Tumor Size, Depth of Myometrial Invasion, and Preoperative Histologic Grade as Prognostic Factors of Lymph Node Involvement In Endometrial Cancer: Analysis of Data*

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Objective: To determine whether the preoperative histologic grade, intra-operative tumor diameter, depth of myometrial invasion may predict the risk of nodal metastasis in patients with endometrial cancer in a tertiary government hospital.

Study Design and Methodology: This is a retrospective analysis of endometrial cancer cases seen in a tertiary government hospital, Out-Patient Department of the Gynecologic Oncology Section from January 2008-June 2014. Preoperative histologic grade, intra-operative tumor diameter, depth of myometrial invasion and nodal involvement were recorded. Pathology reading was done in the institution. The endpoint of this study was pelvic node involvement. Analysis of the different variables was done using the following test statistics: T-test, Chi-square test, Fisher Exact test, Logistic Regression Analysis, Wilcoxon Signed Rank Test.

Results: A total of 127 patients were included in the study. Out of the 127 patients, 12 (9.4%) had pelvic node involvement and 115 (90.6%) did not have pelvic node involvement. There was a significant association between the grade of tumor (grade 3) and pelvic node spread as demonstrated by the p value 0.04. The depth of myometrial invasion and tumor size did not correlate with pelvic node involvement as shown in the univariate and multivariate analysis.

Conclusion: This study showed that endometrial cancer patients with a higher preoperative tumor grade (grade 3) had a higher chance of pelvic lymph node involvement than lower grade tumor (grade 1-2). This study did not show any significant association of intra-operative tumor size, and depth of myometrial invasion with pelvic lymph node involvement.

Key words: endometrial cancer, tumor grade, tumor size, pelvic lymph node involvement, myometrial invasion

Endometrial cancer is the 13th most common cancer in both sexes (2%) and the 7th leading site among women (4%) in our country. It was estimated that 1, 760 new cases were diagnosed in 2010. The incidence rate starts rising steeply at age 40 and continues to increase with increasing age. The estimated

* First place winner, SGOP Research Contest 2014

age-standardized national incidence rate was 4.6 per 1000, 000 in 2008. One out of 100 women would have had a likelihood of getting corpus uteri cancer before age 75.[1]

Majority of patients present with early stage disease, and the prognosis of endometrial carcinoma patients is generally good, with a 5-year overall survival rates of 80 to 85% and cancer specific survival rates of 90% to 95%.[2] Given this good outcome, the surgeon's task is to properly select patients who might benefit from the extensive surgery, adjuvant treatment and to avoid giving unnecessary treatment for low-risk cases.

It has been recommended that surgical staging must include lymphadenectomy, which is the standard of care in most endometrial cancers. But it is not clearly defined if all patients should undergo lymphadenectomy. Some believe that although it improved surgical staging, it did not improve disease free or over-all survival[4,7,8] and some have shown that it may increase operative time, morbidity and increase blood loss.[5,6]

This study is done to know if these specific risk factors may help identify the risk of nodal involvement in a tertiary level government hospital.

Objective

To determine whether the preoperative grade, intra-operative tumor diameter, depth of myometrial invasion may predict the risk of nodal metastasis in patients with endometrial cancer in a tertiary level government hospital.

Methodology

A retrospective analysis of endometrial cancer cases seen at the Out-Patient Department of the Gynecologic Oncology Section of the Jose Reyes Memorial Medical Center from January 2008-June 2014 was collected.

The age, sex, race, year of diagnosis, geographical location, as well as data regarding the stage of the disease, tumor size, tumor histology, preoperative and postoperative histologic grade, depth of myometrial invasion, and lymph node involvement were recorded in the charts.

All patients who underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy, peritoneal fluid cytology, pelvic lymph node dissection and para-aortic lymph node evaluation were included in the study. Histopathology reading was done in the institutions' Department of Pathology. The inclusion criteria are as follows: those age 18 years old and above with endometrial cancer who underwent primary surgery. The exclusion criteria are as follows: those with previous history of gynecologic cancer or evidence of disease (cervix, ovarian, fallopian tube), those with incomplete data regarding the lymph node involvement, tumor size, histologic grade and depth of invasion of tumor and those with previous chemoradiation, or chemotherapy prior to surgery.

Risk was also classified using the Mayo Criteria which defines Low risk group as grade 1 or 2 tumor histology; less than 50% myometrial invasion; and tumor size ? 2cm. High risk group were composed of tumors with grade 3 tumor histology; more than 50% myometrial invasion and tumor size > 2 cm. The primary endpoint for this study is the presence of lymph node involvement based on the histopathology result.

Sample Size Computation

The number of samples collected was computed using a 95% level of confidence. With an estimated prevalence of pelvic node involvement of 9.0%, at least 126 subjects are needed.

Data Processing and Analysis

Data were encoded and tallied in SPSS version 10 for windows. Descriptive statistics were generated for all variables. For nominal data frequencies and percentages were computed. For numerical data, mean ± SD were generated. Analysis of the different variables was done using the following test statistics:

T-test - used to compare two groups with numerical data.

Chi-square test - used to compare/associate nominal (categorical) data

Fisher Exact test - a modification of chi-square used for 2x2 table when there are expected frequencies <5.

Logistic Regression Analysis- a multivariate test use to identify predictors of an outcome variable.
Wilcoxon Signed Rank Test - non parametric statistical hypothesis test that compares two related samples whether their population ranks differ

Results

One hundred eighty-nine (189) endometrial cancer patients seen in a tertiary government hospital, Out-Patient Department of the Gynecologic Oncology Section from January 2008- June 2014 who underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy, peritoneal fluid cytology, pelvic lymph node dissection and para-aortic lymph node evaluation were gathered. Of these, 62 patients were excluded for unknown tumor size and histologic grade, no biopsy prior to surgery, neoadjuvant radiotherapy and incomplete data. A total of 127 patients were included in the study. Out of the 127 patients, 12 (9.4%) had pelvic node involvement and 115 (90.6%) did not have pelvic node involvement. (Table 1)

Table 1. Distribution of subjects according to pelvic node involvement.

	Frequency (n=127)	Percentage (%)
Pelvic Node Involvement		
Positive	12	9.4
Negative	115	90.6

Table 2 shows the association of the patient demographics by pelvic node involvement. The mean age at diagnosis was 55.3 (± 5.14) for subjects with pelvic node involvement and 53.2 (± 8.64) for those without pelvic node involvement (p value=0.38). More subjects with negative lymph node involvement were found to have a lower grade of tumor. Ninety-five percent of grade 1 differentiation had no pelvic lymph node involvement, followed by grade 2 tumor differentiation at 90.5%, as compared with grade 3 tumor which comprised 73.7% of no pelvic node involvement. Conversely, preoperative tumor grade 1 has only 4.5% pelvic lymph node involvement, followed

Table 2. Patient demographic variables by pelvic node involvement.

	Pelvic Node Involvement		Total (n=127)	p-value*
	(+) (n=12)	(-) (n=115)		
Age at diagnosis (in years)				
Mean ± SD	55.33 ± 5.14	53.20 ± 8.64	53.40 ± 8.38	0.38 (NS)
Preoperative Grade				
1	3 (4.5%)	63 (95.5%)	66	0.04 (S)
2	4 (9.5%)	38 (90.5%)	42	
3	5 (26.3%)	14 (73.7%)	19	
Myometrial Depth of invasion				
<50	5 (6. 7%)	70 (93.3%)	75	0.23 (NS)
>50	7 (13.5%)	45 (86.5%)	52	
Tumor Size				
≤cm	1 (4.0%)	24 (96.0%)	25	0.46 (NS)
>2cm	11 (10.8%)	91 (89.2%)	102	
LVSI				
(+)	10 (29.4%)	24 (70.6%)	34	<0.0001 (S)
(-)	1 (1.1%)	89 (98.9%)	90	
Not Demonstrated	1 (33.3%)	2 (66.7%)	3	

by grade 2 tumor at 9.5% pelvic lymph node involvement. The most involved tumor differentiation is the tumor grade 3 which comprises 26.3%. These values were statistically significant (p value = 0.04). The result showed that there was a significant association between the grade of tumor and pelvic node spread as demonstrated by the p value 0.04.

Of the patients with myometrial invasion, 7 (13.5%) with more than 50% myometrial invasion had nodal metastasis while 45 (86.5%) had none. For patients with less than or exactly 50% myometrial invasion, 5 (6.7%) had nodal metastasis and 70 (93.3%) had no nodal metastasis but it was not statistically significant.

Of the patients with intra-operative size of more than 2 cm, there were 11 (10.8%) who had nodal involvement as compared to only 1 (4.0%) for tumors less than or equal to 2cm intra-operative size but it was not statistically significant.

When the patients were classified according to the Mayo criteria (Table 3), the mean age of diagnosis was 54.13 (±8.25) for the high risk and 49.5 (±8.15) for the low risk which was statistically significant (p value = 0.02). Of these categories, 84.3% were high risk and 15.7% were low risk. Eleven out of twelve (11/12) who had lymph node involvement were in the high risk group (91.7%) versus one with lymph node involvement out of 12 in the low risk group (8.3%). The high risk category has an overall lymph node involvement rate of 10.3% as compared to the low risk group which has only 5% rate, but it was not statistically significant (p value = 0.69).

Table 3. Patient demographic variables by Mayo Risk Criteria.

	Risk Category High Risk (n=107)	Low Risk (n=20)	Total	p-value*
Age at diagnosis (in years) Mean ± SD	54.13 ± 8.25	49.50 ± 8.15	53.40 ± 8.38	0.02 (S)
BMI Mean ± SD	25.75 ± 4.93	23.90 ± 5.36	25.43 ± 5.03	0.14 (NS)
Depth of Myometrial Invasion ≤50 >50	55 (73.3%) 52 (100%)	20 (26.7%) 0	75 52	<0.0001 (S)
Histologic Grade 1 2 3	55 (83.3%) 34 (81.0%) 18 (94.7%)	11 (16.7%) 8 (19.0%) 1 (5.3%)	66 42 19	0.45 (NS)
Intraoperative Tumor Diameter ≤2 cm >2cm	5 (20.0%) 102 (100%)	20 (80.0%) 0	25 102	<0.000001 (S)
Lymph Node Involvement Positive Negative	11 (91.7%) 96 (83.5%)	1 (8.3 %) 19 (16.5%)	12 115	0.69 (NS)
Histologic Subtype Endometrioid Non Endometrioid	101 (83.5%) 6 (100%)	20 (16.5%) 0	121 6	0.58 (NS)
LVSI Positive Negative Not Demonstrated	33 (97.1%) 71 (78.9%) 3 (100%)	1 (2.9%) 19 (21.1%) 0	34 90 3	0.01 (S) (between (+) and (-) only)

* p-values >0.05- Not significant; p-values ?0.05-Significant

However, myometrial invasion depth of more than 50% and intra-operative tumor size more than 2 cm, were both significantly associated with the high risk category with a p value of <0.0001 and 0.000001, respectively.

Multivariate logistic regression analysis was done to assess the over-all effects of the three variables, which include preoperative tumor grade, tumor size and the depth of myometrial invasion. It was found in this study that preoperative histologic tumor grade was a significant predictor of nodal involvement. The risk of having a pelvic nodal metastasis with a grade 3 tumor was almost 5 times higher than lower grade tumors (OR = 4.63; 95% CI = 1.27-16.85; p value of 0.02). For the tumor size (>2cm), the risk of nodal metastasis was almost 2 times higher than in those with (≤2 cm), but not statistically significant, with OR = 2.15; 95% CI = 0.25-18.56; p value of 0.48. Myometrial invasion of >50% has almost 2 times higher risk than those <50% myometrial invasion, with OR = 1.78; 95% CI = 0.50-6.26; p value of 0.36 which was also not statistically significant.

Comparing the preoperative and the postoperative tumor grade, majority (81.9%) had the same grade postoperatively. Only 6.3% or 8 out of 127 were upgraded and 11.8 % or 15 out of 127 were even downgraded on the final histopathology. The changes were statistically not significant at p value 0.24 using the Wilcoxon Signed Rank Test.

Table 4. Preoperative Tumor Grade, Tumor Size and Myometrial Invasion as Predictors of Pelvic Node Involvement (Multivariate Analysis).

Variable	OR	95% CI	P value
Grade (3)	4.63	1.27- 16.85	0.02 (S)
Tumor Size (>2cm)	2.15	0.25 - 18.56	0.48 (NS)
Myometrial Invasion (>50%)	1.78	0.50 - 6.26	0.36 (NS)

Table 5. Comparison of the Pre-operative and Post-operative Tumor Grade.

	Median	*p value
Pre-op Grade	1	0.24
(NS)	1	Post-op Grade

* p-values >0.05- Not significant; p-values ?0.05-Significant Wilcoxon Signed Rank Test

Discussion

Surgical Staging is the most accurate way to establish and document the extent of disease spread. From the GOG 33 trial[12], there is roughly an estimated 9% baseline rate of nodal disease. But how can we classify patients with low risk endometrial cancer from the high risk category, which population should be offered lymph node dissection and which population it is safely avoided.[13]

From our Society of Gynecologic Oncologists of the Philippines Clinical Practice Guidelines 2012[3], surgical staging for all endometrial cancer cases must include adequate lymphadenectomy. It is the standard of care in the staging of most endometrial cancers. However, the role of lymph node dissection in early stage endometrial carcinomas has not yet been clearly established. Some studies do not agree on the role of lymphadenectomy in low risk endometrial carcinomas. Milam, et al.[4] found patients belonging to low risk characteristic of endometrial carcinoma, had only 0.8 % rate of nodal metastasis. Patients with high-risk characteristics had 6.3 times the risk of nodal metastasis when compared to lower risk patients. Panici, et al.[7] and Chan, et al.[9] noted that although systematic pelvic lymphadenectomy statistically improved surgical staging, it did not improve disease-free or overall survival and had a higher rate of postoperative complications than those who received only conventional surgery. Kitchener, et al.[8] in the MRC ASTEC trial showed no evidence of benefit in terms of overall or recurrence-free survival for pelvic lymphadenectomy in women with early endometrial cancer.

The main advantage of comprehensive staging is to provide the patient and physician with the greatest amount of information intra-operatively which may result in less use of radiation. Without nodal information, failure to determine the need for postoperative radiation may happen.[13]

A cohort study by Dowdy, et al.[5] in 2012, that included 285 patients who had lymphadenectomy along with hysterectomy, concluded that lymph node dissection significantly and unfavorably

impacted operating room (OR) time, blood loss, length of hospital stay and 30-day morbidity. Complications in the first 30 days occurred in 19.3% versus 37.5% of patients in the non-LND versus LND group, respectively with a $p<0.001$.[5,6] This study also presented a 30-day cost of care as a function of surgical approach and lymph node dissection. The addition of lymph node dissection significantly increased cost for both open and closed approaches. The cost of care correlated directly with increasing severity of the adverse events occurring during the 30 days following surgery.[5]

A retrospective study by Alhilli, et al.[15] wherein preoperative histologic grade and intra-operative tumor diameter were used to stratify the risk groups, but no information on the myometrial invasion was recorded. Their findings showed that grade 1 tumors have a low over all risk (1.3%) lymph node involvement, and regardless of myometrial invasion, did not exceed 2% lymph node involvement until tumor size exceeded to 3 cm.

The result of this study showed that there was a significant association noted with a higher preoperative tumor grade with pelvic node involvement. Preoperative Grade 1-2 tumor has a lower chance of having pelvic node metastasis. There was only a 4.5 chance of pelvic node metastasis for Grade 1 and 9.5% for Grade 2 which was significant. Given a low preoperative tumor grade, the surgeon might preoperatively plan to defer node dissection provided the intra-operative findings concurs that tumor is confined to the corpus. This might decrease the morbidity, operative time, blood loss and even cost of the hospitalization.

There was no statistically significant difference noted between the preoperative and postoperative tumor grades in this study (Table 5). Therefore, we may surmise that the preoperative tumor grade may be used as a basis for doing lymphadenectomy.

The depth of myometrial involvement and the preoperative tumor size did not significantly influence lymph node involvement. Using the Mayo criteria, the high risk group had a higher lymph node involvement (91.7%) when compared with low risk group (8.3%).

Conclusion

This study showed that endometrial cancer patients with a higher tumor grade (grade 3) had a higher chance of pelvic lymph node involvement. This study did not show any significant association of tumor size, and depth of myometrial invasion with pelvic lymph node involvement.

Recommendation

Since there is a lower risk of pelvic lymph nodes metastasis for preoperative tumor grade 1 to grade 2 tumors confined to the corpus, lymph node dissection may be omitted to lessen morbidity, operative time, and further blood loss. It may also lessen the hospitalization cost associated with these complications. A preoperative grade 3 tumor would warrant lymphadenectomy as it has a higher risk of pelvic node involvement.

Further and larger studies may be utilized to associate tumor size, tumor grade and depth of myometrial invasion with pelvic node involvement.

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Association of Risk Factors on Deep Venous Thrombosis Among Patients with Histologically Proven Gynecologic Malignancy and Preoperatively Assessed To Have Ovarian Malignancy*

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Background: Venous thromboembolism (VTE) which comprises deep vein thrombosis (DVT) and pulmonary embolism (PE) represents a major health problem in gynecologic malignancy. Malignancy itself and its therapeutic intervention (e.g. surgery, chemotherapy) increase thrombophilic predisposition. The reported rate of DVT in gynecologic cancer ranges from 11-18% with the rate of pulmonary embolism between 1 and 2.6%. However, in the Philippines, the incidence is unknown, hence the conduct of this study.

Objectives: This study is conducted to determine the incidence, risk factors and their association on DVT among patients with histologically proven gynecologic malignancy and pre-operatively assessed to have ovarian malignancy admitted for surgery in a tertiary government hospital.

Methods: This is a prospective cohort study conducted in a tertiary government hospital, Section of Gynecologic Oncology, Department of Obstetrics and Gynecology. A duplex scan of the lower extremities was performed among patients who met the inclusion criteria.

Results: A total of fifty-two (52) patients with gynecologic malignancy were included in the study: twenty-five (25) ovarian cancer; twenty-three (23) endometrial cancer; two (2) cervical cancer; and two (2) vulvar cancer cases. The incidence of DVT was 13% (7/52). Among the seven cases (7) of DVT, 71.4% (5/7) and 28.6% (2/7) were observed among patients with ovarian cancer and endometrial cancer respectively. No DVT was observed among patients with cervical and vulvar cancer. In terms of risk factors, normal body mass index (BMI) was not associated with DVT at p-value of 0.011. With regards to surgery, the following surgical procedures were associated with a higher rate of DVT namely a) exploratory laparotomy, peritoneal fluid cytology, adhesiolysis, modified radical hysterectomy with bilateral salpingooophorectomy, infracolic

* Third place winner, 2014 Research Contest.

omentectomy, biopsy of adhesions, lymph node palpation; b) exploratory laparotomy, peritoneal fluid cytology, total hysterectomy with bilateral salpingooophorectomy, lymph node palpation and insertion of JP drain; c) exploratory laparotomy, peritoneal fluid cytology, total hysterectomy with bilateral salpingooophorectomy, tumor debulking, biopsy of sigmoid implant, bowel run and insertion of JP drain; and d) exploratory laparotomy, peritoneal fluid cytology, total hysterectomy with bilateral salpingooophorectomy, bilateral pelvic lymph node dissection, para-aortic lymph node sampling, infracolic omentectomy, random peritoneal biopsy, biopsy of implants, appendectomy and insertion of JP drain. All four surgical procedures were performed in patients with ovarian cancer, and was statistically significant (14.3% vs 0.0%) at p=0.01. Moreover, there is a higher rate of DVT among patients with advanced stage ovarian cancer (stage IVB). There was a higher rate of DVT symptoms observed among patients with DVT (57.1% vs 22.2%, p=0.053) which manifested and was identified as edema (57.1%), pain (42.9%), erythema (57.1%) and tenderness (28.6%). None among patients with DVT had varicosities. Furthermore, the significant common specific symptoms associated with DVT were the following: a) unilateral edema (28.6%); b) bilateral pain (28.6%); c) bilateral and unilateral erythema (28.6%); and d) bilateral tenderness (28.6%).

Conclusion: Based on the results of the study, patients with histologically proven gynecologic malignancy and those pre-operatively assessed to have ovarian malignancy with DVT had BMI not within the normal. They was predispostion for those with ovarian or endometrial cancer; with advanced stage of cancer; will undergo extensive cytoreductive surgery and will use compression stockings. In terms of symptoms, they present with edema, pain, erythema and tenderness. In line with this, thromboprophylaxis is recommended to be administered to gynecologic oncology patients and patients preoperatively assessed to have ovarian malignancy who will undergo extensive cytoreductive surgery in order to prevent complications of venous thrombosis.

Key words: deep venous thrombosis, venous thromboembolism

Significance of the study

Venous thromboembolism (VTE) which comprises deep vein thrombosis and pulmonary embolism represents a major health problem in gynecologic malignancy. Malignancy itself which predisposes to hypercoagulable state, as well as its therapeutic intervention (e.g. surgery, chemotherapy) leading to vascular injuries, advancing age, advanced stage, immobility even more increase thrombophilic predisposition.[1-8] The reported rate of DVT in gynecologic cancer ranges from 11-18% with the rate of pulmonary embolism between 1 and 2.6%.[9-10] The presence of a symptomatic DVT is highly linked to the development of a clinically significant pulmonary embolism in nearly one third of patients accounting to approximately 60,000 deaths each year.[11-12] Most patients die within 30 minutes from the time of pulmonary embolism, leaving little room for therapeutic interventions.[13] The development of DVT in conjunction with gynecologic malignancy connotes a poorer prognosis with a two-fold greater risk of dying compared to those without DVT.[14] Thus, clinicians should focus on identifying high-risk patients and thereby instituting consistent and effective thromboprophylaxis to reduce the incidence of this frequent, often preventable cause of death.[13]

Despite the problem posed by VTE in the setting of cancer and recommendations by different institutional organizations internationally (e.g. American College of Obstetrician and Gynecologists, American College of Chest Physicians, American Heart

Association, American Society of Clinical Oncology, Italian Association of Medical Oncology, European Society of Medical Oncology, National Cancer Comprehensive Network),[12-13, 15-20] it is evident that a notable proportion of oncologists do not recognize the need for thromboprophylaxis in selected patient populations.[13] This may be due to the failure to recognize the link between cancer, its treatment, and thrombogenesis.[5] In a study among oncologists on VTE during treatment for cancer, over 27% believe that their patients are not at risk for VTE. Over 60% of them do not believe hormone replacement therapy or chemotherapy increased risk for VTE and lastly, a vast majority of them (80%) do not use thromboprophylaxis routinely. [21] Moreover, in the FRONTLINE STUDY, a comprehensive global survey of thrombosis and cancer, it reveals that 50% of surgical cancer patients and 95% of medical patients do not use thromboprophylaxis.[22]

In the Philippines, there are no previous or current studies as of date on the incidence of DVT in the setting of gynecologic malignancy and no data as to number of cancer patients given thromboprophylaxis. The Society of Gynecologic Oncology of the Philippines (SGOP) as stipulated in their latest Clinical Practice Guidelines (CPG), advocates giving prophylaxis in high risk patients which includes those undergoing surgery whether in the form of definitive treatment or palliative for their malignancy.[23] Despite this advocacy, patients undergoing surgery for malignancy are not routinely given thromboprophylaxis. It is only given as an individualized case to case basis such as patients who are already preoperatively diagnosed with DVT, or have history of stroke. In line with this, results of this study can serve as a benchmark whether or not to routinely give thromboprophylaxis among gynecologic oncology patients admitted for surgery as advocated/ recommended.

Objectives

General Objective:

To determine the association of risk factors on deep vein thrombosis among patients with histologically proven gynecologic malignancy and pre-operatively assessed to have ovarian malignancy admitted for surgery in a tertiary government hospital

Specific Objectives:

1) To determine the incidence of deep vein thrombosis among patients with histologically proven gynecologic malignancy and pre-operatively assessed to have ovarian malignancy admitted for surgery in a tertiary government hospital;

2) To describe the demographic characteristics of patients with histologically proven gynecologic malignancy and pre-operatively assessed to have ovarian malignancy admitted for surgery in a tertiary government hospital in terms of age, gravidity, parity, BMI, site, histology, and stage of malignancy; and

3) To correlate risk factors on DVT among histologically proven gynecologic malignancy and pre-operatively assessed to have ovarian malignancy admitted for surgery in a tertiary government hospital

Review of Related Literature

Venous thromboembolism (VTE) which consists of two related conditions namely deep vein thrombosis and pulmonary embolism represents a major health problem in gynecologic malignancy. Deep venous thrombosis (DVT) is the presence of coagulated blood, a thrombus, in one of the deep venous conduits that return blood to the heart. In 1856, Virchow described the classic triad of predisposing factors for developing thromboembolism which include venous stasis, vessel wall injury and a hypercoagulable state.[24] Gynecologic oncology patients are predisposed to thromboembolism because of alteration in one or more of these factors. Cancer cells secrete procoagulant (e.g. tissue factor and cancer procoagulants) as well as factors that affect endothelial permeability (e.g. vascular endothelial growth factor) and promote fibrin

deposition.[25-27] Elevated coagulation factors (factors I, V, VII, IX, X and XI), activated intermediates (thrombin-antithrombin III complexes), and platelet abnormalities which are found in patients with malignancy also contribute to a hypercoagulable state.[26,28] Vessel wall injury can result from malignant growth of a tumor into vascular tissues. Immobility as well as mass-effect of tumor can adversely affect the drainage of blood from the lower extremity promoting development of DVT.[26] The therapeutic interventions (e.g. surgery and chemotherapy) as well as advancing age, and advanced stage of the disease also predispose to DVT.[1-8, 25-26] Thus, clinicians should focus on identifying high-risk patients and thereby instituting consistent, effective thromboprophylaxis to reduce the incidence of this frequent, often preventable cause of death.[13]

Malignancy is a known independent risk factor for deep vein thrombosis.[29] In a population-based case-control study done by Heit, et al. the presence of malignancy has a 4-fold increased risk of VTE, and cytotoxic or immunosuppresive chemotherapy which increased the malignant neoplasm-associated risk to more than 6-fold.[30] In another study, the risk of developing VTE as well as the risk of dying from VTE is three-fold higher in cancer patients compared to those without cancer.[31] Specifically, in gynecologic oncology, the reported rate of DVT ranges from 11-18% with the rate of pulmonary embolism between 1 and 2.6%.[9-10] The odds ratio of developing DVT with a diagnosis of cancer is 2.82 at p-value of 0.231 when compared to benign gynecological diseases.[3] The presence of a symptomatic DVT is highly linked to the development of a clinically significant pulmonary embolism in nearly one third of patients accounting to approximately 60,000 deaths each year.[11-12] Most patients die within 30 minutes from the time of pulmonary embolism, leaving little room for therapeutic interventions.[13] The development of DVT in conjunction with gynecologic malignancy connotes a poorer prognosis with a two-fold greater risk of dying compared to those without DVT.[14]

The clinical conundrum of DVT is that symptoms are often nonspecific or absent.[32-35] Symptoms suggestive of DVT include unilateral calf, leg, or thigh swelling or pain.[16] In a study by Santoso, et al. leg warmth ($p<0.001$), edema ($p<0.008$), fever ($P<0.012$) and erythema ($p<0.009$) are significant symptoms in diagnosing DVT ($p<0.01$).[3] Furthermore, in patients presenting with symptoms of unilateral pain or swelling with at least one DVT risk factor have an 85% probability of having DVT.[36]

The diagnosis of DVT is generally made by venous ultrasonography. It is considered as the primary non-invasive method of diagnosing DVT[35] as well as safe, readily available and repeatable. Diagnosis of DVT is based on the following criteria: a) failure of vein to compress, b) presence of thrombus; and c) absence of venous flow augmentation during compression of the calf.[32-35] In general, duplex scan ultrasonography has a 100% sensitivity and 98% specificity in diagnosing DVT among symptomatic patients. [33] The sensitivity and specificity of diagnosing proximal DVT is 100% and 98% respectively while for distal venous calf veins, its 94% and 75% respectively. In early and asymptomatic DVT, diagnosis by duplex scanning shows a decrease in accuracy.[33] However, results have improved in recent studies with a sensitivity of 75-85% in the hands of an experienced staff.[32]

Post-operative VTE occurs 2-4 times more frequently in oncology patients than in non-oncology patients[8,14,20] In oncology patients undergoing surgery without prophylaxis, incidence of lower limb deep vein thrombosis ranges from 40-80% and that of proximal DVT from 10-20%. The risk of fatal post-operative pulmonary embolism is about 4 times higher in cancer surgery in comparison to a non-cancer surgery. In oncology patients undergoing surgery for cancer, the most commonly used prophylactic regimen consists of preoperative subcutaneous injection of heparin followed by continued administration starting 12-24 hours after surgery. Unfractionated heparin (UFH) is given two to three times daily while low molecular weight heparin (LMWHs) is given once-daily.[20] In the ENOXACAN study II, it reported a statistically significant reduction from 12% to 4.8% in the rate of DVT after extended prophylaxis (4 weeks) compared with prophylaxis given in the first operative week (7-10 days).[37] In a Cochrane review, extended prophylaxis reduces the incidence DVT by >50% among cancer patients undergoing surgery versus those given within 1st 7-10 days postoperatively.[38]

Despite the problem posed by VTE in the setting of cancer and recommendations by different institutional organizations internationally (e.g. ACOG, ACCP, AHA, ASCO, AIOM, ESCO, NCCN),[12-13, 15-20] it is evident that a notable proportion of oncologists do not recognize the need for thromboprophylaxis in selected patient populations.[13] This may be due to the failure to recognize the link between cancer, its treatment, and thrombogenesis.[5] In a study among oncologists on VTE during treatment for cancer, over 27% believe that their patients are not at risk for VTE. Over 60% of them do not believe hormone replacement therapy or chemotherapy increased risk for VTE and lastly, a vast majority of them (80%) do not use thromboprophylaxis routinely.[21] Moreover, in the FRONTLINE STUDY, a comprehensive global survey of thrombosis and cancer, it reveals that 50% of surgical cancer patients and 95% of medical patients do not use thromboprophylaxis.[22]

In the Philippines, there are no previous or current studies as of date on the incidence of DVT in the setting of gynecologic malignancy and no data as to number of cancer patients given thromboprophylaxis. The Society of Gynecologic Oncology of the Philippines (SGOP) as stipulated in their latest Clinical Practice Guidelines (CPG), advocates giving prophylaxis in high risk patients which includes those undergoing surgery whether in the form of definitive treatment or palliative for their malignancy. [23] Despite this advocacy, patients undergoing surgery for malignancy are not routinely given thromboprophylaxis. It is only given as an individualized case to case basis such as patients who are already preoperatively diagnosed with DVT, or has history of stroke.

Methodology

Study Design

This was a prospective cohort study which included patients with histologically proven gynecologic malignancy and preoperatively assessed to have ovarian malignancy admitted for surgery at the Philippine General Hospital (PGH).

Study Population

a. Target population
Patients with histologically proven gynecologic malignancy and those pre-operatively assessed to have ovarian malignancy admitted for surgery at the PGH were included in the study. Patients pre-operatively assessed to have ovarian malignancy who met the inclusion criteria were included in the study.

b. Inclusion and exclusion criteria

Inclusion Criteria:

1. Patients with histologically proven gynecologic malignancy admitted for surgery at the PGH.

2. Patients who are pre-operatively assessed to have ovarian malignancy with one or more of the following features:
   a) Patients with ovarian new growth/ abdominopelvic mass with ascites
   b) Patients with ovarian new growth, elevated CA125 with or without ascites
   c) Patients with ovarian new growth/ abdominopelvic mass with sonographic features suggestive of malignancy (presence of solid areas, excrescences)

3. Patients medically cleared for surgery

Exclusion Criteria:

1. Patients diagnosed with deep vein thrombosis prior to the study

2. Patients with history of pulmonary embolism

3. Patients with thrombophilia

4. Patients on anti-coagulant therapy prior to the study

5. Patients with IVC filter

6. Mentally incapacitated patients

Diagnostic Criteria

Diagnosis was made using complete duplex ultrasonography of the lower extremities which allowed direct visualization of the deep veins and detection of venous flow. Complete duplex venous ultrasonography was performed by a trained operator and the results were interpreted by a cardiovascular specialist. The patient was examined in supine and sitting positions. With the patient in supine position, the inferior vena cava, iliac veins and the femoral veins were examined while the calf veins which included the posterior tibial and fibular veins, gastrocnemius veins and soleal veins were examined in sitting position. The venous network was screened using two-dimensional real-time images, duplex modality and in some cases Doppler ultrasound. The diagnosis of DVT was based on the following criteria: a) failure of vein to compress, b) presence of thrombus; and c) absence of venous flow augmentation during compression of the calf. The performance of the said procedure was free of charge and paid by the primary investigator.

Therapeutic Regimen

Patients with DVT were referred to the Cardiovascular Service and managed accordingly with emphasis on thromboprophylaxis either in the form of low- molecular weight heparin or unfractionated heparin whatever the patients can afford.

Sample size

A total of fifty-two (52) patients with histologically-proven gynecologic malignancy and pre-operatively assessed to have ovarian malignancy were enrolled consecutively in the study. The sample size was computed using the parameters 2.92% of the expected number of asymptomatic patients with DVT who had gynecologic malignancy, an assumed 3:1 ratio of the expected number of asymptomatic patients over symptomatic patients, 40% of those with DVT were symptomatic (with leg warmth), a two-tailed 5% level of significance and 80% power of test.

Withdrawal criteria

The participant could discontinue her participation in the study at anytime without penalties. In this case, the investigator would withdraw the results obtained from her data in the study.

Procedure

This study was conducted in a tertiary government hospital, Section of Gynecologic Oncology after the approval of the Research Ethics Board. Prior to the scheduled surgery, a duplex scan of the lower extremities was performed among qualidied patients. For those patients with negative DVT result on the first duplex scan, a repeat duplex scan was performed post-operatively prior to discharge. Complete duplex venous ultrasonography was performed by a trained operator and results were interpreted by a Cardiovascular (CV) specialist. The procedure lasted for approximately 15-20 minutes. The patient was examined in supine position for examination of the iliac veins and the femoral veins and in the sitting position for the examination of the calf veins which included the posterior tibial and fibular veins, gastrocnemius veins and soleal veins. The venous network was screened using two-dimensional real-time images, duplex modality and in some cases Doppler ultrasound. The diagnosis of DVT was based on the observation of the absence of complete venous compressibility and absence of blood flow.

Data Collection

Data collection included age, gravidity, parity, body mass index (BMI), presence of hypercoagulable risk factors other than cancer (e.g. prolonged hospitalisation, prolonged immobilization, presence of thrombophilia, morbid obesity, OCP use, myeloproliferative disorders, recent surgery, history of chemotherapy), preoperative/ intraoperative/ postoperative course (length of surgery, blood loss and presence of blood transfusion), site, histology and stage of malignancy were gathered. These data were gathered by means of a checklist via a case registry

form which was filled up by the principal investigator during the study period.

Data Analysis

Descriptive statistics (mean, standard deviation and percentages) were used to summarize the demographic variables. Chi-square test and Fisher's exact tests were applied for the association of risk factors on the incidence of DVT. The test was significant at p-value <0.5. Data processing and data analysis were performed using freeware R software.

Ethics

This study was conducted in a tertiary government hospital, Section of Gynecologic Oncology and only upon approval of the Research Ethics Board. All admitted patients at the Section of Gynecologic Oncology and Department of Obstetrics and Gynecology who met the inclusion criteria and who voluntarily and willingly signed the consent form were included in the study. The consent form emphasized confidentiality of the results as well as the assurance of the respondents of their right to withdraw if and when they want to discontinue in participating the study. Duplex scan of the lower extremities was performed among patients who met the inclusion criteria. Once diagnosed with DVT on duplex scan, they were referred to the Cardiovascular Service for co-management and an appropriate treatment was given accordingly. The principal investigator shouldered the expenses of the duplex scan of the lower extremities.

Results

The incidence of DVT among patients with histologically proven gynecologic malignancy and pre-operatively assessed to have ovarian malignancy who were admitted for surgery in a tertiary government hospital was 13.0% (7/52).

As reflected in Table 1, the average age of the 7 patients with DVT is 53.14 years old +/-7.84. The average gravidity is 3.29 +/- 3.25, while the average age of parity is 3.14 +/- 3.13. On the other hand, among those patients without DVT, the mean age is 50.62 +/-11.84 years old. Meanwhile, the average gravidity and parity is 2.93 +/- 2.13 and 2.69 +/- 1.99 respectively. The differences in the patients' age, gravidity and parity between patients with DVT and without DVT are not statistically significant (p-values $> 0.05\alpha$).

In terms of BMI, higher rate of DVT-negative patients have normal BMI as compared to those patients with DVT (51.1% vs 0%, p=0.011), and the difference is statistically significant. This means that having a normal BMI is not associated with DVT. On the other hand, higher percentages of overweight (42.9% vs 17.8%, p=0.131) and obese patients (42.9% vs 26.6%, p=0.379) are observed among patients with DVT as compared to those without DVT, however, the differences are not statistically significant.

As for the presence of medical illnesses, common for both groups are hypertension (28.6% vs 24.4%, p=0.815) and diabetes mellitus (14.3% vs 13.3% p=0.945), however, these illnesses are not associated with DVT cases. Moreover, there is no history of any cancer (such as colon, breast, and ovarian cancer) among patients with DVT as compared to those without DVT. Hence, history of cancer does not increase the rate of DVT for this study.

Moreover, in terms of the number of patients per organ with cancer, of the 7 DVT positive cases, 71.4% (5/7) has ovarian cancer while 28.6% (2/7) has endometrial cancer. Nevertheless, for those with DVT negative, 51.1% of them (23/45) has endometrial cancer; 40% (18/45), ovarian cancer; 4.4% (2/45), cervical cancer; and 4.4% (2/45), vulvar cancer.

As shown in Table 2, among the 3 cases of DVT positive with noted risk factors for DVT, only the infection (14%) and immobilization (29%) are present. However, presence of these risk factors (infection and immobilization) is not associated with occurrence of DVT in this study.

As shown in Table 3, there is a higher rate of DVT symptoms observed among patients with DVT (57.1% vs 22.2%, p=0.053) which is manifested and identified as edema, pain, erythema and tenderness. None among patients with DVT has varicosities. Moreover, among patients with DVT, the significant common specific

Table 1. Patients' demographic profile among patients with histologically proven gynecologic malignancy and preoperatively assessed to have ovarian malignancy.

Demographic and Baseline Characteristics	DVT (+) n=7		DVT (-) n=45		p-value
Age, years (mean+/-sd)	53.14	7.84	50.62	11.84	0.590
Gravidity (mean+/-sd)	3.29	3.25	2.93	2.13	0.707
Parity (mean+/-sd)	3.14	3.13	2.69	1.99	0.607
Body Mass Index (BMI)					
Normal	0	0.0%	23	51.1%	0.011*
Underweight	1	14.3%	2	4.4%	0.299
Overweight	3	42.9%	8	17.8%	0.131
Obese	3	42.9%	12	26.6%	0.379
ECOG					
0	5	71.4%	30	66.7%	0.803
1	2	28.6%	14	31.1%	0.892
2	0	0.0%	1	2.2%	0.690
Medical Illness					
Hypertension	2	28.6%	11	24.4%	0.815
Diabetes Mellitus	1	14.3%	6	13.3%	0.945
Cholecystolithiasis	0	0.0%	1	2.2%	0.690
Colon carcinoma	0	0.0%	1	2.2%	0.690
Hydatidiform mole	0	0.0%	1	2.2%	0.690
Breast cancer	0	0.0%	2	4.4%	0.569
Ovarian cancer	0	0.0%	3	6.7%	0.482
History of Cancer					
Colon cancer	0	0.0%	1	2.2%	0.690
Breast cancer	0	0.0%	3	6.7%	0.482
Ovarian cancer	0	0.0%	3	6.7%	0.482
Adjuvant treatment					
s/p Cyclophosphamide-Doxorubicin-5FU	0	0.0%	2	4.4%	0.569
s/p BEP IV	0	0.00%	1	2.20%	0.690
s/p Carboplatin-Paclitaxel	0	0.0%	2	4.4%	0.569
Tamoxifen	0	0.0%	1	2.2%	0.690
None	0	0.0%	1	2.2%	0.690
Site of cancer					
Endometrium	2	28.6%	23	51.1%	0.267
Ovary	5	71.4%	18	40.0%	0.119
Cervix	0	0.0%	2	4.4%	0.569
Vulva	0	0.0%	2	4.4%	0.569

Note: (*) means significant at 0.05?
5FU = 5-Fluorouracil; BEP = bleomycin-etoposide-cisplatin

symptoms are the following: a) edema (57.1%) which is unilateral (28.6%); b) pain (42.9%), bilateral (28.6%); c) erythema (57.1%), bilateral and unilateral (28.6%); and d) tenderness (42.9%), bilateral (28.6%).

As to preoperative interventions, 7 patients with DVT, 57.1% (4/7) received blood transfusion prior to surgery. These 4 patients with DVT are all cases of ovarian cancer. None of these 7 patients with DVT had pre-operative paracentesis or thoracentesis.

Of the 6 different surgical procedures done for the 7 patients with DVT, only the following surgeries were significantly associated with the rate of DVT namely: a) exploratory laparotomy, peritoneal fluid cytology, adhesiolysis, modified radical hysterectomy

Table 2. Presence of risk factors among patients' with DVT (+) and DVT (-) .

Presence of Risk Factors	DVT (+) n=7		DVT (-) n=45		p-value
Family history of cancer	0	0%	0	0.0%	1.000
History of surgery	0	0%	7	15.6%	0.262
Types of surgery					
s/p EL, omental biopsy			1	2.2%	
s/p EL, PFC, RSO			1	2.2%	
s/p Modified radical mastectomy			3	6.7%	
s/p sigmoidectomy			1	2.2%	
s/p THBSO			1	2.2%	
History of trauma	0	0%	0	0.0%	1.000
OCP use	0	0%	2	4.4%	0.569
Genetic Predisposition	0	0%	0	0.0%	1.000
Pregnancy	0	0%	1	2.2%	0.690
Smoking	0	0%	6	13.3%	0.304
Infection	1	14%	4	8.9%	0.652
Immobilization	2	29%	4	8.9%	0.129
Chemotherapy/Adjuvant treatment	0	0%	6	13.3%	0.304
Mode of adjuvant treatment					
s/p Carboplatin-Paclitaxel			2	4.4%	
s/p Cyclophosphamide-Doxorubicin-5FU			2	4.4%	
s/p Tamoxifen			1	2.2%	
s/p BEP			1	2.2%	
None			1	2.20%	

EL = exploratory laparotomy; PFC = peritoneal fluid cytology; RSO = right salpingooophorectomy;
THBSO = total hysterectomy bilateralsalpingooophorectomy; 5FU - 5 flourouracil;
BEP = bleomycin-etoposide-cisplatin

Table 3. DVT symptoms among patients with DVT (+) and DVT (-).

DVT Symptoms	DVT (+) n=7		DVT (-) n=45		p-value
Presence of Symptoms	4	57.1%	10	22.2%	0.053
Edema	4	57.1%	10	22.2%	0.053
Bilateral	2	28.6%	8	17.8%	0.608
Unilateral	2	28.6%	2	4.4%	0.026*
Pain	3	42.9%	0	0.0%	0.002*
Bilateral	2	28.6%	0	0.0%	0.016*
Unilateral	1	14.3%	0	0.0%	0.135
Erythema	4	57.1%	1	2.2%	0.001*
Bilateral	2	28.6%	1	2.2%	0.044*
Unilateral	2	28.6%	0	0.0%	0.016*
Tenderness	3	42.9%	0	0.0%	0.002*
Bilateral	2	28.6%	0	0.0%	0.016*
Unilateral	1	14.3%	0	0.0%	0.135
Varicosities	0	0.0%	1	2.2%	1.000
Bilateral	0	0.0%	1	2.2%	1.000
Unilateral	0	0.0%	0	0.0%	1.000

Note: (*) means significant at 0.05α

with bilateral salpingooophorectomy, infracolic omentectomy, biopsy of adhesions, lymph node palpation; b) exploratory laparotomy, peritoneal fluid cytology, total hysterectomy with bilateral salpingooophorectomy, lymph node palpation and insertion of JP drain; c) exploratory laparotomy, peritoneal fluid cytology, total hysterectomy with bilateral salpingooophorectomy, tumor debulking, biopsy of sigmoid implant, bowel run and insertion of JP drain; and d) exploratory laparotomy, peritoneal fluid cytology, total hysterectomy with bilateral salpingooophorectomy, bilateral lymph node dissection, para-aortic lymph node sampling, infracolic omentectomy, random peritoneal biopsy, biopsy of implants, appendectomy and insertion of JP drain. All four surgical procedures are performed in patients with ovarian cancer, and are statistically significant (14.3% vs 0.0%) at p=0.01.

As for stages of cancer, among the 7 DVT positive cases, 2 (28.6%) are cases of endometrial cancer with stage 1A (14.3%) and 1B (14.3%) respectively, while 5 (71.5%) are cases of ovarian cancer with the following stages: one (14.3%) stage 1A, two (28.6%) stage IIC, and two (28.6%) stage IVB. With regards to staging, ovarian cancer stage IVB (liver) is statistically significant at p-value of 0.026 which means that the rate of DVT is higher in patients with stage IVB ovarian cancer.

In terms of histology, the following were observed among the patients with DVT: a) two (28.6%) endometrial adenocarcinoma endometrioid type, b) two (28.6%) ovarian mucinous cystadenocarcinoma; c) one (14.3%) ovarian serous papillary adenocarcinoma; d) one (14.3%) poorly differentiated adenocarcinoma; and e) one (14.3%) ovarian endometrioid adenocarcinoma. With regards to histology, none of the histologic types is significantly associated with DVT.

In terms of the surgery related profiles, the 7 patients with DVT has the following characteristics: for endometrial cancer, the average surgery time is 167.50 +/- 24.75 minutes while that of ovarian cancer has an average surgery time of 202.00 +/-38.99 minutes. This means that ovarian cancer has longer surgery time compared to endometrial cancer due to the additional surgical procedure performed compared to endometrial cancer. With regards to blood loss, the average blood loss for endometrial cancer cases with DVT is 400 cc while 1030 cc +/- 831.87 cc for ovarian cancer with DVT. Moreover, none of the endometrial cancer cases with DVT has received blood transfusion intraoperatively, while 4 (57%) of the ovarian cancer cases with DVT has blood transfusion intraoperatively. Ovarian cancer patients with DVT have more blood loss due to the extent of tumor, type or surgery, and additional procedure performed compared to endometrial cancer. However, the difference is not statistically significant. Furthermore, of the seven DVT positive patients, only 4 of them (1 endometrial cancer and 3 ovarian cancer) use compression stockings intraoperatively. Only usage of compression stockings intraoperatively among ovarian cancer patients with DVT showed a statistically significant difference (43% vs 13%, p=0.055) which means that the rate of DVT is higher among ovarian patients who used compression stockings. None of the seven DVT cases are inserted with central venous catheter prior or during the surgery.

As to the post operative profile of patients included in the study, 3 ovarian cancer patients with DVT were transfused with blood and none for the endometrial cancer with DVT. Moreover, in terms of duration of immobilization post-operatively, endometrial cancer patients with DVT have an average immobilization of 6 hours while ovarian cancer patients with DVT have an average immobilization of 10.80 +/-7.2 hours. Also, 4 of the 7 patients with DVT used compression stockings post-operatively (1 endometrial cancer patient with DVT and 3 ovarian cancer patients with DVT). Specifically, for ovarian cancer patients with DVT, the rate of compression stocking usage is higher compared to DVT-negative, and the difference is statistically significant (43 vs 11%, p=0.030). This means that the rate of DVT is higher among ovarian cancer patients who used compressions stockings. Lastly, for the hospital stay of these DVT positive patients, the average hospital stay for the endometrial cancer group is 3 days while it is 4.00 +/ - 1.22 days for the ovarian cancer group. Ovarian cancer patients with DVT have longer hospital stay because of the post-operative intervention done (e.g. blood transfusion) and prolonged/longer recovery time from the surgery.

Discussion

Venous thromboembolism which comprises deep vein thrombosis and pulmonary embolism represents a major health problem in gynecologic malignancy. Malignancy itself, as well as its therapeutic intervention (surgery, chemotherapy, radiation), advancing age, advanced stage, immobility even more increase thrombophilic predisposition.[1-8, 30] The reported rate of DVT in gynecologic cancer ranges from 11%-18%.[9-10] In another study, the incidence of DVT among patients with gynecologic cancer is only 4 - 4.2%.[3,55] In this study the incidence rate of DVT is 13.0%, similar to the report of Clarke-Pearson, et al.[9-10]

Venous thromboembolism is the second leading cause of in-hospital death, after cancer, in cancer patients. 40 Several risk factors have been implicated to increase the risk of venous thromboembolism which include the following: a) presence of malignancy, b) type / site / extent of malignancy, c) older age, d) surgery (cytoreductive surgery/prolonged surgery >2hrs), e) blood transfusion; f) duration of anesthesia; g) prolonged immobilization, h) debility, i) obesity, j) hospitalization, k) presence of indwelling catheter, l) history of DVT, m) hereditary predisposition (thrombophilia), n) acute medical condition (eg congestive heart failure, stroke), o) radiation therapy, p) use of hormonal replacement therapy (estrogen use), and q) chemotherapy.[1-8, 13-14, 20, 30, 40-48, 50-53, 60-61, 71-72] The risk of thromboembolism is 4.1 times higher in patients with cancer compared to patients without cancer and the risk is increased further to 6.5-fold in cancer patients receiving chemotherapy.[30] Gynecologic oncology patients are predisposed to thromboembolism because of alteration in one or more of the following factors: a) cancer cells secrete procoagulant (e.g. tissue factor and cancer procoagulants) as well as factors that affect endothelial permeability (e.g. vascular endothelial growth factor) and promote fibrin deposition;[25-27] b) elevated coagulation factors (factors I, V, VII, IX, X and XI), activated intermediates (thrombin-antithrombin III complexes), and platelet abnormalities which are found in patients with malignancy contributing to a hypercoagulable state;[26, 28] c) vessel wall injury resulting from malignant growth of a tumor into vascular tissues; and d) immobility as well as mass-effect of tumor that adversely affect the drainage of blood from the lower extremity promoting development of DVT.[26]

Aside from cancer, the risk of venous thromboembolism is also influenced by the type and site of cancer. The following malignancies carry the highest risk: malignant brain tumors, hematologic malignancies, adenocarcinoma of the pancreas, uterus, ovary, stomach, lung, and kidney.[4,6,40-47] For gynecologic oncology patients, ovarian cancer appears to have a higher incidence of venous thromboembolism as compared to women with endometrial or cervical cancer.[56] Fibrin degradation products and vascular endothelial growth factor found in plasma and ascites of these patients have been implicated.[57-58] Also, genes associated with ovarian cancer are linked to the coagulation pathway hence coagulation factors are also upregulated.[59] In Peedicayil, et al. study, ovarian/peritoneal/tubal tumors and hospital stay of 5 days or more are risk factors for venous thromboembolism between 8 and 90 days postoperatively.[55] In this study, out of the seven cases of DVT observed, 71.4% (5/7) are cases of ovarian cancer followed by endometrial cancer 28.6% (2/7). This finding is similar to the previous reports that ovarian cancer has a higher incidence of DVT. However, in this study, site of cancer is not statistically significant.

Thrombotic risk may also be influenced by the extent of malignancy and that advanced metastatic cancer is associated with a higher risk of venous thromboembolism.[4,6,40-47] In a study by Black, et al. the proportion of advanced-stage (III-IV) patients with venous thromboembolism is higher compared to the group with no venous thromboembolism (90% versus 72%, p=0.0078). Furthermore, the proportion of patients with ascites compared to those with none (74% vs 54%, p=0.0045), and the proportion of patients with residual disease >1cm compared to those with </= 1cm (37% vs 19%, p=0.0021 is also higher in those with advanced-stage patients with VTE group compared to the group with no VTE. On multivariate analysis, advanced stage (p=0.0001), the presence of ascites (p=0.0210), and residual disease >1cm (p<0.0001) are significant predictors of poorer survival.[71] In the present study, there is a higher rate of advanced-stage disease observed among patients

with DVT which is statistically significant at p= 0.026. This result confirms the established relationship of an increased risk of venous thromboembolism in ovarian cancer with an advanced stage.[71,64,74]

Surgical interventions place cancer patients at a two-fold risk for postoperative venous thromboembolism compared with non-cancer patients undergoing the same procedure.[47] The risk is further increased because of the concomitant non-cancer-specific venous thromboembolism risk factors such as advanced age, type/site/extent of cancer, debility, prolonged immobilization, hospitalization, surgery, indwelling catheters, hereditary predisposition, radiation, chemotherapy, hormonal replacement therapy and the presence of medical condition such as congestive heart failure.[14,30,48,42,49,50-53] In this study, the following surgeries namely: a) exploratory laparotomy, peritoneal fluid cytology, adhesiolysis, modified radical hysterectomy with bilateral salpingooophorectomy, infracolic omentectomy, biopsy of adhesions, lymph node palpation; b) exploratory laparotomy, peritoneal fluid cytology, total hysterectomy with bilateral salpingooophorectomy, lymph node palpation and insertion of JP drain; c) exploratory laparotomy, peritoneal fluid cytology, total hysterectomy with bilateral salpingooophorectomy, tumor debulking, biopsy of sigmoid implant, bowel run and insertion of JP drain; and d) exploratory laparotomy, peritoneal fluid cytology, total hysterectomy with bilateral salpingooophorectomy, bilateral lymph node dissection, para-aortic lymph node sampling, infracolic omentectomy, random peritoneal biopsy, biopsy of implants, appendectomy and insertion of JP drain are all significantly associated with DVT. All four surgical procedures were performed in patients with ovarian cancer, and are statistically significant (14.3% vs 0.0%) at p=0.01. Gynecologic oncology patients, especially those with ovarian cancer are prone to develop thromboembolism in view of their pelvic surgery, the extensive cytoreductive surgery performed, in association with prolonged duration of surgery, prolonged hospitalization and perioperative blood transfusions.[30, 61,72]

The clinical conundrum of DVT is that symptoms are often nonspecific or absent.[32-35] Symptoms suggestive of DVT include unilateral calf, leg, or thigh swelling or pain.[16] However, according to Agnelli et al, patients with cancer have more frequently bilateral DVT of the lower limbs and venous thrombosis in unusual sites.[20] In patients presenting with symptoms of unilateral pain or swelling with at least one DVT risk factor, the probability of having a DVT is 85%.[36] In a study by Santoso et. al, leg warmth ($p<0.001$), edema ($p<0.008$), fever ($P<0.012$) and erythema ($p<0.009$) are significant symptoms in diagnosing DVT ($p<0.01$).[3] In the present study, there is a higher rate of DVT symptoms observed among patients with DVT manifested and identified as edema, pain, erythema and tenderness. Moreover, the most common specific symptoms are edema (unilateral), pain (bilateral), erythema (bilateral or unilateral) and tenderness (bilateral). In relation to symptoms of DVT, the present study shares similar findings as reported by Agnelli et al and Santoso, et al.[3,20]

With regards to histologic type, the result of this study shows no significant association between histologic type and deep venous thrombosis. This finding is also observed by Black, et al. Though histologic type is not associated with venous thromboembolism, the development of venous thromboembolism per se may reflect a more aggressive malignancy.[71]

In a study by Abu-Rustum, et al.[72] they reported an increased risk of venous thromboembolism in patients who received perioperative blood transfusions after undergoing primary surgery for ovarian cancer. The blood transfusion rate in patients with advanced-stage disease who have undergone primary cytoreductive surgery is as high as 40% due to bleeding secondary to extensive upper abdominal surgical techniques, perioperative blood transfusion and prolonged recovery time.[71,73] Similar to what Black, et al.[71] and Chi, et al.[73] observed in their respective studies, the rate of blood transfusion in this study is higher (57%) both preoperatively and postoperatively, however it is not statistically significant.

Based on all these findings, it would be reasonable to administer venous thromboprophylaxis in gynecologic oncology patients or patients preoperatively assessed to have gynecologic malignancy who will undergo extensive cytoreductive surgery most especially if they are at risk for venous thromboembolism.

Summary and Conclusion

This prospective cohort study included 52 patients with histologically confirmed gynecologic malignancy and preoperatively assessed to have gynecologic malignancy in a tertiary hospital from October 2013 to May 2014 in the Section of Gynecologic Oncology, Department of Obstetrics and Gynecology after appropriate technical and ethical reviews. The incidence of DVT was 13.0%. There were seven cases of DVT observed, 71.4% (5/7) from ovarian cancer while 28.6% (2/7) from endometrial cancer. No deep venous thrombosis was observed among patients with vulvar and cervical cancer. In terms of risk factors, normal BMI showed no significant association with DVT at p-value of 0.011. Furthermore, there were more overweight and obese cases among patients with DVT, however it was not statistically significant. With regards to surgery, the following surgical procedures were associated with a higher rate of DVT namely a) exploratory laparotomy, peritoneal fluid cytology, adhesiolysis, modified radical hysterectomy with bilateral salpingooophorectomy, infracolic omentectomy, biopsy of adhesions, lymph node palpation; b) exploratory laparotomy, peritoneal fluid cytology, total hysterectomy with bilateral salpingooophorectomy, lymph node palpation and insertion of JP drain; c) exploratory laparotomy, peritoneal fluid cytology, total hysterectomy with bilateral salpingooophorectomy, tumor debulking, biopsy of sigmoid implant, bowel run and insertion of JP drain; and d) exploratory laparotomy, peritoneal fluid cytology, total hysterectomy with bilateral salpingoophorectomy, bilateral lymph node dissection, para-aortic lymph node sampling, infracolic omentectomy, random peritoneal biopsy, biopsy of implants, appendectomy and insertion of JP drain. All four surgical procedures were performed in patients with ovarian cancer, and were statistically significant (14.3% vs 0.0%) at p=0.01. Moreover, there was a higher rate of DVT among patients with advanced stage ovarian cancer (stage IVB). With regards to clinical symptoms of DVT, there was a higher rate of DVT symptoms observed among patients with DVT (57.1% vs 22.2%, p=0.053) which was manifested and identified as edema, pain, erythema and tenderness. None among patients with DVT had varicosities. Moreover, the significant common specific symptoms are the following: a) edema (57.1%) which was unilateral (28.6%); b) pain (42.9%), bilateral (28.6%); c) erythema (57.1%), bilateral and unilatera (28.6%); and d) tenderness (42.9%), bilateral (28.6%).

Based on the above results, patients with histologically proven gynecologic malignancy and preoperatively assessed to have ovarian malignancy with DVT are not likely to have a normal BMI. They tend to have ovarian or endometrial cancer; have an advanced stage of cancer; will undergo extensive cytoreductive surgery and will use compression stockings. In terms of symptoms, they will present with edema (unilateral), pain (bilateral), erythema (bilateral or unilateral) and tenderness (bilateral).

Finally, due to the higher incidence of deep venous thrombosis in this study, thromboprophylaxisis recommended to be administered among patients with gynecologic malignancy and preoperatively assessed to have ovarian malignancy who will undergo extensive cytoreductive surgery in order to prevent complications.

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Prevalence of Lymphocyst Formation Among Gynecologic Malignancy Patients Undergoing Pelvic Lymphadenectomy at a Tertiary Hospital*

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Objectives: To determine the prevalence of lymphocyst formation among gynecologic malignancy patients undergoing pelvic lymph node dissection taking into consideration its symptoms, time interval between surgery and its formation, and the influence of factors such as age, gravidity, parity, body mass index (BMI), type and stage of malignancy, peritonealization technique used, number of nodes dissected and positivity of nodes that may influence its formation.

Materials and Methods: The medical records of 58 patients diagnosed with a gynecologic cancer who underwent pelvic lymph node dissection between September 2013 to February 2014 in a tertiary hospital were retrieved and reviewed. Diagnosis of lymphocyst formation was made through ultrasonography. The prevalence was determined and each group (with or without lymphocyst formation) was compared by age, gravidity, parity, type of malignancy, number of nodes dissected and nodes with or without metastasis.

Results: Of the 58 patients, 34 had endometrial cancer (58.62%), 6 had cervical cancer (10.34%) and 18 had ovarian cancer (31.03%). Two (2) patients developed lymphocyst, giving a prevalence of 3.44 per 100 gynecologic malignancies. Both patients were asymptomatic. The mean interval between surgery and lymphocyst formation was 5.5 weeks. The peritonealization technique, as well as the other hypothesized clinical and surgico-pathologic factors showed no influence on the formation of lymphocyst.

Conclusion: The prevalence of lymphocyst formation in this study is 3.44 per 100 gynecologic malignancies. Its formation is not influenced by the peritonealization technique, nor is it influenced by the patient's clinical and surgico-pathologic characteristics.

Key words: Lymphocyst, Pelvic lymph node dissection

* Finalist, 2014 SGOP Research Contest

Through the years, gynecologic oncologists continue to determine ways of improving management and survival of patients with gynecologic malignancies. At present, surgery remains to be the standard form of treatment for most gynecologic malignancies. This form of management is not only essential for proper staging, but also contributes in improved survival outcome.

Surgery remains to be the standard form of treatment for most gynecologic malignancies especially with endometrial and ovarian cancer of all stages. Over time there has been a more widespread use of lymphadenectomy in the management of gynecologic malignancies. Lymph node dissection is prognostically important because it provides the best estimate of spread of disease.

Retroperitoneal lymph node dissection is an essential component of the surgical management of gynecologic malignancies. It provides important information with regards the stage, and appropriate adjuvant treatment approach to patients, and contribute to improved disease specific survival.[1-3] Though the procedure may have its numerous advantages, the process of dissection may in certain conditions result in complications, one of which is the formation of a pelvic lymphocyst.

Pelvic lymphocyst, or lymphocoele consists of a collection of lymph fluid in the pelvic lymphadenectomy site surrounded by a poorly defined fibrous connective tissue capsule.[4] In the normal sequence of events, operative disruption and ligation of the lymphatic trunks makes the lymphatics more permeable, resulting in a continuous outpouring of lymph from the distal segments. The channels proximal to the point of division also remain patent but carry fluid away from the wound. After 24 hours from dissection, the greater portion of the lymph stream is shunted through the collaterals about the periphery of the wound; and within 48 hours, the lymphatic channels are completely occluded.[5] The spontaneous occlusion of severed lymphatics is brought about by the pronounced regenerative capacity of the lymphatic endothelium, with new vessels being formed within 7-10 days.[6] Subsequent restoration of the continuity of lymphatics is achieved by the loose approximation of the severed channels, and the complete patency is achieved in 14-21 days.[6] When a short section of the lymphatic vessel is removed, the restoration of continuity is easily achieved.[5,6] On the other hand, if a long segment of a lymphatic channel is removed, as when pelvic lymphadenectomy is done, the regeneration of the collateral pathways may not occur, resulting in continuous accumulation of the lymph and subsequently a lymphocyst is formed.[5,6] The development and persistence of a clinically significant lymphocyst is, therefore, dependent upon the adequacy of the collateral circulation.[5]

Pelvic lymphocyst normally appear within 3-8 weeks after surgery.[7] In some instances, lymphocyst may persist up to four months from surgery.[5] The clinical importance of the lymphocyst formed is determined by its size and position.[5] Often small, uninfected lymphocyst are asymptomatic and spontaneously resorb. Symptomatic lymphocyst may cause lower abdominal swelling or a feeling of fullness, which localizes lateral to the operative incision. The swelling is usually elliptical and tends to parallel the inguinal ligaments. Eventually, the cyst may become evident as a growing prominence in the lower abdomen. Larger collections may compress adjacent structures resulting in compressive symptoms such as urinary frequency, constipation, edema of lower genitalia and lower extremities.[5] Significant morbidities such as secondary infection of the cyst, leg edema, genital edema, bladder dysfunction, subocclusion, deep vein thrombosis, pulmonary embolism and pelvic pain may likewise occur.[5-7]

Although the described pathophysiology of lymphocyst formation suggests inherent regenerative ability of lymphatic system as the main factor determining its formation, different factors have been implicated to predispose patients to lymphocyst formation. Lymphocyst were reported to be more common among patients more than 60 years old, presumably due to the impeded regenerative capacity of the lymph vessels among older patients.[8] Previous radiation with doses of 2,000-2,500 rads was likewise considered sufficient to cause suppression of lymphatic channel regeneration leading to lymphocyt formation.[5,6,9] The surgical technique, the size and number of lymph nodes surgically removed, and presence of metastatic disease in the lymph nodes have

also been frequently suggested to influence lymphocyst formation.[9] Proper ligation of the tissue pedicles representing the most proximal and distal limits of the dissection may help prevent lymphocyst formation.[5] Others report that the incidence of lymphocyst formation was reported to be a function of the thoroughness of the dissection, with a higher incidence noted when more positive nodes were harvested.[5,6] The peritonealization technique on the retroperitoneal lymph node dissection site has also been implicated in the development of lymphocyst, with most literature favoring non closure of the peritoneum in decreasing incidence of lymphocyst.[6,10,11]

Adequate comprehension of lymphocyst as a complication of radical surgeries for gynecologic malignancies is limited by low accuracy in recognition of this complication. This is evidenced by the wide variation in the reported prevalence of pelvic lymphocyst. Older literature would report a higher prevalence of 49%, while more recent series would report less than 6%.[4] Local experience with lymphocyst formation is even limited as diagnostic efforts to detect these complications are not routinely done postoperatively. At the Philippine General Hospital, particularly at the Cancer Institute, about 12 cases of pelvic lymphocyst among gynecologic oncology patients were reported from 2006-2008 (2 in 2006, 7 in 2007, 3 in 2008).[12] In most instances, incidental finding of lymphocyst were discovered more than a month after the patient's surgery.

The apparent variation in incidence may partly depend on the awareness of and interest of the physician and lack of guidelines regarding post-operative evaluation of lymphocyst formation. This study is thus conducted to increase awareness of this probably benign, but potentially debilitating, condition. The main objective of this study is to assess postoperatively the prevalence of lymphocyst formation among gynecologic malignancy patients undergoing pelvic lymph node dissection with or without para-aortic lymph node dissection. As this study will provide baseline information on the investigation of lymphocyst formation, this can lead to further investigations to evaluate the possible factors contributing to its formation. Furthermore, identification of its local prevalence could provide a more definite understanding of the clinical significance of detected lymphocyst. All these will be significant in the post operative evaluation and formulation of preventive measures against pelvic lymphocyst formation.

Objectives

General Objective:

To determine the prevalence of lymphocyst formation among gynecologic malignancy patients undergoing pelvic lymph node dissection with or without para-aortic lymph node sampling.

Specific Objectives:

1. To determine symptomatology associated with pelvic lymphocyst formation.
2. To determine the mean interval period from surgery to lymphocyst formation.
3. To determine the influence of the peritonealization technique used in the prevalence of lymphocyst formation.
4. To identify factors - age, gravidity and parity, BMI, type of malignancy (cervical, endometrial or ovarian), stage of the disease, number and size of nodes, metastatic nodes - that may contribute to lymphocyst formation.

Methodology

This was a retrospective descriptive study. The study population consisted of patients diagnosed with cervical, endometrial and ovarian cancer at the Philippine General Hospital and who underwent surgery for the gynecologic malignancy in the past 6 months.

The medical records were retrieved and checked for inclusion into the study and patients who underwent the standard surgical procedure, which includes unilateral salpingo-oophorectomy or hysterectomy (intrafascial, extrafascial, radical) with or without bilateral salpingo-oophorectomy and comprehensive lymphadenectomy were included. Lymph node dissection in this study consists of bilateral external

iliac, internal iliac and obturator lymph node dissection with or without para-aortic lymph node sampling.

The case registry forms were completed and variables that were investigated include socio-demographic data of the patients such as age, obstetric score, and BMI, preoperative and final surgico-pathologic diagnosis, complete surgical procedure, peritonealization technique, intraoperative findings, intraoperative stage, histopathologic diagnosis and staging, number of lymph nodes dissected and number of positive lymph nodes were obtained from the histopathologic report.

The postoperative transvaginal ultrasound results were checked for the presence of pelvic lymphocyst. The interval from the surgery to the ultrasound and the time interval from the ultrasound to the adjuvant treatment were noted.

Patients without a postoperative ultrasound were called in to follow up for an ultrasound after an informed consent was obtained. The co-investigator (sonologist) performed the ultrasound on these patients. Presence of lymphocyst was recorded. Patients who underwent serial ultrasound, either secondary to lymphocyst monitoring or during treatment, time of resolution of lymphocyst were also recorded.

The main variable that was measured was the development of lymphocyst. The time interval between surgery and detection of lymphocyst, the size and location of the lymphocyst, the time of resolution of lymphocyst, postoperative symptoms related to lymphocyst formation and intervention done were recorded. All personal and clinical data gathered were kept confidential.

Data Analysis

The data obtained from this study were analyzed using descriptive statistics (mean, range and percentage). Proportions were determined using the Z-test while t-test was used for means. Statistical significance was accepted at P value < 0.05.

Results

In a span of 6 months, from September 2013 to February 2014, a total of 73 patients underwent pelvic lymph node dissection with or without para-aortic lymph node sampling. Among these patients, 15 (20.5%) were lost to follow up or died from the disease and were excluded in the study.

The rest of the 58 patients fulfilled the inclusion criteria and were included in the study. Table 1 summarizes the patient characteristics which include: age, gravidity, parity and BMI. The mean age of the patients was 51.78 (SD = 11.41), with a range of 23 to 74 years of age. The mean gravidity of the patients was 2.67 (SD = 2.05) ranging from gravid 1 to 7 and the mean parity was 2.34 (SD = 1.94), with a range of 0 to 7. The mean BMI of the patients was 25.16 (SD = 4.89), with a range of 13.3 to 37.9 kg/m^2.

Of the 58 patients, 34 had endometrial cancer (58.62%), 6 had cervical cancer (10.34%) and 18 had ovarian cancer (31.03%). Majority (29 patients) of endometrial cancer patients had an early stage disease (85.29%) while 5 patients had stage III disease (14.7%). All 6 cases of cervical cancer patients had stage IB1 disease. Sixteen patients had an early stage ovarian cancer and 2 cases had stage III ovarian cancer.

Thirty five (59.3%) cases underwent extrafascial hysterectomy with bilateral salpingoophorectomy, 15 (25.4%) cases underwent total hysterectomy with bilateral salpingooophorectomy, 5 cases (8.5%) underwent radical hysterectomy with bilateral salpingooophorectomy and 3 (5.1%) cases underwent unilateral salpingoophorectomy. All of these 58 cases underwent pelvic lymphadenectomy with non closure of the peritoneum. The mean number of pelvic lymph nodes dissected was 13.84 (SD = 9.51) and 4 cases (6.9 %) turned out to have positive tumor cells in the nodes dissected.

Twenty six (44.83%) received chemotherapy as an adjuvant treatment, while 10 patients (17.24%) received adjuvant radiotherapy. Five patients (8.62%) underwent chemoradiation. Seventeen patients (29.31%) had no further adjuvant treatment.

The time interval between surgery and ultrasound examination was 12.33 weeks (SD = 8.42). Ultrasonography revealed pelvic lymphocysts in 2 (3.44%) of the 58 patients. The first patient was a 56 years old, G4P2 (2022) diagnosed with endometrial adenocarcinoma, endometrioid type, well differentiated who underwent exploratory laparotomy, peritoneal

fluid cytology, extrafascial hysterectomy with bilateral salpingooophorectomy, infracolic omentectomy, random peritoneal biopsy, bilateral pelvic lymph node dissection and para-aortic lymph node sampling. Nonclosure of the peritoneum was done. Final surgico-pathologic stage was FIGO stage IIIA. She started her chemotherapy 24 weeks post operatively with carboplatin and paclitaxel and to be followed by pelvic external beam radiation therapy (EBRT). A tranvaginal ultrasound done 5 weeks post op showed lymphocysts medial to the right iliac vessels measuring 3.6cm x 2.1cm and 2.1cm x 1.7cm. No symptoms and complications were reported.Follow up ultrasound 24 weeks after surgery showed resolution of lymphocysts.

The second patient was a 41 years old, G4P4 (4004) diagnosed with ovarian malignancy who underwent exploratory laparotomy, peritoneal fluid cytology, total abdominal hysterectomy with bilateral salpingooophorectomy, infracolicomentectomy, random peritoneal biopsy, bilateral pelvic lymph node dissection and para-aortic lymph node sampling. Nonclosure of the peritoneum was done. Final histopathologic result revealed Granulosa cell tumor of the left ovary, adult type, stage IA. No adjuvant therapy was given. A transvaginal ultrasound done 6 weeks postoperatively revealed lymphocyst formation at the right and left iliac vessel measuring 1.5cm x 1.2cm and 1.5cm x 1.1cm respectively. No symptom and complication were reported. A repeat transvaginal ultrasound was done 22 weeks postoperatively showing resolution of the lymphocysts.

Lymphocyst formation was diagnosed in 3.44% (2 of 58) of the total study population, in 5.55% (1 of 18) of ovarian cancer patients, 2.94% (1 of 34) of endometrial cancer patients and none in the 6 cervical cancer patients.

Patients who developed lymphocyst were compared to those without lymphocyst to evaluate for possible influence of clinical factors on lymphocyst formation (Table 2). No significant differences were found with respect to age, gravidity, parity, BMI, type of malignancy, number of nodes dissected and whether the nodes dissected were positive or negative for tumor.

The mean interval between the time of operation and lymphocyst formation was 5.5 weeks (SD = 0.71).

Table 1. Clinical Characteristics

Variables	Values
Age	Mean: 51.78 SD: 11.41 Range: 23 to 74
Gravidity	Mean: 2.67SD: 2.05 Range: 0 to 7
Parity	Mean: 2.34 SD: 1.94 Range: 0 to 7
BMI	Mean: 25.16SD: 4.89 Range: 13.3 to 37.9
Type of Malignancy	
Endometrial	34 (58.62%)
Cervical	6 (10.34%)
Ovarian	18 (31.03%)
Stage of the Disease	
Endometrial (n=34)	
IA	13 (38.24%)
IA (+) LVSI	3 (8.82%)
IB	9 (26.47%)
IB (+) LVSI	4 (11.76%)
IIIA	2 (5.88%)
IIIC1	2 (5.88%)
IIIC2	1 (2.94%)
Cervical (n=6)	
IB1	6 (100.00%)
Ovarian (n=18)	
IA	8 (44.44%)
IB	1 (5.56%)
IC	4 (22.22%)
IIB	3 (16.67%)
IIIA1	1 (5.56%)
IIIC	1 (5.56%)
Procedure	
EHBSO	35 (60.34%)
RHBSO	5 (8.62%)
THBSO	15 (25.86%)
RSO/LSO	3 (5.17%)
Number of Nodes Dissected	Mean: 13.84 SD: 9.51 Range: 2 to 66
Peritonealization Technique	
Closure	0
Non closure	58 (100%)
Metastatic Nodes	
(-)	54 (93.10%)
(+)	4 (6.90%)
Adjuvant Therapy	
None	17 (29.31%)
Chemotherapy	26 (44.83%)
Radiation	2 (3.45%)
Chemoradiation	5 (8.62%)
Brachytherapy	8 (13.79%)
Ultrasound Post-op (weeks)	Mean: 12.33 SD: 8.42 Range: 2 to 44
Lymphocyst Formation	
No	56 (96.55%)
Yes	2 (3.44)*

Table 2. Comparison of Clinical Characteristics of Patients with and without Lymphocyst formation.

Variables	With Lymphocyst formation (N=2)	Without Lymphocyst formation (N=56)	p-value	Remarks
Age	Mean: 48.50 SD: 10.61	Mean: 51.89 SD: 11.51	0.6833	NS
Gravidity	Mean: 4.00 SD: 0	Mean: 2.63 SD: 2.07	0.3551	NS
Parity	Mean: 3.00 SD: 1.41	Mean: 2.32 SD: 1.96	0.6316	NS
BMI	Mean: 22.20 SD: 3.39	Mean: 23.26 SD: 4.92	0.3882	NS
Type of Malignancy				
Endometrial	1 (50.00)	33 (58.93)	0.8011	NS
Cervical	0 (0.00)	6 (10.71)	0.6249	NS
Ovarian	1 (50.00)	17 (30.36)	0.5552	NS
Number of Nodes Dissected	Mean: 10.00 SD: 2.83	Mean: 13.98 SD: 9.65	0.5654	NS
Metastatic Nodes				
(-)	2 (100.00)	52 (92.86)	0.6953	NS
(+)	0 (0.00)	4 (7.14)		
Ultrasound Post-op	Mean: 5.50* SD: 0.71	Mean: 12.57 SD: 8.47	0.2466	NS

Discussion

At present, surgery remains to be the standard form of treatment for most gynecologic malignancies especially with endometrial and ovarian cancer of all stages. Over time there has been a more widespread use of lymphadenectomy in the management of gynecologic malignancies. Lymph node dissection is prognostically important because it provides the best estimate of spread of disease. Patients who are found to have positive or negative nodes may receive different postoperative therapy versus patients with unknown status of lymph nodes. This form of management is not only essential for proper staging procedure, but also contributes in improved survival outcome.[13] The Society of Gynecologic Oncology of the Philippines 2012 clinical practice guidelines in line with the Federation of International Gynecologic Oncologist and American Congress of Obstetrics and Gynecology suggested that women with endometrial, ovarian and early stage cervical malignancies should undergo systematic surgical staging including bilateral pelvic and para-aortic lymphadenectomy.[13,14,15]

In cases of cervical cancer, the standard of treatment is chemoradiation[15], however most literature favors surgical treatment in the form of radical hysterectomy including lymphadenectomy for early stage cervical cancer (stage IA1 to IIA1 except IB2) showing improved overall survival and can guide the clinician on choosing the appropriate adjuvant treatment.

The current trend on the surgical management of gynecologic malignancies which aimed to improve overall survival includes pelvic lymphadenectomy. Aside from its numerous advantages, this procedure is not totally inocuous. One of the most common post operative complication is lymphocyst formation.

In our study, the prevalence of lymphocyst formation is 3.44 per 100 gynecologic malignancy patients. Studies would show that incidence of lymphocyst after pelvic and para-aortic lymphadenectomy is approximately 2 - 48.5% of cases.[13,17] The apparent variation in incidence may partly depend on the awareness of different institutions and lack of strict guidelines in the post operative evaluation of lymphocysts formation after pelvic lymphadenectomy.

Most patients with lympocysts are asymptomatic and these disappear spontaneously as exemplified by the 2 patients in this study. In the literature, symptoms arising from lymphocyst are secondary to infection and compression symptoms. Large lymphocyst may be recognized clinically by palpation of a mass along the pelvic sidewall or in the iliac fossa on abdominal examination while smaller lymphocyst not palpable by pelvic examination can be diagnosed by ultrasonography, computed tomography scan and magnetic resonance imaging.[20] The largest diameter of lymphocyst present in our patient is 3.6 cm which did not cause any symptom. Follow up ultrasonography of both patients showed resolution of lymphocyst. In an ideal setting, patients with lymphocyst should undergo serial ultrasound to monitor its regression. Those that occur later than 1 year after surgery should be suspected of having a recurrent disease. Ideal follow up of post lymphadenectomy patients should include imaging 3 months after surgery, right after adjuvant treatment and yearly thereafter.[15]

Pelvic lymphocyst normally appear within 3-8 weeks after surgery.[7] The mean time interval between the time of surgery and ultrasonography in our patients is 12.33 weeks (SD = 8.42). Thus lymphocyst formation prior to the period of ultrasound may have been missed.

The formation of lymphocyst may be influenced by several factors: body mass index[20], the number of lymph nodes removed[21,22] and the presence of metastases to the lymph nodes.[23] In this study, the mean number of nodes harvested is 13.84. Both patients who developed lymphocyst in this study had no metastasis to lymph node .However the above mentioned factors did not influence the formation of lymphocyst in our study.

Age, gravidity, parity and type of malignancy were also analyzed and did not influence the formation of lymphocyst. Lymphocyst were previously reported to be more common among patients more than 60 years old, this is presumably due to the impeded regenerative capacity of lymph vessels among older patients.[8] The mean age of patients in this study is 51.78 years and somewhat lower than the cited age that could probably influence lymphocyst formation. Other factors which may have significant impact on the development of lymphocyst such as tumor differentiation, ligation of lymphatic channels during lymphadenectomy, pre/postoperative radiation therapy, prophylactic use of anticoagulants were not determined in this study thus were included in its limitations.

Conclusion and Recommendations

This study showed that the prevalence of lymphocyst formation is 3.44 per 100 gynecologic malignancy patients (2 of 58) and these patients were asymptomatic. The mean interval between the time of operation and lymphocyst formation is 5.5 weeks. All patients had non closure of the peritoneum as the only technique performed. Other factors such as age, gravidity, parity, BMI, type of malignancy, number of nodes dissected, nodes either positive or negative for metastasis showed no influence on the formation of lymphocyst among malignancy patients who underwent pelvic lymphadenectomy.

This study reflects the prevalence of lymphocyst formation in this institution. Variables not included in this study which may influence lymphocyst formation may be investigated in future researches. These include tumor differentiation, ligation of lymphatic channels during lymphadenectomy, pre/postoperative radiation therapy and prophylactic use of anticoagulants.

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Placental Site Trophoblastic Tumor, a Rare Gestational Trophoblastic Neoplasia
A Case Report and Review of Literature*

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Placental site trophoblastic tumor (PSTT) is a relatively uncommon form of gestational trophoblastic disease. A 6- year database review from 2008 to 2013 at the Section of Trophoblastic Disease revealed only 1 case of PSST managed.

This is in a 27 year-old who presented with persistent vaginal bleeding three months after a full term delivery. Pelvic examination, and ancillary procedures suggest a primary impression of Gestational Trophoblastic Neoplasia. She underwent emergency laparotomy with total hysterectomy for an impending uterine rupture and started on single agent chemotherapy based on an initial diagnosis of GTN I:6 . Hispathologic examination with immunohistochemistry panel on the hysterectomy specimen revealed a placental site trophoblastic tumor.

This paper presents the clinical presentation and management of a PSTT encountered at the Philippine General Hospital and reviews the latest literature in the diagnosis and treatment of this rare gestational trophoblastic neoplasia.

Key words: Placental site trophoblastic tumor, Gestational trophoblastic neoplasia

Gestational Trophoblastic Diseases (GTD) represents a unique group of lesions with abnormal proliferation of trophoblasts. The various forms of gestational trophoblastic disease can be defined and related to discrete pathological aberrations occurring at different stages of trophoblastic differentiation with specific pathogenesis, morphological characteristics and clinical features.[1]

In the Modified World Health Organization Classification[2], gestational trophoblastic diseases can be broadly divided into molar lesions and nonmolar lesions. The molar lesions include partial and complete hydatidiform moles and invasive moles. The nonmolar lesions include choriocarcinoma and lesions derived from implantation site extravillous (intermediate) trophoblast [exaggerated placental site and placental site trophoblastic tumor (PSTT)] and those from the chorionic-type intermediate trophoblast (placental site nodule and epithelioid trophoblastic tumor).[3,4,5]

There is only one patient confirmed to have PSTT and managed accordingly in a 6- year database review from 2008 to 2013 of the Section of Trophoblastic Disease. This paper aims to: (1) discuss the clinical presentation diagnosis and management of this particular case at the Philippine General Hospital and

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in the process, (2) review the latest knowledge in the pathology, diagnosis and treatment of this rare gestational trophoblastic neoplasia.

The Case

The only reported case for the past 6 years was in a 27 year-old, G1P1 (1001) who presented with persistent vaginal bleeding for three months. She has no comorbidities. Her past medical and family history were unremarkable. She delivered to a full term, a live baby boy with no complications 7 months prior to the admission.

The patient started to have abnormal uterine bleeding described as spotting with intermittent profuse vaginal bleeding, 3 months after her delivery with no initial consult done. Due to the persistence of bleeding, which went on for 4 months, she finally consulted a local hospital where a completion curettage was done. There was no specimen submitted for histopathologic study. Vaginal bleeding persisted even after the curettage. On follow-up, a pelvic ultrasound was requested with findings consistent with a molar pregnancy. Hence, she was referred to a trophoblastic disease center for management. On admission, pelvic exam showed the external genitalia to normal with smooth vagina. The cervix was closed and the corpus was enlarged to 18-20 weeks, with tenderness on deep palpation. There was no adnexal mass nor tenderness and bilateral parametria were smooth and pliable.

Repeat transvaginal ultrasound done revealed that the uterus was anteverted, with irregular contour and heterogenous echopattern measuring 14cm x 10.6cm x 10.3cm. The cervix measures 2.8cm x 3cm x 3cm with homogenous cervical stroma and distinct endocervical canal. There is an irregular vascular solid mass measuring 11.2cm x 8.7cm x 8.7cm involving the full thickness of the anterior and posterior myometrium and bulging at the fundus. The uterine serosal surface is intact (Figure 1). Color flow mapping of the mass showed abundant vascularity with low resistance indices (Figure 2). The impression was a Uterine mass consider GTN, with >50% myometrial invasion, impending uterine rupture at the fundus. Bilateral ovaries were normal. Chest X-ray and holoabdominal ultrasound were unremarkable. Her baseline βhCG value was 7,419 mIU/ml. The admitting impression was Gestational Trophoblastic Neoplasia. Impending uterine rupture.

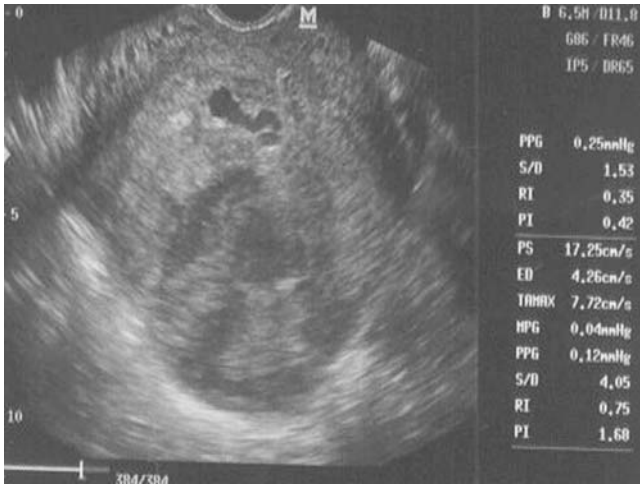

Figure 1. Irregular solid endomyometrial mass involving the full thickness of the anterior and posterior myometrium and bulging at the fundus. The uterine serosal surface is intact.

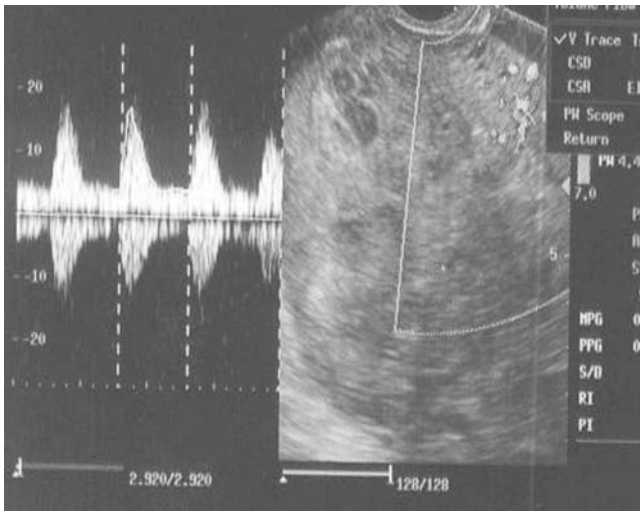

Figure 2. Color flow mapping of the mass showed abundant vascularity with low resistance indices.

The patient underwent emergency exploratory laparotomy, total hysterectomy under spinal anesthesia. Methotrexate 50 mg was given intravenously prior to the operation. Intraoperatively, minimal brownish fluid was noted at the peritoneal cavity. The liver, spleen, subdiaphragmatic surfaces and kidneys were smooth and grossly normal. The uterus measured 15cm x 14cm

x12cm with irregular contour but the anterior surface of the corpus was noted to be bluish (Figure 3). The fundal portion of the mass was covered with serosa only (Figure 4). On cut section, there was a polypoid endometrial mass measuring 10 x 10 x 8 cm, with full thickness myometrial invasion into the anterior myometrium and fundal area. There were areas of hemorrhages and necrosis noted (Figure 5). The cervix measured 2cm x 2cm x 3cm and was smooth. Bilateral ovaries and fallopian tubes were grossly normal. The patient tolerated the procedure well. Her repeat βhCG after 1 week went down to 3,350 mIU/ml. She received 1 cycle of Methotrexate chemotherapy after which she was discharged. She was given another cycle of Methotrexate out- patient. Her βhCG level was normal after her 2nd cycle of Methotrexate. During her last follow up, she was asymptomatic and her latest βhCG values were normal for 2 consecutive determinations. Final histopathologic result of the specimen was Placental Site Trophoblastic Tumor, with infiltration to more than ½ of the myometrial wall with proliferative endometrium and chronic endocervicitis. Immunohistochemistry study showed a negative p63 and a positive Ki-67. Presently she is asymptomatic and no subjective complains.

Discussion

PSTT is a relatively uncommon form of gestational trophoblastic disease. It is composed of neoplastic implantation site intermediate trophoblastic cells.[2-8] In contrast to the normal extravillous (intermediate) trophoblastic cells in which invasion is highly regulated and is confined to the inner third of myometrium, the tumor cells of PSTT are highly invasive as they infiltrate deep into the myometrium of the uterus.[4,6]

PSTT accounts for 3.1/1000 to 2/100 of all trophoblastic diseases. Rate of PSTT to choriocarcinoma has been reported to be 1/138.[9] Based on the Philippine Obstetrical and Gynecological Society statistics, there were only 18 cases reported from 2001-2009.[10] In this particular institution, there were only at least 4 PSTT cases reported since 1998, this case being the latest.

Figure 3. Uterus has an irregular contour with prominent vessels noted at the surface.

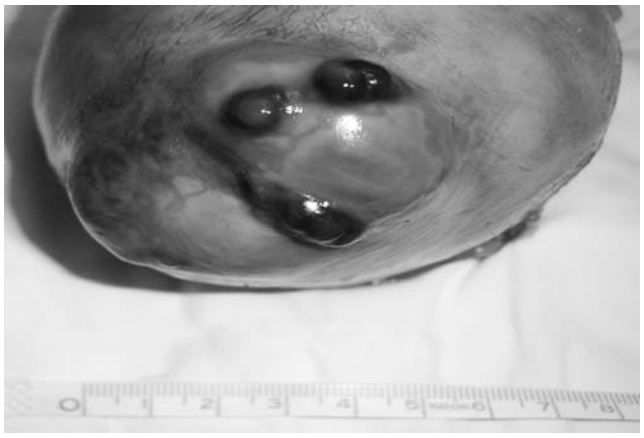

Figure 4. The serosa was thinned out at the fundal area. Large vessels and blood clots were visible underneath.

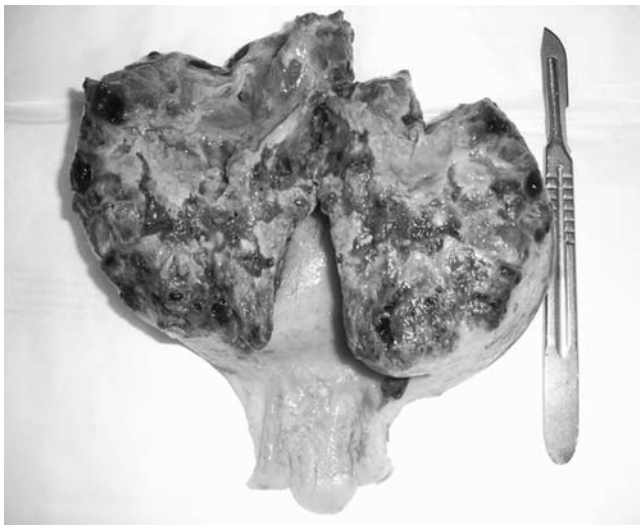

Figure 5. On cut section, the mass showed areas of hemorrhage and necrosis with almost full thickness myometrial involvement.

It was first described by Kurman, et al. in 1976, given the term 'trophoblastic pseudotumor[8] thought to be benign in nature lacking the dimorphic picture of cyto- and syncytiotrophoblast characteristic of choriocarcinoma. Since then, a few cases were reported with similar morphology that proved to be fatal. Because of this, in 1981, Scully and Young, proposed the term Placental Site Trophoblastic Tumor in lieu of the term pseudotumor, to emphasize that the origin of the tumor was the placental site cell and to show the tendency of the tumor to follow a malignant course with disseminated metastasis in 15-30% of cases.[11] A good percentage of patients with PSTT however, may initially show no focus of metastasis implying good prognosis similar to the index patient.

Clinical Presentation

The disease is usually seen in young women as in the index patient, with mean age at diagnosis of 31 to 33 years. There have been cases reported in post-menopausal women with the oldest patient reported by Nigam et al in a 63 year-old woman who was menopause for 12 years.[12]

Very few data are currently available on the genetics of PSTT. Although these tumors are less often associated with an antecedent molar pregnancy, it has been confirmed using DNA analysis that, like choriocarcinoma, they may arise from both hydatidiform mole (21%) and a normal term pregnancy which appears to be the most common antecedent pregnancy of PSTT (53 - 78%).[13-17] Cytogenetic analysis of a single PSTT by Lathrop et al (1988)[14] showed that it was diploid. In a further case reported by Arima et al (1994)[15] two term female pregnancies were followed by a PSTT, which was shown by sex chromosome-specific sequences to have arisen from an unrecognized male pregnancy. Using the X-linked human androgen receptor gene as a polymorphic marker in the nine cases of PSTT showed that most PSTT were derived from the antecedent female conceptus and were likely to have possessed a functional paternal X chromosome.[16,17] Some reports show that an antecedent normal pregnancy with a female fetus is not only a common occurrence but also an independent poor prognostic variable.[18] The index patient delivered to a baby boy prior to the PSTT.

The clinical presentation of patients with PSTT does not differ from the signs and symptoms of patients with other forms of gestational trophoblastic disease. In most of the reviews done, the most prevailing presenting symptom is abnormal vaginal bleeding or amenorrhea. The interval between the antecedent pregnancy and the presentation of PSTT is variable from a few months similar to the index patient, to a number of years. Studies show that the longer the interval (more than 2 years), the poorer the prognosis.[10] Aside from vaginal bleeding, another interesting manifestation in a few patients is galactorrhea induced by the hPL that is produced and secreted by the intermediate trophoblastic cells. It is also the high levels of hPL that is related to hyperprolactinemia that is thought to be the reason of the amenorrhea.[12] The index patient was amenorrheic for 3 months after her normal delivery after which she presented with vaginal bleeding. In some isolated cases, usually in the advanced stages, nephrotic syndrome, sepsis, and erythrocytosis, or symptoms pertaining to the metastatic sites may be the presenting symptoms. PSTT presents with metastases in about 10% of the cases and metastases develop in an additional 10% during follow-up.[9]

Diagnosis

A high index of suspicion is needed in the initial diagnosis of PSTT. Aside from the clinical presentation, the physical examination findings showing a relatively large tumor incompatible with the low level of hCG will lead to the consideration of PSTT. On pelvic examination, the corpus of the index patient was enlarged to 18 - 20 weeks with the tumor measuring 11.8 cm in its widest diameter but the hCG was only 7,419 mIU/ml. Case reports show that serum hCG in PSTT is usually below 1000 mIU/ml in 79% and below 500 mIU/ml in 58% of patients. This is because of the predominance of intermediate trophoblasts in PSTT secreting human placental lactogen (hPL) and producing only a lower amount of hCG compared to syncythiotrophoblasts.[10] However, hCG still remains to be the tumor marker that we use for PSTT. In relation to hCG, some

studies report a high proportion of hCG free ? subunit and ? core fragment which is a degradation product of the free β subunit, but these are not available in our country. The use of hPL is limited only to immunohistochemistry.

As in other types of GTN, ultrasound with Doppler studies to show the extent of the tumor and its vascularity is useful in establishing diagnosis of PSTT. This will help also in the decision regarding the type of surgery that can be done and whether there will be room for a conservative procedure. CT, MRI, and even PET scan are sometimes also requested in case reports abroad and used to evaluate the depth of invasion and the scope of metastasis especially when a more conservative management is planned. The imaging findings of PSTT indicate that it can be divided into two types, a hypervascular type and a relatively hypovascular type. In the hypervascular type, massive bleeding following dilatation and curettage has been reported.[19] When prominent vascularity of the tumor is indicated by imaging findings, dilatation and curettage should be avoided. On the other hand, uterine conservative surgery may be possible in patients with the localized hypovascular type. The ultrasound of the index patient showed an irregular vascular solid mass measuring 11.2cm x 8.7cm x 8.7cm involving the full thickness of the anterior and posterior myometrium with abundant vascularity (Figures 1-2). The result was compatible with impending tumor rupture and involved a greater part of the corpus and therefore not a candidate for a more conservative procedure.

The gold standard for the diagnosis of PSTT remains to be histopathology. The gross appearance of the tumor is variable. It may be an ill-defined mass or a well-circumscribed nodule in the myometrium with or without projection into the uterine cavity. Cut surface of the tumor is mostly yellow or tan, soft, granular and may contain only focal areas of hemorrhage and necrosis. For this particular patient, grossly there was a cream tan fungating mass at the fundal area. Cut section of the mass showed it to be dark brown and friable and revealing gross infiltration up to a depth of 2 cm of the myometrium (Figure 5). Bilateral adnexae and other pelvic organs were unremarkable.

Microscopically, the following features are characteristic of PSTT: 1. sheets of large, polygonal intermediate Trophoblastic cells with irregular, hyperchromatic nuclei, and dense eosinophilic cytoplasm; 2. myometrial infiltration with characteristic separation of muscle bundles by tumor cells; 3. vascular invasion characterized by extensive replacement of blood vessel walls by tumor cells that extend into the vascular lumen from the outside to inside; and 4. abundant extracellular eosinophilic fibrinoid.[12] These particular features were appreciated in the specimen of the index patient. (Figures 6-12).

Immunohistochemistry is significant to establish definitive diagnosis in PSTT. An algorithm using a panel of immunohistochemical markers is useful for the differential diagnosis of trophoblastic lesions. PSTT is highly positive for human placental lactogen (hPL) because of the predominance of the intermediate trophoblasts and only weakly positive (< 10%) for hCG. A negative p63 and a positive hPL indicate that the lesion is either exaggerated placental site or PSTT. These 2 lesions can be differentiated based on the Ki-67 labeling index. A Ki-67 of more than 1% is diagnostic of PSTT [20]. Immunohistochemical staining panel for this case revealed a negative p63 and Ki-67 positivity with moderate nuclear staining in 6-11% of cells of interest (Figures 13-14). hPL was not done because it is not available locally.

Management

Baseline laboratory tests are requested to enable prompt management of complications. These include CBC with platelet count and Typing, Urinalysis, liver function tests, renal function tests and electrolytes, which were all done for the index patient. A baseline ?hCG and a transvaginal ultrasound are done to verify initial diagnosis, which were performed in the index patient (Table 1). Metastatic work-up will include a Chest xray and a whole abdominal ultrasound, which in the index patient showed normal, results. Additional tests include a Chest CT Scan and a Brain CT Scan. Chest CT Scan is done only when Chest xray showed normal result. In the patient, since the initial ?hCG result was low with an admitting impression of GTN, it was deemed not necessary to do a chest CT scan since the

extent of intrauterine tumor already explained the βhCG level. Brain CT Scan is done when Chest xray show a large pulmonary mass 3 cm. and above.[10]

With completion of the work-up, the patient is staged using the FIGO 2000 Staging System (Table 2). The WHO Scoring System is not used as PSTT behaves differently and does not correlate well with the outcome. The FIGO Stage is the most important prognostic factor with FIGO I and II showing a higher survival rate of 93.5% compared to FIGO III and IV with a survival rate of 33.3%. Likewise, a lower recurrence rate is seen in FIGO I and II of 5% and higher for FIGO III and IV of 70% and 90% respectively.[21] The index patient is FIGO Stage I showing the tumor to be confined in the uterus with no site of metastasis.

Table 2. 2000 FIGO Staging for Gestational Trophoblastic Neoplasia.

Stage 1	Disease confined to the uterus
Stage 2	Disease extends to outside the uterus but confined to the pelvic organs
Stage 3	Pulmonary metastases
Stage 4	Metastasis to other sites

Table 1. Laboratory tests performed on admission and on follow up.

Tests	Results
Complete blood count	
Hemoglobin	108
Hematocrit	0.335
WBC	9.87
Segmenters	0.61
Lymphocytes	0.28
ANC	6.02
Platelet count	357
Blood type	O+
BUN	3.39
Creatinine	36
Na	142
K	4.6
AST	44
ALT	41
PT	
Patient	9.9
Control	11.6
Act	>1.0
INR	1.0
APTT	
Patient	36.7
Control	29.5
Urinalysis	Equivocal
βHCG	
10/10/08 (admission)	7,419.75 mIU/ml
10/16/08 (post op)	3,350.5 mIU/ml
11/18/08 (post chemo I)	40 mIU/ml
12/12/08 (post chemo II)	4 mIU/ml
1/13/09	0.239 mIU/ml
2/10/09	<0.10 mIU/ml

Unlike the more common Invasive mole and Choriocarcinoma were the primary mode of management is chemotherapy, surgery is the first line of treatment in PSTT as it is found to be resistant to chemotherapy. The optimal treatment therefore remains to be hysterectomy with or without bilateral oophorectomy depending on the age of the patient. Ovarian micrometastases from the disease apparently confined to the uterus is rare, thus preservation of grossly normal ovaries in premenopausal women who wish to preserve ovarian function is reasonable.[5,7,12,13] The performance of pelvic and para aortic lymphadenectomy is still controversial and has been suggested by some authors because of reports of a tendency to lymphatic spread in PSTT.[22] Younger patients with a lower FIGO Stage, smaller tumor size and still desirous of pregnancy can still be managed conservatively with dilatation and curettage or tumor resection. It is in these patients where a CT Scan or MRI of the pelvis may be helpful to accurately map out the extent of the tumor. The index patient has only one living child but the size of the tumor and the circumstances on admission of impending tumor rupture did not make tumor resection feasible. She underwent hysterectomy showing the tumor to be involving almost the whole corpus with full thickness myometrial invasion.

Chemotherapy in PSTT is advised for patients with a lower stage with poor prognostic factors like a longer interval from the antecedent pregnancy to the manifestation of the disease, higher mitotic count or

higher FIGO Stages.[10] The index patient was initially given a pre-operative dose of Methotrexate with an initial diagnosis of GTN with impending tumor rupture. The rationale of the perioperative chemotherapy is: 1. to reduce the likelihood of disseminating viable tumor cells at surgery; 2. to maintain a cytotoxic level of chemotherapy in the bloodstream and tissues in case viable tumor cells are disseminated at surgery; 3. to treat any occult metastases that may already be present at the time of surgery. The study of Sheong, et al. demonstrated that a single chemotherapy with MTX can be administered safely during the time of hysterectomy without increasing the risk of bleeding or sepsis.[13] For the index patient, treatment with single agent Methotrexate was started after the operation based on an initial diagnosis of GTN I with a low risk score, as the histopathologic result of PSTT was not yet available.

Most cases of PSTT are confined to the uterus like the index patient but it can infiltrate relentlessly and extend into adjacent organs such as the ovary, parametrium, rectum or bladder. Distant metastases can occur in lungs, peritoneum, liver and brain, and some reported observed retroperitoneal and supraclavicular lymph node metastases.[8,11,23,24] Metastases at presentation were occurring in 10-15% of patients, and recurrences develop in 10% of cases. The common sites of metastases are lungs, pelvis and lymph node. Less commonly, the central nervous system, kidney and liver are involved.[24]

For PSTT patients with advanced stages, the first-line chemotherapeutic regimen is EMA/CO as reports have shown complete responses with this regimen.[25] Treatment delay can be best avoided with G-CSF and other types of growth factor.[26] For second-line chemotherapy, EP/EMA may be used, although it is recommended in some studies to be given as first line regimen in PSTT. Other protocols used in case reports are Bleomycin, etoposide and cisplatin (BEP) and Etoposide, ifosfomide and cisplatin (VIP).[10] In cisplatin-refractory cases, Taxanes is added to the regimen as a taxol/cisplatin-taxol/etoposide regimen.[13]

Radiation is reported to be useful in the setting of localized and isolated recurrence or palliative therapy.[27] However, due to limited experience with it, there is still no consensus on radiation in the PSTT treatment.

Follow-Up

After treatment, with normal levels of βhCG, follow-up is advised similar to GTN patients. βhCG is monitored every month for the first 6 months and every other month to complete 1 year. It is taken every 3 months on the 2nd year and every 6 months thereafter. For patients treated conservatively, they are advised to avoid pregnancy 1 year from the first normal βhCG titer. Chest xray is done annually for those with residual lung lesions.[10] The first normal βhCG titer of the index case was noted after her 2nd cycle of chemotherapy. Her βhCG titer was monitored monthly. After 2 consecutive normal values of βhCG, she decided not to continue with her follow up despite advise of her attending physician.

Prognosis

Prognosis was best in cases of disease confined to the uterus, tumor less than 2 years from antecedent pregnancy, and when combination treatment of surgery and chemotherapy was used which are all present in the index patient. In cases of metastasis outside the uterus, and in cases when the interval between antecedent pregnancy and the disease was over 4 years, the outcome was dismal, with a mortality rate of 100% despite all treatment modalities.[13,28]

This recent case portrayed a benign clinical course in contrast to the first case reported in the Philippines, which showed a very poor outcome. This is in a 37-year old, G8P8(5125) who underwent a fractional curettage for vaginal spotting. The histopathology revealed PSTT for which she underwent total abdominal hysterectomy.

The antecedent pregnancy in this case was a normal term delivery with an interval of 6 years up to diagnosis of PSTT. Chemotherapy was not given due to financial constraints. She was readmitted for dyspnea five months after the operation. Work ups showed pulmonary metastasis. She eventually died from respiratory failure despite administration of chemotherapy. Autopsy study showed widespread metastases to lungs, brain, pancreas, adrenals and both kidneys.[29]

Several studies demonstrated that disease extension beyond the uterus is the most significant adverse prognostic factor. However, interval from antecedent pregnancy >2 years and age >40 years are also significant adverse prognostic factors. In the recent study of Papadopoulos, et al.[30] risk factors for death include lung metastatic involvement (50%) and an antecedent pregnancy interval of 4 years or more (100%). In contrast, those with no extrapelvic disease or an interval of less than 4 years had 100% survival. Some authors demonstrated that mitotic count >5 mf/ 10 HPF is also a significant adverse prognostic factor.[31,32] Vascular space involvement and endomyometrial invasion are also considered to be poor prognostic factors.[27,33]

All these factors present in this first diagnosed case of PSTT were poor prognostic variables in contrast to our index patient. On follow up, the index patient was asymptomatic and the βhCG monitoring went down to normal. Latest metastatic work ups were unremarkable. Her course showed a remarkable response from the surgery and chemotherapy. Favorable prognostic factors were present in our patient. Primarily, she's at FIGO stage 1 (confined to the corpus), even if histopathologic features showed vascular space invasion and deep myometrial invasion. The most important prognostic factor in PSTT is the FIGO Stage. Patients who were initially diagnosed as FIGO I and II showed a higher survival rate than FIGO III and IV.[10] The patient was young at 27 and her interval from the antecedent pregnancy was only 7 months. These added to her better prognosis.

Summary and Conclusion

With a patient presenting with symptoms of vaginal bleeding months to years after delivery, an inappropriate uterine size, and a low βhCG levels, the diagnosis of PSTT may be considered. Meticulous metastatic work-up is mandatory. Early diagnosis facilitates treatment planning and prevents occurrence of serious morbidities. The diagnosis of PSTT can be made with H &E stain alone but immunohistochemistry panel is confirmatory.

After completing the work-up, staging is done using the FIGO 2000 Staging System. WHO Prognostic Scoring System is not used in PSTT. The primary mode of treatment is surgery. The desire of future fertility and the extension of the disease are important factors to keep in consideration. Chemotherapy is given to patients with poor prognostic factors and advanced FIGO Stage. First line is EMACO with EP-EMA as primary salvage chemotherapy.

Favorable Prognosis of patients with PSTT depends primarily on the FIGO stage, age and interval from the antecedent pregnancy. The rarity of this tumor, together with variable biological behavior and chemosensitivity, makes it difficult to identify the optimum management. Lifelong follow up with tumor marker and additional clinical assessment will be necessary.

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Leiomyosarcoma of the Cervix in Association with Pregnancy: A Case Report*

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Leiomyosarcoma arising in the uterine cervix is an exceedingly rare tumor accounting for less than 1% of cervical malignancy and 12.5% of cervical sarcomas. Approximately 30 cases of primary cervical leiomyosarcomas have been reported in the literature and none of them were diagnosed during pregnancy. This is the first reported case of leiomyosarcoma of the cervix in association with pregnancy to the author's knowledge. A 40-year-old, gravid 6 para 5, Filipino woman, 17 weeks and 3 days pregnant consulted a private obstetrician due to a 4-month history of post-coital bleeding. She was subsequently referred to our institution due to a finding of a cervical mass. On examination, the cervix was completely converted to a bulky, solid, nodular, polypoid mass measuring 12cm x 12cm occupying and obliterating the vaginal canal up to the lower third of the vagina. Biopsy of the mass with immunohistochemistry showed leiomyosarcoma of the cervix. She underwent extrafascial hysterectomy with bilateral salpingo-oophorectomy, bilateral pelvic lymph node dissection and para-aortic lymph node sampling. On histology, the tumor was very cellular with spindle-shaped cells arranged in fascicles with marked pleomorphism, atypia, and scanty eosinophilic cytoplasm. High power magnification revealed abundant pleomorphic cells with >10 mitosis per high power field and tumor cell necroses. She was then advised postoperatively to receive adjuvant treatment in the form of chemotherapy with doxorubicin. Due to its rarity, little is known of its appropriate modality of treatment. Hence, management is extrapolated from their uterine counterparts consisting of hysterectomy. Prognosis is poor regardless of adjuvant treatment given due its high rate of relapse and recurrence.

Key words: Leiomyosarcoma, cervical leiomyosarcoma

Leiomyosarcoma (LMS) arising in the uterine cervix is an exceedingly rare tumor accounting for less than 1% of cervical malignancy[1-3] and 12.5 % of cervical sarcomas.[3] Approximately 30 cases of primary cervical leiomyosarcomas have been reported in the literature[3-4] and none of them were diagnosed during pregnancy. Histologically, it is diagnosed based on the presence of high grade cytologic atypia, high mitotic rate and presence of tumor cell necrosis.[5-7] Due to its rarity, little is known of its appropriate modality of treatment. Hence, management is extrapolated from their uterine counterparts consisting of hysterectomy.[8]

* First place winner, 2013 SGOP Interesting Case Contest

The objectives of this paper are to report a case of leiomyosarcoma of the cervix diagnosed during pregnancy, to report the pathological, clinical, demographic profile, treatment, prognosis and outcome of leiomyosarcoma of the cervix and to review related literature.

The Case

A 40yo, G6P5 (5005), 17 weeks and 3 days pregnant, from Taguig City, Philippines was referred to our institution for further evaluation and treatment of her cervical mass. She presented with 4 month history of post coital bleeding. One month prior to admission, she consulted a private obstetrician who noted a cervical mass measuring 10cm x 8cm, characterized as bulky and occupying the whole cervix. Assessment was a cervical mass to consider malignancy. Biopsy of this mass revealed malignant spindle cells separated by thin fibrous stroma exhibiting marked nuclear pleomorphism, hyperchormasia, prominent nucleoli, scant cytoplasm, extensive necrosis and mitosis of 10-12 mitosis per high power field. The histopathologic diagnosis was a spindle cell carcinoma versus leiomyosarcoma. Transvaginal ultrasound showed a singleton intrauterine pregnancy 13 weeks and 2 days by CRL and BPD concomitant with a cervical mass measuring 10cm x 8cm, thin-walled with mixed echogenicity. At our institution, internal examination showed the cervix was completely converted to a bulky, solid, nodular, polypoid mass measuring 12cm x 12cm occupying/obliterating the vaginal canal up to the lower third of the vaginal canal, corpus was enlarged to age of gestation, and bilateral parametria were smooth and pliable. She was initially assessed to have malignant spindle cell carcinoma versus leiomyosarcoma of the cervix, stage IB2. Slide review was done showing a malignant melanoma versus leiomyosarcoma. Immunohistochemistry was requested to confirm the diagnosis and it showed positive for smooth muscle actin and vimentin, negative for cytokeratin, S-100 and HMB-45, consistent with leiomyosarcoma. (Figures 1-5) Hence, she was finally diagnosed with leiomyosarcoma of the cervix, stage IB2. Treatment options were thoroughly explained to her and her husband which include the following: a) immediate hysterectomy with fetus-in-situ; b) neoadjuvant chemotherapy while awaiting fetal lung maturity followed by cesarean section then hysterectomy; or c) await fetal lung maturity followed by cesarean section then hysterectomy. She and her husband opted for immediate surgical intervention. Baseline transvaginal ultrasound was done in our institution which showed a cervical mass measuring 10.1cm x 9.3cm x 10.0cm and an intrauterine pregnancy 18 weeks by BPD and 17 weeks and 2 by FL. The sonologic impression was cervical mass consistent with malignancy and a single live intrauterine pregnancy, variable presentation with good cardiac and somatic activities, 18 weeks by BPD, 17 2.7 weeks by FL. (Figures 6-8)

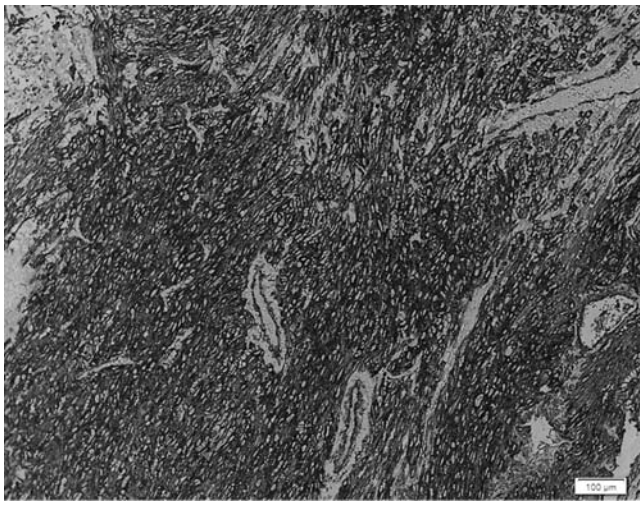

Figure 1. Positive staining for smooth muscle actin.

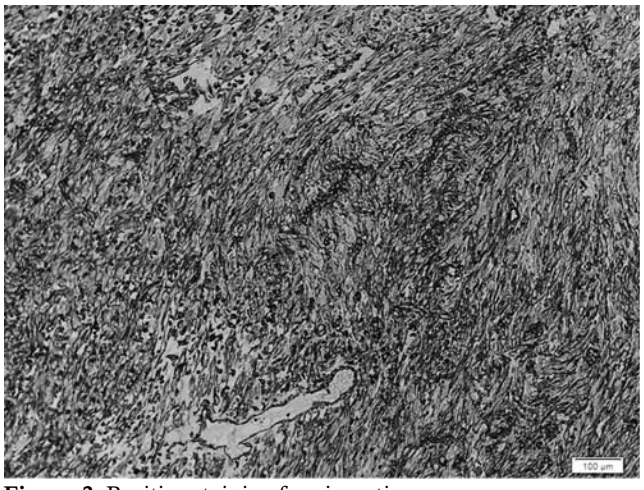

Figure 2. Positive staining for vimentin.

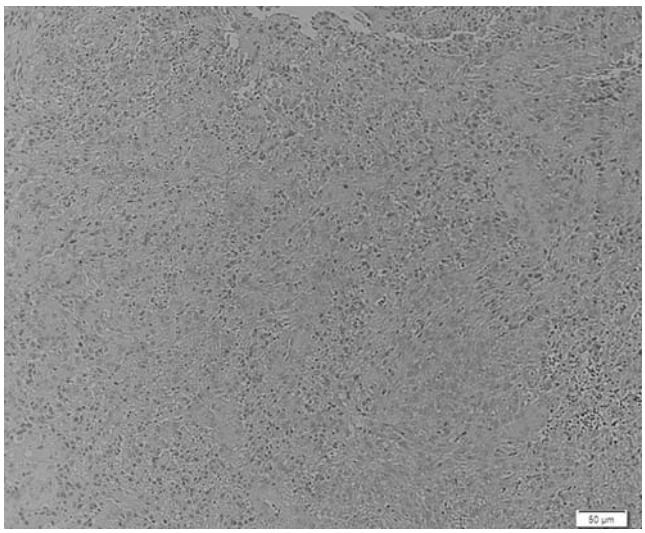

Figure 3. Negative staining for cytokeratin.

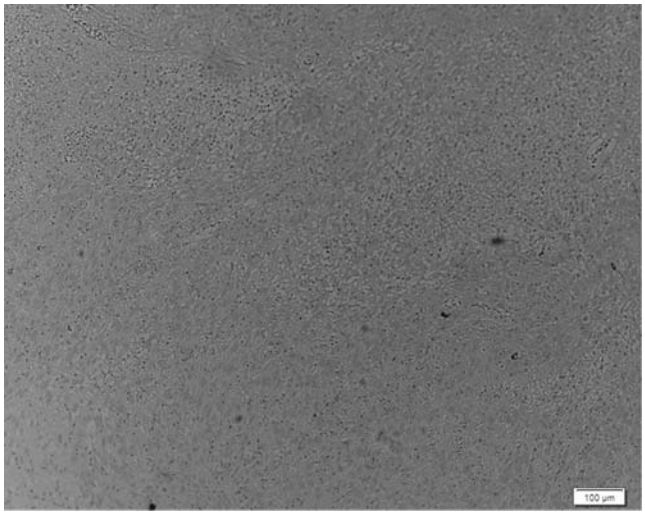

Figure 4. Negative staining for S100.

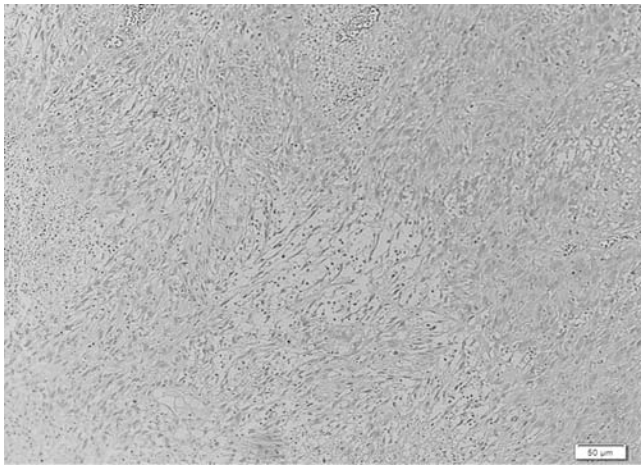

Figure 5. Negative staining for HMB45.

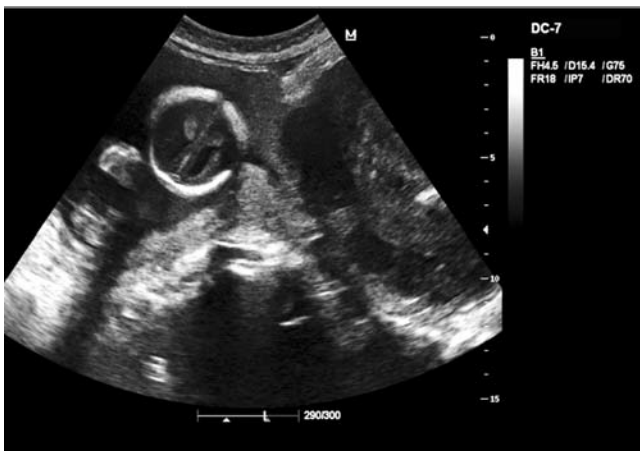

Figure 6. Ultrasound showing fetus within the uterus, 18 weeks by biparietal diameter and 17 weeks and 2 days by femoral length.

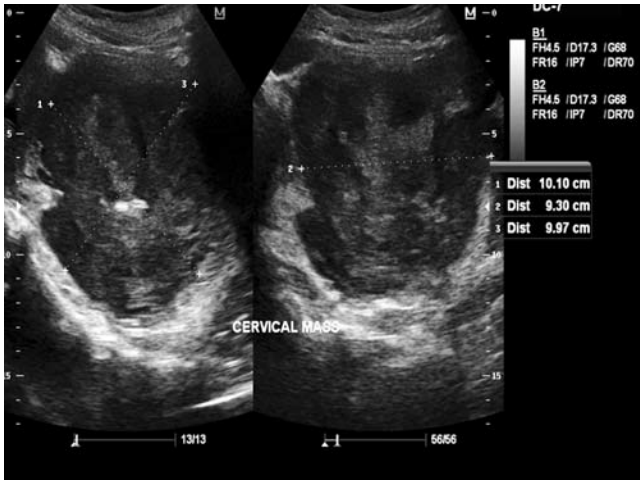

Figure 7. Ultrasound showing cervical mass characterized as irregular heterogenous mass measuring 10.1cm x 9.3cm x 10cm.

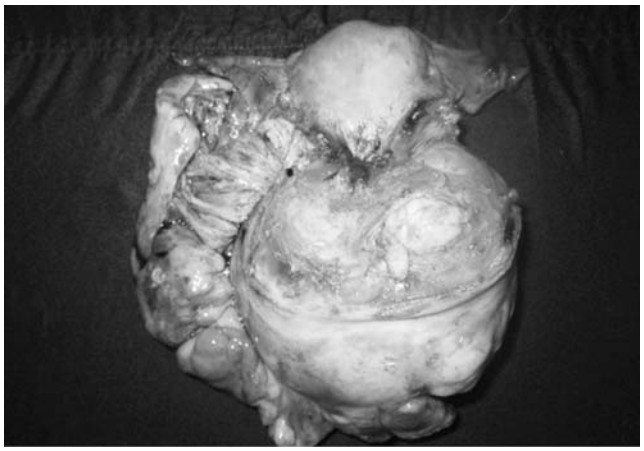

Figure 8. Anterior view of the mass showing a corpus measuring 5cm x 7cm x 4cm while the cervix measured 10cm x11cm x 9cm.

On her 19th week (19 3/7 wks AOG) of pregnancy, she experienced sudden onset of vaginal bleeding associated with crampy hypogastric pain and passage of meaty material. She was admitted in our institution with a diagnosis of incomplete abortion. After spontaneous passage of fetus, she underwent completion curettage. Estimated blood loss after curettage was approximately 500cc. Post curettage, she was transfused with 4 units of blood and was discharged improved.

She was admitted for elective surgery in our institution one month post curettage. She underwent exploratory laparotomy, extrafascial hysterectomy, bilateral lymph node dissection and para-aortic lymph node sampling. Intraoperatively, there was no ascites. The surfaces of the liver, subdiaphragmatic peritoneum, spleen, gallbladder, stomach, kidney surfaces, intestines, omentum, and appendix were all smooth and grossly normal. There were no palpable pelvic or paraaortic lymph nodes. The corpus measured 5cm x 7cm x 4cm with smooth tan serosal surface. On cut section of the corpus, the endometrial cavity measured 5 cm, the endometrium measure 0.2 cm and the myometrium measured 1.5cm. There were two polypoid endometrial masses measuring 2cm x 2cm x 1cm, necrotic, friable and hemorrhagic located in the fundus, while the other one measured 1cm x 1cm, necrotic, and friable located in the posterior corpus. Both masses had no myometrial invasion. The cervix was completely converted to a 10cm x 11cm x 9cm predominantly solid friable necrotic mass which was impacted to the pelvic sidewalls and cul de sac. Cut section of this mass showed areas of necroses and hemorrhages. The bilateral adnexae were smooth and appeared grossly normal. (Figures 9-12) On histology, the tumor was very cellular (Figure 13) with spindle shaped cells arranged in fascicles, marked pleomorphism, bizarre-forms, atypia and scanty eosinophilic cytoplasm. (Figure 14) On high power magnification, (Figure 15) there were abundant pleomorphic cells with >10 mitosis per high power field and tumor cell necroses. The histologic and morphologic features were consistent with leiomyosarcoma. The vaginal cuff, bilateral adnexae and all the excised lymph nodes were free of tumor. The estimated blood loss during surgery was 1.5 L. Two (2) units of blood were transfused intraoperatively. She had unremarkable course in the ward and was discharged improved on the 4th hospital day.

Her final diagnosis was leiomyosarcoma of the cervix stage IB2. She was advised to receive adjuvant chemotherapy in the form of doxorubicin, however, she is still securing funds for treatment.

Discussion

Leiomyosarcoma is one of the most common non-epithelial malignant neoplasm arising in soft tissue and somatic organs.[8] Theoretically, it may arise from

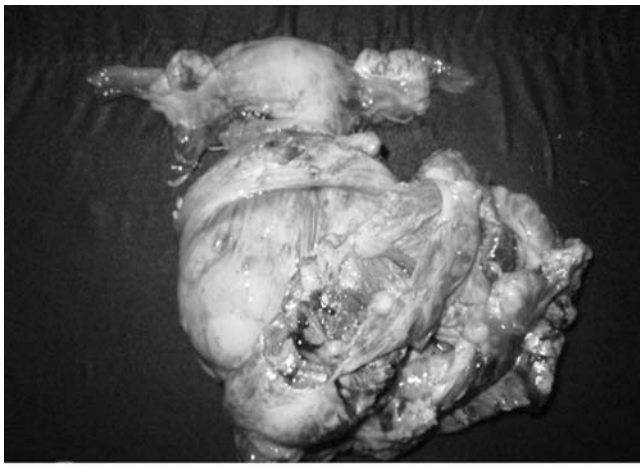

Figure 9. Posterior view of the mass.

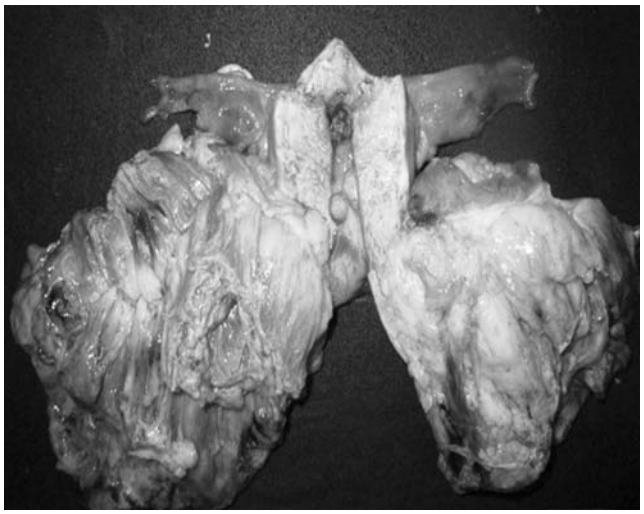

Figure 10. Cut section of the mass (anterior view).

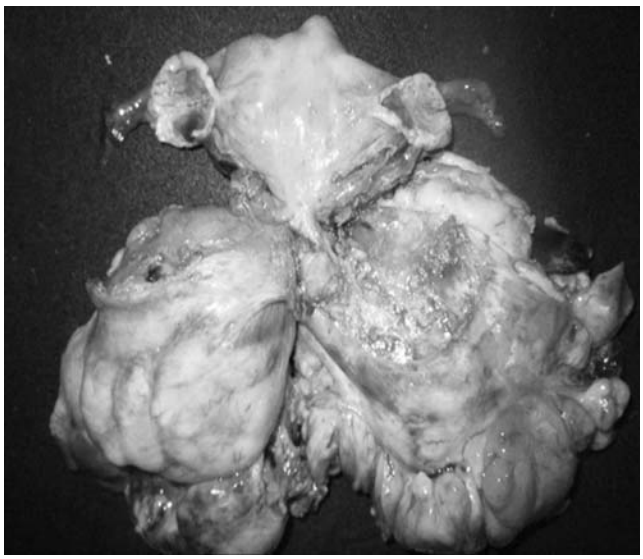

Figure 11. Posterior view showing a grossly normal bilateral adnexae.

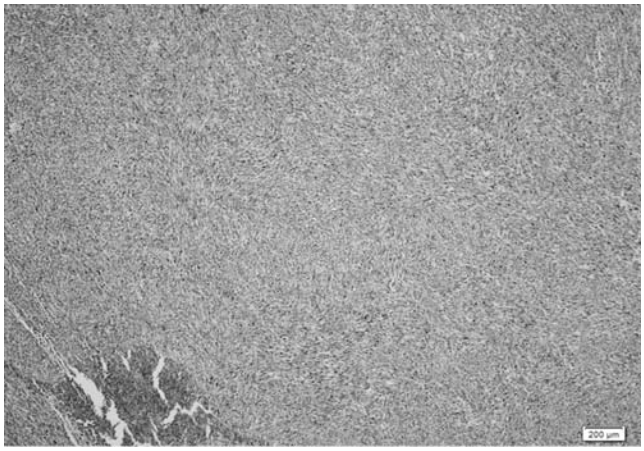

Figure 12. Scanning view of the cervical mass showing high cellularity.

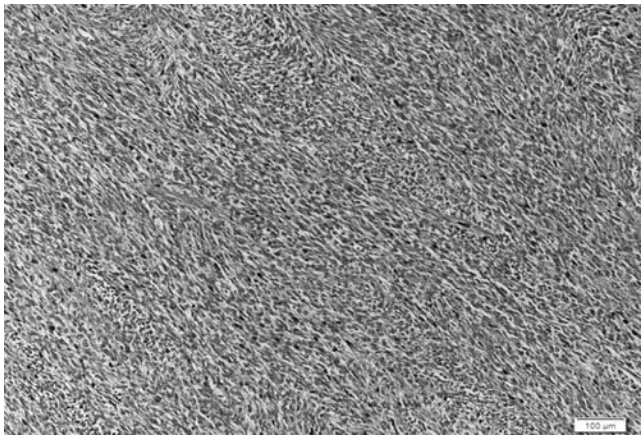

Figure 13. At 10x magnification (LPO) of the cervical mass showing numerous spindle-shaped cells arranged in fascicles.

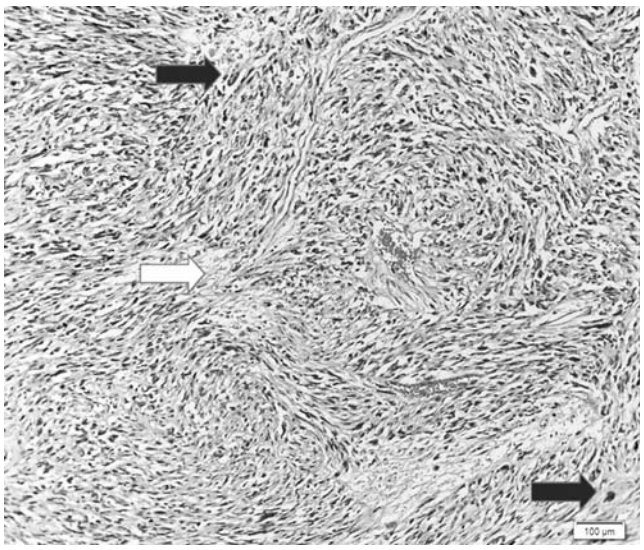

Figure 14. At 10x magnification (LPO) of the cervical mass showing numerous spindle-shaped cells of varying sizes, shapes (light arrow) and mitotic figures (dark arrow)

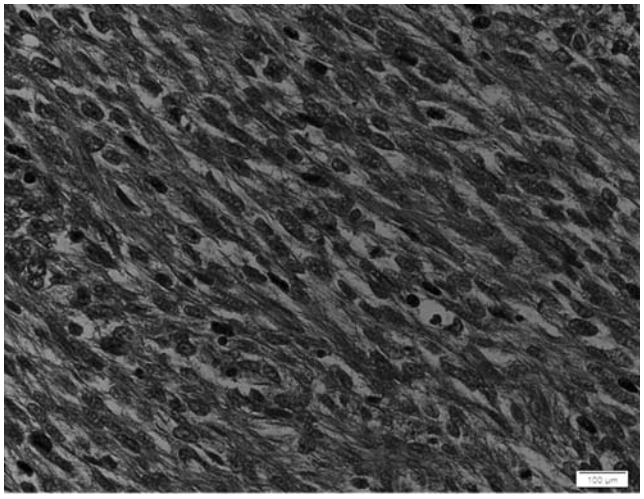

Figure 15. At 40x magnification (HPO) of the cervical mass showing numerous spindle- shaped cells of varying sizes, shapes and mitotic figures.

any of the constituents of the uterus since they are all of mesodermal origin.[9] Leiomyosarcoma arising in the uterine cervix is exceedingly rare accounting for less than 1% of cervical malignancy.[1-3] In a study of Wright, et al. among cervical sarcoma, 12.5% are leiomysarcoma 3 versus 30% in another study done by Abell, et al.[11] There is approximately 30 cases of primary cervical leiomyosarcomas that have been reported in the literature[3-4] and none of them were

diagnosed during pregnancy. In our institution, there are 5 cases of leiomyosarcoma of the cervix reported from 2008 to 2012[12-16] and this is the first case of leiomyosarcoma of the cervix diagnosed during pregnancy.

Cervical cancer is rarely diagnosed during pregnancy but is the most common malignant tumor diagnosed during pregnancy.[44-47] It is reported to occur in approximately one in every 1000-10,000 pregnancies.[47-49] Among patients who present with cervical cancer, it is estimated that only 1% to 3% are pregnant at the time of diagnosis.[50-52] As leiomyosarcoma of the cervix is a rare tumor, its association with pregnancy makes it even rarer, and it is the first reported case to the author's knowledge.

Generally, cervical leiomyosarcoma occurs in the perimenopausal and postmenopausal period.[1,3-4, 8-10] The mean age of diagnosis is 46.[9] Majority of patients complain of vaginal bleeding[3,8-11,17-18,20-22] although some may present with excessive foul-smelling vaginal discharge[18] and urinary retention.[1] In pregnancy-associated cervical cancer, about 50% will present with vaginal bleeding[44] while 30 to 50% of pregnant patients are asymptomatic.[53] Pelvic pain is a less frequent presenting symptom, and maybe associated with more advanced disease.[44] The cervical mass or lesion on the other hand is characterized as either friable, polypoid, bulky, or pedunculated.[1, 3-11,17-22] Our patient is 40 years old, presenting with post-coital bleeding, and the cervical mass is described as polypoid and bulky.

Pregnancy is a good time for cervical cancer screening because cytology is routinely done during prenatal care. A colposcopy with or without biopsy maybe requested when there is any abnormality observed in the cervix on speculum examination, internal examination and cytology. Unfortunately, for this patient, no prenatal care was rendered before the diagnosis of cervical malignancy because pregnancy was not considered at all and it was only an incidental finding on baseline ultrasound. The diagnosis of cervical cancer is primarily based on a biopsy showing malignancy. The diagnosis of leiomyosarcoma of the cervix is extrapolated from its uterine counterpart and is based on the presence of high grade cytologic atypia, high mitotic rate and presence of tumor cell necrosis.[5-7] A constellation of cytologic features including nuclear pleomorphism, hyperchromatism, irregularity in nuclear membranes, high nuclear size, and prominent nucleoli when present are indicative of significant atypia. The presence of 10 or more mitoses per 10 high power fields (HPFs) is considered as key in establishing leiomyosarcoma. Tumor cell necrosis is finding an abrupt transition from necrotic to non-necrotic tumor, without interposed granulation or fibrous tissue.[7] Morphologically, leiomyosarcoma is characterized by cells that form long intersecting fascicles, with eosinophilic cytoplasm and elongated blunted-end nuclei with presence of atypia, high mitotic activity and tumor necrosis.[7] Our patient, on morphology, showed numerous spindled-shaped cells arranged in fascicles with varying sizes and shapes and high mitotic figure of about >14 mitoses per 10 high power field. Spindle cells are pleiomorphic with bizaare forms and presence of tumor cell necrosis. The differential diagnosis for leiomyosarcoma on hematoxylin-eosin (H&E) staining includes malignant melanoma. The diagnosis of leiomyosarcoma in our case is strongly supported by the immunohistochemical staining result showing diffuse and strong expression of smooth muscle actin and vimentin and absence of S-100 and HMB45 and cytokeratin. (Figure 1-5) In contrast, melanoma shows positive for HMB-45 and S-100 protein and negative for smooth muscle actin and vimentin. Available immunohistochemistry results of previously reported leiomyosarcoma cases are summarized in Table 2 with the data of our patient.

Pregnant women with cervical carcinoma are 3.1 times more likely to be diagnosed with early stage disease.[44,54] Most cases (about 70%) of cervical cancer in pregnancy are identified in early stages IA, IB and IIA. These results represent a 2 to 3 fold higher probability of being diagnosed in an operable stage of the disease.[46,55] This is due to the effective early cancer screening such as cytology, speculum examination and internal examination which is routinely done as part of prenatal check up.

Due to the rarity of cervical leiomyosarcomas, little is known of its appropriate treatment modality. Management is extrapolated from their uterine counterparts consisting of hysterectomy8 with or without bilateral salpingo-oophorectomy depending

on the menopausal status of the patient. However, dilemma comes in when it is associated with pregnancy, such in our case, since there is a fetus involved. It is important to consider the possible effects of the pregnancy on the biology of the cancer along with the possible effects of the cancer on maternal and fetal health. Pregnancy per se does not affect progression of cervical carcinoma.[44,48] Zemlickis et al found that stage for stage, 30-year survival of pregnant women with invasive cervical cancer was identical to that of matched controls. The risk of recurrence after delay of treatment of early-stage cervical cancer in pregnancy is reported to be 5% not unlike that of nonpregnant women.[51] Though guidelines for management are not clearly defined, the basis of treatment is similar to that of a non pregnant patient with variations done to achieve the best possible outcome for the fetus without compromising the mother.[44] Moreover, treatment depends on whether the patient desires to continue pregnancy, as well as the stage of the disease, histology of the tumor and gestational age at diagnosis.[47,51] Based on the Guidelines of the Society of Gynecologic Oncologist of the Philippines, treatment depends on the gestational age, stage of disease, lymph node status, desire to continue pregnancy and whether patient has a good or bad surgical risk for operation.[56] Generally, concurrent chemoradiation therapy is given in advanced disease regardless of the age of gestation. If pregnancy is less than 20 weeks age of gestation and early stage, treatment consists of immediate radical surgery as it affords removal of the cervical mass with termination of pregnancy as a consequence of the surgery. If the pregnancy is more than 20 weeks, planned delay of treatment to allow fetal maturity can be a treatment of choice. Neoadjuvant chemotherapy can also be a reasonable option if continuation of pregnancy is desired in early stage bulky locally advanced cervical cancer to be followed by cesarean section with hysterectomy. [56] Neoadjuvant chemotherapy has the following advantages: it is effective before blood flow is disrupted in surgery or radiation therapy, it can reduce cervical tumor bulk and increase operability, it is effective against lymph node metastasis and for prevention of tumor dissemination.[49] Neoadjuvant chemotherapy reported in literature is in the form of cisplatin and vincristine or cisplatin plus vincristine and bleomycin. In a study by Takushi et al, a planned delay of treatment up to 25 weeks does not adversely affect progression of the tumor and showed no clinically apparent side effects to the fetus. In a review by Sadker and Sykes, they also found out that a treatment delay of more than 6 weeks in order to reach fetal viability is safe in patients with early cervical cancer during pregnancy. Chemotherapy during the second and third trimesters has been shown to result in a malformation rate of 1.3% and intrauterine growth restriction.[59,60] The incidence of malformation is similar in the general population when chemotherapeutic drugs are administered after the second trimester.[61] For this patient, she was diagnosed with cervical cancer on her second trimester of pregnancy at 17 weeks age of gestation and had a stage of IB2. Considering the tumor histology, aggressive characteristic of the tumor, financial difficulties, paucity of data on treatment modality of leiomyosarcoma of the cervix and the patient's preference, the initial plan was immediate surgery with the fetus in situ. Thorough explanation of the planned procedure with emphasis of the ethical consideration was given to both patient and her husband. Ethical issue centered on the principle of double effect -- that *"the action is permissible only if it is not wrong in itself and if it does not require that one directly intent the evil result"*.[58] This was understood and accepted by them. However, she had a spontaneous abortion at 19th week of pregnancy.

Several factors have consistently been found to demonstrate value as prognostic indicators predictive of outcome in patients diagnosed with leiomyosarcoma. These include tumor stage, grade, mitotic count, tumor size, age and menopausal status.[9-10,24-28] In the largest clinicopathologic review focusing exclusively upon leiomyosarcoma of the uterus, Guintoli et al retrospectively evaluated 208 patients diagnosed and treated for leiomyosarcoma at the Mayo clinic. They found out that stage, older age (>51 yo), postmenopausal status and larger tumor size (>5 cm) reduced the likelihood of survival.[25] In a recent retrospective study done by Park, et al. postmenopausal status, advanced FIGO stage, deep myometrial invasion, and positive lymphovascular space invasion are associated with poor prognosis.[26] These

identified factors are also considered as predictors of clinical outcome in patients with leiomyosarcoma of the cervix regardless whether it is associated with pregnancy or not. The incidence of lymph node metastasis in leiomyosacoma is noted to be 3.5% - 11%,[10, 29] hence, lymph node sampling at the time of surgery or re-exploration for lymph node dissection is not recommended[10] as disease-specific survival curves is not improved.[29] Adjuvant radiotherapy is associated with improvement of locoregional control, 50% reduction of pelvic relapse[10] and a modest improvement in 5-year survival.[42] However, no statistical significant difference is found on disease-specific survival, recurrence-free survival and overall survival between patients receiving post operative radiotherapy versus no radiotherapy.[29,42] Patients who are at risk for local failure such as those with tumor size >5 cm, high mitotic rate, high cytologic atypia, should be offered radiotherapy for local control.[29] Adjuvant chemotherapy should be given especially in the management of advanced disease due to its propensity to spread hematogenously. Single agents that show moderate activity include paclitaxel (response rate of 33%), doxorubicin (response rate 25%), gemcitabine (response rate 20%), ifosfamide (response rate 17.2%) and intravenous etoposide (response rate of 10.7%).[2-36] Combination of doxorubicin and ifosfamide has been employed more commonly as first line therapy for women with advanced or recurrent leiomyosarcoma.[9,31] As first line chemotherapy regimen with advanced disease, doxorubicin and ifosfamide show the largest response rates which have been reported as high as 30.3% versus combination of hydroxyurea, dacarbazine and etoposide (response rate of 18.4%).[37-38] For patients with recurrent disease, paclitaxel is tested in combination with carboplatin with good outcome.[39-40] Docetaxel plus gemcitabine regimen in a phase II study shows promising results[31, 41] with a 53% response rate.[31]

Recurrence rates of leiomyosarcoma range from 33% to 73%.[3,10,29] Majority of the recurrence occur primarily in the lungs (40.7%) followed by pelvis (13.6%) showing the high propensity of distant spread.[10] Five-year survival rate ranges from 25% to 75%.[24] Patients whose tumors are completely removed have significantly longer disease progression free survival (OR 5.934, 95% CI) and overall survival (OR 4.589, 95% CI).[30] Finally, secondary cytoreductive surgery maybe warranted in patients with recurrence as it shows a prolonged survival in selected group of patients such as those with isolated site of recurrence amenable to complete resection.[43]

Conclusion

Leiomyosarcoma of the cervix is a very rare tumor and its association with pregnancy makes it even rarer. Due to its rarity, no consensus is made with respect to its management. Thus, it is extrapolated from its uterine tumor counterparts. Due to its aggressive nature, immediate treatment is recommended depending on the age of gestation, stage and the desire of the patient to continue pregnancy. More cases and prospective study should be done to determine outcome and prognosis. In the author's knowledge so far, this is the first case of leiomyosarcoma of the cervix in association with pregnancy. Furthermore, it is difficult to concede any effect of pregnancy on tumor growth due to paucity of literature. Prognosis is poor regardless of adjuvant treatment given. Relapse and recurrence are common showing its primary hematogenous route of metastasis.

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Early and Late Stage Neuroendocrine Carcinoma of the Cervix: Experience with Docetaxel-Oxaliplatin and Radiation*

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Uterine cervical cancer is the second most common cancer among women worldwide and accounting 22.5 cases per 100,000 women in the Philippines.[1] The standard of treatment for both early and late stage cervical cancer is concurrent radiotherapy and chemotherapy with an overall 5-year survival rate ranging from 44 - 86%.[1] The most common histologic cell type is squamous cell carcinoma followed by adenocarcinoma, other rare types includes clear cell, glassy cell and neuroendocrine carcinoma.[8] It is very important to determine the specific subtype of cervical cancer because other types are highly aggressive and has a propensity for rapid local and distant metastasis even in early stage, thus the standard treatment may not be enough to treat these patients.[8] The neuroendocrine carcinoma (small cell) type comprising less than 5% of all cases provides a therapeutic challenge for the gynecologic oncologists because it appears to have the poorest prognosis and is characterized by frequent early nodal and distant metastasis. Currently, there is no accepted standard treatment for small cell neuroendocrine cancinoma (SCNEC).

Recently, we have encountered two cases of women affected with an early and a late stage SCNEC, the former was treated with radical surgery with adjuvant chemotherapy followed by radiotherapy while the latter was treated with chemotherapy and radiotherapy.

The Case

Case 1:

A case of a 41-year old, G5P4 (3113) came in with a 10-month history of heavy menstrual bleeding. The patient was hypertensive with good control. Family history was unremarkable. She is a high school graduate, 10-pack year smoker and an occasional alcoholic beverage drinker.

Menarche was at 14 years old with regular monthly cycle consuming 3-5 pads per day with no dysmenorrhea. She had her coitarche at 16 years old. She had 2 monogamous sexual partners. She had history of depot medroxyprogesterone acetate (DMPA) use for 1 year. She had a Pap smear done 2 years prior to consult with allegedly normal result. She is a gravida 5, para 4 (3113), had her first pregnancy at 16 years old which resulted to stillbirth at 7 months. She had one spontaneous abortion and all three pregnancies were carried to term and delivered via cesarean section with no complications.

She has stable vital signs, body mass index of 25 mg/m^2 and body surface area of 1.69 m^2. The rest of the physical examination findings were essentially normal. Internal examination revealed a normal

* Second place winner, 2013 SGOP Interesting Case Paper Contest.

external genitalia, the vagina was smooth and the cervix was converted to a 4cm x 3cm x 3 m nodular fungating mass without forniceal involvement, the corpus was small, there was no adnexal mass and tenderness and the bilateral parametria were smooth and pliable.

Transvaginal and trans-abdominal ultrasound (Figures 1 to 3) revealed that the cervix was converted to an irregular heterogenous mass measuring 5.4cm x 4.9cm x 3.9cm involving the upper one third of the anterior vagina inferiorly and the uterine midcorpus superiorly. Both parametria are intact, normal bilateral adnexae and no pelvic and para-aortic lymphadenopathies was seen.

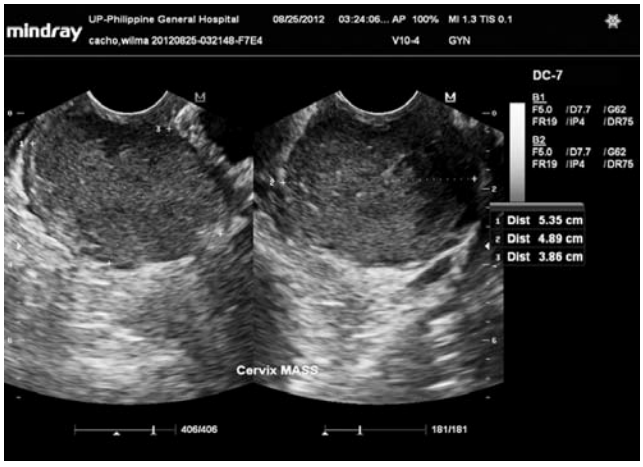

Figure 1. Ultrasound of case 1: The cervix was converted to an irregular heterogenous mass measuring 5.4cm x 4.9cm x 3.9 cm.

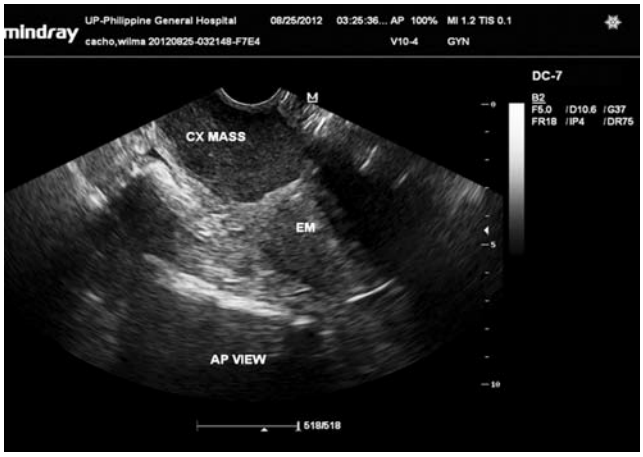

Figure 2. Ultrasound of case 1: The cervical mass involving the upper one third of the anterior vagina inferiorly and the uterine midcorpus superiorly.

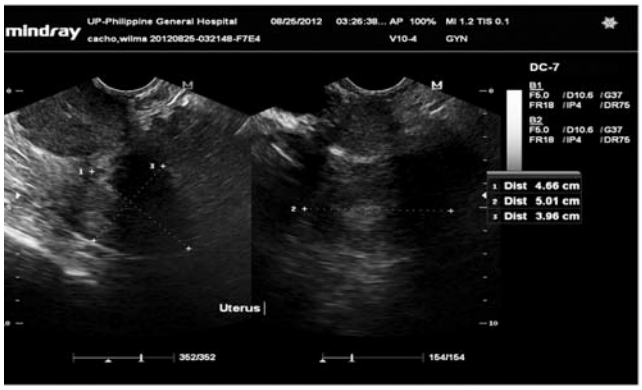

Figure 3. Ultrasound of case 1: The remaining corpus was anteverted with smooth contour and homogenous echopattern measuring 4.7cm x 5.0cm x 4.0cm. The endometrium was hyperechoic measuring 0.2 cm with intact subendometrial halo.

The patient underwent cervical punch biopsy which revealed round cell tumor, to consider small cell carcinoma versus lymphoma. Immunohistochemical studies revealed: Cytokeratin positive, Synaptophysin diffusely positive, Chromogranin focally positive, Leukocyte Common Antigen negative. Results are consistent with neuroendocrine small cell carcinoma. Preoperative diagnosis was neuroendocrine (small cell) cervical cancer stage IB1 (FIGO). She underwent exploratory laparotomy, radical hysterectomy with bilateral salpingo-oophorectomy, bilateral pelvic lymph node dissection and para-aortic lymph node sampling (Figures 4 and 5). Final histopathologic result is small cell carcinoma with neuroendocrine features (Figures 6 and 7), cervix with invasion of more than 2/3 of cervical stroma, positive lymphovascular space invasion with positive metastasis on the external iliac nodes. She received adjuvant chemotherapy with docetaxel at 75 mg/m^2 and oxaliplatin at 100 mg/m^2 every 21 days for 6 cycles followed by extended field radiotherapy (5040 cGy + 4140 cGy at the para-aortic area).

The patient tolerated the treatment with minimal gastrointestinal complaint. No grade 3 or grade 4 anemia and neutropenia were noted. She is currently asymptomatic with the present internal examination revealing a normal external genitalia, smooth vagina with intact vaginal stump, there were no adnexal masses nor tenderness and the bilateral paracolpium were smooth and pliable. Post treatment abdominopelvic computed tomography scan and transvaginal ultrasound results showed no evidence of disease.

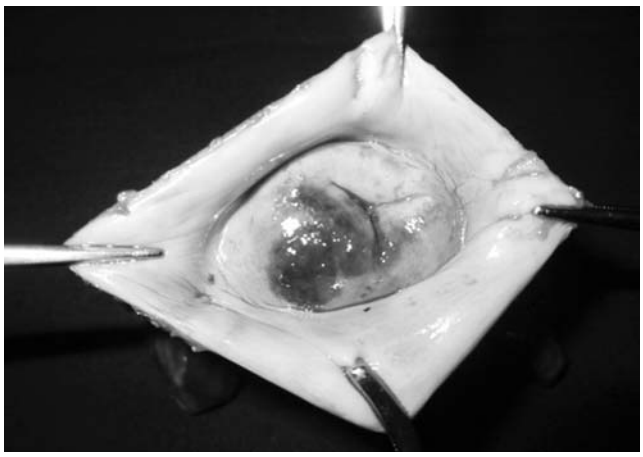

Figure 4. The post radical hysterectomy image of the cervix with a friable necrotic mass at the 6 to 8 o' clock position with vaginal margins grossly free of tumor.

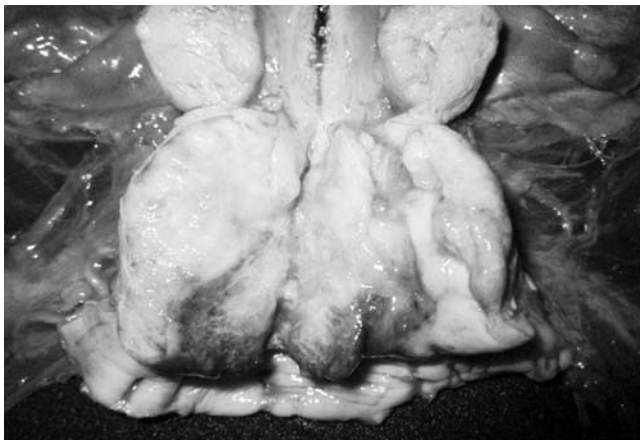

Figure 5. Cut section of the uterus showing the cervical mass with more than 1/3 cervical stromal invasion.

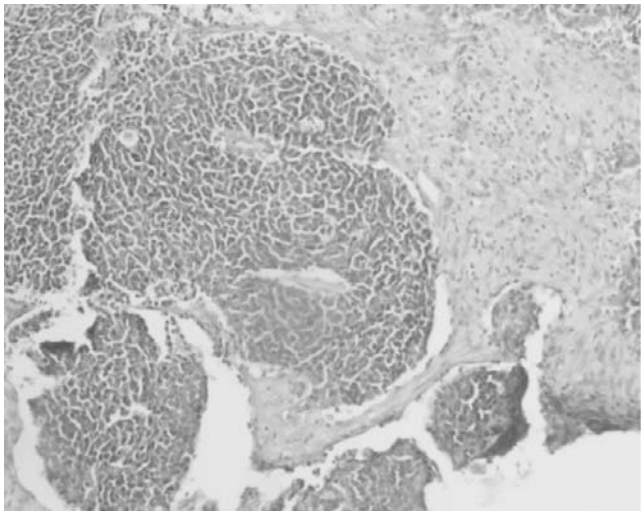

Figure 6

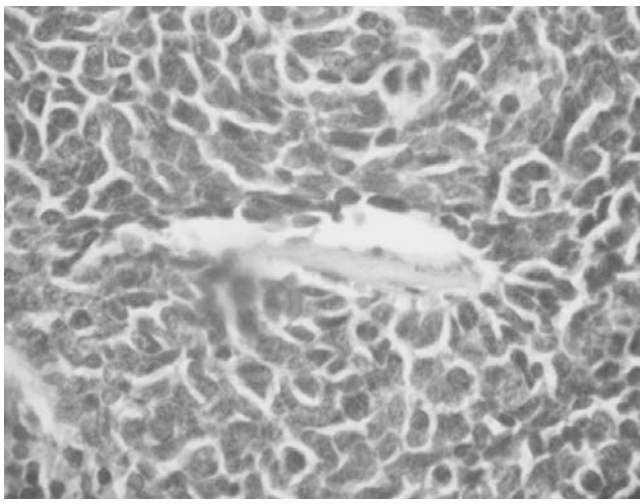

Figure 7

Figures 6 & 7. Tissue sections show sheets of small cells with large, hyperchromatic, irregular nuclei with finely stippled chromatin and inconscipuous nucleoli and scant cytoplasm. Nuclear molding is also seen.

Case 2:

A case of a 40-year old, G5P3 (3023) came in with 2 months history of heavy menstrual bleeding. Past medical and family history were unremarkable. She is a high school graduate, non-smoker and an occasional alcoholic beverage drinker.

Menarche was at 13 years old with regular monthly cycle consuming 2-3 pads per day with no dysmenorrhea. She had her coitarche at 22 years old. She had 7 sexual partners. She had no history of contraceptive use and Pap smear. She is a gravida 5, para 3 (3023) She had her first pregnancy at 22 years old. She had two spontaneous abortions and all three other pregnancies were carried to term and delivered via normal spontaneous vaginal delivery with no complications.

She has stable vital signs, body mass index of 23.6mg/m^2 and body surface area of 1.56 m^2. The rest of the physical examination findings were essentially normal. Internal examination revealed normal external genitalia, the cervix was converted to 8cb x 9cm excavating mass extending to the anterior lower third of the vagina, the corpus was small, no adnexal masses and tenderness were noted and the bilateral parametria was nodular and fixed.

A transvaginal - transabdominal ultrasound (Figure 8) revealed that the vaginal canal was distended by a cervical mass with the lower pole occupying the upper two thirds of the vagina. It has an irregular contour and heterogenous echopattern measuring 7.0cm x 7.1cm x 5.6cm and extends up to the posterior midcorpus and anterofundal area. Both parametria were obliterated with normal bilateral adnexae. There were two hypoechoic masses at the right pelvic area measuring 2.4cm x 1.4cm and 2.3 x 1.0cm respectively representing pelvic lymphadenopathy. Metastatic work-up was negative.

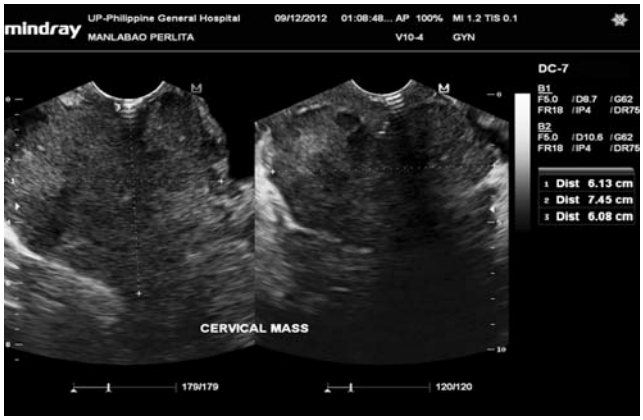

Figure 8. Ultrasound of case 2 showed that the vaginal canal was distended by a cervical mass with the lower pole occupying the upper two thirds of the vagina. It has an irregular contour and heterogenous echopattern measuring 7.0cm x 7.1cm x 5.6cm extending up to the posterior midcorpus and anterofundal area.

The patient underwent cervical punch biopsy which revealed small cell lesion, to consider squamous cell carcinoma, small cell variant versus neuroendocrine small cell carcinoma and malignant lymphoma. Immunohistochemical studies revealed: Chromogranin A positive, Synaptophysin negative, leukocyte common antigen negative and pancytokeratin positive, supporting the diagnosis of neuroendocrine small cell carcinoma.

Final diagnosis was small cell neuroendocrine carcinoma stage IIIB (FIGO). She received six cycles of chemotherapy with combined docetaxel-oxaliplatin and pelvic external beam radiotherapy (5040 cGy + 1000 cGy parametrial boost) and brachytherapy (4000 cGy). Present internal examination revealed normal external genitalia, the vagina was smooth, the cervix measures 1cm x 1cm smooth, the corpus was small, no adnexal masses and tenderness noted and the bilateral parametria was smooth and pliable. Metastatic work up showed no evidence of disease.

Discussion

Neuroendocrine tumors are thought to arise from cells throughout the diffuse endocrine system, originally from the embryonic neural crest cells.[15] They are comprised of a broad family of tumors, and the most common of which are carcinoid and pancreatic neuroendocrine tumors.[15] Neuroendocrine tumors, despite differing embryological origin, have common phenotypic characteristics and are treated as a group of tissue because the cells of these neoplasms share common features, such as histologic characteristics, having special secretory granules and often producing biogenic amines and polypeptide hormones.[20]

Patients with neuroendocrine tumors may or may not have symptoms attributable to hormonal hypersecretion. Patients are classified as having 'functional' or 'non functional' tumor based on the presence or absence of the symptoms. These symptoms include intermittent flushing and diarrhea such as in patients with carcinoid syndrome, hypertension in patients with pheochromocytoma, and symptoms attributable to secretion of insulin, glucagon, gastrin, and other peptides in patients with pancreatic neuroendocrine tumors.[15] They are also classified based on tumor differentiation, well-differentiated, low-grade (G1); well-differentiated, intermediate-grade (G2); and poorly differentiated, high-grade (G3). Small cell carcinoma is considered as a poorly differentiated tumor which has a high mitotic rate and an aggressive clinical course.

The College of American Pathologists and the National Cancer Institute proposed standardized terminology for neuroendocrine tumors of the uterine cervix and identified four categories namely small cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma, typical carcinoid tumor and the atypical carcinoid tumor.[25]

Most neuroendocrine tumors seen in the cervix represent small cell carcinomas. Neuroendocrine cervical cancer is rare representing less than 5% of all cases.[8] It is very important to identify this particular histologic subtype of cervical cancer and to consider innovative approach to treatment because of its poor outcome even at an early stage. They are characterized by cells with scant cytoplasm, inconspicuous nuclei with finely stippled chromatin, nuclear molding, extensive necrosis, crush artifact, and numerous mitotic figures. Single cell infiltration of the stroma is common and lymphovascular space invasion is often, as seen in our patient. These tumors have morphology identical to that seen in small cell carcinoma of the lung and other organs.[8] In the diagnosis, neuroendocrine markers are commonly used to differentiate neuroendocrine small cell carcinoma from other small cell types, with up to 80% of tumors staining for synaptophysin, chromogranin and CD 56 or the neural cell adhesion molecule.

Contrary to the poorly identified risk factor for the development of neuroendocrine carcinoma in other organs, neuroendocrine carcinoma of the cervix identified human papilloma virus (HPV) as a major risk factor in its development. In general, it is well recognized that infection with HPV is required for the development of cervical neoplasia.[8] Presence of HPV deoxyribonucleic acid (DNA) in cervical neoplasia is the first necessary cause of cervical cancer identified.[26] There were about 120 different types of HPV which have been isolated and characterized. The so-called low risk types (6, 11, 42, 43, 44) are mainly associated with benign lesions while high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58) are detected in intraepithelial and invasive cancers.[8] Grayson, et al. investigated the role of human papilloma virus in 12 patients with neuroendocrine (large cell) cervical carcinoma. They concluded that integration of high risk HPV, in particular type 16 and to a lesser extent type 18, were associated with this uncommon variant of cervical carcinoma.[27] Our two patients had several risk factors identified in developing cervical cancer which includes early coitarche and multiple sexual partners which increased their risk of having HPV infection, however HPV typing was not done in our patients. Another important risk factor present in one of our patient is smoking. Smokers maintain cervical HPV infections significantly longer and have a lower probability of clearing an oncogenic infection.[26]

The National Comprehensive Cancer Network (NCCN) published a clinical practice guidelines on the management of neuroendocrine tumors last 2012. Most of the discussion covered neuroendocrine tumors arising from the gastro-intestinal tract, lungs and pancreas and unfortunately, neuroendocrine tumor arising from the cervix was not included. Most of the suggested treatment regimen for neuroendocrine (small cell) cervical cancer was solely based on clinical experience of different institutions and as of this date, there were no published clinical trials and accepted standard of treatment available.

The role of primary radical hysterectomy in patients with neuroendocrine (small cell) cervical cancer is unclear. There were advocates of primary radical hysterectomy for patients with early stage disease and the others prefer to proceed with combined modality treatment when the diagnosis is established. In one Korean retrospective study by Tian et.al., they compared the treatment option of 96 patients with FIGO stage 1B1 to IIA1 neuroendocrine small cell cervical cancer and found out that there was no significant difference in the overall 5 year survival in patients who underwent surgery, surgery plus chemotherapy and surgery plus chemoradiation. They also concluded that adjuvant therapy did not improve the survival.[23]

In a Korean retrospective study, patients with FIGO stage I and II SCNEC underwent radical hysterectomy with bilateral salpingooophorectomy followed with adjuvant chemotherapy while patients with FIGO stage III and IV small cell cervical cancer underwent concurrent chemoradiation. It concluded that primary radical surgery followed by adjuvant chemotherapy is the preferred treatment modality for patients with early stage disease and favorable results have been reported for patients who received concurrent chemoradiation followed by several additional cycles of chemotherapy for late stage disease.[29]

Given the absence of impact on overall survival of chemoradiation and the high risk of distant

metastasis, the role of adjuvant chemotherapy needed further investigation.

Clinical trials with the treatment of neuroendocrine small cell cervical cancer have been scarce and local experience with treatment of these tumors were not promising thus chemotherapeutic agents which were seen to be effective in treating neuroendocrine tumors in other organs such as the lungs, gastric and pancreas were used in the treatment of patients. Surprisingly even with neuroendocrine tumors involving such organs have only few trials which are prospective, randomized and most of these studies include a small number of patients. This is the reason why no standard of treatment can be recommended.

Hoskins, et al. published an institutional experience with multimodality approach in treating small cell carcinoma of the cervix in 31 patients. Patients received either SMCC protocol (etoposide & cisplatin with locoegional irradiation) and SMCC 2 protocol (paclitaxel, cisplatin, etoposide and carboplatin with locoregional irradiation). Comparing the two regimens in this study, they found out that SMCC 2 is more hematologically toxic however it was associated with less hospital admission for nausea and vomiting with less decrease in ECOG scoring. They also found out in the study that radiologic stage was the only predictor of failure free survival. The 3-year overall survival and failure free survival rates were 60% and 57% respectively, thus shifting to SMCC 2 protocol did not improve efficacy but did lessen the toxicity.[11]

Several chemotherapeutic drugs were used in the treatment of neuroendocrine carcinomas, these includes etoposide, streptozocin, doxorubicin, 5-fluorouracil, docetaxel, paclitaxel, gemcitabine, cisplatin, oxaliplatin and other targeted therapies but none has emerged as the standard treatment. Traditional combination chemotherapy regimens containing streptozocin, doxorubicin and 5-fluorouracil used in the treatment of neuroendocrine tumors have yielded disappointing results. The lack of efficacy of these combinations, together with their toxicity, has led to efforts to investigate therapeutic agents that are potentially more active and tolerable. Kulke, et al. assessed the efficacy of docetaxel in the treatment of patients with metastatic carcinoid tumors and results showed biochemical response yet with no radiologic response, only stable disease was achieved in these patients.[14] Gounaris, et al. published a case report regarding a 52 year old woman with neuroendocrine carcinoma stage IV of the lungs, adrenals and brain with marked response using cisplatin, docetaxel and temozolomide.[28]

Oxaliplatin is a platinum analogue with a favorable safety profile in comparison with other platinum derivatives and has shown significant activity against wide range of cancers. Tetzlaff, et al. first reported the response to an oxaliplatin-based regimen in a patient with metastatic carcinoid tumor in 2005.[22] Cassier, et al. conducted a study using gemcitabine and oxaliplatin combination in twenty patients with metastatic neuroendocrine carcinoma which showed promising activity accompanied with decreased toxicity.[6] Several clinical trials are ongoing with the use of oxaliplatin in neuroendocrine tumors, supporting platinum-based regimen as the treatment of neuroendocrine tumors.

Larsson, et al. found out the synergistic effect of the cytotoxic agents like etoposide, oxaliplatin, docetaxel and doxorubicin which are currently used in the treatment of neuroendocrine tumors combined with other pharmacologically active agents.[18] Other therapeutic options have emerged for the treatment of neuroendocrine carcinoma however, the survival was not promising. Thus further researches and identification for the innovative treatment for neuroendocrine carcinoma that will improve survival in our patients should be continued.

Conclusion and Summary

These 2 case reports discussed a rare type of neuroendocrine small cell carcinoma of the cervix, its risk factors and treatment outcome, which has shown good response to treatment with docetaxel and oxaliplatin combined with radiation.

Presently, our patients show no evidence of disease with the instituted treatment regimen. This may not be the standard protocol in the management of such histologic type but may be an alternative one. Prospective studies involving more patients can lead to better evidence of response and toxicity.

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