ORIGINAL ARTICLE

The presence of particular criteria and noncriteria antiphospholipid antibodies in patients with uterine malignancies

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KEY WORDS

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EDITORIAL

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ABSTRACT

INTRODUCTION Currently, there have been limited data on the presence of antiphospholipid antibodies (aPLs) in patients with uterine malignancies (UMs).

OBJECTIVES We aimed to determine whether criteria and noncriteria aPLs are present in patients with UMs and associated with the thrombotic risk, as compared with patients with noncancerous gynecological diseases (NCGDs).

PATIENTS AND METHODS The study involved 151 women scheduled for gynecological surgery. The patients were divided into the UM group (n = 70) and the NCGD group (n = 81). The Antiphospholipid 10 Dot assay was used to detect criteria and noncriteria aPLs before surgery. The study patients were considered positive for thrombosis if they exhibited signs of thrombosis within the 2-year follow-up period after surgery.

RESULTS Positive results for aPLs were obtained in 17/70 patients with UMs (24.3%) and in 6/81 patients with NCGDs (7.4%) ($P = 0.008$). Particular noncriteria aPLs (antiphosphatidic acid, antiphosphatidylserine, anti–annexin V, and antiprothrombin antibodies) yet no criteria aPLs (anticardiolipin and anti–β2-glycoprotein I antibodies) were more frequently found in patients with UMs than in those with NCGDs. Thrombosis was diagnosed in 9/70 patients (12.9%) in the UM group and in 3/81 patients (3.7%) in the NCGD group ($P = 0.03$).

CONCLUSIONS Antiphospholipid antibodies were present at significant levels in patients with UMs. Noncriteria aPLs yet no criteria aPLs were more frequently found in patients with UMs than in those with NCGDs. The incidence of thrombosis was significantly higher in patients with UMs.

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INTRODUCTION Thrombosis is a common complication observed in patients with malignancies.[1-3] Several factors responsible for the development of thrombosis have been identified. Interactions between cancer cells, coagulation mechanisms, and the immune system may play an essential role in initiating thrombotic processes accompanying tumors.[4-9]

Women with reproductive tract malignancies, including uterine malignancies (UMs), are at high risk for thromboembolic complications also because of comorbidities, the advanced clinical stage of the disease at the time of diagnosis, disease duration, the scope of the surgery (performed via laparotomy or laparoscopy), and the need for long-term postoperative immobilization.[10]

The role of the immune system in neoplasia and antitumor defense is well established.[11-15] Furthermore, there have been numerous reports on thrombotic complications associated with the presence of criteria antiphospholipid antibodies (aPLs) in patients with cancer.[16-19] Although the exact relationship between aPLs and malignancies is unclear, the presence of aPLs in cancer patients may contribute to an increased thromboembolic risk. There are limited data on

WHAT'S NEW?

There are limited data on the occurrence of criteria and noncriteria antiphospholipid antibodies (aPLs) in patients with malignancies of the female reproductive tract. Our observations confirmed the frequent presence of criteria and noncriteria aPLs in patients with uterine malignancies (UMs). We found significant differences in the occurrence of the particular aPLs between patients with UMs and those with noncancerous gynecological diseases (NCGDs). The noncriteria aPLs (against phosphatidic acid, phosphatidylserine, annexin V, and prothrombin) are more frequently observed in patients with UMs than in patients with NCGDs. However, the criteria aPLs did not significantly differ between the UM and NCGD groups.

the presence of aPLs and their association with thrombosis accompanying female reproductive tract tumors.[16,20]

Antiphospholipid antibodies are serological markers of immunization and thrombotic risk in patients with antiphospholipid syndrome (APS). The diagnosis of APS usually involves the detection of criteria aPLs including immunoglobulin M (IgM) and immunoglobulin G (IgG) classes of anticardiolipin antibodies, anti–β2-glycoprotein I antibodies, and lupus anticoagulants, as well as thrombotic complications.[21]

As emphasized in the literature, the assessment of the thrombotic complication risk should be supplemented with the detection of noncriteria aPLs, including anti–annexin V and anti-phosphatidylserine / prothrombin complex, the presence of which may be associated with the increased risk of thrombosis.[5,16,22] To date, the role of noncriteria aPLs in the pathogenesis of thrombosis in the course of gynecological malignancies remains unclear.

In our study, we aimed to determine whether criteria and noncriteria aPLs are present in patients with UMs and related to the thrombotic risk, as compared with patients with noncancerous gynecological diseases (NCGDs).

PATIENTS AND METHODS Our study involved 151 women admitted to the Department of Gynecological Oncology and Gynecology in the years 2015 to 2017. The study patients were admitted for the diagnosis and treatment of female reproductive organ lesions suggestive of cancerous or nonmalignant lesions of the adnexa. All patients were deemed eligible for surgical treatment.

The day before their scheduled surgery, a blood sample from each patient was collected in a clot tube. Each blood sample was centrifuged at 1008 relative centrifugal force for 10 minutes, and then the serum was frozen at –70 °C and stored for immunoassays for selected aPLs.

Surgery (via laparotomy or laparoscopy) was performed in 151 women, and the final diagnosis for each patient was based on the postoperative histological examination of the specimens. The postoperative histological diagnoses of the study patients are shown in Supplementary material, *Tables S1* and *S2*.

The patients were divided into 2 groups: the UM group of women with diagnosed UMs (n = 70) and the NCGD group of women with diagnosed nonmalignant genital organ pathology (n = 81). The mean (SD) age of the patients was 59.8 (12.6) years in the UM group and 45.1 (14.7) years in the NCGD group (P <0.001).

The comorbidities and thrombotic risk factors of the study patients are presented in TABLE 1. In patients with UMs, hypertension, obesity, type 2 diabetes, and heart failure—the characteristic features of metabolic syndrome (MetS)–were more frequently recognized than in patients with NCGDs.

The study patients were followed up for 24 months after surgery and were considered "positive" for thrombosis if they exhibited clinical signs of a thrombotic process within that period, such as deep vein thrombosis confirmed by Doppler ultrasound examination and / or a clinical event involving pulmonary embolism or embolism involving other organs, confirmed by radiological examination.

Antiphospholipid antibody determination Antiphospholipid 10 Dot test sets (Generic Assays, Dahlewitz / Berlin, Germany) were used to determine the presence of aPLs. The nitrocellulose membranes with the primary antibody were incubated with patients sera for 20 minutes. After washing with Tris-buffered saline, the binding of aPLs with secondary IgG and IgM antibodies was detected. Finally, the membranes were washed, dried, and read by the Canon Cano Scan LiDE 120 scanner (Dahlewitz / Berlin, Germany). The intensity of the membrane readings was determined in a semiquantitative manner by the DotBlot Analyzer (Generic Assays, Dahlewitz / Berlin, Germany). Specifically, the intensity of the spotting on the membranes was calculated concerning the intensity of the control spotting. The categories of semiquantitative readings applied by the software interpreting the scanner readings were as follows: extremely positive: >80 IgM antiphospholipid units/ml (MPL) or IgG antiphospholipid units/m (GPL); strongly positive: 60–80 MPL / GPL; positive: 40–59 MPL / GPL; barely positive: 20–39 MPL / GPL; and negative: below 20 MPL / GPL.

The DotBlot method was used to detect the following classes of aPLs from each patient's frozen serum:

- noncriteria antiphospholipid antibodies (IgM and IgG class) against: phosphatidic acid, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidylinositol, phosphatidylserine, annexin V, and prothrombin
- criteria antiphospholipid antibodies (IgM and IgG class) against cardiolipin and β2-glycoprotein I.

A total of 3020 immunoassays (20 antibody types in 151 patients) were performed.

TABLE 1 Comorbidities and thrombotic risk factors of the study patients

Comorbidity or thrombotic risk factors	UM (n = 70)	NCGD (n = 81)	*P* value
Hypertension	42 (60)	22 (27.2)	0.001
Obesity (BMI >30 kg/m^2)	24 (34.3)	15 (18.5)	0.043
Type 2 diabetes	10 (14.3)	4 (5)	0.047[a]
Heart failure	16 (22.9)	5 (6.2)	0.007
Miscarriages	6 (8.6)	7 (8.6)	>0.99
Smoking status	8 (11.4)	16 (19.8)	0.24
Another neoplasm	4 (5.7)	2 (2.5)	0.42[a]
Oral contraception	2 (2.9)	9 (11.1)	0.07[a]
Long-term immobilization (over 72 hours) before surgery	9 (12.9)	4 (4.9)	0.15[a]

Data are presented as number (percentage) of patients. Analysis was performed using the Pearson χ^2 test.

a Monte Carlo simulation

Abbreviations: BMI, body mass index; NCGD, noncancerous gynecological disease; UM, uterine malignancy

The software regarded a result of 20 or above as positive. The numerical values of the spotting intensity of the membranes were automatically recorded by the software in a spreadsheet file for further statistical analysis.

Statistical analysis The clinical parameters and laboratory test results were subjected to statistical analysis. The values of the analyzed parameters were characterized using the R programming language. Statistical analysis was carried out at the significance level of $\alpha = 0.05$. The null hypothesis was rejected and an alternative hypothesis adopted when $P < 0.05$.

The χ^2 test was used to check the association between categorical variables. In the case of too few observations, to fulfill the criteria for the χ^2 test, the Monte Carlo method was used (to describe comorbidities and thrombotic risk factors of the study groups). For data presentation regarding aPL occurrence, we used the χ^2 Pearson and Fisher exact tests.

Data were expressed as number (percentage) for categorical variables and mean (SD) or median (interquartile range) for continuous variables.

Ethics The study was approved by the ethics committee (KE-0254/265/2014). All patients provided written informed consent to participate in the study.

RESULTS Significant differences were observed between the UM and NCGD groups with regard to the presence of aPLs in the DotBlot test. More patients with aPLs (with at least a single aPL detection value ≥40) were found in the UM group compared with the NCGD group (17/70 [24.3%] vs 6/81 [7.4], respectively; $P = 0.004$).

The double-positive aPL status was noted in 3 patients from the UM group and in a single patient from the NCGD group. There was only a single case of multipositivity in the UM group (4 positive results in the DotBlot test for MPL and GPL ≥40).

The particular noncriteria aPLs (antiphosphatidic acid IgM, antiphosphatidylserine IgM, anti–annexin V IgM, and antiprothrombin IgM and IgG antibodies) were more frequently detected in patients with UMs than in those with NCGDs. There were no significant differences regarding the detection of criteria aPLs between the study groups (TABLES 2–7).

The assessment of thrombotic complication frequency in individual groups indicated differences in the incidence of thrombosis between the UM and NCGD groups (9/70 patients in the UM group versus 3/81 patients in the NCGD group; χ^2 $P = 0.03$).

DISCUSSION Our study showed that thrombotic complications are relatively common in patients with UMs. The remarkable levels of particular criteria and noncriteria aPLs were present in patients with UMs. Selected noncriteria aPLs, ie, antiphosphatidic acid, antiphosphatidylserine, anti–annexin V, and antiprothrombin antibodies, were more common in patients with UMs than in those with NCGDs.

Our observations confirmed the frequent criteria and noncriteria aPL positivity in patients with UMs. The presence of selected noncriteria aPLs in patients with UMs appears to be a risk factor for thrombosis. However, the causal relationships between criteria and noncriteria aPLs and thrombosis in patients with UM remains unclear. They have not been shown to be clearly related to thrombotic complications in patients with UMs.

Patients with UMs are at higher risk of venous thromboembolism than the general population.[10] The malignancy itself, treatment modalities including medication and surgery, and the increased counts of leukocytes, platelets, and tissue factor–positive microvesicles increase this risk.[23-25] Several authors have shown that aPLs can be detected in the peripheral blood of patients with malignancies[16-22,26-29]; however, whether aPLs can induce thrombosis in patients with UMs or not is still unknown. Further studies should

TABLE 2 DotBlot test results for anti–phosphatidic acid antibodies

Patient group	Anti–phosphatidic acid IgM			Anti–phosphatidic acid IgG		
	<20	≥20 and <40	≥40	<20	≥20 and <40	≥40
UM (n = 70)	58 (82.6)	11 (15.71)	1 (1.43)	69 (98.57)	0	1 (1.43)
NCGD (n = 81)	78 (96.23)	3 (3.7)	0	81 (100)	0	0
P value[a]	0.007			0.46		

Data are presented as number (percentage) of results.

a The χ^2 (Fisher) *P* value with Monte Carlo simulations (based on 2000 replicates) for UM versus NCGD

Abbreviations: IgM, immunoglobulin M; IgG, immunoglobulin G; others, see TABLE 1

TABLE 3 DotBlot test results for antiphosphatidylserine antibodies

Patient group	Antiphosphatidylserine IgM			Antiphosphatidylserine IgG		
	<20	≥20 and <40	≥40	<20	≥20 and <40	≥40
UM (n = 70)	58 (82.86)	12 (17.14)	0	70 (100)	0	0
NCGD (n = 81)	76 (93.83)	5 (6.17)	0	79 (97.53)	2 (2.47)	0
P value[a]	0.041			0.5		

Data are presented as number (percentage) of results.

a The χ^2 (Fisher) *P* value with Monte Carlo simulations (based on 2000 replicates) for UM versus NCGD

Abbreviations: see TABLES 1 and 2

TABLE 4 DotBlot test results for anti–annexin V antibodies

Patient group	Anti–annexin V IgM			Anti–annexin V IgG		
	<20	≥20 and <40	≥40	<20	≥20 and <40	≥40
UM (n = 70)	28 (40)	36 (51.43)	6 (8.57)	62 (88.57)	6 (8.57)	2 (2.86)
NCGD (n = 81)	52 (64.2)	27 (33.3)	2 (2.47)	79 (97.53)	2 (2.47)	0
P value[a]	0.007			0.06		

Data are presented as number (percentage) of results.

a The χ^2 (Fisher) *P* value with Monte Carlo simulations (based on 2000 replicates) for UM versus NCGD

Abbreviations: see TABLES 1 and 2

TABLE 5 DotBlot test results for antiprothrombin antibodies

Patient group	Antiprothrombin IgM			Antiprothrombin IgG		
	<20	≥20 and <40	≥40	<20	≥20 and <40	≥40
UM (n = 70)	12 (17.14)	54 (77.14)	4 (5.71)	51 (72.86)	18 (25.71)	1 (1.43)
NCGD (n = 81)	35 (43.21)	43 (53.1)	3 (3.7)	73 (90.12)	8 (9.88)	0
P value[a]	0.002			0.01		

Data are presented as number (percentage) of results.

a The χ^2 (Fisher) *P* value with Monte Carlo simulations (based on 2000 replicates) for UM versus NCGD

Abbreviations: see TABLES 1 and 2

improve the understanding of the aPL role in thrombotic complications in patients with cancer.

The pathomechanism by which aPLs are generated in patients with malignancies remains unclear. Several mechanisms have been suggested to explain the association between aPLs and cancer,[16,30-33] including the production of antibodies in response to tumor antigens; the secretion of anticardiolipin antibodies from tumor cells; and the production of monoclonal immunoglobulins with lupus anticoagulant activity.

The autoantibodies present in serum may be a direct consequence of tumor presence[16,30,31] and result from specific cancer treatments or various infections.[16,32]

We speculated that, in our group of patients with UMs, selected noncriteria aPLs (against phosphatidic acid, phosphatidylserine, annexin V, and prothrombin) could be potential biomarkers for malignancy.

Antiphospholipid syndrome developed during the chemo- and immunotherapeutic treatment

TABLE 6 DotBlot test results for anticardiolipin antibodies

Patient group	Anticardiolipin IgM			Anticardiolipin IgG		
	<20	≥20 and <40	≥40	<20	≥20 and <40	≥40
UM (n = 70)	59 (84.29)	10 (14.29)	1 (1.43)	61 (87.14)	8 (11.43)	1 (1.43)
NCGD (n = 81)	77 (95.06)	4 (4.94)	0	74 (91.36)	7 (8.64)	0
P value[a]		>0.99			>0.99	

Data are presented as number (percentage) of results.

a The χ^2 (Fisher) *P* value with Monte Carlo simulations (based on 2000 replicates) for UM versus NCGD

Abbreviations: see TABLES 1 and 2

TABLE 7 DotBlot test results for anti–β2-glycoprotein I antibodies

Patient group	Anti–β2-glycoprotein IgM			Anti–β2-glycoprotein IgG		
	<20	≥20 and <40	≥40	<20	≥20 and <40	≥40
UM (n = 70)	19 (27.14)	44 (62.86)	7 (10)	32 (45.71)	38 (54.3)	0
NCGD (n = 81)	43 (53.08)	36 (44.4)	2 (2.47)	57 (70.37)	24 (29.63)	0
P value[a]		0.109			0.127	

Data are presented as number (percentage) of results.

a The χ^2 (Fisher) *P* value with Monte Carlo simulations (based on 2000 replicates) for UM versus NCGD

Abbreviations: see TABLES 1 and 2

of different types of cancer,[16,34-36] and further investigations indicated that aPL-positive IgG from patients with autoimmune disease accelerates cancer angiogenesis and growth through a tissue factor–mediated mechanism.[16,36] There are multiple mechanisms—platelet activation, endothelial activation, and tissue factor expression—which may cause hypercoagulation in cancer patients by disrupting the coagulation pathway and fibrinolysis.[16,37-39] With aPLs present, all of these mechanisms contribute to the development of thrombotic complications in APS.[16,40,41]

Seronegative APS is defined as clinical manifestations suggestive of APS without the presence of criteria aPLs in serum.[16,42-44] The detection of noncriteria aPLs in patients with seronegative APS may indicate an increased thrombotic risk.[44] Our study demonstrated that noncriteria aPLs occur more often in patients with UMs than in those with NCGDs, in particular antibodies against phosphatidic acid IgM, phosphatidylserine IgM, annexin V IgM, and prothrombin IgM and IgG. One of the patients from the UM group with multipositive aPL status had been earlier diagnosed with APS and she died of myocardial infarction 12 months following the surgery. Therefore, screening for noncriteria aPLs in patients with UMs may be useful as a prognostic factor for thrombotic and cardiovascular complications.

It has not been known yet what values of aPL detection should be considered as a "positive" prognostic factor. For instance, even low (<20) MPL / GPL values may play a crucial role in possible thromboembolic complications in pregnant women.[45]

In our study, hypertension, obesity, type 2 diabetes—ie, the typical features of MetS—were more frequently reported in patients with UMs than in those with NCGDs. There is evidence showing that MetS is associated with endometrial cancer and increases the risk of venous thromboembolism.[46-48] Metabolic syndrome was often observed in patients with UMs and might have had an impact on a higher frequency of thrombotic complications than in the NCGD group.

Thrombosis in patients with UMs is also determined by underlying factors not related to aPLs, such as age and MetS. Therefore, the causality between the criteria and noncriteria aPLs in this population and thrombosis is unclear.

Admittedly, our report has some limitations. It was a pilot study; therefore, we attempted to determine the presence of aPLs only in patients with malignancies yet without the diagnosis of APS. Our study was also limited by the fact that we measured the aPL levels only once.

Conclusions Antiphospholipid antibodies are present at significant levels in patients with UMs. Contrary to expectations, noncriteria aPLs (against phosphatidic acid, phosphatidylserine, annexin V, and prothrombin) were more frequently found in patients with UMs than in those with NCGDs. On the other hand, the levels of criteria aPLs did not significantly differ between the UM and NCGD groups. The incidence of thrombosis in patients with UMs was higher than in those with NCGDs, but there has been insufficient evidence yet to establish a direct causal relationship between aPL presence and thrombosis in patients with UMs.

Further conclusions from this study may constitute the basis for future research on the immunological conditions of thrombosis in cancer: 1) noncriteria aPL–mediated mechanisms may

contribute to increased thrombosis in patients with cancer; 2) mean and high reading values for certain noncriteria aPLs (against phosphatidic acid, phosphatidylserine, annexin V, and prothrombin) may indicate their future usefulness as novel cancer biomarkers.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

CONTRIBUTION STATEMENT AM conceived the concept of the study. AM, MM, LGS, and JK contributed to the study design. AM, MD, and PZ were involved in data collection. AM, MM, and MD analyzed the data and prepared the manuscript. MM coordinated funding for the project. All authors edited and approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

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