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Acardius acephalus fetus – report of distinctive anatomical anomalies with regards to pathophysiology of TRAP sequence

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Summary

Acardiac fetuses are consequences of twin reversed arterial perfusion (TRAP). Here the authors present a case of 40-year-old gravida IX who gave birth to a healthy, 2,900 g female child by a cesarean section. Additionally amorphic 1,020 g maldeveloped fetus was removed. There was a diamnion monochorionic type of twin placenta with incorrect single umbilical arteries (SUA) both in umbilical cord of healthy fetus and in atrophic second umbilical cord. A malformed fetus developed a rather well formed lower leg with four digital foot and oval shape amorphous body mass with omphalocele and eventration of the intestines. X-ray picture showed well visible metatarsal and femur bone and anatomically undefined bones cluster in the central part. A cavity of fetal body contained intestines - the only one well-formed organ, nests of heterotopic pilosebaceous residues, remnants of adrenal glands, well-formed ganglia, and nests of neural tissue covered by neuroepithelium.

Key words: Acardius acephalus; Organ underdevelopment; Disruption; Twin reversed arterial perfusion; Hypoxia.

Introduction

Acardiac acephalus twin is a rare fetal malformation that occurs in one to 1.5% monochorionic multiple pregnancies [1-3]. Generally a disturbance of placental circulation could be associated with conjoined twins or more severe malformations as acardiac fetus. In 1850, Meckel first identified the pathogenetic mechanism of reverse fetal perfusion, and next in 1859 Claudius articulated the thesis that after normal initial development, the heart degenerates as result aortal thrombosis [4]. According to updated definition, twin reversed arterial perfusion (TRAP) or twin-twin transfusion syndrome is caused by incorrect intraplacental arterial-arterial and venous-venous anastomoses that convey reversed blood flow in umbilical vessels and aorta in twin fetus that is therefore destined to serious malformation [4,5]. Precisely, twin reversed arterial perfusion (TRAP) is constituted by three determinants: (1) there is no heart or cardiac development is severely impaired; (2) artery-artery shunt conveys arterial blood flow from a normal so-called "pump twin" to the acardiac partner; (3) vein-vein shunt is a way of outflow of venous blood from the acardius back to the normal twin [6]. Dysmorphogenesis has still not be unequivocally defined to be a case or result of reversal of blood flow [6]. In consequence of such circulatory defect, prolonged hypoxia is responsible for a underdevelopment and dysmorphogenesis that are expressed by atrophia and hypoplasia of one of twins that is termed a recipient. Organ agenesis could also be another eventual explanatory mechanism in pathogenesis of this malformation due to the same but more aggravated causative factors as hypoperfusion and hypoxia due to ischemia [2,3]. Thus, growth of upper parts of the body is abolished severely, while development of inferior organs is less impaired in the manner of disruption [5]. In this condition the severity of organ's anomaly depends mainly on the rate of incorrect blood flow, hypoxia level, and the gestational period. A few types of acardiac fetuses can be distinquished on the basis of the stage of undergrowth. They include acardiac acephalus, acardius anceps, acardius ancormus, and acardius amorphous fetus. If severe vascular disturbances commenced within first trimester, it can be a cause of early death of the twin whose fetal relics are vividly termed a fetal papyraceus.

Case Report

A 40-year-old gravida IX without history of multiple pregnancy was admitted to hospital for delivery. Her pregnancy was not under gynecological control until hospitalization. Hence, a suspicion of twin pregnancy with ultrasonography described a pathological amnion tissue mass was diagnosed just before the delivery

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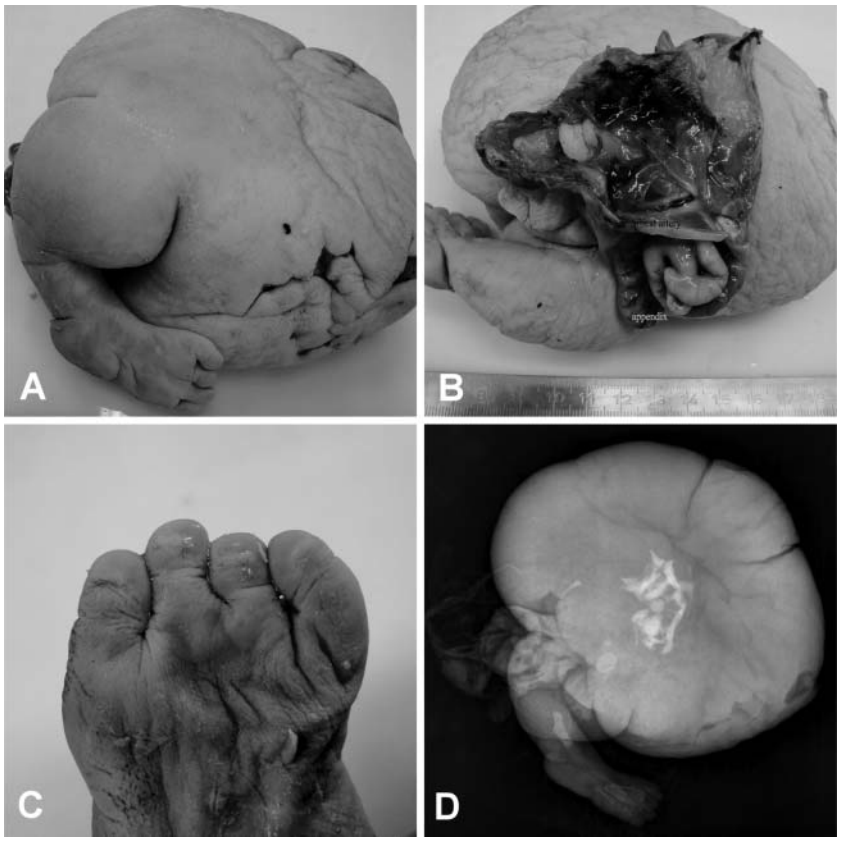

Figure 1. — Macroscopic presentation of the acardiac fetus. A, B: The dorsal and ventral view of acardius acephalus fetus with evident intestinal eventration. C: Four-digit foot. D: X-ray picture of maldeveloped fetus with centrally locked bones cluster.

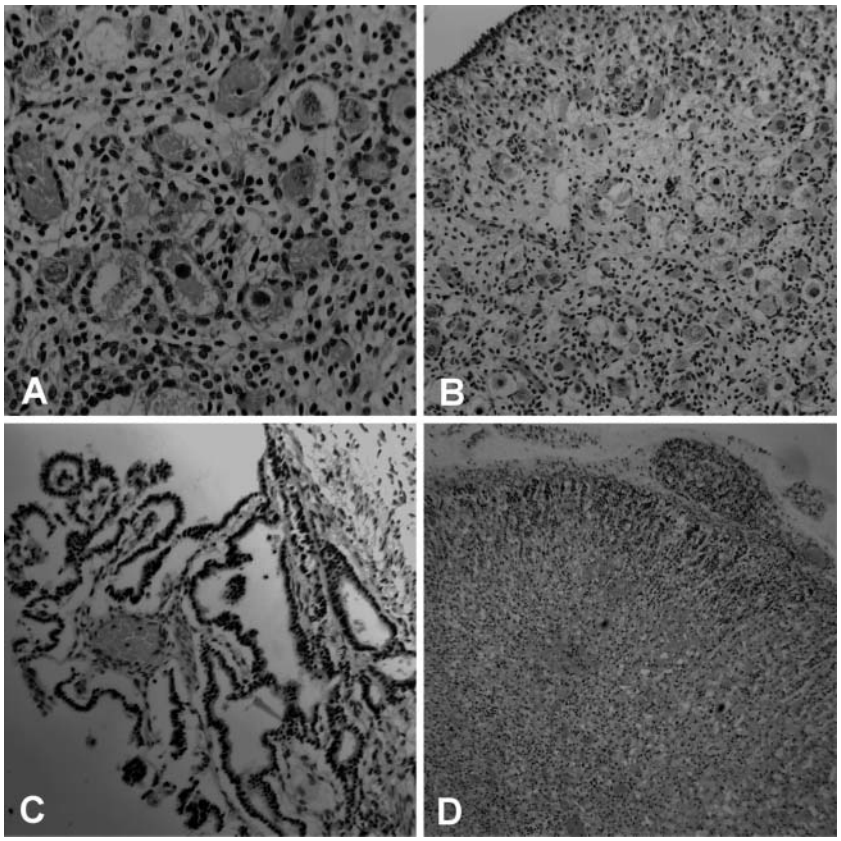

Figure 2. — Microscopic presentation of acardiac fetus. A, B: Rudimentary neural tissue with prominent ganglia cells surrounded by primitive glial tissue and covered by neuroepithelium - H&E stain x20 and x10 magnification. C: Papillary projections of mesothelial surface covered by two-layer cuboidal epithelium - H&E stain x10 magnification. D: Well-formed and nearly matured adrenal gland - H&E stain x10 magnification.

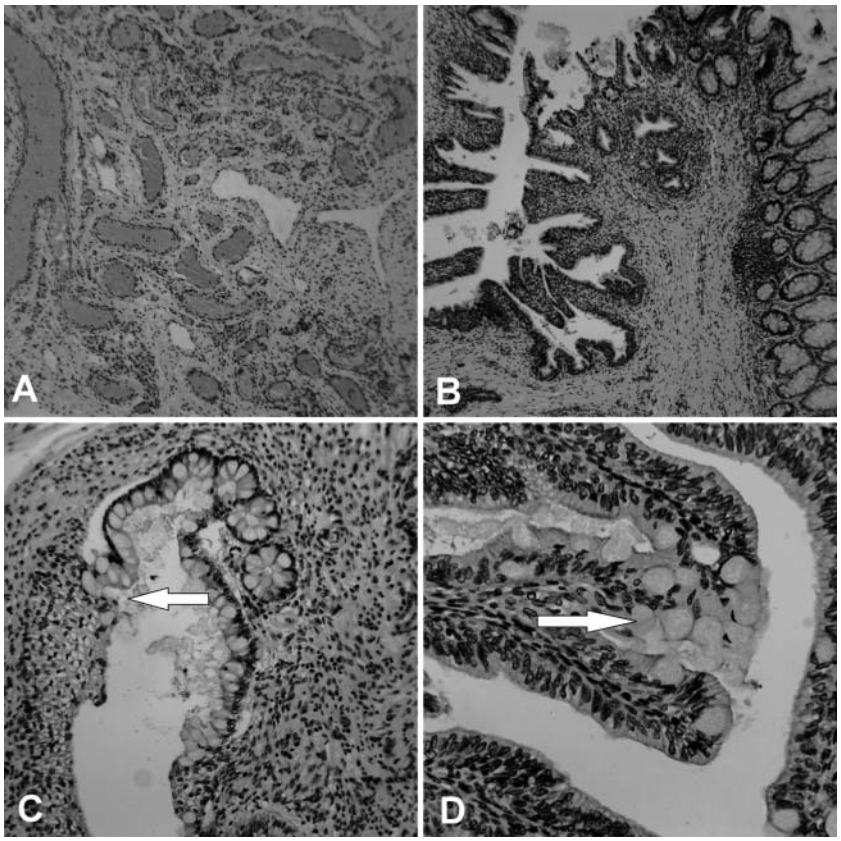

Figure 3. — Microscopic presentation of acardiac fetus. A: Highly vascularized region of body relic - H&E stain x10 magnification. B: The join of colon with meso-nephroidal space - H&E stain x10 magnification. C: The joining of colon and urothelial epithelium with forming a cloacal space - H&E stain x10 magnification. D: A focal goblet cell differentiation in meso-nephroidal epithelium - H&E stain x20 magnification.

at 39 gestational week. A cesarean section revealed a healthy, with absence heart failure signs, 2,900 g female new born child (NBC) and amorphic 1,020 g maldeveloped fetus with discernibly formed only one lower extremity and another rudimentary lower limb in a form of very small process of skin and subcutaneous tissue.

In the histopathological placental report the authors recorded diamnion monochorion type of twin placenta with incorrect single umbilical arteries (SUA) both in healthy fetus and in atrophic second umbilical cord. Microscopic evaluation of placenta denotes indirect signs of anastomosing circulation such as focal villous edema and partial high density of villous vasculature.

Macroscopic evaluation of malformed fetus showed relatively well formed lower leg with four digital foot and oval shape amorphous body mass measuring 16 x 11 x 7 cm with omphalocele and eventration of the intestines (Figure 1A-C). X-ray picture revealed well visible metatarsal and femur bone and anatomically undefined bones cluster in the central part which could be some compounds of axial skeleton and the pelvic girdle (Figure 1D). Most of the body's relics consisted of skin that covered spherical tissue mass with centrally located skeletal cluster.

Anatomical preparation showed many different anomalies. A small cavity was encountered after dissection of skin and edematous soft tissue cover. In this space there were nine-cm long loops of intestines. One of the ends of intestine was conjoined with funicular tissue, which led around the femur into centre of body mass that contained a cavity space. This umbilical cord contained umbilical artery and well-formed urachus with purulent exudates. In maze of disorganized skeleton there were a few long bones which were surrounded by adipose tissue, skeletal muscle fibers, nerves, lacunar lymphatic channels, small lymph nodes, and vessels. There were also rudimentary central nervous system represented by well-formed ganglia, nests of neural tissue with many neurocytes, and covered by prominent neuroepithelium (Figure 2 A, B). Histological examination of the cavity space showed its multilocular appearance with persisting papillary projections of two-layer-thick cuboidal epithelium (Figure 2C) and focal hyperpigmentation due melanin content. Moreover adrenal glands tissue was found to be three mm in length (Figure 2D). The evaluation of intestines, which remained the only one well-formed organ, demonstrated a multifocal lumen atresia, blind terminal ends, but relatively well-formed and persisting appendix. The macroscopic analysis of circulatory system allowed only distinction of umbilical artery that grew into bone cluster. It is worth mentioning that there was a complete lack of fetal large arteries and veins. The authors observed only plenty of other vessels mainly small veins and small muscular arteries. (Figure 3A). Thus, they supposed that arterial supply of bones is continued by anastomosing vascularity type only from the end of umbilical artery.

The intestine directly communicated with tunnel covered by mesonephroidal-like epithelium, which showed a focal goblet cell differentiation. (Figure 3B, D) It was also interesting to note that anatomically ileum –like intestine possessed partially colon texture in a caecum region. Histologically, the authors observed intestine of colon type texture with small nests of heterotopic pilosebaceous units and urothelial epithelium, which interfered with colon epithelium of intestinal mucosa (Figure 3C) and formed primitive cloacal-like space.

Discussion

The present case report is only one of a few descriptions of greatly variable mythic forms of fetal deformation. Atrophy, agenesis, aplasia or dysgenesis are terms which do not com-

pletely explain the pathogenesis of gradually advanced malformation of fetal tissue. The severe anatomical malformations could indicate not only mechanism of atrophy and hypoplasia but rather complex causes with severe disturbances during organogenesis. Hypoxia/ischemia is the mechanism, which is crucial in pathogenesis of this entity according to the majority of the investigators [7]. However, hypoxia is not an mechanism that completely explains fetal malformations with evident hypoplasia of organs and minor tissue structures. The presented observations of intestine wall heterotopy would rather indicate an incorrect tissue differentiation or -what is more likely- disturbances of cell migration during organogenesis. In the present case study the authors did not find a liver at all. In this context it is worth to mention that Giménez-Scherer and Davies rightly noticed that the liver is located first in the circulatory way from the placenta to the fetus so this organ was expected to be relatively well-developed in TRAP syndrome [8]. Taking this into account, hypoxia-ischemia mechanism does not explain absence of liver in the present case of acardiac fetus. The present authors postulated that hypoxia-exposed fetus is more flexible to modeling pressure of the donor twin, whose growth can be expanding enough to compress the twin recipient in uterine cavity. Nonetheless, there are decreased blood oxygen saturation levels in the body of cardiac twin and this could be a triggering factor for hypoxia mediated angiogenesis, which employs such factors as hypoxia inducible factor and vascular endothelial growth factor. Such a process augments vascular bed capacity and simultaneously decreases vascular resistance of the acardiac body that may result in intrauterine fetal death [7]. Conclusions of De Groot *et al.* [7] are supported by the present finding of prominent vascular density in this observation.

The present findings of only rudimentary nervous system are not astonishing in front of the fact that neural tissue particularly brain tissue is the most sensitive to hypoxia-ischemic injury in TRAP sequence. Sergi and Schmitt reported microcephaly and a residual brain anlage, which was consistent with impairment of brain growth at the prosencephalic stage -holoprosencephaly that was accompanied with formation of cystic cavity (hydranencephaly) due to hypoxic injury to the holospheric brain mantle [9]. Their findings were in agreement with the opinion that oxygen deficiency causes disruptions of head-brain and heart development during early embryogenesis on animal experimental model [9]. In other report of severely underdeveloped acardius that constituted ovoid mass with skin, rudimentary legs, and vertebral skeleton, there was a disorganization in structure of brain tissue, which suggested that a hypoxic injury occurred after neurulation to impair the prosencephalic stage of brain development [10]. Namely, cerebellar cortex was the only well-formed element in the present inspection. Moreover, an encountered slit-like space was consistent with the third ventricle that was limited with ependymal covering and choroid plexus [10]. As an evidence to hypoxia induced augmented neovascularization, an area of increased vascular density was also encountered to draw a resemblance to cavernous haemangioma [10]. In comparison to the present findings of more modest neural residues, the authors conclude that this case of acardiac fetus presents with much less developed nervous system than plenty of reports in literature on TRAP syndrome.

There are different subtypes of acardiac fetuses depending on the level of underdevelopment: acardius acephalus, acardius amorphus, and acardius anceps [1]. The present case was classified as acardius acephalus because the malformed twin was devoid of a head, a thorax, and upper limbs but in opposition to acardius amorphous there were relatively well-developed adrenal glands and large intestines in the body of the fetus [11]. Acardius acephalus is also termed with an older name chorangiopagus parasiticus (CAPP) and is found in 1% of monozygous twins. The description of CAPP fetus is the most suitable to the present case as it was an edematous fetus with discernible lower limbs, incomplete pelvis and lower spine elements, incomplete abdominal viscera like intestines, but without any thoracic organs [12]. A case reported by Kakkar *et al.* contained edematous cystic area in upper part of the fetus, similarly to the present case which contained a cystic cavity [12]. The need of ultrasound surveillance and control should be emphasized here because this malformation can be identified by ultrasound as early as 12 weeks gestation [12].

The present case of acardiac fetus seems to resemble slightly the fetus reported by Sharbaf *et al.* [13]. They described a normal fetus and acardiac twin with a underdeveloped lower extremity with a sac containing some intestinal loops [13]. However, the present case better fits this classification on the ground of combined Doppler waveform ultrasound and pathological findings presented by Shih *et al.* [11, 14]. Namely, artery-artery pump-in pattern is one distinguished types and is characterized by two rudimentary lower limbs (in the present case the second one extremity was actually an cutaneous process-like relic), agenesis of upper extremities, underdeveloped visceral organs, and brain and presence of omphalocele [14]. The present case was a subject of differential diagnosis between artery-artery pump-in pattern and collision summation artery–artery pattern [14]. The latter one is defined by presence of cardiac motion in malformed twin because of preserving a cardiac substitute in a form of a rudimentary, contractile heart and artery-artery shunts [14]. Moreover collision summation artery–artery pattern is characterized by an underdeveloped leg, omphalocele, agenesis of liver, spleen, kidneys, lungs, and brain [14]. Both patterns result in live birth of co-twin.

Acardia can occur in an unusual setting with cyclopia and aprosencephaly in a twin fetus because of TRAP [5]. A variety of abnormalities could indeed be very broad to note also that an acardiac, anencephalic twin harbored a serious cardiac type defect, which was a transposition of great arteries [15]. The cardiac development could be impaired at a very varied stage, ranging from a complete lack of the heart through hypoplastic cor triloculare to a malposition of a relatively well-developed heart [16].

Fetal karyotype can be very often normal regardless of subtype of acardiac twin [1]. Nonetheless acardiac fetuses may carry chromosomal abnormalities as trisomy 2 (karyotype 47,XX,+2), which was reported by Blaicher *et al.* with extensive review on cytogenetic defects in acardia [17]. The other chromosomal aberrations like XXY karyotype in Klinefelter syndrome were also recorded at increased rate in monozygotic pregnancies with acardiac twin and twin reversed arterial perfusion sequence [18]. Acardiac twin was also reported in other genetic disorders like Duchenne muscular dystrophy (DMD) [19]. In every case such an acardiac twin recipient causes additional load for heart output of "pump" twin and could result in cardiac insufficiency of the donor twin [19]. Actually, TRAP sequence can be the life-threatening condition also for the mother as in the case of hydropic acardiac fetus in triplet pregnancy [20]. Namely, it is a risk factor for occurrence of mirror syndrome that is defined as simultaneous placental, fetal, and maternal edema with maternal preeclampsia [20].

TRAP sequence could be managed in early fetal life. As acardiac twinning is a complication of at least 1% of monozygotic twins with incidence of one in 35,000 births, a proper protection of pump twin is recommended [21, 22]. This covers prenatal diagnostics with ultrasound Doppler imaging and genetic testing. Nowadays modes of therapy include numerous procedures from hysterotomy with delivery of the acardiac twin to techniques of thermocoagulation and radiofrequency, fetoscope-guided or ultrasound guided occlusive ligation of umbilical cord of acardius, and many others, if only benefit of pump twin is expected to be achieved by the prenatal intervention [21]. Among these methods, the least invasive treatment seems to be intrafetal laser ablation of acardiac fetus that is performed by laser coagulation of pelvic vessels and umbilical cord [22]. This is method of choice particulary at early stage of monochorionic diamniotic twin pregnancy [22].

The present acardiac fetus was in advanced pregnancy which in spite of the lack of gynecological care, resulted in birth of healthy donor twin. Nonetheless, due to possible circulatory complications in acardiac twin pregnancy, this case calls for careful and efficient ultrasonographic screening for early detection of TRAP sequence.

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