

# Budd-Chiari Syndrome as a Manifestation of Antiphospholipid Antibody Syndrome during Oral Contraceptive Therapy: More to Think About

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## Abstract

The association of Budd-Chiari Syndrome (BCS) and Antiphospholipid Antibody Syndrome (APS) has been previously described in literature. We report the case of a 46-year-old woman who was admitted to our Unit of Hepatology for upper abdominal quadrant pain, asthenia and edema of the left upper arm. Her familiar history told about predisposition to Systemic Lupus Erythematosus (SLE) whereas her personal story showed a continuous use of oral contraceptives during the six years preceding diagnosis and the absence of episodes of obstetric complications. At the admission, a Doppler Ultrasound examination showed complete thrombosis of venous axis of the left upper arm and thrombosis of subclavian artery (with the aspect of "subclavian steal syndrome"). Abdominal ultrasonography revealed hepatic lesions (characterized by an abdominal Computed Tomography as ischemic injuries) at seventh and eighth segments and the presence of significant amount of ascites. Abdominal and thoracic Computed Tomography confirmed pleural effusion and pointed out a radiologic pattern of Budd-Chiari Syndrome. To verify the presence of concomitant pericardial effusion, an echocardiogram was performed. It allowed reaching the diagnosis of polyserositis. In order to investigate all potential causes of thrombotic diathesis, specific laboratory tests were performed. Normal level of protein C, S and antithrombin II, absence of JAK-2 mutation and negativity of Ham's test were observed. Positivity was found for anti-SSA (60 kDa) and for antibodies routinely tested for Antiphospholipid Antibody Syndrome (APS), i.e. Lupus-Anticoagulant, Anticardiolipin and Beta2- Glycoprotein I. After the introduction of oral anticoagulant and diuretics a significant improvement of clinical condition of the patient was reached. To conclude, the exact role of oral contraceptives as triggering factor of an undetected APS need to be emphasize, as well as the potentiality of this disease to evolve in a "to happen" SLE in patients with positive familiarity for autoimmune diseases.

## Introduction

Budd-Chiari Syndrome (BCS) is a spectrum of disease states, including anatomic abnormalities and hypercoagulable disorders, resulting in hepatic venous outflow occlusion from the small hepatic veins up to where the inferior vena cava enters the right atrium [1]. Contrary to Asia and Africa, where BCS is caused primarily by an obstructing membranous web, BCS in the western world is considered a thrombotic complication of an underlying hypercoagulable state [2]. BCS may be classified as primary or secondary, depending on the underlying process [3].

A small number of cases about association of BCS and Antiphospholipid Antibody Syndrome (APS) have been reported in literature [4-7]. APS is defined by thrombotic events and/or obstetric complications and the presence of Antiphospholipid Antibodies (APAs), including Lupus Anticoagulant (LAC), Immunoglobuline (Ig) G or IgM anticardiolipin (aCL) and IgG/IgM anti-Beta-2 glycoprotein I antibodies (anti-B2GPI) [8]. LACS are identified by clot-based coagulation tests, whereas aCL and anti-B2GPI antibodies by Enzyme-Linked Immunosorbent Assay (ELISA). To confirm the diagnosis of APS, antibodies should be retested at least 12 weeks after initial positive result. The mechanism of thrombosis in APS patient is still unknown. APAs seem to interfere with endogenous anticoagulant pathways, binding and activation of platelets, expression of adhesion molecules and tissue factor on endothelium and activation of the complement cascade. LAC is known to inhibit the conversion of prothrombin to thrombin, paradoxically inducing an increased tendency to thromboembolic events, despite in vitro prolongation of the activated Partial Thromboplastin Time (aPTT) [9].

## Case-Report

A 46 years-old Caucasian woman was admitted to our Unit of Hepatology for upper abdominal quadrant pain, asthenia and edema of

the left upper arm. Her family story revealed a sister with diagnosis of Systemic Lupus Erythematosus (SLE), whereas her personal story told about a continuously use of oral contraceptives during the six years preceding diagnosis, no smoking habits or alcohol abuse and absence of episodes of obstetric complications. The patient had received diagnosis of uterin leiomyoma several years before.

On admission, in addition to persistence of abdominal pain and edema of the left arm, physical examination showed hepatomegaly, mild ascites and pleuric effusion. Laboratory data pointed out as follows: hypochromic and microcytic anemia (Hb 11,8 gr/dL, MCV: 79,8 fl), low platelet count (118,000/mm<sup>3</sup>), elongation of activated partial thromboplastin time (aPTT: 77 sec), hyperfibrinogenemia (834 mg/dL), hyperferritinemia (483 mg/dL), low level of albumin (2,4 gr/dL) and cholinesterase (691 UI/l), hepatocytolysis (AST 57 UI/l, ALT 57 UI/l), cholestasis (GGT 68 UI/l, FA: 334 UI/l), high hemosedimentation velocity and high level of C-reactive protein. Viral markers and renal function tests were negative.

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Doppler Ultrasound examination showed complete thrombosis of venous axis of the left upper arm (including subclavian, axillary and humeral veins) and thrombosis of subclavian artery (with the ultrasound aspect of “subclavian steal syndrome”). Abdominal ultrasonography revealed the presence of hepatic lesions (later characterized by an abdominal Computed Tomography as ischemic injuries) at seventh and eighth segments of an enlarged liver and the presence of significant amount of ascites. Abdominal and thoracic Computed Tomography confirmed the pleuric effusion and pointed out a radiologic pattern of Budd-Chiari Syndrome. To verify the presence of concomitant pericardial effusion, an echocardiogram was performed, which allowed us to diagnose a condition of polyserositis. Cytology of fluids obtained by paracentesis and thoracentesis was negative for malignant cells, whereas the analysis of their chemical-physical characteristics revealed a transudate and exudate, respectively.

In order to investigate all potential causes of thrombotic diathesis, further laboratory specific tests were performed. Normal level of protein C, protein S, antithrombin II, homocysteine, absence of JAK-2 mutation and negativity of Ham’s test (specific for paroxysmal nocturnal hemoglobinuria-PNH) were observed. Positivity was found for anti-SSA (60 kDa) and for antibodies routinely tested for diagnosis of Antiphospholipid Antibody Syndrome (APS), i.e. LAC (Lupus-Anticoagulant), aCL (anticardiolipin) and Beta2-GPI (Beta2-glycoprotein I) (Table 1). Even if patient did not fulfill criteria for SEL, on consideration of her positive familiarity for this disease, auto antibodies were tested.

During the observation, a diagnosis of autoimmune chronic thyroiditis was reached, basing on unknown condition of hypothyroidism (TSH 36 UI/l). Replacing treatment with thyroid hormones was started.

Symptomatic treatment with heparin (8000 UI twice daily subcutaneously) was suddenly established at the admission, later supplemented and then replaced with oral anticoagulants. Diuretic therapy was also prescribed and allowed to get a complete remission of pleural and abdominal effusions at the moment of discharge from hospital. At that time, the patient was sent home with diagnosis of APS, which was confirmed by the repetition of laboratory tests after a distance of twelve weeks from the first assessment (according to guidelines). She has been constantly visited as outpatient to better assess the anticoagulant therapy and regularly follow her clinical course.

## Discussion

Budd-Chiari Syndrome (BCS) is a rare but potentially life-threatening disorder caused by hepatic venous obstruction, distinct from cardiac causes of hepatic congestion or sinusoidal

obstruction syndrome (formerly known as veno-occlusive disease) [2]. Several conditions have been implicated in its pathogenesis, including myeloproliferative disorders, oral contraceptives, pregnancy, Paroxysmal Nocturnal Hemoglobinuria, the presence of lupus anticoagulant and others [10]. The combination of recurrent thrombosis and antiphospholipid antibodies in patients without features of SLE is called primary Antiphospholipid Antibodies Syndrome [11].

In our patient two risk factors for the development of BCS were present: the use of oral contraceptives and positive familiarity for SEL represented, in fact, two “predisposing” conditions. In order to progressively confirm or exclude all potential causes of APS, appropriated tests were performed: JAK2 mutation for myeloproliferative disorders and Ham’s test for PNH. We also consider a paraneoplastic syndrome as a potential cause of thromboembolic state (endoscopic examinations of gastrointestinal tract were performed, together with an accurate gynecological evaluation and determination of neoplastic markers).

Venous thromboembolism is the most common clinical presentation and affects between 30-70% of APS patients [12]. The deep veins of the extremities are most commonly affected, followed by axillary, retinal, hepatic and cerebral venous sinus thrombosis. Other clinical manifestation includes hepatomegaly, right upper quadrant pain, and abdominal ascites. Specifically, our patient presented all aforementioned conditions on admission, but in addition a polyserositis and chronic thyroiditis could be observed, indicating for the patient an “autoimmune” predisposition. The patient, however, did not fulfill criteria for diagnosis of SLE.

## Conclusion

To conclude, the case we reported should lead clinicians to answer two clinical questions: 1) to consider the possible role of APS as a prodromic condition of a “to happen” SLE in patient with positive familiarity for this disease; 2) to determine what factors are involved in inducing a sudden development of thrombosis in this class of patients.

Oral contraceptive therapy is significantly associated with the development of BCS, but its real burden as triggering factor in inducing appearance of an undetected APS is still unclear. Nothing is known about these aspects, so it needs to be investigated.

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<b>Lupus Anticoagulant (LAC)</b>		
-	LAC screen Ratio	<b>Mildly positive</b> 1.96 (0.8-1.2)
-	LAC ratio N	<b>Mildly positive</b> 1.36 (0.8-1.2)
<b>Anticardiolipin (aCL)</b>		
-	IgG	<b>Mildly positive</b> 32 GPL
-	IgM	<b>Mildly positive</b> 17 MPL
<b>Beta2- Glicoprotein I (Beta2-GPI)</b>		
-	IgG	<b>Positive</b> 25 UI/l
-	IgM	<b>Negative</b> 0,9 UI/l

**Table 1:** A mildly positivity was found for LAC and aCL (both IgG and IgM), a clearly positivity for Beta2-GPI (IgG). These results were confirmed at a second repetition after a distance of twelve weeks from the first assessment.

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