Pulmonary Hemorrhage in Antiphospholipid Antibody Syndrome

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ABSTRACT. ***Objective.*** To characterize the clinical manifestations of patients with antiphospholipid antibody syndrome (APS) and pulmonary hemorrhage (PH).

Methods. We performed a retrospective, single-center analysis of patients with APS who were followed up from 1980 to 2011. Of these patients, only those who fulfilled the Sydney criteria for APS were included. Patients with APS that manifested with PH were called the PHAPS group. The rest of the patients with APS served as controls. Clinical manifestations were compared between the PHAPS group and controls.

Results. Sixty-three patients fulfilled the criteria for APS. Thirteen experienced PH and were included in the PHAPS group. Seventy-five percent of the patients with PHAPS and 22% of the controls had mitral valve disease ($p = 0.001$). Central nervous system (CNS) involvement (cerebrovascular accident, seizures) was present in 61% and 16% of the patients with PHAPS and controls, respectively ($p = 0.001$). Skin involvement (livedo reticularis, chronic leg ulcers) was present in 54% and 8% of the patients with PHAPS and controls ($p = 0.001$). Pregnancy morbidity occurred in 87.5% and 32.5% of the patients with PHAPS and controls ($p = 0.005$). Ninety-two percent and 83% of the patients with PHAPS had high-titer immunoglobulin γ (IgG) anticardiolipin and $ß_2$-glycoprotein I IgG antibodies compared to 43% and 30% of the controls ($p = 0.002$, $p < 0.001$, respectively).

Conclusion. Patients with PHAPS were more likely than controls to have mitral valve disease, skin disease, CNS involvement, and pregnancy morbidity as well as high-titer APS. PHAPS seems to be a unique subgroup of all patients with APS. (First Release July 1 2012; J Rheumatol 2012;39:1628–31; doi:10.3899/jrheum.120205)

Key Indexing Terms:
ANTIPHOSPHOLIPID ANTIBODY SYNDROME PULMONARY HEMORRHAGE
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Antiphospholipid antibody syndrome (APS) is defined by thrombotic events or obstetric morbidity with the persistence of abnormal levels of antiphospholipid autoantibodies (aPL)[1]. Pulmonary injury in APS is common and may be induced by thrombotic events or through nonthrombotic mechanisms. Pulmonary embolism and infarctions are the most common causes of pulmonary injury in this syndrome[2,3]. Pulmonary hemorrhage (PH) is a known yet underrecognized manifestation of APS. We describe 13 patients with APS who were admitted to our medical center with PH. Our objectives were to present their clinical manifestations, comorbidities, and outcome and to determine whether they have increased comorbidities when compared to patients with APS who did not experience PH.

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MATERIALS AND METHODS

We retrieved from the archives of Hadassah-Hebrew University Medical Center details of all the patients who were diagnosed with APS from 1980 to 2011. Of these patients, only those who fulfilled the Sydney criteria for APS were included[1]. A retrospective analysis enabled us to make the diagnosis of APS in patients who presented from 1980 to 1990. Patients with APS that manifested with PH were called the PHAPS group. The remainder of the patients with APS served as controls. PH and comorbidities were ascertained through review of patient records and diagnostic laboratory findings. Diagnosis of PH was made by the rheumatology team, based on the clinical presentation, lung imaging on chest radiograph, computed tomography (CT), and response to therapy. All patients with PH had a CT scan during at least 1 episode. Five patients underwent bronchoscopy and 2 of them also had open-lung biopsy. PH events occurring during acute episodes of catastrophic APS were excluded (1 patient).

Comorbidities. Mitral valve disease was defined as either mild or moderate to severe mitral regurgitation, mitral thrombosis, or mitral vegetations. Central nervous system (CNS) involvement was defined as cerebrovascular accident (CVA) or seizures. All CVA were demonstrated on head CT or magnetic resonance imaging. Patients with seizures had epileptic activity in electroencephalography and were treated with antiepileptic therapy. Dermatological manifestations were defined as livedo reticularis or chronic leg ulcers. Pulmonary hypertension was defined as right atrium-right ventricle gradient above 30 mm Hg by echocardiography or mean pulmonary artery pressure measured by right heart catheterization. Obstetric morbidity was defined according to the Sydney criteria[1].

Laboratory measures considered abnormal were low C4 (percentage < 20

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mg), low C3 (percentage < 50 mg), high-titer anticardiolipin (aCL) immunoglobulin γ (> 40 IgG phospholipid units/ml), and high-titer ß$_2$-glycoprotein I (GPI) IgG (> 40 units/ml). Radial immunodiffusion was used to measure C3 and C4. ELISA was used to measure aCL and ß$_2$-GPI.

Statistical analysis. Descriptive statistics were used to present the segregation of comorbidities among patients with and those without PH. Frequencies were compared between the groups using Fisher's exact test. Statistical significance was determined when 2-sided p values were < 0.05.

RESULTS

Data for 167 patients who carried the diagnosis of possible or definite APS in their admission charts were retrieved from our archive. We excluded 104 patients for whom we could not prove the diagnosis of APS. These included 55 patients who fulfilled clinical criteria but had 1 or 2 of the following: low-titer aCL or ß$_2$-GPI, only 1 test of aPL, negative aPL, or aPL titer unreported. Thirteen patients fulfilled clinical criteria and were reported to have positive aPL elsewhere, but we could not obtain their aPL values. Thirty-six patients did not fulfill clinical criteria (they had either positive or negative serology).

Thorough review of the charts revealed that only 63 patients met the Sydney criteria and were defined as having APS for our analysis. Fifty patients with APS did not have PH and they served as controls. Thirteen of these patients had PH and APS and were called the PHAPS group (Table 1). In the PHAPS group, 6 patients had primary APS (PAPS) and 7 had secondary APS (SAPS) because of systemic lupus erythematosus (SLE). The total number of PH episodes was 72 (median 3). Twenty-four episodes occurred in the SAPS group (median 2) and 48 in the PAPS group (median 3). All episodes were reported as acute respiratory illness manifesting with dyspnea and cough. Hemoptysis was present in 9 patients. On physical examination, low-grade fever and lung rales were frequently reported. All the patients had transient lung infiltrates on chest radiograph and ground-glass appearance on CT. All the acute episodes resolved within hours to 1–2 days. Bronchoscopy was performed in 5 patients (Patients 1, 7, 8, 9, and 10; Table 1) and demonstrated alveolar hemorrhage. Two patients had open-lung biopsy (Patients 8 and 9; Table 1). The first demonstrated macrophages with hemosiderin without evidence of vasculitis. The second demonstrated thrombi in small and medium size blood vessels and neutrophils in alveolar septa. Six patients had 1 episode in which simultaneous pulmonary embolus and ground-glass appearance were demonstrated in the CT (Patients 5, 6, 9, 10, 11, and 13; Table 1). Fifty-eight of the episodes occurred during anticoagulation therapy. International normalized ratio was in most cases in the therapeutic range (in 1 case it was 5.6 and in 2 cases, 4.9). DLCO and DLCO/alveolar volume (VA) were evaluated in 3 patients between episodes of PH. Patient 4 had DLCO of 83% and 63% and DLCO/VA of 97% and 88% in 2004 and 2008, respectively. Patients 9 and 10 had DLCO of 40% and 66% and DLCO/VA of 102% and 63%.

Nine patients with PHAPS had mitral regurgitation. It was moderate to severe in 7 and mild in 2. Eight patients had thickened mitral valve leaflets, 5 patients had vegetations, and 3 patients had intracardiac thrombosis. Two patients required mitral valve replacement. Nine patients with PHAPS had pulmonary hypertension. Three of these patients had severe pulmonary hypertension (Table 1). Livedo reticularis was present in 3 patients and PHAPS and chronic leg ulcers in 4.

Clinical manifestations in the PHAPS group and controls were compared (Table 2). Seventy-five percent of the patients with PHAPS had mitral valve disease compared to 22% of controls (p = 0.001). Pulmonary hypertension was present in

Table 1. Characteristics of patients with PHAPS.

Patients	1	2	3	4	5	6	7	8	9	10	11	12	13
Age at first PH episode, yrs	50	29	36	36	30	41	29	57	31	34	32	42	26
Age at first thrombotic or obstetric event	29	25	34	22	25	33	19	56	30	33	26	32	26
No. PH episodes	5	1	1	10	2	4	1	3	24	14	1	3	3
Sex	F	F	F	F	F	F	F	M	M	M	M	F	M
SLE	+	+	+	+	+	+	+	–	–	–	–	–	–
Pregnancy morbidity	+	+	+	+	–*	+	+	NA	NA	NA	NA	+	NA
Mitral disease	+	ND	+	+	–	+	+	+	+	–	+	+	–
RA-RV gradient by echo (mm Hg)	43	ND	Normal	37**	31	61	50	51	14	38**	63**	51	60**
CNS morbidity	+	–	+	+	–	+	+	+	–	+	+	–	–
Skin involvement	+	–	–	+	–	+	+	+	+	–	+	–	–
C3 level	56	50	50	50	60	98	49	173	67	40	82	111	147
C4 level	25	10	42	7	27	36	6	42	10	16	11	14	27
aCL IgG	120	652	200	100	238	559	160	69	184	120	200	273	220
aCL IgM	ND	ND	10	ND	5	4	19	12	26	100	52	2	20
ß$_2$-GPI IgG	ND	332	110	83	50	190	80	1.7	104	200	352	176	1428
ß$_2$-GPI IgM	ND	29	13	ND	ND	2	2	0.1	31	190	50	2	16
LAC ratio	5.5	ND	3.3	2	1.8	2.5	3.8	ND	Negative	9.5	Positive	3	1.5

* Patient 5 had infertility and had no pregnancies. ** Mean pulmonary artery pressure measured during right heart catheterization. PHAPS: pulmonary hemorrhage and antiphospholipid antibody syndrome; SLE: systemic lupus erythematosus; RA-RV: right atrium-right ventricle; CNS: central nervous system; aCL: anticardiolipin; IgG: immunoglobulin; IgM:immunoglobulin μ; GPI: glycoprotein I; LAC: lupus anticoagulant; ND: not determined; NA: not applicable.

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Table 2. Clinical and laboratory manifestations in patients with PHAPS and in controls. Except for p values, data are n (%).

	PHAPS, n = 13	Controls, n = 50	p
Sex, women	8 (61)	40 (80)	0.14
Mitral valve disease	9 (75)	11 (22)	0.001
CNS disease	8 (61)	8 (16)	0.001
Pregnancy morbidity*	7 (87.5)	13 (32.5)	0.005
Skin involvement	7 (54)	4 (8)	0.001
Pulmonary hypertension	9 (75)	5 (22)	0.004
Low C3	1 (8)	6 (18)	0.65
Low C4	7 (54)	13 (44)	0.03
Lupus anticoagulant	10 (91)	38 (97)	0.39
High ß$_2$-GPI IgG	10 (83)	8 (30)	< 0.001
High-titer aCL IgG	12 (92)	21 (43)	0.002

* Percentage among women. PHAPS: pulmonary hemorrhage and antiphospholipid antibody syndrome; CNS: central nervous system; GPI: glycoprotein I; aCL: anticardiolipin; IgG: immunoglobulin.

75% of the PHAPS group and in 22% of the controls (p = 0.004). It was measured by echocardiography in 12 patients and was confirmed by cardiac catheterization in 4 (Patients 4, 10, 11, and 13; Table 1). Skin involvement was present in 54% of the patients with PHAPS and in 8% of the controls (p = 0.001). CNS involvement was present in 61% of the patients with PHAPS and in 16% of the controls (p = 0.001). Pregnancy morbidity occurred in 87.5% of the women with PHAPS and in 32.5% of the women in the controls (p = 0.005; Table 2). However, all the women in the PHAPS group except 1 had successful delivery of live babies.

Ninety-two percent of the PHAPS group had high-titer aCL IgG compared to 43% of the controls (p = 0.002). High-titer ß$_2$-GPI IgG was present in 83% of patients with PHAPS and in 30% of controls (p < 0.01). Low C4 and C3 were present in 54% and 8% of patients with PHAPS and in 44% and 18% of controls, respectively (nonsignificant; Table 2). Lupus anticoagulant (LAC) was present in 91% of patients with PHAPS and in 97% of controls (p = 0.39).

Mean age at the first event of PH was 36 years. First episode of PH occurred 0–21 years (mean 5.8 yrs) after the first thrombotic or obstetric event (Table 1). In no patient was PH the first manifestation of APS. Patient 13 had his first episode of PH 1 month after he presented with pulmonary emboli. Patients with PHAPS who had primary APS were mostly men (83%). There were 8 women in the PHAPS group and 7 of them had SLE. In these patients, manifestations of SLE were relatively mild and included oral ulcers, malar rash, pleuritis, and arthralgia. One patient with PHAPS had severe lupus nephritis.

Therapy. We differentiate 2 phases of the treatment: acute and subacute/chronic. In the acute phase, our management included withholding anticoagulation, supportive care, and steroids in most cases. Steroids were given in 47 episodes (65%) and were tapered quickly as soon as resolution of symptoms occurred. Prednisone was given in 9 episodes (15–55 mg per day). Intravenous methylprednisolone was given in 14 episodes (60 mg to 1 g per day). Intravenous hydrocortisone was given in 5 episodes (100 mg × 3 per day). In 19 episodes, the dose was not mentioned in the medical file. In 25 episodes, which were less severe, supportive management was given successfully without the use of steroids. Three patients had multiple recurrent attacks (10–24 admissions per patient) and were considered as being in the subacute/chronic phase. They were treated with longterm preventive therapy, which included anticoagulation, azathioprine, cyclophosphamide, intravenous Ig, plasmapheresis, and rituximab (Patients 4, 9, and 10; Table 1)[4]. Nine patients had pulmonary hypertension. Of these, 1 patient was treated with endothelin receptor antagonist and 2 with phosphodiesterase inhibitor. Two patients required pulmonary thrombectomy because of chronic pulmonary emboli (Patients 11 and 13; Table 1).

Outcome. Mean followup was 9 years (range 3–23 yrs). Three patients died. Patient 1 died as a result of massive pulmonary hemorrhage complicated by pulmonary infection. Patient 8 died from endocarditis and sepsis. Patient 4 developed cognitive deterioration because of multiple infarcts resulting from shower of emboli. She died from multiorgan failure, multiple infarcts, and massive pulmonary hemorrhage. Patient 9 developed mild pulmonary fibrosis.

DISCUSSION

We compared clinical manifestations and comorbidity in the patients with PHAPS to 50 patients with APS that did not manifest with PH. Patients with PHAPS had significantly more mitral valve disease, CNS involvement, skin involvement, pulmonary hypertension, obstetric morbidity, and high-titer aCL IgG and ß$_2$-GPI IgG than patients with regular APS. Patients with PHAPS who had primary APS were mostly men (M:F ratio 5:1), whereas all patients with PHAPS who had SLE were women (Table 1). In a review by Deane and West, out of 17 patients with primary APS and PH, 14 were men[2,5,6,7,8,9,10]. PH occurred on average 5.8 years after the first thrombotic or obstetric manifestation and was therefore a relatively late manifestation of APS in most patients (Table 1). In agreement, reports have found that the majority of patients with primary APS and PH had suffered previous thrombotic complications[5,6,7,8,9,10].

It has been suggested that aPL play a major role in the pathogenesis of PH in APS. In a review of 17 cases with primary APS and PH, all the reported cases had either positive LAC medium-titer or high-titer aCL, usually the IgG isotype[2,11]. These authors have suggested that aPL could induce upregulation of endothelial cell adhesion molecules with subsequent neutrophil recruitment and migration into the alveolar septa, with resulting hemorrhage[2]. An interaction between aPL and endothelin-1 may also be the cause for pulmonary hypertension in APS[11]. Therefore, the high prevalence of pulmonary hypertension in the patients with PHAPS could be

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related not only to the selection bias of very difficult patients with comorbidity but also to the high titer of aPL found in this group.

A few major drawbacks should be emphasized. Because this was a retrospective study, we based our analysis on medical files retrieved from our hospital's database. In some of the cases, we did not have access to laboratory tests that were done elsewhere. We therefore might have overlooked valuable laboratory information. For example, among the control group, echocardiography was done in only 27 patients. The rest of the patients did not have signs or symptoms suggesting cardiac disease or pulmonary hypertension and therefore echocardiography was not performed. Pulmonary hypertension was confirmed by cardiac catheterization in 4 patients. In the control group, C3 was measured in 32 patients, C4 in 30 patients, and LAC in 39 patients.

Another shortcoming of the study is that only 5 patients with PHAPS underwent bronchoscopy. An alternative possible diagnosis was pulmonary emboli, which were ruled out in most cases by CT angiography. In 6 episodes that occurred in 6 different patients, PH and pulmonary emboli were demonstrated on CT simultaneously. Another possible diagnosis was pulmonary edema, especially in patients with severe mitral regurgitation. Because orthopnea, neck vein congestion, or leg edema were not demonstrated in these patients, this diagnosis was excluded in most cases. Nevertheless, in some patients with mitral disease it is difficult to discriminate between the immunological component (capillaritis) and the cardiac component (hemoptysis and congestion due to mitral regurgitation). Because pulmonary congestion could not be ruled out in some cases, diuretics were given in these episodes together with steroids. Pulmonary infection was ruled out in some of the cases by negative cultures taken during bronchoscopy. In all cases, PH episodes were short and resolved within hours to 1–2 days. This rapid resolution is suggestive of PH and not of infection or adult respiratory distress syndrome.

The prevalence of PH in our patients was much higher than that shown in the European phospholipid cohort (< 1%)[12]. This may be due to a selection bias of very difficult patients. Our center is a referral center for difficult patients with SLE, APS, and connective tissue diseases. Patients are referred to us from primary care physicians, as well as from rheumatologists. Also, the database that we searched to find patients with APS consists mainly of admitted patients. In the last few years, data from outpatient clinics were added. Ninety-five percent of our patients with APS (60 patients) were admitted at least once during the followup period. Therefore, the prevalence of PH in our patients with APS was high, and it did not represent the prevalence of PH in outpatient clinics.

Treatment recommendations. In the acute phase, our management included withholding anticoagulation and administration of steroids in most cases. In 25 episodes that were less severe, supportive management was given successfully without the use of steroids.

Patients with APS and PH are more likely to have mitral valve disease, CNS involvement, skin involvement, pulmonary hypertension, and high-titer aPL than regular patients with APS.

Patients with PHAPS who have primary APS are invariably men, whereas patients with PHAPS who have SLE are invariably women. The PHAPS group of patients is a unique subgroup of patients with APS, with a distinct clinical and laboratory presentation that distinguishes them from regular patients with APS. Future studies are needed to further assess the role of high-titer aPL in PHAPS.

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