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Letter to the Editor

Antiphospholipid syndrome – a life threatening condition

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Dear Editor,

Antiphospholipid antibody syndrome (APS) is characterized by a state of hypercoagulability leading to the occurrence of thromboembolic complications [1]. The most common subgroups of antibodies involved in APS include lupus anticoagulant (LA), anticardiolipin (aCL) and anti-β_2 glycoprotein-I antibodies ($a\beta_2$GPI) (both IgG and IgM) [2]. Frequently associated with systemic lupus erythematous (SLE), APS can appear as the only autoimmune manifestation in some patients [2].

In order to establish a proper diagnosis of the antiphospholipid antibody syndrome, the international consensus states that the presence of at least one clinical manifestation (vascular thrombosis or pregnancy complication) and one laboratory finding is required. Furthermore, the laboratory abnormality must be observed repeatedly, with a minimum of 12 weeks between determinations [1].

We report the case of a 59-year-old woman, a former heavy smoker (40 pack-years, withdrawn for 10 years), with a history of arterial hypertension and hypothyroidism, without premature birth or abortion. She was admitted to our clinic for muscle weakness, shortness of breath, and mild chest pain – symptoms that were persistent for about two weeks; she also complained about pain and stiffness affecting the hand joints as well as knees bilaterally, associated with low lumbar pain and important functional impairment. The clinical examination revealed an obese patient, with stiffness and swelling of the hand and finger joints bilaterally, with mild pain at this level. The remaining examination was normal.

The laboratory tests (Table 1) revealed a mildly elevated aspartate transaminase (AST) with normal alanine transaminase (ALT). Important elevation of creatine kinase (CK) was noted, associated with a slight increase in CK-MB and in lactate dehydrogenase (LDH) blood levels. Serum creatinine and urea were increased and there was an important inflammatory syndrome with high levels of fibrinogen, C reactive protein, and erythrocyte sedimentation rate (ESR). Laboratory tests also revealed mild leucocytosis (10.53 $x10^3$/ ul) predominantly with neutrophils, and an increased number of platelets (488 $x10^3$/ ul). An electrocardiogram was performed, without repolarization alterations. The chest X-ray revealed cardiomegaly, while transthoracic echocardiography indicated mild dilation of the right heart cavities and moderate tricuspid valve regurgitation, being otherwise normal. Daily proteinuria was determined with a value of 0.7 g of proteins per day.

Coagulation exploration revealed increased levels of D-dimers with normal activated partial thromboplastin time (APTT), prothrombin time (PT) and International Normalized Ratio (INR). For further evaluation, a circulating anticoagulant antibody panel was also performed, showing the presence of lupus anticoagulant, as well as anticardiolipin antibodies. Anti-β_2 glycoprotein-I antibodies were not detected. Serology for anti-neutrophil cytoplasmic antibodies (ANCA), Anti-Sjogren's Syndrome A (SSA), Anti-Sjogren's Syndrome B (SSB), antinuclear antibodies (ANA), anti-double stranded DNA antibodies (dsDNA), Rheumatoid Factor (RF), and anti-glomerular basement membrane antibody was negative.

Table 1. The evolution of biologic parameters and treatment associations in our patient.

Variable	First admission	Second admission (one month apart)	Third admission (one month apart)	Fourth admission (three months apart)
AST	100	67	32	37
ALT	38	34	27	25
CK	1460	78	45	39
CK-MB	35	12	14	12
Creatinine	1.81	1.52	1.39	1.51
24-h proteinuria	0.7	3.28	0.3	0.2
D-dimers	1400	1600	512	218
Fibrinogen	813	428	356	258
CRP	117	24	12	4
Anticoagulation therapy	Enoxaparin for 14 days Rivaroxaban for 3 weeks	UFH for 7 days Enoxaparin for 3 weeks	Enoxaparin for 3 weeks	Enoxaparin for 3 weeks
Immunosuppressive therapy	Methylprednisolone 1g for 3 days Dexamethasone 4mg for 3 weeks	Methylprednisolone 1g for 3 days Methylprednisolone 16mg for three weeks	Methylprednisolone 1g for 3 days Methylprednisolone 16mg for three weeks	Methylprednisolone 1g for 3 days Methylprednisolone 16mg for three weeks

Abbreviations: AST: aspartate transaminase; ALT: alanine transaminase; CK: creatine kinase; CK-MB: creatine-kinase muscle-brain; CRP: C-reactive protein.

Computerized tomography of the thorax revealed partial filling defects within the segmental pulmonary arteries of the inferior right lobe. Venous Doppler ultrasound examination of the legs showed no signs of thrombosis.

The patient was administered parenteral anticoagulation with enoxaparin for 14 days, followed by oral treatment with rivaroxaban (20 mg daily). Furthermore, given the renal impairment, the presence of autoantibodies, as well as the pain and swelling of several joints (that did not improve with the use of nonsteroidal anti-inflammatory drugs), the patient was given corticosteroid pulse therapy with one gram of methylprednisolone per day, for three days, followed by oral therapy with 4 mg of dexamethasone daily. Under therapy, the clinical status of the patient improved significantly, while creatinine and urea slowly normalized, as well as CK, CK-MB, ALT, AST, fibrinogen, C reactive protein and ESR. The patient was discharged, with the recommendation of continuing both anticoagulant therapy with rivaroxaban and corticosteroid therapy with dexamethasone.

After one month of treatment the patient presented for re-assessment. She was in good clinical condition and only complained of mild fatigability and asthenia. Clinical examination was normal. However, D-dimers had a value of 1600 ng/ml and there was also an increase of serum creatinine level and urea. Blood tests revealed leucocytosis of 16.45 $x10^3$/ ul, with neutrophilia, mild anaemia 12.7 g/dl and a normal number of platelets (289 $x10^3$/ ul). The 24-hour proteinuria was also determined and was importantly elevated (3.28 g of proteins per day), by comparison

with the previous determination. Plasmatic level of rivaroxaban was determined by chromogenic assay and the peak concentration was 34.1 μg/L (at the lower limit of efficient concentration range).

The patient underwent a second computerized tomography of the thorax, which revealed the remission of the right segmental pulmonary embolism, while a new filling defect located within the segmental pulmonary arteries of the superior left lobe was described. The oral anticoagulation was replaced by parenteral anticoagulation with unfractionated heparin (UFH). Also, she underwent a second pulse therapy with methylprednisolone followed by 16 mg of methylprednisolone orally daily.

In order to determine the cause of the renal impairment in the presence of lupus anticoagulant, a kidney biopsy was performed. Optical microscopy described glomeruli with ischemic apearance, without mesangial proliferation, as well as interstitial sclerosis and atrophic tubules, hyaline nodular arteriolar deposits, narrowing in the arteriolar lumen, arteriolar media hypertrophy; arterial vessels with lamellar structure of the internal elastic lamina and discrete diffuse interstitial inflammation were also spotted. Electron microscopy evaluation showed glomeruli with permeable capillaries, with some glomerular loops presenting ischemic basal membranes and important narrowing, in association with discrete signs of endotheliosis.

She was discharged in good condition and was recommended enoxaparin 4000 UI twice a day.

One month after the second PE, she was admitted for follow-up, with good clinical status; the control CT scan of the thorax showed no signs of pulmonary embolism. D-dimers, as well as all the other laboratory tests (hemogram, coagulation tests) were within normal range. Increased creatinine and proteinuria persisted, with significant improvement. She was discharged from hospital after another corticosteroid pulse therapy, with the recommendation of therapeutic dose of enoxaparin and 16 mg/ day of methylprednisolone.

On three months follow up, the presence of lupus anticoagulant was verified again and the initial diagnosis of antiphospholipid antibodies syndrome was confirmed, with positive lupus anticoagulant, anticardiolipin antibodies and anti-β_2 glycoprotein-I antibodies. She was therefore advised to indefinitely continue the anticoagulant treatment and the corticoid therapy.

Our patient had recurrent pulmonary embolism, with important renal involvement manifested with proteinuria and nitrogen retention. While many visceral implications of primary APS have been characterized, the renal manifestations of this pathological entity were underestimated and have received scarce attention until recently [3]. Not only can the kidney be affected by APS, but it also represents a major scene in the pathogenesis of this condition. Moreover, renal involvement is a frequent characteristic of catastrophic APS.

The pathway by which antiphospholipid antibodies determine thrombotic events remains yet unclear, although it may involve interactions with beta 2-glycoprotein 1, resulting in endothelial cell activation, in association with antithrombin III inhibition, protein C activation, inhibitory effects on fibrinolysis and interference with tissue factor and thrombin [4]. A recent study has shown that the risk of venous thrombosis in patients with SLE- associated APS can be correlated to high serum levels of IgG antiphosphatidylethanolamine [5]. Furthermore, increased levels of platelet activation markers such as P selectin and soluble CD40L have been found in APS patients with recurrent thrombotic events [6].

The therapeutic approach of APS is focused on three aspects: the identification and treatment of precipitating factors, the prevention and treatment of thrombotic events and the suppression of excessive activity of cytokines. Therefore,

optimal therapy may include: anticoagulants, corticosteroids, plasma exchange, intravenous gamma-globulins and, if necessary, cyclophosphamide [1].

Our patient had a very particular evolution, under treatment. She received anticoagulation therapy after the diagnosis of the first PE, consisting of parenteral anticoagulation with enoxaparin for 14 days, followed by oral treatment with rivaroxaban (20 mg daily) on discharge. While on rivaroxaban, an inhibitor of coagulation Factor Xa, she developed a second PE, with different location from the first one. There are several potential causes reported in the literature for the recurrence of thrombotic events during anticoagulant therapy, such as: malignant tumours [7], myeloproliferative disorders (polycytemia vera and essential thrombocythemia) [8], vasculitis (Behcet disease), paroxysmal nocturnal haemoglobinuria, pregnancy, vascular abnormalities (for example the venous compression in May-Thurner syndrome) and last, but not least, the antiphospholipid syndrome itself may be a cause of anticoagulant therapy failure [9]. However, there is evidence of recurrent thrombotic events while on rivaroxaban even in individuals that do not present with any of the aforementioned conditions, especially in obese patients, although the cause remains unclear [10]. For treating the second thrombo-embolic event, she was given parenteral anticoagulation with unfractionated heparin, followed by enoxaparin. The patient did not repeat any thrombotic events while on enoxaparin. In terms of reducing cytokine activity, corticosteroid treatment was applied, in monthly pulse-therapy, followed by daily oral administration, effectively reducing inflammatory markers and related symptoms.

In conclusion, APS can induce severe organ damage by recurrent embolisms and inflammation, requiring anticoagulation as well as immune suppression for the inhibition of pathogenic pathways. Frequent follow-up with treatment optimization is essential in patients presenting with clinical manifestations of APS.

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Conflict of interest

None to declare.

Informed consent

Informed consent was obtained from the patient prior to the submission of this report

Abbreviations

APS: antiphospholipid antibody syndrome; aPL: antiphospholipid antibodies; LA: lupus anticoagulant; aCL: anticardiolipin; aβ2GPI: anti-β2 glycoprotein-I antibodies; DVT: deep vein thrombosis (DVT); PE: pulmonary embolism (PE); AST: aspartate transaminase; ALT: alanine transaminase; CK: creatine kinase; LDH: lactate dehydrogenase; ESR: erythrocyte sedimentation rate; APTT: activated partial thromboplastin time; INR: International Normalized Ratio; ANCA: anti-neutrophil cytoplasmic antibodies; SSA: Anti-Sjogren's Syndrome A; SSB: Anti-Sjogren's Syndrome B; ANA: antinuclear

antibodies; dsDNA: anti-double stranded DNA antibodies; RF: Rheumatoid Factor; UFH: unfractionated heparin; SLE: systemic lupus erythematosus.

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