The diagnostic conundrum of maternal mirror syndrome progressing to pre-eclampsia – A case report

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ABSTRACT

Mirror syndrome, also called Ballantyne syndrome, is a rare condition in pregnancy, defined by the presence of the clinical triad of fetal hydrops, placentomegaly and maternal oedema. Any aetiology of fetal hydrops, including rhesus iso-immunization, congenital infection, twin-to-twin transfusion, structural anomalies and fetal malignancies, can lead to the syndrome. The pathogenesis, although not well established, mimics trophoblastic damage and maternal vascular endothelial dysfunction, as is also seen in pre-eclampsia, and, hence, the two conditions may have a similar clinical presentation. They may even co-exist, where a patient with maternal mirror syndrome develops features of pre-eclampsia. A timely, accurate diagnosis and prompt interventions are needed to prevent fetal mortality and maternal morbidity.

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1. Introduction

Mirror syndrome, also called Ballantyne syndrome or triple oedema, is defined by the presence of a clinical triad that involves hydrops of the fetus, the placenta and the mother. This rare condition was first described by John William Ballantyne in 1892 with the original thought that rhesus iso-immunization of the fetus was the cause of maternal hydrops. [1] In 1956, O'Driscoll described a similar case and the term 'mirror syndrome' was coined since the oedema in the mother mirrors that of her fetus and its placenta. [2]

However, as recent literature describes, the present thought, with the advent of ultrasound and prenatal diagnosis, is that multiple aetiologies causing severe hydrops fetalis, that is, both immune and non-immune hydrops, can lead to maternal mirror syndrome. [3]. These may be parvovirus B19 infection, as in our case, Cytomegalovirus infection, placental chorangioma, twin-to-twin transfusion, aneurysm of Galen's vein, sacrococcygeal teratoma and even fetal leukaemia. [3].

The pathophysiological mechanism behind the syndrome remains unknown; however, it has been suggested that the hydropic placenta is the likely source, as the correction of fetal hydrops (and, hence, placental hydrops) or the termination of the pregnancy (and removal of placenta) resolves the syndrome. [4]

Mirror syndrome is also referred to as pseudotoxaemia. About half the patients with mirror syndrome develop hypertension and proteinuria, which is consistent with the clinical diagnosis of pre-eclampsia.

The worsening of the imbalance between angiogenic and anti-angiogenic factors is the likely cause of progression towards toxaemia of pregnancy. [5]

We describe a case of maternal mirror syndrome progressing to severe pre-eclampsia, the trigger being fetal hydrops caused by congenital parvovirus B19 infection in the second trimester of pregnancy.

2. Case Report

A 28-year-old healthy woman of South-East Asian ethnicity was booked into the hospital's antenatal clinic early in the first trimester. The pregnancy had been progressing well. The patient had had one pregnancy 5 years prior, which was a rare abdominal pregnancy in the pouch of Douglas, finally resulting in a laparotomy, termination of pregnancy (fetal size of approximately 13 weeks) and salpingectomy. The patient was known to be a carrier of the alpha thalassaemia trait and her partner's screen was negative.

At her first-trimester antenatal screen, she was noted to be Rhesus positive, negative for HIV, hepatitis B, hepatitis C and syphilis. She was also found to be rubella immune. Her combined first-trimester screen was reported as low risk for trisomy 21, 18 and 13.

The 15-week visit was routine. Her blood pressure was noted to be within normal range (around 110/70 mmHg), the uterus appeared adequate for dates and an ultrasound scan revealed an active fetus of normal appearance. The next follow-up visit would be in 3 weeks.

However, at 17 weeks 3 days gestation, the patient presented to the emergency department with swelling in both legs. The patient's blood pressure was 144/92 mmHg, with grade 3 pitting pedal oedema up to

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mid-thigh in both legs. The patient reported mild frontal headache but no blurring of vision or right upper quadrant pain. She also reported a weight gain of 10 kg over 2 weeks. She denied any febrile episodes, history of rash, lower abdominal pain or bleeding per vaginum. Bilateral deep patellar reflexes were brisk but no ankle clonus was demonstrated.

Ultrasound examination revealed fetal death in utero (FDIU) with the bi-pariteal diameter corresponding to 16 weeks and 4 days of gestation. There was evidence of gross fetal hydrops with severe ascites, skin oedema and pleural effusion. Table 1 summarizes the results of further investigations. The urine dipstick revealed 1+ of nitrite-free protein with a protein/creatinine ratio (PCR) of 22 mg/mmol. The B-hCG was >200,000 IU/L, likely due to placental oedema. All FDIU investigations were requested, including a toxoplasmosis, cytomegalovirus and parvovirus B19 serology screen. The patient's blood pressure remained within the higher limits of normal, at 130–140/80–90 mmHg.

Subsequently, labour was induced with a mifepristone-misoprostol regimen. The patient delivered a stillborn female, weighing 127 g. The placenta was pale and on histopathology was noted to have oedematous and immature villous maturation. As the patient's blood pressure remained within normal limits and she was well, she was discharged home on day 1 post-delivery with a clinic follow–up scheduled for 2 weeks. Subsequently, maternal parvovirus B19 serology was reported to be positive for IgM antibodies, which confirmed congenital parvovirus infection to be the cause of fetal hydrops.

On day 3 post-delivery, the patient presented to the emergency department with increasing dyspnoea, worsening since discharge and now present on rest. She reported chest tightness and left-sided chest pain radiating into the neck with worsening of frontal headache. She also reported worsening of upper and lower limb swelling, as well as facial puffiness. She denied any febrile episodes, cough, right upper quadrant pain, any visual symptoms or lower abdominal pain. Her heart rate was 65 beats per minute, blood pressure was 190/90 mmHg and her oxygen saturation was 99% on room air. However, the patient was in tripod position, and appeared uncomfortable and distressed; her respiratory rate was 35 breaths per minute. Grade 2 pitting oedema was elicited in the upper limbs up to the elbows and there was persistent grade 3 pitting oedema up to mid-thigh in the lower limbs. On auscultation, air entry was noted to be reduced in bilateral lung basal lobes, though, with no evidence of crepitations or wheeze. Both heart sounds were audible, with no evidence of murmur. Bilateral patellar tendons revealed hyperreflexia with two beats of ankle clonus bilaterally.

The investigation results are summarized in Table 1. Troponins were significantly elevated, at 234 ng/L. The urine dipstick now revealed 2+ of nitrite-free protein with a PCR of 31 mg/mmol. The urine output was noted to be 30 ml/h during the initial investigation. A chest X-ray revealed bilateral lower lobe pleural effusion and evidence of pulmonary oedema. Transthoracic echocardiography revealed normal biventricular size, normal valvular function and a normal left ventricle with an ejection fraction of 65%. However, a small pericardial effusion was noted (possibly explaining the rise in troponin level). There was no evidence of dilated right ventricle or right heart strain and a computed tomography pulmonary angiogram was negative for pulmonary embolism.

The patient was admitted to the intensive care unit with an unclear diagnosis and multi-system supportive therapy was commenced. She was administered intravenous hydralazine initially for blood pressure control. She was also commenced on intravenous magnesium sulphate (MgSO4) in view of features of atypical severe pre-eclampsia. Several other differential diagnoses were considered, including peri-partum cardiomyopathy and cardiac failure in view of severe dyspnoea; hence, calcium channel blockers and beta-blockers were avoided. Intravenous frusemide was commenced with caution in view of interstitial fluid overload, despite the differential of pre-eclampsia at this stage, as the haematocrit revealed an expanded rather than a contracted intravascular volume.

In retrospect, the diagnosis of mirror syndrome was made in view of the presence of fetal hydrops, maternal anasarca, mild hypertension and maternal haemodilution, which then progressed to severe pre-eclampsia with worsening hypertension, proteinuria, hyperreflexia and persistence of maternal oedema after delivery, which in the scenario of mirror syndrome alone should have resolved with delivery. Similarly, although pre-eclampsia has been thought to resolve with delivery, it can present in the postpartum period of an uneventful pregnancy, but why this occurs is not fully understood.

The patient made a substantial recovery over the next 24–48 h, with decreasing need for supplemental oxygen, normalizing respiratory rate, decreasing oedema and improving biochemical markers. By day 6 post-delivery (day 3 of admission), the patient reported that she experienced almost no dyspnoea on mobilization and that her limb swelling had reduced by over 75%. She was discharged on day 4 of admission on a tapering regimen of low-dose anti-hypertensives for blood pressure control and diuretic therapy was ceased.

At her follow-up visit a week later, she reported being well. Her blood pressure was well within normal limits and no maternal oedema was elicited.

3. Discussion

Our case highlights the importance of recognizing features to accurately diagnose maternal mirror syndrome progressing to pre-eclampsia. Timely intervention is needed to prevent fetal and maternal morbidity.

The incidence of Human parvovirus B19 infection in pregnancy is estimated to be 1–2% during an epidemic but over 50% of patients remain asymptomatic, hence accounting for the typically late presentation [6]. Vertical transmission occurs in 30% of cases and the risk of fetal mortality before 20 weeks is 5–10%. Once fetal hydrops sets in, the prognosis is guarded. [7]

Parvovirus infection leads to severe fetal anaemia by causing cytotoxic apoptosis of the fetal erythroid progenitor cells, hence shortening the half-life of these erythrocytes and causing high-output cardiac failure; therefore, non-immune hydrops fetalis sets in (NIHF) [8]. The P antigen expressed on fetal cardiac myocytes enables the parvovirus B19 to infect myocardial cells and produce myocarditis, which aggravates cardiac failure [8]. This, in turn, leads to placental villous oedema, thereby

Table 1
Trend of investigations.

	Baseline (preconception)	At the diagnosis of FDIU (mirror syndrome)	Admission to ICU (mirror syndrome with pre-eclampsia)	Reference values (for pregnancy) (perinatology.com)
Haemoglobin (g/L)	128	94	103	105–148
Haematocrit (L/L)	0.41	0.30	0.32	0.32–0.42
Platelet count ($\times 10^9$/L)	368	298	374	150–400
Urea (mmol/L)	UA	4.1	4.8	1.1–4.6
Creatinine (μmol/L)	UA	49	70	35–80
Albumin (g/L)	UA	28	28	25–42
ALT (U/L)	UA	91	61	</= 30
AST (U/L)	UA	55	56	</= 35
Urate (mmol/L)	UA	0.35	0.40	0.12–0.37

reducing the intervillous space and blood flow, leading to hypoxia. This hypoxia is responsible for releasing anti-angiogenic factors such as sVEGFR-1 (sFlt-1) into the maternal circulation, hence setting off a cascade of triggers leading to Ballantyne syndrome. It is the same anti-angiogenic factors, which have been studied exhaustively as a cause of pre-eclampsia [9].

So how is the clinical diagnosis of mirror syndrome reached? The clinical picture of Ballantyne syndrome has several characteristics: fetal hydrops is present, maternal oedema is always a key feature; albuminuria is usually mild; and blood pressure may be slightly elevated, or may rise only during labour. [10] It has been suggested that a key criterion in diagnosing mirror syndrome is the presence of a dilutional anaemia, with a low haematocrit level, as was present in our case, different from the haemoconcentration seen in pre-eclampsia. [5] There is evidence to suggest that hyperplacentosis occurs (suggested by significant elevation in hCG concentrations, as in our case, at >200,000 IU/L), which may, in turn, lead to placental ischaemia through the mechanism stated above. As per Umazume T. et al., this placental ischaemia is responsible for increasing plasma renin activity, which in turn increases maternal plasma aldosterone concentration, leading to maternal oedema and haemodilution. [11]

Development of mirror syndrome can increase the risk of pre-eclampsia; there is a common ground for the development of both pathologies, a ground that favours an angiogenic-antiangiogenic imbalance, which might contribute to an even worse prognosis when both entities coexist, as described in our case [4].

In pre-eclampsia, there is pathogenic evidence of placental underperfusion (hypoplacentosis) caused by failure of trophoblastic invasion into the spiral arteries, which suggests involvement of angiogenic modulation in the development of this disease. Increased circulating sFLT-1(sVEGFR-1) levels and decreased PlGF levels have been reported in pre-eclampsia [5]. Recent publications reveal that the imbalance between the same angiogenic and antiangiogenic factors may also be associated with the maternal clinical symptoms in mirror syndrome [5]. In a study by Llurba E. et al., low PlGF levels and high sFLT-1 levels were found in maternal serum at the diagnosis of mirror syndrome, and these values were similar to (but slightly less than) the levels found in 21 patients with pre-eclampsia at the same gestational age. Noteworthy is the fact that after treatment and resolution of fetal hydrops, maternal PlGF and sFLT-1 levels normalized to those in the control group. [12]

Therefore, why do some mothers with a hydropic fetus develop mirror syndrome while others do not, and what determines the severity, i.e., mirror syndrome progressing to pre-eclampsia? As per Espinoza et al., the speculation is that the severity of the villous oedema and the genetic factors responsible for the production, metabolism, and functional control of pro- and anti-angiogenic factors may tip the balance. Moreover, as in any disease, some patients may simply be more susceptible than others; in this case to a given concentration of anti-angiogenic factors. [5]

Fetal prognosis when mirror syndrome develops is poor. As described by S. Allarakia et al. and T. Braun et al., the condition results in intrauterine fetal death in over 50% of cases. [3,13]. Interestingly, unlike pre-eclampsia, where the only effective treatment is delivery, in Ballantyne syndrome the treatment of fetal hydrops in utero, from whatever aetiology, often leads to the resolution of maternal symptoms together with an improvement in perinatal outcome [12]. A. Chimenea et al. describe two cases of maternal mirror syndrome. The first was caused by congenital parvovirus B19 causing fetal anaemia and hydrops. The fetus was treated with intrauterine blood transfusion which progressively resolved both the fetal and maternal hydrops, with a good outcome in both. The second case was caused by fetal bilateral hydrothorax, causing cardiac failure, leading to feto-placental hydrops. A pleuro-amniotic shunt was placed in the hemithorax. Although the mother required diuretics to manage pleural and pericardial effusion that had already developed, shunt placement led to an overall good outcome. [14]. Whether an earlier presentation and diagnosis of parvovirus causing fetal hydrops in our case may have prompted an intrauterine red cell transfusion and resolved both fetal and maternal oedema, hence changing the course of the disease, remains a retrospective reflection.

Parvovirus B19 infection in adults can, rarely, cause heart failure and generalized oedema (a differential diagnosis in the present context) [15]. Therefore, it may be useful to make a qualitative comparison of specific features differentiating mirror syndrome, pre-eclampsia, mirror syndrome progressing to pre-eclampsia (as in our case) and congestive cardiac failure (Table 2).

A key message from our case report is the essentiality of early accurate diagnosis of mirror syndrome to improve both maternal and fetal outcome. Clinical vigilance is required in the postpartum period in view of possible progression to pre-eclampsia and worsening of maternal symptoms. There may be a need for anti-hypertensives, magnesium

Table 2

Differentiating between mirror syndrome, pre-eclampsia, mirror syndrome with pre-eclampsia (our case) and congestive cardiac failure (a qualitative comparison).

Features	Mirror syndrome	Pre-eclampsia	Our case (mirror syndrome with pre-eclampsia)	Congestive cardiac failure
Onset	16–39 weeks	After 20 weeks	17 weeks	At any time
Hypertension	Absent or mild(usually <140/90)	Mild to severe (>140/90)	Highest reading: 190/90; range: 150–190/90–100	May be hypotensive
Proteinuria (>300 mg/day); urine dipstick of nitrite-free proteinuria ≥1+	Usually absent or mild (<300 mg/day)	Almost always present	urine dipstick 2+	Usually absent
Maternal oedema	Present (sometimes anasarca)	Present	Anasarca	Present
Fetal hydrops	Present	Absent (growth restricted fetus)	Present	Unaffected
Amniotic fluid	Polyhydramnios more common	Oligohydramnios more common	Unaffected	Unaffected
Placental size	Large	Small	Histopathology elicited oedema	Unaffected
Haematocrit	Haemodilution	Haemoconcentration	Haemodilution	Haemodilution
Thrombocytopenia (<100,000 × 10⁶/L)	Not present	Can be present (HELLP syndrome)	Not present	Unaffected
Renal function derangement	Absent, mild	Mild to severe	Absent	Unaffected or mild
Liver functions	Normal to mildly elevated	Mild to severely elevated (HELLP syndrome)	Mild elevation	Unaffected
Serum uric acid	Sometimes elevated	Elevated	Elevated	Sometimes elevated
Hyperreflexia	Absent	Usually Present	Present	Unaffected
Pulmonary oedema	Can be present	Can be present	Present	Present
Pleural/pericardial effusion	Can be present	Unusual	Present	Can be present

sulphate to prevent the rare event of eclampsia (described by Espinoza et al) [5] as well as cautious use of diuretics to ease interstitial fluid overload. This may be achieved through continued in-patient post-partum assessment, as is done when pre-eclampsia is diagnosed antenatally in view of often worsening hypertension in the first 48 h after delivery.

Although mirror syndrome is a rare clinical entity, it is likely that it is under-researched and under-reported. Two systematic reviews have been published, one in 2010, reporting 56 cases, and in 2017, reporting 113 cases. [3,13]

As stated above, there is a direct link between trophoblastic damage caused by placental oedema and an imbalance in pro- and anti-angiogenic factors in the maternal circulation that ultimately cause maternal endothelial dysfunction and the clinical manifestation of mirror syndrome. [5,10,12]. However, further research into elevations of these serum markers of placental dysfunction is needed to elucidate the underlying aetiology of mirror syndrome, as well as to formulate management guidelines for this spectrum of disorders.

4. Conclusion

Mirror syndrome, caused by several aetiologies of fetal hydrops, is a rare clinical entity which requires timely and accurate diagnosis. Although mirror syndrome and pre-eclampsia have different aetiologies, they may have similar clinical presentations and can often co-exist as the syndrome worsens. There is a need for clinical vigilance and prompt intervention to prevent fetal mortality and maternal morbidity.

Contributors

Caroline Ruth Mathias acquired data and drafted the case report.
Carmela Rizvi revised the draft case report.
Both authors were responsible for conceptualization of the case report and the literature review, saw and approved the final version of the paper, and take full responsibility for the work.

Conflict of Interests

Both authors declare that they have no conflict of interest regarding the publication of this case report.

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Patient Consent

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