

Catastrophic Antiphospholipid Syndrome: Lessons from the “CAPS Registry”

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Abstract: Although less than 1% of patients with the antiphospholipid syndrome (APS) develop the catastrophic variant, its potentially lethal outcome emphasizes its importance in clinical medicine today. However, the rarity of this variant makes it extraordinarily difficult to study in any systematic way. In order to put together all the published case reports as well as the new diagnosed cases from all over the world, an international registry of patients with catastrophic APS (“CAPS Registry”) was created in 2000 by the *European Forum on Antiphospholipid Antibodies*. Currently, it documents the entire clinical, laboratory and therapeutic data of more than 300 patients whose data has been fully registered. This registry can be freely consulted at the Internet (www.med.ub.es/MIMMUN/FORUM/CAPS.HTM) and it is expected that the periodical analysis of these data will allow us to increase our knowledge of this condition.

Keywords: Catastrophic antiphospholipid syndrome, antiphospholipid antibodies, anticardiolipin antibodies, lupus anticoagulant, antiphospholipid syndrome.

INTRODUCTION

The descriptive adjective “catastrophic” was added to the term antiphospholipid syndrome (APS) in 1992 by Asherson [1] in order to highlight an accelerated form of this syndrome resulting in multiorgan failure. Patients with catastrophic APS (also known as Asherson’s syndrome) have in common: a) clinical evidence of multiple organ involvement developing over a very short period of time; b) histopathological evidence of multiple small vessel occlusions, and c) laboratory confirmation of the presence of antiphospholipid antibodies (aPL), usually in high titre. Furthermore, approximately 60% of the catastrophic episodes are preceded by a precipitating event, mainly infections [1-6].

Although less than 1% of patients with the APS develop this complication [7], its potentially lethal outcome emphasizes its importance in clinical medicine today. The majority of patients with catastrophic APS end up in Intensive Care Units (ICU) with multi-organ failure and, unless the condition is considered in the differential diagnosis by the attending physicians, it may be completely missed, resulting in a disastrous outcome for these patients.

The rarity of this syndrome makes it extraordinarily difficult to study in any systematic way. In order to correlate all the published case reports as well as newly diagnosed cases from all over the world, an international registry of patients with catastrophic APS (“CAPS Registry”) was created in 2000 by the *European Forum on Antiphospholipid Antibodies*, a study group devoted to the development of multicentre projects with large populations of APS patients [8]. Currently, it documents the entire clinical, laboratory and therapeutic data of more than 300 patients whose data has been

fully registered. This registry can be freely consulted through Internet at www.med.ub.es/MIMMUN/FORUM/CAPS.HTM. The analysis of this registry has allowed to characterize the clinical and laboratory features of the catastrophic APS as well as to establish preliminary criteria for its classification and guidelines for its management [9-21].

CLINICAL FEATURES

The detailed analysis of the first 250 patients included in the “CAPS Registry” shows that 70% are female, mean age is 37 years (range, 7 to 76), 46.4% have primary APS, and 40% systemic lupus erythematosus (SLE) (Table 1).

Patients may develop catastrophic APS *de novo* (46.4%), without any previous history of a thrombosis either associated with a primary APS or SLE. However, it can be seen that deep vein thrombosis, fetal loss or thrombocytopenia are the most frequently encountered aPL associated previous manifestations.

The clinical manifestations of catastrophic APS mainly depend on two factors: a) organs affected by the thrombotic event and the extent of the thrombosis, and b) manifestations of the systemic inflammatory response syndrome (SIRS), which are presumed to be due to excessive cytokine release from affected and necrotic tissues. There are thus two separate and distinct sets of manifestations, each of which requires effective therapy.

Thrombotic Manifestations

Intraabdominal thrombotic complications affecting the kidneys, adrenal glands, splenic, intestinal and mesenteric or pancreatic vasculature are most commonly encountered and the patients frequently present initially with abdominal pain or discomfort. Renal disease is present in 70.6% of patients but patients do not succumb from uremia (Table 1).

Pulmonary complications are next in frequency (63.9%), with ARDS [22] and pulmonary emboli accounting for the

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majority, while pulmonary hemorrhage, microthrombi, pulmonary edema and infiltrates occurring in a minority of patients. Dyspnea is a common presenting symptom.

Table 1. Demographic, Clinical and Laboratory Features for 250 Patients of Catastrophic APS

| | N (%) |
|--|------------|
| Demographic characteristics | |
| Gender (F/M) | 177/73 |
| Mean age (yrs ± SD)* | 37 ± 14 |
| Diagnosis | |
| Primary APS | 116 (47.5) |
| SLE | 100 (41) |
| SLE-like | 12 (4.9) |
| Precipitating factors | 143 (56.3) |
| Catastrophic APS as the first manifestation of APS | 116 (46.4) |
| Main organ involved | |
| Kidney | 180 (70.6) |
| Lung | 163 (63.9) |
| Brain | 158 (62) |
| Heart | 131 (51.4) |
| Skin | 128 (50.2) |
| Liver | 85 (33.3) |
| Intestinal | 60 (25.3) |
| Peripheral venous thrombosis | 59 (23.1) |
| Spleen | 48 (18.8) |
| Adrenal glands | 33 (12.9) |
| Peripheral artery thrombosis | 27 (10.6) |
| Pancreas | 19 (7.5) |
| Retina | 17 (6.7) |
| Peripheral nerve | 12 (4.7) |
| Bone marrow | 10 (3.9) |
| Laboratory features† | |
| IgG aCL | 197 (83.5) |
| IgM aCL | 92 (41.6) |
| IgA aCL | 3 (1.2) |
| Lupus anticoagulant | 173 (71.6) |
| Disseminated intravascular coagulation | 33 (14.9) |
| Thrombotic microangiopathic hemolytic anemia | 19 (8.6) |

*Referred at the time of catastrophic APS.

† Lupus anticoagulant was present in 173 (71.6%) patients. In 63 (36.4%) patients, the case records stressed that the LA were detected according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on Lupus Anticoagulants/Phospholipid-Dependent Antibodies). In the remaining case records, it was not available by what method the LA was tested.

aCL: anticardiolipin antibodies; APS: antiphospholipid syndrome; F: female; M: male; SLE: systemic lupus erythematosus.

Cerebral manifestations (infarcts, encephalopathy, seizures or cerebral venous occlusions) are frequent (62%). Small vessel cerebrovascular occlusive disease is probably commoner than has been reported and may be the etiology of the encephalopathic features of the syndrome.

Skin complications, such as *livedo reticularis*, purpura and skin necrosis, are next, occurring in 50.2%.

Cardiac problems occur in 51.4%, with valve defects (mitral, aortic) often present. Myocardial infarctions are a presenting feature in 25% of cases.

Additionally, other organs may be occasionally affected, including testicular/ovarian infarction, necrosis of the prostate, acalculous cholecystitis, bone marrow infarction, esophageal rupture, giant gastric ulceration, colonic ulcerations, thrombotic pancreatitis, and adrenal infarction, among other features.

Recurrent Catastrophic APS

Recurrences/relapses of the condition are distinctly uncommon and have occurred in less than 10 patients [23-25]. Infections, trauma (e.g. minor surgery such as removal of simple cataract), fracture are some of the “triggers” documented, while in others no specific precipitating factors have been identifiable.

Manifestations of the SIRS

This multisystem inflammatory syndrome is due to cytokine activation and has been extensively reviewed [26]. Although actual measurements of cytokine levels in very ill patients with catastrophic APS have not been undertaken, it is assumed that this process is on-going in the acute phase of the illness. Certainly, some of the non-thrombotic manifestations, particularly ARDS [22], are frequently encountered in SIRS. The cytokines involved include tumour necrosis factor (TNF)- α , IL-1, IL-6 and macrophage-migration inhibitory factor and they are responsible not only for ARDS but also for the cerebral edema which may be a factor in the initial confusion and deterioration of consciousness seen in these patients as well as myocardial dysfunction encountered. IL-18 is also implicated in acute lung inflammation *via* increasing neutrophil migration and lung vascular permeability and this cytokine may also be implicated in the pathogenesis of ARDS. This may be superimposed on an underlying infective process, which itself may have been instrumental in “triggering” catastrophic APS. Therefore, in treatment, strong consideration should be given to the early institution of antibiotic therapy.

ARDS associated with septic shock and severe trauma is often complicated by disseminated intravascular coagulation (DIC), a not infrequent finding in patients with catastrophic APS [27].

LABORATORY FEATURES

Thrombocytopenia is usually present and was detected in more than 60% of cases from the “CAPS Registry”. One third have evidence of hemolysis and 14.9% have some of the features of DIC [20]. Schistocytes, if present, are usually scanty, unlike the abundant numbers seen in patients with thrombotic thrombocytopenic purpura (TTP) (28) (Table 1). IgG anticardiolipin antibodies (aCL) are usually positive with IgM being less frequent. Patients with SLE demonstrate positive antinuclear antibodies, antibodies to double stranded DNA and to extractable nuclear antigens (ENA).

During the 10th International Congress on aPL in Taormina, Sicily, Italy, in 2002, proposed preliminary classification criteria for the catastrophic APS (Table 2) were accepted in [9]. This consensus statement is of major importance, as patients with a debatable diagnosis or with less severe disease (“probable” catastrophic APS) may now be classified separately and distinctly from those with a “definite” catastrophic APS. These criteria will now provide a

more consistent diagnostic paradigm and will assist in planning and documenting future multicentre studies.

Table 2. Preliminary Criteria for the Classification of Catastrophic APS

| | |
|----|---|
| 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 vessel occlusion in at least one organ or tissue**. |
| 4. | Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies)*** |

* Usually, clinical evidence of vessel occlusions, confirmed by imaging techniques when appropriate. Renal involvement is defined by a 50 % rise in serum creatinine, severe systemic hypertension (>180/100 mm Hg) and/or proteinuria (>500 mg/24 hours).

** For histopathological confirmation, significant evidence of thrombosis must be present, although vasculitis may coexist occasionally.

*** If the patient had not been previously diagnosed as having an APS, the laboratory confirmation requires that presence of antiphospholipid antibodies must be detected on two or more occasions at least 6 weeks apart (not necessarily at the time of the event), according to the proposed preliminary criteria for the classification of definite APS (9).

Definite catastrophic APS:

- All 4 criteria

Probable catastrophic APS:

- All 4 criteria, except for only two organs, systems and/or tissues involvement.

- All 4 criteria, except for the absence of laboratory confirmation at least 6 weeks apart due to the early death of a patient never previously tested for aPL prior to the catastrophic APS event.

- 1, 2 and 4

- 1, 3 and 4 and the development of a third event in more than a week but less than a month, despite anticoagulation.

PRELIMINARY CLASSIFICATION CRITERIA

From the analysis of the initial 176 patients included in the "CAPS Registry" [1], 89 (51%) of the previously compiled patients with catastrophic APS were classified as having "definite" and 70 (40%) as "probable" catastrophic APS. The sensitivity of these criteria was 90.3% and the specificity 99.4%. Positive and negative predictive values were 99.4% and 91.1%, respectively.

TREATMENT

Management of the catastrophic APS is challenging for all attending physicians. Early diagnosis and aggressive therapies are essential in order to "rescue" such patients from succumbing to this potentially fatal condition. Unfortunately, at this time, despite all therapies advised, the mortality is extremely high (around 50%). An algorithm with treatment guidelines for the catastrophic APS (Fig. 1) has also been proposed [9]. Treatment may be divided into three major categories: a) prophylactic therapy, b) specific therapies, and c) non-specific therapies.

Prophylactic Therapy

As it is unclear why some patients with an APS will develop recurrent episodes and others (a minority) will be "catapulted" into multiorgan failure, therefore, in any APS patient particular attention should be given to the following guidelines:

1. Any infection, however trivial, should be energetically treated with the appropriate antibiotics.
2. APS patients undergoing surgical procedures, however minor, should all receive parenteral anticoagulation

during the procedure instead of remaining on coumadin.

3. The puerperium should be adequately covered for a minimum of 6 weeks with parenteral anticoagulants (e.g. subcutaneous heparin).
4. SLE "flares", although uncommonly associated with catastrophic APS, should also be treated with parenteral anticoagulation.

Specific Therapies

First-Line Therapies

Intravenous heparin: It is usually administered for 7-10 days followed by oral anticoagulants to an INR of approximately 3.

Corticosteroids: They should be administered for a minimum of three days but may have to be continued for longer depending on the patient's response. Steroids are not indicated for the treatment of the ongoing thrombosis or to attempt to reduce the high levels of aPL, but to treat the manifestations of the presumed excessive cytokine release because of the widespread tissue necrosis. ARDS is a prime example of this.

Second-Line Therapies

Intravenous immunoglobulins (IVIG): The daily dose recommended is 0.4 gm/day/kg body weight for 4-5 days. It may specifically be helpful in those patients who have severe thrombocytopenia but also possibly decreases antibody synthesis and increases the catabolism of circulating immunoglobulins in others. There is no evidence, judging from the analysis of treated patients with catastrophic APS, that IVIG on its own improves survival but its combination with plasma exchange might be more effective. IVIG are usually well tolerated, but there are a few reports of thromboembolic events after IVIG infusions and a few cases have been described on the association of acute renal failure with IVIG therapy.

Plasma exchange (PE): Pathogenic IgG aCL and β 2-GPI as well as cytokines such as IL-1, IL-6, TNF- α and complement may be removed by this procedure. It has been reported as improving the outcome in patients with classic APS and, of course, is the treatment of choice in patients with TTP where the emphasis is on small vessel occlusive disease.

Third-Line Therapies

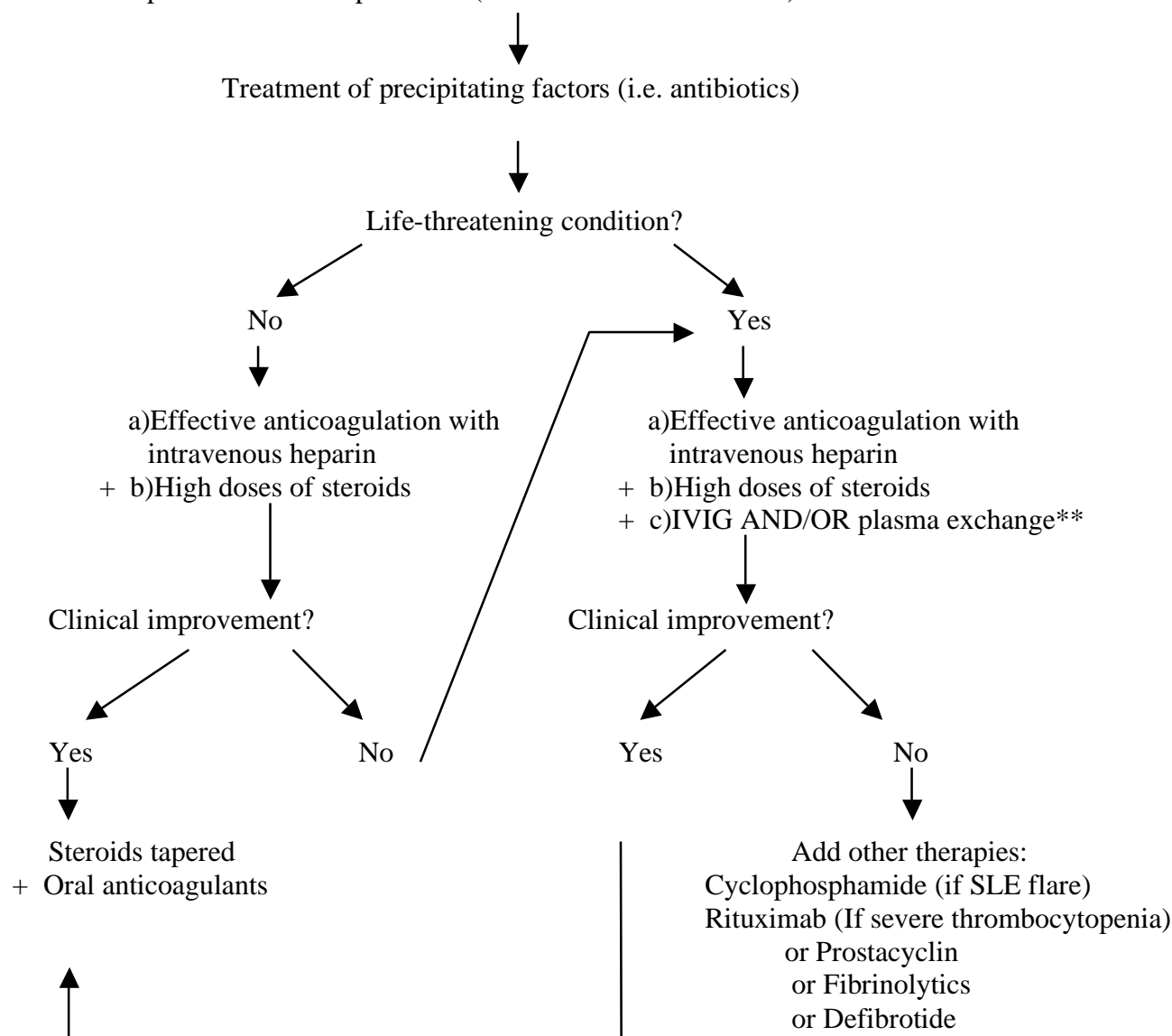
These comprise several compounds that have either been used fairly often (cyclophosphamide) or in a few cases only (rituximab, prostacyclines, ancrod, defibrotide) and may have contributed to the recovery of the patient.

Cyclophosphamide: Theoretically, immunosuppressive therapy might be useful to prevent rebound of the aPL following plasma exchange.

Rituximab: This anti-CD20 monoclonal antibody has now been used with good results in patients with non-responsive severe thrombocytopenia [29].

Prostacyclin: This compound is a potent inhibitor of platelet aggregation and would thus theoretically be of benefit in the ongoing clotting process. It is also a vasodilator. The dose is 5 ng/kg/min for seven days.

Clinical suspicion of catastrophic APS (i.e. 2 classification criteria)*



*Consider exclusion of other microangiopathic syndromes (mainly thrombotic thrombocytopenic purpura and heparin-induced thrombosis/thrombocytopenia)

**With fresh frozen plasma and specially indicated if schistocytes are present.

Fig. (1). Treatment algorithm of catastrophic APS.

Ancoad: It is a powerful fibrinolytic and also corrects plasminogen activator deficiencies. It is seldom used today.

Defibrotide: This is an alkali metal salt of single stranded DNA and has antithrombotic properties. Because of its polypharmacological properties, indications are that it may have an important role to play in the future in the management of refractory patients with catastrophic APS and has been successfully used in one patient.

Other fibrinolytics (e.g. streptokinase, urokinase, tissue plasminogen activators): These compounds, theoretically, might have an important role to play in the management of refractory patients with catastrophic APS but may be associated with hemorrhagic complications. Their judicious use in

these difficult cases where a life-threatening situation is imminent because of ongoing clotting is probably justified.

Non-Specific Therapies

Most patients end up in ICU because multi-organ failure has supervened. If renal failure is present, hemodialysis may be required. Mechanical ventilation for respiratory failure is often indicated particularly if ARDS is present. Inotropic drugs for circulatory failure need to be administered. Severe hypertension due to renal vascular occlusive disease may necessitate aggressive antihypertensive therapy. If hypotension is present due either to myocardial depression (SIRS), microangiopathy of small cardiac vessels or hemorrhagic infarction of the adrenal glands, parenteral steroids are necessary. This is another reason for inotropic drugs.

Table 3. Causes of Death and Necropsy Finding in Patients who Died with Catastrophic APS

| | |
|-------------------------------------|------------------------|
| Total of Patients who Died | 46% (114/250) |
| Clinical Diagnosis of Death | 71.7 % (81/114) |
| Cerebral involvement | 19.5% (22/114) |
| Stroke | 13.3% (15/114) |
| Cerebral haemorrhage | 3.5% (4/114) |
| Encephalopathy | 2.7% (3/114) |
| Cardiac involvement | 14.1% (16/114) |
| Cardiac failure | 12.2% (14/114) |
| Arrhythmias | 1.8% (2/114) |
| Infection | 14.1% (16/114) |
| Bacterial sepsis | 8.8% (10/114) |
| Sepsis by candida | 2.6% (3/114) |
| Cerebral abscesses | 0.9% (1/114) |
| Pneumocystis carinii | 1.8% (2/114) |
| Multiorgan failure | 12.4% (14/114) |
| Pulmonary involvement | 7.1% (8/114) |
| ARDS | 5.3% (6/114) |
| Pulmonary embolism | 0.9% (1/114) |
| Pulmonary haemorrhage | 0.9% (1/114) |
| Abdominal involvement | 4.5% (5/114) |
| Liver failure | 2.7% (3/114) |
| Acute abdomen | 1.8% (2/114) |
| NECROPSY | 52.2% (59/114) |
| Microthrombosis | 89% (53/59) |
| Renal | 62% (37/59) |
| Cerebral | 50.8% (30/59) |
| Pulmonary | 45.7% (27/59) |
| Cardiac | 45.7% (27/59) |
| Intestinal | 30.5% (18/59) |
| Splenic | 28.8% (17/59) |
| Hepatic | 20.3% (12/59) |
| Cutaneous | 20.3% (12/59) |
| Others | 35.5% (21/59) |
| Infarcts | 54.2% (32/59) |
| Cerebral | 33.8% (20/59) |
| Myocardial | 20.3% (12/59) |
| Splenic | 10.2% (6/59) |
| Renal | 8.4% (5/59) |
| Hepatic | 3.3% (2/59) |
| Other | 11.25 (7/59) |
| Other findings at necropsy | |
| Libman Sacks endocarditis | 27.1% (16/59) |
| Pulmonary embolism | 16.9% (10/59) |
| Infection | 10.2% (6/59) |
| Acute respiratory distress syndrome | 6.8% (4/59) |
| Alveolar haemorrhage | 5% (3/59) |
| Budd Chiari | 1.6% (1/59) |

OUTCOME AND PROGNOSIS

The mortality of the condition is high despite present day therapy. Mortality is of the order of 50%. In a recent analysis of the "CAPS Registry" focused on mortality [30], the major cause of death was identified in 81/114 (71.1%) patients (Table 3). Cerebral involvement was the most frequent cause of death, being present in 22 patients (27.2%). They included stroke in 15 (18.5%), cerebral hemorrhage in 4 (4.9%), and encephalopathy in 3 (3.7%) patients. Cardiac involvement was identified in 16 (19.8%) patients as major cause of death, including cardiac failure in 14 (17.3%) and arrhythmias in 2 (2.5%) patients. Infection was described as the

main cause of death in 16 (19.8%) patients, including bacterial sepsis in 10 (12.3%), fungal sepsis in 3 (3.7%), *Pneumocystis carinii* pneumonia in 2 (2.5%) patients, and suppurative peritonitis in one patient (1.2%). Multiorgan failure was identified in 14 (17.3%) patients. Pulmonary involvement was presented as major cause of death in 8 (9.8%) patients, mainly consisting of ARDS in 6 (7.4%), and pulmonary embolism and pulmonary hemorrhage (one case each). Abdominal involvement was incriminated as main cause of death in 4 (4.9%) patients, including liver failure in 3 (3.7%) and acute abdomen in 1 (1.2%), respectively.

Necropsy was performed in 58/114 (50.8%) patients. The main occlusive features were microthrombosis, present in 49 (84.5%) patients, followed by infarcts in 31 (53.4%), thromboses of large vessels in 11 (18.9%), and pulmonary embolism in 7 (12.1%). In order of frequency, the kidneys (65.3%), the heart (55.1%), the lungs (48.9%), the brain (48.9%), the spleen (24.5%), the skin (22.4%), the gut (20.4%), the liver (20.4%), and the adrenal glands (16.3%) were the main organs affected by microthromboses. Others organs where microthromboses were occasionally described included pancreas, uterus, testicles, retina, bone marrow, thyroid, muscles and peripheral nerves.

However, once patients with catastrophic APS have recovered, patients usually have a stable course with continued anticoagulation. A recent paper [31] has documented that 66% of patients with catastrophic APS who have survived the initial event had remained symptom-free for an average follow-up of 62.7 months. Twenty-six percent of the survivors, however, developed further APS-related events but there were no instances of further catastrophic events. Only few patients have suffered "recurrent" catastrophic APS. In these, clear precipitating factors were evident, e.g. recurrent infections and trauma. This is a rare event, unlike patients with the not superficially dissimilar condition of TTP where recurrent episodes are common.

ABBREVIATIONS

IVIG = Intravenous immunoglobulins
SLE = Systemic lupus erythematosus

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