Management of Troublesome Sites in Gestational Trophoblastic Neoplasia

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Objective: To describe and evaluate different adjunctive treatment modalities for troublesome sites in gestational trophoblastic neoplasia.

Design: A retrospective descriptive analysis of data was done using charts of diagnosed case of gestational trophoblastic neoplasia (GTN) from 2006-2010. The patients were classified according to the FIGO staging and WHO prognostic scoring. Surgical procedures were evaluated as to problematic sites, indications for surgery and, remission rate.

Results: Seventy-two patients underwent at least one major surgery in the form of hysterectomy with adjuvant procedure, uterine perforation and profuse vaginal bleeding as indications for surgery. Common indications for adjuvant surgery are completed family size and resistance to chemotherapy. Four patients in remission had surgery for profuse vaginal bleeding due to AV malformation - two underwent embolization while two had wedge resection.

Conclusion: The most common troublesome site remains to be the uterus followed by the lungs then the vagina and the brain. Surgical interventions combined with chemotherapy maximize the benefit that can be derived by patients from our treatment protocol. Surgery significantly reduces tumor burden as manifested by decrease in serum beta hCG postoperatively thus decreasing number of cycles needed for remission. With adjuvant surgery, there is also decreased exposure to toxicity, decreased morbidity, and decreased length of hospital stay.

Key words: gestational trophoblastic neoplasia, adjuvant surgery, hysterectomy

Our understanding of the epidemiology, pathology and clinical management of gestational trophoblastic disease (GTD) has advanced considerably over the past 60 years. Worldwide, gestational trophoblastic neoplasia (GTN) in the form of choriocarcinoma is least prevalent in North America and Europe at 1 in 30,000-40,000 pregnancies but is still quite common in Southeast Asia at 1 in 500-3,000 pregnancies. [1] In the Philippines, studies made at the University of the Philippines-Philippine General Hospital (UP-PGH) showed, for choriocarcinoma and other GTN, a prevalence of 4.3/1000 pregnancies. [2]

Progress made in diagnosis, accurate staging and timely chemotherapeutic interventions have led to marked improvement in outcome, with international literature reporting almost 100% recovery in low-risk cases and 93% even in high risk cases.[3,4,5] Despite this, GTD remains a disease to reckon within the Philippines. Despite good response to chemotherapy, the local survival rate in both low-risk and high-risk GTN at the UP-PGH is lower: 88% for non-metastatic or low-risk GTN using single-agent chemotherapy and 78% for high-risk metastatic GTN using multiple-agent chemotherapy. [6] This problem has been attributed to several factors affecting management including delayed referral or wrong initial management, delay or failure to initiate treatment, delayed subsequent chemotherapeutic cycles due to toxicity and inability to secure drugs and poor follow up.[2,6,7]

Contributing to these factors is the difficulty in managing troublesome sites in GTN. These are sites of resistance, hemorrhage or infection that complicate treatment or prevent cure. Approximately half of high risk GTN will require some form of adjuvant surgical procedure to improve response to treatment or treat complications. In a previous series done by the author, 129 of 420 GTN patients or 32% underwent surgery as part of their management. Fifty-six percent of these patients underwent hysterectomy due to completed family size or are non-desirous of further pregnancy. [8] Other indications for the surgical procedures are as follows : 1) control tumor hemorrhage, 2) remove foci of resistant / persistent disease in the uterus or other metastatic sites, 2) decrease tumor burden, 4) relieve bowel or urinary obstruction, or 5) treat infection.[8,9,10,11,12] Common troublesome sites are the uterus, vagina, lungs, brain and gastrointestinal tract. In this study, we identified the most common troublesome sites in GTN and described the adjunctive treatment modalities used in management.

Study Design and Methodology

A retrospective study was done among patients diagnosed with GTN who were managed at the PGH Trophoblastic Disease Section from January 2006 to December 2010. The medical records of patients who underwent immediate surgery or surgery after chemotherapy during their stay at the institution were reviewed. Clinical data including socio-demographic profile, stage and risk score according to the FIGO 2000 staging system and the WHO scoring system,[13] pre and post operative serum beta hCG, surgical procedures and indications, chemotherapy regimens and remission rates were noted.

Based on the International Federation of Gynecology and Obstetrics anatomic staging and prognostic scoring, patients who had non-metastatic and metastatic low-risk disease were given single agent chemotherapy using methotrexate (MTX) and shifted to actinomycin D (ACT) or combination/ multiple agent chemotherapy in the form of etoposide and actinomycin D (EA), methotrexate, etoposide and actinomycin D (MEA) or etoposide, methotrexate, actinomycin D, cyclophosphamide and vincristine (EMA-CO) when resistance to single agent chemotherapy occurred. Those with metastatic high–risk disease were immediately started on combination chemotherapy preferably EMA-CO. Cycles were repeated after 7-10 days as permitted by toxicity. Taxanes and cis-platinum (EMA-EP and EMA-PT) were added as part of salvage therapy for those who developed resistance to EMA-CO.

Results

From January 2006 to December 2010, a total of 186 patients diagnosed with GTN were admitted at the Philippine General Hospital, Department of Obstetrics and Gynecology, Section of Trophoblastic Diseases. Seventy-two of these patients (38.7%) underwent surgery as part of their management. There were 84 procedures done and 13 of the 72 patients had 2 or more procedures done to manage troublesome sites.

Clinical Features

The patients' age ranged from 17 to 54 years old , with a mean of 33. Thirty-eight (53%) patients had a gravidity of 4 or more and 55 (76%) patients had a parity of 3 or more. (Table 1)

Table 2 shows the preoperative profile of GTD patients who underwent adjuvant surgery. Thirty

(42%) were diagnosed with Stage I disease, 1 (1%) with Stage II, 38 (53%) with Stage III and 3 (4%) with Stage IV disease based on the International Federation of Gynecology and Obstetrics (FIGO) Staging System. Of 72 patients, 43 (60%) belonged to the High Risk group and 29 (40%) were low risk according to the WHO Risk Factor Scoring System.

Table 1. Demographic and obstetric profile of gestational trophoblastic disease patients who underwent adjuvant surgery, UP-PGH, January 2006 - December 2010.

Characteristic	Frequency (n=72)	Percentage (%)
Age (Years)		
Mean ± SD	33 ± 8.5	--
Range	17 - 54	
Gravidity		
1	3	4
2	7	10
3	24	33
≥4	38	53
Parity		
1	4	6
2	13	18
≥3	55	76

Table 2. Pre-operative profile of gestational trophoblastic disease who underwent adjuvant surgery, UP-PGH, January 2006 - December 2010.

Characteristic	Frequency (n=72)	Percentage (%)
Stage of Disease		
I	30	42
II	1	1
III	38	53
IV	3	4
FIGO Prognostic Score		
< 7	29	40
> 7	43	60

Chemotherapy

Chemotherapy remains the cornerstone in the management of GTN. Several treatment regimens involving a variety of chemotherapeutic agents are currently available. Patients classified under Stage I and low-risk Stage II and III were given single-agent chemotherapy using Methotrexate. Those who developed resistance to Methotrexate or experienced toxicity were shifted to Actinomycin D or combination chemotherapy in the form of Etoposide and Actinomycin D (EA), Methotrexate, Actinomycin D and Cyclophosphamide (MAC), Methotrexate, Etoposide and Actinomycin D (MEA) or Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide and Vincristine (EMA-CO). Patients with metastatic high-risk disease were initially treated with multi-agent chemotherapy preferably EMA-CO. Cycles were repeated every 10-14 days. Forty (56%) patients received single agent chemotherapy and 32 (44%) received multiple agent chemotherapy. (Table 3)

Table 3. Chemotherapy regimens of patients with gestational trophoblastic disease who underwent adjuvant surgery, UP-PGH, January 2006 - December 2010.

Chemotherapy		
Single Agent	40	56
Methotrexate	31	78
Actinomycin D	9	12
Multiple Agent	32	44
EMA-CO	27	84
Others	5	16

Adjuvant Procedures

Many patients with GTN undergo some form of surgery to control the disease in troublesome sites by removing the focus of resistance, decreasing tumor burden, controlling hemorrhage, relieving obstruction or by treating infection. Table 4 shows the different adjuvant procedures and their indications. Hysterectomy (82%) remains the most common procedure with adjuvant or planned part of treatment due to completed family size (64%) as the most common indication. Bilateral internal iliac artery ligation (18%) and uterine artery embolization (3%) were done to control hemorrhage. Other procedures performed include wedge resection of arterio-venous (AV) malformation (3%), oversewing of vaginal metastasis (3%), resection of vaginal metastasis (1%), pneumonectomy (1%), pulmonary wedge resection

(1%), pulmonary lobectomy (1%) and brain irradiation (1%). One fifth (14/72) of patients had surgery due to chemoresistance or progression. Twelve patients had surgery for persistent vaginal bleeding and/or uterine rupture. There were 4 patients who were in remission but underwent procedures for persistent vaginal bleeding secondary to AV malformation as complication of the disease and chemotherapy. Two of these had uterine artery embolization while another 2 had wedge resection of the AV malformation. One of the patients who had uterine artery embolization went on to have hysterectomy because vaginal bleeding persisted despite embolization.

Table 4. Adjuvant procedures and indications for procedure of patients with gestational trophoblastic disease, UP-PGH, January 2006 - December 2010 (n=72).

Characteristic	Frequency (n=72)	Percentage
Surgery		
Hysterectomy	59	82
Bilateral internal iliac artery ligation	13	18
Uterine artery embolization	2	3
Wedge resection of AV malformation	2	3
Vaginal oversewing	2	3
Excision of vaginal metastasis	1	1
Pneumonectomy	1	1
Pulmonary wedge resection	1	1
Pulmonary lobectomy	1	1
Whole Brain irradiation	1	1
Indication		
Adjuvant (with completed family size/ Non-desirous of pregnancy)	46	64
Uterine rupture	8	11
Vaginal bleeding	4	6
Resistance /Progression	14	19

Comparison of Pre-operative and Post-operative Beta-HCG in Gestational Trophoblastic Disease

Comparing the overall pre and post operative β-HCG values, a statistically significant reduction in the mean level was noted. (mean pre-operative =177,296 versus post -operative=49,783, P<.001) (Table 5)

Table 5. Comparison of beta-HCG before and after adjuvant surgery in gestational trophoblastic disease, UP-PGH, January 2006 - December 2010.

Beta- HCG*	Pre-Operative Level	Post-Operative Level	Mean Difference p-value**
Mean	177,296	49,783	127,513
SEM	32,288	5,166	P <.001
Range	297 - 1,257,000	18.7 - 341,530	

* Analysis of 65 subjects who had post-operative BCG levels, SEM-standard error of the mean

** Significant difference if p-value is <.05, Wilcoxon Signed Ranks Test

Treatment Outcomes

Of the 59 hysterectomies, 53 were done after at least 1-2 cycles of methotrexate for low risk disease and EMACO for high risk disease. Six patients who underwent hysterectomy had the operation prior to chemotherapy due to uterine rupture and profuse vaginal bleeding. Fifty-four patients achieved complete remission after chemotherapy and adjuvant surgery. Two patients went home against medical advice and did not continue treatment while three patients died. All three patients had stage IV disease. The three patients who had pulmonary resection due to chemoresistance went into remission after the surgery. Overall remission rate for patients who underwent adjuvant treatment was 92%.

Discussion

Troublesome sites, as previously defined, are those sites wherein hemorrhage, chemoresistance, rupture, obstruction or infection that complicate treatment or prevent cure may occur. Management of these sites is dependent on several factors, namely; the desire for future reproduction, the expertise of the clinician and available modalities in the institution where the patient is being managed. Although chemotherapy alone works very well for most cases of GTN, adjuvant surgery remains an important part of management in this subgroup of GTN patients.[8,9,10,11,12,14,15] In a series of 50 patients with high-risk GTN at the John Brewer Trophoblastic Disease Center of Northwestern

University 1986-2005, 24 patients (48%) underwent 28 adjuvant surgical procedures including hysterectomy (17), lung resection (5), salpingectomy (1), uterine wedge resection (1), small bowel resection (1), suturing of the liver or uterus for bleeding (2), and uterine artery embolization (1). [9]

Uterus

The most common troublesome site is the primary lesion site which is the uterus. The Sheffield group recently updated their data on the role of hysterectomy in managing persistent GTN at their institution. Of the 8,860 registered patients, 62 (0.7%) underwent hysterectomy for GTN: 22 (35.5%) for resistance to chemotherapy, 21 (33.9%) for major hemorrhage, while the remainder had hysterectomy as part of their primary treatment for other indications. The overall remission rate in these patients was 93.5%, however, 7 relapsed and 4 (18%) of 22 patients with resistant disease subsequently died.[12] Hysterectomy is not often indicated in the primary management of patients with widely metastatic disease unless there is a very large uterine tumor causing bleeding in a patient with no desire to maintain fertility. High risk patients with evidence of uterine disease but with no or very little extrauterine disease may benefit from hysterectomy with a complete clinical response in 71 – 86 %.[11,16,17] Hysterectomy is not performed when there is disseminated metastasis unlikely to make a significant impact in the survival of patients with high risk or recurrent disease.[11,18] Although most literature report less than one-fourth of their patients undergoing hysterectomy due to a very good response to chemotherapy, hysterectomy remains a major treatment component in our institution and in our country as most patients are multiparous, have limited finances to procure the chemotherapeutic medications, and have diseases which presented with multiple complications on consult.[2,6,7] Hysterectomy has been proven to reduce the number of cycles needed to achieve remission as well as shorten hospital stay and prevent prolonged exposure to chemotherapy and its toxicities.[8]

Conservative management in the form of resection of chemotherapy-resistant disease within the myometrium (wedge resection) can be done in highly selected patients with non- metastatic GTN who wish to preserve fertility. [11,14,15] A thorough evaluation for systemic metastasis should be performed and localization of the tumor with MRI with or without color doppler ultrasound and hysteroscopy. Lesions < 2 -3 cm diameter associated with low hCG levels are more likely to be completely excised. [11] We report two patients who were currently in remission but had wedge resection not for chemoresistance but for AV malformation due to inability to procure needs for embolization. Repeat angiogram post resection showed complete removal of the AV malformation.

Bilateral internal iliac artery ligation can also be done in young patients profusely bleeding but who wish to retain their fertility. In this report, 10 patients had bilateral internal iliac artery ligation alone. Of these 10, 3 had subsequent hysterectomies because bleeding was uncontrolled. Three more patients had elective combined bilateral internal iliac artery ligation and hysterectomy as a maneuver to decrease intra-operative blood loss.

Angiographic embolization can be done for AV malformations and problematic uterine/vaginal bleeding. [11] It is commonly done on the uterine arteries to control uterine or pelvic tumor bleeding in lieu of surgical intervention. [19] It is only quite recently, in 2008, that we started utilizing this technique to control bleeding and report two patients who underwent the procedure. One patient had hysterectomy because of failed embolization. The Charing Cross Hospital group reported on the use of arterial embolization in 14 patients for control of uterine bleeding with GTN. Hemorrhage was controlled in 11 patients, while 2 patients required hysterectomy and 1 patient underwent uterine artery ligation for persistent uterine bleeding. Five pregnancies, including 3 normal full-term deliveries were achieved in these 11 women. [19]

Vagina

Vaginal metastasis accounts for 4-30% of metastasis. Diagnosis is mainly by physical examination with identification of bluish, highly vascular mass on the vaginal wall. They are extremely vascular, friable and replete with abundant venous plexuses. Vaginal

metastasis is not a significant factor for predicting response to therapy but is important as its presence complicate overall treatment and is capable of inducing severe hemorrhagic complications.[20,21,22,23]

While most vaginal metastases respond quickly and completely to systemic chemotherapy, their management often includes surgical and angiographic interventions.[11,20,23] In this report, we had two patients who underwent vaginal oversewing to control bleeding. At the Brewer Center, 13 (36%) of 36 patients with vaginal metastases from GTN had significant bleeding requiring blood transfusion (median 7 units, range 1 – 26 units). Seven of these patients required 1 or more procedures for control of bleeding when vaginal packing was not sufficient. Procedures done include excision (3) or suturing (7) of vaginal lesions, bilateral internal iliac artery ligation (1) and angiographic uterine artery embolization (1).[23] In a review of patients with vaginal metastases from GTN treated at the UP-PGH trophoblastic disease unit from 1998 to 2008, the following procedures were performed: vaginal packing with methotrexate solution (5/11 or 46%), ligation of bleeders with bilateral internal iliac artery ligation (4/11 or 36%), oversewing of bleeding vaginal lesions (2/11 or 18%), ligation of vaginal bleeders (3/11 or 27%), vaginal packing only (6/11 or 54%), methotrexate infiltration of vaginal mass (1/11 or 9%) and external beam radiation (1/11 or 9%).[22]

Lungs

Lungs are the most common site of metastasis and the most commonly encountered problem is chemoresistance.[4,5,11] Before pulmonary resection is even considered, it is important to exclude extrapulmonary disease by scans. A successful resection is more likely if the following criteria are met: 1) good surgical candidate, 2) primary uterine malignancy controlled, 3) no evidence of other metastatic sites 4) solitary pulmonary lesion, 5) hCG level < 1,000 mIU/mL .[24] Ninety-three percent of patients who met these criteria and underwent pulmonary resection were cured. Prompt hCG regression within 1 – 2 weeks of resection of an isolated pulmonary nodule predicts a favorable outcome.[24] Those who underwent pulmonary resection in different centers have the following outcome: Brewer Center: 4/5 or 80% who had drug-resistant disease were cured,[9] Southeastern Regional Trophoblastic Disease Center : 4/9 or 44% of those with resistant choriocarcinoma survived, [16] New England Trophoblastic Disease Center: 10/11 or 91% of drug-resistant pulmonary disease survived,[25] UP-PGH Medical Center: 4/6 or 67% (Mondragon and Estrella, 2008).

Radiographical evidence in the lungs of tumor regression often lags behind hCG level response to treatment. Some patients will have pulmonary nodules for months or years after completion of chemotherapy. Radiologic abnormalities at the end of treatment are of no prognostic significance if the patient is in hCG remission and excision of these lesions is not warranted.[24,25]

Central Nervous System

Central nervous system metastasis accounts for 3-28% of metastasis.[3,4,5,26,27] Rustin, et al. from the Charing Cross Hospital in 1989 recommended an approach of early craniotomy with excision of isolate brain lesions combined with systemic and intrathecal methotrexate.[26] However, at present, most trophoblastic disease centers in the U.S. recommend integration of whole brain or steriotactic irradiation into systemic therapy in an attempt to prevent brain hemorrhage, reserving craniotomy for neurologic deterioration. [11]

Craniotomy is indicated to allow for decompression of intracranial hemorrhage with highly vascular lesions with a tendency for central necrosis and hemorrhage. Resection of drug resistant lesions in the brain is only rarely performed.[4,5] It is important to exclude active disease elsewhere before attempting surgical resection. With the use of intrathecal Methotrexate and brain irradiation, "prophylactic craniotomy" to decrease chance of cerebral hemorrhage has no role in patients with Stage IV disease. [11] Whole brain irradiation with a dose of 3000 – 4000 cGy in 20 fractions is given concomitantly with systemic chemotherapy.[18] The dose of Methotrexate is increased to 1gm/m^2 with Folinic acid 30 mg every 12 hours for 6 doses starting 32 hours after the start of the infusion.[4,5,18] Survival

rates of 50 – 75% at Charing Cross in patients who initially presented with brain metastasis and required combination chemotherapy is a lot higher compared with 27% remission rate in the Philippines. [26,27]

Liver and Other Gastrointestinal Organs

Whole liver irradiation with dose of 2000 cGy is given in 10 fractions concurrently with chemotherapy to minimize the risk of hemorrhage. Higher survival rate of 40 – 50% is reported in patients presenting with primary liver involvement compared to those who develop new liver metastasis during therapy.[4,5,18] Although liver was not a troublesome site is this 5-year review, we previously reported remission in two patients who underwent excision of liver metastasis and chemotherapy. [8]

Conclusion

Intensive multi-agent chemotherapy and adjuvant surgery and radiotherapy remain the main treatment modality for high risk GTN and problematic GTN cases. Adjuvant surgery mainly in the form of hysterectomy still plays a major role. Surgery significantly reduces tumor burden as manifested by decrease in serum beta hCG postoperatively thus decreasing number of cycles needed for remission. With adjuvant surgery, there is also decreased exposure to toxicity, decreased morbidity, and decreased length of hospital stay.

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Peritonectomy in the Management of Pseudomyxoma peritonei Arising From Ovarian Mucinous Tumors: A Case Series*

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Background: Pseudomyxoma peritonei (PMP) is a rare condition that is more commonly seen in females and is characterized by the development of massive amounts of mucinous ascites. It is believed to originate mostly from mucocoeles of the appendix. However, mucin-producing tumors in other organs such as the ovary have been implicated in its etiology. Due to the rarity of this condition, there have been no formal trials to provide guidelines for optimum treatment.

Objectives: To determine the efficacy and safety of peritonectomy procedures in the treatment of patients with pseudomyxoma peritonei.

Methods: A retrospective review of patients diagnosed with pseudomyxoma peritonei was done. Demographic data and clnical outcomes of patients who underwent peritonectomy procedures were compared to those who did not undergo peritonectomy. Descriptive analysis of the data collected using frequency and percentages was used for this study.

Results: There were a total of 14 patients with pseudomyxoma peritonei from 2006-2009. Of the 11 patients with DPAM, 4 patients (43%) underwent peritonectomy while the remaining 7 (67%) did not undergo the said procedure. All 4 patients with DPAM and one patient with benign ovarian mucinous tumor with PMP not otherwise specified as to whether DPAM or PMCA who underwent peritonectomy are currently alive with no evidence of disease. Survival in this group of patients ranged from 18-48 months, with a median survival of 29 months. There were no recurrences noted in this group of patients. Seven patients with DPAM did not undergo peritonectomy: 2 developed recurrent disease, 4 became lost to follow-up, while 1 continued to have no evidence of disease. Recurrences were noted between 13-29 months from the time of diagnosis of PMP. There were 2 cases of PMCA, both arising from malignant ovarian neoplasms. One died 5 months after surgery (without peritonectomy) while the other one who was treated with peritonectomy was lost to follow-up.

Conclusion: Peritonectomy is a safe treatment modality for pseudomyxoma peritonei arising from mucinous ovarian new growths which may have a potential benefit in terms of disease-free interval.

Key words: Pseudomyxoma peritonei, peritonectomy

* Second Place, 2010 SGOP Fellows' and Residents' Research Contest.

Pseudomyxoma peritonei (PMP) is an intriguing but often confusing disease, partly because of its rarity.[1] PMP is a rare disease with an estimated incidence of 1-2 per million per year.[2] It occurs in approximately 2 out of every 10,000 laparotomies, and is more common in women.[3] It is a progressive disease of the peritoneum characterized by the production of copious amounts of mucinous fluid that gradually fills the peritoneal cavity, resulting in the characteristic "jelly belly."[4] Over time, accumulation of mucin in the peritoneal cavity results in massive symptomatic distention and associated mechanical and functional gastrointestinal obstruction.[5] The pathogenesis of this rare disease has generally been attributed to rupture, leakage, or metastasis of an intraperitoneal mucinous neoplasm.[4] The precise origin of the tumor has been debated throughout the years, with both appendiceal and ovarian origins being considered. Interestingly, simultaneous occurrence in both the appendix and ovaries has been noted in the vast majority of women with this condition.[6]

The evolution of treatment strategies of PMP still remains debated though the current mainstay of treatment remains surgical extirpation of the lesion.[7] Observation alone will eventually result in bowel obstruction and consequent death of the patient by cachexia or complications related to obstruction[1]. Traditional treatment of PMP consists of serial cytoreductive surgery with removal of all mucinous ascites with or without additional modalities. In the second half of the previous century, the Memorial Sloan-Kettering Cancer Center (n=17) and the Mayo Clinic (n=56) reported on serial celiotomy and cytoreductive surgery. These studies suggest that survival could be achieved by surgery alone, even though gross disease was present at the end of most procedures. Aggressive surgical debulking as the sole treatment modality was further explored by the Memorial Sloan-Kettering Cancer Center. An analysis of surgical therapy in 97 patients, aiming at symptom management rather than cure, demonstrated a mean of 2.2 debulking operations to reach a complete cytoreduction in 55% of patients. The median overall survival was 9.8 years. Survival was independently associated with low-grade pathologic subtype and the ability to achieve complete cytoreduction.[1]

Cytoreductive surgery involves peritonectomy procedures. Peritonectomy is a surgical technique that allows resection of all parietal peritoneum involved by peritoneal seeding. The visceral peritoneum invaded by tumor may require organ resection. Likewise, these intend to reduce peritoneal surface dissemination to a microscopic level. In brief, peritonectomy procedures are performed on the basis of disease extension by the following steps: 1) greater omentectomy and right parietal peritonectomy with or without right colon resection, 2) pelvic peritonectomy with or without sigmoid colon resection as well as hysterectomy and bilateral salpingo-oophorectomy, 3) lesser omentectomy and dissection of the duodenal-hepatic ligament with or without antrectomy and cholecystectomy, 4) right upper quadrant peritonectomy and glissonian capsule resection, 5) left upper quadrant peritonectomy and left parietal peritonectomy with or without splenectomy, and 6) other intestinal resection and/or abdominal mass resection.[8]

The natural history of this disease has been drastically modified since the introduction of a new surgical approach, proposed by Sugarbaker who defines it as a peritonectomy procedure consisting of the complete removal of the tumor. Surgery is followed by local drug administration aimed at eliminating microscopic and/or minimal residual disease left in the abdominal cavity following surgical manipulations. The additional effects of hyperthermia, through the use of a special pump, increase local tissue drug concentration and consequently antiblastic drug activity. This technique has been defined as hyperthermic intraperitoneal chemotherapy (HIPEC).[9]

The negative side of combined modality treatment is the relatively high morbidity and mortality rate in comparison with less aggressive treatment. Although most complications are related to surgery, intraperitoneal chemotherapy is not performed without any side effects. In particular, the lowest point of the white blood cell count, usually around the tenth day, as a result of bone marrow toxicity, endangers any surgical complication.[10]

Surgical expertise and postoperative management entail the experience of the entire medical team

with all aspects of demanding surgery. Increasing experience with the surgical procedure, postoperative care, and handling complications have been shown to decrease operation duration, blood loss with need for transfusion, treatment-related morbidity and mortality and consequent intensive care unit stay and total in-hospital stay.[19]

Objectives

A. General Objective

To determine the efficacy and safety of peritonectomy procedures in the treatment of patients with pseudomyxoma peritonei.

B. Specific Objectives

1. To determine the prevalence of Pseudomyxoma peritonei.
2. To identify the socio-demographic characteristics of patients with Pseudomyxoma peritonei.
3. To determine the efficacy of peritonectomy procedures in the treatment of patients with Pseudomyxoma peritonei.
4. To determine the safety of peritonectomy procedures in the treatment of patients with Pseudomyxoma peritonei.

Materials and Methods

Clinical records and follow-up data of patients diagnosed with Pseudomyxoma peritonei which originated primarily from the ovary were reviewed. All patients were treated surgically in a single institution. Patients were grouped into those who underwent peritonectomy procedures and those who did not undergo peritonectomy procedures. For the purpose of this study, peritonectomy is defined as stripping and removal of the anterolateral abdominal peritoneum, paracolic gutter peritoneum and pelvic peritoneum. Diaphragmatic peritoneum excision and resection of the gastric, intestinal, liver, gallbladder and/or spleen were not included in this study's peritonectomy procedures. Information on patient demographic characteristics, histologic subtypes of Pseudomyxoma peritonei, nature of the mucinous ovarian tumors, dates of surgery and current status of the patient were collected and entered into a case registry form.

Due to the rarity of the disease, a case series study design was employed and as such, there was no sample size calculated.

Descriptive analysis of the data collected using frequency and percentages was employed for this study.

Definition of Terms

1. Pseudomyxoma peritonei – a rare condition characterized by mucinous ascites and multifocal mucinous tumors on the peritoneal surface and omentum, the origin of which could be a primary appendiceal malignancy with metastasis to the ovary, an ovarian primary malignancy with metastasis to the appendix, or there could be two independent primary disease processes.[12]
2. Disseminated peritoneal adenomucinosis (DPAM) – benign variant of PMP[7]
3. Peritoneal mucinous carcinomatosis (PMCA) – malignant variant of PMP[7]
4. Peritonectomy - the removal and stripping of all tumour tissues involving the parietal and visceral peritoneum[13;] stripping and removal of the anterolateral abdominal peritoneum, paracolic gutter peritoneum and pelvic peritoneum
5. Mucinous tumors of the ovary – may refer to benign ovarian new growths (mucinous cystadenomas), tumors that are of low malignant potential (borderline tumors), and frankly malignant ovarian neoplasms (mucinous cystadenocarcinomas)
6. Current status – refers to the present condition of the patient (i.e. whether they are presently known to be alive or dead; a patient may have an unknown current status if she has been lost to follow-up and has not been contacted despite several attempts to do so)
7. Disease-free interval – the time span (in months) from surgery to time of recurrence of PMP
8. No evidence of disease –no clinical evidence that shows reaccumulation of mucin in the abdomen

Results and Discussion

There were a total of 551 cases of mucinous tumors of the ovary seen at the tertiary government hospital from 2006 to 2009. Majority of these were mucinous cystadenomas (64%). Its malignant counterpart, mucinous cystadenocarcinoma, comprised 22% while the remaining 13% were mucinous tumors of low malignant potential. (Table 1)

Majority of the patients diagnosed with PMP were between the ages of 31-40 years old (36%) and had a mean parity of 1-3 (43%). Majority had no comorbidities (57%). At the time of diagnosis of PMP, 50% of the patients were already postmenopausal while the other half was still menstruating regularly. The most common complaint on admission was abdominal distention or enlargement, occurring in 57% of the cases. (Table 2)

Table 1. Mucinous tumors of the ovary seen in UP-PGH from 2006-2009.

Histology of ovarian new growth	Year				
	2006	2007	2008	2009	Total
Mucinous tumor of LMP	8	19	20	25	72
Mucinous cystadenoma	86	99	94	75	354
Mucinous cystadenocarcinoma	18	36	33	38	125
TOTAL	112	154	147	138	551

Table 2. Socio-demographic characteristics of patients with PMP.

Patients with PMP (N=14)			
Variable		Number	%
Age	20-30	0	0
	31-40	5	36
	41-50	2	14
	51-60	1	7
	61-70	1	7
	>70	5	36
Parity	0	3	21
	1-3	6	43
	4-6	1	7
	7-9	3	21
	≥10	1	7
Civil Status	Single	4	29
	Married	7	50
	Widowed	3	21
Co-morbidities	Hypertension	1	7
	Diabetes mellitus	2	14
	Bronchial asthma	1	7
	Bronchial asthma and hypertension	1	7
	PTB	1	7
	None	8	57
Menstrual status at time of diagnosis	Premenopausal	7	50
	Postmenopausal	7	50
Chief complaint	Vaginal bleeding	1	7
	Hypogastric pain	1	7
	Abdominal pain	3	21
	Abdominal enlargement/distention	8	57
	Abdominal enlargement and abdominal pain	1	7

Half of the cases with PMP had tumors of low malignant potential while 4 had benign ovarian new growths. The remaining 3 had frankly malignant mucinous tumors of the ovary. (Table 3)

An important prognostic factor in PMP is its histology. The classification described by Ronnet, et al. categorized PMP into 2 groups with different prognosis: DPAM, PMCA, and an intermediate/ hybrid group. PMCA seems to behave like peritoneal carcinomatosis and has a very poor prognosis. In their analysis, the authors found that the histologic classification of PMP was found to have prognostic significance with five year age-adjusted survival rates of 84% for DPAM, 37.6% for tumors with intermediate or discordant features and 6.7% for classical PMCA[14] In this study, there were 2 cases of PMCA, both arising from malignant ovarian neoplasms. One died 5 months after surgery (without peritonectomy) while the other one who was treated with peritonectomy was lost to follow-up, thus, her current status is unknown. (Table 3)

Furthermore, Ronnet, et al. found that DPAM was more common, accounting for 59.7% of cases compared to PMCA which accounted for only 25.7%. The remainder were of the intermediate type.[14] In this study, majority (78%) of the patients with PMP had DPAM as the histologic classification on final biopsy result. There were only 2 cases of PMCA (14%) and one case wherein the histologic classification of DPAM was not specified.

Of the 11 patients with DPAM, 4 patients (43%) underwent peritonectomy while the remaining 7 (67%) did not undergo the said procedure.

All 4 patients with DPAM and the patient with benign ovarian mucinous tumor with PMP not otherwise specified as to whether DPAM or PMCA who underwent peritonectomy are currently alive with no evidence of disease. Survival in this group of patients ranged from 18-48 months, with a median survival of 29 months. (Table 3)

Of the remaining 7 patients with DPAM who did not undergo peritonectomy, 2 developed recurrent

Table 3. Patients with PMP diagnosis by selected characteristics.

Patient Code	Date diagnosed with PMP	Nature of mucinous ovarian new growth	Histology of PMP	Peritonectomy done	Follow-up course	Additional treatment	Present status	Date present status noted	Time period from diagnosis to present status (Months)
B	7/5/2006	Malignant	PMCA	No	Lost to follow-up	None	Dead	12/1/06	5
C	1/12/2008	Benign	DPAM	No	Recurrent disease	Herbal/ Alternative meds	Alive with disease	6/17/10	29
D	12/21/2008	Malignant	DPAM	No	Lost to follow-up	None	Alive with NED	7/27/10	20
H	12/9/2008	Benign	DPAM	No	Recurrent disease	None	Dead	1/1/10	13
I	7/10/2009	Benign	DPAM	No	Lost to follow-up	None	Unknown	–	–
L	8/11/2009	LMP	DPAM	No	Lost to follow-up	None	Unknown	–	–
M	5/15/2009	LMP	DPAM	No	NED	None	Alive with no disease	1/22/10	8
N	9/24/2009	LMP	DPAM	No	Lost to follow-up	None	Unknown	–	–
A	2/4/2006	Benign	NOS	Yes	Lost follow-up	None	Alive with NED	5/12/10	48
E	7/9/2008	LMP	DPAM	Yes	NED	None	Alive with NED	7/26/10	36
F	8/14/2008	LMP	DPAM	Yes	NED	None	Alive with NED	4/17/10	20
G	8/6/2009	LMP	DPAM	Yes	NED	None	Alive with NED	7/27/10	23
J	1/30/2009	LMP	DPAM	Yes	NED	None	Alive with NED	6/16/10	18
K	12/2/09	Malignant	PMCA	Yes	Lost to follow-up	None	Unknown	–	–

disease, 4 became lost to follow-up, while 1 continue to have no evidence of disease. Recurrences were noted between 13-29 months from the time of diagnosis of PMP. The sole patient who continues to have no evidence of disease has been disease-free for 8 months. The current status of the 4 patients who were lost to follow-up is unknown.

At present, there is no international consensus regarding the most beneficial treatment strategy for PMP. Due to the rarity of this condition, there have been no formal trials to provide guidelines for optimum treatment. However, proponents of surgical extirpation point out that there are certain features of PMP that makes it amenable to curative surgery. These include early peritoneal dissemination and accumulation in anatomically resectable sites by peritonectomy.[15] Taking into account the considerable morbidity, if not mortality, which combined modalities may entail coupled with the prohibitive cost of chemotherapy, peritonectomy as part of a maximal cytoreductive effort may be a feasible option for this group of patients. This study has shown that the patients with PMP on whom peritonectomy was done as part of the surgical management are currently alive and with no clinical evidence of disease.

Although the cases of PMP treated with peritonectomy at the UP- PGH from 2006 and 2009 have been limited, it can be seen from the results of this study that there may be a therapeutic benefit in doing peritonectomy in this group of patients.

Conclusion and Recommendations

Peritonectomy as a treatment modality for pseudomyxoma peritonei arising from mucinous ovarian new growths may have a potential benefit in terms of disease-free interval. In this study, median disease-free interval was 29 months from the time of diagnosis. Furthermore, no recurrences were noted in this group of patients. However, further follow-up is on-going for 5-year survival analysis.

The following are the recommendations generated from this study:

1. Further accrual of cases for inclusion in a prospective study looking into long-term survival and quality of life of patients with PMP treated with peritonectomy as part of cytoreductive surgery.

2. Inclusion of peritonectomy in the core competencies of the fellowship training program of gynecologic oncology.

Limitations of the Study

This study included patients with Pseudomyxoma peritonei from an ovarian primary treated at a single institution from 2006-2009. Excluded in this study were those patients whose Pseudomyxoma peritonei originated from an organ other than the ovary.

The small number of cases of Pseudomyxoma peritonei precludes the generation of a Kaplan-Meier survival curve at this point of the study.

Lastly, the study was limited by the incomplete entries in the patients' charts. The lack of contact numbers as well as the geographic location of some of the patients made retrieval of pertinent information difficult and sometimes impossible.

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The Accuracy of Grayscale Transabdominal Pelvic Ultrasonography in Detecting Paraaortic and Pelvic Lymphadenopathies*

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Objective: To determine the accuracy, sensitivity, specificity, positive and negative predictive values of using grayscale transabdominal pelvic ultrasonography in detecting paraaortic and pelvic lymphadenopathies in endometrial cancer.

Materials and Methods: All women newly diagnosed with endometrial carcinoma from January to June 2010 that will undergo exploratory laparotomy, bilateral lymph node dissection and paraaortic lymph node sampling were enrolled in the study. All underwent transabdominal pelvic ultrasonography preoperatively. Transverse and longitudinal scans were performed in supine position. The maximum interval from the time of ultrasound to surgery is 30 days. The lymph node status was determined histologically. Values were calculated according to standard formula using the 2 x 2 contingency table.

Results: A total of 46 patients were included in the study. There were 2 cases of true positive, 38 cases of true negative, 5 cases of false positive and 1 case of a false negative result. The sensitivity is 67%, specificity is 88%, positive predictive value is 29% and negative predictive value is 97% with an overall accuracy of 87%.

Conclusion: The use of grayscale transabdominal pelvic ultrasonography in detecting lymph node metastasis is highly specific, with a high negative predictive value and overall accuracy. Size is an important factor to consider in detecting lymph node metastasis. An average of 10mm is readily seen sonographically, less than 5mm is hardly evident and 15mm or more is discriminatory.

Key words: accuracy, transabdominal pelvic ultrasound, lymph node metastasis

Gynecologic cancers are a common cause of morbidity and mortality in women of all ages. While many gynecologic cancers are staged clinically using the International Federation of Gynecology and Obstetrics (FIGO) staging system, imaging can be a useful adjunct to clinical staging. Cross sectional imaging techniques such as ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) have been used to detect and follow patients

* Third Place, 2010 SGOP Fellows' and Residents' Research Contest.

with gynecologic cancer. These imaging modalities can show anatomic detail and morphologic changes in the female genitourinary tract to good advantage. Positron emission tomography (PET) differs in that it shows functional information that is not easily obtained by the other cross sectional imaging techniques. The fusion of PET with CT allows anatomic localization of functional abnormalities in the female genital tract and thereby allows the detection of gross disease in many malignant conditions both within and outside the confines of the female pelvis (Iyer, 2007). However, these procedures are costly and unaffordable to many.

Diagnostic ultrasonography is one of the modalities available for evaluating patients for neoplastic processes or for tumor staging. It is able to present a cross-sectional anatomy without radiation in a non-invasive fashion, relatively inexpensive, requires little patient preparation and produces little discomfort. Lymphomatous nodes may be seen as multiple, relatively echo-free para-aortic masses or as a large mass encasing the aorta in grayscale picture (Mittelstaedt, 1980)

The data obtained from the sonographic examination in tumor detection and staging are extensive. First, the presence or absence of a mass can be determined. Multiple or solitary masses can be localized, and their origin, extent, and sonographic characteristics can be defined. A differential diagnosis can be projected based on these findings. If indicated, the demonstrated mass may be localized with ultrasound and a biopsy performed. These all help to streamline the diagnostic workup with prompt and appropriate treatment (Mittelstaedt, 1980). It is reported that external iliac lymph nodes are the most commonly involved lymph nodes in endometrial cancer, and that paraaortic lymph node metastases spread via a route shared by the common iliac lymph nodes (Mariani, et al. 2006).

According to Fotopoulou in 2008, the proportion of endometrial cancer patients with positive paraaortic lymph nodes is at 76%, considerably high, and more than half of them have affected lymph nodes above the inferior mesenteric artery level.

One aim of the study is to try to provide a cheaper alternative to CT, PET scan and MRI in detecting paraaortic and pelvic lymphadenopathies. The presence or absence of which on grayscale ultrasound in cervical cancer patients are clinically significant. Management differs and ,hence, can be used for prognostication. However, this approach cannot be done on cervical cancer patients since lymphadenopathies cannot be histologically confirmed. Bilateral lymph node dissection and par-aaortic lymph node sampling are not part of routine staging for cervical cancer. With these, the study tried to evaluate the accuracy of grayscale transabdominal pelvic ultrasonography in detecting pelvic and paraaortic lymphadenopathies in patients diagnosed with endometrial carcinoma.

The general objective is to determine the accuracy of using grayscale transabdominal pelvic ultrasonography in detecting paraaortic and pelvic lymphadenopathies in endometrial carcinoma. Specific objectives are to determine the sensitivity, specificity, positive predictive value and negative predictive value of the above.

Materials and Methods

All women newly diagnosed with endometrial carcinoma that will undergo exploratory laparotomy, bilateral lymph node dissection and paraaortic lymph node sampling were enrolled in the study. The study lasted for 6 months from January to June 2010. The eligibility requirements included: 1) histologically-confirmed endometrial carcinoma by means of an endometrial biopsy or curettage and 2) preoperative transabdominal pelvic ultrasonography.

All patients recruited were interviewed and asked to fill up personal data sheet and sign the informed consent. All underwent transabdominal pelvic ultrasonography preoperatively to assess pelvic and paraaortic lymph node metastasis. All were examined with a commercially available static grayscale system using a 2.25- or 3.5-MHz transducer. Transverse and longitudinal scans were performed in supine position. All the patients underwent surgery, including bilateral pelvic lymph node dissection and paraaortic lymph node sampling. The average interval from the time of ultrasound to surgery is 7 days. The lymph node status was determined histologically in all the patients.

The study employed a cross-sectional design. The accuracy, sensitivity, specificity, positive and negative predictive values were calculated according to standard formula using the 2 x 2 contingency table.

Results

A total of 46 patients were enrolled in the study. The age range is 33-70 years, with a median of 57 years. The number of deliveries range from 0-7, with a median of 2. Majority were menopausal. (Table 1)

Table 1. Clinical data of patients.

Median age in years (range)	57 years, (33-70)
Median number of delivery (range)	2, (0-7)
Menopause	39/46 (85%)

Table 2 shows the distribution of patients using the 2 x 2 contingency table. There were 2 cases of true positive results and 38 cases of true negative results. There were 5 cases of false positive results and 1 case of a false negative result. The true positive lymph nodes were sonographically described as hypoechoic masses along the course of the iliac vessels and lateral to the abdominal aorta with an average size of 10mm. Likewise, obliteration of the aortic contour, while the vertebral outline is still preserved, has been proven to be a helpful diagnostic criterion. The first of the 2 true positive cases identified 2/17 obturator nodes while in the second case, it identified 3/12 obturator nodes, 2/3 external iliac nodes and 1/9 paraaortic lymph node. The 5 false positive reported cases were sonographically described as hypoechoic masses along the external iliac vessels. Size ranges from 15-20mm in its widest diameter. The 1 false negative reported case has an aggregate diameter of less than 5mm on gross examination and were identified as 2 external iliac nodes and 1 obturator node on histopathology.

Table 3 shows the computed values using standard formula. The sensitivity is 67%, specificity is 88%, positive predictive value is 29% and negative predictive value is 97%.

Table 2. Contingency table.

Lymph Node	Positive on Histopathology	Negative on Histopathology
Present on ultrasound	2	5
Absent on ultrasound	1	38

Table 3. Diagnostic efficacy of pelvic ultrasonography in detecting lymph node metastasis.

N=46	Accuracy	Sensitivity	Specificity	PPV	NPV
Lymph node metastasis	87%	67%	88%	29%	97%

Accuracy was defined as the percentage of all patients or lymph nodes in which pelvic ultrasound correctly predicted the presence or absence of metastatic tumor. The overall accuracy is 87%.

Discussion

Lymphadenectomy is essential for staging endometrial carcinoma, but it can be omitted for those tumors that are limited to the endometrium because less than 1% of these patients have disease that has spread to the pelvic and/or paraaortic areas. Therefore, the pretreatment determination of lymph node metastasis is important for planning the extent of surgery.

Multiple small metastatic nodes - average of 10mm in diameter - were sonographically identified within normal-sized lymph nodes and appear as rounded, lobular, or sausage-shaped masses distributed along the iliac vessels anterior to the iliopsoas muscle. Single or multiple nodes may be seen anterior to the psoas or iliopsoas and/or impinging on the lateral or posterior aspects of the bladder.

Unexpectedly, very small metastatic nodes – less than 5mm on gross examination were likewise identified histopathologically within normal-sized lymph nodes. These tumors were not sonographically evident (false negative). Such microscopic tumor deposits are below the threshold of detection of any other imaging technique. For comparison, the limit of

detection of tumor deposits in the pelvis on positron-emission tomography (PET scan) is often 6-10mm and on MRI less than 5mm. Another important factor to consider is a history of previous pelvic surgery and adhesion. In large patients with thick abdominal wall and in those with a large amount of bowel gas, there is poor penetration of the sound beam and poor resolution. Patients with an iliostomy, colostomy, incision, or the like may be difficult to examine, as is the uncooperative patient. According to Tanaka in 2006, the common iliac and external iliac nodes were the key lymph nodes in metastasis compared to the obturator node and that the latter is more visible in transvaginal scan. It is noteworthy to emphasize that the study employed only transabdominal scan.

Surprisingly, large masses – 15 to 20 mm – may be mistaken sonographically for a lymph node (false positive). But could actually be a lymphocyst accumulating around the course of the external iliac vessels. Such masses have the same echogenicity as a lymph node. Abscesses, like hematomas, also appear as relatively echo-free, non-specific masses while mesenteric masses are generally changeable in location and position without a specifically consistent echopattern. Other lymphomatous or metastatic nodes appear as multiple relatively echo-free to echodense masses along the distribution of the iliopsoas muscles, hence muscle layering is an important consideration. Also worth mentioning are retroperitoneal non-lymphoid masses which are generally mixed to echo-dense and are usually well-defined. Hence, grayscale pelvic ultrasonographic findings of lymphadenopathy must be cautiously interpreted.

In a study done by Ryoo in South Korea in 2007, it showed that the sensitivity, specificity and accuracy of MRI as a diagnostic tool for predicting lymph node metastasis in endometrial carcinoma are 50%, 97% and 93%, respectively. It parallels with our results.

Sawicki, et al. in 2003 showed that the sensitivity, specificity, positive and negative predictive values of using transvaginal scan to detect lymph node metastasis in endometrial carcinoma are 33%, 100%, 100% and 88%, respectively. According to the authors, transvaginal scan alone because of its low sensitivity did not provide additional information. Combining both transvaginal and transabdominal scan may increase the accuracy.

Dissection of pelvic lymph nodes is the diagnostic standard for detecting metastatic cancer in iliac lymph nodes and is therefore performed with either an open or a laparoscopic technique in most patients deemed candidates for surgery. This approach, however, has several limitations. First, the area of surgical exploration is limited to groups within the external iliac, obturator nodes, but so called skip metastases to the internal and common iliac nodes are not uncommon and go undetected with the use of this method. Second, the rates of morbidity and complications of 4 to 5 percent with this invasive technique are not negligible. Third, dissection of pelvic lymph nodes is expensive and requires hospitalization. Fourth, it is typically a one-time procedure performed at the beginning of treatment.

The routine imaging used in this study is readily available at most secondary and tertiary institutions. Pelvic ultrasonography is of particular help in displaying and analyzing para-aortic and pelvic lymph node metastasis. It is feasible to show both normal and abnormal lymph nodes and their location with respect to important surgical landmarks such as vessels, nerves, and ureters. Our study showed that in the absence of lymphadenopathy on grayscale ultrasound, a full lymph node dissection should still be performed and this is consistent with the current practice.

Summary and Conclusion

The sensitivity, specificity, positive and negative predictive values of transabdominal pelvic ultrasound for detecting lymph node metastasis in endometrial cancer are 67%, 88%, 29% and 97% respectively with an overall accuracy of 87% . Size is an important factor to consider in detecting lymph node metastasis. An average of 10mm is readily seen sonographically. Small masses less than 5mm is hardly evident and larger masses 15mm or more are discriminatory.

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Primary Endodermal Sinus Tumor of the Vulva: A Case Report*

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Extragonadal endodermal sinus tumor (EST) arising from the external genitalia is an exceedingly rare condition. They have a much worse prognosis than primary ovarian germ cell tumors. There were eleven cases reported in world literature, ten cases occurred in premenopausal women and one is a postmenopausal. This is probably the twelfth reported case of vulvar EST.

DC is a 61-year old G3P3 (3003) who sought consult because of an enlarging left vulvar mass of nine months duration. Excision biopsy was done revealing an anaplastic tumor, immunohistochemistry revealed it to be an endodermal sinus tumor. Bleomycin-Etoposide-Cisplatin (BEP) chemotherapy was initiated. There was local recurrence after the second course of treatment. Serum alphafetoprotein (AFP) results were normal. A repeat excision was done and she was shifted to Vincristine-Actinomycin-Cyclophosphamide (VAC) chemotherapy. She is presently on her second course of VAC chemotherapy and remains asymptomatic.

Vulvar EST represents a small number of cases in women premenopausally and is very rare during menopause. Due to its rarity, treatment is usually individualized.

Key words: Extragonadal endodermal sinus tumor, alpha feto-protein

Endodermal sinus tumor (EST) is a rare type of germ cell tumor arising primarily in the gonads. It is the second most common malignant germ cell tumor of the ovary comprising around 10% of cases. Extragonadal endodermal sinus tumor is even rarer. Most cases develop in the sacrococcygeal region of infants. Other sites, in descending order of frequency, include the mediastinum, intracranium, retroperitoneum, and neck. Of these tumors, 70% are said to occur in females and over half arise in infants. Approximately half are benign while one third is frankly malignant. It has also been observed that extragonadal germ cell tumors carry a worse prognosis than primary ovarian germ cell tumors.

Extragonadal tumors of the external genital tract are exceedingly rare, accounting for only 1% of these tumors. The majority occurs in the vagina and cervix, and they are mostly seen in infants and young adolescents.

EST occurs rarely as extragonadal tumors. To our knowledge, there are only eleven reported cases of vulvar EST worldwide. Majority (ten) were seen in

* First Place, 2010 SGOP Fellows' and Residents' Interesting Case Contest.

premenopausal women and only one case was seen in a menopausal woman. Based on our literature search, there are no reported cases of vulvar EST locally. These types of tumors are said to be aggressive, with three deaths occurring within one year from the time of diagnosis and one case developing recurrence within a year. Due to its rarity, treatment of vulvar EST is individualized, of which primary surgical intervention is initiated with or without adjuvant chemotherapy.

We report probably the twelfth case of primary endodermal sinus tumor of the vulva and the second in a postmenopausal woman. The treatment course based on current surgical and chemotherapeutic regimens is described. A review of literature on this rare condition is likewise discussed, including the treatment course and outcome of the previous case reports.

The Case

CD is a 61-year old G3P3 (3003), menopausal for 10 years, who sought consult because of a vulvar mass of nine months duration. Her present condition started nine months prior to admission when she palpated a 1cm x 2cm soft, non-tender mass on her left pubis. The mass progressively enlarged with no accompanying symptoms which prompted consult 5 months prior to admission. She was then advised further work-up.

She is hypertensive for 10 years, with maintenance of irbesartan 300mg and hydrochlorthiazide 25mg daily. She is diabetic for 5 years, with intake of metformin 500mg three times a day and gliclazide 30 mg daily with good compliance. There are no known hospitalizations or any other illnesses other than those mentioned. Family history revealed presence of hypertension and diabetes mellitus in both sides of her family.

She is a nursing graduate and worked as a clinical instructor in a private hospital for several years prior to her retirement.

Menarche at 13 years old with regular interval lasting for 3-5 days consuming 3-4 cloth pads per day. She had her first coitus at 18 years old. She used oral contraceptives for six years.

She is a gravida 3 para 3. All pregnancies were delivered by spontaneous vaginal delivery with no feto-maternal complications. Menopause was at 51 years old.

Transvaginal sonography showed that the uterus is normal in size for age measuring 5.59cm x 3.63cm x 4.5cm. There are 2 intramural myoma nodules at the mid-anterior and low posterior wall of the uterus. The endometrium is thin, isoechoic and intact measuring 0.35cm. The ovaries are atrophic and there is no fluid seen in the cul de sac.

Ultrasound/Doppler study of the pubic mass was likewise done revealing cystic structures with internal echoes and hypervascularities measuring 6.2cm x 4.9cm x 4.8cm located at the left mons pubis area. There was no evidence of bowel herniation noted during resting and Valsalva's maneuver.

Computed tomography (CT) scan of the whole abdomen showed a well-circumscribed enhancing rounded mass density at the left subcutaneous mons pubis region (Figures 1 & 2). Except for the small myomas, the uterus was normal. The ovaries were also normal. The liver, gall bladder, pancreas, spleen, adrenals, kidneys, ureters and urinary bladder appear normal. There is no ascites or enlarged retroperitoneal lymph node. The impression is left pudendal subcutaneous mass density, inflammatory (abscess) versus neoplastic metastasis or primary lesion.

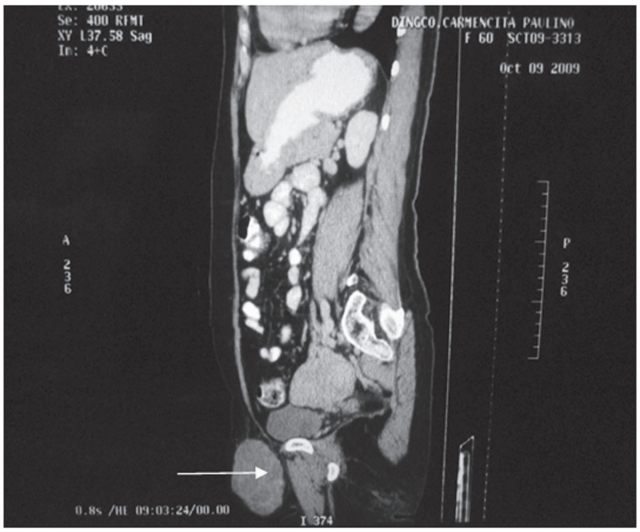

Figure 1. Lateral view of the abdominopelvic CT scan.

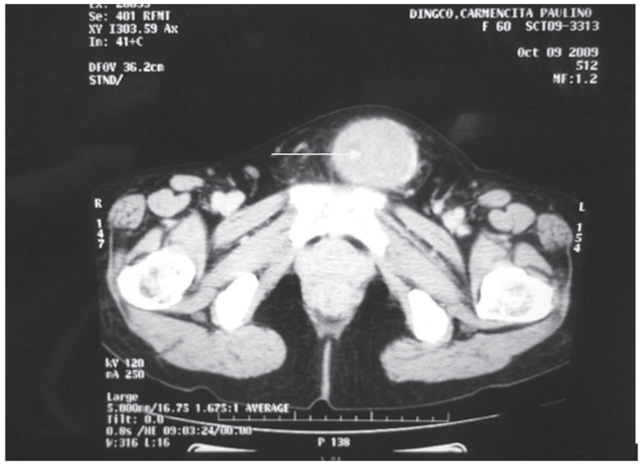

Figure 2. Sagittal view of the abdominopelvic CT scan.

Fine needle aspiration biopsy revealed the presence of malignant cells. She was then referred to a gynaecologic oncologist for further evaluation and management.

Excision biopsy was done revealing a 13cm x 7cm mass tan-red with a thin capsule, prominent blood vessels, which on cut section revealed a tan-yellow fleshy mass with areas of necrosis and hemorrhages (Figures 3-5).

Histologic sections showed a malignant tumor composed of solid cohesive sheets of tumor cells containing pleomorphic vesicular nuclei, prominent nucleoli and abundant eosinophilic cytoplasm (Figure 6). Less frequently seen were papillary fibrovascular projections lined on the surface by a layer of cuboidal to columnar cells with clear to eosinophilic cytoplasm and prominent nucleoli, the Schiller-Duval bodies (Figure 7). Several mitotic figures and areas of necrosis were noted.

The specimen was sent for immunohistochemistry for definitive diagnosis. It stained positive for cytokeratin (Figure 8), Alpha Feto protein (AFP) (Figure 9), and CD 30 (Figure 10) and negative for Placental Alkaline Phosphatase (PLAP), Carcinoembryonic Antigen (CEA), Desmin, S-100, Human Melanoma Black (HMB-45). Characterization as a germ cell tumor with subclassification as a yolk sac tumor is most favored, given the tumor expression of cytokeratin, CD30 and AFP. The absence of S-100 and HMB-45 expression does not favor characterization as a malignant melanoma.

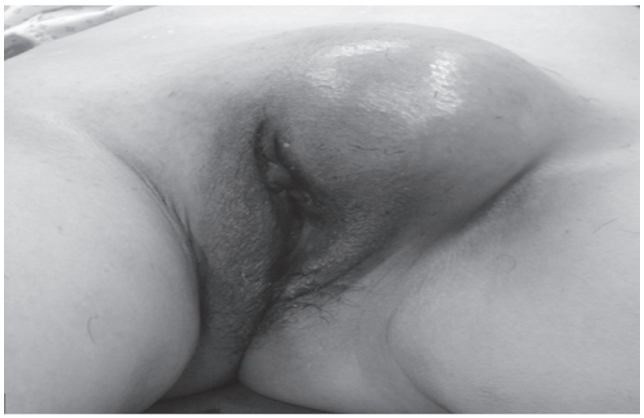

Figure 3. Mass as it occupies the mons pubis area.

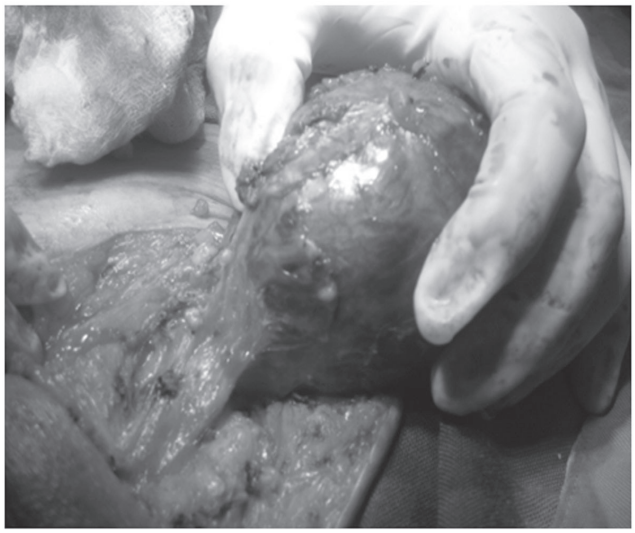

Figure 4. The mass underwent excision here demonstrating its attachment to the subcutaneous tissue.

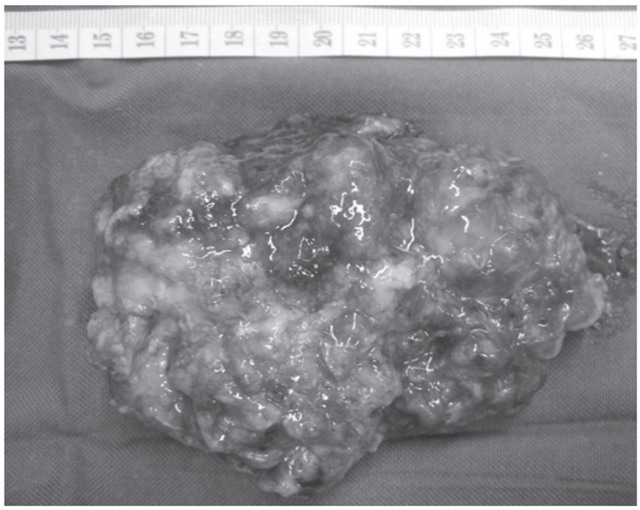

Figure 5. Cut section of the mass.

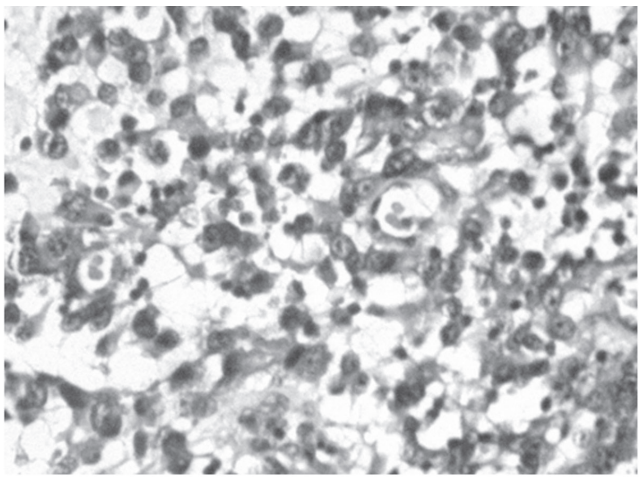

Figure 6. Yolk sac tumor exhibiting hepatoid pattern solid aggregates or cords of polygonal cells with even granular eosinophillic cytoplasm resembling hepatocytes.

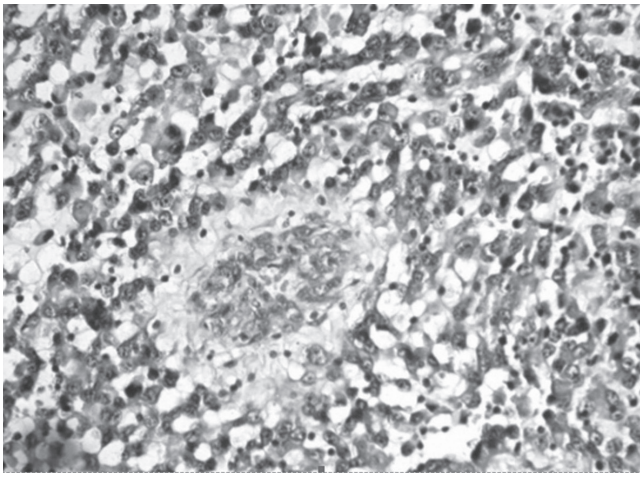

Figure 7. Perivascular formation of the tumor cells(schiller duval body) is a diagnostic for yolk sac tumor which resemble superficial immature renal glomeruli.

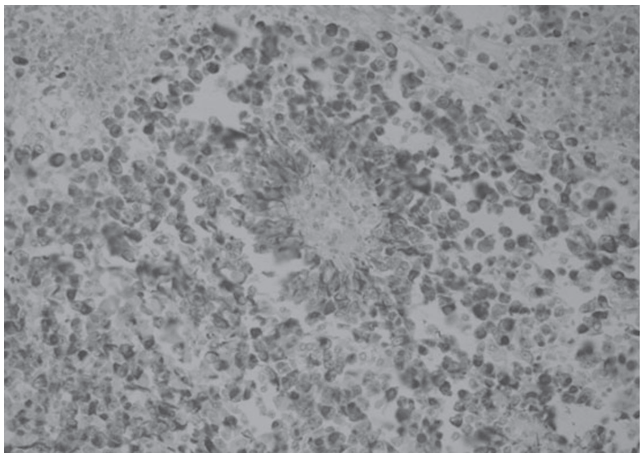

Figure 8. Immunostaining positive for cytokeratin.

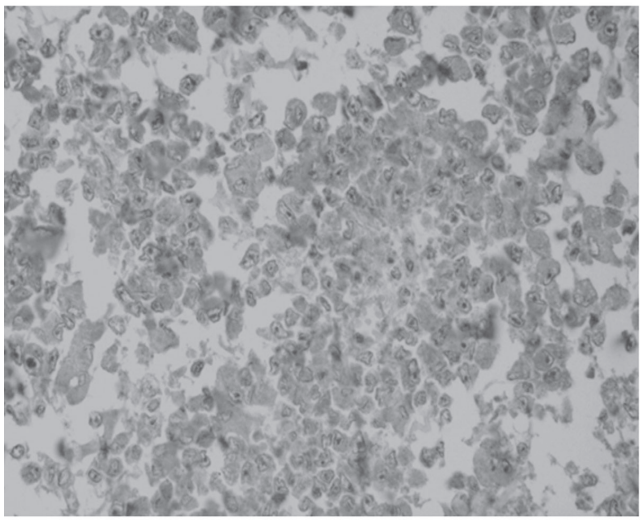

Figure 9. Immunostaining positive for alpha feto-protein.

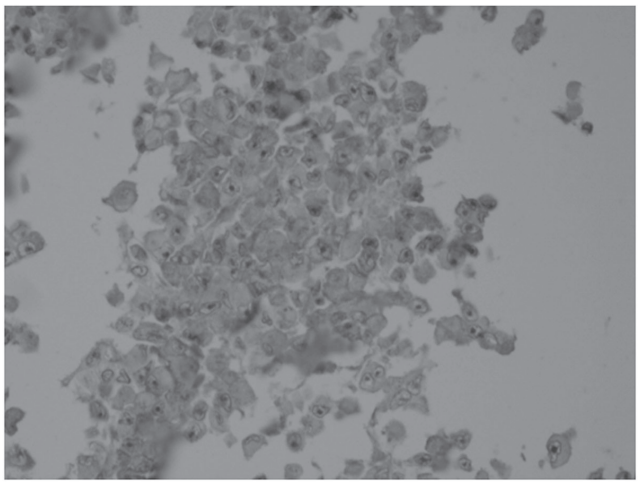

Figure 10. Immunostaining positive for CD 30.

She was lost to follow-up for three months. On subsequent consult, physical examination revealed recurrence of the mass on the same area of the mons pubis: 5cm x 3cm, fluctuant, with limited mobility. She was then started on Bleomycin-Etoposide-cisPlatin (BEP) chemotherapy. Serum AFP level determination revealed normal results (3.45 ng/ml). After the second cycle of BEP, increase in the size of the mass was noted, now measuring 10cm x 5cm. There were no palpable inguinal nodes. A decision to do a re-excision biopsy was made. A 10cm x 5cm tan-red encapsulated mass was excised, cut section revealed fleshy core with areas of hemorrhages and necrosis. Histopathologic

findings were consistent with recurrence of EST. She was then shifted to the Vincristine-Actinomycin-Cyclophosphamide (VAC) regimen. She is presently on her second cycle and is asymptomatic.

Discussion

Germ cell tumors comprise around 20% of all ovarian neoplasms. Ninety five percent are benign cystic teratomas. The younger the patient is, the most likely it is malignant.[1] Endodermal sinus tumor is primarily a neoplasm of children and young adults, with median age of 19 years though it can be seen in the elderly. Twenty-three percent were prepubertal at the time of diagnosis. None presented with precocious puberty, amenorrhea, or hirsutism. Vaginal bleeding occurred only in 1% of cases. Serum alpha-fetoprotein was invariably elevated.

Extragonadal germ cell tumors are rare tumors with most cases occurring in infants in the sacrococcygeal region. Other sites are the mediastinum, intracranium, retroperitoneum and neck. In the female genital tract, majority occurs in the vagina or cervix and occurs in infants and adolescents. So far, there are eleven reported cases worldwide of vulvar EST. Ten cases were premenopausal and one reported case in a menopausal woman in Japan in 2007.[3] Locally, there were no reported cases seen on literature search. Due to the dearth of cases, the reported cases were treated with various types of surgery with or without adjuvant therapy.

Normally, the primordial germ cells arise in the wall of the yolk sac by the fourth week of gestation. At around fifth or sixth week, they migrate into the urogenital ridge. The mesodermal epithelium of the urogenital ridge then proliferates, eventually to produce the epithelium and stroma of the gonad. The dividing germ cells—of endodermal origin—are incorporated into these proliferating epithelial cells to form the ovary. Failure of germ cells to develop may result in either absence of ovaries or premature ovarian failure. Any disruption in the normal migration may account for extragonadal distribution of germ cell midline structures (retroperitoneum, mediastinum, and even pineal gland) and may rarely lead to tumors in these sites.

The pathogenesis of extragonadal germ cell tumors is poorly understood. It was hypothesized that these tumors arise from germ cells that were misplaced during embryogenesis. During the fourth to sixth weeks of development, the germ cells migrate through the midline dorsal mesentery, to the developing gonadal ridge. Some of these germ cells are misplaced along the path of migration. Malignant transformation of these misplaced germ cells lead to the development of primary germ cell tumors at extragonadal sites. Vulvar germ cell tumors are thought to represent misplaced cells that have travelled along the gubernaculum and come to rest in the subcutaneous tissue of the mons pubis and labia.[4] This theory would explain why the majority of vulvar EST were seen on the labia majora in the series below.

From 1978-2007, there were 11 cases reported. The median age of reported cases is 22. Painless right labial mass is the most common symptom. AFP levels were mostly normal. Our patient presented with a similar vulvar mass which progressively enlarged. She also had normal AFP levels.

Table 1a. List of reported cases of Vulvar EST.

Author	Year	Age	Localization	AFP	Symptoms
Ungerleider	1978	15	Labium Majus, right	normal	Painless mass
Castaldo	1980	2	Clitoris	normal	Painless mass
Krishnamurthy	1981	26	Labium Majus, left	normal	Painless mass
Dudley	1983	22 months	Labium Majus, right	?	Painless mass
Penkar	1992	25	Labium Majus, right	335ug/L	Painless mass
Craighead	1993	24	Labium Majus, left	?	Painless mass
Flanagan	1997	18	Labium Majus, right	29.3ug/l	Painless mass
Traen	2003	18	Labium Majus, right	normal	Painless mass
Khunamornpong	2005	30	Labium Majus, right	normal	Painless mass
Basgul	2006	32	Labium Majus, right	normal	Painless mass
Niwa	2007	52	Labium Majus, right	?	Painless mass

Table 1b. The eleven cases with their tumor size and stage.

Author	Pathology	Volume	pTNM	Stage
Ungerleider	EST+embryonal Carcinoma	P.E 4cm x 1cm	T2N0M0	II
Castaldo	EST, undifferentiated	B:1.2cm x1.5cm x 1cm	T1N0M0	II
Krishnamurthy	EST	B:7cm x 6cm	T2N0M0	II
Dudley	EST	B:6cm x 6cm	T4N0M0	III
Penkar	EST	B:10cm x 7cm	-	II?
Craighead	EST	P.E:4cm x 4cm	T2N0M0	II
Flanagan	EST	4cm x 2.5cm x 2cm	T2N0M0	II
Traen	EST+focal immature teratoma	B:3.4cm x 1.4cm x 2cm	-	II?
Khunamornpong	EST	3.5cm	T2N0M0	II
Basgul	EST	3.5cm	T2N0M0	II
Niwa	EST	-	T2N0M0	II

PE: Physical exam; B: biopsy

All eleven patients had primary surgery with or without adjuvant chemotherapy. Two had radical vulvectomy with or without lymphadenectomy, one with modified radical vulvectomy, two hemivulvectomy with lymphadenectomy, one did local wide excision of the clitoris. Three had local excision with no adjuvant chemotherapy. One had excision biopsy. One had resection of the tumor. Local recurrence occurred within one year from the time of diagnosis and within 20 months for distant metastasis. Adjuvant chemotherapy of BEP is commonly used, as is radiotherapy. Further treatment for recurrence include re-excision, lymphadenectomy, radiotherapy and chemotherapy with VAC regimen. Follow-up of patients as they were reported revealed three patients died within 2 years of diagnosis, the rest had no evidence of disease. The longest was reported by Niwa wherein the patient was free of symptoms for 67 months after surgery.

Our patient had excision biopsy of the vulvar mass. She was lost to follow-up for 3 months. While on her second cycle of BEP chemotherapy, tumor recurrence was noted. Thus re-excision of the mass was done. She was then shifted to VAC regimen. Presently, she has completed her second VAC cycle and remains asymptomatic.

The differential diagnoses of vulvar tumors with clear cytoplasm include a wide variety of metastatic tumors and primary cytoplasm. The possibility of metastatic tumors from gynaecologic organs and non-gynecologic organs should be ruled out. To ensure that the vulvar mass is not a metastatic one, imaging studies were done on this patient. Both the ultrasound and abdominal CT scan did not reveal any primary lesion in the gastrointestinal and reproductive organs. Chest x-ray was likewise negative for any lesions.

The initial reading of the specimen revealed amelanotic melanoma. The pathologist suggested immunohistochemistry for definitive diagnosis. This technique uses antibodies targeted to specific antigens in tissue and chromagen to signal the presence of antibody-antigen interaction[5]. An immunohistochemical panel is one that can be used for the workup of an undifferentiated neoplasm. Cytokeratins are excellent markers of epithelial differentiation. AFP stains yolk sac tumors and is frequently focally positive. CD30 stains positive for embryonal carcinoma. Our specimen stained strongly positive for cytokeratin, AFP and CD30. Dysgerminoma stains positive for placental alkaline phosphatase(PLAP). Carcinoembryonic antigen (CEA) stains positive for endocervical adenocarcinoma. Desmin turns positive for endodermal stromal sarcoma while melanomas are positive for S-100. Our specimen did not stain for any of these immunogens, PLAP, CEA, Desmin, S-100. Due to this, melanoma was ruled out. The definitive diagnosis of yolk sac tumor was given based on the results of this panel of immunostains.

In the female genital tract, extragonadal EST commonly occurs in the vagina. The recommended treatment for vaginal EST is conservative surgery followed by cisplatin-based chemotherapy. Though the vulva and vagina are adjacent to each other, vaginal

Table 3. List of 11 cases with their treatment and outcomes.

Author	Initial therapy	Recurrence	Further treatment	Follow-up
Ungerleider	RV+VAC	Inguinal LN (12mo)	Ly + Pelvic RT	DoD 23 mos
Castaldo	Wide excision of clitoris	-	VD	NED 42 mos
Krishnamurthy	Local excision	Local recurrence(6mo) Inguinal node	Local excision+Ly L	DoD 11 mos
Dudley	RT+C+RVBGND Partial excision ramus, pubicus, right, post op C	Bone, epidural	Decompressive laminectomy; VAC	DoD 11 mos
Penkar	Local excision	?	?	?
Craighead	Local excision BEP x 3	Inguinal LN(2mo) Inguinal LN(+)2mo	VAC+BEP+M Wide excision RT 4000Gy	NED 15 mos Post RT
Flanagan	Modified RV, Inguinal LND, right BEP x 3	-	-	NED 18 mos
Traen	Hemivulvectomy Inguinal LND, right; EP x 3	Lung, Pleura (20 mos)	Resection of lung tumor; TIP 3 IP x 3; HDCT (Etoposide+ carboplatin2)	NED 56 mos after primary diagnosis
Khunamornpong	Excision biopsy	Lymph node, right	Cisplatin based chemotx+ pelvic & groin irridiation	Free of disease 90 months after diagnosis
Basgul	Hemivulvectomy Inguinal LND, right	With recurrence; location not stated	BEP x3 Refused RT	Alive with the disease 42 months after first appearance of vulvar mass
Niwa	Resected tumor-no procedure written	-	-	NED 67 mos

V, vincristine; A, actinomycin-D; C, cyclophosphamide; RT, radiotherapy; Ly, lymphadenectomy; DoD, dead of disease; NED, no evidence of disease; B, bleomycin; E, etoposide; P, cisplatin; M, methotrexate; D, doxorubicin; L, left; R, right; m, month; y, year; M,metastasis; T, taxol; I, ifosfamide, HDCT, high-dose chemotherapy.

EST usually occurs in patients less than 2 years old while vulvar EST occurs in the older age group. Our patient is the oldest at 61 years old. According to the literature, vaginal EST can be usually cured by chemotherapy and vulvar EST is said to be resistant to vincristine and sometimes in some cases to cisplatin-based regimen. Our patient did not respond to the initial BEP regimen that was given. After the re-excision, we shifted her to the second line regimen of VAC. So far, there is no recurrence of the tumor although she has only undergone two cycles of this regimen.

The appropriate surgical treatment for vulvar EST is controversial. In the series of the patients above, majority underwent vulvectomy. Appropriate therapy for these tumors remains unclear due to its rarity. Based on the clinical behavior of ovarian EST, we decided to perform conservative surgery for this

patient. Ipsilateral inguinal lymphadenectomy may be justified because inguinal lymph node metastasis is said to be the first evidence of tumor spread outside the vulva in almost all cases. We did not perform inguinal lymphadenectomy anymore on this patient since there are no palpable nodes and the presence of nodal metastasis will not change the planned adjuvant treatment.

The use of serum AFP as a tumor marker has been well established in patients with ovarian EST. Serum AFP levels, however, may not be a sensitive marker for monitoring patients with vulvar EST. In the series cited above, most have normal AFP levels inspite of the fact that some have advanced disease or tumor recurrence. Such was also the case in our patient. The AFP level was normal despite the presence of recurrence.

In summary, a rare case of vulvar EST in a postmenopausal woman was presented. This is probably the twelfth reported case worldwide. She was managed with local excision and adjuvant chemotherapy. A review of previous case reports was also presented. Due to its rarity and highly aggressive nature, there is no standard treatment for this condition. It is our hope that our experience with the management of this disease can help come up with a standard effective treatment that can offer a better outcome for these patients.

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Primitive Neuroectodermal Tumor of the Ovary: A Case Report*

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We report a case of primitive neuroectodermal tumor (PNET) in a 29 year old woman who presented with abdominal pain and enlargement. She underwent exploratory laparotomy with complete surgical staging. Microscopically, the tumor was composed of sheets of primitive small round cells making it difficult to adequately identify the precise histologic diagnosis. Immunohistochemical stains with CD 3, CD 20, chromogranin, synaptophysin, cytokeratin, inhibin, calretinin, CD99 and EMA were done. The results confirmed the diagnosis of primitive neuroectodermal tumor. This confirms the diagnostic validity of primitive neuroectodermal tumor which in the past may have been mistaken for other, more common tumors of the ovary, as well as the value of immunohistochemistry in making the diagnosis.

Key words: primitive neuroectodermal tumor, immunohistochemistry

Primitive neuroectodermal tumors (PNET) was first described in 1973 by Hart and Earl as embryonal small cell tumors of the cerebrum mimicking medulloblastomas.[8] In 1986, the term "peripheral primitive neuroectodermal tumor" (pPNET) was introduced by Dehner for all the PNETs occurring outside of the central nervous system.[9]

PNET, which commonly arises from soft tissues, is considered as one of the small round blue cell tumors and shares morphologic features with that of Ewing's sarcoma, which usually arises from the bone. Peripheral PNET has been reported in publications throughout the years and have involved organs such as the kidneys, lungs, vagina, cervix, mediastinum and even the pancreas.[15,16,17,18] However, PNET of the ovary has been said to be a rare tumor[10] and only a limited number has been reported since the early 1980's.

We report here a case of a woman with primitive neuroectodermal tumor which is a rare, highly aggressive malignant soft tissue tumor of the ovary, where diagnosis was made through the use of immunohistochemistry.

The Case

This is the case of CR, a 29 year old G2P2 (2002) from Caloocan City, separated, who was admitted with the chief complaint of abdominal pain associated with abdominal enlargement.

The patient's past medical history is unremarkable. She has a first degree cousin who was reported to have

* Second Place, 2010 SGOP Fellows' and Residents' Interesting Case Contest.

had an ovarian mass, although the exact diagnosis was not known to the patient.

The patient's personal, social history is non-contributory. She has no history of oral contraceptive or intra-uterine device use. No Pap smear was done previously.

Menarche was at 13 years of age, with subsequent menses occurring at regular monthly intervals, 3 to 4 days duration, moderate flow. She has no amenorrhea.

The patient is a G2P2 (2002). Both pregnancies were carried to term and delivered by spontaneous vaginal deliveries with no known complications.

Symptoms started four months prior to admission when the patient developed abdominal enlargement associated with abdominal pain, anorexia and vomiting. She was seen by a private physician who requested for an ultrasound which showed the presence of ascites, peritoneal implants beneath the hemidiaphragm, multiple solid lesions in the liver, gallbladder polyps, and a solid mass which was noted to be closely related to or adjacent to the uterus. CA 125 levels were taken and was noted to be elevated. The patient was then advised to undergo surgery, hence her consult with a gynecologic oncologist.

Upon admission, the patient had stable vital signs with a body mass index (BMI) of 22.9 kg/m^2 and a body surface area (BSA) of 1.5 m^2. Pertinent physical examination findings include a globular abdomen with an abdominal girth of 96 cm. Internal examination findings revealed normal external genitalia, smooth vagina, the cervix was smooth flushed and pushed anteriorly, the corpus was difficult to assess due to the presence of an abdominopelvic mass palpated anterior to the uterus measuring 12cm x 11cm, solid, the inferior pole of which was palpable at the cul de sac. On rectovaginal examination, the bilateral parametria were smooth and pliable. The admitting impression then was ovarian new growth, probably malignant.

The patient underwent total abdominal hysterectomy with bilateral salpingooophorectomy, infracolic omentectomy, bilateral lymph node dissection and paraaortic lymph node sampling with random peritoneal biopsy. Intraoperatively, there was 1 liter of serous ascitic fluid. There were multiple tumorous masses palpated within the liver parenchyma, the largest of which measured 2cm x 2cm, involving both the hepatic lobes. The subdiaphragmatic surfaces were studded with tumorous implants with an approximate aggregate diameter of 3cm to 5cm. The omentum contained tumorous implants measuring 1cm to 2cm. There was a large extraluminal necrotic mass noted at the small intestine, measuring 5cm x 5cm. The appendix was converted into a 3cm x 5cm solid mass. The spleen and stomach were smooth and grossly normal. There were multiple palpable fixed paraaortic lymph nodes measuring 3cm to 4cm in diameter. There were no palpable pelvic lymph nodes noted. The right ovary was converted into a 12cm x 10cm x 4cm solid, necrotic mass which was densely adherent to the pelvic sidewall, the uterus and the cul de sac. On cut section, it was a predominantly solid mass with areas of necrosis and hemorrhage (Figure 1). The left ovary was likewise enlarged to 10cm x 16cm x 7cm, adherent to the uterus and the pelvic sidewall, with a 2cm point of rupture on its surface. On cut section, it was also predominantly solid with areas of necrosis and hemorrhage. The uterus measured 8cm x 3cm x 2.5cm with multiple tumorous implants noted on the surface of the lower uterine segment at the vesicouterine fold up to the bladder surface. The cervix measured 2cm x 2cm x 2cm and was grossly normal. Bilateral fallopian tubes were grossly normal. The specimens were sent to the Surgical Pathology Section for examination.

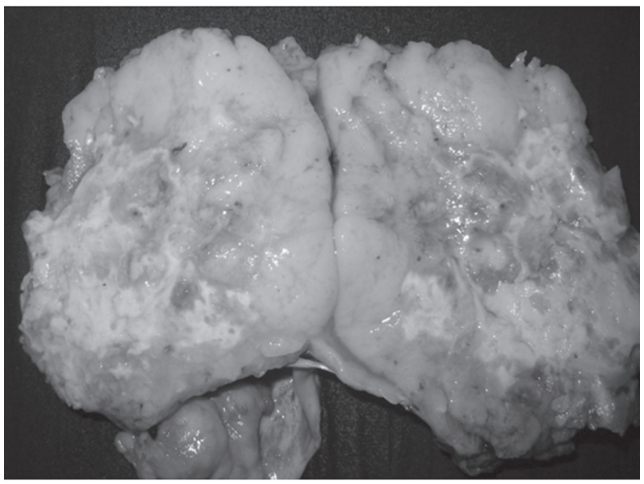

Figure 1. Gross photograph of the ovarian tumor.

The impression then was ovarian new growth, malignant, intraoperative stage IV.

The patient's postoperative course was unremarkable and she was discharged stable and ambulatory.

Initial histopath result of the specimens submitted revealed the following results: Small round cell tumor, considerations - 1) Non-Hodgkin lymphoma and 2) small cell carcinoma involving both ovaries (Figure 2), uterine serosa, specimen labeled "omentum", peritoneum" and "bladder wall"; proliferative endometrium; chronic cervicitis; no diagnostic abnormality recognized, both fallopian tubes. Immunohistochemical stains for CD3, CD20, chromogranin, synaptophysin, and cytokeratin were recommended for tumor differentiation.

On immunohistochemistry, the stains requested included pancytokeratin, CD3, CD20, chromogranin and synaptophysin. All these stains were negative hence the primary consideration then was juvenile granulosa cell tumor. Alpha-inhibin, calretinin and EMA were also done which were negative for staining. Finally, CD 99 was done which revealed positive results (Figure 3). The final diagnosis then was primitive neuroectodermal tumor.

The patient underwent one cycle of adjuvant chemotherapy but succumbed to the disease three months after the diagnosis.

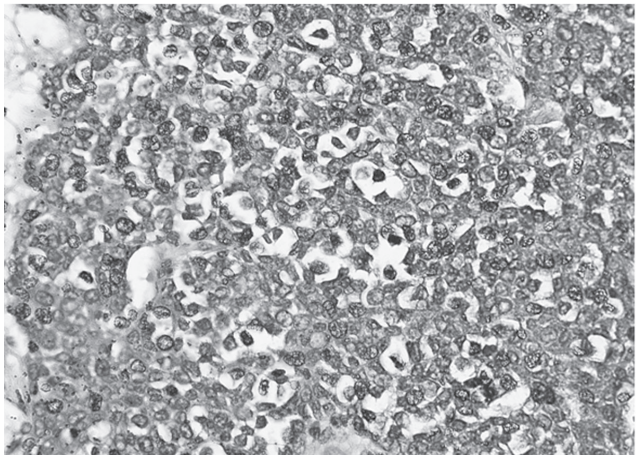

Figure 2. High power magnification of the tumor.

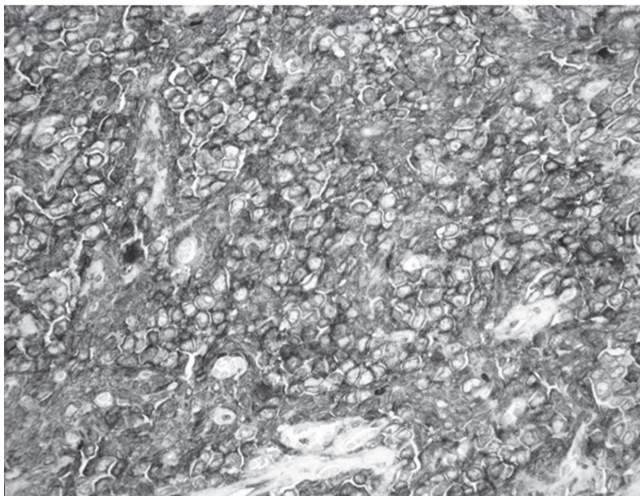

Figure 3. Immunostain positive for CD 99.

Discussion

Primitive neuroectodermal tumor of the female genital system is extremely rare.[1,2] In the recent decades, only 60 neuroectodermal tumors of the ovary have been reported in literature and, of these, only 10 were diagnosed to be primitive neuroectodermal tumors.[3] Local literature search and review of the surgico-pathologic results in our institution for the last 5 years have yielded no cases of this type of tumor having been reported.

Neuroectodermal tumors of the ovary are microscopically identical to their neoplastic counterparts in the nervous system and can be divided as well-differentiated, anaplastic or poorly-differentiated (primitive) tumors.[4] Well-differentiated tumors include astrocytomas and ependymomas, the latter being the most common neuroectodermal tumor of the ovary. Anaplastic tumors are rare and most are classified as glioblastoma multiforme while the poorly-differentiated neuroectodermal forms include medulloblastoma, medulloepithelioma, neuroblastoma and ependymoblastoma. Primitive neuroectodermal tumors belong to this category and are tumors that are composed of small cells that show only rudimentary signs of differentiation. Classification of neuroectodermal tumors are seen in Table 1.

Most women diagnosed with neuroectodermal tumors of the ovary are in their third and fourth decades of life. Occasionally, these tumors may be seen in younger women and there have been reports of these tumors in adolescents and older women.[4,5] In the largest series published to date, the age range

Table 1. Classification of neuroectodermal tumors.

Classification	Diagnosis
Well differentiated neuroectodermal tumors	Astrocytomas Ependymomas
Anaplastic neuroectodermal tumors	Glioblastoma multiforme
Poorly differentiated neuroectodermal tumors	Medulloblastoma Medulloepithelioma Neuroblastoma Ependymoblastoma Primitive neuroectodermal tumor

of the patients was 6 to 69 years of age with a median of 23 years.[6] Anaplastic and primitive tumors were more commonly found in younger patients than well-differentiated tumors. Our patient was 29 years of age during the time of diagnosis.

There are no established predisposing or genetic factors associated with primitive neuroectodemal tumors. There have been studies, however, showing chromosomal abnormalities in patients with these tumors. Comparative genomic hybridization studies have revealed multiple chromosomal abnormalities including losses of chromosomes in 1p, 1q, 4q, 7q, 8q, 13q and 19q as well as chromosomal gains in 1q, 2p, 7p, 9q, 18q and Xq.[11, 13] There have also been reports of balanced chromosomal translocation t(11;22) (q24;q12), that is highly specific for tumors of the PNET family.[12]

The most common clinical presentation of patients with neuroectodermal tumors is abdominal or pelvic pain. This may be accompanied by abdominal fullness, abdominal distention, weight loss, anorexia and vomiting. Other presenting symptoms such as deepening of voice with hirsutism have also been reported in literature.[4,7] Our patient came in with a chief complaint of abdominal pain and abdominal distention.

On gross pathology, most tumors are large and the average size of tumors is 10cm-14cm.[6] The external surface of the tumor is mostly smooth and glistening although tumors with external nodules and surface papillary excrescences have also been reported. Majority of these are solid tumors, with grayish white tissue, but may also be partially cystic and may contain papillary structures protruding into the lumen. Areas of necrosis and hemorrhage may be prominent, especially in large tumors. For our patient, the left and right ovarian masses measured 12cm x 10cm x 4cm and 10cm x 16cm x 7cm respectively. Grossly, they were predominantly solid with glistening cut surfaces. Grayish white tissues were noted as well as areas of hemorrhage and necrosis (Figure 1).

Morphologically, neuroectodermal tumors of the ovary are identical to their counterparts in the central nervous system. Tumor cells show either glial or neural differentiation or correspond to developmentally unclassifiable nervous system precursors. As previously mentioned, histologically, these tumors are classified as ependymoma, astrocytoma, glioblastoma multiforme, medulloblastoma, medulloepithelioma, epyndomoblastoma, glioblastoma multiforme, neuroblastoma and primitive neuroectodermal tumor. Primitive neuroectodermal tumors are composed of primitive neuroblastic or primitive, developmentally uncommitted, precursors of neural and glial cells. They are highly cellular and are composed of small cells with hyperchromatic, round to oval nuclei and scanty cytoplasm. This is similar to the histologic picture of our patient's tumor (Figure 2). However, neuroectodermal tumors may be confused with other ovarian tumors on histologic examination, which makes coming up with the definitive diagnosis difficult, as with the case of our patient. Ovarian ependymomas may be confused with other carcinomas because they contain large gland-like spaces which superficially resemble neoplastic glands in endometrioid adenocarcinomas. Ependymal rosettes may resemble Call-Exner bodies of granulosa cell tumors. Various malignant "small blue-cell" tumors such as small cell carcinoma, malignant lymphoma and leukemia, metastatic round cell carcinoma and others may be mistaken for primitive neuroectodermal tumors because of histologic similarities.[3] Initial histopathologic reading for our patient's tumor was a small round cell tumor with the consideration of a lymphoma or a small cell carcinoma. The difference in the management of these two disease entities necessitates further investigation.

In order to elucidate the precise diagnosis for our patient, presented with the histologic picture of a round cell tumor, immunohistochemical stains were ordered. CD3 and CD20 were requested to confirm the diagnosis of non-Hodgkins lymphoma. Cytokeratin was ordered to confirm small cell carcinoma and chromogranin and synaptophysin were included to diagnose carcinoid tumor. Since all the stains revealed negative results, the consideration then was juvenile granulosa cell tumor. Additional immunostains of alpha-inhibin was requested to confirm the diagnosis however the stain also turned out to be negative. CD99, Calretinin and EMA were then requested. Calretinin is a useful immunohistochemical marker of mesothelial cells and mesothelioma while EMA may also be used as a confirmatory test to differentiate a juvenile granulosa cell tumor from and small cell carcinoma of hypercalcemic type. CD99, on the other hand, is a sensitive immunohistochemical marker of peripheral primitive neuroectodermal tumors.[14] Of these three markers, only the CD99 turned out to be positive (Figure 3). The diagnosis of primitive neuroectodermal tumor was then made.

Just as in any other ovarian malignancy, surgery is the cornerstone of management for primitive neuroectodermal tumors. Most patients with clinical stage I of the disease receive operation as the only treatment while patients in more advanced clinical stages were treated with surgery and subsequent radiation or chemotherapy or a combination of both. Chemotherapeutic agents for this tumor is similar to the drugs used in treating Ewing's sarcoma, namely Vincristine, Adrinamycin and Ifosfamide.[19] This underscores the importance of arriving at the proper diagnosis since chemotherapeutic agents for other diseases with similar histologic features are different. For small cell carcinomas of the ovary, the standard treatment would be chemotherapy with a platinum-based agent followed by radiotherapy.[20] For non-Hodgkins lymphoma of the ovary, treatment would have been chemotherapy with Cyclophosphamide, Doxorubicin, and Vincristine with steroid agents.[21] For juvenile granulosa cell tumor, the recommended therapy would be chemotherapy with Bleomycin, Etoposide, and Cisplatin.[22] Our patient underwent total abdominal hysterectomy with complete surgical staging followed by one course of chemotherapy.

Primitive neuroectodermal tumors, given their poorly-differentiated nature, are known to behave clinically in a very aggressive fashion. Survival rates have been reported to range from 10 months to 3 years but patients with this tumor have even poorer prognosis when extra-ovarian spread has occurred.[6] Due to the paucity of the cases reported in literature, specific survival rates by stage are not available. Our patient was diagnosed with stage IV disease upon surgery and eventually succumbed to the disease 3 months after the surgery.

Summary

We are presented with a 29 year old female who came in with a chief complaint of abdominal pain and enlargement. Surgery was done the intraoperative assessment was a malignant ovarian new growth, stage IV. Initial histopathologic results, however, were non-conclusive, hence necessitating the use of immunostain histochemical studies, which led to the diagnosis of a rare ovarian neoplasm.

Conclusion

Malignant ovarian new growths are a common cause of morbidity and mortality today. Prompt and proper diagnosis is imperative in order to be able to give the proper treatment to the patient. In cases wherein there are diagnostic dilemmas or rare tumors are encountered, ancillary studies such as immunohistochemistry may be employed. Although tedious and quite expensive, these markers may make the difference with regards to the treatment given as well as to the overall survival of the patient.

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Radical Vaginal Trachelectomy: The First Local Experience*

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This is the case of a 32 year old G2P2 (2002) who was diagnosed with squamous cell carcinoma stage IB1. She underwent extraperitoneal lymph node dissection, frozen section, and radical trachelectomy. Histopathology revealed squamous cell carcinoma, with negative margins. The patient is currently being followed up closely, and still has the chance of having another pregnancy because of the conservative treatment done on her.

Cervical cancer is a devastating disease that can take away a woman's chance to fulfill her role of being a mother. Over the past years, management of cervical cancer has evolved, giving an emphasis on the preservation of fertility for early stage disease. As more women are delaying child-bearing, preservation of fertility and reproductive function is a major concern when these young women are counseled on the effects of treatment for cervical cancer. Approximately 15% of all cervical cancers and 45% of surgically treated stage IB cancers occur in women under 40 years of age. These women represent the subset of patients who are candidates for fertility preservation if they are identified as having a low risk of recurrence and a low risk of lymph-node involvement. Radical vaginal trachelectomy is a fertility-preserving procedure that has recently gained worldwide acceptance as a method of surgically treating small invasive cancers of the cervix. This procedure was first described by Daniel Dargent in 1994 and involves the removal of most, if not all, of the cervix, its contiguous parametrium, and vaginal cuff, in addition to a laparoscopic pelvic lymphadenectomy. To date, this is the first case of radical vaginal trachelectomy done in the Philippines.

The Case

The patient is a 32 year old G2P2 from Quezon City with a one year history of intermenstrual vaginal bleeding. Her past medical and family medical history were both unremarkable. She is single and currently works as an airline employee. Her first coitus was at the age of 18 with two lifetime partners. She had no vices. She has an eight-year history of oral contraceptive pill use. She has no history of intrauterine device use or history of Pap smear done.

She had her menarche at 12 years old. Subsequent menses would occur regularly at monthly intervals, lasting for 7 days, soaking 2-3 pads per day. Her last normal menses was from August 13-14, 2007.

One year prior to admission, the patient started to experience intermenstrual spotting lasting for 3 days. No associated symptoms like hypogastric pain,

* Third Place, 2010 SGOP Fellows' and Residents' Interesting Case Contest.

watery discharge or abdominal pain were reported. No consult was done initially. Due to the persistence of the symptoms, she consulted a gynecologic oncologist. On pelvic examination, the patient had a normal external genitalia, a smooth parous vagina, the cervix was 2cm x 2cm. There was a 1cm x 1cm mass at the posterior endocervix while the ectocervix was smooth. The corpus was small, there were no adnexal masses appreciated, and both parametria were smooth and pliable. Cervical punch biopsy was done which revealed squamous cell carcinoma, large cell, non-keratinizing. Since the patient desires to preserve her fertility, she was advised fertility-sparing vaginal trachelectomy.

The patient underwent extraperitoneal bilateral pelvic lymph node dissection, radical trachelectomy, and frozen section under regional anesthesia. Intraoperatively, the cervix measured 3cm x 2.5cm x 3cm with no gross identifiable lesion. The vaginal cuff measured 2cm anteriorly and 1cm posteriorly, grossly free of tumor. The parametria measured 2cm each, grossly unremarkable. Harvested lymph nodes were not suspicious for malignancy. On frozen section, the endocervix, vaginal margins and paracervical margins were negative for tumor.

The final pathologic diagnosis was Squamous cell carcinoma, large cell, non-keratinizing (2 cms in greatest dimension), with more than two-thirds cervical stromal infiltration and lymphovascular space infiltration, ten to three o'clock position, cervix uteri. Negative for tumor: paracervical tissues and vaginal cuff, specimens labeled anterior vaginal biopsy and anterior vaginal wall, all eight right obturator lymph nodes, all four right external iliac lymph nodes, all six left obturator lymph nodes, all two left external iliac lymph nodes.

Discussion

A diagnosis of invasive cervical cancer used to mean the end of a woman's fertility. For women with small, localized invasive cervical cancers, there is now hope for pregnancy after treatment. Each year, about 11,000 new cases of invasive cervical cancer are diagnosed in the United States, and about 3,500 women die of the disease. In the past, a diagnosis of early stage invasive cervical cancer would usually lead to infertility because of the recommended treatment necessary to cure the cancer. Treatment usually includes a radical hysterectomy with or without concurrent chemoradiation for stages no more than IB1. There has been an increased focus towards fertility preservation in the treatment of cervical cancer during the last decade. The driving force is the fact that 15% of all cervical cancers, and 45% of surgically treated stage IB cervical cancers occur in women < 40 years of age. [1]

Radical trachelectomy is a procedure wherein the cervix, the vaginal cuff and the parametria are removed, preserving the uterine body, which in turns preserves the childbearing potential of the patient. This procedure was developed in France in 1987 by Dr. Daniel Dargent to preserve the childbearing potential of young women with FIGO stages 1 and 2 cervical cancers. Women are at higher risk of recurrence if their tumor size is larger than 2 cm.[2] The indications are not definitely established at this point. Eligibility criteria currently used are 1) desire to preserve fertility, 2) no clinical evidence of impaired fertility, (3) lesion is less than 2cm, 4) FIGO stage IA2- IB1, 5) squamous cell carcinoma or adenocarcinoma, 6) no involvement of the endocervical canal as determined by colposcopy, and 7) no metastasis to regional lymph nodes.[3] In the United States and France, the procedure is performed transvaginally with pelvic lymph nodes harvested through a laparoscope. There are, however, institutions in the U.S. that practice abdominal trachelectomy to ensure a wider parametrial surgical margin. Either approach, the standard of care is to perform a frozen section evaluation of the endocervical margin to exclude tumor involvement at the time of surgery. If negative, the vaginal cuff is purse-stringed (by a surgical cerclage) using Prolene 0. With healing, the surgical surface re-epithelialises and creates a smooth vaginal vault. A catheter is often introduced into the endocervical / endometrial canal during the procedure to prevent closure of the canal during healing. Women usually resume normal menstruation within three months. [4]

An important step prior to performing radical trachelectomy is the extraperitoneal lymph node dissection. Due to the limitation of modern

radiologic imaging to accurately detect subclinical lymphatic spread, surgical sampling remains the gold standard. The trend in developed countries is the use of laparoscopy in lymph node dissection. Soon, our institution will be equipped to perform laparoscopic lymph node dissection. Aside from laparoscopic approach in harvesting pelvic lymph nodes, extraperitoneal approach is also an option. In our index patient, extraperitoneal pelvic lymph node dissection was done. Incision is done from the anterior superior iliac spine to the suprapubic area. The transversalis fascia is incised and dissected caudally until the psoas muscle is exposed. Once the psoas muscle is visualized, careful dissection is done to get to the pelvic lymph nodes. Compared to the transperitoneal approach in lymph node dissection, the advantage of extraperitoneal approach is that there is less chance of postoperative bowel adhesion or injury because the peritoneal cavity is not entered.

The role of frozen section is vital in performing radical trachelectomy. A study designed to determine the indications and the best method for evaluating the resection margins of trachelectomy specimens was done from 1991-2002. They recommended doing frozen section, using a longitudinal section only in those specimens with a grossly visible lesion.[5]

Intraoperative complications of radical trachelectomy occurred in 4% of the cases reported in the literature. More than half of the complications were bladder injuries that occurred during the trachelectomy procedure. Vascular injuries were the second most common complication and occurred mainly during lymphadenectomy.[6] Postoperative complications were seen in 12% of the patients reported in the literature, and were mainly related to bladder hypotonia, similar to what is observed after radical hysterectomy.[7]

One of the concerns in doing conservative management for early-stage cervical cancer is whether conservative radical trachelectomy is as effective as the standard radical hysterectomy. It is reassuring that no significant differences have been detected in tumor recurrence rates between pooled series of patients treated with radical trachelectomy and with historical controls.[8] During the 8th International Gynecologic Cancer Society meeting in 2000, Dr. Dargent summarized the data of 224 cases and found out that the recurrence rate after the procedure is only 3.6% One of the studies in the summarized data was the report by Covens, et al. in 1999 wherein there were 58 patients. Out of the 58, only 3 (5.1%) patients had recurrence.[9] The most important risk factors for recurrence are the size of the lesion (≥2cm) and the presence of lymphovacular space invasion.

As for the pregnancy outcomes, pregnancy losses were 42%[10]. The rate of the second trimester losses was higher than that of the third trimester. This was attributed to cervical incompetence as complication of the procedure. Seventy-two percent of pregnancies reached the third trimester. Seventy-eight percent of those who reached the third trimester have successfully borne children at term. Since a permanent cerclage is placed, cesarean section is usually required for delivery. For young patients diagnosed with stage I cervical cancers, this surgical procedure offers young women a chance to retain child-bearing capability despite a cancer diagnosis[11].

Conclusion

We are presented with a 32 year old G2P2 (2002) patient diagnosed with stage 1B1 cervical cancer who expressed her desire fertility preservation. Extraperitoneal pelvic lymph node dissection, frozen section, and radical vaginal trachelectomy were performed. Despite having a stage IB1 cervical cancer, she has been disease-free for 3 years now and still has a chance to get pregnant. To date, this has been the first radical vaginal trachelectomy done in our country. Nowadays, young patients diagnosed with cervical cancer Stage 1B1 or less have an option to preserve their fertility. Unlike before when the diagnosis of cervical cancer would entail losing reproductive ability, we now have a fertlity sparing alternative to offer our patients. Its recurrence rate is almost the same of those who underwent radical hysterectomy. The obstetric outcome is very promising.

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