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Clinical and prognostic significance of antinuclear antibodies in primary antiphospholipid syndrome : French multicenter retrospective study

Laure Ricard (1) ; Charlotte Laurent (1) ; Matthias Papo (2) ; Sophie Deriaz (3) ; Jennifer Catano (1) ; Sonia Alamowitch (4) ; Gilles Kayem (5) ; François Chasset (6) ; Claire De Moreuil (7) ; Jean Jacques Boffa (8) ; Grigorios Gerotziapas (9,10); Ismail Elalamy (9,11) ; Marie Bornes (10) ; François Maillot (3) ; Alexandra Audemard-Verger (3) ; Virginie Planche (12) ; Eric Ballot (13) ; Olivier Fain (1) ; Arsène Mekinian (1)

¹Sorbonne Université, AP-HP, Hôpital Saint Antoine, service de médecine interne et Inflammation-Immunopathology-Biotherapy Department (DMU i3), F-75012, Paris, France

²Médecine interne institut e3m, Groupe Hospitalier Pitié Salpêtrière, Paris; France ;³Médecine

interne, CHRU Hôpitaux de Tours, Tours; France ;⁴Service de neurologie et d'urgences

neurovasculaires, Hôpital Saint-Antoine, Paris; France ; ⁵Obstétrique, Hôpital Armand-

Trousseau AP-HP, Paris; France ; ⁶ Sorbonne Université, Faculté de médecine, Service de Dermatologie, Hôpital Tenon AP-HP, Paris; France

⁷Service de médecine interne, C .H.U. Brest ; France ; ⁸Néphrologie, Hôpital Tenon, Paris;

⁹Sorbonne Université, INSERM UMR-S938 Cancer Biology and Therapeutics, Research Group "Cancer-Hemostasis-Angiogenesis" CRSA, Institut Universitaire de Cancérologie, Paris, France

¹⁰Department of Thrombosis and Haemostasis, Service d'Hématologie Biologique Hôpital Tenon, Hôpitaux Universitaires de l'Est Parisien, Assistance Publique Hôpitaux de Paris, Faculté de Médecine Sorbonne Université, Paris, France

¹¹I M Sechenov First Moscow State Medical University, Department of Obstetrics and Gynecology Russia

¹²Hemostase, Hôpital Saint-Antoine AP-HP, Paris;¹³Immunologie biologique, Hôpital Saint-Antoine, Paris

Correspondence and reprint request to: Arsène Mekinian, ¹AP-HP, Hôpital Saint-Antoine, service de médecine interne and Inflammation-Immunopathology-Biotherapy Department (DHU i2B), Sorbonne Universités, F-75012, Paris, France

Mail : arsene.mekinian@aphp.fr

Abstract:

Introduction: The antiphospholipid syndrome (APS) (1) is defined by the development of vascular thrombosis, or pregnancy morbidity in the presence of persistent antiphospholipid antibodies (aPL). Antinuclear antibodies (ANA) can be detected in primary APS patients without any clinical systemic autoimmune disease. The presence of ANA antibodies could confer a specific phenotype in primary APS.

Objective: To evaluate the characteristics of APS patients with antinuclear antibodies without other autoimmune disease (ANA positive APS patients) in comparison with primary APS without ANA or secondary APS patients with associated systemic lupus erythematosus (SLE)

Methods: Clinical and biologic data from 195 APS were retrospectively collected and patients were classified as primary APS with positive ANA (ANA-positive APS), primary APS without any ANA (ANA-negative APS), and SLE-associated APS (SLE-APS).

Results: Forty patients (21%) were classified into ANA-positive APS group, 77 (39%) in ANA-negative APS and 78 (40%) in SLE-APS. In ANA-positive APS patients, 20 patients (51%) had arterial thrombosis, 14 (41%) had venous thrombosis and 19% had obstetrical complications. There was no difference between the three groups for the frequency of thrombotic manifestations and obstetrical complications. ANA-positive APS patients had more non-criteria manifestations than ANA-negative APS (48% versus 25%; $p \leq 0.01$) ANA-positive APS had more triple aPL positivity (59% versus 18% ; $p < 0.001$) and more thrombosis and obstetrical recurrences (63% versus 36% ; $p < 0.01$) in comparison with ANA-negative APS patients.

ANA-positive APS had more triple aPL positivity than SLE-APS patients (54% versus 33% ; $p < 0.05$). ANA-positive APS and SLE-APS patients had similar clinical manifestations, and recurrences. Despite a limited follow-up (28 months (11-50)) none of the ANA-positive APS develop SLE. Antiplatelet and anticoagulant therapies were similar for the three groups. SLE-APS patients received more immunomodulatory therapies.

Conclusion:

ANA positivity in patients with APS enables to individualize a subset of patients with a more severe phenotype. Whereas the ANA positivity does not seem to be associated with the risk to develop SLE, prospective studies with a longer follow-up are necessary, in particular to evaluate the effect of additional therapies in this subset of APS.

Key words: antiphospholipid syndrome, antiphospholipid antibodies, antinuclear antibodies, outcome

1.Introduction

The antiphospholipid syndrome (1) is defined by vascular thrombosis and/or pregnancy morbidity associated to persistent antiphospholipid antibodies (1). APS can be primary or in association with other autoimmune diseases (associated APS), especially systemic lupus erythematosus (SLE) (2). Even if APL are frequent during SLE, the progression from primary APS to SLE occurs only in 4 to 10% of patients after a ten-year follow-up (3). Otherwise, antinuclear antibodies (ANA) can be detected in primary APS patients without any clinical SLE and are sometimes called “lupus-like” APS (3-5). The presence of ANA could be associated with more pregnancy morbidity and recurrence thrombosis even in the absence of any well-defined associated autoimmune disease (6-8). However, data about the impact of ANA positivity in primary APS remain scarce and clinical phenotype, outcomes and relapses in these patients remain to be determined.

The aims of this study were to evaluate characteristics, outcomes, and management of primary APS patients with positive ANA without any clinical autoimmune disease (ANA-positive APS) in comparison with primary APS without ANA (ANA-negative APS) and SLE-associated APS (SLE-APS).

2.Methods

Data about patients with APS between January 2015 and June 2019 from Saint Antoine, Tenon University Hospitals (Paris) and Brest University Hospital, Tours University Hospital were retrospectively collected. Inclusion criteria were APS (Sydney criteria), without any other systemic auto-immune disease than SLE associated systemic disease (9). APS patients were then classified into three groups: primary APS with positive antinuclear antibodies without any associated autoimmune disease (ANA-positive APS) and which not fulfilled SLE ACR/EULAR classification criteria; primary APS without antinuclear antibodies (ANA-negative APS) and APS patients with SLE (SLE-APS).

Clinical and laboratory data were retrospectively collected as follow: age, sex, cardiovascular risk factors (arterial hypertension, diabetes, overweight (BMI>25) (**Table S1 and S2**, See the supplementary material associated with this article online) , tobacco use (active smoking was defined as regular cigarette smoking (duration >6 months) , hypercholesterolemia), associated SLE (10), types (arterial or venous) and site of thrombosis, type of pregnancy adverse obstetrical events, non-criteria manifestations (such as immune thrombocytopenia, multiple sclerosis like disease, Libman Sacks endocarditis, APS nephropathy, etc.). Treatments were

recorded as follows: steroids, hydroxychloroquine, anticoagulants, antiplatelets, and duration of each therapy.

APS relapse was defined as a new arterial or venous thrombosis or obstetrical adverse event occurring after the diagnosis of APS.

ANA were detected by indirect immunofluorescence. ANA test was considered to be positive when titers were superior or equal to the 1/80 dilution (10).

Lupus anticoagulant (LA) was detected using two tests: diluted Russell's viper venom (dRVVT) and diluted activated partial thromboplastin time in accordance to ISTH recommendations. Anticardiolipin (ACL) antibodies IgG/IgM and anti- β 2GP1 antibodies IgG/IgM were measured by standard ELISA. ACL positivity was defined as a titer superior to 40 UGPL for IgG and 40 UMPL for IgM and anti- β 2GP1 (IgM/IgG) as a value above 99th percentile. Repeated laboratory testing had to be at least 12 weeks apart. Triple positivity was defined by the association of ACL (IgG and/or IgM), anti- β 2GP1(IgG and/or IgM) and LA test.

3. Statistical analysis

Variables with quantitative distributions were tested by Shapiro-Wilk test. Data were expressed according to their distributions as medians with ranges, as means with standard deviation and numbers with their frequencies. The Student t-test or the Mann-Whitney test was used to compare quantitative variables according to the distribution. Qualitative variables were compared by the Chi-2 test or the Fisher's exact test as appropriate. Relapses were compared by using log-rank test and expressed with Kaplan-Meier curves. A p value <0.05 was considered as statistically significative. All analyses were performed using JMP-SAS and GraphPad Prism softwares.

4 Results

4.1 Patients' characteristics

One hundred and ninety-five APS patients were included in the study : 40 patients (21%) with ANA-positive APS, 77 patients (39%) with ANA-negative APS and 78 patients (40%) with SLE-APS.

Among the 117 primary APS patients, the median age at APS diagnosis was at 47 years (IQR [36-58]), with 90 females (77%). Primary APS was purely thrombotic (n=66; 56%), purely obstetrical (n=22; 19%) or mixed (n=29; 19%). 49 patients (43%) had arterial thrombosis and 41 patients (40%) had veinous thrombosis. Triple positivity was noted in 37 cases (32%). Catastrophic antiphospholipid syndrome occurred in three patients with primary APS.

4.2 Comparison of ANA-positive APS with ANA-negative APS

ANA-positive APS (n=40) had a median age at 46 years (IQR[36-55]) with female sex in 85% (**Table 1**). APS thrombotic features were arterial thrombosis in twenty cases (51%) and venous thrombosis in fourteen cases (41%). Adverse obstetrical events were noted in 19 cases (51%), with recurrent miscarriages in five cases, intrauterine deaths in nine cases, preeclampsia and placental insufficiency in seven cases. Non-criteria APS features were noted in nineteen cases (51%): autoimmune cytopenia in eight cases (21%) (thrombocytopenia in six cases and hemolytic anemia in two cases), APS nephropathy in two cases (5%), neurological involvement in five cases (multiple sclerosis like seizure, chorea or migraine), livedo reticularis (n=1) and Libman Sacks endocarditis (n=1). Antiphospholipid antibodies (aPL) were single-positive in seven cases, double- and triple-positive aPL in ten and twenty-three (58%) cases, respectively. The most frequent isolated antibody was lupus anticoagulant (n=27; 87%). Median ANA titers were at 1/320e [IQR 1/320-1/640], 39 (98%) patients have ANA titers \geq 160e and anti-DNA antibodies were $>$ 20 UI in 3 cases (8%).

In comparison to ANA-negative APS, ANA-positive APS patients had significantly more frequent non-criteria features (48% versus 25%; $p \leq 0.01$), whereas other APS features and demographic data were not significantly different (**Table 1**). ANA-positive APS had more anticardiolipin IgG positivity (54% versus 33%; $p < 0.05$), more anti-B2GP1 IgG positivity (54% versus 34%; $p < 0.05$), and more lupus anticoagulant (87% versus 63%, $p < 0.05$), with higher prevalence of triple positivity than ANA-negative APS (59% versus 18%; $p < 0.001$) patients (**Table 1**).

Whereas there was no difference in frequencies of anticoagulant and antiplatelet therapies, ANA-positive APS patients received significantly more corticosteroids (32% versus 9%; $p < 0.01$) and hydroxychloroquine (38% versus 17%; $p \leq 0.01$) than ANA-negative APS. ANA-positive APS patients presented more relapses (63% versus 36%, $p < 0.01$) whereas both groups had a similar follow-up (28 months (11-50) versus 18 months (7-39); non-significant). During the follow-up no patient from ANA-positive APS group declared an associated SLE (ACR/EULAR criteria)(10).

4.3 Comparison of ANA-positive primary APS patients with SLE-associated APS

Clinical and laboratory data of primary ANA-positive APS (n=40) and SLE-APS (n=78) are described in **Table 2**. There was no difference in demographic data, nor in frequency of APS

features. ANA-positive APS patients had significantly more frequent anticardiolipin antibodies positivity (54% versus 33%, $p < 0.05$), lupus anticoagulant (87% versus 67%; $p \leq 0.05$) and triple-positivity than SLE-APS patients (59% vs 32%; $p < 0.01$).

Whereas there was no difference for the frequencies of antiplatelet and anticoagulant therapies, ANA-positive APS patients received less corticosteroids (32% versus 90%; $p < 0.001$), hydroxychloroquine (38% versus 97%, $p < 0.001$) and other immunomodulatory drugs (28% versus 60%; $p \leq 0.01$). There was no difference in the relapse rates between the groups, and ANA-positive APS had a significantly increased mortality (13% vs 2%; $p < 0.05$)(**Table 2**).

4.4 Relapses

Relapse-free survival rate in ANA-positive APS patients was significantly lower than in patients with ANA-negative APS (Hazard Ratio 1.88 [95% CI 1.01-3.48] $p < 0.05$) (**Figure 1**), but was not significantly different from SLE-APS patients (non-significant). In ANA-positive APS patients, there was no difference of relapse-free survival in patients who received hydroxychloroquine and those without hydroxychloroquine (Hazard Ratio 2.14 [95% CI 0.84-5.45] ; non-significant)(**Figure 2**).

5 Discussion

In this study, we raise several important messages about the clinical value of ANA positivity in patients with primary APS. First, the presence of ANA seems to confer a particular clinical phenotype, characterized by more prevalent non-criteria features (notably cytopenia), whereas the usual APS features seem to be similar to those without ANA antibodies. Second, the presence of ANA is associated with increased frequencies of triple-positive APS, which are known to have a particular outcome and increased risk of relapses. Indeed, ANA-positive APS have a significantly increased relapse rates in comparison with ANA-negative APS patients, whereas similar frequencies of antithrombotic therapies have been used in these patients. Last, the use of hydroxychloroquine was not associated in our study with a better relapse-free survival, and studies are necessary to determine the better treatment strategies in ANA-positive APS. Despite increased non-criteria features, ANA and triple positivity, none of ANA-positive APS developed a SLE during the follow-up time.

ANA positivity was associated with more prevalent non-criteria features (4, 11). In Cervera *et al* study, SLE-APS had more livedo and more thrombocytopenia than primary APS (4). Even

if the non-criteria are not specifically observed in APS patients, studies suggested that their presence conferred a particular « high risk » profile for future thrombotic events (12). Some clinical extra-criteria manifestations like livedo reticularis and migraine have been shown to be associated with increased risk of thrombosis. Non-criteria manifestations could also correlate with APS prognosis and seem to confer a more risk of active persistent disease (13, 14).

The presence of ANA was associated in our study with increased frequencies of triple-positive aPL, which are known to have a particular outcome and increased risk of relapses (15-17). The frequencies of triple positive aPL were more important in our patients than usually reported on APS patients, with 10-30% of triple positive according to the APS subtypes. Triple-positivity in asymptomatic patients is associated with first thrombosis and triple positivity in APS patients is associated with recurrent thrombosis (18, 19). Indeed, our ANA-positive APS had a significantly increased relapse rates in comparison to ANA-negative primary APS patients, whereas similar frequencies of antithrombotic therapies have been used in these patients.

The increased risk of thrombosis relapses questions the value of additional therapies in this subset of APS patients. Several studies (20, 21) raised the potential benefit of hydroxychloroquine for the obstetrical and thrombotic APS. Studies suggested that hydroxychloroquine could be effective to prevent thrombosis in patients with SLE and persistently positive aPL antibodies (22, 23). In obstetrical refractory APS, a retrospective European study showed a potential benefit of hydroxychloroquine to reduce the adverse obstetrical outcome (20). In thrombotic APS, adjunction of hydroxychloroquine to vitamin K antagonists reduced the recurrence of thrombosis in a small uncontrolled study (21). Despite these data, we did not find any benefit of hydroxychloroquine in ANA-positive APS, even the low number of patients could limit the definite conclusion from this preliminary report.

Conflicts of interest and findings: none

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Online Material. Supplementary data

Supplementary data (Table S1-S2) associated with this article can be found in the online version at ...

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Figure 1 Comparison of relapse-free survival between ANA-positive APS , ANA-negative APS and SLE-APS patients_ (ANA-positive APS vs ANA-negative APS $p < 0.05$; SLE-APS vs ANA-positive APS $p = 0.86$)

Figure 2. Comparison of relapse-free survival between APS ANA+ patients treated with hydroxychloroquine and those with no hydroxychloroquine

Table 1. Primary APS patients with antinuclear antibodies (ANA-positive APS) (n=40) and those without ANA positivity (ANA-negative APS) (n=77).

Parameters	ANA-positive APS (n=40)	ANA-negative APS (n=77)
<i>General characteristics</i>		
Age at diagnostic (years)	46.5 (36-55)	46.5 (36-55)
Female gender (%)	34/40 (85.0)	57/77 (74.0)
<i>APS features</i>		
Arterial thrombosis (%)	20/39 (51.3)	29/75 (38.7)
Arterial ischemic stroke (%)	11/26 (42.3)	12/38 (31.6)
Myocardial infarction (%)	4/26 (15.4)	4/38 (10.5)
Venous thrombosis (%)	14/34 (41.2)	27/69 (39.1)
Pulmonary embolism (%)	5/34 (14.7)	13/40 (18.6)
Obstetrical adverse events (%)	19/34 (56)	30/57 (53)
« Non criteria » %	19/40 (47.5)	19/77 (24.7)*
APS nephropathy (%)	2/39 (5.1)	1/77 (1.3)
Livedo reticularis (%)	1/39 (2.5)	1/77 (1.3)
Thrombocytopenia/ autoimmune hemolytic anemia (%)	8/39 (20.5)	6/77 (7.8)*
Catastrophic APS (%)	2/39 (5.1)	1/77 (1.3)
<i>Laboratory data</i>		
IgG anti-cardiolipin (%)	19/35 (54.3)	21/63 (33.3)*
IgG anti-β2GP1 (%)	21/39 (53.8)	23/68 (33.8)*
Lupus anticoagulant (%)	27/31 (87.1)	32/51 (62.8)*
Triple positivity (%)	23/39 (59.0)	14/76 (18.4)**
<i>Treatment</i>		
Anticoagulant therapy	25/35 (71.4)	45/71 (63.4)
Antiagregant therapy	18/34 (52.9)	31/70 (44.3)
Hydroxychloroquine (%)	14/37 (37.8)	12/72 (16.7)*
Corticosteroids (%)	11/34 (32.4)	6/68 (8.9)***
Immunomodulatory agents (%)	11/39 (28.2)	11/76 (14.5)
<i>Outcome</i>		

Follow up (months)	66 (21.5-811)	43 (13-227)
Relapse (%)	24/38 (63.16)	26/73 (35.6)***
Death (%)	4/30 (13.3)	2/55 (3.6)

*** p <0.05 ; ** p < 0.001 ; p<0.01**

Parameters	SLE-APS(n=78)	ANA-positive APS (n=40)
<i>General characteristics</i>		
Age at diagnostic (years)	42.5 (28-49)	46.5 (36-55)
Female gender (%)	70/78 (89.7)	34/40 (85.0)
<i>APS features</i>		
Arterial thrombosis (%)	30/77 (39.0)	20/39 (51.3)
Arterial ischemic stroke (%)	20/45 (44.4)	11/26 (42.31)
Myocardial infarction (%)	2/45 (4.4)	4/26 (15.4)
Venous thrombosis (%)	28/65 (43.1)	14/34 (41.2)
Pulmonary embolism (%)	14/66 (21.2)	5/34 (14.7)
Obstetric complications (%)	36/70 (51.4)	19/34 (55.8)
« Non criteria » %	40/78 (51.3)	19/40 (47.5)
Renal manifestations (%)	3/77 (3.9)	2/39 (5.1)
Livedo/ skin ulceration/necrosis (%)	10/77 (13.0)	1/39 (2.5)
Cardiac valve abnormalities (%)	7/77 (9.1)	1/39 (2.5)
Thrombocytopenia/ autoimmune haemolysis (%)	15/76 (19.7)	8/39 (20.5)
Catastrophic APS (%)	2/77 (2.6)	2/39 (5.1)
<i>Laboratory data</i>		
Anti-dsDNA antibodies (%)	41/60 (68.3)	3/30 (10%)**
IgG anti-cardiolipin > 40 (%)	21/63 (33.3)	19/35 (54.3)*
IgG anti-β2GP1 (%)	34/74 (46.0)	21/39 (53.8)
Lupus anticoagulant (%)	33/49 (67.4)	27/31 (87.1)*
Triple positivity (%)	24/74 (32.4)	23/39 (59.0)***
<i>Treatment</i>		
Anticoagulant therapy	58/73 (79.5)	25/35 (71.4)
Antiagregant therapy	36/71 (50.7)	18/34 (52.9)
Hydroxychloroquine (%)	73/75 (97.3)	14/37 (37.8)**
Corticosteroids (%)	54/60 (90.0)	11/34 (32.4)**

Immunomodulatory agents (%)	46/77 (59.8)	11/39 (28.2)***
<i>Outcome</i>		
Follow up (months)	159 (55-333)	66 (21.5-811)
Relapse (%)	46/74 (62.1)	24/38 (63.16)
Death (%)	1/56 (1.8)	4/30 (13.3)*

*** p <0.05 ; ** p < 0.001 ; p<0.01**

Table 2. Primary APS patients with antinuclear antibodies (ANA-positive APS) (n=40) and SLE-associated APS (SLE-APS) (n=78)



