EJGO European Journal of Gynaecological Oncology

Prevalence of pulmonary embolism in gynecological cancer: the experience of a single tertiary center in Okinawa, Japan

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Summary

Purpose: To explore the incidence and outcome of pulmonary embolism (PE) cases in Japanese patients with gynecological malignancy. *Materials and Methods:* The authors reviewed the medical charts of all patients with gynecological malignancy who had a diagnosis of PE at this Hospital between January 2008 and December 2013. *Results:* Twenty patients developed PE during the study period. Nineteen patients had advanced or recurrent cancer. The incidence of PE was 1.8%, and those with ovarian, cervical, uterine corpus, and vulvar cancers were 7.5%, 0.86%, 1.0%, and 7.7%, respectively. PE developed in 12 patients before cancer treatment, six during chemotherapy, and two postoperatively. Three patients died as a result of PE. *Conclusion:* PE more frequently occurred in patients with ovarian and vulvar cancers, and those with advanced/recurrent disease. Patients with active gynecological cancer require thromboprophylaxis throughout hospitalization and not just in the perioperative period, and should be periodically assessed for venous thromboembolism risk.

Key words: Pulmonary embolism; Deep vein thrombosis; Gynecological cancer.

Introduction

The association between cancer and venous thromboembolism (VTE) was first described in 1823 by Bouillaud and later by Trousseau [1, 2]. Active cancer is an independent risk factor for VTE, with an overall four- to seven-fold increase in risk [3, 4], and accounts for 20–30% of all new VTE events [5, 6]. VTE is one of the most common complications seen in cancer patients [7].

It is well established that patients with gynecological cancer are at an increased risk of VTE [8, 9]. There are many risk factors for VTE in gynecological oncology patients, including age, race, pelvic surgery, previous leg edema, presence of venous varicosities and history of VTE, prolonged operative time, intravenous catheterization, chemotherapy administration, radiotherapy, and immobilization [10, 11]. The rate of deep vein thrombosis (DVT) in patients with gynecological malignancy is 11–18% in the published literature, whereas the rate of pulmonary embolism (PE) is 1–2.6% [9–12].

The purpose of this single-institutional retrospective study was to explore the clinical pattern of PE cases in Japanese patients with gynecological malignancy.

Materials and Methods

This retrospective study was carried out with the approval of the Institutional Research Board of the University of the Ryukyus (protocol #947). The authors reviewed the medical charts of all patients with gynecological malignancy treated at their Hospital between January 2008 and December 2013. The types of gynecological malignancy encountered included ovarian, fallopian tube, peritoneal, uterine, cervical, and vulvar cancers. Peritoneal and fallopian tube cancers were classified together as ovarian cancer because of the similarity of these conditions in terms of natural history and treatment. The authors also identified all patients with gynecological malignancy who also had a diagnosis of PE. The diagnosis of PE was confirmed using ultrasonography or computed tomographic (CT) venography. A comprehensive review of all medical documentation was then carried out, and the following data were extracted: age at diagnosis, type of gynecological malignancy, International Federation of Gynecology and Obstetrics (FIGO) stage, histology subtype, date and type of primary surgery, adjuvant treatment, serum D-dimer level, body mass index (BMI), and tumor status at the date of last contact. For cases involving PE, the authors also recorded the date of PE diagnosis, the nature of investigations carried out, along with the timing related to the date of cancer diagnosis and the treatments involved. Patients with gynecological malignancies were considered to be high-risk cases for VTE, and Japanese guidelines recommend a preventive approach according to the risk level of VTE in relation to a surgery [13]. The present study patients were asked to wear thromboembolic deterrent stockings and/or intermittent pneumatic compression bandages postoperatively and were treated using prophylactic anticoagulation therapy (unfractionated

Revised manuscript accepted for publication September 20, 2016

Table 1. — *Demographic and clinical characteristics of patients with pulmonary embolism.*

Site of Cancer	Ovary, tube, peritoneum	Cervix	Uterine	Vulva	Total
No. of patients	9	6	3	2	20
Incidence of PE	7.5% (9/120)	0.86% (6/700)	1.04% (3/288)	7.7% (2/26)	1.8% (20/1110)
Median age (range)	73 (43-80)	64 (46-75)	61 (55-62)	72.5 (60-85)	63.5 (43-85)
No. of patients >60 years	7/9 (78%)	4/6 (67%)	2/3 (67%)	2/2 (100%)	15/20 (75%)
BMI (kg/m^2)	23.8 (20-29)	25.3 (16.1-40.5)	21.3 (20.6-40.7)	26.3 (22.9-29.7)	23.8 (16.1-40.7)
BMI >24	4/8 (50%)	3/5 (60%)	1/3 (33%)	1/2 (50%)	9/18 (50%)
D-dimer					
Elevated	7	5	3	2	17
Non-elevated	0	0	0	0	0
Unknown	2	1	0	0	3
FIGO stage					
Stage I + II	0	0	0	1	1
Stage III + IV	8	4	3	0	15
Recurrence	1	2	0	1	4
Histological subtype					
Squamous cell	0	4	0	2	6
Adenosquamous	0	1	0	0	1
Serous	4	0	1	0	5
Endometrioid	1	1	2	0	4
Clear cell	1	0	0	0	1
Mucinous	1	0	0	0	1
Undifferentiated	2	0	0	0	2
DVT	7	2	2	2	13

PE: pulmonary embolism, BMI: body mass index, FIGO: International Federation of Gynecology and Obstetrics, DVT: deep vein thromboembolism.

Table 2. — *Onset of pulmonary embolism and symptoms.*

	PE + DVT	PE alone	Total
Onset			
Pretreatment	8	4	12
Postoperative	2	0	2
During chemotherapy	3	3	6
Symptoms			
Dyspnea + shock	1	1	2
Dyspnea + chest pain	4	3	7
Leg swelling	8	0	8
Elevated D-dimer	0	3	3

PE: pulmonary embolism, DVT: deep vein thromboembolism.

heparin and low molecular weight heparin) from six hours to five days postoperatively.

Results

Patient characteristics are shown in Table 1. There were 20 patients with gynecological malignancy who developed PE during the study period, involving nine patients with ovarian, fallopian tube, and peritoneal cancers, six with cervical cancer, three with endometrial cancer, and two with vulvar cancer. The incidence of PE amongst the entire cohort of patients with gynecological malignancy in the present institution is 1.8% (20 of 1,110 cases), whereas those with ovarian cancer, cervical cancer, uterine corpus cancer, and vulvar cancer represent 7.5% (nine of 120 cases), 0.86% (six of 700), 1.0% (three of 288), and 7.7% (two of 26), respectively. Median age of the patient cohort was 63.5 (range, 43–85) years. Median BMI was 23.8 (range, 16.1–40.7), and there was no significant difference between the cancerous tissue sites. Serum D-dimer levels were elevated in all 17 patients tested. Nineteen of the 20 patients had advanced or recurrent disease, whereas 13 patients had cancers that were complicated by DVT. Interestingly, only one patient with ovarian clear cell carcinoma developed PE in this study cohort.

Table 2 describes the symptoms and onset of PE during the course of cancer treatment. PE developed in 12 patients before cancer treatment, six during chemotherapy, and two postoperatively. Postoperative PE occurred in two cases of vulvar cancer. One of the patients was a 60-year-old woman who underwent radical vulvectomy and colostomy (operation time, 12 hours and 37 minutes). The other patient was an 85-year-old woman with Stage IB disease who underwent wide radical excision (operation time, one hour and 32 minutes). Both patients were classified with the highest risk for PE in gynecological surgery and were treated with thromboembolic deterrent stockings, intermittent pneumatic compression, and prophylactic anticoagulation therapy. Most events in the present cohort were diagnosed by clinical findings, such as lower extremity pain or swelling, chest pain, shortness of breath, or dyspnea on exertion.

Table 3. — *Clinical features of 20 patients with pulmonary embolism.*

Age, years	BMI	Site of cancer	FIGO Stage	D-dimer	DVT	Onset of PE	Symptom	Treatment for PE	PE outcome	Prognosis
43	20	Ovary	IIIC	Elevated	Yes	Pretreatment	Dyspnea, Shock	Anticoagulation + IVC filter	Improved	NED
80	25.8	Ovary	IIIC	Elevated	Yes	Pretreatment	Leg swelling	Anticoagulation	Improved	DOD
60	NA	Ovary	Recurrence	Unknown	Yes	During chemotherapy	Leg swelling	Anticoagulation	Improved	AWD
64	29	Ovary	IIIC	Elevated	Yes	Pretreatment	Leg swelling	Anticoagulation + IVC filter	Improved	AWD
80	22.2	Ovary	IIIC	Elevated	No	Pretreatment	Elevated D-dimer	Anticoagulation	Improved	NED
56	22.8	Ovary	IIIC	Elevated	No	During chemotherapy	Dyspnea	Anticoagulation	Improved	AWD
75	20.3	Tube	IIIC	Elevated	Yes	Pretreatment	Leg swelling	Anticoagulation	Improved	NED
73	24.7	Peritoneum	IV	Elevated	Yes	Pretreatment	Dyspnea	Anticoagulation + IVC filter	Improved	AWD
74	25.6	Peritoneum	IV	Unknown	Yes	During chemotherapy	Dyspnea	Anticoagulation + IVC filter	Improved	DOD
65	NA	Cervix	IVB	Elevated	Yes	Pretreatment	Leg swelling	Anticoagulation	Improved	AWD
63	16.1	Cervix	Recurrence	Elevated	No	During chemotherapy	Dyspnea, Shock	Anticoagulation	Dead	DID
65	25.3	Cervix	IVB	Elevated	No	During chemotherapy	Dyspnea	Anticoagulation	Dead	DID
46	21.5	Cervix	Recurrence	Elevated	No	Pretreatment	Elevated D-dimer	Anticoagulation	Lost F/U	Lost F/U
75	40.5	Cervix	IVB	Elevated	No	Pretreatment	Dyspnea	Anticoagulation	Improved	AWD
55	32.8	Cervix	IVB	Unknown	Yes	Pretreatment	Leg swelling	Anticoagulation	Improved	AWD
62	20.6	Uterine	IVB	Elevated	Yes	During chemotherapy	Leg swelling	Anticoagulation	Improved	AWD
61	21.3	Uterine	IVB	Elevated	Yes	Pretreatment	Leg swelling	Anticoagulation	Dead	DID
55	40.7	Uterine	IVB	Elevated	No	Pretreatment	Elevated D-dimer	Anticoagulation	Improved	DOD
60	29.7	Vulva	IB	Elevated	Yes	Postoperation	Dyspnea	Anticoagulation	Improved	NED
85	22.9	Vulva	Recurrence	Elevated	Yes	Postoperation	Dyspnea	Anticoagulation	Improved	NED

FIGO: International Federation of Gynecology and Obstetrics, DVT: deep vein thromboembolism, PE: pulmonary embolism, NA: not assessed, NED: no evidence of disease, DOD: dead of disease, AWD: alive with disease, DID: dead of intercurrent disease.

However, elevated levels of serum D-dimer was identified in three patients.

The clinical characteristics of the present 20 patients are summarized in Table 3. Three patients died as a result of PE. Two patients developed PE during chemotherapy, both with a recurrence of cervical cancer Stage IVB. PE disappeared following anticoagulation therapy, but the condition reoccurred two to three months after the initial PE treatment. One patient with Stage IVB endometrial cancer (peritoneal carcinomatosis) developed PE before cancer treatment and was immediately administered with anticoagulation therapy. However, because of deterioration of general condition, she died of PE three days later.

Discussion

The incidence of PE among the entire cohort of patients with gynecological malignancy in the present institution was 1.8%, and those with ovarian, cervical, uterine corpus, and vulvar cancers were 7.5%, 0.86%, 1.0%, and 7.7%, respectively. This is consistent with previous reports in which the reported rate of PE in patients with gynecological malignancy was 1–2.6% [9, 10, 12]. The present study, however, showed that PE more frequently occurred in patients with ovarian and vulvar cancers, advanced/recurrent disease, and elevated serum D-dimer. Ovarian and vulvar cancers were the most common malignancies complicated by PE in the present study.

Ovarian cancer typically presents in the advanced stage with widely metastatic disease. A retrospective review of 253 patients with ovarian cancer treated by a combination of surgery and chemotherapy revealed a 16.6% rate of VTE. Multivariate analysis further demonstrated that residual disease, increasing age, and BMI were independent risk factors for the development of VTE [14]. Rodriguez *et al.* reported that, among 13,031 cases of ovarian cancer, there was a 5.2% rate of VTE within 24 months of diagnosis [15]. Furthermore, measurement of D-dimer levels and subsequent ultrasonography revealed that silent or subclinical VTE frequently occurs before surgery in cases of ovarian cancer [16]. While only one patient with ovarian clear cell carcinoma developed PE in the present study, this particular type of carcinoma is reported to predispose patients to a thrombogenic phenotype [17, 18],

Levels of serum D-dimer were elevated in all the present patients when measured at the onset of PE. However, the validity of D-dimer for oncology patients is compromised because its levels may be elevated even in the absence of thrombosis. Elevation in D-dimer levels may reflect the biology of the underlying tumor. However, the negative predictive value (NPV) and sensitivity of D-dimer testing are known to be high for diagnosing PE among oncology patients. [19]. Di Nisio *et al*. [20] found NPV to be high among 2,066 cancer patients, and PE could be ruled out by a negative D-dimer test. While the major limitation of D-dimer testing for oncology patients is its low specificity, the test retains a high sensitivity and NPV [21]. Although most events in the present cohort of patients were diagnosed by clinical findings, elevated serum levels of D-dimer facilitated clinical decision making for further testing in three patients without any clinical symptoms, which ultimately led to the diagnosis of PE.

Patients with gynecological malignancies are thought to represent high-risk cases for VTE, and the Japanese guidelines recommend prevention according to the risk of VTE in relation to surgery for patients with both benign and malignant gynecological tumors [13]. Accordingly, patients undergoing surgery were asked to perform mechanical and pharmacological prophylaxis according to the level of VTE risk at the present hospital, and those with gynecological malignancy were well controlled in terms of PE. Postoperative PE was observed in only two patients with vulvar cancer.

With regards to the timing of PE episodes, the authors noticed that PE occurred before the treatment of advanced or recurrent cancer more than during the postoperative period. Cancer induces a prothrombotic state by favoring both endothelial dysfunction and vascular inflammation. Other cancer-related factors can act as additional triggers, such as chemotherapy and other supportive therapies [7, 20]. This point was of clinical significance because existing clinical guidelines recommend VTE prophylaxis for cancer patients through hospitalization [22, 23]. The revised American Society of Clinical Oncology (ASCO) guidelines recommend that most hospitalized patients with active cancer require thromboprophylaxis throughout hospitalization and that patients with cancer should be periodically assessed for VTE risk [24]. Physicians should always take this point into account and perform thromboprophylaxis and periodic assessment for patients with gynecological cancer without any symptoms and clinical findings.

There are several limitations in the present study. First, retrospective analysis led to incomplete and ascertainment bias. Second, this study was a single-institutional study involving a small number of patients. Last, the authors only conducted a descriptive analysis of the clinical pattern of PE occurrence.

Conclusion

The incidence of PE in the present entire cohort of patients with gynecological malignancy in this institution was 1.8%. Furthermore, PE more frequently occurred in patients with ovarian and vulvar cancers, and those with advanced/recurrent disease. Patients with active gynecological cancer require thromboprophylaxis throughout hospitalization and not just the perioperative period and should be periodically assessed for VTE risk.

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