Report

Antiphospholipid antibodies in patients with ovarian cancer: A prospective pilot study

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ABSTRACT

Background; Ovarian cancer is associated with a high incidence of thromboembolism, and it has been suggested that the mechanisms, particularly when apoptosis is induced by chemotherapy, share common underpinnings with antiphospholipid syndrome (APS) -associated thromboembolism. A clinical study was conducted to elucidate the expression of antiphospholipid antibody (aPL) in patients undergoing various treatment steps.

Methods; Fifteen patients with newly diagnosed ovarian cancer, primary peritoneal cancer, or fallopian tube cancer were prospectively and consecutively enrolled to measure lupus anticoagulants, anti-cardiolipin antibodies, and anti-PS/PT antibodies. The observational period for thrombotic events after blood sampling ranged from 5 to 13 months.

Results; Six patients received systemic chemotherapy as neoadjuvant or adjuvant therapy before blood sampling; four patients had thromboembolic diseases, including cerebral infarction; and four patients had clear cell carcinoma. None of the patients showed aPL, regardless of chemotherapy induction. Univariate analysis showed no major clinical characteristics (advanced age, history of thromboembolisms, clear cell carcinoma, large tumor diameter, high body mass index, and advanced FIGO stage) that correlated with thrombosis, while the histological subtype of clear cell carcinoma was associated with elevated plasma D-dimer levels above 8.45 mg/L (P=0.03).

Conclusions; Based on this pilot study with a limited number of patients, ovarian cancer and its treatment may have no direct association with the induction of APS or aPL, regardless of the clinicopathological background or induction of chemotherapy with cytotoxic agents. Further research in this area is warranted.

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Key Words
Ovarian Cancer, Antiphospholipid Syndrome, Antiphospholipid Antibody, Chemotherapy

I. Introduction

Cancer-associated thrombosis is the second leading cause of mortality among cancer patients following disease progression [1]. The risk of thromboembolism in individuals with cancer is intricately linked to tumor characteristics, including primary site, histological grade, or tumor node metastasis stage, as well as to cancer treatments, such as surgery, hospitalization, central venous catheter placement, systemic chemotherapy, radiothera-

py, anti-angiogenesis agents, immunomodulatory drugs, hormonal therapy, erythropoiesis-stimulating agents, and red blood cell or platelet transfusions [1]. The mechanisms underlying cancer-associated thrombosis are multifaceted, involving direct activation of platelets by cancer cells and procoagulant molecules such as tissue factor (TF) and P-selectin derived from tumor cell microvesicles [2]. These pathways illustrate the complex interplay between malignancy and hypercoagulability.

Antiphospholipid syndrome (APS) is a systemic autoimmune condition characterized by arterial, venous, or microvascular thrombosis, recurrent pregnancy loss, and non-thrombotic manifestations in the presence of persistent anti-phospholipid antibodies (aPLs) [3]. The pathogenic role of aPLs is well documented. These autoantibodies induce a prothrombotic state primarily through the activation of vascular endothelial cells and monocytes, resulting in increased TF production [4]. This mechanism, known as the procoagulant cell activation theory, underscores the pivotal role of blood-borne TF in APS-associated hypercoagulability. The representative aPL anti-cardiolipin antibodies are auto-antibodies that target plasma proteins, primarily β2-glycoprotein I (GPI), which binds to anionic phospholipids [5][6]. Phosphatidylserine-dependent anti-prothrombin antibodies (aPS/PTs) exhibit structural characteristics similar to those of antiphospholipid antibodies by binding to prothrombin, which undergoes conformational changes upon interaction with negatively charged phospholipids. These antibodies also possess prothrombotic properties, and are increasingly recognized as novel or alternative antiphospholipid antibodies, potentially substituting lupus anticoagulants (LACs) in certain diagnostic contexts [4][7]. Emerging evidence suggests a potential association between APS and thrombosis in cancer patients, possibly mediated by the overexpression of phosphatidylserine on cell surfaces, including in ovarian cancer [8-11]. Although the precise mechanisms remain elusive and may vary by cancer type, this link warrants further exploration.

Ovarian cancer is the most lethal malignancy of the female reproductive system, claiming the lives of over 200,000 women each year [12]. The standard treatment is debulking surgery to achieve no gross residual tumor, followed by adjuvant platinum-based chemotherapy in both primary and recurrent disease [13]. In addition, several clinical trials demonstrated that the anti-angiogenesis agent bevacizumab improved the prognosis of patients with advanced [14] and recurrent ovarian cancer [15], and combination drug therapy with bevacizumab is currently used as a control arm to develop novel treatments in randomized clinical trials [16]. Notably, ovarian cancer has a disproportionately high incidence of thromboembolism relative to other malignancies [17][18] and has been associated with Trousseau syndrome as a cerebral infarction [19]. Chemotherapy has been implicated in the externalization of negatively charged phospholipids, such as phosphatidylserine [20], due to apoptosis in ovarian cancer [21], further increasing the thrombotic risk. The shared pathophysiological underpinnings of APS-associated thrombosis and cancer-associated thrombosis, particularly the formation of fibrin clots, suggest a potential overlap between these conditions [22]. This prompted our hypothesis that aPLs may be more frequently detected in patients with ovarian cancer. Recognizing the critical importance of anticipating thrombotic events and instituting appropriate prophylactic measures, we explored the utility of aPL testing. However, the clinical relevance of aPLs in ovarian cancer remains controversial, as the current data are limited to case reports and small-scale studies. To address this gap, we conducted a prospective study to elucidate the correlation between the expression of aPL and clinical thrombotic events, with a focus on their timing relative to the administration of chemotherapy. Through this investigation, we sought to advance the understanding of thrombotic risk in ovarian cancer and refine strategies for its management.

II. Materials and methods

Ovarian Cancer Patients

From 2016 to 2017, we consecutively invited eligible Japanese patients from Hokkaido University Hospital and its affiliated hospitals to participate in our clinical study. These patients were histologically diagnosed with borderline epithelial ovarian, ovarian, primary peritoneal, or fallopian tube cancer, as confirmed by certified pathologists, irrespective of their clinical characteristics. Body mass index (BMI), history of thromboembolisms before the initial diagnosis of each patient's gynecological tumors, chemotherapy before blood sampling, disease stage, tumor diameter, and disease status were confirmed at registration. All thromboembolic events associated with the diagnosis of each patient's gynecological tumors were confirmed 5 months after the last subjects were registered in November 2017. Thromboembolisms were assessed when they were suspected by ultrasonography or contrast-enhanced computed tomography at the physicians' choice, and we did not perform routine screenings. Certified radiologists checked all the results of imaging tests to diagnose thromboembolism. D-dimer levels were checked in all patients at the same time as blood sam-

pling for this study.

This study was conducted according to the 1964 Declaration of Helsinki. The Institutional Review Board of Hokkaido University approved all experiments on the human genome for this study (Registration ID: 014-0106). Plasma and serum samples were prospectively collected from the patients, and antiphospholipid antibodies were measured as follows. Samples were collected in tubes containing a one-tenth volume of 0.105M sodium citrate and centrifuged immediately at 4℃. Plasma samples were depleted of platelets by filtration and stored at −80℃.

Antiphospholipid antibody (aPL) tests

Clotting tests to determine the activated partial thromboplastin time (aPTT) and dilute Russell's viper venom time (dRVVT) were performed for LAC determination using a semiautomated hemostasis analyzer (STart 4; Diagnostica Stago) according to the guidelines recommended by the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis 23. IgG and IgM anti-cardiolipin antibodies (aCL) were assayed using a standard enzyme-linked immunosorbent assay (ELISA) [24]. Anti-PS/PT antibodies were detected by an ELISA as previously described [25].

Statistical analysis

Using a univariate analysis, we analyzed any correlations between the clinical parameters and thrombosis or high D-dimer values and set P values of 0.05 as being statistically significant for Fisher's exact test. All statistical analyses were performed using the JMP® Pro software program (ver. 14.0.0; SAS Institute, Cary, NC, USA).

III. Results

Disease characteristics of the study patients

We prospectively enrolled 15 patients with newly diagnosed ovarian, primary peritoneal, or fallopian tube cancer. All approached patients agreed to participate, resulting in complete consecutive enrollment. The clinical characteristics of the patients are summarized in **Table 1**. The median age and BMI at registration were 63 years (range 41 – 82) and 23.4 kg/m^2 (range 16.1 – 34.3), respectively. Blood samples were collected either before or during treatment for the primary disease, except for one patient with recurrent disease. None of the patients had a history of thromboembolism unrelated to their current treatments for gynecological tumors, nor did they have untreated severe hypertension, diabetes, or hyperlipidemia. Two patients in the cohort were smokers; neither had experienced thromboembolism before blood sampling was conducted. None of our patients used pro-coagulant drugs at the time of blood sampling. We histologically diagnosed gynecological tumors using surgical specimens in 14 patients (93.3%) and a pleural effusion cell block in one patient (6.7%). The distribution of histological subtypes among the patients was as follows: serous carcinoma (33.3%), clear cell carcinoma (26.7%), mucinous carcinoma (20.0%), and endometrioid carcinoma (13.3%). Forty percent of patients (n=6) received systemic chemotherapy as neoadjuvant or adjuvant therapy before blood sampling. The median number of chemotherapy cycles was 3 (range, 1–7), and the regimen included tri-weekly paclitaxel and carboplatin (TC), dose-dense TC, tri-weekly TC with bevacizumab, gemcitabine as a single agent, and a combination of irinotecan and nedaplatin. **Figure 1** illustrates each patient's treatment course and the timing of the blood sampling. One patient (no.2 in **Figure 1**) received chemotherapy with bevacizumab before blood sampling. None of the patients had previously undergone radiotherapy. The follow-up period for thrombotic events after study registration ranged from 5 to 13 months. Three patients had preoperative deep venous thrombosis (DVT). In these three patients, blood samples were obtained from two patients before the diagnosis of DVT. In the other patient, we obtained a blood sample after the diagnosis of DVT, and this patient was not taking anti-coagulant drugs because the thrombi were organized. In addition, another patient with systemic thrombosis and cerebral infarction was diagnosed with Trousseau's syndrome and was taking warfarin during blood sampling for this study. The remaining 11 patients either had no thromboembolisms (n=8) or had temporal operation-related DVT (n=3).

Results of blood examinations and aPLs

None of the patients tested positive for syphilis at the time of the diagnosis of the gynecological tumor. The D-dimer level at study registration ranged from 0.5 to 24.96 mg/L, and 10 of 15 patients (66.7%) were positive when we set the cutoff value to the general threshold up to 1.0 mg/L. Regarding aPLs, only one patient was positive for the dRVVT screening test (**Table 2**). However, this patient was negative for all the other screening tests (no.9 in **Figure 1**). Therefore, none of the patients–including one with cerebral infarction of Trousseau's syndrome and six who were registered after chemotherapy–showed the presence of aPLs (**Table 2**). We subse-

Table 1 Disease characteristics and antiphospholipid antibody expression of the study patients (n=15)

Characteristic			
Age - year	Median (range)	63	41 - 82
Race	Asian - no. (%)	15	100.0%
Body mass index (kg/m^2)	Median (range)	23.4	16.1 - 34.3
	≤ 25 - no. (%)	12	80.0%
	> 25 - no. (%)	3	20.0%
History of thromboembolisms			
	Yes - no. (%)	2	13.3%
	No - no. (%)	13	86.7%
Smoker at diagnosis			
	Yes - no. (%)	2	13.3%
	No - no. (%)	13	86.7%
Surgery for diagnosis and/or debulking of present disease			
	Yes - no. (%)	14	93.3%
	No - no. (%)	1	6.7%
Complication of thromboembolism			
	Preoperative DVT - no. (%)	3	20.0%
	Multiple thrombosis with cerebral infarction - no. (%)	1	6.7%
	Postoperative DVT - no. (%)	3	20.0%
	None - no. (%)	8	53.3%
Use of anticoaglants at blood sampling			
	Yes - no. (%)	1	6.7%
	No - no. (%)	14	93.3%
Chemotherapy before blood sampling			
Yes - no. (%)		6	40.0%
	Number of cycles (median, range)	3	1-7
	Interval between last chemotherapy and blood sampling (week, median and rage)	5	0-33
No - no. (%)		9	60.0%
Histologic features			
	High-grade serous carcinoma - no. (%)	5	33.3%
	Clear cell carcinoma - no. (%)	4	26.7%
	Mucinous carcinoma - no. (%)	3	20.0%
	Endometrioid carcinoma - no. (%)	2	13.3%
	Unspecified - no. (%)	1	6.7%
FIGO stage			
	I / II - no. (%)	7	46.7%
	III / IV - no. (%)	8	53.3%
Maximal tumor diameter			
	> 15 cm - no. (%)	4	26.7%
	≤ 15 cm - no. (%)	11	73.3%
Disease status			
	primary - no. (%)	14	93.3%
	recurrent - no. (%)	1	6.7%
D-Dimer			
	< 8.5 mg/L - no. (%)	11	73.3%
	≥ 8.5 mg/L - no. (%)	4	26.7%
Syphilis test			
	positive - no. (%)	0	0.0%
	negative - no. (%)	15	100.0%
Antiphospholipid antibody			
	negative - no. (%)	15	100.0%
	positive - no. (%)	0	0.0%

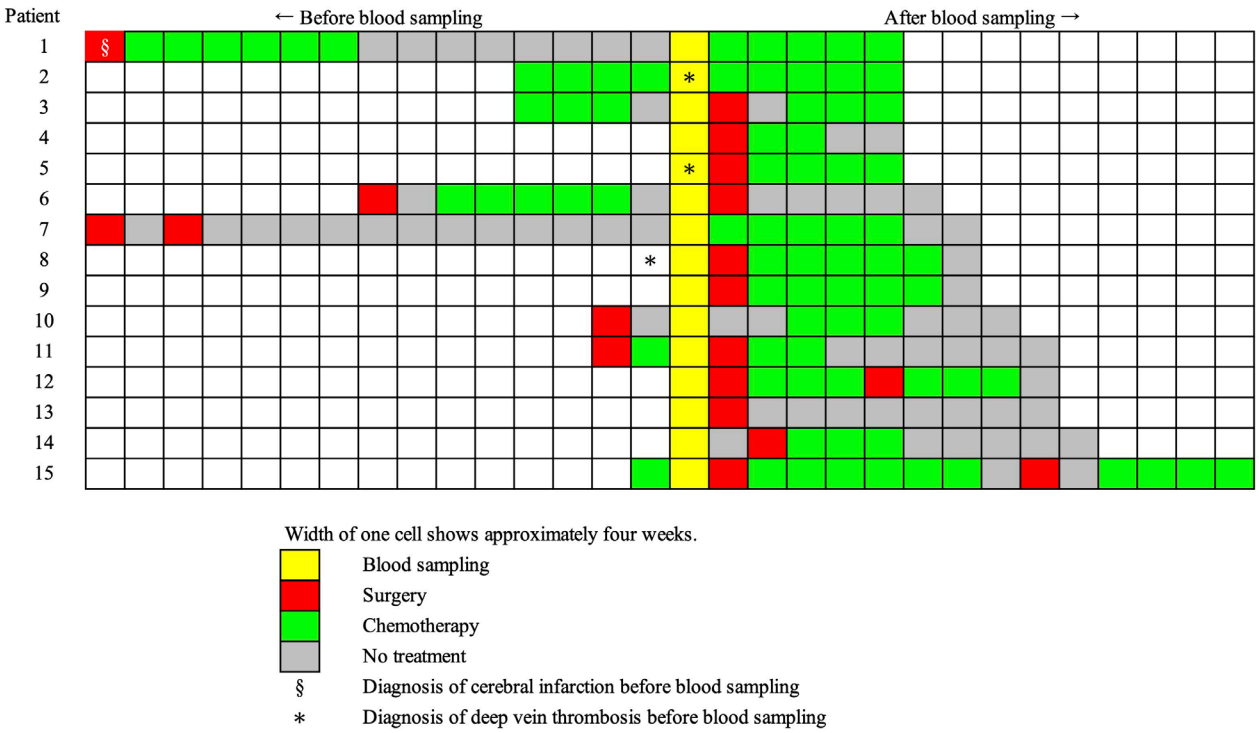

Figure 1 Clinical course and the timing of blood sampling

Table 2 Results of antiphospholipid antibodies (n=15)

	Antiphospholipid antibody (> normal range)					
Patient	PTT-LA	dRVVT >1.3	aCL-IgG >19.2	aCL-IgM >23.4	aPS/PT-IgG >1.2	aPS/PT-IgM >5.2
1	negative	1.16	low	low	low	low
2	negative	1.11	low	3.7	low	low
3	negative	1.02	6.1	low	low	low
4	negative	1.17	low	2.3	low	low
5	negative	1.11	low	low	low	low
6	negative	1.13	3.0	low	low	low
7	negative	1.21	low	low	low	low
8	negative	1.19	low	low	low	low
9	negative	1.43	low	low	low	low
10	negative	1.01	low	low	low	low
11	negative	1.07	11.2	low	low	low
12	negative	1.14	8.1	low	low	low
13	negative	1.15	8.3	10.5	low	low
14	negative	1.13	3.1	low	low	low
15	negative	1.06	low	low	low	low

quently asked 5 of the 15 (33.3%) patients to provide additional blood samples from 1 to 6 months after the first sampling, regardless of the timing of cancer treatment, and no patients had aPLs again (not shown in **Figure 1**). We also measured the expression of aPLs in four patients with mucinous borderline ovarian tumors using the same methods, and none of these patients had aPLs (data not shown).

A univariate analysis for risk factors of elevated D-dimer

Age (> 60 years), history of thromboembolisms, large tumor diameter (> 150 mm), high body mass index (> 25), histological subtypes of clear cell carcinoma, and ad-

vanced FIGO stage (III of IV) were not significantly correlated with thrombosis during the study period. These factors were also not significantly correlated with an elevated plasma D-dimer level at study registration when we set the cutoff value to the general threshold up to 1.0 mg/L. On the other hand, when we set the cutoff value of D-dimer to 8.45 mg/L, which was the mean value of acute phase patients with Trousseau's syndrome in a previous study 26, the histological subtype of clear cell carcinoma was significantly correlated with an elevated plasma D-dimer level ($P = 0.03$, **Table 3**). Although the limited sample size and heterogeneity of clinical backgrounds preclude definitive conclusions regarding the correlation between thrombotic events and prognosis, the 5-year overall survival rate was comparable at 57.1% among patients with and without thrombotic events, except for patient 4 in Figure 1, whose prognosis remains unknown.

IV. Discussion

To our knowledge, this study included the largest cohort of ovarian cancer patients to be investigated in this context. Clinically significant thrombotic events, excluding postoperative DVT, a common complication of abdominal surgery, were observed in 4 of the 15 patients. This finding aligns with existing reports indicating a high incidence of thrombotic events in ovarian cancer. The lack of detectable aPL in ovarian cancer patients in this study may be explained by several factors. First, ovarian cancer cells, whether treatment-naïve or following chemotherapy, might not prominently expose negatively charged phospholipids on their cell surfaces, which are essential for aPL production. Second, even if such phospholipids are expressed on cell surfaces, additional genetic predispositions associated with autoimmune diseases may be necessary to trigger the generation of aPL. Further basic and clinical investigations are required to confirm these hypotheses. Finally, the current finding–that ovarian cancer, despite its strong association with thrombosis, exhibits minimal aPL expression–raises the possibility that aPLs may have relatively limited involvement in cancer-associated thrombosis in other malignancies as well. However, this remains to be validated. This cohort included four patients with clear cell carcinoma, a rare histologic subtype in Western countries. This subtype is reported to carry the highest risk of serious thromboembolism among ovarian carcinomas [19], probably due to an excessive production of tissue factor [27]. Although our study was unable to demonstrate the risk factors for thromboembolism in patients with ovarian cancer due to the small number of subjects, the findings of our univariate analysis did suggest a correlation between clear cell carcinoma and elevated plasma D-dimer levels which strongly correlate with an increased risk of thrombosis, particularly venous thromboembolism, in ovarian cancer patients [28].

Previous studies have shown that treatment with chemotherapy is an independent risk factor for symptomatic and incidental venous thromboembolism in patients with endometrial, cervical, ovarian, tubal, or peritone-

Table 3 Univariate analysis of the factors associated with high D-dimer values

Univariate analysis of the factors associated with thrombosis

	n	Any thrombosis (%)	Odds ratio	95% confidence interval	P value
Age > 60	11	45.5 % (5/11)	0.83	0.08 - 8.24	0.77
History of thromboembolisms	2	50.0 % (1/2)	1.17	0.06 - 22.94	0.73
Large tumor diameter (> 150 mm)	4	25.0 % (1/4)	0.28	0.02 - 3.57	0.95
FIGO stage III / IV	8	62.5 % (5/8)	4.16	0.47 - 36.73	0.21
Body mass index > 25	3	0.0 % (0/3)	0.00	-	1.00
Clear cell carcinoma	4	50.0 % (2/4)	1.20	0.12 - 11.86	0.66

Univariate analysis of the factors associated with high D-dimer values

	n	D-dimer > 8.45 mg/L	Odds ratio	95% confidence interval	P value
Age > 60	11	27.3 % (3/11)	1.12	0.08 - 15.50	0.73
History of thromboembolisms	2	50.0 % (1/2)	3.33	0.16 - 70.90	0.47
Large tumor diameter (> 150 mm)	4	25.0 % (1/4)	0.89	0.06 - 12.3	0.76
FIGO stage III / IV	8	37.5 % (3/8)	3.60	0.28 - 46.36	0.34
Body mass index > 25	3	33.3 % (1/3)	1.50	0.10 - 23.06	0.64
Clear cell carcinoma	4	75.0 % (3/4)	30.00	1.41 - 638.2	0.03

al cancer [29)30)]. In addition, it has been suggested that chemotherapy, which is a mainstay in the treatment of ovarian cancer, may induce aPL via the externalization of negatively charged phospholipids due to apoptosis. Regarding elevated anionic phospholipid expression associated with tissue damage, aPLs are known to transiently appear during acute infections such as COVID-19 [31)]. Therefore, we hypothesized that aPLs could potentially be expressed at various stages in ovarian cancer, where prolonged tumor growth or treatment-related modifications may induce high anionic phospholipid expression levels. However, our study found no significant correlation between aPLs and thromboembolic events in general patients with ovarian cancer, and no aPL induction by chemotherapy with cytotoxic agents. Therefore, with the exception of infrequent situations suspicious for serious catastrophic anti-phospholipid syndrome–characterized by the rapid chronological development of fulminant thrombotic complications leading to multi-organ failure [32)] –clinicians do not need to routinely check aPLs during chemotherapy with cytotoxic agents in patients with ovarian cancer. However, we cannot discuss the influence of bevacizumab because of the small number of patients.

Although aPLs are generally reported to be present in 1–12% of healthy individuals 31, no positive cases were identified among the 15 patients in this cohort. The presence of aPLs has been proposed to be a potential risk factor for malignancy and mortality. A previous study demonstrated a 2.6-fold increase in the risk of cancer-related mortality in patients positive for anti-cardiolipin antibodies [33)]. Additionally, a prospective study of 1,000 APS patients with APS identified malignancies as one of the most frequent causes of death in this population [34)]. A recent large-scale study on obstetric APS (n=517) reported a significant association between aPL positivity and an increased incidence of malignancy after long-term follow-up (hazard ratio, 2.22), although no ovarian cancer cases were observed [35)]. However, the frequency of aPL induction in ovarian cancer remains poorly understood. Few case reports have documented patients with ovarian cancer who incidentally test positive for aPLs [36)-38)]. Fewer reports suggest that APS, characterized by the rapid onset of severe thromboembolisms, may arise as a paraneoplastic syndrome in ovarian cancer [36)39)]. For other malignancies, prior research reported an aPL positivity rate of 5.7% among patients with various solid tumors, with higher rates observed in VTE-positive colon cancer (11.3%), breast cancer (7.9%), head and neck cancer (7.7%), and lung cancer (4.7%) [40)]. However, it found no significant difference in thrombosis-free survival between aPL-positive and aPL-negative patients [41)]. Data specific to ovarian cancer were notably absent from these reports, suggesting that aPL positivity may remain infrequent in patients with ovarian cancer.

The tumor microenvironment of ovarian cancer is suggested to be procoagulant, where tumor cell-induced activated platelets interact with endothelial cells, pericytes, mesenchymal stem cells, cancer-associated fibroblasts, adipocytes, immune cells, and extracellular matrix elements through direct interactions or by releasing various modulatory factors and platelet microparticles [42)]. In this study, we did not evaluate intratumoral thrombosis induced by procoagulant factors other than aPLs and its association with systemic thrombosis, including pre-operative DVT or cerebral infarction, and further study is needed. Our study showed that aPLs are not generally associated with systemic venous and arterial thrombosis. Antiphospholipid antibody detection encompasses various types (including lupus anticoagulant), which require multiple tests for confirmation. Another key marker, aPS/PT, is a frequently observed and characteristic autoantibody of APS; however, its diagnostic utility has only recently been established. This study was associated with the common limitations of antiphospholipid antibody testing. However, based on this pilot study with a limited number of patients and previous studies, ovarian cancer and its treatment may have no direct association with the induction of APS or aPL. Further research in this area is warranted.

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Authorship Contributions

Takashi Mitamura (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Validation; Writing - original draft), Kenji Oku (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Writing - original draft), Yuichiro

Fujieda (Methodology; Supervision; Validation; Writing review & editing), Hiroshi Asano (Data curation; Formal analysis; Investigation; Supervision; Validation; Writing - review & editing), Chisa Shimada (Data curation; Investigation; Writing - review & editing), Ayako Nozaki (Investigation; Validation; Writing - review & editing), Daisuke Endo (Investigation; Writing - review & editing), Hidemichi Watari (Supervision; Writing - review & editing).

Disclosure of Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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