CASE REPORT

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Multidisciplinary approach of assessing malformed fetuses exemplified in a rare case of pentalogy of Cantrell associated with craniorachischisis, pulmonary extrophy and right-sided aortic arch with aberrant brachiocephalic artery

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Abstract

We present the imagistic and pathological assessment of a unique case of complete pentalogy of Cantrell associated with craniorachischisis, pulmonary extrophy and right-sided aortic arch with aberrant brachiocephalic artery. For this particular case, the complete and correct diagnosis required a post-mortem imagistic high-resolution magnetic resonance imaging (MRI) at 7 T and detailed stereomicroscopic autopsy. Also, we discussed the pathogenesis and possible etiology of pentalogy of Cantrell and the associated malformations of the case presented.

Keywords: pentalogy of Cantrell, craniorachischisis, right-sided aortic arch, post-mortem MRI, stereomicroscopic examination.

Introduction

Pentalogy of Cantrell (PC) is an extremely rare and complex congenital abnormality that was first described in 1958 [1]. Complete spectrum of the syndrome, consist of supraumbilical abdominal wall defects, deficiency of the anterior diaphragm and lower sternum, defects in the diaphragmatic pericardium and congenital intracardiac malformations [1]. Complete PC has an incidence between 1:65 000 to 1:200 000 live births [2, 3].

In 1972, Toyama proposed a classification for this syndrome in three classes: class 1 – definite diagnosis meeting all five defects; class 2 – probable diagnosis meeting four defects including intracardiac and ventral abdominal wall defects; and class 3 – incomplete expression with sternal abnormality associated with other combinations of anomalies [2].

Although the pathogenesis is not yet elucidated, most cases are sporadic and thought to be the result of an abnormal differentiation of the intraembryonic mesoderm between 14 to 18 days after conception and failure of fusion of the transverse septum of diaphragm and lateral fold of the thorax [1, 4].

Still, fetal chromosomal analysis and proteomic studies are needed, thus some cases seem to be linked to genes mutations, located on the X chromosome [5] or associated with Turner syndrome and trisomies [6]. On the other hand, using chromosome microarray analysis, was describe a microduplication of chromosome 15q21.3 (57,529,846 to 58,949,448) in one male newborn prenatally diagnosed with PC. More specific the duplicated region was *ALDH1A2* gene, encoding the enzyme retinaldehyde dehydrogenase type 2 [7], essential for the conversion of dietary retinol to retinoic acid, an important factor in early embryological development of axial patterning [8]. Also, recent studies highlight the role of bone morphogenetic protein 2 (BMP2) in early embryogenesis, cardiogenesis, and skeletogenesis, and his involvement in normal neural tube closure [9] and body wall closure [10].

Usually, the prenatal diagnosis is suggested by the unveiling of omphalocele and ectopic fetal heart at the first or second trimester ultrasonography [11, 12], but when more complicated anomalies are associated for example: anomalies of central nervous system (CNS) [13], abdominal organs defects [14], or limb defects [15] the complete diagnosis requires thorough pathological analysis.

Prenatal magnetic resonance imaging (MRI) may help in better visualization of the fetal anomalies in order to have a clear picture before a possible repair surgery [16]. Several cases of surgical repairment of newborns with PC were reported with promising results [17, 18].

For the cases with no therapeutic solution, the pathological examination is crucial, as correct assessment of the associated anomalies of a malformed fetus has an important role in finding the recurrence risk for future pregnancies [19].

Therefore, using multidisciplinary investigation teams and resources (imagistic and pathological), can add more accuracy to the final diagnosis.

Pentalogy of Cantrell with craniorachischisis and

lung extrophy is exceptional finding and was previously described in only one case of incomplete PC [13].

We present a case of a fetus diagnosed with class 1 PC associated with craniorachischisis and pulmonary extrophy at 17.5 weeks of gestation. The fetus was analyzed by prenatal ultrasound, *in vivo* MRI, post-mortem MRI and conventional autopsy.

Case presentation

A 32-year-old healthy nulliparous, Caucasian woman was referred to our Prenatal Diagnosis Centre, at 17 weeks and five days of gestation for fetal posture anomaly discovered at the first prenatal ultrasound. It was a poorly monitored pregnancy. The mother's personal history revealed one early first trimester miscarriage (no pathological investigations have been performed), no exposure to teratogenic drugs or infections during pregnancy. Also, family medical history and blood tests were not remarkable. She was a heavy smoker with more than 10 cigarettes per day, living in a mountainous mining region, rich in natural radioactive metals. The patient denied consumption of alcohol during pregnancy.

Prenatal ultrasound demonstrated a single live fetus presenting *ectopia cordis*, with intraventricular defect and large omphalocele. The cervical spine was markedly retroflexed, causing the fetus to gaze upward in a position similar to iniencephaly. The nervous system analysis revealed a large spinal dysraphism. The limbs and placenta had a normal appearance and the umbilical cord, although short presented two umbilical arteries and one vein. Also, excess amniotic fluid was noticed and no amniotic bands (Figure 1, a and b).

To complete the prenatal clinical picture, the investigations were continued with an *in vivo* MRI using a 3 T machine. The examination was limited by the small size of the fetus and fetal motions. Still, in addition to the ultrasound information was described left lung extrophy (Figure 1c). The chromosomal analysis of the amniotic fluid identified a female fetus with normal karyotype.

After informing the mother upon the fetal prognostic, with her written consent was performed the therapeutic interruption of the pregnancy.

The patient delivered a small for gestational age female fetus, weighting 100 g, without viability signs, with craniorachischisis, large midline thoraco-abdominal defect, with an extensive omphalocele sac containing the heart, left lung, the liver, stomach, spleen, pancreas and bowels loops and a 4 cm length umbilical cord (Figure 2).

Prior to conventional autopsy, after a 24-hour setting in formaldehyde solution, the fetus was scanned using a 7 T Bruker Biospec machine as part of part of a larger project created to evaluate the value of post-mortem imaging to improve the quality of the post-mortem examination of small gestational age fetuses. The study protocol was approved by the local Ethics Committee and written informed consent was obtained before the procedures.

Additionally to ultrasound findings, the post-mortem imagistic evaluation revealed all the cervical and thoracic vertebrae and pituitary gland agenesis (Figure 3).

Pathological examination confirmed the anomalies found on the imagistic examinations.

At the cephalic extremity, histology certified the presence of meninges and a small fragment of cerebral cortex, therefore the diagnosis of exencephaly was accepted (Figure 4).

The stereomicroscopic examination of fetal thorax revealed a ventricular septal defect and right-sided aortic arch, with aberrant brachiocephalic artery. The aortic valve was situated above the ventricular septal defect and connected to both the right and the left ventricle. The right common carotid artery emerged from the aortic arch, while left common carotid artery emerged from the pulmonary artery. The *ductus arteriosus* was absent (Figure 5).

Furthermore, all organs had normal histological structure.

The case was interpreted as complete pentalogy of Cantrell with pulmonary extrophy, craniorachischisis and right-sided aortic arch with aberrant brachiocephalic artery.

Discussions

PC is a complex cluster of malformations with yet unknown pathogenesis. We use multidisciplinary diagnostic teams and investigation resources, in order to investigate the fetal anomalies and build a comprehensive picture of an abnormal arrangement. As we continuously seek to understand the morphogenesis of congenital malformations, such information is of inestimable value.

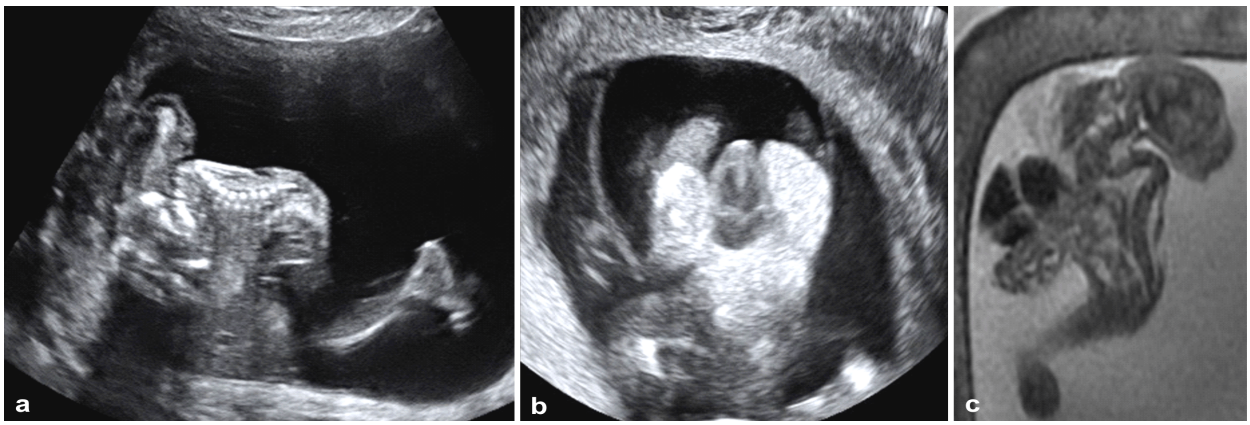

Figure 1 – ***(a) Ultrasound examination depicting a 17 weeks and five days fetus with posture anomaly; (b) Ectopia cordis and large VSD and large omphalocele; (c) In vivo MRI depicting a single live fetus with the cervical spine markedly retroflexed, presenting ectopia cordis and large omphalocele containing the heart, left lung, the liver, stomach, spleen, pancreas and bowels loops. VSD: Ventricular septal defect; MRI: Magnetic resonance imaging.***

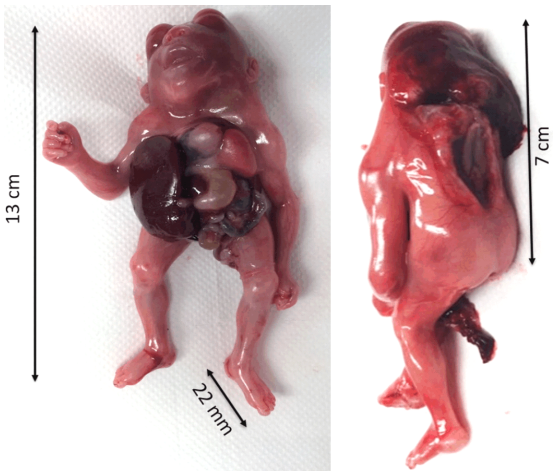

Figure 2 – *Macroscopic pathological examination: anterior and posterior view of the fetus with biometrical data.*

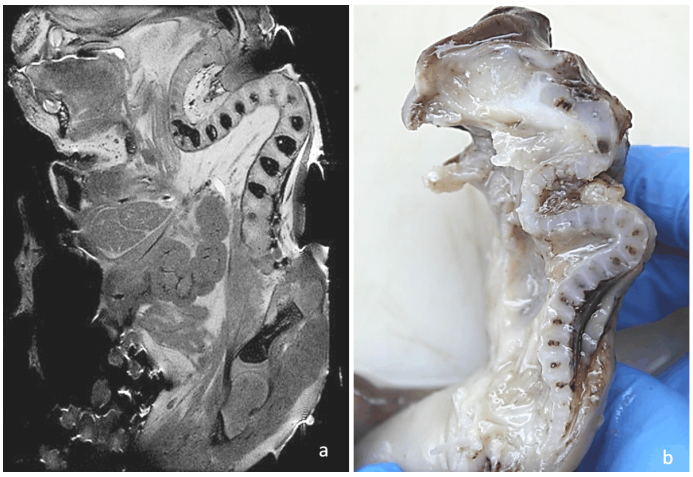

Figure 3 – *(a) 7 T pm-MRI, T2WI, sagittal view depicting retroflexion of the cervical spine, excessive kyphosis and of the thoracic – all the cervical and thoracic vertebras can be identified; (b) Macroscopic pathological examination – sagittal section of the spine and base of the skull, confirming the pm-MRI findings. pm-MRI: Post-mortem magnetic resonance imaging; T2WI: T2-weighted image.*

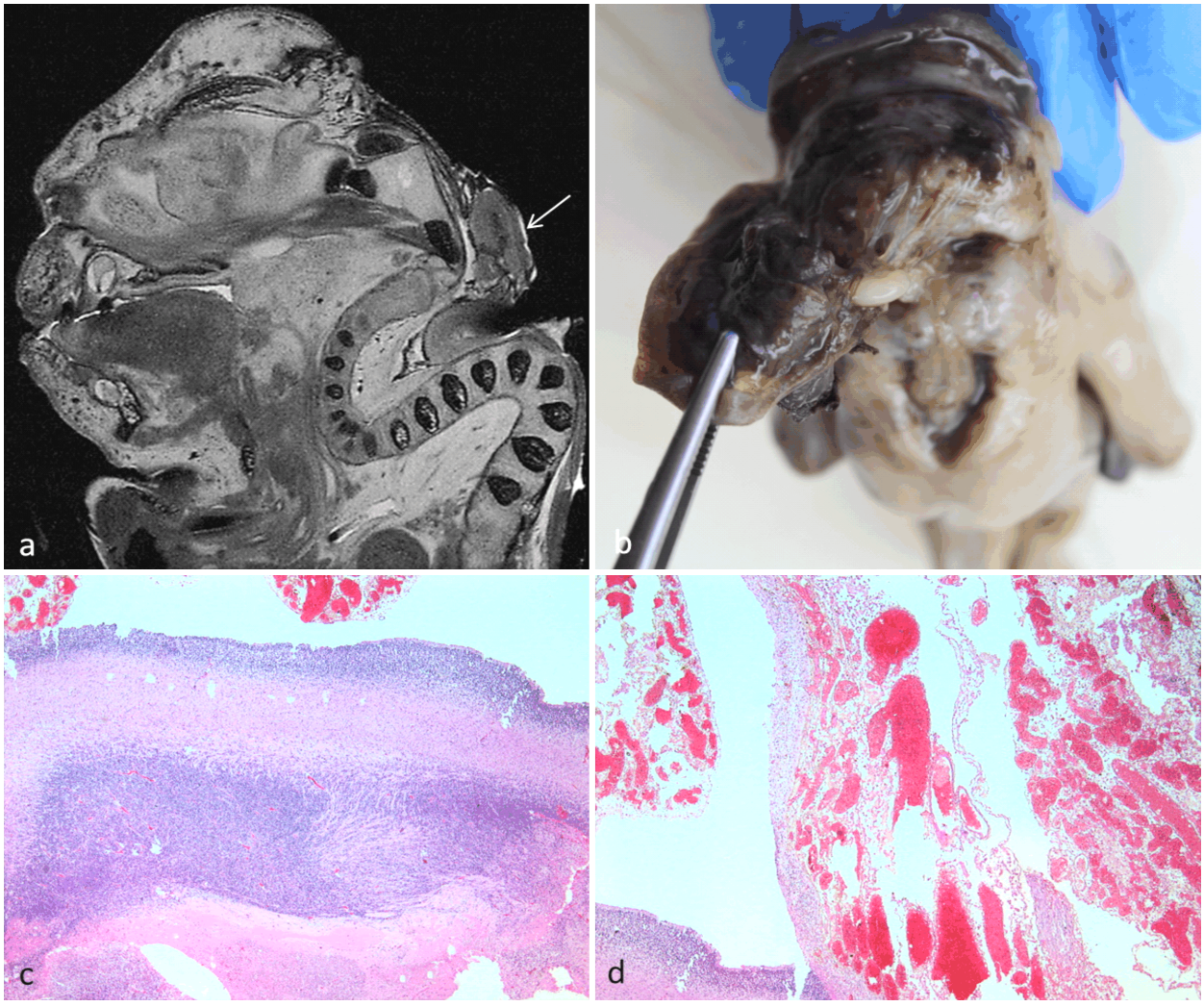

Figure 4 – *(a) 7 T pm-MRI revealed at the cephalic extremity; (b) Macroscopic pathological examination of the cephalic extremity revealed inside the vascular tissue attached to the base of the skull a small tissue fragment with color and consistency similar to cerebral tissue; (c) Microscopic examination of the small tissue showing a fragment of cerebral cortex, with migrating neurons and cortical layers; (d) Microscopic examination of the vascular tissue showing multiples enlarged capillaries with marked congestion surrounded by connective tissue. Hematoxylin–Eosin (HE) staining: (c and d) ×100. pm-MRI: Post-mortem magnetic resonance imaging.*

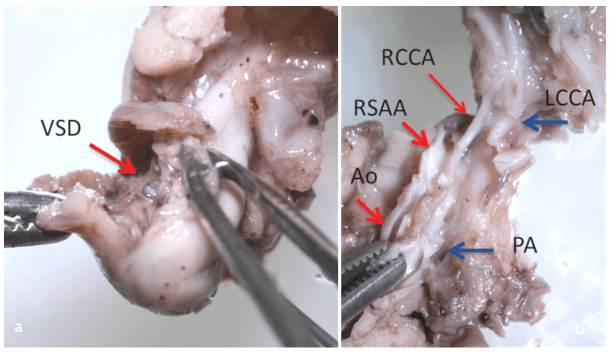

Figure 5 – ***(a) Stereomicroscopic examination of fetal heart showing a VSD and (b) right-sided aortic arch with aberrant brachiocephalic artery. Ao: Aorta; RSAA: Right-sided aortic arch; RCCA: Right common carotid artery; PA: Pulmonary artery; LCCA: Left common carotid artery; VSD: Ventricular septal defect.***

Our case had normal karyotype, but maternal history and the residence in a mining region known for increased residual load of heavy metals in the soil and vegetation [20] associated with the presence of environmental radioactivity, raise a question mark concerning the potential teratogenic effect of radiation exposure resulted consequently to mining operations.

The hypothesis that higher birth-defect rates are present in mountaintop mining regions is a current issue worldwide. Also, Ahern *et al.*, in 2011, highlight the relations between maternal residence in mining areas and the increased prevalence of circulatory, respiratory, central nervous system, musculoskeletal, gastrointestinal, urogenital birth defects [21].

At the prenatal evaluation was discussed the possibility of *ectopia cordis* associated with iniencephaly, *ectopia cordis* associated with amniotic band syndrome and body-stalk anomaly syndrome.

The associated craniorachischisis, complex anomaly characterized by an opened cranial defect (anencephaly or exencephaly) that continues with a completely open spine (spinal dysraphism) was reported in association with PC in less than 10 cases [22–26].

An important differential diagnosis taken into consideration was iniencephaly, due to the overall position of the fetus. Iniencephaly has a prevalence of 1–2 in 2000 births [27], being one of the rarest forms of neural tube defects. Classical sonographic features for iniencephaly are: occipital bone defect with consecutive enlargement of foramen magnum, irregular fusion of malformed vertebrae, and incomplete closure of vertebral arches and bodies leading to extreme retroflexion of cervical spine and upward turned face with chin continuous with chest due to the absence of the neck (star-gazing appearance) [28]. More than 75% of iniencephaly cases present concomitant anomalies, most frequent being anencephaly, omphalocele or holoprosencephaly [29].

In our case, the post-mortem examinations, revealed a complete spine, with all vertebral bodies normally developed, without fusion between adjacent vertebrae. The existing occipital bone defect combined with the incomplete closure of the vertebral arches that also associate, a very short umbilical cord, forced the spine in an excessive kyphosis of the thoracic region and lordosis of the lumbar region.

Due to the presence of a short umbilical cord and associated anomalies, body-stalk anomaly syndrome was another differential discussed. The syndrome is a rare pattern of multiple malformations that include abdominal wall defect, scoliosis, extremity defects, and absent or short umbilical cord [30]. The most characteristic finding of this pathology is the scoliosis that can be revealed starting with the first trimester [31]. Our case presented excessive kyphosis of the thoracic region and lordosis of the lumbar region and no limbs anomalies, therefore the diagnosis of body-stalk anomaly syndrome was excluded.

Ectopia cordis was previously described associated with anomalies secondary to aberrant fibrous amnion bands formation due to early membrane rupture [32], therefore the amniotic band syndrome was carefully ruled out at the prenatal imagistic investigations.

Continuous development of ultrasound machines and techniques, leaded to an increase number of diagnosed or suspected anomalies in fetuses increasingly smaller [33].

Therefore, the need for adequate investigation protocols of small gestational age fetuses has increased.

High-resolution post-mortem MRI begins to detach as a reliable method to identified and describe subtle fetal anomalies [34] and in the future, is emerging as a viable alternative for the parents who refuse conventional autopsy or, as in our case, to guide difficult autopsies.

Still, the imagistic investigations were not capable to describe all the cardiac and vascular anomalies, to identify these structures a stereomicroscopic examination being necessary.

The right aortic arch with aberrant brachiocephalic artery found is an extremely rare anomaly. Jesse Edwards theory of the "double aortic arch" [35] that can be interrupted from the origins of the vessels at any point, provides a logical explanation for all the variants of aortic arch and vascular rings anomalies, known so far. Also, the migration of neural crest cells to the pharyngeal arches is thought to play a role in the mechanisms that lead to regression, or to persistence and development of the aortic arch segments [36].

Conclusions

We have presented antenatal imagistic and corresponding virtual and conventional autopsy findings of an extremely rare association of complete pentalogy of Cantrell with craniorachischisis, pulmonary extrophy and right-sided aortic arch with aberrant brachiocephalic artery. To our knowledge, there are no records in the literature of this particular anomalies association. Nowadays, the demand for a detailed prenatal diagnosis is higher than ever, therefore clinicians must be aware that these anomalies may occur simultaneously with a classic PC in order to improve the diagnosis of the fetal malformative pathology, pregnancy management and further patient counseling.

Declaration of interests

The authors report no conflict of interests. The authors alone are responsible for the content and writing of the paper.

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