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The impact of antiphospholipid antibodies in Takayasu arteritis

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Background/aim: The significance of antiphospholipid antibodies (aPL) is controversial in Takayasu arteritis (TA). This study was conducted to explore the frequency of aPL and their association with disease-related complications in TA.

Materials and methods: This cross-sectional study was conducted to investigate the presence of anti-cardiolipin (aCL), anti-beta 2 glycoprotein- 1(aβ2G1) antibodies, and lupus anticoagulant (LA) in TA patients. TA patients admitted to the Department of Rheumatology of Hacettepe University Faculty of Medicine between December 2015 and September 2016 who fulfilled the American College of Rheumatology (ACR) classification criteria for TA were consecutively enrolled in the study. Patients were grouped according to aPL positivity and compared in terms of disease manifestations, type of vascular involvement at diagnosis, and vascular complications/interventions attributable to TA.

Results: Fifty-three TA (49 female) patients were enrolled in the study. We detected 9 (16.9%) patients with IgM and/or IgG aβ2G1 and/or LA positivity. There were no patients with positive aCL. All aβ2G1 titers were low. There were no differences in terms of symptoms, signs, type of vascular involvement, the number of patients with disease-related complications or vascular interventions/surgery between aPL (+) and aPL(-) groups ($p > 0.05$ for all). The number of patients with thrombotic lesions was similar between the groups ($p > 0.05$). There were no patients with a history of venous thrombosis or on anticoagulant treatment in the aPL(+) group. Only 1 patient with IgM aβ2G1 (+) had a history of pregnancy loss.

Conclusion: Our results indicate that aPL positivity is not rare in TA. On the other hand, all aPL titers were low and no differences were found in the frequency of disease-related complications between aPL(+) and aPL(-) patient groups. Only TA patients with atypical manifestations with high suspicion of aPL-related complications should be considered to be investigated for aPL.

Key words: Takayasu arteritis, anti-beta 2 glycoprotein-1 antibodies, anti-cardiolipin antibody, lupus anticoagulant, antiphospholipid antibody syndrome

1. Introduction

Takayasu arteritis (TA) is a granulomatous large vessel vasculitis characterized by the involvement of the aorta and its branches. The disease is more common in Asia than in western populations and mainly affects young women. TA is considered to be a slow-progressing disease and the 10-year survival rate has been reported to be over 85% [1]. However, TA has an unpredictable clinical course with frequent disease exacerbations. Vascular involvement in TA can cause permanent organ dysfunction, even death in a significant number of patients in the short term. Therefore, identifying poor prognostic factors is crucial in TA.

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by recurrent thrombosis and pregnancy complications due to autoantibodies [2]. It is reasonable to think that the presence of antiphospholipid antibodies (aPL) may increase vascular damage in the course of a vasculitic disease such as TA due to their thrombotic effects. Although there were studies and case reports supporting the association of aPL and TA severity in the literature, the clinical importance of these antibodies in TA is still controversial [3–7]. This study was conducted to explore the frequency of aPL and its association with disease-related complications in TA.

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2. Materials and methods

Patients with TA admitted to the Department of Rheumatology of Hacettepe University Faculty of Medicine between December 2015 and September 2016 and who fulfilled the American College of Rheumatology (ACR) classification criteria for TA were consecutively enrolled in this cross-sectional study [8]. Pregnant patients or patients aged (<18) years were excluded. Medical histories of all TA patients; including both the history of thrombotic events and the obstetric complications (for female patients) in detail were reevaluated by face-to-face interview. Complete physical examinations were performed in all subjects. Medical records of the patients were reviewed retrospectively. The type of vascular involvement and involved arteries of the patients at diagnosis were determined by using the reports of imaging modalities (computed tomography angiography (CTA) and/or magnetic resonance angiography (MRA) and/or conventional angiography) [9]. The presence or history of hypertension, retinopathy, cerebrovascular accident, transient ischemic attack, severe aortic regurgitation, aortic valve replacement, aneurysm formation, vascular interventions (angioplasty and/or stent implementation), and vascular surgery were considered as disease-related complications and data about these were recorded as well. TA patients were also grouped according to the presence or absence of major complications (hypertension and/or aneurysm and/or aortic regurgitation and/or retinopathy) [10]. TA patients with arterial thrombotic lesions were also noted. TA patients who received cyclophosphamide and/or biological agents at any time were considered as treatment-resistant cases or severe diseases [11,12]. A history of antiaggregant and/or anticoagulant use was also recorded.

All subjects gave written informed consent and the institutional ethical committee approved this study.

2.1. Autoantibody analysis

Blood samples for testing autoantibodies were collected on the day of the evaluation of TA patients for the study. Tests for IgM/G anti-cardiolipin antibodies (aCL) and IgM/G anti-beta 2 glycoprotein-1 antibodies (aβ2G1) were performed by using a standardized enzyme-linked immunosorbent assay (ELISA) (Orgentec Diagnostika *515 and 521 commercial assays, respectively, ORGENTEC Diagnostika, Germany). The normal reference range for IgG/IgM aCL was <10 U/mL and <7 U/mL, respectively (range 0–100 U/mL, for both). The normal reference range for IgG/IgM aβ2G1was <5 U/mL (range 0–100 U/mL, for both). Screening for lupus anticoagulant (LA) was performed by using the diluted Russell's viper venom time assay in accordance with standard methods (Siemens Healthcare Diagnostics*, Germany). Confirmatory tests used a combination of mixing studies and correction with the addition of phospholipids. A LA ratio of 1.2 was considered to be positive (low positive: 1.2–1.5, medium positive 1.5–2.0, high positive >2.0).

2.2. Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences software (version 21.0; IBM Corporation, Armonk, NY, USA). Unless indicated otherwise, values are expressed as mean ± SD. Fisher's exact and chi-square tests were used for the comparison of categorical variables or percentages. Student t-test and Mann-Whitney U test were used to compare parameters among the groups whenever appropriate. A p-value of less than 0.05 was considered statistically significant.

3. Results

We included 53 TA (49 female) patients. The mean age of the TA patients was 40.8 ± 12.7 years. The mean age of the patients at diagnosis was 33.3 ± 11.4 years and the median disease duration was 48 months (interquartile range (IQR); 30.75–108.0 months). Constitutional symptoms (fever and/or fatigue and/or weight loss), extremity claudication, dyspnea, carotidynia, and palpitation were the most common complaints at the time of diagnosis in TA patients with the rate of 92.2% (n = 47), 64.7% (n = 33), 43.1% (n = 22), 31.4% (n = 16), 31.4% (n = 16), respectively. The age of symptoms onset was <40 years in all subjects. Decreased brachial artery pulses, bruits over subclavian arteries or aorta, and the blood pressure difference between the arms, were present in 49.1% (n = 26), 75.5% (n = 40), and 17.1% (n = 9) of patients, respectively. We detected 9 TA (16.9%) patients with IgM/G aβ2G1 and/or LA positivity. There were no patients with positive aCL. Of the 9 antibody positive patients; 7 had positive IgM aβ2G1, 3 had IgG aβ2G1 and 1 had positive LA. One had both positive IgM and IgG aβ2G1. Additionally, one had both IgM aβ2G1 and LA (Table 1). The mean serum level of IgM aβ2G1 was 6.6 ± 1.3 U/mL in antibody positive patients. The IgG aβ2G1serum levels of 3 patients were 5.0 U/mL, 7.2 U/mL, and 6.4 U/mL. Detected LA levels were considered as borderline positive with a ratio of 1.2. There were no patients with the infectious disease when blood samples were collected for antibody testing.

Demographic, clinical features and types of vascular involvement of aPL(+) and aPL(-) patients are represented in Table 2. There were no differences among the aPL(+) and aPL(-) patient groups in terms of age and gender. The median disease duration in the aPL(+) group was longer than the aPL (-) group (p = 0.02). The frequencies of the symptoms and signs were similar between two groups. The most frequent vascular involvement type was type V in both aPL(+) and aPL(-) groups. There were no differences in types of vascular involvement between the two groups (Table 2).

Table 1. Detected antiphospholipid antibodies in Takayasu arteritis patients.

Anti-beta 2 glycoprotein-1 IgM (+) patients, n (%)	7 (13.2)*
Anti-beta 2 glycoprotein-1 IgG (+) patients, n (%)	3 (5.7)*
Lupus anticoagulant (+) patients, n (%)	1 (1.9)**
Anti-cardiolipin IgM (+) patients, n (%)	0 (0.0)
Anti-cardiolipin IgG (+) patients, n (%)	0 (0.0)
Total number of patients with any positive test results, n (%)	9 (16.9)
Anti-beta 2 glycoprotein-1 IgM concentration (U/ml), median (IQR)	5.7 (5.3–7.9)
Anti-beta 2 glycoprotein-1 IgG concentration (U/ml), median (IQR)	6.8 (6.4–7.2)

*One patient had both positive IgG and IgM anti beta 2 glycoprotein-1 antibodies.
** One patient had both IgM anti beta 2 glycoprotein-1antibody and Lupus anticoagulant test positivity.

Table 2. Demographic, clinical features, and types of vascular involvement in aPL(+) and aPL(-) TA patients.

	aPL(+) TA patients, (n = 9)	**aPL(-) TA patients, (n = 44)**
Gender (female/male)	7/2	42/2
Age (years ± SD)	42.5 ± 14.7	40.4 ± 12.4
Age at diagnosis (years ± SD)	30.9 ± 12.8	33.8 ±10.8
Disease duration, months (IQR)	108 (66–240)	48 (24–84)*
Symptoms and signs at diagnosis, n (%)**		
Constitutional symptoms	8 (88.8)	39 (92.8)
Extremity claudication	5 (55.5)	28 (66.6)
Dyspnea	5 (55.5)	17 (40.4)
Carotidynia	4 (44.4)	12 (28.5)
Palpitation	4 (44.4)	12 (28.5)
Decreased brachial artery pulses	5 (55.5)	21 (50.0)
Bruits over subclavian or aorta	6 (66.6)	34 (80.9)
Blood pressure difference between the arms	0 (0.0)	9 (21.4)
Type of vascular involvement at diagnosis, n (%)		
Type I	1 (11.1)	14 (31.8)
Type IIa	1 (11.1)	4 (9.1)
Type IIb	0 (0.0)	5 (11.4)
Type III	0(0.0)	1 (2.3)
Type IV	1(11.1)	0 (0.0)
Type V	6 (66.7)	20 (45.5)
Coronary arteries	1 (11.1)	2 (4.5)
Pulmonary arteries	2 (22.2)	7 (15.9)

$p > 0.05$ for all except * $p = 0.02$, **data is available for 51 patients
aPL: antiphospholipid antibodies, TA: Takayasu arteritis, IQR: interquartile range

3.1. Complications

Among 52 TA patients (1 patient excluded from the analysis because of insufficient data) a total of 45 complications occurred in 28 patients during their follow-up. The rates of disease-related complications including vascular interventions or vascular surgery were not different

between the aPL(+) and aPL(-) patients (p > 0.05 for all) (Table 3). No difference was found between the number of patients with complications or major complications (hypertension, aneurysm, aortic regurgitation, and retinopathy) between the groups (p > 0.05 for all). Forty-five patients were evaluated at least once by transthoracic echocardiography during their follow-up. Three patients had pulmonary hypertension (systolic pulmonary arterial pressure >40 mmHg). There was one patient with pulmonary hypertension in the aPL(+) and 2 in the aPL(-) group.

3.2. Immunosuppressive treatment

All TA patients were treated with steroids and immunosuppressive agents except one. The initial immunosuppressive agents were as follows; methotrexate in 29 (54.7%), azathioprine in 13 (24.5%), cyclophosphamide in 9 (16.9%), and mycophenolate mofetil in 1 (1.8%). One (1.8%) patient was treated initially with steroids and tocilizumab and was followed up with the diagnosis of ankylosing spondylitis, and was already on tumor necrosis factor alpha antagonist. During the follow-up period, a total of 15 (28.3%) patients were treated with cyclophosphamide and 16 (30.2%) patients with biologic agents. The number of patients treated with cyclophosphamide and/or biologic agents was not different between aPL (+) and aPL (-) groups (p = 0.29) (Table 4). There were 38 (71.6%) patients who were on low-dose acetylsalicylic acid. There was no difference between aPL(+) and aPL(-) patients who were on low-dose acetylsalicylic acid (77.7% vs. 70.4%; p = 1.00).

3.3. Thrombotic events and pregnancy loss

There were 9 patients with thrombotic lesions. All had systemic arterial thrombotic lesions except one who had documented pulmonary arterial thrombosis and pulmonary arterial involvement. This patient with pulmonary thrombosis was aPL (-). There was no difference in the number of patients with thrombotic lesions between aPL (-) and aPL (+) groups (6/42 vs. 3/9; p = 0.18). None of the aPL (+) patients had venous thrombotic events in their disease course. There were 4 patients who were on anticoagulant treatment (1 for atrial fibrillation, 1 for aortic valve replacement, 1 for immobilization due to severe pulmonary hypertension, and 1 for after bypass surgery). None of the patients who were on anticoagulant treatment were aPL (+).

Pregnancy loss occurred in 5 among 73 pregnancies in 49 female TA patients. Three of 5 pregnancy losses occurred after TA diagnosis and 4 of 5 pregnancy losses occurred >10 weeks of gestation. There were no patients with a history of recurrent pregnancy loss. There was only one pregnancy loss in aPL(+) TA patients. This patient was aCL IgM (+) and had a pregnancy loss >10 weeks of gestation. Only 3 (6.1%) patients stated that they had HT during pregnancy.

4. Discussion

In this study, aPLs were detected in 16.9% of the TA patients. All the antibody positive patients had IgM and/or IgG aβ2G1, there was only one patient with a positive

Table 3. Frequency of disease-related complications in aPL(+) and aPL(-) TA patients.

	aPL(+) TA patients, (n = 9)	**aPL(-) TA patients, (n = 43)**
Total number of complications, n (%)	7 (77.7)	38 (88.3)
Cerebrovascular accident, n (%)	1 (11.1)	3 (6.9)
Transient ischemic attack, n (%)	0 (0.0)	3 (6.9)
Severe aort regurtation, n (%)	0 (0.0)	3 (6.9)
Aortic valve replacement, n (%)	0 (0.0)	1 (2.3)
Angioplasty or stent, n (%)	0 (0.0)	4 (9.3)
Bypass surgery, n (%)	2 (22.2)	2 (4.6)
Aneurysm, n (%)	0 (0.0)	8 (18.6)
Hypertension, n (%)	4 (44.4)	13 (30.2)
Retinopathy, n (%)	0 (0.0)	1 (2.3)
Number of patient with complications, n (%)	6 (66.6)	22 (51.1)
Number of patients with major complication*, n (%)	4 (44.4)	20 (46.5)

p > 0.05 for all

*Hypertension and/or aneurysm and/or aort regurgitation and/or retinopathy

** Data is available for 52 patients

aPL: antiphospholipid antibodies, TA: Takayasu arteritis

Table 4. Patients treated with cyclophosphamide or biologic agents in aPL(+) and aPL(-) TA patients.

	aPL(+) TA patients, (n = 9)	**aPL(-) TA patients, (n = 44)**	**p**
Neither cyclophosphamide nor biologic agent*, n (%)	3 (33.3)	24 (54.5)	0.29
Cyclophosphamide, n (%)	3 (33.3)	12 (27.2)	0.70
Biologic agent*, n (%)	4 (44.4)	12 (27.2)	0.43
Cyclophosphamide and/*or* biologic agent*, n (%)	6 (66.6)	20 (45.4)	0.29

* Tumor necrosis factor-α antagonist and/or interleukin-6 receptor antagonist
aPL: antiphospholipid antibodies, TA: Takayasu arteritis

LA test and there were no aCL positive patients. Serum concentrations of the antibodies were low in all patients with aβ2G1 positivity.

There are few studies in the literature investigating the frequency of aPL in TA patients. Most of those studies were cross-sectional and had a limited number of patients; they were conducted with 22, 28, 21, 19, and 47 TA patients, respectively [4,7,13–15]. The frequency of aPL was reported between 0% and 45%. Only in one study antibodies were evaluated more than once during the disease course and the frequency of persistent aPL positivity was found to be 45% (10/22 patients). In the same study, aPL were detected only once during the disease course in 7 of the remaining 12 patients [4]. Not all the aPL were evaluated in all studies. In our study, the frequency of aPL was 16.9% which was compatible with the literature. All the antibody positive patients had IgM and/or IgG aβ2G1 except one with LA positivity. Our results were similar to the Mexican study where the authors reported that there were no patients with positive aCL but detected low titers of IgM or IgG aβ2G1 in 39.2% (11/28 patients) of their TA patients [7].

The clinical significance of the presence of aPL in the course TA is controversial. Although severe cases with TA and aPL had been reported, the thrombotic events in these patients were usually detected in the arterial circulation, and the number of cases with venous thrombosis or recurrent pregnancy losses, which are more typical for APL, were low. A venous thrombotic event (in 3 patients) or recurrent pregnancy (in 4 patients) loss was only present in 7 of the 19 reported cases in the literature [5,6,16–34]. In studies where aPL were screened more systematically, it has been suggested that aPL in TA patients were associated with disease activity or an increased number of vascular interventions [3,4]. On the other hand, there were studies that reported no clinical association with aPL in TA [7,13–15]. Moreover, antibody titers were usually low in all of those studies; which were not enough to fulfill Sapporo classification criteria for definite antiphospholipid syndrome [2,4,7,15,35]. In the study where authors suggested an association between aPL and more frequent vascular interventions; there was only 1 out of 10 who met Sapporo criteria, in the aPL(+) group [4,35]. In our study, there were no differences in the symptoms, signs, type of vascular involvement, and number of patients with complications including vascular interventions or surgery between aPL(+) and aPL() groups. Moreover, the number of patients treated with cyclophosphamide and/or biological agents was not different between the groups. This result suggests that the rate of severe or treatment-resistant cases is similar in both groups. Therefore, it is hard to conclude that the presence of aPL is associated with a severe TA course according to our results.

Not all the aPL are pathogenic and they can be detected in several conditions such as infectious diseases, inflammatory disorders, malignancies, and usage of particular drugs [2]. The antibodies that do not cause thrombosis are usually of IgM type and their titers are low [2,36]. In this study, most of the patients had IgM type aβ2G1 and all the antibody titers were low. Therefore, the antibodies we detected might be nonpathogenic and it could be an explanation for not observing an association between aPL and TA manifestations in our study.

The number of patients with thrombotic lesions was similar between aPL(+) and aPL(-) patient groups in our study. All the thrombotic lesions were on the systemic arterial circulation except one in pulmonary arteries. The patient who had pulmonary thrombosis was aPL(-) and had severe pulmonary artery involvement. Moreover, there were no aPL(+) patients with a history of venous thrombosis or on anticoagulant treatment for thrombotic lesions. There was only one patient who had a >10-week pregnancy loss with low titer IgM aβ2G1. Recurrent venous thrombosis and pregnancy loss are the most common manifestations of APS [2]. Therefore, our findings regarding the absence or rarity of venous thrombosis and pregnancy loss, which were unexpected for the presence of APS; might support the nonpathogenic character of these antibodies in TA patients who are aPL(+). Actually, the presence of TA is a satisfactory explanation for the development of arterial thrombosis alone. Vascular damage, blood flow

disturbances due to aneurysms or narrowed arteries, and prothrombotic state can all contribute to the development of arterial thrombosis in TA patients [37,38]. In situ thrombosis can occur in pulmonary arteries during the disease course [39].

In this cross-sectional study, we tested patients for aPL only once and had no control group. However, we tested the antibodies with well-known, commonly used methods in the context of high clinical correlations. In addition, as all the antibody titers of our patients were low, there was no need for a second test except for the LA positive patient. On the other hand, although they are unlikely to affect the aPL titers, it should be kept in mind that most of our patients were on immunosuppressive therapy. Differences in clinical approach to TA patients between the countries may have affected the number of vascular interventions and surgeries performed. Although we evaluated more patients compared to similar studies in literature, the limited number of the patients tested and retrospective data collection may have affected our results. Lastly, we did not evaluate TA disease activities which may have an impact on antibody titers.

In conclusion, our results indicate that aPL positivity is not rare in TA. On the other hand, all aPL titers were low and no difference was found in the frequency of arterial thrombotic lesions or disease-related complications between aPL(+) and aPL(-) groups. There were no patients with a history of venous thrombosis in aPL(+) group. We do not suggest routine evaluation of TA patients for the presence of aPL. We suggest performing these tests only in TA patients with atypical manifestations highly suspected of aPL-related complications.

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The authors report no conflicts of interest.

Informed consent
Non-Interventional Clinical Research Ethics Committee of Hacettepe University approved this study (2015/336-16).

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