A Challenging Case of Peripartum Cardiomyopathy Complicated by Thromboembolism

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Abstract:
Peripartum cardiomyopathy (PPCM) is a rare and potentially life-threatening heart condition that occurs in previously healthy women in the last month of pregnancy or within five months post-delivery. Diagnosis is made by identifying left ventricular systolic dysfunction and excluding other common causes of heart failure. The presence of intracardiac thrombus is associated with increased adverse events, mortality, and high risk of thromboembolic events. Here, we describe a case of a 37-year-old mother presenting with shortness of breath on exertion and orthopnea. Echocardiography revealed LV systolic dysfunction and a large organized thrombus, among other findings. She was treated with bromocriptine, anticoagulants, and guideline-directed medical therapy for heart failure with reduced ejection fraction. Over the next two months, she recovered with adequate ejection fraction and complete thrombus resolution, evident on echocardiography.

Introduction:
Peripartum cardiomyopathy (PPCM) is a rare disorder in which left ventricular systolic dysfunction and symptoms of heart failure occur between the last month of pregnancy and the first five months postpartum. The primary causative agent has been identified as a 16-kDa prolactin fragment formed by the cleavage of prolactin molecule by cathepsin D (induced by oxidative stress). This 16-kDa prolactin fragment has angiostatic and proapoptotic properties responsible for the pathophysiology of PPCM. Bromocriptine is a central dopamine-D2-receptor agonist that decreases the production of prolactin, hence counteracts the inflammatory cascade triggered by the secretion and cleavage of prolactin.

The formation of left ventricular thrombus in patients with PPCM complicates the management of associated heart failure because of the underlying risk of thromboembolism. The peripartum period is a hypercoagulable state, likely a natural response to minimize the risk of postpartum hemorrhage. Given the high risk of thromboembolism, anticoagulation is advised in patients with PPCM during and two months after pregnancy. We present a case of PPCM treated with bromocriptine with a large LV thrombus on echocardiography, with evidence of embolism, which was managed with anticoagulation.

Case Description:
A 37-year-old hypothyroid woman (G2P2) (on levothyroxine 50mcg) initially presented to her general practitioner (GP) 4 months after her last childbirth with complaints of gradually worsening shortness of breath on exertion and inability to lie down flat for the past three weeks, along with complaints of epigastric, back pain, and development of bilateral leg

swelling from the last week. During her pregnancy, she was diagnosed with gestational hypertension in the 3rd trimester, but she was noncompliant with her medications. She started taking antihypertensive drugs two days before her delivery and stopped after one month postpartum. Otherwise, her pregnancy was uneventful. She had stopped breastfeeding after visiting the GP.

Echocardiography at GP visit revealed global hypokinesia with dilated LV cavity, impaired LV and RV systolic function, LVEF = 32%, grade III diastolic dysfunction (E/a = 2.5, E/e' = 21), TAPSE = 15, Pulmonary Hypertension, PASP = 48 with no evidence of intracardiac thrombus. She was presumptively diagnosed as a case of peripartum cardiomyopathy. She was started on loop diuretics, mineralocorticoid receptor antagonist, ARNI, and beta-blocker from her primary care team and referred to a higher center for further management.

She then presented to the Cardiology Outpatient Department and was advised in-patient admission because of worsening symptoms. She was started on bromocriptine (initially 2.5 mg BD for two weeks) and continued on loop diuretics, MRA, ARNI, and beta-blocker. Her repeat echocardiographic evaluation revealed dilated LA and LV, Global hypokinesia, depressed LV systolic function, Grade III diastolic dysfunction, LVEF= 45%, average GLPS= -5%, and a large organized thrombus (10 X 31 X 11mm) attached to the LV apex. Anticoagulation was promptly started with LMWH (40mg SC BD).

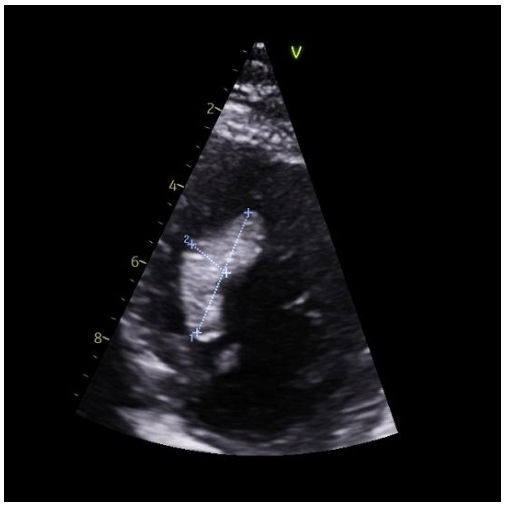

Fig. 1: *View of LV showing the thrombus In situ*

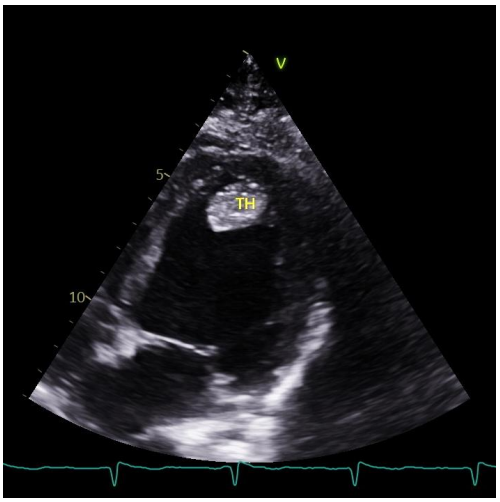

Fig. 2: *Apical four-chamber view showing Cardiomyopathy & thrombus in situ.*

On the 4th day of her stay, she suddenly developed an episode of dizziness, slurred speech, and sweating, with spontaneous recovery within 24 hours. The NCCT brain revealed no evidence of bleeding. Subsequent MRI of the brain revealed small left-sided parietal cortical and subcortical infarct. 24-hour Holter monitoring revealed no evidence of arrhythmia. Cardiac thrombus was presumed to be the source of the thromboembolic event. A neurology opinion was taken, and a decision to continue bromocriptine with therapeutic anticoagulation was made.

Anticoagulation with low-molecular-weight heparin (LMWH) was bridged with an oral vitamin K antagonist (acenocoumarol), and the dose was directed by daily INR monitoring. She was

discharged on a stable INR between 2.5 and 3.5. She was released after two weeks with bromocriptine 2.5 mg OD, loop diuretics, ARNI, MRA, beta-blocker, SGLT2i, and oral anticoagulant (acenocoumarol).

After six weeks, she felt much better on her next follow-up visit to the Outpatient Department. Check echocardiography showed that the LV thrombus had dissolved entirely, the average GLPS improved to -10.2%, and LVEF= 46%. Bromocriptine was stopped, and acenocoumarol and other standard heart failure medications were continued till the subsequent follow-up.

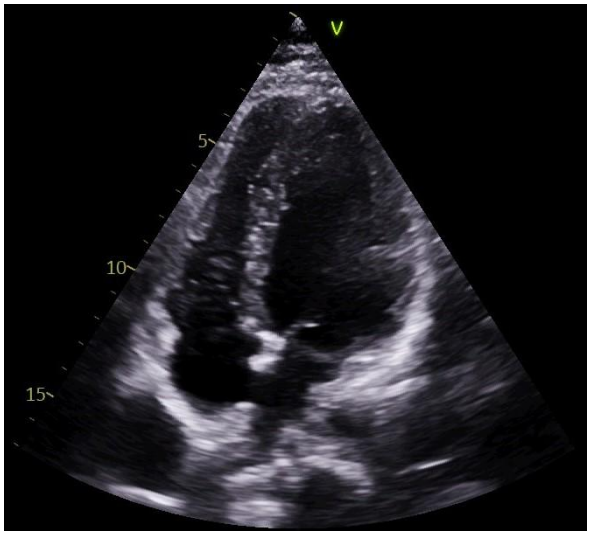

Fig. 3: *Apical four-chamber view showing no evidence of the previous thrombus.*

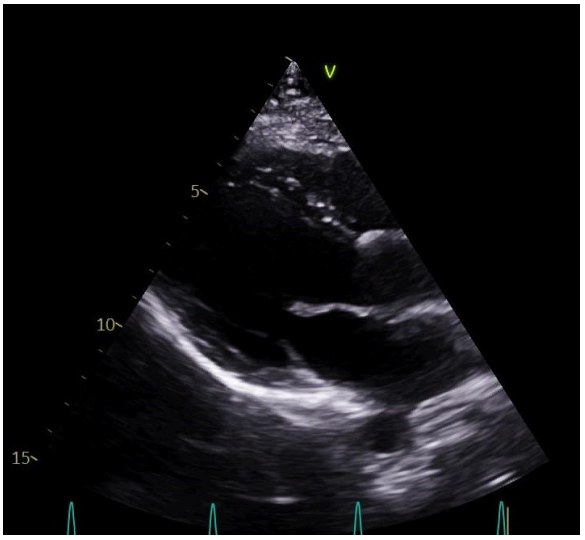

Fig. 4: *PLAX view showing no evidence of the previous thrombus.*

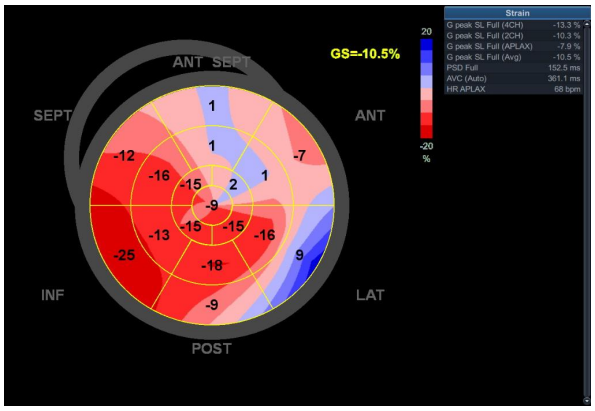

Fig.6: *AGLS = -10.5%*

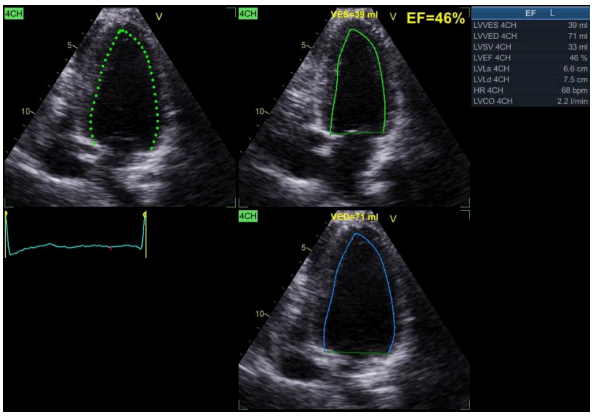

Fig.5: *LVEF = 46% measured by the modified Simpson Biplane method.*

On her subsequent follow-up after eight weeks, she had no fresh complaints and was doing well. Repeat echocardiography revealed LVEF = 55%, average GLPS = -17%, no evidence of pulmonary hypertension and LV thrombus, and normal chamber dimensions. Acenocoumarol was discontinued, and the dose of loop diuretic was reduced.

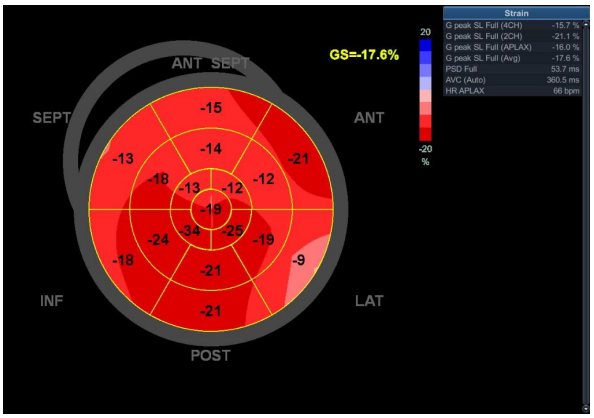

Fig.7: *Improved AGLS = -17.6%*

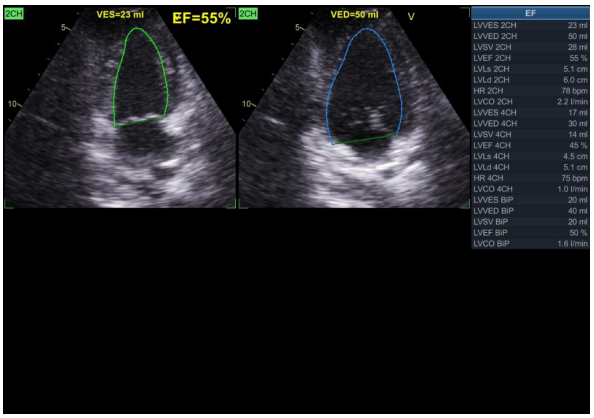

Fig.8: Improved LVEF 55% measured by Modified Simpson biplane method

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Discussion:

Peripartum cardiomyopathy affects women in the last month of pregnancy up to 5 months postpartum.[1,2] Most of the time, the diagnosis of peripartum cardiomyopathy is presumed, as preexisting cardiac imaging is seldom available in these young age groups.[3] Peripartum cardiomyopathy is a diagnosis of exclusion. Healthy pregnant mothers presenting with signs and symptoms of heart failure in the last month of pregnancy or months following may be considered cases of peripartum cardiomyopathy in the appropriate clinical context.

A “multiple hit” model for peripartum cardiomyopathy has been described by the European Society of Cardiology (ESC).[4] Associated risk factors include age over 30 years, race, pre-eclampsia, hypertension, smoking, and multiparity and multifetal gestation. Mutations involving the titin gene (TTN), which is also involved in the development of DCM, are present in European and American populations having PPCM.[5,6] Angiogenic imbalance, physiological cardiac stress, neurohormonal alterations, genetic predisposition, and other risk factors culminate in developing PPCM.

Women present with symptoms of heart failure in the last month or postpartum months. It is sometimes a challenging task to differentiate symptoms of PPCM from regular pregnancy-related changes. Orthopnea and paroxysmal nocturnal dyspnea are more specific in these women over mild shortness of breath and bipedal edema. PPCM patients are often in NYHA class III or IV at the time of presentation.

A thorough history and proper investigations help us to differentiate between PPCM and other causes of LV systolic dysfunction. The fundamental studies include ECG, NTproBNP, echocardiography, chest X-ray, and routine blood investigations. Obtaining an echocardiography not only helps us to identify LV systolic dysfunction but also identifies any

intracardiac thrombus. Cardiac MRI is sometimes functional to differentiate PPCM from preexisting/familial DCM, ARVD, and myocarditis once a patient is stabilized. However, the benefit of obtaining cardiac MRI in these women over echocardiography remains uncertain.[8] Genetic testing can be advocated, though routinely not done.[4]

Early diagnosis and prompt treatment are crucial as PPCM can cause severe morbidity and mortality. Postpartum women with PPCM are generally treated with heart failure modifying agents such as beta-blockers, ACEIs/ARBs/ARNIs, and MRAs, along with loop diuretics. Hydralazine and nitrates can replace ACEIs/ARBs/ARNIs/MRAs during pregnancy.[4] Beta-blockers[8] and loop diuretics can be cautiously used during pregnancy.[4]

Notable complications of PPCM are thromboembolism secondary to LV thrombus formation and sudden cardiac arrest due to ventricular arrhythmias. The rate of thromboembolism[9] is much higher in PPCM than in other forms of cardiomyopathy because of the hypercoagulable [10] state associated with pregnancy. Heparin and oral vitamin K antagonists are the best prophylactic or therapeutic anticoagulants in PPCM. Heparin is preferred during pregnancy because of its safety profile. NOACs are generally avoided because of a lack of evidence of safety in pregnant and lactating mothers.[11] The use of permanent ICDs to prevent ventricular arrhythmias is controversial, given the reversible nature of PPCM. However, wearable cardioverter/defibrillator can be used in patients with EF<30%.[3]

Bromocriptine Is an experimental but proposed therapy in PPCM. A previous study on PPCM management with bromocriptine and standard heart failure therapy in Germany revealed reduced mortality. However, this study had no placebo arm. A cohort study in Canada showed improvement in LVEF after six months following bromocriptine therapy, which is hypothesis-generating and suggests the need for further multicenter RCT.[12] Bromocriptine therapy is associated with an increased risk of thromboembolism and should always be accompanied by therapeutic anticoagulation.[9] There is limited data on bromocriptine therapy in PPCM patients with LV thrombus, and it should always be given after an expert opinion. The impact of bromocriptine on breastfeeding should be discussed with lactating mothers. 2010 European statement advised against breastfeeding in PPCM patients.[4] However, recent IPAC data showed no increased adverse events in continuing breastfeeding.[13] So, breastfeeding is advisable for mothers, especially in the developing world, because of the lack of availability of appropriate formula feed.

Contraception using progesterone-containing contraceptives and barrier methods is advisable. Combined OCPs are generally avoided due to the increased risk of thrombosis. Cardiologists and obstetricians/gynecologists should encourage the choice of appropriate contraception as per patients' wishes.[14] Risks with subsequent pregnancies depend mainly on the prepregnancy LV function. Subclinical LV dysfunction can be assessed by stress testing and strain imaging.[15,16] Women with reduced LV function (LVEF<50%) should be informed regarding the higher chance of recurrent HF. Women with PPCM (recovered/non-recovered) should be closely followed up during their subsequent pregnancies with a multidisciplinary approach.

Conclusion:

Though peripartum cardiomyopathy is rare, a high index of suspicion should always be there, given the high morbidity and mortality rate associated with delayed diagnosis. Most of the time, patients present to midwives and primary care doctors in resource-poor settings. Prompt decisions regarding transferring care to a higher center should be taken.

Though bromocriptine induces the risk of thrombus formation and embolism during the management of PPCM, it is safe if given with therapeutic anticoagulation. If LV thrombus is already present, using bromocriptine may create a dilemma. In this case, using bromocriptine, guideline-directed medical therapy (GDMT), and anticoagulation proved very beneficial for the patient. Further studies regarding the safety profile of bromocriptine in PPCM with preexisting LV thrombus are needed. If bromocriptine is used in PPCM patients with LV thrombus, multidisciplinary decisions and continuous monitoring for probable complications are mandatory.

Conflict Of Interest:
There was no conflict of interest regarding the management of this patient among the treating doctors.

Consent:
Appropriate consent was taken to publish this case report from the patient and her family. All acceptable measures were taken to maintain confidentiality.

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