Catastrophic antiphospholipid syndrome in a patient with V Leiden variant

Silvio Buscemi, Daniela Rallo, Sergio Siragusa, Maurizio Li Vecchi

Dipartimento di Medicina Interna e Specialistica, Policlinico "P. Giaccone", University of Palermo, Italy

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Corresponding author:
Silvio Buscemi MD
Dipartimento
di Medicina Interna
Malattie Cardiovascolari
e NefroUrologiche
Policlinico "P. Giaccone"
Via del Vespro 129
90127 Palermo, Italy
Phone: +39-091-6554580
Fax: +39-091-6552144
E-mail: silbus@tin.it

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by a thrombophilic state with pregnancy complications and the presence of circulating antiphospholipid (aPL) antibodies, namely lupus anticoagulant (LAC), anticardiolipin (aCL), and/or anti-β_2-glycoprotein I (anti-β_2 GPI) [1]. Antiphospholipid syndrome may occur in association with systemic lupus erythematosus (SLE-APS) or as primary APS. This syndrome rarely may present with rapidly recurring thrombotic events involving predominantly small vessels of many organs; this presentation is defined as catastrophic APS (CAPS) or Asherson's syndrome [1].

We report a case of a woman with multi-systemic dysfunction consisting of cerebral symptoms, cardio-pulmonary disease, and renal insufficiency, who tested positive for aPL antibodies and factor V Leiden variant.

A 44-year-old woman with a history of pregnancy losses and evidence of LAC positivity and a pre-eclamptic syndrome during the final pregnancy was transferred to our department for acute lung failure and a suspected stroke. On admission, the patient presented with coma, fever (37.5°C), normal diuresis (1250 ml), blood pressure 150/110 mm Hg, pulse rate 106/min and a respiratory rate of 50/min. On physical examination, she exhibited truncal ecchymoses and late inspiratory crackles were auscultated bibasally. Laboratory studies demonstrated leukocytosis (22 000/mm^3, with 93% neutrophils), fibrinogen 522 mg/dl (normal values: 150-350), antithrombin (AT) 99% (80-120), BUN 22 mg/dl (8-20), and creatinine 1.2 mg/dl (0.7-1.1). Urinalysis revealed 2+ protein, 5-9 HPF red blood cells, and 24-hour proteinuria was 2400 mg. The chest radiograph revealed diffuse infiltrates in the bilateral lung fields with mild cardiomegaly. Echocardiography showed normal left ventricular contractility with an ejection fraction of 65% and mild enlargement of the right atrium and the right ventricle. Computed tomography (CT) imaging of the brain revealed a right subcortical nucleobasal and deep fronto-temporal highly hypodense extended area arising from a not-yet-stabilized ischemic lesion (Figure 1). The time course of routine coagulation screening and renal function are displayed in Table I.

The patient was treated with antibiotics, anti-hypertensive medications and mannitol, in addition to pressure support ventilation. On the fourth day, the patient was hemodynamically stable but a moderate fever continued which increased subsequently in the absence of positive cultures. Renal function worsened and transaminases increased (ALT 74 and AST 35 IU/l; normal values: < 35). Considering the patient's history and the laboratory data, we suspected CAPS. Immune and coagulation systems with

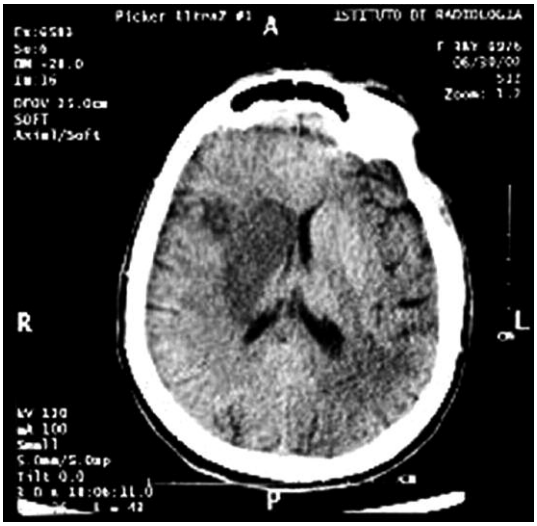

Figure 1. Brain basal CT demonstrating right subcortical nucleobasal and deep fronto-temporal highly hypodense extended area

APL antibodies and a complete coagulative screening, including protein C, were assessed. Serology investigation excluded the presence of anti-nuclear antibodies (ANA), anti-double stranded DNA antibodies (anti-ds-DNA) and anti-neutrophil cytoplasmic antibodies (ANCAs), thus suggesting the presence of primary APS. Therapy with intravenous heparin and steroids (methylprednisolone 1 g /day) was initiated. Until day 6, the clinical parameters and serum blood chemistry tests gradually indicated deterioration and cardiorespiratory failure persisted in association with hyperthermia. On day 9 the patient's hemodynamics worsened and laboratory tests revealed raised cardiac enzymes. Renal function quickly deteriorated, but a kidney biopsy was not performed due to the patient's critical condition. Continuous veno-venous hemodiafiltration treatment was initiated but the patient expired during this procedure. The immuno-coagulative results showed a protein C level of 82%, aCL IgG and LAC highly positive and the presence of heterozygous factor V Leiden.

Fewer than 1% of APS patients present with the life-threatening condition known as CAPS, attributable to multiple organ thromboses and failure. In classic APS, single venous or arterial medium-to-large blood vessel occlusion usually dominates the clinical picture and recurrences are rare with adequate anticoagulation. Catastrophic APS, however, is characterized by severe multiple organ dysfunction for the rapid, diffuse small vessel ischemia and thromboses. The organs most frequently involved are the kidneys (78%), lung (66%), central nervous system (56%), heart (50%), and skin (50%). In CAPS, acute respiratory distress syndrome is an expression of systemic inflammatory response syndrome, mainly caused by release of cytokines [2]. Preliminary CAPS classification criteria (Table II) were proposed during the 10th International Congress on aPL held in Taormina (Italy) in 2002 [3]. It remains unknown why some patients develop CAPS rather than classic APS: the role of trigger factors (e.g., infection, surgery, or oral contraceptive use) is evident in patients with classic APS; however, the proposed "double-hit" or "triple-hit" hypothesis may be applicable to CAPS patients. Furthermore, CAPS is fatal in approximately half of all cases despite treatment.

The case described here appears to be an example of CAPS (probable CAPS according to criteria). She had a positive LAC but an absence of risk factors, although she had an inherited thrombophilic condition (factor V Leiden).

Activated factor V is necessary for prothrombin activation and its activity is regulated by activated protein C (APC), which cuts the V factor into three parts (Arg 506 is one of the cleavage sites). The presence of factor V Leiden results in a prothrombotic status. This variant arises from a genetic mutation known as G1691A and is characterized by a GLN 506; this mutation makes factor V resistant to cleavage by APC, resulting in increased levels of factor V and thrombin. Heterozygous status increases the risk for thrombosis by about 8-10 fold in comparison to wild-type, whereas patients who are homozygous carry an 80-100-fold higher risk for venous thrombosis.

Many studies have reported an increased venous thromboembolic risk in patients with APS and associated congenital thrombophilia. Brouwer *et al*. [4] confirmed previous studies demonstrating in

Table I. Time course of laboratory examinations during the hospitalization

Parameter	Day								
	1	2	3	4	5	6	7	8	9
Serum creatinine [mg/dl]	1.3	1.6	1.8	2.3	1.6	2.7	4.2	8.7	10.6
Blood urea nitrogen [mg/dl]	44	62	70	91	93	180	259	386	447
Platelet count [thousands/mm^3]	279	179	243	238	200	191	221	198	215
PT [%]	90	50	57	49	72	58	58	61	57
APTT [s]	18	21	29	40	37.9	44.7	44.7	50	39

APTT – activated partial thromboplastin time, PT – prothrombin time

144 patients with LES that the presence of aPL doubled the risk of venous thromboembolic events; in the patients with a V Leiden mutation this risk was trebled. Many studies on patients with primitive APS have shown an increased risk if a V Leiden mutation was present [5]. The coagulative pattern of the patient (prolongation of the activated partial thromboplastin time (aPTT) as an expression of LAC and not of a hemorrhagic disorder) and the multi-organ failure suggest a common pathogenesis supported by the presence of APL antibodies, although in these cases, a moderately low platelet count is frequent. In a series published by Asherson *et al*. [2] of 80 patients with CAPS, 50 of them had thrombocytopenia. Laboratory results and imaging excluded other diagnoses.

This case demonstrates the difficulties involved in identifying and treating the condition, with organs and clinical parameters deteriorating rapidly. Early diagnosis and treatment is fundamental, even if not always decisive. Even a slight prolongation of aPTT (based on clinical status) should suggest a focus on LAC more than aCL, which is not correlated with thrombotic risk. A combination of high doses of *i.v.* heparin, *i.v.* steroids and repeated doses of *i.v.* gamma globulins or plasma exchange is the treatment of choice in patients with this severe condition. Despite this multi-modal treatment, CAPS is often associated with high mortality; unfortunately, evidence-based management recommendations are not available because of an absence of controlled studies. In most cases only patient-based management has been performed.

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