Ovarian Involvement in Cervical Cancer

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While cervical cancer involves women in their forties and fifties, a significant number of women who are under 40 years of age, are diagnosed to have invasive cervical cancer. It is in these young women whom radical surgery with ovarian preservation has been advocated to enable them to maintain continued ovarian function, preventing the complications of surgical menopause. Considering that most of these patients belong to the lower socio-economic strata and thus the cost of hormonal replacement therapy would be prohibitive, ovarian preservation will be an inexpensive alternative. The benefit of continued ovarian function must, however, be weighed against the risk of microscopic metastatic disease and the later development of ovarian malignancy.

Objective

General Objectives

To confirm whether ovarian preservation is justified in young patients who undergo radical hysterectomy for early stage cervical carcinoma.

Specific Objectives

1. To determine the incidence of ovarian metastasis in early stage carcinoma of the cervix.
2. To determine whether the stage of the disease, histologic cell type or lymph node involvement affect the incidence of ovarian metastasis.
3. To determine the incidence of ovarian recurrence in patients whose ovaries were retained after radical hysterectomy.

Materials and Methods

The medical records of 215 patients who underwent radical hysterectomy with bilateral pelvic lymphadenectomy for invasive cervical cancer between January 1986 to August 1993 at the Philippine General Hospital were reviewed. Of the 215 patients, 136 had unilateral or bilateral salpingo-oophorectomy and 79 had ovarian preservation with or without transposition. Seventeen cases of cervical cancer patients who had bilateral adnexectomy after exploration for ovarian new growth were also included. The records were reviewed with emphasis on the age, gravidity, parity, stage of the disease, histologic cell type and ovarian and lymph node involvement.

Results

Table 1 shows the profile of patients who underwent radical hysterectomy with bilateral lymph node dissection and bilateral salpingo-oophorectomy. Radical surgery was limited only to Stage IB and IIA disease.

Table 2 shows the profile of patients who underwent laparotomy and bilateral salpingo-oophorectomy. This group included patients with advanced disease.

Only 111/136 (81.6%) of the patients who had radical surgery received postoperative radiotherapy. All of those who had bilateral adnexectomy received complete radiotherapy.

There were no metastasis to the ovaries on histologic review in all 153 patients who had radical surgery or bilateral salpingo-oophorectomy. (Tables 1 & 2). It may be of interest to know that patients in the advanced stages of the disease who only had bilateral salpingo-oophorectomy had no ovarian involvement. (Table 2).

In spite of the presence of lymph node metastasis in 27 (23.3%) patients with Stage IB disease and 4 (20%) with Stage IIA disease, no involvement of the ovaries among these patients was found. (Table 3).

Regardless of the histologic cell type of the cervical lesion, ovarian metastasis was not seen.

Non-metastatic ovarian neoplasms identified in this series included the two patients with serous cystadenoma and one each with endometrial cyst, fibroma and oophoritis with pyosalpinx. These patients represented 3.2 percent of the total subjects in this study.

Table 1. Profile of patients who had radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy (n = 136 patients).

Age	44.8	(30-60 y.o.)	
Gravidity	5.11	(0-16)	
Parity	4.7	(0.13)	
Stage			Ovarian Mets
IB	116	(85.3%)	0
IIA	20	(14.7%)	0
Histologic Type			
Squamous cell	100	(73.5%)	0
Adenocarcinoma	30	(22%)	0
Adenosquamous	5	(3.6%)	0
Small cell CA	1	(0.7%)	0

Table 2. Profile of patients who had laparotomy with bilateral salpingo-oophorectomy (n = 17 patients).

Age	44.4	(32-57 y.o.)	
Gravidity	4.9	(0.10)	
Parity	4.4	(0.9)	
Stage			Ovarian Mets
IB	7	(41.1%)	0
IIA	3	(17.6%)	0
IIB	5	(29.4%)	0
IIIB	1	(5.8%)	0
IVA	1	(5.8%)	0
Histologic Type			
Squamous cell	14	(82.4%)	0
Adenocarcinoma	3	(22%)	0

Table 3. Incidence of lymph node and ovarian metastasis in relation to stage (n = 136 patients).

Stage	LN Mets	Ovarian Mets
Stage IB	27/116 (23.3%)	0
IIA	4/20 (20%)	0
Total	31/136	0

Table 4. Incidence of lymph node and ovarian metastasis in relation to histologic cell type (n = 136 patients).

Histologic Cell Type	LN Mets	Ovarian Mets
Squamous cell	25/100 (25%)	0
Adenocarcinoma	5/30 (16.6%)	0
Adenosquamous	1/5 (20%)	0
Small cell CA	0/1	0

Upon review of the 215 patients who underwent radical surgery, 79 patients had one or both ovaries retained with or without ovarian transposition. Only 9 patients who had no ovarian transposition received postoperative radiotherapy, leaving 70 patients at theoretical risk from undetected micrometastases in the retained ovaries. In 13 (18.6%) of these 70 patients, recurrence with pelvic component did develop occurring as follows: 8 in the vagina, 3 in the pelvic wall and 2 in the parametria. The high cost of diagnostic procedures like the CT-scan and MRI, which most of our patients could not afford, limited our assessment of recurrent disease. We therefore cannot totally rule out the possibility that the recurrence from the pelvic wall or parametria were not from the ovaries.

As to the histologic cell type, pelvic recurrence occurred as follows: clear cell carcinoma 0/1, adenosquamous carcinoma 1/1, adenocarcinoma 3/17 and squamous cell carcinoma 9/51.

For those patients who underwent ovarian transposition and therefore at risk for abdominal recurrence if ovarian metastases were present, no abdominal recurrence was found regardless of stage or histologic cell type.

Discussion

Several recent studies confirmed the impression in the older literature that ovarian spread of squamous cell carcinoma is rare.[5,7]

The incidence of subsequent development of ovarian malignancy after hysterectomy has been estimated to be 0.2 percent to 1.3 percent. Reoperation for new pathologic material arising in ovaries retained at radical surgery was required in 7.6 percent to 1.2 percent of patients. It would seem that the development of subsequent ovarian malignancy is not a prohibitive risk in terms of ovarian preservation at the time of radical surgery for carcinoma of the cervix.

McCall, et al. were unable to find a case of ovarian metastasis in early stage squamous carcinoma of the cervix. His finding was confirmed by Yagi, Webb[7] and Parents.[5] McCall, Baltzer and Shingleton-Orr[6] recommend ovarian preservation based on their incidence of ovarian metastasis in early stage cervical carcinoma.

Recent studies however dispute these findings. In a large scale study done by the Gynecologic Oncology Group in 1992,[7] they identified ovarian involvement in 0.5 percent of patients with squamous cell carcinoma and 1.7 percent of those with adenocarcinoma. No patient with adenosquamous carcinoma (82) or other histologic types (17) had ovarian metastasis. Although the frequency of metastasis was greater among patients with adenocarcinoma, this was not statistically significant.

In conclusion, the present study confirmed reports in literature that the incidence of ovarian metastasis in early stage cervical cancer is nil. We did not find microscopic foci of ovarian metastasis in early stage cervical cancer among patients who had radical surgery or even in patients with advanced stage disease who only had bilateral salpingo-oophorectomy.

The histologic cell type also did not affect the incidence of ovarian metastasis. No increased risk of pelvic or abdominal recurrence was demonstrated in this series of patients with retained ovaries whether the cell type is adenocarcinoma or squamous cell carcinoma. Even in the presence of lymph node metastasis, ovarian metastasis was absent.

Based on all these findings, it would be reasonable to conserve normal-looking ovaries in young women undergoing radical hysterectomy for early stage cervical cancer regardless of histologic cell type. Preservation of the ovaries among young patients who made up 33.8 percent in this series, will prevent surgical menopause. Since most of the these patients belong to the low socio-economic strata, ovarian preservation would save them the expense of hormonal replacement therapy.

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Fate of the Transposed Ovaries in Early Cancer of the Cervix Following Radical Hysterectomy and Radiation Therapy

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Ovarian preservation is one of the most compelling reasons for choosing radical hysterectomy as primary treatment instead of radiation in young women with early stage cervical cancer.[1] Loss of ovarian function interferes seriously with the normal life of a young woman. In the past, complete castration, whether by irradiation or by surgery was ordinarily accepted as inevitable in the course of treating cancer of the cervix, regardless of the patient's age. This attitude arose due to the gynecologists' fervent desire to offer patients the greatest possible chance for cure, the development of minor or even major side effect notwithstanding. The primary goal of any gynecologist treating a patient with malignancy is to cure his patient, if it is at all possible.

Although cancer of the cervix commonly occurs in women aged 40-60 years old, more recent years have shown a steady rise in the incidence of cervical intraepithelial neoplasia and cancer of the cervix in women in their '20s and '30s,[2,3,4] necessitating further the need to offer a means of ovarian conservation. Surgery alone, in the form of radical hysterectomy and pelvic lymph node dissection may not always be enough as the sole means of management for cervical cancer. In some patients, adjuvant pelvic radiation may be recommended for large lesions (> 2 cm),[5] deep stromal invasion, involvement of resection margin with tumor and/or pelvic nodal metastasis.[6] This, however, should not hinder the practice of ovarian conservation. Another point to ponder upon is the rate of ovarian metastasis in cervical cancer. Is it negligible enough to make the practice of retaining the ovaries feasible? The answer to this is yes- Henriksen,[7] McCall[8] and Sutton[9] all have stated it would seem reasonable to conserve normal-appearing ovaries in young women undergoing radical hysterectomy for cervical cancer whether it be squamous cell, adenocarcinoma, adenosquamous carcinoma or clear cell carcinoma provided there are no other extracervical spread.

It is primarily for these reasons that this study was undertaken. Our specific objectives were as follows:

1. To evaluate function of the transposed ovaries after radical hysterectomy and adjuvant radiotherapy using clinical parameters and laboratory parameters like the maturation index (MI) in Pap smears and serum estradiol assay.
2. To determine the levels of the transposed ovaries and to correlate their positions relative to the radiation field in maintaining ovarian function.
3. To look into the complications encountered with transposition of the ovaries.
4. To offer information for improvement of the technical procedure of ovarian transposition in women with cervical cancer in whom ovarian conservation is deemed necessary.

There are two phases involved in this study. Phase I is a preliminary report written in 1993 by Dr. Wilma Torres, et al.[10] covering 10 patients who underwent radical hysterectomy and pelvic lymphadenectomy with transposition of one or both ovaries from August 1990

to January 1992. All 10 patients had one or both ovaries transposed lateral and caudal beyond the pelvic brim. Results were evaluated in only 8 of the 10 patients and revealed that 4 (50%) out of the 8 patients had estradiol levels within the pre-menopausal range while the other 4 (50%) had levels in the menopausal range - 2 of whom had menopausal complaints and were placed on estrogen replacement therapy. Three out of the 4 patients with menopausal estradiol levels had ovaries within the radiation field. No complications were noted from the said procedure of ovarian transposition. To increase the success of ovarian conservation, an improved technique was suggested and carried out for ovarian transposition whereby the ovaries are transposed 4 cms beyond and lateral to the iliac crest. This report represents the results of ovarian transposition using the modified technique and covers Phase II of the study. (Figures 1, 2 & 3)

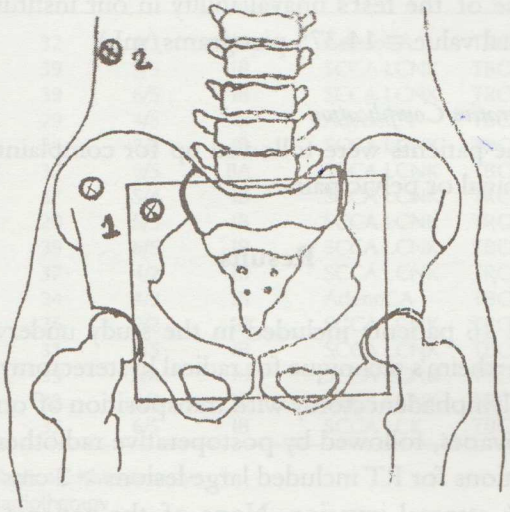

Figure 1. Diagramatic representation showing the (AP-PA) whole pelvic radiation therapy field relative to the position of the transposed ovary.

Position 1: Represents Suboptimal Placement (Phase 1)
2: Represents Optimal Placement (Phase 2)

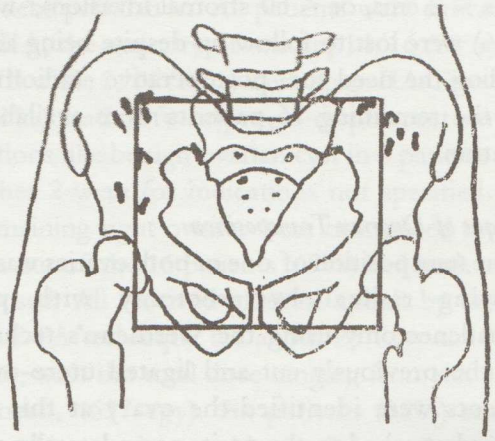

Figure 2. Liga clip markers representing the transposed ovaries schematically presented in a single pelvis. (Phase 1).

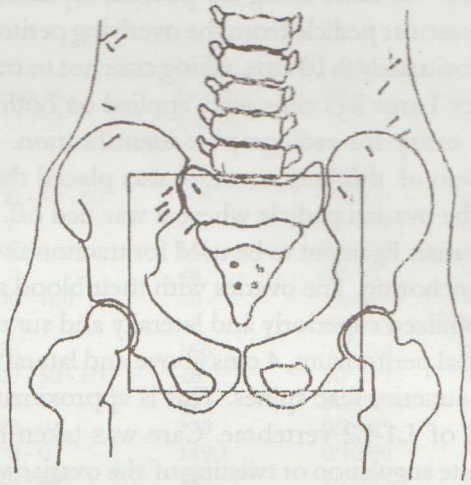

Figure 3. Liga clip markers representing the transposed ovaries schematically presented in a single pelvis. (Phase II).

Materials and Methods

Patients

Between February 1992 and 1995, ovarian transposition was carried out in 27 patients with stage IB-IIA cervical cancer in the section of Gynecologic Oncology, Department of Obstetrics and Gynecology, Philippine General Hospital. Patients' requirements for inclusion in the study were: 1) patients with histologically proven diagnosis of invasive cervical cancer Stage IB through IIA who underwent radical hysterectomy with pelvic lymphadenectomy and transposition of one or both ovaries with post-operative radiotherapy and 2) age less than 40 years.

Of the 27 patients who underwent radical hysterectomy with ovarian transposition 7 (25%) did not require postoperative radiotherapy (had small

lesions < 2 cms, or < 50 stromal invasion),[5] while 4 (14.8%) were lost to follow up despite being advised regarding the need for postoperative radiotherapy. Only the remaining 16 patients were available for evaluation.

Technique of Ovarian Transposition

The transposition of one or both ovaries was done following radical hysterectomy with pelvic lymphadenectomy using the Wertheim's technique. First, the previously cut and ligated utero-ovarian ligaments were identified-the ovary at this point remained attached to the peritoneum laterally and to its own vascular pedicle (the infundibulopelvic ligament). The ovary was elevated and its vascular pedicle kept tense as the ureter was identified. Dissection was done along the pedicle, separating the ovarian vascular pedicle from the overlying peritoneum for approximately 8-10 cms, taking care not to transect the ureter. Large liga clips were applied on both poles of each ovary for radiographic identification. Upon completion of this step, a suture was placed thru the end of the ovarian pedicle where it was tied off at the utero-ovarian ligament to be used for traction and later on, for anchoring. The ovaries with their blood supply were mobilized superiorly and laterally and sutured to the parietal peritoneum, 4 cms above and lateral to the anterior superior iliac spines. This is approximately at the level of L1-L2 vertebrae. Care was taken not to cause acute angulation or twisting of the ovarian vessels at the time of transposition. Simulation x-rays were taken postoperatively to determine the level of the ovaries as indicated by the liga clip markers attached to them.

Radiotherapy and Docimetry Calculation

External radiation was given to the patients using the Cobalt 60 AP-PA technique. The doses ranged from 4000-5600 centigray (cgy), in fractions of 180-200 cgy/day. The size of the radiation field varied from 15-18 x 15-18 cms. The upper margin of the field was at the level of the sacral promontory, while the lower margin was at the level of the inferior border of the symphysis pubis. The right and left lateral margins were along the inner third of the right and left femurs respectively. All patients had simulation x-rays. Port films were taken to check the port size and the location of the transposed ovaries. For the docimetry, the ovaries transposed within the radiation field received 100 percent radiation. As the distance of the transposed ovaries increased away from the radiation field, the scatter doses received by the ovaries decreased from 90 to 100 percent.

Subjective Evaluation of Menopause

The menopausal state was ascertained by subjective complaints of hot flushes, dyspareunia and dryness in the vagina.

Laboratory Evaluation

Three or more months after the last dose of radiotherapy, vaginal and cervical smears were evaluated for maturation index (MI) using the Papanicolau stain. Evidences of the pre-menopausal state include high levels of intermediate and superficial cells. Serum estradiol levels were also taken at this time. Sera of patients were ran at the St. Luke's Medical Center because of the test's unavailability in our institution. (Normal value = 14-375 picograms/mL).

Postoperative Complication

The patients were followed up for complaints of abdominal or pelvic pain.

Results

All 16 patients included in the study underwent the Wertheim's technique for radical hysterectomy and pelvic lymphadenectomy with transposition of one or both ovaries, followed by postoperative radiotherapy. Indications for RT included large lesions > 2 cms and > 50% stromal invasion. None of the patients had positive tumor in the pelvic lymph nodes. The age range was 24-39 years with a mean age of 33 years. (Table 1). All women were multigravidas with 2-6 pregnancies achieved (mean = 4.6). Cervical cancer was associated with pregnancy in 2 patients. Case no. 4 was first seen at 25 1/7 weeks age of gestation for vaginal bleeding. Gross examination of the cervix revealed a fungating, friable cervical mass which on biopsy revealed adenocarcinoma. Pregnancy was allowed to continue until 33 4/7 weeks age of gestation when a primary classical cesarean section was done and delivered a live baby girl with Apgar score of 7-8, a weight of 1850

gms and a pediatric age of 33 weeks. She subsequently underwent a radical hysterectomy with pelvic lymph node dissection and transposition of both ovaries as well as postoperative complete radiotherapy (External Cobalt + Brachytherapy). Unfortunately, there was disease recurrence 8 months after treatment and the patient was lost to follow up and presumed to have succumbed after 10 months of follow up. Case no. 11 had a first trimester spontaneous abortion, 3 months before the diagnosis of cervical cancer was made. She was given external cobalt postoperatively but developed recurrent disease 4 months after RT and was lost to follow up soon after. Twelve (75%) patients had SCCA LCNK, while only 1 (6%) had SCCA LCK. Endocervical adenocarcinoma was seen in 3 (19%) of the patient population. All patients were either Stage IB or IIA, the majority of whom, 14/16 (88%) were Stage IB while 2/16 (12%) were Stage IIA. Five out of 16 (31%) had left salpingo-oophorectomy for indications like benign ovarian cyst in 3 patients while the other 2 were for indications not specified. Only the remaining right ovaries were transposed in them. Eleven out of the 16 patients (69%) had both ovaries transposed. All received external cobalt by the two-field AP-PA technique for about 25 days at 180-220 cgy/day, with the total dose ranging from 4000-5600 cgy (mean, 4637 cgy). Six patients (38%) received additional brachytherapy. None of the patients in this study had positive pelvic lymph nodes, therefore, none received extended field radiotherapy. (Table 1)

Table 1. Profile of women who underwent RH + ovarian transposition + RT.

Case No.	Age	G/P	Stage	Hx Type	OR	RT Dose Received	Dosimetry R - L (%)	Estradiol (pg/mL)	MI	Menopausal S & S
1	32	4/3	IIA	AdenoCA	TRO	5000	50 - 60	112	0/95/5	N
2	39	5/5	IB	SCCA LCNK	TBO	5600	100 - 50 - 60	140	3/22/75	N
3	39	6/5	IB	SCCA LCNK	TRO	4600	100	<8	90/10/0	N
4	29	4/3	IB	AdenoCA	TBO	11320	10 - 0	116	0/80/20	N
5	24	2/2	IB	SCCA LCNK	TBO	4500	0	<8	0/5/95	N
6	32	5/5	IIA	SCCA LCNK	TBO	4400	100 - 100	<8	12/48/40	Y
7	37	5/4	IB	SCCA LCNK	TRO	5000	100	<8	0/35/65	N
8	29	5/3	IB	SCCA LCNK	TRO	5000	20	150	0/50/50	N
9	39	6/5	IB	SCCA LCNK	TBO	10100	100 - 50 - 60	<8	50/30/20	Y
10	37	4/2	IB	SCCA LCNK	TRO	5000	80	<8	50/40/10	Y
11	24	4/3	IB	AdenoCA	TBO	5000	20 - 0	128	0/25/75	N
12	26	2/2	IB	SCCA LCNK	TBO	9990	0 - 0	149.1	0/10/90	N
13	31	6/5	IB	SCCA LCNK	TBO	7800	20 - 30	125	5/70/25	N
14	35	6/4	IB	SCCA LCNK	TBO	7495	10 - 10	91.6	0/10/90	N
15	32	3/3	IB	SCCA LCNK	TBO	5110	0 - 10	110	0/20/80	N
16	37	6/5	IB	SCCA LCK	TBO	9990	10 - 0	140	0/25/75	N

RH - Radical Hysterectomy
RT - Radiotherapy
TRO - Transposition, Right Ovary
TBO - Transposition, Both Ovaries
SCCA LCNK - Squamous Cell CA, Large Cell Non-Keratinizing
SCCA LCK - Squamous Cell CA, Large Cell Keratinizing
Case No. 4 & 11 - Associated with Pregnancy and lost to follow-up with recurrent disease
Case No. 8 & 16 - Lost to follow-up with no evidence of disease
Case No. 5, 6, 7, 9 & 10 - on estrogen replacement therapy

Of the 16 patients, docimetries as described ranged from 0-50 percent in more than half [n = 10 (62.5%)] of them and all belonged to the pre-menopausal group. These 10 patients had only an average of 20% scatter dose to their ovaries. Cases no. 12, 14 & 15 received blocks to the pelvis during radiation therapy. Case no. 2 who had both ovaries transposed had 100% radiation exposure to her R ovary vs. 50-60% to the L ovary. The R ovary was noted to be within normal levels of estradiol. These data ran compatible to the

absence of subjective menopausal signs and symptoms in this group as well as within normal levels of serum estradiol at 91.6 - 149.1 pg/mL (mean = 126.1 pg/mL). The MI also taken from their Pap smears show predominantly intermediate and superficial cells - also indicators of estrogen secretion, although this alone may not be conclusive evidence of ovarian function.

Six of the 16 patients (37.5%) had menopausal levels of serum estradiol at < 8 pg/mL. Five out of the 6 patients had docimetries ranging from 80 - 100% (mean = 96%) with only one having 0% radiation exposure and yet with menopausal estradiol levels. Despite these values 3 (50%) of these 6 patients did not manifest with any signs nor symptoms of the menopause while the other 3 (50%) experienced either hot flushes, dyspareunia or dryness in the vagina. Maturation indices showed equivocal results, with 2 patients (Case no. 5 and 7) showing predominantly superficial cells. Case no. 5 is the 24 y.o. patient with 0% docimetry to both ovaries and yet with < 8 pg/mL of estradiol. Five of the 6 patients with menopausal estradiol levels have since been given estrogen replacement therapy and have remained asymptomatic since then.

In this phase of the study, mean follow up was 23 months. Four have since been lost to follow up for more than 1 year - 2 with recurrent disease and presumed to have succumbed and 2 with no evidence of disease. None of the patients had developed any complications resulting from the ovarian transposition itself-like torsion of the ovaries, injury to the ovarian vessels, bowel strangulation and other complications like ovarian cyst formation. Case no. 9 however, developed a rectovaginal fistula secondary to radiation therapy and now has a colostomy but is otherwise asymptomatic. Case no. 14, on the other hand, developed a ureterovaginal fistula postoperatively requiring surgical correction. She is alive and well today.

Discussion

Since the mid - 1800's, surgeons have relocated ovarian tissue. First, in the treatment of uterine retrodisplacement, later to avoid entrapment of scar tissue and more recently, for placement out of a radiation field. In 1958, McCall, et al.[8] have demonstrated that preservation of the ovaries at the time of radical hysterectomy and pelvic lymphadenectomy for Stage I and II cancer of the cervix would not compromise patient survival. Since then, several procedures have been introduced to preserve ovarian function in patients undergoing radiation. This study depicts one such procedure whereby the ovaries are transposed outside the radiation field in the pelvis, above the anterior superior iliac spine. Permanent sterilization of the ovaries would require a single acute dose of about 400 cgy or a fractionated regimen consisting of about 1500 cgy over 10 days.[11] With the use of computer dosimetry, Webb, et al.[12] calculated the dose to transposed ovarian tissue that would result from various treatment conditions on a 6 megavolt linear accelerator treating a pelvic field to a central dose of 4500 cgy. In a patient with a 17 cm anteroposterior separation (similar to our patients), the dose to the ovaries would be 158 cgy (AP field). Positioned above the iliac crest, as was done in our study patients, there is little danger of the ovarian tissue falling within the direct portal beam. The calculated doses to the transpositioned ovarian tissue results only from scatter and is spread over the total course of treatment, usually 5 - 6 weeks. With this in mind, the dose to the ovaries would be well below that believed to suppress ovarian function. In ideal set ups where linear accelerators are used and pelvic blocks are readily available, success rates for ovarian transposition are almost 100 percent. In our study, only 10 (62.5%) out of 16 study subjects demonstrated normal estradiol levels but this is a significant indicator of success for the modified technique of ovarian transposition described. Phase I of this study revealed a salvage rate for the ovaries of only 50 percent. Failure of ovarian function in the 6 patients (37.5%) may have been secondary to the fall of the ovaries from the parietal peritoneum it was anchored so that they entered the radiation field, or these may have been secondary to faulty technique. Also, because of the lack of adequate pelvic blocks in our institution, scatter to the transposed ovaries may be higher than expected. These data are comparable to the data gathered by Husseinzadeh, et al. in 1994[13] where 7 (64%) of their patients had preserved ovarian function after transposition and radiation therapy. All patients received ≤ 500 cgy to the ovaries.

The use of estradiol levels is a good index to test ovarian function since this hormone is secreted chiefly by the ovaries. On the other hand, vaginal cytologic smears are not a reliable index of the amount of estrogen necessary to keep the patient comfortable or symptoms free. Randall[14] has shown that over 50 percent of women 5 - 10 years after a normal menopause will show some estrogen effect in their vaginal smears. This has been thought to be due to secretions by the adrenal cortex and peripheral conversion of androstenedione to estrone in adipose tissues. It is generally conceded, however, that estrogens from sources other than the ovary are usually not adequate to prevent the typical catabolic sequelae associated with aging.

Although complications can occur as a result of ovarian transposition - including torsion of ovarian pedicle and direct injury to the vessels, these complications are practically nil in the hands of good and able surgeons.

Survival rate of patients studied may only be obtained after years of observation following radical hysterectomy. The longest observed survival in this series was only 49 months.

Conclusions

Ovarian transposition should be considered as part of the treatment plan for young patients with invasive cervical cancer receiving pelvic radiation. Ovaries should be moved superiorly and laterally at about L1-L2 vertebral levels for optimal benefit. This procedure of ovarian transposition is generally easy to do and does not interfere with radical hysterectomy.

Radiation doses to the ovaries should be limited to < 500 cgy. Regardless of shielding, if the para-aortic area is treated with extended field radiation for metastatic disease, the ovaries will receive a higher dose of radiation. Thus, transposition should not be done.[13] In our country, ovarian transposition plays a pivotal role in alleviating the added financial burden that may be brought about by castration. With the rising cost of hormonal replacement therapy, many young patients are left to suffer the effects of early menopause because of their inability to procure these drugs. Ovarian transposition should therefore be done when indications are present, to do so - not only to abate further financial burden, but also to maintain the patient's sense of well being and health. Dr. McCall in 1958 stated so well when he said, "Anatomically adequate but less heroic 'en bloc' dissections might permit us to report the number of years our patients have lived, rather than the number of years they have survived,"[8]

Recommendations

1. Use of pelvic blocks should be done routinely in all patients with transposed ovaries and even in those young women who did not have the benefit of ovarian transposition but do undergo pelvic radiation.
2. Further study should be made to determine applicability of ovarian transposition in young patients with more advanced Stage IIB - III lesions and/or pelvic nodal metastasis.

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The Effects of Early Removal of Indwelling Foley Catheter After Radical Hysterectomy

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Traditionally, indwelling foley catheter is retained for 3 weeks after radical hysterectomy with pelvic lymphadenectomy in patients with cervical cancer or endometrial cancer with cervical extension. This catheter is associated with urinary tract dysfunctions as well as patient discomfort. Our objective was to determine the effect of early removal of indwelling urinary catheter after radical hysterectomy. Specifically, 3 groups were compared based on subjective pain assessment, first spontaneous void, post void residual (PVR) urine and rate of recatheterization. **Methods**: From January, 2005 to July, 2005, 21 patients were distributed into a matched controlled clinical trial which includes one week (Group 1), two week (Group 2), and three week (Group 3) catherized groups. Total urine volume as well as post voiding residual volume was determined before and after surgery. Percentage of PVR urine was computed. At the OPD, on the basis of the study assignment, the catheter was permanently removed depending on the PVR percent. First spontaneous voiding and pain assessment were considered. **Results**: Based on pain assessment, Group 2 showed a statistically significant report before and after radical hysterectomy with a mean score of 2.0 (SD 1.4) to 0.5 (SD 0.8). (Paired t test, p value = 0.01). There was an increase in urine volume, either total or residual, when it was measured before and after surgery, however, both revealed non-statistically significant findings (One way ANOVA, p value = 0.23 vs 0.40; p value = 0.41 vs. 0.23) Percentage of post voiding residual urine was the basis of permanent removal of foley catheter. In Group 1, there was an increase of PVR percent from 25.2% to 45.3% noted before and after radical hysterectomy. This finding was statistically significant (Paired t test, p value = 0.04). At the outpatient department, the indwelling foley catheter was removed and the patient was allowed spontaneous voiding. The time of first voiding of urine after removal of catheter was measured. The shortest mean time interval from the removal of foley catheter to spontaneous voiding was noted in Group 2 at 71.5 min (SD 41.4) while Group 1 and Group 3 had 152.4 min (SD 53.1) and 120.2 min (SD 58.7), respectively. This finding was statistically significant. (One way ANOVA, p value = 0.03.) Among all groups, the rate of the catherization was inversely proportional to the duration of catheter removal however the result was not statistically significant. **Conclusion:** There was no significant change in the urine volume, post void residual urine volume and post void residual urine percent before and after radical hysterectomy as well as the rate of re catherization. However, the time of first voiding was shortest in Group 2. In this same group, pain assessment was significantly improved based on Wong Scale and Self Report Scale. Both findings were statistically significant.

Key words: Foley catheter, radical hysterectomy

Radical hysterectomy with pelvic lymphadenectomy plays a significant role in the treatment of selected gynecologic malignancies. One of the preoperative preparations routinely done for extensive hysterectomy is the placement of indwelling urinary catheter and keeping it for 3 weeks after the procedure, changing of which is on a weekly basis. Its uses include improvement of the exposure of the urinary bladder and reduction of injury to the urinary system during the surgery, assessment of urinary output and prevention of postoperative urinary retention. This indwelling catheter, however, is associated with patient discomfort, urinary tract infection, delayed ambulation and moderate cost.[1] In the study of Kelleher, some women were offered cesarean delivery without the use of an indwelling foley catheter and these women were generally pleased and satisfied with this method.[2] In addition, in the study of Ghoreshi, randomized trials have shown that women in the uncatheterized group had a shorter mean ambulation time and a shorter hospital stay by nearly 18 hours.[3] These findings encouraged us to determine among patients who will undergo radical surgery for gynecologic malignancy if we can remove the indwelling catheter on an earlier date.

Among women who underwent radical surgery, other than the maternal discomfort, lower urinary tract dysfunction is commonly observed as a result of this extensive dissection. Urinary retention, detrussor hypertonicity, hypotonicity, stress incontinence and fistula formation remain the most frequently reported postoperative complications. Improved surgical technique, use of perioperative antibiotic prophylaxis and drainage of the retroperitoneal space are believed to be responsible for the decrease rate of serious urinary tract complications. The contribution of prolonged indwelling catheterization to bladder dysfunction remains unclear.

Thus, the general objective of this study was to determine the effects of early removal of indwelling urinary catheter after radical hysterectomy. Specifically, we compared the effects of removal of the urinary catheter on the first week, second week and third week post surgery using the following parameters:

1. Subjective pain assessment based on the Wong scale and the self report scale.
2. First spontaneous void
3. Post void residual (PVR) urine
4. Rate of recatheterization

Materials and Methods

From January, 2005 to July, 2005, thirty women were admitted in our institution for an elective radical hysterectomy with bilateral lymph node dissection for cervical malignancy or uterine malignancy with cervical extension. These subjects were distributed into a matched controlled clinical trial. Participation is voluntary and an informed consent was obtained for all subjects.

Patients with concomitant renal, hepatic and urologic disease, with preoperative RT or chemotherapy, who had abandoned radical hysterectomy and with no informed consent were excluded in the study. Patients received one pre-operative and three postoperative doses of a second generation of cephalosporin.

Demographic information were recorded and clinical data include indication for radical hysterectomy, type of anesthesia used, time when anesthetic agent was given, length of operation and amount of blood loss. One day prior to operation, the subject was allowed to void and record the total amount of urine for 2 consecutive occasions. Then, a straight catheter was introduced transurethrally into the bladder to withdraw residual urine volume. Percentage of PVR urine was computed based on the total volume of urine and PVR urine volume. The indwelling foley catheter was latex, 16F with a 10cc balloon, which is the standard catheter used in this hospital's operation room. This catheter was inserted at the time of surgery and was left in place for either one week (Group 1), two weeks (Group 2) or three weeks (Group 3).

The radical hysterectomy was performed by senior fellows in our section. The duration of surgery (defined as the time from the onset of surgery to the completion of skin closure), amount of intraoperative blood loss and the occurrence of any organ injuries were recorded. The length of hospital stay was noted as well. The return of bowel function, documented by a bowel movement or passage of flatus, was the determining factor for discharge in most cases.

During follow up at the outpatient department, on the basis of the study assignment, the foley catheter was permanently removed depending on the PVR percent. If more than 30% of PVR urine was established, re catheterization was made, either re insertion of indwelling foley catheter or intermittent straight catheterization depending on patient's preference. The time of first voiding (defined as the time interval between the removal of the catheter and first spontaneous voiding) was considered. Pain was assessed with a pictorial questionnaire (Figure 1). These scales measure the level of pain and location (ie, bladder or urethra vs the surgical site) The questionnaire was site specific for pain. Pain assessment was completed by the investigator during the patient's stay in the ward and repeated on the time of her first spontaneous voiding during follow up.

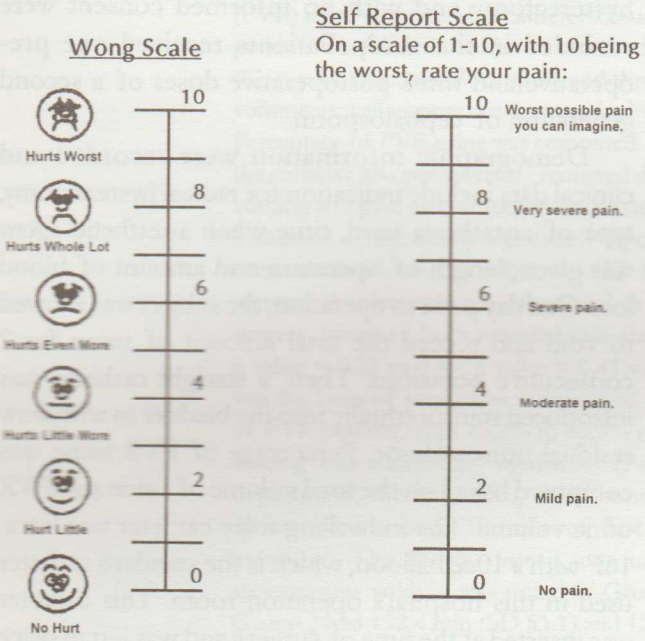

Figure 1. The Wong scale and the self report scale.

Data were analyzed by SPSS statistical software using the chi square and paired t-test to compare mean days and urine volume.

Results

Among 30 women who underwent radical hysterectomy, 5 had previous radiotherapy, 3 had an abandoned planned surgery for lymph node metastasis and 1 had an intraoperative finding of left renal agenesis, hence, they were excluded from the study. Twenty one patients were included in this study. Three patients were operated for endometrial cancer and 18 for cervical cancer. Among patients with cervical cancer, 14 had squamous cell carcinoma, 2 had small cell carcinoma and 2 had adenocarcinoma (endocervical and endometrioid). The mean ages, gravidity and parity among subjects were not statistically different (Table 1). All patients included in the study received continuous epidural anesthesia.

Table 1. Baseline characteristics of patients.

	1 week (Group 1)	2 weeks (Group 2)	3 weeks (Group 3)	p value*
Age	51.3 (5.1)	46.0 (7.1)	51.7 (12.9)	0.57
Gravidity	4.0 (2.0)	3.0 (2.0)	4.0 (5.0)	0.61
Parity	4.0 (2.0)	2.0 (2.0)	4.0 (5.0)	0.54
Duration of surgery	268.0 (54.2)	261.2 (55.8)	290.6 (67.4)	0.61
EBL	586.0 (399.9)	612.5 (195.9)	600 (261.9)	0.98

Values are Mean (SD)
* One-way ANOVA

The mean duration of surgery was noted to be longest in Group 3 at 290.6 min (SD 67.4 min) while the mean estimated blood loss was greatest in Group 2 at 612.5 ml (SD 195.9 ml). Both findings were not statistically significant. In the three-week catheterized group, one patient had bowel injury and another one had obturator nerve transection. There were no bladder, urethral and ureteral injuries incurred during the operation.

Pain assessment was measured based on the Wong scale and Self Report scale. Among the three groups, Group 2 showed a statistically significant report before and after radical hysterectomy with a mean score of 2.0 (SD 1.4) to 0.5 (SD 0.8). (Paired t test, $p = 0.01$). These changes were observed in both scale. (Tables 2 & 3) (Figures 2 & 3)

Total urine volume as well as the amount of post void urine volume were monitored before and after the radical hysterectomy. There was an increase in urine volume, either total or residual, when it was measured before and after surgery, however, both revealed a non

Table 2. Wong score monitoring.

	Before	After	p value
1 week (Group 1)	1.8 (1.8)	0.4 (0.8)	0.13
2 weeks (Group 2)	2.0 (1.4)	0.5 (0.8)	0.01
3 weeks (Group 3)	1.5 (1.3)	0.1 (0.4)	0.71
p value	0.55	0.29	

Values are Mean (SD)
* One-way ANOVA
** Paired t-test

Table 3. Self-report monitoring.

	Before	After	p value
1 week (Group 1)	1.8 (1.8)	0.4 (0.9)	0.13
2 weeks (Group 2)	2.0 (1.4)	0.5 (0.8)	0.01
3 weeks (Group 3)	1.6 (1.6)	0.1 (0.4)	0.71
p value	0.66	0.29	

Values are Mean (SD)
* One-way ANOVA
** Paired t-test

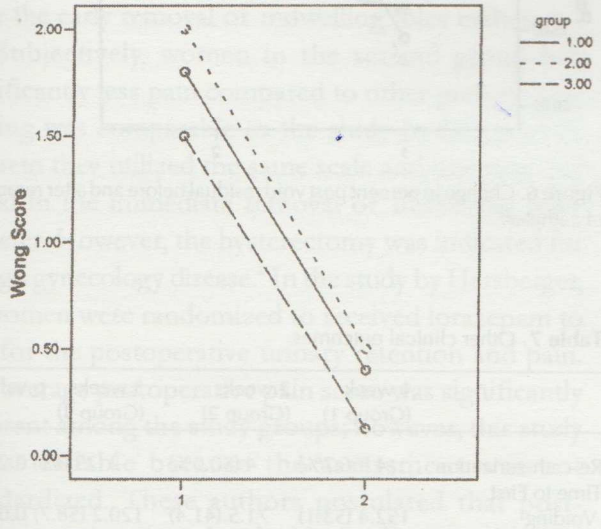

Figure 2. Change in Wong score before and after removal of catheter.

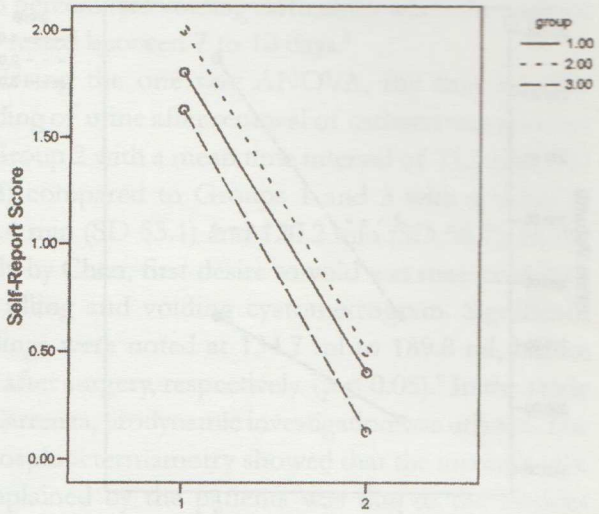

Figure 3. Change in self-report score before and after removal of catheter.

Table 4. Urine volume monitoring.

	Before	After	p value
1 week (Group 1)	198.0 (66.1)	214.0 (99.71)	0.64
2 weeks (Group 2)	230.0 (32.9)	228.1 (72.9)	0.62
3 weeks (Group 3)	214.4 (35.4)	255.0 (110.9)	0.25
p value	0.66	0.40	

Values are Mean (SD)
* One-way ANOVA
** Paired t-test

Table 5. Post voiding residual (PVR) urine monitoring.

	Before	After	p value
1 week (Group 1)	47.0 (22.8)	88.0 (66.1)	0.12
2 weeks (Group 2)	51.9 (10.7)	90.6 (35.3)	0.61
3 weeks (Group 3)	56.2 (10.9)	62.2 (43.3)	0.56
p value	0.41	0.23	

Values are Mean (SD)
* One-way ANOVA
** Paired t-test

statistically significant findings (One way ANOVA, p value = 0.23 vs 0.40; p = 0.41 vs. 0.23). Using the paired t test, these urine volumes were compared among the study groups. There was a slight decrease in urine volume in Group 2 from 230 to 228.1 ml. This result however showed non statistically different findings. (Tables 4 & 5) (Figures 4 & 5)

Permanent removal of foley catheter was based on percentage of post voiding residual urine. In Group 1, there was an increase from 25.2% to 45.3% of PVR noted before and after radical hysterectomy. This finding was statistically significant (Paired t test, p = 0.04). Increase of PVR percent was also noted among

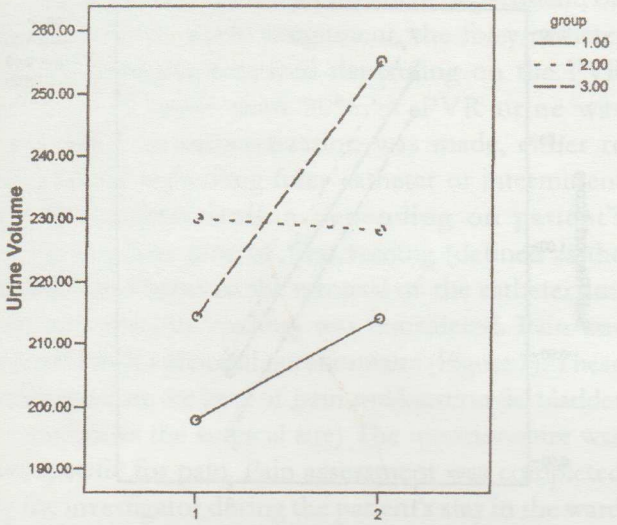

Figure 4. Change in urine volume before and after removal of Foley catheter.

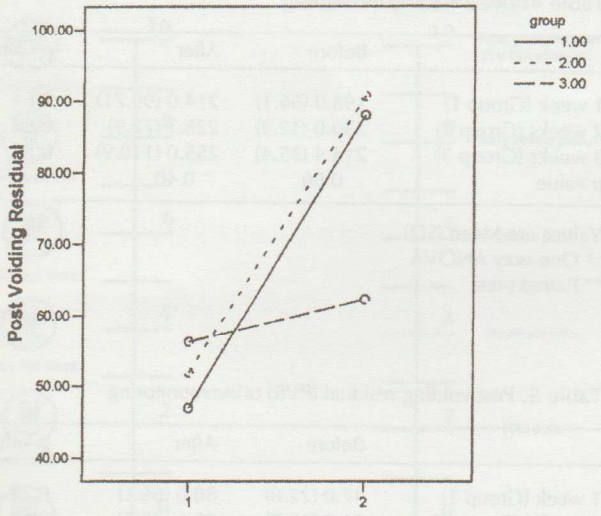

Figure 5. Change in post voiding residual urine volume before and after removal.

Groups 2 and 3, however these results were non statistically significant. (Paired t test, p = 0.69 and 0.65, respectively) (Table 6) (Figure 6)

At the outpatient department, the indwelling foley catheter was removed and the patient was allowed spontaneous voiding. The time of first voiding of urine after removal of catheter was measured. The shortest mean time interval of 71.5 min (SD 41.4) was noted in Group 2 while Group 1 and Group 3 had 152.4 min

Table 6. Post voiding residual (PVR) percent monitoring.

	Before	After	p value
1 week (Group 1)	24.5 (9.7)	88.0 (66.1)	0.04
2 weeks (Group 2)	22.9 (5.7)	42.2 (17.4)	0.69
3 weeks (Group 3)	26.4 (3.8)	28.9 (24.8)	0.65
p value	0.54	0.35	

Values are Mean (SD)
* One-way ANOVA
** Paired t-test

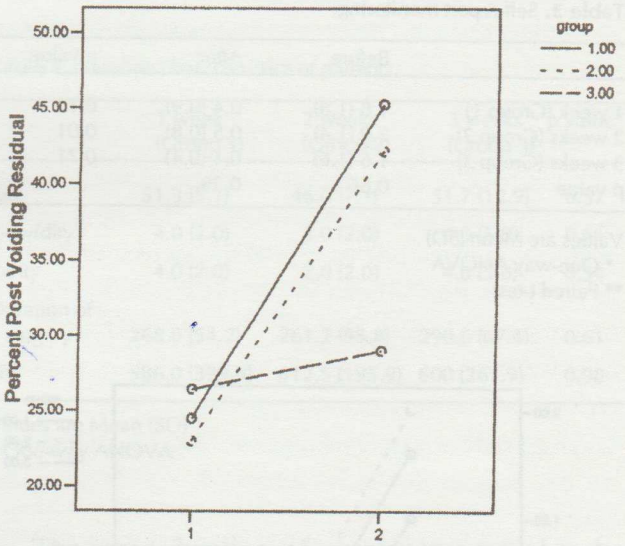

Figure 6. Change in percent post void residual before and after removal of catheter.

Table 7. Other clinical outcomes.

	1 week (Group 1)	2 weeks (Group 2)	3 weeks (Group 3)	p value*
Re-catheterization	4 (66.7%)	4 (50.0%)	2 (25.0%)	0.28**
Time to First Voiding	152.4 (53.1)	71.5 (41.4)	120.2 (58.7)	0.03*
Length of Stay	5.2 (0.4)	6.9 (0.8)	6.9 (1.2)	0.01*

Values are Mean (SD) or Frequency (%)
* One-way ANOVA
** Pearson chi-square

(SD 53.1) and 120.2 min (SD 58.7), respectively. (Table 7). This finding was statistically significant. (One way ANOVA, p = 0.03).

Among all groups, the rate of re-catheterization was inversely proportional to the duration of catheter

removal, however, the result was not statistically significant. (Pearson chi square, $p = 0.28$). In contrast to the hospital stay, wherein Group 1 has the least mean stay of 5.2 days (0.4%) compared to Groups 2 and 3 with 6.9 days (0.8%) and 6.9 days (1.2%), respectively (Table 7). These findings were statistically significant. (Paired t test, $p = 0.01$)

Discussion

Lower urinary tract dysfunction remains the most commonly encountered adverse sequelae following radical hysterectomy. Prolonged catheterization may contribute to bladder dysfunction. Long term catheterization prevents the bladder from expanding and emptying in its usual fashion and acts as a chronic irritant, possibly contributing to vesical pathology. Our findings suggest that the total urine volume, post voiding residual urine and PVR urine percent has no significant change before and after radical hysterectomy. However, the quality of life was significantly affected after the early removal of indwelling foley catheter.

Subjectively, women in the second group had significantly less pain compared to other groups. This finding was comparable to the study by Dunn, et al. wherein they utilized the same scale and less pain was noted in the immediate removal of indwelling foley catheter. However, the hysterectomy was indicated for benign gynecology disease.[4] In the study by Hersberger, 90 women were randomized to received lorazepam to test for the postoperative urinary retention and pain. The average postoperative pain score was significantly different among the study groups; however, this study is less reliable because the assessment was not standardized. These authors postulated that post-operative pain is associated with the time to void. One of the proposed mechanisms was pelvic floor muscle spasm.[5] This was supported by the report of Green in 623 patients. They concluded that if the catheter was left in place for 7 to 14 days, the incidence was approximately 25 percent and if left for 6 to 8 weeks, the incidence dropped to approximately 5 percent.[6] Roberts and Homesley concluded that if bladder cystometry was performed immediately postoperatively, 100 percent of the patients showed abnormal bladder function.[7] On the other hand, Lee and Park cited that 26.3 percent had voiding difficulties when the patients was tested between 7 to 10 days.[8]

Using the one way ANOVA, the time of first voiding of urine after removal of catheter was shortest in Group 2 with a mean time interval of 71.5 min (SD 41.4) compared to Groups 1 and 3 with a value of 152.4 min (SD 53.1) and 120.2 min (SD 58.7). In the study by Chen, first desire to void was measured thru the filling and voiding cystometrogram. Significant findings were noted at 134.7 ml to 189.8 ml, before and after surgery, respectively. ($p \leq 0.05$).[9] In the study by Carrenza, urodynamic investigation was utilized. The cystosphinctermamotry showed that the incontinence complained by the patients was due to the bladder pressure exceeding that of the urethra without voiding reflex and proprioseptive sensation.[10] Scotti, et al. demonstrated long term effect on postoperative vesical dysfunction. They showed that by 3 months, no significant difference in first sensation, fullness sensation, maximum capacity, voiding pattern residual volumes or flow rates existed compared to those at preoperative evaluation.[11] On the other hand, Ghoreishi showed that first postoperative voiding was commonly observed at 8-11 hours in 42.5 percent and 5-8 hours in 40.9 percent.[3] In the study by Hershbergert, benzodiazepines were used. There was no significant difference in the mean time to void between lorazepam (3.1 ± 1.2 hours) and placebo (2.8 ± 2.0 hours) groups ($p = 0.5$).[5]

In this study, there was an increase in residual urine volume when it was measured before and after surgery; however, this was not statistically significant (One way ANOVA, $p = 0.41$ vs 0.23). Notably, in Group 1, there was an increase in the percentage of PVR urine. This was a statistically significant findings (Paired t test, $p = 0.04$) in contrast to the increase of PVR (%) in groups 2 and 3. According to Bentash, et al., abnormal post voiding residual volume was 4 percent during the first visit (2 weeks) among patients who underwent radical surgery compared to simple hysterectomy.[12] In the study of Chamberlaine, residual urine volume was checked at 12 hours using fluorodynamicly (FUDS), prior to discharge from the hospital and monthly thereafter. Eight patients (31%) required continued measurement of PVR and among these, 3 patients had

PVR monitoring which lasted for 165 days.[13] Forney demonstrated that patients had increased postvoid residuals and decreased sensation for an extended period following radical hysterectomy. He correlated the duration of increased PVRs with the extent of cardinal ligament resection and found that residuals remained high, longer in patients with completely resected ligaments.[14] Same findings were observed by Farquazon, et al. They postulated that the degree of vesical function was related to the "radicality" of the procedure and that autonomic innervation via the cardinal and uterosacral ligaments was interrupted during the dissection and advocated long term catheterization.[15] According to Hohenfeller, different types of surgery cause different voiding disorders. It is reasonable to suppose that, although the same type of radical surgery is performed, each case has its own peculiarities which make it unique. This explains the large variety of voiding disorders caused by the same type of surgery without taking into consideration, hypothetically at least, the effect of traumatic factors.

In the study by Kerr Wilson, terbutaline resulted in a statistically significant increase in the volume of urine voided.[16] In our study, the increase of total urine volume as well as the post voiding residual urine volume noted before and after surgery was parallel, however, result was not statistically significant. (One way ANOVA, p = 0.23 vs 0.40; p = 0.41 vs. 0.23) These two parameters were used to compute for the percentage of post voiding residual (PVR) urine. This percentage was the basis for re catheterization in our study. Unlike other studies, they utilized PVR of more than 75 ml[13] or more than 100 ml.[8]

Using the Pearson chi square, recatheterization rates of 66.7%, 50% and 25% were noted in Groups 1, 2 and 3, respectively. (p = 0.28). This was observed even in patients who underwent hysterectomy for benign disease. Their findings were 4.8 percent for those group where removal of foley catheter was done immediately after surgery and 2.4 percent for those patients where the removal of foley catheter was done 24 hours after surgery.[4]

Many women undergo radical hysterectomy as treatment for early stage cervical cancer or endometrial cancer with cervical extension. They may be working and have families, so that prolonged catheterization after surgery can be a considerable inconvenience. Any means by which bladder function can be restored, therefore will hasten return to a normal lifestyle.

Conclusion

Among the three groups, there was no significant change in the urine volume, post void residual urine volume and post void residual urine percent before and after radical hysterectomy as well as the rate of re catheterization. However, the time of first voiding was shortest in Group 2. In this same group, pain assessment significantly improved based on Wong Scale and Self Report Scale. Both findings were statistically significant.

Limitations of the Study

The degree of surgical difficulty which may have affected the results could not be assessed. Pain perception is a subjective measure, which could result in variations of perceived pain. This study did not have enough information whether pre and post operative urinary infections could lead to postsurgical voiding pain. Lastly, because of its unavailability, the complete urodynamic study was not performed in foreseeing the amount of damage caused by the radical hysterectomy to the normal bladder-sphincter functions.

Recommendation

Based on the above findings, this study recommends that the removal of an indwelling foley catheter after radical hysterectomy from cervical carcinoma or endometrial carcinoma with cervical extension can be done 2 weeks after surgery.

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Editor's Note:

A more extensive study including, among other things, the "radicality" of the radical hysterectomy will be necessary to change a long established practice of retaining the catheter for three weeks after the surgery. More studies on "nerve sparing radical hysterectomy" may also be necessary.

Malignant Melanoma of the Vagina

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Malignant melanoma of the vagina is a rare form of neoplasm that comprises less than 3 percent of all vaginal malignancies. It is primarily a disease of postmenopausal women and generally portends a poor prognosis with a 5-year survival rate of 5 to 25 percent. Contributory to this poor survival rate is the fact that most cases diagnosed are in their advanced stages. Several staging schemes with prognostic significance have been developed based on different histologic and clinical criteria. There are various treatment modalities in the management of vaginal melanomas and these include wide local excision, radical excision with inguinofemoral lymphadenectomy, irraditation and chemotherapy. We describe a premenopausal woman diagnosed with vaginal melanoma treated with wide local excision as well as adjuvant chemoradiotherapy.

Key words: vaginal melanoma, pelvic exenteration, wide local excision

The Case

SR, a 33 year old G3P3 (3003) from Angeles City, was admitted for the first time to the Philippine General Hospital for the chief complaint of vaginal mass.

Her past and family medical histories were unremarkable. She is married and works as a teacher. She had no vices and she had her first coitus at 26 years old with a single nonpromiscuous partner. She had no history of infection with sexually transmitted disease. She denies intake of oral contraceptives, or use of intrauterine device.

She had her menarche at the age of 13 and her subsequent menstrual periods came at regular monthly intervals, lasting for 2-3 days, using 3-5 pads per day. She had occasional dysmenorrhea. Her last normal menstrual period was on March 24 to 25, 2004.

She was a G3P3 (3003). All her pregnancies were terminated at term by cesarean section for cephalopelvic disproportion. She underwent bilateral tubal ligation during her last delivery in 2002.

Her illness started three months prior to admission, when she noted a friable vaginal mass that bled even on slight manipulation. One month prior to admission, increase in the size of the mass prompted consult with a gynecologist. She underwent urethroscopy and biopsy of the mass. Biopsy revealed melanosarcoma. She was thus referred to this institution for further management.

On admission, she was ambulatory and not in cardiorespiratory distress. Her vital signs were within normal limits and she was afebrile. She had a soft, flabby abdomen that was non-tender. Palpation of the inguinal area revealed a 3 cm x 2 cm fixed node on the left inguinal area and a 0.5 cm x 0.5 cm movable node on the right inguinal area. The rest of the systemic physical examination was essentially normal. On speculum examination, there was a 4 cm x 3 cm grayish to black mass at the anterior lower third of the vagina beneath the urethra. On internal examination, she had normal external genitalia and parous vagina. The vaginal mass was nodular, nonfriable, with well-delineated borders.

The cervix was closed and smooth and the corpus was small. No adnexal mass or tenderness was appreciated. Rectovaginal examination revealed good sphincter tone, smooth rectovaginal septum and intact rectal vault. The parametria were smooth and free.

The admitting impression was vaginal melanocarcinoma Stage IV.

Laboratory examinations revealed normal blood count and blood chemistry levels. Urinalysis was likewise normal. Chest x-ray showed nodulocalcific densities at the left upper lung field. The radiographic impression was a possible pulmonary granuloma.

CT scan of the pelvis done with contrast showed the uterus to be anteverted measuring 6.8 cm x 5.9 cm x 4.8 cm. The endometrial stripe was hypodense. There was no definite focal parenchymal mass seen but immediately distal to the cervix was an inhomogenous predominantly hypodense lesion that measured 3.5 cm x 2.7 cm. The ovaries were normal in size. Seen in the left ovary was a 1.8 cm x 1.6 cm non-enhancing hypodensity. There were slightly enhancing nodular densities in the lateral pelvic area, the largest was on the right measuring 2.4 cm x 2.5 cm. There were also slightly enhancing nodular densities in the left inguinal area, the largest measuring 2.3 cm x 2.4 cm. There was no free fluid in the pelvic cavity. The distended urinary bladder had smooth outline and had no abnormal intraluminal filling defects. The rest of the visualized structures including the bowel loops did not appear unusual. The axial tomographic impression was "Paracervical inhomogenous predominantly hypodense mass; pelvic and left inguinal lymphadenopathies."

She underwent wide local excision, with a 1 cm margin, of the vaginal mass. The vaginal defect was repaired by primary closure. She tolerated the procedure well and was discharged after a few days.

The Department of Pathology received a specimen labeled "vaginal mass" which consisted of a 4 cm x 3 cm x 2.5 cm cream-white, firm, ulcero-fungating mass attached to a 5 cm x 1.5 cm sheet of cream-tan tissue. Cut section showed a smooth, cream-white surface. The mass was 0.3 cm to 1 cm from the line of resection.

Scanning views show areas of normal vaginal epithelium with intact layers. The surface epithelium of the mass as well as the junction between the mass and the normal vaginal epithelium are eroded (Figure 1). The mass is composed of scattered epithelial-like cell in sheets and nests supported by a fibrovascular stroma (Figure 2). Higher magnification of these cells shows large oval to elongated hyperchromatic nuclei with prominent nucleoli (Figure 3). Seen in a different plane from the cells is a single spot of melanin (Figure 4).

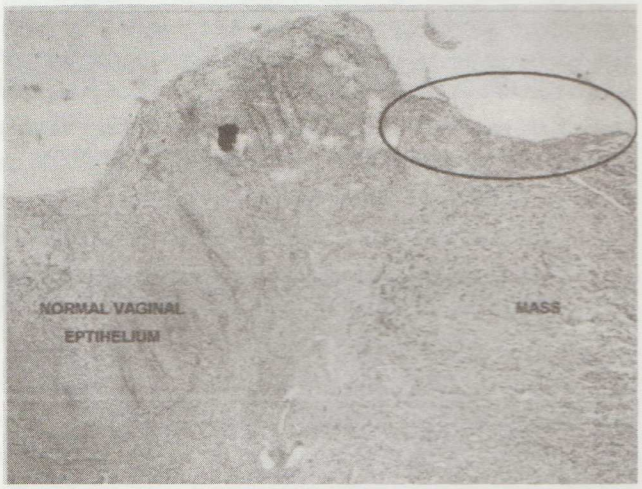

Figure 1. Scanning view of the vaginal mass. There are areas of normal vaginal epithelium with intact layers. The surface epithelium of the mass and the junction between the mass and the normal vaginal epithelium are eroded.

Figure 2. High power view of the vaginal mass. The mass is composed of scattered epithelial-like cells in sheets and nests supported by a fibrovascular stroma.

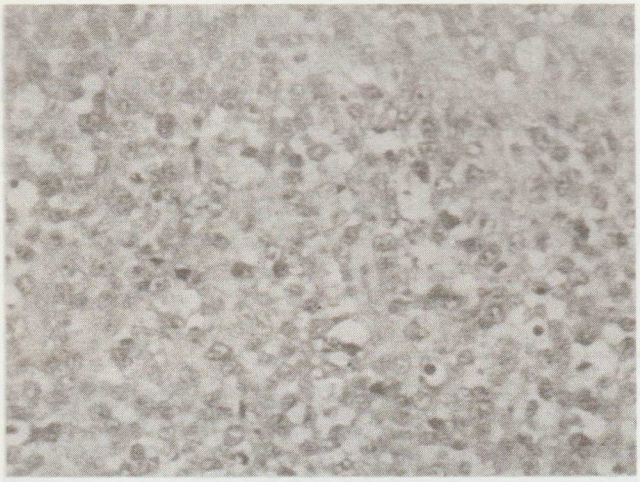

Figure 3. Oil immersion field view of the vaginal mass. There are large oval to elongated hyperchromatic nuclei with prominent nucleoli.

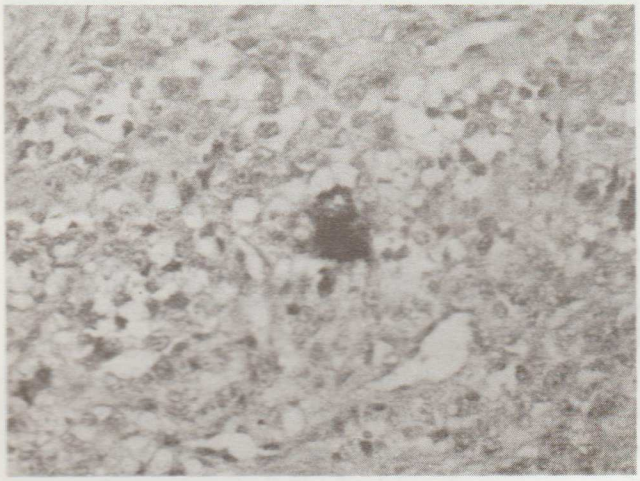

Figure 4. Oil immersion field view of the vaginal mass. There is a single spot of melanin pigment.

The histopathologic diagnosis was malignant round cell tumor. Germ cell tumor (germinoma) and melonoma were being considered. Immunohistochemical studies in the form of homatropine methylbromide 45 (HMB45) and human placental lactogen (HPL) were suggested.

HMB45 immunostaining was done and showed a primarily cytoplasmic with sporadic nuclear staining pattern (Figure 5). This confirmed the diagnosis of melonoma of the vagina.

The patient underwent radiotherapy with concomitant chemotherapy. She however succumbed to multiple metastases to the bone, breasts, liver and cervical lymph nodes. She died five months after the diagnosis of her illness. The possible cause of death was massive pulmonary embolus secondary to disseminated disease secondary to malignant melanoma of the vagina stage IV.

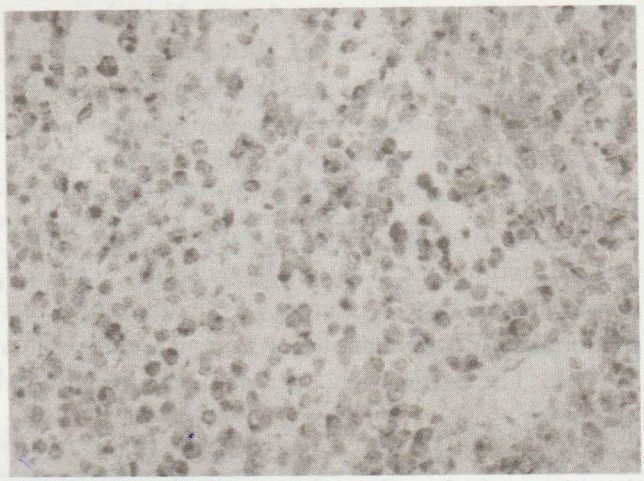

Figure 5. Oil immersion field view of the mass with homatropine methylbromide 45 (HMB45) immunostain. There is a primarily cytoplasmic with sporadic nuclear staining pattern.

Discussion

Malignant melanoma is a rare form of neoplasm that originates from melanocytes. The term malignant melanoma is used synonymously with melanocarcinoma and melanoma. Around 4-5 percent of melanomas are extracutaneous and may come from the mucous membranes lining the respiratory, digestive, genitourinary tracts, eyes and cerebral meninges (Thoelke, et al). Malignant melanoma of the vagina is a very rare entity. It accounts for less than 1 percent of all melanomas in women, less than 10 percent of all female genital tract melanomas and less than 3 percent of all vaginal malignancies (Piura, et al. 2002).

The first reported case of primary melanoma of the vagina was in 1887 by Paronas and the first comprehensive review of the subject was in 1948 by Mino, et al. (Sepidoza, 1985). Since then and up to the year 2002, less than 250 cases have been reported worldwide (Piura, et al. 2002). In the Philippines, to

date, there have only been three published cases. The first case was reported by Dr. Bernabe Marinduque in 1985. The melanoma was diagnosed in a 55 year old G2P2 (2002). Also in 1985, Dr. Nora Sepidoza reported the second case of vaginal melanoma in a 38 year old G2P1 (1011). The third was reported by Dr. Benjamin Cuenca in 1994 and it involved a 34 year old nulligravid.

Hasume, et al. in 1978 found that 3 percent of normal females have melanocytes in the vagina. These cells are presumed to undergo malignant transformation (Manlucu, et al, 1998). As for the possible cause of the malignant transformation, Davis in 1976 proved that melanoma need not be actinic-related. Genetic factor may come into play, as with the 11 percent familial incidence in Queensland. Some authors believe that it may evolve from pre-existing junctional or compound nevi (Droegemueller, et al. 1992). Presently, no relationship has been established between the disease and exposure to airborne or work-related carcinogens. It may be possible, that in certain instances, trauma may stimulate an active growth phase of pre-existing melanoma (Cuenca, 1993).

Vaginal melanoma is primarily a disease of postmenopausal women with 75 percent of patients being 50 and older (Manlucu, et al. 1998). It may however occur in any age group, with the youngest reported case being 22 years old (Cuenca, 1993).

The more common symptoms include vaginal bleeding, discharge and tumor mass (Liu, et al. 1996). The lesion commonly occurs at the distal third of the anterior vaginal wall (Reid, et al. 1989). The index patient was just 33 years old when she noted a tumor mass at the distal third of the anterior vaginal wall.

The lesions may vary in presentation, from single to multiple and from microscopic to several centimeters. Their characteristic hallmark is color variegation. Various shades of red, white and blue are admixed with brown, black or tan lesions (Cuenca, 1993). Six percent of these lesions, however, are not pigmented or are amelanotic. These variants may be flesh, red or purple-colored. Vaginal melanomas may be flat, nodular, polypoid or fungating. The overlying epithelium is frequently eroded or ulcerated which helps to explain their frequent confusion with squamous cell carcinoma (Manlucu, et al. 1998).

Although LDH is not specific for melanoma, it may be useful at diagnosis and also in the follow-up care of patients with melanoma. A markedly elevated level may indicate distant metastases, especially in the lungs and liver. Although the specificity and sensitivity of this test are low, multiple studies show an elevated LDH level to be an independent predictive factor for poor prognosis. LDH level now is considered part of the staging system for melanoma. LDH level determination was not done on the patient because the patient had already advanced disease when she was seen by her attending physician.

In the management of patients with melanoma in stage I or II of the disease, a chest radiograph will likely be negative. To date, no studies support obtaining a radiograph in these patients, but a normal chest radiograph finding at diagnosis provides a baseline for future comparison. Patients with stage III disease or local recurrence should have a chest radiograph or CT scan because the lungs are common sites of metastatic disease.

Chest and cranial CT scans are used in patients with known distant metastases to detect additional asymptomatic metastasis disease. Chest and cranial CT scan in patients without known metastatic disease are reserved for those who are symptomatic (Brick, 2004). CT scan of the pelvic and abdomen is indicated to detect metastasis to the pelvic and abdominal lymph nodes.

A complete excisional biopsy is preferred and should include a 1-2 mm margin of healthy vaginal mucosa to include all layers of mucosa and some submucosal fat to ascertain the following information:

1. Assessment of tumor depth (Breslow depth)
2. Ulceration
3. Anatomic level of invasion (Clark level)
4. Presence of mitoses
5. Regression
6. Lymphatic/vessel invasion or vascular involvement
7. Host response (tumor-infiltrating lymphocytes) (Swetter, 2004)

If the suggestive lesion is large or situated in a cosmetically sensitive area, an incisional or punch biopsy may be appropriate. The incisional biopsy should be taken from the most abnormal area of the lesion. Because all layers of the vaginal mucosa must be included in the biopsy, a shave biopsy is contraindicated.

Patients with clinically enlarged lymph nodes and no evidence of distant disease should undergo a complete regional lymph node dissection (LND). For years, patients without clinically enlarged nodes underwent LND. Recent studies show that, in patients with melanomas that are 1-4 mm thick, LND may not yield a significant survival advantage. The only patients who seem to benefit from LND are those with lesions 1.1-2 mm thick and who are younger than 60 years. Patients with lesions greater than 4 mm in thickness, as in the case of the index patient, are widely considered not to benefit from removal of clinically negative nodes.

Microscopically, the lesion of malignant melanoma of the skin shows proliferation of atypical melanocytes along the dermoepidermal junction with extension into the epithelium. The atypical melanocytes may be epithelioid, spindled or mixed and may occur singly or in clusters. The infiltrative component is usually nevoid or spindled. The nuclei are pleomorphic with macronucleoli and intranuclear inclusions. The cytoplasm is abundant and granular with or without melanin pigment. These microscopic findings are also seen in germinomas, hence, the pathologist placed the said disease as one of the differentials.

Homatropine methylbromide or HMB45 is a monoclonal antibody that has a chromogenic reaction with a glycoconjugate present in the cytoplasm of melanoma cells. This examination was positive in the patient. Another immunostain being used in the diagnosis of melanomas is S-100. Although this test is highly sensitive, it is not specific for melanoma, whereas the HMB45 is highly specific and moderately sensitive for melanoma. The 2 stains, in concert, can be useful in diagnosing poorly differentiated melanomas.

The criteria for the diagnosis of a primary malignant melanoma of the vagina as set by the International Federation of Gynecology and Obstetrics are the following:

1. Absence of a primary malignant melanoma elsewhere in the body.
2. Histopathologic features seen on tissue sections are consistent with malignant melanoma.
3. The tumor is situated clearly above the hymen and below the cervix, thus, discounting the possibility of a primary vulvar or cervical melanoma.

All these criteria were met in the index case.

Malignant melanoma is one of the disease entities wherein several staging schemes have been developed.

In 1969, Clark, et al. introduced a staging system based on the depth of invasion of the tumor in relation to the skin layers.

Level I: Confined to epidermis (in situ); never metastasizes; 100% cure rate
Level II: Invasion into papillary dermis; invasion past basement membrane (localized)
Level III: Tumor filling papillary dermis (localized), and compressing the reticular dermis
Level IV: Invasion of reticular dermis (localized)
Level V: Invasion of subcutaneous tissue (regionalized by direct extension)

In 1970, Breslow proposed a pathologic staging based on measurement of tumor invasion of dermis using the micrometer on the microscope.

- 0.75 mm (comparable to Clark Level II)
- > 0.75 - 1.5 mm (comparable to Clark Level III)
- > 1.5 - 4.0 mm (comparable to Clark Level IV)
- > 4.0 mm (comparable to Clark Level V)

The Clark level and Breslow index were designed primarily for cutaneous melanomas. Since extracutaneous sites lack the dermal layer, the two staging systems may not always be applicable (Thoelke, et al). Thus, Chung, et al. suggested a staging system for mucosal sites of melanoma.

Level I - tumor confined to the surface epithelium
Level II- invasion of 1 mm or less
Level III - invasion of 1-2 mm
Level IV - invasion of greater than 2mm. Most tumors are deeply invasive.

The American Joint Committee on Cancer (AJCC), has adopted a primary tumor nodes metastases (pTNM) staging system for melanoma, which incorporates the histologic characteristics of the primary tumor. In 2003, revisions to the system have been made, adding ulcerations and LDH since these factors have been proven to affect the prognosis of melanomas.

This staging system more accurately assesses the metastatic potential of the majority of melanoma patients who present with clinically localized disease. Although the AJCC system has been recommended

for staging of these tumors (Trimble, 1996), the usefulness of the system remains controversial because there are no prospective studies addressing its prognostic significance (Irvin, et al. 1998).

Stage TNM	Criteria
I pT1, N0, M0	Primary melanoma < 0.75 mm thick and/or Clark's level II No nodal or systemic metastasis
pT2, N0, M0	Primary melanoma 0.76-1.50 mm thick and/or Clark's level III No nodal or systemic metastasis
II pT3, N0, M0	Primary melanoma > 1.51-4.00 mm thick and/or Clark's level IV No nodal or systemic metastasis
III pT4, N0, M0	Primary melanoma > 4.0 mm thick and/or Clark's level and/or satellite(s) within 2 cm of the primary tumor No nodal or systemic metastasis
Any pT, N1, M0	Regional nodal metastasis ≤ 3 cm in greatest dimension No nodal or systemic metastasis
Any pT, N2, M0	Regional nodal metastasis > 3 cm in greatest dimension or in-transit metastasis No systemic metastasis
IV Any pT, Any N, M1	Systemic metastasis

In the Clinical Practice Guidelines of the FIGO Committee on Gynecologic Oncology published in 2000, no staging system was mentioned particularly for vaginal melanoma. The FIGO staging was for carcinoma of the vagina in general.

Stage 0	Carcinoma in situ; intraepithelial neoplasia grade 3
Stage I	The carcinoma is limited to the vaginal wall
Stage II	The carcinoma has involved the subvaginal tissue but has not extended to the pelvic wall
Stage III	The carcinoma has extended to the pelvic wall
Stage IV	The carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum; bullous edema as such does not permit a case to be allotted to Stage IV
IV A	Tumor invades bladder and/or rectal mucosa and/or direct extension beyond the true pelvis
IV B	Spread to distant organs

Presently, Clark, Breslow and Chung Schemes are used for microstaging. When the melanoma has spread beyond the primary tumor, the FIGO staging is employed.

Extracutaneous melanomas are considered to be biologically more aggressive than cutaneous melanomas (Thoelke, et al). Vaginal melanoma, in particular, is notoriously more aggressive, with a 5-year survival rate ranging from 5 percent to 25 percent (Piura, et al. 2002). Contributory to this poor survival rate is the fact that most cases diagnosed are often in their advanced stages.

Metastasis occurs initially via the lymphatics. Regional lymph node involvement has been demonstrated in as high as 54.5 percent of cases (Marinduque, 1985).

Many factors, such as the size, histologic type, mitotic count, tumor thickness and status of the regional lymph nodes have been reported to influence survival. However, more and more emphasis is being placed on the tumor thickness (Disaia, 1993), tumor size and mitotic counts (Moodley, et al. 2004). Reid, et al. in their meta-analysis of 15 patients and review of literature in 1989, concluded that tumor thickness of 6 mm or less significantly affected the disease-free interval. Patients with tumor size < 3 cm are reported to have a significantly greater mean survival of 41 months compared to 12 months for patients with tumor size ≥ 3 cm (Buchanan, et al. 1998). Patients with mitotic counts < 6 per 10 HPF have a better survival (21 months) than patients with mitotic counts greater than 6 per 10 HPF (7 months) (Borazjan, et al. 1990).

The vaginal lesion of the patient, on excision, already measured 4 cm in its widest diameter. There were already ulcerations and though the margins of resection were free of tumor, at the time of surgery, there already seemed to be lymph node involvement. All these factors pointed to a very dismal prognosis for the patient.

Various treatment modalities are described in the management of vaginal melanomas and these include wide local excision, radical excision with inguinofemoral lymphadenectomy, irradiation, chemotherapy and immunotherapy (Moodley, et al. 2004). Historically, primary treatment of vaginal melanomas meant pelvic exenteration wherein all pelvic organs such as ovaries and tube, uterus, bladder, vagina and rectum are

removed; an ileal bladder or conduit is created plus a colostomy for the patient. Patients with primary melanoma of the vagina who undergo exenteration as primary therapy may experience 50% 5-year survival if the pelvic nodes are free of metastases. However, the overall 5-year survival for vaginal melanoma remains at 15 percent (Geisler, et al. 1995).

Therefore, many authors have been discouraging surgery as the primary therapy since the patient will just spend the first half of her remaining years recuperating from the disease and the last half deteriorating from metastasis and recurrences (Sepidoza, 1985). Neven, et al. even asserted that conservative procedures in the management of invasive melanoma of the lower female genital tract should be the rule and the radical procedures should be reserved for palliation rather than cure (Neven, et al. 1994).

The use of wide local excision followed by high-dose fractionation teletherapy (> 400 cGy/fx) in the primary management of vaginal melanoma appears to provide excellent locoregional control, without the attendant morbidity and physical disfigurement associated with more radical surgical resection (Irvin, et al. 1998). Radiotherapy may be a limited valuable alternative or adjunct to surgery in patients with primary melanoma of the vagina 3 cm or less in diameter (Petru, et al. 1998).

Chemotherapy has been reported to produce good results in melanoma cases. Seigler, et al. in 1980 suggested the BOLD regimen (Bleomycin, Oncovin, Lumocin or CCNU and DTIC) which produced marked improvement in the patients' condition when used in combination, but were less effective when used singly.

On the frontier of treatments for melanoma have been investigations of novel therapies, including the use of interferon-α, interleukin-2 and interferon-α2b. Interferon-α has been shown to confer survival benefits in patients with nodal disease (Trimble, 1996). High-dose bolus interleukin-2 has been useful in selected patients with stage IV melanoma, showing tumor responses in 16 percent of patients (Atkins, et al. 1999). Interferon-α2b given to patients with stage III melanoma has been shown to delay recurrence but did not affect the overall patient survival.

The attending physician for this case elected to do wide local excision for local control followed by chemoradiation for systemic control of the disease. However, because of the already advanced state of the patient's disease, little control over the systemic spread of the carcinoma was achieved.

More recent literatures show no significant difference in survival among patients treated by surgical resection, irradiation or surgical resection plus irradiation. The type of surgery, whether radical or conservative, also did not influence survival (Reid, et al. 1989). In general, the prognosis in women with this malignancy is poor regardless of type of surgery (Panek, et al. 2001).

Summary and Conclusions

The patient was just 33 years old when she was diagnosed with malignant melanoma. The presenting symptom was vaginal mass. Even with aggressive management, the patient died just 5 months after the diagnosis of her illness. This case underlines the fact that the rare disease of malignant melanoma of the vagina is a rapidly growing tumor that carries a poor prognosis regardless of treatment modalities employed. Early detection and prompt diagnosis are very essential. It is unfortunate however that this disease has ill-defined characteristics. Therefore, only a high index of suspicion plus definite biopsy would assure us of the right diagnosis.

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A Mimic of Malignancy: Hidradenoma Papilliferum

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Hidradenoma papilliferum, a benign vulvar condition, possesses clinical and histologic features that may be likened to a malignancy. In the eyes of the inexperienced, such benign condition may be diagnosed as malignant, with the unfavorable consequence of subjecting a patient to unnecessary radical procedures. This is a case of a 43 year old nulligravid with a 5-year history of recurrent vulvar mass. Initial vulvar biopsy showed a well-differentiated adenocarcinoma. The patient subsequently underwent radical vulvectomy with bilateral groin node dissection. Histopathologic result of the surgical specimen still revealed adenocarcinoma. However, subsequent slide reviews by gynecologic pathologists revealed a benign condition - hidradenoma papilliferum. This report emphasizes familiarity with such a rare condition to avoid the perils of unnecessarily undergoing a radical operation for benign condition.

Key words: hidradenoma papilliferum, vulvar adenocarcinoma, radical vulvectomy, bilateral groin node dissection

A clinician should observe extreme caution before designating a vulvar mass as malignant, especially in a young patient. An example of a condition that may mimic a malignancy based on its clinical and histologic features is hidradenoma papilliferum. This is a case of such a rare lesion, which although clearly benign may be mistaken as a malignancy.

The Case

J.D., a 43 year old nulligravid, Filipino, married, was admitted for the first time last August 22, 2003 for a nonhealing vulvar wound.

She was a known hypertensive. Her highest blood pressure was 150/100 and her usual blood pressure was 140/90. She had no maintenance medications.

She was a housewife with no vices. She had one sexual partner. She had no history of oral contraceptive pill use and no history of sexually transmitted disease.

She had her menarche at 13 years of age. Subsequent menses occurred at regular monthly intervals, with each cycle lasting for 3-4 days. Her last normal menstrual period was August 16-20, 2003 and previous menstrual period was July 16-20, 2003.

Present illness started 5 years prior to admission, when she noted a vulvar mass. No consult was done at that time and no medications were applied over the area.

One year prior to admission, with the repeated recurrences of the vulvar mass, the patient consulted a private physician, who performed a wide excision of the mass. Unfortunately, the histopathologic result was not known to the patient.

One month prior to admission, she noted another recurrence of the vulvar mass, presenting as a nonhealing vulvar wound. She consulted another private physician, who did a punch biopsy of this nonhealing wound. Histopathologic result showed a well-differentiated adenocarcinoma with low mitotic index. She was then referred to a gynecologic oncologist and was subsequently advised radical vulvectomy with bilateral groin node dissection.

She had no fever, no headache and no blurring of vision. She did not have any urinary or bowel disturbances. She had no menstrual irregularities, no abnormal vaginal bleeding, no vulvovaginal discharge and no pruritus vulvae.

Physical Examination

On admission, the patient was fairly nourished and was not in cardiorespiratory distress. She had a blood pressure of 150/90 mmHg, a heart rate of 80 beats per minute and a respiratory rate of 20 cycles per minute. She was a febrile. She had pink conjunctivae and anicteric sclerae. There were no cervical lymphadenopathies. She had clear breath sounds, with no rales or wheezes. She had distinct heart sounds. No murmurs were appreciated. The abdomen was soft and non-tender with no organomegaly. She had pink nail beds, with no edema and no palpable groin lymph nodes.

On pelvic examination, there was a 0.5 cm x 0.5 cm reddish elevated mass with irregular borders at the left labia majora about 2.5 cm lateral to the urethra. The clitoris was grossly normal (Figure 1). Internal examination showed a smooth nulliparous vagina. The cervix measured 2 cm x 2 cm, was smooth and non-tender. The corpus was anteverted and small. There were no adnexal masses or tenderness. Both parametria were smooth and pliable.

Admitting Impression

Vulvar adenocarcinoma G1, stage II
S/P Wide excision of vulvar mass (MCM, 2002)
S/P Punch biopsy of nonhealing vulvar wound (July 2003)
Hypertension stage IA

Course in the Ward

On the second hospital day, the patient underwent radical vulvectomy and bilateral groin node dissection (Hacker's Incision) under epidural anesthesia. Intraoperatively, there were no palpable superficial lymph nodes. The harvested nodes at the deep inguinal chains were enlarged and were suspicious for malignancy. The vulvar specimen measured 10 cm x 7 cm x 4 cm with a 0.5 cm x 0.5 cm red excavated lesion at the left labia between the majora and minora, with no gross extension to the clitoris, urethra and vagina. There was a 4.0 cm margin of normal tissue from the edge of the tumor to the surgical margins.

The patient had an unremarkable postoperative course and was discharged after seven days.

Histopathologic Description

The vulvar specimen measured 10 cm x 7 cm x 4 cm. The labia majora and clitoral hood were identified. There was a 0.5 cm x 0.5 cm x 0.3 cm cream white, fibrotic nodule at the left labia minora located 4 cm from the lateral surgical margin and 1 cm from the vaginal surgical margin. The tumor invaded into the superficial soft tissue but was grossly 0.2 cm from the deep soft tissue margins. The remainder of the epidermal surface was unremarkable (Figure 1).

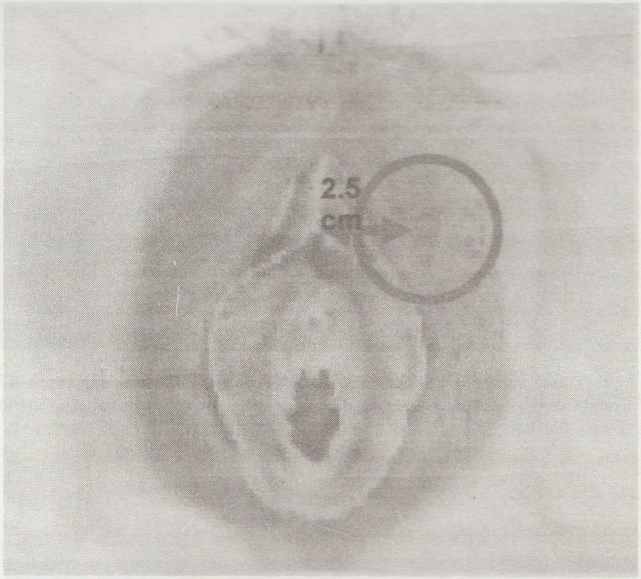

Figure 1. This is a diagrammatic representation of the vulvar lesion removed from the index patient.

Histopathologic examination showed that the tumor was located in the dermis, attached by a stalk to the invagination of the epidermis (Figure 2). The interface between the normal epithelium and that of the tumor was clearly seen (Figure 3). The tumor was composed mostly of papillary structures (Figure 4). There was scanty stroma in between the epithelium lining the papillae (Figure 5). The lining epithelium consisted of 2 layers. The inner layer was a tall to

cuboidal epithelium, while the outer layer, called the "myoepithelial cell layer", was evident (Figure 6). Deep in the stroma was a focus of the tumor suggestive of an invasive process (Figure 8). The surgical margins were negative for tumor (Figure 9). All lymph nodes were likewise negative for tumor (Figure 10).

Final histopathologic diagnosis was papillary adenocarcinoma, vulva. Negative for tumor: all surgical margins, four lymph nodes labeled "right superficial inguinal", specimen labeled "left superficial inguinal", three lymph nodes labeled "right deep inguinal", five lymph nodes labeled "left deep inguinal", clitoris and fibrofatty tissues.

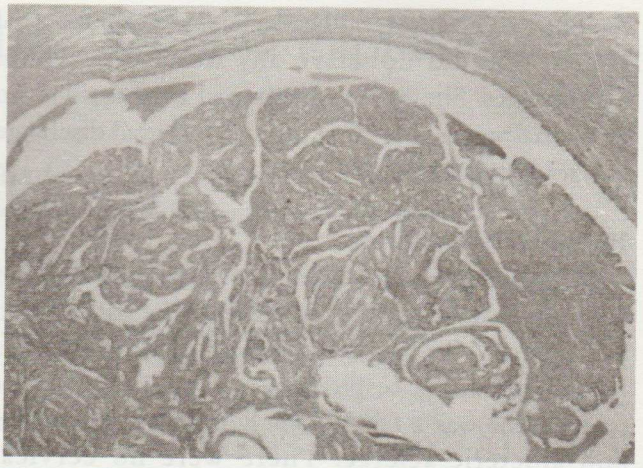

Figure 4. This is another scanning view showing the papillary pattern of the tumor.

Figure 2. This is the bird's eye view of the lesion. There is an invagination on the surface of the epithelium. The lesion is located in the dermis and is connected to the underlying tissue by a stalk.

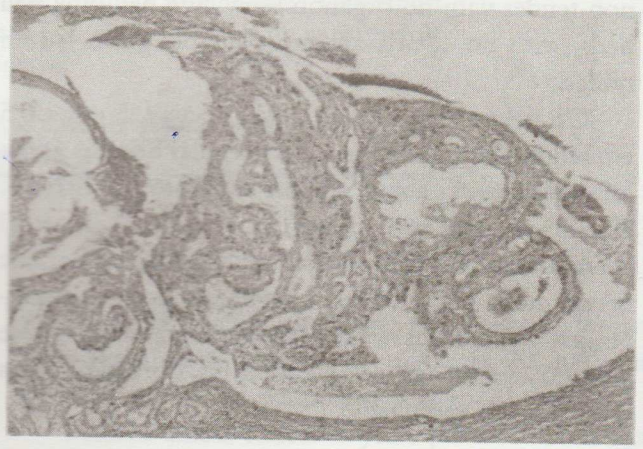

Figure 5. This is a low power view of the tumor. This shows the stroma being scanty in between the papillary structures.

Figure 3. This is a scanning view of the specimen showing the interface between the lesion and the epithelium.

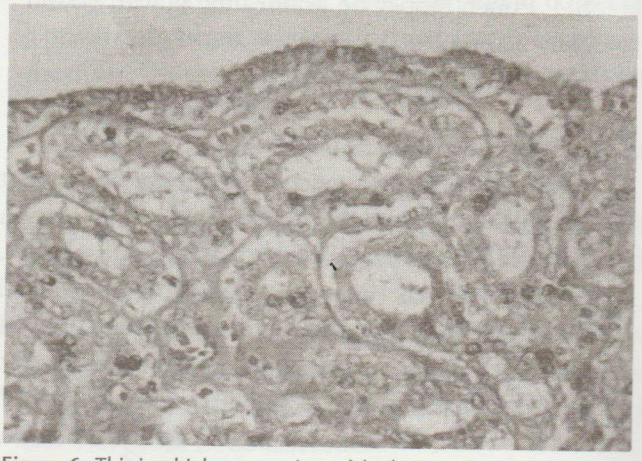

Figure 6. This is a high power view of the lesion. This slide shows the lining epithelium. It has 2 layers. The inner layer is a tall to cuboidal epithelium. The outer layer is called the "myoepithelial cell layer".

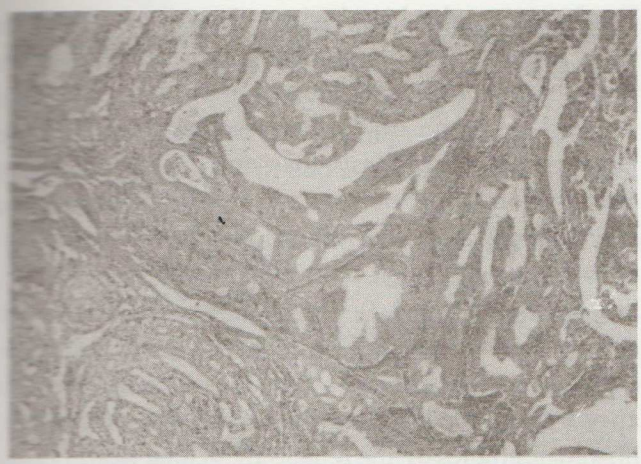

Figure 7. This is another high power view showing an area of the lesion wherein the epithelium underwent apocrine metaplasia.

Figure 8. This slide shows a focus of the lesion in the stroma. This is called the "pseudoinvasive" property of hidradenoma papilliferum.

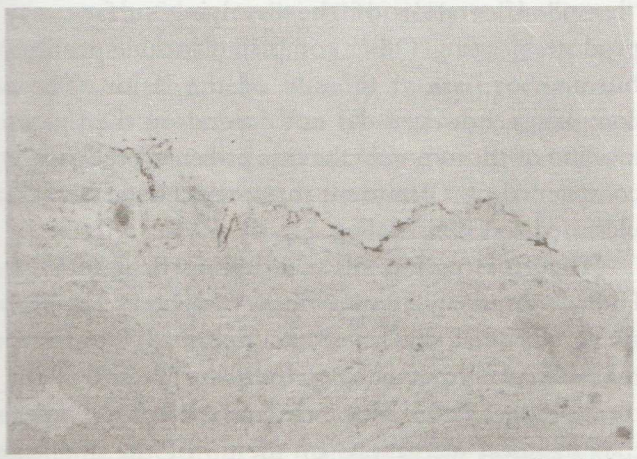

Figure 9. This slide shows a representative surgical margin which is negative for tumor.

Figure 10. This slide shows a representative lymph node which is negative for tumor.

To determine the exact tissue of origin, the attending physician requested for a slide review. Review of slides revealed that although the morphologic feature of the papillary carcinoma favored more a Bartholin's gland origin, the anatomic location did not support such gland as a possible origin.

With the tumor of origin still undetermined, the attending physician requested for a second slide review of both the preoperative biopsy specimen and vulvectomy specimen. Four gynecologic pathologists read the slides as follows: there was a circumscribed dermal tumor composed of tubules, acini and in areas, papillary-like structures, lined by columnar to cuboidal epithelium. The cells had bland vesicular nuclei. Mitotic figures were not increased. In the peripheral portion of the tumor, glands were entrapped in the compressed connective tissue producing a pseudo-infiltrative appearance. These lands, however mostly showed a distinct myoepithelial cell layer. Sections from the adjacent tissue showed focal chronic inflammation. The lymph nodes showed reactive features. Final histopathologic diagnosis was hidradenoma papilliferum. The tumor was of sweat gland origin.

With the difference in reading between initial histopathologic result and the slide review, the attending physician requested for a third review of slides from another gynecologic pathologist. Review of slides revealed a tumor showing a papillary pattern, within an invagination of the epithelium and partly connected

to the epidermis. The epithelium had 2 layers and a myoepithelial layer was prominent. Focal oncocytic change was present. There was no atypia in the epithelium. The area near the epidermis showed pseudoinvasion. The stroma around the "trapped glands" did not show any invasive changes. Final histopathologic diagnosis was papillary hidradenoma. All nodes were negative for tumor.

Discussion

Hidradenoma papilliferum is a benign neoplasm mainly affecting the vulva and anogenital skin. A variety of terms, including adenoma hidradenoides, hidradenoma tubulare, apocrine adenoma, hidrocystadenoma papilliferum and apocrine hamartoma, has previously been used to refer to this tumor.[4]

Hidradenoma papilliferum is an uncommon neoplasm. To date, only approximately 200 cases have been described.[4] In 1971, Woodworth, et al. reported that from 1905 to 1965, a median of 1.15 cases were diagnosed per year.[10] More recently, Virgili, et al. (2000), reported a higher incidence of 3.14 cases diagnosed per year, based on the documented cases in Italy from January 1989 to June 1999.[9]

The first hidradenoma papilliferum described was probably the vulvar lesion reported by Werth in 1878. He believed the lesion was derived from aberrant epithelium. In 1892, Braun described a similar lesion and was the first to mention the possibility of a sweat gland origin. It was not until 1904, though, that the team "hidradenoma" was first used by Pick to refer to this tumor.[4]

Since the publication of Pick's paper in 1904, the hypothesis of a sweat gland origin has been generally accepted. However, whether the apocrine sweat glands or the eccrine sweat glands are primarily involved is still a subject of debate. The human sweat gland may manifest histologic variations or even forms intermediate between the apocrine and eccrine types. Such variations and transitional forms may be partially responsible for the difficulty of relating these tumors to a specific type of sweat glands. McDonald was the first to suggest an apocrine sweat gland origin.[4] He observed large, eosinophilic cells in these tumors that resembled the cells of apocrine sweat glands. Furthermore, the histologic and cytologic features along with the sites of predilection noted in most of the subsequent reports strongly suggest an apocrine sweat gland origin of the hidradenoma papilliferum. However, the hypothesis that this tumor originates directly from apocrine sweat glands conflicts with its main clinicopathologic features, namely: 1) it has not been reported in men, 2) it does not develop in the axillary regions, and 3) it does not appear to occur among black women. The common factor in these exceptions is the presence of high concentrations of apocrine sweat glands.[6] In recent years, several histologic studies of the female anogenital region have carefully examined a new variant of cutaneous glands, the so-called "anogenital sweat glands," which are presently considered the most likely source of hidradenoma papilliferum.[6]

In all the so far described cases, these lesions occurred in the adult, postpubertal women. In a study by Meeker, et al. (1962), the youngest patient was 25 years of age and the oldest 66 years.[4] In the study by Ioannides (1966), likewise showed the predilection of this tumor in the vulva and perineum.[3] In addition, his case series suggested a distinct predilection for the right side of vulva (11 lesions) as contrasted with the left (1 lesion). Rarely, this tumor is noted in other parts of the body. However, lesions located in "ectopic" sites such as the face, axilla and the back would best be classified currently as apocrine papillary cystadenomas.[8] In the case presented, the lesion is located in the interface of the labia majora and minora.

Hidradenoma papilliferum usually is asymptomatic. At other times, the patients would complain of a "lump". Ulceration of the overlying surface may produce bleeding. Other complaints include pruritus, burning, or pain at the site of the lesion. These complaints, however, did not depend on the size or location of the tumor. In the case presented, the patient complained of a recurrent mass, which later became ulcerated and non-healing.

The gross picture of such lesions is of interest. Hidradenoma papilliferum usually presents as a benign, single, unilateral, small, well-circumscribed, firm, freely movable papule or nodule in the skin. The size of the tumor ranges between 0.1 cm and 1.0 cm. At times, they manifest ulcerations of the tip of the nodules, the surface of which is rough and bluish-raspberry-

red in color - a feature common among malignant lesions. Thus, in such instances, these lesions are mistaken to be malignant. The case presented is an example of a seemingly malignant presentation of this tumor. The index patient had a reddish elevated mass with irregular borders.

Microscopically, hidradenoma papilliferum consists of an intradermal, non-capsulated, neoplasm characterized by glandlike structures with intraluminal papillary projections. All tumors exhibit both papillary and glandular patterns. The glandular structures vary in size. Towards the periphery of the lesion, they are large and occasionally cystic and towards the center, usually smaller. In most lesions, the glandular lumen contains faintly eosinophilic, amorphous material. The glandular structures frequently manifest a double layer of epithelial cells resting on a well-defined, thin basement membrane. The papillary structures are usually slender and covered by a single or double layer of epithelial cells.

The epithelium in both the papillary and glandular structures is of 2 general types. Most frequently, the lining cells are tall and columnar, with faintly eosinophilic cytoplasm and moderately large, distinct nuclei parallel with the long axis of the cell. Nipple-like cytoplasmic projections are often present on the surface of these cells. These lining cells often rest on a second layer of smaller cuboidal cells having a contrasting clear cell cytoplasm and round or oval nuclei. Pick referred to the outer layer of cell as "ectodermal muscle cells" and several others have thought that these cells have features observed in smooth muscle cells.[4] The second type of epithelium is composed of large cells with brightly eosinophilic cytoplasm and small, basilar nuclei. The cytoplasm in the apex of the cells usually contains coarse, eosinophilic granules. The nuclear chromatin is compact, with a distinct nuclear membrane. An occasional small nucleolus is present. This epithelium is generally only a single cell in thickness and morphologically resembles the cells of apocrine metaplasia. This type of epithelium is present only in approximately one-third of the lesions.

The stroma, constituting the interglandular and periglandular tissue and the stalk of the papillary projections, is scanty in the majority of the tumors and consists of delicate connective tissue strands with scattered capillaries. Foci of hyalinization, acute and chronic inflammation, or foreign body reaction are seen in the stroma of a few tumors.

In the case presented, the presence of a papillary lesion, lined by 2 layers of epithelial cells, with note of a distinct myoepithelial layer, stromal pseudoinvasion and the absence of cellular atypia and necrosis all support a histopathologic diagnosis of hidradenoma papilliferum.

It was unfortunate that in the case presented, this benign lesion was initially mistaken for a malignant condition. The possibility that hidradenoma papilliferum might be mistaken for adenocarcinoma was mentioned by Pick in 1904.[4] In early literature, there is frequent reference to cases that were mistaken as malignant. Ruge in 1905 described a nodule in the labium majus with the usual complex papillary and glandular pattern, but said that it was certainly malignant.[4,5] Schiffmann in 1920 reported a lesion from the labium majus with a papillary pattern and with metaplastic squamous cells with pearl formation.[4,5] He believed the lesion to be an incipient carcinoma based on the presence of these epithelial pearls. However, in 1945, Novak and Stevenson indicated that both these lesions clearly represent examples of hidradenoma papilliferum.[5] The highly papilliferous pattern or glandular crowding, marked adenomatous hyperplasia, irregular acini without lumen formation and apparent "early invasion" of surrounding stroma are common features that argue towards a malignancy. However, the regular frond-like papillary and glandular proliferations lined by a two-layered epithelium as well as the lack of cytologic atypia, pleiomorphism, necrosis and mitosis throughout the lesion favor a biologically benign condition.

The described histologic features of hidradenoma papilliferum are characteristic and can enable one to accurately diagnose the lesion from the routine sections. Histochemical or electron microscopic evaluation is unnecessary for diagnosis. If one is familiar with the frequent stratification and the frequent papilliferous ingrowths which characterize this benign tumor, one would avoid misdiagnosing such lesion as adenocarcinoma and consequently avoid subjecting the patient to radical procedures such as vulvectomy, as what happened in the case presented.

On the other hand, even if hidradenoma papilliferum is considered a benign tumor, the

possibility of malignant transformation should not be discounted. Exceptional cases of malignant changes have been reported. Cunningham and Hardy were the first to suggest the possibility of malignancy of this tumor.[4] However, it was only in recent years that malignant transformation of hidradenoma papilliferum to adenocarcinoma has been reported. Bannatype, et al. in 1989 reported a case of vulvar adenosquamous carcinoma arising in a hidradenoma papilliferum.[2] In 1991, Pelosi, et al. reported a case of an intraductal carcinoma of mammary-type apocrine epithelium arising within a hidradenoma papilliferum.[7]

The practical lesson when dealing with such vulvar lesions is that although the histologic features often characterize entirely benign lesions of sweat gland origin, one should not treat these growths too lightly. Excision biopsy is mandatory to achieve a correct diagnosis and rule out malignancy. When they are small and slow growing or quiescent, simple but complete excision is adequate to effect cure. It is always advisable, however, especially in lesions showing high degree of epithelial proliferation and a markedly papilliferous pattern, to keep the patients under observation.

It is also important for clinicians to correlate biopsy results with essential features of the case. The index patient just entered her fifth decade of life, with a 5-year history of recurrent vulvar mass with no associated vulvovaginal discharge, bleeding or pruritus. Such clinical features are ideally not consistent with a vulvar malignancy. In retrospect, when in doubt, a slide review of the initial biopsy, and/or a wider incision of the mass might be prudent.

Summary

In summary, a case of a 43 year old nulligravid who underwent vulvectomy for a nonhealing wound misdiagnosed as a carcinoma was presented. The diagnosis of hidradenoma papilliferum is made difficult by the fact that it is an uncommon tumor. For this reason, physicians do not gain enough experience to enable them to recognize this lesion. To one not familiar with its histologic appearance, the microscopic picture is apt to be rather startling and perhaps lead to the wrong diagnosis of adenocarcinoma. It is thus hoped that with this discussion, one has become familiar with clinical and histopathologic presentation of hidradenoma papilliferum and thus prevent the disservice of flat-footedly designating these tumors as adenocarcinoma and subsequently subjecting the patients to unnecessary radical procedures.

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Vulvo-Vaginal Sarcoma in Prepubertal Females: A Case Series

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Embryonal rhabdomyosarcoma (RMS) of the genital tract among prepubertal females is rare, accounting for 3.5 percent of all pediatric rhabdomyosarcoma cases. The Intergroup Rhabdomyosarcoma Study Group included four generations of studies conducted from 1972-1997 involving 3,000 children afflicted with rhabdomyosarcoma. Its purpose was to improve treatment-related outcome and survival rate while decreasing mortality and morbidity. It is through these studies that the manner of therapy of RMS has shifted from radical surgery to a multimodal, less radical treatment. Two cases are reported involving prepubertal females with embryonal rhabdomyosarcoma, a multimodality approach is the key to achieving complete response to treatment.

Key words: vulvovaginal sarcoma, embryonal rhabdomyosarcoma

Childhood rhabdomyosarcoma, a malignant tumor originating from soft tissue of skeletal muscle origin, is a biologically diverse tumor considered as the most common soft tissue sarcoma in children. It comprises 3.5 percent of the cancer cases seen in the 0-14 years age group and 2 percent in the 15-19 age group.[1] Considered as the most common pediatric soft-tissue sarcoma, these tumors account for 50 percent of soft-tissue sarcoma and 10-12 percent of malignant solid tumors in children.

Rhabdomyosarcoma is a curable disease especially in children presenting with localized disease and who are subjected to combined modality therapy.[1] The outcome primarily depends on the site of the primary tumor and its extent. Outcome among patients with primary vulvar or vaginal sarcomas is superior than among patients with primary uterine sarcomas or sarcomas involving adjacent anatomic areas.[2] With the greater efficacy of new combinations of chemotherapeutic drugs, it is possible to achieve complete remission in some patients.[3] Rhabdomyosarcoma has four pathologic subtypes with the embryonal type comprising 57 percent. It usually occurs at 3-12 years of age. It occurs in any anatomic location of the body where there is skeletal muscle as well as in sites with no skeletal muscle. The primary sites of involvement include the orbits, parameninges, bladder, prostate, vagina, uterus, extremities and trunk.[4] Most cases of childhood rhabdomyosarcoma occur sporadically although a small proportion are found in genetically-predisposed children. The most common presenting signs and symptoms are vaginal bleeding and grape-like clustered masses protruding through the vaginal or cervical opening.

Two cases of childhood perineal sarcomas consulting at our institution in 2003-2004 are presented.

Case I

C.S., a 1 year old female from Tarlac consulted because of a 5-month history of an enlarging grape-

like vaginal mass. Her birth, past medical and developmental histories were unremarkable. There were no associated bowel or bladder disturbances. On physical examination, there was a 6 cm x 4 cm x 3 cm solid, polypoid mass protruding from the vagina. There were also bilateral 0.5 cm x 0.5 cm movable inguinal lymph nodes. Transabdominal ultrasound revealed normal infantile uterus, no adnexal masses, with a vulvar mass measuring 2.6 cm long and 0.7 cm high. The upper third of the vagina was smooth. Abdominal CT scan showed a 4.5 cm x 3.5 cm x 6.5 cm mildly enhancing tissue mass protruding externally and arising from the vagina with associated fat stranding. There were also enlarged left superficial inguinal lymph nodes. The liver, kidneys, gallbladder, spleen, pancreas, urinary collecting systems and bladder were normal. She subsequently underwent excision of the said mass under general anesthesia. Two fleshy polypoid masses were obtained which were read histologically as embryonal rhabdomyosarcoma after immunostaining with desmin and actin. (Figure 1) The base of the mass which measured 2 cm x 0.5 cm was left. The patient belongs to Stage I using the Intergroup Rhabdomyosarcoma Study Group (IRSG).

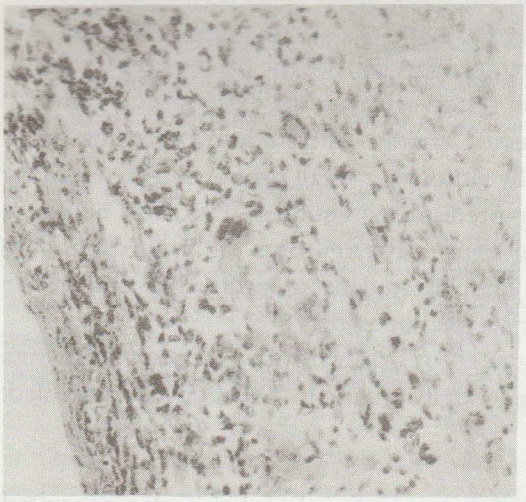

Figure 1. Immunostaining of case 1 with desmin and actin.

Pretreatment Staging, showed she has localized disease involving the genitourinary region. She, however, belongs to Group III in the IRSG grouping system since a grossly visible residual disease due to incomplete resection was present. She is now undergoing chemotherapy with vincristine, actinomycin and cyclophosphamide under the care of the Pediatric-Oncology Service and will undergo radiation therapy subsequently. She is asymptomatic and tolerates the chemotherapy well. A repeat abdominal CT scan was requested after the eighth week of chemotherapy and this showed a decrease in the size of the vaginal mass to 1.5 cm x 2.2 cm x 4.5 cm. Physical examination after completing 22 weeks of chemotherapy showed no hepatosplenomegaly and no vaginal mass.

Case 2

R.G., a 1 year 6 month old female from Cagayan consulted at the Pediatric Oncology Clinic of this institution because of a 9-month history of vaginal mass. Birth, past medical as well as developmental histories were unremarkable. On physical examination, there was a 6 cm x 2 cm polypoid fleshy, erythematous vaginal mass. (Figure 2) Biopsy was done which revealed embryonal rhabdomyosarcoma. A transabdominal ultrasound was requested which showed that the uterus was converted into a heterogenous mass with cystic spaces measuring 3.2 cm x 3.3 cm x 3.3 cm with no adnexal masses. CT scan correlation was suggested and it revealed polypoid cystic masses measuring 3.3 cm x 3.7 cm x 10 cm in the pelvic cavity extending to the vagina. There were also small nodules in the mesentery. The rest of the abdominal organs, vascular and osseous structures were normal. She was then referred to the Gynecologic Oncology Service for possible surgical intervention. The plan of the service was to perform primary surgical resection. The patient, however, acquired pneumonia and was not cleared for the procedure. She is also staged as Group III using the IRSG Clinical Posttreatment Staging since only a biopsy was done. She then underwent chemotherapy in the form of vincristine, actinomycin and cyclophosphamide. The Pediatric Oncology Service Protocol for VAC consists of 43 weeks of chemotherapy with the following dosage: vincristine - 0.05 mg/kg/dose, actinomycin - 0.045 mg/kg/dose and cyclophosphamide - 73 mg/kg/dose. She is now on her fifteenth week of chemotherapy with a

decrease in the size of the mass from 6 cm x 2 cm to 4 cm x 2 cm. A repeat abdominal CT scan showed a decrease in the size of the heterogenous mass with septations now measuring 2.5 cm x 3 cm x 2.1 cm compressing the posterior urinary bladder. She is scheduled for surgical excision after the sixteenth week of chemotherapy.

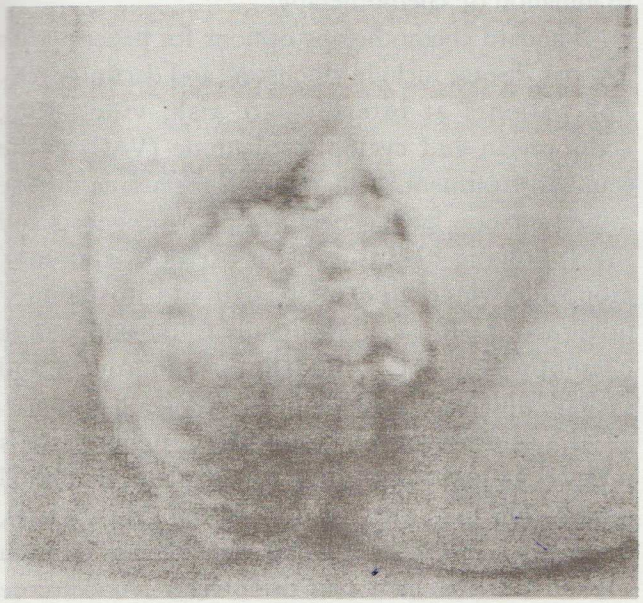

Figure 2. Polypoid fleshy vaginal mass of Case 2.

Discussion

The prognosis for children with rhabdomyosarcoma depends on the following factors: site of origin, histopathology, presence and number of metastases and resectability.[1] The site with more favorable survival rates include the orbit, nonparameningeal head and neck, paratestis, non-bladder, non-prostate genitourinary tract and biliary tract. The initial size of the tumor especially when < 5 cm carries improved survival compared to larger-sized tumors, more so if accompanied by distant metastases. Similarly, patients with metastatic genitourinary primary tumors have a more favorable outcome compared to primary and metastatic tumors at other sites. Presence of regional lymphadenopathy also worsens prognosis for these children.[1] Histologically, the alveolar subtype is more prevalent in patients who also present with unfavorable clinical features such as age less than 1 year old, > 10 years old, metastatic disease and unfavorable primary sites. Preoperative evaluation of a suspected tumor mass includes baseline laboratories such as complete blood count, urinalysis, serum electrolytes, renal and liver function tests. Imaging studies such as chest x -ray, CT scan of the chest, bone marrow biopsy and aspirate and CT scan of the abdomen and pelvis are indicated to determine the extent of the disease.[4]

The original staging system of the IRSG consists of four clinical groups based on the extent of surgical resection:[4] (Table 1) The recently completed IRS Trial IV incorporated size, invasiveness, lymph node involvement and primary site into a new TNM staging system which is used pre-operatively.[6] (Table 2)

Both of the cases presented were Stage 1 by pretreatment staging because the disease was localized to the genitourinary tract. They were both under Group III due to the presence of gross unresected residual disease. The extent of residual disease after surgical resection correlates with outcome. The journal on the IRS III reported a 5-year survival rate of 70 percent for patients in Clinical Group III (with gross residual disease) as compared to 80 percent for patients in Clinical Group II (microscopic residual tumor). In the series by Blakely, et al., the overall 5-year Failure Free Survival (FFS) for 71 eligible patients diagnosed with rhabdomyosarcoma of the perineum was 45% and the overall survival rate (OS) was 49%.[5] There was significant survival difference between the different clinical groups and between stages. (Table 3) Patients less than 10 years old had OS rate of 71% as compared to 18% in children more than 10 years of age. Survival also was related to tumor size and nodal status with tumors < 5 cm having OS of 74% versus 37% in > 5 cm. The absence of regional node involvement (OS 71% vs 33% in node positive patients) also predicts good prognosis.[5]

Childhood rhabdomyosarcoma requires an integrated multimodality therapy. From 1972-1976, traditional management of perineal rhabdomyosarcoma was early radical surgery preceding irradiation and chemotherapy.[2] The IRSG started the goal of eliminating pelvic exenteration as initial therapy by 1974.[5] By 1975, primary pelvic exenterations,

primary hysterectomy/vaginectomy were abandoned in favor of primary chemotherapy or primary chemotherapy/radiotherapy regimen.[9] This entails surgical resection then adjuvant chemotherapy followed by second look surgery in cases with residual tumors. Radiation therapy is reserved for achieving local tumor control in patients with gross residual or microscopic disease after initial surgical resection or chemotherapy. Despite less radical surgery, prognosis of pediatric patients with these kinds of tumor has improved with 5-year survival rate of up to 80%.[7,9]

The primary aim of initial surgical treatment of children with rhabdomyosarcoma is complete resection of the primary tumor with margin of normal tissue and lymph node sampling of the draining nodes. Patients with microscopic residual disease after the initial surgical resection would have improved prognosis if complete removal of tumor can be achieved prior to initiation of chemotherapy.[5]

Standard chemotherapy options for patients with low risk disease include vincristine and dactinomycin. For patients at intermediate risk, vincristine, actinomycin and cyclophosphamide (VAC) is the standard treatment.[1] Patients with metastatic disease at presentation have generally a poor prognosis and the following agents can be used: Ifosfamide/etoposide, vincristine/melphalan and ifosfamide/doxorubicin.[1] Both of our patients are undergoing chemotherapy with vincristine, actinomycin and cyclophosphamide and they both show good response.

It is of utmost importance that the tumor tissue is reviewed by pathologists with experience in childhood tumors. Furthermore, the diversity of primary sites, the distinct surgical and radiation treatments for each site and the rehabilitation of these children underscore the importance of treating these children in medical centers equipped with the appropriate experience in all the treatment modalities required.

Table 1. IRSG clinical group (Posttreatment) staging system.

Clinical Group	Definition
I	Localized tumor, complete resection with pathologically negative margins and no lymph node involvement
II	Localized tumor, grossly removed with: A. microscopically positive margins B. involved, grossly resected regional lymph nodes C. both microscopically positive margins and tumor-involved, grossly resected regional nodes
III	Localized tumor with gross residual disease after attempted resection, or after biopsy only
IV	Distant metastases

Table 2. IRSG pre-treatment staging system.

Stage 1	Localized disease involving the orbit or head and neck (excluding parameningeal sites), or genitourinary region (excluding bladder/prostate/sites), or biliary tract (favorable sites)
Stage 2	Localized disease of any other primary site not included in the stage 1 category (unfavorable sites). Primary tumors must be less than or equal to 5 cm in diameter and there must be no clinical regional lymph node involvement by tumor.
Stage 3	Localized disease of any other primary site. These patients differ from stage 2 patients by having primary tumors greater than 5 cm and/or regional node involvement.
Stage 4	Metastatic disease at diagnosis.

Table 3. Overall survival by clinical group and stage.

Clinical Group	OS	Stage	OS
1	100	1	
2	63	2	94
3	43	3	48
4	25	4	45

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