

A "PRIMITIVE" CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

Paolo Vivaldi[°], Cristina Andreotti^{*}, Cristina Mazzon[#], Mauro Pedrazzoli[°]

[°]Second Medical Division; ^{*}Dept. of Nephrology; [#]Transfusion and Hematology Center, St. Chiara General Hospital, Trento, Italy

ABSTRACT

A female patient affected by a thrombotic syndrome due to non SLE-related antiphospholipid antibodies (APA), developed a serious, non inflammatory, thrombotic macroangiopathy and uremic-hemolytic syndrome during oral anticoagulant therapy. She was treated with aspirin, dipyridamole iv and with a total of 14 fresh frozen plasma exchange (PEX), but the thrombotic syndrome only showed a partial response with the APA titre dropping considerably. Renal failure did not improve because of acute cortical necrosis. The patient died from infective complications.

Key words: antiphospholipid antibodies, extensive thrombosis, plasma exchange

Both IgG and IgM antiphospholipid antibodies (APA) seem to be laboratory data frequently associated with systemic lupus erythematosus (SLE),¹ or with other autoimmune diseases.² They are sometimes associated with intake of drugs such as chlorpromazine.³ APA include anticardiolipin antibodies (aCL) and lupus anticoagulant antibodies (LAC); aCL are recognized by their ability to bind anionic phospholipids in solid-phase immunoassays, while LAC cause prolongation of phospholipid-dependent coagulation tests.¹⁸

APA are often associated with both venous and arterial vessel thrombosis, giving rise to the *APA thrombotic syndrome* (APS).⁵ Great interest surrounds *primitive* APS that are not associated with other diseases, but due only to the presence of idiopathic APA.^{6,7}

APS can evolve dramatically in the *catastrophic antiphospholipid syndrome* (CAS), which is characterized by thrombotic occlusion of arterial vessels.⁸⁻¹⁰ CAS requires differential diagnosis from thrombocytopenic thrombotic purpura (TTP) and uremic-hemolytic syndrome (UHS); its therapy is not yet well defined,¹¹ and often proves to be ineffective.

We report the clinical case of a female patient

affected by CAS in the course of primitive APS that was characterized by micro-macroangiopathy associated with acute renal failure.

Case report

A 46-year-old female was admitted to our hospital.

At the age of 23 and 28 she had experienced spontaneous abortions. Two years before this admission she suffered acute ischemia of the right leg with thrombotic occlusion of the popliteal artery. This condition proved irreversible even after thrombolytic therapy and surgical treatment with a Fogarty catheter. In the end, her lower right leg had to be amputated.

Laboratory tests revealed the presence of an APS due to IgG type anticardiolipin antibodies whose titre was 285 U/mL (normal value inferior to 15 U/mL). Prothrombin time INR was 0.95, and activated partial thromboplastin time (APTT) of patient plasma (PP) showed a ratio of 1.23; APTT of a PP/normal plasma (NP) mixture gave a ratio of 1.06 at time 0 of incubation at 37°C and 1.45 at time +1 hour of incubation at 37°C (inhibitor of coagulation present after 1-hr incubation at 37°C). Antithrombin

III (103%), protein C (150%), protein S (125%) and plasminogen (138%) were normal. During hospitalization the patient suffered a cerebral ictus with resulting right hemiparalysis. She was discharged on oral anticoagulant therapy with warfarin.

Six months later she was again hospitalized for abdominal pains. At that time laboratory data were the following: hemoglobin (Hb) 10.1 g/dL, white blood cells (WBC) $5.92 \times 10^9/L$, platelets (Plt) $133 \times 10^9/L$; PT (with oral anticoagulant therapy) INR was 3.17 and APTT 2.01; PT INR of PE/NP mixture was INR 1.41 and the APTT ratio of this mixture was 1.68. The level of coagulation factor II was 35%, of factor V 83% and of factor VIII 40% (two coagulation factors, one of which was FVIII, were not vit. K-dependent: probably connected to the presence of a lupus-like inhibitor). The aCL IgG titre exceeded 400 U/mL. Antinucleoproteic antibodies (ANA) were negative.

The patient continued oral anticoagulant therapy at home. She had been followed up with periodic checks of PT, which with treatment had maintained an INR range between 2.5 and 3.5 until three months before hospitalization. In those final three months, the patient stopped checking PT values.

Laboratory tests from one month before admission to our department gave the following values: Hb 11 g/dL, WBC $5.6 \times 10^9/L$, Plt $115 \times 10^9/L$, blood urea 25 mg/dL and serum creatinine 1.0 mg/dL.

The patient was admitted to our unit because she had already been experienced cold cyanosis in the fingers on her left hand for 15 days. This finally led to painful dry gangrene. Diuresis also diminished during the last two days. Clinical evaluation confirmed dry gangrene of the fingers of her left hand, especially on the distal phalanges of the second finger with the absence of left radial and humeral pulses. Femoral pulses were also absent bilaterally.

Doppler echocardiography confirmed occlusion of the left subclavian artery and the femoral arteries. The internal jugular veins and the right subclavian artery were also occluded. Cardiopulmonary and respiratory parameters appeared normal. Clinical lab values were the

following: ESR 127 at the first hour, Hb 6.2 g/dL, WBC $7.92 \times 10^9/L$ with normal differential count, Plt $22 \times 10^9/L$; transaminases GOT 125 U/L and GPT 187 U/L, G-GT 463 U/L, alkaline phosphatase 415 U/L. PT INR was 8.0, APTT 4.63, fibrinogen 720 mg/dL, antithrombin III 124%; blood urea 124 mg/dL and serum creatinine 5.2 mg/dL. Warfarin was stopped. Lactate dehydrogenase (LDH) was 1770 U/L, haptoglobin less than 10 mg/dL, reticulocytes 130%, and 15% schistocytes were found in the peripheral blood. Direct and indirect Coombs' tests were negative.

Coagulation tests performed two days after suspension of warfarin yielded the following results: aCL IgG 150 U/mL, PT INR 3.6, APTT ratio 2.97, APTT PP/NP mixture ratio 1.53; direct Russell viper venom test (DRVVT) PP ratio *did not coagulate* and DRVVT PP/NP ratio was 1.83; DVV confirmation test ratio was 2.7. The same tests repeated in the hospital 15 days later, gave the following values: PT INR 1.35; APTT PP ratio 1.35, APTT PP/NP ratio 1.01, DRVVT PP ratio 2.4 and DRVVT PP/NP ratio 1.78; DVV confirmation test ratio 1.47. Lupus-like inhibitor was positive and ANA search negative. The patient became anuric the second day of hospitalization.

We proposed following therapeutic treatment: aspirin iv 10 mg/Kg of body weight (bw)/day, dipyridamole iv 10 mg/Kg bw/day, daily plasma exchange with fresh frozen plasma for 7 consecutive days. Hemodialysis was performed when necessary. On the 7th day of treatment the patient was given methylprednisolone 4 mg/Kg bw/day and cyclophos-

Table 1. Clinical data of patient during treatment.

IgG aCL	150 U/mL	100	150	30
LDH	1770 U/L	726	848	535
Left radial pulse	absent	present	absent	present
days	1	8	15	22

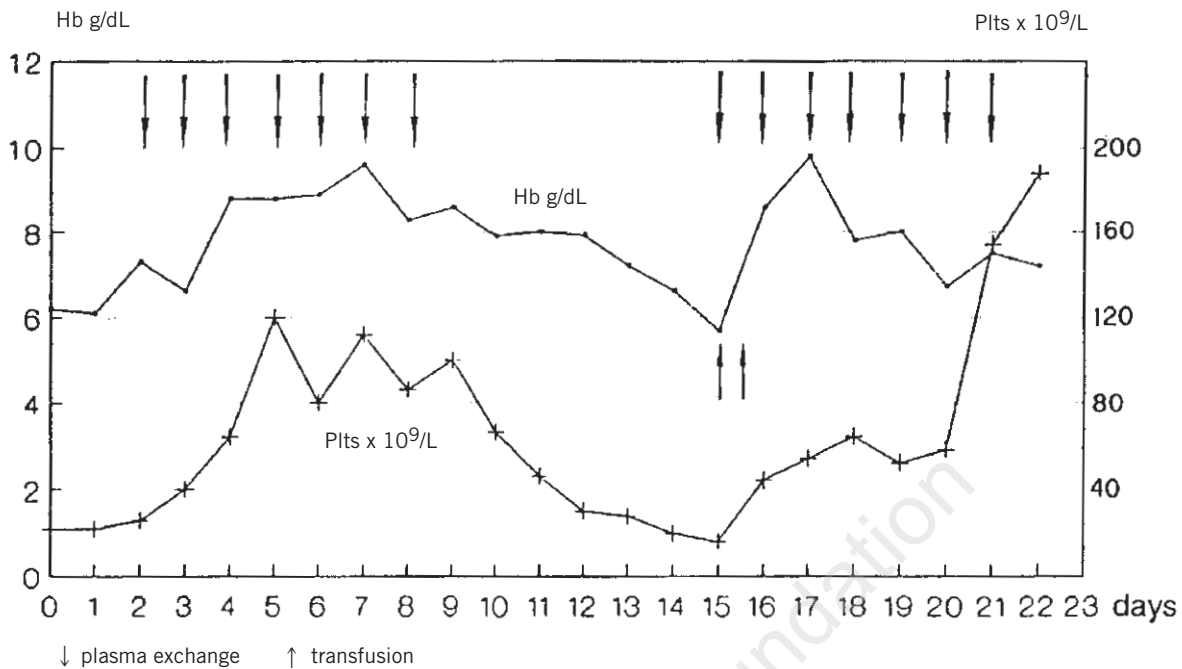


Figure 1. Hematological data of patient during treatment.

phamide 500 mg/m².

Figure 1 and Table 1 report the hematological values, significant clinical (left radial pulse) and lab data registered during treatment. Table 1 also shows that another 7-day cycle of PEX was necessary. Only after this intensification of PEX was there a significant decrease in IgG aCL to 30 U/mL. Platelets reached a normal value of $188 \times 10^9/L$, Hb remained 7.2 g/dL, LDH was 535 U/L and reticulocytes were 49%.

This hematological improvement was not followed by an improvement in diuresis. Therefore, on the 23th day of hospitalization we performed a renal percutaneous needle-biopsy.

Histological examination of renal tissue revealed a picture of acute cortical necrosis described as follows: "about 20 glomeruli were present, mostly characterized by ischemic collapse of vessels and the arteriolas were thickened and contained fibrin thrombi. Some vessels were in expansion and took on a glomeruloid aspect. Vast areas of tubular necrosis with interstitial inflammatory infiltrates were evident".

The patient's general condition worsened due to fever caused by catheter-related staphylococcal sepsis. She died 26 days after admission.

Autopsy confirmed thrombosis of the left subclavian artery, the presence of thromboembolism in the right inferior pulmonary lobe artery and multiple hepatic infarcts.

Discussion

CAS has been reported as a rare clinical entity characterized by diffuse thrombosis with multiple vascular occlusions that often causes patient death.⁸⁻¹⁰

It presents as a dramatic evolution of APS, almost always associated with an autoimmune disease such as SLE, and shows a high titre of IgG type aCL.¹⁰

Other signs commonly present include cutaneous lesions, acute ischemia with gangrene of the fingers, thrombotic occlusion of large vessels, vascular hepatic necrosis and renal failure due to microvascular thrombosis.¹⁰

Our patient suffered thrombotic occlusion of the large vessels with gangrene of the 1st and 2nd distal phalanges on the left hand. Transaminases were increased as a result of ischemic hepatic lesions and renal failure was caused by cortical necrosis, an expression of thrombotic microangiopathy.

It is interesting to note that the IgG type aCL titre was also rather high in our case, but the thrombotic syndrome was not associated with an autoimmune disease. Furthermore, together with the thrombotic ischemic manifestations, the patient developed a TTP-UMS condition with microangiopathic hemolytic anemia. The renal vascular microthrombi led to acute cortical necrosis and irreversible acute renal failure.

Our patient's condition evolved into CAS during oral anticoagulant therapy. Must we admit that the treatment was ineffective? It is impossible to know for sure the answer to that question because the patient's PT values for the last three months are unavailable. It is certain that three months earlier her PT-INR was in the therapeutic range, and when she was hospitalized she even showed an excess of warfarin. Therefore it is very possible that a different thrombotic event occurred during oral anticoagulant therapy.

CAS is difficult to treat because of the gravity of the clinical picture and because no precise therapy has yet been defined, since the patho-

genesis of the syndrome is still unknown.⁸⁻¹⁰

Several treatment schedules have been reported but plasma-exchange and antiaggregants is the most common one.¹⁰

Unfortunately, no treatment has proved to be effective so far.

References

1. Italian Registry of Antiphospholipid Antibodies (IR-APA). Thrombosis and thrombocytopenia in antiphospholipid syndrome (idiopathic and secondary to SLE): first report from the Italian Registry. *Haematologica* 1993; 78:313-8.
2. Vermynen LO, Blockmans D, Spitz B et al. Thrombosis and immune disorder. *Clin Haematol* 1986; 19:505-6.
3. Canoso RT, Sise HS. Chlorpromazine induced lupus anticoagulant and associated immunologic abnormalities. *Am J Hematol* 1982; 13:121-29.
4. Galli M, Barbui T, Zwill RFA, Confurius P, Bevers EM. Antiphospholipid antibodies: involvement of protein cofactors. *Haematologica* 1993; 78:1-4.
5. Petri M. The clinical syndrome associated with antiphospholipid antibodies. *Clin Haematol* 1992; 19:505-6.
6. Alarcon-Segovia D, Sanchez-Guerrero J. Primary antiphospholipid Syndrome. *J Rheumatol* 1989; 16:482-8.
7. Asherson RA. A "primary" anti-phospholipid syndrome. *J Rheumatol* 1988; 15: 1742-6.
8. Ingram SB, Goodnight SH, Bennet RM. An unusual syndrome of a devastating non-inflammatory vasculopathy associated with anticardiolipin antibodies: a report of two cases. *Arthritis Rheum* 1987; 30:1167-72.
9. Harris NE, Phil M, Bos K. An acute disseminated coagulopathy-vasculopathy associated with the antiphospholipid syndrome. *Arch Intern Med* 1991; 19:231-3.
10. Asherson RA. The catastrophic antiphospholipid syndrome. *J Rheumatol* 1992; 19:508-12.