

Antiphospholipid Syndrome in Patient with Portal Venous Thrombosis: Case Report

Ljubinka Damjanovska¹, Ruse Rajcevski²

¹University Rheumatology Clinic, Faculty of Medicine, University "Ss Cyril and Methodius", Skopje, Republic of Macedonia; ²General Hospital "8 of September", Transfusiology, Skopje, Republic of Macedonia

Abstract

Citation: Damjanovska L, Rajcevski R. Antiphospholipid Syndrome in Patient with Portal Venous Thrombosis: Case Report. *Maced J Med Sci*. doi:10.3889/MJMS.1957-5773.2011.0178.

Key words: antiphospholipid syndrome (APS); portal venous thrombosis (PVT); anticoagulant therapy; anticardiolipin antibodies (aCL); lupus anticoagulant (LA).

Correspondence: Dr. Ljubinka Kiril Damjanovska, University Rheumatology Clinic, Faculty of Medicine, University "Ss Cyril and Methodius", Vodnjanska 17, 1109 Skopje, Republic of Macedonia. Phone: 38923147366. E-Mail: ldamjanovska@gmail.com

Received: 09-May-2011; Revised: 23-May-2011; Accepted: 24-May-2011; Online first: 01-Jun-2011

Copyright: © Damjanovska L. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Competing Interests: The author have declared that no competing interests exist.

Antiphospholipid syndrome (APS) is defined by the presence of arterial and venous thrombosis, recurrent fetal death, cerebrovascular accidents, hemolytic anemia, thrombocytopenia and various manifestations on different organs in the presence of anticardiolipin antibodies (aCL) and or lupus anticoagulant (LA).

It was reported in early 1980's. This syndrome is the most common cause of acquired thrombophilia. There is no consensus for treatment among physicians. Overall there is a general agreement that patients with recurrent thrombotic episodes require life-long anticoagulation therapy and those with recurrent spontaneous abortions require anticoagulation therapy (low molecular weight heparin) and low dose aspirin during most of gestation. Immunosuppression seems to be ineffective except in patients with fulminate multiple organ failure i.e. catastrophic antiphospholipid syndrome where plasmapheresis can also be used.

We present a case of 31 year old woman with primary APS and portal venous thrombosis (PVT), without any recognizable autoimmune disease. She has 4 spontaneous abortions, calf thrombosis, gangrene of one toe, refractory cutaneous ulcer on the heel and livedo reticularis. She is positive for aCL and LA, with hypergammaglobulinemia.

Introduction

Antiphospholipid syndrome (APS) is characterized by venous or arterial thromboses, fetal losses and thrombocytopenia, in the presence of antiphospholipid antibodies (aPL) (namely lupus anticoagulant (LA)), anticardiolipin antibodies (aCL) or antibodies directed to various proteins, mainly beta 2 glycoprotein I (beta2GPI), or in the presence of all three. Both lupus anticoagulant (LA) and anticardiolipin (aCL) immunoglobulin isotype G (IgG) and M (IgM) are maintained as laboratory APS

criteria, and IgG and IgM anti-β2 glycoprotein-I (anti-β2GPI) assays are added in the revised criteria. Laboratory criteria should be positive on two or more occasions at least 6 weeks apart and anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e. >40 GPL or MPL (or > the 99th percentile) [1].

Diagnosis is based on the presence of at least one clinical and laboratory criterion each, according to International Consensus Statement on preliminary classifi-

cation criteria. However, APS can be diagnosed in individuals even in the absence of some of the classification criteria [2].

APS occurs 2-5 times more frequently in women than in men. Currently, two major forms are recognized: primary and secondary APS. Primary form exists without associated underlying illnesses, while the secondary form is associated with definable underlying illnesses or inciting factors. It can be found in 10-40% patients with SLE.

Nowadays, it is not recommended to use the terms primary and secondary APS because secondary APS is usually associated with SLE [3].

Women with serologically positive IgG aPL antibody and/or LAC, and/or thrombosis may lose approximately 80% of all subsequent pregnancies. Criteria have recently been proposed for APS and pregnancy. They suggest that women with positive aCLs greater than or equal to 20 GPL or LA and any of the following should be diagnosed with APS: One or more otherwise unexplained fetal death at 10 weeks or more of gestation, loss of one or more morphologically normal neonates due to complications of prematurity after delivery because of severe pre-eclampsia or evidence of severe placental insufficiency, three or more consecutive pre-embryonic or embryonic losses, without anatomic, genetic, and hormonal abnormalities. Early fetal loss, late fetal loss, premature births, and pre-eclampsia are the most frequent fetal and obstetric manifestations [4].

Deep vein thrombosis is the most frequently reported manifestation in this syndrome. Conversely, cerebrovascular accidents are the most common arterial thrombotic manifestations [5].

Major-vessel occlusion has been described in virtually every vessel, including the aorta, branches of the aorta, inferior vena cava, hepatic vein, portal vein, intra-abdominal and intracranial vessels, and the peripheral vasculature of the extremities (organ infarctions). Liver thrombosis was a feature of the original clinical description of the syndrome. Liver function abnormalities are common in APS patients.

Approximately 40 % of patients will present with cutaneous manifestation as the first indicator of the APS. These are as follows: livedo reticularis, superficial thrombophlebitis, cutaneous necrosis, digital ischemia and gangrene, stasis ulcers of the ankles, epidermal atrophy, splinter hemorrhages of the nailbeds, non-necrotizing purpura, and blue-toe syndrome [6].

Cardiac lesions may occur in as many as 22% to 36% of patients. Demonstrable lesions on echocardiography include aortic and mitral regurgitation, valvular thickening, diminished valvular mobility, and valvular vegetations.

Neurological symptoms such as diplopia, memory loss, headache, ataxia and "multiple sclerosis like syndrome", are also frequent.

Antiphospholipid antibodies correlate with lesions of renal small-artery vasculopathy and chronic renal ischemia. Platelet counts in APS may vary from normal to severe thrombocytopenia [1].

Accurate laboratory investigations are crucial for APS diagnosis and treatment. LA measured by diluted viper venom test (dRVVT) and activated thromboplastin time assay (aPTT) are among the most sensitive tests. Lupus anticoagulants increase the risk of venous and arterial events to the same extent, particularly if cerebral stroke and deep vein thrombosis are considered. Anticardiolipin antibodies are not such strong risk factors for thrombosis as lupus anticoagulants. They are associated with cerebral stroke and myocardial infarction but not with deep vein thrombosis.

All aCL assays detect antibodies to negatively charged phospholipids bound to a plasmatic cofactor with natural anticoagulant activity known as β 2-glycoprotein 1 or apolipoprotein H (β 2-GP or apo H). It seems that the pathogenic antibodies are those directed towards beta 2-GP 1. Anti- β 2GPI antibodies are an independent risk factor for thrombosis and pregnancy complications. Anticardiolipin antibodies and anti- β 2GP 1 are detected with ELISA technique. Patients may also have anti-protrombin antibodies [1, 7].

Materials and Methods

We present a case of 31 years old white Muslim female, who presented with primary APS with portal vein thrombosis .

The data were taken from the patient, from her family and from her past medical records.

Report of the case

Identification: 31-year-old, white Muslim female.

Chief complaints: Fatigue, abdominal pain, pain and tenderness in her right calf, painful ulcer on the

bottom of the right feet. The ulcer resolved few times with periods of rest, antibiotics, and local care. The current ulcer has been treated without improvement with oral and topical antibiotics.

History of the present illness: She suffered 3 spontaneous abortions in her second trimester of pregnancy, during 1996/1997 in a period of 15 months. Once she was noted to have blighted ovum and missed abortion. After her third abortion she developed recidivant right calf thrombosis, and because of that she was treated with parenteral and oral anticoagulant therapy (warfarin) for a total period of 3 years.

The fourth spontaneous abortion happened in 2001 in the 12-th week of her pregnancy. Eight months before this admission her right calf became tender and painful, and she noticed a painful ulcer on the bottom of her right feet. Since then she suffers from malaise and feels frank pain in her right flank. In addition due to arterial thrombosis she suffered gangrene on the second toe of her left foot, which was amputated.

This time she was referred to specialist because of recidivated calf thrombosis, prolonged aPTT, and coagulation factor deficit. She was not taking anticoagulants for 4 years and her family physician suspected hepatic lesion and APS.

Psychosocial History: Housewife, married since 1996 without any children, she finished elementary school. She denies cigarette smoking and alcohol drinking. She does not take any drugs.

Physical Exam. General: Conscious white female, lying comfortably supine in the bed. Vital signs: Temp 37 DC, Respirations. 20, HR 100, BP 110/70. Skin: pale, livedo reticularis on the extremities, ulcer on the bottom of the right feet, measuring 2 x 2 cm, with fibrinoid debris over the ulcer surface. Head, ears nose and throath (HEENT): Normal without lesions. Neck: Full range of motion, no masses or lymphadenopathy. Chest: Symmetrical expansion. FP equal bill. Lung fields clear to percussion. Breathing sounds normal. Heart: No cardiac impulse visible. Normal S1, S2, no murmurs, no rub. Abdomen: Distended, diffuse tenderness, without splenomegaly and hepatomegaly. Musculoskeletal exam: No joint swelling, warmth and tenderness. Range of motion within normal limits.

Peripheral vascular: Right calf tenderness, Homans's sign positive, palpable pulses on a. dorsalis pedis ECG: HR 100, normogram, sinus rhythm. Chest X-ray: Without any abnormalities.

Dopler echosonography of the abdomen: Old portal thrombosis with numerous varicosities with slow circulation around the liver, gall bladder and pancreas.

Laboratory results: ESR: 79...105 mm/h, HGB: 107...88 g/L, Er 3.7 x 10¹²/L Htc: 0.33...0.29 Le 4.1x10⁹/L, Plt 126x10³/L Urine analysis: Negative.

Protrombin time 17 sec. (RV 15 sec), Thrombin time normal, aPTT prolonged 95 sec (RV 32 sec) FDP: <250 (RV 0-250).

Lupus anticoagulant – positive (APTT based assay), cardiolipin IgG antibody 22 gpl (< 20) Coagulation factors: Factor II Prothrombin 45% (60-120%), Factor V Proaccelerin 42%, Factor VIII AHG 8.7%, Factor XI Christmas 13%. Blood Group: O, Rh positive.

SMA-12: AP 31 U/L, SGOT: 32 U/L SGPT: 45U/L, LDH 21 U/L; CPK 22 U/L, Glucose: 4.8 mmol/L Urea: 3.3 mmol/L Creatinin 55 mcg/mL, Total proteins: 86 g/L, Albumin 47, Globulin 49, IgG 23, cryoglobulines negative, C3 0.64, C4 0.06, Clk 0.13, ANA negative, Lupus cells phenomenon - negative, RF 320 IU/L (> 30 IU/L), CRP negative.

Treatment: The patient was further referred to hematologist who treated her with oral anticoagulants and aspirin.

Discussion

We presented a case of the 31 year old white female with primary APS and portal venous thrombosis, without any recognizable autoimmune connective tissue disease. She had 4 spontaneous abortions in the first and second trimester, deep venous thrombosis, arterial thrombosis manifested as a gangrene of one toe, refractory cutaneous ulcer on the heel and livedo reticularis.

She presented with mild anemia, thrombocytopenia, prolonged a-PTT, and she was positive for LA, aCL and anti - CMV antibodies.

Systemic arterial and vein thrombosis are typical features of APS. Vianna et al reported typical cases of arterial thromboses in deep vein thrombosis in 54% of cases and arterial occlusions in 44%. However, portal vein thrombosis in APS is rare [8].

Portal vein thrombosis (presinusoidal venous obstruction) is the second most common cause of portal hypertension after cirrhosis. It may develop in a variety

of hypercoagulable states (polycythemia vera, essential thrombocytemia, deficiencies of protein C, S or antithrombin III), including APS. Normal pressure in the portal vein is low -10 to 15 cm saline (portal hypertension > 30 mmHg saline). The major clinical manifestations of portal hypertension include hemorrhage from gastroesophageal varices, splenomegaly with hypersplenism, ascites and hepatic encephalopathy. Therapy is directed towards surgical and non surgical decompression (TIPS). Beta-adrenergic blockade with propranolol (propranolol reduces cardiac output and has vasodilatory effects on both splanchnic arterial bed and the portal venous system) can be used [9-11].

The treatment of APS still remains controversial and it should be individualized depending on the clinical manifestations and the underlying disease.

It is consensus to indicate life-long oral anticoagulation therapy with warfarin with an INR target of 2.5-3.5 for those with recurrent venous thrombosis and INR of 3-4 for those with past arterial thrombosis. These patients should also receive low dose 65-100 mg of ASA. The combination of low molecular weight heparin and low dose aspirin is recommended in pregnant patients with past thrombosis or fetal loss, because of significantly higher rate of live births in the patients who received both aspirin and heparin [13].

Glucocorticoids have been associated with increased maternal and fetal morbidity. They sometimes may be useful in PVT with esophageal varices.

The treatment of patients with APS and portal venous thrombosis is difficult because of the risk of bleeding and the recurrent thrombosis if they don't receive appropriate long-term anticoagulant therapy [10, 11].

Prophylactic anticoagulation therapy is not justified in patients with high titers of aPL with no history of thrombosis. Treatment of associated risk factors (avoidance of smoking, oral contraceptives, obesity, invasive vascular procedures, treatment of hypertension and hypercholesterolemia, avoidance of prolonged immobilization etc.) should be recommended [14].

This case report suggests that APS has heterogeneous clinical presentation and a high index of suspicion for any signs of abdominal involvement should be considered in patients with APS. In addition screening for aPL should be carried out in patients who present with hepatic vein occlusion and unexplained signs of intestinal angina.

References

1. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, Derksen RH, DE Groot PG, Koike T, Meroni PL, Reber G, Shoenfeld Y, Tincani A, Vlachoyiannopoulos PG, Krilis SA. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006;4:295-306.
2. Tripodi A, de Groot PG, Pengo V. Antiphospholipid syndrome: laboratory detection, mechanisms of action and treatment. *J Intern Med*. 2011 Feb 15. doi: 10.1111/j.1365-2796.2011.02362.x.
3. Hughes G. Hughes Syndrome: the antiphospholipid syndrome-a clinical overview. *Clin Rev Allergy Immunol*. 2007;32(1):3-12.
4. Carp HJ. Antiphospholipid syndrome in pregnancy. *Curr Opin Obstet Gynecol*. April 2004; 16(2):129-35.
5. Espinosa G, Cervera R. Antiphospholipid syndrome. *Arthritis Res Ther*. 2008;10(6):230.
6. Di Francesco LM, Burkart P, Hoehn JG. A cutaneous manifestation of antiphospholipid antibody syndrome. *Ann Plast Surg*. 2003;51(5): 517-22.
7. Galli M, Luciani D, Bertolini G, Barbui T. iLupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. *Blood*. 2003;101:1827-1832.
8. Vianna JL, Khamashta MA, Ordi-Ros J, et al. Comparison of the primary and secondary antiphospholipid syndrome: a European Multicenter Study of 114 patients. *Am J Med*. 1994;96(1):3-9.
9. Hirohata Y, Murata A, Abe S, Otsuki M. Portal Vein Thrombosis Associated With Antiphospholipid Syndrome. *J Gastroenterology*. 2001;36(8):574-8.
10. Uthman I, Khamashta M. The abdominal manifestations of the antiphospholipid syndrome. *Rheumatology (Oxford)*. 2007;46(11):1641-7.
11. Marchante Cepillo I, Romero Gómez M, López Lacomba D, Grande Santamaría L, Grilo Reina A. [Primary antiphospholipid syndrome presented with portal vein thrombosis]. *Rev Esp Enferm Dig*. 1999;91(9):650-2. Spanish.
13. Pabinger I, Grafenhofer H. Anticoagulation during pregnancy. *Semin Thromb Hemost*. 2003;29(6):633-8.
14. Levy R. APS: From benchtop to bedside. *Ann Rheum Dis*. 2003;62(1):12.