Preoperative Evaluation of Serum C-Reactive Protein and CA-125 in Differentiating Benign from Malignant Ovarian Masses*

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Background: Ovarian carcinoma is a leading cause of death among the gynecologic malignancies. At present, no definite premalignant lesion has been identified and the goal of screening tool is limited to detection of asymptomatic, early stage disease. **Objective:** This study was conducted to determine the validity of C-reative protein (CRP) and CA 125 in differentiating a benign from a malignant ovarian mass. Subsequently, the study aimed to establish a cut off level for CA-125 and CRP which would best effectively distinguish a benign from a malignant ovarian mass. **Methods:** This is a prospective cross sectional study which included patients diagnosed with ovarian masses admitted for exploratory laparotomy at the Philippine General Hospital. Peripheral venous blood samples each were taken for CA-125 and CRP examinations prior to scheduled operation. CA-125 and CRP results were correlated with the final histopathologic results. Descriptive statistics using means and standard deviation were used for continuous variables and frequency and percentage for categorical variables. The validity of sensitivity, specificity and predictive values of CRP (cut-off - 9.9 mg/L) and CA 125 (cut-off - 35 U/ml) were computed using a given cut-off. A receiver operating characteristic curve (ROC curve) was created to determine and compare the ability of CRP and CA 125 in differentiating malignant and benign ovarian masses. Using the ROC curve, a new cut-off was derived using optimum sensitivity and specificity. **Results:** From the ROC curve, a cut-off of $\geq$6.6 mg/L for CRP and $\geq$61.6 U/ml for CA-125 were derived which will most effectively distinguish between benign and malignant ovarian masses. The sensitivity of CA-125 is 78.6% while the specificity is 65.2%. The sensitivity of CRP is 77% while the specificity is 78.3%. **Conclusion:** CRP is comparable with CA 125 as a tumor marker in differentiating benign from malignant ovarian masses.

Key words: serum CA-125, serum C-reactive protein, ovarian mass

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Ovarian carcinoma is the second most common gynecologic cancer but the leading cause of death from gynecologic malignancies. Its incidence rate is 9 to 17/100,000 and is highest in industrialized countries. Accurate methods of early detection are lacking, with only 25 to 30 percent of these cancers diagnosed at an early stage. To this date, no precursor lesion has been identified. Available potential screening techniques which include transvaginal ultrasound, CA-125 and other tumor markers have limited their goal to detection of asymptomatic, early stage disease.[1]

Among the tumor markers studied for ovarian cancers, CA-125 is the most well-characterized. Its role as a sole screening device is not recommended since several studies showed that elevated levels by itself does not sufficiently distinguish benign from malignant masses.[2,3,4,5] However, its value in monitoring treatment and progression of ovarian cancer has been well- established.[6] Its role as a predictor of clinical and surgical outcome has also been reported. In a recent study done by Cooper, et al, it was shown that preoperative CA-125 is an independent risk factor for death due to ovarian cancer, but not a reliable predictor of optimal cytoreduction.[7]

C-reactive protein is an acute phase protein that is produced by the hepatocytes as a component of the acute phase response. It is mainly induced by Interleukin – 6 which is a pleomorphic cytokine involved in hematopoiesis and regulation of immune response.[8] These substances are released into the circulation in response to tissue damage and inflammation. Serum levels of IL-6 correlate with levels of C- reactive protein.[10,11] Studies demonstrated significant correlation between serum IL- 6 and CRP values in patients with malignant tumors such as esophageal and gastric cancer.[8] Several studies have also been conducted to determine its usefulness in ovarian cancer particularly of epithelial origin. A recent study done by McSorley, et al. showed higher circulating CRP concentration in women who subsequently developed ovarian cancer.[12] The inflammation hypothesis for ovarian cancer was theorized because of its indirect association with endometriosis,[13] pelvic inflammatory disease[13] and polycystic ovarian syndrome.

Recent evidences show that IL-6 may be a useful tumor marker in some patients with epithelial ovarian cancer, as it correlates with the tumor burden, clinical disease status and survival.[11] Although less sensitive than CA-125 as tumor marker for ovarian cancer, it may be related to tumor aggressiveness.[10] Because of its association with IL- 6, studies have been conducted using serum C- reactive protein as tumor marker for ovarian cancer. Two studies done by Kobola, et al. and Hefler, et al. suggested that serum CRP may be an adverse prognostic factor in patients with epithelial ovarian cancer.[8,9] Two studies comparing CA-125 and acute phase proteins showed that CRP is an additional helpful procedure for monitoring patients with malignant ovarian tumors.[15,16]

This study aimed to validate the usefulness of serum C reactive protein as a tumor marker for ovarian masses. Although recent studies proved its usefulness in monitoring response to treatment to ovarian cancer, no prior studies have been conducted using CRP as a marker for discriminating between benign and malignant ovarian masses. If proven, it can be used as an alternative or a complementary tumor marker of CA-125 in the diagnosis of ovarian cancer especially because its measurement is easy and inexpensive.

Objectives

General Objective

1. To determine the validity of CRP and CA 125 in differentiating between benign and malignant ovarian mass.

Specific Objectives:

1. To determine the clinico-pathologic characteristics of the patients with ovarian mass.
2. To determine the sensitivity, specificity, positive predictive value and negative predictive value of CRP and CA 125 in differentiating between benign and malignant ovarian mass.

3. To determine the association of tumor stage with CRP and CA-125.
4. To compare the ROC curve of CRP and CA-125.

Materials and Methods

Patients who were admitted at the PGH from February to August 2008 who satisfied the following criteria were included in this analysis and formed the study population:

1. Patients, regardless of age, documented with ovarian mass by ultrasonography
2. medically fit to undergo exploratory laparotomy, unilateral or bilateral salpingooophorectomy, with or without total hysterectomy, peritoneal fluid cytology, bilateral pelvic lymph node dissection, paraaortic lymph node sampling, random peritoneal biopsy, infracolic omentectomy
3. not pregnant
4. no acute inflammatory disease or autoimmune disease
5. no previous or concomitant malignant disease
6. with informed consent

A case registry form containing the sociodemographic data of the patient (i.e., age, gravidity, past illnesses, family medical history, age at menarche, irregularity of menstrual flow, age at menopause, age at first coitus, history of infertility, history of oral contraceptive pill use) was properly filled up.

Peripheral venous blood was extracted for serum CA-125 and CRP determination at most 5 days prior to surgery. All blood samples were submitted to the Immunopathology Laboratory for CA-125 testing using a chemiluminescent enzyme immunoassay (CLEIA) and CRP testing using VITROS CRP slide method based on an enzymatic heterogenous, sandwich immunoassay format.

All patients underwent exploratory laparotomy, unilateral or bilateral salpingooophorectomy with or without complete surgical staging, which included peritoneal fluid cytology, total hysterectomy, bilateral pelvic lymph node dissection and para-aortic lymph node sampling, random peritoneal biopsy and infracolic omentectomy. All tissue specimens were submitted to the Surgical Pathology Laboratory for processing. The stage of the disease was determined based on the final histopathologic reading.

All serum CA-125 and CRP results and histopathologic reports were collected. The data were pre-coded, entered to digital format using MS Excel software.

Statistical Analysis

Descriptive statistics using mean and standard deviation were used for continuous variables and frequency and percentage for categorical variables. The validity of sensitivity, specificity and predictive values of CRP (cut-off 9.9 mg/L) and CA-125 (cut-off 35 U/L) were computed using a given cut-off.

A receiver operating characteristic curve (ROC curve) was created to determine and compare the ability of CRP and CA-125 in differentiating malignant and benign ovarian masses. Using the ROC curve, a new cut-off was derived using optimum sensitivity and specificity.

Results

Forty-four patients with ovarian masses were included in the study. The mean age was 42.8 with a wide standard deviation. The patients were multigravid and multiparous. There were more patients with malignant than benign ovarian mass. Most patients with malignant ovarian mass were in Stage IA. The most frequent tumor histology were mucinous cystadenoma among the benign ovarian masses and mucinous cystadenocarcinoma of low malignant potential among the malignant ovarian masses. (Table 1)

The validity of the two tests is shown in Table 2. Using a test cut-off of 9.9 for CRP, the sensitivity of CRP in detecting malignant ovarian mass is 57.1% while the specificity is 87.5%. On the other hand, with a test cut-off of 35 U/ml for CA-125, the sensitivity in detecting malignant ovarian mass is 78.6% and a specificity of 62.5%. The predictive values are likewise shown in Table 2.

Table 1. Clinico-pathologic characteristics of patients with ovarian mass.

Variable	Mean (SD) N=44
Age	42.8 (14.1)
Gravida	3.3 (2.9)
Parity	3.0 (2.6)
	Frequency (Percent) N=44
Benign ovarian mass	17 (38.6)
Malignant ovarian mass	27 (61.4)
Tumor stage	
Stage IA	12 (27.3)
Stage IB	1 (2.3)
Stage IC	6 (13.6)
Stage IIIA	1 (2.3)
Stage IIIC	6 (13.6)
Stage IV	1 (2.3)
Histology	
Benign	
Benign epithelial cyst	1 (2.3)
Mucinous cystadenoma	9 (20.4)
Serous adenoma	2 (4.5)
Endometriotic cyst	5 (11.4)
Malignant	
Serous tumor of LMP	1 (2.3)
Mucinous tumor of LMP	9 (20.4)
Endometroid adenocarcinoma	5 (11.4)
Mucinous cystadenocarcinoma	8 (18.2)
Serous adenocarcinoma	4 (9.1)

Table 2. Validity of CRP and CA-125.

	Sensitivity	Specificity	Positive Predictive Value	Predictive Predictive Value
CRP Cut-off=9.9	57.1%	87.5%	88.9%	53.8%
CA-125	78.6%	62.5%	78.6%	62.5%

Table 3 shows the association of the diagnostic tests with tumor stage. There is significant difference (CRP $p=0.006$; CA 125 $p=0.009$) in distribution of patients with malignant and benign ovarian mass in the different tumor stages. Patients with abnormal diagnostic test were more frequent in the higher tumor stages while normal test results were more frequent in patients with benign ovarian mass.

Receiver operating characteristic (ROC) analysis was used to quantify the accuracy of diagnostic tests. A good test will have its curve approaching the upper left hand of the graph while a poor test approaches the reference line (diagonal line). The CRP and CA-125 test is far from the reference line and approaches the upper left hand part of the graph. (Figure 1)

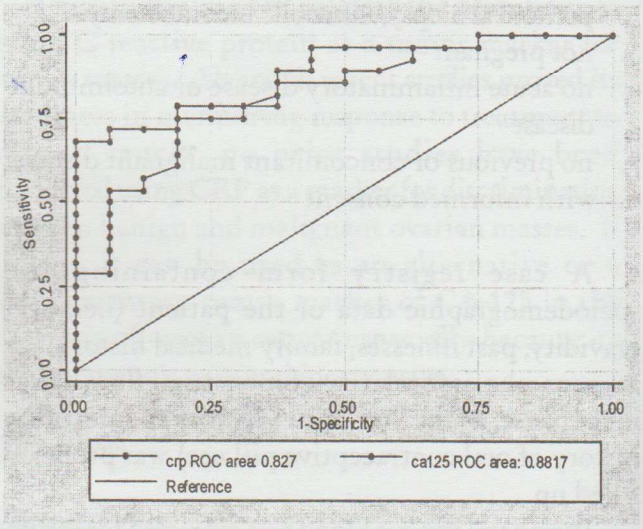

Figure 1. Comparison of receiver operating characteristic (ROC) curve of CRP and CA-125.

Table 3. Association of CRP and CA-125 with tumor stage.

	Benign	Stage IA	Stage IB	Stage IC	Stage IIIA	Stage IIIC	Stage IV	P value
CRP								
Normal (n=26)	14	6	1	4	0	1	0	0.006
Abnormal (n=18)	3	6	0	2	1	5	1	
CA-125								
Normal (n=16)	10	4	0	1	0	1	0	0.009
Abnormal (n=28)	7	8	1	5	1	5	1	

The global performance of a test is commonly summarized by the area under the ROC curve (AUC). The greater the area under the ROC curve, the better the global performance of the test. The AUC for both CRP and CA-125 is above 0.80. There is no statistical difference (P = 0.39) between the AUC of CRP and CA-125.

From the ROC curve, a new cut-off for the 2 tests which will optimize sensitivity and specificity was derived. That cut off will give the highest number of correctly classified cases. For CRP, the cut-off for the patients included in the study is $\geq$6.4 while for CA-125, the cut-off for the patients included in the study is $\geq$61.6. (Table 4)

Table 4. Derived cut-off level for CRP and CA-125 in ovarian malignancy.

Test	Cut -off	Sensitivity	Specificity	Correctly Classified
CRP	≥ 6.4	71.4%	81.2%	75.0%
CA-125	≥61.6	75.0%	81.2%	77.3%

Discussion

In this study, the authors confirmed the validity of CA-125 and evaluated C-reactive protein as preoperative determinant of the benign or malignant nature of ovarian masses. When a cut off of 35 U/l is set, the present study showed a sensitivity of 78.6% with a specificity of 62.5% in detecting malignant masses. The finding on sensitivity is consistent with previous studies which showed a sensitivity ranging from 60-78%.[3,4,16] However, the specificity was low in this study. Previous studies conducted showed specificity ranging from 80-93%. [3,4,16] The low specificity and positive predictive value of CA-125 used as the sole screening test for ovarian cancer were in part due to the marker being elevated in other cancers e.g. pancreatic, breast, bladder, liver, lung as well as in benign disease e.g. diverticulitis, fibroids, endometriosis and physiologic conditions e.g. pregnancy and menstruation.[18]

C-reactive protein as a tumor marker in differentiating benign from malignant ovarian masses has not been explored in the past. Although, there were several studies done proving its usefulness in monitoring treatment response and progression from ovarian carcinoma, no studies confirmed its usefulness in differentiating the nature of such masses. Thus, it could be an alternative tumor marker in discriminating between benign and malignant masses. The study showed that the sensitivity of CRP in detecting malignant ovarian mass is 57.1% while the specificity is high at 87.5% using the cut-off of 9.99mg/L which is the quantitative CRP test available in PGH.

Using the ROC curve, a cut-off of 61.6U/ml for CA-125 was set which increased the sensitivity to 78.6% while the specificity increased to 65.2%. This cut-off approximates the 65 u/ml cut-off used by other previous studies to differentiate most effectively the nature of pelvic masses, although, sensitivity and specificity proved to be higher than what was shown in our study.[2,3,4]

The study, likewise, derived a cut-off of 6.6mg/L for CRP which can most effectively distinguish benign from malignant masses. It increased the sensitivity from 57.1 to 71.4%. however, there was a decrease in specificity from 87.5% to 81.2%.

Conclusion

CA-125 is not sufficiently sensitive to be used alone as a screening tool for detection of epithelial ovarian cancer. But its utility in combination with other modalities such as bimanual vaginal examination and transvaginal ultrasonography has been well-recognized. Although not specific to ovarian cancer because of its elevated levels with other non-gynecological cancer and certain conditions such as endometriosis, pregnancies and infections, it is still the most widely used tumor marker requested by clinicians in determining the nature of ovarian masses. Morever, its preoperative

level when determined is used as a baseline in the monitoring for tumor response in those patients already diagnosed with ovarian cancer and undergoing treatment. Similarly, C-reactive protein is being investigated for its possible use in ovarian cancer. Few studies have already been undertaken and has shown that CRP can also be a useful tool in monitoring tumor response to ovarian cancer. Like CA-125, CRP is also non-specific and can be elevated in other various conditions such as acute and chronic inflammation and connective tissue diseases. However, with the results shown in the study, CRP showed to be a valid tumor marker in determining the nature of ovarian masses. It may prove to be an option and a cheaper alternative tumor marker for CA-125 in the detection and diagnosis of ovarian cancer and monitoring of treatment response. Like CA-125, it may not be sensitive or specific enough to be used as a sole screening tool, but it may find its value when combined with other modalities.

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Correlation of Frozen and Histopathologic Diagnosis of Borderline Ovarian Tumors in a Tertiary Hospital: A Retrospective Study*

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The aim of intraoperative frozen section diagnosis for ovarian tumors is to correctly diagnose malignancy which is very important for younger women. where fertility preservation is paramount and to enable the surgeon to choose the correct operation type. Borderline tumors of the ovary are epithelial tumors distinguished from benign ovarian tumors and frankly invasive ovarian cancers. Due to good prognosis of most women with borderline ovarian tumors, radical surgical management of premenopausal women with borderline ovarian tumors has been replaced in last decades of conservative, fertility-sparing surgery. From January 1998-May 2008, 46 ovarian specimens were submitted for frozen section examination at The Medical City. Forty-two tumors were histologically mucinous, two were serous and two were endometriod. Of the 46 cases reviewed, 36 (78%) correlated with its frozen section diagnosis and final histopathologic diagnosis. However, there were 10/46 (22%) patients that were underdiagnosed with frozen section analysis of benign tumor but definitive histology of borderline ovarian tumor. Our data confirm that frozen section evaluation is an accurate method for the surgical management of patients with an ovarian mass. In conclusion, the frozen and permanent pathology reports of diagnosis of borderline tumor at The Medical City hospital between January 1998 to May 2008 were consistent 78 percent of the time.

Key words: borderline ovarian tumor, frozen section diagnosis, definitive histopathologic diagnosis

Ovarian tumor is the leading cause of death among gynecological cancers, and the fifth cause of cancer death among women.[1] Borderline tumor is a term used to describe an epithelial carcinoma of low malignant potential.[1] It occurs in approximately 20 percent of ovarian epithelial cancers and usually have an excellent prognosis.[2] The most common of

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borderline tumors are the serous and mucinous varieties but other epithelial types can occur.

Surgical excision with total abdominal hysterectomy and bilateral salpingo-oophorectomy has been the primary treatment for borderline tumors. Due to excellent prognosis of patients and its occurrence in women of reproductive age, fertility sparing surgery is of great importance. Thus, accurate intraoperative assessment is important if the patient is highly considering pregnancy in the future.

The accuracy of frozen section diagnosis of epithelial ovarian tumors is generally good but little has been published on frozen section accuracy for borderline ovarian tumors.[3] This retrospective study was undertaken to evaluate the correlation between frozen section and histopathologic diagnosis of borderline tumors of the ovary from January 1998-May 2008 at the Department of Obstetrics and Gynecology, at The Medical City. It likewise aimed to evaluate the accuracy of frozen sections in diagnosing borderline ovarian tumors and to discuss the reasons of discordance, to determine the sensitivity, specificity, positive predictive value and negative predictive value of frozen section diagnosis in borderline ovarian tumors.

Materials and Methods

A retrospective cross sectional study was utilized for this study. Analysis of patient's records between January 1998-May 2008 for borderline ovarian tumors was performed. Pathology reviews of all consecutive patients with ovarian tumors, with either a frozen section or histopathologic diagnosis of borderline tumor of the ovary were obtained. The cases that did not have frozen sections were excluded from the study. The main sources were the database of the Department of Obstetrics and Gynecology and the records of the Department of Pathology of The Medical City. Records were examined for information including frozen section diagnosis, histologic type, final histologic diagnosis and the attending pathologist responsible for the frozen section and for the final diagnosis.

The tissues for frozen section were obtained and processed following a standard protocol. All frozen section specimens were diagnosed by a Pathology consultant. Following inspection, each specimen had 1 or 2 representative sections sampled for frozen section. In cases of non-uniform tumors, representative samples of suspicious areas were submitted for frozen section evaluation. In cases of large tumors, number of sections, one section per centimeter, based on the size of the tumor, were taken for frozen section evaluation. An attending pathologist performed the final pathologic review, not necessarily the same individual who examined the frozen section. For the purpose of the study, the final histopathologic diagnosis was assumed to be accurate.

For each biopsy, the frozen section diagnosis and definitive histology diagnosis were compared. The results were divided into three groups benign, borderline, or malignant. The sensitivity, specificity, and positive and negative predictive values of the frozen section diagnosis were calculated.

Results

This study reviewed 56 cases with final histopathologic findings of borderline ovarian tumors. Ten cases were automatically excluded from the study because frozen section procedures were not requested. Forty-six patients were identified with ovarian borderline carcinoma on frozen section and final pathology reports. Forty-two (91%) tumors were histologically mucinous, 2 (4%) were serous and two (4%) were endometriod. Thirty-nine (85%) patients had fertility-sparing surgery, 6 (15%) patients underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy. There were 4 (9%) bilateral diseases noted. The left ovary was noted to be more frequently affected in 29 (63%) of cases than the right ovary which was only involved in 13 (27%). Agreement between frozen section diagnosis and definitive histology was observed in 34/46 (78%) patients, yielding a sensitivity and positive predictive value of 44% and 78%,

respectively (Table 1). Underdiagnosis, however was identified in 10/46 (22%) patients with frozen section analysis of benign tumor but definitive histology of borderline ovarian tumor (Table 2). The 10 underdiagnosed frozen section diagnoses occurred in mucinous ovarian tumors. None of the patients had a frozen section analysis of malignant ovarian cancer but definitive histology of borderline ovarian tumor was identified. Of the 10 with a frozen section diagnosis of benign tumor and definitive histological diagnosis of borderline ovarian tumor, there were focal borderline changes not sampled during frozen section analysis but were all staged during the initial surgery, none had to undergo a second surgery for staging purposes.

Table 1. Sensitivity, specificity, positive predictive value, negative predictive value for borderline ovarian tumors.

	Borderline Ovarian Tumors			
	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Frozen Section Diagnosis vs. Final Histopathologic Diagnosis	44	0	78	100

Table 2. Frozen diagnosis compared with permanent pathology diagnosis of ovarian tumors.

	Final Diagnosis			
Frozen Section	Malignant	Borderline	Benign	Total
Malignant	0	0	0	0
Borderline	0	36	0	36
Benign	0	10	0	10
Total	0	46	0	46

Patient characteristics and tumor characteristics is shown in Table 3. The mean age for all patients was 32.5 years (range 12-61 years). The mean diameter overall was 14.5cm (range 3.83-35.5cm). Mucinous tumors had a mean diameter of 17.5cm while serous tumors had a mean diameter of 10.5cm and endometriod tumors had a mean diameter of 11cm.

Table 3. Patient characteristics and tumor characteristics.

Characteristics	
Age	
≤ 35	22
> 35	24
Histology	
Serous	2
Mucinous	41
Mixed	0
Endometriod	3
Size	
≤ 20cm	30
>20cm	16

Discussion

Borderline epithelial ovarian tumors or tumors of low malignant potential were first described in 1929.[2] Surgical excision with total abdominal hysterectomy and bilateral salpingo-oophorectomy has been the primary treatment, with a trend toward fertility conservation in young women. Particularly this relates to the accurate diagnosis of borderline tumors on frozen section as half of them occur before the age of 40.[5] In these, women fertility can be preserved without radical surgery or chemotherapy. Excellent long-term survival has been reported with conservative surgery for borderline ovarian tumors, so accurate intraoperative diagnosis is imperative.

The rapid frozen section technique was introduced by William Welsh in 1891.[4] Although

the technique remains essentially the same, refinements for more accessible and timely results have made frozen section diagnosis standard in many surgical procedures.[4] Frozen section diagnosis should not be seen merely as a microscopic examination of the tissue. Rather, it is an intraoperative consultation method in which other diagnostic tests such as a gross examination and fine needle aspiration cytology are used in combination.[6] Careful gross examination of the specimen is of utmost importance for both correct sampling and arriving at the correct diagnosis.

A frozen section report can dramatically influence a patient's life. The risk of inadequate staging for what is believed to be borderline lesion but reported by final pathology as invasive cancer is the potential concern of using frozen section. During the course of data gathering for this study, it was observed that at present frozen section is more frequently requested by surgeons as compared to previous years. Overdiagnosis of borderline ovarian tumors will result in even more serious morbidity while underdiagnosis may result in subsequent additional surgical intervention or possible tumor spread. Gynecologic surgeons fully stage ovarian tumors that are borderline by frozen section because of concern of diagnosis of invasive cancer by permanent sections. Frozen section examination has a high accuracy rate in ovarian tumors, reported at greater than 90%.[7] Frozen section analysis of borderline ovarian tumors is notoriously difficult with a significantly lower sensitivity and specificity of 45-78% compared to benign tumors of the ovary and ovarian cancers.[10] A study by Twaalfhoven, et al. in a series of 311 ovarian tumors, 11 had a disagreement between frozen section analysis and a definitive histology. Seven of these had either a frozen section or final diagnosis of borderline ovarian tumor.[10] However, in a study by Rose, et al. reported a sensitivity and positive predictive value of 87% and 100%, respectively for borderline ovarian tumors making overtreatment an unlikely event.[6]

Most cases in the study had completed families however, two of the cases reviewed were that of a 12 year old and a 16 year old, both nulligravids with frozen section diagnoses of mucinous tumor of borderline malignant potential. Fertility preservation was done. Peritoneal fluid cytology and partial omentectomy results revealed negative for malignancy. Women, as such, can now enjoy fertility preservation without radical surgery or postoperative chemotherapy because of accurate frozen section technique. Most tumors in the study were mucinous. Most surgeons required frozen sections for tumors that were questionable on ultrasound or intraoperative examination of the tumor. Diagnostic problems can be overcome in mucinous and borderline tumors during frozen section examination if there is a good communication between clinicians and pathologists. A study by Houck, et al. shows that frozen section is most reliable for small serous tumors and that mucinous histology, spread outside the ovary, bilateral disease and diameter each had significant effects on accuracy of diagnoses.[8] Increased inaccuracy of frozen section diagnosis for mucinous tumors is likely because of the larger average diameter of mucinous tumors and the need for larger samples. Mucinous tumors typically contain a range of tissue types from benign to malignant and have diameters larger than 20 cm were more likely to be under diagnosed by frozen specimen because of the decreased number of sections done relative to the size of the tumor. According to a study by Twaalfhoven, et al. in their evaluation of a small number of borderline tumors, that those of the mucinous type were potential diagnostic problems.[10]

The ten cases excluded from the study did not request for a frozen section. Fortunately, surgical completion was done for all the cases.

Conclusion

The most important question is whether or not a frozen section diagnosis of borderline tumor of the ovary should lead the surgeon to abort the operation and wait for a definitive histology report. Understanding the prognosis and treatment of borderline tumors over the years has allowed

conservative therapy of young women. Frozen section evaluation of ovarian masses provides mostly accurate diagnosis and guides the surgeon in planning the management of the operation and to do fertility preserving surgery if appropriate. Frozen and permanent pathology reports of diagnosis of borderline tumor from January 1998-May 2008 at The Medical City were consistent in 36 of 46 cases (78%) of the time. The mean age of patients in the study was 32.5 years in whom fertility is an important issue.

Limitation of this study is the limited number of subjects available. Since borderline ovarian tumor is a rare entity comprising only 10 percent of epithelial ovarian malignancies[2], studies investigating the accuracy of frozen section analysis are characterized by a limited number of patients. Another possible limitation of this study is the interobserver bias in cases of the characteristic differences in reading of specimens sent for frozen section evaluation by pathologists.

Like other diagnostic methods in medicine, frozen section has its pitfalls, and surgeons must be aware of the limitations of this procedure. Frozen section appears most helpful when the lesions are solid or cystic or completely solid.[7] However, malignant or borderline tumors and also metastatic tumors may show completely cystic features on gross examination. For this reason, adequate sampling is mandatory especially in cases of large ovarian tumors and the macroscopic evaluation of inner and outer surfaces of the cyst must be done in great scrutiny. Large ovarian tumors, as in cases of mucinous tumors should be investigated very carefully and intraoperative frozen section diagnosis of large tumors should be interpreted with caution. This study recommends that frozen sections should be examined by an experienced pathologist with expertise in gynecological oncology.

The data also indicate that large tumors should be grossly examined thoroughly and multiple sections may be appropriate to increase the sensitivity for focal borderline changes. This study also recommends a more thorough research because of the impact of frozen section diagnosis with regards to its reliability will give surgeons the option to request the procedure when the need arises. Follow-up of patients to determine incidences of pregnancy after fertility sparing procedure is also recommended.

In conclusion, frozen section evaluation to identify a malignant, borderline of benign ovarian tumor is an important and reliable tool in the clinical management of patients with ovarian tumors. However, surgical management of borderline ovarian tumors based on intraoperative frozen section diagnosis should be used prudently because this strategy will result in an undertreatment or overtreatment of a substantial number of women.

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Giant Condyloma Acuminata of Buschke and Lowenstein Tumor in Pregnancy*

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Giant Condyloma Acuminata or Buschke and Lowenstein Tumor is a rare sexually transmitted disease. It is characterized by invasive growth, recurrence after treatment and potential for malignant transformation.[1,2] This tumor grows to a large size and has a fungating cauliflower-like appearance.[3,4] Buschke and Lowenstein tumor has a clinically intermediate presentation being histologically benign while behaving malignantly. Its early recognition as a different clinical entity to ordinary Condyloma acuminata is important for its adequate management.[5]

This case is the first recorded in our institution and in the country, of Buschke and Lowenstein tumor in pregnancy with syphilis infection. The patient is a 21-year old commercial sex worker, G2P1(0101) presented at 20-21 weeks of gestation with a rapidly enlarging infected cauliflower-like vulvar mass. Infection and anemia were managed and followed by surgical excision of the vulvar mass. One week postoperatively intrauterine fetal demise occurred and the patient delivered spontaneously after two weeks (beginning tumor regrowth was seen at this time). Preliminary histopathologic findings showed Condyloma acuminata and treatment with an immune modifier cream was started but there was no response. Further evaluation of histopathologic result led to the final diagnosis of giant condyloma acuminata of Buschke and Lowenstein/Verrucous Carcinoma. There was rapid enlargement of the tumor in six weeks, despite medical treatment, with enlargement of bilateral inguinal lymph nodes. A radical vulvectomy with bilateral groin node dissection was done. This successfully treated the tumor with no recurrence on her 6th month follow up.

Key words: Giant condyloma acuminata, pregnancy, verrucous carcinoma, Buschke and Lowenstein tumor, radical vulvectomy, syphilis

* First place, 2009 SGOP Interesting Case Contest (tie); Won also first place in the POGS Interesting Case Contest and was published in the Philippine Journal of Obstetrics and Gynecology, vol. 33, Oct-Dec. 2009

Gynecologists are very familiar with the condylomatous lesions associated with the low-risk Human Papilloma Virus subtypes. Rarely, a very rapidly growing condylomatous tumor, called giant Condyloma acuminata or Bushke and Lowenstein tumor (BLT), presents as an enormous mass on the anogenital area. Biopsies of the lesion will show unremarkable benign histologic findings, but the tumor exhibits a malignant clinical course with rapid growth and a recurrence after minimal surgery. This case report is the medical and surgical account of a young pregnant patient afflicted with the giant Condyloma acuminata and concomitant venereal infections.

There are conflicting opinions among authors whether the tumor is a benign or malignant lesion. Some authors consider the giant Condyloma acuminata or Buschke and Lowenstein as a benign lesion distinct from verrucous carcinoma.[3,6] Others consider it to be an intermediate lesion between benign and malignant- a precancerous lesion with propensity to transform into verrucous carcinoma or squamous cell carcinoma.[1,4,5,7,8,9] Finally, some authors believe that the Buschke and Lowenstein tumor is synonymous to verrucous carcinoma.[7] The tumor may start like a typical Condyloma acuminata which changes into a giant Condyloma acuminata due to poor hygiene, chronic irritation/ inflammation, promiscuity and immunosuppression (the latter brought about either by medications, organ transplantation medication, HIV, alcohol abuse or pregnancy).[10] All these conditions were present in our patient. The malignancy that arises has a locally invasive nature and if left untreated may lead to death in 20%. Early recognition and wide surgical treatment is effective in treating the disease.

The Case

This is the case of a 21-year old, commercial sex worker, G2P1(0101), 20 weeks and 1 day gestational age who presented with a rapidly enlarging vulvar mass.

Her condition started at 4-6 weeks gestational age, when she noticed a small growth of two flesh-colored, soft, non-tender, non-pruritic, round, 0.5cm x 0.5cm papules on each labia majora. She manipulated the papule and noted watery discharge. She did not seek any consultations nor take any medications.

At 8-10 weeks gestational age, she noted a rapid increase in the size of the papules to about 5cm diameter, described as non-tender, pebble-like papules. There was associated erythema and foul smell prompting consultation at a tertiary hospital. A biopsy was done which revealed Condyloma acuminata. She was advised treatment post partum and was given paracetamol for pain.

Between 10-16 weeks gestational age, the mass continued to rapidly increase in size (now occupying the entire vulva and extending to the anal area). She disregarded her symptoms until she had difficulty in urination, defecation and ambulation. She consulted the same tertiary hospital and was given the same advice and medication for pain. At 20 weeks gestational age, there was continued growth of the mass (to the size of two palms of her hand) such that she had problems ambulating. Due to her worsening accompanying symptoms- she developed fever and severe pain- she consulted at our institution.

The patient presented with easy fatigability and intermittent fever, but denied anorexia, and weight loss. She did not have cough, colds, or diarrhea.

Her past medical history was unremarkable. There were no heredofamilial diseases in the family. She was a smoker using 1 to 3 sticks of cigarettes per day for 6 years. She is an occasional alcoholic beverage drinker. She had her first coitus at age 16 years old to a promiscuous sexual partner. She had a live-in partner at age 19 who likewise, was promiscuous. The patient, born to poverty and poor family support- on top of being unskilled and uneducated, was pushed to a life of prostitution. Without the knowledge of her family, she started work as a commercial sex worker at the age of 18 up until the appearance

of the present vulvar mass. She claims to have had more than a hundred sexual partners with unknown sexual histories and engaged in sex without using condom. She has had no gynecologic consultations or any pap smear done. She is a Gravida 2 Para 1 (0101). She had her first pregnancy at age 19, and delivered preterm via spontaneous vaginal delivery at a local hospital with no fetal and maternal complications.

On her admission, she was wheelchair-borne, poorly nourished, in distress due to a painful massive fleshy mass on the perineal area. Walking or sitting was difficult. She had multiple tattoos on her body. She had stable vital signs, and had pale palpebral conjunctiva. Her systemic findings were unremarkable. Abdominal findings showed the uterine size was 20 cm by fundic height, compatible to age of gestation. There was good heart tone of 140 beats per minute. Her pelvic examination showed a huge cauliflower-like mass occupying the entire perineum, from the mons pubis down to the peri-anal area, overlying the midline and hiding the urethra, vagina and the anus. The mass measured 20cm x 8cm x 8cm. (Figure 1)

The vulvar mass had necrotic areas and foul-smelling, muco-purulent discharge. The upper portion of the mass had dry hyperpigmented scaly nodules (giving cauliflower-like look to the entire mass). The lower half was moist with mucopurulent discharge. (Figure 1) Further probing showed that the mass was soft, velvety, and composed of three contiguous growths emanating from the two labia majorus, and perineum/ peri-anal area. (Figure 2) The three masses grew out from these sites with "button mushroom" like configuration. The base of each outgrowth had short but thick pedicle with width of about 3-4 cms on each labia with wider overlying mass surface. There was easy bleeding and severe tenderness on gentle manipulation. The urethra and vaginal canal were barely visible and the rectum was not seen due to technical difficulties (speculum and rectovaginal examination could not be performed initially due to severe tenderness and the huge size of the mass covering the vulvar, vaginal and anal areas).

The admitting diagnosis: Vulva condyloma acuminata with secondary bacterial infection. Pregnancy in 20 weeks gestation G2P1 (01-01).

Figure 1. A huge cauliflower-like mass occupied the vulva from the mons pubis down to peri-anal area. Hyperpigmented scales, necrotic areas and mucopurulent discharge were noted.

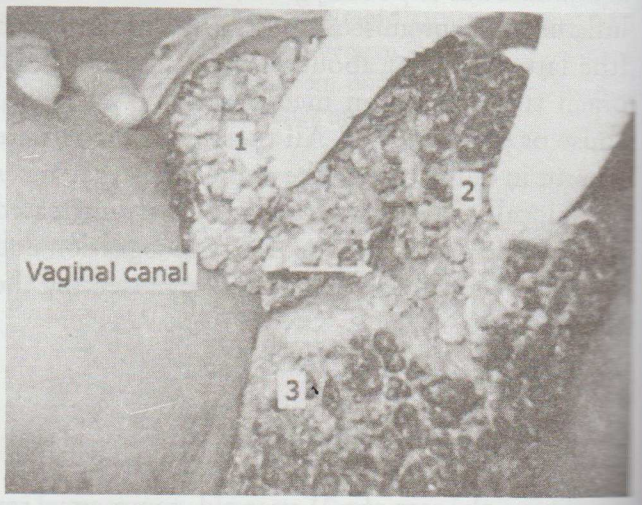


Figure 2. A huge cauliflower-like mass occupies the vulva from the mons pubis down to peri-anal area. Hyperpigmented scales, necrotic areas and mucopurulent discharge were noted.

Figure 3. Examination under anesthesia. The mass was attached by a short, but thick pedicle, to the whole surface of the vulva.

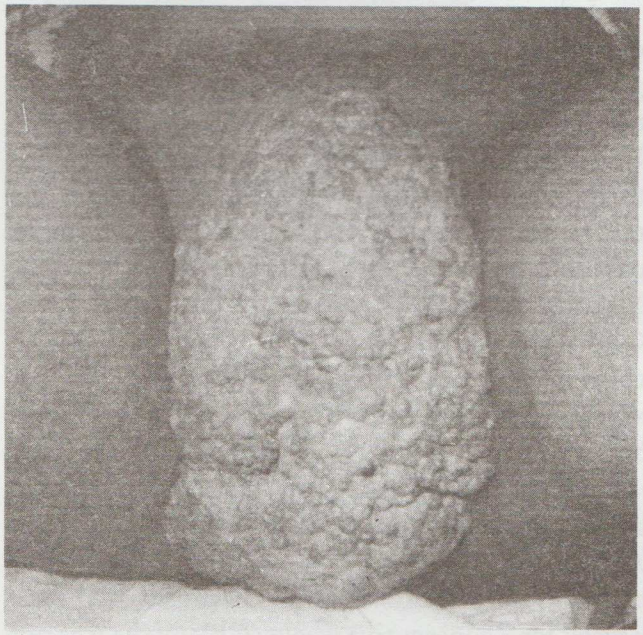
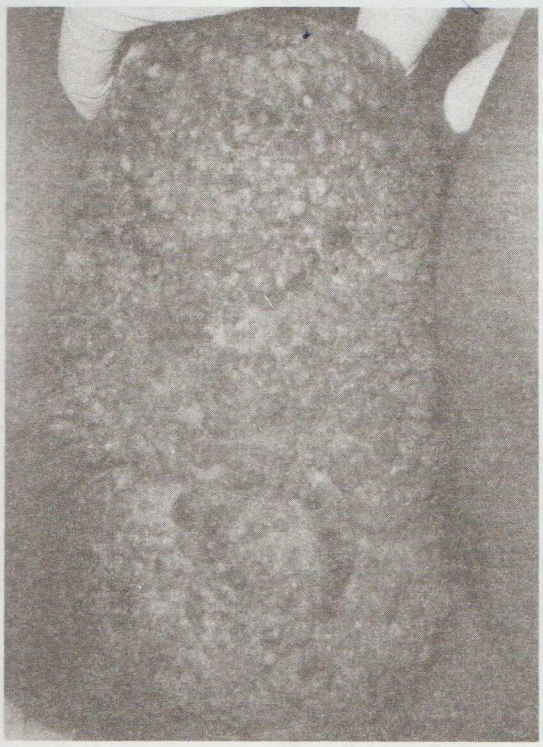


Figure 4. At 21-22 weeks AOG, there was a decrease in the necrotic areas and mucopurulent discharge after 1 week of antibiotic and perineal washing with povidone-iodine wash.



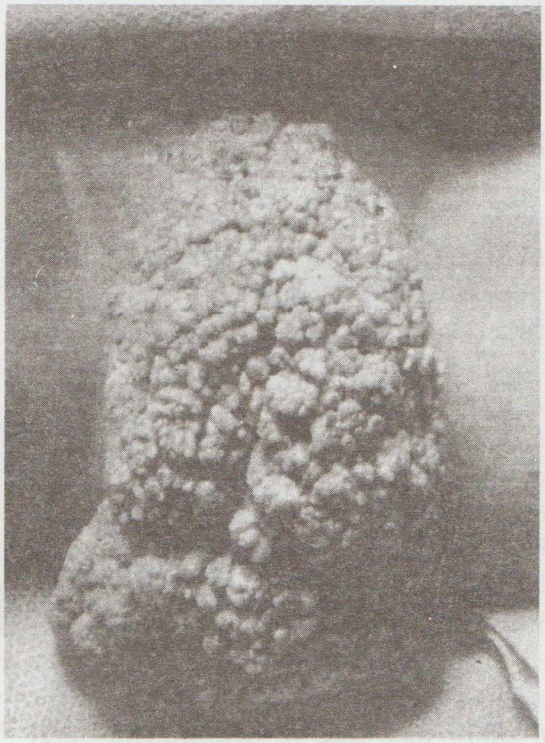


Figure 5. There was rapid growth of the mass at (Left) 21-22 weeks AOG and at (Right) 23-24 weeks AOG.

Laboratories on admission revealed hemoglobin of 7 mg/dl and leucocytosis with neutrophilic predominance. Anemia was corrected with transfusion of 3 units packed red blood cells. Urinalysis showed Trichomonas infection. She was treated initially with co-amoxiclav 625mg/tab one tablet per orem every 8 hours and twice daily perineal washing with povidone iodine wash. Metronidazole 2000 mg single dose was given. Gonorrhea was treated syndromically with ceftriaxone 1gm intramuscularly for 1 dose. Patient was tested for other sexually transmitted infections. She tested negative for human immunodeficiency virus and hepatitis B, but tested positive on screening and definitive test for syphilis infection. At 23 weeks AOG, she was treated as late latent syphilis with penicillin 2.4 mU intramuscularly once a week for 3 consecutive weeks. Chlamydia was not tested due to lack of funds. Punch biopsy of the mass showed Condyloma acuminata. Rectal and bladder involvement was considered, thus was referred to the Department of Surgery. The extent of surgery planned was only a simple excision due to the biopsy result and the narrow pedicle like. Ultrasound showed a fetus that was appropriate for gestational age with good cardiac and somatic activities.

The electro-surgical excision of the vulvar mass under epidural anesthesia was done at 24 weeks age of gestation after the infection on the mass was controlled. Tocolysis with an isoxuprine drip was started preoperatively. Intraoperatively, the mass was excised section by section down past the base down to the subcutaneous layer of the labia majora and profuse bleeding was encountered. All visible lesions were removed. Hemostasis was done by suture ligation or electro-coagulation leaving behind a 5cm x 4cm x 0.5cm raw area left open for secondary healing. (Figure 6) The urethra and the rectum were identified and had no tumor involvement. The patient had 3 units of blood transfused but otherwise had a relatively unremarkable recovery period. At 25 weeks age of gestation, 1 week post operation, there was note of intrauterine fetal demise. Prior to induction of labor, wounds were allowed to heal and anemia was corrected. (Figure 7) She had a spontaneous breech delivery at 26 weeks age of gestation delivering a macerated baby girl with a birth weight of 850gm. Postpartum, there was note of regrowth of a warty lesion on the upper mid portion of both labium majus. Treatment with immune modifier Imiquimod™ was done by applying three times a week at bedtime, and washed off after 6-8 hours from application. Despite medical management, the rapid enlargement of the mass progressed with enlargement of bilateral inguinal lymph nodes.(Figure 8).

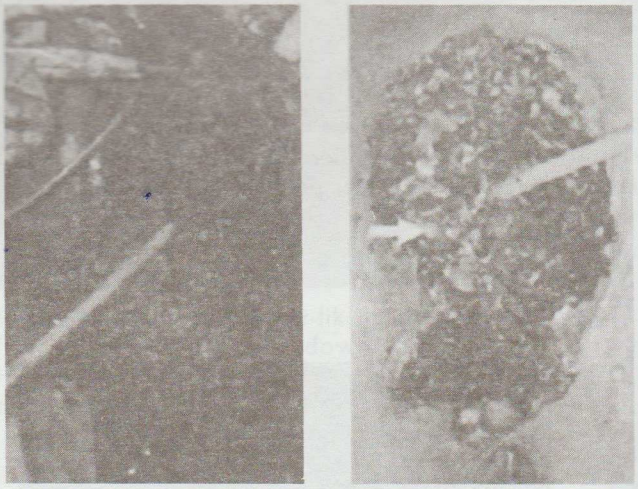


Figure 6. Excision cautery was done section by section down to the base and the subcutaneous layer of the labia majora leaving behind a raw area left open for secondary healing.

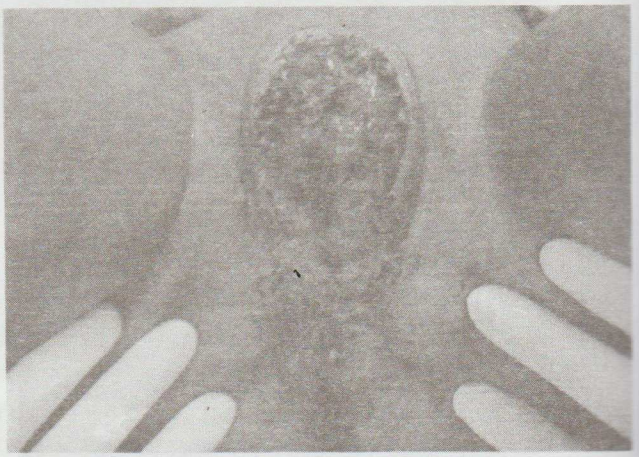


Figure 7. Granulation tissues were present after two weeks from excision.

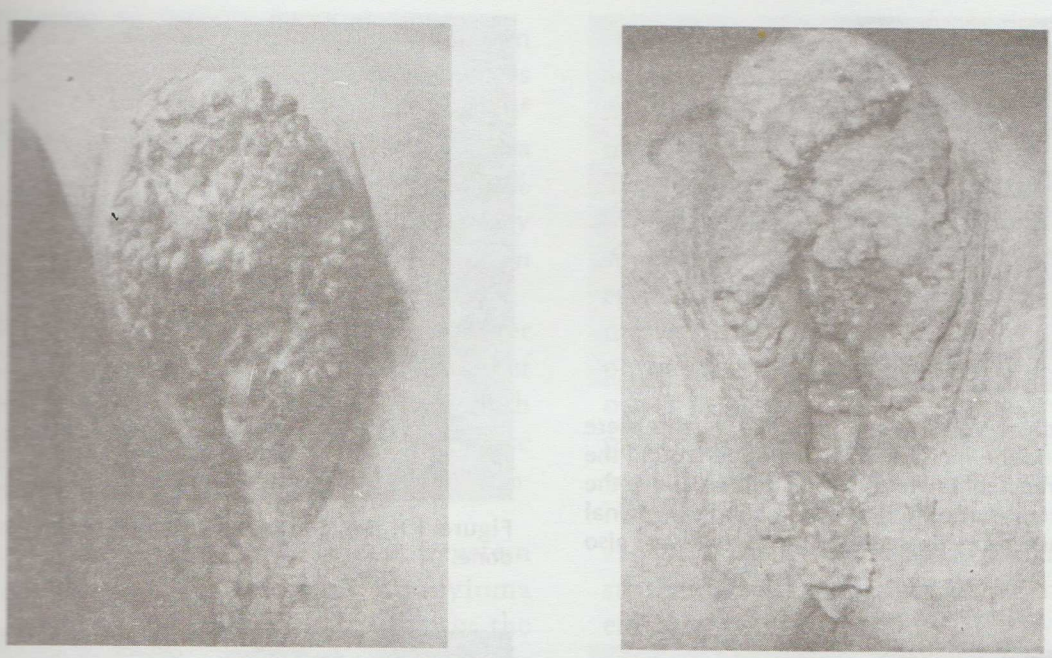


Figure 8. There was regrowth of a warty lesion on the upper-portion of both labia majora at four weeks (left) and further enlargement after six weeks post operation (right).

Because of the unusual clinical course, further work up was done on the specimen. Initial and repeated histopathologic results from the specimen revealed only the findings of condyloma acuminata. While HPV-DNA test by genotyping was positive for HPV 11, it was negative for high risk HPV types. Pap smear showed inflammation. However, when the H & E slides were reviewed by the institution's five pathology consultants, their final impression was giant condyloma acuminata of Buschke and Lowenstein/ verrucous carcinoma.

A radical vulvectomy with bilateral groin node dissection was done using Hacker's 3-incision technique. (Figures 9-14). All the groin nodes and all 1cm margins were negative for metastasis. This successfully treated the tumor with no recurrence at the patient's 6th month follow-up. Final histopathology revealed all lymph nodes negative for metastasis, giant Condyloma acuminata of Buschke and Lowenstein AKA verrucous carcinoma.

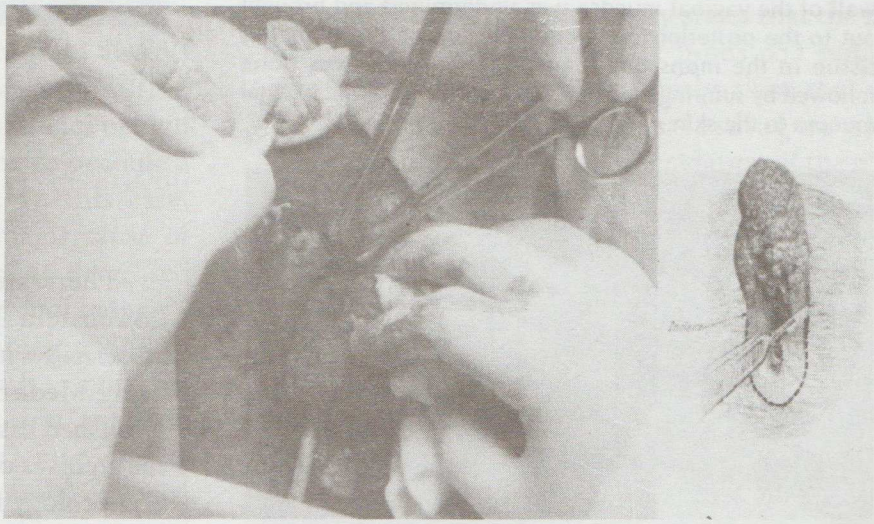


Figure 9. Radical Vulvectomy. An elliptical incision was made down to the fascia. The incision started from above the labial folds on the mons pubis and was extended down the lateral fold of the labia majora and across the posterior fourchette.

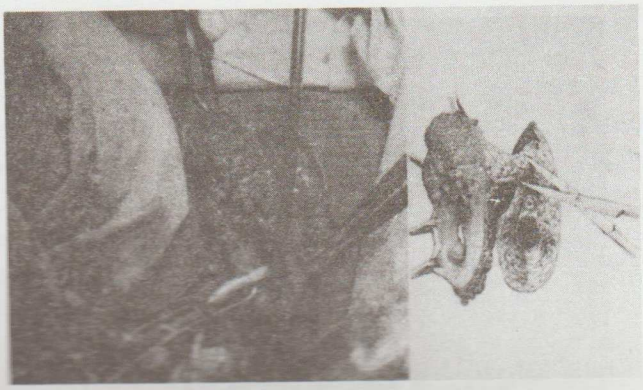


Figure 10. Radical Vulvectomy. Pudental vessels were securely tied, and the incision was continued around the entire circumference of the lesion; The incision above the urethral meatus was started and carried around the vaginal introitus. The suspensory ligaments of the clitoris were also transected.

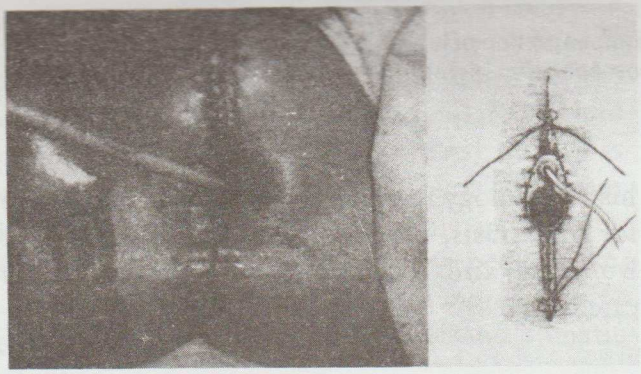


Figure 11. Primary closure of the wound was done. Posterior wall of the vaginal mucosa was undermined and brought out to the posterior fourchette. Closure of subcutaneous tissue in the mons pubis and perineal area was done followed by suturing of the periurethral mucosa and vaginal mucosa to the skin.

Figure 12. Cautery of the lesion located on the anal area by surgery. Wound was left to heal by secondary intention.

Figure 13. Bilateral inguinal lymph node dissection was done.

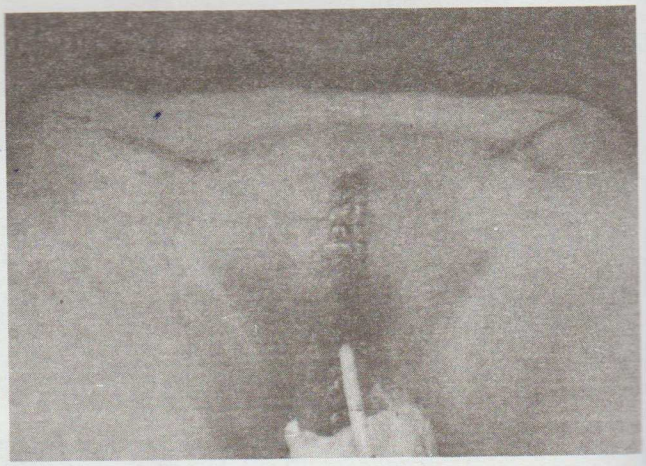


Figure 14. Post radical vulvectomy with bilateral groin node dissection.

Discussion

There are 58 published articles on Buschke Lowenstein Tumor worldwide, with only 8 cases associated with pregnancy, seen in a literature search using Medline from 1960 to 2009. There are no published cases of BLT in the Philippines based on the archives of Philippine Journal of Obstetrics and Gynecology from 1978 to 2008 and this is the first reported case in our institution.

Giant Condyloma acuminata or Buschke and Lowenstein tumor was originally described as a

genital lesion by Buschke in 1896 and Lowenstein in 1925.[1] It is a rare sexually transmitted disease. It is more common in males, with an incidence of 3.3:1[8] In males, it is located in the penis, anorectal area and urethra in 84% to 91%, 10%-17%, and 5% respectively. In females, the location is chiefly the vulva in 90 percent of the time,[1] as witnessed in our patient.

Buschke and Lowenstein tumor is observed after puberty, usually between the 4th and 6th decades of life.[9] The mean age of BLT patients is 43 years, with malignant transformation in 30%-56%,[7] recurrence rate of 18%-67% and overall mortality of 20%-30%.

Histologically, the Buschke and Lowenstein tumor is similar to the common Condyloma acuminata. The main differences are, firstly, the presence of local infiltration to adjacent structures by a cauliflower-like exophytic lesion.[8] Secondly, its giant form and rapid growth[4] and thirdly, its higher potential for malignant transformation.[5]

The etiology of Buschke and Lowenstein tumor commonly involves HPV types 6 and 11, and rarely subtypes 1 and 18. HPV type 11 was seen in our patient. It has a clinically intermediate condition: it is histologically benign but manifests a malignant behavior (rapid growth, recurrence, and extensive destruction of local tissue). It is locally aggressive and extremely morbid.[5]

Buschke and Lowenstein tumor is always preceded by Condyloma acuminata. Suppression of the immune system, along with presence of high risk factors, causes that condyloma to become a Buschke and Lowenstein tumor.[1] In this case, pregnancy was identified as the major cause of immunosuppression, primarily due to decreased lymphocyte function, decreased level of helper T cells[11] and accelerated viral replication due to physiologic changes in pregnancy such as increased vascularity, increased moisture, and elevated estrogen levels.[12,13] High risk factors for developing a Buschke and Lowenstein tumor are multiple sexual partners, prostitution, poor personal hygiene and chronic genital infections,[1] all of which were notably present in our patient.

Histologically, there is absence of the most basic and typical of feature of malignancy- basement membrane invasion (as well as vascular and neural invasion)[9,14] in the Buschke and Lowenstein tumor. The typical condylomatous features of an exuberant proliferation of stratified squamous epithelium supported by fibrovascular papillae, and superficial epithelial cells containing irregular, hyperchromatic nuclei surrounded by the characteristic clear perinuclear halo (koilocytosis) is seen, as well as other benign histologic characteristic such as parakeratosis, hyperkeratosis, papillomatosis, and acanthosis. There is active papillary proliferation in Buschke and Lowenstein tumor causing local expansion, penetration, and invasion of the adjacent structures with a pushing rather than infiltrating effect.[9,14]

Buschke and Lowenstein tumor is mainly recognized for its thicker stratum corneum and marked papillary proliferation which tends to invade deeply, displacing the underlying tissues. For this reason. Buschke and Lowenstein tumor is also known by some authors as "verrucous carcinoma". It however, rarely presents with histologic features of malignancy, which differentiates it from squamous cell carcinoma.[15]

The pathophysiology and biologic behavior of Buschke and Lowenstein tumor is still not completely known.[9] One theory states that the E6 protein of HPV-6 and HPV-11 binds p53 tumor suppressor protein less efficiently than that of HPV-16 and HPV-18, thus leading to the intermediate acceleration in degradation of the p53 protein. The E6 protein also has been shown to inhibit p53 transcription.[9] Another theory suggests that a mutation may occur in the p53 protein, leading to clonal proliferation.[16]

Symptoms of Buschke and Lowenstein tumor are brought about by destruction of local tissue and mechanical obstruction. Local tissue destruction causes severe pain, bleeding, itching, and fistula formation. Mechanical obstruction causes difficulty in defecation, minimal food intake, and cachexia.[5] In our case, the patient was in severe pain, with a foul-smelling mass and with

mucopurulent discharge. Due to these findings, a secondary bacterial infection was considered, thus antibiotics were given to prevent progression to sepsis. As stated by Mudrikova, fistulas colonized with bacteria can cause the formation of abscesses which can eventually lead to sepsis.[5] Other concomitant sexually transmitted infections were treated accordingly.

All authors agree that the first line of treatment is surgical excision which is most effective when executed during the early stage of disease. Early intervention prevents local spread, extensive tissue destruction and malignant transformation.[1]

Surgery during pregnancy poses a risk to both fetus and mother. This however, can be safely undertaken with adequate preparation.[17] Preoperative fetal surveillance was done to ensure fetal well being and the pregnancy was to be maintained with IV tocolysis during surgery. High vascularity of the mass seen by Doppler prompted preparing blood for transfusion and to use electrosurgical equipment for the excision. Intra-operatively, standard universal precautions were followed. Since Condyloma acuminata aqnd syphilis are highly contagious through the breaks in mucus membrane[18], double glowing was done and goggles and boots and water proof gowns were also employed. The extent of surgery was deliberated and proper referral to surgery was done.

Due to its rarity, there is scarce information available regarding its biologic behavior, diagnosis, treatment options, and prognosis.[9] Currently, there is no therapeutic guideline or consensus on the treatment of a Buschke and Lowenstein tumor. A definite therapeutic modality has yet to be defined.[5] To date, no randomized controlled trials have been performed.

For this case, surgical as well as medical therapy was initiated with both the patient and fetus in mind. Antibiotic treatment was initially given for the secondary bacterial infection and the concomitant sexually transmitted infections. Daily perineal washing with povidone iodine was done. Within a week, the mass was less painful and had a significantly decreased odor.

The use of the immune modifier after surgery proved successful in 2 case reports.[5,19] Unfortunately this did not work in our patient.

Recurrence is a consequence of a more limited procedure.[4] As with our case, a wide radical excision was not initially performed due to the very large and highly vascular mass, the biopsies that did not show any malignancy, and her pregnant state. Regrowth of the warty mass was noted four weeks after the initial surgery even with the application of the immune modifier Imiquimod™. During this lull, an new histologic consensus was reached indicating verrucous carcinoma. A second surgical intervention was therefore done with more adequate surgical margins, producing a more successful result. A similar case was described by Bergleiter, et al. where an extended giant condyloma of the vulva was removed, with the patient cured after several surgical interventions.[20]

One study of perianal/ anogenital Buschke and Lowenstein Tumor, with treatments ranging variously from podophyllin to pelvic exenteration, showed a 68% recurrence rate with a 21% mortality rate.[21] A high rate of recurrence correlates with a long duration of the disease.[16] Vulvar recurrence was related to tumor diameter and condition of the resection borders.[22] In our case, there is short duration of disease and resection borders were negative for tumor.

In a study done by Paraskevas, et al. the extent of surgery is based on the size of lesion, penetration to adjacent structures and lymph node involvement.[14] Lymph node enlargement causes suspicion of malignant transformation.[1] The enlarged lymph nodes present in our patient after regrowth of the tumor with the shift of pathologic diagnosis to verrucous carcinoma confirmed our suspicion of a malignant conversion. Thus, a radical vulvectomy using Hacker's 3-incision technique (Figure 6-12) with bilateral groin node dissection was done emphasizing on the removal of the entire lesion with an adequate tumor-free margin and removal of lymph nodes from the inguinal area. The single most important predictor of death from vulvar cancer is the presence of inguinal femoral

lymph node metastases and separate groin dissection significantly reduces its morbidity.[19] Groin dissection was warranted in our case, because of enlarged bilateral inguinal nodes. Histopathologic study of the harvested lymph nodes showed negative for tumor. It was therefore concluded that the enlarged lymph nodes were primarily due to infection arising from the previous surgery's secondary intention closure. This is supported by Kauffman, et al. who noted that regional lymphadenopathy is common and is primarily due to infection and not metastases.[16]

Unfortunately, despite all precautionary measures, the fetus had an unexpected demise. A possible cause identified is the syphilis infection, which results in perinatal morbidity and mortality in 50 percent of cases.[23] Another unfavorable perinatal condition that might have been contributory is the presence of anemia. Histopathologic examination of the placenta only revealed an aging placenta in a preterm fetus. Autopsy did not yield findings consistent with congenital syphilis. Dark field microscopic examination to visualize the spirochetes could have helped confirm this possibility[18] or cord blood examination could have been done to indicate significant immunoglobulin production.

Syphilis infection adversely affects pregnancy[24] and may result to fetal death in utero or stillborn infant at term.[18] More recent studies during the last epidemic of congenital syphilis confirmed the devastating effects of untreated or inadequately treated syphilis including high rate of still birth, congenital infection and preterm delivery. Transplacental infection occurred only after 16 weeks of gestation but it has been documented as early as 6 weeks of gestation.[24] Estipona states that the atrophy of the Langhan's layers of placental chorion of the placenta at 20 weeks gestational age causes transfer of spirochetes to the fetus. Treatment before 18 weeks age of gestation is therefore recommended.[18] Our patient when detected with syphilis infection, was at 22-23 weeks of pregnancy. Although treatment was immediately started this may have been already too late. Prompt treatment once diagnosis is established therefore cannot be overemphasized.[18]

Secondly, fetal death from surgical complications may occur in 2.7 percent of cases.[25] To minimize complications, the patient's preoperative condition was optimized, and the epidural anesthesia chosen well, that with the least-systemic-effect, in mind.

HPV infection, on the other hand, has yet to be incriminated by recent literature, as a possible cause of fetal demise. There is no data to support that HBV, HSV and HPV significantly contributes to transmitted intrauterine disease leading to pregnancy wastage.[26]

Other factors that could be taken into consideration for the demise of the fetus is anemia, poor nutritional status and low socioeconomic status. As revealed in observational studies of famine and controlled supplementation trials, energy supplementation may reduce the risk of still birth and neonatal death.[27]

Malignant transformation of Buschke and Lowerstein tumor occurs in 30-50 percent of cases usually within 5 years. Viral factors or host factors may affect the oncogenic potential of HPV subtypes 6 and 11, to cause the giant condyloma to turn malignant.[8]

Co-infection with syphilis can cause chronic granulomatous lesions to degenerate into carcinoma.[28] Immunocompromised states (HIV, post-transplantation, malignancy, diabetes, pregnancy, alcoholics, Herpes simplex infection) are also of importance[10] stating that the immunological condition at the time of virus acquisition may worsen during the immunosuppression.[5]

Vulvar carcinoma is an uncommon disease with an incidence of 1.8 per 100,000 women. It afflicts women in the seventh and eighth decade of life and is rare in women below thirty years of age,[29] as in the patient.

Verrucous carcinoma is a highly differentiated squamous carcinoma that has a verrucous pattern and invades with a pushing border in the form of bulbous pegs of neoplastic cells. It is a papillary exophytic growth that has the appearance of an

exophytic, broad-based Condyloma acuminatum. Microscopic features include prominent acanthosis with a pushing tumor-dermal interface and bland cytologic features. Parakeratosis and hyperkeratosis usually are prominently present.[30] These findings were also seen in our case, thus the final histopathological diagnosis was giant condyloma acuminata of Buschke and Lowenstein/verrucous carcinoma.

Verrucous carcinoma may recur locally after excision. Prognosis is excellent if removed completely.[30] Evidences show that wide surgical incision [3,14] is the sole treatment and that radiotherapy is contraindicated because it may induce anaplastic transformation with subsequent regional and distant metastases.

The usual complications of surgery are large tissue defects, fecal contamination of the wound,[5] wound breakdown, leg edema, and infections. In this patient, a month after the second surgery, the incision site had minimal pus-like discharge. Application with mupirocin ointment was done and metronidazole 500mg tablet one tablet three times a day for 7 days was instituted.

Wide radical excision with plastic reconstruction of skin defects is the best treatment in patients with Buschke and Lowenstein tumor. [25] As described by Adolfo, a case at 3 months post operation of Buschke and Lowenstein tumor, a non-epithelialized area on the large residual was seen wherein an advancement flap using gluteal skin was performed .[24] In our patient, we were able to close the tissue defect with primary closure on the second surgery performed.

On follow-up, one month postoperatively, the wound was intact with no evidence of dehiscence. (Figure 16) On six months, there was no recurrence of the tumor. (Figure 17) Wounds were completely healed with restoration of bowel, bladder and sexual function. As mentioned, recurrence rate for an adequately treated Buschke and Lowenstein tumor is low therefore prognosis is excellent. The presence of malignancy does not indicate a poorer outcome. Prognosis is mainly related to complications associated with local invasion rather than the presence of malignant histology.[3] The success of treatment lies in early recognition and intervention. Delayed treatment is mainly due to poor recognition of the invasive nature of the disease, alongside with the patient's refusal to seek consult due to embarrassment and fear of the consequences of the therapy.

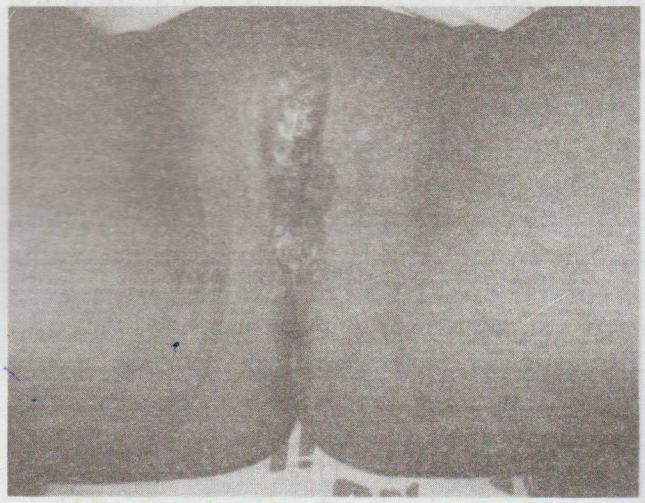


Figure 16. On one month follow-up, the wound was intact no evidence of dehiscence. There was noted moist area with edema, and minimal pus-like discharge.

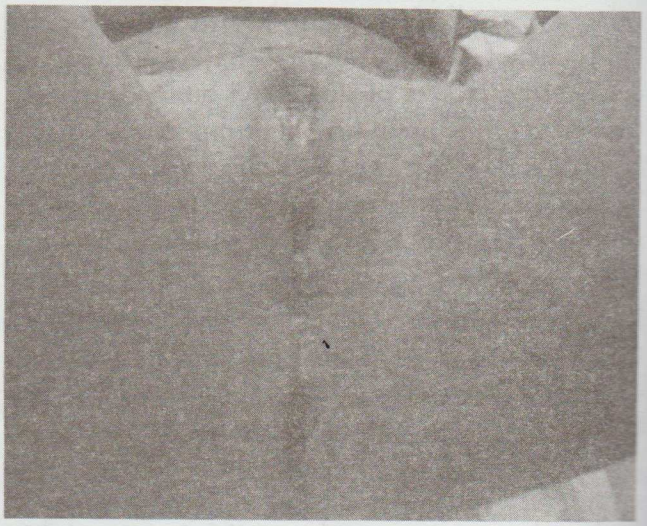


Figure 17. On six months follow-up, wound was completely healed with no tumor recurrence.

This patient should be closely-followed up regularly to ensure no disease recurrence.[14] Patient was properly and adequately advised on the importance of sexual education, contraception, and sexually transmitted diseases prevention.[2] Serologic screening for syphilis using quantitative VDRL at 1, 3, 6, and 12 months for the first year, then 6 month interval on 2nd year is recommended.[18] Human immunodeficiency virus testing should be repeated after six months. Cervical cytology examinations should be done regularly. Counseling regarding high risk sexual behaviors should be reiterated, including the impact of incurring sexually transmitted diseases on succeeding pregnancies and the high probability of infecting sexual partners. Vulvar and vaginal cancer leave obvious residual effects, disfigurement and dysfunction will forever be a part of these women's lives. Pscyhosocial support is thus of utmost importance. Husbands and partners are also affected, and adjustments of both the patient and partner are expeted to continue for years.[30]

Treatment lies not only on the removal of the diseased organ. The patient was an ailing mother, physically and emotionally burdened from the disease and the loss of her child. Having surpassed all these undertakings, the patient is now disease-free but her scars do not remain skin deep. She still continues to suffer from poverty, and may once again face the consequences of lost opportunities. Love and support from family and health care professionals are much needed by this patient.

Summary and Conclusion

Giant Condyloma Acuminata of Buschke and Lowenstein behaves as a clinical malignancy due to rapid growth of the mass and invasion of nearby structures but appears benign on histopathology. Immunocompromised state of pregnancy and concomitant venereal infections may cause its rapid growth. Recognition of this disease entity and prompt treatment with wide surgical excision is warranted.

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ERRATUM

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Growing Teratoma Syndrome*

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Growing teratoma syndrome (GTS) is a rare phenomenon characterized by conversion of a malignant germ cell tumor into a benign germ cell despite chemotherapy, with only 37 cases presented in world literature. Presented is the first documented case of GTS in the Philippines. A 22 year old nulligravid, diagnosed with immature cystic teratoma of the ovary, stage IA, underwent 4 cycles of bleomycin-etoposide-cisplatin. In spite of normal tumor markers, there was growth of a new pelvic mass after the fourth cycle. On debulking surgery, what was initially thought of as tumor progression showed mature teratomatous implants, suggestive of conversion from immature to mature implants on histopathologic examination. The case fulfilled the three criteria of GTS, namely: 1) enlargement of the primary tumor or development of a new one during or after chemotherapy, 2) normal tumor markers, and 3) metastases consisting of pure mature teratoma. This condition was hypothesized to be the result of either the induction of differentiation of the malignant cells into mature cells, or the selective destruction of the malignant tissues with concomitant resistance, persistence and further growth of the mature components. The presence of benign elements with neuroepithelial tissues are identified predictive factors for its development. Surgery is the mainstay in the diagnosis and management of the condition. Proper management of this condition is necessary to prevent known complications such as mechanical obstructive effects and malignant transformation of the resulting mature teratoma. After debulking surgery, the patient, until present, has no evidence of disease.

Key words: immature teratoma of the ovary, growing teratoma syndrome, chemotherapeutic retroconversion

Immature teratomas of the ovary are malignant germ cell tumors that are highly chemosensitive and are associated with a very good prognosis. In the presence of persistence or recurrence, however, these tumors may be difficult to manage. Infrequently, growth of the tumor despite chemotherapy, which may suggest malignancy persistence or recurrence, are in fact benign growths that resulted from the retroconversion effects of chemotherapy.

* Third Place, 2009 SGOP Interesting Case Contest.

Growing teratoma syndrome of the ovary is a rare phenomenon. To date, there are only 37 cases reported worldwide. In the Philippines, the presented case is the first documented case. This report discusses the criteria for diagnosis, pathogenesis and proper management of this condition. Although a rare entity, there should be awareness of its possibility when tumor growth is observed despite normalization of tumor markers during chemotherapy of a malignant germ cell tumor of the ovary.

The Case

The Case A. A., a 22 year old nulligravid, from Imus, Cavite, was admitted last September 17, 2007 at the Philippine General Hospital for debulking surgery.

Her past medical and family medical histories are unremarkable. The patient is a first year medical student. She is a non-smoker, non-alcoholic beverage drinker. She has no coitus. She has no history of oral contraceptive pills and no history of intrauterine device use. She has no history of Pap smear.

She had her menarche at 11 years old, with subsequent menses occurring at regular monthly intervals, each cycle lasting for 5-7 days duration, using 3-5 pads per day. The patient has been amenorrheic ever since the primary cytoreductive surgery and during adjuvant chemotherapy. She is nulligravid.

History of present illness started 8 months prior to admission. The patient was diagnosed to have an ovarian mass. She underwent exploratory laparotomy by a surgical oncologist. Intraoperatively, there was 1 liter of ascitic fluid evacuated. There was a complex mass at the left adnexal area with the largest diameter of 20 cm. The rest of the abdominopelvic organs were grossly normal. Left salpingo-oophorectomy was done and the specimen was sent for frozen section, which revealed immature teratoma. The patient then underwent surgical staging procedures, which included peritoneal fluid cytology, omentectomy, pelvic and paraaortic lymph node sampling and peritoneal surface biopsies. Final surgico-pathologic diagnosis was immature teratoma, grade II, ovary, stage IA (Figures 1A & 1B).

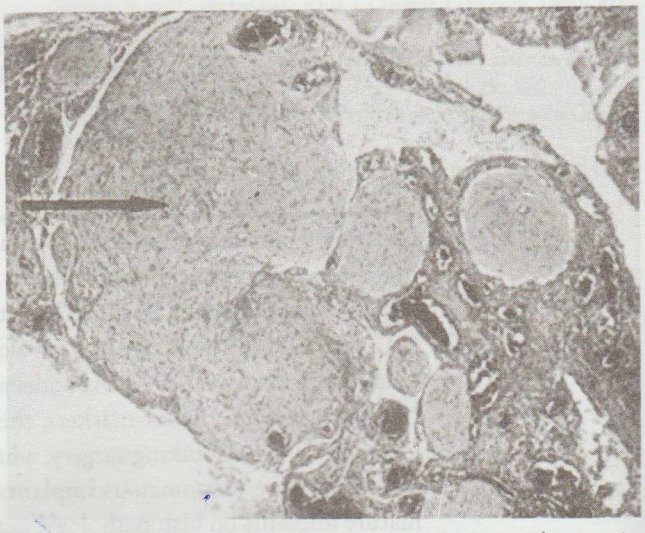

Figure 1A. Immature Teratoma, Ovary. The main component of the tumor is neurogenic.

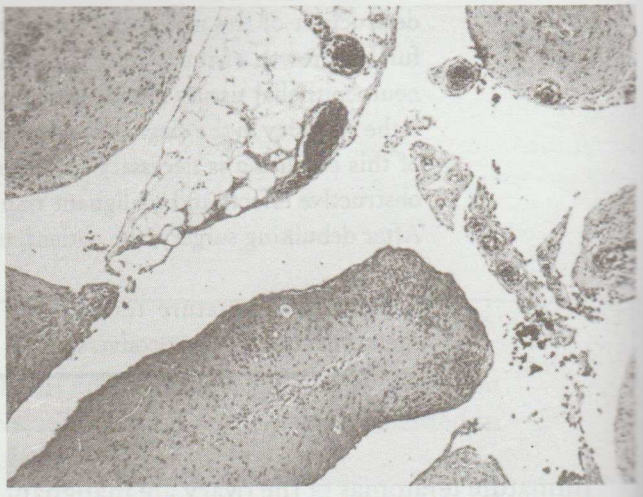

Figure 1B. Gliomatosis Peritonei, Omentum. These represent innumerable implants of mature brain tissue.

The patient subsequently underwent four courses of adjuvant chemotherapy with Bleomycin-Etoposide-Cisplatin (BEP) (February to May 2007). Ultrasound done after the fourth cycle of

chemotherapy showed a complex lesion in the left adnexa, measuring 3.8cm x 2.5cm x 3cm. Abdominopelvic computed tomography (CT) scan showed a tumoral focus at the left adnexa measuring 4cm x 5cm x 3cm. There was also note of hepatic focus measuring 3.5cm x 1.5cm and multiple subdiaphragmatic metastatic foci with an aggregate size measuring 7cm x 3cm. Tumor markers done at that time were within normal limits. Nonetheless, the patient was diagnosed to have progressive disease.

The patient sought second opinion with a gynecologic oncologist. She was started on second-line chemotherapy with Carboplatin-Paclitaxel (TC) (July 13-August 24, 2007). After the third course of chemotherapy, repeat CT scan showed further increase in tumor bulk, with hepatic masses now measuring 3.6cm x 3.2cm x 4cm and the pelvic mass measuring 8.1cm x 9cm x 6.2cm. Tumor markers remained within normal limits. The patient was diagnosed to have persistent progressive disease and was then advised debulking surgery.

On review of systems, the patient had no weight loss, no anorexia, no bowel or urinary disturbances. She had no vaginal bleeding or vaginal discharge.

On admission, the patient had stable vital signs, with a blood pressure of 100/70, heart rate of 70 beats per minute, and respiratory rate of 18 cycles per minute. She was afebrile. She had a body mass index (BMI) of 22. She had pink conjunctivae and anicteric sclerae. There were no cervical or inguinal lymphadenopathies. She had alopecia. Chest examination showed equal chest expansion and clear breath sounds, with no rales nor wheezes appreciated. She had an adynamic precordium, with distinct heart sounds; there were no murmurs noted. The abdomen was flabby and non-tender. She had pink nail beds and full pulses. There was no bipedal edema.

On pelvic examination, the external genitalia was grossly normal. The vagina was nulliparous and smooth. The cervix measured 2cm x 2cm; it was smooth and non-tender. The corpus was small. There was an 8cm x 6cm nodular, non-tender, slightly movable left adnexal mass, with the inferior pole palpable at the cul de sac.

Admitting impression was Immature teratoma, left ovary, grade 2, stage IA. S/P Peritoneal fluid cytology, left salpingo-oophorectomy, frozen section, omentectomy, pelvic and para-aortic lymph node sampling, random peritoneal biopsies (January 30, 2007), S/P Bleomycin-Etoposide-Cisplatin IV (February to May 2007), Progressive Disease, S/P Carboplatin-Paclitaxel III (July 13-August 24, 2007), Persistent Progressive Disease.

The patient was referred preoperatively to Urology and General Surgery Services for co-management and possible intraoperative referral. The Urology Service performed a cystoscopy preoperatively which showed normal findings.

On the fourth hospital day, the patient underwent exploratory laparotomy, tumor debulking, and appendectomy under epidural-general anesthesia Intraoperatively, there was no ascites. The surfaces of the liver, gallbladder, stomach, spleen and kidneys were all smooth (Figure 2A). The subdiaphragmatic peritoneum was studded with cobblestone-like implants and had 2 pedunculated solid masses on its left and right aspects measuring 7cm x 5cm x 2cm and 4cm x 3cm x 1.5cm, respectively (Figure 2B). Cut section of both masses revealed sebum, hair and cartilage. There were superficial, necrotic implants on the anterior abdominal wall and small intestines. There was a 0.8cm fecalith noted in the tip of the appendix. There were no enlarged lymph nodes in the pelvic and paraaortic chains. There was a 9cmx 6cm x 2.5cm irregular, solid, necrotic mass wedged in the cul de sac. Both pelvic sidewalls, rectosigmoid and bladder peritoneum were likewise studded with cobblestone-like implants (Figure 2C). Superficial necrotic implants were noted on the surface of the right ovary with an aggregate diameter of 0.7cm. The right fallopian tube measured approximately 8cm x 0.5cm and was grossly normal. The corpus was not enlarged and had a smooth serosa. The left adnexa was surgically absent. Histopathologic examination of the specimens showed mature (90%) and immature (10%) teratomatous implants. These findings were suggestive of conversion of implants from immature to mature tissues following chemotherapy in immature teratoma (Figure 3).

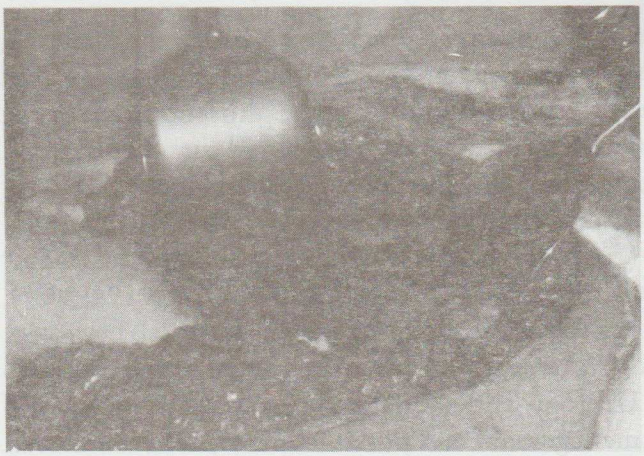

Figure 2A. The surfaces of the liver, gallbladder, stomach, spleen and kidneys were all smooth.

Figure 2B. The subdiaphragmatic peritoneum was studded with cobblestone-like implants and had 2 pedunculated solid masses on its left and right aspects measuring 7cm x 5cm x 2cm and 4cm x 3cm x 1.5cm, respectively.

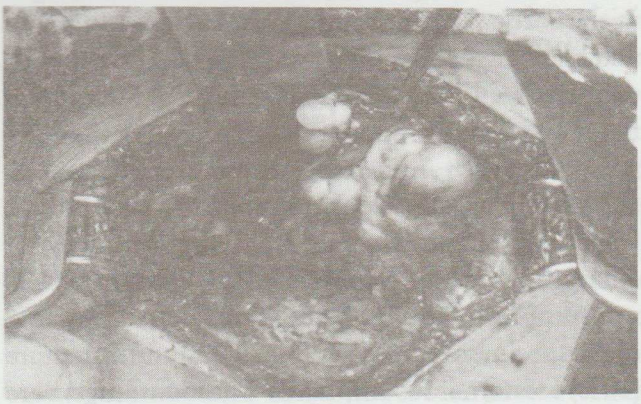

Figure 2C. There was a 9cm x 6cm x 2.5cm irregular, solid, necrotic mass wedged in the cul de sac. Both pelvic sidewalls, rectosigmoid and bladder peritoneum were likewise studded with cobblestone-like implants.

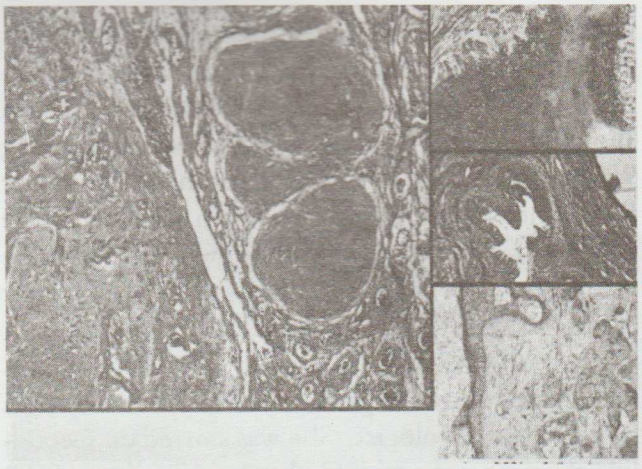

Figure 3. Mature (seen at right) teratomatous elements comprise 90% of the tumorous implants with only 10% focal areas of immature (above) teratomatous elements.

Postoperatively, the patient was advised continuation of three more cycles of Carboplatin-Paclitaxel, which the patient completed from October 15 to December 24, 2007. After the sixth course, the patient underwent a third operation, which showed no evidence of disease. Random peritoneal biopsies and biopsy of pelvic adhesions were done. Histopathologic examination showed gliomatosis peritonei (Figure 4). Since then, the patient had no evidence of disease.

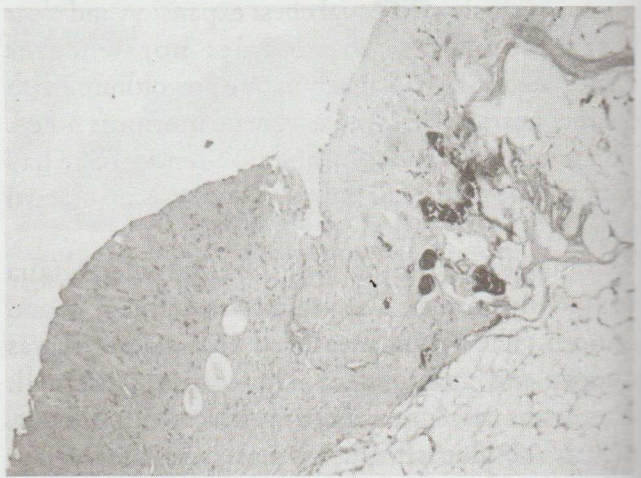

Figure 4. Gliomatosis peritonei.

Discussion

Immature teratomas are malignant tumors that make up approximately 20 percent of the primitive germ cell tumors.[1] These tumors are composed of tissues derived from the three germ layers and contain immature or embryonal structures, which are almost always neuroectodermal.[1] In some instances, immature teratomas may be combined with mature elements or other neoplastic germ cell elements.[2]

With the advent of chemotherapy, immature teratomas have become highly curable tumors. These tumors are highly chemosensitive and are associated with a very good prognosis. However, in cases of recurrences, the prognosis becomes less favorable with a 5-year survival of less than 30%. Although enlargement of the primary tumor or development of a new mass despite chemotherapy may suggest malignancy persistence or recurrence, this may not always be the case. When this phenomenon is observed in the presence of normal tumor markers, a benign condition called growing teratoma syndrome should be a consideration.

Growing teratoma syndrome is an infrequent complication observed in cases of germ cell tumors of the ovary treated with chemotherapy. This condition was first defined in 1982 by Logothetis, et al., when they observed persistent extratesticular masses of mature teratoma in 6 male patients treated for testicular non-seminomatous germ cell tumor.[2,3] In 1989, Tonkin, et al. were the first to report the occurrence of growing teratoma syndrome in a series of 6 women.[4] Subsequently, Kattan, et al. were the first to use the term "growing teratoma syndrome" to describe this phenomenon in a woman with immature teratoma of the ovary.[4,5]

Following Logothetis' definition, other authors subsequently described three criteria required for the diagnosis of growing teratoma syndrome. These include: 1) clinical or radiological evidence of enlargement of the primary tumor or development of a new tumor during or after chemotherapy, 2) normalization of previously elevated tumor markers (alpha fetoprotein and human chorionic gonadotropin, or both), and 3) metastases consisting of pure mature teratoma without malignant cells on histologic examination.[2,3,4,5,6]

Growing teratoma syndrome should not be confused with another similar condition called chemotherapeutic retroconversion. The latter term was first defined by DiSaia, et al. in 1976, when he described this condition in a series of three female patients affected by immature teratoma.[2,3] Chemotherapeutic retroconversion is defined as a chemotherapy-mediated transformation of a metastatic immature teratoma into mature teratoma.[3] Chemotherapeutic retroconversion meets only two of the three criteria for growing teratoma syndrome. In growing teratoma syndrome, not only must the immature teratoma nodules have undergone chemotherapeutic retroconversion, the resulting mature elements should also have the ability to grow, whereas in chemotherapeutic conversion the nodules do not increase in size. The difference emphasizes the proliferative ability of the GTS cells despite being terminally differentiated.[3] In addition, chemotherapeutic retroconversion is applicable only to immature teratomas of the ovary and has not been applied subsequently to mixed germ cell tumors of either the ovary or the testis.[3]

The case presented fullfilled the criteria of a growing teratoma syndrome. After the fourth cycle of BEP, the patient was noted to have the growth of a pelvic mass despite normal alpha fetoprotein (AFP) and cancer antigen (CA-125) levels. Although the histopathologic result of the debulking surgery still showed 10% immature elements, which may be in contrast to the third criteria requiring pure mature teratoma elements, the chemotherapy-induced conversion may still be an ongoing process during the time of surgery. The process of conversion was further proven during the third operation wherein the histopath result of the biopsy sample all showed gliomatosis peritonei, a benign condition characterized by presence of mature neural glial tissue.

The pathogenesis of growing teratoma syndrome remains unclear. Different authors hypothesized two possible mechanisms to explain the process. The first hypothesis is that chemotherapy may induce

malignant cell differentiation of immature teratoma into mature teratoma. The second hypothesis is that chemotherapy can induce a selective destruction of immature components, whereas mature elements, resistant to chemotherapy, persist and grow alone as growing teratoma syndrome. Cytokines, growth factor, or steroid hormones were reported to regulate the enlargement and stabilization of the mature teratomatous components.[7] The second hypothesis is favored by the fact that most often, the primary ovarian immature teratoma is often associated with a mature teratoma component.[2,6,8] Growing teratoma syndrome of the ovary is an extremely rare condition. To date, there are only 37 cases that have been described in international literature.[9] In the local setting, review of records showed that this could be the only documented case of a growing teratoma syndrome arising from an immature teratoma of the ovary. As in the index patient, growing teratoma syndrome is reported in literature to be commonly observed among women 20-22 years of age.[3,9,10]

Growing teratoma syndrome can occur anytime from the commencement of chemotherapy until two years, with an average of eight months. The tumor nodules most commonly remain confined in the pelvis, abdomen or retroperitoneal area.[2,3,4,8] The retroperitoneum is the single most common site of regrowth being involved in 80 percent of cases.[8] This limited distribution of growing teratoma syndrome is a reflection of the lack of tendency of malignant ovarian germ cell tumors to metastasize to distant locations. In addition, since the tumor nodules consist of mature tissues, they lack the ability to metastasize or to invade surrounding tissues. In the case presented, the growing teratoma was initially noted 3 months from the time of initiation of chemotherapy, with the tumor nodules confined in the abdominopelvic area.

Because of its rarity, it is difficult to characterize factors predicting the development of growing teratoma syndrome. Andre, et al., considered that the presence of mature teratomatous elements in the primary tumor is highly predictive.[6] Zagame, et al. also reported that the presence of predominantly immature neuroectodermic components in the primary tumor, as well as presence of peritoneal involvement, seem to be commonly associated with the development of growing teratoma syndrome.[2] Another identified predisposing factor is incomplete resection of the primary tumor.[9] In the case presented, the presence of gliomatosis peritonei with primitive neuroepithelial tissue in the omentum and peritoneal surfaces noted during the primary surgery may be responsible for the subsequent development of growing teratoma syndrome.

The question of whether the type of chemotherapeutic agent influences development of growing teratoma syndrome remains unclear. In the series reported by Andre, et al., the patients who developed growing teratoma syndrome were primarily treated with platinum-based chemotherapy (cisplatin or carboplatin).[6] The index patient was initially given the BEP regimen followed by TP regimen, both platinum-based chemotherapy. In both regimens, a steady growth of the tumor was observed.

Imaging studies are critical in the diagnosis of growing teratoma syndrome. Computed tomography (CT) scans and magnetic resonance imaging (MRI) are the preferred imaging modalities.[11] CT features suggestive of maturation include increased density of mass lesions, whose margins become better circumscribed in relation to adjacent tissues, presence of new onset or increased number of calcifications and fatty tissues, and presence of cystic areas.[6,7,11,12] MR imaging sequences using fat saturation, gradient echo-imaging with an echo time in which fat and water are in opposite phase, and chemical shift artifact are useful in distinguishing fat from other tissue types.[11] A limitation of these imaging modalities is that some of the mentioned features may overlap with those seen in immature teratomas, making the distinction difficult.[11,13] Typically, however, immature teratomas are larger, less well-defined, have a prominent solid component and are associated with foci of hemorrhage.[11] The CT scan findings of the index case is an example of a situation wherein distinction of a mature from immature growth is difficult.

Although peripheral enhancement may suggest a benign tumor, the extensive spread of the mass and the presence of suspicious infiltration into the bladder may be confused for a malignant growth.

Management of growing teratoma syndrome primarily involves complete surgical resection of the tumor. The reason for surgical resection is threefold. First, it is important to confirm the diagnosis of growing teratoma syndrome and to exclude malignancy. Second, complete resection is necessary to relieve a possible pressure from adjacent organs. Mechanical complications may occur due to the growth of the tumoral masses which can compress the surrounding organs.[6] Depending on the site and extent of the residual tumor, this may result in pain, biliary and duodenal obstruction, renal failure by ureteral compression, thrombophlebitis, vena cava compression and mesenteric compression with small bowel necrosis.[2,4,6]

A third possible theoretical reason for complete resection is to prevent a future malignant transformation.[2,4,6,8] Malignant transformation has been reported to occur in as much as three percent of the cases.[6] Different case reports have shown that the residual mature teratomas possess a malignant potential and may transform into another ovarian immature teratoma, a sarcoma, squamous cell carcinoma, adenocarcinoma, carcinoid tumor, or primitive neuroendocrine tumor.[2,6] Andre, et al. suggested that mature teratoma cells retain an intrinsic biological malignant potential, despite their benign appearance.[6]

In the index case, the repeat surgical operation, although initially performed for a suspicion of tumor persistence, was a necessary procedure. It provided a definite diagnosis for the condition of the patient, thus alleviating concerns of a persisting tumor. Secondly, it obviated the possibility of both mechanical obstruction and malignant transformation.

The prognosis of inoperable growing teratoma syndrome is poor. Interferon, steroids or differentiational agents were evaluated as non-surgical treatment options for growing teratoma syndrome.[4,6,14] Treatment with α-interferon has been shown to result in either stabilization of the mass or a decrease in size of less than 50%. However, very prolonged exposure is necessary and discontinuation results in progression of the disease.[9] A case report by Mego, et al. suggests the role of Bevacuzimab, a multikinase inhibitor that induces continuous inhibition of angiogenesis, in the treatment of growing teratoma syndrome.[14]

With complete surgical resection of the tumor, prognosis of growing teratoma syndrome is excellent. However, follow-up of patients treated for growing teratoma syndrome must be continued for many years. Reports show that recurrences may occur in as long as 14 years from treatment.[2] The compressive effects of a recurrence and the possibility of a secondary non-germ cell neoplasm should not be underestimated.

Summary

In summary, presented is a rare case of a growing teratoma syndrome in a 22 year old nulligravid undergoing adjuvant chemotherapy for an immature teratoma of the ovary. The presence of neuroepithelial tissue elements in the primary tumor may be a contributing factor in the development of the syndrome. Although imaging studies and tumor markers may help in the initial evaluation, definite diagnosis can only be done through surgery and histopathologic examination of the tumor nodules. Management consists primarily of surgical debulking of the tumor. Although female growing teratoma syndrome is extremely rare, there should be an awareness of its possibility when obvious tumor growth is observed despite normalization of tumor markers during chemotherapy for a germ cell tumor of the ovary.[7]

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Intraperitoneal Carboplatin in Combination with Intravenous Paclitaxel in Optimally Debulked Advanced Stage Epithelial Ovarian Carcinoma: A Local Experience*

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Ovarian carcinoma is the leading cause of death among women with gynecologic malignancy worldwide. Current standard of treatment after primary maximal cytoreduction is systemic administration of combination platinum-based and taxane chemotherapy. Recent trials have proven the significant impact on over-all survival of intraperitoneal (IP) cisplatin-based chemotherapy compared to the standard intravenous (IV) chemotherapy. However, cisplatin-associated toxicity is one of the limiting factors for its global acceptance. Carboplatin, a less toxic platinum-based agent may be a good alternative. A 37 year-old, multigravid, with optimally debulked advanced stage epithelial ovarian carcinoma who was given IP carboplatin with IV paclitaxel is presented. The toxicities encountered during treatment will be discussed.

Key words: intraperitoneal chemotherapy, intraperitoneal carboplatin, ovarian carcinoma

Ovarian carcinoma is the leading cause of death among women with gynecologic malignancies worldwide.[1] In the United States (US), about 21,650 new cases were diagnosed in 2008 making it the 8th most common malignancy of the female. It is also the 5th leading cause of female deaths in the US with 15,520 cases dying from it last 2008.[2] In the Philippines, ovarian cancer is the fifth leading cancer site among females with an incidence of 6.0%, based on the 2005 Philippine Cancer Facts and Estimates. In 2005, about 3,283 new cases were diagnosed and 1,918 died from it.[3] This high death rate is attributed to tumor spread beyond the ovary at the time of diagnosis.

Current standard of treatment after primary maximal cytoreductive surgery, i.e. total abdominal hysterectomy with bilateral salpingooophorectomy, infracolic omentectomy, lymphadenectomy and tumor debulking for patients with advanced stage

* Finalist, 2009 SGOP Research Contest

epithelial ovarian cancer, is systemic administration of a combined platinum-based agent and taxane (paclitaxel).[4] Patients most often respond well after the primary treatment. However, majority of them will have a persistent disease or will develop a recurrence and later die of the disease due to emergence of drug resistance.

Attempts have been made to improve the outcome of these patients which include the use of various and/or additional systemic IV chemotherapeutic agents or the use of regional chemotherapy through IP route.[5]

Delivery of chemotherapy using the IP approach has been investigated as consolidation therapy after a negative second-look reassessment, as second-line treatment for persistent disease and as primary treatment for ovarian cancer.[6] Based on the results of three multicenter randomized phase III trials, IP cisplatin-based chemotherapy regimen has shown to significantly improve the overall survival outcome of diagnosed ovarian cancer cases with reasonable certainty compared to standard intravenous chemotherapy in the primary chemotherapeutic management of small volume, residual, advanced epithelial ovarian cancer.[7] Limiting factors, however, are its high cost, toxicity, poor quality of life during treatment and the lack of technical expertise with the peritoneal administration and the catheter placement technique.[8]

Majority of the trials on IP-IV chemotherapy have used cisplatin as the primary platinum intraperitoneal chemotherapeutic agent in combination with cyclophosphamide and paclitaxel. Only a few have investigated the potential of carboplatin, another platinum agent with known lesser nephrotoxic potential, as an alternative to cisplatin.

This is a case of a 37 year old, multigravid, with advanced stage, optimally debulked epithelial ovarian carcinoma, who was given combination IP-IV carboplatin-paclitaxel.

This paper aimed to share the authors' experience in combination IP-IV carboplatin-paclitaxel, its administration, complications and toxicities encountered during the treatment in comparison with the standard of IP cisplatin.

The Case

The patient, E.Y., is a 37 year old G4P4 (4004), married, Filipino, Roman Catholic from Tanza, Cavite admitted last December 2008 due to gradual abdominal enlargement. Family history was unremarkable. She is a known asthmatic since childhood with last attack when she was 12 years of age. She has nodular non-toxic goiter for five months with no maintenance medication. She is clinically and biochemically euthyroid. She is a non-smoker, and occasional alcoholic beverage drinker.

Menarche was at the age of 11 with subsequent menstrual periods at regular monthly intervals, lasting four days per cycle, consuming two to three pads/day with no associated dysmenorrhea. Her first coitus was at 18 years old and claimed to be in a monogamous relationship. She denied history of oral contraceptive use or any form of birth control method and had no history of undergoing Pap smear.

She is a G4P4 (4004). All pregnancies were carried to term. The first two pregnancies were delivered spontaneously. The third pregnancy was by low segment cesarean section and the last pregnancy was an assisted delivery.

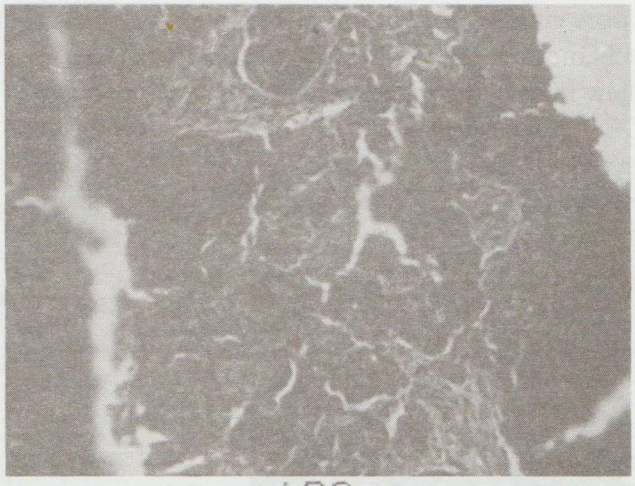
Her condition started five months prior to admission when she had gradual abdominal enlargement with no associated signs and symptoms. There was no consultation done and no medication taken. Until, one month prior to admission, still with the same condition, now associated with early satiety and occasional abdominal pain, the patient consulted at a tertiary government hospital.

She came in conscious, coherent, ambulatory, not in respiratory distress. Physical examination was essentially normal and was centered on the abdomen which was globularly enlarged, with an abdominal girth of 101 cm, hypoactive bowel sounds, non-tender, and with fluid wave. Speculum examination showed a pinkish smooth cervix with no bleeding and discharge. Internal examination revealed a 2cm x 2cm smooth, firm cervix; corpus and adnexae cannot be properly assessed due to the enlarged abdomen. Both parametria were smooth and pliable.

A combined transabdominal and transvaginal ultrasound were done and showed massive ascites. The uterus was anteverted and normal in size (5.48cm x 5.88cm x 5.23cm) with no myometrial lesions. The endometrium was thin (0.96cm) and intact. Posterior to the uterus was a complex mass measuring 11.7cm x 8.83cm x 8.72cm, thick-walled with papillarities, no septa, and a solid component at the medial portion measuring 6.57cm x 3.80cm was noted probably the right ovary with sassone score of 10. The left ovary was normal and closely adherent to the uterus and pelvic wall. The impression was an ovarian new growth with non-benign sonologic features. Her CA-125 was elevated at 328.60 u/ml. The rest of the laboratory work-ups were normal.

On the third hospital day, she underwent exploratory laparotomy. Intra-operatively, eight liters of ascitic fluid was drained. The right ovary was enlarged to 10cm x 8cm, with implants on the surface of its intact thick-walled capsule. The left ovary was normal in size with implants on the external surface. There were palpable pelvic lymph nodes. The largest which measured 2cm was noted on the left external iliac nodal chain. Multiple peritoneal implants on the abdominal wall were *also seen and the largest implant measuring 5cm* was located on the rectosigmoid area. The rest of the abdominal structures were unremarkable. Total abdominal hysterectomy with bilateral salpingooophorectomy, infracolic omentectomy, *peritoneal fluid cytology, sampling of peritoneal* implants and bilateral lymph node evaluation were done. Residual tumor on the rectosigmoid area was about 1 cm. Patient tolerated the procedure well. Postoperative stay was unremarkable. She was discharged improved on the sixth postoperative day.

Histopathological examination revealed serous carcinoma of the ovary, bilateral (Figure 1). The omentum and implants on the right and left fallopian tubes and peritoneum were positive for malignancy. Peritoneal fluid cytology was also suspicious for malignant cells to consider *adenocarcinoma.*



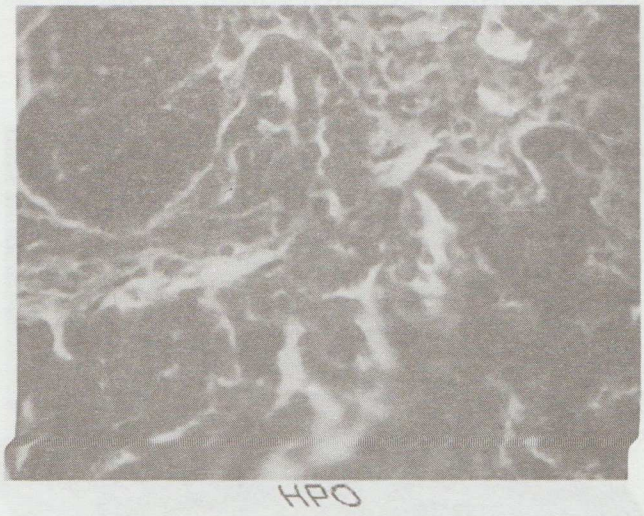


Figure 1. Microscopic section of the ovary shows complex papillary glandular pattern of malignant cells in a lace-like *appearance with loss of the intervening stroma. Cells show marked atypia, hyperchromatic nuclei and prominent nucleoli.*

The option of adjuvant treatment with IP-IV chemotherapy was explained. The patient and husband agreed to the procedure. While waiting for funding for the intraperitoneal port, standard *combination IV paclitaxel-carboplatin was given* two weeks postoperatively. She tolerated the procedure well. Repeat serum Ca-125 decreased to 75.58 u/mL after the first cycle of chemotherapy. *The patient then had insertion of intraperitoneal*

port via minilaparotomy three weeks after the first chemotherapy (Figures 2-6). IV paclitaxel was given few hours postoperatively.

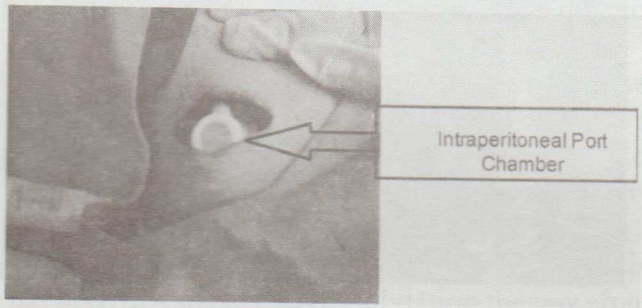


Figure 2. Insertion of IP port chamber 2-3 fingerbreadths below the right ribcage, midclavicular line at the subcutaneous fat which is anchored on the scarpa's fascia.

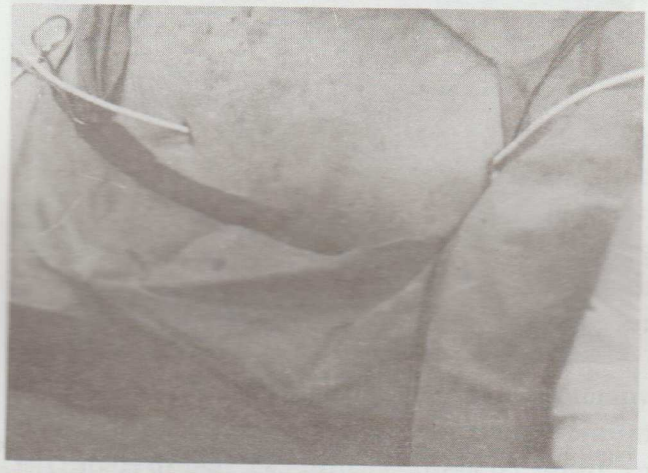
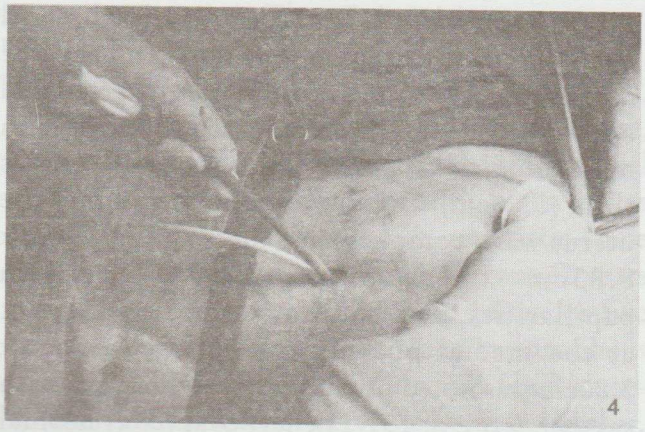
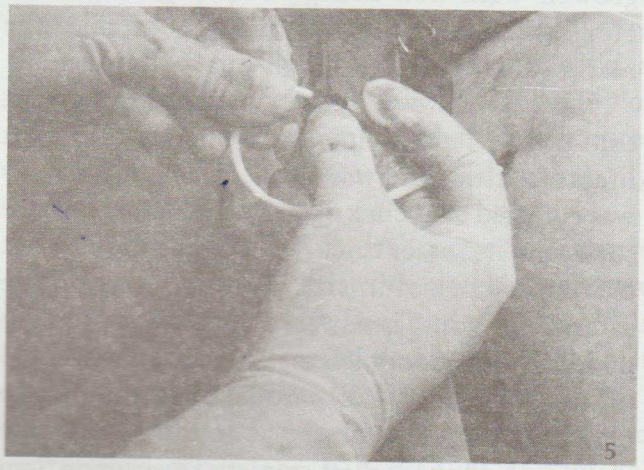
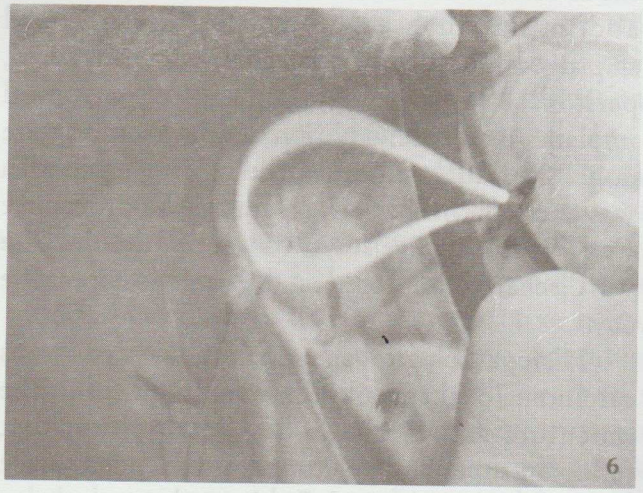


Figure 3. French 8.4 sillicone catheter inserted subcutaneously above the fascia.

IP chemotherapy was started with application of EMLA (2%) to the skin over the IP port site. (Figure 7) Signs of redness, swelling and leakage were checked prior to insertion of Huber non-coring needle. The patient was asked to void prior to procedure and was placed on a semi fowler position afterwards. Standard anti-emetic therapy and dexamethasone were administered. IP carboplatin was given following the Fujiwara protocol: infusion of 1 liter 5% glucose solution







Figures 4, 5 & 6. Insertion of fine catheter into the peritoneal cavity using a tunneling device leaving 10 cm of the catheter within the peritoneal cavity.

followed by bolus infusion of a calculated dose of carboplatin at AUC 5 (*Figure 8*). The dose was calculated using the Calvert formula and creatinine clearance was computed using the Cockcroft-Gault formula. Both infusions were done via gravitational flow as fast as possible. Patient was advised to move side to side to diffuse the fluid inside the peritoneal cavity after the infusion. She did not complain of any abdominal pain/cramping, difficulty of breathing or respiratory distress during the infusion. After chemotherapy, 10 ml of Heparin solution 100u/ml was flushed to the IP port prior to the removal of the needle. She was sent home after the procedure and subsequent chemotherapy was scheduled every three weeks.

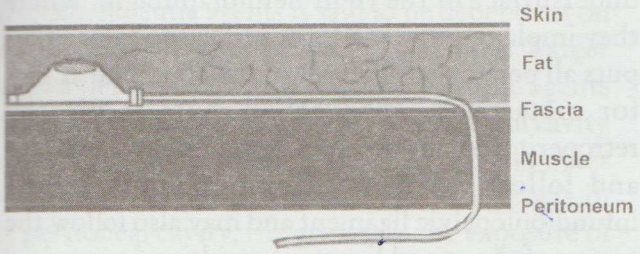


Figure 7. Preferred site of IP port placement underlying the subcutaneous fat tissue and just above the fascia.[11]

One week after the first cycle of IP-IV chemotherapy, work-ups revealed anemia with hemoglobin of 9 g/dl. Two units of packed RBC were transfused which increased the hemoglobin to 11 g/dl. Chemotherapy was given three weeks apart and after the third cycle repeat CA-125 was 76.88 u/mL. Second to fifth cycles of IP-IV chemotherapy were given with no accompanying toxicity noted.

One week prior to the sixth IP-IV chemotherapy, the patient complained of right upper quadrant pain and clear fluid coming out of the port site. Physical examination showed a skin break about 1.0 cm in greatest diameter over the IP port site (Figure 9) and the liver edge was 3 cms below the rib, slightly tender on palpation. Work-up revealed almost 3-fold increase in AST (104.2 U/L) and 5- fold increase in ALT (229.6 U/L). Ultrasound of the whole abdomen revealed hepatomegaly and the rest of the structures were unremarkable. She was seen by the Gastroenterology Service and was started on N-ornithine-L-carnitate one tablet three times a day. Topical antibiotic was also started over the port site. The sixth cycle of IP-IV chemotherapy was given and was well tolerated by the patient. Repeat CA-125 after this cycle was 75.46 u/mL and CT scan of the whole abdomen showed fatty liver, and no enlarged retroperitoneal and pelvic nodes.

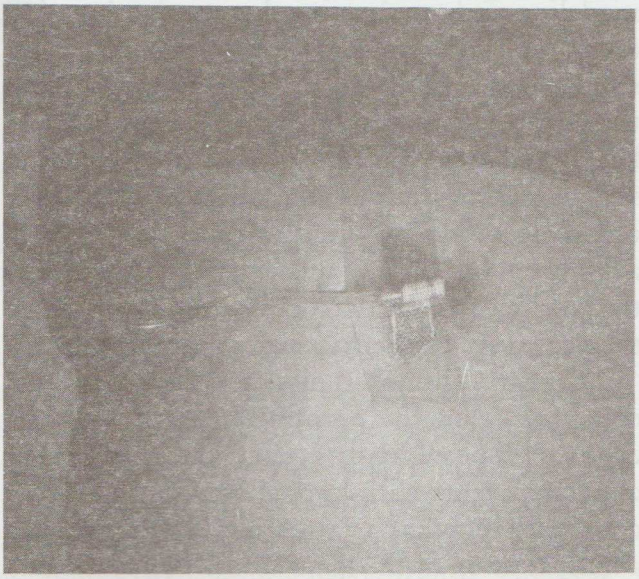


Figure 8. Infusion of chemotherapy at IP port site.

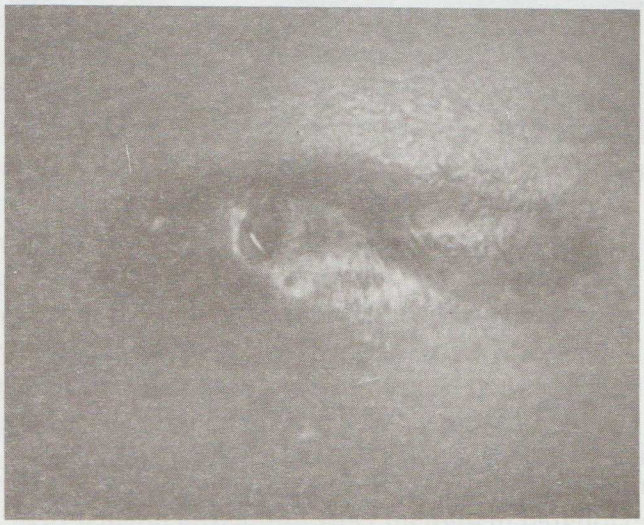
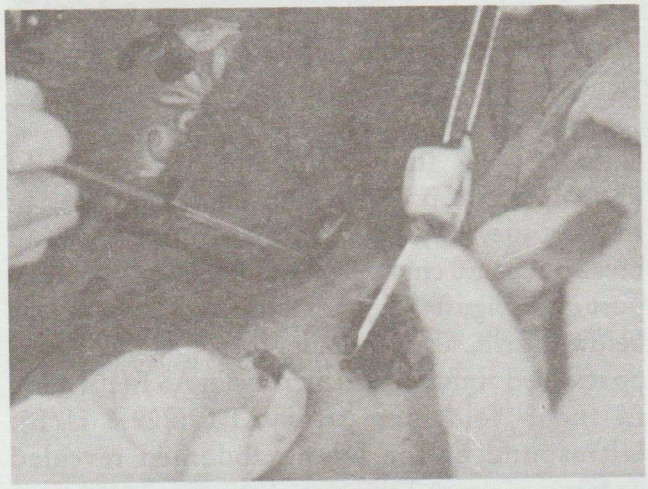
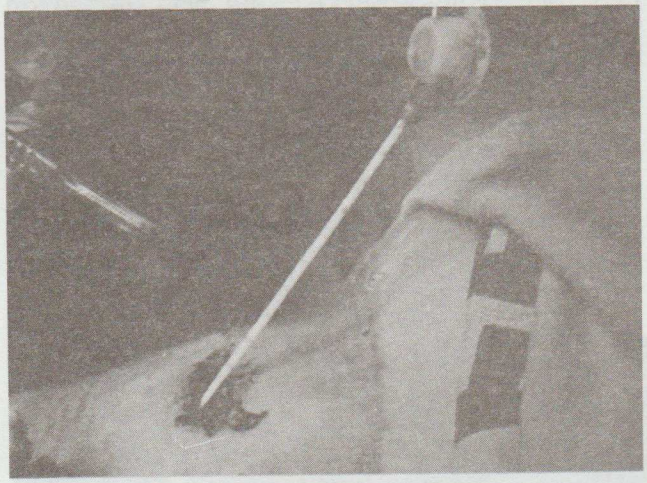


Figure 9. Skin dehiscence (1.0 cm in greatest diameter) over the IP port site. A portion of the port is visible through the dehiscence.

Three weeks post chemotherapy, the patient underwent removal of the IP port (Figures 10, 11 & 12). She was sent home improved and was advised follow-up after a month.





Figures 10 & 11. Removal of IP port.

Figure 12. Closure of wound.

Discussion

Epithelial ovarian carcinoma is known to spread primarily through exfoliation and implantation of malignant cells to the peritoneal cavity. These exfoliated malignant cells follow the normal flow of fluid inside the peritoneal cavity, i.e. in a clockwise manner: up the right paracolic gutter, then to the undersurface of the right hemidiaphragm, where they implant, grow and form surface nodules. This puts all peritoneal surfaces of the abdomen at risk for metastasis. The other route is via the retroperitoneal group of nodes that drain the ovary and follow the ovarian blood supply in the infundibulopelvic ligament and may also follow the course of the round ligament resulting in inguinal lymphadenopathies.[9] These theories have sparked the development of various treatment modalities for ovarian carcinoma.

In 1978, Dedrick, et al. presented the theoretical modeling study supporting the examination of IP anti-neoplastic drug delivery as a management strategy for ovarian cancer. They suggested that tumors present within the peritoneal cavity could be exposed to cytotoxic drug concentrations one to several logs greater with regional treatment than could be safely attained with systemic drug administration.[7] This stimulated the interest to start the preclinical evaluation of this strategy and begin the phase I studies of this treatment approach.

The early clinical studies by Markman in 1993 confirmed that the peritoneal cavity could be exposed to substantially greater concentrations of cytotoxic agents with known activity in ovarian cancer than what is possible with systemic administration of the same agent.[10] The rationale

for this approach is that the peritoneum which is the principal site of disease in ovarian cancer has direct sustained exposure to high concentrations of antitumor agents through perfusion inside the peritoneal cavity while normal tissues like the bone marrow are relatively spared. Some of these agents will go into the capillaries adjacent to the peritoneum and systemic circulation, and then return to the inner core of tumour tissue through tumour microcirculation. Thus, the factors that determine the effect of IP chemotherapy are direct penetration of anticancer agent into the tumour tissue from tumour surface/periphery, diffusion of anticancer agent into the inner core of tumour tissue through systemic blood circulation, and most importantly, the antitumor effect of the agent for ovarian cancer.[11]

The pharmacologic behaviour of IP chemotherapeutic agents is said to be dependent on its molecular weight and water solubility. Larger and heavier molecules and water insoluble agents were observed to stay longer in the peritoneal cavity than agents with smaller molecular weight and water solubility. Therefore, the longer a drug stays in the peritoneal cavity, the greater is the exposure of the peritoneum to the said drug. In effect, the ratio of the drug levels in the peritoneum and serum becomes higher for agents that stay longer in the peritoneal cavity.[11,12]

Platinum-based chemotherapeutic agents, like cisplatin and carboplatin, that are used for ovarian carcinoma are relatively small molecules and are water-soluble. Though not ideal as an IP drug, these agents easily enter the systemic circulation and may be considered as one route for systemic chemotherapy with the added benefit of peritoneal and tumour exposure to high drug concentration while in the abdominal cavity.[11,12]

Phase II trials were mainly cisplatin-based and showed that a proportion of patients with small-volume residual ovarian cancer could achieve surgically documented complete response to second line IP chemotherapy when this clinical state had not been achieved after primary platinum-based systemic chemotherapy. A subset of these patients was observed to have prolonged survival. However these did not prove superiority of IP approach with systemic drug delivery.[12,13]

Two phase III randomized controlled trials by the Gynecologic Oncology Group (GOG) and the Southwest Oncology Group (SWOG) on second-line IP chemotherapy of ovarian cancer compared intravenous and intraperitoneal cisplatin. Both received intravenous cyclophosphamide. Results showed that patients with small-volume disease (largest residual tumor nodule < 2cm in maximum diameter) after surgical cytoreduction given intraperitoneal cisplatin experienced lower incidence of neutropenia and tinnitus but a higher incidence of abdominal discomfort and statistically significant improvement in overall survival (median of 49 vs. 41 months $p = .02$).[14]

In 2006, the third phase III randomized trial of IP cisplatin for the treatment of newly diagnosed stage III ovarian cancer (GOG-172) was published. Comparison of IP regimen (IV paclitaxel at 135 mg/m^2 over 24 hours on day 1 + cisplatin at 100 mg/m^2 IP on day 2 + paclitaxel at 60 mg/m^2 on day 8) to the IV regimen (paclitaxel at 135 mg/m^2 over 24 hours IV on day 1 + cisplatin at 75 mg/m^2 IV on day 2) showed improved overall survival in the IP regimen, having a longer median survival of 65.6 months vs. 49.7 months for the IV therapy ($p = 0.3$). However, higher toxicities and worse quality of life before cycle four and three to six weeks after the treatment were observed in the IP arm. But, the quality of life a year after the treatment was similar to those women treated with the standard IV chemotherapy.[8]

Despite these results and with the concurrent publication of the National Cancer Institute encouraging the use of IP cisplatin combined with IV only or IV plus IP taxane in women with optimally debulked epithelial ovarian cancer, this treatment modality has not gained wide acceptance from both the clinicians and patients worldwide. One of the reasons was attributed to the toxicity associated with cisplatin i.e. nephrotoxicity, neurotoxicity and gastrointestinal toxicity.

Another platinum agent, carboplatin, presently used as the standard treatment in the IV regimen in combination with paclitaxel is known to be as

effective as cisplatin but with lesser toxicity, can also be a safer and better alternative to cisplatin when given intraperitoneally. Use of carboplatin as an IP agent however, has been ignored because of early studies by Los, et al. that showed approximately six to ten times more carboplatin was needed to achieve comparable amount of platinum tissue concentration in the tumor of animal models.[15] Markmann, et al. in a retrospective study claimed that carboplatin was inferior to cisplatin when used intraperitoneally. The dose used in this study for carboplatin was too low at 200mg/m^2 compared to a relatively larger dose of cisplatin at 100mg/m^2.[16]

A prospective study by Polyzos, et al. comparing IP carboplatin and IV carboplatin with cyclophosphamide, on the other hand, showed that significantly more patients in the IV carboplatin group than in the IP carboplatin group had grade 3 or higher leukopenia ($p < 0.01$) and grade 3 thrombocytopenia ($p < 0.09$). Morbidity due to infectious complications in the IP group was also minimal. Complete clinical response rate was 48% for the IP group and 45% in the IV group. Time to tumor progression was 18 months for the IP group and 19 months for the IV group and median survival was 26 months and 25 months, respectively. Thus, he concluded that IP carboplatin was equally effective to IV administration in terms of response and survival with less myelotoxicity.[17]

Fujiwara, et al., likewise, believed in the potential value of carboplatin as an intraperitoneal agent in the treatment of ovarian cancer. In their studies, chemotherapy was given using IV administration of paclitaxel at 175 mg/m^2 given as a 3-hour drip infusion followed by IP administration of carboplatin. Administration of IP carboplatin was started with infusion of 500 ml – 1 liter of 5% glucose during the paclitaxel administration, and then the calculated dose of carboplatin was given in a bolus infusion.[18,21,22,23] Unlike GOG-172, paclitaxel was given by IV route alone. This was done to reduce the IP paclitaxel-related toxicity i.e. severe abdominal pain and greater neurotoxicity.[11,22] Although the optimal volume of infusate is not known, the volume of fluids infused intraperitoneally was also decreased to 500 ml to 1 liter to improve tolerability of the treatment by Asians who generally have smaller stature compared to Caucasians.

In 2003, a retrospective study by Fujiwara, et al., on the long term survival of 165 patients given IP carboplatin showed median survival was 51 months when carboplatin was 400 mg/m^2 or more but was only 25 months if the dose was less than 400 mg/m^2 implying that the dose of IP carboplatin was a significant prognostic factor in long term survival.[18]

In 2004, during the Annual Meeting of the American Society of Clinical Oncology (ASCO), which was later published in 2006, Miyagi, et al. reported the pharmacological advantage of IP carboplatin using the three-compartment mathematical model. The rate constants of platinum diffusion from the peritoneal cavity to serum, serum to peritoneal cavity, serum to peripheral space, peripheral space to serum, and elimination were 0.9 ± 40.79 (mean ± SD), 1.28 ± 2.50, 16.50 ± 9.26, 0.99 ± 0.62, and 4.14 ± 1.45, respectively indicating that 24-h platinum area under the curve (AUC) in the serum was exactly the same regardless of intraperitoneal or intravenous administration of carboplatin. However, the 24-h platinum AUC in the peritoneal cavity was approximately 17 times higher when carboplatin was administered by the intraperitoneal route. They then concluded that intraperitoneal infusion of carboplatin was feasible not only as an intraperitoneal regional therapy but also as a more reasonable route for systemic chemotherapy.[19]

A retrospective study by Fujiwara, et al. on the preliminary toxicity analysis of escalating doses of IP carboplatin at AUC 5-7.5 with fixed dose of IV paclitaxel at 175 mg/m^2 was initiated to provide the preliminary data for the future Phase I study of the Gynecologic Oncology Group (GOG). Results showed grade 2-3 gastrointestinal toxicity and neuropathy and grade 3-4 neutrocytopenia and anemia (based on the GOG Common Toxicity Criteria Grade) which were not related to carboplatin dose. Incidence of Grade 3 thrombocytopenia however increased with

increasing carboplatin dose as follows: AUC 5 – 0%, AUC 6 – 31.6%, AUC 6.5 – 44.4%, AUC 7 – 25% and AUC 7.5 – 80%. Dose limiting toxicity was primarily thrombocytopenia less than 2.0 x 10^4/mm^3 requiring platelet transfusion which was observed in 3/6 patients under AUC 7.5. They suggested that the recommended dose of IP carboplatin in combination with 3-h IV paclitaxel infusion at 175mg/m^2 could be AUC of 6.0–7.0.[20] Currently, GOG is conducting a Phase 1/feasibility study of IP carboplatin to determine the optimal dose with IV paclitaxel for future study. Our patient was given IP carboplatin at AUC 5. Maximal toxicity noted based on the GOG CTC Grade were grade 2 anemia and liver toxicity and grade 1 skin toxicity. Except for these, treatment was well tolerated.

Last 2008, a case of an optimally debulked advanced stage ovarian cancer that was given IP-IV cisplatin-paclitaxel following the GOG 172 protocol was first reported in the Philippines. Treatment was completed not without toxicities and concomitant use of costly measures to decrease the IP-IV chemotherapy related effects. During her chemotherapy, the side effects encountered were nausea with vomiting, abdominal discomfort, abdominal muscle cramping, and diarrhea with maximal GOG CTC grade of 4. The occurrence of grade 4 toxicity was the reason for discontinuing the IP Paclitaxel during the fifth and sixth cycles. Hematological abnormalities like anemia, leukopenia and renal insufficiency were also observed which caused the delay in her chemotherapy. Supportive care was administered by IV hydration, diuresis, use of probiotics (Erceflora), blood transfusion, use of immunostimulators (Pegfilgrastim), renal cytoprotectant (Amifostine), potent anti-emetics (Aprepitant, Ondansetron), and pain relievers.[21]

A recently concluded phase II trial using IP carboplatin and IV paclitaxel in sub-optimally debulked epithelial ovarian cancer by the Sankai Gynecologic Cancer Study Group Study confirmed the earlier retrospective study of Nagao, et al., that intraperitoneal administration of carboplatin combined with IV paclitaxel was well tolerated and showed satisfactory response (83.3%) in patients with bulky residual tumor.[22,23]

Future studies by the Japanese GOG on a large-scale randomized phase III trial comparing the progression-free survival (PFS) and over-all survival (OS) of IP carboplatin plus IV paclitaxel with the standard IV carboplatin-paclitaxel regimen will help elucidate clearly the potential benefit of using IP carboplatin in both optimally and sub-optimally debulked epithelial ovarian carcinoma.[11,12]

IP catheter related toxicities such as infection, in-flow obstruction, leakage, extrusion, and severe pain attributed to catheter material may further limit the acceptance of this approach. Use of a Bardport catheter is more acceptable than a Port-A-Cath.[11] There is also information that inflow obstruction can be prevented by using an IV port system rather than using IP catheter. The type of catheter and port system has yet to be explored to make the IP chemotherapy more tolerable. Our patient used a fully implanted IP port system attached to a single lumen catheter. This prevented kinking and obstruction. No abdominal pain was observed during infusion of chemotherapy. However, a skin dehiscence about 1.0 cm in greatest diameter overlying the IP port with passage of clear fluid was observed prior to the 6th cycle of IP-IV chemotherapy. The clear fluid collection may be a seroma which drained after a skin break secondary to multiple punctures on the skin over the IP port site. It was also speculated that the technique of imbedding the port may have something to do with the dehiscence. It was observed that the port was immediately overlying the skin. Imbedding the port under the subcutaneous tissue might provide additional protection from multiple punctures. There was no redness, swelling or tenderness noted. The blood picture did not show any sign of infection either. Hence, the chemotherapy was continued but utmost care was observed by avoiding the dehisced portion during application of the needle in order to prevent further dehiscence.

Optimal timing for the insertion of IP catheter has not been established. However, it may be done

at the time of initial laparotomy just before closing the abdomen or a few weeks after primary maximal cytoreduction. The port was inserted after the patient underwent one cycle of standard IV treatment, the reason being financial.

The most recommended and preferred site of port placement is two to three fingerbreadths above the right or left lower costal margins in the midclavicular line. In this case, the port was placed on the right lower costal margin at the midclavicular line. A transverse incision was made overlying the right lower rib along the midclavicular line (*Figure 2*). The port was placed directly above the rib to add support during application of the needle. Anchoring the port on the soft tissue in the upper abdomen without the rib support which is the practice of Fujiwara et al may cause rotation of the port and a more difficult insertion of the needle. A subcutaneous pocket above the fascia and a subcutaneous tunnel from the catheter entry to the portal pocket were made. The catheter was tunneled subcutaneously, above the fascia, 6 cms lateral to the umbilicus (*Figures 3 & 7*) and pulled into the peritoneal cavity through a small hole the size of the catheter using a catheter tunneling device (*Figure 4*). With the fascia punctured and using a guide, the catheter is allowed within the peritoneal cavity at a length of approximately 10 cms (*Figure 5*), the other end of the catheter is pulled up and attached to the port. Only 10cm of catheter is allowed within the abdominal cavity because a longer catheter may cause entanglement with the intestines. The port is then sutured to the fascia. Heparin (100 units per cc) was transdermally flushed to determine that flow is not obstructed, and then the incision is closed.

Likewise, the optimum time of IP port removal is still unknown. In this case, the IP port removal with wound debridement was done three weeks post-chemotherapy under local anaesthesia/IV sedation.

Summary

A case of a Stage III serous carcinoma of the ovary managed with maximal cytoreductive surgery followed by combination chemotherapy of intraperitoneal carboplatin and intravenous paclitaxel using the Fujiwara protocol was presented. The treatment modality offered to the patient was well-tolerated. Minimal hematologic, liver toxicity and catheter-related problems were encountered which caused the slight delay in the chemotherapy. Treatment response at the present time cannot be properly established because the patient has just finished her chemotherapy. Although her CA-125 levels during and after the regional chemotherapy plateaud, previously palpated nodes are now not evident by radiologic imaging modality (CT scan).

Conclusion

Intraperitoneal chemotherapy significantly improves the overall survival outcome of diagnosed ovarian cancer cases compared to standard intravenous chemotherapy in the primary chemotherapeutic management of small volume residual, advanced stage epithelial ovarian cancer. Its use has to be encouraged and considered as a standard treatment armamentarium for these cases. One of the limitations preventing its wide acceptance is cisplatin-induced toxicity. Carboplatin, another platinum-based agent, which is less toxic, with proven same efficacy and is the standard systemic platinum agent for ovarian cancer, may actually be a safer and better option to cisplatin as an intraperitoneal agent. Based on retrospective studies and the case presented, carboplatin may be a reasonable alternative to cisplatin for intraperitoneal therapy, having less toxicities encountered and therefore better quality of life during treatment. Hopefully, the results of a forthcoming randomized trial on IP carboplatin vs. cisplatin will give some definite answers.

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Keynote Address*

Luciano SJ Sotto, MD**

Distinguished guests, officers and members of the Society of Gynecologic Oncologists of the Philippines, ladies and gentlemen, friends.

It is indeed a great honor, and a rare privilege to stand here before you, to deliver the silver jubilee keynote address to this very prestigious society. This touches me deeply because this society has a permanent and very important niche in my professional life. My sincere and devoted involvement in this society during the past two and a half decades is well known to everybody. We are here today to give an accounting of what the society has accomplished during the twenty-five years of its existence. The main objective for which the society was organized was, and still is, - "TO PROVIDE THE BEST QUALITY CARE POSSIBLE, TO ALL WOMEN WITH GYNECOLOGICAL CANCER." Needless to say, such care embraces education, prevention, diagnosis, treatment, and rehabilitation. This address will trace its conception, birth growth, development, its activities and accomplishments. This address will try to answer the question of whether or not, we have attained and realized the primary goal of the society. Before I proceed any further, however, please allow me to recognize and thank the few brave colleagues who worked with me, to organize this society.

To Dr. Genara Limson, Dr. Augusto M. Manalo, Dr. Angeles Padilla-Cruz, Dr. Manuel Borja, Dr. Isidro Benitez, Dr. Rainerio Abad, and Dr. Virgilio Oblepias, the founders of this society, I salute you all. You are the nicest people I have worked with, for over 30 years. Thank you very much. Please let us give them a big hand.

I took my residency in Obstetrics and Gynecology at the Millard Filmore Hospital in Buffalo, New York, which, at that time had the busiest OB-GYN department in the whole New York state outside of New York City. In the last few months of my residency, I felt there was something lacking in my training. I was not satisfied. Having seen the very inadequate preparation of the general Obstetrician/Gynecologist to diagnose and treat gynecological cancer cases, gave me the idea of pursuing further training in this specialty. It so happened that the oldest and one of the biggest cancer hospitals in the United States of America was, and still is, in the city of Buffalo, New York. This is the Roswell Park Memorial Cancer Institute. At that time, this hospital had a special post-residency program for those who wanted to learn more about cancer. All the departments had this special program. The program was for a period of one to two years. Gynecology was under the Surgical program and was allotted one slot per year. I applied for this position, and I was lucky to get it. The program that I requested, entailed a rotation of 6 months in Gynecology, 2 months in Breast Surgery, 2 months in Lower G.I. and 2 months in Urology.

* Delivered during the silver anniversary celebration of the Society of Gynecologic Oncologists of the Philippines (SGOP), held last August, 2009 at the Hotel Intercontinental Manila.

** Founding President, SGOP.

My first rotation was Gynecology, which started in July 1, 1957. The chairman of Gynecology was a young surgeon imported from Harvard and Massachusetts General Hospital in Boston, Massachusetts. His name was Dr. John B. Graham, a protégé of the famous Dr. Joe Vincent Meigs, who was the recognized father of Radical Pelvic Surgery in America. Dr. Graham was a real master surgeon, who devoted his entire life to cancer research. He and his wife, Dr. Ruth Graham, a world reknown cytologist, were the investigators of the Sensitization Response and the Radiation Response in Cancer of the Cervix (S.R. and R.R. - for short). The theory was, "Cytology could predict the response of cervical cancer to radiation prior to, as well as, during radiation." This was the hottest research project at the time worldwide. This study was started at the Massachusetts General Hospital and the Pondoille Hospital in Boston, then at the Radiumhemmet in Stockholm, Sweden, and continued in Buffalo, New York.

After 6 months in Gynecology, Dr. Graham asked me to stay on in his department. He promoted me to attending gynecologist status - with the title of Senior Cancer Research Gynecologist. He designated me as Assistant Chief of the department - in - charge of all the activities of the department especially the research projects of which there were numerous. I was the only one who could do the radical operations. We wrote papers, just like all the other doctors in this hospital. The research output and publications from this hospital were enormous. There was a saying then that in this type of hospital you either publish or perish, which meant that you had to do research, you write and you publish or else, you are out. It was at this time that we started writing our book - CARCINOMA OF THE CERVIX - by Graham, Sotto, and Paloucek, which was published by W.B. Saunders in 1962. This was the only book of its kind.

It was at this time also when I had a dream, a vision, to organize and manage a Gynecologic Oncology Clinic in the Philippines. It was my desire and hope to apply all these new knowledge and expertise on Filipino women. How to do it, I had no idea. It was a very wild dream after all. I had no idea of what we had in the Philippines by way of radiation facilities, doctors with enough knowledge of Oncology, operating room facilities and so forth. I spent a total of 3 years at the Roswell Park Cancer Research Institute. I was very happy and felt prepared for any challenge. In June 1961, the late Dr. Constantino P. Manahan, the Chair of the Department of Gynecology of the UP-PGH Medical Center appointed me as Instructor and Consultant in his department. In our first solo meeting, this was his instruction, and I quote "Dr. Sotto, I will give you 10 beds, organize a malignancy service," end of quote. I was stunned. I could not say anything. I could not believe what I heard. I did not expect it. This to me, marked the birth of Gynecologic Oncology in the Philippines. All of a sudden, it dawned on me that this could be the fulfillment of my dream. It was time to work, and I did. The first thing I did was to examine what we had in PGH. Was there a policy on how to treat cancer cases? There was none. How about radiation facilities? The Cancer Institute had one 250KV X-ray machine which was used to treat all kinds of cancer. There were a few radium tubes used in brachytherapy. Was there a standard radiation dose for each type of cancer? None. How about qualified personnel? Dr. Manahan and a few of his residents were doing radical hysterectomy for cervical cancer. Dr. Isidro Benitez was one of them. How about a system of follow-up of patients treated? There was no such thing. In other words, I had to start from NOTHING.

The first thing I did was to talk to the residents: Dr. Florante Gonzaga, the chief resident, Dr. Genera Limson, Dr. Augusto Manalo, Dr. Angeles Padilla-Cruz, Dr. Rainerio Abad and Dr. Virgilio Oblepias. We decided on a plan of action - a set of policy guidelines. The first thing we did was to organize a weekly Cancer Clinic in the OPD, where all patients with gynecologic cancer would be seen, examined, and decide on a treatment. This will also serve as a follow-up clinic. All new patients would be admitted in the ward for work-up and treatment. Most of the patients we saw were

cervical cancer patients - mostly far advanced cases - Stages III and IV. Those who were treated before coming to us were treated with total or even subtotal hysterectomy, a cardinal sin in my book. There was very little we could do for them. All the operable cases (Stages I and II) were admitted for radical hysterectomy. The patients with Stages II-B, III and IV were sent to Manila Doctors' Hospital for External Beam Irradiation. The Manila Doctors' Hospital had a Cobalt 60 unit. We had this special arrangement with Dr. Manahan, who was the Director of Manila Doctors' Hospital, to treat these indigent patients gratis et amore. All the other types of cancer - endometrial, ovarian, vulvar and others, were treated with primary surgery. In due time, we were swamped with patients. In 1965, the Cancer Institute acquired a Cobalt 60 and a Cesium 137 External Beam units. Dr. Paterno Chikiamco, Director of the Cancer Institute and I, designed a new treatment protocol, which was patterned after the Roswell Park technique. We finally had the facilities to offer patients a decent chance of cure.

The weakest link in our set-up was the Chemotherapy Unit. At that time, there were only 2 agents used for ovarian cancer, Chlorambucil or Alkeran and Triethylene Thiophosphoramide or Thiotepa. The response rate to these agents was quite poor. At around this time - mid 1965, Dr. Graham and his wife visited Manila as my guests. When he saw our set-up in PGH - and the huge number of patients we had, he gave up the idea of getting me back to the Roswell Park Cancer Center. Dr. Graham did a radical hysterectomy on a thin patient with cervical cancer. The surgery was perfect, just like in the book, done by the master surgeon and artist, BUT he accidentally cut the ureter. Of course, he did not panic, as most of us would. He just implanted the ureter in the dome of the bladder. The surgery was so radical and clean that the patient could not void for over a year. We had to teach her how to catheterize herself, using the ordinary soft drink straw. A similar incident happened to Dr. Joe Vincent Meigs while demonstrating radical hysterectomy to a group of doctors visiting him in Boston. After the ureter was accidentally cut, he announced to the audience how lucky they were because they would also see how a ureter is implanted on the bladder.

Dr. Ruth Graham suggested that I organize all the bar maids in Olongapo City so that we could examine them regularly and do Pap smear on them, to detect early cervical cancer. She would get me all the grants that would be needed. I politely declined. I didn't want to be known as the doctor of bar girls.

In the late sixties, the Malignancy Service got a big boost when the young residents who took a fellowship training in America returned after their training. Dr. Manalo spent a year at the M.D. Anderson in Houston, Texas under Dr. Felix Rutledge. Dr. Limson worked with Dr. Masterson at King's County Hospital in New York City. Dr. Abad spent 2 years at the Roswell Park Cancer Center with Dr. Graham. Dr. Oblepias was trained by Dr. John D. Thompson in Georgia and Dr. McKelvey at the University of Minnesota. Dr. Cruz was trained in cytology by Dr. Ruth Graham at the Roswell Park Cancer Center. I felt quite good - to see a concentration of talents in the Malignancy Service of the Department of Gynecology of the UP-PGH Medical Center. They were the new superstars of Gynecologic Oncology in the Philippines.

In 1975, the U.S. State Department discontinued the Exchange Visitor's Program which was started after World War II. It became difficult to get residency and fellowship positions in America. We therefore decided to put up a Fellowship Program in Gynecologic Oncology. It was easy enough since we had plenty of patients, complete facilities for radiotherapy, and the training personnel. This was a 2-year program, whose centerpiece was radical pelvic surgery. Radiotherapy and chemotherapy were major components of the program. The only requirement to get into the program was to be a graduate of an accredited residency program in Obstetrics and Gynecology. Preference was given to the following: 1) those practicing in government hospitals especially in the

provinces or cities outside Metro Manila; 2) those affiliated with medical schools and university hospitals; and, 3) graduates of prominent private hospital programs. The only problem was the absence of funding for this program. It was a huge sacrifice on the part of the candidates. We started the program in January 1981, and by the end of 1982, we had our first batch of graduates - a total of two. Since then, we have revised, and improved the program to what it is today. As of the end of December 2008, we have graduated a total of 75 trainees, and all of them have passed the certification examination given by the Philippine Board of Gynecologic Oncology.

Sometime in the early part of 1984, the consultants in the Malignancy Service floated the idea of organizing our own society during a merienda after our follow-up clinic. Everybody was so excited and enthusiastic except me. I was afraid that it might collapse even before it could start because of the very small number of prospective members. After some encouraging discussions, we decided to go for it. The first organizational meeting was held at a French restaurant (Leou Vive) on Otis Avenue in Paco, Manila. At that time, Dr. Borja happened to have a Chinese friend from Taiwan, Professor Chen Tien Hsu, who was visiting Manila. He was a prominent Gynecologic Oncologist in Taiwan. Dr. Borja invited him to the meeting. When he heard about our plan, he thought it was an excellent idea, and that he would likewise organize his colleagues in Taiwan.

We then prepared the By Laws and subsequently elected the officers. The Society of Gynecologic Oncologists of the Philippines was born. We were even ahead of the International Gynecologic Cancer Society - by three years. I attended its first meeting in 1987 in Amsterdam. Another Filipino was there, Dr. Deogracias Custodio, a medical oncologist.

The officers were inducted into office at a dinner meeting in Via Mare Restaurant in Makati City. Dr. Manahan was the guest of honor and inducting officer.

The main objective of the society then, as it is now, is to provide and maintain the highest quality care to patients with gynecologic cancer. We also decided to incorporate in order to have a legal personality. When the Board of Directors of the Philippine Obstetrical and Gynecological Society learned about this, they did not like it. I was the target of their displeasure since I was the president. They wanted us to be just a committee on Cancer under the POGS.

The first scientific meeting was held at the Ledesma Hall of the Makati Medical Center. Everybody worked hard so that the Society would succeed. Scientific meetings were organized within the city and later on, outside. Annual as well as midyear conventions were organized. Prominent foreign guests were invited to share with the Society their expertise. Today, these conventions are the main scientific, cultural and social activities of the Society. What amazes me to this day, is the enthusiasm of all the members to see that the society lives on and on. The camaraderie is contagious. Our By Laws provide a certifying body which will conduct written, oral and even practical examinations to candidates, towards a Diplomate in Gynecologic Oncology. One year after passing the examinations, they can be elected as Fellows of the Society of Gynecologic Oncologists of the Philippines.

Another provision in the By Laws is to inspect and accredit future training programs. I hope the Board will be very strict about this, in order to maintain high quality specialists. Quality should be the primary aim of our training programs.

Now, for the present membership of the society as gathered from the Society of Gynecologic Oncologists of the Philippines office, we have three categories of members: Fellows, Affiliate Fellows, and Honorary Fellows. The gynecologists belong to the first category. To the second category are the trophoblastic tumor specialists, the pathologists, cytologists, radiation oncologists, medical oncologists, and others. Outstanding foreign guests belong to the 3rd category. As of today, we have a total of 115 members; 84 Fellows, 26 Affiliate Fellows, and 5 Honorary Fellows. The geographical distribution of the Fellows is as follows:

Metro Manila	46 (55%)
Region I	4
Region II	1
Region III	7
Region IV	9
Region V	2
Region VI	3
Region VII	4
Region VIII	0
Region IX	1
Region X	1
Region XI	4
Region XII	2

The lopsided distribution is quite clear. This can, and should be addressed by the Society.

For the past 25 years, our Society has been leading the incessant fight against gynecological cancer. All of you were taught and prepared for the difficult and many times frustrating task, to provide quality care to our women afflicted with cancer. It is also your duty to educate in your own way, colleagues in the medical profession, medical students, paramedical personnel, patients, and their relatives, and everybody. Those of you who are connected with medical schools have a bigger task, and this is your responsibility. Participating in medical meetings and conventions, as speakers or resource persons offers an excellent chance to share your expertise. What I would like to see in this society is to be involved in more clinical research. We can organize a Philippine Gynecologic Oncology Group (P.G.O. G.) - patterned after the G.O.G. of America - suited for local conditions.

Now, in the twilight of my career, and after more than fifty years since I had that wild dream and vision of providing quality care to thousands and thousands of women with gynecological cancer by training physicians and fielding them to the four corners of the Philippines, I ask myself and all of you this very serious question: Is there a realization of that dream? With all honesty, modesty and sincerity, I can say YES. All of you here are the characters in this dream. You made this dream come true. I sincerely thank you all my friends for your dedication and sacrifice to this noble lifetime commitment. Maraming, maraming salamat po.