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case of the month

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Reversible adult respiratory distress in primary antiphospholipid syndrome

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ABSTRACT

Antiphospholipid antibody syndrome (APS) is a disorder caused by circulating antibodies reacting with biological membranes and characterized by recurrent thrombosis, chronic thrombocytopenia and miscarriages. It has been reported to occur either as a primary syndrome or secondary to systemic autoimmune disorders. We describe a case of primary APS in a young patient, in whom the clinical course was particularly severe and complicated by a respiratory distress syndrome. The patient was resistant to a number of treatments, and eventually responded to intravenous high dose corticosteroids.

Key words: antiphospholipid syndrome, acute respiratory distress, high dose corticosteroids.

The antiphospholipid syndrome (APS) is a disorder characterized by the presence of circulating immunoglobulins reacting with phospholipids, the main component of biological membranes. Patients who develop this syndrome have an increased tendency to thrombosis, chronic or recurrent thrombocytopenia and (in women) repeated fetal loss.[1] Antiphospholipid antibodies may be detected in the serum of patients suffering from systemic lupus erythematosus (SLE) or other autoimmune diseases; they can also be found in subjects with no evidence of other autoimmune disorders (primary APS). In some instances, patients with APS may develop life-threatening complications. In 1992, Asherson *et al.*[2] described *catastrophic* APS, an acute and often fatal syndrome characterized by multiple vascular occlusions involving different organs (kidney, lung, central nervous system, deep veins). The treatment of this condition has not been conclusively defined.

We report the case of a young patient with primary APS complicated by acute respiratory distress syndrome (ARDS), successfully treated by high dose methylprednisolone.

Case report

In January 1998 a 15-year old boy from Benevento was admitted to a local hospital after two weeks of fever unresponsive to antibiotic treatment. Physical examination did not contribute diagnostic information. Laboratory findings showed a hemoglobin (Hb) of 70 g/L and platelet count of 35×10^9/L; antiphospholipid antibodies were detected in the serum. Broad spectrum antibiotics, low-dose corticosteroids and fresh frozen plasma (FFP) infusions (4 units) were all ineffective. Two weeks later he developed thrombosis of the left popliteal vein, treated by subcutaneous heparin (12,500 IU every 12 hours). A few days later, the patient showed a severe hemorrhagic syndrome associated with thoracic pain and respiratory distress. CT scan and pulmonary scintigraphy suggested right pulmonary embolism.

Referred to our Hematology Unit, the patient was conscious on admission, with a high-grade fever and severe hemorrhagic status (massive skin ecchymoses, nose bleeding). Bilateral pleural effusions and pulmonary micro-infiltrates were documented by chest X-ray. Blood gas analysis was normal. Routine laboratory tests showed Hb 77 g/L; platelets 25×10^9/L; erythrocyte sedimentation rate 145 mm/hour; AST 120 U/L (n.v. <40), ALT 240 U/L (n.v. <40), LDH 633 U/L (n.v. 220-450). Reticulocyte count was 384×10^9/L. Red cell morphology from a peripheral blood smear showed the presence of a small number of schistocytes, suggesting the presence of a microangiopathic condition. Direct and indirect Coombs' tests were negative, ruling out Fisher-Evans syndrome. Microbiological cultures from blood and mucosae were negative. PT and APTT were prolonged; fibrinogen level was slightly increased. PT and KCT mixing ratios were both prolonged, confirming the presence of a high titer of lupus anticoagulant antibodies. More detailed coagulation tests showed activation of the hemostatic pathway, documented by elevated thrombin-antithrombin (T-AT) complexes and fibrinopeptide-A (FPA), and signs of endothelial damage, as suggested by the release of plasminogen activator inhibitor-1 (PAI-1) (Table 1). The presence of lupus anticoagulant (LAC) was documented by prolonged KCT and dRVVT tests. Both IgG and IgM anticardiolipin antibodies (ACA)-β_2-glycoprotein type 1 (β_2-GPI) were present (Table 1). Serologic tests performed to investigate the presence of serum antibodies characteristic of SLE (ANA- Hep-2 cells; anti-ENA–SSA, Sm; anti-DNA ds) were all negative. When second line antibiotics (meropenem and teicoplanin) and repeated FFP infusions (4 units for three days, for a total volume of infused plasma of about 1,800 mL) failed to modify the clinical status, methylprednisolone 200 mg/day i.v. was given for five days, without success. The patient was restless and markedly

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Table 1. Selected coagulation and immunologic data.

Test	*Results*	*Reference range**
Screening analysis		
PT (INR)	1.45	1.0±0.15
PT mixing 1:1 test (ratio)	1.40	≤1.2
APTT (ratio)	2.25	1.0±0.17
Fibrinogen (mg/dL)	447	265.5±40.4
Fibrinolytic activity		
PAI-1 (AU/mL)	16.5	6.2±3.8
Activation peptides		
T-AT (µg/L)	4.8	2.2±1.46
FPA (nM)	4.6	1.2±1.05
Lupus anticoagulant		
PT ratio	1.45	≤1.2
KCT ratio	3.42	≤1.2
KCT mixing test ratio	4.12	≤1.2
DRVVT ratio	2.10	≤1.2
DRVVT mixing ratio	1.87	≤1.2
DRVVT confirm ratio	1.48	≤1.2
ACA-Ig β_2-GPI (GPL U/mL)	44	<9.5
ACA-Ig β_2-GPI (MPL U/mL)	12	<7.0
ACA-IgA β_2-GPI (APL U/mL)	1.5	<9.0

**From our general population (n= 400 healthy subjects). PT: prothrombin time; PAI-1: plasminogen activator inhibitor type 1; T-AT: thrombin-antithrombin complexes; FPA: fibrinopeptide A; KCT: kaolin clotting time; dRVVT: dilute Russell viper venom time; ACA (IgG/IgA/IgM)–β_2-GPI: anticardiolipin antibodies β_2-glycoprotein type I.*

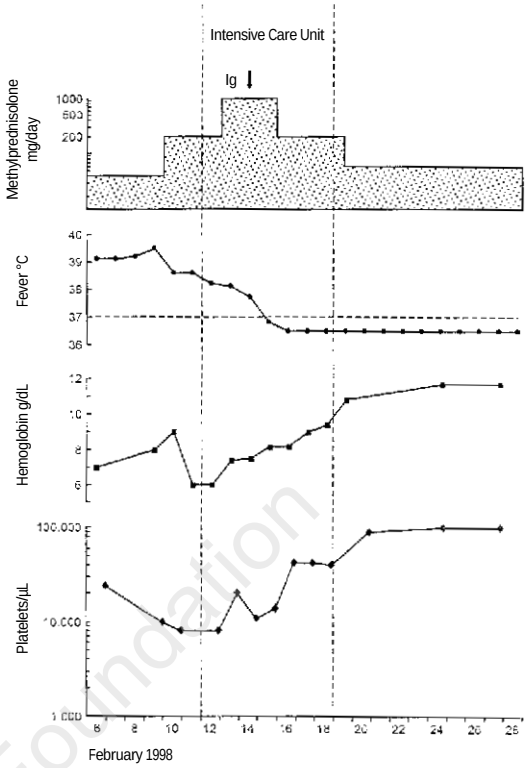

Figure 1. Effect of high dose methylprednisolone on essential clinical and hematologic parameters.

dyspneic; blood gas analysis showed severe hypoxia; chest X-ray and CT scan showed bilateral multiple pulmonary infiltrates consistent with ARDS. The patient was transferred to the Intensive Care Unit and was intubated. A single shot of high dose (0.4 g/kg, i.e. 20 g) intravenous immunoglobulins was given. We then gave high dose methylprednisolone (1 g/day i.v. for 3 days), which produced immediate improvement of the respiratory status and blood count and disappearance of the fever; the patient was extubated three days later, and after a week returned to the ward in good general condition, afebrile, with normal blood counts and blood gas analysis (Figure 1). Intravenous glucocorticoid treatment was tapered down, and then substituted with low-dose oral prednisone. The patient started oral anticoagulant therapy to mantain PT INR between 2 and 3 and was discharged. Three months later clotting tests showed the persistence of circulating LAC antibodies. No recurrence has occurred after a year of follow-up.

Discussion

Primary APS is an immunologic disorder that can be asymptomatic or associated with arterial and venous thromboses. In APS catastrophic thrombocytopenia due to a TTP-like syndrome or disseminated intravascular coagulation may occur, leading to the association of severe hemorrhagic and thrombotic events. This was the case in our patient, who showed hemolysis, thrombocytopenia, schistocytes, a normal fibrinogen level and severe bleeding associated with popliteal vein thrombosis and pulmonary embolism. Pulmonary embolism and pulmonary hypertension secondary to recurrent emboli have already been reported.[3,4] In a few cases catastrophic APS may ensue, which can be triggered by infections or drugs.[5] We were unable to identify the triggering agent in our patient, who had thrombosis of a popliteal vein followed by pulmonary embolism and developed ARDS a week later. In the past years, ARDS in patients with APS has been reported on rare occasions;[2,6,7] however, in a recent review by Asherson,[8] ARDS was observed in about one third of cases, being reported in 17 out of 50 patients with APS. The mechanism of ARDS in patients with APS is still poorly understood. It is likely that extensive small vessel thromboses followed by an acute increase of hydrostatic pressure causes exudation of fluids from blood vessels into the lung parenchyma, resulting in acute respiratory distress.[6] In our patient increased TAT, FPA, and PAI-1 levels indicated a hypercoagulable state associated with extensive endothelial damage, possibly responsible for the ARDS.

Catastrophic APS is characterized by a high mortality,[8] and the therapeutic approach is still a matter of debate. Repeated plasmapheresis is considered the treatment of choice,[9] but since adequate venous access may be difficult to obtain in a patient with a severe hemorrhagic tendency, we reserve this approach to failure of other treatments. The efficacy of high-dose intravenous corticosteroids is uncertain. Ghosh *et al.*[6] reported successful treatment of two

patients with APS complicated by ARDS, using intravenous steroids. In our patient no benefit was obtained by FFP and a standard dose of prednisone, while a rapid improvement of the clinical status and of blood counts was obtained by a shot of i.v. immunoglobulins followed by high-dose methylprednisolone for three days. Our case report supports the use of high dose methylprednisolone in catastrophic APS, when plasmapheresis is contraindicated or not possible. Anticoagulant therapy is mandatory once the control of the acute phase has been obtained.[10]

Contributions and Acknowledgments

AC and SR were responsible for the clinical management of the patient and wrote the manuscript; DDL performed coagulation tests; GS had clinical responsibility for the patient during his staying in the ICU; SC and AL collected clinical, laboratory and literature data; GV was the Rheumatology Consultant and with BR revised the manuscript and gave final approvation for its submission.

Disclosures

Conflict of interest: none.

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