FETAL MYOCARDIAL CALCIFICATION – NECROPTIC IDENTIFICATION

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FETAL MYOCARDIAL CALCIFICATION – NECROPTIC IDENTIFICATION (Abstract) : The detection of fetal intracardial foci of calcifications was firstly reported in 1987. These foci are most commonly seen in the left ventricle and occasionally in the right ventricle, while diffuse or intra-atrial myocardial calcifications are rare. Usually, heart defects or malformations are associated with fetal chromosomal abnormalities. We report a case of fetal myocardial calcification in a newborn who led to death within several hours after birth. These lesions occurred due to the presence of an intrauterine growth restriction associated with myocardial ischemia related to a short and thin umbilical cord. Autopsy and microscopic examinations have provided a better understanding of the clinical symptoms that led to the death in this case. **Key-words :** FETAL CARDIAC FIBROSIS, MYOCARDIAL CALCIFICATION, AUTOPSY

INTRODUCTION

The heart is the organ with the highest oxygen consumption reported to its weight, in the human body. The deposit of calcium salts into myocardium is correlated to a process of dystrophic calcification in areas of bleeding, necrosis or fibrosis of the heart (1, 2)(Baysal, 2008 ; G Veldtman 1999).

Myocardial ischemia in the perinatal period is rather determined by low rates of perfusion than by an acute ischemic incident. The myocardial areas which are mostly involved are the papillary muscles and the subendocardial zone (3, 4)(Donnelly 1987, Wax 2000).

Only few cases with focal myocardial calcifications and few other with extensive calcifications of the fetal heart associated with significant myocardial dysfunction have been described in literature (5, 6) (Hajdu, 1998, Rodriguez 2013). In some cases, fetal myocardial calcifications have been associated with infections, early maternal drug abuse or genetic anomalies, as trisomies 21 or 13 (7-10)(Mitra, 2004, Sahlin 2015, Yap 1994, Huang SY 2010).

In this context, we are presenting a rare case of myocardial calcifications in a premature newborn which has been diagnosed after postmortem microscopic examination.

CASE PRESENTATION

We report the case of a male newborn, 37 weeks gestational age, which died a few hours after birth. Ultrasound examinations performed during pregnancy have revealed a fetal growth restriction according to the measurements of the abdominal circumference, with an anatomically normal fetal heart and no other major malformations. No chronic alcohol or drugs consumption have been registered in maternal history.

The newborn had a low Apgar score, a weight of 2480 g, a height of 42.5 cm, and 28 cm thoracic perimeter. The gross features of the placenta have been apparently normal, except for a short and thin umbilical cord, with 30 cm length and 1.3 cm diameter.

The infant has shown forceful intercostals retraction and has used accessory neck muscles at about 60 minutes after birth, becoming progressively obtunded, flaccid, dying few hours later.

Autopsy revealed the presence of a cerebral edema, along with kidney, liver, spleen and

Fig. 1. Compact gross features of the lungs and of the heart

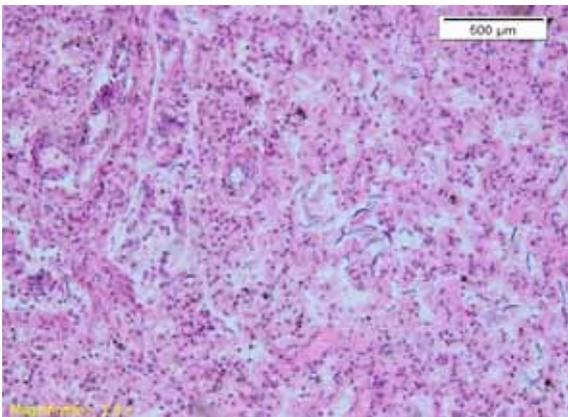**Fig. 2.** Apparently normal gross features of the heart

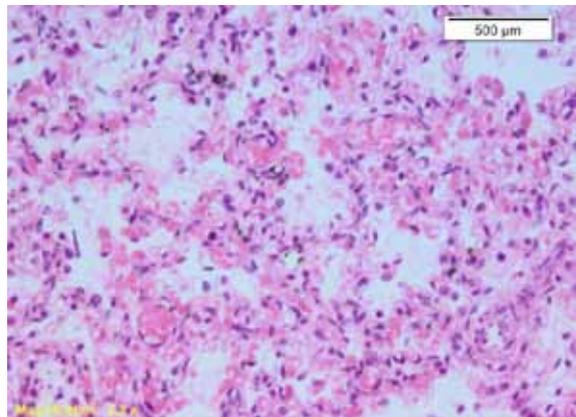**Fig. 3.** Insufficient alveolar expansion with fetal squames in alveolar spaces, H.E. x 100

Fig. 4. Intra-alveolar red blood cells, capillary congestion and interstitial edema, H.E. x 200

adrenal gland hyperemia. The lungs were heavy, compact, reddish- purple in color, and their texture resembled that of the liver (Fig. 1). These features have been associated with about 250 ml of serous fluid in the pleural and peritoneal cavity. The lung hydrostatic test has shown partial flotation of the fragments.

External examination of the heart has shown no gross abnormalities. The pericardium and endocardium have been smooth and glossy, heart cavities without blood content, and valvular apparatus integrity and elasticity have been preserved.

Although the heart was anatomically normal, with a weight of 17 g, an area of subendocardial myocardial fibrosis of 20/40 mm (Fig. 2) associated with foci of calcification have been observed in the left ventricle.

Fetal anatomy has been otherwise normal and no other areas of abnormal calcification have been detected. No external traumatic lesions have been noticed.

Necroptic examination has been associated to the collection of representative tissue specimens for microscopy. Paraffin-embedding followed by routine, hematoxylin-eosin (HE) and trichromic Masson stainings have been performed. The microscopic examination has been done and illustrative images have been captured.

Routine microscopy confirmed the cerebral edema, the meningo-cerebral congestion associated to focal perivascular hemorrhages and a prominent, dense aggregation of neuroblasts and immature neurons in the periventricular and subpial zones and subjacent to the ependimal epithelium.

Lung alveoli have been collapsed in some areas, containing fetal squames in alveolar spaces, along with retarded epithelial differentiation (Fig. 1) ; capillary congestion, interstitial edema, focal necrosis of bronchial and bronchiolar epithelial cells and intra-alveolar hemorrage have been also noticed in other areas (Fig. 2).
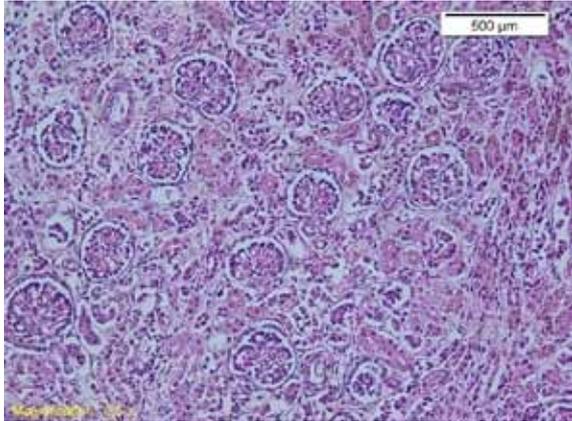
Fig. 5. Fetal renal corpuscles and autolysis of epithelial renal tubules, H.E. x 100
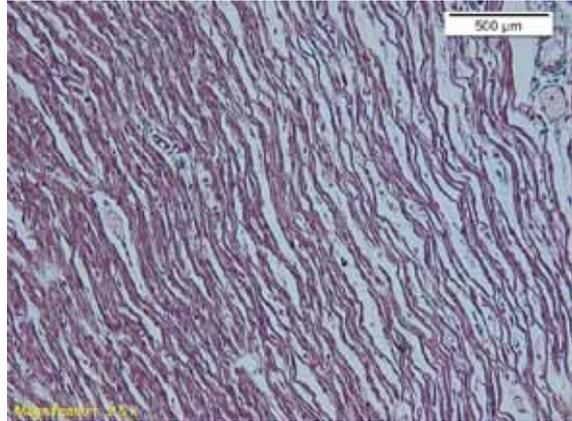

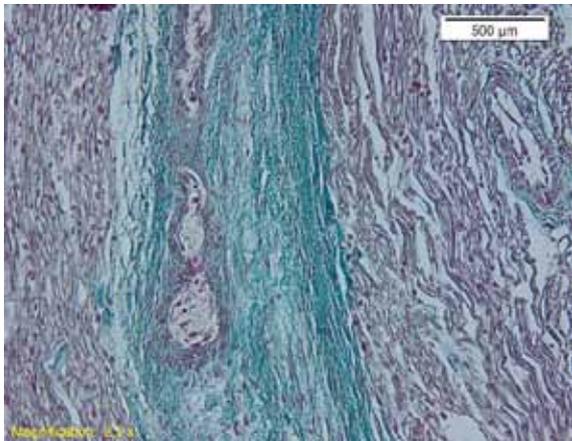**Fig. 6.** Ischemic cardiac striated muscle fibers, trichrome Masson x 200

Fig. 7. Myocardial fibrosis and ischemic cardiac striated muscle fibers, trichrome Masson x 100
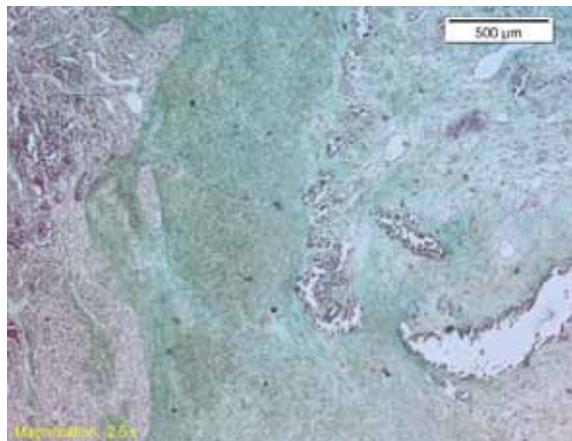

Fig. 8. Large area of subendocardial fibrosis, trichrome Masson, x 40

Kidney parenchyma revealed the presence of fetal renal corpuscles, glomerular capillaries hyperemia, and postmortem autolytic lesions of the epithelial renal tubules (Fig. 3).

Microscopically, capillary congestion, perivascular microhemorrhages, focal myocardial ischemia, small areas of perivascular fibrosis, and calcifications have been noticed in the myocardium (Fig. 4, 5).

Supplementary, an area of subendocardial fibrosis (Fig. 6, 7) associated with foci of calcification and discrete microhemorrhages have been identified (Fig. 8).

Few dispersed mononuclear inflammatory cells and sections of coronary arteries without apparent lesions have been noticed in the pericardium.

Supplementary, adrenal edema, along with spleen and sinusoid liver congestion have been observed.

DISCUSSIONS

Calcification of the heart and vessels in fetuses is a condition with heterogeneous etiopathogeny (5, 11) (Hajdu 1998, Murphy H 2015). About 3.5% to 5% of routine pregnancy ultrasounds may detect isolated echogenic intracardiac foci in the fetus (Murphy, 2015).

Myocardial calcifications were firstly described in literature in 1987, by Schechter and colleagues, who observed the echogenic cardiac focus, in 6 of the 26 fetuses on neonatal echocardiography (12) (Schechter, 1987). These have been considered dystrophic or metastatic and generally were associated with chromosomal abnormalities, intrauterine infections, early maternal drug abuse or ischemia (13, 14) (Pipitone 2015, Simchen 2006). A recent study performed on 9270 second-trimester obstetric sonograms (16-28 weeks) on middle Eastern population has shown 2.5% myocardial calcifications prev-
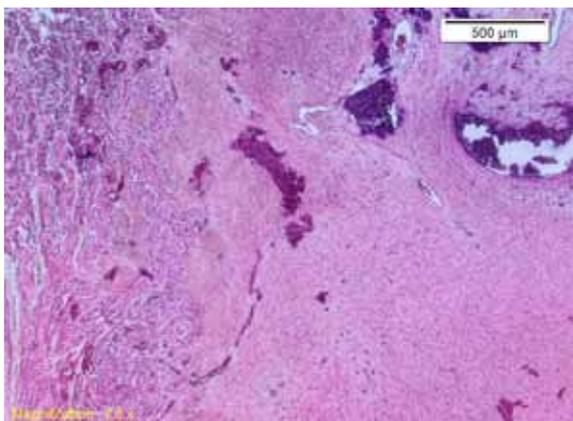
Fig. 9. Subendocardial fibrosis
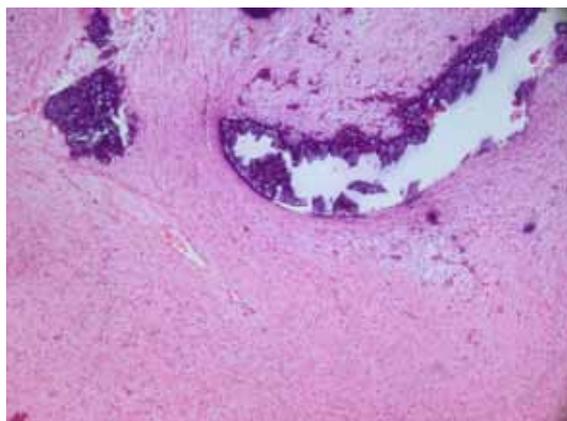and calcifications, H.E. x 40

Fig. 10. Myocardial fibrosis associated with foci
of calcification and microhemorrhages, H.E. x 100

alence (95 % CI : 2.2-2.8 %), without any association with trisomy 21 (0/163 *versus* 1/163 ; p value = 1.00) (MIRZA 2016).

Cardiac calcifications have been described in fetuses with different gestational ages, from of 18-22 weeks (14)(Simchen 2006), as disseminated or as foci.

Most cases have been reported in prenatal ultrasound examinations, but the clinical significance of intracardiac foci of calcification has been just recently associated with intrauterine ischemia or congenital heart defects (8) (Sahlin 2015).

Although most foci of calcification have been registered within the left ventricle (15) (Merati R, 1996), right ventricle (0-25 % cases) or both ventricles (1.5-7.6 % cases) have been rarely noticed as alternative locations (16, 17) (Petrikovsky 1995, T. Yee Khong 2015).

Several authors have described extensive myocardial calcifications in premature fetuses, being associated with cardiac dysfunctions (8, 14) (Chan, 2005, Simchen 2006).

Even more frequently, massive or focal myocardial calcifications have been accompanied by cardiac dysfunction or heart abnormalities but, nonetheless, a normal perinatal outcome has been reported (14) (Simchen 2006, Murphy 2015).

A study conducted on three fetal hearts from perinatal autopsy specimens (including spontaneous abortions, stillbirths, and perinatal deaths) revealed the presence of a discrete calcification in papillary muscle of the left ventricle (19) (Brown, 1994). Similar small Calcium deposits, located in the papillary muscles and exhibiting a linear feature have been reported in a retrospective study in 15 % of 149 fetuses with chro-

mosomal anomalies and in 2 % of 209 fetuses without chromosomal anomalies (20) (*Sepulveda, 1998)*.

It has been suggested that the main cause of these calcifications would be the abnormal development of the microvasculature, involving terminal branches of the coronary arteries, leading to early ischemic changes in the papillary muscles (19) (Brown1994).

Papillary muscles calcifications may indicate an increased chance of the fetus harboring a chromosomal anomaly but some authors consider that these may be quasinormal variants of development due to the lack of cardiac anomalies (Murphy 2015).

Moreover, cardiac calcifications occur at sites of myocardial necrosis, and are probably just one feature of a severe generalized ischemic insult.

It is known that premature infants with chronic lung disease are susceptible to myocardial ischemia. The subendocardial zone or papillary muscles are the most likely areas to be affected by ischemia and secondary by fibrosis and calcification (21) (Tennstedt C,2000).

As in adults, myofibers injured by ischemia become swollen and show eosinophilic granularity of their cytoplasm, with loss of normal striations. As the lesion is progressing, the nuclei become pyknotic and disappear by karyolysis. Sometimes these lesions may be associated with extravasations of erythrocytes. Occasionally, the calcification of individual necrotic myocytes may be identified (17) (T. Yee Khong 2015).

In our case, routine antenatal ultrasound examinations have not revealed myocardial echogenic foci or other heart malformations but,

during the delivery, a short and thin umbilical cord was noticed.

Excessively long cords occur in 4–6% of placentas, while abnormally short cords have an incidence of approximate 1–2% (17) (T. Yee Khong 2015). The cord length is determined by several factors as : gestational age, genetic or fetal movement. Decreased fetal movements are associated with fetal skeletal dysplasia, ectopic pregnancies, amniotic bands, and alcohol or drug abuse (22, 23).

In general, short and thin cords are associated with fetal distress, low Apgar scores, low intelligence quotient or different degrees of developmental anomalies (T. Yee Khong 2015) (17, 23).

In our case, the fetal growth restriction that was apparent at birth was confirmed by the autopsy and histology examinations. While the occurrence of fetal renal corpuscles or dense aggregations of neuroblasts and immature neurons in subpial zones and subjacent to the ependimal epithelium are normal morphological features in newborn, the presence of collapsed alveolar areas associated with fetal squames in alveolar spaces, along with retarded epithelial differentiation represent the expression of pulmonary immaturity. Focal ischemic myocardial fibres, areas of fibrosis, and foci of calcifications identified during microscopic examination are considered as injuries secondary to an in-trauterine chronic ischemia. All these histopathologic findings occurred most probably due to a short and thin umbilical cord.

This is the first case of fetal myocardial calcifications that has been diagnosed in our service and, according to our knowledge, there is only one report in Romanian literature, with 94 fetuses which have been diagnosed with focal intra-myocardial calcifications, in the second trimester of pregnancy. According to this study, the most numerous areas of calcifications have been observed in the left ventricle (81 cases), 8 in right ventricle, and 5 bilateral cases, involving both ventricles. Other supplementary sonographic abnormalities have been identified in 21 of these cases, such as short femur, single umbilical artery, choroid plexus cyst or mild pyelectasis (Tica, 2016).

CONCLUSIONS

Chronic intrauterine ischemia is associated with growth restriction and delay in organ development. The lung immaturity may represent the major cause leading to death, as in this case report.

Additionally, chronic intrauterine ischemia associated to a short and thin umbilical cord may lead to myocyte necrosis, fibrosis, and foci of myocardial calcification which may remain undiagnosed during the pregnancy and may be revealed by autopsy examination, as in the reported case.

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