A Hospital-based Study on the Knowledge and Attitude of Mothers of Adolescents in the Philippine General Hospital Regarding *Human Papillomavirus* Infection and its Potential Vaccine*

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Cervical cancer remains to be the second leading cancer and the leading cause of cancer-related deaths among Filipino women despite the development of the Papanicolaou testing. Epidemiologic research strongly implicates human papillomavirus as the major risk factor for cervical cancer. Given the substantial disease and death associated with HPV and cervical cancer, vaccine development and immunologic-based therapeutics for HPV infection are currently exciting and are rapidly progressing. However, before an HPV vaccination program is successfully implemented, social, cultural and political issues will need to be addressed. Acceptance of a potential HPV vaccine will depend highly on the knowledge and attitude of people with regards the risks associated with HPV infection, as well as, the benefits of the vaccine against it. One scenario that has to be addressed is the parents' acceptability of administering the vaccines among their teenage daughters. **Methods**: A survey was carried out in a sample of 195 mothers with daughters aged 12 to 15 years who consulted at the Philippine General Hospital General OB-GYN Clinic and Gynecologic Cancer Clinic at the Cancer Institute for the month of July, 2006. These women were made to answer a self-administered questionnaire that includes sociodemographic, reproductive and sexual history variables, vaccine usefulness and knowledge of cervical cancer etiology. The possible acceptability of an HPV vaccine for their teenaged daughters was assessed in association with these sociodemographic and reproductive factors. **Results**: The respondents had little knowledge regarding human papillomavirus. Only 14.4 percent has heard of HPV prior to this study and most of them got their information from the television, followed by the doctors. Only 31.8 percent has identified HPV as a specific risk factor for the development of cervical cancer although more than 56.4 percent think that it is caused by an infection that is sexually transmitted. Acceptability of a potential HPV vaccine in this study population was high at 75.4 percent. The main factor associated with the acceptance of such vaccine was the knowledge of the general usefulness of vaccines in preventing illnesses, in this case, the cervical cancer. Fifty-five percent of those who accept the HPV vaccine think that it should be given at any age prior to any sexual activity while 27 percent think that it should be given between 12 to 15 years of age. The main reason for non-acceptance of the vaccine is its prohibitive cost, although most of them explained that if only their resources would allow it, they would be willing to have their children vaccinated. Another reason for non-acceptance is that it might promote or encourage unsafe sexual behavior among the adolescents. Majority

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of the respondents think that men should also be vaccinated against HPV in order to protect their partners from the contracting the infection. **Conclusion**: Increased education of Filipino women regarding HPV and its association with cervical cancer is needed. Initiation of an immunization campaign that targets adolescents who are not sexually active might be quite difficult and should include educational programs aimed at mothers of these individuals. Knowledge of the benefits of a preventive vaccine should be emphasized. Inclusion into widespread government immunization programs should also be targeted for it to be successful.

Key words: adolescents, human papillomavirus

The use of Papanicolaou testing has been highly effective in preventing cervical cancer. Between 1973 to 1995, the Surveillance Epidemiology and End Results (SEER) Program (sponsored by the National Cancer Institute) documented a 43% decrease in incidence and a 46% decrease in death from cervical cancer.[1] Such reductions, however, have only been observed in developed nations where organized and widespread screening is carried out. The cost of nationwide routine Pap testing may be too high for many developing countries including ours, hence, cervical cancer still remains a major health problem. It is still the second leading cancer and the leading cause of cancer-related deaths in Filipino women. The age-standardized rate is 22.5/ 100,000 population - a rate that has not changed for many years.[2]

Epidemiologic research strongly implicates *Human papillomavirus* as the major risk factor for cervical cancer. Ninety-nine percent of invasive cervical cancers are HPV DNA positive. HPV types 16 and 18 account for 2/3 of all cases. In the Philippines, the prevalence of HPV among cervical cancer patients is 93.8%.[3] Given the substantial disease and death associated with HPV and cervical cancer, vaccine development and immunologic-based therapeutics for HPV infection are currently exciting and are rapidly progressing. In fact, prophylactic vaccines are in the late phase clinical trials with evidence that they prevent HPV infection.

Based on the presence of neutralizing antibodies against capsid proteins of HPV, a vaccine consisting of virus-like particles containing the L1 protein alone or the L1 and L2 proteins have been developed and used in various studies.[4] A controlled trial of a Human Papillomavirus type 16 vaccine was conducted by Koutsky[5], et al. in 2002. In this double-blind study, 2,392 females between the ages 16-23 years were randomly assigned to either the placebo group who will receive 3 doses of placebo or the HPV vaccine group who will receive HPV-16 virus-like particle vaccine, given at day 0, month 2 and month 6. Genital samples for HPV-16 DNA were obtained at enrolment, one month after the third vaccination and every six months thereafter. The primary endpoint was persistent HPV-16 infection, defined as the detection of HPV-16 DNA in samples obtained at 2 or more visits. The primary analysis was limited to women who were negative for HPV-16 DNA and HPV-16 antibodies at enrolment and HPV-16 DNA at month 7. After follow-up of a median of 17.4 months after completion of the vaccination regimen, the incidence of persistent HPV-16 infection was noted to be 3.8 per 100 women-years at risk in the placebo group while 0 per 100 women-years at risk in the vaccine group (100% efficacy; 95% confidence interval, 90-100; $P<0.001$). All nine cases of HPV-16 related cervical intraepithelial neoplasia occurred among the placebo recipients.

DM Harper, et al. conducted a randomized double blind controlled trial in North America and Brazil to assess the efficacy, safety and immunogenicity of a bivalent L1 virus-like particle vaccine in the prevention of infection with HPV 16 and 18 in young women. One thousand one hundred thirteen women aged 15-25 years were randomized to receive 3 doses of the vaccine on a 0, 1 and 6 month schedule. The women were assessed for a total of 27 months after the last dose and the results reveal that the vaccine efficacy was 91.6% (95% CI 64.5-98) against incident infection and 100% (47-

100) against persistent infection with HPV 16 and 18. In the intention to treat analysis, the efficacy was 95.1% (63.3 – 99.3%) against persistent cervical infection and 92.9% (70-98.3%) against cytological abnormalities associated with HPV 16 and 18 infections. The vaccine was generally safe and well-tolerated and highly immunogenic. Vaccination against such infection was therefore concluded to substantially reduce the incidence of cervical cancer.

Currently, the Human Papilloma Trial against Cervical Cancer in Young Adults is being conducted among women ages 15-25 years in study regions that include the Asia Pacific (the Philippines included)-Europe, Latin America and North America. It is focused on the vaccine against the two high risk types HPV 16 and 18 with emphasis on its efficacy, safety and immunogenicity. Preliminary results are very promising.

The cost-effectiveness of such potential vaccines has also been studied by Sanders[1], et al. in 2003. They evaluated the usefulness of a potential vaccine against high-risk HPV types administered to adolescent girls and found it to be cost-effective as compared to current practice that includes routine Pap tests every 2 years starting at the age of 16 years. Although the increase in quality-adjusted life expectancy from a vaccination program is modest for the individual, the increase aggregates to substantial numbers of HPV infections, cases of cervical cancer and prevented cancer-related deaths. Furthermore, the life expectancy gains are similar to those realized by current vaccination programs. Vaccination against high-risk HPV saved 2.8 life days and 4.0 quality-adjusted life days per person. In comparison, vaccinations against measles, mumps, rubella and pertussis each save 2.7, 3.0, 0.3 and 3.3 life days, respectively. Sensitivity analyses found that the HPV vaccine would be cost effective, even assuming vaccine efficacy as low as 40% or that booster shots would be required every 3 years.

From the data gathered in this cost-effectiveness analysis study, several assumptions about the target vaccination population and program implementation were made. First, a school-based rather than a clinic-based vaccination program is proposed since school-based programs provide an infrastructure in which to vaccinate adolescents and the three-dose HPV vaccination regimen can be fitted into the academic year which will increase the compliance while containing the costs. Second, it is proposed that a universal vaccination program be provided rather than targeting specific high-risk groups since identification of these high-risk groups may not always be feasible. Lastly, it is proposed that vaccination be given to girls at an early adolescent age of 12 years. A significant proportion of adolescents are sexually active by 15 years, therefore, vaccination at 12 years of age aims to include as many girls as possible before sexual activity begins and HPV infection risk increases. In addition, studies using Hepatitis B vaccines as proxy have found better immune responses in younger persons and have shown that younger children require lower doses. Finally, it is believed that a 3-dose school-based vaccination program aimed at 12-year olds will result in greater compliance because adolescents of this age have more consistent school attendance. It is, therefore, hoped that such vaccine would eventually become part of the childhood vaccination program of each country so that it may be available to everyone especially the low-income group who may not be able to afford the high cost of such vaccine.

The Advisory Committee on Immunization Practices (ACIP) recommends that the HPV vaccine be routinely given to girls when they are 11-12 years old. The ACIP recommendation also allows for vaccination of girls beginning at nine years old as well as vaccination of girls and women 13-26 years old. According to the ACIP's recommendation, three doses of the new vaccine should be routinely given to girls when they are 11 or 12 years old. The advisory committee, however, noted that the vaccination series can be started as early as nine years old at the discretion of the physician or health care provider. The recommendation also includes girls and women 13-26 years old because they will benefit from getting the vaccine. The vaccine should be administered before onset of sexual activity (i.e., before women are exposed to the viruses), but females who are sexually active should still be vaccinated.[8]

Several institutions, including Merck Research Laboratories and GlaxoSmithKline are developing

and testing prophylactic HPV vaccines. In fact, these vaccines will be commercially available soon. However, before an HPV vaccination program is successfully implemented, social, cultural and political issues will need to be addressed and agreed upon by stakeholder groups, including pediatricians, public health officers, parents, adolescents, school administrators and community leaders[1]. Acceptance of a potential HPV vaccine will depend highly on the knowledge and attitude of these groups of people with regards the risks associated with HPV infection, as well as, the benefits of the vaccine against it.[5,6,7]

Objectives of this Study

This study is undertaken in order to determine HPV knowledge and priorities and HPV vaccine acceptability among mothers of adolescents in the Philippine General Hospital. Specifically, this study aims to evaluate the relationship between acceptability of an HPV vaccine and sociodemographic, reproductive and sexual history variables, vaccine usefulness and knowledge of cervical cancer etiology.

Materials and Methods

Overview of Study Design

The study employed a cross-sectional design to determine the knowledge of Filipino mothers regarding illnesses caused by Human Papillomavirus as well as their attitude regarding the administration of HPV vaccine to their adolescent daughters.

Study Population and Selection of Respondents

The target population was composed of Filipino mothers with daughters aged 12 to 15 years old, seeking consult at the OB-GYNE Clinic of the Outpatient Department and at the Gynecologic Clinic of the Cancer Institute of the Philippine General Hospital. Excluded in the study were those who refused to participate.

Recruitment of the subjects was voluntary and a written, informed consent was obtained from the respondents.

Sample Size

A total of 195 participants were included in this study.

Description of Study Procedure

This study was conducted in the Outpatient Department and Cancer Institute of the Philippine General Hospital. Recruitment of subjects was done over a one-month period.

A self-administered survey instrument or questionnaire was developed for this study using sociodemographic, reproductive and sexual history variables, vaccine usefulness and knowledge of cervical cancer etiology. The questionnaire was then translated to the vernacular. The initial questionnaire form was pre-tested among Filipino mothers with daughters aged 12-15 years in the Cancer Institute of the Philippine General Hospital. Revisions were then made prior to final administration.

The questionnaire forms were distributed to the respondents. The questionnaires were self-administered under the supervision of a clerk, intern, resident or fellow of the department in case clarifications were needed and to check the completeness of forms.

The research protocol was submitted to the Research Implementation and Development Organization and Ethical Review Board for approval.

Statistical Analysis

The continuous variables were initially examined in terms of their original distribution before being analyzed as categories. Acceptability of HPV vaccine was used as the dependent variable for evaluation and quantification of associations.

To evaluate the relationship between the acceptability of an HPV vaccine and sociodemographic, reproductive and sexual historical variables and knowledge of cervical cancer etiology, P values were estimated using the Pearson's chi-square test or the Fisher's exact test. Eta, a measure of association was also employed.

Results

A total of 195 mothers participated in the study conducted during the month of July 2006, with a

mean age of 42 years, 6.58 SD (range of 28-59 years). Only half of the participants were employed. Seventy-eight percent were married, 11 percent were separated, 6.3 percent were widowed and 4.2 percent were common-law partners. Twenty four percent finished elementary schooling, 33 percent were high school graduates, 32 percent had college degree and 11 percent finished a postgraduate course. Approximately 75 percent were in the low income bracket with gross family income of less than P15,000.00 per month, 15 percent were earning between P15,000 – P30,000 per month and only 9 percent had monthly earnings more than P30,000.00.

The mean age of first coitus among the partipicants was 22 years, SD 4.9 (range 12-39 years), with the mean number of sexual partners at 1.21 SD 0.518 (range 1-5). Thirty-nine percent never had a Pap smear yet while the rest had at least one. The mean number of livebirths is 3.4 SD 1.843 (range of 1-11). Sixty percent had not used any form of contraception while the rest had tried various forms, with oral contraceptive pills as the most common, followed by the use of the withdrawal method.

Of the 195 participants, only 14.4 percent have heard of the Human papillomavirus prior to the conduct of this study. Eighty-four percent never heard of it before while 1.5 percent did not respond to the question. Knowledge of HPV was obtained from the television, followed closely from the doctors.

Only 31.8 percent have identified HPV as a specific risk factor for the development of cervical cancer although 56.4 percent think that it is caused by an infection that is sexually transmitted. Acceptability of a potential HPV vaccine in this study population was high at 75.4 percent. The main reason for the acceptance of such vaccine was the knowledge of its general usefulness in preventing illnesses, in particular, the cervical cancer. Fifty-five percent of those who accepted the HPV vaccine thought that it should be given at any age prior to any sexual activity while 29.3 percent thought that it should be given between 12 to 15 years of age. The main reason for non-acceptance of the vaccine was its prohibitive cost. In fact, for those who responded affirmatively to giving the vaccine to their daughters, only 51.8 percent would still agree to giving it if it will cost as much as P15,000.00, although most of them explained that only if their resources would allow it, they would be still be willing to have their children vaccinated. Another reason for non-acceptance is that it might promote or encourage unsafe sexual behavior among the adolescents. Majority of the respondents (87.8%) thought that men should also be vaccinated against HPV in order to protect their partners from contacting the infection.

The relationship between acceptability of an HPV vaccine and the participants' sociodemographic, reproductive and sexual history variables were evaluated using either the Pearson Chi-square or the Fisher's Exact Test. Although no significant association was found between acceptability of an HPV vaccine with any of these variables, it is noteworthy that there is decreasing percentage of acceptability as the gross family income increases, meaning, the lower the gross family income, the higher the acceptability for an HPV vaccine. There were also higher rates of acceptability in patients who finished at the most secondary schooling only compared to those who were able to finish a college degree or a postgraduate course.

Eta, a measure of association that ranges from 0-1 (0 indicating no association and values close to 1 indicating a high degree of association), was also used for dependent variables measured on an interval scale (i.e. age). Among the dependent variables included in the questionnaire, it was noted that a participant's knowledge of HPV and cervical cancer has direct, although weak association with her acceptance of an HPV vaccine (Eta score of 0.159), followed by the number of livebirths (Eta score of 0.121). Other variables such as the participant's age, number of sexual partners, age at first coitus and the number of times that the patient had a Pap smear has less than 0.1 Eta scores.

Discussion

The success of a vaccination campaign strongly depends on the acceptance of the population for which it was developed. Given the fact the HPV vaccines are prophylactic and will provide the

greatest public health benefit prior to infection with the virus, the major targets of HPV vaccination campaigns should be pre- and early adolescents. Parental consent will therefore be required. The acceptability of adolescent HPV vaccination to parents, therefore, is a critical issue.[6]

The findings of this study suggest that although knowledge regarding Human papillomavirus, as well as its causal relation to cervical cancer, is low, the acceptance of a vaccine against it is remarkably high. This finding is consistent with other studies, particularly those conducted among mothers in Cuernavaca, Mexico[5] and in two qualitative studies conducted in the United States.[9,10] The main reason for the acceptance of such vaccine was the knowledge of its general usefulness in preventing illnesses, in particular, the cervical cancer. There is a direct, however weak, association noted between acceptability of the HPV vaccine and the knowledge of the participants regarding the virus and its causation in cervical cancer. The number of livebirths is also weakly associated with acceptability of the vaccine. Other sociodemographic, reproductive and sexual history variables were not significantly associated with the vaccine acceptability, although it is noteworthy that in this group of women, there seems to be a higher acceptability for women in the low income group and those who finished at most, secondary education only.

Although some parents are concerned regarding the sexual transmissibility of HPV and that allowing their daughters to be vaccinated against the virus may be misinterpreted as consenting to risky sexual behavior at an early age, this is not their main reason for non-acceptance of the vaccine. It is actually the prohibitive cost of the vaccine that hinders them from agreeing to vaccinate their children. This is another issue that needs to be addressed if a successful campaign against cervical cancer is aimed. Pap testing has been highly effective in preventing cervical cancer but not in developing countries such as the Philippines. This may also be the case for HPV vaccination if it does not become a public health priority. It is, therefore, hoped that such vaccine would eventually become part of the country's childhood vaccination program to make it available especially to those in the low-income group who may not be able to afford the high cost of such vaccine.

Conclusion

Increased education of Filipino women regarding HPV and its association with cervical cancer is needed. Knowledge of the benefits of a preventive vaccine should be emphasized. Initiation of an immunization campaign that targets adolescents who are not sexually active might be quite difficult and should include educational programs aimed at mothers of these individuals. Inclusion in government programs for widespread immunization of children and preadolescents might answer the problem of the high cost of the vaccine and may contribute significantly to the success of this endeavor.

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Sexual Behavior of Gynecologic Cancer Survivors and Their Partners

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Sexuality is an integral part of a woman as a person. This is most often neglected among women afflicted with gynecologic cancers. Sexual dysfunction during and after treatment for gynecologic cancers has been widely studied. Only a few though have involved the partners to participate actively in such studies. **Objective**: This study aims to determine the physical and emotional aspects of sexual behavior among cancer patients and their partners. **Methods**: Nintey-six gynecologic cancer patients and their partners were interviewed individually using a standardized questionnaire. Their sexual practices and other emotional aspects of sexuality prior to, during, and after treatment were included in the questions. **Results**: Mean age of patients was 41.66 years while 49 years for partners. Patients included cervical, endometrial, and ovarian cancer cases (a third each). Prior to treatment, there was sexual bliss in more than ½ of patients and more than 80 % of partners. Only 24 % of patients had sexual intercourse during treatment. The most common reason for avoidance is fear and anxiety. Post-treatment, there were decrease in sexual activity, orgasm, and satisfaction among patients but to a less degree among their partners. Analysis by organ involvement showed that the greatest dysfunction was seen among cervical cancer patients. Analysis according to treatment showed that the patients who underwent surgery plus radiotherapy had the greatest dysfunction. **Conclusion**: Sexual dysfunction appeared during and after treatment including decrease in frequency of sexual activity, decrease in orgasm, and diminished sexual satisfaction. Cervical cancer patients exhibited the greatest dysfunction. Surgery plus radiation combination treatment was associated with the greatest dysfunction. The patients exhibited a greater dysfunction compared to their partners.

Key words: sexual dysfunction, gynecologic cancer

The emergence of the best possible treatment modalities for gynecologic malignancies has made oncologists and patients alike optimistic of complete cure. Surgery, radiotherapy and the newly discovered chemotherapeutic agents alone or in combination are considered the mainstay therapy. Most institutions report better survival rates among patients who receive such treatments. It is indeed the cure from cancer the utmost goal of any practicing oncologist for his patient but there are other aspects in the holistic management of person inflicted with cancer. Unfortunately, these are often relegated to as minor and often been neglected.

One particular aspect of treatment of gynecologic cancer patients that have been most often neglected is her sexuality. It is an integral part of a woman as a person, integrating the physical, emotional, intellectual and social aspects of her being. Borg in his lecture described it as "much more than sex, which therefore cannot be destroyed by cancer or cancer treatment, yet often significantly changed in inhibited."[1] Sexual dysfunction during

and after treatment for gynecologic cancer had been recognized and reported in previous years. At the Philippine General Hospital, Cardenas, et al.[2] have reported that women treated for cancer have abandoned sexual activities because of anxiety, fear of recurrence and low sex urge. Decrease in the frequency, desire and satisfaction, difficulty in achieving orgasm and dyspareunia have all been experienced by these women. Frequency of intercourse decreased by 31 percent because the desire for sex has decreased by 50 percent. In their 100 patients, almost one third were completely shunning sex because of anxiety on recurrence and low sex urge.

The impact of cancer diagnosis and treatment likewise affect not only the physical aspect of sexuality. Borg, reported that change in self-image, crisis related to loss and sin and shame have all contributed to the negative impact of cancer on sexual health.[1] The way one perceives oneself or one's body can be destroyed by cancer. The psychological experience of the loss of an organ is dependent upon the meaning this organ has been given as part of the person's own identity (e.g. breast) and this can result to depression, isolation and withdrawal. It was also known that patients see the occurrence of cancer as punishment for past behavior. In a European study by Veronesi in 1999, patient's perception on the treatment of their cancer have been identified and has shown that women's knowledge about cancer before diagnosis is poor and they are not being adequately prepared and educated about what to expect from treatment.[3] It was emphasized in the study that although the family provides support to them, they also derive considerable support from healthcare professionals.

Most studies conducted on sexuality among cancer patients have been solely among the patients themselves. Sexual partners were often not recruited to actively participate, knowing that they play an important role in providing support and care to their loved ones. Better perception and more concrete description of the problems arising from cancer can be unearthed if the constant life partner can collaborate.

This study aims to determine the changes in the physical and emotional aspects of sexual behavior among cancer patients and their partners. This will likewise compare the difference among the treatment modalities and lesion types on their impact on the patient's sexuality.

Materials and Methods

Subjects

Ninety-six gynecologic cancer patients and their sexual partners from the Gynecologic Oncology Section of the Cancer Institute of the Philippine General Hospital fulfilled the following inclusion criteria:

1. Sexually active prior to the appearance and diagnosis of cancer
2. Has completed the recommended treatment protocol on the specific type of gynecologic cancer
3. Currently no evidence of disease
4. No contraindications for sexual intercourse on both the patient and her sexual partner
5. Sexually active at the time of interview

Of the 96 patients, 32 (33.3%) were cervical cancer patients, 32 (33.3%) were endometrial cancer and 32 (33.3%) were ovarian cancer patients. Fifty-five were treated with surgery with or without chemotherapy, 27 were treated with surgery plus radiotherapy with or without chemotherapy and 14 were treated with radiotherapy with or without chemotherapy (Table 1).

Table 1. Diagnosis and treatment.

	Surgery	Radiotherapy	Surgery + Radiotherapy	Total
Cervix	6	14	12	32
Endometrium	17		15	32
Ovary	32			32
	55 (57.29%)	14 (14.58%)	27 (28.13%)	96

Methods

This study used the standardized questionnaire, each for the patient and the sexual partner. Personal data such as age, gravidity and parity, age of onset of first intercourse, and number of sexual partners were determined. Each of the couple was interviewed separately. The purpose of the study was discussed with the couples and they were encouraged to answer as truthfully as possible. Establishing rapport with each subject was initially difficult because of the too personal queries in the questionnaire. However, the subjects after sometime became relaxed and readily answered each question. They were asked to recall their sexual practices before the diagnosis and compare them to their present sexual practice. The frequency of sexual activity, how often they achieved orgasm and their satisfaction were asked. The emotional aspect of sexuality was discussed by asking the perceived changes of each couple towards each other, both during and after treatment.

Results

The mean age of all patients was 41.66 years and all the partners, 49 years. The ovarian cancer patients were generally younger (mean = 30) and the endometrial cancer patients were generally older (mean = 53). Younger age of first sexual intercourse was seen among the cervical patients. They also had the most number of sexual partners (mean = 1.4). The average number of months of no evidence of disease was 23 months. The longest no evidence of disease was in early stage (IA) well differentiated endometrial adenocarcinoma.

Prior to the diagnosis, the couples were enjoying sexual bliss. In their 3.6 per week sexual intercourse, all patients and their partners experienced orgasm in every sexual activity. All the couples engaged in foreplay (kissing, necking and petting). More than half of the patients and over eighty percent of the partners were always satisfied. No one among the subjects were never satisfied in their sexual activity. Only 11.45 percent of the patients experienced dyspareunia (crampy hypogastric pain, during and after sex) and none among their partners. Their usual method of sexual gratification was genital intercourse (55.2%). Only 37 (38.5%) patients practiced combined genital and oral sex. Other forms of sexual gratification combined with genital and oral sex were practiced by 6 (6.24%) of them. Masturbation although practiced predominantly by the partners was likewise practiced by 1 5(15.62%) patients.

In general, the patient experienced greater changes in the sexual behavior after treatment. The frequency of sexual activity diminished from 3.6/ week to just 2.1 per week. Orgasm diminished by more than ten percent. Those patients who were experiencing dyspareunia increased more than three times after the treatment. Four (4.16%) of the partners who never had dyspareunia had occasional pain after treatment. Satisfaction among the patients also decreased. Only 50 (52.08%) women were always satisfied, the remaining women were either sometimes satisfied or often satisfied. Six (6.25%) women were never satisfied after treatment. Most partners however were still always satisfied, and all were having orgasm. The method of sexual gratification had very slight changes. Masturbation was still being practiced but to a less degree.

Table 2. Comparison of sexual behavior in all subjects (n = 96).

	Before Diagnosis	After Treatment
Frequency	3.6 / week	2.1 / week
Method		
Genital only	53 (55.2%)	51 (53.12%)
Genital + oral	37 (38.5%)	42 (43.74%)
Genital + oral + others	6 (6.24%)	3 (3.1%)
Foreplay	96 (100%)	96 (100%)
Orgasm		
Patient	96 (100%)	84 (87.5%)
Partner	96 (100%)	96 (100%)
Dyspareunia		
Patient	11 (11.45%)	36 (37.5%)
Partner	0.0%	4 (4.16%)
Satisfaction		
Patients		
Always	53 (55.2%)	50 (52.08%)
Often	19 (19.79%)	21 (21.91%)
Sometimes	24 (25%)	19 (19.79%)
Never	0 (0.0%)	6 (6.25%)
Partner		
Always	80 (83.33%)	86 (89.58%)
Often	16 (16.67%)	8 (8.3%)
Sometimes	0.0%	2 (2.8%)
Never	0.0%	0.0%
Masturbation		
Patient	15 (15.625%)	6 (2.8%)
Partner	93 (96.87%)	87 (90.62%)

During treatment, only 23 (23.95%) patients had sexual intercourse, 71 (73.95%) did not and two couples tried but failed (Table 3). Of those who had sex, 17 (73.9%) of the patients and 23 (100%) of the partners had orgasm (Table). The most common reason of avoiding sexual intercourse was fear or anxiety [79 (55.6%)] (Table 5). Twenty two (15%) were because the partner refused to have sex. Decreased libido, genital pain and "may hurt partner" got 7.7%, 9.8% and 8.4% votes, respectively. Other reasons were weakness and "as advised". During treatment, 6 (6.25%) women and 95 (98.95%) of their partners practiced masturbation.

During treatment, the most commonly perceived change in sexual behavior among the patients was decrease in libido (60.41%) (Table 6). After treatment, this decreased to 43.75% percent, 6.25 percent noted improvement and 13.54 percent returned to normal. As perceived by their husbands, 46 (47.9%) had decreased libido during treatment but decreased to 19.8 percent after treatment. Fourteen percent had low self-esteem during treatment but 30.72 percent returned to normal and 6.25 percent improved after treatment.

Table 3. Summary of sexual behavior during treatment.

Couples who had sex	23 (23.95%)
Couples who did not have sex	71 (73.95%)
Couples who tried but failed	2 (2.08%)

Table 4. Comparison of sexual behavior during treatment.

	Orgasm (n = 23)	Masturbation (n = 96)
Patient	17 (73.9%)	6 (6.25%)
Partner	23 (100%)	95 (98.95%)

Table 5. Summary of reasons for not having sexual activity during treatment. n = 142 (71 + 71)

Fear / anxiety	79 (55.6%)
Partner refused	22 (15.99%)
Genital pain	14 (9.8%)
Did not want to hurt partner	12 (8.4%)
Decreased libido	11 (7.7%)
Weakness	3 (2.1%)
As advised	1 (0.7%)

Table 6. Perceived changes in all patients during and after treatment.

	During Treatment		After Treatment	
As perceived by				
Patient (herself)	Decreased libido	57 (59.37%)	Decreased libido	42 (44.7%)
	No change	36 (37.5%)	No change	34 (35.41%)
	Increased orgasm	3 (3.12%)	Increased orgasm	1 (1.04%)
			Improved	6 (6.25%)
			Returned to normal	12 (13.54%)
Partner (husband)				
	Decreased libido	46 (47.9%)	Decreased libido	19 (19.8%)
	No change	36 (37.4%)	No change	41 (42.8%)
	Low self esteem	14 (14.58%)	Returned to normal	29 (30.72%)
			Improved	7 (7.29%)

As for the husbands (partners), they perceived themselves to have no change in their sexual behavior during treatment (83.33%). Only 16.67% noted decreased libido. Their wives agreed that there were no changes in their partners' behavior (85.41%). After treatment, the husbands noted improvement of their sexual behavior (13.54%) but according to their wives, only 6.25 percent had improvement. 82.29 percent of the husbands still mentioned that they did not change at all and 75 percent of their wives agreed. (Table 7).

When analyzed by organ involvement, cervical cancer patients were distinctly sexually dysfunctional. They resumed sexual intercourse after an average

of 18.2 weeks. Frequency decreased by 50 percent, orgasm decreased by 20 percent, dyspareunia increased by more than ten times (6% to 65%), and satisfaction decreased by more than half. All partners however did not show any significant change. (Tables 8, 9 & 10)

When the data were analyzed according to the treatment received, the 27 patients who underwent surgery plus radiotherapy had the most dysfunctional sexual behavior. They had a lower rate of orgasm [19 (70.37%)] and a higher rate of dyspareunia [18 (66.67%)]. No patient was always satisfied sexually and had the highest rate of dyspareunia [18 (66.67%)]. No patient was always satisfied sexually and had the highest rate of no sexual satisfaction at all [5 (18.5%)]. Although all their partners still had orgasm, 3 (11.1%) experienced dyspareunia, resulting from a narrow, short and dry vagina. Only 19 (70.37%) reported to be always satisfied.

Discusion

Cancer remains one of the leading causes of death among women. Its cost to women's lives is staggering. It is not only economically but more importantly physically and emotionally devastating. Diagnostic and treatment modalities drain one's coffers but the emotional and physical damage it brings deplete one's self-confidence, self-esteem and self-worth.

As treatment modalities of gynecologic cancer improve, survivors can only be expected to increase in number. These survivors are eager to go back to the mainstream and resume normal life again. But having to do so, they have to face and conquer the damage that cancer brought.

Table 7. Perceived changes in all partners during and after treatment.

	During Treatment		After Treatment	
As perceived by				
Patient (wife)	Decreased libido	9 (9.37%)	No change	72 (75%)
	No change	82 (85.41%)	Increased libido	14 (14.58%)
	Increased libido	2 (2.08%)	Depressed	4 (4.1%)
	Depressed	3 (3.12%)	Improved	6 (6.25%)
Partner (himself)				
	Decrease libido	16 (16.67%)	Decreased libido	4 (16%)
	No change	80 (83.33%)	No change	79 (82.29%)
			Improved	13 (13.54%)

Table 8. Comparison of couples' sexual behavior according to organ involvement.

	Cervix		Endometrium		Ovary	
	Before Diagnosis	After Treatment	Before Diagnosis	After Treatment	Before Diagnosis	After Treatment
Interval time before resumption of regular sex after treatment in weeks		18.2		14		10.6
Frequency of sexual activities (per week)	4	2	3.7	2.1	3.1	2.3
Method of sexual gratification (n = 32)						
Genital	24 (75%)	20 (62.5%)	18 (56.25%)	20 (62.5%)	11 (34.37%)	11 (34.37%)
Genital + Oral	7 (21.8%)	9 (28.1%)	12 (37.5%)	12 (37.5%)	18 (56.25%)	21 (65.62%)
Genital + Oral + Others	1 (3.2%)	3 (9.3%)	2 (6.25%)	0.0%	3 (9.37%)	0.0%

Table 9. Comparison of patients' sexual behavior according to organ involvement.

	Cervix		Endometrium		Ovary	
	Before Diagnosis	After Treatment	Before Diagnosis	After Treatment	Before Diagnosis	After Treatment
Foreplay	32 (100%)	32 (100%)	32 (100%)	32 (100%)	32 (100%)	32 (100%)
Orgasm	32 (100%)	26 (81.5%)	32 (100%)	26 (81.5%)	32 (100%)	32 (100%)
Dyspareunia	2 (6.25%)	21 (65.62%)	3 (9.37%)	8 (25%)	6 (18.75%)	7 (21.87%)
Satisfaction						
Always	14 (43.75%)	5 (15.62%)	18 (56.25%)	17 (53.12%)	21 (65.62%)	18 (56.25%)
Often	10 (31.25%)	12 (37.5%)	6 (18.75%)	6 (18.75%)	3 (9.37%)	4 (12.5%)
Sometimes	8 (25%)	12 (37.5%)	8 (25%)	7 (21.87%)	8 (25%)	10 (31.25%)
Never	0.0	3 (9.3%)	0.0	2 (6.25%)	0.0	0.0
Masturbation	2 (6.25%)	0.0	4 (12.5%)	0.0	9 (28.125%)	2 (6.25%)

Table 10. Comparison of partners' sexual behavior according to organ involvement.

	Cervix		Endometrium		Ovary	
	Before Diagnosis	After Treatment	Before Diagnosis	After Treatment	Before Diagnosis	After Treatment
Foreplay	32 (100%)	32 (100%)	32 (100%)	32 (100%)	32 (100%)	32 (100%)
Orgasm	32 (100%)	32 (100%)	32 (100%)	32 (100%)	32 (100%)	32 (100%)
Dyspareunia	0.0	1 (3.125%)	0.0	1 (3.125%)	0.0	2 (6.25%)
Satisfaction						
Always	20 (62.5%)	32 (100%)	32 (100%)	24 (75%)	28 (87.5%)	30 (93.75%)
Often	12 (37.5%)	0.0	0.0	6 (18.75%)	4 (12.5%)	2 (6.25%)
Sometimes	0.0	0.0	0.0	2 (6.25%)	0.0	0.0
Never	0.0	0.0	0.0	0.0)	0.0	0.0
Masturbation	30 (93.75%)	24 (75%)	32 (100%)	32 (100%)	31 (96.87%)	31 (96.87%)

One of the most damaging effects of cancer treatment is on sexuality. Sex is one of the most precious elements of life that brings pleasure and harmony among couples. Losing one's sexuality and the ability to reciprocate is undeniably a blow to one's self esteem. For this reason, providing sexual rehabilitation for gynecologic cancer survivors is a very important part of treatment. However, are the gynecologic oncologists prepared to give what their patients are clamoring for?

Knowledge about patients' sexual behavior should be comprehensive. Most literatures have already recognized the sexual dysfunction among gynecologic cancer survivors. They have identified and predicted sexual difficulties and have provided suggestions for preventing and treating sexual morbidities. Evidently lacking are studies regarding the sexual functions or dysfunctions of the gynecologic cancer survivors' sexual partners. It is imperative that the partner should be included in whatever rehabilitation is provided to the patient. Obviously, treatment will not be as effective as it should be if only one of the couples is being treated. This study aims to determine the changes in the physical and emotional aspects of sexuality among gynecologic cancer patients and their partners.

Sexual dysfunction results both from the physical and psychological effects of treatment. The physical

changes that occur in gynecologic cancer patients are physical injury to the female genitalia, radiation changes resulting to vaginal dryness, urinary problems and pain/discomfort after hysterectomy. The psychological effects are secondary to change in self-image, crisis related to loss of an organ and sin and shame wherein patients see the cancer as retribution or punishment for past behaviors.[4]

The physical changes in the vagina are either loss of lubrication secondary to radiotherapy or a shortened vagina secondary to surgery. In a study made by Bergman K, et al., they have noted that twenty six percent of women reported insufficient vaginal lubrication, and another twenty six percent noted short vagina among cervical cancer patients.[5] These changes resulted a compromised sexual activity and result in considerable distress. In our study population, an increase in the number of patient experiencing dyspareunia was noted after treatment. This observation was also noted in most patients who have cervical cancer who underwent surgery and received radiotherapy. This set of patients also noted less orgasm and less satisfaction. Achieving orgasm among the patients was likewise affected by these physical changes. Cervical and endometrial cancer patients had difficulty achieving orgasm. Most of these patients received radiotherapy as either their primary or adjuvant treatment. Satisfaction was highly altered in the cervical cancer group. Their physical changes had little impact on the partners' sexual behavior. Some of them experienced dyspareunia. All of them achieved orgasm and most of them were always often satisfied with the sexual activity.

The psychological changes among patients are rooted on the change of self-image. Some patients assume that the loss of the uterus and ovaries rendered them "less of a woman. This notion eventually results to less sexual desire during and after the treatment period. Andersen in her paper "Predicting and Treating the Sexual Difficulties of Gynecologic Cancer Survivor" stated that "Of all the phases of the sexual response cycle, sexual excitement undergoes the greatest disruption."[6] She described the disruption to involve dysfunctional self-image, lowered arousability and reduced awareness of physiologic signs of arousal. From these disruptions, women tend to have orgasmic difficulty and increased level of dyspareunia. Of the 96 patients we interviewed, it was noted that only 23 (23.95%) of them had sexual intercourse during the treatment period. The most common reasons for not having sex are fear or anxiety and decreased libido, all related to the psychological changes mentioned above. Evidently, when asked about changes in their sexual behavior during the treatment period, we noted that 60 percent of the patients had decreased libido. Only 47 percent of their partners however noticed this change. What the partners noticed was their wives' low self-esteem (14%). After treatment, most patients and their partners noted improvement of the patients' sexual behaviour.

The psychological changes were not exclusive to the patients. On partners' response to the question, "what changes have you noticed about yourself during the treatment?", some noted decreased libido however, a bigger number noted 'no change'. Their wives likewise noted depression among their husbands. Unmistakably, the psychological problems of sexuality are more common among the patients. However, the 'no change' answers of the husbands and some with decreased libido are too remarkable not to be reassessed.

None of the 96 patients and their partners shunned sexual activity completely during treatment. Most patients and their partners who did not have sex during the treatment period practiced other types of sexual activity other than genital to genital contact. Some patients performed oral sex to satisfy their partners' needs. Likewise, the partners practiced other forms of sexual gratification to please their wives. Mutual or self-masturbation was practiced every so often. The couples were regularly performing necking, petting and kissing as forms of foreplay. This is very encouraging since most patients were aware of each other's needs and they were willing to discover and explore other forms of sexual gratification.

Voluntarily, some patients and most partners expressed the need for counseling. Some partners confided that their physicians did not discuss sexual

function to them and they were likewise hesitant to ask. They indicated that sexual activity could have been resumed earlier if they were advised. Most of them resumed genital intercourse on their own decision.

Conclusion

The sexual behavior of the gynecologic cancer survivors and their partners before diagnosis, during and after treatment has been described.

Pertinent conclusions include the following:

1. Sexual dysfunctions appeared during and after treatment. These included decrease in frequency of sexual activity, decrease in achieving orgasm, increased dyspareunia and diminished sexual satisfaction.
2. Cervical cancer patients appeared to be more sexually dysfunctional than endometrial and ovarian cancer patients during and after treatment.
3. The form of treatment is greatly related to the degree of dysfunction.
   a. Surgery + Radiotherapy greatly caused sexual dysfunction among the gynecologic cancer survivors.
4. Both patient and partner exhibited sexual dysfunction but in a less degree among the partners.

Recommendation

Knowledge of the sexual behavior for gynecologic cancer patients and their partners is pertinent in the holistic treatment of cancer. Further studies that will identify specific physical and psychological changes may lessen sexual dysfunction. Questionnaires containing specific queries about the partners'viewpoint will greatly improve the results.

Counseling should be a fundamental part of the gynecologic oncologists' treatment scheme. Brief sexual counseling includes[7]:

a. Educating patients about treatment-related sexual problems
b. Encouraging patients to resume sex during and after treatment
c. Encouraging open sexual communication between partners
d. Helping patients cope with physical handicaps
e. Advising patients on overcoming specific sexual dysfunctions

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A Successful Pregnancy After Conservative Management of Endometrial Cancer Associated with Polycystic Ovary Syndrome*

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Endometrial cancer can occur in patients less than 40 years of age. The classical treatment is total abdominal hysterectomy with bilateral salpingo-oophorectomy with lymphadenectomy. This surgical treatment is unacceptable in women who wish to preserve their family. Conservative management of early-stage, well-differentiated endometrial carcinoma is possible. In this paper, a case of a successful pregnancy in a patient with PCOS and subsequently diagnosed with endometrial cancer managed conservatively was presented and similar cases in the literature were reviewed. The risk factors, pathophysiology, criteria for patient selection, treatment and pregnancy outcomes were described.

Key words: endometrial adenocarcinoma, conservative treatment, fertility preservation, progesterone/hormonal therapy

Endometrial adenocarcinoma is the most common gynecologic malignancy diagnosed in the United States. In the Philippines, it ranks 9th among the leading female cancer sites with a 3.2 percent incidence rate.[1] Although endometrial cancer is more common in postmenopausal patients. About 1.5 – 14 percent of cases occur in women younger than 40 years of age.[2] In a local study done on endometrial carcinoma in women 40 years old and younger, the incidence is 12.4 percent.[3] In this premenopausal group, endometrial cancer is more common in those with chronic anovulation, obesity or estrogen-producing tumors.

Typical treatment consists of total abdominal hysterectomy with bilateral salpingo-oophorectomy, peritoneal fluid cytology and lymphadenectomy[4], an option which may be unacceptable to those desirous to preserve childbearing potential. In fact, some of these patients initially consulted in an infertility context. Since it has been previously shown that endometrial adenocarcinoma in young women are typically associated with good prognosis because of early stage and high tumor differentiation at diagnosis[5], conservative therapy may be recommended to preserve fertility in carefully selected cases.

Multiple reports have proposed that such patients may be treated with hormonal therapy.[6-10] Although there is no standard regimen of medical management to allow subsequent pregnancy, the literature has identified several patients who were managed with high-dose progestational agents.[2] A recent retrospective study evaluated the efficacy of high-dose progestins in the treatment of complex

* Won second place in the SGOP Interesting Case Paper Contest for Fellows and Residents 2006.

hyperplasia with atypia and well-differentiated adenocarcinoma.[6] In the series by Randall and Kurman, 5 (20%) of 25 women who attempted conception following conservative treatment of endometrial cancer had successful full-term pregnancies. These findings were consistent with other case series of a similar nature.[7] However, no controlled studies have evaluated pregnancy rates in endometrial cancer managed as such.

This paper presents a patient with PCOS conservatively treated for endometrial adenocarcinoma with subsequent conception and successful delivery.

The Case

This is the case of RA, a 32 year old, G0, from Bulacan who consulted a tertiary hospital for primary infertility of six years.

The patient has no history of hypertension, diabetes, bronchial asthma, pulmonary tuberculosis, allergies or any previous hospitalization.

There is diabetes and hypertension in the patient's parents.

The patient is married, a college graduate, a housewife with no vices. Her first coitus was at age 24 with a single, non-promiscuous sexual partner. She has a history of oral contraceptive pill use for 1 year (1993).

The patient's menarche was at 13 years of age, with subsequent menstrual periods occurring at irregular intervals, of 4-5 days duration, and with associated dysmenorrhea. She used 3-4 pads a day.

The patient has been married for 6 years, with regular coitus but no children. She had a transvaginal ultrasound done previously which revealed normal findings. Persistent infertility prompted initial consult.

Physical examination shows an overweight female (BMI=28) with essentially normal physical findings. Initial internal examination shows normal external genitalia, a nulliparous vagina, closed and smooth cervix, a small corpus, and no adnexal masses or tenderness.

Fertility work-up was done. Transvaginal ultrasound revealed polycystic ovaries and a thickened endometrium (endometrial thickness of 1.5 cm) (Figure 1). Hysterogram demonstrated mucosal irregularities (interpreted as likely due to myomata) and an obstructed right oviduct. Left oviduct was patent. Semen analysis showed asthenoteratospermia (Table 1). The patient was then started on Clomiphene citrate for ovulation induction, starting at 50 mg once a day on day 2 to day 5 of cycle and was gradually increased to 150 mg once a day on day 2 to day 5 of cycle since there was no initial response. She was also started on Metformin 500 mg, three times a day. Six months later and without successful conception, Clomiphene citrate and Metformin were discontinued and diagnostic laparoscopy, diagnostic hysteroscopy, ovarian drilling, chromotubation, endometrial and endocervical curettage were performed. Intraoperative findings showed no ascites and no pelvic lymphadenopathy. The uterus was anteverted and small. There was note of a 0.5 cm x 0.5 cm fleshy, polypoid mass located at the anterofundal area, and both ovaries were polycystic. On chromotubation, there was no egress of dye from the right fallopian tube but the left fallopian tube was patent. Histopathology of the curettings revealed an endometrial polyp and scanty endocervical tissues (Figures 2 & 3). A repeat transvaginal ultrasound was done a month later and it showed a normal uterus and left ovary, with a physiologic right ovarian cyst. Clomiphene citrate and Metformin were thus resumed after two months and intrauterine insemination was done a month later. After 2 months of amenorrhea, test for pregnancy was positive. However, ultrasound during her monthly prenatal check up revealed a blighted ovum. Dilatation and curettage were performed and histopathology of the placental tissues revealed a well-differentiated adenocarcinoma, endometrioid type (Figures 4, 5 & 6). A transvaginal ultrasound done one week post-curettage revealed a possible endometrial pathology with normal uterus. The patient was subsequently referred to a gynecologic oncologist.

Considering the patient's age, her histologic diagnosis, laparoscopic and ultrasound findings, and as well as her desire for future childbirth, conservative management of the endometrial carcinoma was pursued. A fractional curettage for thorough endometrial sampling was performed a

Table II. Semen analysis report.

	Reference value	Patient's value
Volume (ml)	3 - 5 ml	2.5 ml
Total count (M/ml)	60 - 150 M/ml	53.7 M/ml
Viscosity		Normal
Motility %		
Rapid		25%
Sluggish		14%
Non-progressive		5%
Non-motile		56%
Total progressively %		
Motile %	> 50%	39%
Normal forms %	> 50%	34%
Cellular elements		
Presence	Mild	Moderate debris
Type		Mild-epithelial cells
White Blood Cells	1-3 hpf	3 - 5 hpf
Others	Mild	None found

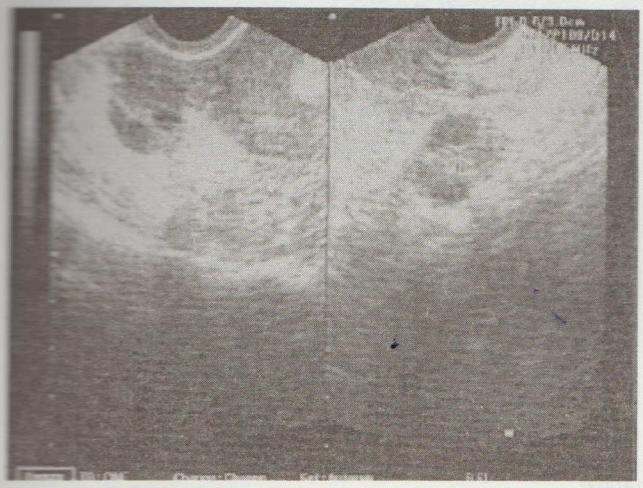

Figure 1. An ultrasound picture showing a thickened endometrium and polycystic ovaries.

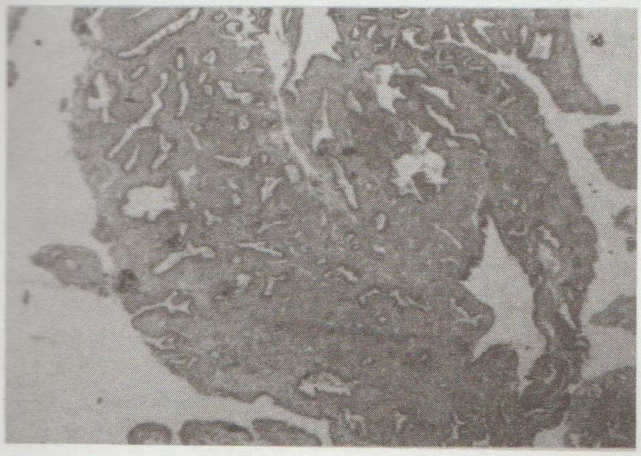

Figure 2. Histopathologic results of diagnostic hysteroscopy, endometrial and endocervical curettage revealing an endometrial polyp (100x).

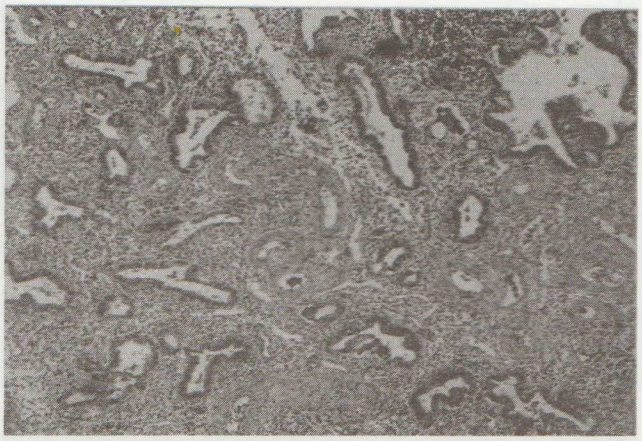

Figure 3. Histopathologic results of diagnostic hysteroscopy, endometrial and endocervical curettage revealing an endometrial polyp (400x).

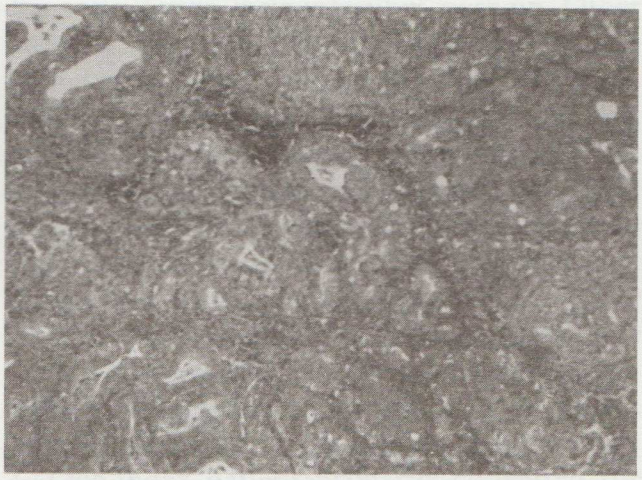

Figure 4. Endometrial curettings after a blighted ovum showing endometrial adenocarcinoma, well-differentiated (100x).

Figure 5. A higher magnification showing a well-differentiated endometrial adenocarcinoma (400x).

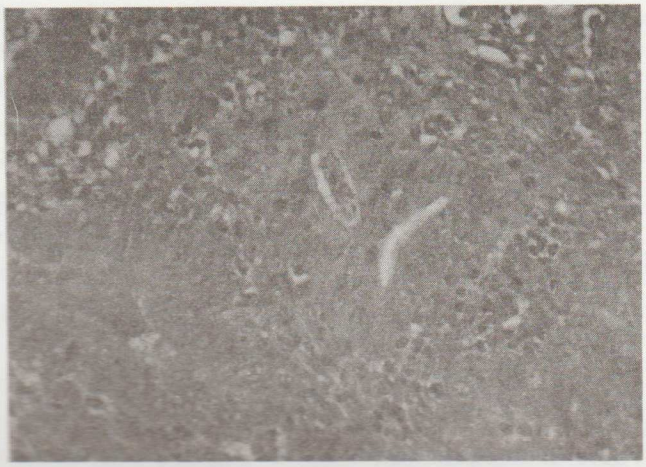

Figure 6. A higher magnification showing a well-differentiated endometrial adenocarcinoma (400x).

month later and histopathology revealed a secretory endometrium and chronic endocervicitis with focal squamous metaplasia. The patient was then started on Megestrol acetate 160 mg daily. Three months later, the patient reported vaginal bleeding. Transvaginal ultrasound during this time demonstrated an ill-defined hypoechoic mass measuring 0.9 cm x 0.7 cm within the endometrial cavity. Repeat fractional curettage revealed an asynchronous endometrium: secretory phase glands (Figure 7) and proliferative phase glands (Figure 8). She was then shifted to a GnRH agonist, Leuprolide acetate 3.75 mg intramuscularly, once a month which was given for 6 months. Another transvaginal ultrasound and fractional curettage were performed thereafter, which showed polycystic ovaries with normal uterus. Histopathology revealed no evidence of malignancy for both endometrial and endocervical tissues (Figures 9 and 10). With the latter finding, the patient was once again resumed on Clomiphene citrate and Metformin, taken for 3 months but without success. She was put on therapeutic rest for 3 months. On the 4th month, she was given FHS (Puregon). Transvaginal ultrasound was done and findings were as previously reported. Her CA-125 level was determined to be normal (5.2 U/mL). The patient was then placed on therapeutic rest for 10 months. During this time, she was having irregular menses, occurring every 2 months. She later experienced amenorrhea lasting for 3 months, and fortunately, 5 years and 3 months after the first consult, she became pregnant without any active management. She subsequently delivered via low segment cesarean section for non-reassuring fetal status a live baby girl, 3700 gm, 38 weeks by PA, with an APGAR score of 9-9. Intraoperatively, the endometrium was not suspicious for malignancy. No tumor could be identified in the placenta.

The patient refused hysterectomy post-delivery.

Presently, she has no evidence of disease and is pregnant with her 2nd child.

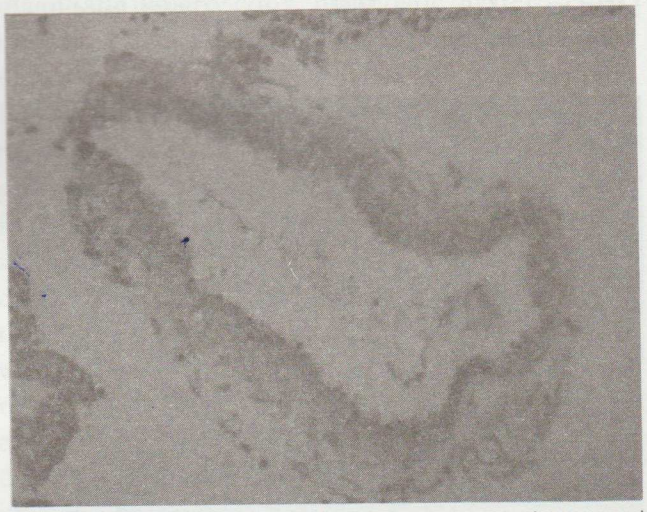

Figure 7. Curettage specimen taken after treatment with Megestrol acetate showing asynchronous endometrium - secretory phase (400x).

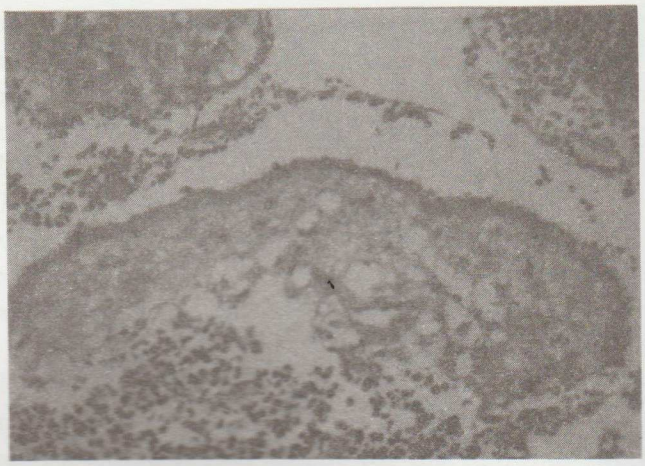

Figure 8. Curettage specimen taken after treatment with Megestrol acetate showing asynchronous endometrium - proliferative phase (400x).

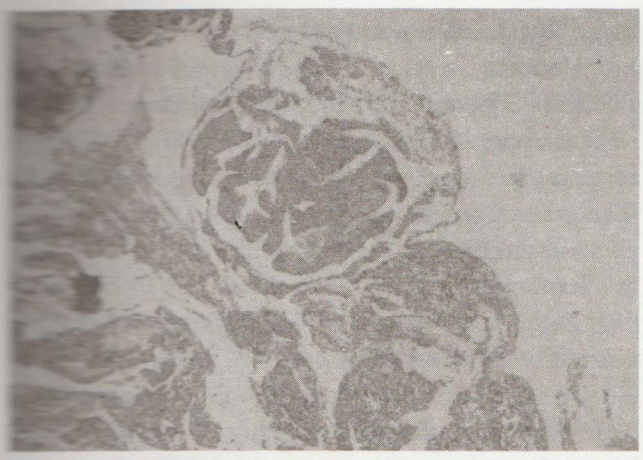

Figure 9. Curettage specimens taken after treatment with GnRH agonists showing no evidence of malignancy (100x).

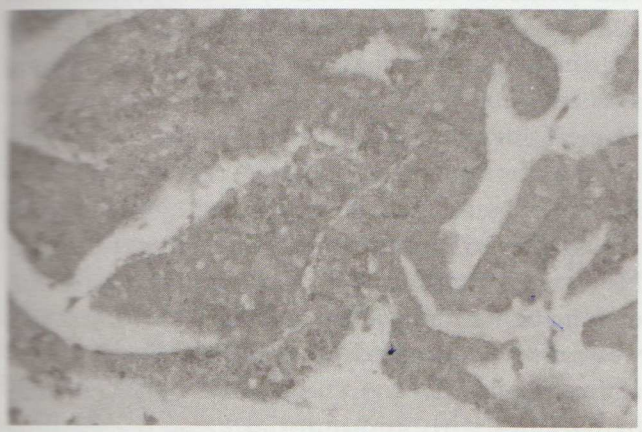

Figure 10. A higher magnification of the curettage specimens taken after treatment with GnRH agonists showing no evidence of malignancy (400x).

Discussion

Risk Factors

Advanced age, anovulatory cycle, hypertension, diabetes, obesity, unopposed use of estrogens, and tamoxifen are the most cited risk factors for endometrial cancers.

Several reports support the observation that age is one of the most important dependent risk factors for endometrial carcinoma.[6] Several authors have compared young women with endometrial adenocarcinoma with older women with the same disease and have shown that endometrial cancer is biologically different in young women. One study comparing obesity between younger and older women showed that there is a higher incidence of obesity in the younger population, probably making obesity a significant risk factor in the younger group. In five reviews, nulliparity was more frequent in the younger population which most likely makes it also a risk factor for the younger patients. In a study done by Fernando, et al. endometrial cancer patients $\leq$ 40 years old had a higher median weight and twice more likely to be nulliparous than >40 years old.[3]

Majority of women who develop endometrial cancer at a young age have a history of chronic anovulation, irregular menses and infertility. They usually present with polycystic ovary syndrome (PCOS) and some of the patients will have such diagnosis during their infertility work-up. Other premenopausal patients will present with irregular or heavy bleeding prompting investigation. Indications for endometrial biopsy vary greatly, with some recommending biopsies only in patients over 35 to 40 years. However, in a high risk patient with abnormal uterine bleeding, regardless of age, one should consider performing an endometrial biopsy. Age at presentation is variable and patients as young as 15 years of age have been reported to have endometrial cancer. The youngest patient with endometrial adenocarcinoma seen at our institution is 23 years old.[11]

Our index patient primarily consulted for infertility and was subsequently found to have endometrial adenocarcinoma. She was 32 years old at the time of diagnosis. On history, she had irregular menses and on work-up, transvaginal ultrasound revealed that she had polycystic ovaries. Based on the Rotterdam criteria (Table 2)[12], the patient has polycystic ovary syndrome (PCOS). Save for being only overweight and not obese, the patient's profile matches the majority of women who develop endometrial cancer at a young age.

Pathology and Pathophysiology

The diagnosis of endometrial carcinoma in the premenopausal patient should be thoroughly investigated. The slides should be reviewed by a pathologist experienced in gynecologic cancers

before suggesting any form of treatment. Care should be taken to rule out endometrial hyperplasia and cervical carcinoma, which are more prevalent in this age group. Endometrial hyperplasia is considered a precursor of endometrial carcinoma and has a risk of progression estimated around 25-29%.[6,7] It can also be very difficult to differentiate between well-differentiated endometrioid adenocarcinoma and complex hyperplasia with atypia. Pathologists actually have poor interobserver agreement when it comes to diagnosing atypical hyperplasia and endometrial cancer.[7,13]

Table 2. Revised 2003 diagnostic criteria for polycystic ovary syndrome.

Revised 2003 criteria (2 out of 3)
1. Oligo- or anovulation,
2. Clinical and / or biochemical signs of hyperandrogenism,
3. Polycystic ovaries
And exclusion of other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome)

There appears to be two histogenic types of endometrial cancers. The first type usually presents in pre – and post-menopausal women, mostly obese and nulliparous. It is associated with atypical hyperplasia and hyperestrogenism. Histopathologically, this type is usually well-differentiated, endometrioid type with minimal or superficial myometrial invasion. Prognosis is favorable in this type. The second type presents in the thin, post-menopausal, multiparous woman. It is unrelated to unopposed estrogen and hyperplasia. Histopathologically, this second type is poorly differentiated with an aggressive histologic type (papillary serous or clear cell) and deep myometrial invasion. Consequently, prognosis is unfavorable.

Based on this classification, our index patient would belong in the first histogenic type.

Endometrial Carcinoma and PCOS

An association between PCOS and endometrial carcinoma was first suggested in 1949. in a study done by Jackson and Dockerty in 1957, the prevalence of endometrial cancer in women with PCOS is 37 percent.[14] Up to the present no other studies have challenged this observation. The are three possible mechanisms which are assumed to be responsible for any increased risk of endometrial adenocarcinoma in women with PCOS.[14] The first mechanism states that women with PCOS have prolonged anovulation with consequent continued secretion of estrogen unopposed by progesterone. The second mechanism implicates the hypersecretion of leutenizing hormone (LH) which is prominent in most women with PCOS. Receptors for LH and human chorionic gonadotropin (hCG) are overexpressed at both mRNA and protein levels in endometrial cancer. A study done by Konishi, et al. concluded that overexpression of receptors for LH and hCG is a feature of endometrial hyperplasia and endometrial cancer in younger, anovulatory women, including those with PCOS.[15] The third mechanism that links endometrial cancer with PCOS is hyperinsulinemia. Diabetes mellitus is a well-recognized risk factor for endometrial cancer. Nagamani, et al. found insulin-binding sites in the endometrial stroma of premenopausal women and women with endometrial cancer[16] and Bershtein, et al. found increased concentrations of plasma insulin in patients with endometrial cancer.[14] Insulin upregulates aromatase activity in endometrial glands and stroma, thus endogenous estrogen production is enhanced. As expected, therefore, insulin and insulin-like growth factor I, concentrations of which are increased with PCOS, accelerate the growth of endometrial cells in vitro.

Our patient fits the diagnosis of PCOS based on the Rotterdam criteria. Aside from it contributing to her infertility, her PCOS may also have increased her risk of developing endometrial cancer based on the above-mentioned mechanisms.

Patient Selection

Not all young patients with early stage endometrial carcinoma strongly desirous of fertility preservation should be offered medical treatment. The appropriateness of conservative treatment for young women with endometrial adenocarcinoma

relies on a correct diagnosis as well as knowledge of the prognosis of the disease. Conservative treatment is only offered to patients who have the following: 1.) well-differentiated tumor (endometrioid type) 2.) no or minimal myometrial invasion 3). no cervical involvement 4). negative peritoneal fluid cytology and 5). no evidence of lymph node metastasis[17] Aside from these, fertility chances, patient compliance and follow up and informed consent should also be considered before any form of conservative management be undertaken since this is not the standard of treatment.

As with all cancers, the diagnosis of endometrial adenocarcinoma must be made on histopathologic grounds, which raises some concerns. First, the biopsy or curettage at the origin of the diagnosis may not sample the entire endometrium and areas of the greatest histological or cytological severity may escape histological identification. In this regard, hysteroscopic evaluation of the endometrium with guided biopsies may help. Sardi, et al. believe that hysteroscopy can address this concern, ultimately determining candidates for hormonal treatment and in treatment follow-up.[7] Other authors have used hysteroscopy to monitor treatment response. Secondly, myometrial invasion is not usually apparent in biopsies and curettings, and in this regard, magnetic resonance imaging (MRI) may be of help. Kinkel, et al. (1991) and Frei and Kinkel (2001), reviewed the literature on the use of ultrasound, computed tomography, non-enhanced MRI, and contrast-enhanced MRI and showed significantly better assessment of myometrial invasion by contrast-enhanced MRI ($p<0.02$).[8, 17] In the local setting, however, the more commonly used imaging modality in the diagnosis of endometrial cancer is the ultrasound. Two studies have been done showing the accuracy of ultrasound in detecting myometrial invasion and cervical involvement. In the study done by San Juan, et al., the sensitivity and specificity for myometrial invasion is 76.47% and 82.35%, respectively while the sensitivity and specificity for cervical involvement is 85.71% and 92.29%, respectively. In a more recent study done by Benavides, et al. the sensitivity and specificity for myometrial invasion is 83.3% and 75%, respectively while the sensitivity and specificity for cervical involvement is 83.3% and 75%, respectively while the sensitivity and specificity for cervical involvement is 66.7% and 95.4%, respectively.[18]

The tumor marker CA-125 should also be a part of the investigation.[7, 10, 19] Although less reliable in the premenopausal patients compared to postmenopausal patients, a high value could alert the physician to the possibility of more extensive myometrial infiltration or extrauterine disease. Because of the occurrence of synchronous versus metastatic ovarian disease in patients with early-onset endometrial cancer, an ovarian evaluation must be performed. Patients should have at least a pelvic ultrasound. Some authors, however, recommend laparoscopic surgery for more precise evaluation of the adnexa.[7, 20] The ovaries are thoroughly evaluated and sampled if deemed necessary and a peritoneal cytology can be done as well as peritoneal examination of the pelvis and abdominal cavity to rule our presence of extrauterine disease. If more advanced disease is discovered, this approach has the advantage of not delaying definitive surgery and altering prognosis.

Another important factor to consider in selecting patients for conservative management of endometrial carcinoma is the fertility status. Thus appropriate fertility evaluation should be done prior to treatment.

If medical treatment of presumed early endometrial carcinoma is entertained, a careful and thorough consent of the treatment contemplated should be done. For the informed consent to be valid, it is important to have the following critical elements: the patient must be competent to begin the informed consent process; the physician must disclose all relevant information to the patient; the patient must comprehend all the information given her; the patient must agree voluntarily to the proposed treatment with the knowledge that she can withdraw from the treatment anytime.[21] Response rates to conservative management of endometrial cancer vary from 50 percent to 80 percent.[7] It should be emphasized that delaying treatment for cancer can have serious implications and risks to the patient. The estimated risk of progression during and after treatment is about 5 percent.[7] The patient must be

made aware of the risks of such treatment for her to arrive at an informed decision.

In our index patient, the histologic finding of endometrial carcinoma was confirmed by four pathologists to ascertain correct diagnosis. MRI was not performed in this case although serial pelvic scans have repeatedly shown no evidence of myometrial invasion and cervical involvement. The results of the diagnostic laparoscopy, although performed for her infertility problem, are significant in retrospectively ruling out pelvic lymphadenopathy and the presence of peritoneal fluid. Her CA-125 level, at 5.2 U/mL, was normal. Lastly, hysterogram demonstrated a patent left oviduct. After thorough counseling of the adverse effects, risk of progression, risk of recurrence and the importance of adherence to close follow up, patient opted for conservative therapy.

As recommended in literature, the patient was evaluated by a multidisciplinary team, with a gynecologic oncologist and a fertility specialist on board.

Treatment

The preferred medical treatment is a progestational agent. However, because of the rarity of this condition, prospective trials are lacking. Most of the literature relies on a few case reports with a small number of patients. There is still no consensus on which progestational agent, duration of treatment and dosage is the most suited. In literature, six studies using progestin agents are of interest.[7] The first study on medical treatment of endometrial carcinoma was published in 1985 by Bokhman, et al. Delalutin (Oxyprogesterone acetate) 500 mg/day for 3 months followed by endometrial sampling was used. Success rate was 79 percent. A prospective study was done by Wang, et al. and they used Megestrol acetate 160 mg/day and Tamoxifen 30 mg/day for 6 months. The overall success of initial response was 77 percent. Randall and Kurman's study consisted of patients with endometrial hyperplasia and carcinoma. Patients were treated with Megestrol acetate 80-160 mg/day (median 160 mg) for 3-18 months (median 9 months). Regression was obtained in 79 percent of patients. The fourth study by Imai, et al. used Medroxyprogesterone acetate 400-800 mg/day (median 600 mg) for 4 to 16 months (median 7.5 months). In this study, more than 50 percent of patients were clinical stage II. Fifty-three percent of patients responded initially, however, if stage I disease only was considered, the response rate would have been 83 percent. In Kim, et al's series, patients were treated with Megestrol acetate 160 mg/day for 3 months. Response rate was 57 percent. Sardi, et al. treated 4 patients with Medroxyprogesterone acetate 200-500 mg/day (median 500 mg) for 3 to 9 months. Seventy-five percent responded to treatment.

There have been other case reports of other hormonal agents used with some success in endometrial hyperplasia (gonadotropin-releasing hormone analogues, danazol, oral contraceptives, Tamoxifen).[6, 8, 17, 22] However, no literature to date supports their use in the primary treatment of endometrial carcinoma.

Patients must be counseled regarding adverse drug reactions prior to starting the treatment as these may lead to cessation of therapy. Reported side effects of hormonal treatment include weight gain, new onset headaches, bloating, premenstrual tension, increased appetite, vaginal dryness, deep vein thrombophlebitis and pulmonary embolism.[7,9]

During the treatment period, regular endometrial sampling (every 2-3 months), pelvic examination and ultrasonography must be done.[7] Following successful reversal of the adenocarcinoma with hormonal treatment, patients should be monitored closely. Recurrence may occur several months and even up to several years after treatment.[5-8,10,23] Sampling of the endometrium at regular intervals of 3-6 months would be reasonable.[6, 10, 24] The endometrium should cycle spontaneously or artificially with hormonal manipulations to prevent recurrence of cancer. It should be emphasized that the consequence of hormonal disturbances (endometrial carcinoma) may have been successfully treated, but not the underlying cause. The condition may recur and must be detected early if it does. Some authors recommend definitive hysterectomy when childbearing is completed or abandoned. The question as to whether to remove or not to remove the ovaries is still a subject of a lot of debate since there are few data available in the literature. On one side, because of the increased

incidence of ovarian lesions in these subsets of patients ranging from 5-29%[3,6-8,10,17,25-26], perhaps it would be preferable to remove them. However, a study by Chen, et al. favors ovarian preservation but suggests hysterectomy and lymph node sampling.[7] This should be discussed in detail with the patient.

The index patient was successfully treated with Megestrol acetate 160 mg/day for 3 months and Leuprolide acetate 3.75 mg intramuscularly once a month for 6 months. Although Metformin was initially given for the treatment of PCOS, theoretically, it may also have a role in preventing endometrial hyperstimulation by lowering insulin concentrations and restoring ovulation.[14] Endometrial biopsies after treatment showed no evidence of disease. She is presently pregnant with another child and is contemplating on a cesarean-hysterectomy at the completion of her pregnancy.

Pregnancy after Conservative Treatment of Endometrial Adenocarcinoma

Between 1968 and 2003, 52 patients <40 years of age underwent conservative treatment of endometrial adenocarcinoma with subsequent pregnancy. Fifty-six livebirths were obtained in these 52 patients.[10] In a study done by Jadoul, et al. they reviewed 70 articles on the treatment, follow-up, and evolution of conservative management in young women with endometrial cancer to assess the risks posed by a conservative approach and to try to define the indications and standard treatment.[17] In their analysis, Megestrol acetate and Medroxyprogesterone acetate were the most frequently used drugs with doses ranging from 80 to 160 mg/day for Megestrol acetate and 200-800 mg/day for Medroxyprogesterone acetate. The duration of hormonal therapy ranged from 2 months to 6 years. Most investigators treated their patients for 3 to 6 months before allowing pregnancy attempt. At least 17 pregnancies were obtained in 15 women after ovarian stimulation and IVF. However, two patients experienced recurrent adenocarcinoma. Both recurrences were diagnosed after pregnancy and delivery and both underwent total hysterectomy. Both patients at the time of review are in remission.

Our patient was treated with Megestrol acetate 160 mg/day for 3 months then with Leuprolide acetate 3.75 mg intramuscularly for 6 months. Thereafter, ovarian stimulation was done using Clomiphene citrate with addition of Metformin. She conceived and delivered a live baby girl three years after being diagnosed with endometrial carcinoma and is presently pregnant with her 2nd child.

Effects of Pregnancy on Endometrial Cancer and Endometrial Cancer on Pregnancy

Twenty-four cases of endometrial cancer associated with intrauterine pregnancy have been reported in literature since 1927. Of these cases, most were diagnosed incidentally at the time of curettage for abortions (15 cases) and 9 were pregnancies in patients known to have endometrial cancer.[8]

The human blastocyst attaches itself to the endometrial epithelium and implantation occurs approximately 6 days after fertilization. This is made possible by a complex series of events, both biochemical and physiological. Any interference in this series of events may result in the failure of implantation.[27] It is interesting to note that ovulation only occurs in a normal cyclical milieu. It is unlikely for a progestational endometrium to be associated with adenocarcinoma, an entity which has its highest rate of occurrence in a persistently estrogen-stimulated endometrium, unopposed by periodic progesterone influence. It is usually recognized that the hormonal milieu of pregnancy, with high levels of progesterone, protects the woman from endometrial cancer.[22, 24] How then did these two conditions co-exist?

Several studies have tried to explain the co-existence of these two conditions. As early as 1924, Novak and Matzloff described and documented areas of progesterone unresponsive endometrium. These areas were located within the functional layers of the endometrium. These progesterone unresponsive areas of the endometrium were immature and have not acquired the capacity to respond to progesterone and hence exhibit a proliferative and hyperplastic pattern despite a

biphasic cycle. These areas, which may become neoplastic, were also described by Risberg, et al. in 1983.[28] It is then presumed that the endometrial cancer represent localized fragments of the endometrium that remain refractory to the progesterone but continue to respond to estrogenic stimulation.[24] Schneller and Nicastri in 1994 postulated that in pregnancy-associated endometrial carcinoma, part of the endometrium undergoes gestational change while another part becomes neoplastic. The portion of the endometrium which becomes neoplastic may be sensitive to estrogen but unresponsive to progesterone. It would exist in an environment of continuous although waxing and waning estrogen stimulation in the non-pregnant state. When pregnancy occurs, these estrogen-responsive, progesterone-refractory areas undergo hyperplasia and ultimately become neoplastic.[28]

What then are the effects of pregnancy on endometrial cancer? Due to the limited number of cases, it is difficult to draw conclusions as to the exact effects of the pregnancy on the cancer. In cases reviewed by Schammel, et al. the cancer tended to be of higher grade and associated with ovarian carcinomas and to have poorer prognosis.[24] Conversely, in cases wherein after delivery of the baby, no evidence of cancer was seen, it is possible that the hormonal milieu of pregnancy, with high levels of progesterone, induced complete regression of the tumor. In a case report by Ayhan, et al. they stated that during the first trimester of pregnancy, the high levels of hCG downregulates tumor proliferation, thus making the co-existence of pregnancy and cancer possible.[29] A case described by Mitsushita, et al. wherein there was remaining endometrial carcinoma after term pregnancy, they postulated that neoplastic areas that were refractory under the high progesterone environment during pregnancy may have started regrowing under the influence of estrogen after delivery.[22]

What then are the possible effects of endometrial cancer on pregnancy? The number of livebirths associated with endometrial cancer is limited, only 56 were reported so far[10] and only 9 were co-existent with cancer.[8] It is due to this small number of cases that no conclusion can be drawn as to the effects of endometrial cancer on pregnancy. In general, any malignancy may be associated with malnutrition thus causing a possible adverse neonatal outcome such as intrauterine growth restriction. Also, the cancer patient has an increased tendency to experience febrile illnesses from the infection or from the tumor itself and hyperthermia may have an effect on fetal brain development.[30] Placental and fetal metastases may also be possible, although rare in other reported cancers associated with pregnancy.[31]

Our patient initially had endometrial cancer co-existent with pregnancy which was diagnosed during curettage for a blighted ovum which was majority of the cases reported in literature. After conservative treatment of endometrial cancer, patient subsequently became pregnant after 2 years of no evidence of illness. Since the patient delivered via cesarean section for non-reassuring fetal status, intraoperative assessment was possible and no evidence of disease was seen. Likewise, the placenta submitted for histopathology did not show any evidence of tumor. Also, no adverse neonatal and fetal outcomes were observed.

Prognosis

In general, endometrial cancer in the young treated conservatively shows a good prognosis with response rates ranging from 50%-80%[7] and an estimated risk of progression of 5%[7, 24]. However, because of lack of appropriate controlled studies, several issues remain unresolved, such as, the optimal treatment regimens – drug, dose, duration, and manner of administration, the safety of fertility treatments, the need for hysterectomy after childbearing, and the need for oophorectomy at the time of hysterectomy.

The different drugs used in the medical management of endometrial cancer have been mentioned earlier in the paper. No drug has been proven superior over the other.

Several reports have been cited regarding the different fertility treatments and assisted reproductive techniques. Again, no treatment or technique has been proven superior in its safety profile over the other.

The need for hysterectomy and the need for oophorectomy at the time of hysterectomy remain unresolved. Several authors have strongly proposed

hysterectomy, with or without ovarian removal after childbearing is completed to avoid a long and stressful follow up and possible morbidity and mortality due to a delay in detecting recurrence.[6-7,17, 32] Until guidelines have been established, this option would still largely depend on the patient and her acceptance of her disease and the risks that go with it.

Ethical Considerations

The principle of free and informed consent is unquestionably one of the most important principles in medical ethics because it is at the heart of the physician-patient relationship. Responsible consent to therapy must be informed consent, that is, the patient must be told of the nature of the proposed therapy, its risks and benefits, and other treatment alternatives. The information must be given in terms understandable to the patient and will feedback from the patient to make sure that she understands what is being said.[36] A patient who is well-informed about her condition and therapeutic options has a greater capacity for autonomous decision-making. The physician should also pay attention to the patient's values and beliefs so he or she can better determine a management plan that would be consistent with the woman's perspective of her best interests. This will prevent conflicts between maternal autonomy-based and beneficence-based obligations of physicians.

Conservative management of endometrial cancer is not the standard of treatment. In the end, management is still a case to case basis. As clinicians, we must always go back to our Hippocratic Oath, the duty to care and do no harm.

Summary

A case of a 32-year old woman initially consulted and worked up for infertility and later diagnosed with PCOS and well-differentiated endometrial carcinoma was presented. Owing to the patient's desire for pregnancy, coupled with a good prognosis based on her young age, histopathologic evaluating and imaging findings, she was offered and eventually opted for conservative management of the cancer. To date, there is still no consensus on the ideal hormonal agent, dose and duration but our index patient was given Megestrol acetate at 160 mg/day for 3 months then shifted to Leuprolide acetate 3.75 intramuscularly for 6 months - similar to doses given in several case series.

Serial transvaginal scans demonstrated initial endometrial thickening becoming normal after progestin/GnRH intake. Nine months after, endometrial sampling showed regression of disease, and she attempted conception with success and subsequent delivery. Post-childbirth placental biopsy result was negative for malignancy. A hysterectomy was recommended after childbirth but the patient refused. She is presently on her 2nd pregnancy but is considering the aforementioned surgical procedure after delivery of her 2nd child.

Our patient has been in remission for 3 years since first diagnosed with cancer. Her positive response rate shows a promising therapeutic alternative to patients of similar profile and diagnosed with the same disease.

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Ovarian Carcinoma with Metastasis to the Vulva

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The vulva is an uncommon site of metastatic deposit. Among the different reproductive organs, only in the vulva does metastasis account for a significant number of lesions that could mimic a primary tumor.

A 55-year old multigravid presented with postmenopausal bleeding, vulvar pruritus, and a vaginal mass. Examination revealed the presence of a left adnexal mass with sonographic features of a malignancy. She underwent a complete surgical staging procedure for an intraoperative assessment of a probable synchronous tumor of the ovary and the vulva. Histopathologic diagnosis was a primary serous cystadenocarcinoma of the ovary with metastasis to the vulva.

Ovarian carcinoma with vulvar metastasis is a rare phenomenon. Spread from one tumor to the other may be through the extensive lymphatic network draining the ovary, through the vascular channels, or by direct extension. Alternatively, all of these routes of spread may be involved. Clinical presentation may vary, with the metastatic tumor in the vulva representing the first manifestation of the disease, prompting consult, diagnosis and identification of the primary tumor.

Management must be tailored based on the primary site of disease. Regardless of the primary origin, however, metastatic tumors of the vulva are associated with a poor prognosis.

Key words: ovarian carcinoma, serous cystadenocarcinoma, vulvar metastasis, metastatic tumors of the vulva

Primary vulvar cancer is rare, accounting for 3-5 percent of all malignancies of the female genital tract.[1] Metastatic tumors of the vulva are even rarer, and often pose diagnostic problems to both clinician and pathologist. More commonly, they represent the initial manifestation of disease which prompts consultation, work-up and subsequent identification of a primary tumor.

The Case

A.S. is a 55 year old multigravid from Cavite who consulted because of postmenopausal vaginal spotting. Her past and family medical histories are unremarkable. She is a non-smoker and an alcoholic beverage non-drinker. She finished elementary school, got married, and is presently a housewife. Menarche was at the age of 14 with subsequent menstrual periods at regular monthly intervals, lasting 7 days, consuming 2 clothpads per day, with no dysmenorrhea. She experienced menopause at 50 years old. Her first coitus was at the age of 19

* Won third place in the SGOP Interesting Case Paper Contest for Fellows and Residents 2006.

with a single monogamous sexual partner. The patient's first pregnancy was at the same age. She used an intrauterine device for 17 years, but never used oral contraceptive pills. She had no history of sexually transmitted diseases. The patient is a gravida 5 para 3 (3023). She had 3 uncomplicated term vaginal deliveries assisted by a traditional birth attendant at home. Her third and fourth pregnancies terminated into spontaneous abortions. Her last delivery was in 1980.

Her history started five months prior to admission when she noted intermittent vaginal spotting associated with vulvar pruritus. No consult was done and no medications were taken at this time. One month later, she noted a pea-sized firm, nontender vaginal mass. She consulted at the Outpatient Department of a tertiary hospital where internal examination revealed a 2 cm x 2 cm left lateral vaginal wall mass, extending up to 0.5 cm from the urethral meatus. This was assessed to be probably malignant. Punch biopsy of this mass was done, which revealed a malignant tumor, to consider 1) malignant melanoma, or 2) squamous cell carcinoma, poorly differentiated. She was subsequently referred to the Section of Gynecologic Oncology for further management and was then admitted for surgery.

Review of systems was unremarkable.

On admission, the patient was conscious, coherent, ambulatory, with an ECOG performance score of zero. She had stable vital signs. She stands 155 cm and weighs 51.8 kg, giving her a BMI of 21.35 kg/m^2 and a BSA of 1.49 m^2. Systemic physical examination findings were essentially normal. On pelvic examination, there was note of a 0.2 cm nevus on the left labia majora (Figure 1). Internal examination revealed a parous vagina, with a 4 cm x 3 cm nodular, movable, nontender mass at the lower third of the left lateral vaginal wall extending to the 10 o'clock position of the introitus and suburethral area (Figure 2). The cervix measured 2 cm x 2 cm and was smooth. The corpus was small. There was an 8 cm x 8 cm movable, nontender, predominantly cystic mass superior and to the left of the uterus. No mass or tenderness was appreciated on the right. Rectovaginal examination revealed a smooth septum. Both parametria were likewise smooth and pliable.

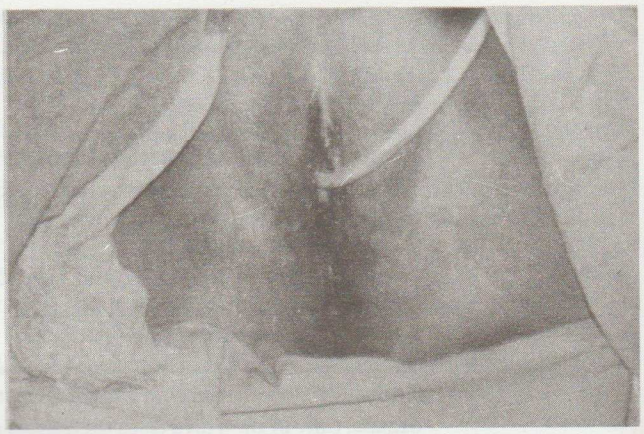


Figure 1. A 0.2 cm nevus was noted on the left labia majora.

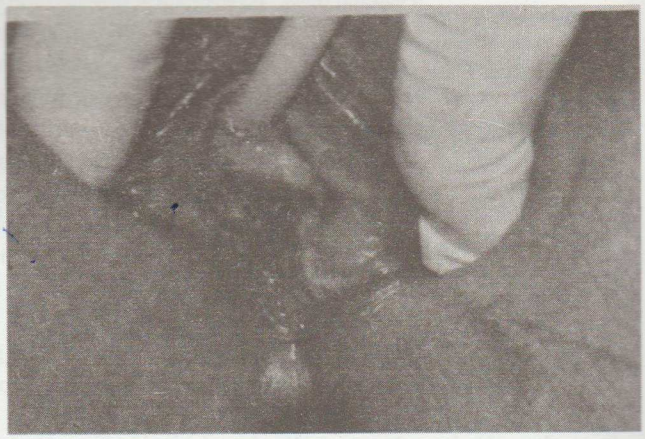


Figure 2. A 4 cm x 3 cm nodular, movable, nontender mass at the lower third of the left lateral vaginal wall extending to the 10 o'clock position of the introitus and suburethral area was appreciated on internal examination.

Admitting impression was a vulvar carcinoma, consider poorly differentiated squamous cell carcinoma vs malignant melanoma, stage III, with an ovarian new growth, left, probably malignant.

Transperineal ultrasound revealed an irregular solid hypoechoic mass extending from the perineum and into the left vaginal wall measuring 1.7 cm wide and 3.8 cm thick (Figure 3), involving 3.7 cm of the lower end of the vagina and encroaching into the posterior outlet of the urethra (Figure 4). On transvaginal sonography, there were two well-circumscribed heterogenous uterine masses as follows: (M1) 3.8 cm x 3.3 cm x 3.0 cm, located at the anterior midcorpus, subserous, and (M2) 0.5 cm x 0.5 cm x 0.5 cm, located at the anterior isthmus, intramural (Figure 5). Anterosuperior to the uterus

and more to its left was a multiloculated anechoic cystic pelvic mass measuring 9.2 cm x 8.9 cm x 6.8 cm with several solid masses within, the largest of which measured 5.8 cm x 4.0 cm x 3.9 cm (Figure 6). Color flow mapping of the solid mass showed scanty central vascularity with high resistance indices (PI 1.52, RI 0.79) (Figure 7). Sonographic impression was a vaginal mass, probably malignant; left pelvic mass, consider ovarian new growth, probably malignant (Sassone 12, Lerner 5); myoma uteri.

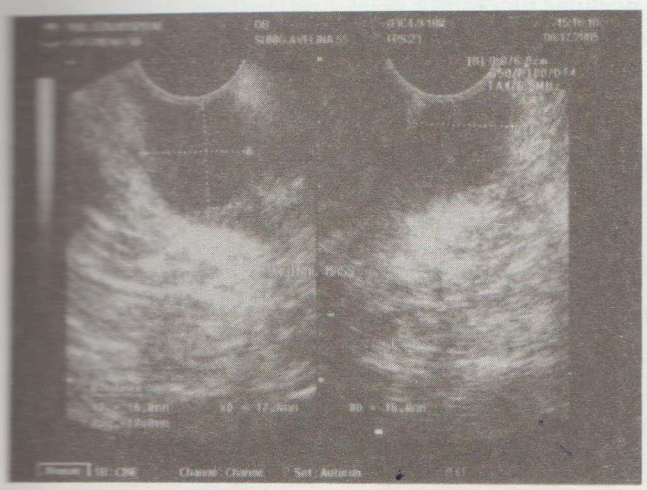


Figure 3. Transperineal ultrasound showing an irregular solid hypoechoic mass extending from the perineum and into the left vaginal wall measuring 1.7 cm wide and 3.8 cm thick.

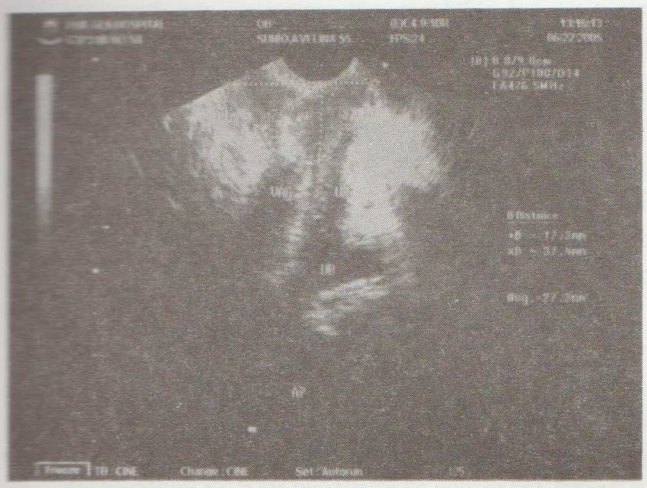


Figure 4. Transvaginal ultrasound demonstrating involvement up to 3.7 cm of the lower end of the vagina with encroachment into the posterior outlet of the urethra.

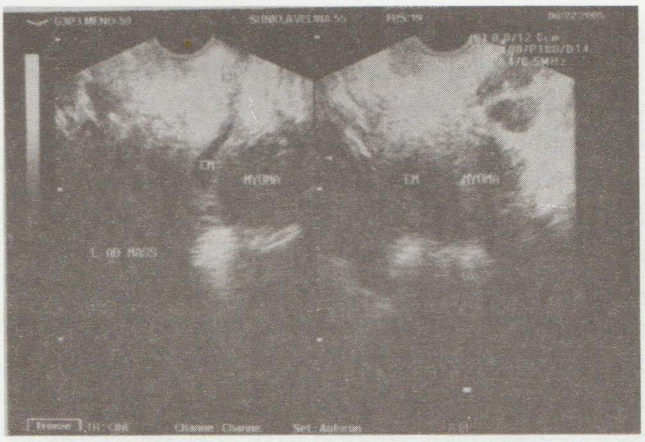


Figure 5. Vaginal sonography showing two well-circumscribed heterogenous uterine masses: (M1) 3.8 cm x 3.3 cm x 3.0 cm, located at the anterior midcorpus, subserous, and (M2) 0.5 cm x 0.5 cm x 0.5 cm, located at the anterior isthmus, intramural.

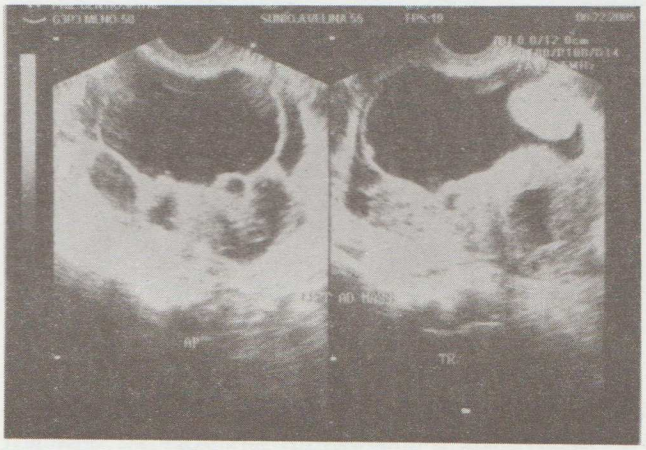


Figure 6. Sonographic picture of a multiloculated anechoic cystic pelvic mass anterosuperior to the uterus and more to its left, measuring 9.2 cm x 8.9 cm x 6.8 cm with several solid masses within, the largest of which measured 5.8 cm x 4.0 cm x 3.9 cm.

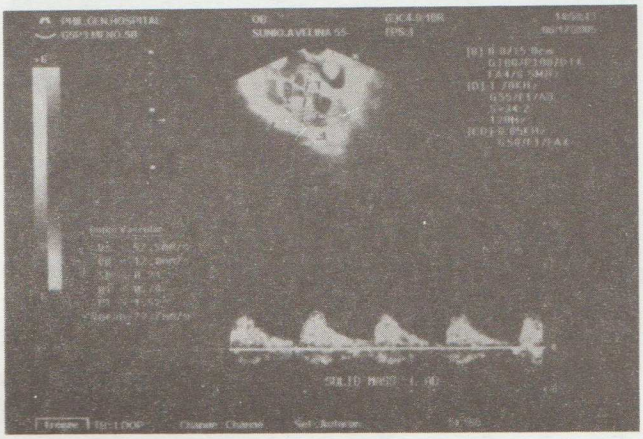


Figure 7. Color flow mapping of the solid mass showed scanty central vascularity with high resistance indices (PI 1.52, RI 0.79).

Colposcopy was likewise performed which showed normal findings. Immunostaining with HMB45 was requested, with negative results, thus ruling out a malignant melanoma.

A referral to Urology was done. She underwent cystoscopy and was cleared by the service from any bladder involvement. Another referral was given, this time to the Colorectal Surgery Service. Proctosigmoidoscopy was performed, with the scope inserted up to 13 cm only, due to difficulty pushing the endoscope forward probably secondary to the extraluminal mass. However, no bleeding, polyp or mass was noted.

She was subsequently scheduled for surgery and underwent laparotomy and vulvectomy on her 14th hospital stay. On exploratory laparotomy there was no ascites. The liver, gall bladder, spleen, subdiaphragmatic surfaces, kidneys, stomach, omentum and peritoneum were all smooth and grossly normal. The left ovary was converted to a predominantly solid mass with some cystic areas measuring 8 cm x 9 cm x 5 cm (Figure 8). On cut section, the solid areas measured 7 cm x 5 cm, creamy white, with fleshy consistency, with yellowish necrotic and hemorrhagic areas. The cystic areas were filled with yellowish serous fluid (Figure 9). The left ovary was adherent to the left pelvic side wall and cul de sac. The right ovary measured 2 cm x 1.2 cm x 1 cm and was grossly normal. The left fallopian tube measured 9 cm x 0.3 cm while the right measured 7 cm x 0.3 cm, both of which were grossly unremarkable. The uterus measured 8.5 cm x 5 cm x 3 cm with smooth serosal surface. The cervix measured 2.5 cm x 3.5 cm x 1.5 cm. On cut section, the uterine cavity measured 6.5 cm, 2.5 cm of which was the endocervical canal. The myometrium measured 2 cm with a 3 cm x 2 cm intramural myoma located at the left fundal area. The endometrium measured 0.1 cm. There was a 3 cm x 2 cm fixed solid lymph node over the para-aortic area. There were no suspicious lymph nodes harvested from the external iliac and obturator chains. An exploratory laparotomy, total hysterectomy with bilateral salpingooophorectomy, infracolic omentectomy, bilateral pelvic lymph node dissection, fine needle aspiration biopsy of the para-aortic lymph node and peritoneal fluid sampling were performed. This was followed by radical vulvectomy, bilateral groin node dissection, distal urethrectomy and lower vaginectomy. No suspicious nodes were harvested from the superficial inguinal and deep femoral areas. The vulvar specimen measured 10 cm x 12 cm x 2 cm, and consisted of the whole vulva, clitoris, distal 1 cm of the urethra, and distal 1 cm of the vagina (Figure 10). There were multiple, firm, nodular masses on the left labia minora with an aggregate diameter of 3 cm x 2.5 cm x 0.5 cm, extending to the hymenal ring from 12 to 6 o'clock positions (Figure 11a). Another brownish-black nodular ulcerating mass measuring 1.5 cm x 1.2 cm was noted located 0.5 cm below the urethral orifice (Figure 11b). Both masses had full stromal invasion. The urethra was grossly normal. Estimated blood loss was 1.2 L. Two units of blood was transfused intraoperatively.

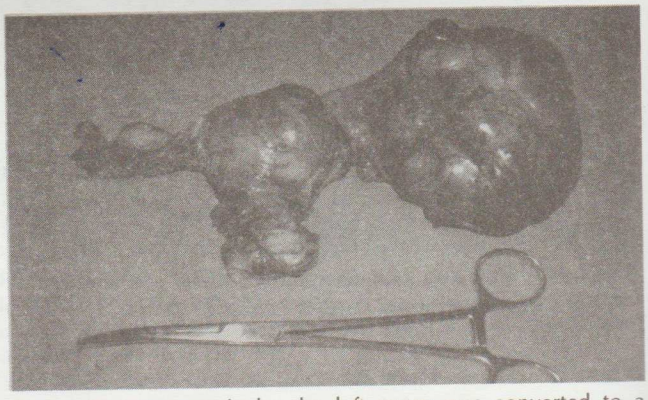


Figure 8. Intraoperatively, the left ovary was converted to a predominantly solid mass with some cystic areas measuring 8 cm x 9 cm x 5 cm.

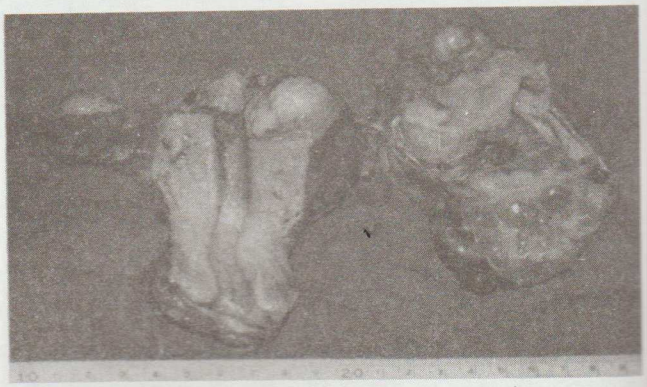
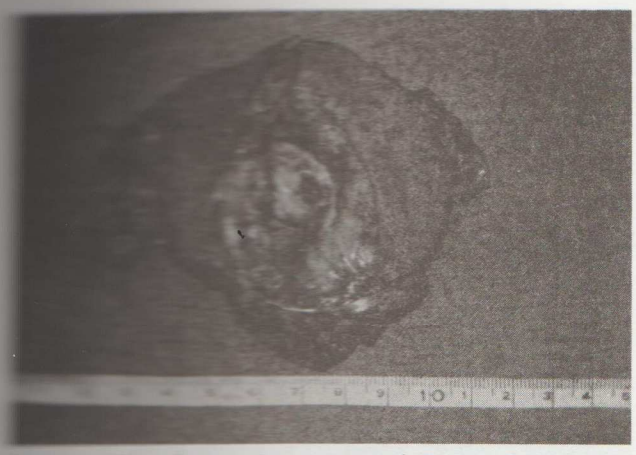


Figure 9. Cut section revealed solid areas measuring 7 cm x 5 cm, creamy white, with fleshy consistency, with yellowish necrotic and hemorrhagic areas. There were also cystic areas within, filled with yellowish serous fluid.



The vulvar specimen measured 10 cm x 12 cm x 2 cm, ... the whole vulva, clitoris, distal 1 cm of the urethra, ... cm of the vagina.

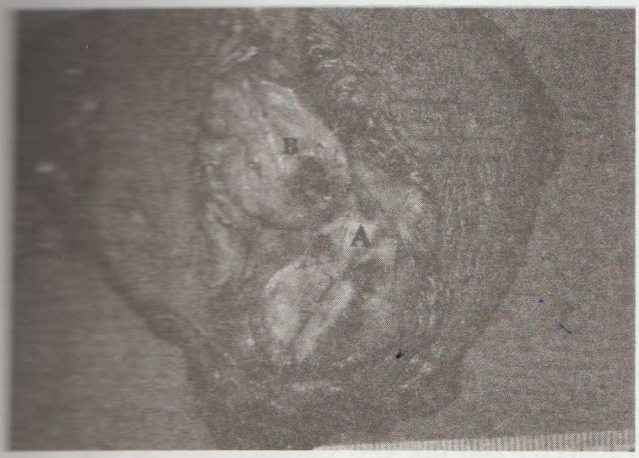


Figure 11. (A) There were multiple, firm, nodular masses on the left labia minora with an aggregate diameter of 3 cm x 2.5 cm x 0.5 cm, extending to the hymenal ring from 12 to 6 o'clock positions. (B) Another brownish-black nodular ulcerating mass measuring 1.5 cm x 1.2 cm was noted located 0.5 cm below the urethral orifice. Both of these masses had full stromal invasion.

Intraoperative diagnosis was a synchronous tumor (poorly differentiated squamous cell carcinoma of the vulva, stage III, and a malignant ovarian new growth, stage IIIC), or a primary vulvar carcinoma.

Microscopic examination of the left ovary revealed papillary projections formed by neoplastic cells invading the stroma with desmoplastic reaction (Figure 12). The tumor cells have large reticular nuclei and prominent nucleoli (Figure 13). Similar neoplastic cells were seen in the sections taken from the left fallopian tube (Figure 14) and vulva (Figure 15). This was read as Serous cystadenocarcinoma, poorly differentiated, left ovary, with extension to the left fallopian tube and metastasis to the vulva. The para-aortic lymph node was positive for tumor (Figure 16). All the other 35 lymph nodes harvested from the pelvic and inguinofemoral chains, as well as the omentum and peritoneal fluid, were free of tumor. There was leiomyomata uteri, senile cystic endometrium, and chronic cervicitis. No diagnostic abnormality was recognized from the right ovary and right fallopian tube. All vulvar and urethral surgical resection margins were negative for tumor.

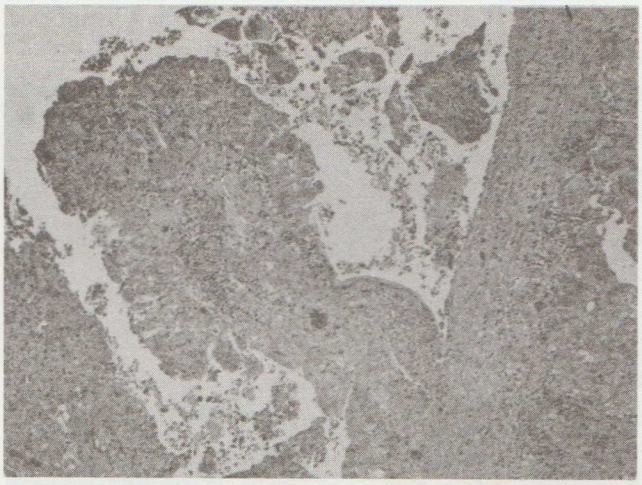


Figure 12. Section from the left ovary showing papillary projections formed by neoplastic cells invading the stroma with desmoplastic reaction, characteristic of serous cystadenocarcinoma.

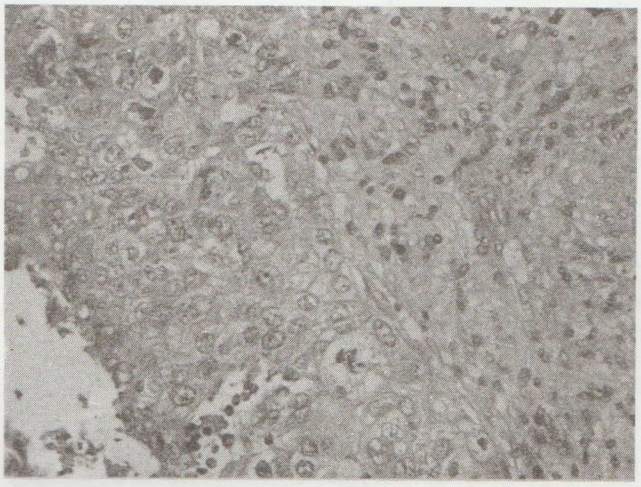


Figure 13. Higher magnification of a section from the left ovary revealing large reticular nuclei and prominent nucleoli.

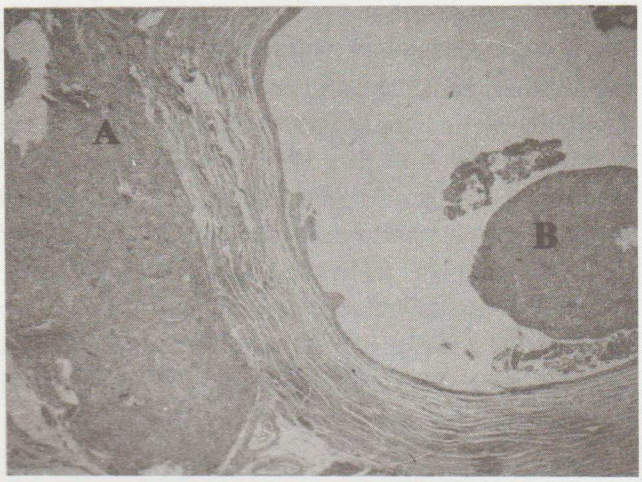


Figure 14. (A) Tumor cells were seen infiltrating the wall of the left fallopian tube. (B) Same neoplastic cells within the lumen of the tube.

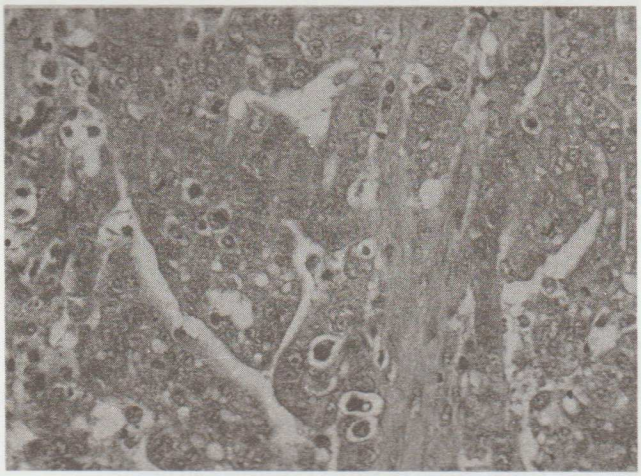


Figure 15. Cells from the left ovary characteristic of serous cystadenocarcinoma were likewise found in the vulva.

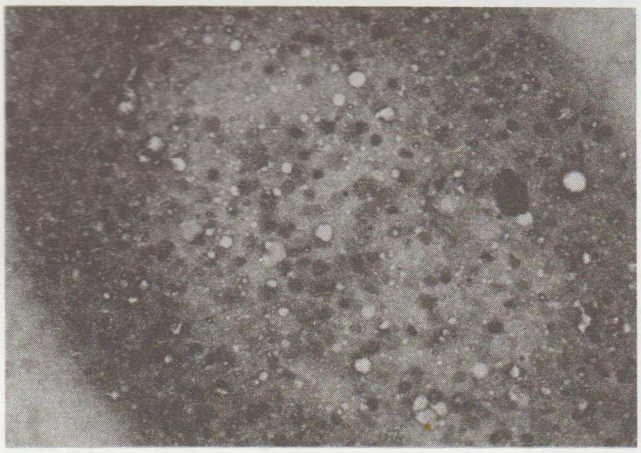


Figure 16. Fine-needle aspiration biopsy of para-aortic lymph node demonstrating the presence of tumor cells.

A review of the punch biopsy slides side by side with the final specimen was requested. The biopsy specimen revealed a metastatic poorly differentiated carcinoma (Figure 17).

Figure 17. Punch biopsy of the vulva showing metastatic poorly differentiated carcinoma.

The final diagnosis was Serous cystadenocarcinoma of the ovary, poorly differentiated, stage IV.

She was started on adjuvant chemotherapy with Paclitaxel 260 mg and Carboplatin 450 mg. She received her first course of chemotherapy prior to discharge. CA 125 levels after the third chemotherapy was 37.12 U/mL. She was last seen six months postoperatively, after receiving her fourth course of chemotherapy. At that time, she has an ECOG performance score of zero with no clinical or radiologic evidence of disease recurrence.

Discussion

The finding of malignancies in two separate organs poses a diagnostic challenge. Determining whether such is a case of synchronous tumors or whether one malignancy is metastatic to the other is of utmost importance. Three possibilities exist in the case presented: 1) the ovarian and vulvar cancers are independent entities and occur as double primary carcinomas, 2) the ovarian cancer is metastatic from

primary vulvar carcinoma, or 3) the vulvar cancer metastatic from a primary ovarian carcinoma.

Synchronous tumors are defined as tumors that were either diagnosed concurrent with the primary tumor, discovered at the primary surgical procedure, or occurred within one year of the primary tumor diagnosis.[2] A set of criteria have been proposed for the diagnosis of multiple primary malignancies. Warner and Gates[3] stated that 1) each of the tumors must present a definite picture of malignancy, 2) each must be distinct, and 3) the probability that one is a metastatic lesion from the other must be excluded. In our case, both tumors are distinct and clearly malignant. An intraoperative assessment of a probable double primary neoplasm from the ovary and the vulva was considered. Although the para-aortic node involvement may give a clue as to the advanced stage of the disease, an intraoperative diagnosis of a metastatic nature of either the vulva or the ovary cannot be made with absolute certainty since a synchronous tumor of advanced stages is still a possibility. The latter condition thus is difficult to entirely rule out intraoperatively. Alternatively, the probability that one is metastatic from the other likewise cannot be entirely excluded, such that the criteria proposed by Warner and Gates cannot be fulfilled. The fixed solid para-aortic lymph node that was positive for tumor is indicative of an advanced disease, such that lymphatic spread may have already occurred from one tumor to the other. Furthermore, histologic examination of both the ovarian and vulvar masses showed poorly differentiated carcinoma, thus the probability of metastasis of one to the other cannot be entirely ruled out.

Approximately 3 percent of ovarian cancers arise outside the ovary, with the breast, large intestines, endometrium, and stomach as the most common primary sites.[4] A primary vulvar carcinoma metastasizing to the ovary is thus a rare phenomenon. Gross features of tumors that are metastatic to the ovary vary greatly. Majority of ovarian metastases show bilateral involvement. The presence of multiple nodules or implants on the ovarian surface, or minute foci of tumor within the parenchyma may also provide clues to the metastatic nature of the ovarian masses.[4] In the case presented, only the left ovary was pathologic. Nodules or implants within the ovarian surface were likewise not observed. The likelihood of a primary vulvar cancer with metastasis to the ovary is thus remote. Nevertheless, it had been an intraoperative consideration in this case owing to the original biopsy result of a squamous cell carcinoma, the occurrence of which is more common in the vulva than the ovary. It was unfortunate though that review of the initial vulvar biopsy specimen showed a different finding. It should be kept in mind, however, that examination of a poorly differentiated tumor from a small piece of tissue poses difficulties, as in our case, since the histologic architecture characteristic of the tumor is lost and is thus difficult to identify with certainty.

This leaves us with the third possibility of this case being a primary ovarian carcinoma with metastasis to the vulva. Such is a strong consideration, the ovarian mass being larger, measuring 8 cm x 9 cm x 5 cm, compared with the vulvar mass. Furthermore, involvement of the vulva was noted to be in the form of multiple nodular masses, characteristic of a metastatic process. Histologically, examination of the vulvar mass showed the presence of neoplastic cells similar to those found in the ovary, which were characteristic of a serous cystadenocarcinoma type of tumor.

Mazur, et al. noted that among the different reproductive organs, only in the vulva does intragenital metastases account for a significant number of lesions that could mimic a primary tumor. The metastatic tumor in the vulva may represent the first manifestation of disease, and may be diagnosed before identification of the primary tumor[1,5], the vulvar mass being a more obvious lesion. This is compatible with the case presented, since the symptoms that were referable to the vulvar involvement prompted consultation and subsequent recognition of the primary malignancy. Conversely, identification of the metastatic foci may occur subsequent to the excision of the primary lesion.[5] In other cases, the primary tumor and the metastatic lesion may be diagnosed simultaneously.[1]

Metastatic tumors account for approximately 5-8 percent of all cancers of the vulva.[1,6] Its incidence thus ranges from 0.15 to 0.40 percent of all

gynecologic malignancies.[1] The largest series of metastatic vulvar cancers in the English literature was reported in 2003 by Neto, et al. They described the clinicopathologic features of 66 cases over a 57-year period (1944-2001) and found that half of these cases were of gynecologic origin, majority of which arose from a primary squamous carcinoma of the cervix (22.7%), followed by ovarian (12.1%) and endometrial (9%) carcinomas. Among the cases with primary ovarian origin, papillary serous histology was the most common. Other histologic types that have been reported in literature include clear cell[1], granulosa cell[7], and a poorly differentiated adenocarcinoma[6]. In our institution, this is the first reported case of ovarian carcinoma with vulvar metastasis.

Tumor spread from the ovary to the vulva may have occurred in a number of ways. The first route of spread is via the vast network of lymphatics that drain the ovary.[7] These vessels are noted to converge at the hilar area to form the sub-ovarian lymphatic plexus. From this plexus, there are three different routes of lymphatic drainage. The main pathway consists of trunks located along the ovarian vessels bilaterally, terminating into the aortic nodes surrounding the renal vessels. The second route of lymphatic spread involves the trunks that run along the broad ligaments. These vessels drain towards the lateral pelvic side walls, and terminate in the external iliac and interiliac lymph nodes. From there, the lymph reaches the common iliac then the aortic group of nodes. Less frequent is the third pathway that involves trunks along the round ligaments, subsequently draining into the external iliac and inguinal lymph nodes. The case presented demonstrated metastasis in the para-aortic lymph node which was shown to be positive for tumor (Figure 16). This was further demonstrated by the presence of tumor cells within the lumen of the lymphatic vessels of the left ovary (Figure 18). However, it is difficult to conclude which among the lymphatic pathways was involved, since any one of them is possible. In a study by Tsurnura et al, they demonstrated that the para-aortic lymph nodes are the primary sites of nodal metastases and may be considered as the sentinel node in ovarian carcinomas.[9]

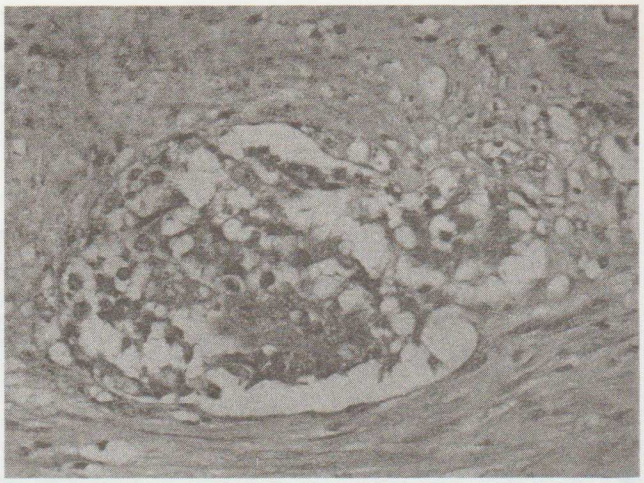


Figure 18. Tumor cells were seen within the lumen of lymphatic vessel in the left ovary.

A number of factors have been identified as predictive of lymph node involvement. Stage of the tumor has been described as the most important, with nodal positivity occurring in as high as 87 percent of patients with stage IV disease.[10] Likewise, the involvement of the omentum, uterus and fallopian tubes were observed to be independent factors predictive of para-aortic node involvement, with a relative risk of 18.48.[10] Tumor differentiation also plays a role in predicting lymph node metastasis.[11,12,13] Approximately, 20 percent of grade 1 and 2 tumors, and 45 percent of grade 3 tumors will demonstrate para-aortic lymph node involvement.[10] Histology has also been found to play a significant role in the incidence of metastases, with the highest percentage found among undifferentiated or anaplastic tumors, followed by clear cell, serous, endometrioid and mucinous types.[14,15] In the study by Tsuruchi et al, they found serous histology to show the highest correlation with positive para-aortic lymph node metastasis, with a rate of 42%. Our patient had stage IV poorly differentiated serous cystadenocarcinoma of the ovary with extension to the fallopian tube and metastasis to the vulva. It is thus not surprising to find para-aortic lymph node involvement in this case.

Spread to adjacent pelvic tissues by direct extension and exfoliation of tumor cells into the peritoneal cavity has also been proposed as a possible

mechanism of tumor spread.[16] Circulation of the peritoneal fluid may cause migration of the tumor cells from the surface of the ovary into and along the surfaces of the pelvic and mesenteric peritoneum. In our case, the demonstration of tumor cells within the lumen of the left fallopian tube and the involvement of the tube itself attests to this route of spread.

Spread to other tissues through the vascular channels is the least common route of spread.[17] Less than 5 percent of patients will demonstrate parenchymal metastases, indicative of hematogenous spread of the disease.[18] Dehner noted that a constant finding in nearly all biopsies was the presence of tumor within the vascular spaces, some of which were attached to the vascular endothelium, while others were lying free within the lumen. In our case, the presence of tumor cells within the lumen of the blood vessels of the vulva is proof of this route of spread (Figure 19).

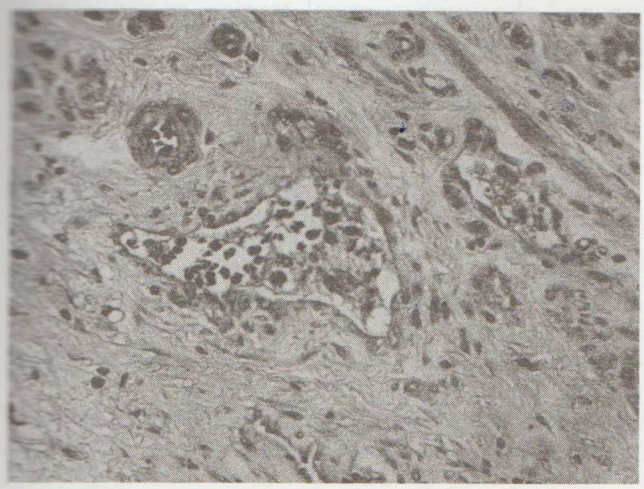


Figure 19. Tumor cells were seen within the lumen of blood vessels in the vulva.

Patients with epithelial ovarian carcinomas had a mean age of 55 years[19], while the median age at diagnosis was 63[20]. Those with ovarian carcinoma who developed metastases to the vulva ranged from 32 to 70 years of age.[1] Majority (89.3%) were in the peri- and postmenopausal age groups[1]. Our patient is 55 years old and is 5 years past her menopause.

Signs and symptoms most often associated with ovarian cancer are secondary to intraperitoneal spread, which include vague abdominal pain, decreased appetite, early satiety, or abdominal distention. Physical examination would usually reveal the presence of ascites or abdominal or pelvic mass.[17] On the other hand, majority of patients with metastatic tumors to the vulva presented with a vulvar mass or nodule (59%)[1]. Some complained of pain or ulceration over the vulvar area.[1,6] Others experienced painless bleeding[6], pruritus, swelling, vulvar discomfort and a cystic lesion[1]. Symptoms lasted from 14 days to 72 months[1]. Our index patient presented with symptoms referable to the vulvar involvement, such that her first manifestation of disease that led to the diagnosis was the metastatic lesion. She initially complained of vaginal spotting associated with vulvar pruritus. A vaginal mass was noted a few months after. No sign or symptom attributed to her primary malignancy was ever noted.

Metastatic lesions were noted to vary in size, ranging from 0.5 cm to 11.9 cm[1]. In our case, the vulvar involvement was noted to be in the form of multiple firm nodular masses on the left labia minora with an aggregate diameter of 3 cm x 2.5 cm x 0.5 cm, extending to the hymenal ring from the 12 to 6 o'clock positions, and a 1.5 cm x 1.2 cm ulcerating mass below the urethral orifice.

Majority of the vulvar metastases involved the labium majus (67%). Vulvar involvement was demonstrated from the epidermis down to the subcutis, regardless of the histologic type. None of the vulvar lesions involved the epidermis alone.[1] Dehner reported that the most prominent gross characteristic of the specimens was the replacement of the dermis by either a firm homogenous process or multiple areas of necrosis, with no notable correlation between the gross appearance and histologic feature of the metastatic lesion. However, in majority of the cases, tumor differentiation of both the primary and metastasis were alike. In our case, both the primary ovarian carcinoma and its vulvar metastasis were poorly differentiated.

Management of primary ovarian carcinomas is through a thorough staging laparotomy with removal of all obvious sites of tumor wherever possible, with maximal attempt at optimal cytoreduction, in

addition to total hysterectomy and bilateral salpingooophorectomy. Furthermore, the ometum, pelvic and para-aortic lymph nodes should also be removed for histologic examination with the objective of optimal debulking for advanced disease.[21] Treatment options for the vulvar involvement may vary, which included local excision, wide local excision, vulvectomy, chemotherapy, and radiotherapy, or a combination of these modalities[1]. One study cited the use of whole pelvis irradiation therapy and interstitial radium needle implants to the clitoral metastasis[6]. Our patient underwent a complete surgical staging procedure for an intraoperative diagnosis of a probable synchronous tumor of the ovary and the vulva. Exploratory laparotomy, total hysterectomy with bilateral salpingooophorectomy, infracolic omentectomy, bilateral pelvic lymph node dissection, fine needle aspiration biopsy of the para-aortic lymph node, and peritoneal fluid sampling were performed, followed by radical vulvectomy, bilateral groin node dissection, distal urethrectomy and lower vaginectomy. Had the vulvar mass been diagnosed as metastatic from an ovarian primary on laparotomy, a less radical procedure could have been substituted for the vulvar involvement. However, it is unfortunate that this information could only be obtained upon microscopic examination of the diseased organs, at the time of which, excision has already been performed.

Mazur, et al. noted that metastasis to the female genital tract was usually reflective of widespread and advanced stage of disease. Adjuvant treatment should be tailored based on the primary site of disease. Systemic chemotherapy for advanced ovarian carcinomas is in the form of a combination of Paclitaxel and Carboplatin.[21] However, regardless of the site of the primary lesion, metastatic tumors of the vulva were associated with an extremely poor prognosis, with only a handful of patients surviving 5 years after diagnosis.[5,6] Most of the patients in Dehner's series died of widespread disease within 12 months of the detection of the vulvar metastasis. In the series reported by Neto, of the 7 patients with vulvar metastases from an ovarian primary who were available for follow-up, 5 died of the disease at 3-81 months from the diagnosis of the metastasis, while 2 were alive with disease at 2 and 30 months. The patients who underwent wide local excision of the vulvar lesion and subsequently received chemotherapy and radiotherapy were noted to survive the longest. However, it is difficult to conclude which adjuvant therapy is ideal due to the limited number of reported cases in the literature[1]. Our patient was advised adjuvant chemotherapy with Paclitaxel and Carboplatin. She was last seen six months post-operatively, after receiving her fourth course of chemotherapy. At that time, she has an ECOG performance score of zero with no clinical or radiologic evidence of disease recurrence.

In summary, we are presented with a rare case of vulvar metastasis from a primary ovarian carcinoma. Review of the histopathologic specimen revealed an extensive manner of spread from one organ to the other. Although metastases to the female genital tract are rare, these tumors can nevertheless be insidious and can masquerade as primary disease at the metastatic site. A high index of suspicion coupled with an extensive patient work-up and thorough surgical staging at the time of laparotomy is thus necessary.

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Paraganglioma of the Uterine Cervix in a 7 year-old: A Case Report

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A 7 year old Filipino child who had vaginal bleeding episodes underwent excision biopsy of a paraganglioma of the uterine cervix. This is a tumor of the female reproductive system with only 15 cases reported worldwide, and probably the first report in the Philippines. The absolute criterion for malignancy is the presence of tumor at sites where paraganglionic tissue is not normally found. Neuron specific enolase (NSE) is the most useful immunostain and marker for the definitive diagnosis of the tumor. Surgical excision is the preferred mode of treatment whenever possible. But there have been reports of use of 131 I-metaiodebenzyl-guanidine radionuclide therapy, radiotherapy and chemotherapy for other extra-adrenal paragangliomas. Prognosis for cure is usually good. However, median survival for metastatic disease is 4.5 years and overall survival rate is 44%.

Key words: paraganglioma, pheochromocytoma, extra-adrenal pheochromocytoma, neuron-specific enolase, ^{131} I-metaiodebenzyl-guanidine

Vaginal bleeding in childhood is always clinically significant. It is uncommon in prepubertal girls but warrants careful and appropriate medical evaluation. The variable etiologies of vulvovaginitis are the most common causes. Trauma, urologic factors such as urethral prolapse and foreign bodies can be related to external blood loss. Precocious menstruation in itself or as a part of precocious puberty must be suspected. Genital bleeding also alerts one to the possibility, though rare, of a genital tract tumor. In the process of investigation, one may occasionally stumble upon something rarer than rare.

Case History

This is a case of R.H., 7 years old who consulted for vaginal bleeding. She has no previous medical illnesses and has no known allergy to any food or drug. Her developmental milestones are at par with children her age. There is a history of Hodgkin's lymphoma in the father. There are histories of hypertension and cerebrovascular disease in the maternal grandfather.

She is the fifth among six siblings. Both her parents are unemployed. She discontinued her studies after grade 2 level due to financial constraints. Menarche has not occurred. She has no history of coitus.

One week prior to hospital admission, there was onset of vaginal bleeding for one week consuming two diapers per day. Persistence of bleeding prompted consult with a private obstetrician-gynecologist. Pelvic ultrasound revealed a mildly enlarged uterus with apparent internal calcifications and hypervascularity. It exhibited very hypoechoic internal echo pattern within multiple intervening, highly echogenic foci with

[illegible] posterior shadows in the uterus. Exuberant [illegible] vascularity was depicted on color flow imaging. A possible uterine vascular tumor or vascular malformation was the sonologic impression. She was then referred to this institution for further evaluation and management.

On examination, the patient was pale. Breast growth was classified under Tanner stage I. The rest of the systemic findings were within normal limits. There were no palpable lymph nodes and abdominal masses. Pubic hair growth was classified under Tanner stage I. There was vaginal bleeding. Rectal examination showed a 2 x 2 cm mass, doughy, non-tender, extraluminal, which seemed adherent to the uterus posteriorly. Admitting impression was uterine mass rule out malignancy; rule out precocious puberty. The patient was co-managed with the Pediatrics service. Work-ups were requested.

She had a baseline hemoglobin of 89 and hematocrit of 0.265 with a WBC of 11.85 and platelet count 401,000. Peripheral blood smear showed slight anisocytosis, normochromic cells and slight poikilocytosis. No toxic changes were seen in the polymorphonuclear cells. Protime and activated partial thromboplastin time were normal. Urinalysis showed normal values. Blood chemistry profile was within normal.

Cranial CT Scan showed normal brain and sellar region. Anterior and posterior xray views of the left hand showed delayed skeletal maturity since the patient's left hand and wrist most closely resembled those of a standard 5 to 6 year old female (Greulich-Pyle method). Free T4 and TSH IRMA were normal. Serum FSH was <0.28 mIU/L while serum LH was <0.03 mIU/L. 17 OH Progesterone was 1.6 ng/ml while estradiol RIA was 0.38 pg/ml. DHEA-S level was determined and showed normal result. Precocious puberty was ruled out.

A transabdominal and transperineal ultrasound were performed on admission.

The vaginal canal was smooth with no masses within while the cervix measured 1.2 cm x 1.1 cm x 1.1 cm (Figure 1). The uterus was anteverted with smooth contour and heterogenous echopattern measuring 3.3 cm x 1.9 cm x 1.8 cm. The endometrium was indistinct. There was a heterogenous mass at the fundal area of the uterine corpus measuring 1.0 cm x 1.0 cm x 0.8 cm. with ill-defined border with echogenic areas peripherally, depicted in anteroposterior and transverse views (Figure 2). Color flow mapping showed a vessel arising from the posterior aspect of the uterus into the mass. Doppler studies, revealed low resistance indices (PI=0.74, RI=0.51) (Figure 3). Both ovaries were not visualized. There were no adnexal masses and no free fluid in the cul de sac. Impression was a uterine mass, cannot totally rule out endometrial involvement as described.

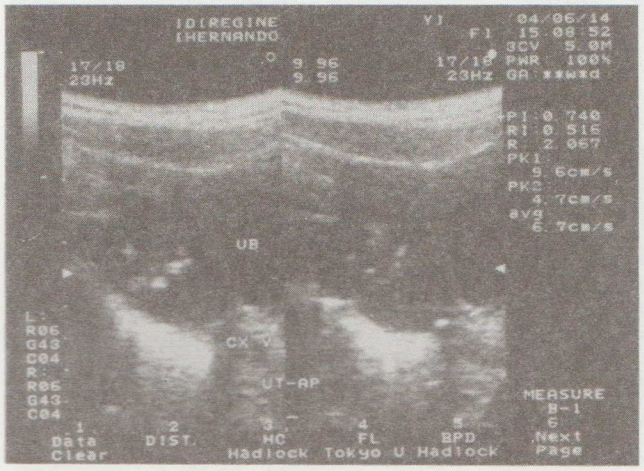

Figure 1. Transabdominal ultrasound anteroposterior view shows the characteristic of the vagina, cervix and uterus.

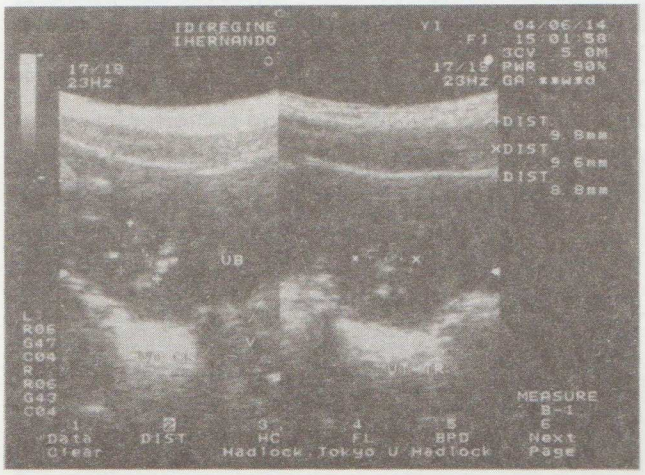

Figure 2. Transabdominal ultrasound anteroposterior and transverse views showing a fundal mass with echogenic areas.

A pelvic MRI showed an ill-defined mass seen in the cervix measuring 1.2 cm x 0.9 cm with marked enhancement after contrast infusions. Minimal

infiltration was noted in the adjacent fat. Small amount of fluid was seen posterior to this mass. Infantile uterus was deviated to the left. Visualized portion of both kidneys appeared unremarkable. There were no significant lymphadenopathy or osseous changes. Figure 1 depicts a schematic representation of these findings.

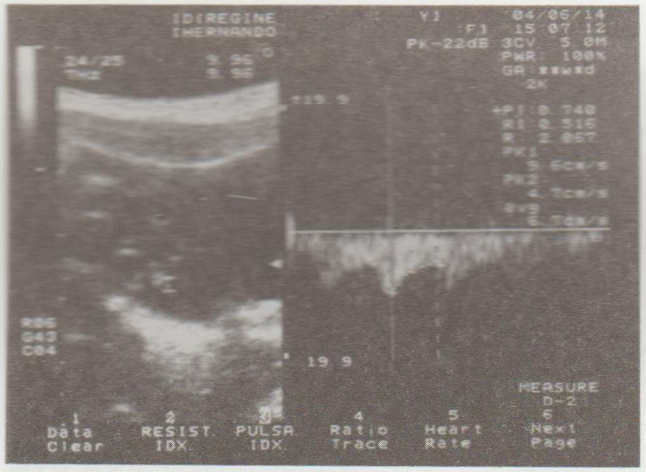

Figure 3. Doppler studies showing pulsatile and resistance indices.

On the fourth hospital day, she underwent internal examination under general anesthesia. External genitalia appeared grossly normal. Vaginal walls were smooth. There was a 1.5 cm x 1.0 cm x 2.0 cm fleshy, well-circumscribed erythematous mass, with a wide base attached to the anterior and posterior lip of the cervix at the at the 6- 10 o'clock position. The external os was also partially covered by the mass. The corpus was small. There were no adnexal masses. Intraoperative impression was a cervical mass probably polyp rule out malignancy. An excision biopsy of the cervical mass was performed.

Two specimens were sent to the surgical pathology laboratory and both were labeled "uterine mass." They consisted of several brown irregular tissue fragments with an aggregate diameters of 1.2 cm and 1.5 cm, respectively. Hematoxylin-eosin (H & E) stained microscopic pictures showed a vascular tumor. Networks of capillaries were seen among polygonal cells (Figure 4). Several fields revealed the presence of staghorn blood vessels. Final histopathologic diagnosis was:

Intermediate grade vascular tumor.
Hemangiopericytoma is a strong consideration
Note: Reticulin stain supports the vascular nature of the lesion. However, immunostains for CD34 is recommended.

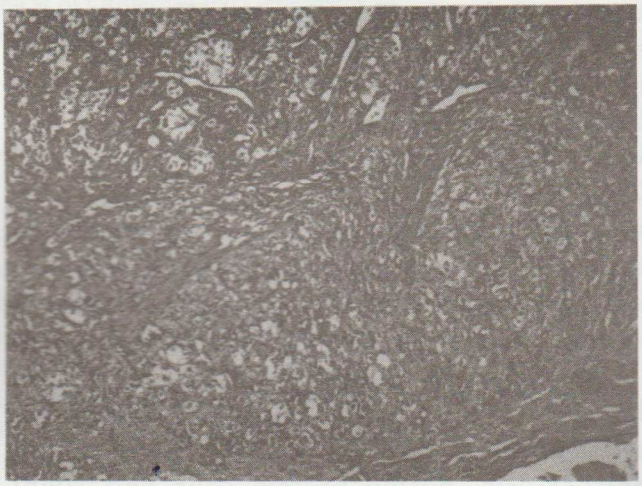

Figure 4. H & E preparation showing zellbalen pattern of cells with multiple capillaries, 100x.

After correction of the anemia and completing the work-ups, the patient was discharge improved. After five weeks, she followed up at the oncology subspecialty clinics of this institution. The patient and her relatives were advised that adjuvant treatment might be instituted in the form of combination chemotherapy with vincristine, adriamycin and cyclophospamide if hemangiopericytoma was confirmed by tissue immunostaining.

Tissue immunostaining for definitive diagnosis was requested. Review of the H & E preparation showed an organoid arrangement of polygonal cells with relatively abundant eosinophilic, focally clear cytoplasm and fairly uniform nuclei (Figures 5 & 6). The tumor showed strong diffuse immunoreactivity to neuron-specific enolase (NSE) (Figure 7). The tumor stained negative to Factor VIII (Figure 8), HMB 45 (Figure 9), actin (Figure 10), keratin (Figure 11), CD 34 (Figure 12), desmin (Figure 13), chromogranin (Figure 14) and synaptophysin (Figure 15). Final diagnosis was:

Paraganglioma, uterus
Note: Although necrosis, mitotic activity and vascular invasion are not evident, the reliable prediction of biologic behavior of

paragangliomas on the basis of histopathologic features is extremely difficult.

Unfortunately, the patient was lost to follow-up.

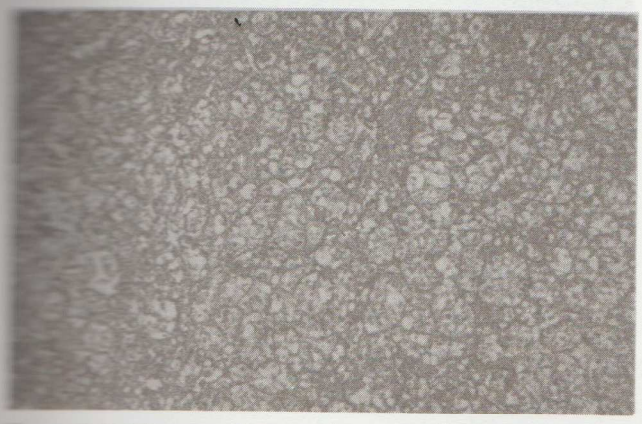

Figure 5. H & E preparation showing a magnified view of an area with zellbalen pattern, 400x.

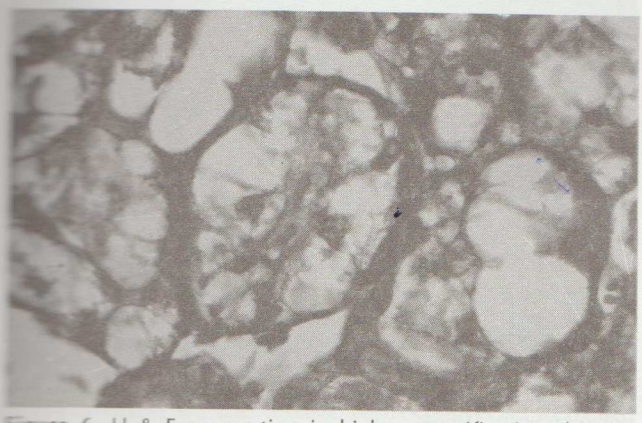

Figure 6. H & E preparation in higher magnification showing details of the polygonal cells in the zellbalen clusters. 1000x

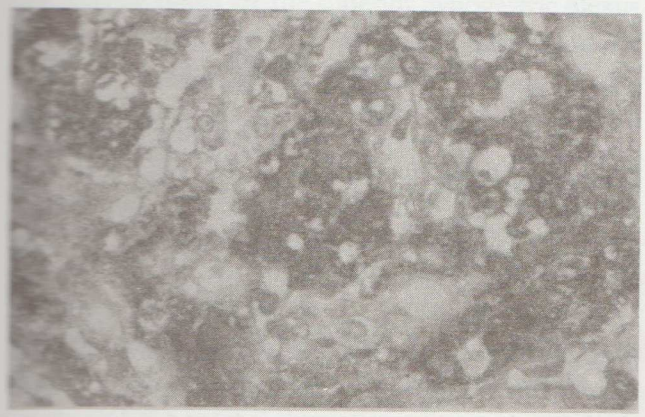

Figure 7. The tumor exhibiting positive immunostaining with NSE, 1000x.

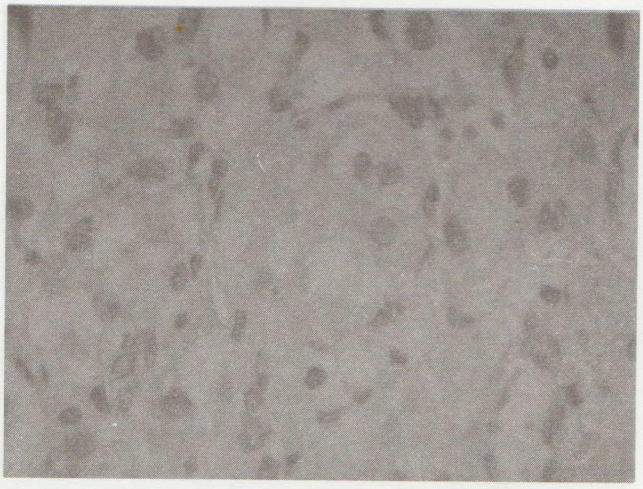

Figure 8. The tumor exhibiting negative immunostaining with Factor VIII, 1000x.

Figure 9. The tumor exhibiting negative immunostaining with HMB 45, 1000x.

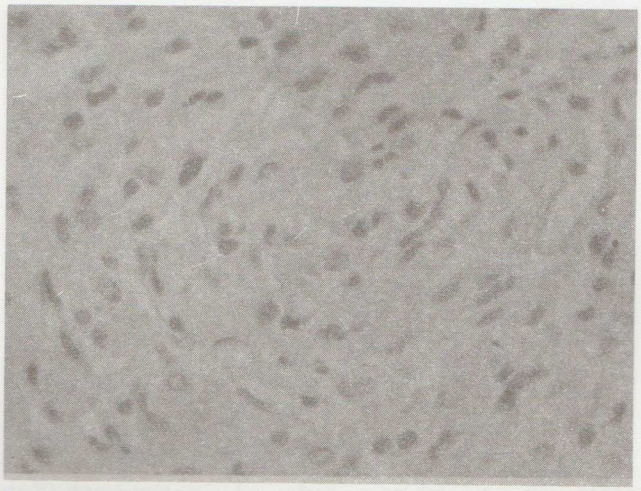

Figure 10. The tumor exhibiting negative immunostaining with actin, 1000x.

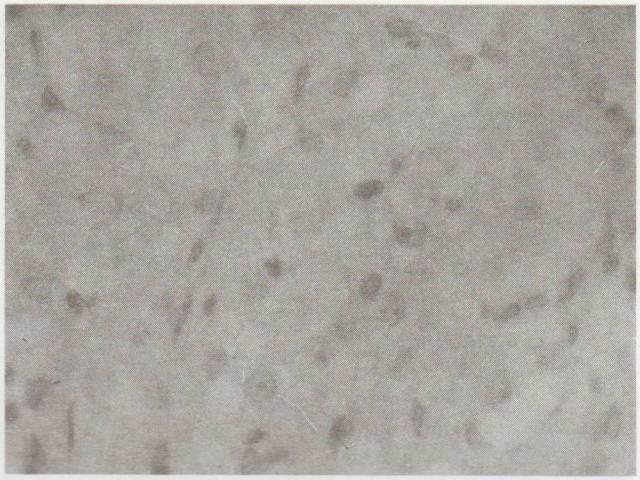

Figure 11. The tumor exhibiting negative immunostaining with keratin, 1000x.

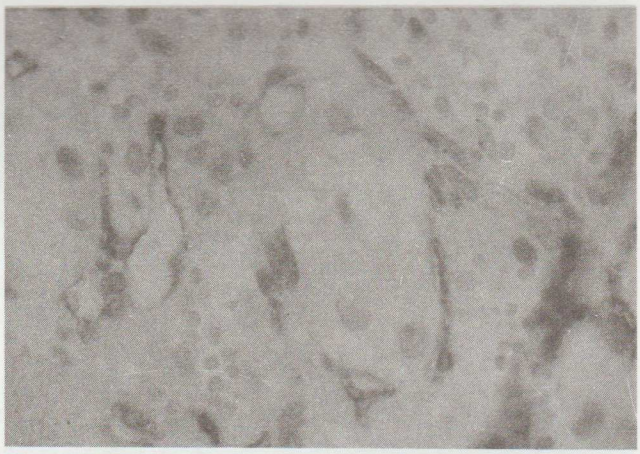

Figure 12. The tumor exhibiting negative immunostaining with CD 34, 1000x.

Figure 13. The tumor exhibiting negative immunostaining with desmin, 1000x.

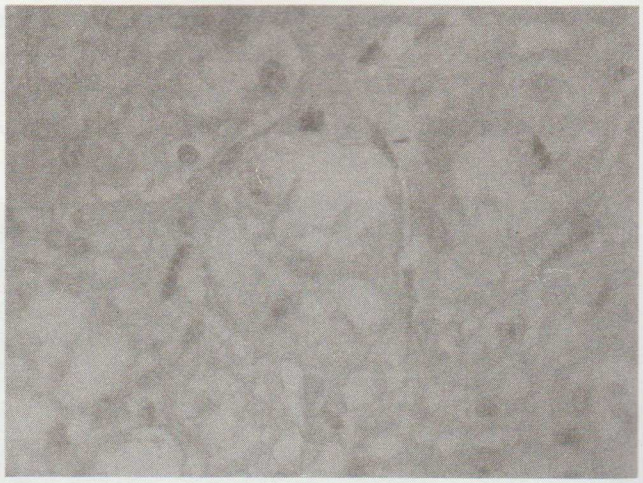

Figure 14. The tumor exhibiting negative immunostaining with chromogranin, 1000x.

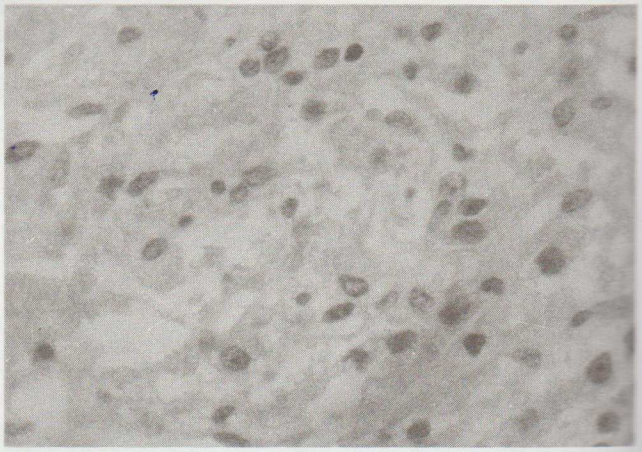

Figure 15. The tumor exhibiting negative immunostaining with synaptophysin, 1000x.

Case Discussion

Paragangliomas are neuroendocrine tumors arising from paraganglia which are groups of cells arising from the neural crest origin belonging to the extraadrenal chromaffin and nonchromaffin cell system.[1] They are also referred to as extraadrenal pheochromocytomas and comprise about 5-18 percent of all pheochromocytomas.[2,3] The failure of involution of the chromaffin tissue may be the best explanation for the development of extraadrenal pheochromocytomas.[4]

During embryogenesis, neural crest cells migrate from the neural tube to form the parasympathetic system in the head and neck, the sympathetic nervous system in the thoracic and abdominal region and the adrenal medulla. Those arising from the sympathetic system usually have no endocrine activity. However, those arisng from the adrenomedulla and sympathetic ganglia may be functional and secrete catecholamines.[3]

Paragangliomas may occur at any location in the sympathetic system. The most common location is the retroperitoneal region (between the diagphragm and the inferior renal poles). Approximately 46 percent of the extraadrenal tumors have been located in this region, particularly in and around the renal hilus. Twenty-nine per cent of cases have been found in the abdominal paraaortic area arising from the organ of Zuckerkandl which consists of paraganglia found in the retroperitoneal region.[4]

It is difficult to explain paragangliomas in an unusual location such as the female genital tract specifically the cervix. However, it can still be best explained by the dispersed migratory property of the neural crest cells.[6]

The female pelvic structures receive innervation from the autonomic nervous system. There are several points from where this migration of paraganglionic cells may be initiated, leading to the formation of a collection of cells in the uterine cervix. Sympathetic efferent fibers of the female reproductive system are derived from the T12 to L1-2 of the spinal cord, which run over the lumbo-aortic vessels. Components of the sympathetic fibers are the superior hypogastric plexus at the level of the aortic bifurcation, middle hypogastric plexus at the level of the sacral promontory and the inferior hypogastric plexus also known as the Lee Franchenauser ganglia. From the middle plexus arise two hypograstric nerves running craniocaudally and 2 cm mediodorsally to the ureters, in the posterior and lateral layer of the uterosacral ligament. The Lee Franchenauser ganglia, on the other hand, has both sympathetic and parasympathetic fibers and stretches from an area anterolateral to the rectum, passes the cervix and the vaginal fornix laterally and extends to the base of the bladder.

Parasympathetic efferent fibers come from the S2-S4 levels of the spinal cord. They supply motor fibers to the detrusor muscle and inhibitory fibers to the sphincter vesicae. The first 3 cm of the parasympathetic fibers is covered by the pelvic parietal fascia. Three groups of fibers identified in the pararectal space : first: runs along the lateral side of the pararectal space to the dorsomedial part of the cardinal ligament; second: crosses through the pararectal space over the pelvic floor and third: runs from the sacrum along the medial side of the pararectal space, parallel to the uterosacral ligament.

In the female genital tract, paragangliomas are exceptionally rare, with fewer than 15 cases reported since its first delineation in 1926. Four cases presented in the vagina,[7-10] another five were documented in the uterus, two of which were melanotic, [11-14] one in the ovary, [15] one in the vulva, [16] and one in the broad ligament.[17] There was also a report of a gangliocytic paraganglioma arising from a mature cystic teratoma of the ovary in 2003.[18] In this literature search, no detailed report or citation of a case of paraganglioma in the uterine cervix, whether primary or metastatic, was found. In the Philippines, this is probably the first report of a case of a paraganglioma in the female genital tract.

Extra-adrenal paraganglioma are more common in children, 30-40 percent of all pheochromocytomas versus about 10 percent in adults.[19] The first report of a paraganglioma in child within the female reproductive system was in 1998.[10] The tumor was located in the vagina of an 11 year-old. The said study investigated the incidence of tumor in the childhood population of the West Midlands region of the United Kingdom since 1957. Four other cases were found, all outside the genital tract: 2 abdominal, 1 para-aortic, and 1 carotid body.

Like the vast majority of cancers, paraganglioma occurs sporadically but has a hereditary or familial equivalent in 30 percent of cases. Imprinting, a mode of inheritance less well understood was observed in a subset of families with inherited paraganglioma. [20] Familial paraganglioma is caused by a germline mutation in one of the genes encoding succinate dehydrogenase. In this condition, multiple paragangliomas can arise in the same individual and

must be distinguished from metastatic disease, which may coexist.[21] It is usually characterized by an early onset and a more severe presentation. They are usually bilateral and multiple in location and may be recurrent or malignant. Although the hereditary form is worth-mentioning in a paranganglioma in a child, the lack of multiple tumor sites and a single family history of lymphoma in the father would not convince one to proceed with genetic studies.

These tumors are slow growing and are believed to be present for months or years prior to the onset of symptoms that lead to the diagnosis. They are multicentric in 43% of cases and there seems to have no specific distribution.[22] Multicentric paragangliomas are frequent in children.[4] However, it is rare for a functional and non-functional pheochromocytoma or paragangliomas to coexist.

Symptoms of paragangliomas can be divided into two categories. The first category includes symptoms due to an excess of catecholamines similar to their adrenal counterpart. The second category includes symptoms that are due to the specific location of the tumor and may help in localizing the tumor.

Paragangliomas in extragenital sites usually present with headache, palpitations, sweating and hypertension which are signs of norepinenephrine overproduction. But unlike the adrenal type, most extraadrenal pheochromocytomas (36-60%) do not secrete epinephrine since high local concentrations of cortisol required to stimulate the expression of 4-phenylethanolamine-N-methyltransferase, which catalyzes the conversion of norepinephrine to epinephrine is not present in these tumors.[21] Few cases have demonstrated some hormonal activity in the female reproductive system, one in the broad ligament.[17] and one in the vagina.[8] The patient with the said vaginal paraganglioma presented with episodes of acute hypertension before, during and after manipulation of the tumor, myocardial infarction and pulmonary edema warranting alpha blockade therapy.[8]

Abnormal vaginal bleeding is the most common manifestation of paragangliomas in the female genital tract.[7] A vaginal mass may be also be the first presenting sign.[8] Vulvar pain and nodule at the labia minora manifested in a 58 year-old woman with documented paraganglioma of the vulva.[16] It has also presented as a persistent right adnexal mass in a case arising from a mature cystic teratoma of the ovary.[18]

The patient presented with heavy vaginal bleeding and a well-circumscribed cervical mass which on imaging studies indicated a highly vascular tumor. No symptom or sign of catecholamine production was documented. Ultrasound findings suggested possible endometrial foci. The MRI though showed no definite masses in the uterus.

Diagnosis is difficult considering the relative rarity of the tumor, much more in the genital tract. Preoperative identification is unfortunately rare. Gross appearance is variable. For a tumor located in the vagina, the initial diagnosis was rhabdomyosarcoma.[10] Another mass located in the uterine cavity was initially thought of as leiomyoma in necrobiosis.[11] In our patient, even the visualization of the gross tumor did not provide clues to the diagnosis. Intraoperatively, a cervical polyp was the impression because the mass was fleshy, well-circumscribed with a broad base. The hypothesis of origin of polyps is usually secondary to inflammation or abnormal focal responsiveness to hormonal stimulation[23] which makes it also uncommon in children.

Biochemical studies may only help in the diagnosis if the tumor is hormonally functional. Elevated levels of fractionated urinary catecholamines, metanephrines and creatinine may be confirmatory.[21] None of the reported cases in the female genital tract have used biochemical parameters. In clinical practice though, the diagnostic and therapeutic issues raised with paragangliomas of the female reproductive system are quite different from tumors capable of catecholamine hypersecretion.

Imaging studies may aid in localizing the primary tumor and its other foci. The best localizing study for malignant paraganglioma is ^{123} I-Metaiodebenzyl-guanidine (MIBG) scanning with SPECT (single photon emission computed tomography.[19,21] MIBG is an adrenergic tissue localizing agent, particularly for extra-adrenal lesions. This can be combined with CT scanning. However, MIBG scintigraphy alone is superior to CT scan and MRI in the diagnosis of these tumors. It has a sensitivity of over 90 percent in detecting metastatic paragangliomas.[24] MIBG is structurally similar to noradrenaline and is taken into chromaffin cells by an active transport mechanism and concentrated in storage granules.[123] I dye has superior image quality and smaller amount of exposure and is

recommended. The test is not perfect though because at least 30 percent of malignant paragangliomas do not concentrate MIBG. This test is not available in the local setting and thus, an MRI was done.

MRI scanning is particularly useful for visualizing abdominal and bone tumors. Imaging results of the patient showed no abdominal masses, nor significant adnexal changes. CT scanning is most useful for visualizing lung and abdominal tumors. The intravenous contrast used in CT scans can provoke hypertensive crisis in paragangliomas which secrete norepinephrine. These patients are thus prepared beforehand with alpha-adrenergic blockers and are closely monitored.[21]

Gold standard for diagnosis is routine histology with immunohistochemical studies. Review of the patient's H & E slides showed findings consistent with a paraganglioma. Microscopically, the classic description are uniform small round cells arranged in discrete cohesive lobules known as zellbalen pattern which are surrounded by extensive vascular channels.[1,6,12] The tumor in this patient exhibited this classic zellbalen pattern. The nuclei are usually round, oval, spindly and epitheloid with moderate to scanty granular eosinophilic cytoplasm, with smooth nuclear membranes, fine evenly dispersed chromatin, slight hyperchromasia, and mild pleomorphism.[25] Reticulin stain can confirm the "zellbalen" nature of the neoplasm. Neoplastic cells may show moderate argyrophilia on Grimelius stain.[16]

Immunohistochemically, the tumor stains with neuron-specific enolase (NSE), chromogranin, protein gene product 9.5 and synaptophysin.[12] NSE is the best tumor marker for paragangliomas. It is elevated in 80 percent[26] of patients and has a sensitivity of 92.1%.[18] Chromogranin on the other hand is elevated in 40 percent of patients,[26] with a sensitivity of 84.2%.[18] The least sensitive (73.0%) and specific marker was met-enkephalin. Combinations of NSE and chromogranin with met-enkephalin identified chief cells in all cases as cited in a review of prognosis by histologic, immunohistochemical and ultrastructural techniques of paraganglioma in general done in 1989.

To arrive at the diagnosis, several panels of immunostains were used. The diagnostic considerations for a malignant neoplasm that does not exhibit clear evidence of differentiation include carcinoma, lymphoma, melanoma and sarcoma. Cytokeratins are excellent markers for epithelial differentiation. They are intermediate filaments classified on the basis of molecular weight and pH. Desmin has a high sensitivity in differentiating highly cellular leiomyomas from endometrial stromal tumors. Leiomyosarcomas however, frequently express CD 10. Smooth muscle actin (SMA) may be helpful for epitheloid smooth muscle tumors because it is more sensitive than desmin in marking those tumors. Chromogranin and synaptophysin are used for the diagnosis of large cell neuroendocrine carcinoma of the cervix. This is not a requirement, though for small cell carcinoma. NSE is not specific enough to reliably determine neuroendocrine differentiation for these tumors.[27]

It was necessary to distinguish this tumor from other tumors with prominent vascular patterns such as a hemangiopericytoma, which was the initial histopathologic consideration. CD 34 stains the cytoplasm and membrane, and may be used in identifying endothelial or myofibroblastic differentiation in tumors. CD 34 is one of the few immunostains that is positive for hemangiopericytomas in about 60-70 percent of cases. It may not be specific, but can be very useful in context with other features. Factor VIII is expressed by normal pericytes and may be used as a marker of fibrohistiocytic differentiation in hemangiopericytomas. It was found to focally stain the endothelial cells of the tumor.[28]

HMB 45 is a marker for melanoma. Even in cases reported with pigmented extraadrenal paragangliomas, HMB 45 antibodies were negative The presence of the melanin pigment, although a pitfall in diagnosis, does not appear to alter the biologic behavior of paragangliomas.[29]

Ultrastructural studies with electron microscopy indicated two cell types within the neoplasm: chief cells with numerous small neurosecretory granules and peripheral slender sustentacular cells.[16] Electron microscopy, however, may be of less value in delineating sustentacular cells because of scarcity and the absence of specific features.[18] In a few studies, stains for chromogranin and NSE were strongly positive in the chief cells while S-100 antibody and glial fibrillary acid protein (GFAP) confirmed the

finding of sustentacular cells by identifying many slender cellular processes among the chief cells. [16,19] Sustentacular cell density and chief cell staining intensity were both inversely related to tumor grade. [19]

Paragangliomas may be benign or malignant tumors. In adults, the rate of malignancy was 30-40 percent of cases versus 2 percent in children although conflicting data add to the uncertainty at this point. Malignant behavior of paraganglioma in sites other than the genital tract ranges between 15-50 percent.[18] It was reported that malignancy is more common in paragangliomas, around 30-50 percent of cases than in pheochromocytomas, 10-15 percent of cases.[21] Thus, in the absence of malignant behavior, it may be misleading to regard cases as benign.

Several authors have attempted to define malignancy based on histologic markers including central necrosis, vascular invasion, and mitosis or nuclear atypia. However, these parameters did not appear to be correlated with metastasis or true invasion. Even signs of local compression and erosion of surrounding structures generally are not accepted signs of malignancy. [1]

The only hallmark of malignancy is evidence of metastasis where paraganglionic tissue is not normally found.[4] This may include the presence of local invasion, destruction of adjacent vertebrae, and distant metastasis to the lungs, liver, lymph nodes, skin and bones. Malignancy, however, must be distinguished from peritoneal seeding of tumor that can occur spontaneously or during the resection of a retroperitoneal paraganglioma, yielding multiple intra-abdominal tumors. [21] Of the five cases reported previously reported in the uterus, only one was malignant. [11]

The challenge lies in distinguishing those tumors which are actually malignant due to metastasis versus tumors which are multicentric. Presently, there are no clear answers.

The patient's symptomatology, the clinical behavior of the tumor, as well as the absence of microscopic evidence of necrosis, mitotic activity and lymphovascular invasion, extrauterine involvement and lymphadenopathy may point to a benign condition. The coexistence of an endometrial focus documented in several ultrasound studies, the presence of an intermediate grade vascular tumor on H & E and ill-defined mass with minimal infiltration to the adjacent fat in MRI provide clues to possible local invasion and malignancy. In these tumors, however, there is no apparent relationship between true invasion and clinical behavior, as well as true invasion and histologic features such as nuclear pleomorphism, vascular invasion, mitotic activity or perineural invasion. Unfortunately, the child did not follow-up.

The American Joint Committee on Cancer (AJCC) has no formal staging system for paraganglioma. In some studies, general summary was used which classified the tumor as local, regional or distant.[1]

For benign paragangliomas, surgical excision may be sufficient. Irradiation as a form of treatment has also been reported in benign tumors. This slows or halts the tumor growth or cause partial tumor shrinkage but usually does not result in complete resolution of the tumor. [21]

Even in the presence of distant metastasis, it is best to resect and debulk the primary tumor whenever possible. [21] Preoperative factors univariately associated with adverse perioperative events included larger tumor size, prolonged duration of anesthesia and increased levels of preoperative urinary catecholamines and catecholamine metabolites. [4] A multidisclipanary approach is necessary whenever the tumor has metastasis or multicentric. For most of the cases of genital paraganglioma worldwide, surgical excision was the primary mode of treatment whenever possible. The child in this case would have benefited to a planned complete surgical removal of the tumor if only she followed up after the definitive diagnosis.

Hysterectomy has been done for a paraganglioma of the uterus with clinically malignant behavior. The clinical outcome was characterized by early regional recurrence in the left fallopian tube with subsequent vertebral and lung metastasis, leading to death 22 months after the initial diagnosis. [11] Moreover, hysterectomy with bilateral salpingooophorectomy has been performed in a 55 year-old with ovarian paraganglioma with benign features.[18]. The same report suggested surgical staging and retroperitoneal lymphadenectomy if histopathology is suggestive of invasive disease and enlarged lymph nodes are noted.

High dose [131] I-MIBG therapy or radioactive MIBG has been moderately successful in treating these cases.

resembles norepinephrine, and iodine is tagged to it, producing ^{131} I-MIBG, a targeted radionuclide. As the iodine 131 decays, it releases local high-energy beta particles that damage or destroy the tumor cell; concomitant release of gamma rays allows post-therapy whole-body scanning. Majority of cases experience partial remission and stabilization of disease. With very high doses, 3 of 12 patients achieved complete remissions.[21] Approximately 73 percent of patients show at least partial tumor response, hormonal response or symptomatic improvement.[21] Complete remission is rare. Tumor shrinkage is achieved in metastatic disease and small lesions tend to resolve while larger ones usually persist. Its use for genital tract paragangliomas, however, has not been documented.

External radiation therapy has been useful for patients with painful bone metastasis. However, irradiated tumors lose their avidity for ^{131} I-MIBG. Thus, radiation is administered after. Radiotherapy is ineffective in intra-abdominal paragangliomas.[21] In some reports, RT has been considered partially efficient as it diminishes tumor growth and induce partial regression especially as adjuvant treatment post surgical excision.[22] A cure however, should not be expected. There has been no report of RT use in a paraganglioma in the genital tract.

Experience with chemotherapy as primary or adjuvant treatment modality is limited to extragenital paragangliomas. It is reserved for those with residual disease after surgery and for metastatic disease. In a fifteen-year review by Patel et al. in 1995, combination chemotherapy with cyclophosphamide, vincristine and dacarbazine (CVD) every 21 days appears to be the most effective chemotherapeutic regimen for metastatic paraganglioma and even pheochromocytoma.[30] Analysis of 23 patients treated with CVD showed 61 percent had objective evidence of tumor regression and 74 percent had evidence of biochemical response.[31] There was no evidence that chemotherapy contributes to improved patient survival.

There are no detailed reports on chemotherapy use as treatment modality in paragangliomas of the uterus, ovary, and vagina. The patient was initially advised chemotherapy with VAC since this is the regimen of choice for the initial histopathologic diagnosis of hemangiopericytoma. If she followed up when the immunostaining results were released, the appropriate regimen would have been advised.

Patient follow-up with a few months interval is necessary as the tumors may metastasize after initial resection. Can one monitor a tumor marker for such a case? NSE is best tumor marker for paraganglioma. There have been no studies however, regarding its correlation with tumor burden. Blood chromogranin A may give additional information during the monitoring of patients in I-MIBG especially for the functional type, since this correlate well with urine catecholamines.[22] Urinary catecholamines may also be monitored if the tumors are functional.

A case report of a recurrent paraganglioma of the carotid body with lung and bone metastasis compared metabolic imaging with positron emission tomography (PET) scanning and anatomical imaging with CT scanning to monitor response to chemotherapy. Response to chemotherapy was demonstrated on PET scan alone and the patient had remained disease-free for 24 months after chemotherapy completion.[32] This is worth-mentioning since PET scanning can also be helpful in malignant genital tract paragangliomas which are multifocal, recurrent or metastatic.

Among paraganglioma patients in general, global survival is 62 percent although 36.7 percent remain free of disease.[22] Prognosis for cure is usually good, but for the malignant types, the survival for a malignant pheochromocytoma is 44 percent.[19] For paragangliomas with metastatic disease, median survival is 4.5 years.[21]

Conclusion

It has been two years since the patient has been diagnosed with this rare tumor. She stays in the province and is currently well. Her relatives have been called a few times for follow-up, but financial constraints have deterred them form going back for consult.

Paragangliomas have an indolent course and many cases present with a benign clinical picture. Although unusual in the pelvis, much more in the cervix, paragangliomas should be included in the differential diagnosis of a well-circumscribed pelvic mass with features suggesting a vascular lesion. As highlighted by this case, biologic behavior is variable and may not be correlated with symptomatology and histologic features.

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Pseudomyxoma Peritonei: A Revisit

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The term Pseudomyxoma peritonei or PMP was [illegible] by Werth in 1884 in reference to mucinous [illegible] within the peritoneal cavity associated with a [illegible] tumor. Literally translated to mean "false [illegible] tumor of the peritoneum", the term was [illegible] by Dr. Fraenkel in 1901 in the case of a [illegible] of the appendix associated with mucinous [illegible]. Since then, the term has been broadly [illegible] to any slowly progressive disease whereby the [illegible] cavity becomes filled with thick gelatinous [illegible], hence its monicker "jelly belly".[1] Unfortunately, the indiscriminate use of the term PMP resulted in considerable debate and controversy regarding its definition, pathology, origin and prognosis. The past decade, however, has seen tremendous advances in research on the various points of contention about PMP. This article aims to focus on these recent breakthroughs.

Pathology

The term "pseudomyxoma peritonei" was [illegible] used as a pathological diagnosis applied to the chronic accumulation of intra abdominal mucus most often associated with an indolent mucinous neoplasm. It has also been used, however, for mucin deposition seen in cases of clinically aggressive metastatic carcinoma of the peritoneum, and cases of ruptured ovarian mucinous tumors. This lack of a uniformly accepted definition caused diagnostic confusion and unreliable data on prognosis.[2]

In 1995, Ronnett, et al.[3] studied 109 cases of PMP defined[3] prognostically distinct groups of patients based on the pathologic features of their peritoneal lesions. Disseminated peritoneal adenomucinosis or DPAM is characterized by superficial, non-invasive peritoneal lesions composed of abundant extracellular mucin associated with fibrosis and scanty bland to low-grade mucinous epithelium. This epithelium is non-stratified with minimal cytologic atypia and mitotic activity. The primary site of origin is usually a mucinous adenoma of the appendix. Intra-operatively, DPAM appears as a mucinous ascites with a characteristic distribution along the peritoneal surfaces while sparing the small bowel serosa.[4]

In contrast, Peritoneal mucinous carcinomatosis or PMCA presents with more abundant mucinous epithelium in its extracellular mucin. This epithelium forms glands and/or signet ring cells, and exhibit marked atypia warranting a diagnosis of mucinous carcinoma. Many of these lesions were associated with a primary mucinous adenocarcinoma of either the appendix or colon. On surgery, PMCA presents as carcinomatosis with invasive peritoneal implants and frequent lymph node and parenchymal organ metastases.[4]

The PMCA-Intermediate category (PMCA-I) included cases derived from well-differentiated mucinous adenocarcinomas whose peritoneal lesions show features of DPAM with focal areas of mucinous carcinoma. In contrast, cases with discordant features originated from atypical appendiceal adenomas but had peritoneal lesions uniformly composed of mucinous carcinoma.[4]

A follow-up study in 2001 revealed statistically significant differences in the survival of patients in the 3 pathological categories with DPAM patients having the best survival figures and PMCA the worst. Patients in the Intermediate or Discordant category had survival rates intermediate to DPAM and PMCA.[5]

Ronnett, et al. interpreted DPAM as a pathological term for the disease entity often labeled in the past as

PMP, characterized by slowly progressive reaccumulation of mucinous ascites.[5] In 2003, participants in the Borderline Ovarian Tumor Workshop[2] held in Bethesda, Maryland agreed that the term "DPAM" be used as the specific pathological diagnosis for these low-grade peritoneal mucinous tumors. For historical continuity, they recommended restricting the use of the term "PMP" as a clinical descriptor for the syndrome of mucinous ascites accompanied by these low-grade mucinous tumors.

Table 1. Pathological categories of mucinous peritoneal tumors.[5]

	DPAM n = 65	PMCA - I / D n = 14	PMCA n = 29
5-year Survival Rate	75%	50%	14%
10-year Survival Rate	68%	21%	3%
Median Survival	Not reached	51 mos.	16 mos.
No. of deaths (%)	20 (31 %)	11 (79 %)	28 (93 %)

Before the 1990s, much debate also occurred over the site of origin of PMP among women. Whereas in men, the gastrointestinal tract was always considered the only site of origin, in women, it was assumed that PMP could originate from the GI tract or the ovaries. Recent morphological, immunohistochemical, and molecular genetic studies, however, have provided compelling evidence that virtually all cases of PMP in women are derived from appendiceal mucinous tumor and that the ovarian involvement is only secondary. Table 2 shows the distinguishing features of metastatic ovarian mucinous tumors in PMP versus Primary ovarian mucinous LMP tumors or atypical proliferative mucinous tumors (APMTs).[6]

The Borderline Ovarian Tumor Workshop group[2] recommends that ovarian tumors associated with PMP: 1.) should be reported as metastatic to the ovary from a primary tumor of the appendix or GI tract; 2.) and should not be labeled with the same diagnostic terms used for primary ovarian tumors in order to avoid confusion as to the suspected site of origin of the PMP. They also recommend that if an ovarian mucinous tumor is noted on frozen section in the setting of PMP, the need for appendectomy should be conveyed to the surgeon and the pathologist should step section and examine the entire appendix microscopically so as not to miss out on a microscopic foci of tumor here.

Table 2. Features of both metastatic mucinous ovarian tumors in PMP versus primary ovarian mucinous LMP tumors.

Feature	Metastatic Mucinous Ovarian Tumors in DPAM & PMCA	Primary Ovarian Borderline Mucinous Tumors or APMTs
Size (mean)	7 cm	19 cm
Laterality	Bilateral 80 % Unilateral 20 %, R > L	Unilateral 93%
Gross appearance	Mucinous nodules 90%	Multiloculated cyst 100%
Location of tumor	Surface + stroma 77%	Stroma only 97%
Pseudomyxoma ovarii	Often prominent	Infrequent
Associated appendiceal or intestinal tumor	Very frequent	Rare
Histochemical markers	· Diffusely CK 20 (+) · CK 7 (-), HAM 56 (-)	· Patchy CK 20 (+) · CK 7 (+), HAM 56 (+)
K-ras mutations	Identical mutations between ovarian & appendiceal tumors	

Pathogenesis

The sequence of events leading to the development of PMP is best described by the "redistribution phenomenon".[7] Here, the primary tumor in the appendix enlarges and obstructs the appendiceal lumen and stretches its walls to bursting point. Eventually, the appendix perforates and leaks tumor cells into the peritoneal cavity. Such peritoneal spread usually occurs before the involvement of lymph channels or venules in the appendix wall, thus, lymph node and parenchymal metastases in cases of PMP rarely occur.

The extruded benign adenomatous cells are relatively free of adhesion molecules. As a result, these cells are easily carried along with the mucin and aggregate in certain predetermined areas within the peritoneal cavity as determined by fluid flow, absorption, and the gravitational forces therein. Most of the fluid is absorbed by the lymphatic lacunae in the subdiaphragmatic region and the omentum where cells are subsequently deposited. There is preferential involvement of the right subdiaphragmatic peritoneum as the falciform ligament impedes cell transgression until late in the disease process.[7] Cells then settle by gravity within the dependent portions of the abdomen such as the pelvis, right retrohepatic space, left abdominal gutter and at the ligament of Treitz.

Another important feature of this redistribution phenomenon is the concept of visceral sparing.[8] Because the small bowel is in relatively constant motion, it will not be involved early in the disease process. In contrast, areas where the bowel is fixed such as in the pylorus, proximal and distal colon are more commonly involved. This unique pattern of mucin deposition and visceral sparing has allowed for the recognition of PMP on diagnostic imaging studies, and more importantly, has led to the development of potentially curative surgical approaches to PMP.

Clinical Presentation

PMP is a very rare disease with estimated incidence of 1 case per 1 million per year.[9] Two-thirds of patients present in the 4th to 5th decades of life with most studies showing a mean age of 53 to 58 years. Previously, PMP was thought to occur more in women with a female to male ratio of 3:1. However, more recent studies do not reflect such preponderance for women.

Table 3.

Author (Year)	No. of Subjects	Mean Age (age range)	No. of Females (%)
Van Ruth S, et al. (2003)[10]	62	58 (30 - 77 yrs)	38 (61.3%)
Deraco M, et al. (2004)[11]	33	53 (30 - 76 yrs)	12 (36.4%)
Gunes Z, et al. (2005)[12]	28	56 (28 - 79 yrs)	17 (60.8%)
Miner TJ, et al. (2005)[13]	97	53 (19 - 84 yrs)	45 (46.4%)
Smeenk RM, et al. (2006)[9]	103	57 (30 - 77 yrs)	69 (67%)
Sugarbaker PH, et al. (2006)[14]	356	48 (29 - 72 yrs)	153 (43%)
		TOTAL	334 females (49.2 %)

The most common symptom of PMP is a gradually increasing abdominal girth. Another common presenting feature is appendicitis, a clinical manifestation of a ruptured appendiceal mucocele with local inflammation. Women often develop an ovarian mass, usually on the right side, while men can have new-onset hernia.[14]

Diagnostic Tools

Pre-operative diagnosis of PMP used to be difficult and indeterminate up until the patient underwent laparotomy. Fortunately, reports published in the past decade have shown the increasing usefulness of radiological imaging techniques in diagnosing PMP pre-operatively. The least expensive and more widely available of these is whole abdomen ultrasound, which is usually the first diagnostic procedure done on patients with abdominal enlargement.[16] Typical findings of PMP on sonography include: a) nonmobile ascites with multiple echogenic masses, b) multiple septations and, c) scalloping of the hepatic and splenic margins.[16]

Table 4. Frequency of symptoms and signs of PMP.

Symptom / Sign	Esquivel & Sugarbaker (2000)[15] n = 217	Miner TJ, et al. (2005) n = 97
Increased abdominal girth	49 (23%)	53 (55%)
Appendicitis	58 (27%)	20 (20%)
Ovarian mass	44 / 112 (39%)	-----
Hernia	30 (14%)	6 (6%)
Ascites	5 (5%)	-----
Abdominal pain	5 (5%)	3 (3%)
Other	5 (5%)	2 (2%)

Computed tomography is increasingly becoming the most widely used imaging technique to diagnose PMP. All cases of PMP present with the characteristic low attenuation mucinous ascites exhibiting the same density as fat. In addition, Sulkin, et al.[17] noted that this mucinous ascites contained septae and calcifications and caused visceral scalloping as well as posterior / central displacement of the small bowels. However, they considered scalloping of the visceral surfaces, particularly the liver to be the diagnostic sign that distinguishes mucinous ascites from fluid ascites on CT.

Table 5. CT scan findings of PMP.[17]

CT Features	Number & Percentage of Cases (n = 17)
Visceral scalloping	17 (100%)
Septae in PMP	15 (88%)
Small bowel displaced centrally / posteriorly	8 (47%)
Calcification in PMP	4 (23.5%)
Right ovarian mass	2 of 9 women (2%)
Appendiceal tumor	1 (6%)

Sulkin also noted the distribution of lesions in the early and late stages of PMP.[17] In patients with small-volume disease or early PMP, the deposits were noted in the pouch of Douglas, subphrenic spaces, liver and spleen surfaces, and paracolic gutters. As the disease progresses, it spreads to those sites where peristalsis is limited by peritoneal attachments such as the stomach, duodenum, sigmoid colon / Morison's pouch / lesser sac before it finally goes to fill the rest of the peritoneal cavity. This pattern of distribution of lesions on CT reflects the progression of PMP according to the redistribution phenomenon and the pattern is considered characteristic enough to suggest the diagnosis of PMP, especially in the early stages of the disease process.

Table 6. Distribution of lesions on CT scan of PMP cases.[17]

Distribution of PMP	Number & Percentage of Cases (n = 17)
Right subphrenic space	15 (88%)
Liver surface	15 (88%)
Left subphrenic space	15 (88%)
Spleen surface	15 (88%)
Right paracolic gutter	14 (82%)
Pouch of Douglas / rectovesical pouch	17 (100%)
Left paracolic gutter	12 (70.6%)

In more advanced cases of PMP, the CT findings are more non-specific. However, several clues remain to suggest the diagnosis of PMP and these clues include: 1) pressure effects, a prominent feature seen as posterior or central displacement of the small bowels + universal abdominal distention + compression of retroperitoneal structures and 2) absence of abdominal / pelvic lymph node and visceral metastases.[17]

In some cases, the diagnosis of PMP may be made through paracentesis or laparoscopy with biopsy. Dr. Sugarbaker, a known expert on PMP, advises that these procedures be done directly within the midline and through the linea alba since these areas can be excised as part of a midline abdominal incision during the definitive surgical procedure of the patient. Lateral puncture or port sites should be avoided since these could cause tumor seeding into the abdominal wall and greatly reduce the likelihood of optimal surgical resection later on.[14]

Treatment

Debulking surgery with a primarily palliative intent was the mainstay of treatment for pseudomyxoma peritonei. Before the 1990s, the options for adjuvant treatment varied widely ranging from radiotherapy, mucolytic agents, and even immunotherapy.[18] Of these, chemotherapy was the only option that gained wide acceptance.

Traditionally, PMP was managed by serial debulking surgery to achieve optimal palliation of the patient's symptoms. This usually consisted of an appendectomy or right hemicolectomy, bilateral salpingoophorectomy in women, omentectomy, and debulking of as much gross mucin as possible.[13] After 2 to 4 years, the tumor usually recurs and debulking is repeated but is now more difficult.

Gough, et al. of the Mayo Clinic[19] reported that with each successive surgery, the proportion of patients achieving total mucus removal decreased and the surgeries became increasingly palliative in intent.

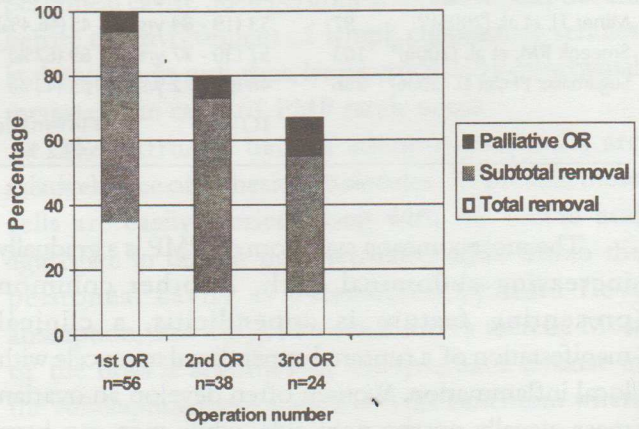

Figure 1. Proportion of patient outcomes from surgery for PMP.[19]

A similar experience was shown by the group from Memorial Sloan Kettering Cancer Center in their 2005 report.[13] They also found that durability

symptom control decreased after each operation. After 3 or 4 debulking procedures, the small bowel loops became encased in scar tissue and mucinous tumor such that further surgery is impossible. This eventually restricts gastrointestinal tract function and the patient succumbs from long-term starvation.

More recently, some surgical oncologists noted that PMP had certain features that made it amenable to curative and not just palliative surgery.[8] These features include: A) The low biological aggressiveness of appendiceal cancer with rare metastasis to the lymph nodes and viscera; B) Early peritoneal dissemination occurring even before venous and lymphatic channels in the appendix wall are invaded; C) The accumulation of mucinous tumor in anatomically resectable sites with sparing of the small bowel and D) Lastly, its location in a local body cavity amenable to high-dose intraperitoneal chemotherapy to augment the surgical tumor removal.

With these features in mind, Dr. Paul Sugarbaker and his colleagues from the Washington Cancer Institute proposed the following changes in the therapeutic approach to PMP: 1) They suggested peritonectomy procedures instead of surgical debulking; 2) Intraperitoneal rather than intravenous chemotherapy using drugs with a high molecular weight for slower peritoneal absorption and rapid systemic clearance; 3) Change in the timing of chemotherapy by giving it perioperatively so that chemotherapy drugs can be more evenly distributed since postoperative intestinal adhesions have not yet developed; and lastly 4) better patient selection by choosing to give chemotherapy only to those patients with negligible residual peritoneal surface disease.[8]

These changes led to the development of what is now known as the Sugarbaker procedure.[14] It involves aggressive cytoreductive surgery (CRS) to treat macroscopic disease, followed by intraoperative intraperitoneal chemotherapy (IPC) to treat microscopic residual disease, thus eradicating pseudomyxoma completely in a single step.

For the CRS, an incision is made from the xiphoid to pubis and abdominal exposure is maximized using a Thompson self-retaining retractor. The surgical procedure is started with dissection of the parietal peritoneum from the abdominal wall. Using a ball-tip electrosurgical hand piece on pure cut at high voltage, CRS was then carried out to remove all grossly diseased peritoneum.

Basically, when the tumor involves parietal peritoneal surfaces, parietal peritonectomy or peritoneal stripping is done. When it involves visceral peritoneal surfaces, organ resections are done. Complete parietal peritonectomy usually involves the following dissections as outlined by Sugarbaker: 1) greater omentectomy + splenectomy; 2) LUQ (left subphrenic peritonectomy); 3) RUQ peritonectomy + Glisson capsule resection; 4) lesser omentectomy + dissection of hepatoduodenal ligament ; and 5) pelvic peritonectomy $\pm$ THBSO.

The thoroughness of surgery is defined using the Completeness of Cytoreduction Score (CC Score) devised by Sugarbaker.[8] This scoring system is based on the size of the largest tumor implant left as residual. For PMP, a level 0 or level 1 cytoreduction is considered a complete resection because 2.5 mm is the maximum tumor size that is theoretically penetrable by IPC. Patients with tumor greater than 2.5 mm are considered incompletely cytoreduced. Thus, meticulous CRS is necessary prior to IPC instillation.

After cytoreduction but before intestinal anastomoses or repair of seromuscular tears, 4 silicone catheters are placed in the abdominal cavity in the areas shown here and the abdomen and pelvis are irrigated with a warm mitomycin C solution (using 1.5% dextrose peritoneal dialysate as its carrier solution).[14] Heating the chemotherapy perfusate to 40°C - 44°C is justified by the known cytotoxic property of heat and by its enhancement of the drugs' antitumor effects. Thermocouples inserted into the peritoneal cavity monitor temperature, while a heat exchanger keeps the perfusate at 42°C - 44°C. The procedure lasts 60-90 minutes after which the perfusate is quickly drained, bowel anastomoses and repair is performed, and the abdomen is closed.

Early postoperative IPC with 5-FU (at 600 mg/m^2 in 1L 1.5% dextrose peritoneal dialysate) is instilled using the same silicone catheters and distributed by gravity for the next 6 hours. Systemic chemotherapy was reserved only for patients with PMCA on histopathological examination.

Extensive CRS and HIPEC present a major physiological insult to the patient. It entails an average OR time of 6-9 hours, mean of 4-16 blood units transfused, mean ICU stay of 3-15 days and a mean hospital stay of 21-29 days. At the Washington Cancer Institute, as much as 21 percent of patients had a temporary jejunostomy / ileostomy, and 13 percent retained a permanent ileostomy.

Studies on the complications associated with this treatment regimen showed morbidity rates ranging from 12-55 percent and mortality rates of up to 12 percent.[20,21] Centers with longer and more extensive experience with the Sugarbaker procedure had lower morbidity and mortality rates as refinements in the procedure and in postoperative critical care were instituted throughout their learning curve.

Table 7. Survival rates for PMP.

Author (Year treated)	n	Treatment	5 yr Survival	10 yr survival
Gough D, et al.[19] (1957-83)	56	Repetitive debulking surgery ± chemo ± RT	53%	32%
Misdraji, et al.[23] (1950-2000)	107	NA	86% DPAM 44% PMCA	45% DPAM
Miner TJ, et al.[13] (1980-2002)	97	Repetitive debulking surgery ± chemo		70% overall 90% DPAM
Sugarbaker & Chang[8] (1989-99)	385	CRS + IPC	86% DPAM 50% PMCA I/D; 20% CC-2 or 3	80% overall 0% CC-2 or 3
Van Ruth, et al.[10] (1996-2002)	62	CRS + IPHP	38% overall	
Deraco M, et al.[11] (1996- 2003)	33	CRS + IPHP	96%	
Lougnarath R, et al.[22] (1997-2003)	27		100% DPAM 32% PMCA or hybrid	
Smeenk RM, et al.[9] (1996-2004)	103	CRS + IPHP	60% overall 72% DPAM + CC 0-1	

The main morbidities associated with the Sugarbaker procedure are caused by complications of surgery represented by intestinal perforations or fistulas, anastomotic leakages, and hemorrhage.[21] The main morbidity from IP chemo is hematological in nature, mainly severe neutropenia. Aside from its profound systemic toxic effects, intraperitoneal chemotherapy may also have adverse effects on wound healing as shown by increased incidence of fistula and anastomotic leakage in these studies.

Survival data of PMP patients treated with traditional repetitive debulking and the aggressive locoregional approach are shown in this table with note of better 5-year survival in the aggressively treated group of patients.

The main prognostic indicators of pseudomyxoma peritonei are the histopathological grade, the completeness of cytoreductive surgery based on the CC score, and the extent of any surgery prior to CRS with patients receiving more extensive but incomplete surgery doing worse tan those whose prior surgery was limited.[8]

Data from the following studies show that recurrence rate remains high with a slightly longer DFI in the aggressively treated group. Unlike overall survival, the DFI was not associated with pathologic subgroup, or extent of surgery. The recurrence data viewed alongside the overall survival rates suggest that a disease-free state is not an absolute requirement for long-term survival in PMP.

It also underscores the limitations of using overall survival as the principal endpoint in evaluating patients with PMP, as it fails to characterize the impact of disease recurrence, ongoing treatment, and treatment-related toxicity on the quality of life of patients with this insidious, slowly progressive disease.

The proponents of the Sugarbaker procedure believe that it should be the new standard of care for PMP. Other authors, however, prefer to apply this regimen cautiously and selectively due to its associated morbidity and mortality, the high cost of the procedure for patients, treatment centers and service care providers, and doubt whether the survival benefit they claim is due to the aggressive approach or simply due to better selection of patient and tumor type.

Table 8. Disease free survival and recurrence data on PMP.

Author	n	Treatment	Median survival (ff up)	Median DFI (DFS rate)
Gough D, et al.[19] (1957-83)	56	Repetitive debulking surgery ± chemo ± RT	5.9 yrs (12 yrs)	2.5 yrs 76% recurred regardless of completeness of debulking
Misdraji, et al.[23] (1950-2000)	107	NA	6 yrs DPAM 2.5 yrs PMCA	44% recurred; 56% NED, 12% AWD, 32% DOD
Miner TJ, et al.[13] (1980-2002)	97	Repetitive debulking surgery + chemo	9.8 yrs overall 12.8 yrs DPAM vs 4 yrs PMCA 12.8 yrs CC0-1 vs 8 yrs CC2-3	2 yrs 91% recurred
Van Ruth, et al.[10] (1996-2002)	62	CRS + IPHP	4 yrs.(2.8 yrs)	2.8 yrs (3yr DFS = 43%)
Deraco M, et al.[11] (1996- 2003)	33	CRS + IPHP	W/ mean ff up 2.4 yrs (range: 0.03 - 6 yrs): 74% NED, 23% AWD, 3% DOD	4.8 yrs (5yr DFS = 43%)
Guner Z, et al.[24] (1995-2003)	28	CRS + IPHP	4.25 yrs overall 6.1 yrs CC 0-1 2.2 yrs CC 2-3, 1 yr unresected	

In summary, PMP remains a disease of the peritoneum from an appendiceal tumor primary that follows "an unremitting but prolonged clinical course." Great strides have been made in the past 20 years in determining the real pathologic features and pathogenesis of this condition. These developments, in turn, have had great influence on the changes incorporated in the treatment approach towards PMP. Even though aggressive locoregional treatment seems to confer longer overall survival, disease recurrence is common and the real survival benefit attained with such aggressive procedures remain shrouded in doubt.

Dr. Blake Cady, former President of the Society of Surgical Oncology,[13] once wrote that, "in the world of surgical oncology: Biology is King; selection is Queen, and the technical details of surgical procedures are the Princes and Princesses of the Realm. Occasionally, the prince and princess try to usurp the throne. They almost always fail to overcome the powerful forces of the King and Queen." In the future, randomized trials using relevant clinical endpoints and appropriate control groups could provide the basis for a better understanding of the role of surgery and chemotherapy in PMP. Although many have concluded that the rarity of the condition prevents such a trial, reports now documented in the literature suggest that such efforts in a multi-center setting might be possible.

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