Right Ventricular Thrombosis Combined With Fetal Death and Acrocyanosis in Pregnancy

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Abstract- Prepartum or postpartum right ventricular thrombosis (RVT) is an exceedingly rare and potentially lethal phenomenon in pregnancy. We here report a case of a pregnant patient with near term pregnancy admitted for dyspnea, amniotic fluids discharge and labor pain in a gynecology center that an eight-month dead fetus was diagnosed and delivered vaginally by induction. A post delivery period was complicated by aggravation of her dyspnea and pleuritic chest pain that she referred for further evaluation in our cardiac center. Physical exam revealed normal head and neck exam, and history taking revealed that her fetus had intra-uterine growth failure as reported by her gynecologist. Chest exam except to left lung crackle was normal. Lower and upper left extremities were normal. However, acrocyanosis was found in tips of 4 and 5th right-hand digits. Chest x-ray revealed some linear consolidation in left lower lung lobes, and the precordial exam was normal. ECG was normal. Post delivery transthoracic echocardiography (TEE) showed a 1.5×1.5 cm mobile right ventricular clot. C-T angiography revealed obstruction of left upper lung pulmonary artery branches. Complete thrombophilia assay showed the presence of high titer of antiphospholipid, anticardiolipin antibody, and β1 glycoprotein antibody. However, others test were normal. The patient was scheduled for cardiac surgery, and her hemodynamic was monitored by left radial artery line and central pressure venous line, and thrombus was removed from the right ventricle (RV), and subsequent anticoagulation therapy constituted. Six-month follow-up revealed no recurrence of thrombus and recovery of patient's symptoms.

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Keywords: Pregnancy; Thrombus; Thrombophilia

Introduction

Intra cardiac clot formation in pregnancy could be related to multiple underlying local or systemic disorders affecting myocardium or coagulation system (1). Thrombus formation in right cardiac chambers or left cardiac chambers is serious situations as they may be embolized to pulmonary arteries or to systemic circulation (2). Exceedingly rare cases of cardiac chamber thrombosis were reported in the pregnancy, the, however, the right ventricular thrombus is even rarer, especially when it associated with some types of thrombophilia such as antiphospholipid antibody. The antiphospholipid antibody disease is a complex syndrome defined as an acquired and autoimmune disorder explained by occurrences of clot formation in microcirculation or veno-arterial system and pregnancy. It also was defined as a case of cardiac chamber thrombosis, associated with the persistent presence of anti phospholipids auto antibodies that, documented at least in two fold at 3 months interval. This antibody was suspected to be performed and directed toward the molecular structures of plasma phospholipids and serum proteins. Antiphospholipid antibody as a complex syndrome should also keep in mind as a potential cause of thrombotic event especially in pregnant patients presenting with a history of miscarriage in the course of pregnancy or thromboembolic episodes, especially when others acquired predisposing factors or congenital thrombophilic states were ruled out by appropriated assays and by physical exam and good history taking (3). Multiples another disease could be able to mimic

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sign and symptoms of this syndrome, so a wide variety of alternative differential diagnoses should be assayed and ruled out during workup. Nonthrombophilia conditions that have been reported with right ventricular clotting including. pregnancy-induced cardiomyopathy, congestive heart failure, central vein catheter for monitoring or dialysis, right ventricular pacing lead, right ventricular infarction. The pregnancy has been described as a thrombophilia state and if occurred in the setting of autoimmune disease or others hypercoagulability states, the risk of thromboembolism is tenfold increased (4).

Case Report

A 23-year-old pregnant woman without history of thrombophilia or thrombophlebitis or miscarriage or cardiomyopathy or left or right ventricular dysfunction was admitted to our cardiac center following vaginal delivery of the eight-month expired fetus with intrauterine growth retardation (IUGR) for further evaluation of her dyspnea, pleuritic chest pain and purple digits (Figure 1). He was not drug abuser or smoker or a drinker. She had been continuously followed in the gynecologic clinic, and repeated abdominal ultrasound showed IUGR (Figure 2) that contributed to the placental position. However, no treatment or preventive measures were explained or emerged, and she eventually abandoned follow-up till the labor pain was started. At the recent admission to gynecology center, she presented with cough, pleuritic left hemithorax pain, dyspnea, and mild hemoptysis. She was not hypotensive, and her blood pressure was 120/67 mmHg with, heart rate of 111 s beats per minute and peripheral oxygen saturation was 96%. Her precordial auscultation showed no any murmur, and she had crackles in the lower left lung half. There was not any evidence of lower extremity pitting edema, digital cyanosis, thrombophlebitis or embolic event. The ECG exhibits normal sinus rhythm and no evidence of chamber hypertrophy of bundle branch block. The chest X-ray showed signs linear consolidation in the left lung. The complete blood count showed microcytic hypochromic anemia with of hemoglobin 9 g/dL and abnormal elevated anticardiolipin/IgG/CLIA>280 GPLU/ml (>80 highly positive confirmed by repeated analysis). The results of others thrombophilia screening revealed: Antiphospholipid/IgM/ELISA 10.7 U/ml (normal range,>18), ANAs (screening assay) IgG 0.8U/ml (negative<1.5), Anti dsDNA/IgG 17.6/u/ml (positive>25), anti–β_2-glycoprotein-1 (anti–β_2-GP1) antibodies. β2 GPI IgG: 43(normal≤20 SGU U/mL) .β2 GPI IgM: 32 (normal≤20 SMU U/mL), p-ANCA(MPO/IgG/ELISA) 0.90 (<5 negative), c-ANCA(PR3/IgG/ELISA) 0.98 (<10 negative), Anit-phospholipid/IgG/ELISA) 25.8 u/ml (negative<12, positive>18),Anticardiolipin/IgG/CLIA>280GPLU/ml (>80 highly positive confirmed by repeated analysis), Lupus anticoagulant (second) 51 (normal,31-44). Serum protein C, S and Leiden factors were normal. Transthoracic echocardiography revealed mild dilatation of right ventricle, normal left ventricular function (ejection fraction was 60%) associated with the normal right ventricular function, mitral and tricuspid function also were normal. In the posterior inferior wall of the right ventricle, there was an hypo dense echo image suggestive of a clot, however main pulmonary artery and its branches were clear (Figure 3,4). It was observed that thrombus to be large, mobile and round (maximum dimensions of 15 mm x 15 mm). The patient hemodynamically was stable requiring no any inotropic drugs, intravenous diuretics. The patient was scheduled for emergency cardiac surgery, and by full heparinization and bi-cava and aortic cannulation and by mid sternotomy, right atrium was opened, and a large round and organized clot was found in the base of the posterior papillary muscle of tricuspid valve that removed and sends to the histological exam (Figure 5,6). the operation was the uneventful course. The pathology revealed fibrin strand with clot formation (Figure 7). Unfortunately, the placenta was not available for the further histological exam to confirm placental venous thrombosis. The C-T angiography revealed obstruction of pulmonary artery branches of the lower lobe of left lung (Figure 8). The presence of antiphospholipid antibody was confirmed with rule out of others multiple causes of congenital or acquired thrombophilia, and then intravenous heparin and oral anticoagulation was started, and she was eventually discharged, with clinically stable condition and relief of dyspnea, with remaining mild purple digits under warfarin 7.5 mg per day, Metoral® 25.5 mg per day, aspirin 80 mg per day, the patient strictly monitored to maintain her INR at limits of 3-3.5 at home and she continued to follow up. Thrombophilia screening assay showed high serum level of antiphospholipid antibody at 12 weeks later. Six-month follow-up showed no evidence of cardiac chambers thrombus and also elevated serum level of antiphospholipid.

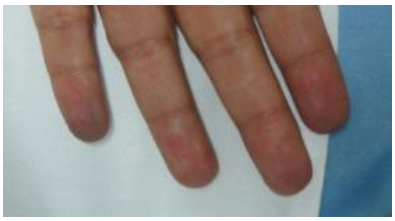

Figure 1. Purple tips of left hand

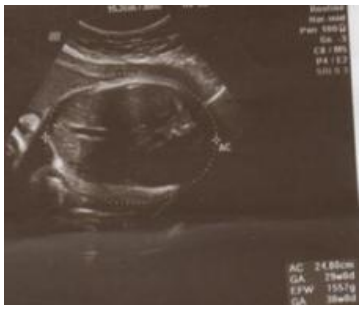

Figure 2. An 8 months dead fetus in an abdominal ultrasound

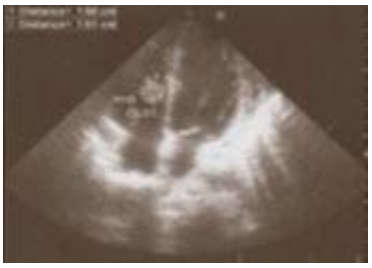

Figure 3. Right ventricular clot and normal main pulmonary artery and its branches

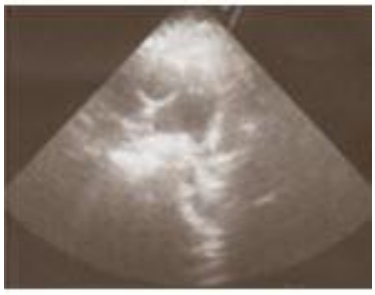

Figure 4. Right ventricular clot and normal main pulmonary artery and its branches

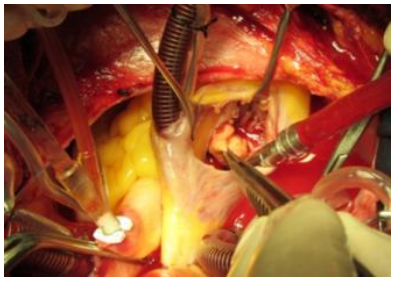

Figure 5. An intra operative view of right ventricular thrombus

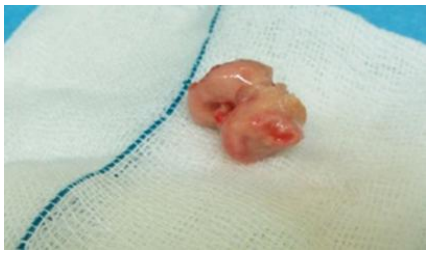

Figure 6. Resected right ventricular thrombus

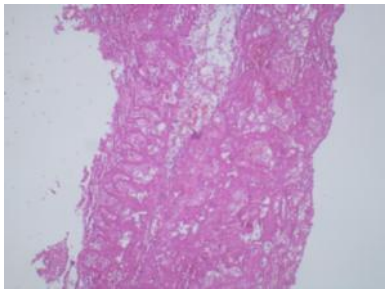

Figure 7. Histological exam of thrombus with fibrin strand and red blood cells (H,E 40)

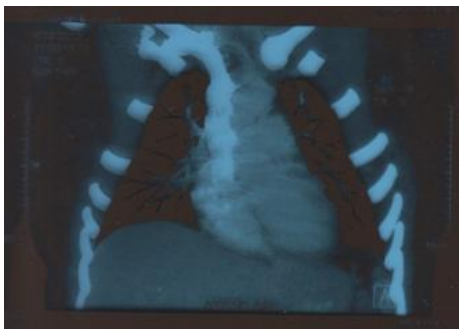

Figure 8. Cut off of left upper lobe pulmonary artery branches

Discussion

RVT has been attributed to wide range of causes that some of them aggravated or facilitated by pregnancy that considered as thrombophilia state. These includes, local and anatomic predisposing factors such as right ventricular myocardial infarction (MI) right ventricular muscular defect as seen in Ules anomaly, right ventricular aneurysm or thrombophilia states such as protein C-S deficiency, factor V of Leiden, antithrombin ш deficiency, autoimmune diseases likes, the presence of anti phospholipids antibody, the presence anti cardiolipin antibody, anti nuclear antibody, anti double strand antibody, and both types of restrictive and dilated cardiomyopathy (5,6). Echocardiography was considered as main gold standard for assigning type of thrombus that allowing clinician to determine chance of further thromboembolic to pulmonary system. In opposed to congenital or acquired thrombophilia, some cardiac disorder imposed an anatomic or physiologic

disturbances that aggravates thrombogenic condition. The conditions such as congestive heart failure (by stasis and anatomic defect of internal wall of chambers), low cardiac output state (stasis), and one or more cardiac chamber dilatation (Ebstein anomaly) contributes to thrombophilia state. However, the thromboemboli is leading cause of pre or postpartum mortality in pregnancy but risk of cardiac chamber and deciduas vein thrombosis in pregnant with congenital thrombophilia is exceedingly rare event (7). In one study, thrombus was found in right atrium in pregnant patients who her fetus died from concomitant decidual venous system thrombosis. In case of Antithrombin III deficiency; 45% of thrombi were in the left ventricle, 25% in the right ventricle, 20% in the right atrium, and 8% in the left atrium (8). Velicki L explained that conventional pregnancy contributed to changes in the coagulation and fibrinolytic system toward a thrombophilia state and reported a case of a woman with post partum right ventricular thrombosis, which was successfully removed by surgery however no evidence of others congenital of acquired thrombophilia were reported (9). Matos V reported a case of antiphospholipid syndrome in a pregnant woman with a right atrial clot detected by TEE. This case was complicated by thromboemboli and recurrence of the clot within four months. Pathological exam showed it to be thrombotic in nature. APS Patients should be classified into four groups: 1-APS Patients with typical clinical pictures of syndrome combined with high level of antiphospholipid antibodies (aPL*)*: thrombotic events occurred in typical locations lower extremity thrombophlebitis, lung embolism, myocardial infarction, and CVA or pregnancy morbidity (10). This typical case should be differentiated from microangiopathic syndromes or systemic lupus erythematosus (SLE*)*. 2-APS Patients with unusual clinical features of of APS combined with high serum level of aPL*:* in this case thrombotic events occurred, in unusual territories such as hepatics vein, renal vein, adrenal vein, and mesenteric vessels or cerebral venous sinuses with pregnancy complications with difficult differential diagnosis (11). 3-APS patients with incomplete clinical manifestations of obstetric APS associated with positivity of aPL: pregnancy disorders not completely fulfilling Miyakis criteria (e.g., 2 consecutive abortions before the 10^{th} week of gestation or 3 or more nonconsecutive abortions before the 10th week). 4-Patients that did not fulfilled clinical criteria of APS however associated with positivity of aPL and, non-thrombotic lung or cardiac disease, or eye, brain, skeletal, joint, and hematological manifestations (12). In second, third and fourth types, the patient presenting with atypical clinical manifestation, but suspected sign and symptoms, need a careful serological assay and precise follow-up to ascertain early clinical sign and symptom to establish early anticoagulant therapy. Differential diagnosis of APS includes: TTP *(*thrombotic thrombocytopenic purpura), HUS (hemolytic uremic syndrome), and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets syndrome), HIT (Heparin Induced Thrombocytopenia) DIC (Disseminated intravascular coagulation) (13). All of above-mentioned syndrome is defined by small vessel thrombosis, probably contributing to consumptive coagulopathy and hemorrhage, which could be lead to others, organ failure. In oppose to APS that usually caused by pregnancy, the above syndrome created by surgical intervention, chronic inflammation, carcinoma, and infection. Histopathologically they are defined by micro vascular occlusion with hyaline and fibrin deposition in vessel walls and, noteworthy, that aPL antibody has not been detected or rarely detected in aforementioned syndromes and on the other hand, the degree of microvascular embarrassment, in APS syndrome is very lower than microangiopathic syndrome (14). Another's differential diagnosis is Behçet syndrome (BS) that as a vasculitis syndrome defined by the involvement of eyes, skin, mucous membrane, and central nervous system embarrassment. Like to APS large numbers of Behçet patients are prone to rebounding vascular thrombosis, due to inflammation of the vessel walls that is opposed to APs requiring prednisolone or immunosuppressive drugs rather than anticoagulation which should be considered for APS. Vascular thrombosis in BS are associated with elevated serum markers of disseminated intravascular coagulation as increased D-Dimer', thrombocytopenia, prolonged PT. PTT activating clotting times, elevated serum levels of FDP (fibrin degradation products), and reduced serum level of fibrinogen and normal level of antiphospholipid antibody. In opposed to APS, these syndromes are defined by platelet utilization, hemolysis lead to schistocytes formation due to red cell fragmentation. Some author believe that systemic lupus erythematosus and APS syndrome may be considered as a different clinical spectrum of the same disease, and showing the strict association existing between these syndromes (15). Like to APS patients, SLE patients could have a positive serum level of aPL in the presence of vasculitis or obstetrical morbidity, and in a rare case it also could be associated with some SLE properties, including, hemolytic anemia with schistocytes formation and mild

plasma complement reduction, and anti-nuclear antibodies (ANA). These SLE patients may be defined as APS cases that probably will emerge into SLE in the future. In addition to conventional clinical sign and symptoms of APS such as thrombotic cardiac manifestation. There are many unconventional clinical manifestations of APS including: 1-brain ischemic cases as a main characteristic of APS, that caused by cerebral venous thrombosis. It is a rare events but should be considered in diagnostic workup of cerebral veins thrombosis2-renal complication of APS are very rare than in SLE patients and in opposed to SLE is caused by renal vein thrombosis than secondary glomerular damage developed in SLE. In addition to histological manifestation of thrombotic vasculopathy resulting from inflammatory vasculitis (16), presence of aPL and brilliant histopathologic finding, are the hallmarks of APS nephropathy and renal biopsy is required for proper diagnosis 3-gastrointestinal manifestation: Thromboses of veno-arterial tributaries such as hepatic, IVC, portal, splenic and mesenteric veins are the main complications of gastrointestinal tract in APS cases; in differential diagnosis, disease such as polyarteritis nodosa, myeloproliferative disorders and Henoch-Schönlein purpura could be kept in mind with APS that usually is not associated with increased plasma levels of inflammatory markers. 4-Adrenal dysfunction secondary to venous thrombosis is the rare, characteristics of APS 5-Pregnancy morbidity such as recurrent miscarriage may warn presence of the of APS; however, other disorders such as connective tissue disease, anatomic defect of uterine, endocrine dysfunction, thrombophilia, SLE, thyroiditis, and celiac disease could be excluded. 6-acrocyanosis as in our patient represent the most common cutaneous sign of APS. That histologically revealed by partial or complete occlusion of small or medium size arteries of the skin without perivascular inflammatory reaction that was seen in others connective tissue disease associated with acrocyanosis and absence of circulatory antibody in them. 7-Nonthrombotic (17). Cardiac and Pulmonary Involvement: The most common manifestation of cardiac involvement in APS syndrome related to involvement of Heart valves usually of the mitral valve, as nonbacterial thrombotic endocarditis (Libman-Sacks endocarditis) followed by rare case of Cardiomyopathy by vascular thrombosis and pulmonary involvement manifested by alveolar bleeding, acute respiratory distress syndrome, and fibrosing alveolitis chronic thromboembolic pulmonary hypertension8-Ocular Involvement: In opposed to connective tissue disease that ocular involvement caused by vasculitis in APS syndrome, eye's involvement such as Amaurosis fugax as a most common symptom, usually are not associated with abnormal funduscopic sign that found in inflammatory connective tissue disorders indeed severe ophthalmologic sign and symptoms which may observed in APS cases are related to veno-arterial thrombosis that caused retinal detachment and ischemic optic neuritis by vascular occlusion (18). In opposed to other connective tissue disease, serum inflammatory targets in APS are normal. 9-Hematological Involvement: Thrombocytopenia, is not considered as diagnostic clinical criteria, and is observed in approximately 35% of APS cases. Interestingly, APS-related thrombocytopenia is usually milder than severe thrombocytopenia in SLE ones that needs emergent management. In oppose to APS, thrombocytopenia related to lupus DIC, TTP, and HIT are always associated with hemolytic anemia that is rare in APS syndrome. 10-Musculoskeletal embarrassment: Joint involvement is very rare among others the APS properties and, if present, should also raise the suspicion of n combined connective tissue disease. That caused by thrombosis of perfusing small vessels of joints (19).

Here we report a case of APS with thrombotic cardiac manifestation associated with vascular thrombosis in placenta (manifested as fetal death) and acrocyanosis and right ventricular thrombus that associated with very high serum level of anti phospholipid antibody and β1 anti-glycoprotein .

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