Catastrophic Antiphospholipid Syndrome: A Case Series

Shachaf Shiber MD and Yair Molad MD

Rheumatology Unit, Rabin Medical Center (Beilinson Campus), Petah Tikva, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

ABSTRACT: **Background:** Antiphospholipid syndrome (APS) is an autoimmune disease with clinical manifestations of arterial and venous thrombosis, obstetric manifestations, and the presence of antiphospholipid antibodies or lupus anticoagulant. Catastrophic APS is a rare variant of APS, defined as acute failure of at least three tissues, organs or systems caused predominantly by small vessel thrombosis confirmed by histopathologic evidence. Catastrophic APS develops rapidly and leads to death in 30% of cases.

Methods: We evaluated 11 patients with catastrophic APS – 8 of them with a probable diagnosis of catastrophic APS and 3 with a definite diagnosis – admitted to Beilinson hospital during the period 2003–2011.

Results: Overall venous events numbered 18 and overall arterial events 10. The event duration per patient was 2.6 ± 1.2 weeks (mean ± SD). Deep vein thrombosis of the legs was quite common (7 events), as was venous intraabdominal thrombosis (10 events). Eight patients had microangiopathic anemia with schizocytes seen in the blood smear. The mean ± SD hemoglobin level was 10.3 ± 3.6 g/dl and the mean ± SD creatinine level 0.98 ± 0.78 mg/dl. All our patients had high acute-phase reactant and all had lupus anticoagulant positivity, The most common positive antibodies were immunoglobulin G anticardiolipin (8 patients) and IgG β2-glycoprotein (7 patients). During the events warfarin was stopped and the patients were given intravenous heparin. All the patients received steroids in variable doses. Five patients underwent plasma exchange, two patients received rituximab and two patients intravenous immunoglobulin.

Conclusions: Catastrophic APS, a rare syndrome, is important because of its major morbidity and mortality among young patients.

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KEY WORDS: antiphospholipid syndrome (APS), catastrophic antiphospholipid syndrome, arterial and venous thrombosis, obstetric manifestations

The "catastrophic" variant of the antiphospholipid syndrome was described by Ronald Asherson in 1992 [1] as a condition characterized by multiple vascular occlusive events, usually affecting small vessels and developing over a short period. According to the criteria published in *Lupus* in 2003 [2], catastrophic APS is the most severe form of APS with clinical evidence of multiple organ involvement developing over a short time, histopathological evidence of small vessel occlusions, and laboratory confirmation of antiphospholipid antibodies (lupus anticoagulant test, anticardiolipin antibody enzyme-linked immunosorbent assay, and anti-β2-glycoprotein-I antibody ELISA). The classification criteria for catastrophic antiphospholipid syndrome are summarized in Table 1.

Although fewer than 1% of patients with APS develop this complication [3], its potentially lethal outcome underlines its importance in clinical medicine today. The majority of patients with catastrophic APS end up in intensive care units with multiorgan failure and, unless the condition is considered in the differential diagnosis by attending physicians, it may be completely missed, resulting in a disastrous outcome [4]. In this article we describe 11 patients with catastrophic APS admitted to the Rabin Medical Center during the years 2003–2011.

CASE SERIES

This series comprises 11 patients admitted to our hospital with a picture compatible with catastrophic APS. Their age at diagnosis was 38.25 ± 14.8 years (mean ± SD). The male:female ratio was 2:9. The mean ± SD duration of follow-up was 3.45 ± 2.5 years. Five patients had primary APS syndrome and six

APS = antiphospholipid syndrome
ELISA = enzyme-linked immunosorbent assay

Table 1. Preliminary criteria for the classification of catastrophic APS [2]

Evidence of involvement of ≥ three organs, organ systems or tissues (usually confirmed by imaging techniques; renal involvement defined as a 50% rise in creatininemia; severe arterial hypertension or proteinuria)
Development of manifestations simultaneously or within 1 week
Confirmation by histology of small vessel occlusion in at least one organ or tissue (confirmation of thrombosis is necessary; at times vasculitis may coexist)
Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies)
Definite diagnosis = 4 criteria Probable diagnosis = any of the following: 2 + 3 + 4 criteria and involvement of two organs, organ systems or tissues 1 + 2 + 3 criteria (without confirmation of APS due to early death of a patient never tested for APA before catastrophic APS 1 + 3 + 4 criteria and the development of a 3rd event between 1 week and 1 month after presentation, despite anticoagulation

Table 2. Epidemiological, clinical and laboratory manifestations of catastrophic APS patients

Patient #	Age at diagnosis (yr)	Gender	Years of follow-up	Primary/ secondary APS	ANA	Anti-DsDNA	APS serology	Clinical manifestation	Treatment	Episode length (wk)	Outcome	Eligible for CAPS criteria
1	18	F	3	SLE	+	+	LAC, β2GP IgG	Leg DVT, PE, IVC thrombus, Budd-Chiari syndrome	Heparin, steroids	2	–	Probable
2	66	F	1	Primary	+	+	LAC, β2GP IgG, ACL IgM, ACL IgG	PE, splenic infarct, CVA, ARF	Heparin, steroids, rituximab	2	Paraplegia	Definite
3	43	F	9	SLE	+	+	LAC, β2GP IgG, β2GP IgM ACL IgM, ACL IgG	PE, AION, Liebman-Sachs endocarditis, CVA	Heparin, steroids, IVIG	4	Death	Probable
4	22	M	1	Primary	+	–	LAC	Thrombotic MI, PE, renal thrombus	Heparin, steroids	1	CHF, ARF	Definite
5	33	M	2	Primary	+	–	LAC, β2GP IgG	Leg DVT, adrenal hemorrhage, IVC thrombus, sinus vein thrombosis, ischemic ulcer	Heparin, steroids, PE	2	Adrenal insufficiency	Definite
6	28	F	4	SLE	+	–	LAC, ACL IgG	Leg DVT twice, portal thrombosis, PE, AION	Heparin, steroids	3	Blindness Rt eye	Probable
7	34	F	3	SLE	+	+	LAC, β2GP IgG, ACL IgG	PE, leg DVT, livedo, ARF reticularis	Heparin, steroids	4	Chronic renal failure	Probable
8	62	F	2	Lupus-like	+	–	LAC	CVA, ischemic ulcer, IVC thrombus	Heparin, steroids	2	Death	Probable
9	35	F	2	Primary	+	–	LAC	ARF, leg DVT, Budd-Chiari	Heparin, steroids	4	–	Probable
10	39	F	7	Primary	–	–	LAC, β2GP IgG	Leg DVT, CVA, portal vein thrombus	Heparin, steroids, IVIG	4	–	Probable
11	40	F	4	Lupus-like	+	–	LAC, β2GP IgG, ACL IgG	CVA, livedo reticularis, ARF	Heparin, steroids, PE	1	Right hemiplegia	Definite

CAPS = catastrophic antiphospholipid syndrome, ANA = antinuclear antibody, LAC = lupus anticoagulant, ACL = anticardiolipin; β2GP = beta 2 glycoprotein antibody, DVT = deep vein thrombus, PE = pulmonary embolism, ARF = acute renal failure, CVA = cerebrovascular accident, IVC = inferior vena cava, MI = myocardial infarction, AION = anterior ischemic optic neuropathy, PE = plasma exchange

had secondary APS syndrome (four with systemic lupus erythematosus and two with lupus-like syndrome). Two patients died from catastrophic APS. Table 2 lists the epidemiological, clinical and laboratory manifestations of the 11 patients in this series.

BASELINE CLINICAL CHARACTERISTICS

Venous or arterial thrombosis was seen in 10 of our patients before the catastrophic APS occurred. The most common venous thrombosis was deep vein thrombosis of the legs (n=4) and the most common arterial thrombosis was stroke (n=3). Obstetric manifestations were also common and were seen in six of our nine female patients. The most common manifestation was premature abortions (in five).

CLINICAL MANIFESTATIONS DURING THE CATASTROPHIC APS EPISODE

Overall venous events numbered 18 and overall arterial events 10. The event duration per patient was 2.6 ± 1.2 weeks (mean ± SD). DVT of the legs was quite common (7 events), as was venous intraabdominal thrombosis (10 events). There were six events of pulmonary embolism. Sinus vein thrombosis occurred in one patient. Arterial thrombosis was also common, but the most common was stroke (five events). There were two events of acute ischemic optic neuritis and two of ischemic ulcer. Other manifestations were livedo reticularis (n=2), thrombotic myocardial infarction (n=1), Liebman-Sachs endocarditis (n=1) and adrenal hemorrhage (n=1).

DVT = deep vein thrombosis

LABORATORY MANIFESTATIONS DURING THE CATASTROPHIC APS

Of the 11 patients, 10 were thrombocytopenic during the acute event with a mean ± SD of 145.7 ± 132.1/μl. Eight patients had microangiopathic anemia with schizocytes seen in the blood smear. The mean ± SD hemoglobin level was 10.3 ± 3.6 g/dl. The mean ± SD creatinine level was 0.98 ± 0.78 mg/dl. All our patients had high acute-phase reactant. Other mean ± SD levels were erythrocyte sedimentation rate 76 ± 22 mm/hr and C-reactive protein 9.62 ± 6.21 mg/dl.

All our patients had lupus anticoagulant positivity. The most common positive antibodies were immunoglobulin G anticardiolipin (8 patients) and IgG β2-glycoprotein (7 patients).

Ten patients received warfarin before the catastrophic APS event because of a previous thrombosis and 6 patients (those with systemic lupus erythematosus and lupus-like syndrome) received hydroxylchloroquine. During the events warfarin was stopped and the patients were given intravenous heparin. All the patients received steroids in variable doses. Five patients underwent plasma exchange; two patients received rituximab and two patients intravenous immunoglobulin.

DISCUSSION

The diagnosis of catastrophic APS can be challenging. Sometimes the differential diagnosis cannot be narrowed to a single disease during the acute period and thus continuous assessment of patients is warranted [6-8].

Similar to our observations, the CAPS Registry of 280 patients shows that 72% were female, with a mean age of 37 years (range 11–60). Approximately 46% had primary APS and 40% SLE . However, contrary to the literature where most patients are reported to have CAPS de novo [5,9], 10 of our patients had prior thrombotic or obstetric manifestations. Similar to the 11 intraabdominal events in our series, in the registry [5] the vast majority of patients had intraabdominal manifestations. Table 3 compares the epidemiological, clinical and laboratory data of our case series with the CAPS registry. Thrombocytopenia usually presents in catastrophic APS [4] and was detected in 10 of 11 patients; 8 had hemolysis and 6 had schizocytes in the peripheral blood smear.

In the absence of a clinical randomized control trial, anticoagulation together with corticosteroids is the most commonly used regimen (19.8%), followed by AC + CS + and/or IVIG (17.4%). The highest recovery rate is achieved by the combination of AC + CS + PE (77.8%), followed by AC + CS + PE and/or IVIG (69%) [10]. AC is usually given in the form of heparin, which is the mainstay of treatment in patients with catastrophic APS [11]. Analysis of the CAPS Registry shows that CS alone does not improve outcome. However, CS inhibits nuclear factor-κB, which is an important mediator in both systemic inflammatory response syndrome [13] and aPL-mediated thrombosis. PE removes aPL (most likely transiently), as well as cytokines, tumor necrosis factor-alpha, and complement products. Based on a literature search of PE use in patients with catastrophic APS [12], as well as the CAPS Registry analysis [15], the use of PE clearly improves patient survival.

Table 3. Comparisons of the epidemiological, clinical and laboratory data in our case series and the CAPS Registry

Characteristics	Current series	CAPS registry [5]
Age for diagnosis (mean + SD)	38.25 ± 14.8	37 ± 14
M:F ratio	2 (18%):9 (82%)	79 (28%):201 (72%)
Primary APS	5 (45.4%)	129 (46%)
Secondary APS	6 (54.6%)	151 (54%)
Death	2 (18%)	123 (44%)
Thrombocytopenia	10 (91%)	129 (46%)
Hemolytic anemia	8 (72%)	143 (51%)
Lupus anticoagulant positivity	11 (100%)	230 (82%)
Anticardiolipin IgG (U/ml)	5 (45%)	232 (83%)
Anticardiolipin IgM (U/ml)	2 (18%)	106 (38%)
ANA titer >160	10 (91%)	185 (66%)
Intraabdominal manifestations*	7 (63.6%)	60 (25%)
Leg deep vein thrombus	6 (54.6%)	64 (23%)
Pulmonary manifestations∞	6 (54.6%)	163 (64%)
Cerebrovascular manifestations**	6 (54.6%)	158 (62%)
Kidney manifestations©	5 (45%)	180 (71%)
Skin manifestations▪	4 (36%)	128 (50%)
Retinal manifestations◊	2 (18%)	17 (7%)
Cardiac manifestations$	2 (18%)	122 (51%)
Adrenal manifestations$$	1 (0.9%)	3 (1%)

Values presented are number of patients and percentage

*Intraabdominal manifestations: IVC thrombus, Budd-Chiari syndrome, portal vein thrombus, splenic infarct

∞Pulmonary manifestations: acute respiratory distress syndrome and pulmonary embolism

**Cerebrovascular manifestations: encephalopathy, cerebrovascular accidents, seizures, headache, silent brain infarcts

©Kidney manifestations: kidney infarct, renal involvement defined as a 50% rise in creatininemia, severe arterial hypertension or proteinuria

▪Skin manifestations: livedo reticularis, leg ulcers, necrotic lesions, digital gangrene, purpura, splinter hemorrhages, and multiple ecchymosis

◊Retinal manifestations: anterior ischemic optic neuropathy, optic neuritis

$Cardiac manifestations: cardiac failure, thrombotic myocardial infarction, valve lesions (Liebman-Sachs endocarditis)

$$Adrenal manifestations: adrenal infarct, adrenal hemorrhage

IgG = immunoglobulin G
SLE = systemic lupus erythematosus
CAPS = catastrophic APS
AC = anticoagulation
CS = corticosteroids
IVIG = intravenous immunoglobulin
PE = plasma exchange

aPL = antiphospholipid antibodies

IVIG has multiple therapeutic actions and improves the outcome according to the CAPS Registry [16]. When IVIG and PE are used simultaneously in the same patient, IVIG is usually administered after the last day of the PE in order to prevent the removal of IVIG by PE.

There is growing evidence that treatment with rituximab, an anti-CD20 monoclonal antibody is effective in catastrophic APS, as evidenced in two patients in our series treated with rituximab during the event [17].

Two female patients in our series died, one from infection and the other from cerebral infarct. In the literature, older age (over 36 years old), SLE, pulmonary and renal involvement, and positive antinuclear antibody titer are associated with higher mortality in patients with catastrophic APS [4,18].

The only study on the prognosis of patients who survive the initial catastrophic event demonstrated that 66% of them remain free of thrombosis and 17% develop further APS-related manifestations during a follow-up of approximately 6 years [19]. Although relapse in catastrophic APS is uncommon, there have been a few case reports of catastrophic APS relapse [20-24].

In conclusion, this rare syndrome is important because of its major morbidity and mortality among young patients.

Corresponding author:
Dr. S. Shiber
Rheumatology Unit, Rabin Medical Center (Beilinson Campus), Petah Tikva 49100, Israel
Phone: (972-3) 937-6947
Fax: (972-3) 937-7062
email: sofereret@gmail.com

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"Anyone who has ever struggled with poverty knows how extremely expensive it is to be poor"

James Baldwin (1924-1987), American novelist, essayist, playwright, poet and social critic, whose essays, such as the collection *Notes of a Native Son*, explore palpable yet unspoken intricacies of racial, sexual, and class distinctions in western societies, particularly in mid-20th century America

"You can tell whether a man is clever by his answers. You can tell whether a man is wise by his questions"

Naguib Mahfouz (1911-2006), Egyptian writer and Nobel laureate, regarded as one of the first contemporary writers of Arabic literature, along with Tawfiq el-Hakim, to explore themes of existentialism. He published 34 novels, over 350 short stories, dozens of movie scripts, and five plays over a 70-year career. Many of his works have been made into Egyptian and foreign films