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CLINICAL CASE

"Seronegative" catastrophic antiphospholipid syndrome in pediatrics: Clinical case

Síndrome antifosfolípido catastrófico "seronegativo" en pediatría: Caso clínico

Ericka Vargas-Quevedo[a], Eduardo Ordoñez-Gutiérrez[a], Jorge Enrique Trejo-Gómora[b], Lénica Anahí Chávez-Aguilar[c], Rubén Peña-Vélez[a,d]

[a]Department of Pediatric Internal Medicine, Centro Médico Nacional 20 de Noviembre. Mexico City, Mexico
[b]Blood Bank. Centro Médico Nacional 20 de Noviembre. Mexico City, Mexico
[c]Department of Pediatric Hematology. Centro Médico Nacional 20 de Noviembre. Mexico City, Mexico
[d]School of Medicine, Universidad Nacional Autónoma de México, Mexico City, Mexico

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Abstract

Introduction: The antiphospholipid syndrome is an acquired autoimmune thrombophilia, characterized by arterial and/or venous thrombosis. Rarely, this condition can have a catastrophic presentation, with high mortality, and presence of microangiopathy and involvement of three or more organs. **Objective**: To describe the clinical presentation and evolution of a pediatric patient with catastrophic antiphospholipid syndrome, with a seronegative onset form, whose response to aggressive therapy was favorable. **Clinical case:** Adolescent female, with a one-week history of pain, increased abdominal volume and edema in the lower extremities. Generalized lupus erythematosus was diagnosed and the neoplastic process was ruled out. During its evolution, she presented various thrombotic events, initially with the presence of negative antiphospholipid antibodies, which were subsequently positive. The patient presented multisystemic failure secondary to multiorgan thrombosis, required hemodynamic and ventilatory support. It was managed with low molecular weight heparin, plasmapheresis, anticoagulation, immunosuppression and boluses of rituximab with excellent response. **Conclusions:** We consider this case interesting because it is an infrequent diagnosis in the pediatric age and whose suspicion, timely and aggressive intensive management, can change the poor prognosis and high mortality of these patients.

Keywords: Antiphospholipid Syndrome; Catastrophic Antiphospholipid Syndrome; Generalized Lupus Erythematosus.

Correspondence:
Dra. Ericka Vargas-Quevedo
ericka_enfa@yahoo.com.mx

Introduction

Antiphospholipid syndrome (APS) is an acquired thrombophilic disorder, considered a multisystemic autoimmune disease, in which autoantibodies against a variety of phospholipids and their transporting proteins are persistently formed. The clinical picture is characterized by arterial and/or venous thrombosis, recurrent abortions (in women of reproductive age), as well as positivity of antiphospholipid antibodies, lupus anticoagulant, and anti-β2-glycoprotein I antibodies (β2GPI).[1] This syndrome may be primary or associated with other autoimmune pathology, mainly with generalized lupus erythematosus, in which it appears in up to 20-30% of these patients, with positive antiphospholipid antibodies found in 54% of patients with lupus[2,3].

Rarely, this condition can be treated with microangiopathy, and when the involvement of three or more organs occurs, it is called catastrophic antiphospholipid syndrome (CAPS), with a frequency of less than 1% of APS and a high mortality rate[4].

The pathogenesis of this condition is not well understood, but it involves the presence of antibodies against different plasma proteins (β2 glycoprotein I, prothrombin, annexin, and high and low molecular weight kininogens) or circulating phospholipid microparticles. The reaction of these antibodies with a corresponding antigen present in platelets, monocytes, tumor cells, or endothelium may result in activation and induce a procoagulant state by expressing different adhesion molecules and promoting thrombosis. In addition, these antibodies can interfere with different clotting factors such as factor V and VIII, causing increased thrombin production[5]. It is unknown why some patients develop the classical syndrome and others develop the catastrophic one, although some factors such as surgery or infections that trigger CAPS have been recognized[6].

The objective of this report is to describe the clinical presentation and evolution of a pediatric patient with catastrophic antiphospholipid syndrome, with seronegative onset form, whose response to aggressive therapy was favorable.

Clinical case

12-year-old female patient, originally from Morelos, Mexico. She has history of polycystic ovary syndrome, treated since she was nine years old with antiandrogens. With no other relevant medical history.

The patient consulted due to a one-week history of pain, increase of abdominal volume and edema in the lower extremities, therefore, she was referred to our hospital due to suspicion of abdominal malignancy.

At admission, the patient had anasarca, with multiple cervical and inguinal lymphadenopathy, abdominal wall edema and ascites. In the initial evaluation, an elevation of the ovarian tumor marker was found CA-125 (1,613 U/ml) (Reference Value [RV]: 35 U/ml). Pelvic ultrasound showed free fluid in the abdominal cavity with morphological loss of the right ovary. Chest CT scan revealed a right solitary pulmonary nodule and bilateral pleural effusion. A cervical lymph node biopsy and bone marrow aspiration were performed, both without evidence of malignancy, therefore, tumor activity was ruled out. Serologies for Toxoplasma, Rubella, Cytomegalovirus, Herpes, human immunodeficiency virus, hepatitis C virus and hepatitis B virus were negative.

In the connective tissue disease approach, she presented four criteria according to *Systemic Lupus International Collaborating Clinics* (SLICC) 2012, one clinical criterion: proteinuria (> 500 mg/24 hours), and three immunological criteria: increase of antinuclear antibodies (fine speckled pattern 4+), anti-DNA (659.92 IU/ml), and C3 hypocomplementemia (46.6 mg/dl) (RV: 87-177 mg/dl), C4 (6.3 mg/dl) (RV: 15-45 mg/dl), therefore, generalized lupus erythematosus was diagnosed, a determination of antiphospholipid antibodies was requested and it was negative. Renal biopsy was performed which reported class IV lupus nephritis, thus, three methylprednisolone boluses (30 mg/kg/dosage) and one cyclophosphamide bolus (750 mg/m^2 sc) were administered; the patient presented hematuria which was treated with mesna and hyperhydration. She continued the treatment with prednisone (1 mg/kg/day) and mycophenolic acid (1 g mycophenolate mofetil/24 h).

A week later, the patient developed left subclavian vein thrombosis, which was treated with enoxaparin and acetylsalicylic acid. Subsequently, an increase in D-dimer levels was found (42.97 µg/ml) (RV): <0.4 µg/ml), a decrease in antithrombin III (26.6%) and protein C (59%), in addition to thrombocytopenia, consequently, enoxaparin was suspended and dabigatran anticoagulation was initiated. APS was re-evaluated showing moderate positive lupus anticoagulant, increased titers of anti-cardiolipin antibodies and anti-beta 2-glycoprotein antibodies.

Despite anticoagulant treatment, two weeks later the patient presented Hunter's canal thrombosis and generalized seizures, thus a brain magnetic resonance imaging was performed, which showed ischemic events of the posterior cerebral artery and superior cerebellar artery, as well as small vessel disease. The electroencephalogram showed generalized slow waves and probable partial seizures. Probable catastrophic antiphospholipid syndrome was diagnosed. Due to the clinical instability of the patient, no biopsy was perfor-

med to confirm microangiopathy due to histopathological study.

The first session of plasmapheresis was performed, subequently she presented neurological alterations (hallucinations and seizures), ventilatory deterioration due to pulmonary hemorrhage and restrictive thorax with ascites, which required mechanical ventilation for sixteen days; she developed acute renal failure with a decrease in glomerular filtration rate below 20 ml/min/1.73 m^2, in addition to difficult-to-control arterial hypertension, she required high doses of antihypertensive agents (prazosin 6 mg every six hours, amlodipine 5 mg every 12 hours, enalapril 10 mg every 12 hours), Mahurkar catheter was placed and three hemofiltration sessions were performed; the patient had three plasmapheresis sessions and intravenous immunoglobulin at 2 g/kg/dosage was administered, with poor clinical response, therefore, treatment with rituximab was initiated at 375 mg/m^2 SC/weekly dose. Mechanical ventilation was removed. Subsequently, she developed pancreatitis and bleeding from the upper and lower gastrointestinal tract, with a decrease of hemoglobin levels to 5.4 g/dl, a circulating volume loss of 26% and transrectal output up to 25 g/kg/day were attributed to multifactorial etiology; the possible precipitating drugs such as acetylsalicylic acid, mycophenolic acid, and dabigatran were suspended. A colonoscopy was performed which showed an important inflammatory process and bleeding in layers, endoscopy showed erosive pangastritis and an aggressive treatment was initiated with high doses of omeprazole, sucralfate, mesalazine, and infusion of octreotide adjusted to renal function, a *Clostridium difficile* infection was ruled out due to negative AB toxins.

The administration of rituximab continued in three additional doses, with progressive improvement and recovery of neurological status, gastrointestinal tract bleeding remission, and recovery of renal function with glomerular filtrate higher than 120 ml/min/1.73 m^2, recanalization of thrombosis sites were found and there was no evidence of new thrombotic events. The patient was discharged in appropriate clinical condition, she continued with quarterly rituximab administration according to protocol, with monthly gamma globulin boluses and immunosuppressive management with mycophenolate and prednisone (Table 1).

Table 1. Laboratory tests performed at the patient's entrance, during the course of the catastrophic antiphospholipid syndrome and hospital discharge

Laboratory test	Entrance	Evolution	Discharge	Reference Value
Hemoglobin (gr/dl)	8.4	7.4	11	11.5-13.5
Leukocytes (109/L)	4.66	3.11	7.74	4.5-13.5
Platelets (109/L)	174	90	180	150-350
PT (s)	10.8	13.5	12.9	12.7-16.1
aPTT (s)	26	32.1	30.4	33.9-46.1
Antithrombin III (%)	68	73	106.5	
Dimero D (µg/ml)	22	34.2	5.2	
Creatinine (mg/dl)	0.49	2.35	0.39	0.5-1
Albumin (g/dl)	2.1	2	2.8	
C3 (mg/dl)	46.6	52.7	110	87-177
C4 (mg/dl)	6.3	16.7	29	15-45
AC anti DS DNA (UI/mL)	716.6	959.7	323.23	
ANA	Homogeneous diffuse 4+	Homogeneous diffuse 4+, fine speckled 4+, cytoplasm 1	Fine speckled 3+, mitochondrial pattern 2+, homogeneous diffuse 3+	
AC anti SM (U)	8.5	9.2	4.482	
AC anti cardiolipines G (GPL)	10.5	5.5	3.99	
AC anti cardiolipines M (MPL)	37.7	13.2	7.03	
BETA-2 microglobulin (mg/dl)	0.7	3.1	0.7	
BETA 2 glicoprotein IGG (SGU)	4.70	2.1	2.1	
BETA 2 glicoprotein IGM (SMU)	19.44	8	3.2	

PT: Prothrombin time; aPTT: Activated partial thromboplastin time; C3: Complement component 3; C4: Complement component 4; AC ANTI DS DNA: anti-double-stranded DNA antibodies; ANA: Antinuclear antibodies; AC ANTI SM: Anti-Smith antibody.

Discussion

It is referred to seronegative APS when there are clinical manifestations, but antiphospholipid antibodies titers are negative, and they should be re-evaluated as they can be positive weeks or months later[7]. The catastrophic presentation usually has an acute onset and it is characterized by the involvement of at least three organs or different systems with an interval of days or weeks. The clinical presentation is usually conditioned by an aggressive microvascular occlusive disease that affects kidneys, liver, central nervous system, heart, lung, and skin. Since CAPS has 50% of mortality despite treatment, it is important to recognize the condition early and give an aggressive and intensive therapy (Table 2)[6,8,9].

Table 2. Criteria for the catastrophic antiphospholipid syndrome

1. Evidence of involvement of three or more organs, systems and/or tissues
2. Development of manifestations simultaneously or in less than a week
3. Confirmation by histopathology of small vessels occlusion in at least one organ or tissue
4. Laboratory confirmation of the presence of antiphospholipid antibodies

Catastrophic antiphospholipid syndrome is defined if all four criteria are present. Evidence of vascular obstruction should be confirmed by imaging techniques.

The early treatment with steroids and anticoagulation is recommended in all patients in whom the definitive or probable diagnosis of CAPS has been established[10].The use of anticoagulation therapy has proven to increase survival in patients who receive it (63 vs. 22%; $P < 0.001$)[11]. The use of unfractionated heparin is recommended as the anticoagulant of choice, given its reversibility. Direct thrombin inhibitors have also been evaluated with good results and recently dabigatran has been proposed as a new line of anticoagulation therapy in thrombosis due to CAPS[12-13]. Due to the decrease in antithrombin III in our patient, dabigatran was initiated, thus prevent new thrombosis events. It is postulated that plasmapheresis, through the elimination of cytokines or other mediators, interrupts the interaction between phospholipid-protein complexes and endothelial cells, and is therefore proposed as a potential therapy in CAPS[10]. A retrospective study showed 78.8% of survival of 18 patients treated with anticoagulants, corticosteroids and plasma exchange, compared to 55.4% of 43 patients treated only with anticoagulants and steroids ($P < 0.083$)[14].

The administration of intravenous immunoglobulin, along with the above-mentioned therapeutic strategies, has been associated with a decrease in mortality. Its effect is immunomodulatory and favors mainly to patients with thrombocytopenia[10].

Recommendations for immunosuppressive therapy include cyclophosphamide (intravenously administered at doses of 500 mg-750 mg/m^2), mainly in patients with systemic lupus erythematosus, resulting in better survival outcomes[10]. Due to the history of hemorrhagic cystitis secondary to cyclophosphamide, this drug was not administered again in our patient.

Rituximab is a chimeric monoclonal antibody, which binds specifically to CD20, a surface antigen expressed in B lymphocytes. The described action mechanisms are: complement-induced cytotoxicity, antibody-dependent cell cytotoxicity acting through the recruitment of macrophages, natural killer cells, and cytotoxic T lymphocytes, and apoptosis directly induced by the binding of rituximab to CD20[15]. It has been reported as a successful treatment for refractory manifestations of generalized lupus erythematosus, such as nephritis, neuropsychiatric disease, and autoimmune hemolytic anemia[15]. A study that included 20 patients with CAPS showed 80% of survival[16]. Given the refractory nature of the symptoms in our patient, it was decided to start rituximab, which showed gradual improvement, allowing removal of mechanically assisted ventilation, organic brain syndrome remission, and bleeding of the digestive tract, as well as improvement of renal function and hematological recovery.

Eculizumab is a humanized monoclonal antibody that prevents C5 complement activation, it has been used as a last resort treatment, and success cases are reported in patients with combination therapy failure who have even received rituximab, however, more studies are still needed to evaluate its effectiveness[17].

Conclusion

The CAPS is a serious manifestation of the antiphospholipid syndrome, with high mortality and varied presentations, which require a high clinical suspicion in order to make the diagnosis, start an early intervention and a systematic management, intensive and timely, carried out by a multidisciplinary group. There are currently established protocols, with new therapies which include the use of biological agents such as rituximab used in our patient, and more recently described the use of eculizumab, with promising results.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

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Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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