CASE REPORT

Catastrophic antiphospholipid syndrome

Agnieszka Furmańczyk[1], Ewa Komuda-Leszek[1], Wioletta Gadomska[2], Jerzy Windyga[2], Magdalena Durlik[1]

1 Department of Transplantation Medicine and Nephrology, Transplantation Institute, Medical University of Warsaw, Warszawa, Poland
2 Department of Hemostasis Disturbances and Internal Diseases, Institute of Hematology and Transfusiology, Warszawa, Poland

KEY WORDS

catastrophic antiphospholipid syndrome, human immunoglobulins, plasmapheresis

ABSTRACT

Antiphospholipid syndrome (APS) is an autoimmune disease with clinical manifestations of arterial and venous thrombosis, concomitant fetal loss and the presence of antiphospholipid antibodies (APLA). This report focuses on the challenges of optimal treatment involving plasma exchange and intravenous human immunoglobulin infusions that is administered in patients with catastrophic APS (CAPS).
CAPS is a rare variant of APS defined as acute failure of at least three tissues, organs or systems caused predominantly by small vessel thrombosis confirmed by histopathologic evidence. CAPS develops rapidly and leads to death in 50% of cases.
We present the case of a 39-year-old male patient with APS with worsening renal function. Positive lupus anticoagulant, markedly high concentrations of anticardiolipin and anti-β_2-glikoprotein I antibodies have been observed. According to the criteria introduced by Asherson, a catastrophic form of APS was diagnosed and the patient had been treated with low-molecular-weight heparin, glucocorticosteroids, and plasmapheresis. In order to maintain clinical improvement, the patient was given human immunoglobulins i.v. (1g/kg body weight). After the procedure, gradual clinical improvement was observed and renal function remained stable (serum creatinine level of 1.5 mg/dl).

INTRODUCTION Antiphospholipid syndrome (APS) is a clinical disorder described in the 1980s by a number of investigators, including Harris.[1,2]

Since then, new discoveries regarding APS, its pathogenesis, diagnostic evaluation and treatment, have been made. Currently, APS is recognized as an autoimmune disease presenting with venous and/or arterial thrombosis with concomitant fetal loss in the presence of antiphospholipid antibodies (APLA). Anticardiolipid antibodies (ACL) in IgG and IgM classes, antibodies against β_2-glycoprotein I (β_2-GPI) and lupus anticoagulant (LA) detected on two or more occasions at least 12 weeks apart with the use of standardized tests are crucial in establishing the diagnosis of APS. The presence of these antibodies correlates with propensity to in vivo thrombosis, and the strongest association is characterized by lupus anticoagulant and anti-β_2-GPI.

APS displays a wide spectrum of variable symptoms. Given the unusual course of our case, particular attention should be paid to the potential renal lesions; the kidney is an organ that is most commonly affected by APS. Renal artery or vein thrombosis is less common than APS nephropathy, and than thrombotic microangiopathy documented by histopathology. Kidney involvement is manifested as a constellation of symptoms of nephrotic or nephritic syndromes with acute or chronic renal insufficiency.[3]

Catastrophic APS (CAPS, Asherson's Syndrome) is a rare variant of APS defined according to the criteria published in Lupus, 2003[4] as an acute insufficiency of at least three tissues, organs or organ systems caused by small vein thrombosis detected in histological examinations. Risk factors of CAPS include infections, surgery, trauma, stress, malignancies, and drugs including ineffective anticoagulation. The condition has a dramatic clinical course with a mortality rate of 50%.[5,6]

CASE REPORT We present the case of a 39-year-old male patient with APS, admitted to our department in 2008 because of deterioration

Correspondence to:
Agnieszka Furmańczyk, MD, Klinika Medycyny Transplantacyjnej i Nefrologii, Warszawski Uniwersytet Medyczny, ul. Nowogrodzka 59, 02-006 Warszawa, Poland,
phone: + 48-22-502-12-32,
fax: + 48-22-502-21-26,
e-mail: afurmanczyk@gmail.com
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TABLE Classification criteria for catastrophic antiphospholipid syndrome[4]

1	evidence of involvement of ≥3 organs, organ systems or tissues (usually confirmed by imaging techniques; renal involvement defined as a 50% rise in creatininemia, severe arterial hypertension or proteinuria)
2	progression of manifestations simultaneously or in less than 1 week
3	confirmation by histology of small vessel occlusion in ≥1 organ or tissue (confirmation of thrombosis is necessary, at times vasculitis may coexist)
4	laboratory confirmation of the presence of APLA
definite diagnosis = 4 criteria	
probable diagnosis = any of the following:	
– 2 + 3 + 4 criteria and involvement of 2 organs, organ systems or tissues	
– 1 + 2 + 3 criteria (without confirmation of APLA owing to the early death of a patient never tested for APLA before CAPS	
– 1 + 3 + 4 criteria and the development of a 3rd event between 1 week and 1 month after presentation, despite anticoagulation	

Abbreviations: APLA – antiphospholipid antibodies, CAPS – catastrophic antiphospholipid syndrome

in renal function. The diagnosis of APS was established 12 years earlier (LA present, increased ACL titer, recurrent vein thrombosis). He was at the time the patient of the Hematology and Transfusiology Institute and suffered deep vein thrombosis of the lower limbs four times, complicated by pulmonary embolism and suspected lung infarction, and one episode of acute ischemia of the lower left limb.

The patient required chronic anticoagulation therapy (coumadin derivatives). This treatment was complicated by two episodes of upper gastrointestinal bleeding and by spontaneous bleeding to the right knee joint. Recurrent lower leg ulcers have been observed over the past 5 years, and they had not healed in the 6 months preceding present hospital stay.

Gradual increase in creatinine levels to the peak value of 5 mg/dl (442 micromol/l), with concomitant daily protein loss up to 2 g without hematuria has been observed since October 2007. In January 2008, the patient was admitted to the Department of Hemostasis Disturbances and Internal Diseases. To exclude or confirm the suspicion of systemic lupus erythematosus and vasculitis, autoantibodies have been determined; tests for anti-dsDNA, ANA, c-ANCA, p-ANCA, anti-ribosome, anti-ENA/SM, anti-RNP, anti-La/SS-A, anti-Ro/SS-A, anti-PM-Scl, anti-Scl-70, and anti-Jo1 antibodies gave negative results. Anti-platelet and anti-lymphocytotoxic antibodies were absent. Doppler ultrasonography showed normal venous and arterial flow in the kidneys. A dose of low-molecular-weight heparin (LMWH) was increased, 120 mg/d enoxaparin was administered with body weight of 96 kg, with anticoagulant effect monitored with serum anti-Xa activity. No features of anticoagulant cumulative effect was observed (maximum level of anti-Xa 4 hours after enoxaparin administration – 0.8 u/ml). Additional tests performed on admission showed creatinine level of 4.3 mg/dl (380.12 μmol/l), platelet count (PLT) 88 G/l, international normalized ratio (INR) – 1.3, activated partial thromboplastin time – 74.2 s, fibrinogen – 8.73 g/l. A highly positive ACL titer was obtained – >120 GPL (u/ml) in IgG class (normal value <10), 13.71 MPL (u/ml) in IgM class (normal value <7); and anti-β_2-GPI – >100 u/ml in IgG class (normal value <8), 10.69 u/ml in IgM class (normal value <8). Moreover, in coagulation tests based on the measurement of coagulation time (dilute Russell viper venom time), the presence of strong LA was demonstrated. Biochemical parameters of hemolysis measured every few days were normal, haptoglobin levels were 297 (before plasmapheresis), 166, 257 mg/dl (reference range, 30–200), bilirubin levels remained between 0.13–0.23 mg/dl (reference range, 0.1–1.0 mg/dl). Lactate dehydrogenase levels were 255, 250 U/l (reference range, 80–248). Levels of complement components were: C3 – 108 mg/dl (reference range, 90–207), and C4 – 15.7 mg/dl (reference range, 17–52).

Due to deterioration in renal function of unknown cause, kidney biopsy was performed after excluding renal flow disturbances and obstructed urine outflow, and despite thrombocytopenia and previously introduced anticoagulation treatment. In the specimen, 13 glomeruli with features of active chronic thrombotic microangiopathy were found. Immunofluorescence examination revealed no deposits of immunoglobulins, light chains or C3 component. The amyloid test was negative. The result was not confirmed by the immunohistochemistry with antiplatelet antibodies due to unavailability of a reagent.

In view of a significant deterioration in the course of illness, despite continued antithrombotic prophylaxis, and having taken into consideration the rapidly progressive renal insufficiency, it has bee established that the patient fulfilled 2 + 3 + 4 criteria (**TABLE**) with two organs involved, i.e. the kidneys and the skin. Small vessel thrombosis was histologically confirmed. The available data led to the diagnosis of a probable CAS (according to Asherson). Intensive treatment in line with the standards was initiated. In addition to the previous LMWH therapy, glucocorticoids (GC) and plasmapheresis procedures were administered. The patient had nine plasmapheresis procedures with plasma exchange of 2400 ml each time and received 3.0 g of i.v. SoluMerol in pulse therapy of 500 mg, followed by 80 mg/d prednisone treatment (0.8 mg/kg body weight). Initially, plasmapheresis procedures were performed every other day; a decrease in creatinine levels to 2.5 mg/dl (221 μmol/l) with accompanying transient polyuria up to 5500 ml without the use of diuretics, and the healing of the ulceration were observed. However, a gradual decrease in PLT from initial 123 to 55 G/l was observed for 4 days since the 4th day after the last (7th) plasmapheresis procedure. Therefore, in the course of 2 successive days, additional plasmapheresis procedures were performed with plasma exchange of 2400 ml as previously, and a significant increase in PLT up to 92 G/l was achieved.

At the same time, creatinine level varied between 2.4–2.8 mg/dl (212–247 μmol/l). To enhance the therapeutic outcome, the patient was transferred to the Department of Hemostasis Disturbances and Internal Diseases for further treatment with intravenous immunoglobulins (IVIGs). After finishing plasmapheresis series but before IVIG application, APLA measurements were not repeated, a short-term clinical improvement suggested their continuous production. A single i.v. infusion of IVIG of 1 g/kg body weight was performed. A gradual clinical improvement was noted and renal function stabilized, serum creatinine level was 1.8 mg/dl (159 μmol/l) and PLT remained stable at approximately 120 G/l. The patient received prednisone of gradually tapered doses, eventually it was discontinued in September 2008 (after 6 months of treatment). During follow-up serum creatinine level was 1.5 mg/dl. Currently, the patient receives acenocoumarol (INR 2.0–3.0) and an antiplatelet drug, aspirin.

DISCUSSION The diagnosis of APS is based on the presence of at least one clinical and one laboratory criteria. Criteria for diagnosing CAPS include insufficiency of at least three organs, tissues or organ systems along with laboratory or histological data that take into consideration time index and the dynamics of symptom progression. The number and constellation of measured parameters allow to establish a definite or probable diagnosis.

Our patient presented a history of renal insufficiency, arteriolar thrombosis confirmed by histological examination of kidney specimen and idiopathic, deep, persistent skin ulcer on the thigh with accompanying *livedo reticularis*. The above symptoms occurred despite the long-term antithrombotic therapy (LMWH and acenocoumarol). After the first procedure of plasmapheresis and application of GC, a significant clinical improvement was observed, which was thought to be associated with the decrease in circulating APLA. After a few days since plasmapheresis discontinuation, an increase in creatinine level and a decrease in PLT were again observed. Despite GC therapy, autoantibody production might persist and therefore, two successive plasmapheresis procedures were performed and the rate of creatinine level increase was reduced. Because of the short-term effect of plasmapheresis and insufficient suppression of antibody production and also considering notably high APLA titers, IVIGs were introduced in an attempt to consolidate the therapeutic effect. The aim of such management was to maintain protective activity of immunoglobulins during their half-life in the patient's circulation. The next application was planned at 3–4 weeks. However, the patient did not require additional doses of IVIG as no signs of renal insufficiency or features of CAPS deterioration were observed after 2 months from treatment completion.

In approximately 50% of cases no precipitating factors of CAPS have been identified, whereas infections are the most common known trigger. In our case, prior to the the CAPS symptom onset no features of infection and inflammatory markers were observed. At the time of establishing the diagnosis of APS in 1996, all coagulation investigations were performed, which excluded congenital trombophilia. Remission time is difficult to establish because the precipitating factor of CAPS is unknown. There are scarce data available concerning CAPS relapse. Undas et al. described the case of a female patient with CAPS secondary to systemic lupus erythematosus, who died of pulmonary embolism and multiorgan failure after the third episode of CAPS recurrence.[7] Asherson reported three cases of CAPS recurrence with concomitant features of hemolytic anemia after approximately 1 year.[8] Erkan et al. described a group of 58 patients with CAPS with no relapse during more than 67 months of follow-up, but 11 patients presented APS-related symptoms and/or deterioration of the underlying disease.[9]

In our opinion therapeutic efficacy could be achieved through a prompt introduction of intensive treatment involving not only administration of LMWH and GC but also repeated plasmapheresis procedures and IVIG therapy which protects from multiorgan failure.

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OPIS PRZYPADKU

Katastrofalny zespół antyfosfolipidowy

Agnieszka Furmańczyk[1], Ewa Komuda-Leszek[1], Wioletta Gadomska[2], Jerzy Windyga[2], Magdalena Durlik[1]

1 Klinika Medycyny Transplantacyjnej i Nefrologii, Instytut Transplantologii, Warszawski Uniwersytet Medyczny, Warszawa
2 Klinika Zaburzeń Hemostazy i Chorób Wewnętrznych, Instytut Hematologii i Transfuzjologii, Warszawa

SŁOWA KLUCZOWE

katastrofalny zespół antyfosfolipidowy, ludzkie immunoglobuliny, plazmaferezy

STRESZCZENIE

Zespół antyfosfolipidowy (*antiphospholipid syndrome* – APS) jest chorobą autoimmunologiczną, objawiająca się zakrzepicą żylną lub tętniczą z towarzyszącymi niepowodzeniami położniczymi przy obecności przeciwciał antyfosfolipidowych. W pracy przedstawiany jest problem optymalizacji leczenia pacjentów z katastrofalnym zespołem antyfosfolipidowym (*catastrophic APS* – CAPS) z zastosowaniem plazmaferezy i wlewów ludzkich immunoglobulin.

CAPS to rzadka postać APS definiowana jako ostra niewydolność minimum 3 tkanek, narządów lub układów, spowodowana zakrzepicą głównie małych naczyń stwierdzoną w badaniu histologicznym. Choroba postępuje gwałtownie i doprowadza w 50% przypadków do zgonu.

Przedstawiamy przypadek 39-letniego mężczyzny z APS hospitalizowanego z powodu pogorszenia czynności nerek. Stwierdzono obecność silnego antykoagulantu tocznia i wybitnie dodatnie miano przeciwciał antykardiolipinowych i przeciwciał przeciwko β_2 glikoproteinie I. Kierując się kryteriami Ashersona, rozpoznano prawdopodobny CAPS. Terapię heparyną drobnocząsteczkową poszerzono o glikokortykosteroidy i zabiegi plazmaferezy. W celu utrwalenia efektu terapeutycznego, podano jednokrotnie ludzkie immunoglobuliny dożylnie w dawce 1g/kg mc. Uzyskano stopniową poprawę kliniczną i ustabilizowanie się czynności nerek (stężenie kreatyniny 1.5 mg/dl).

Adres do korespondencji:
lek. Agnieszka Furmańczyk, Klinika Medycyny Transplantacyjnej i Nefrologii, Warszawski Uniwersytet Medyczny, ul. Nowogrodzka 59, 02-006 Warszawa,
tel.: 022-502-12-32,
fax: 022-502-21-26,
e-mail: afurmanczyk@gmail.com

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