Primary antiphospholipid syndrome and hepatitis B and C infections

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ABSTRACT

Objective: The objective of the present study was to evaluate the prevalence of hepatitis B and C serology in patients with primary antiphospholipid syndrome (APS). **Methods:** This is a transversal study with 47 patients with primary APS (Sapporo's criteria). Demographic and clinical data, medications, and hepatitis B and C serologies, with PCR in positive cases, were evaluated. **Results:** The study population had a mean age of 38±11 years, 80.8% were females, and 68% Caucasian. The mean duration of the disease was 67 ± 61 months (ranging from 1 to 240 months). Arterial events were seen in 61.7% of the patients, venous events in 51%, and obstetric events in 38.3%. Five (10.6%) patients with primary APS had positive serologies for hepatitis B or C. Three of them were positive for anti-HBs, and only one was anti-HBc positive; the other two patients were positive for hepatitis C. Qualitative PCR did not detect hepatitis C viral RNA in neither of the positive patients. **Conclusion:** A small percentage of patients with primary APS had positive serology for hepatitis B and C, and all represented cases post-vaccine or serology scar.

Keywords: antiphospholipid syndrome, primary antiphospholipid syndrome, seroprevalence, hepatitis, hepatitis B, hepatitis C.

INTRODUCTION

Primary antiphospholipid syndrome is an acquired autoimmune thrombophilia characterized by the presence of vascular thrombosis and/or obstetric events, associated or not with thrombocytopenia, in the presence of moderate and persistent levels of antiphospholipid antibodies.[1]

Antiphospholipid antibodies have been detected in patients with infectious diseases and associated with the use of several medications.[2] Infectious agents have been implicated in the pathophysiology of APS, especially the catastrophic type.[3] Although the role of hepatitis B and C virus in APS has not been thoroughly studied, several studies have demonstrated the association of those viral agents with several autoimmune disorders, such as Sjögren's syndrome,[4] rheumatoid arthritis,[5] and systemic erythematosus lupus.[6] On the other hand, even though the presence of antiphospholipid antibodies is common in chronic hepatitis C, this association is seldom related with thrombotic phenomena.

Only one study describing the presence of hepatitis C in patients with APS was found in the literature.[7] Thus, the objective of the present study was to evaluate the frequency of seropositivity for hepatitis B and C in patients with primary APS.

PATIENTS AND METHODS

Forty-seven consecutive patients of both genders, 18 years or older, with the diagnosis of primary APS, according to Sapporo's criteria, were included in this study.[8] All patients had primary APS, *i.e.*, not associated with other autoimmune diseases. Those patients are followed at the APS outpatient clinic of the Rheumatology Department of the Hospital das Clínicas of the Medical School of Universidade de São Paulo.

Data used in this study was collected both during the evaluation visit and reviewing medical records. Clinical arterial and venous events were confirmed by imaging methods, such

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as Doppler, ventilation-perfusion scintigraphy, CT, MRI, arteriography, angiotomography, and angio-MRI. The presence of anticardiolipin antibodies (aCL) and lupus anticoagulant (LA) was confirmed at the time of the clinical diagnosis of the syndrome. A venous blood sample was collected for laboratorial tests. The samples used in this study were obtained from a serum library of a previous study, according to the approval of the previous study, number 240/07, by the Ethics on Research Committee.

Diagnostic tests: Commercial kits to detect antibodies against hepatitis C virus (Vitros, USA), were used for all serologies by amplified chemiluminescence. Polymerase chain reaction (PCR) (Roche) was used for detection of the hepatitis C viral RNA in positive cases. *Serology for hepatitis B* (total anti-HBc, AgHBs, anti-HBs, AgHBe, anti-HBe, and anti-HBc IgM) was done by microparticle immunoenzyme assay (MEIA, AxSym, Illinois, USA). Total anti-HBc and anti-HBs, the latter to detect vaccinated patients, were used for the initial screening.

Statistical analysis: Data are presented as means, standard deviation, or percentage. Descriptive analysis was used to present the data.

RESULTS

Patients included in this study had a mean age of 38.0 ± 11 years, 68% were Caucasian, and 80.8% females. The mean disease duration was 67 ± 61 months (Table 1).

Arterial thrombotic events were seen in 61.7% of the cases, venous events in 51%, and obstetric events in 38.3%. Strokes were seen in 42.5% of the patients, ischemia of the extremities in 12.7%, and deep venous thrombosis in 60%.

As for antiphospholipid antibodies, 59.6% of the patients were positive for aCL IgG with a median of 20 (from 20 to 120) GPL, and 53.1% aCL IgM positive with a mean of 20 (from 20 to 120) MPL. Thirty-eight patients (80.8%) were LA positive.

Approximately 80% of the patients were using oral anticoagulant, and 34% were taking acetyl salicylic acid. Ten patients (21.2%) were taking chloroquine diphosphate.

Five patients were positive for hepatitis B or C. Two patients (4.2%) had antibodies for the hepatitis C virus, but their PCR were negative in three separate occasions. Both were asymptomatic for gastrointestinal involvement, and their liver enzymes were normal. Cryoglobulins were negative in those patients. Both patients were females, and one of them had a history of porto-splenic thrombosis and secondary esophageal varices with normal liver function tests (Table 2).

Total-anti-HBs was positive in 6.4% (3/47) of the patients. One of them was also positive for total anti-HBc, demonstrating prior exposure to the virus, and the other two had been vaccinated (Table 2).

DISCUSSION

The present study demonstrated a low frequency of positive hepatitis B and C serologies in patients with APS.

This study included a restrict group of patients with primary APS who fulfilled the international classification criteria for this thrombophilia,[8] excluding secondary APS, since the association of systemic lupus erythematosus and rheumatoid arthritis with hepatitis C has already been demonstrated.[5]

Hepatitis C is considered one of the greatest viral epidemics in the world in the last two decades, with an increasing tendency for the description of autoimmune phenomena associated with this disorder. Several studies have demonstrated that anticardiolipin antibodies can be present in 3.3 to 46% of the patients with hepatitis C infection.[9-11] In the study by Zachou *et al.*, who evaluated 174 patients with hepatitis C, 50 with hepatitis B, and 267 healthy controls, the authors detected aCL IgG in 21.3% of the patients with hepatitis C and in 14% of patients with hepatitis B. Patients did not have clinical manifestations of the antiphospholipid syndrome.[12] The presence of antiphospholipid antibodies in hepatitis B and C viral infections raises the possibility of a common mechanism leading to their production. Induction of neoantigens by chronic hepatitis due to the rupture of the membrane of hepatocytes is one possibility. The presence

Table 1
Demographic and clinical data and positivity for antiphospholipid antibodies of 47 patients with primary APS

	n = 47
Mean age, (range), years	38.0 ± 11 (18-60)
Females, n (%)	38 (80.8)
Caucasian, n (%)	32 (68.0)
Duration of the disease, (range), months	67 ± 61 (1-240)
Arterial events, n (%)	29 (61.7)
Venous events, n (%)	24 (51.0)
Obstetric events, n (%)	18 (38.3)
Positivity for aCL IgG, n (%)	28 (59.6)
Positivity for aCL IgM, n (%)	25 (53.1)
Positivity for LA, n (%)	38 (80.8)

Data presented as mean ± standard deviation or percentage; aCL: anticardiolipin antibody; LA: lupus anticoagulant.

Table 2
Summary of the demographic, clinical, and laboratorial data of five patients with primary APS and positive viral serologies

Patients	Age (years)	Gender	Virus	Antibody	RNA-PCR	Duration of APS (months)	Clinical manifestations	LA	aCL	Cryoglobulins	Liver changes (clinical and laboratorial)
1	34	F	C	Anti-HCV	N	24	DVT, *livedo reticularis*	+	+	N	No
2	37	F	C	Anti-HCV	N	10	PTE, spontaneous abortion, angina	N	+	N	No
3	18	M	B	Anti-HBs	-	11	DVT	+	N	N	No
4	60	M	B	Anti-HBs	-	60	Strokes, thrombocytopenia	+	+	N	No
5	57	F	B	Anti-HBs, total anti-HBc	-	120	Strokes, DVT, PTE, spontaneous abortion	N	+		No

F = Female; M = Male; DVT = Deep Venous Thrombosis; PTE = Pulmonary Thromboembolism; aCL = Anticardiolipin Antibodies; LA = Lupus Anticoagulant.

of aCL antibodies could result from the recognition of those neoantigens by the immune system. Induction of apoptosis by hepatotropic virus leading to a redistribution of membrane phospholipids and their increased expression on the surface of apoptotic cells, resulting in the production of antiphospholipid antibodies, would be another possibility.[11,13,14]

In an interesting study, the authors evaluated the Hispanic-American data base of autoimmune manifestations in chronic viral diseases (HISPAMEC) and described 45 patients with chronic hepatitis C presenting a spectrum of APS clinical manifestations, as well as antiphospholipid antibodies.[15]

In a study with 40 patients with hepatitis B, 17 (42%) of the patients had aCL, and the IgM and IgA isotypes were more frequent.[16] It has been proposed that mechanisms of molecular mimetism between infectious agents and the beta-2-glycoprotein I molecule, a cofactor of antiphospholipid antibodies, are capable of inducing the formation of anti-beta-2-glycoprotein I antibodies.[17] Besides, cellular receptors for lipid components of the hepatitis B virus envelope include anexin V and beta-2-glycoprotein I, which could be the antigens for the production of antiphospholipid antibodies.[16]

In a classical study, Prieto et al. investigated the presence of aCL antibodies in 100 patients with chronic hepatitis C and compared it with a control group of 52 healthy individuals and 73 patients with thrombotic conditions (36 aCL positive). The authors observed a higher incidence of aCL antibodies in the hepatitis C group (22%) than in the healthy population and, more interestingly, they found, through logistic regression, that the presence of thrombocytopenia, portal hypertension, and history of thrombosis in patients with hepatitis C (HCV) was related to the presence of aCL antibodies.[18] One of our patients with positive HCV serology also had portal hypertension, although the disease hepatitis C was not confirmed in any of our patients; this finding seems to implicate common pathophysiological mechanisms.

On the other hand, studies on the frequency of infection with the hepatitis C virus in patients with APS are not common. On a study by Cervera *et al.* with 100 patients with APS, 68 with primary APS and the remaining with APS associated with other autoimmune disorders, 13% of the patients had infection with the hepatitis C virus.[7] However, this study did not discriminate whether those 13 individuals had primary APS or associated with other disorders.

Summarizing, this study demonstrated that patients with primary APS had a low frequency of hepatitis B and C seropositivity, and in all cases presented this immunological positivity was secondary to serological or vaccinal scar.

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