CASE REPORT

Intracerebral hemorrhage in a patient with SLE and catastrophic antiphospholipid syndrome

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A 31-year-old woman was admitted to the hospital for the investigation of left lower limb thrombophlebitis. History revealed one 1st trimester abortion, arthralgias, photosensitivity and leucopenia during the last months. Laboratory investigation showed positive antinuclear antibodies (ANA) and high titers of anticardiolipin antibodies (ACA). The patient was diagnosed to suffer from SLE and secondary APS. Treatment included steroids, azathioprine, aspirin and low molecular weight heparin (LMWH). Sixty-three days later, she was admitted to the hospital again because of high fever, macroscopic hematuria and dyspnea. Laboratory testing showed anemia and impaired renal function. High-resolution chest CT revealed bilateral multiple peribronchial infiltrates with hemorrhage. MRI angiography of the kidneys revealed left renal vein thrombosis combined with ischemia of the left kidney. Cyclophosphamide and methylprednisolone pulse treatment as well as intravenous immunoglobulins were started immediately. On day 3, the patient developed acute respiratory failure and was transferred to the ICU. Despite intensive immunosuppressive and supportive treatment, she suffered three relapses of alveolar hemorrhage and died on day 40, due to severe intracerebral bleeding. Final diagnosis was catastrophic APS with diffuse alveolar hemorrhage and kidney involvement. The rarity and individuality of the patient, concerning disease aggressiveness and therapeutic interventions is discussed.

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Originally defined in 1992, catastrophic antiphosholipid syndrome (CAPS) represents an accelerated form of thrombosis, primarily affecting the microvasculature of many organs. It consists of a rare condition, since patients with CAPS comprise about 0.8% of the patients with antiphosholipid syndrome (APS)[1,2]. In the present study, a case of CAPS is analyzed in regard to the clinical and laboratory findings and the impact of applied therapy. Additionally, disease manifestations and applied modalities are compared to other cases presented in the literature.

Presentation of the patient

A 31-year old woman was admitted to the hospital for the investigation of three recurrent episodes of deep vein thrombosis (DVT) of the left lower limb during a six month period. She had a first trimester abortion of unknown etiology twelve months. Thereafter, she was previously complaining of fatigue, migraine-like headaches, arthralgias, photosensitivity and revealed mild leucopenia (WBC=3X10^9/L).

At presentation, physical examination revealed a mild systolic murmur of the mitral valve. Patients' vital signs were normal. Laboratory investigation performed is shown in Table 1. Analysis of the autoantibody profile revealed that ANA were positive (1/80 dilution, speckled pattern) and ACA were detected in high titers twice. Coagulation test showed that serum levels of proteins C and S, antithrombin III, plasminogen, fibrinogen and factor V Leiden were normal. Electrocardiogram and chest X-rays were normal. Ophthalmologic examination revealed micro-hemorrhage of the left retinal artery, while heart ultrasonography showed prolapse and mild regurgitation of the mitral valve.

According to the clinical and laboratory findings, she fulfilled the criteria for the diagnosis of SLE and secondary APS[3,4]. Treatment including methylprednisolone (32 mg/day), azathioprine (100 mg/day), aspirin (100 mg/day) and low molecular weight heparin (LMWH) was administered.

Sixty three days later, she was re-admitted to the hospital because of high fever (maximum temperature 40°C, duration 7 days), macroscopic hematuria, dyspnea, chest discomfort and bilateral visual symptoms (amaurosis). Patients' heart rhythm was 105/minute, respirations 21/minute and blood pressure 135/85 mmHg. Oxygen saturation of the arterial blood was 99%; Hct was 23, WBC 8.3X10^9/L, PLT 239X10^9/L. Further investigation of the coagulation mechanism remained unchanged, direct and indirect Coombs' tests were nor-

Table 1. *Blood, biochemical and immunological parameters at first admission*

Blood-biochemical parameters		Immunological parameters	
WBC	4.1X10^9/L	IgG, IgA, IgM	normal
Hb	11.4 mg/dl	ICs	normal
PLT	369X10^9/L	C_3/C_4	normal
ESR	23 mm/h	RFs	77 (0-9)
INR	1,1	ANA	1/160 (+), speckled
aPTT	31/27	ASMA	1/160 (+)
CRP	5,62 (< 5)	anti-dsDNA	negative
BUN/Creatinine	32 / 0,7	anti-ENA	negative
Cr. Clearance	89	ACA-GPL	49 (0-15)
24h urine protein	206	ACA-MPL	25 (0-15)
Urinalysis	25 – 30 RBC	anti-β_2GPI	negative
Other parameters	normal	ANCA (PR3-MPO)	negative

mal, while ESR was 44 mm/h and CRP was 84 μg/ml. The electrocardiogram showed sinus tachycardia. Auscultation of the lungs revealed basal bilateral crepitations. Chest X-ray showed regions with atelectasia in the base of the left lung, bilateral pleuritic effusion and slight interstitial edema. Urinalysis revealed many RBCs and renal function was impaired (creatinine 1.6 mg/dl, BUN 68 mg/dl). Although blood and urine cultures were negative and procalcitonin levels were low in three sequential measurements, wide-spectrum antibiotics were added to treatment.

Intravenous pulse methylprednisolone (1000 mg) and RBCs (packed cells), transfusions were also administered. On day 2, high resolution CT (HRCT) of the lungs was performed (Picture 1, A, B) and cyclophosphamide pulse treatment (500 mg) was added. On day 3, MRI angiography of the kidneys was performed (Picture 1, C, D).

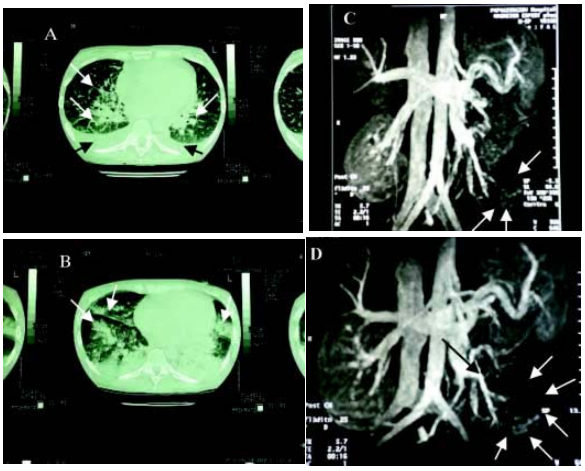


Figure 1. *A. High resolution computed tomography (HRCT) of the thorax revealed multiple peribronchial hemorrhagic infiltrates (ground glass opacification) and unilateral pleuritic effusions. B. HRCT during alveolar hemorrhage relapse when the patient was hospitalized in the ICU. C, D. Magnetic resonance imaging (MRI) angiography of the kidneys revealed left renal vein thrombosis and ischaemia of the lower part of the left kidney in the toxoid arteries region.*

The patient was diagnosed to suffer from diffuse intraalveolar hemorrhage and left renal vein thrombosis and ischemia of the left kidney in the background of secondary APS to SLE. Therapy was continued with intravenous pulses of high doses of methylprednisolone and cyclophosphamide, while low molecular weight heparin (LMWH) and intravenous immunoglobulins (IVIGs) were added. A few hours later on day 3, patients' general status deteriorated rapidly, acute respiratory failure supervened (pO_2 50mmHg, SaO_2 88%); she was intubated and carried to the Intensive Care Unit (ICU). Despite continuous aggressive immunosuppressive, anticoagulant and supportive treatment, the patients' general status deteriorated with three recurrent episodes of massive alveolar hemorrhage. A second HRCT and bronchoscopy was performed on 2nd recurrence. Total therapeutic approach is shown in Table 2.

The patient died on day 40, due to severe intracerebral hemorrhage. Diagnosis was CAPS in the background of SLE, affecting the lungs, the kidneys and the brain.

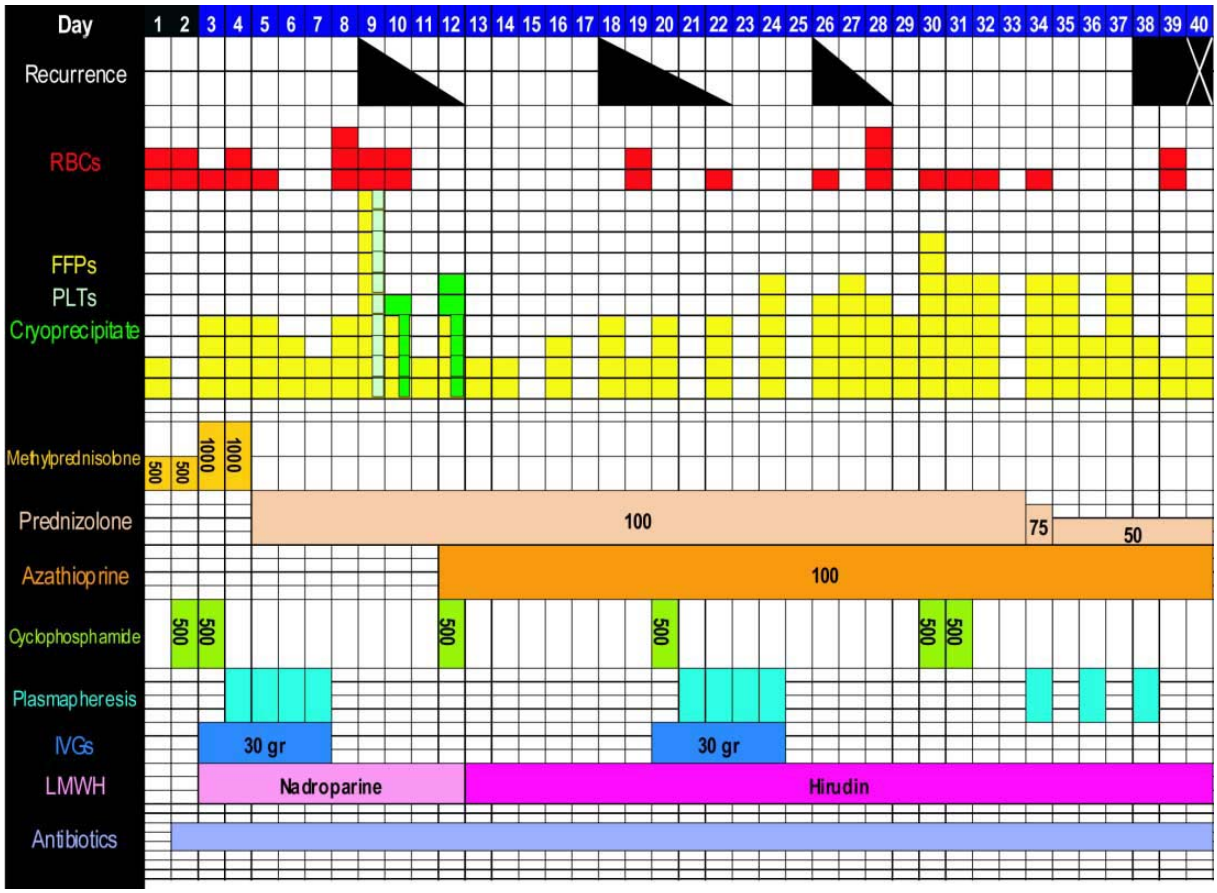
Discussion

Few cases of CAPS have been reported in the literature. The largest series consisted of a meta-analysis of 80 case reports, underlining the rarity of CAPS as well as the variety of the clinical manifestations of these patients[5]. Our previous experience consisted of one patient who presented with pulmonary embolism, mesenteric artery thrombosis, Budd-Chiari syndrome and thrombotic stroke who, finally, survived[6].

The patient discussed in this paper presented with thromboembolic disease and alveolar hemorrhage, clinically expressed as dyspnea, haemoptysis and respiratory failure, which, along with acute pulmonary edema and pulmonary embolism represent the main pulmonary manifestations of CAPS[7]. Intra-alveolar hemorrhage has been reported only in three patients with CAPS, due to thrombosis in the micro-vasculature of the lung[5]. High resolution CT revealed 'typical' pulmonary lesions appearing as ground glass opacifications and patchy hemorrhagic infiltrates as it is discussed in the literature previously (three cases)[8]. Differential diagnosis included lupus pneumonitis, but low levels of complement fragments C_3 and C_4 or high levels of immunocomplexes were not observed throughout the course of the disease (as it would be expected)[8].

Renal involvement was characteristic of APS, as hematuria and impaired renal function were present, resulting from renal thrombotic micro-angiopathy[9]. Although anti-dsDNA antibodies are highly spesific for SLE, they are not always present and predictive of disease activity. A prevalence of approximately 65% for anti-dsDNA and a sensitivity of 71% for the diagnosis of SLE has been recently discussed in the literature[10]. Lupus nephritis was excluded based on negative anti-dsDNA, normal C_3, C_4 and immunocomplexes and normal blood pressure. In the literature, 72% of the CAPS

Table 2. *Schematic representation of the overall therapeutic approach during the 40-day hospitalization of the patient*



patients presented with renal involvement[5].

The existence of high fever complicates the clinical evaluation of these patients. It is suggested that this can be due to an infection that either precipitates the pathogenetic mechanism or aggravates the clinical course, leading to septic shock[5]. Use of wide-spectrum antibiotics is recommended by several investigators, although only 3 out of 80 patients in Ashershon's meta-analysis were proved to suffer from bacterial infection[5]. In our patient, there were no laboratory data suggesting infection existence based on negative blood/urine/BAL cultures and low procalcitonin levels in sequential measurements. Other precipitating factors, present in almost 50% of the patients, include withdrawal of the anticoagulant treatment, trauma and gynecological operations and were carefully excluded, according to history.

Causes of death in CAPS include usually cardiopulmonary complications, such as myocardial infarct, pulmonary embolism, ARDS and alveolar hemorrhage, while main clinical manifestations from CNS include strokes, multi-infarct dementia and seizures[5,11]. The presented patient is the third case with intracerebral hemorrhage reported in the literature[12,13,14]. Our patient had no neurological complications and intracerebral hemorrhage could not be associated with disseminated intravascular coagulopathy, thrombopenia or coagulation factors disorders, based on detailed laboratory investigation. However, the patient died 40 days after her admission, despite the highly offensive immunosuppressive and anti-coagulant therapy.

Mortality reaches 48-50% in CAPS patients, despite various therapeutic interventions used in the last years[5,15,16]. Intensive anti-coagulant treatment with LMWH combined with intravenous pulses of steroids seems to be beneficial in CAPS, as mortality rate was 36%, compared with 62% in patients which had not received such treatment[5]. Other therapeutic choices include IVIGs, cyclophosphamide pulse treatment, plasmapheresis and supportive treatment (mechanical ventilation, blood and FFP transfusions, oxygen)[17].

The impressive variety of clinical manifestations and the potential fatal outcome in these patients necessitates immediate initiation of treatment, although optimal therapy remains controversial. Assiduous study of the cases reported in the literature will help clinicians for better understanding and managing patients with CAPS.

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