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Case Report

Catastrophic Antiphospholipid Syndrome (CAPS) in Patient with Lupus Erythematosus Systemicus: A Case Report - ə

Evgeny Farber[1]*, Nakhoul Nakhoul[2], Hanut Anam[1,3], Maria Gershovich[3], Michael Jerdev[4], Soboh Soboh[3], Nakhoul Farid[1,5] and Sabbah Firas[3]

[c]Nephrology & Hypertension Division, Baruch Pageh Poriya Medical center, Azrieli Faculty of Medicine bar Ilan University Ramat Gan Israel

[2]Ophtalmology Division, Baruch Pageh Poriya Medical center, Azrieli Faculty of Medicine bar Ilan University Ramat Gan Israel

[3]Internal Medicine, Baruch Pageh Poriya Medical center, Azrieli Faculty of Medicine bar Ilan University Ramat Gan Israel

[4]Imaging Department, Baruch Pageh Poriya Medical center, Azrieli Faculty of Medicine bar Ilan University Ramat Gan Israel

[5]Faculty of Medicine, Baruch Pageh Poriya Medical center, Azrieli Faculty of Medicine bar Ilan University Ramat Gan Israel

***Address for Correspondence:** Evgeny Farber, Nephrology & Hypertension Division, Baruch Pageh Poriya Medical center, Azrieli Faculty of Medicine bar Ilan University Ramat Gan Israel, Fax: 972-466-2393; E-mail: Efarber@poria.health.gov.il

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ABSTRACT

Antiphospholipid syndrome is an autoimmune disease, involving multiple organs, characterized by an increased risk of thrombosis due to persistently positive antiphospholipid antibodies in the circulation. Antiphospholipid syndrome is classified as idiopathic when it occurs in the absence of other autoimmune diseases, or as secondary when it occurs in association with several other autoimmune disorders, mostly Systemic Lupus Erythematosus (SLE). Catastrophic antiphospholipid syndrome is a lethal disease characterized by multi-organ failure due to diffuse thrombosis in the microvascular system, occurring over a short period of time. Although less than 1% of patients with antiphospholipid syndrome develop this complication, the outcome is potentially lethal.

In recent years, there has been a significant improvement in the treatment of patients with catastrophic antiphospholipid syndrome, unfortunately the overall morbidity and mortality is still remarkably high. The use of rituximab has been reported in the treatment of refractory cases of catastrophic antiphospholipid syndrome, but the data is still insufficient due to a small number of patients treated with this medication. Physicians should be able to diagnose this syndrome in a patient presenting with thrombosis in multiple organs for early treatment. We report a case of a 37-year-old female patient with long standing, untreated SLE and secondary antiphospholipid, presented with lupus nephritis and kidney injury, thrombosis of the pulmonary artery, the liver and spleen, and neurological involvement. She was treated with anticoagulants, glucocorticoids, intravenous immunoglobulins, Cytoxan and systemic antibiotics. Later on, she was treated with rituximab due to a deterioration in her general condition. Despite her intensive treatment and care, the patient passed away. The patient's family disagreed to an autopsy. We report here a case of catastrophic antiphospholipid associated with lupus treated with rituximab with lethal outcome.

Keywords: Antiphospholipid syndrome; Lupus erythematosus systemicus; Catastrophic antiphospholipid syndrome; Cyclophosphamide; Rituximab

INTRODUCTION

The Antiphospholipid Syndrome (APS) is an autoimmune disease characterized by the presence of circulating antiphospholipid antibodies (aPLs), vascular thrombosis with multiple organ involvement [1,2]. The clinical manifestations consisting of either thrombosis in arterial, venous, or small vessels, and the sustained detection of at least 1 of the 3 main types of aPLs, namely Lupus Anticoagulant (LA), anti-cardiolipin (aCL), or anti–b2 glycoprotein I antibodies. The APS is classified further as primary when APS occurs in the absence of other autoimmune diseases, or as secondary when it occurs in association with a number of autoimmune disorders, mostly Systemic Lupus Erythematosus (SLE) [3-6]. The clinical spectrum of the anti-phospholipid syndrome includes thrombocytopenia, heart valve disease [7], renal, and neurologic manifestations that can result in high mortality rate. Large renal vessel and microarchitecture were recognized as site of involvement.

Large-vessel thrombosis with infarcts represents a well-defined manifestation of APS, and all of the vascular beds may be sites of thrombosis especially the lung, kidney, liver and spleen. The coagulation pathways and inflammation are the main players involved, with the complement system activation [8], emerged as an important pathophysiologic player in APS.

The treatment of Catastrophic Antiphopholipid Syndrome (CAPS) depends on the presence of associated other diseases [9,10]. All patients should be treated with anticoagulants such as unfractionated heparin, corticosteroids, and possibly plasma exchange or intravenous immunoglobulin (IVIG). This regimen seems to be associated with reduced mortality. In patients with SLE, cyclophosphamide should be considered. In refractory or relapsing cases, new therapies, such as rituximab may be utilized [11-15].

CASE REPORT

A 37 years old Arabic female, married +2, had been well until 4 years prior to her admission to our hospital. In 2004 she was referred to the rheumatologist in her village for diffuse arthralgia. Her medical record could not be obtained but the laboratory results revealed a positive ANA and anti-DNA, along with very low complement levels. Patient was lost to follow up. May 2019, she started suffering from peripheral pitting edema, weight gain and arterial hypertension. Her family physician initiated treatment with calcium channel blockers, Lercanidipine (Vasodip), 10 mg twice daily. Her first admission was at another hospital on July 2019 due to edema and nephrotic range proteinuria. On presentation, she was hypertensive with a blood pressure of 160/100 mmHg, tachycardia with a heart rate of 100 beats per minute, without tachypnea, a respiratory rate of 24 breaths per minute, and she was afebrile. Her examination was remarkable for jugular venous distension and a grade III/VI diastolic apical murmur, and breath sounds were detected throw-out the upper and low lung fields, and severe pitting edema. Initial work-up revealed acute kidney injury with serum creatinine of 4.2 mg/dl.

During her admission she suffered from abdominal pain, vomiting, diarrhea, and general weakness. Laboratory results at the local hospital showed a plasma creatinine of 4.2 mg/dl, ANA, Anti-DNA were positive, very low complement level and negative ANCA. She was discharged and advised to be readmitted for elective kidney biopsy. Closed kidney biopsy was performed 2 weeks later, but the renal tissue was accidentally kept in formalin and no information was issued. Because of uremic symptoms, hemodialysis was performed via femoral vein catheter. No cytotoxic or corticosteroid treatment were initiated, and she was discharged.

A deterioration in her general condition ensued and she was admitted to our department in Poriya Medical center. Due to a deterioration in her renal function and high suspicion of proliferative lupus nephritis, Intravenous Solumedrol 1 gram daily for five days was initiated. Despite high dose steroids, plasma creatinine increased progressively to 7 mg/dl, and a Jugular vein catheter was inserted for acute hemodialysis treatment, however, was removed because of fever due to Enterobacter bacteremia. Wide spectrum intravenous antibiotics were administered, and she was discharged one day later. On August 2018, upon her readmission she presented with severe stress and a very poor general condition, without dyspnea, temperature was 37.6˚C, blood pressure of 150/90 mmHg and heart rate was 72 beats per minute, malar flash with jugular vein congestion, severe apical diastolic murmur III/IV, and anasarca. Echocardigraphy showed severe pulmonary hypertension with severe mitral regurgitation and moderate aortic regurgitation.

Chest CT-Angiography with IV contrast media injection was performed (Figure 1) demonstrating multiple filling defects in the segmental and subsegmental arteries of both lungs, especially notable in the left lower lobe with dilatation of the pulmonary trunk and bilateral pleural effusion. Mediastinal lymphoadenopathy was noted. Subcutaneous Clexane 40 mg twice a day was initiated due to pulmonary embolism. Abdominal CT with IV and PO contrast media (Figure 2) showed hypodense areas in the liver and spleen suspected for infarcts due to emboli, huge ascites and diffuse soft tissue edema of the whole scanned body. Brain CT revealed no pathology. Lung X-Ray demonstrated cardiomegaly, bilateral pulmonary edema with pleural effusion (Figure 3). Electrocardiography was normal. Due to persistent fever, blood cultures were done and intravenous Vancomycin and Fortum were administered.

Immunological testing showed severe hypocomplementemia (C3, C4) with positive anti-DNA. A second closed kidney biopsy was performed to rule out diffuse proliferative lupus nephritis. Soon after biopsy we start a second protocol (ALAMS TRIAL) of intravenous Solu-Medrol with 1000 mg oral Mycophenolate daily (Cellcept) and Plaquenil. Due to suspected bacteremia, NIH protocol was hold. Kidney biopsy showed glomerular sclerosis with mesangial cell proliferation and sclerosis, severe tubule-interstitial fibrosis of 70%. We continue the treatment due to extra-renal manifestation of the APLA and SLE. Transtorachic Echocardiography (TTE) at our center on August 2019 (Figure 4) showed Ejection Fraction (EF) of 55%, severe mitral regurgitation, severe tricuspid regurgitation and severe Pulmonary Hypertension (PAP) of 65 mmHg and without vegetations.

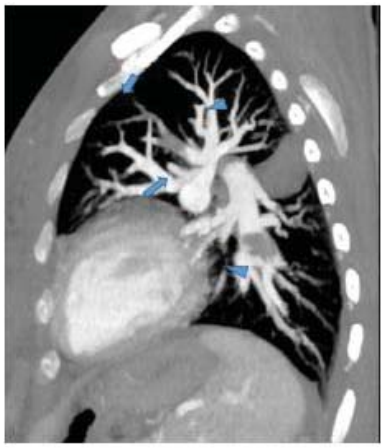

Figure 1: The sagittal MIP reformation of the CT-Angiography showing filling defect (arrows) in the segmental arteries of the left lower and upper lobes and pleural effusion (arrowheads).

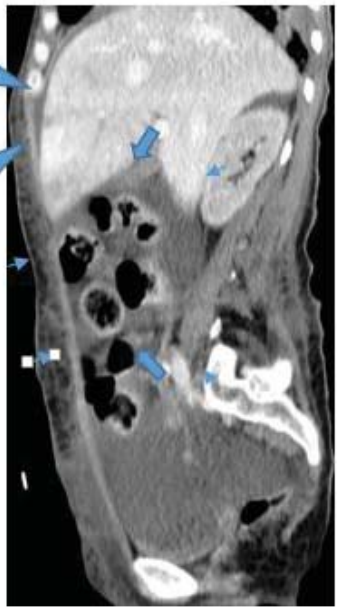

Figure 2: The sagittal MPR reformation of the abdominal CT showed hypoperfusion defects (arrowheads) in the liver suspected infarcts due to emboli, huge ascites (arrows) and diffuse soft tissue edema(small arrows).

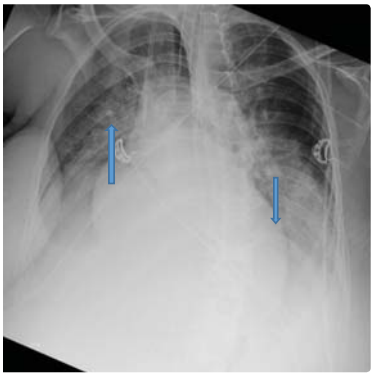

Figure 3: Lung X-Ray showing cardiomegaly, bilateral pulmonary edema with pleural effusion. ETT, NGT and Right Jugular CVP in proper positions.

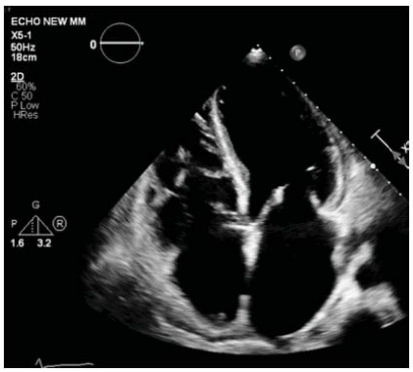

Figure 4: Transtorachic echocardiography showed Ejection Fraction (EF) of 55%, severe mitral regurgitation, severe tricuspidal regurgitation and severe pulmonary hypertension (PAP) of 65 mmHg and without vegetations.

During her admission despite the steroids and chemotherapy, a severe general condition deterioration occured with severe muscle weakness (motor type) and disrupted liver enzyme function with direct hyperbilirubinemia until 4.5 mg/dl, ALT 300 AST 200 with increased alkaline phosphatase of 300 IU/L (Normal range for serum ALP level is 20 to 140 IU/L), compatible with hepato-cellular injury with cholestasis. After consultation with a rheumatologist, drug induced hepatitis, lupus hepatitis and auto-immune hepatitis were taken in consideration as the etiology of the cholestasis. Accordingly, we decided to stop Plaquenil and Cellcept due to the suspicion of drug induced hepatitis, or lupus hepatitis, and rapid tapering in prednisone daily dose.

Due to increased INR (7%) probably secondary to hepatic-cellular

damage, or drug induced, intravenous Vitamin K 10 mg was injected, and later the liver function tests improved with near normalization of the INR level. Because of general muscle weakness, an EMG-NCV was performed showing peripheral axonal neuropathy with motor and sensorial involvement. Urgent thoracic and abdominal CT showed diffuse thrombosis in the pulmonary artery, liver and spleen. Due to the neurological and abdominal involvement, and without dysmorphic peripheral blood cells, CAPS diagnosis was suspected. Due to multi-organ involvement from APLA and SLE, we decided to initiate treatment with IV Solumedrol, IVIG for 5 days and only one dose of Maptera 500 mg. Plasmapheresis was not performed because of severe thrombocytopenia of 20000. No improvement was noted, therefore we decided to stop all medications. Her general condition continued to deteriorate with high fever. Permacath was removed and blood cultures were drawn. Later the blood cultures showed Candida albicans and Enterobacter Cloace. Treatment with intravenous Fluconazole, Vancomycin and Meropenem were started immediately. Multiple organ failure appeared later, and the patient passed away. Autopsy was not performed due to a family decision.

LAB RESULTS SUMMARY

White-cell count was 7000 per microliter with neutrophil count of 45%, hemoglobin = 6.5 gr% (*n* = 12-15), Platelets = 150,000 uL/1000 (*n* = 150-400). Lymphopytes 0.1 ul/1000 (*n* = 0.9-5.2), Ferritin 6850 ng/ml (*n* = 5-204). Bloos smear few dysmorphic red blood cells. INR = 7.19 (*n* = 0.9-1.3) Fibrinogen = 63 mg/dl (*n* = 200-400), PT = 40% (N-70-120), PTT = 31 second (*n* = 27-38). Glucose, Electrolytes were normal. Plasma Creatinine = 7 mg/dl (*n* = 0.6-1), Blood Urea Nitrogen (BUN) = 80 mg/dl; Phosphorus = 8 mg/dl (*n* = 2.3-4.7), Calcium = 7.6 mg/dl (*n* = 8-10), Lactic Acid, bicarbonate were normal. Liver function tests: Alkaline Phosphatase 0f 400 IU/L, Bilirubin direct = 2.8 mg/dl (*n* = 0.0-0.5), Albumin = 2.3 gr% (*n* = 3-5), Gamma Glutamyltransferase (GGT) = 680 U/L (*n* = 9-36), Lactate Dehydrogenase (LDH) = 260 U/L (*n* = 125-200). , TSH, TT4 normal. Bone marrow biopsy without erythrofagocytes.

Immunology Tests results: Antinuclear antibody (ANA), double stranded DNA Positive 530, SSA postitive. Complement C3 = 61 (*n* =), C4 < 2.9 (*n* =). Cardiolipin IgG, Lupus anticoagulant, Anti-Smoth muscle abs, Mitochondrial Ab- Anti-Cytoplasmic Antibody were negative. HbcAb IgM- HbsAb-negative. Ceruloplasmin and liver kidney microsomial antibodieas were negative. ADAMTS ACTIVITY 35%, ADAMS ab Negative. Ceruloplamin, Smooth muscle antibodies and Anti-Liver-Kidney Microsomal antibody (LKM) were negative

DISCUSSION

Anti-Phospholipid Syndrome (APS) [16,17] is an autoimmune condition, often occurring with lupus erytematosus systemicus, that is characterized by the hypercoagulability syndrome and consequent thrombosis in both the arterial and venous circulation with persistent presence of antiphospholipid antibodies. APS can present with multiorgan failure, a condition known as Catastrophic Antiphospholipid Syndrome (CAPS). CAPS accounts for less than 1% of all patients with APS, but it carries a significant mortality estimated to be approximately 37% [17,18]. Cardiac manifestations occur in half the cases of CAPS and primarily consist of valvulopathy (Libman-Sacks endocarditis) [7]. The differential diagnosis between CAPS, thrombotic thrombocytopenic purpura and disseminated intravascular coagulation is difficult [18,19]. The normal blood level of ADAMS 13 and the absence of dismorphic blood cells in the circulation, is in favor of CAPS diagnosis.

Our patient was a 37-year-old female, with underlying untreated SLE involved the kidney and joints, with APLA syndrome appearing later in her admission with severe secondary CAPS. Her first presentation was renal insufficiency and arthralgia due to untreated lupus diagnosed two years prior to her last admission. During her admission, pulmonary artery thrombosis, endocarditis, worsening kidney function and cholestasis developed. Steroids in high doses are life-saving and should be given empirically before the diagnosis as our patients was treated. In the literature, we found that female-to-male ratio was 8.5:1 in SLE-CAPS and 1.5:1 in P-CAPS patients, with a CAPS event occurring at a significantly younger age in SLE-CAPS patients as in our case. This younger onset of CAPS event in patients with SLE-CAPS can be attributable to the early-age onset of SLE and/or increased incidence of thrombosis in SLE patients independent of antiphospholipid antibodies. Different cases were described CAPS and APLA with negative antiphospholipid antibodies.

The patient discussed in the present paper is of interest. Primarily, because she presented two years before her last admission to our center, with edema state, uncontrolled arterial hypertension, renal failure and positive anti-DNA abs and low complement, consistent with systemic lupus erythematosus, unfortunately she was neither treated nor followed up by a rheumatologist or nephrologist for one year. In addition, she developed acute multi-organ failure with catastrophic APS, including thromboembolic disease such pulmonary thrombosis, valvulopathy (mitral and aortic) and neuropathy with cholestasis. In the literature there are only few cases of CAPS with lupus that were treated with rituximab and IVIG, and our case can add recommendation to diagnose and treat the patients early, with review of this catastrophic syndrome.

In conclusion CAPS is life threatening systemic disease and is associated with high mortality. Early diagnosis and immediate combination of anticoagulation and antiplatelets, high dose steroids, IVIG or plasma exchange, cyclophosphamide and Rituximab should be given, because it has been found to be effective [20,21].

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