A catastrophic case of skin gangrene

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We describe the case of a 70-year-old male with the catastrophic antiphospholipid syndrome admitted for skin gangrene of the fingers. The initial diagnosis was antiphospholipid antibody syndrome in a patient with rheumatoid arthritis and a history of deep vein thrombosis of the lower limbs. Liver involvement, the characteristic skin gangrene, pneumonia and worsening severe renal failure were determinant to make the final diagnosis of catastrophic antiphospholipid syndrome that led the patient to death.

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Introduction

Antiphospholipid antibodies directed against the antigen cardiolipin were first described in patients who tested positive for syphilis without signs of infection. Subsequently, a prolongation of various coagulation tests such as activated partial thromboplastin time (aPTT) and prothrombin time due to a circulating anticoagulant was described in patients with systemic lupus erythematosus and a link between recurrent pregnancy loss and the lupus anticoagulant was established1,2. In 1983 Hughes and his colleagues2 first described the association between antiphospholipid antibodies and thrombosis, identifying the antiphospholipid antibody syndrome (APS) as a disorder characterized by the presence of multiple autoantibodies associated with both arterial and venous thrombosis1,3,4. There are two main types of APS: primary APS in patients with no underlying autoimmune disorders and secondary APS, in patients with underlying autoimmune disorders or neoplastic diseases3,4. In the early 1990s Asherson et al. described a new subset of APS: an uncommon and often fatal condition termed “catastrophic antiphospholipid syndrome” (CAPS)5-7. The disease, that prevails in the female sex with a female/male ratio of 2.5 at an average age of onset of approximately 39 years, has been described in association with systemic lupus erythematosus, rheumatoid arthritis, polychondritis, ulcerative colitis and malignancy. Precipitating factors for the onset of CAPS are infections (pneumonia, hepatitis C virus-HCV, human immunodeficiency virus-HIV, Cytomegalovirus, varicella, syphilis, leishmaniasis, malaria and others), surgery, drugs (oral contraceptives, captopril, thiazides) and anticoagulant withdrawal. The most frequent clinical manifestations are renal insufficiency due to the presence of thrombotic microangiopathy in the microvasculature of the kidney with features of lupus nephritis and hypertension. Cardiac involvement consists of myocardial infarction, cardiac valve thrombi, vegetation heart failure. Pulmonary complications range from multiple pulmonary emboli to acute respiratory distress syndrome, whereas central nervous system involvement consists of stroke, consciousness disorders ranging from confusion and disorientation to coma, chorea, sometimes seizures and even status epilepticus. Gastrointestinal symptoms are often present, usually due to ischemia of the gastrointestinal tract resulting in angina abdominis, bowel infarction and pancreatic failure. Transaminases are often elevated as a consequence of cardiac failure or thrombotic microangiopathy of the liver and there may also be adrenal infarctions and hypoadrenalism. Venous thromboembolism and peripheral arterial occlusions resulting in digital necrosis or gangrene is a characteristic finding5,7,8. Laboratory findings include thrombocytopenia, Coombs negative hemolysis with schistocytes, high anticardiolipin antibody titers (usually IgG), lupus anticoagulant positivity and anti-dsDNA. Features of disseminated intravascular coagulation (DIC) may be present, with thrombocytopenia, low fibrinogen levels and increased fibrinogen degradation products or D-dimer. The prognosis is very poor, with death occurring in 50% of cases. Death is generally due to severe renal failure, malignant hypertension, acute respiratory distress syndrome, DIC, myocardial infarction and stroke. Standard therapy consists in the administration of high doses of corticosteroids and intravenous heparin followed by oral anticoagulants, with the goal of keeping the INR not lower than 3. Fresh-frozen plasma is recommended in...
the presence of DIC and antibiotics for infective complications, while the therapeutic usefulness of immunosuppressants, intravenous immunoglobulins, plasma exchange and antiplatelet drugs is still controversial.

Case report

A 70-year-old male was admitted to the Division of Emergency Medicine because of fever and gangrene of the second, third and fourth fingers of the left hand and of the third finger of the right hand (Fig. 1). His medical history included an episode of deep vein thrombosis of the lower limbs at the age of 63 years and since that episode the patient was on anticoagulant treatment with acenocoumarol that he had autonomously suspended 2 weeks prior to admission.

Laboratory analysis revealed a moderately severe hypochromic microcytic anemia (erythrocytes 3,460,000/mm³, hemoglobin 8.7 g/dL, mean corpuscular volume 75 µm³, mean corpuscular hemoglobin 25.9 pg, iron 14 µg/dL, ferritin 550 ng/mL), thrombocytopenia (platelet count 87,000/mm³), leukocytosis (white blood cells 12,500/mm³, with 70% neutrophils), increased serum titers of aspartate aminotransferase (AST), alanine aminotransferase (ALT) (226 and 123 U/L, respectively), γ-GT (198 U/L) and C-reactive protein (14.6 mg/dL) and an increased erythrocyte sedimentation rate (107 mm/hour). On the other hand, the hepatitis and HIV markers, antinuclear, anti-mitochondrial, anti-smooth muscle antibodies, anti-DNA and extractable nuclear antigens, perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA), P3-anti-neutrophil cytoplasmic antibodies (C-ANCA) and circulating immune complex were all negative. Coagulation testing revealed markedly increased fibrinogen levels (1.435 mg/dL) and a prolonged prothrombin time (INR 1.77) and aPTT (48 s); the C3 and C4 titers were normal; the anticardiolipin antibody IgG [231 GPL (normal range < 10 GPL; high positivity > 40)] and IgM [91 GPL (normal range < 10 GPL; high positivity > 30)] levels as well as the rheuma test (29.6 UI/mL) were markedly abnormal. ECG and chest radiography were normal. Abdominal echography showed hepatomegaly and steatosis; gastroscopy revealed a duodenal scar with gastroesophageal reflux.

Treatment with cephalosporins, levofloxacin, prednisone and acenocoumarol resulted in hemodynamic improvement, resolution of the fever and reperfusion of the left hand fourth finger (Fig. 2). A diagnosis of secondary APS in a patient with rheumatoid arthritis was made. Admitted to the Maggiore Hospital of Milan for further evaluation, he underwent a total body computed tomography scan which was negative and a bone marrow biopsy which yielded evidence of reactive dyserythropoiesis with capillaroscopy suggestive of rheumatoid arthritis. Positivity for anticardiolipin antibodies was confirmed. During hospitalization the patient developed progressive jaundice (bilirubin 3 mg/dL) with further increases in the serum levels of AST, ALT and γ-GT. His overall conditions worsened significantly. Acute hepatitis due to herpetic infection was diagnosed on the basis of the presence of high titers of herpes simplex virus IgM and IgG and of biopsy. A new episode of deep vein thrombosis of the left leg complicated the clinical picture, but was successfully resolved with heparin and acenocoumarol therapy. At the same time signs of renal failure were noticed (urea 120 mg/dL, creatinine 3.2 mg/dL, potassium 5.6 mEq/L, creatinine clearance 40 mL/min). Two weeks later the patient presented with pneumonia and consequently a further impaired renal function, severe anemia and thrombocytopenia, decreased fibrinogen levels and high titers of fibrinogen degradation products. In spite of heparin and fresh frozen plasma treatment, the patient finally died of DIC.
Discussion

CAPS is a rare and potentially fatal subset of APS characterized by acute multiorgan thrombosis mainly of the microvasculature but not unusually also of the large vessels. Precipitating factors for the onset of CAPS are infections (pneumonia, HCV, HIV, Cytomegalovirus, varicella, syphilis, leishmaniasis, malaria and others)\textsuperscript{13-15}, surgery, drugs (oral contraceptives, captopril, thiazides) and anticoagulant withdrawal. The etiology of CAPS is so far unknown, but in the last years, many hypotheses have been made to unravel this syndrome. Among these an infectious origin seems to be the most probable\textsuperscript{16,17}. The patient herewith described had a secondary APS associated with rheumatoid arthritis, initially controlled by oral anticoagulant therapy. We assume that sudden withdrawal of acenocoumarol and the related hypercoagulability probably triggered CAPS. This condition is related to the inhibition of the vitamin K-dependent synthesis pathway of some coagulation factors which include C protein. CAPS expressed itself initially with skin gangrene, and subsequently with a new episode of deep vein thrombosis. Hepatitis and pneumonia rapidly worsened this severe form of CAPS, causing renal failure and fatal DIC that were unresponsive to therapy. CAPS should be always suspected in the presence of rapidly worsening symptoms and signs of APS, although prompt treatment is not always sufficient to rescue these patients.

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References


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