

Gangrene as the Initial Manifestation of a Catastrophic Antiphospholipid Syndrome

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Catastrophic antiphospholipid syndrome (CAPS) is an unusual form of presentation of antiphospholipid syndrome with a poor prognosis, so early diagnosis and treatment are necessary. We report a patient who had gangrene as the initial manifestation of CAPS.

Key words: Catastrophic antiphospholipid syndrome. Gangrene. Early diagnosis and treatment.

Gangrena como manifestación inicial de un síndrome antifosfolipídico catastrófico

El síndrome de anticuerpos antifosfolipídicos catastrófico (SAAFC) es una forma rara de presentación del síndrome de anticuerpos antifosfolipídicos, de mal pronóstico, por lo que son necesarios un diagnóstico y un tratamiento precoces. Presentamos un paciente que tuvo gangrena como manifestación inicial de un SAAFC.

Palabras clave: Síndrome de anticuerpos antifosfolipídico catastrófico. Gangrena. Diagnóstico y tratamiento precoces.

Introduction

The antiphospholipid antibody syndrome (APS) is an autoimmune process whose catastrophic variant (CAPS) represents 1% of all cases, and is defined as multiple thrombotic events that can lead to multiorgan failure. CAPS can be primary or secondary, depending on the

presence or absence of autoimmune disease. The disease most frequently associated is systemic lupus erythematosus (SLE).

We present the case of a woman whose initial manifestation and cause of hospitalization was forefoot gangrene. Her progression led to the diagnosis of CAPS.

Case Report

A 19-year-old woman attended the emergency department of our hospital due to distal right foot necrosis and an ulcer on the left foot. She had a personal history of one third trimester abortion 4 months before and had required hospitalization in intensive care (ICU) a month later in a hospital in her country of origin (Morocco) due to severe anemia, receiving several transfusions. She presented, in that moment, lesions on both feet (we have no data on the hospitalizations). Due to the absence of improvement, the patient decided to come to our hospital for evaluation. Upon hospitalization, the patient had no fever and was hemodynamically stable. Physical examination showed livedo reticularis (Figure 1), necrosis of all of the toes and the right forefoot as well as an ulcerated lesion on the internal side of the left foot with distal ischemic lesions.

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Figure 1. Livedo reticularis.

A**B****Figure 2.** A: toe and right forefoot gangrene. B: ulcerated lesion and ischemia of the left foot.

(Figure 2); pulses and mobility were normal. Other analysis only showed an elevation in acute phase reactants; the chest x-ray, electrocardiogram, and the echo-Doppler of the inferior extremities were all normal. Throughout her evolution she had persistent fever with negative blood cultures and a pharyngeal exudate culture positive for *Staphylococcus epidermidis*, *S aureus*, and *Citrobacter freundii* sensitive to antibiotics administered since the first day (intravenous [iv] ceftriaxone, 2 g/24 h; clindamycin, 600 mg/6 h iv). She then presented a progressive descent in her hemoglobin levels, reaching 6.5 g/dL; the direct Coombs test was positive. Other findings were: haptoglobin 74 mg/dL, LDH 13 056; spherocytes, poikilocytes, and fragmented erythrocytes, without schistocytes, detecting also panagglutinin. All of this evidence indicated autoimmune hemolytic anemia, without us being able to discard the presence of alloantibodies.

Anticardiolipin antibodies (aCL) (IgG, 17 GPL/mL; IgM, 100 U MPL/mL), lupus anticoagulant (LA), and anti-beta-2 glucoprotein I antibodies (>5) were positive. The diagnosis of a probable APS was reached, starting treatment with corticosteroids (5 doses of bolus methylprednisolone, 1 g iv every 24 hours followed by prednisone, 1 mg/kg/day), low molecular weight heparin at a therapeutic dose (beforehand it had been employed at prophylactic doses), and a transfusion in spite of its inherent risks.

Forty-eight hours after her hospitalization, the patient presented general health and renal deterioration requiring hemofiltration. She also presented liver failure with an increase in cytolysis and cholestasis as well as respiratory distress syndrome (Figure 3), requiring orotracheal intubation and transfer to the ICU. Due to a situation of multiorgan failure, treatment with iv sodium heparin, iv cyclophosphamide (750 mg/m² of body mass area pulse) and then orally (at 1 mg/kg/day), as well as iv immunoglobulin, at a 400 mg/kg/day dose for 5 days, experimenting progressive improvement of the creatinine and hepatic enzyme readings. No plasma exchange was undertaken because this technique is not available at our hospital and her transfer was not possible.

After 10 days in the ICU she presented an episode of bradycardia, hypotension, non-reactive mydriasis, and absence of tendon and trunk reflexes. A cranial computerized tomography (Figure 4) observed left occipital infarctions with hemorrhagic transformation, one right frontal, edema, cistern obliteration, and complete erasing of brain sulcus. Antinuclear antibody (AAN) and native anti-DNA antibody results arrived 2 days later showing high positive titers, allowing for the diagnosis of a probable secondary catastrophic antiphospholipid antibody

Figure 3. Chest x-ray: bilateral alveolar infiltrate.

syndrome. No autopsy was performed due to religious motives.

Discussion

We are faced with a case of CAPS that was probably secondary to SLE, starting with skin manifestations (ischemia, ulcers, gangrene) and to which liver, kidney, lung, and central nervous system dysfunction were added in an acute and simultaneous manner. This multiorgan affection, associated to the positivity for antiphospholipid antibodies (aPL), without the possibility of doing a second determination due to the patients' death, led us to the diagnosis of probable CAPS. Positive AAN and native anti-DNA antibodies, as well as the hemolytic anemia make us think of associated lupus.

APS is characterized by the appearance of recurrent thrombosis (both venous and arterial or small vessel thrombosis), pregnancy associated morbidity (fundamentally abortions, recurrent fetal loss, and premature births), and hematologic alterations (thrombocytopenia and hemolytic anemia), associated to the presence of aPL (LA, aCL) and antibodies to beta-2-glycoprotein I.¹⁻³

CAPS, which is also denominated Asherson's syndrome, is a variant of APS that is characterized by multiple thrombosis of acute appearance and an extremely severe course. In comparison with primary CAPS, SLE associated CAPS is more frequent in women, is present in younger patients, and affects the brain and pancreas more frequently, having a reduced prevalence of high titers of IgG isotype

Classification Criteria for Catastrophic Antiphospholipid Antibody Syndrome

1. Clinical evidence of affection in 3 or more organs, systems, or tissues. Clinical evidence of confirmed thrombosis through imaging techniques. Kidney affection is defined as an increase in 50% of creatinine, severe arterial hypertension (>180/100 mm Hg), and/or proteinuria >500 mg/24 h
2. Simultaneous development of affection or taking less than 1 week
3. Pathology lab confirmation of the small vessel occlusion in at least 1 organ. Signs of thrombosis must be present, though vasculitis may coexist
4. Analysis confirmation of the presence of aPL (LA or aCL). If the patient has not been diagnosed previously with antiphospholipid antibody syndrome, analytic confirmation requires that the presence of aPL be detected in 2 or more occasions with at least 12 weeks of interval between one and another (not necessarily at the time of thrombosis)

Definitive catastrophic antiphospholipid antibody syndrome:
4 criteria

Probable catastrophic antiphospholipid antibody syndrome:
4 criteria, excepting the affection of 2 organs, systems or tissues

4, except the confirmation in a second determination of aPL at least 6 weeks later due to premature death

Criteria 1, 2, and 4

Criteria 1, 3, and 4 and the development of a third thrombosis after the first week, but before 1 month, in spite of anticoagulation

aCL and is associated with a larger age, gender, affected organ, and treatment adjusted mortality.⁴

CAPS usually affects small caliber vessels in a simultaneous way, in a short period of time, and in multiple localizations, while in non-catastrophic APS, the thrombotic events have place in larger caliber vessels, sporadically and often in a single localization.^{5,6} The criteria proposed in 2002 for the classification of CAPS (definite and probable) appear on Table.⁷

CAPS can potentially affect any large organ or system, including the skin. The skin lesion most frequently seen is livedo reticularis, but ulcers, finger and toe gangrene, nail splinter hemorrhages, superficial venous thrombosis, thrombocytopenic purpura, pseudovasculitic manifestations, extensive skin necrosis, and primary anetoderma can also be found. Superficial necrosis of the skin has been described, with a predominance on the inferior extremities and buttocks, in up to 3% of patients with APS.^{8,9} Skin lesions are more frequently observed in CAPS, with this being characterized by extensive microvascular occlusions that can affect multiple organs at the same time. Histologically, it is a thrombosis of small vessels with vascular proliferation and minimal inflammatory changes.³

Figure 4. Cranial computerized tomography: ischemic lesions with hemorrhagic transformation in the right frontal and left occipital lobes with edema and sulcus erasing.

CAPS fortunately represents only 1% of APS cases. Its mortality is approximately 50%.^{5,6,10} Age over 36 years, the diagnosis of SLE, lung, kidney, and adrenal affection, as well as an elevated number of affected organs and the need for hemodialysis are all risk factors associated to a poor prognosis.² The most frequent causes of death are cerebral affection (27%), cardiac affection, and infections (20%). An increase in survival has been achieved with combined treatment using anticoagulants, glucocorticoids, plasma exchange, and/or iv immunoglobulin.¹¹

Treatment for CAPS must be started as soon as the diagnosis is suspected and includes iv unfractionated heparin, with an initial bolus of 5000 U, followed by a continuous perfusion of 1500 U/h, with serial partial activated thromboplastin time serial controls. If the course of disease is satisfactory, it is maintained for 7 to 10 days and is then substituted for oral anticoagulants, with the intention of maintaining an INR between 2.5 and 3.5. From the start, prednisone is added at 1 to 2 mg/kg/day, preceded in severe cases of iv boluses of 1 g de methylprednisolone for 3 days.

In cases of worsening or risk of death, plasmapheresis can be added for 3 to 5 days minimum, as well as intravenous immunoglobulin at a dose of 400 mg/kg/day for 5 days and, in case of a lack of response to this treatment, cyclophosphamide.^{6,7,8}

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