Case **report**

FETAL MACROSOMIA, POLYHYDRAMNIOS AND CARDIAC ANOMALIES MAY BE HELPFUL TO PREDICT POOR OUTCOME IN NEONATE – CASE REPORT OF A POSSIBLE FETAL RASOPATHY WITH SONOGRAPHIC AND NEONATAL FINDINGS AND GENETIC EVALUATION.

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Prenat Cardio 2017 Jan; 7(1):73-82
DOI: 10.1515/pcard-2017-0011

Abstract

This is a case report about very rare findings in 2nd half of pregnancy (after normal 1 trimester scan) at 18th week of gestation fetal macrosomia was detected unrelated to maternal diabetes, and acceleration fetal growth later on with unusual cardiac abnormalities (fetal cardiomegaly, cardiomyopathy, partial abnormal venous connection). Progressive features of congestive heart failure with polyhydramnios in a fetus with estimated 5500 g predicted a poor outcome and severe neonatal condition, which was presented and discussed with the parents to be. Casearean section was performed at 33rd weeks of gestation due to maternal dyscomfort, severe legs edema and her tachypnoe. Baby boy was delivered with birth weight of 5050g, Apgar 4 with mutiple tumors. Conservative care was introduced and neonated died on the 3rd day. Differential diagnosis was discussed with special attention to Costello syndrome however without proved by genetic make-up from neonatal blood.

Key words: *Costello -like-Syndrome, fetal heart cardiomegaly, superior vena cava dilatation, partial abnormal venous connection, neonatal tumors*

INTRODUCTION

Fetal macrosomia, polyhydramnios and overgrowth with prenatal cardiac abnormalities usually suggest maternal hyperglycemia. However in case of fetal weight exceeding 5000g at 32 weeks of gestation a rare genetic syndrome should be taken into consideration and multispecialist team at the referral center might be helpful in making diagnosis and prognosis for the family.

How to cite this article:
Respondek-Liberska M, Węgrzynowski J, Oszukowski P, Gulczyńska E, Nykiel E, Jakubowski L, Grzesiak M, Czichos E, Romanowicz H. Fetal macrosomia, polyhydramnios and cardiac anomalies may be helpful to predict poor outcome in neonate – case report of a possible fetal RASopathy with sonographic and neonatal findings and genetic evaluation. Prenat Cardio 2017 Jan; 7(1):73-82

CASE REPORT

It was the first pregnancy of a 39 years old woman, who had a normal first trimester scan and nuchal translucency (NT) at 13 wk of gestation of 1,7 mm. At the 18th week of gestation, fetal macrosomia was detected and, after excluding maternal diabetes and thyroid disease, the pregnant woman was referred to our tertiary center for further evaluation. At the 28th week of gestation fetal biometry was consistent with the 35th week of gestation and suggested fetal weight based on basic parameters such as biparietal diameter, head circumference, abdominal circumference and femur length (BPD, HC, Ac and FL) was 3666 +/-535g and the subcutaneous tissue at the femur level was 6 mm thick (Fig. 1, 2, 3). In 3D ultrasound fetal face seemed relatively mature without evidence of dysmorphic features, however probably with a deep and broad nasal bridge (Fig. 4).

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Submitted: 2017-03-16; accepted: 2017-06-25

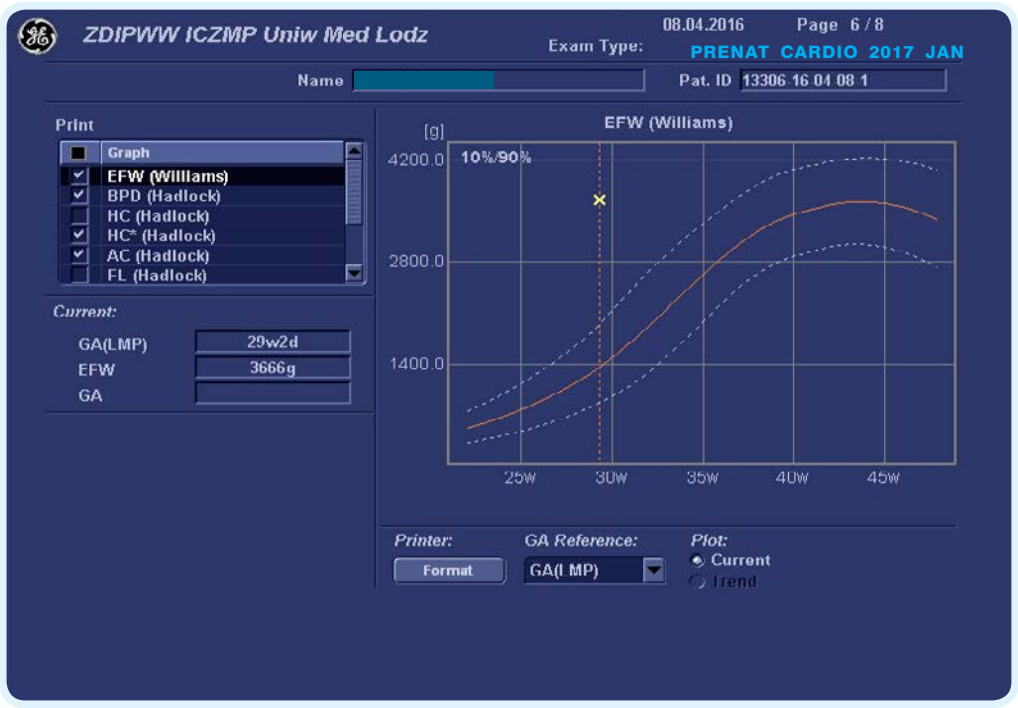

Fig. 1. Fetal biometry

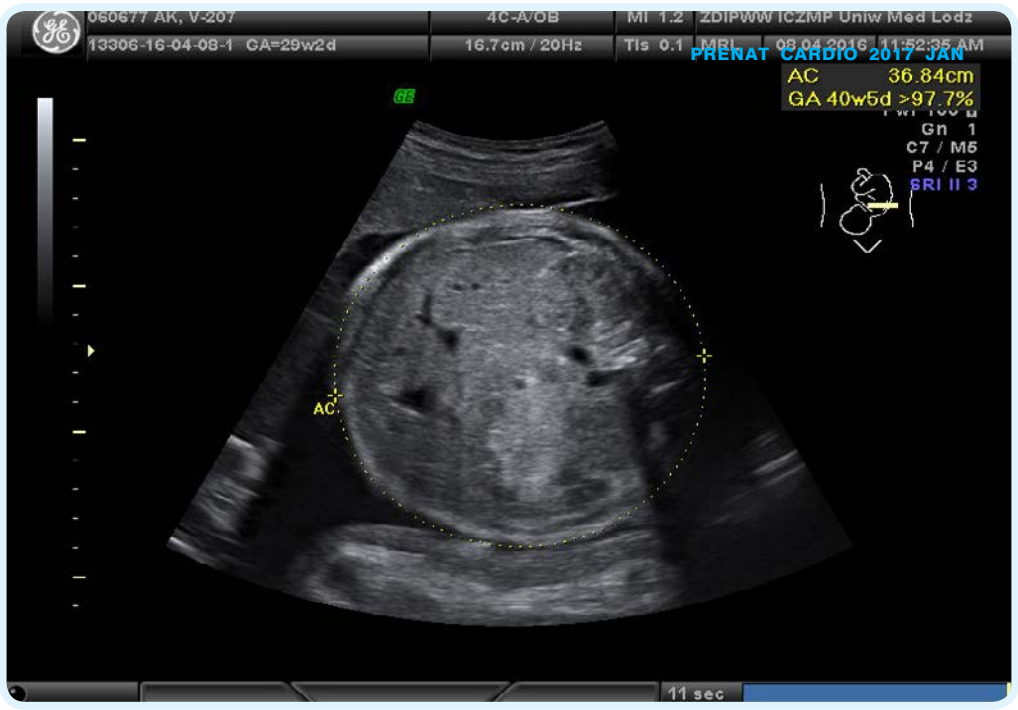

Fig. 2. Fetal abdomen

Fetal echocardiography showed a normal fetal heart anatomy (Fig. 5, 6), however the cardiac axis was 90 degrees, (possibly due to hepatomegaly) and there was mild cardiomegaly with heart area/chest area ratio (HA/CA) was 0,4, but the heart diameter at the level of mitral and tricuspid valves was 48 mm. There was significant dilatation of superior vena cava up to 7,8 mm and pulmonary outflow tract at the level of the mediastinum was 12 mm.

The shortening fractions of LV and RV based on M-mode were 32% and 28%, respectively. The Tei index for the LV 0,45 and for the RV was 0,5.

Due to polyhydramnios (AFI =30 cm) the patient was referred for amnioreduction as an in-patient.

The next ultrasonography and echocardiography exam in our center was performed 4 weeks later as an out-patient again. At that time there was maternal right leg edema due to thrombosis of her popliteal vein. The fetal biometry suggested an estimated fetal weight of approximately 6000 g, polyhydramnios (AFI= 40cm), increasing ascites, increased fetal kidney size (57 mm long), (Fig. 7, 8). There was also polydactyly of the right hand (Fig. 12).

Fetal echocardiography showed cardiomegaly, with a heart diameter at the level of mitral and tricuspid valve of 55 mm, disproportion at the atrial level (RA > LA), disproportion at the ventricular level (RV > LV) and again there was an abnormal mediastinal view with dilatation of the SVC up to 9, 6 mm . Prenatal findings suggested significant macrosomia, fetal / myocardial hypertrophy consistent with neonatal congestive heart failure and a severe neonatal condition after delivery with a poor prognosis for survival.

Due to increasing maternal discomfort with dyspnea and leg oedema 4 days later , at 33 weeks of gestation, an elective cesarean section was performed and a baby boy was delivered with a birth weight of 5050 g and Apgar score of 4. There was an unusual appearance of the fetal face,

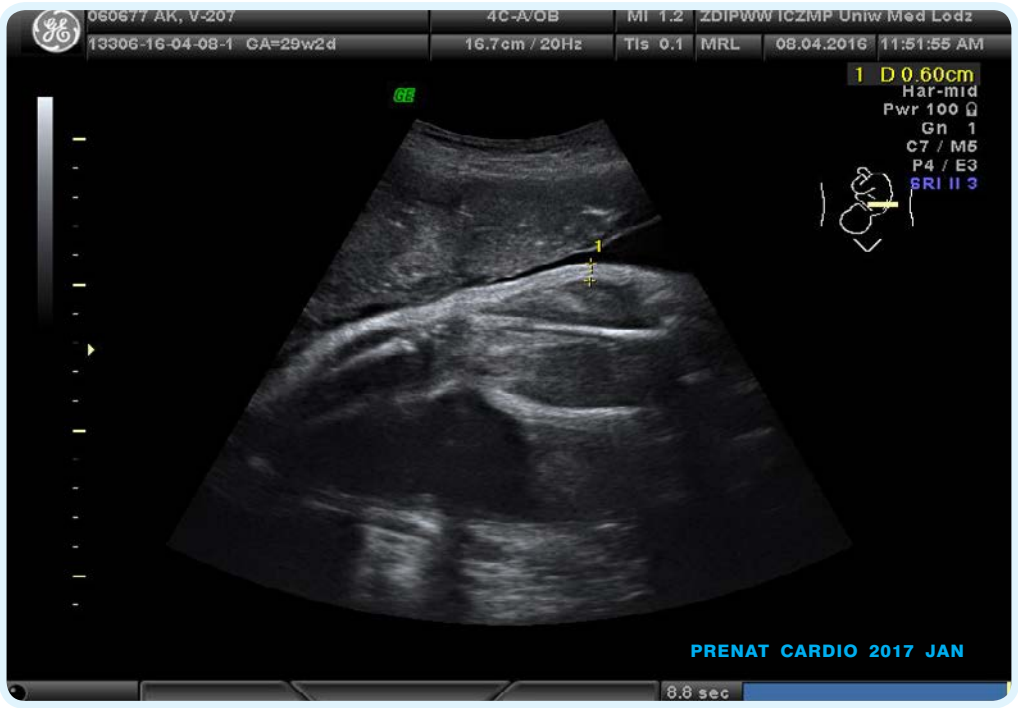

Fig. 3. The 2D ultrasound scan of the fetal thigh which looks enlarged and bulky. Subcutanoues tissue was 6 mm

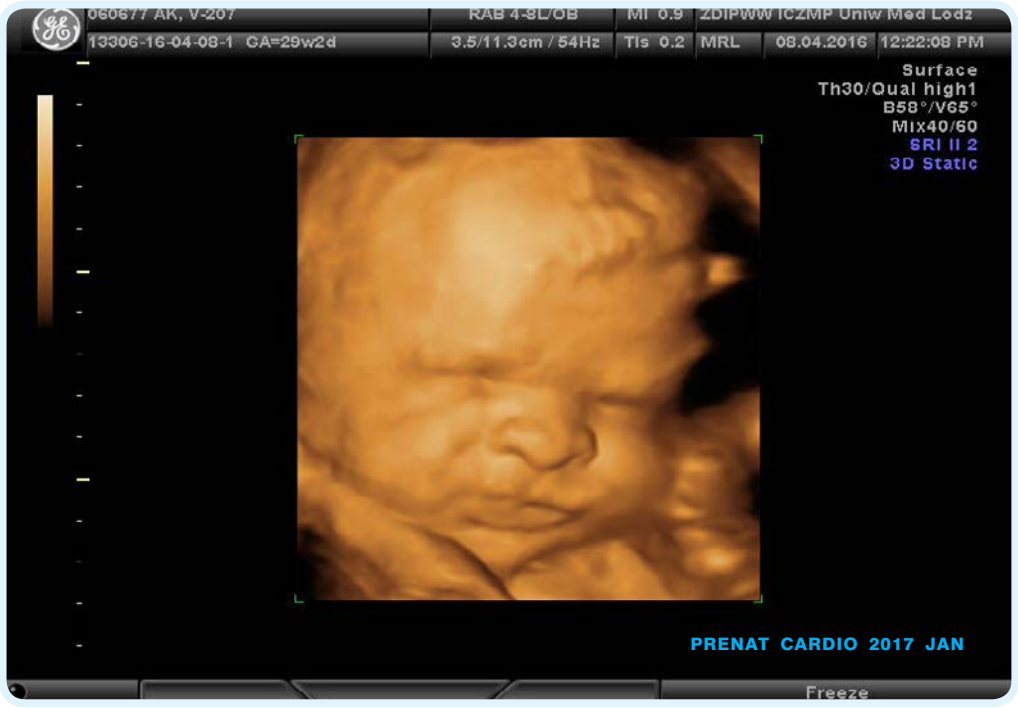

Fig. 4. Fetal face in 3D at first evaluation in our tertiary center

and a superficialfacial haemangioma. He had also several deep skin tumors and polydactyly (Fig. 12) a protuberant abdomen, and abnormally thick skin. There was maternal and medical consensus for conservative management and not to treat the congestive heart failure. On the 3rd day of postnatal life there was a neonatal demise. The autopsy revealed at 6 cm capillary angio tumor below the liver, 3 cm capillary vascular tumor of the right thigh, partial anomalous venous connection (right pulmonary veins to the superior vena cava and left pulmonary veins to the left atrium).

Taking into consideration the possibility of Costello syndrome, a genetic evaluation was performed in our institute. DNA was extracted from whole peripheral blood using the MagCore Genomic DNA Whole Blood Kit (RBC Bioscience), with informed consent of the child's mother. Amplification of the coding exons and flanking intronic sequences of the *HRAS* gene was performed using the primer pairs designed based on the reference genomic sequence NM_005343 GRCh38/hg38 (Table 1).

Exon		Primer Sequence
Exon 2	- Forward	5'-GCTGCACAGGTAGGCACG-3'
	- Reverse	5'-CTCCTGGGGTGCTGAGAC-3'
Exon 3	- Forward	5'-GAGTCCCTCGTCTCAGCAC-3'
	- Reverse	5'-GCAGAGAGGACAGGAGGC-3'
Exon 4	- Forward	5'-TGCCATCAACAACACCAAGT-3'
	- Reverse	5'-CTGTGTCAAGGGAGAGGGTC-3'
Exon 5	- Forward	5'-GGAAGTGGCTGGTGGAGTC-3'
	- Reverse	5'-CACCTCCATGTCCTGAGCT-3'

Table 1.Primers used for sequencing coding regions of HRAS:

PCR contained 50 ng of genomic DNA as template, 10 pmol of each primer (2,5 µl), 200 µM of dNTPs (0,5 µl), and 0,2 µl FastStart Taq DNA polymerase (Roche) in 10x PCR buffer contains 20 mM $MgCl_2$ (2,5 µl). PCR was carried out with initial enzyme activation at 95°C for 4 minutes, followed by 30 cycles of denaturation at 95°C for 30 seconds, annealing at 55°C for exon 2, 56°C for exons 3 and 4, 53°C for exon 5 for 1 minute and extension at 72°C for 45 seconds, with a final extension at 72°C for 7 minutes. The quality and quantity of PCR products were checked by 2% agarose gel electrophoresis.

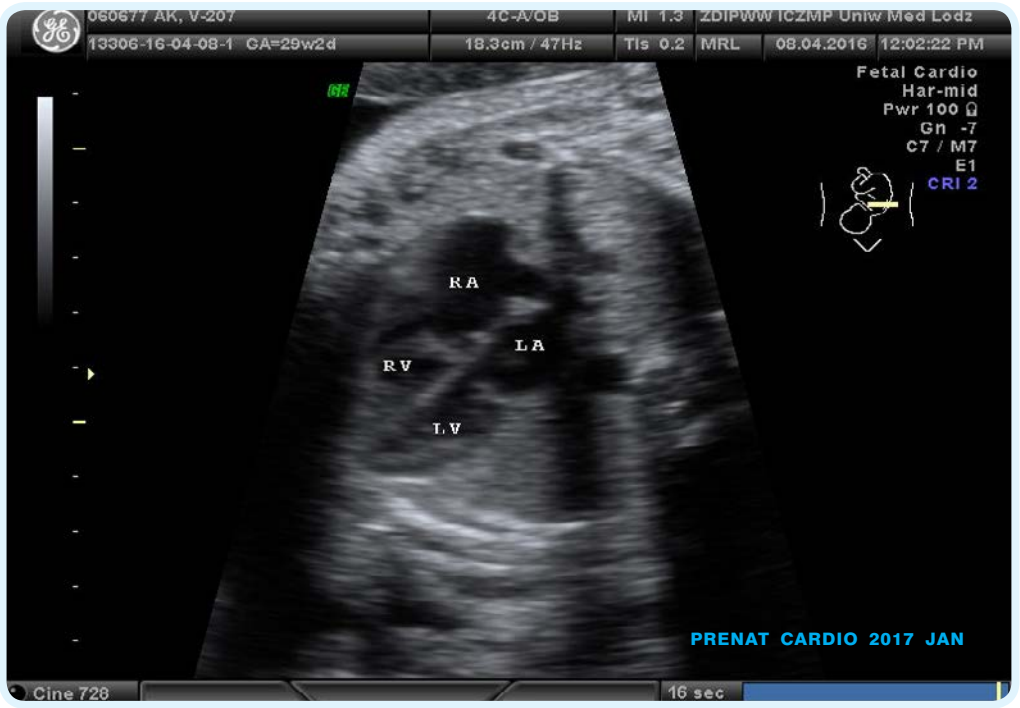

Fig. 5. Fetal heart 4 chamber view at the first fetal echocardiography in our center

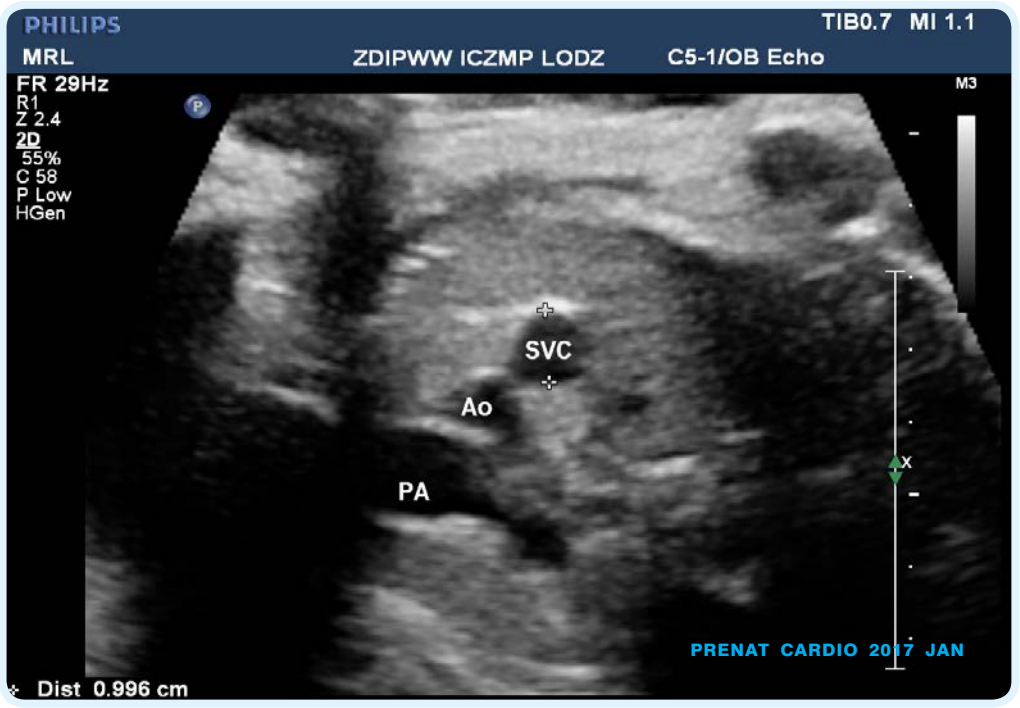

Fig. 6. Fetal mediastinum with dilatation of SVC and Right ventricular outflow tract

PCR products were used for sequencing reaction by BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems). Sequencing products were analysed by capillary electrophoresis on an ABI 3500 Genetic Analyzer (Applied Biosystems). The alignment to reference sequence was performed using Mutation Surveyor 5.0.1 software. No pathogenic mutations were detected in the analyzed gene.

DISCUSSION:

In the case of prenatal ultrasound findings such as increased nuchal translucency[1] and polyhydramnios, macrosomia, and cardiovascular abnormalities a group of developmental disordersdue to defects in the Ras/Mitogen-Activated Protein Kinase (RAS/MAPK) signaling pathway named RASophaties should be considered in the differential diagnosis, including Costello syndrome, Noonan syndrome, and Cranio-Facio – Cutaneous Syndrome[2]. All the RASopathies share similar clinical features; their molecular characterization is complex, time consuming and expensive[3].

Based on the clinical findings , other diagnoses were also taken into consideration, such as Leopard Syndrome, Beckwith –Wiedemann Syndrome, Perlman Syndrome and Simpson-Golabi-Behmel Syndrome (Table 2). The difficulties are related to overlaping symptoms and sonographic findings. The clinical features described for these syndromes in Omim and in Pub-Med are usually related to postnatal findings in infancy or later. Therefore the presented case recognized from prenatal life provides important data, although the final genetic diagnosis was not clear..

Based on the clinical findings, the most likely diagnosis in our case may be Costello Syndrome (Table 3)

In 1977, Costello [4] described 2 unrelated children with a syndrome comprising short stature, redundant skin of the neck, palms, soles, and fingers, curly hair, papillomata around the mouth and nares, and mental retardation. The genetic background of Costello Syndrome was established in 2005 by Aoki and coworkers It is a heterozygous mutation in the HRAS gene on chromosome 11p15. A variant of Costello syndrome, congenital myopathy with excess of muscle spindles, is also caused by a mutation in HRAS. Since 1977 several cases have been reported diagnosed both in children and adults , however very few have been described based on prenatal findings.

Costello syndrome, according to the OMIM definition, is a rare multiple congenital anomaly syndrome associated in all cases with a characteristic coarse facies, short stature, distinctive hand posture and appearance, severe feeding difficulty, and failure to thrive. Other features include cardiac anomalies (hypertrophic cardiomyopathy with arrhythmias) and developmental disability. Facial warts, particularly nasolabial, are often present in childhood. Complications include failure to thrive, and benign and malignant tumors. While the postnatal presentation of this group of disorders is well known (with 590 reports in Pub Med), the prenatal findings are less widely recognized (with less than 10 reports in Pub Med to the present day)[6-12].

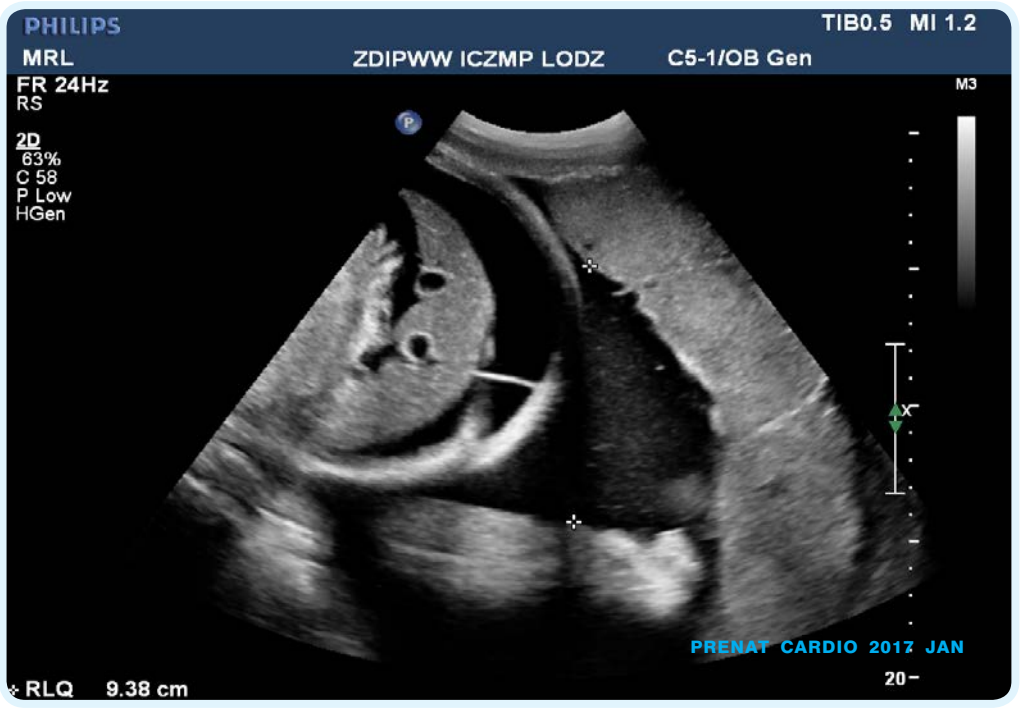

Fig. 7. Fetal ascites at 30 week of gestation and polyhydramnion

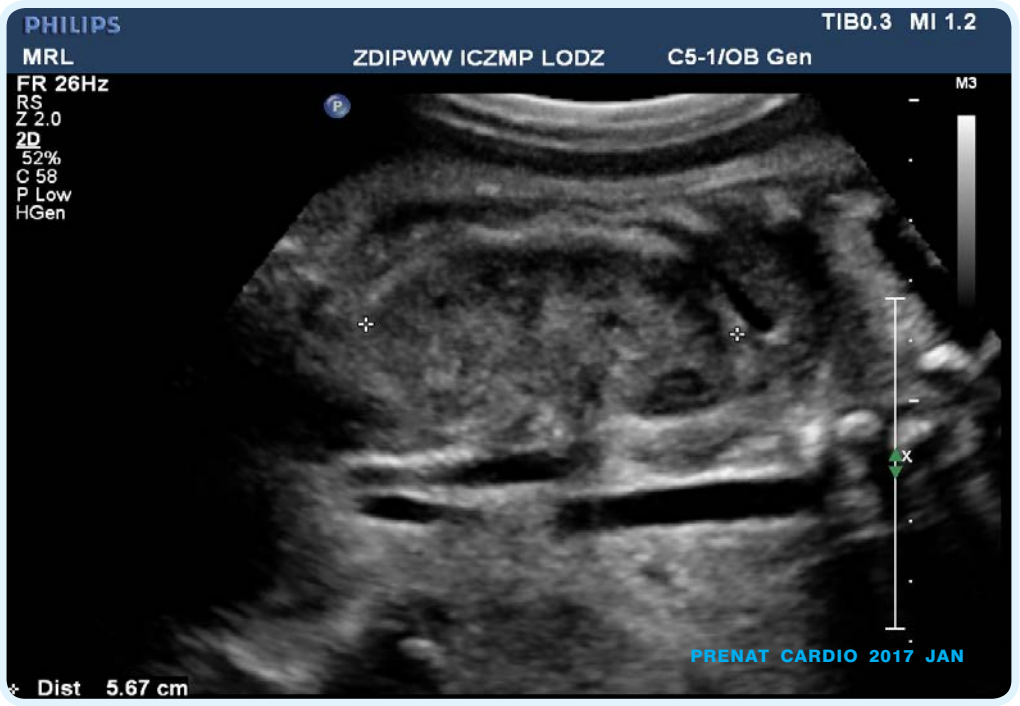

Fig. 8. Fetal large kidney, 56 mm lenght, suggesting visceromegaly

Prenatal diagnosis of Costello Syndrome was first reported less than 10 years ago, in 2008 by Kuniba (case report) [6], in 2009 by Lin and coworkers (3 cases) [7] , and in 2016 by Uemura [8] (Table 2).

The main reason for referral in the presented case was fetal cardiomegaly and myocardial hypertrophy at the 24th week of gestation (after a normal 1st trimester scan in a high risk pregnancy due to advanced maternal age) detected by an obstetrician trained in fetal echocardiography. During a subsequent targeted examination in our tertiary unit, in addition to cardiomegaly and myocardial hypertrophy, the dilatation of superior

Fig. 9. Neonate in the 1st day after birth (photo thanks to maternal agreement)

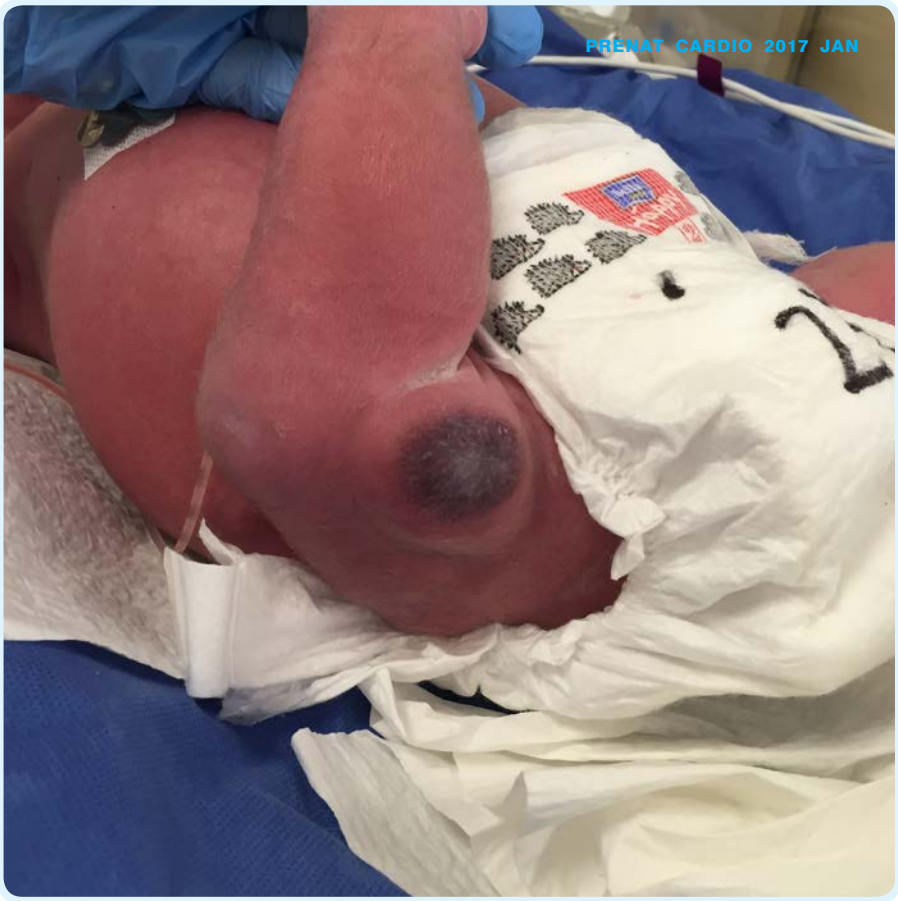

Fig. 10. Neonatal skin tumor in the right leg

vena cava was present suggesting partial anomalous pulmonary venous connection [13] later confirmed by autopsy.

The importance of fetal echocardiography in fetuses with extracardiac anomalies has been demonstrated many times[14,15] and associated with different malformations[16-19].

Further important sonographic features were acceleration in fetal growth up 5000 g at 32 week of gestation, the rapid progression of ascites and of polyhydramios, which all caused maternal dyspnea and leg edema, leading to elective cesarean section. This observation exemplifies our previous study and recommendations concerning the important role of the fetal echocardiographic study in the third trimester[20,21]. Also multiple huge tumors (capillary haemangiomas) both in the skin and abdomen are important and important to report as they are very rarely seen in newborns.

Skin and tumor manifestations in neonates are rare and also have been reported in Costello Syndrome as rhabdomyosarcoma [22,23]

Smith and coworkers [24] compiled from parent surveys that the most common prenatal findings in the literature in this cohort were polyhydramnios and fetal overgrowth with relative macrocephaly. Lurie (1994) [25] They also found a significant increase of mean paternal age (38.0 years); in our case, the paternal age was 40 years.

Other diagnoses included also Noonan Syndrome (often with an increased NT in the 1st trimester), Sotos syndrome, mucopolysaccharidoses and brain abnormalities (Gripp) [26] .

Generation Prenatal Diagnosis (NGPD), a new targeted approach that allows to concurrently investigate all the genes involved in the RASopathies were not available for us. Their molecular characterization is complex, time consuming and expensive.

Fig. 11. Postaxial polydactyly

The lack of confirmation of a mutation in HRAS gene does not exclude disorders in the whole RAS gene family (mostly protooncogens). The phenotype of the fetus was most suggestive of Costello Syndrome, but, the most common syndrome in this family of disorders is Noonan Syndrome, usually with an increased NT in the first trimester., In RAS/MAPK signaling pathways an important role is also played by gene NF. This gene acts like a suppressor gene and it can also influence many other genes in the chain KRAS/MAPK, so it can trigger a wide phenotypic variety.

Despite that in our referral center the final diagnosis was not established , we considered it important to report this case in order to add information to the medical literature from the natural history study as suggested by Lin[27].

	Costello S	Neuro-cardio-facial-cutaneous syndromes	Leopard S	Beckwith-Wiedeman	Perlman S	Simpson-Golabi-Behmel
Overgrowth	Yes		Growth retardation	Yes Visceromegaly	Yes Nephromegaly Nephroblastomosis	Yes
Ascites	Yes				Yes	
Heart – tachycardia	Yes					
Structural heart defect	Yes	PS, ASD	Yes			Yes
Hypertrophic cardiomyopathy	Yes	Yes	Yes	Yes		
Large gestational age	Yes		No	Yes		
Tumors: **Papillomas** **Rhabdomyosarcoma**	 Yes No	"Ichtyosis – like condition"	"Multiple lentigines"	Exomphalos Umbilical hernia Wilms tumor Hepatoblastoma Adrenal carcinoma	Wilms tumor	Vascular malformations
Facial appearance	Yes	Yes		Macroglossia	Yes	"Coarse"
Polidactyly	Yes					Yes

Table 2: Differential diagnosis based on prenatal ultrasound and echocardiographic findings in case of fetal overgrowth, ascites, polyhydramnios and fetal cardiac abnormalities

	Kuniba (Nagasaki)	Lin Case 1	Lin Case 2	Lin Case 3	Uemura Osaka case	This case:?
Year of publication	2008	2009	2009	2009	2016	2017
Maternal/ paternal age (years)	31	29-/ 40	33/31	39 / 41		39 / 40
1st trimester (12/13 wks)	?	?	An increased risk for Down syndrome (1:237)	Thickened nuchal fold,	NT increased, Small Nasal Bone, Low set ears,TR, DV reversal flow	NT 1, 2
2nd trimester	23rd 1300g	28th		SVT at 24 weeks treated successfully with maternal digoxin and sotalol.		Cardiomegaly + HKMP
Polyhydramnios	Yes	Yes	AFI 52	Yes	Yes	Yes
Amniodrenage			yes		Yes	Yes
Overgrowth	Yes			Hepatomegaly, macroglossia Shortended limbs		18/22 28/35
Macrocephaly	Yes	Yes				+
Cardiomegaly						+
Cardiomyopathy					+	
Heart axis						90 degree
Other cardiac		SVT FHR 200–230 / bpm	PAC	SVT	Cor triatriatum	SVC dilatation
DV		?	?	?		DV normal
Ascites/ Pericardial effusion, Hydrothorax	No	Ascites	Hydrothorax Edema	hepatomegaly, thickened nuchal fold, macroglossia and shortened limbs.		Ascites
3D fetal face	Full cheeks, wide nasal bridge, low set ears				Micrognathia and low-set ears	No strong dysmorphic features
Polydactyly						Yes
Thickened subcutaneous tissue					In the thorax	Femur
Delivery	CS	Vaginal	CS		Vaginal	CS
Gest age at delivery	31	36	32	36	31,4	33,1
Neonatal birth weight (g)	2926	3300	2700	2800	2112	5050
Skin tumors	No					Yes
Gender	Male	Male		Female	Female	Male

Table 3: Prenatal findings of Costello Syndrome; part 1 of 2

	Kuniba (Nagasaki)	Lin Case 1	Lin Case 2	Lin Case 3	Uemura Osaka case	This case:?
Neonatal face		Hypertelorism, prominent eyes, pinpoint cataracts, low-set ears, overfolded helices, short neck,		Coarse facial features, a prominent forehead, periorbital fullness, epicanthal folds, small midface with an upturned nose, dysplastic and thickened ears	Coarse face, high forehead, broad nasal tip, thick lips and low-set	Coarse face, high forehead, broad nasal tip, thick lips
Other clinical findings	Respiratory failure after delivery	Deep palmar creases, hyperextensible digits, tightly clenched fists with overlapping first and third fingers, spoon-shaped nails	Wide QRS tachycardia (198–203 bpm)	Short neck with a wide chest, widely spaced nipples, and short thickened hands		Polydactlyly and syndactyly
Neonatal outcome	Died „soon after birth"	Died at age 4 months	Died at age 40 days	Died at age 13 months	Died at 35 days	Died on 3rd day
	HRAS c.35G>A,p.G12D	Missense mutation in the HRAS gene, p.Gly12Ser.	HRAS mutation p.Gly12Cys	HRAS mutation p.Gly12Ser mutation.	Missense mutation (c.35 T > C, p.G12D) in the HRAS gene.	
Autopsy	Not performed		Lung hypoplasia, Nephromegaly Liver hemangioma	Mild subaortic stenosis.		Cardiomyopathy + partial anomopuls venous connection Capillary tumors

Table 3: Prenatal findings of Costello Syndrome; part 2 of 2

It is also worth noting that normal sonographic findings in the first half of pregnancy does not rule out lethal complex malformations which may develop in the second half of pregnancy. On the other hand survival in Costello Syndrome or RASopathies is possible and both parents and pateints have created a support group such as in France (http://afscostello- cfc.asso.fr/category/association/

CONCLUSIONS:

1. Significant acceleration of fetal growth in second half of pregnancy and polyhydramnios were the first symptoms of abnormal fetal growth and development despite normal first half of pregnancy (both clinically and sonographically).
2. Fetal echocardiography revealed cardiomegaly, myocardial hypertrophy, dilatation of the superior vena cava suggesting partial anomalous venous return and was helpful to predict the poor outcome.

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Conflict of interest: The authors declare no conflict of interest

Authors do not report any financial or personal links with other persons or organizations, which might affect negatively the content of this publication and/or claim authorship rights to this publication

Special Acknowledgment for Steward Weiner MD, PhD from Jefferson University off Philadelphia for his English correction of the manuscript.

This manuscript was partially supported by Medical University Research Fund: 503/8-144-02/503-81-004