Preventing Death in the Catastrophic Antiphospholipid (Asherson) Syndrome

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In 1992, Ronald Asherson [1] proposed a new and potentially fatal subset of the antiphospholipid syndrome that was named catastrophic APS, which is characterized by acute multi-organ failure (three or more damaged organ systems and histopathological evidence of multiple microthrombosis). Later, in 2003, his name was formally linked to the condition.

The trigger is most commonly an infection [2], but other causes have been recognized, such as trauma, surgical procedures, malignancies, low international normalized ratio or warfarin withdrawal, obstetric causes and lupus flares. The "double" or "treble" hit hypothesis, applicable to patients with multi-organ failure in general, is also evident in some patients with catastrophic APS. Thus, a combination of two or three triggering factors has been evident in several cases. The mortality rate is about 50%, even in seemingly adequately treated patients. Among the causes of death, renal, pulmonary and multi-organ failure has been reported, but the most common cause of death is stroke. We describe here two cases in which death from catastrophic APS was prevented due to early detection of trigger factors, promptness in suspecting the diagnosis, and aggressive treatment in the intensive care unit.

Patient Descriptions

Patient 1

A 28 year old woman with the diagnosis of systemic lupus erythematosus who was not treated for 1 year presented to our department in the third trimester of her fifth pregnancy, with fever (38.5°C), hypertension (150/100), renal involvement (creatinine 1.7), livedo reticularis, seizures, and loss of consciousness with a Glasgow coma scale of 5 points. The patient had a history of two previous miscarriages and two normal vaginal deliveries. Immunological assessment revealed positive antinuclear antibodies, anti-dsDNA, anticardiolipin antibodies of the immunoglobulin G type, and lupus anticoagulant. There was no evidence of hemolytic anemia or thrombocytopenia. Urinanalysis showed no proteinuria.

We suspected catastrophic APS and transferred the patient to the ICU. Treatment consisted of intravenous methylprednisolone, i.v. immunoglobulins, low molecular weight heparin and cefotaxime plus amikacine due to the high suspicion of an infection that may have triggered the catastrophic APS. On further workup, urine and blood cultures were positive for *Escherichia coli*, which was susceptible to our current antibiotic regimen. The patient remained in the ICU for 2 weeks. During her stay in the unit her condition improved, cultures were negative by the end of the first week, and kidney function improved substantially. The patient was transferred to the ward where she stayed for 3 more days and was discharged in good condition on anticoagulants and steroids.

Patient 2

A 22 year old woman with the diagnosis of SLE, lupus nephropathy WHO class IV, and associated APS presented to our unit with a lupus flare after excessive sun exposure. At initial assessment cutaneous vasculitis was observed. The patient's previous treatment included prednisone at low doses, hydroxychloroquine, azathioprine, acenocoumarin and low dose aspirin.

We admitted the patient to the ICU with the suspicion of catastrophic APS due to worsening of kidney function (creatinine 2.5), without any other sign of acute renal failure of prerenal or postrenal etiology; also, the patient presented with confusion, fever (38°C), lower leg edema and sudden-onset dyspnea. The initial treatment of low molecular weight heparin was targeted at possible pulmonary embolism. In addition, lower extremity Doppler scans showed deep vein thrombosis and V/Q scan reported a high probability of pulmonary embolism. The patient was also started on i.v. methylprednisolone, i.v. immunoglobulins and cefotaxime. Urine and blood cultures were taken but since they were negative cefotaxime was suspended.

The most likely trigger in this patient was the lupus flare; therefore, we continued the treatment for 10 days until the

APS = antiphospholipid syndrome
ICU = intensive care unit
SLE = systemic lupus erythematosus

patient recovered fully. She was discharged to the ward in good condition.

Comment

Catastrophic APS usually occurs in less than 1% of patients with APS. Currently, there is an attempt to compile all the published case reports as well as the new diagnosed cases from all over the world in an international registry of patients suffering from catastrophic APS (the CAPS Registry). This registry can be freely accessed at www.med.ub.es/MIMMUN/FORUM/CAPS.HTM [3].

The management of catastrophic APS is challenging, and early diagnosis and aggressive therapies are essential to prevent the patient from succumbing to this potentially fatal condition. In the two cases described here, we used the same approach – early diagnosis and aggressive therapy. These strategies are the two single most important issues in the patient's survival. The main purpose of the treatment is to decrease and even stop the "cytokine storm," which has been described in catastrophic APS as massive cytokine release in a certain point, with tumor necrosis factor-alpha being the main cytokine involved.

A few years ago an algorithm with treatment guidelines was accepted at the Tenth International Congress on Antiphospholipid Antibodies in 2002 [4]. In general, experts divided the treatment into three categories: prophylactic, primary, and secondary. For years infections have been involved in the pathogenesis of catastrophic APS, as we reported earlier [5]; thus any infection, however trivial, should be energetically treated with the appropriate antibiotics. In our first patient the suspicion of infection was strong enough for broad-spectrum antibiotic therapy. It is crucial that cultures be taken and therapy adjusted accordingly.

Intravenous heparin, usually by means of a heparin drip, has been the cornerstone of anticoagulation therapy for catastrophic APS. In our two patients we performed anticoagulation by this method to a goal INR of 3. We believe that heparin drips and any other i.v. medications that need to be administered should be in the setting of an ICU where closer monitoring is granted. Steroid therapy is usually needed to arrest the "cytokine storm" since this is the pathophysiological basis of catastrophic APS. The uncontrolled and massive release of cytokines should be stopped early in the course of this disease. Intravenous immunoglobulins are also important in the management of catastrophic APS [5]. We used this therapy for both our patients and we again stress the need for the ICU setting for better monitoring. The daily dose we used was 0.4 g/kg/per day. Therefore, most patients will be on steroids, IVIG, intravenous heparin and prophylactic therapy depending on the case.

Other therapies have been described in catastrophic APS patients, including plasma exchange, immunosuppressors such as cyclophosphamide, and prostacyclin. But since prostacyclin has a major side effect: it increases the risk of thromboembolism, we do not recommend its use as standard therapy. Fibrinolytics and antithrombotic medications such as defibrotide have also been used, but only limited evidence exists.

The two patients reported here improved with our initial treatment in the ICU, thus we recommend that aggressive therapy be started as soon as the diagnosis is suspected. Nevertheless, not all patients respond to the initial aggressive therapy, and for those patients conventional therapies directed to specific problems should be used (hemodialysis, mechanical ventilation, inotropic drugs, etc.) [5]. In our opinion most patients positive for antiphospholipid antibodies and clinical suspicion of catastrophic APS should be admitted to the ICU and treated aggressively with antibiotics, steroids and anticoagulation to prevent further multi-organ failure. Moreover, we believe immunoglobulin therapy or plasma exchange should be started as soon as the diagnosis is suspected, as we did with our two patients. It is essential to identify risk factors that may initiate this variant of the APS, such as increased sun exposure, low steroid doses, infections, surgery, and labor.

In conclusion, catastrophic APS should always be suspected in patients previously diagnosed with APS or any disease that might develop secondary APS. A prompt diagnosis will enable physicians to take measures to prevent death from this syndrome, namely aggressive treatment with steroids, anticoagulation and IVIGs in the ICU setting, thereby preventing the progression of organ failure or the development of septic shock in the infected patients.

INR = international normalized ratio
IVIG = intravenous immunoglobulin

References

1. Asherson RA, The catastrophic antiphospholipid antibody syndrome. J R*heumatol* 1992;19:508–12.
2. Asherson RA, Shoenfeld Y. The role of infection in the pathogenesis of catastrophic antiphospholipid syndrome-molecular mimicry? J R*heumatol* 2000;27:12–14.
3. Cervera R, Espinosa G, Bucciarelli S, Gómez-Puerta JA, Font J. Lessons from the catastrophic antiphospholipid syndrome (CAPS) registry. A*utoimmun* R*ev* 2006;6:81–4.
4. Asherson RA, Cervera R, de Groot P, et al. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. L*upus* 2003;12:530–4.
5. Asherson RA. Acute respiratory distress syndrome and other unusual manifestations of the catastrophic antiphospholipid (Asherson's) syndrome. IMAJ 2004;6:360–3.

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