Placental Chorangiosis: An Important Pattern of Placental Injury

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OBJECTIVE: Chorangiosis is an infrequently diagnosed placental lesion characterized by placental capillary proliferation. In this study we present 10 cases of chorangiosis with histological and immunhistochemical features and described the clinical effects on fetal outcome.
STUDY DESIGN: Ten cases of chorangiosis (7%) diagnosed in 150 placentas examined at our institution between 2002 and 2004 were evaluated. Chorangiosis was defined as the presence of a minimum of 10 villi, each with 10 or more vascular channels, in 10 or more areas of three or more random areas when using an x10 objective. Beside histopathological criteria, histochemical and immunohistochemical staining was also applied.
RESULTS: Chorangiosis was most commonly associated with cesarean section (60%), preterm birth and neonatal intensive care (40%), Apgar scores of 5 minute or less (30%), maternal disease and drug ingestion (30%). Also intervillous hemorrhage (80%), placental calcification (60%), placentomegaly (40%), umbilical cord knots (40%), chorioamnionitis (40%), perivillous fibrin (40%) and umbilical vein dilatation (40%) were commonly observed placental findings in chorangiosis cases.
CONCLUSION: Chorangiosis should be considered as an important sign of placental injury associated with hypoxia in utero. Histopathological recognition of these lesions might help to determine the underlying and proximate causes of fetal injury.
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Key Words: Chorangiosis, Chorangiomatosis, Chorangioma, Villous capillary, Angiogenesis

Villous capillary lesions of the placenta are a heterogeneous group of possibly interrelated lesions. Among these, chorangiosis is defined as an alteration of the terminal villous characterized by an abnormal growth of fibrous and vascular tissues with an increased number of capillaries in placental areas.[1] Chorangiosis has not been studied extensively; its etiology is unknown, but believed to be related to chronic hypoperfusion and hypoxia.[1,2]

In this study, we evaluated 10 cases of chorangiosis and determined the clinical, placental and histopathologic features, and emphasized the importance of recognizing these lesions.

Material and Methods

From January 2002 to December 2004, 150 placentas received in the Zonguldak Karaelmas University Hospital Pathology Department were examined. Clinical features, placental histopathological and gross findings were reviewed for each case which was diagnosed as chorangiosis.

The placentas were weighed after removal of the cords and membranes. Multiple sections from each placenta, including one from the cord and one from the membrane roll, were examined microscopically. The tissue was fixed in 10% buffered formalin, embedded in paraffin, and stained with hematoxylin-eosin.

Chorangiosis was diagnosed as the presence of a minimum of 10 villi, each with 10 or more vascular channels, in 10 or more areas of three or more random, noninfarcted placental areas when using a x10 objective according to the criteria established by Altshuler.[1]

Subsequently, for each case one representative placental sections was evaluated by histochemical stains for reticulin (Gomori's reticulin stain) and by immunohistochemical studies by using streptavidin biotin peroxidase method and antibodies specific for CD31 (monoclonal, mouse, clone: JC/70A, NeoMarkers, CA, USA) and PD-ECGF (monoclonal, mouse, clone: P-GF.44C, NeoMarkers, CA, USA).

Results

Of the 150 placentas examined 10 (7%) had chorangiosis. None of the case had multiple gestations. The gestational ages of the associated newborns ranged from 28 to 40 weeks; one case (10%) in 20 to 32 weeks, 5 (50%) in 33 to 37 weeks and 4 (40%) in 38 to 40 weeks.

The evaluated clinical and placental data of mothers and fetuses whose placentas were diagnosed as having chorangiosis was listed in Table 1.

The incidences of clinical conditions most commonly associated with chorangiosis were; cesarean section, 6 (60%);

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Table 1. The evaluated clinical and placental data

Clinical data	Placental data	
Gestational age	Gross	Placental weight
Poor obstetric history		Placental shape and color
Diabetes mellitus		Infarction
Eclampsia/preeclampsia		Umbilical cord abnormalities
Maternal infection		Meconium staining
Maternal drug ingestion		Amnion nodosum
Other maternal disease		Cyst and tumors
Cesarean section	Histopathologic	Chorioamnionitis
Oligohydroamnios		Villitis
Multiple birth		Calcification
Birth weight		Chorangiosis
Prematurity/postmaturity		Fetal nucleated erythrocytes
Neonatal intensive care		Perivillous fibrin
Neonatal/perinatal death		Dysmaturity
Premature rupture of membranes		Umbilical vasculopathy

preterm birth and neonatal intensive care, 4 (40%); Apgar scores of 5 minute or less, 3 (30%); maternal disease and drug ingestion, 3 (30%); premature rupture of the membranes, 2 (20%); toxemia or maternal hypertension, 2 (20%); neonatal death, 1 (10%); congenital anomaly, 1 (10%); diabetes mellitus, 1 (10%).

Of the 10 placentas with chorangiosis, the incidence of each of the following items were; intervillous hemorrhage 8 (80%), placental calcification 6 (60%), placentomegaly, 4 (40%), umblical cord knots 4 (40%), chorioamnionitis 4 (40%), perivillous fibrin 4 (40%), umblical vein dilatation 4 (40%), placental infarction 2 (20%), meconium staining of membranes 2 (20%), placental cyst 1(10%); umbilical vein thrombosis 1 (10%).

Chorangiosis was defined in terms of the number of the capillary vascular loops in the terminal villi. Histopathologically we diagnosed chorangiosis (Figure 1a-b) by applying the critera of Altshuler described above.[1]

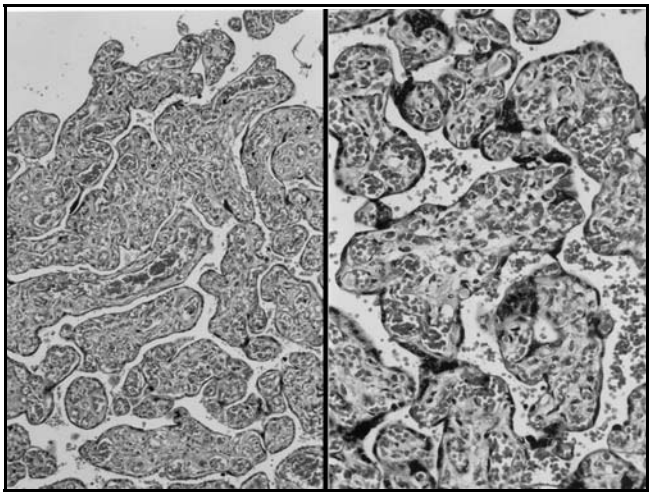

Figure 1. Hypercapillarized terminal villi, each having 10 or more capillary (a) H&E, x100, (b) H&E, x200.

Histochemical stain for reticulin revealed a thin, well-defined basement membrane that surrounds capillaries (Figure 2).

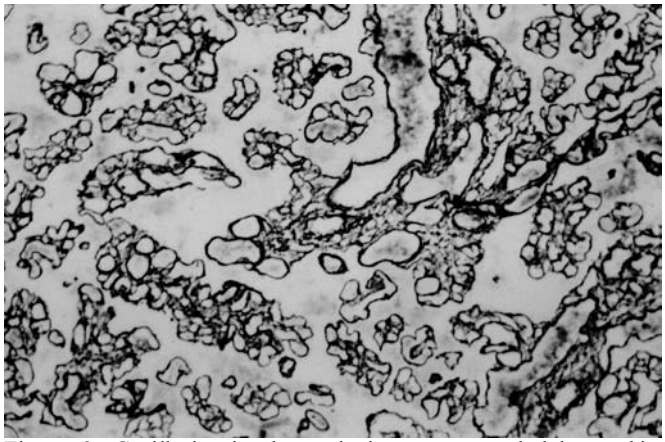

Figure 2. Capillaries in chorangiosis are surrounded by a thin basement membrane (Reticulin, x100).

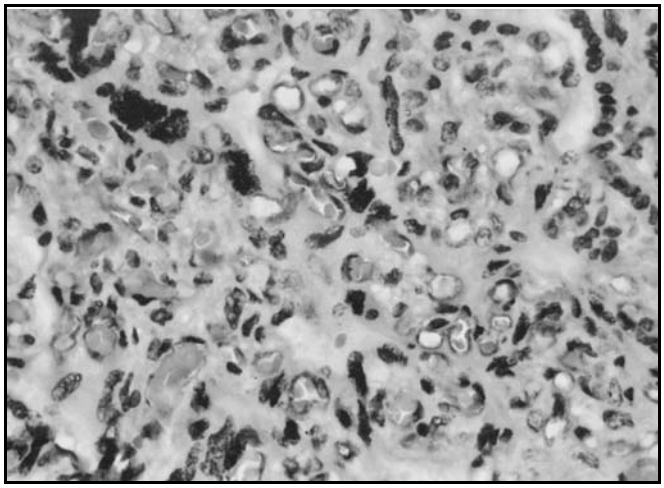

Figure 3. Immunostaining with CD 31 demonstrates more capillaries (Biotin streptavidin peroxidase, DAB, x400).

Immunohistochemically capillary endothelial cells showed uniform positivity with CD31; demonstrating more capillaries than were easily discernible by hematoxylin-eosin stain (Figure 3). The expression of PD-ECGF in the endothelial cells was present in five of our cases (Figure 4).

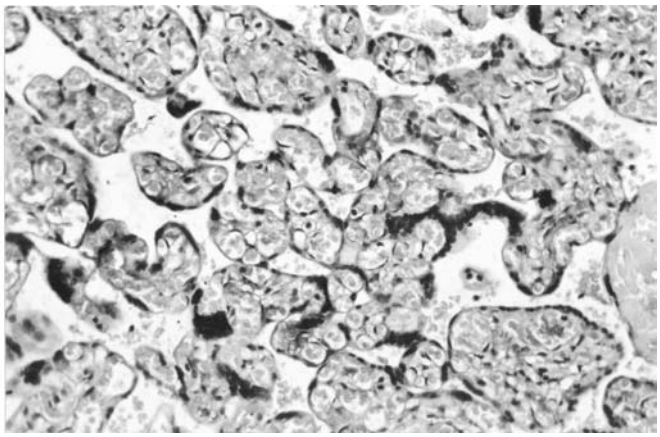

Figure 4. PD-ECF positivity of capillary endothelia (Biotin streptavidin peroxidase, DAB, x200).

Discussion

In this study, we determined chorangiosis in approximately 7% of examined placentas, comparable to other reported series.[1,2] Most placentas with chorangiosis were delivered ≤37 weeks' gestation and it was not seen at less than 28 weeks. It may probably take time to develop chorangiosis, so this hypothesis would explain why we had seen chorangiosis in the advanced weeks.

Chorangiosis has been correlated with increased neonatal death, major congenital malformations, preterm delivery and placental abruption.[1,3,4] It is frequently encountered in medical centers that care for high risk pregnancies1. However we had only one case with major congenital anomalies and neonatal death; but 40% of our cases with chorangiosis showed preterm delivery and required neonatal intensive care.

Association of chorangiosis with maternal disease and drug ingestion were also noted.[5,6] In the present study, of the ten cases with chorangiosis, one patient had multiple sclerosis and two had thyroid dysfunction and had medical treatment throughout their pregnancies. Also a case with oligohydroamnios and a case with polyhidroamnios was present in our series.

Pre-eclampsia may also lead to chorangiosis by giving rise to tissue hypoxemia.[1,5] Also in woman with hypertension, the frequency and extent of infarction are increased.[7] Two of our cases showed pre-eclampsia and at the same time showed placental infarction.

The incidence of chorangiosis is higher in women living in high altitudes; this event seems to result from placental hypoperfusion. Hypoxia appears to stimulate both placental capillary proliferation and cytotrophoblast and can result in elevated maternal serum hCG levels.[3]

Chorangiosis is predominantly a lesion of terminal villi. A number of angiogenic factors, vascular growth factors are thought to have a part in terminal villogenesis. Capillary and stromal overgrowth is characteristic of placentas in diabetes mellitus and Beckwith-Wiedemann syndrome, which can show mesenchymal dysplasia and villous capillary lesions.[8,9] Although we found high frequency of placentomegaly (60%) among placentas with chorangiosis, just one of our cases had diabetes mellitus.

Chronic hypoperfusion or tissue hypoxemia is the well-known stimulus that cause growth factors such as VEGF, PDGF and TGF-β, produced by mesenchymal and trophoblastic cells. Initiation of angiogenesis depends on VEGF, while continued capillary growth and development depend on PDGF dependent differentiation of pericytes, which produces angiopoetins that control remodeling of the primary vascular plexus into a mature capillary bed. Finally endothelial cells and pericytes lead to the activation of TGF-β, which inhibits further growth and promotes terminal differentiation of the mature capillary.[10,11] We demonstrated PD-ECGF reactivity in 5 of 10 cases. In negative cases, we might hypothesize that angiogenesis has become stable or perhaps is presently going on.

Another alternative proposal for the pathogenesis is that, the increase in the macrophage-derived growth factors, such as tumor necrosis factor-α may play a role in chorangiosis.[2] In some series, villitis was demonstrated in chorangiosis cases.[1,2] We noted an increase of the percentage of chorioamnionitis (40%) in our series; however villitis or necrotizing funisitis were not accompanied.

Increased intramural pressure related to venous obstruction at the umbilical cord and fetal cardiac level is thought to have part for the pathogenesis of chorangiosis and associations of cord anomalies, such as long umbilical cord, thrombosis of vessels and nuchal cord have been reported.[4,12] And we observed three false and one true umbilical cord knots (40%) in ten of our cases that in our knowledge it had not been reported before. Also four of our cases showed dilatation of umbilical cord and one umbilical vein thrombosis.

In our study 60% of placentas with chorangiosis were associated with cesarean section, which was also proposed previously by Altshuler.[1] In that study it was proposed that chorangiosis might result from placental circulatory changes or from factors that lead to obstetric decision for cesarean section.

The differential diagnosis between chorangiosis and other villous capillary lesions like chorangiomatosis and chorangioma is based on some histological criteria. Chorangioma is defined as an expansive nodular lesion composed entirely of capillary vascular channels some of which can con-

tain mitotically active cells, intervening stromal cells and surrounding trophoblasts and are analogous to hemangiomas at other body sites. Chorangioma is ascertained both at gross examination and an incidental findings at microscopic examination.[7,13] Chorangiomatosis is a more heterogeneous and less well-defined lesion with features described as having intermediate features between chorangioma and chorangiosis.

Chorangioma and chorangiomatosis is distinguished from chorangiosis by the presence of increased stromal collagenization and cellularity, and surrounding perivascular cells. Also reticulin network will aid the differential diagnosis between chorangiomatosis and chorangiosis. While the former had a loose poorly cohesive lattice of fibrils, capillaries in the latter were each surrounded by a thin, well-defined basement membrane, histochemically demonstrated by reticulin, as in our cases.[2,6]

Chorangiosis should also be differentiated from congestion, and from tissue ischemia with shrinkage of villi. Normal villi contain no more than five vascular channels[1,14] and in congestion vasculature is numerically normal.

Features associated with chorangiosis in this study generally agree with other studies including placentomegaly, umbilical cord problems, preterm birth and neonatal intensive care, low (5 minute or less) Apgar scores, maternal disease and drug ingestion and the presence of cesarean section. We had also demonstrated chorangiosis cases together with umblical cord knots, chorioamnionits, placental calcification and perivillous fibrin deposits with a high percentage.

In summary, the cause of chorangiosis is still not well-known, but chronic hypoperfusion or tissue hypoxemia combine with maternal, placental and fetal factors may produce this pathologic condition. Whatever its cause it should be considered as an important clinical sign of fetal injury. Histopathological recognizing of these lesions might help to clarify the causes of many adverse pregnancy outcomes and would aid the improvement in the management of the subsequent pregnancies.

References

1. Altshuler G. Chorangiosis. An important placental sign of neonatal morbidity and mortality. Arch Pathol Lab Med 1984; 108:71-4.
2. Ogino S, Redline RW. Villous capillary lesions of the placenta: distinction between chorangioma, chorangiomatosis, and chorangiosis. Hum Pathol 2000; 31:945-54.
3. Smith AS, Huang WY, Wong G, Levine D. Placental chorangiosis associated with markedly elevated maternal chorionic gonodotropin. A case report. J Reprod Med 2003; 48:827-30.
4. Franciosi RA. Placental pathology casebook. Chorangiosis of the placenta increases the probability of perinatal mortality. J Perinatol 1999; 19:393-4.
5. De La Ossa MM, Cabello-Inchausti B, Robinson MJ. Placental chorangiosis. Arch Pathol Lab Med 2001; 125:1258.
6. Calderalla A, Buccoliero AM, Taddei GL. Chorangiosis: report of three cases and review of the literature. Pathol Res Pract 2003;199:847-50.
7. Gersell DJ, Kraus FT. Diseases of the placenta. In: Kurman RJ ed. Blaustein's Pathology of the Female Genital Tract. New York: Springer-Verlag, 2002:1103-91.
8. Zygmunt M, Herr F, Munstedt K, Lang U, Liang OD. Angiogenesis and vasculogenesis in pregnancy. Eur J Obstet Gynecol Reprod Biol 2003; 22:10-8.
9. Evers IM, Nikkels PG, Sikkema JM, Visser GH. Placental pathology in woman with type 1 diabetes and in a control group with normal and large-for gestational age infants. Placenta 2003; 24:819-25.
10. Distler JH, Hirth A, Kurowska-Stolarska M, Gay RE, Gay S, Distler O. Angiogenic and angiostatic factors in the molecular control of angiogenesis. Q J Nucl Med 2003; 47:149-61.
11. Cao R, Brakenhielm E, Li X, Pietros K, Widenfalk J, Ostman A. Angiogenesis stimulated by PDGF-CC, a novel member in the PDGF family, involves activation of PDGFR-alphaalpha and alphabeta receptors. FASEB J 2002; 16:1575-83.
12. Redline RW, Pappin A. Fetal thrombotic vasculopathy: the clinical significance of extensive avascular villi. Hum Pathol 1995; 26:80-5.
13. Mesia AF, Mo P, Ylagan LR. Atypical cellular chorangioma. Arch Pathol Lab Med 1999; 123:536-8.
14. Schwartz DA. Chorangiosis and its precursors: underdiagnosed placental indicators of chronic fetal hypoxia. Obstet Gynecol Surv 2001; 56:523-5.