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Early onset Mirror Syndrome associated with foetal sacrococcygeal teratoma: a rare entity

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ABSTRACT

Early onset Mirror Syndrome associated with foetal sacrococcygeal teratoma: a rare entity.

In the mirror syndrome, maternal symptoms mime foetal and placental oedema. The pathogenesis is unknown. The most common etiologic associations are rhesus isoimmunization, twin-twin transfusion syndrome and viral infections. Few reports are associated to foetal tumors and particularly to sacrococcygeal teratoma (SCT). Based on several published series, foetal SCT with placentomegaly and hydrops is almost universally fatal; foetal surgery is not typically offered for hydropic fetuses beyond 26 weeks of gestational age. Delivery of the foetus is the choice treatment when mirror syndrome is present with supporting the pregnancy until delivery is necessary for maternal indications or the foetus is 30 weeks old. The management of a patient with large foetal sacrococcygeal teratoma, hydrops foetalis and early onset mirror syndrome is presented.

Key words: mirror syndrome, Ballantyne syndrome, sacrococcygeal teratoma, hydrops foetalis, placentomegaly.

INTRODUCTION

In 1892, John W. Ballantyne first described serious maternal oedema in pregnancy associated with fetal hydrops (skin oedema, ascites, pleural and pericardial ef-

SOMMARIO

Insorgenza precoce della Mirror Syndrome associata con il teratoma fetale sacro coccygeo: un evento raro.

Nella *mirror syndrome*, i segni e sintomi materni mimano la condizione di edema fetale e placentare. La patogenesi del fenomeno non è ancora conosciuta. I fattori etiologici più comunemente implicati sono l'isoimmunizzazione materno-fetale, la sindrome tra trasfusione feto-fetale e alcune infezioni virali. Pochi sono i casi descritti associati alla presenza di un tumore fetale ed in particolare ad un teratoma sacro coccygeo (SCT). Dai dati presenti in letteratura risulta che l'associazione di SCT con placentomegalia e idrope esita generalmente nella morte fetale; inoltre, va considerato che l'intervento chirurgico non viene proposto per i feti idropici prima delle 26 settimane di gestazione. Quando si manifesta il quadro di mirror syndrome, l'unico trattamento definitivo è il parto; in tal senso, quindi, si supporta la gravidanza finché il parto non diviene necessario per indicazione materna o il feto raggiunge le 30 settimane di gestazione. Riportiamo un caso di *mirror syndrome* instauratasi precocemente in presenza di un voluminoso teratoma sacro coccygeo fetale e idrope.

Key words: mirror syndrome, Ballantyne syndrome, Teratoma Sacrococcygeo, idrope fetale, placentomegalia.

fusion) and placentomegaly due to rhesus isoimmunization (1). This syndrome is defined as mirror syndrome as the mother's symptoms mirror the general edema presented by compromised foetus and placenta (2). Today, this pathology is also defined as Ballantyne syndrome, pseudotoxemia, maternal hydrops syndrome or triple edema. Given the rarity of the phenomenon, it is very difficult to determine the true inci-

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dence of mirror syndrome.

Pathogenesis is still unknown and the relationship with foetal hydrops is undefined (3, 4). After the first case related to rhesus alloimmunization, other causes of foetal and placental hydrops have been associated with the disease, such as viral infection (Cytomegalovirus or Parvovirus B19 infections), foetal malformations, foetal or placental tumors, and twin-twin transfusion syndrome.

It is difficult to make a distinction between mirror syndrome and preeclampsia as they have many characteristics in common (5). In this manuscript, we describe a case of mirror syndrome that was associated with a growing foetal sacrococcygeal teratoma (SCT), diagnosed and managed at our Department.

CASE REPORT

A 37-year-old woman, gravida 0, para 0, group 0 rhesus-positive, was transferred from another hospital at 24 weeks and 3 days of gestation to our Department due to the foetus having a voluminous SCT, cardiomegaly, a dilated inferior and superior vena cava, scalp oedema, hydrothorax, initial cardiovascular failure with foetal anemia secondary to third space fluid shifting. On admission, physical examination revealed a relatively good general state, normal blood pressure (110/70 mmHg), weight, 63.5 Kg and body temperature, 37.5 °C. She had no history of tobacco, alcohol or drug abuse.

Abdominal examination showed a gravid uterine fundus equivalent to gestational age. On physical examination, the pregnant woman exhibited peripheral oedema.

A fetal ultrasound showed an 11.0 x 8.4 cm fetal SCT (type 1, or peduncolated) that appeared vividly vascularized by high caliber vessels, and polyhydramnios; cardiac activity and active fetal movements were present. Middle cerebral artery, umbilical artery and venous ductus flow was normal. Foetal biometry corresponded to gestational age.

Maternal laboratory tests revealed mild anemia (hemoglobin 8.8 gr %, hematocrit 26.8%), hypoalbuminemia (2.7 g/dL) and

mild proteinuria. Renal (creatinine 0.66 mg/dL, uric acid 5.0 mg/dL) function was normal. Liver tests (alanine transaminase 61 U/L, aspartate transaminase 48 U/L) were mildly elevated. Other maternal signs and symptoms such as oliguria, headache, visual disturbances and low platelets were absent. Studies on foetal thalassemia, Parvovirus B19, Coxsackie were all normal. Amniocentesis showed a normal karyotype. TORCH serology was negative. The patient started therapy with albumine (1 fl x2/die) after hospitalization.

Conception was spontaneous; the patient and her husband were not consanguineous, were apparently healthy and there was no family history of congenital malformations.

In consideration of peripheral edema, hypoalbuminemia, proteinuria, normal blood pressure, hemodilution and the evidence at US examination, a diagnosis of mirror syndrome was made. Patient continued albumin administration and was treated with antibiotics for suspected cystitis; in addition, small doses of analgesic were used to mitigate her discomfort. After counseling, it was decided to continue observation and carry on with the pregnancy for as long as maternal clinical conditions consented.

Two days after admission, the patient presented dyspnea, chest pain, mild fever (37.5°) and a need for oxygen. Contemporarily, she developed an increased peripheral oedema, reduction of diuresis and spoke of asthenia; she was normotensive with sinusal rhythm. Echocardiogram showed a mild mitral and tricuspid failure. Laboratory investigations showed regular renal function, but worsening anemia (7.3 g/dL) and hypoalbuminemia (2 g/dL). Given the clinical picture it was decided to start diuretic therapy.

Foetal echocardiography showed an increase of pericardial effusion and foetalis hydrops. Fewer fetal movements were observed. Fetal prognosis was estimated by the obstetrical and pediatric staff to be very poor, due to congestive heart failure. Given the development of generalized maternal oedema and the onset of labour pains, the decision for vaginal delivery was taken. An



Figure 1 - Dead hydropic foetus at the time of delivery.

epidural anesthesia was induced at the L3-4 vertebral interspace without complication. During labour, fetal cardiac activity was suddenly no longer seen.

At 24 weeks 6 days of gestation, a girl, 1,350 g, was spontaneously delivered, dead (Figure 1). The placenta was cm 16 x 16, and weighed 570 g. The fetus showed a multi-lobed neof ormation in the sacrococcygeal area (14x10x6 cm) partially covered by anal skin and perineum, with anterior displacement of the anus. There was hydrops and hydrothorax. The heart had atrial situs solitus, with concordant atrioventricular and ventricular-arterial connections. There was heart disease characterized by parachute mitral valve. Situs viscerus addominalis solitus.

After delivery of the foetus, maternal blood pressure was normal, proteinuria disappeared, and liver function tests returned to normal by the 5th day. Therapy with albumin was continued, small doses of diuretics were administered to reduce the generalized oedema. On the 7th day maternal oedema resolved and the patient was then discharged.

DISCUSSION

The most consistent clinical characteristics of mirror syndrome are maternal hypertension, generalized edema, and proteinuria associated with fetal hydrops and placental enlargement (6). The gestational age in which the disorder usually appeared ranges from 22 to 28 weeks of gestation in the literature (7). The incidence of mirror syndrome and its mechanism are still unknown and the relationship with fetal hydrops is not well understood (4). Furthermore, recent data suggests that placental hydrops alone may also cause the syndrome (8, 9).

Causes of hydrops fetalis are myriad, ranging from immune to structural to metabolic. Definitive treatment for mirror syndrome is delivery of the fetus, regardless of gestational age, or correction in utero of the causes of hydrops (6). This often leads to a resolution of maternal symptoms together with an improvement in perinatal outcome: there have been cases in which the spontaneously or selective loss of a hydropic twin resulted in a pregnancy with good maternal and perinatal outcome (10).

Mirror syndrome which is related to fetal hydrops and large placental mass has several clinical characteristics, but maternal oedema, as in our case, seems to be a key symptom.

Arterial hypertension represents the second most common symptom (58% of cases) associated with mirror syndrome and explains the difficulty in differentiating this syndrome from preeclampsia. On the other hand, one critical clinical distinction is that mirror syndrome is associated with hemodilution, whereas hemoconcentration is a typical pathophysiological feature in preeclampsia (11). Furthermore, preeclampsia diagnosis before 24 week's gestation is extremely rare. Our case report is an anomaly compared to the main data in literature as our patient did not develop hypertension, not even post-partum. Instead, she presented hemodilution, polyhydramnios, proteinuria, and progressive shortness of breath. This data was useful in making the differential diagnosis.

In preeclampsia, there is pathogenic evidence of placental underperfusion caused

by failure of trophoblastic invasion into the spiral artery, which suggests an angiogenetic modulator involvement in this disease (12).

With regard to this aspect, recent studies have shown that the imbalance between angiogenic and antiangiogenic factors might be responsible for maternal clinical symptoms also in mirror syndrome. In particular, the authors found increased circulating sFlt-1 (soluble fms-like tyrosine kinase-1) and sEng (soluble endoglin) levels and decreased PlGF (free placental growth factor) levels in maternal blood at diagnosis of mirror syndrome; this has already been observed in preeclampsia (13, 14). Mirror syndrome shares a common hypothesis with preeclampsia in that the dysfunctional placenta releases anti-angiogenic factors into the maternal circulation. The relationship between increased anti-angiogenic circulating factors and mirror syndrome is supported by Llorba et al, who describe normalization of levels after treatment, and resolution of fetal hydrops (12).

Only two published studies have looked specifically at the placental expression of antiangiogenic factors, demonstrating more intense immunostaining for VEGFR1 and Endoglin in the syncytiotrophoblast of placenta with mirror syndrome compared to normal placental tissue (15, 16).

Hydrops is believed to be a manifestation of foetal heart failure, which is associated with placentomegaly and villous edema, with an impaired placental exchange. Trophoblast hypoxia could be associated with the increased output of angiogenic factors, such as Flt-1, that initiate a series of events which could lead to maternal endothelial injury and the clinical picture of mirror syndrome. These data suggest that an anti-angiogenic state, similar to that of preeclampsia, induce 'mirror manifestation', regardless of the specific causes of fetal hydrops. This observation opens new scenarios for a deeper understanding of the disease and for its management.

SCT is the most common fetal tumour, but is a rare condition and is benign in 90% of cases (17). Large or rapidly growing tumours are associated with a poor prognosis

in relation to the development of high output cardiac failure due to the large artero-venous shunt (18). Based on several published series, foetal SCT with placentomegaly and hydrops is almost universally fatal and for this reason foetuses affected with SCT are observed very closely to facilitate intervention before the development of hydrops (19). Generally, there are 2 options for survival for the foetus with SCT and non-immune hydrops: *in utero* intervention for foetuses with pulmonary immaturity precluding delivery or delivery after 30 weeks with postnatal resection (20). *In utero* surgery may be attempted to arrest the vascular shunt due hysterotomy with tumour debulking or radiofrequency ablation of the main blood supply (17).

Outcomes for the 26-to-30-week gestational age foetus with SCT and late hydrops are poorly defined. Although it has been demonstrated that infant hydrops is reversible after postnatal resection, only one report has confirmed a successful long-term outcome in an infant of this gestational age (19). Foetal SCT with hydrops complicated by the development of maternal mirror syndrome, must necessarily consider the balance between maternal and foetal wellbeing, and in presence of maternal degeneration, delivery is mandatory. In our experience, maternal clinical worsening made delivery necessary, regardless of gestational age of the foetus.

In literature, there have been cases in which foetus cannot be delivered vaginally due to the size of the teratoma (18). In our case, the tumour had a maximal dimension of 14 cm but a vaginal delivery was decided for, considering other options more risky for the mother.

There are few cases of foetal SCT and hydrops associated with maternal mirror syndrome in medical literature. Finamore et al. described the first case report in which a foetus with SCT at 29+5 weeks started to show an enlarged heart, thickened placenta and mild polyhydramnion. Later, the classic symptoms of maternal mirror syndrome appeared. A caesarean section was performed at 30 weeks, along with surgical treatment

Table 1 -Details of foetal SCT related to mirror syndrome in medical literature and the present case.

| Authors | Time of diagnosis | Foetal symptoms | Time of maternal symptoms | Maternal symptoms | Treatment | Gestation at delivery | Foetal outcome |
|---------------|-------------------|--|---------------------------|--|---|-----------------------|---|
| Finamore 2007 | 29 w | 29 w increased cerebral flow; 29+5 w enlarged heart, thickened placenta, increased liver length, mild polyhydramnios | 30 w | pruritic rash, edema, hypertension, epigastric pain, proteinuria, anemia, thrombocytopenia | intrauterine blood trasfusion | 30 w | cesarean section, successful surgery after delivery |
| Ibele 2008 | 25+3 w | mild pericardial effusion, 27 w: placentomegaly, polyhydramnios, scalp oedema, ascites, pericardial and pleural effusion | 27+2 w | hypertension, oedema, highly elevated liver enzymes | not reported | 27+5 w | emergency cesarean section, foetal surgery |
| McCann 2009 | 21 w | hydrops, polydramnios, placentomegaly, scalp oedema, cardiomegaly, pericardial effusion | 21 w | severe abdominal pain, anxiety, anemia, proteinuria, peripheraloedema, hyperthyroidism | morphine, lorazepam, lactated ringer's solution | 21 w | induction of labor, nonviable foetus |
| Kafali 2010 | 16 w | placentomegaly, polyhydramnios, oedema, ascites, pericardial pleural effusions, hydrops, anemia | 28 w | mild peripheral oedema, right lumbar pain, proteinuria, hypertension, hydronephrosis, ovarian vein thrombosis | not reported | 28 w | cesarean section, nonviable foetus |
| Perino 2012 | 24+3 w | cardiomegaly, initial cardiovascular failure, hydrops, anemia, polyhydramnios, placentomegaly | 24+3 w | peripheraloedema, mild anemia, proteinuria, hypoalbuminemia, mild elevated liver enzymes; 24+5: dyspnea, chest pain, mild fever, worsening anemia, generalized oedema, hypoalbuminemia | albumina, diuretic therapy | 24+6 w | spontaneous delivery, nonviable foetus |

of teratoma, with good foetal outcome (9).

Ibele et al. report their experience with a hydropic SCT foetus delivered at 27 weeks for maternal indications who survived post-natal resection, with a good long-term outcome (19). Kafali et al. describes the only case of association between mirror syndrome, ovarian vein thrombosis, and SCT (21). Finally, McCann et al. showed the anaesthetic management of a parturient with foetal sacrococcygeal teratoma, hydrops fetalis, and mirror syndrome complicated by markedly elevated maternal serum human chorionic gonadotropin and subsequent clinical hyperthyroidism (17). All details of these cases are described in Table 1.

Our case is the fifth case of foetal SCT associated with mirror syndrome in international literature. There are some singularities; associated foetal cardiac malformation, very precocious maternal symptoms, and absence of maternal hypertension, which is quite common in this syndrome.

Given the scant level of knowledge on the mechanisms of cause and development of mirror syndrome, the publication of a new experience should be useful. In addition, in the light of new data, we believe it would be useful to focus future studies on the characterization of the upstream pathogenic events that lead to this angiogenic dysfunction.

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