Placental Teratoma, Omphalomesenteric Duct Remnant, or Intestinal Organoid (Enteroid) Differentiation: A Diagnostic Dilemma

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Abstract

Keywords

- placental teratoma
- omphalomesenteric duct
- organoid differentiation

We report an unusual case of fully developed fetal intestinal segment(s) within a nodule on the chorionic plate of the placenta of a 27-year-old female patient at 37 weeks gestation with spontaneous vaginal delivery. Gross examination of the placenta revealed a chorionic plate nodule near the insertion of the umbilical cord, which, upon microscopic evaluation, raised the differential diagnostic possibilities of placental teratoma, vitelline/omphalomesenteric duct anomaly, and intestinal organoid differentiation. We discuss the distinguishing features, morphogenesis, and clinical significance of the aforementioned entities and review the pertinent medical literature.

Introduction

Placental teratoma is a rare nontrophoblastic benign tumor, which is thought to arise from embryonic germ cells. It contains elements derived from multiple germ cell layers. The omphalomesenteric duct is an embryonic structure, which connects the yolk sac to the midgut, and failure of its resorption results in various anomalies. Intestinal organoid differentiation is the presence of simplified intestinal tissue, arising from pluripotent stem cells having the capacity of differentiation and self-renewal. These entities have overlapping features, and a definitive diagnosis can be very challenging. In this article, we present our case and discuss the differential diagnostic possibilities, their morphogenesis, and clinical implications.

Case Presentation

A 27-year-old female patient, G5P3013, presented with a significant past medical history of thyroid cancer status

postpartial thyroidectomy, history of gestational diabetes in a previous pregnancy, hyperemesis gravidarum, gastroparesis, celiac disease, asthma, spina bifida occulta, and renal calculi. Her obstetric history is remarkable for 3 prior term pregnancies with spontaneous vaginal deliveries. Fetal growth has been appropriate this gestation despite maternal gastrointestinal symptoms. She had a spontaneous vaginal delivery at 37 weeks of gestation. Gross examination of the placenta revealed a 365-g (10–25th percentile), 37-week singleton discoid placenta, measuring 15 × 15 × 3.3 cm. The external membranes were gray-yellow semitransparent to opaque and inserted marginally. The umbilical cord was tan-gray, eccentrically inserted, trivascular, and measured 21 × 1.5 cm. There is minimal amount of subchorionic fibrin deposition identified along the fetal surface (3% of fetal surface). A chorionic plate nodule near the insertion of the umbilical cord measuring 1.2 × 0.8 × 0.3 cm was identified. Histopathological examination revealed a third trimester placenta with multiple areas of avascular and near-vascular chorionic villi suggestive of fetal vascular malperfusion. The

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villi also showed delayed maturation with predominance of mature intermediate chorionic villi. Features of meconium exposure in the form of meconium pigmented macrophages were seen. Histological examination of the chorionic plate nodule revealed fully formed fetal intestinal segment(s) (mucosa, muscularis propria, and serosa with vascularization) (►Fig. 1) located between the amnion and the chorion. The mucosa appeared to be colonic type. Adjacent to the intestinal structures within the chorionic plate, there was a small vitelline duct remnant (►Fig. 2). Serial sections of the umbilical cord did not show vitelline/omphalomesenteric duct structures or other embryonic remnants. Immunohistochemical staining with calretinin highlighted the myenteric plexus of the intrinsic intestinal innervation without noticeable staining of muscularis mucosae or lamina propria (►Fig. 3). The mother did not have a history of similar findings in a placenta of a previous pregnancy. The baby is currently doing well with no complications.

Discussion

In this case, multiple intestinal segment(s) were seen microscopically, located on the fetal surface of the placenta, close to the umbilical cord insertion. The mucosa of the intestinal segment(s) was mainly composed of crypts. Villi were not

seen. The crypts were lined by low columnar to cuboidal cells with numerous goblet cells. Paneth cells were not seen. There was intraluminal mucin secretion. The muscularis mucosa was appropriately developed. The submucosa was well-vascularized with loose connective tissue and minimal inflammatory infiltrate. The muscularis propria showed the inner circular layer and the outer longitudinal layer. The intrinsic intestinal innervation is highlighted by calretinin immunohistochemical stain (►Fig. 3). The serosa showed a single layer of flat-to-low cuboidal mesothelial cells and adjacent fibroelastic tissue. No immature tissue or other tissue types were identified within the nodule. Differential diagnostic possibilities include placental teratoma, vitelline/omphalomesenteric duct anomaly, and intestinal organoid differentiation. These entities may have overlapping features and can pose a diagnostic challenge.

Placental teratomas are rare nontrophoblastic tumor of the placenta. In 1925, Morville reported the first case report of placental teratoma in the English literature.¹ It is composed of multiple types of tissues that are foreign to the part in which it arises.² This distinguishes teratomas from other mixed tumors, including hamartomas and embryonal tumors, such as nephroblastomas, in that the latter tumors contain elements that are normally found at their sites of origin. The sites at which teratomas occur, in order of

Fig. 1 (A,B) Low power view illustrating intestinal segment(s) located between the amnion and the chorion (2x). (C,D) Illustrate the well-formed intestinal wall with colonic type mucosa, muscularis propria, serosa, and vascularization (10x and 20x, respectively).

Fig. 2 (A) Low power view illustrating the vitelline duct remnant adjacent to the intestinal segment(s) (2x). (B,C) The vitelline duct (10x and 20x, respectively).

frequency, are the ovaries, testes, anterior mediastinum, retroperitoneum, and presacral and coccygeal regions. Infrequent sites of occurrence include the skull, pineal gland, brain, neck, posterior mediastinum, body walls, and limbs.² Placental teratomas, like umbilical cord teratomas, are rare. To our knowledge, only 34 cases of placental teratoma have been reported so far in English literature. Some of the reported cases described the presence of epidermis with occasional attached adnexa of varying maturity, pilosebaceous units, and hair follicles. Mature adipose tissue, osteoid

Fig. 3 Immunohistochemical staining with calretinin highlights the myenteric plexus of the intrinsic intestinal innervation without noticeable staining of muscularis mucosae or lamina propria (10x).

tissue/bony trabeculae, islands of cartilage, skeletal and smooth muscle bundles, ganglion cells, neuroglial and neuroepithelial tissue, blood vessels, lymphocyte aggregates, calcifications, and stromal myxoid change have also been described. Placental teratomas always lie between the amnion and the chorion, usually on the fetal surface of the placenta, but sometimes within the membranes.³ Several theories have been proposed to explain the occurrence of teratomas in the placenta.^{3,4} The favored hypothesis is that proposed by Fox and Butler-Manuel, that is, aberrant germ cell migration.⁵ This theory is supported by the occurrence of teratomas along this line of migration.⁵

During the third week of development, primordial germ cells are located in the dorsal wall of the yolk sac, near the allantois. They begin migration by amoeboid movement along the dorsal mesentery of the hindgut, completing their journey to the genital ridge by the sixth week.⁶ Embryonic germ cells at this point during their migration may go astray and arrive at a more distant midline structure, such as the mediastinum, giving rise to a teratoma at that location. Fujimoto et al demonstrated that by the sixth week of embryonic development, some primordial germ cells remain in the dorsal mesentery or in the mesenchyme at the coelomic angle.⁷ The primordial germ cells in the extragonadal location are probably migrating or have failed in their migration to the gonad. Most teratomas—gonadal, retroperitoneal, sacrococcygeal, and cranial—arise in tissues that developmentally occupy preaxial median or closely paramedian positions.² This lends support to the theory that teratomas arise from germ cells that migrate aberrantly during their journey from the dorsal wall of the yolk sac to the gonad. In early development, the primitive gut herniates into the base of the umbilical cord. Usually, well-formed loops of intestine can be seen in the cord until the third month of development.^{6,8} Umbilical teratomas are believed to arise from germ cells that migrate out of the wall of the invaginated gut into the loose connective tissue of the umbilical cord. If these germ cells continue their

migration, they may arrive at the placenta between the amnion and chorion and can give rise to a teratoma at this location.⁸

Placental teratomas do not have an umbilical cord attachment to the placenta; they may have a vascular pedicle but without the features of an umbilical cord, that is, Wharton's jelly and amniotic membrane.⁹ The prenatal diagnosis of placental teratoma is based on the presence of tissues of varied echogenicity such as fat, calcification, and fluid on ultrasound.¹⁰

Fetiform teratoma (homunculus) is a term that has been given to a rare form of teratoma that resembles a malformed fetus. There are very few reported cases in the English-language literature of this entity. The age distribution of the patients ranged from 9 to 65 years.^{11–13} However, most of them present in the third or fourth decade of life. It is common that the caudal portion, including the lower extremities, of the fetiform structure is better developed than the cephalic portion. External sexual organ development, most often phallus-like, is not an uncommon finding.^{11–13} A bony skeleton is typically present with varying degrees of limb formation, but visceral organ tissue and skeletal muscle are generally inconspicuous or absent.

The omphalomesenteric duct is an embryonic structure, which connects the yolk sac to the midgut, and failure of its resorption results in various anomalies including Meckel's diverticulum, patent vitelline duct, fibrous band, sinus tract, umbilical polyp and cyst, enteric fistula with ileal intussusception prolapsing over the umbilicus, or hemorrhagic umbilical mass. These anomalies occur in approximately 2% of the population, and may remain silent throughout life or may present incidentally with an intra-abdominal complication.¹⁴ Microscopically, these remnants are usually discontinuous, located peripherally, and lined by columnar cells resembling intestinal epithelium. Occasionally, they have muscular wall with ganglion cells. Rarely, omphalomesenteric remnants include epithelium from the liver, pancreas, stomach, or small intestine. Omphalomesenteric remnants are frequently accompanied by vitelline ducts, which are usually paired but sometimes clustered and lined by endothelium lacking a muscular coat.¹⁵

Could the intestinal segment(s) seen in our case represent an intestinal organoid differentiation?

Reviewing the literature, Pages et al described a similar finding in a placenta they were examining, with fully developed intestinal segment in a subamniotic location. They raised a possible differential diagnosis of organoid differentiation versus a placental teratoma. They concluded that it is most likely an organoid differentiation, but they can still accept a teratoma as a potential diagnosis in case the organoid differentiation hypothesis is rejected.¹⁶

During early development of the mammalian embryo, the three germ layers, ectoderm, endoderm and mesoderm, are formed upon gastrulation. In humans, the development of internal organs from the endoderm begins during the third week of gestation. The endoderm becomes patterned by molecular cues from the microenvironment, such as retinoic acid,¹⁷ fibroblast growth factors,¹⁸ and Wnt ligands.¹⁹ The

cross-talk between the endoderm and mesoderm has a major role in guiding the formation of the gut-tube structure,²⁰ which becomes further patterned by the expression of different fate-specifying transcription factors, such as *Sox2* and *Hhex* in the anterior endoderm (foregut) and *Cdx2* in the posterior endoderm (hindgut). The posterior endoderm will eventually give rise to the small and large intestine.

In the past, discussions of both placental and umbilical cord teratomas by several authors^{8,21} have led to consideration of some of these minors as misdiagnosed fetal acardius amorphus. Fetus acardius amorphus is a rare fetal malformation, occurring in 1 in 35,000 deliveries.²¹ It is characterized by the total absence of heart and displays no resemblance to a human embryo.^{22,23} It is always accompanied by the presence of a cotwin since it needs the functioning heart of the other embryo to provide circulation for both of them.²² The pathogenesis of this condition seems to be that there is an existence of artery-to-artery anastomoses between the circulations of the twins, leading to reversal of the circulation (twin reversed arterial perfusion syndrome) and subsequent impairment in the development of the heart and other organs.²⁴

Fetus acardius amorphous is one of the main differential diagnoses of placental teratomas. The main distinguishing criteria proposed by Fox and Butler-Manuel are the following: (1) placental teratomas do not have an umbilical cord attachment to the placenta; they may have a vascular pedicle but without the features of an umbilical cord, that is, Wharton's jelly and amniotic membrane, whereas fetus acardius usually has an umbilical cord which is usually bivascular (with one artery and one vein) even though it can be rudimentary, and (2) fetus acardius amorphous usually has some degree of axial organization, either as cranial-caudal poles, central skeletal development with vertebral column formation, internal organs formation, or recognizable limbs formation, whereas teratomas usually have a disorganized collection of mature tissue including bone and cartilage.⁷

In this case, no microscopic features suggesting fetus acardius amorphous were identified, such as additional umbilical artery or skeletal organization. The intestinal segment(s) seen were located between the amnion and the chorion in the chorionic plate of the placenta. As mentioned previously, omphalomesenteric duct remnants are lined by columnar mucosa with goblet cells, occasionally with muscular layer and ganglion cells. Contrary to placental teratomas, omphalomesenteric duct remnants are more commonly located at the fetal end of the cord, near the umbilicus of the baby rather than in the placental as seen in this case. Therefore, we favor the notion that the intestinal segment(s) seen microscopically in our case represent an intestinal organoid (enteroid) differentiation. However, given the location of these bowel segment(s) between the amnion and the chorion in the placenta, the hypothesis of this being a placental teratoma is still acceptable and cannot be ruled out. **Table 1** summarizes some helpful distinguishing features between the various entities we considered in our differential diagnosis.

Table 1 Some distinguishing features between placental teratoma, omphalomesenteric duct remnants, intestinal organoid differentiation, and fetus acardius amorphous

Distinguishing feature	Placental teratoma	Omphalomesenteric duct remnants	Intestinal organoid differentiation	Fetus acardius amorphous
Clinical history of multiple pregnancy	May or may not be present	May or may not be present	May or may not be present	Present
Presence of a separate umbilical cord	Not present (may have a vascular pedicle but without the features of an umbilical cord)	Not present	Not present	Present
Umbilical cord vascularity	Trivascular	Trivascular	Trivascular	Usually bivascular May be rudimentary
Common location	Fetal surface of the placenta: Usually between the amnion and the chorion Rarely within the membranes	Fetal end of umbilical cord	Placenta between the amnion and chorion ^a	N/A
Histology	Multiple types of tissues that are foreign to the part in which it arises	Columnar cells resembling intestinal epithelium; may have muscular wall with ganglion cells; rarely include mucosa from the liver, pancreas, stomach, or small intestine	Fully developed intestinal segments with well-developed mucosa (colonic type), muscularis mucosa, submucosa, muscularis propria, and serosa	Malformed fetus with complete absence of the heart and failure of development of several organs
Axial organization	No (disorganized various tissues)	No	No	Yes

Abbreviation: N/A, not applicable.
^aTo our knowledge, other than our case, the only reported case of intestinal organoid differentiation in the placenta (Pages et al¹⁶) was reported to be in a subamniotic location. In our case, the colonic segment(s) lie between the amnion and chorion close to the umbilical cord insertion into the placenta.

Conclusion

Some cases of placental teratoma, fetus acardius amorphous, omphalomesenteric duct anomalies, and intestinal organoid differentiation have overlapping features, creating a diagnostic challenge. Separating these entities is of importance to the parents. They need to know whether the mass is a teratoma, that is, a neoplasm, a fetus acardius, that is, a dead twin fetus with fetal malformation, or if an omphalomesenteric duct, that is, a vestigial remnant. From the clinical standpoint, placental teratoma is a benign nontrophoblastic tumor that has a favorable prognosis and no serious complications. Omphalomesenteric duct, on the other hand, despite being a benign condition requiring no treatment, may have some associations. Those infants may have Meckel's diverticulum, patent vitelline duct, fibrous band, sinus tract, umbilical polyp and cyst, and/or enteric fistula. Therefore, close clinical follow-up of those infants is usually recommended. Intestinal organoid differentiation is not known to be associated with clinical sequelae. In conclusion, distinction between these entities, albeit difficult on some occasions, should always be attempted and largely depends

on the radiographic, gross, and microscopic features of the specimen.

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Conflict of Interest
None.

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