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Case Presentation

Fetal Myocardial Calcification: An Unusual Pathological Finding which Needs Usual Attention - A Case Report and Literature Review

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Abstract

Fetal myocardial calcification is an unusual pathological finding. During the past decades, more cases with fetal myocardial calcification due to a variety of causes are being reported. For most of times, due to the indistinct symptoms and very low prevalence, it is almost impossible to identify the distinctive cause for a specific case. Here we reported a recent case with fetal myocardial calcification at full term. The possible causes are discussed with reviewing the literature and correspondingly for the maximal benefits more attentions are needed on the purpose of its prevention, early diagnosis, and better management of the disease for patient benefits.

Keywords: Myocardium; Calcification; Degeneration; Fetus

Introduction

Fetal myocardial calcification is a rare pathological finding in clinical practice. However, during the past decades, more and more cases are persistently being reported [1,2]. The consequences may include intrauterine fetal demise, organ dysfunction, and severe developmental delay in living survivors [2]. So it is of utmost importance to identify and understand the pathological cause and result and thereafter to prevent, early diagnose and better manage it.

Case Summary

A 12-day-old male infant was delivered *via* stat C-section due to intrauterine fetal bradycardia at 39 4/7 weeks of gestational age. After delivery, the infant was found to have no heart rate with Apgar 0 for 1, 5, and 10 min. Intubation and chest compression were immediately administered and transferred to NICU with more than 60 bpm heart rate. However, resuscitation efforts were finally unsuccessful and the baby was pronounced expired. Autopsy found foci (0.5 cm in diameter) of myocardial calcification located at the jointing area of the right posterior heart wall and septum. The calcification is highlighted with Von Kossa stain (Figures 1 and 2) except accompanying subacute myocardial ischemic changes (Figure 3). The other main findings include respiratory distress syndrome (organizing phase), persistent pulmonary hypertension, bilateral acute renal tubular necrosis, and diffuse severe subacute hypoxic changes in central nervous system. Pathological examination of placenta and membranes revealed focal acute chorioamnionitis, focal chorionic vasculitis, blood vessel thrombi associated with acute inflammation within vessel wall at the fetal surface of placenta, focal funisitis of the umbilical cord, a single placenta parenchymal infarct, and pigment-laden macrophages in the fetal membranes.

The mother was 34 years old, G2P1, with a very limited history due to noncompliance with doctor's follow-ups. For this current pregnancy, the significant blood workups include decreased protein S activity 22(reference range: 60-140% normal, Quest Diagnostics), drug screening with high delta-9-Tetrahydrocannabinol (THC) 40 (<5 ng/ml) (Quest Diagnostics). Early stage pregnancy examination revealed varicella IgG 2473.0 (>165 index as positive), rubella IgG 4.8 (>1.0 index as positive), and evidence for vulvovaginal candidiasis. The previous pregnancy was 2 years ago with varicella IgG 3891.0 (>165 index as positive) and rubella IgG 3.8 (>1.0 index as positive). Placenta and membrane examination also found focal mild acute funisitis and focal mild acute subchorionitis.

Discussion

In obstetrical practice, fetal bradycardia in the trimester stage of pregnancy is usually due to fetal hypoxia from umbilical compression or placental insufficiency. In this report the infant was delivered *via* stat C-section due to fetal bradycardia, which could not rule out the similar usual pathological processes. However, autopsy findings of the infant and pathological findings from placenta and membranes suggested more complicated causes in this case. By literature review, we have noticed that most reported cases of fetal myocardial calcification occurred in the second trimester of pregnancy with fatal consequences. Generally speaking calcification is a secondary relatively slow process based on some other primary pathological bases. This infant survived to full term without significant acute or chronic infection identified in other tissues particularly in the heart or lungs from autopsy findings, which ruled out sepsis as the cause of his death. Acute chorioamnionitis, chorionic vasculitis, funisitis of the umbilical cord, and blood vessel thrombi associated with acute inflammation within vessel wall at the fetal surface of placenta did exist but very focally. Certainly, intrauterine infection existed but obviously myocardial calcification did not start after delivery or when the focal infection happened. It must have already been there for a while based on some other pathological causes or during the process of calcification, fetal bradycardia finally broke out at some point of threshold or at the time when infection started to synergize the effect. So fetal myocardial calcification basically hints another underlying chronic pathological process before delivery in our case. Currently

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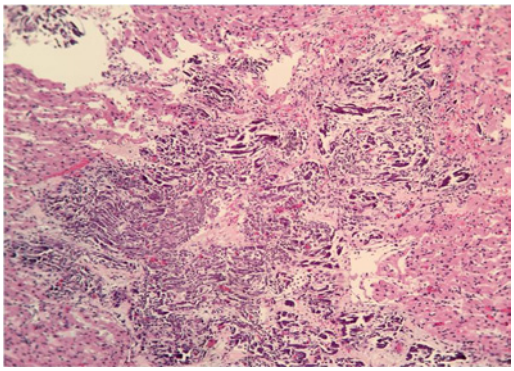
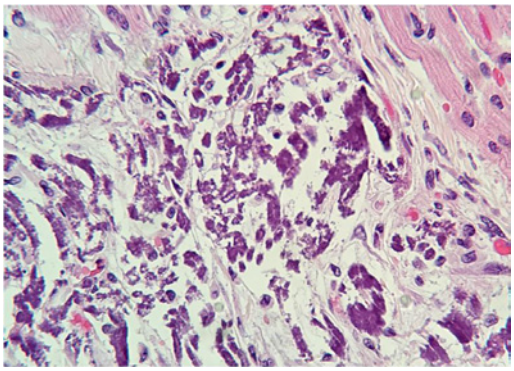


(Von Kossa stain, x 20).

Figure 1: Highlighted fetal myocardial calcification with Von Kossa staining (x20). Coarse calcified deposition was admixed with adjacent fibrosis and in some areas the calcified myocardial cells still kept the original myocardial texture, implying previous coagulation necrosis. The surrounding live myocardial cells were showing disrupted waving myofiber. Mild dispersed lymphocytes and occasional neutrophils could be identified.



(Von Kossa stain, x40).

Figure 2: Higher magnification of myocardial calcification (Von Kossa staining, x40) showing calcified necrotic myocardial cells admixed with dispersed fibrosis. The remnant live myocardial cells on the upper right corner showing myofiber waviness.

the definite cause of myocardial calcification is still unclear. However, the basic pathological process is believed to result from calcium deposition in areas of necrosis, fibrosis, inflammation, infection, and/or hemorrhage of the myocardium. Some researchers call it dystrophic calcification due to its occurrence in the presence of normal serum levels of calcium and phosphorus. Dystrophic calcification of the myocardium is a nonspecific reflection of severe myocardial injury. This may include many possible causes as the follows:

Fetal myocardial infarction-based calcification

This is seen in intrauterine myocardial infarction. Coronary artery occlusion or glycogen storage disease of the heart could cause it as examples. Bernstein et al, [3] reported that perinatal cardiac infarction was usually associated with congenital heart lesions or isolated coronary artery abnormalities. Intrauterine asphyxia and thromboembolic coronary occlusion by a paradoxical embolus usually arised from a thrombus in the ductus venous or umbilical vein and reached the coronary circulation *via* normal fetal circulatory pathways. In our case thrombi were found in umbilical vein but no coronary occlusion was found. Other causes for intrauterine cardiac infarction include idiopathic [4], ventricular aneurysms [5], and twin-to-twin transfusion syndrome [6]. In 2006, a case study reported dystrophic calcification accompanied with severe and extensive myocardial necrosis that suggested intrauterine origin. in a female neonate who suffered from cardiopulmonary arrest at birth presenting with refractory cardiogenic shock and died. No thrombus was identified but both the circumflex artery and anterior descending coronary artery presented with very narrow calibers. It was presumed that sympathomimetics administered to the mother could have played a role in the development of fetal myocardial infarction and consequent calcification [1]. Usually fetal myocardial necrosis is an uncommon event that occurs only under unusual circumstances. However, the histologic changes associated with ischemia and myocardial necrosis are not uncommon as we thought and are frequently overlooked at autopsy. Ischemic changes including coagulation necrosis, myofiber waviness, or contraction band necrosis, were seen in 21% of stillbirths and 32% of live births [7]. In our case, distinctive ischemic changes like necrosis, myofiber waviness, and consequent fibrosis were identified and extensive myocardial vacuolar degeneration was also found (Figure 4), which is considered as a nonspecific finding and could be seen in 43% of stillbirths and 84% of live births [7].

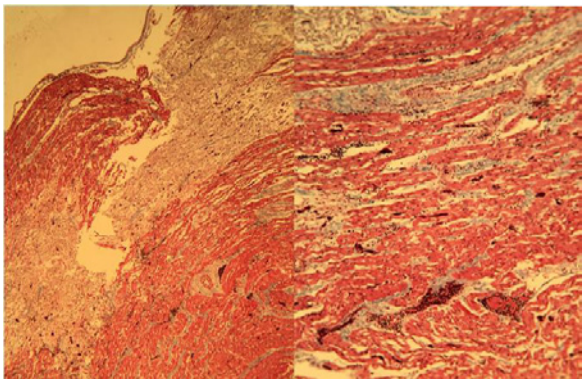
Thromboembolism-based calcification

Thrombus has been reported as a direct factor to cause myocardial necrosis and calcification [3]. Factor V Leiden is the most common inherited form of thrombophilia. It is estimated that 3 ~ 8 percent of people with European ancestry carry one copy of the factor V Leiden mutation in each cell, and about 1 in 5,000 people have two copies of the mutation. This mutation is less common in other populations. Parker et al reported that if fetal myocardial calcification was found accompanying with other calcifications at multiple sites of the body, genetic thromboembolic conditions, for example Facor V Leiden homozygosity, should be considered [8].

Protein S is a vitamin K-dependent anticoagulant which acts as a nonenzymatic cofactor to activate protein C. Protein S deficiency, with decreased protein S activity or level, is a rare inherited thrombophilia disorder associated with increased risk of venous thrombosis and fetal losses in pregnancy. However, decreased free protein S level could be seen in normal pregnancy as a physiological change from first trimester and then all through the pregnancy period. Research suggested the free protein S level during the second trimester could decrease to about half level of that in first trimester and then kept relatively stable until 38th gestational week [9]. This patient's mother had a significant decrease of protein S activity (almost 3 times less than the lower cutoff value), which could play a role in the change of the placental and fetal pathology. Research suggested that late pregnancy loss appeared to be most strongly associated with protein S deficiency [10]. However, in our case the reliable diagnosis on protein S deficiency is impossible due to limited available study.

Inflammation-based calcification

In 1962, Coleman et al [11] reported the first case of infant myocardial calcification. They did not find any occlusion or aberration of the coronary vessels but based on the finding of multinucleated giant cells and granulation tissue they believed an underlying inflammatory basis for the lesion. Many autoimmune



A(x10) B(x20)

(Von Kossa stain).

Figure 3: Highlighted dispersed fibrosis with trichrome stain showing blue fibrotic tissue between the separated waving and / or disrupted myocardial cells in adjacent areas. A: The main pale area admixed with sparse light blue fibers is the original calcification area which could be highlighted with Von Kossa stain(x 10); B: Diffuse fibrosis between distorted waving myocardial cells with dispersed lymphocytes and newly generated small vessels (x 20).

diseases, such as SLE, scleroderma and rheumatoid arthritis, could cause pericarditis. Autoantibodies like La/SSB antibodies can bind apoptotic cardiomyocytes and thus increase immunoglobulin deposition in the heart. The tissue damage could consequently lead to fibrosis and calcification of the myocardial tissue. Once the AV-node gets involved, complete congenital heart block can occur [12]. From this specific process of calcification, we can easily understand that calcification is a chronic process based on inflammation. AV block and endocardial fibroelastosis associated with dilated cardiomyopathy are the most common clinical manifestations of anti-Ro/SSA-mediated fetal cardiac disease. Recent research showed fetal antibody-mediated cardiac inflammation is an underestimated complication and papillary muscle biopsy specimens have demonstrated severe atrophy with fibrosis and dystrophic calcification, showing the significant inflammatory effect from autoantibodies and their role in myocardial calcification [13,14].

Intrauterine infection-associated calcification

As we are already familiar with, TORCH infection in pregnancy, particularly with Cytomegalovirus (CMV), toxoplasmosis, herpes encephalitis, HIV, and rubella, is associated with periventricular calcification of the brain. However, not only for that, more and more observations and studies have reported that many intrauterine infections could also cause fetal myocardial calcification:

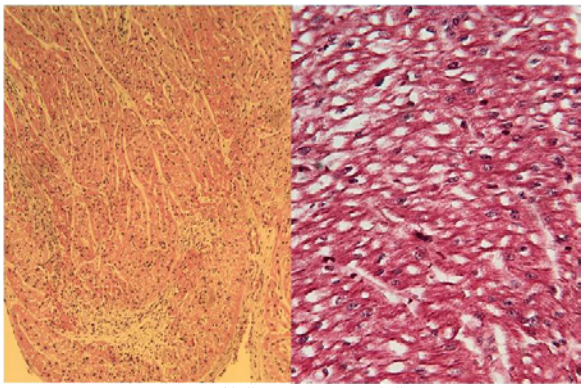
Herpes simplex virus (HSV, type II) infection: Congenital herpes simplex infection is a rare but potentially devastating disease. In most cases, the neonate is infected intrapartum *via* direct exposure to infectious maternal body fluid as it passes through the birth canal. Under these circumstances, manifestations of infection do not occur until the first week of life. Very rarely, vertical transmission occurs antenatally *via* transplacental spread at the time of a maternal viremia or from ascending infection from the lower genital tract into the uterus. A case of in utero transmission of herpes simplex type II viral infection was reported recently which had the striking and distinctive sonographic appearance of dystrophic myocardial calcification associated with an unexplained elevation of the maternal serum α-fetoprotein (AFP) level. In utero fetal death occurred in the late second trimester [15].

Adenovirus infection: Oyer et al, [16] reported a case of fatal hydrops fetal is owing to adenoviral endomyocarditis with aortic and pulmonary valve stenosis. Autopsy confirmed hydrops and showed thickened, fibrotic semilunar valves with stenosis. The myocardium was focally fibrotic with areas of calcification. PCR study of myocardial and aortic valve tissue was positive for adenovirus. This report suggests a broader group of causative agents.

Varicella infection: The first reported case of fetal varicella infection following the diagnosis of maternal varicella infection at 13 weeks of pregnancy. Anomalies noted sonographically at 26 weeks' gestation included oligohydramnios, symmetrically impaired fetal growth, limb anomalies, a thin placenta, and widespread dystrophic calcification of the abdominal cavity and chest, including the lungs and myocardium [17]. The second case of fetal varicella infection was reported following the diagnosis of maternal infection at 16 weeks of gestation. Diagnosis was based on serology testing and prenatal ultrasound, confirmed by DNA PCR detection in amniotic fluid. Sonographic anomalies included borderline ventriculomegaly, intracerebral, intrahepatic and myocardial calcifications. The newborn showed a severe encephalopathy and could not be stabilized sufficiently and died 23 days after birth. These two reported cases showed the very serious consequences of fetal varicella infection and prenatal ultrasound is helpful to evaluation the severity of the infection [18]. As part of multiple sites of calcification, myocardial calcification is noted in both cases of varicella infection.

CMV infection: CMV is the most common congenital infection in the United States, affecting as many as 40,000 newborns each year.

Approximately, 10% of these infants are symptomatic at birth and most of these will suffer permanent neurologic sequelae such as neurodevelopmental delays, motor disabilities, deafness, and blindness [19]. Also CMV infection is notoriously well known associated with peri-ventricular calcification. Even though it is thought that congenital CMV infection does not cause heart defect [19], however, some evidence showed that CMV infection in utero was also associated with cardiomyopathy presenting dilated Left Ventricle (LV), poor LV systolic function, and intraventricular thrombus in a 2-month-old infant [21]. This pathological change could be the basis for dystrophic calcification. Another reported case was a female infant born at 28 weeks of gestation, who died of fatal arrhythmia 50 days after birth. Cytomegalic cells were frequently found in the vascular endothelial cells in the myocardium and occasionally in muscle fibers. Immuno fluorescent microscopy showed the presence of CMV antigen in both endothelial cells and muscle fibers. So it is believed that the endothelial damage is a cause of the myocardial lesion in addition to the direct invasion of the muscle fibers by the virus [21]. Therefore, both cases above did demonstrate the effect by CMV on the heart. Any inflammation or secondary fibrosis or degeneration could be the basis for myocardial calcification. Furthermore, an animal test study established the direct evidence between murine CMV infection and dystrophic myocaridial calcification. Their findings showed that murine CMV could cause acute myopericarditis which varied from a focal lymphohistiocytic inflammation to intense inflammation with necrosis and cytomegalic inclusion-bearing cells. Sublethal doses



(H&E stain).

Figure 4: Diffuse vacuolar degeneration in the myocardial cells. A: Lower power showing diffuse vacuolated degeneration with focal fibrosis(x10); B: High power showing the diffuse myocardial vacuolation (x40).

caused focal transient nonspecific chronic inflammation, followed months later by an increased frequency and extent of dystrophic myocardial calcification [22].

Other viruses: Several other viral etiologies of dystrophic calcified myocarditis have also been reported. Among them included Coxsackie B1, 2, 3, and 4, Coxsackie A3, echovirus II and other enteroviruses, toxoplasma [15], parvovirus B19 [16].

Our review of the literature suggests that fetuses and neonates who have apparently calcified areas of myocardium should be evaluated for possible viral or parasitic infection.

Chromosomal Abnormality and Myocardial Calcification

To identify whether myocardial calcification is associated with specific chromosomal anomalies, some authors reported in 415 cases of abortions, stillbirths, and perinatal deaths, discrete central papillary muscle calcification was present in 14 of 85 (16%) cases with trisomy 21, in 7 of 18 (39%) cases with trisomy 13, but only in 6 of 255 (2%) controls (P <0.001); In a restricted prospective study of the hearts of fetuses with trisomy 21, papillary muscle calcification was demonstrated by specimen radiographs in 4 of 6 (67%) cases [23].

To identify factors associated with calcifications, recently another research has performed a case-control study on the largest cohort of fetuses with calcifications. They found calcifications were mainly located in the liver, but also in heart, bowel, and other tissues. Fetuses with calcifications showed a significantly higher proportion of chromosomal abnormalities than controls: 50% *vs.* 20% (p<0.001). The most frequent aberrations among cases included trisomy 21 (33%), trisomy 18 (22%), and monosomy X (18%). The presence of fetal calcifications is associated with high risk of chromosomal abnormality in combination with malformations [24].

The fetal Intracardiac Echogenic Foci (ICEF) by ultrasound was first reported in 1987 and the current understanding of ICEF is microcalcification of the papillary muscles. It may represent a special type of myocardial calcification. ICEF are observed in 0.5 to 20% of fetuses, with an overall frequency of 5.6%. These small, discrete structures near the papillary muscles and chordae tendinae move in synchrony with the intraventricular valves. ICEF are most commonly seen in the left ventricle and occasionally in the right ventricle or bilaterally. Intra-atrial or diffuse ICEF are rare. The presence of ICEF in fetuses represents a high risk for chromosomal abnormalities, particularly with trisomy 21. The significance of ICEF in fetuses at low risk for aneuploidy is less clear and represents an area for future research [24]. Of course in this study, it is papillary muscle microcalcification, not atrial, ventricular or septal muscle calcification that was emphasized. Generally speaking, the association between cytogenetic abnormality and myocardial calcification is still not clear and not confirmed [26].

Maternal Illicit Drug Use

Cocaine use is associated with myocardial ischemia and infarction [27]. Maternal cocaine use has also been implicated as a possible cause of fetal myocardial damage and subsequent calcification [28].

The mother of this infant denied history of cocaine use. However, high Delta-9-Tetrahydrocannabinol (THC) use was confirmed on the mother. THC is the primary psychoactive ingredient in marijuana. With the legalization of recreational marijuana in many states, it can be anticipated that more women will be using marijuana in pregnancy. Marijuana is probably the most common illicit drug used in pregnancy, with a prevalence of use ranging from 3% to 30% [29]. Marijuana freely crosses the placenta and even though at much lower level relative to the serum level, THC has been demonstrated that it can cross the placenta and cannabinoid receptors are also found to be expressed in the fetal brain, which provides a biologic rationale for potential fetal effects of maternal use [30]. While marijuana exposure alone was not associated with significant perinatal adverse outcomes, co-use with cigarette smoking could cause significant pregnant complications [30]. And while using THC, it has potential high risk to use other drugs, or smoking, or drinking alcohol. It may have adverse effects on both perinatal outcomes and fetal neurodevelopment, particularly on fetal growth restriction, stillbirth, and preterm birth [29]. Based on these knowledge, the mother in our case was a THC user and the effect on the infant's death could be to some degree direct or indirect by THC and/or other co-used illicit drugs.

Familial Fetal Cardiomyopathy

Haug et al, described three male sib fetuses with isolated myocardial calcifications resulting in Intrauterine Fetal Death (IUFD) as early as the second trimester. No evidence for an underlying mitochondrial cytopathy, dystrophinopathy or myopathy was found. There were no signs of inflammation or a metabolic disorder, and the mother had no prenatal exposure of teratogenic drugs. Furthermore, no mutation in the Barth syndrome gene (G4.5) could be detected. Because this isolated calcification of the heart and IUFD are not typical of any previously described inherited cardiomyopathy, it may represent a new familial fetal cardiomyopathy [31].

Differential Diagnoses

Idiopathic Infantile Arterial Calcinosis (IIAC)

IIAC is a rare disease of unknown etiology, which is characterized by arterial calcification. An ultra-sonographic examination can show diffuse arterial calcifications involving the aorta, pulmonary artery, common iliac arteries, renal arteries, and common carotid arteries

[32]. It is important to note that not all calcified areas within the heart are myocardial.

IIAC is an example of calcification that occurs primarily in the vasculature rather than the myocardium.

Generalized Arterial Calcification of Infancy (GACI)

GACI should be considered in the differential diagnosis in infants presenting with arterial calcifications and congenital anomalies of the gastrointestinal tract. It is a rare genetic disorder consisting of diffuse arterial calcification and intimal proliferation. GACI is associated with mutations in ENPP1 in the majority of the cases. The disease typically results in progressive arterial stenosis and frequently leads to death from myocardial ischemia by 6 months of life. Affected infants are usually diagnosed before birth or in the neonatal period with symptoms of congestive heart failure. Therapy with bisphosphonate has been used to treat the condition, but with inconsistent results [33].

Fetal cardiac tumors

Dystrophic calcification of the myocardium may much closely mimic the ultrasound appearances of cardiac tumors but may have very different implications for fetal outcome. Rhabdomyoma is the most common type of neonatal cardiac tumor. Approximately 40% of rhabdomyomas present in fetal life are associated with tuberous sclerosis [34]. This should be considered when counselling parents after detection of masses in the fetal heart, particularly when considering the risk of associated tuberous sclerosis. Except rhabdomyoma, the other cardiac tumors which may appear echogenic or calcified include fibromas and pericardial teratomas [15]. In a recent case report, the fetal echocardiography of a 26-year-old pregnant woman at 20 weeks' gestation revealed an echogenic mass in the post wall of the left ventricle. The pregnancy was terminated. The histopathology of the necropsy material revealed dystrophic calcification. Therefore, the dystrophic calcification of myocardium must be kept in mind in prenatal differential diagnosis of intracardiac masses for patient management and genetic counseling [2].

Conclusion

The present article aims to report our recent case of fetal myocardial calcification as an unusual pathological finding and to review literature with special emphasis on potential causes, which includes fetal myocardial infarction, autoimmune inflammation and viral infections, maternal drug use, and/or chromosomal abnormalities, etc. Even though currently most cases with fetal myocardial calcification are ultimately fatal, however, the cause analysis for the purpose of feasible prevention and even early stage of diagnosis and management may significantly contribute to the best prognosis in the corresponding clinical arenas [35].

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