Immunosuppression therapy in the management of peripartum cardiomyopathy: A case series and literature review

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Abstract

Peripartum cardiomyopathy is a heart failure syndrome occurring late in pregnancy or during the early post-natal period. The pathophysiology of peripartum cardiomyopathy is not fully understood and various mechanisms have been postulated including an underlying inflammatory process. We here report four cases presenting with acute left ventricular systolic dysfunction. Three out of four of the patients presented with a left ventricular ejection fraction <30% and one with a left ventricular ejection fraction of 35%. All made a full clinical recovery following treatment with high-dose intravenous steroids. This case series adds to the growing body of evidence for the role for immunosuppressants in the management of peripartum cardiomyopathy.

Keywords

Immunology, cardiology

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Introduction

Peripartum cardiomyopathy (PPCM) is an idiopathic cardiomyopathy presenting with heart failure secondary to LV systolic dysfunction towards the end of pregnancy, or in the months following delivery, where no other cause of heart failure is found. It is a diagnosis of exclusion. The left ventricle may not be dilated but the ejection fraction is nearly always reduced below 45%.¹

Cardiomyopathy was first associated with pregnancy as early as 1937.² PPCM patients typically present with symptoms of heart failure, which may resemble common symptoms of the late stages of pregnancy. These include shortness of breath, paroxysmal nocturnal dyspnoea, orthopnoea, peripheral oedema and occasionally chest pain and palpitations.

There is significant geographical variance in the incidence of PPCM (1 in 4000 in the USA,³ 1 in 1000 in South Africa⁴ and 1 in 300 in Haiti.⁵ It develops in women without a previous history of cardiovascular disease and is thought to be caused by general risk factors for cardiovascular disease, as well as factors related to pregnancy (tocolytics, parity, gravidity and malnutrition).⁶

Although, the pathophysiology of PPCM is not fully understood, various mechanisms have been postulated, such as oxidative stress involving cardiomyocytes.⁷ This causes inappropriate inflammatory activation of cathepsin D which processes prolactin into an antiangiogenic and pro-apoptotic 16 kDa fragment. The ensuing disruption to the cardiac microvasculature combined with increased apoptosis of the cardiomyocytes leads to impaired function. Bromocriptine, which inhibits prolactin secretion, has been proposed as a therapeutic option in PPCM patients. Other postulated mechanisms include systemic angiogenic imbalance,⁸ and autoantibodies against cardiac tissue.⁹ Viruses may also play a role but the data are far less conclusive. Moreover, an inflammatory process has been found to underlie PPCM in between 29%^{10,11} and 78% of patients.¹² This has led to a possible role for immunosuppressants in the management of this condition.

We present four consecutive patients diagnosed in the first few days of their illness, who developed PPCM and received immunosuppressive therapy with methylprednisolone. In our unit this is standard practice, once alternative causes for myocardial pathology have been excluded.

All patients made a satisfactory recovery and are in good health. This supports the possibility of an underlying inflammatory process in PPCM and a potential role for immunosuppression in its management.

Case series

Case 1

A 50-year-old woman, presented 12 days post emergency caesarean section (CS) delivery of IVF (donor egg) twins, following a diagnosis of pre-eclampsia. She had no other significant cardiac history. As part of the donor egg protocol, she had been assessed by a cardiologist pre-conception and declared healthy. She had developed increasing shortness of breath since her delivery. On examination, there was gross peripheral oedema with bibasal crepitations and a pansystolic murmur on auscultation. A CT pulmonary angiogram (CTPA) had demonstrated interstitial oedema and bilateral pleural effusions suggestive of heart failure. Echocardiography demonstrated a left ventricular ejection fraction (LVEF) of 30%. She was diagnosed with PPCM and commenced on furosemide, aspirin, catopril, and digoxin. She was acutely immunosuppressed with 1 g IV methylprednisolone. Two days later, there was a slight improvement in LV function and a further dose of 500 mg IV methylprednisolone was administered. Clinically there was evidence of significant improvement with a clear

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chest to auscultation and no pedal oedema. Spironolactone and carvedilol were also added.

An MRI performed a week after her initial presentation showed a stable LVEF of 32%. She was discharged home with dalteparin. Over the following months, she continued to improve and echocardiography performed in clinic after her initial presentation, showed only a mild impairment of LVEF, and within six months restoration of normal systolic function.

Case 2

A 37-year-old woman, parity two gravida two, presented eight days post CS, following a normal pregnancy, with acute onset hypoxia secondary to pulmonary oedema. She had no other significant cardiac or medical history. Due to acute onset hypoxia postnatally, a CTPA was performed to exclude pulmonary embolism. This demonstrated interstitial oedema and bilateral pleural effusions suggestive of heart failure. Echocardiography showed her LVEF to be 15%. A diagnosis of PPCM was considered likely and she was commenced on aspirin, furosemide, ramipril, and spironolactone. She was acutely immunosuppressed with IV methylprednisolone. Due to recurrent atrial tachycardias, she was commenced on digoxin and bisoprolol. Echocardiography performed a few days later showed an improvement of the LVEF to 37%. She was discharged home with dalteparin. At a clinic appointment one month post discharge, her LVEF had improved to 40–50% and had normalised by two months.

Case 3

A 31-year-old woman presented two days postpartum (fifth pregnancy), following a normal pregnancy, in pulmonary oedema following a blood transfusion. She had no other significant cardiac history but was asthmatic. A CTPA demonstrated interstitial oedema and bilateral pleural effusions. Echocardiography showed her LVEF to be 35% with moderate mitral regurgitation. On examination, she had clinical evidence of pulmonary oedema and a pansystolic murmur on auscultation. A diagnosis of PPCM was considered to be the most likely and she was prescribed furosemide, aspirin and spironolactone. As she was also hypertensive with a systolic blood pressure of over 160 mmHg, nifedipine was administered. Due to a labile blood pressure, ramipril was also added. She was acutely immunosuppressed with IV methylprednisolone and within days there was no clinical evidence of heart failure. Repeat echocardiography showed a slight improvement of LVEF.

However, in view of persistent hypertension, investigations for pheochromocytoma were performed; 24-h urinary collection and an MRI of the adrenal glands were negative. She was commenced on ivabradine instead of a beta blocker in view of her asthma and discharged on dalteparin. Within three months her LVEF had improved to 45% and had fully normalised by eight months.

Case 4

A 41-year-old woman presented in preterm labour at 33 weeks. She had no other significant cardiac history but had a history of migraines. She was pregnant with IVF twins and had a history of increasing shortness of breath over the preceding two weeks. She was given beclomethasone and nifedipine (tocolytic), whereupon she developed severe hypotension and was fluid resuscitated. Shortly following this, she developed pulmonary oedema, becoming acutely hypoxic and underwent an emergency CS under general anaesthesia. A CTPA following delivery demonstrated a single filling defect representing a small pulmonary embolus, four chamber cardiomegaly, interstitial oedema and pleural effusions.

She remained intubated overnight post CS and received furosemide. Echocardiography showed an LVEF of 35% with moderate to

severe mitral regurgitation. She was successfully extubated the following morning. At this early stage, it was not clear if her clinical state was simply due to the haemodynamic burden of a twin pregnancy complicated by premature labour and fluid resuscitation following the administration of tocolytic drugs, or that she was developing PPCM. However, rather than improving, her clinical state deteriorated over the next two days with clinical signs of congestive cardiac failure, and a repeat echocardiography showed worsening LVEF estimated to be 20% with a very poorly contractile, thickened and echogenic left ventricle and mitral regurgitation. Pulmonary artery pressure (PAP) was estimated to be 52 mmHg with a systemic pressure of 115/65 mmHg. The diagnosis of PPCM was considered very likely in this elderly primipara with twin pregnancy and rapidly worsening heart failure. She was acutely immunosuppressed with IV methylprednisolone. She was commenced on enalapril and aspirin. The following day her clinical state was markedly improved and bisoprolol was cautiously added. Echocardiography two days later showed a small improvement in LV function but a striking reduction in PAP of 25–30 mmHg. The sudden rise in PAP implies severe but transient LV restrictive physiology perhaps due to myocardial cellular infiltration reversed by immunosuppression. A second dose of IV methylprednisolone was administered.

An MRI performed a day later showed an LVEF of 32%. Late gadolinium contrast images showed a very unusual appearance with uptake in the mid part of the myocardium; appearances not typical of idiopathic dilated cardiomyopathy. Five days later, the LVEF on echocardiography was 40%. On discharge, she was commenced on warfarin for three months in view of her pulmonary embolism. A month later her LVEF had improved to 45%. A repeat MRI at five months showed LVEF comparable to that shown on the echocardiogram and interestingly again, predominantly subepicardial late gadolinium enhancement.

Discussion

While the diagnosis of PPCM is one of exclusion, none of these patients had any evidence of pre-existing LV dysfunction and all had risk factors for PPCM as all were either older mothers, two with twin pregnancies or with multiple previous pregnancies, and one with preeclampsia.

Patients with PPCM should be managed with established treatment for acute heart failure from other causes with oxygen, intravenous diuretics and ACE inhibitors with intravenous nitrates and inotropes if required. Beta adrenergic blockers should be added when acute heart failure has been stabilised. Patients with a reduced LVEF have a higher thrombotic risk; therefore, low-molecular weight heparin should also be administered.

This case series demonstrates impressive recovery of cardiac function following very early administration of high-dose systemic immunosuppressive therapy in addition to standard management of acute heart failure in four patients with PPCM. Causality cannot be proven, but the outcome was excellent for all four women and there was no evidence of adverse effects. This adds to the growing body of evidence for the role for immunosuppressants in the management of PPCM. Several studies have shown beneficial effects. Patients with PPCM treated with immune modulators demonstrated greater recovery of LVEF during early follow-up at six months, compared to control subjects with PPCM who did not receive immunoglobulins.¹³ In patients treated with prednisolone and azathioprine for eight weeks following a biopsy proven diagnosis of PPCM, there was notable improvement following treatment.¹²

Moreover, inflammatory cytokines have been implicated in the pathogenesis of PPCM.¹⁴ Inflammatory markers such as C-reactive protein, interleukin 6 and interferon gamma are increased in patients with PPCM.^{7,15,16} Furthermore, use of anti-inflammatory agents such as pentoxifylline, an inhibitor of tumour necrosis factor α , have been shown to be of benefit in patients with PPCM compared to patients

with PPCM treated with standard treatment alone.¹⁷ Interestingly, persistently raised inflammatory markers such as interferon gamma are associated with poor prognosis.¹⁵

Despite the evidence for a beneficial effect of immunosuppressive therapy in the management of PPCM, other authors have shown no difference in patients managed with immunosuppressants compared to standard therapies.¹⁸ Furthermore, immunosuppression with ciclosporin and prednisolone did not improve outcome in patients with acute myocarditis.¹⁹ It must be noted that although the myocarditis treatment trial failed to demonstrate any benefit of immunosuppressive therapy, this was not trialled in patients with PPCM.

In our cases series, all patients managed with immunosuppressive therapy recovered good LV function. As a general rule, it has been quoted that greater than 50%²⁰ of patients recover LV function. If patients have an LVEF of greater than 30% at presentation, the likelihood of recovery is high. If on the other hand the patient does not show an improvement in LVEF at six months postnatally, prognosis is poor.²¹ Three out of four of the patients in our case series fell into a poor prognostic category (LVEF <30%) with the remaining presenting with a severely reduced LVEF of 35%, yet all have made full clinical recovery with three out of four returning to normal LV function. Although this was not a controlled study, comparing patients who did not receive immunosuppressive therapy, and our numbers were small the evidence suggests that there may be a beneficial effect of immunosuppressive therapy. Further research is required to determine if immunosuppression should become a standard treatment in the management of PPCM.

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