively, they may constitute large masses that displace villous tissue. They are typically fleshy, dark red to tan, and are often congested but can have a variable appearance on macroscopic examination, particularly if infarcted (Fig. 30.3). Depending on their composition, they may appear fibrotic, myxoid, or hemorrhagic. Small chorangiomas are often incidental and found only on microscopic examination.

Chorangiomas arise within a single stem villus and thus are invariably covered by trophoblast; one may envisage them to be the proliferation of fetal capillaries of a villus whose surface thus expands to accommodate the increase in size (Fig. 30.4; [112]). Chorangiomas are nodular and composed of anastomosing fetal blood vessels that are usually supported by only scant connective tissue. The network of vessels is surrounded by pericytes within a collagenous stroma which contains variable numbers of fibroblasts and macrophages [112]. The vessels comprising this tumor may be capillary or sinusoidal (Fig. 30.5) and occasionally show collapsed lumina. The endothelial cells lining vascular spaces will stain positively for CD31 and CD34, and the continuous layer of pericytes around each vessel can be highlighted with muscle specific actin (MSA). Reticulin stains highlight a lattice-like pattern of fibers (Redline 2000, Amer 2010). At times, the stromal component will be abundant, and the lesion will consequently resemble a fibroma (Fig. 30.6). When Wharton's jelly-like material participates in the formation of the tumor, the appearance is that of a myxomatous neoplasm (e.g., [8]). The latter is particularly common when a chorangioma arises near the base of the

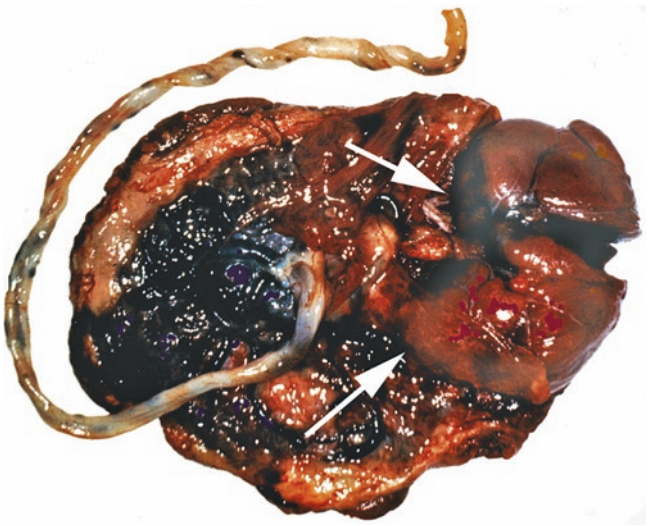

Fig. 30.1 Typical chorangioma (right), bulging on the fetal surface (white arrows). Fetus and pregnancy were normal; there is slight circumvallation of the placenta at left

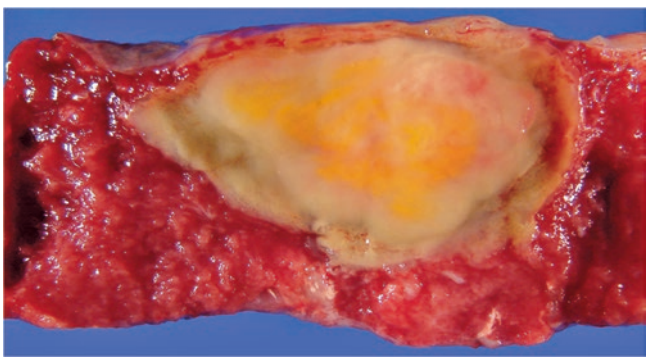

Fig. 30.2 Partially infarcted 1-cm chorangioma underneath the chorionic surface of an otherwise normal, mature placenta. It had a *golden-yellow* appearance and could easily have been mistaken for an infarct

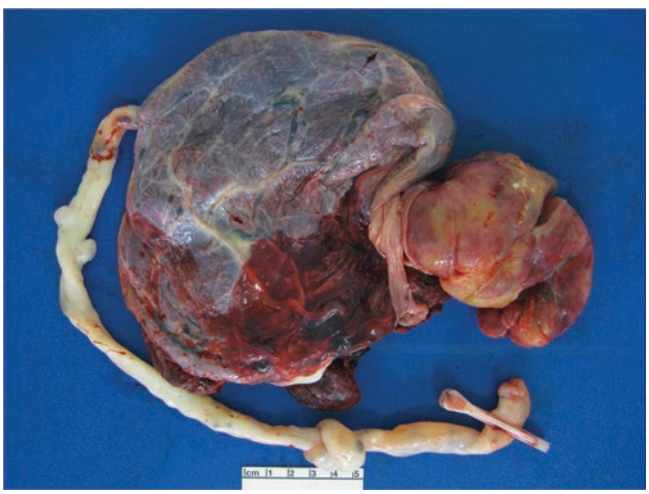

Fig. 30.3 Chorangioma with a more myxoid appearance. Note the true knot in the cord

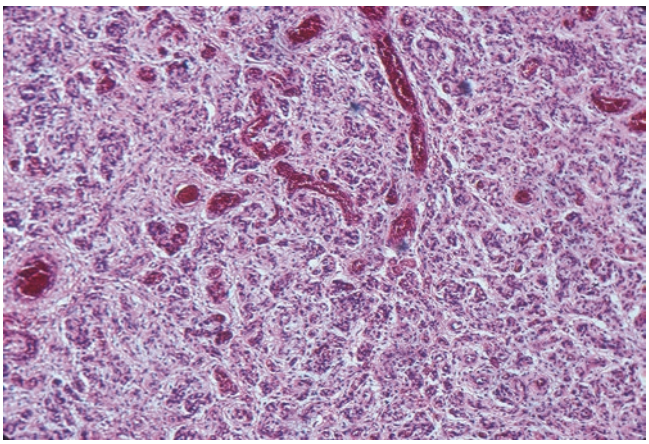

Fig. 30.4 Chorangioma with primarily typical appearance consisting of proliferation of small vessels within a stem villus. H&E × 200

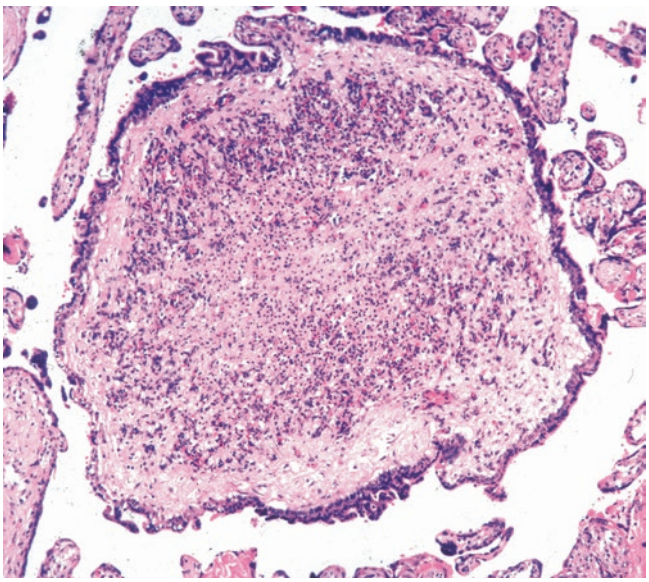

Fig. 30.5 Small incidental chorangioma. H&E × 160

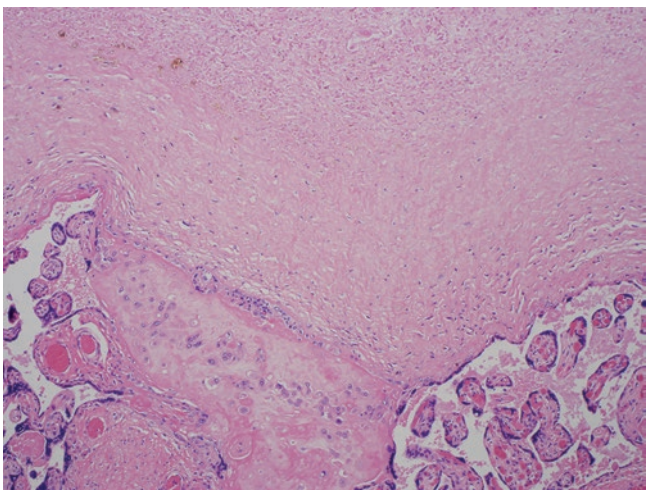

Fig. 30.6 This chorangioma displays the feature a more fibrous stroma which, here, is partially infarcted. H&E × 100

umbilical cord. In such cases, a mucicarmine stain reveals the presence of mucus [41]. The tumors often have degenerative changes, calcification, infarcts, and thromboses, which may leave hemosiderin behind [41]. Rarely, they may be associated with umbilical artery thrombosis as described by Sen [128].

Variability of the histological appearance, often within the same tumor, has confused many authors and is likely the source of the abundance of monikers over the years. Capillary, cavernous, endotheliomatous, fibrosing, and fibromatous tumors have been included in the nomenclature suggested by Schulz-Hetzel [126]. Williams labeled these tumors as hemangioendothelioblastomas in early studies [149]. We believe that such precision regarding nomenclature is unwarranted as the clinical outcome is almost always the same, and outcomes depend more on the size of the mass(es) than on the composition of the tumor(s). Approximately 40% of the tumors have prominent trophoblastic proliferation; these variants are described in greater detail below. Placentomegaly may occur, often with hydropic villi, and is probably directly related to the potential fetal sequelae of cardiac failure, anemia, and hypoproteinemia.

The differential diagnosis for chorangiomas primarily includes chorangiomatosis (particularly of the focal and segmental types), chorangiosis, and albeit less frequently, atypical lesions including chorangiocarcinoma. In chorangiomatosis, the abnormal villi are interspersed between normal villi, rather than as a discrete mass. Chorangiosis involves the terminal villi, shows distinct basement membrane surrounding capillaries, and lacks MSA-positive pericytes and the lattice-like reticulin staining seen in chorangiomas. When otherwise classic chorangiomas show multilayering and proliferation of surface trophoblast (as opposed to the more common single layer), as well as trophoblast atypia and pleomorphism, concern is raised for the atypical chorangioma and/or chorangiocarcinoma. These entities are all discussed in greater detail below.

Chorangioma: Clinical Features

Chorangiomas are seen more commonly in term, near-term, or post-term pregnancies. Multiple gestations and pregnancies associated with maternal preeclampsia also have higher rates [17, 112]. As previously stated, they are seen with increased frequency in association with vascular tumors of the neonate and certain malformations (Visentin et al. 2013). Froehlich et al. [53] found these tumors occur more frequently in White than in African American mothers, more often with twins, and also more often with malformed neonates. Soma [133] found them to be more common in Japanese women (2.5–7.6%) and in populations at high altitude such as Nepal, the latter finding of which was also supported by earlier literature by Reshetnikova et al. [121]. Bashiri et al. [13] found a significant risk of associated preterm delivery and several authors have noted that chorangiomas were seen in association with preeclampsia (e.g., [67]), as mentioned above. Sonographic diagnosis has repeatedly been made of chorangiomas and was well described by Dao et al. [36] (see also [68]). It is now common to make the diagnosis of placental chorangioma by sonography [45, 141].

Chorangioma: Prognosis

The relation of chorangioma to polyhydramnios and fetal hydrops has been known at least since Siddall's extensive review in 1924. He observed that hydramnios was associated with large tumors in particular, but that the prognosis for the gravida was otherwise excellent. Isaacs (2008) also drew attention to the fact that hydrops relates to the size of the tumor mass, as has long been known from sacrococcygeal teratomas [89]. There are many reports of large chorangiomas associated with hydramnios, hydrops fetalis, and fetal death ([29, 71, 88, 96, 122, 125, 140, 143, 147], and [113]). These authors highlight the common cardiac failure from large chorangiomas, multiple chorangiomas, and the associated arteriovenous shunting. Four cm has been cited as a clinically relevant size cutoff portending an increased risk of complications (Amer 2010, Mubiayi 2002).

Fetal growth restriction, preterm delivery, and stillbirth have also been associated with large tumors, perhaps due to the significantly increased fetal circulation that does not participate in maternal–fetal exchange [47, 85, 94, 103, 105, 114]. Large chorangiomas may also affect the fetal circulation directly by increasing the load significantly without providing oxygen exchange, as was probably the case in the patient with a 7-cm tumor whose premature neonate had periventricular leukomalacia [65]. Platelet sequestration within the tumor may lead to neonatal thrombocytopenia [52, 53] and Kasabach-Merritt syndrome (Jones et al. 1972), as well as disseminated intravascular coagulation [1, 58]. Prenatal cerebral embolism [55] has also been described. Additional complications include abruptio placentae [7, 137] and elevated maternal human chorionic gonadotropin (hCG) titers. Altered levels of pregnancy hormones with large chorangiomas have also been described.

"Giant chorangiomas" have been alluded to in several publications (e.g., [21]); the record is probably held by the 1500-g (30 × 20 × 5-cm) tumor described by Arodi et al. [6]. It was associated with breech presentation, placenta previa, hydramnios, preeclampsia, and abruptio placentae. The 32 weeks' gestation fetus weighed 1000 g and died from anemia and asphyxia. Due to the arteriovenous shunting which may occur in these tumors, the hearts of affected newborns are often enlarged and hydrops may develop due to fetal heart failure [30, 31, 35, 106, 110]. The neonates may

also be severely anemic. Cardiomegaly alone was reported with the 542 g chorangioma described by Benson and Joseph [18]. High-output cardiac failure and hydramnios also occurred with a 9 × 8 × 8 cm mass studied sonographically by Eldar-Geva et al. [43].

Size alone, however, may not be the decisive factor. In Fig. 30.7, we show a 900-g chorangioma (14 × 13 × 10 cm) seen in a 950-g placenta of a neonate who survived with virtually no associated problems. The umbilical cord was massively edematous (110 g) and the neonate had normal platelet counts, 14 NRBCs/100 WBCs, mild hepatic enlargement, and minimal edema. There had been no hydramnios, and the neoplasm was first discovered at the Cesarean section done for breech presentation. The large artery supplying this tumor was mostly occluded by an old thrombus with calcification. This presumably was the reason for the infarction of approximately 80% of the tumor and may be the reason the fetus was apparently unaffected. At times, these tumors may undergo extensive thrombosis and infarction which can lead to cessation of maternal symptomatology, such as hydramnios, as well as a reduction in fetal shunted blood flow through the tumor. Chazotte et al. [27] observed such a lesion sonographically; when the chorangioma shrank, which was ultimately determined to be due to infarction, there was some improvement of the hydramnios.

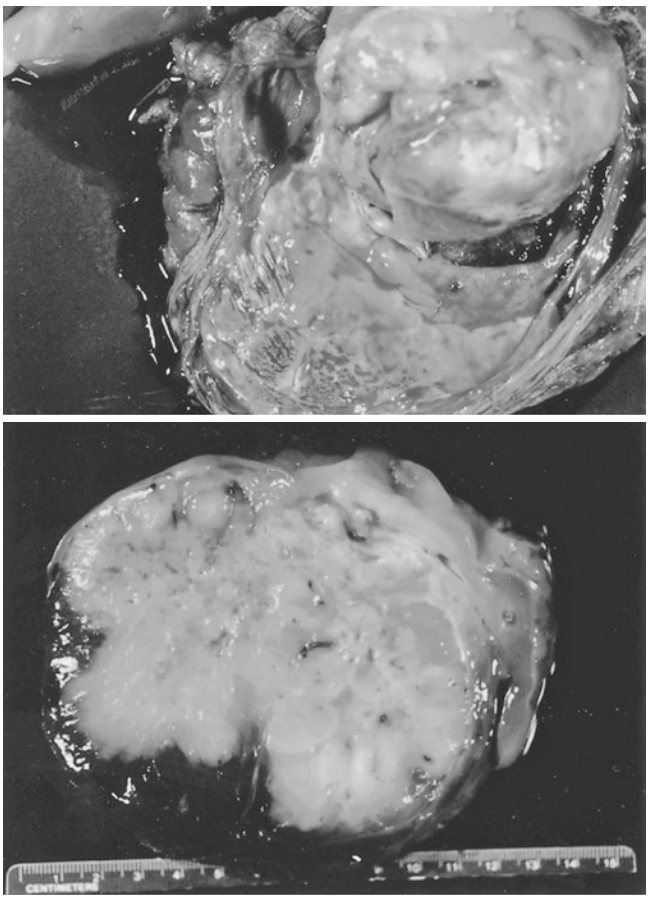

Fig. 30.7 A 900-g subchorionic chorangioma with marked edema of the umbilical cord and thrombosis of the nourishing chorionic artery. Four fifths of the tumor was infarcted; there were villous edema and minimal neonatal cardiac failure. The infant did well

Dorman and Cardwell [40] were the first authors to present a description of the "Ballantyne syndrome" associated with a large chorangioma. This syndrome, also referred to as maternal hydrops syndrome, pseudotoxemia, triple edema, and mirror syndrome, occasionally exists in a variety of conditions, such as both immune (rhesus isoimmunization) and non-immune hydrops, moles, teratoma, etc. The term "mirror syndrome" or "triple edema" refers to the maternal edema and similarly hydropic appearance of both the fetus and placenta. The patient described by these authors had severe hypertension, proteinuria, and edema, and delivered a hydropic fetus with an associated 9 × 6 × 8 cm chorangioma at 19 weeks' gestation. After delivery, the placenta was found to have numerous infarcts in addition to the chorangioma. There are clinical similarities between this syndrome and preeclampsia, and in fact they may coexist, further confounding diagnosis and possibly compounding outcomes. However, while understanding of the pathogenesis of preeclampsia has dramatically deepened, data is limited regarding the pathogenesis of Ballantyne Syndrome. As the association with chorangiomas indicates, it remains important to distinguish these two, since an identifiable source may dictate potentially curative treatment prenatally (Navarro-Perez 2019).

As noted above, maternal thrombocytopenia and fetal anemia have also been associated with these tumors. Platelet consumption and/or sequestration by the tumor may result in thrombocytopenia, and fetal anemia typically occurs as a result of hemodilution and/or destruction of erythrocytes within the tumor, which may ultimately result in fetal cardiac failure [72]. Limaye and Tchabo [91] observed maternal thrombocytopenia during the course of a pregnancy that was complicated by a 5-cm chorangioma. They believed that the thrombocytopenia was the result of necrosis in the chorangioma. Hirata et al. [68] attributed the severe anemia in their case (hematocrit of 17%) to "microangiopathic hemolytic anemia," a form of non-immune related intravascular hemolysis characterized by RBC fragmentation occurring in the microvasculature. Fetal anemia has been also associated with transplacental bleeding or fetomaternal hemorrhage which may account for many cases with anemia and subsequent hydrops [124] ([135]). In some cases, there has been associated fetal exsanguination [124].

Repetitive multiple chorangiomas have been noted by multiple authors [14, 26, 92] and reviewed by Benirschke [17]. Many of these cases resulted in fetal demise. Gallot et al. [54] have reported a case of recurrent chorangiomas in which they compared mRNA expression of various angiogenic factors and found extremely variable expression. No single, outstanding factor for the excess angiogenesis was

detected. In all these cases, the recurrent "chorangiomas" were composed of multiple lesions and probably best defined as chorangiomatosis (see below). Whether isolated chorangiomas can occur repetitively is unknown.

It is now also possible to laser-ablate the vessels that supply the symptomatic chorangiomas and thus prenatally treat the hydrops fetalis at its root cause [19, 116, 129]. Another modality of therapy, the injection with alcohol, has been suggested by Nicolini et al. [108]. These authors injected 1 mL of absolute alcohol into the central veins of two patients' large tumors (5 and 6 cm) whose pregnancies were complicated by hydramnios. It was followed by immediate cessation of blood flow; a second injection was necessary in both patients. Both eventually delivered normal infants, though the state of the tumors at delivery was not described. A case similar to this was treated by colleagues in Wisconsin (courtesy R. Franciosi 2002) and eventuated with a large placental infarct. More recently a "giant chorangioma" was treated successfully by microcoil embolization, a minimally invasive procedure [44].

Interestingly, chorangiomas have been described in placentas of other species. Hydropic bovine and canine fetuses have been associated with chorangiomas [32, 136], and Kirkbride et al. [86] found an aborted calf with dermal, oral, and placental angiomas. A stillborn bongo (Tragelaphus eurycerus) with four huge chorangiomas (weighing up to 975 g) has been described, in which some smooth muscle fibers were frequent along with bizarre multinucleated cells whose origin remains obscure [151].

Chorangioma Variants

Several variants of chorangioma have been described including chorangioendothelioma, atypical chorangioma, cellular chorangioma, atypical cellular chorangioma, chorangioma with trophoblastic proliferation, and chorangiocarcinoma. With rare exception, these tumors have been associated with a benign outcome.

Two tumors with histologic features of hemangioendothelioma have been described in the literature [75, 97]. The first case [97] described a fetus with multifocal hemangioendotheliomas involving the liver and adrenal gland as well as the placenta. The baby was delivered at 28 weeks for fetal hypoxia and showed generalized edema, anemia, hypoproteinemia, as well as cerebral, gastrointestinal, and pulmonary hemorrhage. She died at 2 days of age and the autopsy showed numerous hemangioendotheliomas in the liver and one tumor in the adrenal. The placenta weighed 1000 g and contained numerous firm white nodules. On microscopic examination, numerous vascular spaces with endothelial lining were present, often showing proliferation and budding into the lumina. The nuclei were pleomorphic and showed moderate mitotic activity and there were focally large capillaries embedded in hyalinized fibrous stroma, consistent with a hemangioendothelioma. The authors could not rule out metastasis from the fetus to the placenta. In the second case [75], the fetus developed hydrops with cardiomegaly and the pregnancy was terminated at 24 weeks. At autopsy there was no evidence of vascular tumors. The placenta showed an 8 cm tumor with a similar histology to the first case and the authors termed the lesion a "chorangioendothelioma." Although no fetal involvement was identified, hemangioendotheliomas in comparison to benign chorangiomas are thought to exhibit borderline biological behavior, recurring locally with low metastatic potential.

Jauniaux et al. [76] described what they referred to as a chorangiocarcinoma and suggested that this tumor was the "missing link" between chorangiomas and choriocarcinomas. They described a lesion in a 35-week placenta consisting of a solitary small nodule fairly typical of a chorangioma. Its surface, however, was covered by a marked proliferation of an admixture of syncytiotrophoblast and cytotrophoblast with nuclear abnormalities usually associated with trophoblastic tumors. The mother and child did well and there was no other chemical or cytochemical evidence of choriocarcinoma. They considered it to be a combined lesion of chorangioma and choriocarcinoma. An additional 5 cases of "chorangiocarcinoma" have been described [5, 46, 63, 64, 70, 142]. In retrospect, several cases appear to be variants of chorangioma with trophoblastic proliferation, demonstrating a benign clinical course as described above [63, 64, 142] (vide infra). A subsequent report by Faes et al. [46] presented a similar histology, again with benign follow-up. However, a case reported by Ariel et al. [5] showed a chorangioma with a more exuberant proliferation of nodules of pleomorphic, atypical trophoblast associated with necrosis and high mitotic activity. Although there was no evidence of metastases, they interpreted the findings as an "unequivocal malignant trophoblastic component in a benign chorangioma," closely related to choriocarcinoma. Thus, in some cases, the term chorangiocarcinoma may be warranted. Most convincingly, Huang et al. [70] reported the first case of a chorangiocarcinoma with maternal metastasis documented by pulmonary CT scan and elevated serum beta-hCG. After three courses of postpartum chemotherapy, her serum beta-hCG dropped to the normal range and 36-month follow-up showed resolution of the pulmonary lesions.

Those chorangiomas with a robust proliferation of surface trophoblast but to a lesser degree than the "chorangiocarcinoma" and without significant atypia have been called "atypical chorangioma" or "chorangioma with trophoblastic proliferation" [82, 95, 99, 144](Fig. 30.8 courtesy of Dr. Yee Khong). They have variably been reported in up to 40% of tumors [82], and for the most part appear to be only an exag-

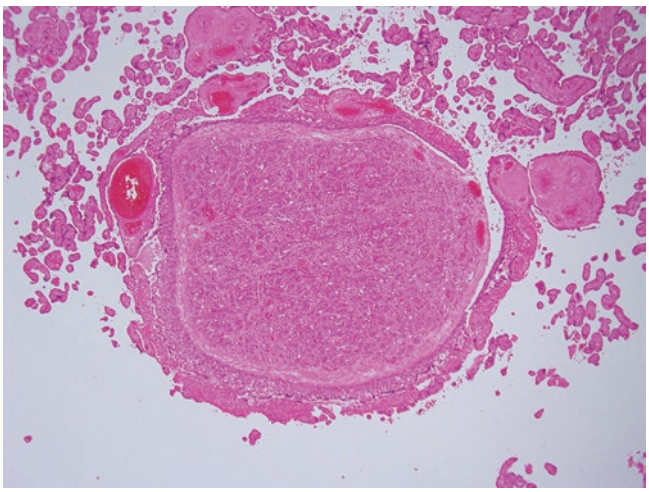

Fig. 30.8 A atypical chorangioma with unusual proliferation of trophoblast surrounding the tumor. (Courtesy of Dr. Yee Khong, Adelaide Australia). H&E 40. ×

gerated proliferation of the normal trophoblastic cover of these tumors. They have all been associated with a benign prognosis. Similar observations were made by Mesia et al. [99] who described an atypical case that was "mitotically active." Despite this feature and their review of the other rare cases described with similar findings, neither invasion nor metastases was identified. Several other cases of atypical cellular chorangioma have been described with similar benign outcomes [95, 144].

Previous authors, impressed with mitoses and the great cellularity of some tumors, suggested that occasional chorangiomas represent sarcomas. Metastases and true invasion, however, have never been seen. Cary [23] considered his case of "sarcoma" to be "well authenticated," but no images were provided at that time. Moreover, mother and infant did not suffer any known deleterious consequences from the 6.5 × 4.0 × 3.0 cm, focally calcified tumor. To date, no true sarcomas of the placenta have been documented.

Other unusual variants include a case depicted by Earn and Penner [42] of a chorangioma that was separate from the placenta, attached by a long vascular pedicle whose vein was diffusely calcified. More recently, a giant chorangioma was identified without a normal placenta, fetal membranes, umbilical cord, or a fetus [117]. Documentation included immunostains for CD34 and beta-hCG which were positive in the blood vessels and trophoblastic cover, respectively. No explanation of this curious phenomenon was provided.

Chorangiomatosis

In the past, terminology and studies describing chorangiosis and chorangiomatosis have overlapped. Over time, distinctions between these entities have evolved. Chorangiomatosis can have a heterogenous appearance and has been described as exhibiting histology intermediate between chorangioma and chorangiosis [112]. However, ultrastructural studies have shown both chorangioma and chorangiomatosis to be lesions of stem villi. While the histology of chorangiomatosis may mimic multiple chorangiomas, the pathogenesis appears to differ. It has been proposed that both lesions may arise from the subtrophoblastic rim of connective tissue of immature stem villi and are differentiated based upon the directionality of growth. Chorangiomatosis grows extending lengthwise and around the stem villus preserving its core, while a chorangioma primarily grows eccentrically, displacing the villus [112]. The incidence of chorangiomatosis has been quoted at 0.55% and its concurrence with chorangioma has been noted at up to 10%.

Chorangiomatosis has been separated into three primary groups based upon the extent of villous involvement: (1) focal (defined as 1–5 involved villous cross sections); (2) segmental (more than 5 villous cross sections); and (3) diffuse multifocal (involvement of multiple separate areas of the placenta) (Redline and Ogino 2000). The focal and segmental types have been noted to share commonalities with chorangiomas beyond the proposed origin in stem villi, including late preterm birth (between 32 and 37 weeks) and an association with multiple births and preeclampsia. However, diffuse multifocal chorangiomatosis is noted to be more strongly associated with adverse outcomes including extreme prematurity (less than 32 weeks gestation), intrauterine growth restriction, congenital malformations, abnormal villous maturation, and fetoplacental vascular abnormalities. Advanced maternal age was also a noted association (Redline and Ogino 2000, Bagby 2011). In the same study, chorangiomatosis was said to be less common in primigravidas and African American mothers and no association with diabetes or preeclampsia was seen.

In chorangiomatosis, the placenta may be unusually large and bulky, particularly in multifocal cases (Figs. 30.9 and 30.10). Because of this massive enlargement and the abnormal amount of gonadotropin that may thus be produced, chorangiomatosis has occasionally led to an excess of luteinized ovarian cysts [123]. Histologically, chorangiomatosis is characterized by a proliferation of anastomosing small vessels involving stem villi, often with interspersed normal terminal villi. The growth is non-expansile in the sense that it does not form a discrete mass. Like chorangiomas, chorangiomatosis shows a contiguous layer of MSA-positive pericytes and a loose stromal reticulin network. However, villi of chorangiomatosis may show a vimentin positive dense central core surrounded by dense reticulin, consistent with the makeup of mature intermediate villi (Redline 2000). Larger vessels as seen in intermediate villi may be identifiable at the core of the involved villi, surrounded by the smaller proliferative vessels of the lesion. Distinct basement

Fig. 30.9 Gross appearance of the maternal surface of a case of multifocal chorangiomatosis. Note the multiple, grossly identifiable nodules on the surface and within the parenchyma with disruption of the surface

Fig. 30.10 Cut section of a placenta diffusely involved with chorangiotic lesions. The nodular, pale lesions represent chorangiotic lesions, which comprise approximately 50% of the placenta. The distinction between multiple chorangiomas and diffuse multifocal chorangiomatosis can at times be difficult. In addition, the lesions could easily have been mistaken for infarcts. The placenta weighed 430 g and was accompanied by a 3200-g infant with cardiomegaly, anemia (hematocrit 40%), and thrombocytopenia at birth. Chromosomes were normal. (Courtesy Dr. P. Bromburger, Kaiser Hospital, San Diego)

membranes surrounding the abnormal vessels are not typically seen (Fig. 30.11). The peripheral changes in diffuse chorangiomatosis may more closely mimic those seen in chorangiosis.

Cases of recurrent chorangiomatosis have been documented [17]. For example, a case of a 2205 g boy born after 39 weeks' gestation to a 17-year-old gravida 2 with Apgar scores of 9/9 had a good clinical outcome. The 430-g placenta had numerous typical chorangiomatous nodules, was markedly congested, and had numerous nucleated red blood cells in the fetal circulation. Sonographically, "unusual notching of the umbilical vein" had been reported. A previous pregnancy, 1 year earlier, was also complicated by multiple placental chorangiomas.

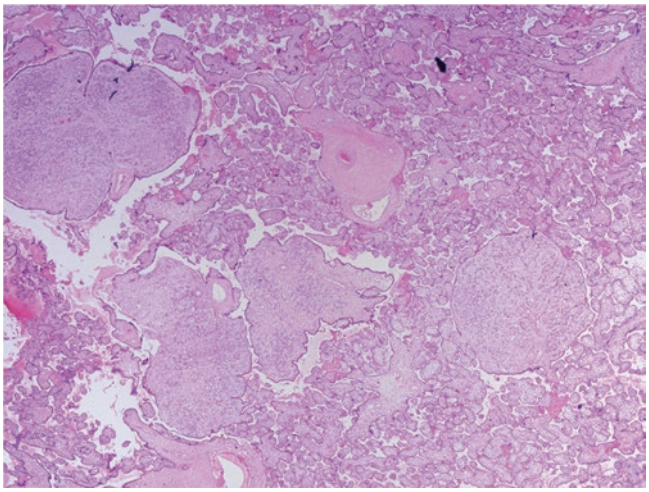

Fig. 30.11 Microscopic appearance of chorangiomatosis. Note the presence of multiple lesions which permeate the villous tissue. H&E 40×

Chorangiosis

While vascular proliferations of the placenta have long been of interest to investigators, they were not always as aptly named as they are today. Meyenburg [100] had considered the proliferation of capillaries that we now call chorangiosis as "diffuse hemangiomatosis of the placenta," and Marchetti (1939) considered that chorangiosis was merely a diffuse ectasia of placental villous capillaries. It was not until 1958 that Hörmann coined the term chorangiosis. In contrast to chorangiomas and chorangiomatosis, chorangiosis arises in the terminal villi of the placenta. A seminal study by Altshuler [4] of 1350 placentas quoted a rate of 5.5%, and since then it has been reported at rates up to 7% [112]. It is most common in term deliveries (at least 37 weeks gestation) and is not typically seen in gestations less than 32 weeks. It is seen with increased frequency in patients residing at high altitudes, those with anemia, and smokers, supporting the proposed stimulus of placental hypoxia. Associations with gestational diabetes and hypertension, preeclampsia, placental abruption, delayed villous maturation/distal villous immaturity, and large placental size have also been noted (Redline 2000, [139]).

The primary pathogenesis of chorangiosis is postulated to relate to hypercapillarization secondary to chronic placental hypoxia. Excessive villous angiogenesis mediated by growth

factors (VEGF, FGF, and PDGF) is thought to occur in response to low oxygen levels and capillary exchange. A more detailed consideration of the placental villous adaptation to hypoxia can be found in the contribution by Kaufmann et al. [79], and the paper by Kadyrov et al. [78] provided information on how anemic women produce increased placental angiogenesis in early development. The control of angiogenesis is complex, but it is an essential aspect of placentation and regulation during anemia, preeclampsia, and other pathologic states in pregnancy. It has also been proposed that vascular proliferation may be related to increased intratumoral pressure, possibly related to umbilical or fetal cardiac venous obstruction. Bernirshke [16] noted an association of chorangiosis with cord abnormalities, a finding which lends credence to this as a possible secondary etiology. Excessive growth factors (such as those seen in diabetes) and increased cytokine production have also been cited as possible alternative etiologies. However, the relationship of chorangiosis to hypoxia is more widely accepted as the primary inciting factor at the current time. There are numerous factors still being explored, and many have significant impact on the villous vascularization. A detailed review of placental response to hypoxia was provided by Sherer and Abulafia (2001) that is too complex, however, for the brief consideration possible in this chapter.

The placentas of patients with chorangiosis may appear grossly normal. Given their reported association with maternal disease states, umbilical cord abnormalities, and placental abruption, attention to these details with thorough gross examination should always be performed. Microscopically, there is prominent vascular proliferation arising in terminal villi (Fig. 30.12). The capillaries have distinct basement membranes and a discontinuous layer of pericytes, in contrast to chorangiomatosis and chorangiomas. The stem villi are also spared in chorangiosis. It was not until Altshuler [4] examined this entity in considerable detail that some clarity was established regarding its histologic nature and diagnosis. He defined chorangiosis as more than 10 capillaries in more than 10 terminal villi in at least 10 different microscopic fields viewed with the 10× objective in three non-infarcted/non-ischemic areas of the placenta. It was chorangiosis from grades 1 to 3, depending on the profusion of vessels within villi. Because of the frequency and importance of this condition, overtime refinements of the numerical assessment have been made. Mutema and Stanek [107] found that chorangiomatous villi may often show 20 or more capillaries within a single terminal villous. They also addressed that, when counting is done on slides stained with CD34 immunohistochemistry (endothelial marker), more vessels were counted in nonchorangiomatous villi (8–15), and thus, when H&E staining only is performed, the frequency of chorangiosis may be overestimated. More recently (and more commonly in clinical practice), it has been acknowledged that there are cases which fall short of Altshuler's criteria, particularly with respect to the diffuse nature, which still portend clinical significance. We use the term "focal chorangiosis" to describe these cases [139].

One must be careful not to overinterpret vascular congestion as chorangiosis, as both may cause a low power appearance of enlarged, rounded terminal villi with prominent vasculature, but careful examination will show the former to be lacking in the classic capillary proliferation (Fig. 30.13). Placental villous congestion is particularly prominent with uncontrolled diabetes and, in our experience, it may mask chorangiosis if one is not careful (see also [37]). In chorangiosis, there is an obvious numerical increase of the vessels

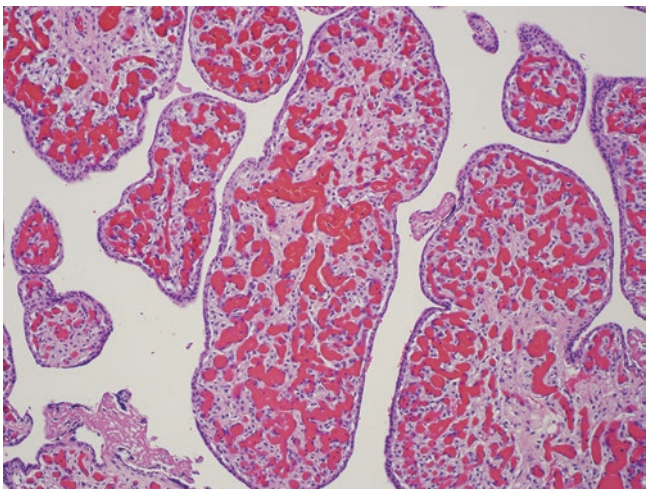

Fig. 30.12 High power view showing chorangiosis in a severely growth restricted infant with presence of numerous capillaries expanding and filling the terminal villi. This is a diffuse process involving terminal rather than more proximal villi. H&E 200×

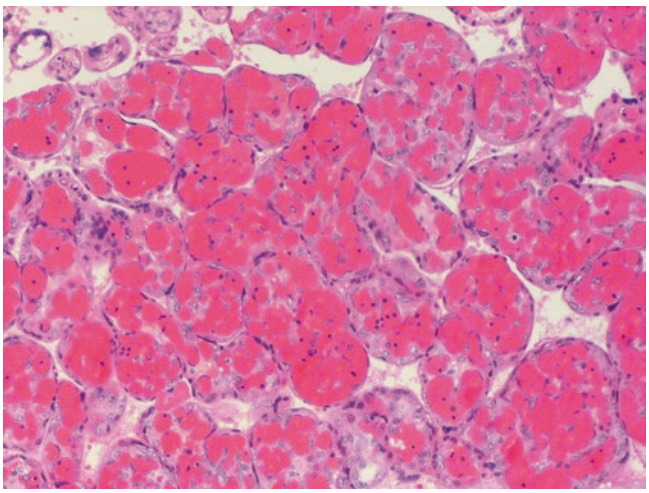

Fig. 30.13 Severe villous congestion in which the capillaries are expanded in size but not in number. May be mistaken for chorangiosis; however, the villi are not enlarged and the capillaries are largely peripheral. H&E × 160

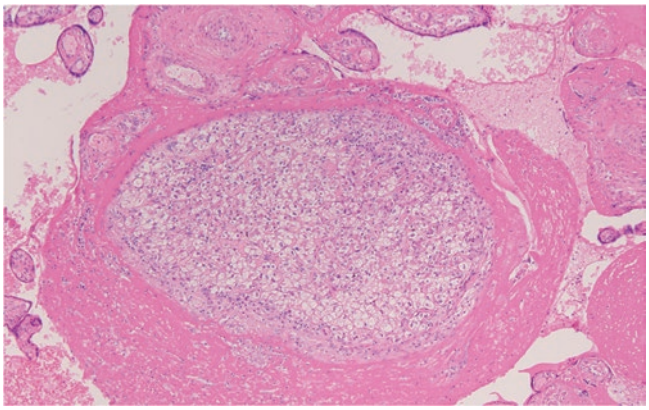

Fig. 30.14 Hepatocellular adenoma in a term placenta. Immunohistochemistry was positive for Hep Par 1 confirming differentiation. H&E × 160

per villus (Fig. 30.14); with congestion, the vessels are merely distended. It must also be cautioned that removal of blood from capillaries renders villi relatively bloodless and thus to appear as being without vessels, while infusion distends the capillaries and may produce pictures like chorangiosis. Care must be taken in interpreting the lesion properly.

The clinical outcome of chorangiosis varies widely, ranging from no abnormalities to increased rates of stillbirth, intrauterine growth restriction, congenital malformations, cerebral palsy, and low Apgar scores ([4], Bernirshke 2012, [139]). Though not overly common, given these associations, its presence can have an ominous connotation. The increase in capillary lumen cross sections seen in this lesion comes about, we believe, through endothelial proliferation. It thus takes time to develop. Perhaps it takes as much as weeks to develop full-blown, marked chorangiosis. Its presence betrays a deleterious intrauterine environment for the fetus, and we see in its manifestation an attempt (teleologically speaking) of the placenta to enlarge its diffusional surface. Altshuler saw it associated with high frequency in stillbirths and many perinatal circumstances that suggested to him long-standing hypoxia. Thus, it is more commonly observed in the placentas of babies who develop cerebral palsy, and perhaps, it is related to smoking and air pollution, as suggested by Akbulut et al. [2]. As previously mentioned, we find it more often with cord problems of one kind or another ([16, 51]; see also [59]). Additional authors found that chorangiosis correlated significantly with perinatal deaths (39%) (e.g., [80]) and congenital anomalies (27%) and was thus deemed to be an important signal for scrutiny, particularly in cases of placentomegaly.

It is thus not surprising to note that somewhat similar observations were made in placentas from high altitude when they were quantitatively compared with those of lower strata ([73, 119–121], and many others). When Ali [3] compared stereologically the villous structure of placentas from high altitude (3000 m) with those at sea level, his main finding was an increase in the number of cytotrophoblast at altitude. Birth weights, placental weights, and placental index were all lower at altitude. The increased recruitment of cytotrophoblast was thought to result from relative hypoxia and increased syncytial turnover. Although not discussed, the microscopic picture of villi shown suggests an increase in capillaries as well. Interestingly, diffuse hemangiomatosis was described in the fetuses (skin, liver) of a patient with twin transfusion syndrome [57].

The exact final etiology, if a specific one really exists, remains to be fully elucidated. While there are certainly associations with adverse perinatal outcomes, it must be cautioned that not all infants whose placentas show diffuse chorangiosis are significantly affected. The case reported by de la Ossa et al. [38] had, as its only complication, severe preeclampsia that necessitated a Cesarean section. Despite the chorangiosis, the infant developed normally, and no other features that might have induced chorangiosis were known. Madazli et al. [93] investigated placentas with chorangiosis in gestational diabetes by an ascertainment of circulating levels of malondialdehyde (MDA) and endothelial vascular growth factor (VEGF) both in maternal and fetal circulations. While MDA levels were elevated in both samples, that of VEGF was not higher or decreased, thus leaving the complexity of the findings still in doubt.

"Heterotopias," Nodules, and Other Benign Tumors

Heterotopic tissues, such as adrenocortical tissue and liver tissue, have occasionally occurred in the placenta as an incidental finding, most commonly in the third trimester. Ectopic liver tissue has often been presumed to be a hepatocellular adenoma but evidence of neoplastic growth is lacking and no malignant sequelae have been reported. Chen et al. [28] described an intraplacental hepatocellular adenoma consisting of a 7.0 × 4.2 × 2.7 cm firm mass. The lesion was tan white, sharply delimited, and composed of polyhedral cells that had the appearance of hepatocytes. There was no bile pigment, but the cells contained glycogen, and some reacted with antibodies to α-fetoprotein and α1-antitrypsin. Study by electron microscopy showed structures that strongly resembled bile canaliculi. The authors believed that the lesion was a "monodermal teratoma," although it was not on the placental surface. The fetus and mother had an entirely benign course. Four additional hepatic "adenomas" were described in some detail by Khalifa et al. [81]. They were benign as well; two had an intravillous and two a subchorionic location. Their histology and special staining characteristics were similar to the previous case and extramedullary hematopoiesis was a consistent finding. Whether subchorionic or intraplacental, the lesions are usually well-circumscribed nodules

with cells resembling hepatocytes but without portal tracts, bile pigment, central veins, or bile duct structures (Fig. 30.14). Extramedullary hematopoiesis may be present, as noted above. The differential diagnosis includes decidua, X-cell islands (extravillous trophoblast), chorangioma, and metastatic tumors of fetal or maternal origin. Immunohistochemistry is usually definitive in distinguishing these diagnoses.

Heterotopic adrenal cortical tissue has also been described. Guschmann et al. [62] described a 2-mm nodule in the twin placenta of a mosaic Turner syndrome patient and interpreted it as a heterotopic adrenal lesion. The five prior reported cases of this entity are reviewed in their report, all of which were present as small islands resembling the zona fasciculata of the adrenal gland (Fig. 30.15). In all cases, the ectopic tissue was seen in a villus near the fetal plate and never in the intervillous space. They postulate that these lesions may be underrepresented in the literature due to their small size, focality, and the fact that they are likely not identified on gross examination without extremely meticulous examination.

The origin of these nodules has not yet been confirmed, and it has been suggested that they may represent monodermal teratomas ([28], Vesoulis and Dimitri 1998), displacement or aberrant migration of cells from the hepatic bud or coelomic epithelium (which differentiates into adrenocortical tissue), respectively (Saluja et al. 2018; Cox 1980), displaced yolk sac [81], vanishing twin, autonomic and erroneous differentiation of mesenchymal cells of the placenta (Bozic 1974), and access to blood vessels during migration [62]. Most cases have been reported in the third trimester, though they have occasionally been reported earlier. The hepatic nodules have been located both in the subchorionic location (Yee et al. 2016, Vesoulis and Dimitri 1998) and intraplacentally (Saluja et al. 2018). Although the lesions of ectopic liver tissue do not appear to be neoplastic, they have been associated with a fetal demise in one case (Salufa et al. 2018). One other unusual case of co-occurrence of a chorangioma and hepatic adenoma was noted in a twin gestation (DeNapoli 2015). The heterotopic adrenocortical tissue does not appear to bear any clinical significance.

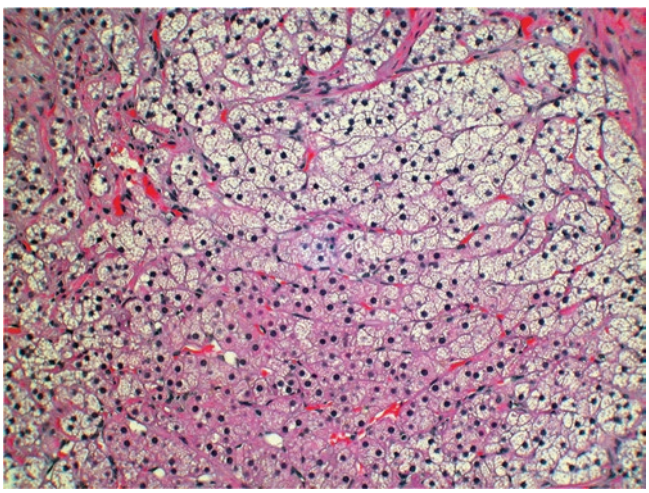

Fig. 30.15 Adrenal cortical rest. (Courtesy of Dr. Debra Heller, Newark New Jersey). H&E 200×

Placental teratomas have also been rarely described, most recently in 2012 by Prashanth. They were first reported by Morville in 1925. Multiple authors have suggested that they should always reside on the fetal surface of the placenta, most commonly located between the amnion and the chorion, though they may occur in the membranes ([50]; Prashanth 2012, Elagoz 1998). They are thought to originate from the abnormal migration of embryonic germ cells (Shimojo 1996). They may be suspected on prenatal imaging based on the presence of varied echogenicity of the components (Ahmed 2004), though the diagnosis can be challenging. The primary pathologic differential is distinction from a fetus papyraceous, which typically will show some organized growth, and clinical review may elicit history of a twin or multiple reduction, spontaneous or otherwise. They have a favorable prognosis, but may present challenges on prenatal imaging.

Harirah et al. [66] reported on an intraplacental smooth muscle tumor, but it is not at all certain that this was not a modified cellular chorangioma. Murtoniemi et al. (2009) and Ernst et al. (2001) both reported cases of smooth muscle tumors involving the placenta which on molecular analysis were ultimately determined to be an entrapped maternal leiomyomas. Both were associated with male fetuses. There are two older reports of primary smooth muscle tumors of the placenta (Misselevich 1989, Tapia 1985). Both were benign leiomyomas, one of the fetal membranes, thought to be arising in the chorion, and one primary parenchymal leiomyoma, likely arising from the mesenchyme of the chorionic villi (fetal vascular smooth muscle). However, a limiting factor is that neither of these studies incorporated molecular data.

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