CASE REPORT

Mirror syndrome associated with fetal cardiomyopathy

Petra Glad Štritof[1], Lucija Zanze[2], Paulo Zekan[1,*], Gordana Horvat[3], Vladimir Blagaic[1]

[1] Department of Obstetrics and Gynecology, University Hospital "Sveti Duh", Zagreb, Croatia. [2] School of Medicine, University of Zagreb, Zagreb, Croatia. [3] Special Hospital Agram, Zagreb, Croatia.

*Correspondence: Paulo Zekan, Department of Obstetrics and Gynecology, University Hospital "Sveti Duh", Sveti Duh 64, 10000, Zagreb, Croatia. Email: paulo.zekan@gmail.com

How to cite this article: Strifof PG, Zanze L, Zekan P, et al. Mirror syndrome associated with fetal cardiomyopathy. Arch Clin Cases. 2023;10(4):191-195. doi: 10.22551/2023.41.1004.10273

ABSTRACT

Mirror syndrome is a rare condition of generalized maternal oedema caused by fetal hydrops. A 37-year-old patient was admitted to our hospital because of suspected mirror syndrome caused by fetal cardiomyopathy. At 26th week of gestation patient developed bilateral pulmonary oedema as her condition rapidly deteriorated. Consequently, preterm labor was induced, percutaneous evacuation of fetal ascites was performed, and the patient finally vaginally delivered stillborn fetus. Although the initial postpartum period was severely complicated by hemorrhage, the condition of the patient significantly improved later, and she was discharged seven days after delivery. We believe this case is worth presenting due to its rarity and significant perinatal and obstetric challenges in treatment of those patients. Furthermore, preimplantation genetic testing could be performed to prevent at least some of the cases.

KEYWORDS: Mirror syndrome; nonimmune fetal hydrops; prenatal diagnosis

INTRODUCTION

Mirror syndrome also known as Ballantynes syndrome is a condition of fetal hydrops (two or more fluid collections in fetus including serous cavities and generalized skin oedema) that is "mirrored" by generalized maternal oedema. It occurs at any time during pregnancy and can persist postpartum. Its presentation is similar to preeclampsia, but with maternal hemodilution (compared to hemoconcentration in preeclampsia), polyhydramnios (compared to oligohydramnios in preeclampsia), and signs of fetal hydrops. Furthermore, mirror syndrome is associated with a high rate of fetal mortality, which was reported to be as high as 62% [1]. It is most commonly associated with nonimmune fetal hydrops (NIFH) but can be caused by immune fetal hydrops as well. Aneuploidy is the most common etiology of NIHF prior to 24 weeks of gestation. After 24 weeks it is predominantly caused by fetal cardiac abnormality and fetal infection [2]. Mirror syndrome is a very rare condition. Previous systematic review reported only 113 cases between 1956 and 2016 [1]. Therefore, exact incidence of the condition cannot be precisely determined.

CASE REPORT

A 37-year-old patient, gravida 2, para 1 was referred from a local hospital because of fetal ascites. Four years before referral she gave birth to a child with right ventricular non-compaction dilatative cardiomyopathy, which died at age of 2. Genetic testing of the child showed *MYOM1* homozygosity variant of uncertain significance associated with autosomal dominant hypertrophic cardiomyopathy and *TPM1* variant of uncertain significance associated with autosomal dominant hypertrophic cardiomyopathy, dilatative cardiomyopathy and left ventricular non-compaction cardiomyopathy. The current pregnancy was achieved through IVF/ET. Preimplantation testing had not been offered to the mother. She had regular prenatal care in a local clinic – first trimester ultrasound was negative for cardiac abnormalities and TORCH screen was negative. Next ultrasound examination at 22 + 4 weeks of gestation showed: fetal ascites, bilateral pleural effusion, hepatomegaly, enlarged placenta (4.6 cm) and suspected major fetal cardiac abnormality. Mother was therefore then (at 23 weeks of gestation) referred to our hospital where fetal echocardiography was performed and further revealed dilatative restrictive cardiomyopathy with tachycardia and heart insufficiency. We tried to correct fetal tachycardia with digoxin and amiodarone but both medications were discontinued two days after initiation because of maternal side effects. At 25 + 1 weeks of gestation the patient was admitted to the hospital due to worsening of her condition (new onset orthopnea and pretibial oedema). Physical examination on admission showed normal blood pressure (110/70 mmHg) and weight gain of 7 kg in the last 2 weeks. Laboratory findings suggested maternal anemia (Hgb 110 g/l), hemodilution (Htc 0.315), proteinuria (2 +) and elevated sFlt-1/PIGF ratio. Throughout the next few days fetal condition significantly deteriorated (total fetal hydrops, ascites,

Received: September 2023; **Accepted after review:** November 2023; **Published:** December 2023.

DOI: 10.22551/2023.41.1004.10273

Table 1. Laboratory values during hospitalization.

Index	Admission	Third day	Fourth day	Fifth day	Delivery	First day after delivery	Second day after delivery	Sixth day after delivery	Normal value	Unit
Serum										
CBC										
RBCs	**3.43**	**3.15**	**3.14**	**3.08**	**3.17**	**3.7**	**3.18**	**2.96**	3.86-5.08	10^12/l
WBCs	8.6	6.4	7.9	7.5	8.8	**16**	7.3	4.5	3.4-9.7	10^9/l
Hb	**110**	**96**	**99**	**96**	**97**	**112**	**98**	**92**	119-157	g/l
Htc	**0.315**	**0.286**	**0.288**	**0.284**	**0.286**	**0.333**	**0.292**	**0.27**	0.356-0.470	l/l
MCV	91.9	90.9	91.9	92	90.3	90.85	91.7	91.2	83.0-97.2	fl
PLTs	**145**	**114**	**123**	**113**	**120.3**	**147**	161	227	158-424	10^9/l
Neutrophils	**79.9**	**76.6**	**78.1**	**75.3**	**79**	**88.7**	**72.6**	66.3	44-72	%
Coagulation										
PT	>138	-	-	-	>138	>138	>138	-	>70	%
aPTT	23	-	-	-	23.6	23.7	24.3	-	23.0-31.9	s
Fibrinogen	**5**	**-**	**4.5**	**-**	**5**	**4.6**	**4**	**-**	1.8-3.5	g/l
Liver function										
ALT	17	-	16	-	-	25	-	-	8-41	iu/l
AST	25	-	29	-	-	**35**	**-**	-	11-34	iu/l
GGT	13	-	-	-	-	13	-	-	9-35	iu/l
ALP	65	-	-	-	-	83	-	-	54-119	iu/l
Kidney function										
Creatinine	58	61	67	-	72	87	**96**	-	49-90	μmol/l
Urea	3.2	3.4	-	-	4.5	4.6	6.2	-	2.8-8.3	mmol/l
Glucose	4.2	-	-	-	-	4.2	4.1	-	3.9-5.6	mmol/l
Total bilirubin	6	-	-	-	-	5	-	-	3-20	μmol/l
LD	231	-	219	-	-	-	-	-	25-241	iu/l
Electrolytes										
Na	139	-	-	-	139	137	142	-	137-146	mmol/l
K	4.4	-	-	-	4.1	4.8	4.8	-	3.9-5.1	mmol/l
Cl	108	-	-	-	**109**	-	-	-	97-108	mmol/l
Ca	-	2.27	-	-	2.14	-	-	-	2.14-2.53	mmol/l
Mg	0.69	-	-	-	-	-	-	-	0.65-1.05	mmol/l
Urine										
Glucose	<5.5	-	-	-	-	-	-	-	<5.5	mmol/l
Bilirubin	negative	-	-	-	-	-	-	-	negative	
Ketones	<1.5	-	-	-	-	-	-	-	<1.5	mmol/l
Proteins	**2+ (1-3)**	**-**	-	-	-	-	-	-	<0.3	g/l
Nitrites	<16.2	-	-	-	-	-	-	-	<16.2	μmol/l
Eritrocytes	**1+ (25-80)**	**-**	-	-	-	-	-	-	<25	10^6/l
Leukocytes	**1+ (15-70)**	**-**	-	-	-	-	-	-	<15	10^6/l
pH	5.5	-	-	-	-	-	-	-	5.0-9.0	
Specific weight	1.016	-	-	-	-	-	-	-	1.002-1.030	kg/l
Sediment										
Eritrocytes	**15**	**-**	-	-	-	-	-	-	<10	10^6/l
Leukocytes	**36**	**-**	-	-	-	-	-	-	<10	10^6/l
Bacteria	**873**	**-**	-	-	-	-	-	-	<130	10^6/l

Continued to next page

Table 1 - Continued.

Index	Admission	Third day	Fourth day	Fifth day	Delivery	First day after delivery	Second day after delivery	Sixth day after delivery	Normal value	Unit
Volume (24 h)	-	700	-	-	-	-	-	-	600-1800	ml
Proteins (24 h)	-	**893**	-	-	-	-	-	-	<150	mg/24h
Creatinine (24 h)	-	13	-	-	-	-	-	-	5.9-14.1	mmol/24h
ABS (arterial blood)										
pH	-	-	**7.454**	-	-	-	-	-	7.35-7.45	
pCO2	-	-	**3.62**	-	-	-	-	-	4.7-6.4	kPa
pO2	-	-	11.2	-	-	-	-	-	10-13.4	kPa
BE	-	-	**-3.8**	-	-	-	-	-	-2-3	
Total bicarbonates	-	-	**17.2**	-	-	-	-	-	23-27	mmol/l
SaO2	-	-	0.968	-	-	-	-	-	0.94-0.98	
Transfusiology										
IAT		neg								
sFlt-1/PlGF		1281								

hydropericardium, anasarca, brain edema, enlarged heart and completely reduced fetal dynamics). At 25 + 6 maternal condition significantly deteriorated when she developed bilateral pulmonary edema, leg swelling and fluid retention of 1600 ml in 24 hours which were unresponsive to diuretics. Laboratory values throughout hospitalization are shown in Table 1.

Hence at 25 + 6 weeks of gestation in the interest of maternal health due to rapidly developing severe mirror syndrome the labor was induced. Mother agreed with comfort care for the fetus owing to poor perinatal prognosis. The labor was induced by amniotomy and oxytocin infusion and the patient received epidural analgesia. We periodically checked for fetal heart rate which had become negative before full dilatation. However, second stage of labor was obstructed due to enlarged fetal abdominal circumference as o consequence of massive ascites. Percutaneous evacuation of fetal ascites was performed. 280 mL of serous content was evacuated from fetal abdomen (Figure 1). After evacuation, she delivered a stillborn hydropic female infant (1360 g, 32 cm). The placenta was macroscopically enlarged (1330g) (Figure 2). Labor was further complicated by retained products of conception so instrumental evacuation of uterine cavity was performed. The patient was discharged on the seventh day after labor in good condition and with improved laboratory values.

DISCUSSION

Mirror syndrome is a rare complication of fetal hydrops. Although usually associated with nonimmune hydrops fetalis, it can also occur with immune-mediated hydrops. Fetal disorders associated with NIHF are typically grouped into etiologic categories e.g., chromosomal, hematologic, cardiothoracic, neoplastic. The proportion of hydrops cases attributable to each etiologic category depends, in part, on the gestational age at presentation. NIHF before 24 weeks of gestation is usually related to an aneuploidy, while cardiac, pulmonary, and infectious etiologies account for most cases after 24 weeks [2]. Accordingly, our patient belongs to the second group, presenting in the 25th week with fetal hydrops due to cardiomyopathy. Furthermore, cardiovascular disorders are the main causes of nonimmune hydrops fetalis (21.7%) [3]. Probable etiology in our case – dilatative restrictive cardiomyopathy falls into the category of cardiothoracic abnormalities usually seen in later pregnancy. The most usual structural abnormalities causing NIHF are atrioventricular septal defect, hypoplastic left and right heart, and isolated ventricular or atrial septal defects [4]. In our case the etiology of heart insufficiency was cardiomyopathy – probably due to genetic mutation.

The pathogenesis of mirror syndrome has not been firmly established, but at least in some cases, the hydropic placenta increases the production of soluble fms-like tyrosine kinase (sFlt1), which is an important mediator of maternal endothelial and vascular abnormalities in preeclampsia [5]. In our case the ratio of sFlt-1 to PlGF ratio was high (1281). Sflt-1 is an antiangiogenic factor usually binding to PIGF, a cytokine that promotes vascularization. Usually, in women with preeclampsia this ratio is elevated due to imbalance between proangiogenic and antiangiogenic processes [6]. This could imply that mirror syndrome is also a consequence of the pathology of the placenta. When compared to preeclampsia mirror syndrome commonly presents with similar symptoms including

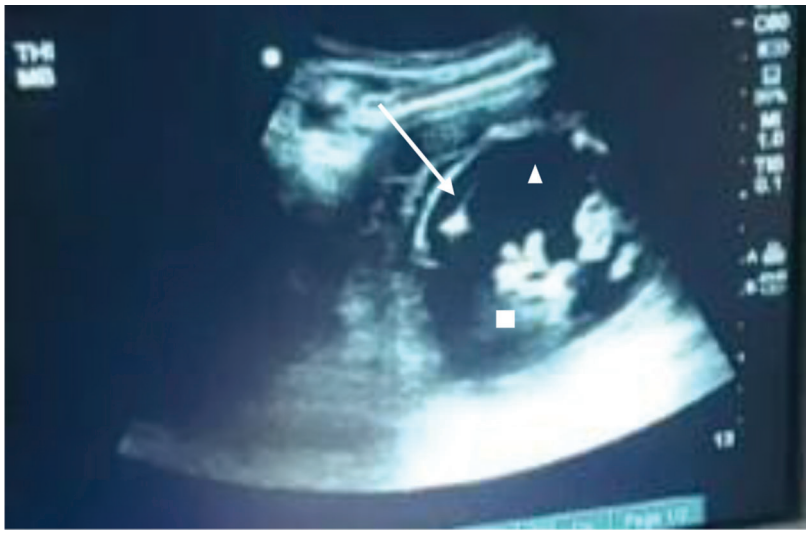

Fig. 1. Ultrasound guided percutaneous evacuation of fetal ascites. Transverse section through fetal abdomen filled with ascites is shown in the picture. Arrow – top of the needle used for evacuation. Arrow head – hypoechoic fetal ascites. Square – hyperechoic fetal bowels floating in the ascites.

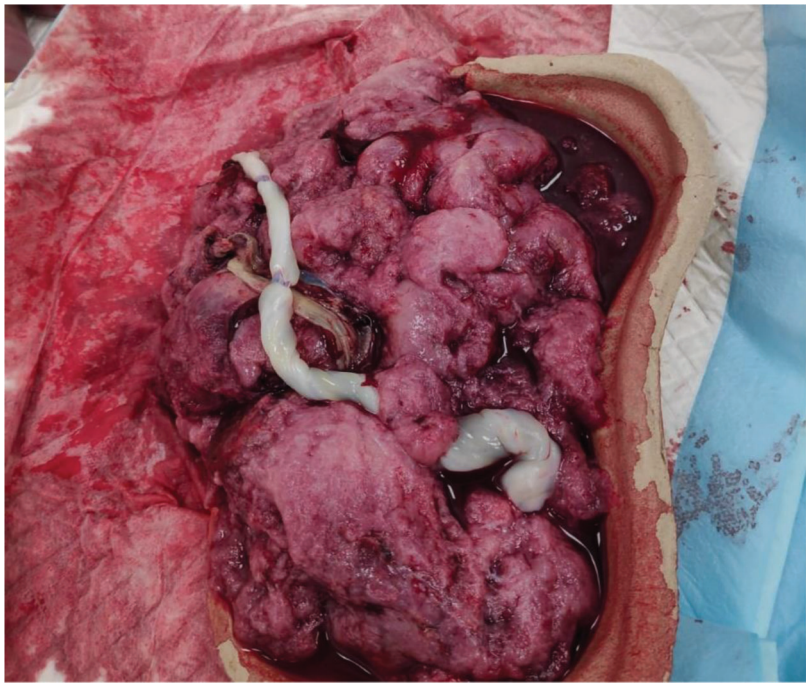

Fig. 2. Enlarged placenta (after delivery aspect).

elevated arterial blood pressure, edema, weight gain and proteinuria. On the other hand, mirror syndrome is associated with hemodilution and polyhydramnios opposed to hemoconcentration and oligohydramnios in PE and also younger gestational age at presentation (more than 50% of cases diagnosed between 26.5 and 27.5 weeks) [2,3]. The youngest patient noted in reports presenting with mirror syndrome was in her 14th week of pregnancy [7]. A systematic review of reports on mirror syndrome noted that key maternal signs were edema (80 to 100%), hypertension (57 to 78%), and proteinuria (20 to 56%), and the overall rate of fetal death was 56%. Severe maternal complications, such as pulmonary edema, occurred in 21 percent of cases [8]. Most of the symptoms in our case overlap with the reported cases, excluding hypertension and polyhydramnios. Our patient was normotensive and had normal AFI.

CONCLUSION

Although mirror syndrome is a rare consequence of fetal hydrops, in this case we could strongly establish diagnosis since obstetric anamnesis, ultrasound findings, laboratory

values and patient's symptoms suggested rapidly progressing mirror syndrome. Furthermore, this case is an example of obstetric and professional challenges associated with Mirror syndrome. Hence, we want to emphasize importance of preimplantation testing after IVF/ET procedures in patients with positive family history since it can prevent development of pregnancy related complication, including mirror syndrome, in at least some cases.

Conflict of interest

The authors declare that they have no competing interests.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

REFERENCES

1. Allarakia S, Khayat HA, Karami MM, et al. Characteristics and management of mirror syndrome: a systematic review (1956-2016). *J Perinat Med*. 2017;45(9):1013-1021. PMID: 28315852. doi: 10.1515/jpm-2016-0422.
2. Nonimmune hydrops fetalis - UpToDate. [https://www.uptodate.com/contents/nonimmune-hydrops-fetalis, available at 11/13/2023]
3. Teles Abrao Trad A, Czeresnia R, Elrefaei A, et al. What do we know about the diagnosis and management of mirror syndrome? *J Matern Fetal Neonatal Med*. 2022;35(20):4022-4027. PMID: 33722118. doi: 10.1080/14767058.2020.1844656.
4. Yinon Y, Chitayat D, Blaser S, et al. Fetal cardiac tumors: a single-center experience of 40 cases. *Prenat Diagn*. 2010;30(10):941-949. PMID: 20721876. doi: 10.1002/pd.2590.
5. Stepan H, Faber R. Elevated sFlt1 level and preeclampsia with parvovirus-induced hydrops. *N Engl J Med*. 2006;354(17):1857-1858. PMID: 16641410. doi: 10.1056/NEJMc052721.
6. Zeisler H, Llurba E, Chantraine F, et al. Predictive Value of the sFlt-1: PlGF Ratio in Women with Suspected Preeclampsia. *N Engl J Med*. 2016;374(1):13-22. PMID: 26735990. doi: 10.1056/NEJMoa1414838.
7. Banoth P, Chaudhary K. Proteinuria: A presenting manifestation of mirror syndrome in pregnancy. *Clin Nephrol*. 2018;90(1):60-63. PMID: 29633703. doi: 10.5414/CN109299.
8. Braun T, Brauer M, Fuchs I, et al. Mirror syndrome: a systematic review of fetal associated conditions, maternal presentation and perinatal outcome. *Fetal Diagn Ther*. 2010;27(4):191-203. PMID: 20357423. doi: 10.1159/000305096.