EXTENDED REPORT

The acute respiratory distress syndrome in catastrophic antiphospholipid syndrome: analysis of a series of 47 patients

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Background: The acute respiratory distress syndrome (ARDS) is a non-cardiogenic form of pulmonary oedema characterised by severe hypoxaemia refractory to oxygen therapy, with diffuse pulmonary infiltrates on chest radiographs. It can be precipitated by various serious medical and surgical conditions, including systemic autoimmune diseases. The ''catastrophic'' variant of the antiphospholipid syndrome (APS) is an accelerated form of this systemic autoimmune condition which results in multiorgan failure because of multiple small vessel occlusions.

Objective: To analyse the clinical and laboratory characteristics of patients with catastrophic APS who develop ARDS.

Methods: Cases with ARDS were selected from the web site based international registry of patients with catastrophic APS (CAPS registry) (http://www.med.ub.es/MIMMUN/FORUM/CAPS.HTM) and their characteristics examined.

Results: Pulmonary involvement was reported in 150 of 220 patients with catastrophic APS (68%) and 47 patients (21%) were diagnosed as having ARDS. Nineteen (40%) of these patients died. Pathological studies were undertaken in 10 patients and thrombotic microangiopathy was present in seven. There were no differences in age, sex, precipitating factors, clinical manifestations, or mortality between catastrophic APS patients with and without ARDS.

Conclusions: ARDS is the dominant pulmonary manifestation of catastrophic APS. Thus the existence of ARDS in the context of an APS makes it necessary to rule out the presence of the catastrophic variant of this syndrome.

The acute respiratory distress syndrome (ARDS) is a non-cardiogenic form of pulmonary oedema characterised by severe hypoxaemia refractory to oxygen therapy, with diffuse pulmonary infiltrates on chest radiographs.[1] It can be precipitated by various serious medical and surgical conditions.[2] Common causes include pneumonia, aspiration of gastric contents, sepsis, severe trauma with shock, and multiple transfusions.[1 2] In the context of autoimmune diseases, several case reports have suggested that systemic lupus erythematosus (SLE) may be linked to ARDS.[3–7]

In 1992, a new subset of the antiphospholipid syndrome (APS) was described, termed ''catastrophic APS''[8] or Asherson's syndrome,[9] which has an acute and accelerated course. It is characterised by multiple vascular occlusive events, usually affecting small vessels, presenting over a short period of time, with laboratory confirmation of the presence of antiphospholipid antibodies (aPL).[10] Several reviews have been published on a growing number of patients with this condition over the past few years.[11–13] As more and more cases are documented, it has become obvious that there is an inordinately high frequency of pulmonary manifestations in the syndrome (particularly, ARDS), not seen with simple or ''classic'' APS.

Our objective in the present study was to analyse the clinical and laboratory characteristics of patients with catastrophic APS who develop ARDS.

METHODS

We analysed the web site based international registry of patients with catastrophic APS (the CAPS registry; http://www.med.ub.es/MIMMUN/FORUM/CAPS.HTM) which, until February 2004 included 220 patients: 153 female and 67 male; mean (SD) age, 38 (14) years, range 7 to 74; 106 with primary APS, 88 with SLE, 11 with lupus-like syndrome, and 15 with other diseases.

We selected those patients diagnosed by their physicians in charge as having ARDS (ratio of Pao_2 to fraction of inspired oxygen (Fio_2) less than 200; evidence of bilateral infiltrates on chest radiographs; and no reason to suspect that the pulmonary oedema was cardiogenic).[14 15] We included only cases with well documented clinical reports and fulfilling the classification criteria for catastrophic APS. Briefly, these criteria include evidence of involvement in three or more organs, systems, or tissues, development of manifestations simultaneously or in less than a week, confirmation by histopathology of small vessel occlusion in at least one organ or tissue, and laboratory confirmation of the presence of aPL.[10]

We summarised data from these patients using a standardised form, including sex, age, diagnosis of the underlying disorder, main clinical manifestations, immunological features, treatment, and outcome. To facilitate synthesis of the data, we categorised patients into three major diagnoses according to their underlying disease or syndrome:

- SLE if they met four or more of the American College of Rheumatology criteria[16];

Abbreviations: aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; ARDS, acute respiratory distress syndrome; BALF, bronchoalveolar lavage fluid; SIRS, systemic inflammatory response syndrome

- ''lupus-like'' syndrome if they met two or three American College of Rheumatology criteria;
- primary APS if they met criteria of the International Consensus Statement on preliminary classification for definite APS[17] and did not meet the above criteria for SLE or lupus-like disease.

Fisher's exact test (bilateral) was employed for the statistical analysis, using the SPSS 10.0 statistical program.

RESULTS

General characteristics

Among the 220 patients included in the CAPS registry, pulmonary involvement was described in 150 patients (68%), and data suggesting ARDS were reported in 56 (25%). However, nine patients were excluded: three because of the presence of pneumonia as a cause of the ARDS, three because features of cardiac insufficiency were present, two because diffuse alveolar haemorrhage was revealed by biopsy, and one because necropsy revealed carcinoma of unknown origin. Thus 47 patients in all (21%) were considered to have ARDS, representing nearly one third (31%) of those having pulmonary involvement. The mean (SD) age of the patients with ARDS was 34 (16) years (range 9 to 74). Thirty six (77%) were female, 22 (47%) had SLE, 19 (40%) had primary APS, and 5 (11%) had lupus-like disease (in one case, this information was not available).

Precipitating factors and clinical manifestations

The general characteristics and precipitating factors of the catastrophic APS are summarised in table 1. In 17 patients (36%), precipitating factors were not identified. The most striking precipitating factor, found in 15 patients (32%), was infection, ranging from upper respiratory tract infections to gastrointestinal infections and other septic conditions such as urinary tract infection. Common causes of ARDS such as pneumonia or sepsis appeared to be precipitating factors of catastrophic APS in three patients. The second most frequent precipitating factor, found in six patients (13%), was surgery and invasive procedures, ranging from an endoscopic retrograde cholangio-pancreatography to various major operations. Others were associated with drug treatment (11%), obstetric complications (9%), SLE flares (4%), or withdrawal of anticoagulants (2%).

Intra-abdominal involvement was identified in 42 patients (89%), mainly consisting of renal (81%), hepatic (26%), gastrointestinal (19%), pancreatic (10%), adrenal (17%), and splenic (5%) manifestations. Thirty six patients (77%) had evidence of cerebrovascular complications, mainly encephalopathy and cerebrovascular accidents, but occasionally seizures or transverse myelitis. Skin manifestations were also frequent (55%) and consisted of livedo reticularis, ulcers, digital gangrene, purpura, and microthrombosis of small vessels. Twenty four patients (51%) had cardiac involvement, mainly cardiac failure and confirmed myocardial infarction, Libman-Sacks non-bacterial endocarditis, or silent valve lesions. Peripheral venous thrombosis was present in 12 patients (26%) and peripheral arterial occlusive disease in five (11%).

Other abnormalities occasionally encountered were retinal, pleural, and peripheral nerve lesions.

There were no differences in age, sex, precipitating factors, or clinical manifestations between catastrophic APS patients with and without ARDS.

Laboratory features

The IgG isotype of anticardiolipin antibodies (aCL) was reported as positive in 38 patients (81%) and the IgM aCL in 16 (34%). Lupus anticoagulant was present in 34 patients (72%).

Pathological features

Histopathological study of lungs was undertaken in 10 patients (necropsy in eight, lung biopsy in two). The main finding was non-inflammatory thrombotic microangiopathy which was present in seven patients; intra-alveolar haemorrhage and hyaline membrane formation were each present in two cases. In all cases, pathological examination ruled out vasculitis.

Treatment and outcome

The treatment and outcome of the 47 patients with ARDS and catastrophic APS are shown in table 2. Data on treatment were not available for three patients. Finally, 44 episodes of ARDS were analysed. Anticoagulation was the most frequent treatment, used in 42 patients (95%), followed by steroids in 39 (89%). Immunosuppressants were used in 19 patients (43%) (cyclophosphamide in 18 and vincristine in one), intravenous immunoglobulins were used in 21 patients (48%), and plasma exchange in 15 (34%). Intravenous prostaglandin was used in one case. Nineteen patients died (40%). There was no statistically significant difference in mortality between catastrophic APS with ARDS and without ARDS. No differences were found in the recovery rate depending on the use or not of a particular treatment.

DISCUSSION

ARDS is associated with a variety of clinical disorders. These can be divided into two categories: those associated with direct injury to the lung, with direct effects on pulmonary cells (pneumonia, aspiration of gastric contents, pulmonary contusion, near drowning, and inhalational injury); and those that cause indirect lung injury in the setting of a systemic process through acute systemic inflammatory responses (sepsis, severe trauma with shock and multiple transfusions, cardiopulmonary bypass, drug overdose, and acute pancreatitis).[18] Overall, sepsis is associated with the greatest risk of progression to ARDS (approximately 40%).[19] ARDS has also been documented in patients with SLE,[3–7] which may be complicated by pulmonary hypertension,[4] as well as in adult Still's disease.[20 21] Its occurrence in catastrophic APS is a completely new association. In the present study, we found a frequency of 21% of ARDS in the patients with catastrophic APS.

Although alveolar haemorrhage may be responsible for dyspnoea in patients with catastrophic APS, it is infrequently encountered, probably because it is difficult to diagnose.[22] Once other causes (such as cardiac failure, pneumonia, and recurrent pulmonary emboli) have been excluded clinically and by the appropriate investigations, ARDS is by far the commonest underlying pulmonary condition encountered.

An intriguing question is whether aPL may play a role in the development of ARDS in patients with catastrophic APS or, conversely, whether ARDS is produced by the same factor that precipitates the catastrophic APS—that is, infection or surgery. Although it is difficult to draw any firm conclusion because of the sparse data, several findings point towards a direct link between aPL and ARDS.

The first of these is that the acute phase of ARDS is characterised by an influx of protein-rich oedema fluid, with associated red cells and neutrophils, into the air spaces secondary to increased permeability of the alveolar–capillary barrier.[23] This increase in endothelial and epithelial permeability allows higher molecular weight proteins, such as IgG and IgM, to enter the air spaces.[24] Maneta-Peyret *et al*[25] have reported an increased amount of IgG in the bronchoalveolar lavage fluid (BALF) of patients with ARDS in comparison

Table 1 General characteristics of patients with acute respiratory distress syndrome plus catastrophic antiphospholipid syndrome

Case*	Sex	Age (y)	Diagnosis	Previous APS manifestations	Precipitating factor	Other organ involvement at the time of catastrophic APS	LA	IgG aCL	IgM aCL
1 (2)	M	22	Lupus-like			PVT, CNS, kidney, skin	+	+	+
2 (3)	F	22	Lupus-like			Heart, CNS, kidney, skin, retina	+	+	+
3 (14)	F	11	SLE	Epilepsy	Intestinal infection	CNS, skin, liver	+	−	−
4 (16)	F	23	SLE		ERCP	Heart, CNS, kidney, liver	+	Moderate +	−
5 (20)	F	43	PAPS	DVT, fetal losses		Heart, kidney, GI tract, adrenals	+	276 GPL	−
6 (26)	M	45	SLE	DVT, PE, SVC thrombosis		CNS, central retinal vein thrombi	−	20	−
7 (33)	F	52	Lupus-like	Fetal loss	Diuretic	CNS, kidney, liver, GI tract, pancreas	NR	High +	High +
8 (36)	F	36	PAPS	DVT		Heart, kidney, GI tract, adrenal glands, thyroid, muscle, peripheral nerves	+	95 GPL	−
9 (41)	F	35	PAPS	Fetal loss, PAT, skin ulcers		CNS, kidney	+	46 GPL	4 MPL
10 (43)	M	47	PAPS			CNS	+	−	−
11 (46)	M	55	Lupus-like	DVT	ACE inhibitor	PVT, heart, kidney, skin	+	High +	−
12 (49)	F	74	PAPS	DVT, PE, LR, skin ulcers		Heart, CNS, kidney, retina	+	200 GPL	NR
13 (62)	F	48	PAPS	DVT	Cholectomy, sepsis	Liver, GI tract, peripheral nerves	NR	Moderate +	Moderate +
14 (63)	M	47	PAPS	TIA, CVA, myocardial infarction	Leg ulcer infection	PAT, CNS, kidney, skin	+	+	NR
15 (69)	F	28	SLE		Pneumonia	Heart, kidney, skin, GI tract	NR	+	NR
16 (72)	F	42	SLE	Fetal loss, CVA, LR, thrombocytopenia		Heart, CNS, kidney, skin, liver, spleen	+	72 GPL	NR
17 (74)	F	16	PAPS		Upper respiratory infection	PVT, CNS, skin, peripheral nerves	+	100 GPL	−
18 (76)	F	21	SLE		Upper respiratory infection	PVT, heart, CNS, kidney, skin, transverse myelitis	−	88 GPL	−
19 (77)	F	54	SLE		Cutaneous and urinary infection, abdominal surgery	PVT, heart, skin, liver, transverse myelitis	−	−	96 MPL
20 (78)	F	17	PAPS		OC, sun exposure	PVT, heart, CNS, kidney, skin, transverse myelitis	−	104 GPL	−
21 (82)	F	26	SLE	DVT	Post-fetal loss	CNS, kidney, skin	NR	24 GPL	NR
22 (94)	M	18	SLE			Heart, CNS, kidney, skin, pleura	NR	+	NR
23 (99)	F	33	PAPS	Fetal loss, superficial venous thrombosis	Pregnancy, caesarean section	Heart, CNS, kidney, skin	+	>100 GPL	−
24 (104)	F	28	SLE	DVT, thrombocytopenia		PVT, heart, CNS, kidney	+	+	−
25 (106)	F	67	PAPS		Urinary infection	Heart, CNS, kidney	+	High +	−
26 (108)	F	20	PAPS		Throat infection	PVT, CNS, kidney, skin	−	+	−
27 (110)	F	22	SLE	Fetal loss	HELLP	CNS, kidney, cranial nerve	+	+	+
28 (121)	F	27	PAPS	DVT, fetal loss	Post-fetal loss	Heart, liver	−	72 GPL	−
29 (125)	F	39	Lupus-like	Fetal death, amaurosis fugax, TIA		Heart, CNS, kidney, skin	+	High +	−
30 (127)	F	49	SLE		Major abdominal surgery	PAT, heart, CNS, kidney, skin, GI tract, pancreas	+	128 GPL	−
31 (132)	M	39				Heart, CNS, kidney, skin, adrenal glands	+	174 GPL	−
32 (134)	F	21	PAPS	DVT	Vascular surgery	CNS, kidney, liver	+	High	High +
33 (149)	F	18	SLE	Thrombocytopenia	Respiratory infection	CNS, kidney, spleen, pancreas, thyroid	+	164 GPL	−
34 (158)	M	55	PAPS	DVT	ACE inhibitor	PVT, heart, kidney, skin	+	−	High +
35 (176)	F	47	SLE	LR, thrombocytopenia	Anticoagulation withdrawal	PAT, CNS, skin, adrenal glands	+	NR	NR
36 (177)	F	38	SLE	CVA, Budd-Chiari syndrome, thrombocytopenia	Sepsis	PAT, CNS, skin, adrenal glands	+	Moderate +	High +
37 (178)	F	63	SLE	Fetal loss, LR, Renal microangiopathy, thrombocytopenia,	Major abdominal surgery	PAT, CNS, skin, GI tract, adrenal glands	+	Moderate +	High +
38 (183)	M	15	PAPS			PVT, liver	+	44 GPL	12 MPL
39 (184)	M	33	PAPS	Livedo reticularis, skin ulcers		Heart, CNS, kidney, skin	+	860 GPL	NR
40 (185)	F	52	PAPS	Fetal loss, CVA		CNS	−	Moderate +	−
41 (199)	M	11	SLE			PVT, heart, kidney	+	36 GPL	−
42 (200)	F	9	SLE	LR, digital ulceration	Lupus flare, urinary infection	CNS, skin	−	100 GPL	−
43 (201)	F	31	SLE		Oestrogens	Heart, CNS, kidney, liver, pancreas, myometrium	+	+	+
44 (204)	F	38	SLE		GI infection	CNS, kidney, skin	+	+	+

Table 1 Continued

Case*	Sex	Age (y)	Diagnosis	Previous APS manifestations	Precipitating factor	Other organ involvement at the time of catastrophic APS	LA	IgG aCL	IgM aCL
45 (207)	F	20	PAPS		GI infection	Kidney, GI tract	+	72 GPL	–
46 (211)	F	27	SLE	LR, skin ulcers	Lupus flare	PVT, CNS, kidney, skin, adrenal glands	+	High +	–
47 (213)	F	27	SLE		Upper respiratory infection	Heart, CNS, kidney, liver	+	Moderate +	–

*The numbers in parentheses correspond to the order of the cases in the CAPS registry.
ACE, angiotensin converting enzyme; aCL, anticardiolipin antibodies; APS, antiphospholipid syndrome; CNS, central nervous system; CVA, cerebrovascular accident; DVT, deep venous thrombosis; ERCP, endoscopic retrograde cholangio-pancreatography; F, female; GI, gastrointestinal; HELLP, Haemolysis, Elevated Liver Enzymes, and Low Platelets syndrome; LA, lupus anticoagulant; LR, livedo reticularis; M, male; NR, not recorded; OC, oral contraceptives; PAPS, primary APS; SLE, systemic lupus erythematosus; SVC, superior vena cava; PAT, peripheral artery thrombosis; PE, pulmonary embolism; PVT, peripheral venous thrombosis; TIA, transient ischaemic attack; y, years.

with mechanically ventilated control patients. These antibodies were directed mainly against anionic phospholipids. However, it is difficult to determine whether the presence of these autoantibodies was associated with modifications of the lipid composition of the surfactant or whether they were produced in response to damage to the alveolar or other cell membranes. Furthermore, these antibodies may be produced locally or be provided from plasma following the increased capillary–alveolar permeability present in ARDS. The same group showed that the aPL detected in the BALF of a patient developing ARDS during catastrophic APS did not have the same specificity towards the different phospholipids as aPL in the serum.[26] This supports the hypothesis of local production of aPL. Additionally, a quantitative as well as a qualitative deficiency of surfactant phospholipids was also observed.[26] The investigators suggested that antibodies directed against surfactant phospholipids could cause surfactant abnormalities and a resulting inflammatory reaction. Unfortunately, so far there are no experimental data on a possible effect of aPL on the function of the surfactant.

Table 2 Treatment and outcome of patients with acute respiratory distress syndrome plus catastrophic antiphospholipid syndrome

Case*	Treatment	Outcome
1 (2)	AC, S, CP, PE	Recovery
2 (3)	AC, S, CP, PE	Recovery
3 (14)	AC, S	Recovery
4 (16)		Death
5 (20)		Death
6 (26)	AC, S, CP, PE, GG, vincristine, splenectomy	Death
7 (33)	AC, S, GG	Recovery
8 (36)	S, HD	Death
9 (41)	AC, S, PE, HD	Recovery
10 (43)	AC	Recovery
11 (46)	AC, fibrinolytics	Recovery
12 (49)	AC, S, GG	Recovery
13 (62)	AC, S	Recovery
14 (63)	AC, S, GG	Recovery
15 (69)		Death
16 (72)	AC, S, CP, PE	Death
17 (74)	AC, S	Recovery
18 (76)	AC, S, CP	Death
19 (77)	AC, S, CP	Recovery
20 (78)	AC, S, CP	Death
21 (82)	AC, S, CP	Recovery
22 (94)	S, CP, PE	Death
23 (99)	AC, S, GG	Death
24 (104)	AC, S, GG	Death
25 (106)	AC, S	Death
26 (108)	AC, S, CP, GG	Recovery
27 (110)	AC, S, GG	Recovery
28 (121)	AC, S	Recovery
29 (125)	AC, S, CP, GG, prostacyclin	Recovery.
30 (127)	AC, S, CP, PE, HD	Death
31 (132)	AC, S, PE, GG	Recovery
32 (134)	AC, S, PE, GG, HD	Recovery
33 (149)	AC, S, CP, GG, HD	Death
34 (158)	AC, aspirin	Recovery
35 (176)	AC, S, CP, GG	Death
36 (177)	AC, S, CP, GG	Death
37 (178)	AC, S, GG	Death
38 (183)	AC, S, GG	Recovery
39 (184)	AC	Recovery
40 (185)	AC, S	Recovery
41 (199)	AC, S, CP, PE, GG	Recovery
42 (200)	AC, S, CP, PE, GG	Recovery
43 (201)	AC, S, PE	Recovery
44 (204)	AC, S, PE, HD	Death
45 (207)	AC, S, GG	Recovery
46 (211)	AC, CP, PE, GG	Recovery
47 (213)	AC, S, PE, GG, HD	Death

*The numbers in parentheses correspond to the order of the cases in the CAPS registry.
AC, anticoagulation; CP, cyclophosphamide; GG, intravenous gamma globulin; HD, haemodialysis; PE, plasma exchange; S, steroids S, steroids.

The systemic inflammatory response syndrome (SIRS) secondary to cytokine activation could be another pathogenic mechanism of indirect injury in the ARDS associated to catastrophic APS. A complex network of cytokines initiate and amplify the inflammatory response in ARDS. The extensive tissue damage caused by catastrophic APS results in the liberation of excessive amounts of cytokines. Some of the major clinical manifestations of catastrophic APS resulting from multiple small vessel occlusive disease and consequent tissue necrosis (that is, ARDS and decreased cardiac function) may be directly attributable to SIRS.[27] In support of this is the recent report of a study in which the cytokine levels of a patient with catastrophic APS were evaluated. The study showed that vascular endothelial cell injury might play a major role in the pathogenesis of catastrophic APS.[28] The cytokines involved in ARDS include tumour necrosis factor α, interleukin 1 (IL1), IL6,[29] and macrophage migration inhibitory factor.[30] These have been found to be increased in both sera and BALF of ARDS patients, and they are responsible not only for ARDS but also for the cerebral oedema which may be a factor in the initial confusion and deterioration of consciousness seen in patients with SIRS, as well as the myocardial dysfunction encountered.[30] There appears to be a massive influx of neutrophils into the damaged tissues. The concentration of potent neutrophil chemoattractants, such as IL8, is also increased in BALF.[31] Additionally, IL18—a proinflammatory cytokine which induces the production of several other cytokines—including interferon γ—and enhances T cell and natural killer cell toxicity as well as neutrophil migration and degranulation. It may also be implicated in acute lung inflammation by increasing neutrophil migration and lung vascular permeability. This cytokine may also be implicated in the pathogenesis of ARDS.[29]

Finally, pathological examination of lung specimens from patients with ARDS in catastrophic APS showed extensive

small vessel thromboses, intra-alveolar haemorrhage, and hyaline membrane formation.[32] Interestingly, in our study, the main pathological finding was non-inflammatory thrombotic microangiopathy, present in 70% of the patients with lung specimens. This may produce an increase in vascular permeability, surfactant deficiency, and intra-alveolar inflammation. It is another probable pathogenic mechanism of ARDS and is closely linked to activation of inflammation and coagulation, which is characterised by fibrin deposition in the pulmonary parenchyma, vasculature, and air spaces. This procoagulant state is tissue factor dependent and is associated with increased elaboration of inflammatory cytokines.[33]

Conclusion

ARDS is the dominant pulmonary manifestation of catastrophic APS. Our study shows that catastrophic APS is a major risk factor for the development of ARDS. The presence of ARDS in the context of an APS makes it necessary to rule out the catastrophic variant of this syndrome.

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APPENDIX

THE CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME REGISTRY PROJECT GROUP

The members of the Catastrophic APS Registry Project Group who contributed to this study are as follows:

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