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# An Acephalus Acardius Amorphous Fetus in a Monochorionic Pregnancy With Sex Discrepancy

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*Acephalus acardia* is among the most severe malformations described in fetuses, with an incidence of about 1 in 35,000 births and is due to twin-to-twin transfusion syndrome, frequently occurring in monochorionic twin pregnancies. The severity of the syndrome depends upon the type of the anastomoses arising between the vascular networks of the two fetuses, usually configuring the 'twin reverse arterial perfusion syndrome'. No clear and univocal etiological explanation is known, though few cases with chromosomal abnormalities have been reported so far. In some cases the fusion of two or more separate placentae of dizygotic fetuses occurs, leading to monochorionic twinning. Few cases of acardius amorphous with complete autoptical examination have been described so far. We report a case of acephalus acardius amorphous fetus, showing features of extremely severe systemic immaturity with very few structured organs. Defined external and autoptic examinations have been performed on the dismorphic twin, along with the histological examination of tissue samples. Karyotype analysis showed sex discrepancy between the twins, as a normal female karyotype had been detected in the acephalus acardius while the living co-twin was a normal healthy male. The analysis of the placenta showed the vascular anomalies leading to the twin-to-twin transfusion syndrome.

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*Acephalus acardia* is among the most severe malformations described in fetuses, with an incidence of about 1 in 35,000 births reported in the original description (Gillim & Hendricks, 1953). This condition can be observed in 1% of monochorionic twins and is probably due to twin-to-twin transfusion syndrome (TTTS), frequently occurring in multiple pregnancies, when vascular anastomoses arise in the fused placenta. The pathogenetical explanation of such cases of acardia resides in the hemodynamic consequences of the fused placentation and the severity of the syndrome depends upon the type of the

anastomoses arising between the vascular networks of the two fetuses (Aggarwal et al., 2002; Van Allen et al., 1983). Acardia is in fact supposed to develop during early embryogenesis as a result of extensive artery-to-artery and vein-to-vein anastomosis through the monochorionic placentation with reverse umbilical arterial circulation in the direction of one of the fetuses, which severely impairs the development of the cardiovascular apparatus (Abboud et al., 2000). Therefore, the circulation is provided by the heart of the normal fetus ('pump'), while the acardiac twin ('perfused') receives only low pressure and hypoxigenated blood, resulting in the dysmorphic sequence (Van Allen et al., 1983). Due to the parasitic hemodynamic dependence of the acardiac twin on the pump twin, the monitoring of such cases is aimed at guaranteeing the pump-twin's survival, by interrupting vascular supply to the acardiac twin as any sign of decompensation occurs (Sullivan et al., 2003; Wong & Sepulveda, 2005).

The most severe type of acardius malformation is represented by the acardius acephalus amorphous (AAA) and few cases with complete autoptical examination have been described so far in the international literature (Aggarwal et al., 2002; Rajesh et al., 2004; Robie et al., 1989).

We report a case of monochorionic twins, one being an AAA fetus showing features of extremely severe systemic immaturity with no structured organs.

## Clinical History

A 33-year-old primigravida presented with a twin pregnancy, proceeded until 32 weeks with spontaneous delivery. The ultrasound performed at 27 weeks of amenorrhea revealed the presence of one severely

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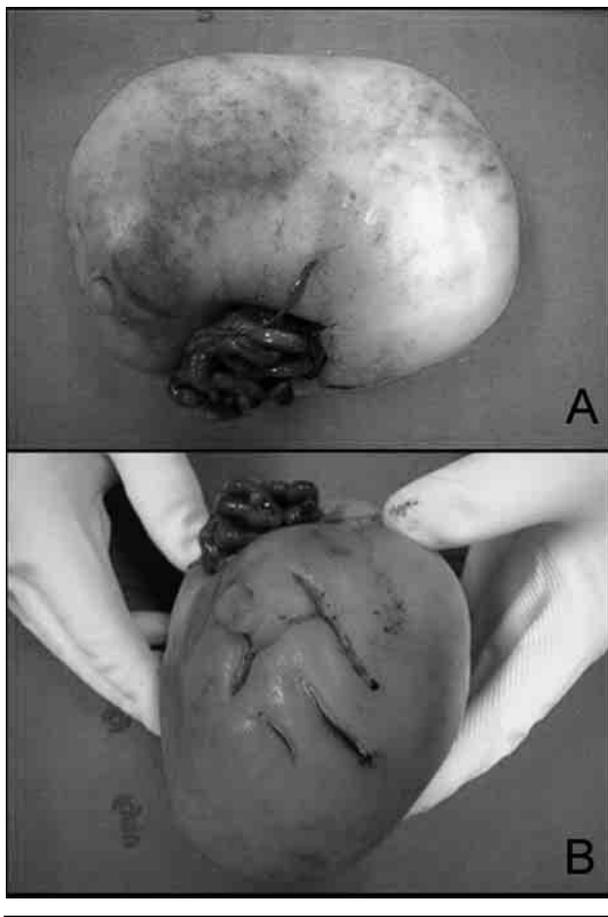
malformed fetus in the upper uterine cavity, appearing as an inhomogeneous mass without cardiac activity containing large cystic spaces and no other recognizable visceral structures. The normal fetus presented with normal-for-gestational-age dimensions, regular cardiac activity and normal visceral and bony structures.

The first twin was a healthy, phenotypically male baby, weighing 1850 g, showing no external malformations (Apgar score = 8). The sex of the normal twin was confirmed by cytogenetic analysis on peripheral blood, which revealed a normal male karyotype. The second twin was represented by a 33 × 40 cm globular mass of tissue, coated by skin with hairs and hair glands, weighing 1070 g (Figure 1), and without either upper or lower limbs.

The mother gave written consent for further analysis on the amorphous fetus.

### Materials and Methods

The analysis of this case was performed starting with the external examination of the AAA fetus. A CT-scan analysis of the globular mass was performed prior to autopsy in order to identify structured internal organs



**Figure 1**

External appearance of the AAA foetus. A: globular mass coated by skin and intestinal loops protruding along the midline, B: linear skin folds are visible in the caudal portion.



**Figure 2**

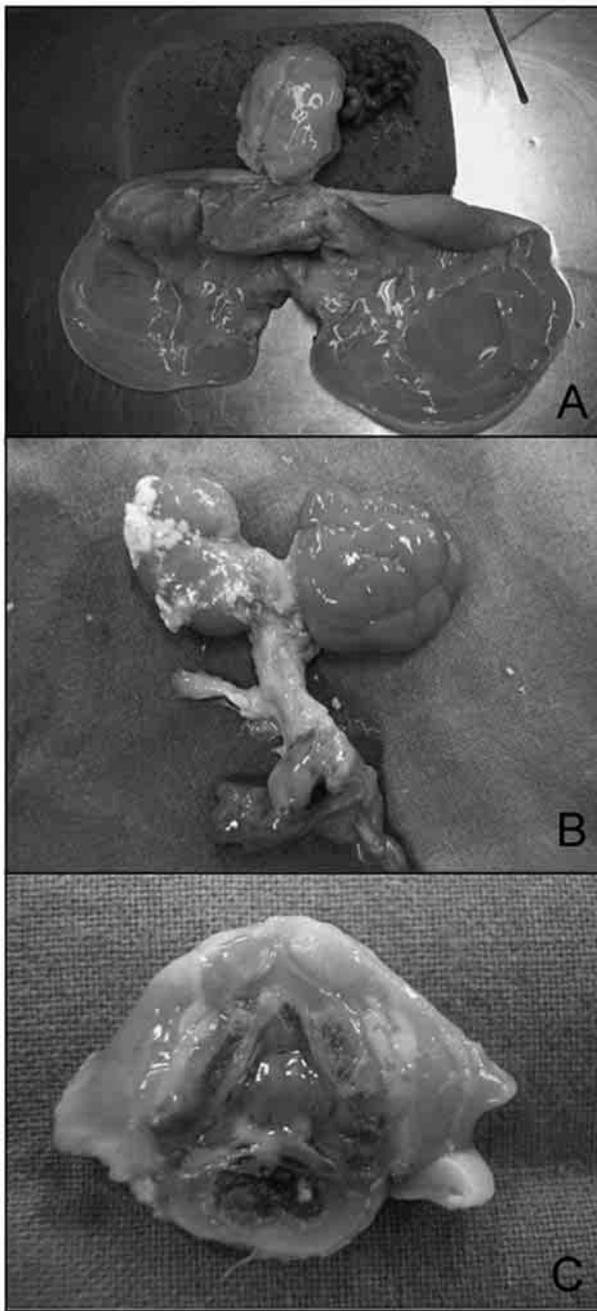
CT-scan image showing immature skeletal features of the abdominal spine and of the pelvic girdle. A radio-opaque structure is also visible in the upper portion of the spine bud.

and to drive the following procedures. The autoptical examination was then performed and sample specimens were obtained for the histological examination, carried out by means of haematoxylin-eosin staining, and for karyotype analysis, performed by standard G-banding.

### Results

On the external surface the mass showed only few features: linear skin folds in the caudal portion and intestinal loops protruding along the midline (Figure 1). CT examination was performed before autopsy and revealed the presence of immature skeletal features resembling the abdominal tract of the backbone and the pelvic girdle. In addition, a radio-opaque structure with undefined rims was visible above the upper portion of the spine bud (Figure 2).

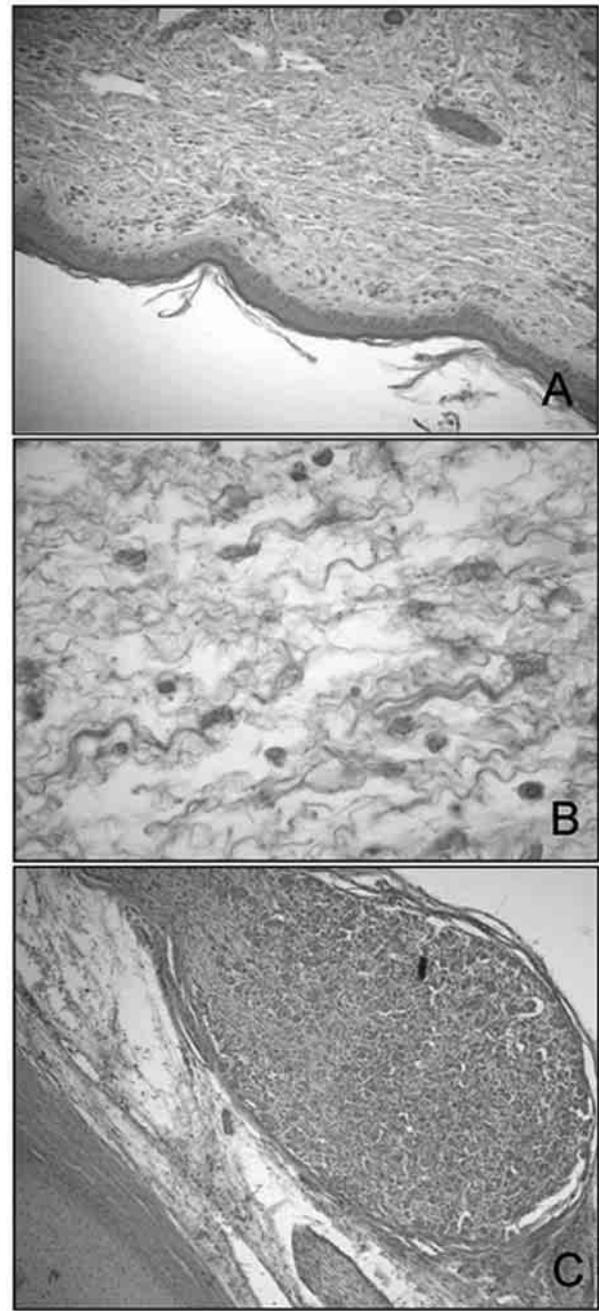
The autopsy of the proximal portion disclosed underneath the skin surface the presence of a multilocular thin-walled cyst filled with a gelatinous yellowish fluid (Figure 3A). In its medial portion the dysmorphic mass presented bilaterally structures macroscopically recognizable as immature kidneys (Figure 3B). The intestinal loops were represented by both the small and large bowel terminating in a cul-de-sac. The resection of the skeletal buds, performed after removing the viscera, enabled detection of the ossification points in the vertebral body and the spinal cord within the spine canal (Figure 3C). The histological examination of the tissues obtained from the dysmorphic fetus showed an extremely thin skin layer where pilosebaceous units were present while dermal papillae were not evident (Figure 4A). The subcutaneous layer was mainly represented by brown adipose tissue with few striped muscle fibers. The analysis of the multilocular cyst disclosed the presence of loose connective tissue with immature cartilaginous elements surrounding a central vascular axis. The walls of the intestinal loops were normally structured and showed the presence of nervous features resembling the



**Figure 3**

Autoptic section images of the AAA foetus. A: the inner content of the multilocular cystic mass revealed the presence of a gelatinous yellowish fluid, B: structures resembling immature kidneys are visible bilaterally in the medial portion of the dysmorphic mass after section, C: a structured vertebra was discovered into the skeletal bud.

myenteric plexus. The gelatinous tissue recovered from the inner mass of the amorphous fetus was composed of loose connective tissue with elastic fibers (Figure 4B), venous and distended lymphatic vessels and some perivascular lymphocytes. The kidneys presented an immature morphology, along with an organized nephrogenic cortex. In addition, structures corresponding to an immature ovary were detected close to the kidneys.



**Figure 4**

Ematoxylin-eosin stainings showing histological details of the dysmorphic mass. A: skin layer covering the mass, B: loose connective tissue with elastic fibers in the gelatinous content, C: a spinal ganglion.

Nervous tissue, with no evidence of ependymal canal and gray matter, was detectable inside the vertebral column, while spinal ganglia were present (Figure 4C).

The cytogenetic examination was carried out on cells obtained from both the skin biopsy and inner mass connective tissue and revealed a homogenous 46, XX karyotype, proving sex discordance with the healthy co-twin.

The placenta measured  $14 \times 12 \times 3$  cm, weighed 590 g and was monochorionic diamniotic, showing superficial anastomoses between the normal and the acardiac twin's umbilical vessels. The umbilical cords were 9 cm and 6 cm in the normal and dysmorphic twin respectively, composed of one artery and one vein in the second one. The histological examination showed concentric 'onion-skinned' hyperplasia in the vascular axis of the placental villi and fibrin deposits. Moreover evident signs of hydrops of placental villi were noticed on the portion of placenta belonging to the acardiac-amorphous fetus.

## Discussion

Twins have been traditionally classified as monozygotic (identical), originating from the splitting of the inner cell mass of a single zygote, and dizygotic (fraternal) when different spermatozoa simultaneously fertilize separate oocytes or the same oocyte. Other rare mechanisms leading to twinning gestation can occur involving separate simultaneous fertilization events, including the possibility of a polar body (Bieber et al., 1981). Monozygotic twins usually share the same placenta (monochorionic), while in 10% of cases they present as dichorionic, being erroneously considered as dizygotic. Nonetheless the placentae of twins derived from separate conceptional events (monovular dispermic twins or simultaneous fertilization of separate oocytes) can merge if the implantations of two separate embryos are close to each other in the uterine lining (Bieber et al., 1981; Rajesh et al., 2004). Monochorionic twins present high risk of complications, ranging from premature delivery to fetal death. In particular, TTTS is a severe complication due to placental vessels anastomoses leading to circulatory predominance of one twin ('pump twin') and gross malformations in the perfused twin, including holoacardia and acephalus. The mortality rate is around 50% to 75% in the pump twin, mostly due to heart failure, and 100% in the perfused one (Czichos et al., 2005; Fries et al., 1992; Malinowski & Szwalski, 2004; Moore et al., 1990; Rajesh et al., 2004; Torres Borrego et al., 2000). In the case here reported we observed gross dysmorphic features in the malformed twin and extensive vascular anastomoses in the fused placenta, suggesting that the low pressure and hypoxigenated blood which nourished it could explain the extremely severe dysmorphic sequence as suggested in previous reports (Buntinx et al., 1991; Cardwell, 1988; Coulam & Wright, 2000; Goh et al., 1994; Kosno-Kruszewska et al., 2003; Malhotra et al., 2004; Moore et al., 1987; Platt et al., 1983; Rajesh et al., 2004; Robie et al., 1989; Sergi et al., 2000; Sharma et al., 1993; Torres Borrego et al., 2000).

The causative event of the acardia acephalus is controversial as divergent hypotheses have been pointed out, such as primary cardiac dysmorphogenesis versus hemodynamical mechanism, based on the abnormal vascular communication between embryos

resulting secondary atrophy of the heart and dependent organs (Abboud et al., 2000; Chanoufi et al., 2004; Coulam & Wright, 2000; Ersch & Stallmach, 1998; Malhotra et al., 2004; Shih et al., 1999; Umur et al., 2004; van Gemert et al., 2005). Chromosomal abnormalities have been identified in isolated cases, mainly represented by aneuploidies and polyploidies (Blaicher et al., 2000; Deacon et al., 1980; Masuzaki et al., 2004; Moore et al., 1987). Moreover cases of acardiac acephalus in pregnancies obtained through assisted reproduction techniques have been described, as a higher rate of multiple gestations is inherent with some of the adopted procedures (Aytoz et al., 1998; Haring et al., 1993; Martinez-Roman et al., 1995). Discordant karyotypes between the dysmorphic fetus and the normal co-twin have been reported in several cases and can be explained by either postzygotic nondysjunction leading to mosaicisms or the fusion of two separate placentae of dizygotic twins (Benirschke, 1995; Chaliha et al., 1999). In the case here reported discordant sexes between the twins, as indicated by the karyotype analysis of the AAA, suggest that the fusion between two originally separated placentae occurred and finally led to the vascular anomalies configuring the twin reverse arterial perfusion syndrome and the following dysmorphic sequence. The present case provides an exhaustive autoptical description of an AAA fetus originating from a monochorionic twin pregnancy. The chromosomal discordance with the normal alive co-twin suggests that they originate from separate conceptional events involving different gametes (monovular dispermic twins).

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