J. Fetal Med. (December 2022) 9:101–104
https://doi.org/10.1007/s40556-022-00351-9

CASE REPORTS

Fetal Endocardial Valvular and Supravalvular Calcification as a Manifestation of Anti-Ro/SSA-La/SSB Antibody Mediated Cardiac Phenotype

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Received: 11 February 2022 / Accepted: 13 July 2022 / Published online: 22 August 2022

Abstract Neonatal Lupus syndrome is caused by the placental transfer of maternal autoantibodies to the fetus. Maternal anti-SSA/Ro-SSB/La antibodies may result in congenital heart block in 1–2% of exposed fetuses. However, fetal valvular calcification is rarely reported. We report a 20 weeks fetus with multiple intracardiac calcifications, valvular calcification in the pulmonary valve and supravalvular calcification at the origin of the main pulmonary artery along with calcification in the chordae of mitral and tricuspid valve in a structurally normal heart. The mother was asymptomatic but strongly positive for anti-SSA/Ro-SSB/La antibodies. Fetal cardiac valvular calcification is an uncommon phenotype of neonatal lupus syndrome. It is important to suspect, recognize and screen for maternal autoimmune disorders even in the absence of congenital heart block.

Keywords Prenatal diagnosis · Fetal calcification · Fetal echocardiography · Neonatal lupus · Anti-Ro and anti-La antibodies

Introduction

Neonatal lupus (NL) consequent to exposure to maternal anti-SSA/Ro-SSB/La autoantibodies affects 1–2% of offspring exposed in utero with considerable morbidity and mortality [1]. The hallmark of cardiac NL is Atrio-Ventricular node fibrosis resulting in congenital heart block [2, 3]. We report a fetus at 20 weeks gestation with multiple valvular chordae calcifications in the presence of normal cardiac structure, rhythm and function in an asymptomatic mother diagnosed to have autoimmune antibodies after the identification of the fetal abnormality.

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Materials and Methods

Patient Report

A 27 year primigravida with non-consanguineous marriage presented at 20 weeks gestation with ultrasound findings of multiple fetal intracardiac calcifications. This was a spontaneous conception with no history of fever, rash, fatigue, oral ulcers, dryness of the mouth or eyes, photosensitivity or joint pains. There was no history of flu like illness, diabetes, maternal phenylketonuria, drug intake, alcohol or substance abuse during pregnancy. There was no history of sudden death or unexplained mortality in the family. The first trimester ultrasound scan was normal with nuchal translucency of 1.4 mm at a CRL of 68.3 mm. The combined first trimester screen was low risk. The mid-trimester anomaly scan showed multiple intracardiac calcifications. There was no other fetal anomaly noted including flat facies, short tubular bones, growth restriction or soft markers. Amniotic fluid volume was normal. Fetal echocardiography revealed multiple fetal intracardiac calcifications, calcification at the level of pulmonary valve annulus, leaflets and origin of the main pulmonary artery (supravalvular) along with calcification in chordae of mitral and tricuspid valve (Fig. 1).

There was no structural cardiac malformation or significant hemodynamic changes (including absence of any

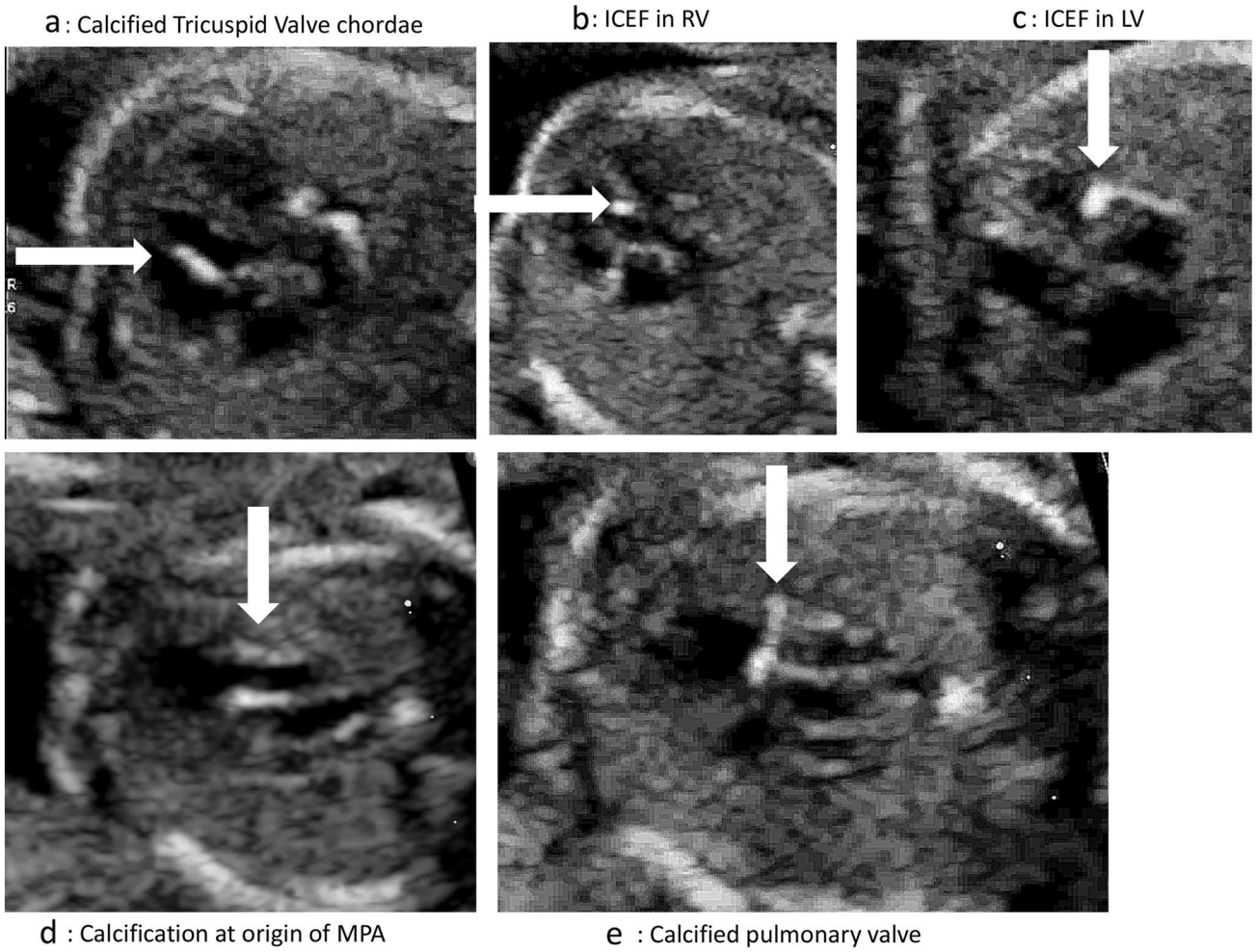

Fig. 1 Fetal Echocardiogram at 20 weeks showing calcified tricuspid valve chordae (**a**); ICEF in RV (**b**) and LV (**c**); calcification at the origin of MPA (**d**) and pulmonary valve (**e**). *ICEF* intracardiac echogenic focus, *RV* right ventricle, *MPA* main pulmonary artery, *LV* left ventricle

valvular regurgitation/stenosis) and the fetal heart rate was 150/min with a normal sinus rhythm and normal mechanical PR interval of 112 ms. The AV node was intact. In view of these findings, the mother was evaluated for infections, autoimmune disorders and fetal chromosomal abnormalities. IgM was negative for TORCH antigens and IgG was positive for Rubella and Cytomegalovirus. Extractable nuclear antigen (ENA) profile by semi-quantitative line immunoassay showed Anti SS-A+++, Ro52+++, SS-B+, PM-Scl 100+, RNP/Sm:++, Sm+. These reports suggested an asymptomatic state for these autoimmune markers with a need for careful monitoring of the fetus in view of the potential for developing a fetal congenital heart block (CHB) in around 1–2% of pregnancies, endocardial fibroelastosis (EFE) or rarely valvular insufficiency [1, 4]. After extensive counseling about the disorder and outcomes, the parents opted to discontinue the pregnancy.

Results

The fetus was examined. Fetogram showed a dense speck of calcification over the cardiac region. The fetus weighed 501 g with no apparent facial dysmorphism or external anomalies. Internal examination showed a grossly normal heart weighing 2.9 g corresponding to 20–21 weeks gestation. The four chambers of the heart appeared normal in size and shape and the major vessels were normally placed. No gross visible calcifications were seen on the external surface. Sections of the heart on microscopic examination showed calcification in both mitral and tricuspid valves. The rest of the internal examination was normal and no calcifications were present in the liver, kidney or lungs. There was no evidence of inflammation or fibrosis on histopathological examination of fetal organs and placenta. Chromosomal microarray was normal.

Discussion

We describe a low risk patient with antenatally identified cardiac valvular calcification in the 20 weeks scan, confirmed by fetal histopathology and associated maternal autoimmune antibodies where the mother was asymptomatic. The finding of cardiac valvular, supravalvular and chordae tendinae calcification was unusual in the fetus as the predominant presentation of maternal Anti-Ro and Anti-La antibodies related neonatal lupus (NL) syndrome. This is characterized by congenital heart block in fetal life in 2% of fetuses of antibody positive mothers [3]. The risk of anti-Ro- and anti-La antibody-related fetal heart block increases to 15% in pregnancies with a previously affected fetus or neonate [1, 5].

Fetal cardiac calcification is a rare ultrasound finding, seen as diffuse hyperechogenicities affecting primarily the myocardium in a diffuse or patchy manner. The calcifications may also involve the epicardium or visceral pericardium. Dystrophic deposition of calcium is a non-specific reflection of severe myocardial injury in areas of necrosis, bleeding or fibrosis [6]. Multiple causes of fetal cardiac calcification were evaluated and excluded in this patient (Table 1). Calcifications can also be a consequence of thromboembolic events due to Factor V Leiden homozygosity or protein S deficiency and these were normal in this case. In addition, idiopathic infantile arterial calcinosis, generalised arterial calcification of infancy and fetal cardiac tumors can also cause fetal calcifications and were excluded on histopathologic examination in the fetus [6–8]. Finally, inflammation based calcification may be seen in maternal autoimmune diseases like SLE, scleroderma and rheumatoid arthritis and though asymptomatic, the lady was positive on screening.

Maternal anti-Ro and anti-La antibodies are rarely reported to be associated with valvular and chordae calcification with involvement of the pulmonary artery as seen in the current case. Fetal exposure to autoimmune maternal antibodies is the most common cause of isolated congenital complete heart block (CCHB) in a structurally normal heart [9, 10]. In a series of 85 patients with positive anti-SSA/Ro and/or anti-La/SSB antibodies and CHB, the Italian registry recorded 89 cases with CHB and a live birth rate of 80%. In addition dilated cardiomyopathy, impaired left ventricular function, endocardial fibroelastosis, hydrops and isolated pleural and pericardial effusion were the associated morbidities. No valvular involvement was noted in this series [1]. In an autopsy series of 18 cardiac NL cases, the predominant finding was heart block along with atrioventricular node, sinoatrial node and bundle of His calcification, endocardial fibroelastosis (EFE), papillary muscle fibrosis,

Table 1 Causes of fetal cardiac calcification

Mechanism	Common causes	Associated features
Intrauterine infections	Rubella	It may be associated with cardiac malformations
	Varicella	IUGR, limb anomalies, multiple intracerebral, intrahepatic calcifications, ventriculomegaly
	CMV	
	HSV 2	Periventricular calcifications, cardiomyopathy
	Adenovirus	In-utero or peripartum
	Others: toxoplasma, coxsackie A and B, Echovirus, Enterovirus, Parvovirus B19	Hydrops fetalis, aortic stenosis, pulmonary stenosis
Chromosome abnormality	Trisomy 21	Papillary muscle calcification
	Trisomy 13	Malformations
	Trisomy 18	Intracardiac echogenic foci
	Monosomy X	
Inflammation based calcification	SLE, scleroderma, rheumatoid arthritis	Fetus can be affected even if mother has no overt clinical symptoms
	Anti Ro/SSA, anti La/SSB	
Hypercalcemia	Maternal Hyperparathyroidism	Maternal nephrocalcinosis and calcifications, Neonatal hypocalcemia
Thrombo-embolism	Factor V leiden homozygosity	Calcifications at multiple sites
	Protein S deficiency	
Myocardial infarction	Coronary artery occlusion	May be associated with structural heart disease or coronary artery abnormalities
	Glycogen storage disorder	
Maternal drug abuse	Cocaine	May be associated with alcohol/smoking
Familial fetal cardiomyopathy		Single case report with three male sibs affected
Arterial calcification and tumors	Idiopathic infantile arterial calcinosis	Involves Aorta, renal, pulmonary, common iliac, carotid artery
	Generalized arterial calcification of infancy	Mutations in ENPP1 gene, progressive arterial stenosis, fatal by 6 months; may be treated with bisphosphonates
	Fetal cardiac tumors	Rhabdomyomas (Tuberous sclerosis)
		Fibroma
		Pericardial teratoma

valvular disease, calcification of the atrial septum and mononuclear pancarditis. The valvular involvement included stenosis, insufficiency and hypoplasia of the cusp leaflets, but calcification of the valves is not reported. They also noted valvular findings in the third trimester and in some patients only at autopsy [3]. This is unlike our case where there was isolated calcification of the valves identified antenatally and confirmed on autopsy. Discordance between echocardiographic and pathological findings at the SA node, AV node and endomyocardium have been noted before and we also observed the same in the present case [3]. Valvular disease due to dysfunction of tensor apparatus is a rare severe complication of autoimmune CHB [11]. Areas of patchy echogenicity in the papillary muscle are detected at 19–22 weeks and affect the mitral and tricuspid valves. Severe valve insufficiency has been reported to develop prenatally or postnatally, requiring valve surgery [4, 12].

It is important to suspect and recognize treatable maternal autoimmune disorders and screen for the antibodies even in the absence of CHB. Early diagnosis is vital for appropriate medical management and follow up. The consequences may range from fetal arrhythmias especially bradycardia, first degree heart block, congenital complete heart block (CCHB), endocardial fibroelastosis (EFE), hydrops fetalis, intrauterine fetal demise to severe organ dysfunction and developmental delay in the surviving neonate. A definitive etiological diagnosis is important for appropriate management and counseling for future pregnancies.

In conclusion, we report an uncommon phenotype of maternal Anti-Ro and Anti-La antibodies in the fetus presenting with valvular calcification. We also show that fetal cardiac calcification is an uncommon presentation and assert that alongwith infections, chromosomal disorders, thrombosis and other rarer causes, treatable maternal connective tissue disease should be considered in the differentials of fetal cardiac calcification. A definitive etiological diagnosis is important for appropriate management, follow up and counselling for future pregnancies. The risk of anti-Ro- and anti-La antibody-related fetal heart block increases to 12–19% in pregnancies with a previously affected fetus or neonate [1].

Acknowledgements We are grateful to the parents for the kind permission to use ultrasound images for this publication.

Author Contributions All authors contributed to the study conception and design. SB drafted the article and performed the literature review. RDP drafted the article, contributed to patient management and reviewed the final draft. NA contributed to echocardiography studies and literature review. AV contributed to imaging studies and literature review. All authors read and approved the final manuscript.

Funding Nil.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Consent Parents signed written informed consent regarding publishing the data and images.

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