The Correlation of Lower Uterine Segment Involvement with Lymph Node Metastasis in Edometrial Carcinoma: A Retrospective Analysis

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Objective: To determine the relationship between lower uterine segment involvement (LUSI) and lymph node metastasis in surgically staged endometrial carcinoma patients. **Study Design:** A retrospective analysis was done on all patients diagnosed with endometrial carcinoma from April 1999 to February 2008. Patients who underwent complete surgical staging and were found to have lower uterine segment involvement were included. Slides were reviewed by a single pathologist. The primary endpoint is the presence of nodal involvement. Comparison/association of the different variables under study was done using the following test statistics: Chi-square test, Fisher Exact test and logistic regression. Odds ratios (OR) with 95% confidence interval were calculated. **Results:** A total of 199 patients were included in the review. Forty-five were found to have lower uterine segment involvement, 16 (35%) of which had nodal metastasis. Out of the 154 patients without LUSI, 16 (10%) were found to have nodal metastasis ($p = 0.0001$). Both for univariate and multivariate analysis, lower uterine segment involvement, lymphovascular space invasion and deep myometrial invasion were found to be predictive of nodal spread. **Conclusion:** Lower uterine segment involvement may be an important predictive factor of lymph node metastasis for endometrial cancer patients with epithelial type of endometrial cancer.

Key words: endometrial carcinoma, lower uterine segment involvement, lymph node spread

Endometrial carcinoma is the most common malignancy of the female pelvis in the United States. It was estimated that about 40,800 women in the United States developed uterine malignancy in 2005, making it the fourth most common malignancy.[1]

In the Philippines, it is the 15th most common malignancy overall with an incidence of 1.7 percent and ranks 9th among the leading cancer sites in women (3.2%). In 2005, it was estimated that there were 1,777 new cases and 546 deaths in our country.[2]

Vaginal bleeding is the most common symptom. Majority of patients would be symptomatic early in the course of the disease with tumor usually confined to the corpus (upper two thirds of the uterus above the level of the internal cervical os) which allows for early detection and early institution of treatment. Thus, there is better survival.

Prognostic factors are recognized as predictive of nodal metastasis and correlates well with recurrence and survival. Stage is said to be the most important prognostic factor. Other factors include tumor grade, histologic subtype, lymphovascular space invasion (LVSI) and depth of myometrial invasion. Location of the tumor at the lower uterine segment (LUS), defined histologically as the transition from endometrial to endocervical tissue, was previously known to increase loco regional recurrence due to its similar prognostic significance as cervical involvement regardless of other risk factors.

In the 1997 and 2002 editions of the clinical treatment guidelines of the Society of Gynecologic Oncologists of the Philippines (SGOP), involvement of the LUS or the lower 1/3 of the uterine cavity (isthmic involvement) or if the base of the tumor is less than 1 cm from the internal os entails postoperative adjuvant radiotherapy either brachytherapy or complete radiotherapy regardless of histologic grade or depth of myometrial invasion.[3,4] However, a study by Gerner, et al. in 2004 showed that LUS involvement has no impact on patient's outcome.[5] Thus postoperative adjuvant therapy was not justified. Hence, this recommendation was removed in the revised 2005 SGOP treatment protocol.[6] However, there was renewed interest in this area since its presence may also be a predictor of lymph node spread as demonstrated in a study done by Madom, et al. in 2007.[7]

The objective of this study was to determine if lower uterine segment involvement in endometrial carcinoma is predictive of lymph node spread in complete surgically staged patients.

Materials and Methods

A retrospective analysis of cases of endometrial carcinoma seen at the Out Patient Department of this institution from April 1999 to February 2008 was done. All patients who underwent complete surgical staging, defined as total abdominal hysterectomy with bilateral salpingooophorectomy, peritoneal fluid cytology and pelvic and paraaortic lymph node dissection were included in the study. Lower uterine segment involvement was defined by macroscopic and microscopic pathologic evaluation i.e. there is visible endometrial tumor present less than 1 cm above the internal cervical os on pathologic specimen and there is presence of malignant cells invading less than 1 cm above the internal cervical os histologically. Slides were reviewed by a single pathologist. The charts were reviewed and data were collected on the patient's type of surgery, lymph node involvement, histology, lower uterine segment involvement, depth of myometrial invasion, and lymphovascular space invasion (LVSI). The primary endpoint for analysis was the presence of lymph node involvement. Data were encoded and tallied in SPSS version 10 for Windows. Descriptive statistics were generated for all variables. For nominal data, frequencies and percentages were computed. Comparison/ association of the different variables under study was done using the following test statistics: Chi-square test – used to compare/associate nominal data; Fisher Exact test - a modification of chi-square used to compare/associate nominal data in a 2 x 2 contingency table; and logistic regression – a multivariate test used to identify predictor of an outcome variable. Odds ratios (OR) with 95% confidence interval were calculated.

Results

Records of 305 patients diagnosed with endometrial carcinoma at the Out Patient Department of this institution between April 1999 and February 2008 were reviewed. Of the 305

patients, 203 underwent complete surgical staging. Of the 203 patients, 4 had non-epithelial histologic type and were excluded. One hundred ninety nine patients were included in the study. Out of the 199 subjects included, 32 (16.1%) had nodal involvement and 167 (83.9%) did not have nodal involvement.

Table 1. Distribution of patients according to nodal involvement.

	Frequency (n= 199)	Percentage (%)
Nodal Involvement		
Present	32	16.1
Absent	167	83.9

Table 2 shows the association of lower uterine segment involvement, lymphovascular space involvement and myometrial invasion with nodal spread. The results showed that there was a significant association between LUS, LVSI and myometrial invasion with nodal spread as proven by the *p* values <0.05.

Of the 45 patients with lower uterine segment involvement, 16 (35.6%) had nodal spread as compared to the 16 (10.4%) patients without LUS who had nodal spread ($p<0.0001$).

Of the 25 patients with lymphovascular space involvement (LVSI), 8 (32%) had nodal spread while 24 (13.8%) of those without LVSI had nodal spread. Comparing the proportion of patients with nodal spread, there was a significant difference noted ($p=0.04$).

Of the 60 patients with deep myometrial invasion (>50%), 15 (25%) had nodal spread while 17 (12.2%) of the 139 patients with <50% myometrial invasion had nodal spread.

Table 3. Multivariate logistic regression.

	OR	95% CI	P value
LUS	4.76	2.14 - 10.59	<0.0001 (S)
LVSI	2.94	1.14 - 7.56	<0.05 (S)
>50% Myometrial Invasion	2.39	1.10 - 5.18	<0.05 (S)

Multivariate logistic regression analysis was performed to evaluate the combined effects of all variables found to be significant on univariate analysis. These included LUSI, LVSI and myometrial invasion. Both in the univariate and multivariate analyses, all three variables were found to be significant predictors of nodal involvement. The risk of patients with LUSI for nodal spread was almost five times higher than in patients without LUSI (OR=4.76; p5% CI = 2.14 - 10.59; $p<0.0001$). Among those with lymphovascular space involvement (LVSI), the risk was almost three times higher than those without LVSI (OR=2.94; 95% CI = 1.14 - 7.56; p value <0.05) and those with myometrial invasion of >50% have a two times

Table 2. Predictor of nodal involvement: Univariate analysis.

Risk Factor	Present (N) Node positive/total (%)	Absent (N) Node positive/total (%)	P value
LUS	45 16/45 (35.6%)	154 16/154 (10.4%)	<0.0001 (S)
LVSI	25 8/25 (32.0%)	174 24/174 (13.8%)	0.04 (S)
Myometrial Invasion	60 15/60 (25.0%)	139 17/139 (12.2%)	0.02 (S)

higher risk for nodal involvement than those with < 50% myometrial invasion.

Discussion

The significance of lower uterine segment involvement at the time of surgical staging of endometrial cancer and its role in lymph node spread has not been clearly defined. Lymphatic dissemination is considered an important mechanism of vaginal and pelvic recurrence in endometrial cancer. Recurrence in the vaginal vault or central pelvic region after extrafascial hysterectomy may be caused by residual microscopic disease in the resection margins or in intervening lymphatic vessels within the adjacent paracervical area and broad ligament. Pelvic nodal recurrence typically arises from unrecognized tumor spread to obturator, internal iliac, external iliac, or other pelvic lymph nodes. Similarities in lymphatic drainage may provide an explanation for the similarities in the rate of local failure between patients with LUSI and those with cervical involvement. Two mechanisms by which lymphatic vessels that originate in the LUS gain access to those that drain the cervix have been postulated. First, microscopic lymphatic networks at the border of the cervix uteri and corpus uteri have numerous anastomoses. Second, large lymphatic collecting trunks within the broad ligament that drain the lower portions of the corpus may merge with those that originate from the upper cervix. These collecting vessels may terminate in the paracervical-parametrial area, such as the parauterine node, or continue along the normal course of cervical lymphatic vessels to the obturator and internal iliac nodes or the external iliac chain.[8]

The value of lower uterine segment was initially evaluated by Creasman, et al. in 1987 when he compared tumor location and lymph node metastases in patients presumed to have early stage endometrial cancer. Of the 621 patients evaluated, those with lower uterine segment involvement had higher rate of node positivity than those with endometrial cancer confined to the fundus.[9] Hachisuga, et al. in 1989, on the other hand, evaluated 12 lower uterine segment carcinomas compared to 196 endometrial cancer of the uterine corpus. They noted that lymph node spread was not associated with lower uterine segment disease. However, LUSI when compared to carcinoma of the corpus involving the fundus was associated with lower median age, higher histologic grade, less favorable histologic type and deeper myometrial invasion.[10] Mayr NA, et al. in 1995 evaluated the involvement of the lower uterine segment in endometrial carcinoma and patterns of treatment failure. Two hundred four patients with endometrial cancer underwent hysterectomy and postoperative adjuvant radiotherapy was administered for adverse histologic types, depth of myometrial invasion, high grade and LUSI. Nineteen percent had tumor at the LUS, 14 percent had cervical involvement and 67 percent were confined to the corpus. Distant metastasis occurred in 3 percent of patients with tumor at the LUS and 17 percent with cervical extension. Local recurrence was as high as 50 percent for those with no postoperative adjuvant radiotherapy and 3 percent for those who had radiation therapy. They then concluded that early loco-regional spread was the primary mechanism for treatment failure in patients with LUSI. Thus, aggressive management, including postoperative radiotherapy, is necessary.[8] A recent study by Gerner, et al. evaluated outcome in relation to lower segment involvement. Their study included 80 patients with stage I disease. Twenty five of these patients had LUSI. In their population, the presence of LUSI did not impact outcome and therefore did not justify adjuvant postoperative radiotherapy.[5] Madom LM, et al. evaluated 299 patients with LUSI. Forty-four had nodal metastases compared to 10 patients without LUSI. It demonstrated that LUSI is a predictor of lymph node metastases.[7] Brown, et al., on the other hand, claimed that in patients with negative nodes the disease within the lower uterine segment does not imply a worse prognosis.[11]

In this study, 35 percent of patients with LUSI also had nodal involvement compared to 10 percent of patients without LUSI who also have nodal involvement. It showed significant association between LUSI and the presence of nodal metastasis

in patients with epithelial histologic type. Thus, it confirmed the earlier study of Madom, et al. that LUSI is a predictor of lymph node spread. It also showed the value of LVSI and deep myometrial invasion in the development of nodal metastasis. Outcome and prognosis however were not investigated as well as the need for adjuvant therapy in these cases.

Conclusion

This retrospective study shows that endometrial cancer patients with epithelial histologic type (endometrioid) and lower uterine segment involvement have a greater chance of lymph node metastasis. Lower uterine segment involvement then, may be considered as a predictive factor for nodal spread. However, its impact on patient's outcome, its role as a prognostic factor and indication for adjuvant therapy remains unclear.

Recommendation

Further studies must be done to clearly elucidate the true relationship between lower uterine segment involvement and nodal spread, which may have an impact on the postoperative management as well as prognosis in endometrial cancer patients.

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Radical Hysterectomy Following Neo-Adjuvant Therapy in Bulky Stage I-IIA Cervical Cancer: A Tertiary Hospital Experience

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The treatment for bulky early-stage cervical cancer remains controversial. This paper aimed to 1) review the different treatment options for bulky early- stage carcinoma of the uterine cervix and, 2) compare the disease-free interval (DFI) of bulky early-stage cases of cervical cancer in the different treatment arms. **Methodology**: All histologically diagnosed cases of cervical cancer with clinical FIGO stages IB to IIA seen from January 2000 to December 2005 whose minimum tumor dimension was measured to be >4.0 cm were included. Patients were grouped according to the treatment arms received. Of the 37 cases included, 16 patients underwent neo-adjuvant pelvic external beam radiation therapy (EBRT) with Cisplatin followed by radical hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymphadenectomy (RHBSO, BLND), 11 patients received complete radiotherapy (RT), 6 patients were given complete radiotherapy with concurrent chemotherapy and 4 patients underwent neo-adjuvant EBRT followed by RHBSO, BLND. **Results**: The overall survival rate of early-stage cervical cancer was shown to be 96% at 12 months of observation. Neo-adjuvant chemoradiation followed by radical hysterectomy demonstrated the best survival rates of 97% and 85% in 1- and 5-years, respectively. The group which received complete radiotherapy (RT) alone showed 91% and 56% survival rates at 1- and 5-years, respectively. **Conclusion**: This retrospective study has shown that neo-adjuvant chemoradiation followed by radical hysterectomy is the best alternative option in the treatment of bulky early-stage carcinoma of the uterine cervix. Larger sample size, however, is essential to validate the role of this treatment modality with the inclusion of the associated toxicities.

Key words: bulky tumor, early-stage, neo-adjuvant, chemotherapy, complete radiotherapy

Cervical cancer is the second most common malignancy in women worldwide and ranks fourth in the United States.[1] In the Philippines, it continues to cause significant morbidity and mortality. In 2005 alone, 7,277 new cases were recorded and 3,807 deaths were estimated to occur from the disease. The survival rate remains at 51.7% and 44.5% at 5 and 10 years, respectiviely.[2]

Majority of cases in the developed countries are diagnosed in early stages, if not in the pre-malignant state. Among the 13,456 cases registered by the SEER program from 1973 to 1987, 71 percent were in FIGO stages I-IIA.[2] But, in the unpublished report of Cabanela, et al. (2003) in a local tertiary hospital the stage distribution was as follows: Stage I, 16.13%; Stage II, 35.98%; Stage III, 46.03% and Stage IV, 1.25.[18]

The survival rate and recurrence rate of bulky early stage cervical cancer comparing both local and foreign figures are as follows:

	Local	Foreign
Survival rate	56% - 63%[3,5]	75-83%[11,14]
Recurrence rate	20-30%[5]	10-20%[4]

One of the factors seen in recurrent cases was the tumor volume (>4 cm) at the time of RH (bulky early stages). Many studies have shown that tumor volume is correlated with the prognosis. Hence, this study presented the various neo-adjuvant therapies for bulky early stage cervical cancer.

Traditionally, bulky (> 4 cm volume) early-stage cervical cancers were treated either with chemoradiation alone or radical surgery, which were thought to be equally effective. Considering the recurrence rate, there are currently a number of treatment arms being proposed in the effort to address and thereby improves survival rate. These include the use of chemotherapy alone, chemoradiation and radiotherapy alone in the neoadjuvant setting.

The authors found meager reports on these neoadjuvant regimens. Except for the local report of Toral, et al. (2004), no substantial data have, so far, been reported on which treatment arm yield the best DFI and overall survival (OS). The authors, therefore, deem it necessary to report their initial experience on different neoadjuvant treatment arms for bulky early-stage cervical cancer.

This paper is, therefore, aimed at the following objectives:

1. To review the different treatment options for bulky early- stage cervical cancer.

2. To compare the disease-free interval of bulky early-stage cervical cancer in the different treatment arms.

Materials and Methods

All histologically diagnosed cases of cervical cancer with clinical FIGO stage IB to IIA, with tumor dimension of >4 cm, who registered in this institution from January 2000 to December 2005 were included in the study. Demographic characteristics like age, gravidity, histologic type, stage and tumor size were evaluated and analyzed. Patients with stages IIB and above, prior chemotherapy or radiotherapy, and with primary tumors other than cervical cancer were excluded.

Patients were grouped according to the treatment arms received. Group A includes patients who received neoadjuvant EBRT with concurrent Cisplatin followed by RHBSO BLND; Group B includes those who were given Radiotherapy (RT) alone; Group C includes those who received complete RT with concurrent Cisplatin and Group D includes those who underwent neoadjuvant EBRT followed by RHBSO BLND.

Patients in Groups A and D underwent the definitive surgery with radical hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic lymph node dissection within 3-6 weeks after the completion of neo-adjuvant treatments.

Patients' response was measured according to the following criteria: Complete response, persistent disease, recurrent disease and progressive disease.

Pathological response was likewise measured in terms of complete response, near complete response and partial response. Disease free interval (DFI) was estimated from the time of completion of treatment until disease progression or patients' last follow-up. The overall survival ratio was estimated from the date of diagnosis until the patient's death or date of last follow-up.

The study is mainly descriptive and analysis was based on percentages. However, disease free interval (DFI) and survival rates (SR) were estimated using Kaplan Meier method of analysis.

Results

Thirty seven patients were enrolled in the study after having satisfied the inclusion criteria. The demographic characteristics were shown to be comparable (Tables 1-3). Overall, the mean age was 44.91 (ranges 30 – 67). All patients had ECOG Performance Score of 0-1. Based on the histological type, squamous cell type accounted for 26 (70.27%) and only 27.03 percent were adenocarcinoma.

Forty-three percent of patients underwent neoadjuvant EBRT plus concurrent Cisplatin chemotherapy followed by RH BSO, BLND. Eleven patients (30%) received complete radiotherapy alone, 6 (16%) underwent Cisplatin chemotherapy plus complete radiotherapy and 4 (11%) were given neoadjuvant EBRT followed by RH BSO, BLND.

Based on the tumor size, 29 (78.38%) have tumor size < 8 cm and 8 (21.62%) with size > 8 cm (Table 4).

Table 1. Age

	Neoadjuvant EBRT + Cisplatin + RH BSO BLND n = 16 (X = 43.25)	Complete RT n = 11 (X = 45.73)	Complete RT + Cisplatin n = 6 (X =51.17)	Neoadjuvant EBRT + + RH BSO BLND n = 4 (X = 39.5)
≤ 30	0	1 (9.09%)	0	1 (25%)
31-40	6 (37.5%)	0	1 (16.67%)	2 (50%)
41-50	9 (56.25%)	8 (72.72%)	2 (33.33%)	0
51-60	1 (6.25%)	2 (18.18%)	1 (16.67%)	1 (25%)
> 60	0	0	2 (33.33%)	0

Table 2. Gravidity

	Neoadjuvant EBRT + Cisplatin + RH BSO BLND n = 16	Complete RT n = 11	Complete RT + Cisplatin n = 6	Neoadjuvant EBRT + + RH BSO BLND n = 4
0-3	8 (50%)	4 (36.36%)	3 (50%)	1 (25%)
4-6	8 (50%)	6 (54.54%)	2 (33.33%)	2 (50%)
7-9	0	1 (9.09%)	1 (16.67%)	1 (25%)
>10	0	0	0	0

Table 3. Histologic type.

	Neoadjuvant EBRT + Cisplatin + RH BSO BLND n = 16	Complete RT n = 11	Complete RT + Cisplatin n = 6	Neoadjuvant EBRT + + RH BSO BLND n = 4
Squamous Cell	10 (62.5%)	9 (81.82%)	4 (66.67%)	3 (75%)
Adenocarcinoma				
Endocervical	2 (12.5%)	0	1 (16.67%)	1 (25%)
Endometrioid	2 (12.5%)	1 (9.09%)	0	0
Clear cell	2 (12.5%)	1 (9.09%)	0	0
Adenosquamous	0	0	1 (16.67%)	0

Table 4. Tumor size.

Tumor size (cm)	Neoadjuvant EBRT + Cisplatin + RH BSO BLND n = 16	Complete RT n = 11	Complete RT + Cisplatin n = 6	Neoadjuvant EBRT + + RH BSO BLND n = 4
5	8 (50%)	3 (27.27%)	2 (33.33%)	3 (75%)
6	2 (12.5%)	2 (18.18%)	1(16.67%)	0
7	3 (18.75%)	2 (18.18%)	3 (50%)	0
8	2 (12.5%)	3 (27.27%)	0	1 (25%)
9	1(6.25%)	0	0	0
10	0	1 (9.90%)	0	0

Pathological evaluation of tumor was based on the surgical specimen removed. The response was registered as follows: patients with no residual tumor cells in the surgical specimen (primary tumor and lymph nodes) were classified as having a pathological complete response (pCR); near complete or microscopic response was defined with the presence of one or more foci of malignant viable cells and partial response when there is gross residual tumor. Out of the 20 patients who underwent surgery, 12 (60%) had pathological complete response and 8 (40%) with microscopic residual tumor (Table 5).

Patients in the chemoradiation and the radiotherapy group had comparable follow-up with a mean of 42 and 41.22 months, respectively (Table 6). Those in the neo-adjuvant chemoradiation with surgery had the shortest duration of follow-up at 23.625 months which may be attributed to the duration of the treatment instituted.

Comparing the response to treatment of the different modalities, 14 (87.5%) patients in the neoadjuvant chemoradiation group (D) were disease-free, 6 (66.67%) in the radiotherapy group, 4 (80%) in the chemoradiation and 2 (50%) in the neoadjuvant EBRT. Overall, 70.27 percent (26 out of 37) of patients had no evidence of disease, 5 (13.51%) of patients had tumor recurrence and there were 3 (8.11%) patients each for persistent and progressive disease. One patient in the chemoradiation group eventually underwent surgery for central persistent disease (Table 7).

Table 5. Pathological response.

	Neoadjuvant EBRT + Cisplatin + RH BSO BLND n = 16	Neoadjuvant EBRT + + RH BSO BLND n = 4
No residual tumor	10 (62.5%)	2 (50%)
Minimal residual tumor	6 (37.5%)	2 (50%)

Table 6. Duration of follow-up.

	Duration of follow-up (months)
Neoadjuvant EBRT + Cisplatin, RH BSO BLND	4 - 63 mean - 23.625
Complete RT	8 - 79 mean- 41.22
Complete RT with Cisplatin	16 - 64 mean - 42
Neoadjuvant EBRT, RH BSO BLND	8 - 85 mean - 35.25

Table 7. Response to treatment.

	Neoadjuvant EBRT + Cisplatin + RH BSO BLND n = 16	RT n = 11	Chemorad n = 6	Neoadjuvant EBRT + + RH BSO BLND n = 4
No evidence of disease	14 (87.5%)	6 (54.54%)	4 (66.67%)	2 (50%)
Persistent disease	1 (5.25%)	1 (9.09%)	1 (16.67%)	0
Progressive disease	0	2 (18.18%)	1(16.67%)	0
Tumor recurrence	1 (5.25%)	2 (18.18%)	0	2 (50%)

About 75 % of patients with recurrent disease are those with tumors less than 8 cm (Table 8). Histologically, both squamous cell carcinoma and adenocarcinoma had no significant difference in recurrent and persistent disease (Table 9).

The risk of recurrent disease or hazard ratio (HR) was noted to be lowest in the neoadjuvant chemoradiation group at 0.5% percent month with the highest at 2.98% percent month for the neoadjuvant EBRT. Neoadjuvant chemoradiation had the longest mean disease-free interval (DFI) at 196 months, followed by chemoradiation at 111 months and with the neoadjuvant EBRT the shortest at 33.5 months (Table 10).

Table 8. Response to treatment compared to tumor size.

	< 8 cm			> 8 cm		
	NED	Recurrent disease	Persistent/ progresive disease	NED	Recurrent disease	Persistent/ progressive disease
Neoadjuvant EBRT with Cisplatin, RH BSO BLND	12	1	0	2	0	1
Complete RT	3	2	2	3	0	1
Complete RT with Cisplatin	4	0	2	0	0	0
Neoadjuvant EBRT, RH BSO BLND	1	2	0	1	0	0

Table 9. Recurrent/Persistent disease based on histologic type.

	Recurrent disease	Persistent disease
Squamous Cell	2	2
Adenocarcinoma		
Endocervical	1	0
Endometrioid	1	0
Clear cell	1	1
Adenosquamous	0	0

Table 10. Hazard ratio and mean disease free progression.

	HR (per month)	Mean DFI (mos.)
Neoadjuvant EBRT with Cisplatin, RH BSO BLND	.5%	196
Complete RT with Cisplatin	.9%	111
Complete RT	1.3 %	74.4
Neoadjuvant EBRT, RH BSO BLND	2.98%	33.5

The Kaplan Meier product limit estimates of the different treatment modalities were computed and compared. From the dates of diagnosis, dates of recurrence and dates of last follow-up, the duration of follow-up (observational period) were determined. The cumulative disease-free rates were plotted against the duration from date of diagnosis to date of recurrence. From Figure 1, the cumulative disease-free rates of those who had complete RT was the lowest among the four after one year of treatment. However, it became similar to the cumulative disease-free rates of the chemoradiation

and neoadjuvant EBRT after 3 years. The highest cumulative disease-free rate was observed in the neo-adjuvant chemoradiation group. At seven months after treatment, the cumulative disease- free rate for neo-adjuvant chemoradiation was 94 percent, while those in the RT group was 72 percent, chemoradiation at 83 percent and neo-adjuvant EBRT was a little over 75 percent.

The fatality risk for neoadjuvant chemoradiation was 0.25 percent per month as compared to RT which was higher at 0.75 percent. However, combining all the treatment modalities, it was reported at 0.34 percent (Table 11). Extrapolating these figures to the overall survival rate, neoadjuvant chemoradiation has a better survival at 97 percent in 1 year and 85 percent at 5 years while RT was 91 percent at 1 year and almost 56 percent at 5 years. Overall, the survival rate for all treatments was 96 percent at 1 year and 79.6 percent at 5 years.

Table 11. Survival ratio.

	RT	Neoadjuvant chemorad	Overall survival rate
Survival ratio	0.74%	0.25%	0.34%
Mean survival rate in months	134.7	396	291.5

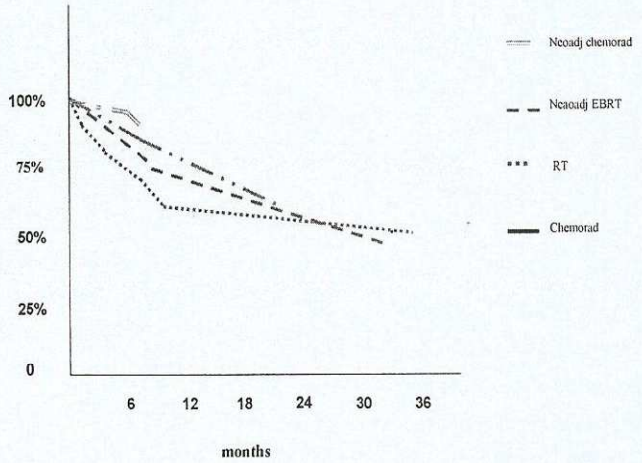

Figure 1. Comparison of Kaplan Meier product limit estimates of disease free progression of the four treatment modalities.

Figure 2 shows the Kaplan Meier curve for survival ratio. From this figure, the overall survival rate of early stage cervical cancer showed a 97% survival in almost 1 year. However, at 19th month, RT has a comparable survival rate as compared to the overall survival ratio at 90.9% and 94.6%, respectively. At almost 3 years, the RT arm was below the overall survival ratio in all treatment regimens at 72.7% and 89.2%, respectively (Figure 2).

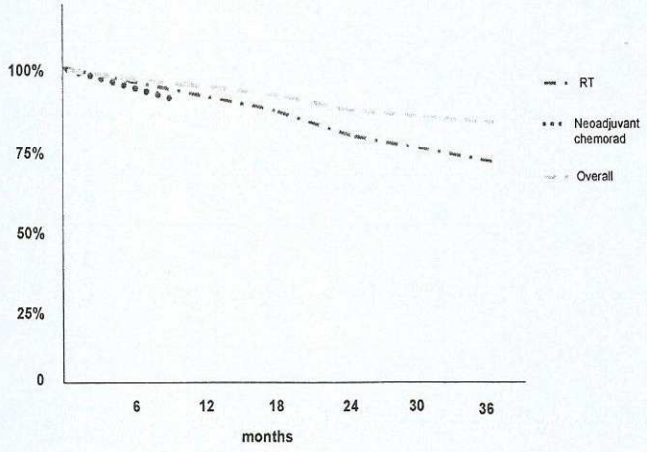

Figure 2. Kaplan Meier curve for survival ratio.

Discussion

Cervical cancer remains as one of the main killers of women worldwide. On a global scale, it is the second most common cancer in women and is the most prevalent female malignancy in many developing countries. In the United States, the majority of cervical carcinoma patients are diagnosed with early stage disease. Among the 13,456 staged patients with cervical carcinoma registered by the SEER program between 1973 and 1987, 71 percent were diagnosed with FIGO stages I-IIA tumors.[7] Cabanela, et al. (2003) reported it at 16. 13 percent and 35.98 percent for Stages I and II, respectively.[18]

Among the major factors that influence the prognosis are stage, volume and grade of tumor,

histological type, lymphatic spread, and vascular invasion. In a surgical-pathological study done by the Gynecologic Oncology Group (GOG) in patients with clinical stage IB disease, the factors that predicted most prominently for lymph node metastases and a decrease in disease-free survival were capillary-lymphatic space involvement by tumor, increasing tumor size, and increasing depth of stromal invasion, with the latter being most important and reproducible. In that study, wherein 1,028 patients were treated with radical surgery, the survival rates correlated more consistently with tumor volume than clinical or histologic stage.[11]

The International Federation of Gynecology and Obstetrics (FIGO) staging system for stage I cervical carcinoma was modified in 1995 to separate stages IB1 and IB2 based on tumor size of 4cm. Most investigators agree that cervical tumor size is a significant negative prognostic factor. Bulky tumors (diameter > 4cm) are associated with a high incidence of lymph node metastasis as well as recurrence compared to smaller sized tumors. For these reasons, the best and most effective therapeutic strategies for bulky stage IB to IIA cervical cancer is still uncertain. This study showed the different treatment modalities instituted in patients with bulky early stage cervical cancer.

Whether adenocarcinoma of the cervix carries a significantly worse prognosis than squamous cell carcinoma of the cervix remains controversial. Most studies suggest no difference in survival when adenocarcinoma is compared to squamous carcinomas after correction for stage. Histologically, in this study, 26 (70.27%) were squamous cell carcinoma and 27.3 percent were adenocarcinoma. However, there were no significant differences in the recurrence rate between the two histologic types.

Most patients in the developed countries present with early disease either confined to the cervix or with limited extension beyond it, FIGO Stage IB1 to IIA. In the past, the standard treatment was usually radiotherapy (RT) or radical hysterectomy, with node dissection (RH LND), each giving 5 year survival rates of around 80% to 90%.[8]

In a report by National Cancer Institute (NCI), in either radiation therapy or radical hysterectomy and bilateral lymph node dissection, the cure rates for Stage IB is 85% to 90% for patients with small volume disease and 75% to 80% for Stage IIA. GOG 123 reported 83% survival for bulky stage IB cervical cancer and Lucely Cetina, et al. (2006), reported an 82% survival rate for stage IB to IIA.[14] Other studies showed a 5 year survival rate exceeding 90% for stage IB1 disease and 60% to 70% in patients with stage IB2 disease. [10]

Twenty patients (54.05%) included in this study underwent adjuvant radical hysterectomy. Twenty six (70.27%) had no evidence of disease. These showed an overall survival rate of 89.2% at 3 years and almost 80% in 5 years.

Pelvic radiotherapy by itself fails to control the progression of cervical cancer in 35% to 90% of patients with locally advanced disease.[15] It has been stated that the most important prognostic factor associated with pelvic tumor control and survival following radiation therapy for stage IB cervical cancer is tumor size. Such that, the ability of radiotherapy to cure locally advanced cervical cancer is limited by the size of the tumor, because the doses required to treat large tumors exceed the limit of toxicity in normal tissues. Intracavitary radiation for central pelvic disease and external-beam radiation therapy for lateral parametrial and pelvic nodal disease are combined with an appropriate radiation dose while sparing the bladder and rectum from receiving full doses. The addition of intracavitary radiation to external-beam radiation is associated with improved pelvic control and survival over external radiation alone, as the combination can achieve high central doses of radiation.

In this study, 54.54 percent of patients (6 out of 11) who received radiotherapy alone had no evidence of disease with a disease-free progression of 74.4 months. The RT regimen showed a fatality ratio of 0.74% per month and a 3-year survival rate of almost 73%.

The central pelvic control rate with radiotherapy alone is excellent for tumors < 8 cm (97%), with total pelvic control and survival rates of 93% and

82%, respectively.[16] For bulky cervical cancers > 8 cm, pelvic control and survival rates decreased to 57% and 40%, respectively.[16] Many experts have argued that adjuvant hysterectomy is unnecessary for tumors < 8cm but may potentially improve local control and survival rates for bulky tumors > 8cm.

All patients with recurrent disease had a tumor size of < 8 cm. However, 4 out of 6 patients (66.67%) identified with recurrent and persistent disease were those with tumors less than 8 cm.

In 1999, a National Cancer Institute (NCI) Alert based on the results of five randomized trials recommended that a "strong consideration should be given to the incorporation of chemotherapy into radiotherapy in women who require radiotherapy for the treatment of cervical cancer".[8] The meta-analysis confirmed that chemoradiation showed a 30%-50% reduction in the risk of death rate which translated into an overall survival benefit of 12% at 5 years.[8,11,14] As a result, concurrent chemoradiation has become a standard of care for women with locally advanced disease.

Theoretically, chemotherapy and radiotherapy could have a synergistic effect. The greater the volume, the larger is the hypoxic and resting phase population with resultant resistance to chemotherapy. Concurrent chemotherapy serves as a radiosensitizer by inhibiting the repair of sub-lethal damage from radiation and synchronizes cells to a particularly radiosensitive phase of the cell cycle.

Neoadjuvant chemotherapy given prior to surgery may present as an alternative to surgery and irradiation as initial treatment of locally advanced cervical cancer. The potential benefits of such an approach include: it can eradicate or biologically alter micrometastases, debulk the tumor, and thus render inoperable tumors operable or improve the outcome of radiotherapy. It also resulted in a longer overall and progression-free survival.

In the RTOG trial (RTOG 9001) for advanced cervical cancer (stage IB or IIA with tumor > 5cm or with biopsy proven pelvic lymph node involvement and stage IIB-IV A), comparing concurrent chemotherapy and radiation versus radiation alone, there was an improvement in the 5 year survival from 58% to 73% and disease free survival from 40% to 67% by reducing rates of both local recurrence and distant metastases.[16]

Eighteen out of 26 (69.23%) patients with no evidence of disease were given concomitant Cisplatin chemotherapy. Patients with recurrent and persistent disease were those who did not receive concomitant chemotherapy [7/11 (63.63%)].

In an Italian Multicenter Randomized Study by Pierluigi Benedetti-Panici, et al. 2002, sequential Neoadjuvant Chemotherapy (NACT) and Radical Surgery (RS) were more effective than exclusive RT in the cure of locally advanced squamous cell cancer. The study showed a 10% to 15% survival advantage for NACT with RS at 5 years.[9] Another study by Youn Seok Choi, et al. (2006) showed a 5 year survival rate of 91.7% and 10-year survival rate of 83.3% in patients with bulky stage IB to IIA cervical cancer who received NACT followed by RS.[10]

In a study by Toral, et al. in 2004, comparing neoadjuvant EBRT concurrent with Cisplatin followed by RHBSO, BLND and neoadjuvant complete RT with Cisplatin followed by EHBSO BLND, both treatment regimens are comparable with slightly higher percentage of cure and less toxicity in the RHBSO, BLND regimen but with higher complete histologic responses in the EHBSO BLND regimen.

In the Gynecologic Oncology Group (GOG) trial, women with bulky stage IB disease, a marked reduction in the local recurrence rate (9% vs 21%) and a slight decrease in the distant recurrence rate (10% vs 13%) were observed in patients who received concurrent radiation and cisplatin compared with those who received RT alone.[12] All patients in the study underwent extrafascial hysterectomy.

Local recurrence was more pronounced in our patients at 80% (4 patients) and distant spread was at 20% (1 patient) with lung metastasis. One patient with local recurrence belongs to the neoadjuvant chemoradiation group.

The study by Keys, et al. (1999) showed a 3-year survival rate of 83% for combined

chemoradiation and adjuvant hysterectomy as compared to RT and adjuvant hysterectomy reported at 74%.[13] The study concluded that combined chemoradiation followed by surgery reduced the risk of disease recurrence and death in women with bulky stage IB cervical cancers.

Patients in this study who underwent neoadjuvant chemoradiation followed by adjuvant radical hysterectomy showed a hazard ratio of 0.5% per month and with the longest disease-free progression at 196 months. This study showed the benefit of adjuvant radical surgery in bulky early stage cervical cancer. However, combination of treatment (neoadjuvant chemoradiation followed by surgery) showed a better response. The neoadjuvant chemoradition in this study has a better outcome when compared to other treatment regimens. This has a survival rate of 97% in 1 year and 85% at 5 years while RT was 91% at 1 year and almost 56% at 5 years.

In 2000, Ting-Chang Chang, et al. estimated the 5-year survival rate for NACT (Cisplatin, Vincristine, Bleomycin) followed by RS and RT alone were 70% and 62%, respectively.[12] The result on the disease-free survival and the overall survival did not differ significantly between the two treatment options.

The study proved that neoadjuvant chemoradiation has a better survival rate at 97% in 1 year and 85% in 5 years while RT was 91% at 1 year and almost 56% at 5 years. Overall, combining all the treatment regimens, the survival rate for bulky early stage cervical cancer was reported at 96% in 1 year and 79.6% in 5 years.

The recognition that patients with bulky stage IB cancers had higher rates of recurrent disease within the cervical area led to the inclusion of adjuvant extrafascial hysterectomy in the treatment regimen for these patients. However, the use of adjuvant hysterectomy is still controversial for small (< 8cm) stage IB2 cervical cancer, since dose-intense external pelvic and intracavitary radiation plus chemotherapy may obviate the need for adjuvant surgery. The GOG trial suggests that adjuvant hysterectomy reduces the recurrence rate but does not affect survival.

This study showed the benefit of adjuvant surgery as demonstrated by the patient's response to treatment and the duration of disease-free progression. However, the author recommends increasing patient population so as to conclude that neoadjuvant chemoradiation followed by RHBSO BLND is indeed the better option for bulky early stage cervical cancer. This study did not include the complications that patients experienced during the course of treatment.

Numerous studies have shown the potential benefit of adjuvant hysterectomy. However, at present, concurrent radiotherapy and chemotherapy (Cisplatin-based) is still the standard approach for bulky stage IB2 cervical cancer. Further study is recommended to define the optimal regimen for bulky early stage cervical carcinoma.

Conclusion

The result of this retrospective study showed that neoadjuvant chemoradiation followed by radical hysterectomy may be a better alternative in treating bulky early stage cervical carcinoma until such time that a definite regimen is established.

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Malignant Mixed Tumor of the Vulva in a Young Patient*

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Vulvar cancers comprise only 5 percent of all genital tract tumors. Most tumors are invasive squamous cell carcinomas. We describe a case of malignant mixed tumor of the vulva which, in our literature search, is the first case described in a young patient. We report a case of a 22 year old nulligravid complaining of a vulvar mass. Excision biopsy showed adenosquamous carcinoma. When she was seen at our institution, there was a 15 cm x 8 cm x 5 cm predominantly solid mass with cystic areas on the left labia majora extending up to the left mons pubis. The clitoris and urethra were grossly uninvolved. Colposcopy of the cervix was normal. She underwent radical hemivulvectomy with bilateral groin node dissection, anterolateral thigh fasciocutaneous rotation flap and split thickness skin grafting. Histopathology of the specimen was Malignant Mixed Tumor, vulva (left). All resection margins, superficial inguinal and deep femoral nodes were negative for tumor except for a lymph node on the lateral margin of the tumor. The plan was to institute adjuvant chemotherapy in the form of Cisplatin and Ifosfamide. However, she did not seek treatment until 2 months postoperatively when she presented with malignant pleural effusion. The optimal management of malignant mixed tumor of the vulva remains to be determined. However, it would seem that early and aggressive surgical resection provides the best possibility for cure. The role of HPV in the histogenesis is promising for possible prevention of this tumor.

Key words: vulva, malignant mixed tumors

The Case

JM, 22 years old, nulligravid from Oriental Mindoro, was admitted with a chief complaint of vulvar mass. Past and family medical histories were unremarkable. She was a high school graduate with no vices. She initially denied any sexual relations but later on admitted to having coitus at 17 years of age to a single non-promiscuous sexual partner. She had no history of contraceptive use nor previous sexually transmitted disease. She never had a Pap smear. Menarche was at 14 years of age with regular monthly intervals with no dysmenorrhea.

History of present illness began when she noted a 1 cm x 1 cm non-tender left vulvar mass. Six months prior to admission, due to increase in the

* 1st Place, 2008 SGOP Fellows' and Residents' Interesting Case Contest.

size of the mass, she consulted a local physician. The mass was excised but not submitted for histopathological examination. She was given antibiotics and pain medications. Two months later, there was regrowth of the mass and she underwent excision biopsy. Initial histopathology was squamous cell carcinoma, vulva. She was advised surgery. She was then referred to our institution. A slide review done in our institution showed adenosquamous carcinoma, vulva. Review of systems was unremarkable. On physical examination, she had an ECOG performance score of 0. She had stable vital signs, with a body mass index of 20 kg/m^2, and body surface area of 1.41 mg/m^2. Systemic physical findings were normal. There was a 15 cm x 8 cm x 5 cm predominantly solid mass with cystic areas on the left labia majora extending up to the left mons pubis. The clitoris and urethra were grossly uninvolved. (Figure 1). The vagina was nulliparous and smooth, the cervix measured 1 cm x 1 cm, smooth, corpus was small, with no adnexal masses or tenderness. Both parametria were smooth and pliable. Colposcopy of the cervix was normal. The admitting impression was Adenosquamous carcinoma of the vulva, stage II. On transvaginal and transperineal scan, the uterus was normal with proliferative endometrium. Both ovaries were polycystic and contained more than 12 subcapsular follicles per scanning field, each measuring less than 1.0 cm and with dense ovarian stroma. There was no adnexal masses seen or free fluid in the cul de sac. There is a solid irregular mass at the left vulvar area measuring 5.0 cm x 4.2 cm x 4.9 cm (Figure 2).

Our initial impression in this case was an HPV-related invasive type of squamous cell carcinoma. Although the patient denied sexual relations, as the patient is unmarried and conservatism is still very prevalent in Filipino culture, this was our primary consideration pre-operatively. We planned to send paraffin blocks of the definitive specimen for HPV DNA in-situ hybridization.

She underwent radical hemivulvectomy with bilateral groin node dissection under regional anesthesia. Intraoperatively, there were no palpable inguinal lymph nodes. Intraoperative referral was made to plastic surgery for anterolateral thigh fasciocutaneous rotation flap and split thickness skin grafting (Figure 3).

Pathologic Findings

The vulvar specimen measured 11 cm x 15 cm x 2.5 cm. There was a 7 cm x 6 cm x 2.5 cm mass at the left anterior labial area and a 6 cm x 6 cm x 2 cm mass at the left posterior labial area. The surrounding free margins were 2 cm distal from the tumor. Nodes were not suspicious for malignancy (Figure 4).

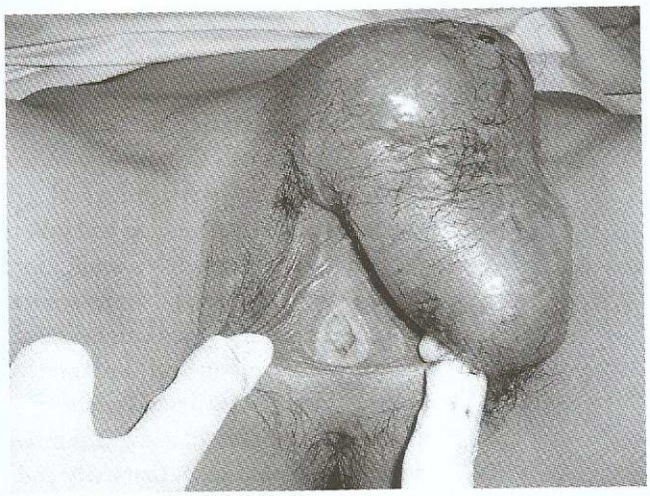

Figure 1. Vulvar mass.

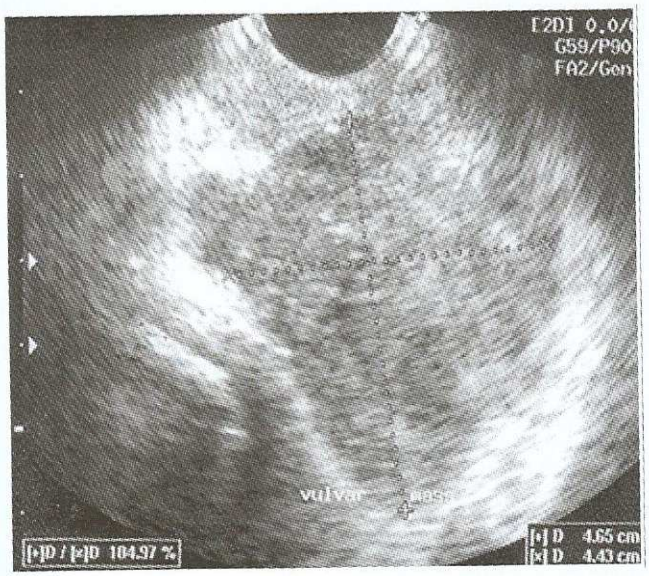

Figure 2. Transperineal ultrasound.

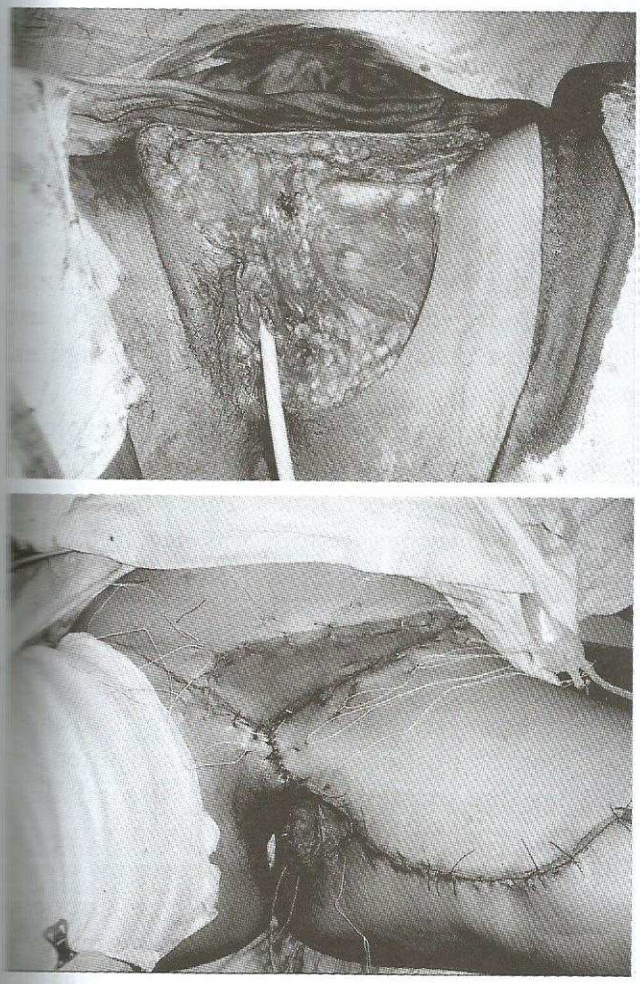

Figure 3. Post-vulvectomy defect and post-skin grafting.

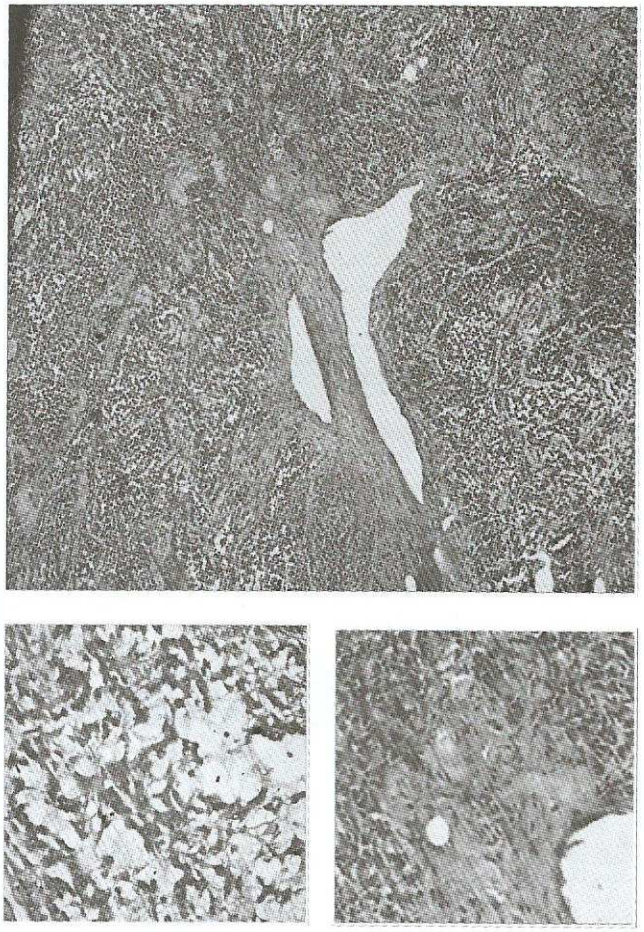

Figure 5. (Topmost): Scanning view of the tumor showing sheets of tumor cells (H & E). Top (left): High power view showing nuclear pleomorphism in the background of myxoid stroma. Top (right): Glandular component of the tumor.

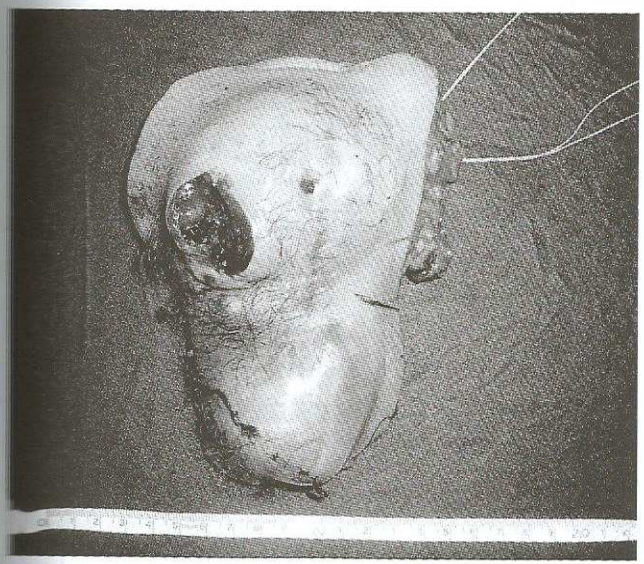

Figure 4. Vulvar specimen.

On hematoxylin and eosin staining, the tumor is cellular, with infiltrating sheets of tumor cells, as shown on scanning view (Figure 5). On high power view, the nuclei show increasing degree of pleomorphism, surrounded by eosinophilic cytoplasm in the background of myxoid stroma. A glandular component of the tumor is also visualized. Figure 6 shows the same neoplastic cells depicting a chondromyxoid appearance. There is a fusion of the cytoplasm of some cells which appear characteristically rhabdoid with mitotic figures. Harvested lymph nodes were not suspicious for malignancy; however on microscopic examination, one lymph node showed tumor infiltration and necrosis (Figure 7).

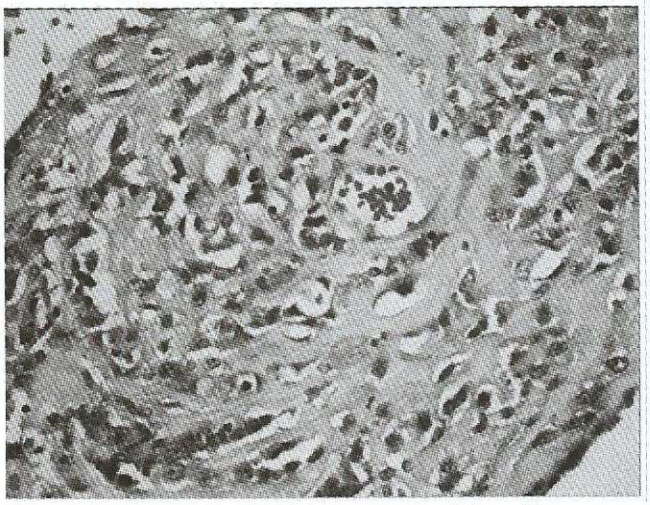

Figure 5. Chondromyxoid appearance of the cells.

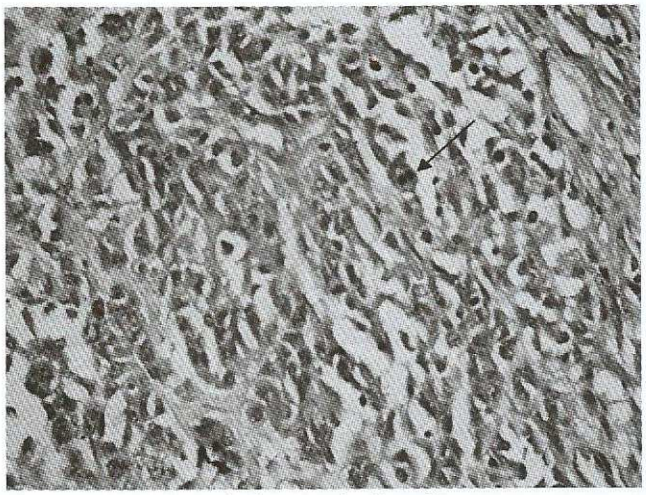

Figure 6. Arrow pointing to mitotic cells.

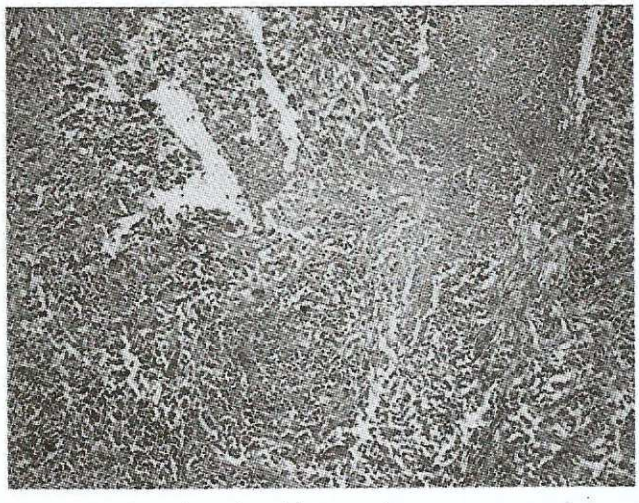

Figure 7. Lymph node with necrosis.

The final histopathology of the specimen was Malignant Mixed Tumor, vulva (left). Positive for tumor: one lymph node near lateral margin of the specimen. Negative for tumor: all resection margins, all four lymph nodes identified as superficial inguinal and deep femoral, all eight lymph nodes labeled "right superficial inguinal", one lymph node labeled "right deep inguinal", both lymph nodes labeled "left deep inguinal", and fibroadipose tissue labeled "left superficial inguinal node."

The slides were reviewed by a gynecologic pathologist. Immunostains for desmin, S-100 and pancytokeratin were performed. Pancytokeratin and S-100 were positive, desmin was negative. The diagnosis of Malignant Mixed Tumor, vulva was maintained.

The plan was to institute adjuvant chemotherapy in the form of Cisplatin and Ifosfamide. The patient, however, was lost to follow-up. Two and a half months post-operatively, the consulted for dyspnea due to pleural effusion. Pleural fluid samples were consistent with malignant effusion. She underwent chest tube thoracostomy which evacuated 2L of fluid and eventually, pleurodesis was done. Days after, the patient and her relatives refused further treatment and went home against advice.

Recent studies have linked carcinosarcomas of the vagina and cervix to HPV. Thus, the paraffin blocks were sent abroad for HPV DNA in situ hybridization. Methodology was as follows: DNA was extracted from a paraffin embedded tissue block that was cut in 5 μm sections which equaled to a total area of approximately of 1cm^2 of tissue. DNA extraction was performed using Proteinase K digestions at 56^{0}C for 18 hours. PCO3/PCO4 primers that amplify a 115 base-pair fragment of the human β–globin target gene were run to determine specimen adequacy. 5μl of the DNA extract, used direct and diluted to 1:10, was used in a final PCR reaction volume of 25μl. β-globin amplification was visualized by 2% agarose gel electrophoresis. SPF10 PCR was performed using 10μl of the DNA extract, used direct and diluted to 1:10, in a final reaction volume of 50μl. The

amplified PCR product was tested using probe hybridization with a cocktail of conservative probes recognizing at least 54 mucosal HPV genotypes in a microtiter plate format. Optical densities (OD_{450}) were read on a microtiter plate reader. HPV DNA was negative. Re-testing was performed, however it was still negative.[1,2]

Discussion

Vulvar cancer is a rare tumor comprising 5 percent of all cancers of the female genital tract. Ninety percent of these primary vulvar cancers are invasive squamous cell carcinoma (ISSC). The disease is predominantly seen in older women (seventh or eighth decade of life) and is rarely seen in patients younger than 35 years of age. Epidemiological and clinicopathologic observations show that there are two general groups comprising vulvar ISSC. The first is the predominant group, seen in older women (55-85 years old), which develop a keratinizing-type ISCC that is associated with lichen sclerosus, squamous hyperplasia, differentiated vulvar intraepithelial lesions (VIN) and p53 mutation. They are not related to the human papillomavirus infection. The second group of ISCC is seen in younger women (35-65 years old). Tumors are basaloid or warty, less invasive and is associated with high risk HPV. There is also a high risk of squamous neoplasia in other areas of the lower genital tract, most commonly the cervix. Prognosis of this group is better than the first.[3,4]

Recent reports suggest that there is an increasing trend toward the younger age group. A retrospective study by Joura, et al.[5] involving 366 women in Central Europe showed that over the last decade, striking increase occurred in the incidence of VIN and an increase in invasive vulvar SCC in young women. In women less than or equal to 50 years old, the incidence of high grade VIN increased by 392% (n = 12 vs. 59) and of invasive vulvar cancer by 157% (n = 7 vs. 18). The British Columbia Cancer Agency likewise conducted a population-based tumor registry to examine clinical and pathologic features of invasive squamous cell carcinoma (ISSC) in women younger than 40 years old. They found that incidence of vulvar ISSC in young women had also increased over time and this increase could not be accounted for by immunocompromised states. Most tumors were associated with HPV, such that HPV DNA was detected in 17 of 20 cases.[3]

Our case is a 22 year old presenting with a vulvar mass with apparent rapid growth in a period of 6 months. She consulted a local physician and the mass was excised but not sent for histopath. It was only when the mass recurred and increased in size that the initial physician who handled the case was alerted that a biopsy should have been done. It is perhaps the rarity of these tumors that makes medical practitioners hesitant and conservative in their initial management. More so that the belief that vulvar cancers are predominantly an illness of the postmenopausal woman. Malignancy in a young patient was not highly entertained.

The second excision biopsy was sent for histologic examination and revealed squamous carcinoma. A slide review in our institution showed it was adenosquamous carcinoma. As the patient is young, it could be surmised that she belonged to the HPV-related group of ISCC. Although cases of ISCC in the young are usually multi-focal, the patient's disease was confined to the vulva. Initially, it was difficult to reconcile the etiology of her tumor as she denied having sexual contact. Later on, the patient disclosed having sexual debut at age 17 with a single non-promiscuous partner, which was within 3 years of her menarche, placing her at risk for HPV infection.

After the vulvectomy, the final histopathology revealed Malignant Mixed Tumor of the vulva. Discrepancy of the excision biopsy and definitive specimen may be explained by the biphasic characteristic of malignant mixed tumor in which the initial biopsy only sampled the epithelial component which was not representative of the entire tumor.

Carcinosarcomas are rare biphasic malignant neoplasms, composed of an admixture of malignant epithelial and mesenchymal elements. They originate in the uterus, ovaries, fallopian tubes, cervix and vagina in descending order of frequency.[6]

The case presented had epithelial elements and mesenchymal elements (chrondomyxoid and rhabdoid components). To our knowledge, this is the case of malignant mixed tumor described in the vulva in a young patient.

The histogenesis of these tumors is controversial. A number of theories have been proposed, including the "collision," "combination," and "composition" theories. The collision theory postulates that the carcinosarcomas have a biclonal origin with two separate, synchronous, neoplastic proliferations fusing to form one collision tumor. The combination theory suggests that carcinomatous and sarcomatous cells share a common "stem cell" origin. The composition theory favors also a monoclonal origin for these tumors and infers that the mesenchymal component originates from the carcinomatous component via a metaplastic process. In this theory, the mesenchymal component is reactive rather than neoplastic and is the result of a proliferative response induced by paracrine factors derived from the carcinomatous component. The composition theory has been largely dismissed because mesenchymal component of the carcinosarcomas have always been found to be overtly malignant on histopathologic examination.[6,7,8]

A fourth histogenic theory known as "metaplastic carcinoma theory" has emerged. It also favors a common cell of origin and postulates that the epithelial or mesenchymal component precedes and gives rise to the other component via metaplasia of a subclonal population, with resultant divergent neoplastic differentiation. This theory is currently favored and is supported by studies with immunophenotypic or ultrastructural observations.[7,9]

The role of human papillomatous virus in the evolution of carcinosarcomas has not been clearly defined. Several studies have tried to find an association of carcinosarcomas of the cervix and vagina with HPV. Grayson, et al.[7] detected by PCR, HPV in all 8 cases of carcinosarcomas of the cervix in their series. HPV 16 DNA was found to be integrated in both epithelial and sarcomatous components of 3 of the 8 cases analyzed. The concept that HPV may be involved in the pathogenesis of carcinosarcomas lends additional support to the metaplastic theory.

Sotiropoulou, et al.[6] described a case report of a 74 year old woman with a vaginal mass which was malignant mixed mullerian tumor with squamous and spindle cell stromal components, associated with high grade vaginal intraepithelial neoplasia (VaIN 3). Though not tested for HPV, the finding of koilocytic atypia and VaIN 3 indicates HPV infection was present. Likewise, Sebenik, et al.[9] described a 57-year old woman with an ulcerated vaginal polyp. Histology showed MMMT composed of invasive squamous cell carcinoma with deeper areas of undifferentiated pleomorphic sarcoma. VaIN 3 was also seen overlying the carcinoma. In situ hybridization showed positivity for HPV DNA in both carcinoma and the sarcoma components.

These studies illustrate a potential role of HPV in the histogenesis of carcinosarcomas in the female genital tract. The possibility that this may have been the mechanism involved in our young patient was explored; especially so that she has a risk factor for HPV infection. Paraffin blocks of the index patient were sent abroad for HPV hybridization in the hope that this would elucidate a correlation. HPV DNA testing however was negative. Other mechanisms may have come into play that led to the metaplastic change in this tumor. P53 mutations have also been implicated and demonstrated in other carcinosarcomas.[8] Although HPV may not have been involved in the pathogenesis of this tumor, its association with other carcinosarcomas in the female genital tract is intriguing necessitating further studies.

Vulvar carcinosarcomas are exceedingly rare. To our knowledge, this is the third case described in literature. The first case reported was a malignant vulvar neoplasm that contained both carcinomatous and osteosarcomatous elements. The second case documented by Adam, et al. showed vulvar carcinosarcoma with squamous carcinomatous and leiomyosarcomatous differentiation. Genetic analysis of the latter demonstrated common clonal origin of both carcinomatous and sarcomatous components.[10]

Ordonez, et al. describes two cases of benign mixed tumor of the vulva probably arising from a Bartholin's gland. Both mixed tumors were of salivary gland type. One of these tumors was histologically comprised of a mixture of epithelial and pluripotential myoepithelial cells which had the capacity to undergo mesenchymal metaplasia, to produce myxochondroid and cartilaginous ground substance. Three other cases of benign mixed tumor are seen in literature. Two arose in the vestibular glands, and the third arose in cutaneous sweat glands.[11] By location, the tumor in the index patient is laterally located and seemed to arise from the left labia majora extending into the mons pubis. Histopathologic analysis failed to reveal any relationship to the Bartholin's gland. This is not surprising as any correlation may no longer be apparent in a highly metaplastic and aggressive tumor that its original morphology may have been lost. Our case of vulvar malignant mixed tumor arising from a Bartholin's gland is still a distinct possibility.

Prognosis of carcinosarcomas of the genital tract is generally poor. These tumors are very aggressive, with most patients dying within a few years of diagnosis. It is often locally advanced at the time of presentation. The case was no exception to the aggressiveness of the tumor. The carcinomatous component represents the dominant factor in determining the biological behavior of these neoplasms.[8] The behavior of the tumor in this case was locally infiltrating with metastasis to the lymph nodes, expected in carcinomatous tumors. Later on, despite vulvectomy, the patient developed malignant pleural effusion.

Management options in vulvar sarcoma are not well-established. Primary surgery is done in the form of wide local excision with or without inguinal-femoral lymph node dissection in early stage and radical vulvectomy with inguinal-femoral lymph node dissection in advanced cases. The efficacy of radiation therapy and /or chemotherapy in this histologic type of cancer of the vulva was not well-defined and even in other parts of the female genital tract. Although the efficacy of radiation and or chemotherapy was not proven in the literature, the rapid course and high mortality of this disease may support the early aggressive strategy such as adjuvant radiation with or without chemotherapy after primary surgery.

Due to its rarity and its seemingly benign appearance, the diagnosis of vulvar cancer often escapes the unsuspecting clinical eye of the examining physician more so when presented with the same case in the young. Early diagnosis entails timely diagnosis of the patient, appropriate intervention of the primary physician and a definitive histopath by the pathologist. These efforts will maximize the window of opportunity for cure. The possibility of carcinosarcomas of the female genital tract being an HPV-related tumor is very promising. Lifestyle changes, sexual practices and vaccination may give hope for prevention of this otherwise dismal and problematic tumor.

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A Case of Ovarian Tumor Induced Pseudo-precocious Puberty in an Eighteen Month Old Child*

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Sex cord stromal tumors represent approximately 8 percent of all ovarian tumors. Granulosa Cell Tumors, the most common malignant tumors of sex cord and stromal origin, represent 2-3 percent of all ovarian tumors. Juvenile Granulosa Cell Tumors (JGCT), which account for about 1-2 percent of all ovarian tumors in children, is a rare cause of sexual precocity.

This is an 18 month old female child who presented with vaginal bleeding and premature thelarche (Tanner II). Prolactin, TSH and cortisol were normal with the following respective values: 0.46 ng/ml, 2.56 uIU/ml and 8.16 μg/dL. LH and FSH were low at 0.48 mlU/ml and 0.109 mlU/ml, respectively. Estradiol was markedly elevated at 722 pg/ml. A left adnexal mass was noted on pelvic ultrasound which was confirmed by a CT scan of whole abdomen. CA 125 and LDH were elevated at 58.26 U/ml and 230 U/L, respectively. Alpha-fetoprotein was normal (2.43 ng/mL) while β-hCG was low (0.24 mlU/ml). The child underwent peritoneal fluid sampling, left salpingo-oophorectomy and omentectomy. Histopathology report revealed Juvenile Granulosa Cell Tumor Stage IA. Ten days after operation, the patient's breast budding had subsided and her estradiol level had dramatically decreased to normal value. A month after surgery, both CA 125 and LDH were within normal values. Monitoring of CA 125, LDH and estradiol was advised monthly for the next 6 months then quarterly to yearly for the next 5 years.

Key words: ovarian tumor, pseudo-precocious puberty

Juvenile granulosa cell tumors (JGCT) of the ovary are rare gonadal stromal tumors that occur mostly in children, adolescents and young adults.[1] JGCT is also a rare cause of sexual precocious puberty and clinical manifestations are associated with hyperestrogenism. Clinical examination, serum estradiol and pelvic imaging studies have been used to diagnose these tumors. The majority of patients with JGCT are diagnosed with early-stage disease (FIGO I) and conservative surgery, which is salpingoophorectomy, is the primary treatment modality. Event free survival rate of greater than 90% with surgery alone was observed.[1,11,12,15]

The Case

This is an 18 month old female child who had spontaneous vaginal bleeding four days prior to

* Second place, 2008 SGOP Fellows' and Residents' Interesting Case Contest.

admission. The mother described the vaginal bleeding as moderate, soaking half a diaper three times a day. There was mucoid watery vaginal discharge noted prior to the vaginal bleeding. There was no history of trauma and there were no other associated signs and symptoms like fever or vomiting noted. The patient was brought to a local hospital in General Santos City three days prior to admission and was subsequently admitted. A pelvic ultrasound was done which showed an enlarged uterus for age and there was no mention of an adnexal mass. The patient was diagnosed to have precocious puberty and she was referred to a pediatric endocrinologist, thus was admitted in this institution.

The patient was the second child of the family and was delivered full term via spontaneous vaginal delivery. She doesn't have any known medical illness. Her mother was diagnosed to have hypothyroidism recently. No medical illness was noted during her mother's pregnancy.

On admission, the patient was examined awake and playful with normal vital signs. Systemic physical examination findings were essentially normal save for breast budding, Tanner stage II (Figure 1). There was no pubic hair noted (Tanner stage I). Vaginal examination done using a nasal speculum under anesthesia revealed a pinkish vaginal mucosa with no malodorous discharge nor active vaginal bleeding.

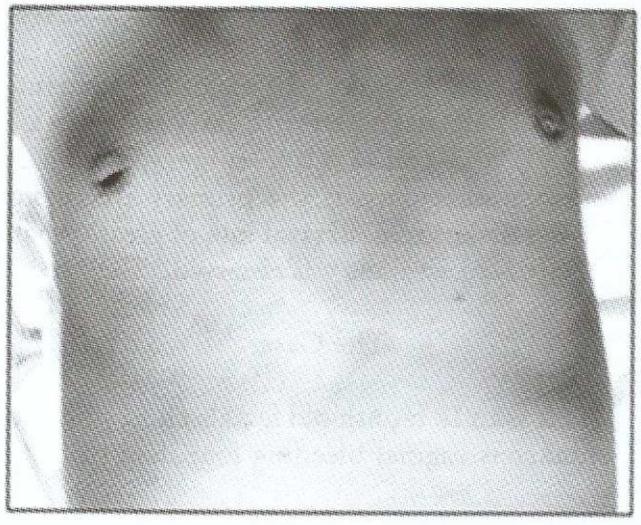

Figure 1. Premature thelarche (tanner stage II).

The admitting impression was Incomplete Precocious Puberty.

A series of blood tests were taken. Prolactin, TSH and Cortisol were normal with the following respective values: 0.46 ng/ml, 2.56 uIU/ml and 8.16 μg/dL. LH and FSH were low at 0.48 mlU/ml and 0.109 mlU/ml, respectively. Estradiol was markedly elevated at 722 pg/ml.

X-ray of the left hand and wrist was done for bone aging which revealed delayed skeletal maturity (by Waterhouse, Pyle and Greulich), as shown in figure 2. The bone age of the patient was for a 10 to 14 month old child. Having two standard deviations, for an 18 month old patient, it is still within normal range of $\pm$ 7 months.

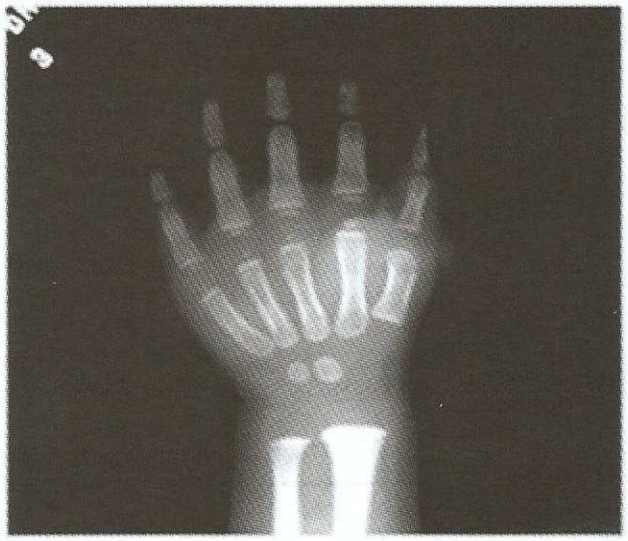

Figure 2. X-ray of left and wrist.

Ultrasound of the adrenals was normal. Pelvic ultrasound revealed a solid left adnexal mass measuring 4 cm x 3 cm x 3 cm (Figure 3). Vascularity was noted at the periphery with high resistance flow.

The patient was referred to a gynecologic oncologist for further management.

The gyne-oncologist requested for ovarian tumor markers such as CA 125, LDH, α feto protein and βhCG. Alpha fetoprotein was normal at 2.43 ng/mL while β hCG was low at 0.24 mlU/ml.

CA 125 was 58.26 U/ml and LDH was elevated at 230 U/L.

CT scan of the pelvis was done which revealed an enhancing lobulated mass in the left adnexal region and which measured 4.4 cm x 2.5 cm x 3.4 cm probably ovarian in origin as shown in figure 4. Uterus was noted to be enlarged measuring 4.2 cm x 2.2 cm x 2.8 cm, and kidneys and adrenals were normal. The patient was scheduled for exploratory laparotomy.

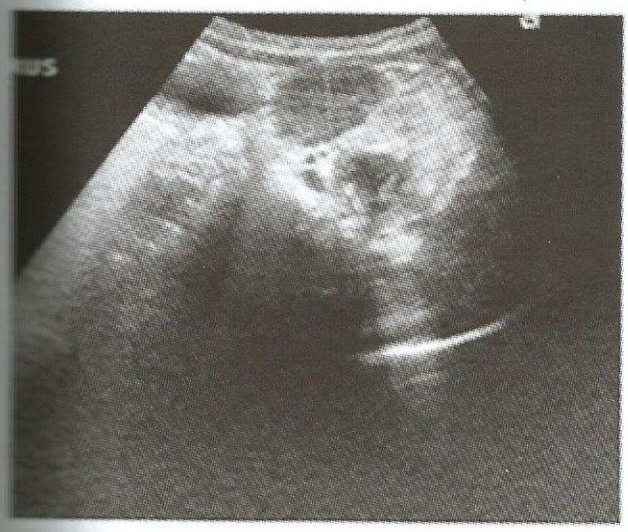

Figure 3. Pelvic ultrasound revealing a left adnexal mass.

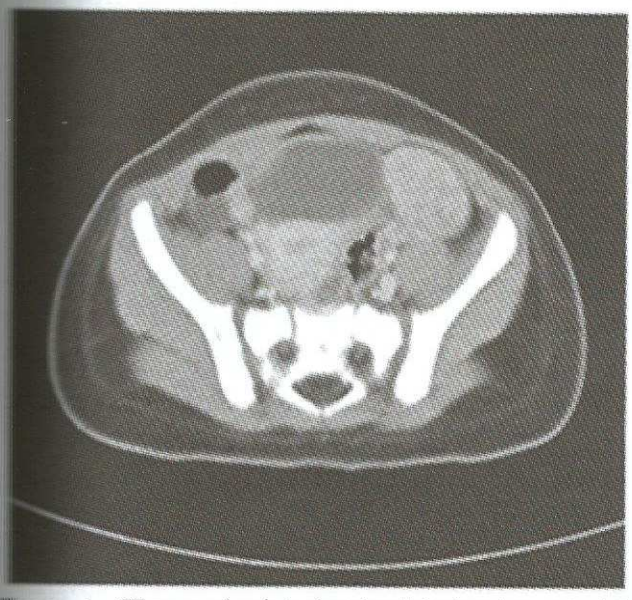

Figure 4. CT scan of pelvis showing lobulated mass in left adnexal region.

At laparotomy, peritoneal fluid was collected. The uterine corpus was noted to be enlarged for age and measured 4 cm x 3 cm x 3 cm (figure 5). A 4 cm x 4 cm x 3 cm solid left ovarian mass with smooth intact external capsule was found (figures 6 & 7A). The right ovary appeared grossly normal with a follicle (figure 8). Left salpingo-oophorectomy with omentectomy was done. The left ovary was sent to the laboratory for frozen section. On cut section of the mass (figure 7B), a solid tan to yellowish "brain gyrus-like" structure was noted. Hemorrhagic areas were not seen. The report was juvenile granulosa cell tumor.

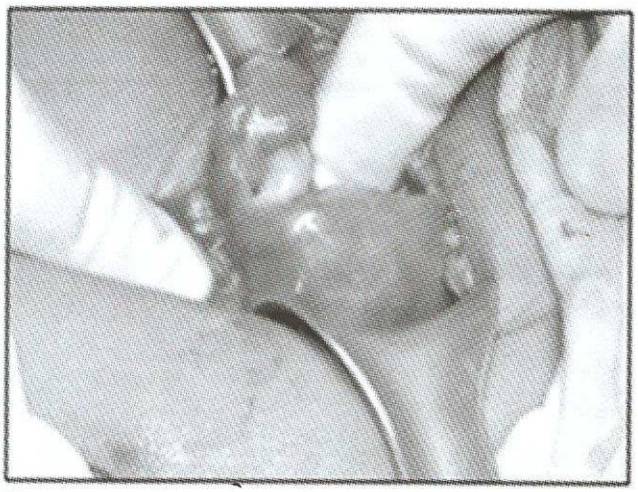

Figure 5. Uterine corpus enlarged for age.

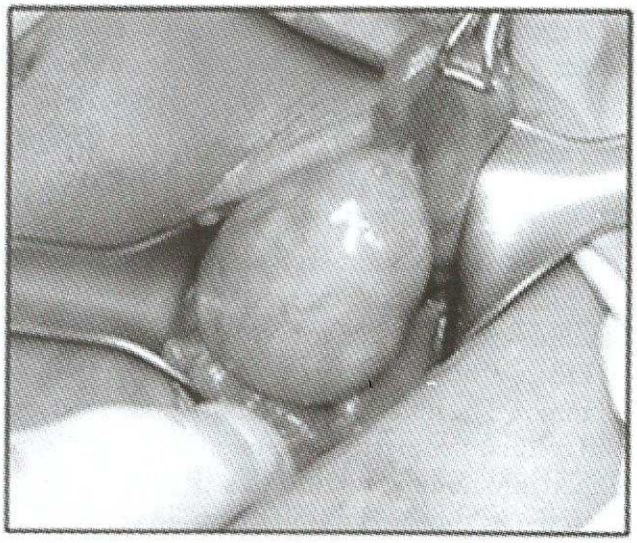

Figure 6. Left ovarian mass seen at laparotomy.

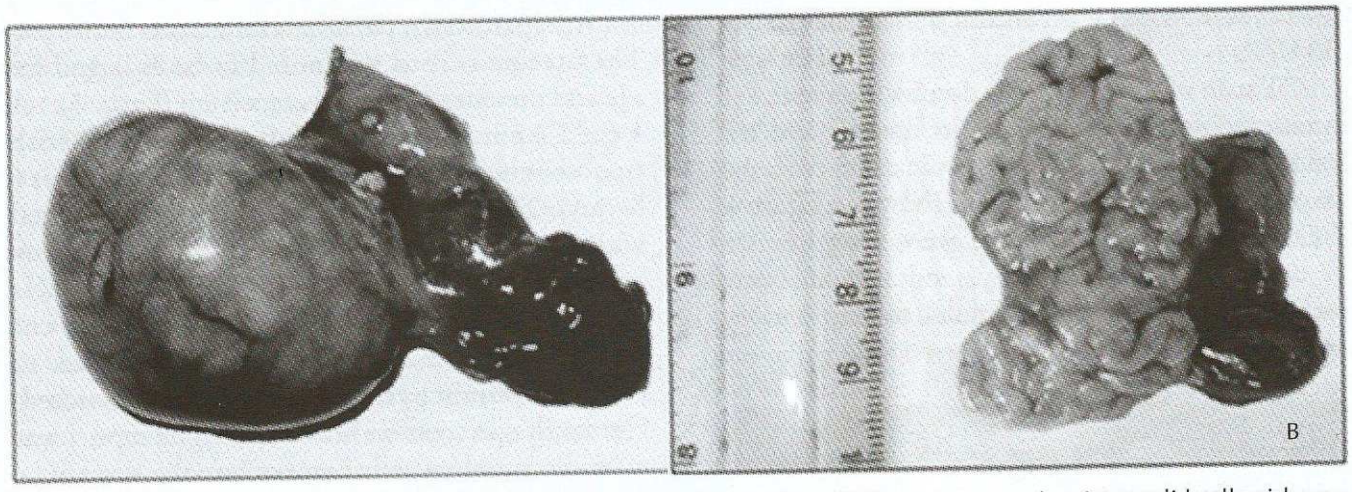

Figure 7. A - Left ovarian mass with smooth external capsule. B - Cut section of left ovarian mass showing a solid yellowish mass without hemorrhagic areas.

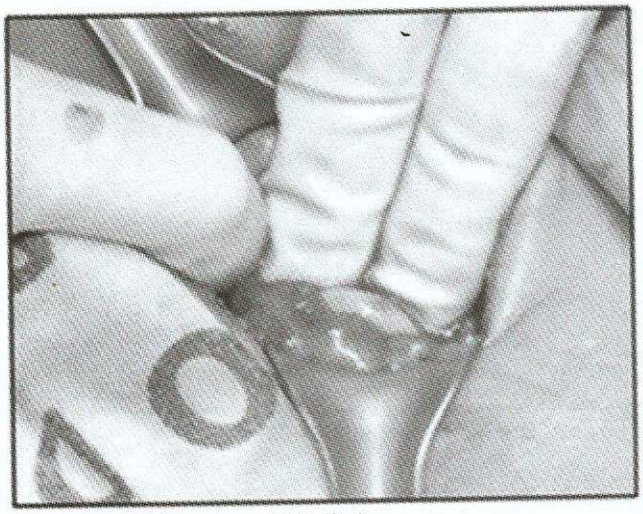

Figure 8. Right ovary with follicle.

The postoperative course of the patient was uneventful and she was discharged on her 3rd post-operative day with the final diagnosis of Incomplete Isosexual Precocious Puberty Secondary to Juvenile Granulosa Cell Tumor Stage IA. CA 125, LDH and estradiol were requested for outpatient follow up.

Histopathology report was juvenile granulosa cell tumor. The microscopic examination revealed a solid cellular neoplasm. The neoplastic cells were divided into nodules by fibrous septae (figure 9A). The follicles appeared round to oval in shape. The cells had abundant cytoplasm with hyperchromatic nuclei, without grooves and exhibit 8-11 mitotic activities per 10 high power fields (figure 9B). The analysis of the peritoneal fluid and omentum were negative for carcinoma cells.

The patient had follow up check up 10 days after operation. The patient's premature thelarche had subsided noticeably. The repeat blood tests were as follows: LDH – 275 U/L and CA 125 – 66.34 U/ml, which were slightly elevated compared to pre-operative values while estradiol has markedly decreased to normal at a value of 3 pg/mL. LDH and CA 125 were again repeated a month after operation and revealed normal results, with the following values: 191 U/L and – 32.92 U/ml respectively. Her gynecologic oncologist advised regular follow up every month with CA 125, LDH and estradiol monitoring for six months then quarterly to yearly for the next five years.

Discussion

Sex cord stromal tumors represent approximately 8 percent of all ovarian tumors. Granulosa cell tumors are the most common malignant tumors of sex cord and stromal origin and represent 2-3 percent of all ovarian tumors.[1,7,8] They are, however, considered low-grade malignancy.[16] Between the two histological forms known: the adult and the juvenile, the latter is more rare accounting for less than 5

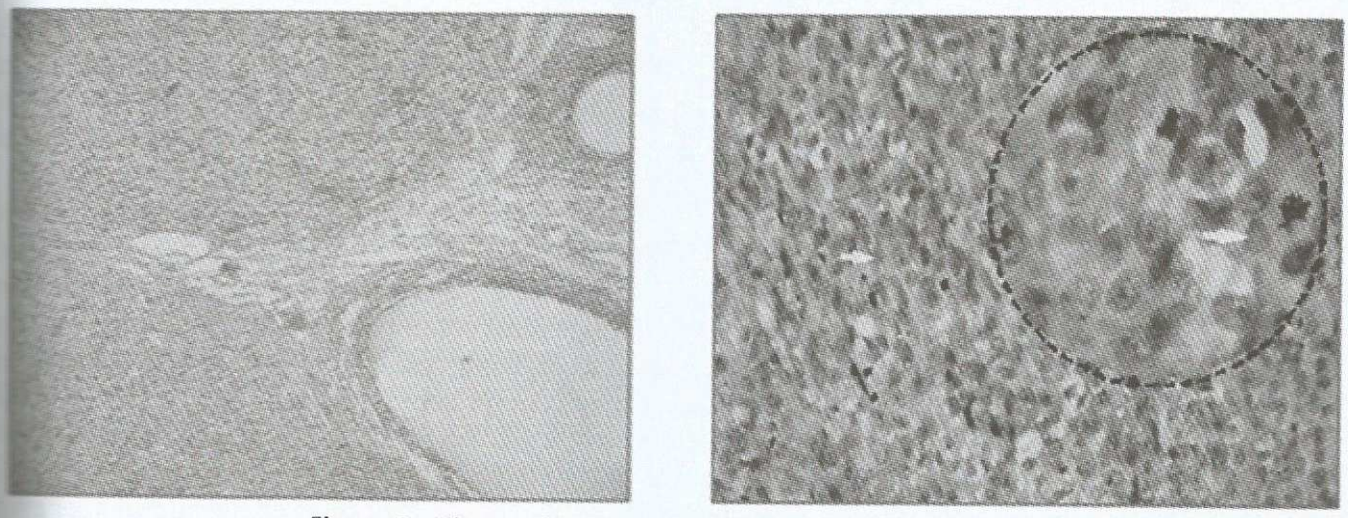

Figure 9. Microscopic appearance of juvenile granulosa cell tumor.

percent of granulosa cell tumors.[2,7,8,12,16] Overall, Juvenile Granulosa Cell Tumors (JGCT) accounts for about 1-2 percent of ovarian tumors in children. Almost all of these tumors are found in pre-pubertal girls and young women under the age of 30 years old.[1,5,7,11]

All ovarian sex-cord stromal tumors are derived from the stroma of the developing ovary. Two theories account for its etiology hypothesizing that they develop either from mesenchyme of the developing genital ridge, or precursors of the mesonephric and coelomic epithelium. No definite etiology has been established, although chromosomal abnormalities and abnormal autocrine and endocrine signaling have been suggested.[17] According to the studies conducted by Lee-Jones, et al. and Tanyi, et al. trisomy 12 is a non-random chromosome abnormality in juvenile granulosa cell tumors.[17,18] In addition, in a study conducted by Maryr, et al. trisomy 12 and 14 and monosomy 22 are the genetic lesions of granulosa cell tumor. Monosomy 22 non-random change was more prevalent than trisomy 12 wherein the loss of chromosome 22 may be associated with tumor progression of granulosa cell tumor and trisomy 14 have been involved in the regulation of cell proliferation and cell death.[16]

Approximately 80 percent of JGCT occurring in children result in isosexual precocity. The more common isosexual precocity are those of central in origin, with premature release of gonadotropins from the anterior pituitary gland and those resulting from apparently autonomous formation of one or more follicle cysts. The precocity caused by granulosa cell tumors is more specifically designated pseudoprecocity because there is no associated ovulation or progesterone production.[1] The patient presented with isosexual precocious puberty manifested by breast budding and vaginal bleeding which is an expression of hyperestrogenism consistent with the findings of 70-82 percent of granulosa cell tumors in general.[4,7,11] Increased whitish mucoid vaginal secretions are believed to originate in the stimulated endocervical glands.[1] This was observed in this patient prior to the vaginal bleeding. Other secondary sexual characteristics, which can occur but were not present in this patient include increased linear growth, clitoral enlargement and pubic hair development.[1,5,7,11]

Somatic and skeletal development are typically accelerated.[1] Bone age of the patient is 14 months which is obviously not advanced but neither delayed significantly (nomal value ± 7 months[13]). This absence of the typical advanced skeletal maturation

may be due to the early diagnosis of the patient such that high estrogen level has not yet stimulated acceleration of skeletal development.

Pelvic mass is the most consistent finding on pelvic and rectal examination in all ages with granulosa cell tumors.[1,7] A palpable mass can be found in 85-97 percent of patients.[7] However, rectal examination was not done in this patient but a pelvic mass was appreciated during abdominal examination when the patient was relaxed after induction of general anesthesia. After puberty, the JGCT usually present with abdominal pain or swelling, sometimes associated with menstrual irregularities or amenorrhea. Approximately 6 percent of all the patients presents with acute abdominal symptoms because of rupture and hemoperitoneum. About 10 percent of cases appears ruptured at operation. It is bilateral in only about 2 percent of cases.[1]

The initial laboratory blood tests were requested to establish the cause of the precocious puberty. These tests include LH, FSH, estradiol, prolactin, cortisol, TSH, T_3, T_4 and testosterone.[14] Prolactin, TSH and cortisol levels in the patient were normal, hence, neither the pituitary, thyroid nor adrenals were the causes of the precocious puberty. In JGCT, hyperestrogenism can be present typically at diagnosis, resulting to an expectedly low LH and FSH because of the negative feedback produced by a markedly elevated serum estradiol as seen in our patient. A very high estradiol level of more than 100 pg/ml such as in this patient, generally indicates an ovarian tumor.[19]

Upon establishing that the cause of markedly elevated estradiol was an ovarian mass, alpha fetoprotein (AFP), beta-hCG, CA 125 and lactate dehydrogenase (LDH) were done to narrow down the type of ovarian mass. Levels of AFP and β-hCG were normal for this patient, which was typical for granulosa cell tumors.[5] LDH and CA 125 may be elevated[7] as seen in this patient. The specific tumor marker for juvenile granulosa cell tumor is serum inhibin, which is a peptide hormone produced by ovarian granulosa cells. Mullerian-inhibiting substance (MIS) or antimullerian hormone (AMH) has recently been studied as a tumor marker for granulosa cell tumor. This hormone is produced exclusively by granulosa cells. Normally, MIS/AMH is found in low levels in females and functions in decreasing ovarian follicle response to FSH.[7] Both serum inhibin and MIS were not done since these were not available in this institution.

The size of the tumor ranges from 3 to 32 cm with an average of 12.5 cm.[1] For this patient, the tumor size was 4 cm in its biggest diameter. The single most common presentation of the tumor is as a solid and cystic neoplasm in which the cysts may contain hemorrhagic fluid. Uniformly solid and uniformly cystic neoplasms are also encountered.[1,9] A mixture of both can also be seen.[7] The solid component typically is yellow-tan or gray and occasionally exhibits extensive necrosis, hemorrhage or both.[1,2] The left ovarian mass seen in this patient was purely solid with no hemorrhagic areas and the yellow-tan appearance was consistently present.

JGCT have characteristic histologic features and consist of nests of granulosa cells interspersed with follicles.[2] Mitosis are numerous and cells have distinct appearance with round hyperchromatic nuclei, most often lacking nuclear grooves found in adult type.[7,11] These histologic findings were consistent with the patient. JCGT rarely demonstrate Call-Exner bodies, which particularly is diagnostic for the adult type.[11] All these histologic characteristics were present in our patient.

The vast majority of JGCT present as localized disease confined to the ovary and that these tumors usually behave in a benign manner despite having histopathologic features of malignancy.[15] This patient was diagnosed as having stage I JGCT which accounts for 70 to 90 percent of cases.[2,8,10,11,12] For early stage tumors, conservative surgery, preserving the possibility of a future pregnancy, is performed by salpingooophorectomy.[5,8,12] Spread beyond the ovary is unusual; only 2 percent of tumors are stage II; rare tumors are stage III.[1] For women with stage IA or IB sex cord stromal tumors, no adjuvant therapy is recommended because of the low risk for relapse.[9] For patients with high-risk early-stage sex cord stromal tumors such as Stage IC or II, there is no standard post-operative

treatment. A JGCT that is confined to the ovary appears to have an excellent prognosis.[1,11,12]

Granulosa cell tumors are radiosensitive but the role of radiotherapy has not yet been defined.[8] The chemosensitivity of these tumors has been demonstrated by the numerous responses observed in the context of palliative therapy: responses of short duration to alkylating agents, frequent responses to adriamycin-bleomycin, actinomycin-fluorouracil-cyclophosphamide combinations added to cisplatin. The highest response rate (80%) was obtained with cisplatin-vinblastine and bleomycin.[8] Although there are no randomized controlled trials to determine the best schedule or drug combination, case series suggest that cisplatin-based regimens have benefit in higher FIGO stages as front line therapy as well as in relapsed disease.[6]

The patient's age and size of tumor (>5 cm) have less certain prognostic value. Among the cytological factors, the number of mitoses has the highest prognostic value, with prognosis being uncomplimentary beyond 5 or 10 mitoses per 10 high power fields.[8] The one year survival rate was lower in JGCT patients with more than 10 mitoses/ 10 hpf, about 81%, compared with patients with fewer than 5/10 hpf about 100%.[10] Unfortunately for this patient, mitotic figures were more than 10 per 10 hpf, a higher recurrence rate is possible. Cellular atypia and poor differentiation have a lower prognostic value.[8] Despite these histological features, stage is the only reliable prognostic factor in these tumors.[17] Hence, there is still a greater chance of survival for our patient since the tumor was diagnosed early.

Recurrence of JGCT is most often seen within the first year after the initial diagnosis.[2,5] These recurrences are usually rapid, leading to death within 13 to 16 months. In contrast, adult granulosa cell tumors tend to have a protracted course and recur 4 to 6 years after initial diagnosis.[2] Young, et al. followed up 23 patients with JGCT for 5 to 10 years and 10 additional patients for 10-21 years without recurrence.[3] Most of the previous studies have reported that it is very uncommon for JGCT to recur after 3 years. Therefore, some authors have recommended that close surveillance is only necessary for up to 3 years after definitive therapy. However, Frausto, et al. reported a case of recurrence of JGCT after left salpingoophorectomy without adjuvant chemotherapy after 4 years. Thus, close surveillance may be warranted for a longer duration.[2] In our patient, close surveillance was advised for 5 years. Because of its rarity, there is no standard and proven treatment for patients with advanced-stage or recurrent non-resectable JGCT.[10]

Raising a child is probably the most challenging responsibility faced by a parent. Having presented with a very rare tumor occurring in a child, the psychological impact on the family should also be addressed. Like other parents, they would want their child to grow normally. Hence, when confronted with situations like a diagnosis of cancer in their child, emotional distress sets in. Especially in our patient, who is the only girl among three siblings. The mother sought several opinions before submitting her daughter for surgery. There was a fear that her daughter might lose the chance of bearing a child in the future because of this life threatening disease.

As a physician, the information of the etiology and management must be provided explicitly to the parents for them to understand and help them cope with the situation and take care of their child accordingly. Therefore, a holistic approach should be provided by the physician, providing appropriate management and follow up care.

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The Uncertain Primary: Definitive Diagnosis of a Pelvic Malignancy Utilizing Immunohistochemistry

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A 49-year old G4P3 (3013) had a 2-month history of menorrhagia accompanied by increase in abdominal girth. Transvaginal ultrasound showed massive ascites and bilateral adnexal masses suggestive of ovarian malignancy. Preoperative impression was advanced ovarian carcinoma. On exploratory laparatomy, there was a finding of essentially normal ovaries, a slightly enlarged uterus, with two solid masses at the cul de sac and sigmoid colon. Tumor debulking of these pelvic masses did not seem to indicate a primary colonic origin. Total abdominal hysterectomy with bilateral salpingo-oophorectomy and bilateral pelvic and paraaortic lymph node palpation were performed. Cut section of the uterus revealed a hemorrhagic and necrotic mass at the cervicocorporeal junction. Initial histopathologic diagnosis was a poorly-differentiated adenocarcinoma. The pathologist was unable to determine the exact origin of the tumor by surgical pathology. Immunohistochemistry using vimentin, cytokeratin Ae1/Ae3, desmin and smooth muscle actin were then used to reveal a final diagnosis of poorly differentiated endometrial adenocarcinoma. She was thus staged as Endometrial Cancer Stage IIIA Grade 3. This case illustrates a dilemma in diagnosis occurring pre-operatively, intraoperatively and postoperatively, finally culminating in the use of immunohistochemistry to pinpoint the origin of the primary tumor.

Key words: Immunohistochemistry, vimentin, cytokeratin

Invasive neoplasms of the female pelvic organs account for almost 15 percent of all cancers in women. In 2005, approximately 80,000 women in the United States were predicted to develop a type of gynecologic malignancy.[19] In the Philippines, the three ranking gynecologic cancers are cervical, ovarian and endometrial carcinoma.[18] In most cases, the patient's profile, clinical history, physical examination, and diagnostic imaging modalities are sufficient to pre-operatively determine the type of pelvic malignancy a woman may possess. This would aid the gynecologist in planning and tailoring the surgery appropriate for the particular cancer. Intraoperative findings and the corresponding histopathologic results usually confirm the pre-operative diagnosis of a gynecologic malignancy.

There are instances, however, when the intraoperative findings are not congruent to the pre-

operative impression. Intraoperative judgment and knowledge on the biologic behavior of specific pelvic malignancies then play an important role in determining the particular type of cancer and managing it appropriately.

Surgical and pathological findings are usually the final determinant of the type of pelvic malignancy a woman may possess. However, there are also rare situations where equivocal findings may prompt the pathologist to utilize other diagnostic procedures that may definitely pinpoint the histologic origin of the tumor. In practice, many pathologists have used immunohistochemical panels composed of markers against certain antigens for determining the exact site of origin and particular type of malignancy. The importance of determining the particular type of pelvic malignancy lies in its ability to affect the subsequent adjuvant treatment these patients will eventually receive.

This report demonstrates the dilemma a gynecologist may face when the pre-operative, intraoperative and postoperative pathologic findings do not seem to point to a particular type of pelvic malignancy. What we thought was a clear-cut case of advanced ovarian carcinoma was ruled out with the intraoperative findings suggestive of either a colonic, endometrial, or endocervical cancer. Though we thought surgical pathology would resolve this dilemma, the initial histopathologic report was also unable to definitely diagnose which among these cancers is the primary site. We thus had to rely on immunohistochemical studies to finally resolve the question of the uncertain primary.

The Case

C.E., a 49-year old, G4P3 (3013) was referred to the Department of Obstetrics and Gynecology by Internal Medicine due to difficulty of breathing and increase in abdominal girth.

She was diagnosed with hypertension in 2006 and is on unrecalled maintenance medications. She was also diagnosed with hypothyroidism in 1997 and is presently maintained on Thyroxine.

She has a history of hypertension, asthma and goiter on both sides of her family. Her daughter has pulmonary tuberculosis. Two maternal aunts have breast cancer.

She has been married for the past 22 years. She never had a Pap smear. She took oral contraceptive pills for 8 years. She denied dyspareunia and postcoital bleeding.

She had her menarche at 12 years of age with menses occurring every 30 days, lasting for 3 days, consuming 4-5 pads per day. She experiences dysmenorrhea on days 1 and 2 of her cycle. Her last menstrual period was November 17, 2006.

She is a Gravida 4 Para 3 (3013) with 3 full term pregnancies delivered spontaneously without complications. She had a non-septic, non-induced abortion where completion curettage was performed.

History of present illness started 2 months prior to admission when she experienced menorrhagia described as heavy menstruation consuming 8-10 fully soaked pads per day. She did not experience abnormal abdominal symptoms and changes in bowel and bladder habits. She did not consult a physician or take any medications.

One month prior to admission, still with persistence of the menorrhagia, she noted an increase in abdominal girth, anorexia and 6-pillow orthopnea. She still did not seek medical advice.

Two days prior to admission, with persistence of vaginal bleeding, increasing abdominal girth, anorexia, and orthopnea, she consulted a private physician who requested an ultrasound of the whole abdomen. This revealed the following findings: Normal liver, gallbladder, pancreas, spleen, and urinary bladder; the uterus measured 4.3 cm x 3.2 cm x 2.5 cm, with heterogenous echotexture; solid structure in right adnexa measuring 8.5 cm x 7.5 cm and a septated cystic structure seen in the left adnexa measuring 6.7 cm x 6.1 cm; massive collection of free fluid in the peritoneal cavity. Sonographic impression was **Ovarian New Growth, bilateral; Massive Ascites.** Chest radiograph done revealed pleural effusion on both lung fields. Patient was advised transfer to our institution where she was subsequently admitted.

On admission, she was conscious, coherent, wheelchair-borne, not in cardio-pulmonary distress

with stable vital signs. She weighed 61.5 kg in a 5-ft frame. She had a BMI of 26.5. Significant physical examination findings revealed pale nail beds, a 2 cm x 2 cm palpable anterior neck mass that moves with deglutition, symmetrical chest expansion, no retractions, decreased breath sounds on both mid- to lower-lung fields. Abdomen was globular with normoactive bowel sounds, soft, non-tender, no palpable mass, with positive fluid wave. She had grade 2 bipedal edema. Speculum and internal examinations could not be performed due to the inability of the patient to lie in a lithotomy position.

Our admitting impression was anemia secondary to perimenopausal bleeding rule out endometrial pathology; bilateral pleural effusion and massive ascites, probably secondary to bilateral ovarian new growth, malignant; hypothyroidism, controlled.

On the 2nd hospital day, CA-125 was markedly elevated with a value of 2,011.3 U/ml (normal range of 0-35 U/m). Her complete blood count showed a hemoglobin value of 7.4 g/dL and a hematocrit of 23. She was thus transfused two units of packed red blood cells.

An advanced-stage ovarian carcinoma was the main consideration at this time because of the findings of abdominal distention, abnormal vaginal bleeding, ascites, bilateral adnexal masses on ultrasound and an increase in CA-125. A CT scan of the whole abdomen and chest were initially requested to determine the extent of the disease but the patient refused due to financial constraints.

On the 5th hospital day, ultrasound-guided thoracentesis was done, evacuating serosanguinous fluid, 650 cc and 480 cc from the left and right lungs, respectively. Pleural fluid cytology revealed atypical mesothelial cells. Post-thoracentesis ultrasound showed approximately 30 cc of remaining fluid in the left lung. The patient was then scheduled for exploratory laparotomy and transfused with 1 unit packed red blood cells, pending cardio-pulmonary clearance.

On the 7th hospital day, she became febrile at 38.3 °C, thus the operation was postponed. Blood culture and sensitivity studies were taken and she was started on antibiotics. Results showed no growth after a 1-week incubation period.

She was afebrile on the 9th hospital day and was cleared to undergo the contemplated procedure.

On the 10th hospital day, she underwent exploratory laparotomy. After induction of anesthesia, pre-operative internal examination showed a parous and smooth vagina, cervix firm, closed, and smooth measuring 4 cm x 3 cm; the uterus and adnexae were difficult to assess due to the distended abdomen; rectovaginal examination showed a smooth and pliable parametria.

Intraoperative findings showed the following: There was approximately 3.5 liters of serosanguinous peritoneal fluid. The liver, subdiaphragmatic area, stomach, spleen, small intestines, omentum, and parietal peritoneum had smooth surfaces and were grossly normal. Both ovaries were grossly normal (Figure 1). There was a yellow friable, necrotic, irregular mass measuring 15 cm x 12 cm x 12 cm at the cul-de-sac adherent to the posterior wall of uterus, right ovary and anterior wall of the rectosigmoid (Figure 2). The uterine corpus measured 5 cm x 5 cm x 4 cm with smooth serosa at its anterior surface. The right ovary measured 2 cm x 1 cm x 0.5 cm and was adherent to the cul-de-sac mass. The left ovary was grossly normal and measured 2.5 cm x 1 cm x 0.5 cm with a smooth capsule. Both fallopian tubes were grossly normal. Another complex mass measuring 8 cm x 6 cm x 6 cm was noted to be adherent to the sigmoid colon. There were no palpable pelvic or para-aortic lymph nodes.

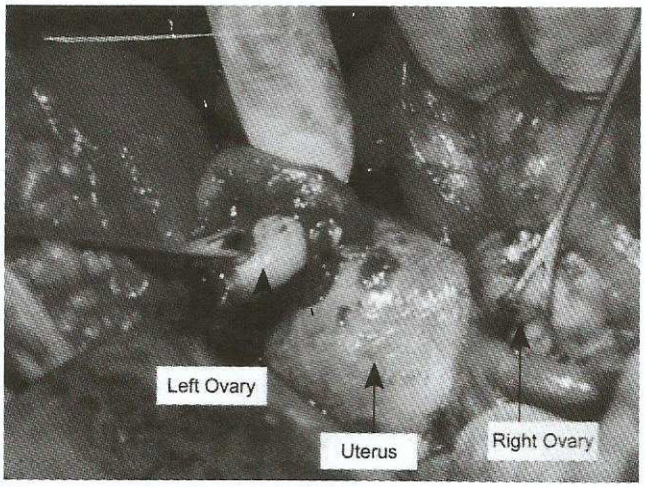

Figure 1. Both ovaries and fallopian tubes were grossly normal.

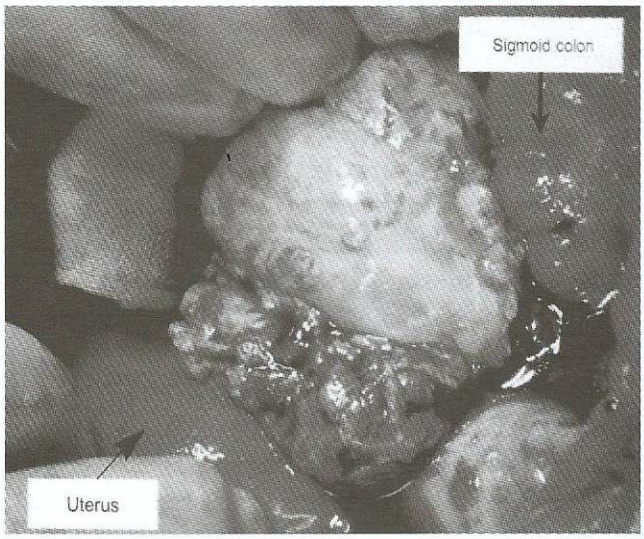

Figure 2. A yellow, friable, necrotic irregular mass measuring 15 cm x 12 cm x 12 cm located at the cul de sac, adherent to the posterior wall of the uterus, right ovary and anterior wall of the rectosigmoid.

At this point, our intraoperative impression was a primary gastrointestinal carcinoma, probably colonic in origin with a possible second primary cancer in the endometrium. We proceeded to perform tumor debulking of the two pelvic masses using blunt and sharp dissection and electrocautery. The masses were easily dissected away from the colon, uterus, right ovary and other surrounding structures. The adjacent serosal surfaces where the tumors were implanted had irregular surfaces, but there was no note of infiltration into the muscularis layer of the large intestine. Primary colonic malignancy was not a strong consideration at this time.

We proceeded to perform total abdominal hysterectomy with bilateral salpingooophorectomy (TAHBSO), and bilateral pelvic and para-aortic lymph node assessment.

Cut section of the uterus revealed a 4 cm x 4 cm x 3 cm friable, hemorrhagic and necrotic mass extending from the uterine isthmus to the endocervical area with almost full thickness involvement of their respective walls (Figure 3). An intramural mass measuring 1 cm x 1 cm x 1 cm was noted at the anterior wall. Cut section showed tan-white, whorled parenchyma. The myometrium at the uninvolved area measured 2 cm and the endometrium at the mid to fundal area of the uterus was thickened. Cut section of both ovaries showed white homogenous parenchyma.

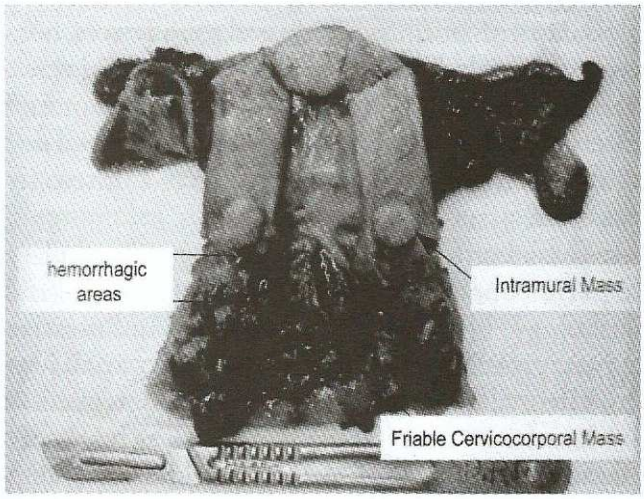

Figure 3. (ANTERIOR VIEW)
Cut section of the uterus revealed a 4 cm x 4 cm x 3 cm friable endocervical mass at the cervico-corporal junction with note of hemorrhagic areas. There is note of a 1 cm x 1 cm x 1 cm intramural mass with tan-white, whorled parenchyma on cut section.

Estimated blood loss during the entire operation was 1.3 liters and she was transfused 2 units of fresh whole blood and 1 unit of packed red blood cells. There was no gross residual tumor after the debulking.

On the 2nd postoperative day, she had 1 episode of dyspnea, accompanied by 5-6 pillow orthopnea and cough. Crackles on both lung fields were appreciated. She was given oxygen at 2-3 liters per minute via nasal cannula and was nebulized with Salbutamol. Furosemide 20 mg/IV was given. A chest x-ray was done revealing an increase in pleural effusion in both lung fields. An ultrasound-guided thoracentesis was done draining serosanguinous fluid, 620 cc and 100 cc from the right and left lungs, respectively. Pleural fluid cytology still showed atypical mesothelial cells. Post-thoracentesis ultrasound revealed very minimal fluid on both lung fields. The rest of the postoperative course was

uneventful and she was discharged on the 10th postoperative day.

Histopathologic Report showed:
Adenocarcinoma, poorly differentiated, with tumor infiltrating the outer half of the myometrium and involving the endocervical stroma and glands up to 1 cm from the external os; With Lymphovascular Space Invasion;
Uterine serosa was uninvolved with tumor
Metastatic Carcinoma, external surfaces of right and left ovaries, bilateral parametria, and cul de sac and sigmoid masses (Figures 4 & 5)
Peritoneal fluid, positive for malignant cells
Complex hyperplasia, endometrium
Fallopian tubes, unremarkable
*Endometrial vs endocervical vs gastrointestinal primary are considerations. Suggest immunohistochemistry studies with cytokeratin, vimentin, desmin and smooth muscle actin.

Immunohistochemistry studies utilizing Cytokeratin (Ae1/Ae3), Vimentin, Desmin, and Smooth Muscle Actin were subsequently performed. Cytokeratin (Ae1/Ae3) and Vimentin stained positive (Figures 6 & 7, respectively). Desmin and Smooth Muscle Actin stained negative (Figures 8 & 9, respectively). These results were consistent with an endometrial cancer as the primary tumor (Table I).

Based on the immunohistochemical panels, we diagnosed her to have Endometrioid Adenocarcinoma of the Endometrium, Poorly-Differentiated Stage IIIA. She was advised adjuvant treatment in the form of combination chemotherapy and pelvic radiotherapy. Unfortunately, she was lost to follow-up.

The final diagnosis of our patient is Endometrioid Adenocarcinoma, Endometrium Stage IIIA, Grade 3; S/P Total Abdominal Hysterectomy with Bilateral Salpingoo-ophorectomy, Tumor Debulking, Peritoneal Fluid Cytology and Bilateral Pelvic and Para-Aortic Lymph Node Evaluation.

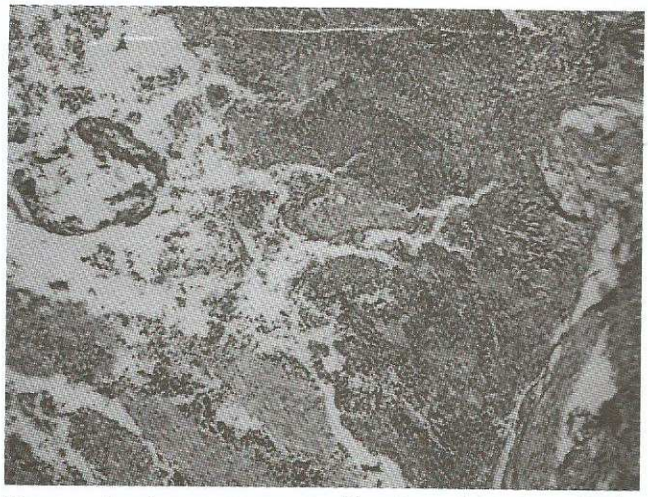

Figure 4. Low power magnification of section of the cervicoporal mass.

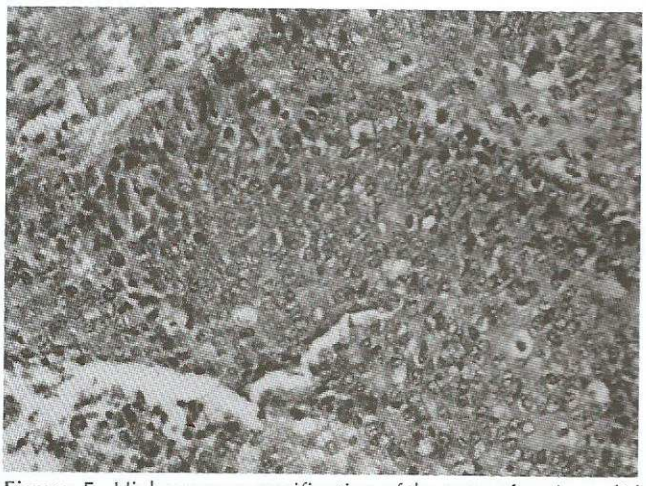

Figure 5. High power magnification of the tumor forming solid sheets of malignant cells without any glandular structure formation.

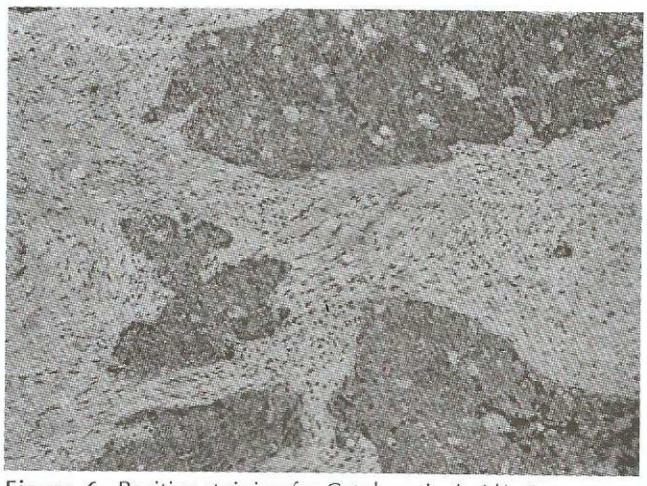

Figure 6. Positive staining for Cytokeratin Ae1/Ae3.

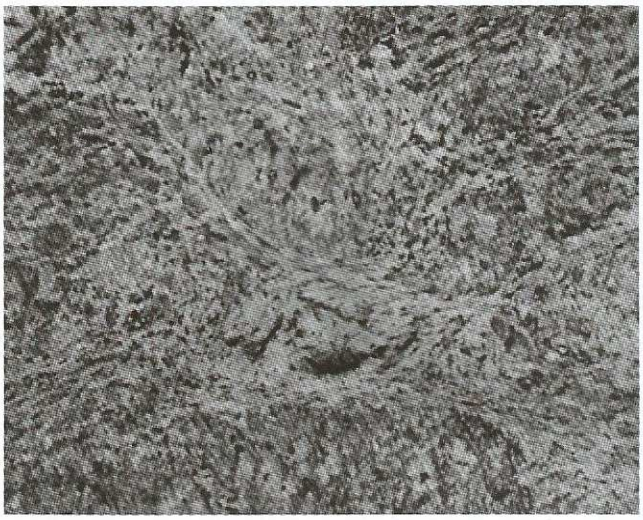

Figure 7. Positive staining for vimentin.

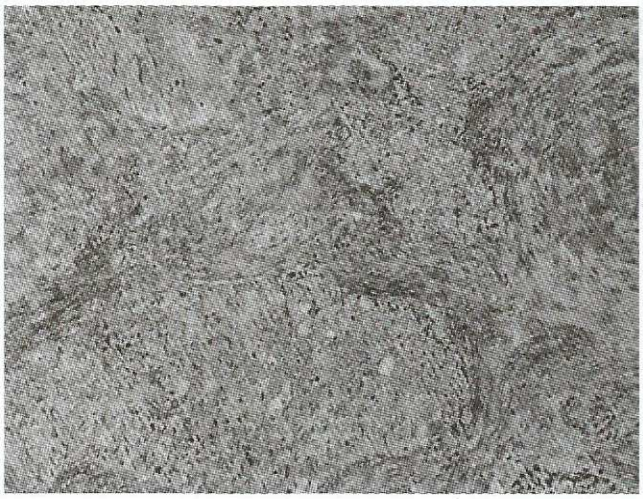

Figure 9. Negative staining for smooth muscle actin.

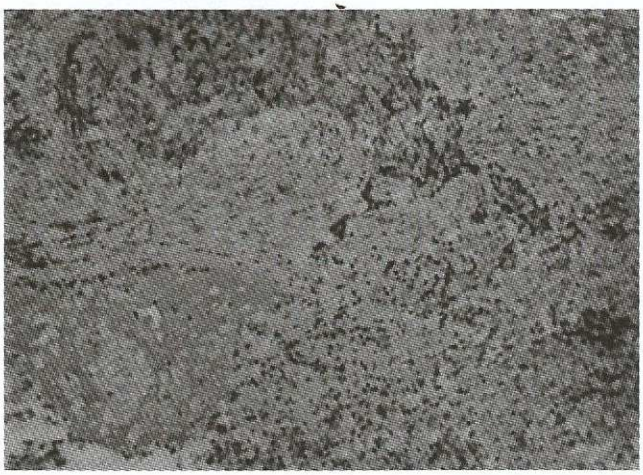

Figure 8. Negative staining for desmin.

Discussion

We are presented with a 49-year old, G4P3 (3013), with a history of menorrhagia and increase in abdominal girth, with findings of bilateral adnexal masses and massive ascites on ultrasound and pleural effusion by chest x-ray. CA-125 showed markedly elevated results.

Pre-operatively, the clinical presentation of abdominal distention secondary to ascites, abnormal vaginal bleeding, pleural effusion and diagnostic procedures showing bilateral adnexal masses, ascites, and a highly elevated serum CA-125 level were strong evidences for advanced ovarian carcinoma. A concomitant or second primary endometrial cancer was considered because our patient was perimenopausal, obese with abnormal vaginal bleeding. An elevated CA-125 could still point to endometrial carcinoma because it is usually elevated in advanced cases (Stage III/IV) of uterine cancer.[8] A differential diagnosis of metastatic carcinoma from a gastrointestinal source was also entertained because of ultrasound findings of bilateral solid adnexal

Table 1.

Antibody	Endometrial Adenocarcinoma	Endocervical Adenocarcinoma	Gastrointestinal Adenocarcinoma
CK Ae1/Ae3	(+)	(-)	(+)
Vimentin	(+)	(-)	(-)
Desmin	(-)	(-)	(-)
Smooth Muscle Actin	(-)	(-)	(-)

(Adapted from Diagnostic Immunohistochemistry. 2002. Ed. David Dabbs)[17]

masses (indicative of Krukenberg tumor). However, this was not a strong consideration because there were no gastrointestinal symptoms commonly associated with gastrointestinal carcinoma such as melena, hematochezia or intestinal obstruction.

In light of the clinical presentation of the patient and the various laboratory and diagnostic imaging tests performed, we highly considered advanced ovarian cancer as the major disease entity that could explain the entire clinical picture of the patient. The presence of pleural effusion and ascites indicate pleural and peritoneal reactions, respectively from tumor deposits. Vaginal bleeding from an endometrial pathology may also be due to direct metastases from an infiltrating ovarian carcinoma. On the other hand, a functioning ovarian tumor, such as a granulosa cell tumor, may also stimulate hyperplastic and dysplastic changes in the endometrium leading to abnormal uterine bleeding. A CT scan would have been helpful in determining the extent of the cancer. Had this procedure been employed, it might have shown findings different from the abdominal ultrasound. A CT scan could have shown normal bilateral ovaries, highlighted the abdominal masses and further elaborated on characteristics of the uterus. In advanced cases of pelvic malignancies, it may also determine retroperitoneal lymphadenopathy. These would enable us to choose the appropriate surgical management for the case. Financial constraints on the patient's part, however, prevented its use.

Since the patient presented with menorrhagia, an endometrial sampling was initially considered. However, since the patient would eventually undergo exploratory laparotomy with tumor debulking, performance of this diagnostic procedure would be moot and academic since the uterus would be removed as part of the cytoreductive process. Involvement of the uterus can be assessed intra- and post-operative and any specific procedure necessary for cases of endometrial cancer would be performed anyway because of the debulking surgery required of advanced ovarian cancer.

During surgery, intraoperative findings revealed both ovaries to be grossly normal (Figure 1), thus our initial consideration of ovarian carcinoma was ruled out. Upon further exploration, there was note of a mass at the cul-de-sac (Figure 2) and another mass adherent to the sigmoid colon. We were now faced with the possibility of a primary colonic malignancy. While awaiting the general surgeons to assess the patient, we decided to attempt cytoreduction of these pelvic masses. With the ease of removal of the sigmoid masses and the determination that there was probably only serosal involvement of the tumors (no infiltration into the muscularis layer), the consideration of a primary colonic malignancy posed an even bigger question. With symptoms of menorrhagia and an initial consideration of a concomitant endometrial carcinoma, we thus proceeded to perform TAHBSO. Cut section of the uterus showed a mass located in the cervicocorporeal junction (Figure 3). The location of the tumor further complicated our dilemma regarding the primary origin of the tumor. Since the lower third of the uterine corpus and the upper endocervical areas were involved, we were considering the possibility that the primary tumor could either be endometrial or endocervical in origin. Despite the relative ease in removing the tumors from the colon, primary gastrointestinal carcinoma still could not be totally ruled out.

The primary consideration was an advanced case of endometrial cancer. Our basis for this impression is the profile of our patient (perimenopausal and obese), symptoms of menorrhagia, and presence of a mass at the cervicocorporeal junction. Though ascites and pleural effusion are not common findings in endometrial cancer, they may be present in advanced cases. The presence of complex hyperplasia in the uninvolved endometrium also favors a primary endometrial carcinoma. It is not uncommon to see the spectrum from pre-invasive lesions (hyperplasia) to carcinoma in cases of endometrial adenocarcinoma.

Cervical cancer (endocervical type), on the other hand, may likewise present with abnormal vaginal bleeding. These tumors are usually of the adenocarcinoma type because they originate from endocervical glands, unlike the squamous cell type where its origin is from the ectocervical squamous

cells. Lateral parametrial spread of the cancer commonly occurs in these cases, a finding which was not present in our patient. Moreover, it is uncommon to have ascites and pleural effusion in cases of cervical carcinoma without parametrial or pelvic sidewall involvement.

Symptoms of primary colonic cancer are numerous and non-specific. Primary colonic malignancy was also considered as a differential diagnosis because of the presence of masses at the rectosigmoid area and the sigmoid colon. This was the least kind of pelvic malignancy considered in our patient's case for the following reasons. She did not have any abnormal signs and symptoms suggestive of a GI malignancy, such as melena, hematochezia or bowel obstruction. Furthermore, the biologic behavior of colonic malignancy shows intraluminal growth causing some form of obstruction prior to involvement of the muscularis and serosal layers and subsequently, intraperitoneal spread. Colonic cancer with intraabdominal spread (ascites and pleural effusion) is not compatible with the clinical picture and intraoperative findings of the patient.

We were thus faced with a problem regarding the origin of the primary tumor. Usually, the clinical presentation, physical examination and diagnostic imaging modalities allow the clinician to narrow down the possibilities and make a logical initial impression. This will aid in planning the definitive surgical procedure. The intraoperative findings then usually confirm the pre-operative impression. In this case, the intraoperative findings actually refuted the initial impression and left us with the predicament of not having a definitive diagnosis. The need to determine whether the tumor is of endometrial, endocervical or gastrointestinal origin is clinically important because the initial surgery may differ among these tumors. Moreover, adjuvant treatments vary among the three pelvic malignancies.

The distinction whether this is a primary endocervical, endometrial or colonic carcinoma can usually be made based on histopathologic findings. We can identify their respective precursor lesions or by the predominance of tumor in either the endocervical, endometrial or the colorectal component of the specimen. Initial histopathology though only revealed adenocarcinoma, poorly differentiated. This result did little to resolve the diagnostic dilemma regarding the question of primary tumor site.

In diagnostic surgical pathology, light microscopic evaluation of routine hematoxylin and eosin (H&E) stained sections provide sufficient information for accurate diagnosis in more than 90 percent of cases. Infrequently, however, the H&E findings alone fail to offer adequate diagnostic and prognostic information. The morphologic overlap of endometrial and endocervical adenocarcinoma can make these distinctions difficult in H&E.[14] In these cases, the use of ancillary techniques such as immunohistochemistry enables the surgical pathologist to extract additional information from fixed, deparaffinized specimens and to provide data critical to the clinical management of the patient.[19] In practice, immunohistochemical panels composed of markers against certain antigens have been used by many pathologists for determining the site of origin. In our case, we employed the use of immunohistochemistry to determine the origin of the primary tumor.

Immunohistochemistry combines anatomical, immunological and biochemical techniques for the identification of specific tissue components by means of a specific antigen/antibody reaction to provide a clearer diagnosis and to ensure optimal management of the patient's malignancy.[5] Suggested antibody panels to be tested in determining whether the origin of the tumor is endocervical, endometrial or colorectal adenocarcinoma include cytokeratin (CK), vimentin (VIM) and carcinoembryonic antigen (CEA). Endocervical adenocarcinoma has been reported to express p16 and carcinoembryonic antigen (CEA), whereas endometrial adenocarcinoma frequently shows estrogen receptor (ER), progesterone receptor (PR), and vimentin expression.[16] Colorectal cancer, on the other hand, typically stains with cytokeratins. There is good evidence that a limited immunohistochemical panel that includes VIM, ER, and CEA can determine the site of origin for the majority of these

problematic cases. The assumption is that an ER(+), VIM(+), and CEA (–) tumor is "almost certainly of endometrial origin," while "an endocervical source is very likely for the tumor that is ER(–), VIM(–), and CEA(+)."[16]

CEA has been touted as a good discriminatory marker for endometrial carcinoma versus histologic mimics, including endocervical carcinoma, because endometrial carcinoma is usually CEA-negative and endocervical carcinoma is usually positive.[14] CEA is more commonly expressed in endocervical adenocarcinoma (up to 100%) than in endometrial adenocarcinoma (up to 50%). However, some studies reveal that although endometrial adenocarcinoma is largely negative for CEA, the rate of CEA positivity varies in endocervical adenocarcinoma.[4] Moreover, it is a known fact that colorectal carcinoma also shows strong and diffuse staining to CEA. In our case, CEA was not used because the great degree of overlap precludes its clinical utility on an individual case basis.

Cytokeratin Ae1/Ae3 is a mixture of two different clones of anti-cytokeratin monoclonal antibodies, Ae1 and Ae3.[17] Both of these individual clones detect certain high and low molecular weight keratins. By combining these two reagents, a single reagent with a broad spectrum of reactivity against both high and low molecular weight cytokeratins is obtained.

Vimentin is an intermediate filament, and expressed in normal proliferative endometrial epithelial cells and also in the majority of endometrial carcinomas. Vimentin is characteristically positive in endometrial cancer. Vimentin staining may be a more useful immunohistochemical aid, as co-expression of low molecular weight cytokeratin and vimentin is seen in the majority of endometrial adenocarcinomas, but not in endocervical adenocarcinomas.[16] The co-expression of vimentin and low molecular weight cytokeratin can aid in the diagnosis of an endocervical versus an endometrial adenocarcinoma. Many endometrial adenocarcinomas, particularly those of the endometrioid type, express estrogen receptors (ER), progesterone receptors (PR) and vimentin. This typical immunophenotype is frequently considered a standard against which others are compared when immunohistochemistry is used for differential diagnosis. A study done by Reid-Nicholson, et al. demonstrated that although ER and PR were expressed in many endometrioid adenocarcinomas, a significant portion of these tumors were negative with vimentin expression as typical of endometrial carcinomas regardless of histologic subtype.[16] ER, PR and p16 expression are more illustrative of tumor type and degree of differentiation than they are of endometrial origin.[15] In contrast, the vimentin-positive/CEA-negative phenotype remained constant among all endometrial cancers. Studies also reveal that ER and PR expression in endometrioid carcinoma is significantly associated with both well-differentiated and early-stage tumors.[12] Our case involved a poorly-differentiated tumor and advanced stage disease. Therefore, the use of immunohistochemical stains for ER and PR would have been impractical and not very helpful since poorly-differentiated tumors stain very poorly or not at all for ER and PR.

In our patient, immunohistochemistry panel was positive for CK Ae1/Ae3 and Vimentin (Figures 6 & 7). This classifies the tumor under endometrial cancer because endometrial cancer stains positively for CK Ae1/Ae3 and vimentin as opposed to endocervical cancer which stains negative for CK Ae1/Ae3 and vimentin while colorectal cancer stains positive for CK Ae1/Ae3 but not for vimentin.

Other immunohistochemistry stains done on our patient were desmin and smooth muscle actin (SMA) which both came out negative (Figures 8 & 9). These immunohistochemistry markers are generally used to diagnose uterine sarcomas, particularly endometrial stromal sarcoma and leiomyosarcoma. Smooth muscle actin can be expressed in both stromal and smooth muscle cells but a lack of desmin expression is usually, but not always, sufficient to support endometrial stromal differentiation.[17] Desmin and SMA were done to rule out these uterine malignancies because the intraoperative findings showed an aggressive type of cancer suggestive of a sarcoma. The results of these stains, though, refuted sarcoma as the histologic type of our patient.

Some studies suggest that another immunostain, CD10, could be recommended for use in problematic cases. CD10 has been shown in several studies to be a reliable marker of endometrial stromal differentiation and thus might help in identifying the stroma accompanying an adenocarcinoma as endometrial versus endocervical.[9] Unfortunately, this hypothesis has not been thoroughly investigated in present studies and a recent article has noted that the stroma surrounding normal glands in the endocervix is often CD10-immunoreactive.[9]

Our final diagnosis after histopathology and immunohistochemistry was Endometrial Adenocarcinoma, Stage IIIA G3. Staging for endometrial carcinoma is surgico-pathologic and follows the FIGO classification (Appendix I). Our patient was diagnosed as Stage III because of the masses found in the sigmoid and cul-de-sac areas. These masses were metastases from the primary endometrial tumor.

How then could we explain the presence of these tumors from an endometrial primary? Metastases in endometrial carcinoma have four routes of spread: by direct extension, by lymphatic spread, by hematogenous spread, and through transtubal implantation. Direct extension of endometrial cancer is commonly seen as invasion into the myometrium and serosa and/or spread to the endocervix. This route is unlikely in our case because there was no direct invasion from the endometrium through the uterine serosa. Lymphatic spread occurs when tumor is present at the retroperitoneal (pelvic and/or para-aortic) and intraabdominal (mesenteric) lymph nodes. In our patient, palpation of the pelvic and para-aortic areas did not reveal any signs of lymphadenopathy. There were also no mesenteric lymph nodes adjacent to the cul de sac and sigmoid tumor.

The other two routes of metastases are more likely the possible reason for extension of the tumor beyond the uterus. Transtubal passage of exfoliated malignant cells from the endometrium may result in intraperitoneal implants that may continue to grow and proliferate. Usually though, the fallopian tube may have pathologic evidence of this form of spread, as in presence of microscopic or gross tumor within its lumen. Though there were no signs of tumor within the fallopian tubes, the ovaries were positive for metastatic carcinoma on their external surfaces, another evidence supporting transtubal spread. The metastases could have also occurred via hematogenous dissemination. This type of spread is responsible for metastases to the lungs, liver, bone and, in some cases, the brain. This could possibly been the route that brought about the sigmoid and cul-de-sac masses.

Primary surgical treatment for endometrial carcinoma is total abdominal hysterectomy with bilateral salpingooophorectomy (TAHBSO), peritoneal fluid cytology (PFC) and bilateral pelvic lymph node dissection (BLND) and para-aortic lymph node assessment. Advanced cases of endometrial carcinoma are treated on an individualized basis, with performance of cytoreductive surgery if technically feasible. Tumor debulking with TAHBSO would have been sufficient surgical procedures to perform in our patient.

Pelvic and para-aortic lymph node evaluation is essential in the staging of gynecologic malignancies. For advanced ovarian carcinoma, lymph node dissection may be considered as part of maximal cytoreduction. However, for advanced cases of cervical or endometrial cancers, lymph node dissection is mainly for staging purposes and its performance as part of tumor debulking has not shown survival benefits. For our patient, we elected not to perform pelvic and para-aortic lymph node dissection or sampling for two reasons. First, we ruled out primary ovarian carcinoma so any removal of lymph nodes will not offer any survival benefit as part of the tumor debulking process. Second, we already incurred a significant amount of blood loss intraoperatively so we decided to forego its performance because it has the potential for additional unwanted hemorrhage.

Postoperative adjuvant treatment also depends on the stage of the patient. For endometrial adenocarcinoma Stage IIIA G3, adjuvant treatment is also individualized depending on the patient's performance status, the location of metastatic and

residual tumor, and the patient's (and family's) desire for further treatment. It is not uncommon that palliative treatment gives way to supportive treatment since the prognosis for this stage is poor. For our patient, since she does not have any gross residual tumor, we planned on giving her combination chemotherapy followed by pelvic radiotherapy. The best choice of chemotherapeutic regimen is a combination of Cisplatin plus Doxorubicin or Carboplatin plus Paclitaxel. Unfortunately, she was lost to follow-up.

According to the FIGO Annual Report, endometrial cancer has an average five-year survival rate of 87.3% for stage I disease, 75% for stage II, 47.3% for stage III, and 16% for stage IV (Table 2). Five-year relative survival rates for endometrial adenocarcinoma also decline as the grade of the tumor increases (Table 3). Our patient, classified as stage IIIA G3, has a poor prognosis because although the overall five-year survival rate in stage IIIA is 60%, the presence of a poorly-differentiated tumor would definitely make her prognosis worse

Table 2. Five-year overall survival rate of endometrial carcinoma.

Stage	Survival %
IA	91%
IB	90%
IC	81%
IIA	79%
IIB	71%
IIIA	60%
IIIB	30%
IIIC	52%
IVA	15%
IVB	17%

(Adapted from FIGO Annual Report, years 1996-98. S. Pecorelli)[15]

Table 3. Five-year overall survival rate of endometrial carcinoma, stage I (surgical).

Grade	Survival (%)
1	91%
2	90%
3	81%

(Adapted from FIGO Annual Report, years 1996-98. S. Pecorelli)[15]

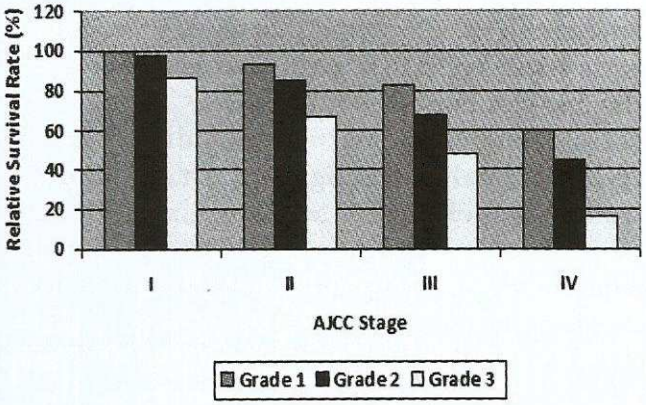

Figure 10. Adenocarcinoma of the corpus uteri: 5-year relative survival rate (%) by grade and AJCC stage (SEER modified, 3rd edition).
(Adapted from SEER Survival Monograph Cancer of the Corpus Uteri. Carol Kosary)[11]

(Figure 10).

Conclusion

In most cases of women with an abdominopelvic mass, a comprehensive clinical history and thorough physical examination together with appropriate diagnostic procedures are satisfactory to come up with an initial impression. This diagnosis is then usually confirmed through intraoperative findings. However, not all cases have textbook presentations regarding signs and symptoms. At times, there is a need to approach the case from all possible angles to come up with the best possible impression. Our patient had a variety of signs and symptoms that included the presence of ascites and pleural effusion with diagnostic examinations showing bilateral ovarian new growths and an elevated CA-125. These manifestations pointed towards a diagnosis of advanced ovarian carcinoma. Our initial impression, though, was refuted with intraoperative findings of normal-appearing ovaries and the presence of sigmoid and cul de sac masses. Our thoughts regarding the origin of the primary tumor were further complicated by the finding of a mass bordering the uterine isthmus and endocervix. Initial histopathology was unable to pinpoint the origin of the primary tumor. In this case,

immunohistochemistry studies were the crucial pathologic tests that provided the definitive diagnosis for our patient.

Although the majority of diagnoses in gynecological pathology are established on examination of routine hematoxylin- and eosin-stained sections, additional tests are occasionally required for diagnostic dilemmas. Immunohistochemistry is thus an important diagnostic adjuvant procedure that can be utilized to provide additional information in select problematic cases.

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Keynote Address, 2008 Joint Annual Convention, SGOP, PSCPC and PSSTD

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Thank you for the honor and pleasure of speaking to you today. When Dr. Rey delos Reyes and Dr. Gil Gonzalez asked me to give the keynote address in this year's convention, I asked "why me"? Then I realized that last year it was Dr. Manalo who was the keynote speaker and the year before that, it was Dr. Sotto. "Perhaps", I said, "You are asking me to give my valedictory address as well". Actually, I am deeply honored by this kind gesture of the organizers.

It was almost a quarter of century ago, in 1984 I think it was, that ten gynecologists under the inspired leadership of Dr. Luciano S. J. Sotto, got together at the Philippine Columbian to organize what is now the Society of Gynecologic Oncologists of the Philippines. I recall that for a while Dr. Sotto was somewhat reluctant but because of our enthusiasm and insistence, he was prevailed upon to go ahead with his idea and so our Society was born. Our vision then, as it is now, was a Filipino nation with its women free of gynecologic cancers. In order to accomplsh this goal we thought that we should first deepen our knowledge of gynecologic oncology and continue to professionally develop ourselves and others who share our vision. This mission is reflected in the objectives of the Society as you see here:

1. To establish, maintain and continously upgrade the standards of practice of gynecologic oncology in the Philippines
2. To disseminate basic and advanced knowledge about gynecologic cancers
3. To set standards of and support training in gynecologic oncology
4. To promote research in gynecologic oncology
5. To maintain good relationship with other societies of similar interests, both local and international
6. To promote the general welfare of its members

By the time we had the induction of our first set of officers with Dr.Constantino P. Manahan as our inducting officer we were nineteen including a pathologist, a radiation oncologist and a medical oncologist. Today, the Society has grown to a membership numbering one hundred seven (84 regular members and 23 affiliates) spread all over the country. Almost all of you, if not all, are graduates of the Gynecologic Oncology Program in the Philippine General Hospital. You perhaps, still recall that one of the criteria for admitting applicants to the program was to choose those from various regions of the country and from training and teaching institutions with the idea of spreading the specialty --- an idea which is consistent with the national health policy.

How have we fared with respect to our vision and our objectives? We, certainly, are still far from fulfilling our dream of the Filipina free from women's cancers; however, the superior scientific programs during our annual conventions and midyear seminars, the postgraduate courses that we offer not only to our members but also to physicians interested in our discipline, our research contests

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midyear seminars, the postgraduate courses that we offer not only to our members but also to physicians interested in our discipline, our research contests that, we hope, would stimulate our members and would be members to do more researches are all in fulfillment of our Society's goal to enhance its members' professional growth and welfare. It is not enough, however, that we engage in activities that will enhance our individual members' professional growth. We have to be relevant as well. The choice of some of our topics during our scientific meetings, our quarterly tumor conferences held in the different hospitals and attended by residents, the consultancy and the outreach programs that we do plus our participation in the information and educational health campaigns such as those sponsored by the Philippine Cancer Society are efforts of our Society to effectively diffuse the utilitarian knowledge of gynecologic oncology.

In my Baldomero Roxas lecture before the Philippine Obstetrical and Gynecological Society in 1999, I spoke about cancer of the cervix which as you very well know is the most common genital tract cancer and the most common cause of cancer deaths among our women. I emphasized then the importance of collaboration with the Department of Health and other civic and non-governmental organizations in the screening and early diagnosis of cervical cancer rather than do sporadic, opportunistic screening which many times result in wasteful and repeated screening that often targets the same population. With organized collaboration, more of the target population of women are reached which should result in reducing the morbidity of and mortality from this killer yet preventable disease.

I am very glad that of late our Society has allied itself with the Cervical Cancer Prevention Network Program (CECAP) in the latter's endeavor in organized screening, early diagnosis and treatment of cervical cancer. This, indeed, is one specific way of furthering national health good.

So, my dear esteemed colleagues, we are on the right path of fulfilling our objectives but we should not rest on our laurels. Let us continue and try to do even more.

Before I close, I would like to tell you that it warms my heart, as I am sure, it does the hearts of Dr. Sotto, Dr. Manalo, Dr. Borja, Dr. Benitez and the others, everytime a young colleague expertly gives a lecture in scientific meetings or ably expound on a topic during interactive discussions. This assures us that we need not worry about fading away because the Society will be in good hands.

Finally, do you know that our Society is admired by many? It is because of the wonderful fellowship among our members. I hope and trust that you will continue the admirable work ethics that we have observed, the culture of friendly competition and refreshing camaraderie that our Society is known for.

Indeed, my dear colleagues you do us, your elders, proud.

Again, thank you and good morning.