Case report on peripartum cardiomyopathy in a patient with Schmidt syndrome with twin pregnancy for emergency lower segment cesarean section

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ABSTRACT

Peripartum and autoimmune cardiomyopathy is an uncommon rare disorder associated with pregnancy. When it occurs association with autoimmune thyroid disorder and autoimmune adrenal insufficiency, it is eponymously referred to as Schmidt syndrome or autoimmune polyendocrine syndrome type 2 (APS type 2). Peripartum cardiomyopathy (PPCM) can be difficult to diagnose as the symptoms can be masked or misinterpreted due to the normal physiological changes during pregnancy, as the symptoms of heart failure can mimic those of pregnancy. PPCM is associated with considerable morbidity and mortality and so should not be underestimated. In this report, we are discussing the management of 32-years-old female with hypothyroidism and Addison’s disease (polyglandular syndrome type 2- Schmidt syndrome) who came for emergency lower segment cesarean section (LSCS) due to twin pregnancy (abnormal doppler of the second twin) and during the period developed pulmonary edema and was diagnosed as peripartum cardiomyopathy.

Keywords: Peripartum cardiomyopathy, Lower segment cesarean section, Schmidt syndrome, Diagnosis, Treatment, Heart failure

INTRODUCTION

Peripartum cardiomyopathy (PPCM) is an uncommon disorder associated with pregnancy where the heart dilates and weakens leading to symptoms of heart failure. Affected women may recover normal heart function, stabilize on medications, or progress to severe heart failure requiring mechanical support or heart transplantation. Even when the heart recovers, another pregnancy may be associated with a risk of recurrent heart failure. A reversible form of dilated cardiomyopathy can develop from alcohol drinking, pregnancy, chronic uncontrolled tachycardia, hypothyroidism, hyperthyroidism, drug use, Addison’s disease and other endocrine dysfunction. Thyroid hormone has a great effect on the heart and vascular system. Cardiac disorders are commonly associated with both hyper and hypothyroidism as the heart is sensitive to the changes in thyroid hormones. According to review of literatures, diastolic dysfunction is most commonly found seen in patients with hypothyroidism, LV systolic function is minimally decreased with decreased EF and Stroke volume. DCM is a rare presentation and most common form of cardiomyopathy usually progressive and associated with poor prognosis. It is uncommon to identify a metabolic etiology responsive to specific therapy, rendering the cardiomyopathy potentially reversible.

Addison’s disease also known as primary adrenal insufficiency is associated with decrease in production of glucocorticoid and mineralocorticoid hormone from the adrenal cortex. Although auto immune adrenalitis is considered to be the major cause of Addison’s disease in up to 90% individuals and most commonly occurs in
females between 30-50 years, other etiologies include infections, drug induced or genetic factors.\textsuperscript{4}

Peri-partum cardiomyopathy is an idiopathic cardiomyopathy that presents with heart failure secondary to left ventricular systolic dysfunction toward the end of pregnancy or in the months after delivery, in the absence of any other cause of heart failure according to Heart Failure Association of the European Society of Cardiology Working Group on PPCM 2010. PPCM is a diagnosis of exclusion. Although the left ventricle may not be dilated, the ejection fraction is nearly always reduced below 45%.\textsuperscript{5}

In contrast to other definitions, the Heart Failure Association’s definition specifically excludes women who develop cardiomyopathy early in their pregnancy and explicitly notes that not all cases present with left ventricular dilation. Pre-eclampsia, hypertensive disorders, and multiple gestations are associated with occurrence of this cardiomyopathy.

The severity of symptoms in patients with PPCM can be classified by the New York Heart Association system as follows: (a) Class I- disease with no symptoms; (b) Class II- mild symptoms/effect on function or symptoms only with extreme exertion; (c) Class III- symptoms with minimal exertion; and (d) Class IV- symptoms at rest.\textsuperscript{5}

This report is a case of Schmidt syndrome in a 32 year pregnant woman, gravi\textsuperscript{2} para\textsuperscript{1} with twin pregnancy who came for emergency LSCS (indication PROM, leaking, abnormal fetal Doppler for the second twin) who developed pulmonary edema during her intra-operative period. She was diagnosed as PPCM by echocardiography, was treated adequately after which she improved and was discharged home. On regular follow up her echocardiogram showed the resolution of the cardiomyopathy and her heart function improved gradually over a period of 1 month after being started on cardiac medications and continuation of the hormonal therapy when her hormonal levels normalized.

**CASE REPORT**

The patient was a 32-years-old female with co-existing hypothyroidism and Addison’s disease on medication was scheduled for emergency LSCS (PROM and twin pregnancy- abnormal doppler of 2\textsuperscript{nd} twin) who developed pulmonary edema during LSCS. She was diagnosed as peripartum cardiomyopathy and treated with anti-failure medication. She improved in condition and was discharged home safely on the treatment. On follow up after 1 month, we noticed that the cardiac function had returned to normal.

Our patient, a 32-years-old female, Gravida 2 para 0, abortion 1, IVF pregnancy, with twin’s h/o hypothyroidism on 100 mcg thyroxin and prednisolone 7.5 mg per day (5 mg during day and 2.5 mg at night), GDD on diet control. It was a precious pregnancy and the patient was seen in the pre-anesthesia clinic as was scheduled for an elective LSCS. An endocrine reference was requested but as the patient got admitted to the hospital in an emergency situation of PROM and leaking with abnormal fetal Doppler, her referral could not be completed. Blood investigations were within normal limits but she did not have any reports of the thyroid profile or cortisol levels.

She came in for an emergency LSCS due to premature rupture of membranes and leaking and had an abnormal fetal doppler and the second twin was transverse lie. After discussion with the obstetrician and on call consultant anesthesiologist, it was decided to give her 200 mg hydrocortisone iv bolus and then the patient was shifted to the operation theatre. She had taken her morning dose of thyroxine (100 mcg) and 5 mg of prednisolone. She was not adequately fasting, and it was decided to give her spinal anesthesia and consent was taken for the same. She was premedicated with 30 ml of sodium citrate and antibiotic prophylaxis with 2000 mg cefazolin was given IV diluted in 100 ml normal saline.

As she came in an emergency, it was not possible to get an endocrine review.

The patient was shifted to the operation table at 09.53 hours and monitors attached- ECG, pulse oximeter and NIBP. Measures to prevent hypothermia were also kept in place. An intravenous access was secured with 2,18 G cannulas one on each metacarpal vein in the right and left hand respectively and warm Ringers’ lactate 10-15 ml/kg was co-loaded. The patient was placed in sitting position and with strict aseptic precautions the back was cleaned and draped and local anesthesia with 100 mg, 1% lidocaine was infiltrated followed by spinal anesthesia given in L3-L4 space with 26 G spinal needle in the first attempt at 10.08. 10 mg of bupivacaine 0.5% heavy mixed with 15 mcg (0.3 ml) fentanyl was injected intrathecely after confirming a clear and free flow of CSF. The patient was made to lie down in supine position with right sided wedge under the hip and phenylephrine infusion started at 5 mcg/kg/hr to maintain SBP within 20% of the baseline. The NIBP was measured at 1 min intervals during and after the delivery of the babies. O\textsubscript{2} was administered with O\textsubscript{2} mask- 5 l/min

The 1\textsuperscript{st} twin was delivered (baby boy- 3180 g, Apgar-9/10 at 10.19) and subsequently followed by the delivery of the 2\textsuperscript{nd} twin (baby girl- 2892 g, Apgar- 9/10 at 10.20) which was followed by delivery of placenta. Oxytocin 5 units stat was given followed by infusion of 30 units by an infusion pump at rate of 125 ml/hr. Methylergometrine 0.2 mg IM and tranexamic acid 1000 mg IV also was given.

Mid way towards the procedure, at 10.35, the patient developed difficulty in breathing became tachypnoeic and she complained of feeling some noises in her chest. The patient started desaturating and SPO\textsubscript{2} dropping to 88-89%. The oxygen concentration was increased from 5 l/min to 10 l/min then again increased to 15 l/min. On auscultation of the chest, there were bilateral crepitation
more towards the bases and posteriorly and occasional ronchi.

At 10.50, 20 mg furosemide was given IV. Patient was placed in a slightly propped up position to ease her breathing.

The surgery was completed with the patient slightly in a propped-up position. The total fluid intake was 2450 ml (ringer lactate) with a blood loss of 1200 ml and urine output of 100 ml.

After the surgery, the patient was shifted to the PACU (10.55). In the PACU also the patient continued to have the difficulty in breathing and she continued to be tachypneic and orthopneic (breathless in supine position). Oxygen was restarted as it was discontinued while shifting her from OT to PACU. Initially in the PACU, the SPO₂ was 90% off O₂ and when oxygen was reconnected, SPO₂ improved to 95-96%.

Another dose of furosemide 20 mg was repeated at 11.20 hours, dexamethasone 8 mg given and nebulization with salbutamol (5 mg) and saline was given at 12.10. After some time O₂ concentration was decreased from 10 l/min to 5 l/min when the patient was maintaining her SPO₂. An arterial blood gas was sent which showed low pO₂-79 and pCO₂ of 34, pH-7.461, SPO₂-96.37 at 13.12.

An X-ray chest was requested, an ECG done, and physician called for at 13.20. Then again 20 mg frusemide was repeated after about 1 hr. The urine output was 3100 ml in the recovery from 11.00 to 16.30 hours. Total VF in PACU was 500 ml (Ringers) and 250 ml PPF and oxytocin 30 U at rate of 125 ml/hr.

XRC at 15.30- heart size difficult to assess. Accentuated broncho vascular markings and peri-hilar marking with bilateral haziness in mid and lower zone s/o pulmonary infiltration.

The physician ordered to continue hydrocortisone 100 mg 8th hourly and thyroxine and advised. Also, referral to the cardiologist was made at 16.00. The cardiologist came at 17.00 and at 17.30 a bed side echocardiography was done which showed a dilated LA and LV and global hypokinesia and an EF- 30% it also showed mild to moderate MR and mild AR. The ECG taken at 14.15 showed sinus rhythm with no significant ST-T changes. He made a differential diagnosis of acute pulmonary edema due to peripartum cardiomyopathy was made and it was decided to shift the patient to SICU for non-invasive ventilation, incentive spirometry, chest physiotherapy and for continuous monitoring and also to start anti-failure treatment.

Arterial line was inserted for serial ABGs under local in SICU at 21.30 and patient was started on iv frusamide 40 mg IV 12th hourly and PRN. In the SICU she was started on intermittent CPAP 12/8 and O₂ with rebreathing mask with O₂ 10 l/min. Also, frusamide and chest physiotherapy and incentive spirometry were continued with a series of investigations blood, ECG and echocardiography. Urine output was measured and was 100-180 ml/hr. Serial ABGs showed low pO₂ and subsequently improved with CPAP, O₂ therapy, chest physiotherapy and medications.

XRC showed the same findings taken at 5.52 am.

2D echo next morning at 06.55 am showed- dilated LV, severely decreased LV function with global hypokinesia of LV with EF of 30% grade 3 diastolic dysfunction, decreased RV function, moderate MR, trivial AR mild TR and RVSP- 33 mmHg and min pericardial effusion which confirmed our diagnosis of peri-partum cardiomyopathy.

There was also e/o pleuritic chest pain and increased troponin enzymes. Also, we had to rule out myocardial ischemia, pulmonary embolism and myo-pericarditis and these were ruled out by a normal ECG.

The patient was started on aspirin 100 mg, metoprolol 12.5 mg bid, enoxaparin 80 mg bid and serial ABGs, Trop T, CRP and her cortisol and thyroid levels repeated. Doppler ultrasound was also done to rule out DVT.

The patient improved over a period of 3-4 days with CPAP and on the POD 4 she was maintaining her saturation without O₂ and even the pO₂ improved in her ABG. She was later transferred from the SICU to the ward and next day was discharged home on beta- blockers, aspirin and ACE inhibitors (anti-failure medication). Bisoprolol 2.5 mg oral, levolthyroxine- 100 mcg, ramipril- 2.5 mg and aspirin 75 mg oral and was advised a cardiac follow up. Her blood sugars were also monitored and were within the range of 4.5 to 6.9.

During the post-operative period, renal profile and electrolytes were normal. Her cortisol level on 16/12 at daytime was 277 which were normal, while her thyroid levels were- 6.202 (TSH- high levels) and free T4- 11.8 which was within normal range.

Her troponin levels were 1031.0, 858.0, 316.80, 224.6, 225.0, 239.0 and pro BNP were 2750.0, 4948.0 ,2852.0, 2561, 1905 and 1703 on 0, 1, 2 and 3 post-op days respectively which were high initially and lowered when patient condition improved. Also, her D- dimer levels were high (4.48 mg/ml) which was high. Her CRP levels were also high and went as high as 76.3 and later reduced to 46.5 and then subsequently to 25.5.

The patient was again readmitted with post CS wound infection, took treatment on admission and discharged after 3 days. She continued to be on regular follow ups with the obstetrician and cardiologist and when she came for follow up after 4 weeks her cardiomyopathy had completely resolved as her repeat ECG and echocardiography were normal. ECG- sinus rhythm-normal, echo- no RWMA, normal diastolic function and EF- 56%.
And TSH-0.620 and free T4-19.0. She also continued her regular endocrine and cardiac follow ups and also continued her medications- thyroxine, prednisolone, beta-blockers, ACE inhibitors and aspirin.

Figure 1: ECG of patient immediate post-operative period- normal.

Figure 2: X-ray chest of the patient postoperative period. Heart size difficult to assess. Accentuated broncho vascular markings and peri-hilar marking with bilateral haziness in mid and lower zone s/o pulmonary infiltration.

Figure 3: Echo of patient on the post- operative day 1- dilated LV, severely decreased LV function with global hypokinesia of LV with EF of 30% grade 3 diastolic dysfunction, decreased RV function, moderate MR, trivial AR mild TR and RVSP- 33 mmHg and min pericardial effusion.

DISCUSSION

PPCM is an idiopathic cardiomyopathy that presents with heart failure secondary to left ventricle systolic dysfunction towards the end of pregnancy or in the post-partum period. Approximately 75% of cases are diagnosed within the first month peri-partum, and 45% present in the 1st week.5 PPCM is associated with considerable mortality and morbidity and hence, should not be underestimated. At least 7% of cases may be a part of spectrum of familial dilated cardiomyopathy. It should be dealt with accordingly and when suspected one must establish a diagnosis rapidly.5

The Heart Failure Association’s definition specifically excludes women who develop heart failure early in pregnancy and notes that not all cases present with left ventricular dilatation like pre-eclampsia, hypertensive disorders and multiple gestations are associated with the occurrence of this cardiomyopathy.5 Also, other risk factors like older maternal age, multifetal pregnancy,
African descent, prior toxin exposure (cocaine), use of certain medications to prevent premature labor are also associated with tendency to develop PPCM. It is more likely to occur in patients over 30 years. who is pregnant with twins or who is multiparous. PPCM can also be familial, or secondary to several acquired conditions including pregnancy, alcoholism, chronic anemia, adriamycin and other chemotherapeutic agents, IHD, infectious causes (autoimmune or viral myocarditis).

Autoimmune polyglandular syndromes consist of failure of two or more endocrine glands together requiring hormonal treatment. Type 2 APS which consists of Addison’s disease in combination with autoimmune thyroid disease and/or type 1 diabetes was described by Schmidt in 1926 is the commonest type of APS in pregnancy.

Adrenal insufficiency during pregnancy is rare, which may be attributable to the decreased rate of fertility in these patients. The decreased fertility is usually multifactorial and related to other autoimmune conditions associated with primary adrenal insufficiency, including autoimmune thyroid disease, premature ovarian failure, and Type 1 diabetes. These patients are subject to chronic anovulation and lack of adrenal androgen production, which may be necessary for folliculogenesis. Despite its rarity, adrenal insufficiency can increase the risk of unfavorable pregnancy outcomes. If undiagnosed, it can also lead to maternal and fetal morbidity and mortality. Furthermore, the signs and symptoms of adrenal insufficiency can be obfuscated by symptoms normally attributed to pregnancy, particularly in the first trimester, including fatigue, nausea, vomiting, food aversions and dizziness.

Pregnancy is a period that places great physiological stress on both the mother and the fetus in the best of times. However, if pregnancy is compounded by endocrine disorders such as hypothyroidism, the potential for maternal and fetal adverse outcomes can be immense.

The most notable change is the increase in thyroxine-binding globulin (TBG). This is due to stimulation of TBG synthesis by elevated maternal estrogen levels, and more importantly, due to a reduced hepatic clearance of TBG because of estrogen-induced sialylation. This increased TBG concentration leads to an expansion of the extrathyroidal pool and results in elevated total T3 and T4 levels due to an increase in maternal thyroid hormone synthesis. Maternal thyroid hormone synthesis is also increased due to an accelerated renal clearance of iodide resulting from the increased maternal glomerular filtration rate.

Women with hypothyroidism have decreased fertility; even if they conceive, risk of abortion is increased, and risk of gestational hypertension, anemia, abruptio placenta and postpartum hemorrhage is increased. The risk of these complications is greater in women with overt, rather than subclinical hypothyroidism. The prevalence of hypothyroidism during pregnancy is estimated to be 0.3-0.5% for overt hypothyroidism and 2-3% for subclinical hypothyroidism.

Autoimmune thyroiditis is the commonest cause of hypothyroidism during pregnancy. Signs and symptoms which suggest hypothyroidism include inappropriate weight gain, cold intolerance, dry skin and delayed relaxation of deep tendon reflexes. Other features like constipation, fatigue, and somnolence are usually attributed to pregnancy. The signs and symptoms can be masked due to normal physiological changes in the thyroid gland due to pregnancy.

An auto-immune basis for PPCM is suggested by the fact that sera from PPCM patients contain high titers of autoantibodies against normal cardiac tissue proteins 37, 33 and 25 kD that are not present in the sera of patients with idiopathic cardiomyopathy (IDCM). In addition to the autoantibodies, the PBMC’s from PPCM patients demonstrate a heightened level of fetal micro chimerism, an abnormal cytokine profile, decreased levels of CD4+ CD25lo regulatory T cells, and a significant reduction in the plasma levels of progesterone, estradiol and relaxin in PPCM patients as compared with other normal pregnant non-PPCM patients. A potential role for reduced plasma levels of selenium in the pathogenesis of select PPCM patients was also noted. These findings for the first time suggest that such abnormalities may in concert lead to the initiation and perpetuation of an autoimmune process, which leads to cardiac failure and disease.

In our patient, both hypothyroidism and Addison’s disease co-existed. Also, she had infertility and became pregnant after a successful IVF after a previous history of abortion. Due to the polyendocrine syndrome type 2 and due to the multiple gestations, she was prone for developing PPCM which was picked up early and managed appropriately to prevent a fatal outcome. Also, during follow up with the cardiology and endocrinology it became evident that due to proper administration of hormonal treatment and anti-failure treatment her PPCM was transient and resolved completely which was proven in her blood tests, hormonal profile and 2D echocardiography report after 4 weeks. It shows that myocardial function can be reversed with restoration of normal thyroid function and cortisol levels and the management of heart failure.

We also have several case reports, which show association of poly glandular autoimmune syndrome type 2 with cardiomyopathy. In one such patient, the treatment of CHF was complicated by the coexisting Addison’s disease due to which the heart failure progressed rapidly and the patient required inotropic support, placement of an IABP and later LVAD and last but not the least a cardiac transplantation.

Other case reports are in pregnant patients with Schmidt syndrome who developed PPCM in the peripartum period. And another case in a patient who developed PPCM in the postpartum period who needed inotropic support.
support and anti-failure treatment and later had a slow and gradual recovery.5

Several studies have suggested that approximately 50% patients with PPCM recover normal heart function, 25% have persistently reduced heart function but remain stable on medications, and 25% progress to severe heart failure. Early improvement in EF (i.e.; within the first 3-6 months) predicts a good outcome, some women will have slow, gradual improvement in EF over years. The decision of when to stop medications after full heart recovery still remains controversial. However, most physicians agree that ACE inhibitors and beta blockers should be continued for at least one year after normalization of EF.1

In some cases of PPCM, the association appears to occur on an autoimmune basis, arguably due to the fact that PPCM is sometimes characterized by the sera which contain high titers of autoantibodies against human cardiac tissue proteins that are not present in the sera of patients with idiopathic cardiomyopathy. Accordingly, PPCM might be thought of as an autoimmune condition affecting multiple organs concomitantly. This argument might hold true for the association of PPCM and autoimmune hypophysis, the latter characterized by homogeneous enlargement of the pituitary gland followed by development of an ‘empty sella’. It might also hold true for the association of PPCM and type II autoimmune polyglandular syndrome, the latter characterized by primary hypoadrenalism, primary hypothyroidism and type 1 diabetes. However, even in the absence of stigmata of autoimmunity, PPCM can coexist with endocrinopathy.12

CONCLUSION

PPCM is a diagnosis of exclusion after other causes of heart failure are ruled out. It is defined when heart failure occurs in the last month of pregnancy or within 5 months of delivery, absence of an identifiable cause, absence of known pre-existing heart disease and LV systolic dysfunction. There are various proposed etiologies including endocrinopathy and autoimmune etiology.

Recognition of this link should prompt clinicians to heighten their awareness of potential risk of PPCM in women with other autoimmune conditions. Conversely, if a patient develops PPCM, investigation for concomitant autoimmune condition must also be indicated.

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