Case Report

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Website: www.pogsjournal.org
DOI: 10.4103/pjog.pjog_15_21

Malignant transformation of a mature teratoma with concurrent cervical carcinoma versus squamous cell carcinoma of the cervix with ovarian metastasis: A diagnostic dilemma

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Abstract:

Mature cystic teratoma of the ovary may occur in 10%–20% of women during their lifetime. Its biological behavior is benign, while 0.17%–2% of them may undergo malignant transformation. Various histological types of malignant transformation include Squamous cell carcinoma (SCC), adenocarcinoma, small cell carcinoma, sarcoma, malignant melanoma, and mixed histology. SCCA of the cervix occurs more commonly at ages 45–55. This is mainly caused by human papillomavirus 16 and 18. This tumor spreads to local then regional lymph nodes and can have hematogenous spread to bone and lungs, rarely to the ovaries. This report is of a 75-year-old Gravida 9 Para 9 (9009) with an enlarging pelviabdominal mass, managed as a case of ovarian new growth with later findings of cervical cancer. The case merits presentation because of the dilemma in diagnosis.

Keywords:

Cervical cancer, malignant transformation, mature cystic teratoma, squamous cell carcinoma

Introduction

Mature cystic teratoma (MCT) of the ovary, commonly known as a dermoid cyst, has been known since antiquity. MCT is the most common type of ovarian germ cell neoplasm. It occurs relatively frequently and comprises approximately 20% of all ovarian neoplasms.[1] The diagnosis is easy to make; an ovoid cyst with a grey external surface containing yellow to brown sebaceous material and hair. Bone, cartilage, brain, and adipose tissue may be detectable at first examination. The cyst appears to be lined by keratinized epithelium with sebaceous glands, sweat glands, and hair follicles.[2] Malignant transformation of an MCT is an uncommon complication occurring in approximately 0.17%–2% of all MCTs.[3] Although any of the constituent tissues of teratoma has the potential to undergo malignant transformation, squamous cell carcinoma (SCC) is the most commonly associated cancer. SCC of the cervix is one of the most common gynecological malignancies and usually presents with vaginal or postmenopausal bleeding. This can involve the uterine corpus by direct extension or through parametrium by lymphatic invasion to the uterine wall. In most cases, the spread is restricted to the endometrium with very few cases of spread to fallopian tubes or ovaries.[4]

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Submitted: 27-Jan-2021
Revised: 26-Feb-2021
Accepted: 15-Jul-2021
Published: 09-Sep-2021

*Finalist, PHILIPPINE OBSTETRICAL AND GYNECOLOGICAL SOCIETY (Foundation), INC. (POGS) Residents' September 17, 2020, Online Platform: ZOOM Webinar

How to cite this article: Ramajo IF, Gaddi AM, Gueco CG. Malignant transformation of a mature teratoma with concurrent cervical carcinoma versus squamous cell carcinoma of the cervix with ovarian metastasis: A diagnostic dilemma. Philipp J Obstet Gynecol 2021;45:122-7.

Case Report

This is a case of a 75-year old Gravida 9 Para 9 (9009), Filipino, Roman Catholic, who consulted at the outpatient department for the first time due to a palpable pelviabdominal mass. Family and past medical history were noncontributory. She was a known smoker with 6 pack years.

She had her menarche at 13 years old occurring irregularly lasting for 3 days, soaking 3 pads per day with no associated dysmenorrhea, and had her menopause at the age of 48 years.

One year prior to consult, the patient noticed a palpable pelvic mass about 10 cm × 10 cm in size with no other associated symptoms such as abdominal enlargement, vaginal bleeding, changes in the frequency of bowel movement, the caliber of stool, weight loss, anorexia, easy fatigability, early satiety, and hematochezia. She consulted a private OB-GYN and a transvaginal ultrasound was requested which revealed a unilocular cystic pelvic mass measuring 11.7 cm × 10.6 cm × 9.0 cm with benign sonographic features. She was advised to undergo surgery but due to financial constraints, the patient refused and was lost to follow-up.

Two weeks prior to consult, the patient still complained of a palpable abdominal mass now with on and off hypogastric pain, with a pain scale of 6/10, crampy, and associated with rectal discomfort. She consulted at the local health center and was advised surgery but she and her family were undecided.

One week prior to consult, due to the persistence of the above symptoms, and worsening pain of 8/10, the patient consulted at the outpatient department. A metastatic workup was requested and done revealing slightly elevated CA-125 of 36.2 U/mL and normal alpha-fetoprotein of 1.50 ng/mL. On physical examination, the patient was ambulatory, conscious, coherent, afebrile, normotensive, nontachycardic, and nontachypneic. Her abdomen was flabby, soft, had normoactive bowel sounds, and with a 15 cm × 12 cm cystic, movable, nontender, pelvic mass palpable on the left lower quadrant. External genital examination showed normal-looking female genitalia. Speculum examination showed pink and smooth vaginal wall and cervix with no lesions or erosions. On internal examination, the cervix was closed, smooth, and pulled up; the uterus could not be assessed due to the pelviabdominal mass. The rectovaginal septum was intact, with fullness at the cul-de-sac; parametria were free and pliable. On transvaginal ultrasound, the cervix measured 2.94 cm × 1.75 cm × 1.56 cm, uterus measured 3.54 cm × 2.62 cm × 1.03 cm anteverted, with homogenous abnormalities of calcified myometrial vessels. Endometrium was intact, isoechoic, and measures 0.26 cm, thin compatible with abnormalities. The left and right ovaries were visualized and both were normal. There was a large unilocular cystic mass in the pelvic cavity with a smooth outline measuring 11.7 cm × 10.6 cm × 9.0 cm [Figure 1]. There were fine internal calcifications noted within the cystic mass. An incomplete septum was noted in its anterior aspect. No color flow noted in the color Doppler scan. There was also hyperechoic mass left to the cystic mass with lobulated border measuring 4.8 cm × 4.6 cm × 3.37 cm which maybe colonic in origin. No fluid in the cul-de-sac. The impression on ultrasound was unilocular cystic mass with morphologic features suggestive of a MCT left, small anteverted uterus, thin and intact endometrium.

The patient was diagnosed preoperatively with ovarian new growth, probably benign, cannot totally rule out malignancy; Gravida 9 Para 9 (9009). She underwent exploratory laparotomy, peritoneal fluid cytology, total abdominal hysterectomy with bilateral salpingo-oophorectomy, bilateral lymph node dissection, para-aortic lymph node sampling, random peritoneal biopsy, and infracolic omentectomy under combined spinal and epidural anesthesia.

Intraoperative findings revealed that the left ovary was converted to a 15 cm × 15 cm cystic mass with a 5 cm × 5 cm solid mass on its capsule adherent to the posterior lower uterine segment [Figure 2]. On cut

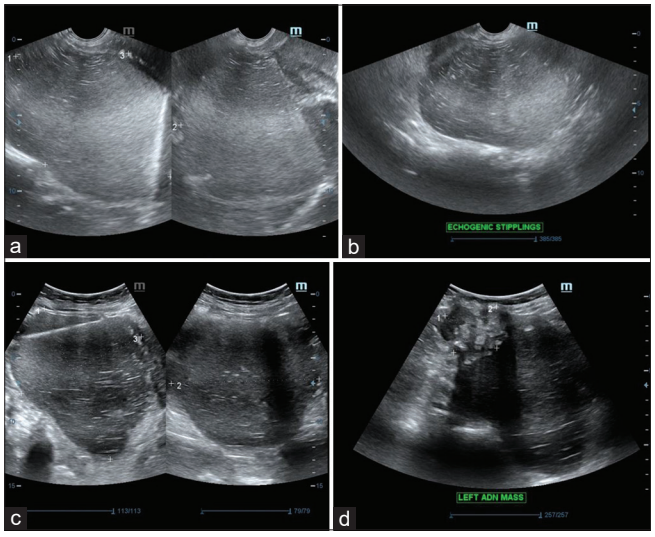

Figure 1: (a) Transvaginal ultrasound. Large unilocular cystic mass in the pelvic cavity with smooth outline measuring 11.7 cm × 10.6 cm × 9.0 cm. An incomplete septum is noted in its anterior aspect. No color flow noted in color Doppler scan. There is also hyperechoic mass left to the cystic mass with lobulated border measuring 4.8 cm × 4.6 cm × 3.37 cm which maybe colonic in origin. (b) Transvaginal ultrasound. Echogenic stipplings were noted. (c) Transvaginal ultrasound. Heterogenous cystic mass is 12 cm × 11 cm × 10cm with echogenic stippling. (d) Transvaginal ultrasound. Echogenic core measuring 4.1 cm × 4.2 cm

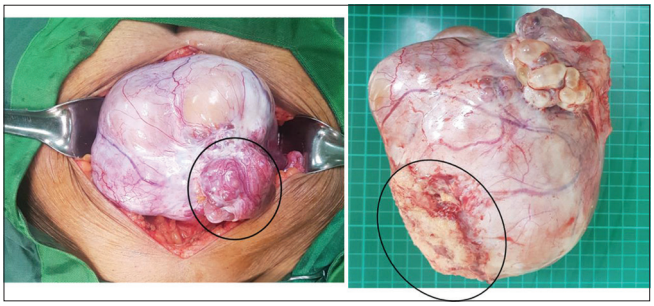

Figure 2: Gross specimen showing left ovary was converted into a 15 cm × 15 cm cystic mass and 5 × 5 × solid mass on its capsule adherent to the posterior lower uterine segment

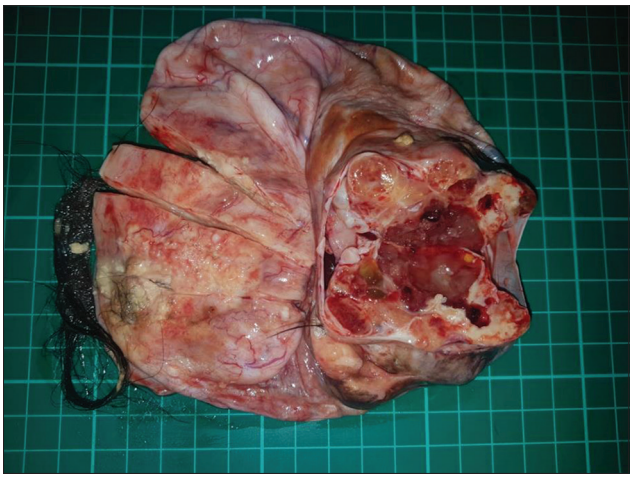

Figure 3: Cut section of the left ovary. There was egress of sebum and hair. There were teeth, cartilage and bone noted

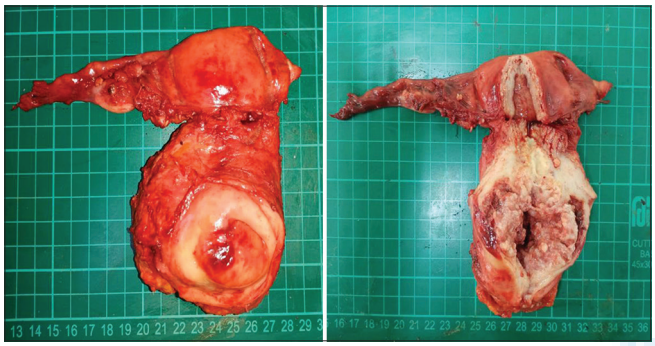

Figure 4: Gross picture of cervix, uterus and right fallopian tube. There was a 8 cm × 7 cm friable mass on the lower uterine segment and the cervix. Uterus measured 12 cm × 8 cm. anterior and posterior myometrium measured 1 cm each. The endometrium measured 0.2 cm. The right fallopian tube measured 8 cm × 0.5 cm × 0.5cm. The right ovary measured 2 cm × 2 cm × 1.5 cm

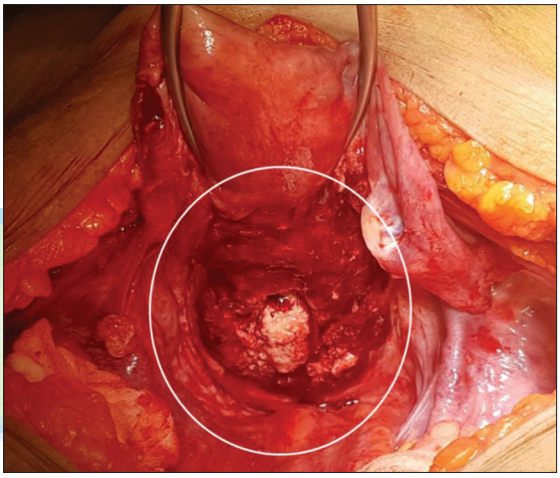

Figure 5: A 6 cm × 6 cm mass noted on the posterior lower uterine segment involving the cervix fixed on the cul de sac

section, there was egress of sebum and hair. There were teeth, cartilage and bone noted [Figure 3]. The liver, gall bladder, stomach, small intestine, peritoneal surfaces, and omentum were smooth. There was an 8 cm × 7 cm friable mass on the lower uterine segment and the cervix. Other findings unremarkable [Figure 4]. After performing left salpingo-oophorectomy, there was a 6 cm × 6 cm mass noted on the posterior lower uterine segment involving the cervix fixed to the cul de sac [Figure 5]. The specimens were submitted to the department of pathology for the histopathologic report. Microscopic examination of the left ovary showed parts of MCT with an invasion of neoplastic cells similar to those of the cervical area [Figure 6]. Sections of the MCT composed parts of the stratified squamous epithelium, hair follicle, and fat [Figure 7]. The microscopic examination of the cervix showed a cervical tumor consisting of diffuse sheets of neoplastic cells. The neoplastic cells were characterized by pleomorphic enlarged nuclei with prominent nucleoli set in an eosinophilic cytoplasm. Several scattered mitotic figures were noted [Figure 8]. The histopathologic report revealed SCC, moderately differentiated involving the cervix, lower uterine segment, and left ovary. The right parametrium was positive for tumor. The omentum, cul-de-sac mass, cul-de-sac, and serosal implants were also positive for tumor metastasis. The peritoneal fluid was positive for atypical cells, giving the high suspicion of malignancy. Lymph nodes were negative for metastasis. Other findings include MCT with struma ovarii, left; atrophic right ovary; cystic atrophy, endometrium, and unremarkable fallopian tubes.

The postoperative diagnosis was MCT with malignant transformation, Left Ovary Stage IIIC versus SCC, moderately differentiated, Cervix stage IVB. The patient was advised systemic chemotherapy of carboplatin-paclitaxel every 21 days for 6 cycles, and underwent 1 cycle but then decided to undergo palliative care. On follow-up at the outpatient department, there was a 6 cm × 5 cm palpable mass on the hypogastric area with associated on and off pain. She was advised on nutritional build-up and continuation of chemotherapy. The patient was however lost to follow-up.

Discussion

Carcinoma of the cervix is initially a locally infiltrating

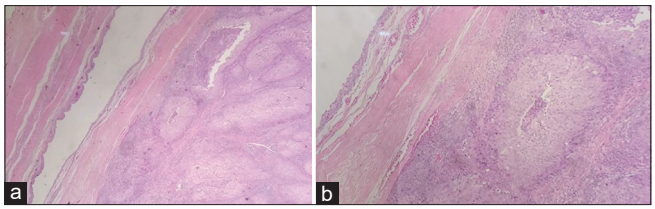

Figure 6: Microscopic examination, left ovary. (a) Scanner view, on your left side is the left ovary which is part of the mature cystic teratoma and on the right side is the invasion of the neoplastic cells similar to that seen in the cervix. In which there are sheets composed of your neoplastic cells, keratinized. (b) High power field view, shows infiltration of keratinized neoplastic cells similar to those of the cervical area

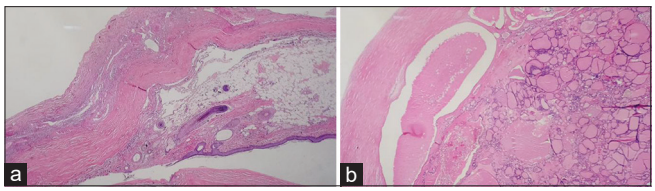

Figure 7: (a) Microscopic examination of mature cystic teratoma. (b) Microscopic sections of the mature cystic teratoma with parts of the stratified squamous epithelium, hair, follicles and fat

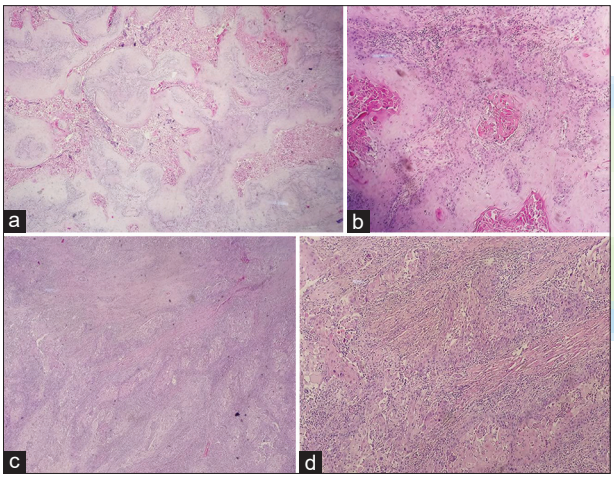

Figure 8: Microscopic examination cervix. (a) Scanner view the cervical specimen has diffuse sheets and nests of neoplastic cells surrounded by several keratinized areas. (b) Low power field, a closer view of the cervical tumor still consisting of diffuse sheets of neoplastic cells. The neoplastic cells are characterized by pleomorphic enlarged nuclei with prominent nucleoli set in an eosinophilic cytoplasm. Several scattered mitotic figures are noted. (c) Another field on low power view which also illustrates the same neoplastic cells but in a more solid area thus assigning it as moderately differentiated. (d) High power field view, showed more solid pattern in this particular area which is still composed of the same neoplastic cells but in a more packed version

cancer that spreads from the cervix to the vagina and paracervical and parametrial areas. Grossly, the tumors may be ulcerated and may have an exophytic growth pattern or cauliflower-like appearance extruding from the cervix. Alternatively, they may be endophytic, in which case they are asymptomatic, particularly in the early stage of development, and tend to be deeply invasive when diagnosed. These usually start initially from an endocervical location and often fill the cervix and lower uterine segment, resulting in a barrel-shaped cervix.[5] This endophytic type of cervical cancer is rarely encountered which may contribute to the nondiagnosis as in the patient's case.

Cervical carcinoma was not detected nor considered during the patient's outpatient consults due to the absence of the usual symptoms of cervical cancer as well as abnormal physical examination and ultrasound findings related to the cervix. Intraoperatively, there were findings of an endophytic type of cervical tumor up to the lower uterine segment partly attached to the cul-de-sac. This type of tumor is often more advanced than the exophytic variety mainly because of the late diagnosis. In addition to the nodal spread, hematogenous spread of cervical carcinoma occurs primarily to the lung, liver, and less frequently, bone.[5] Other areas of metastatic spread are rare.

Mature teratomas are generally a benign tumor with cystic, solid, or mixed component.[5] The patient was preoperatively diagnosed with an MCT, however, intraoperatively, in addition to the ovarian mass, the cervix and lower uterine segment consisted of brainy tissue which pointed to a malignancy. This posed a dilemma in the diagnosis of either a primary cervical carcinoma with ovarian metastasis or a primary ovarian carcinoma with cervical metastasis.

Ovarian cancer rarely metastasizes to the uterine cervix, vagina, or vulva. A review conducted by Guidozzi *et al*. showed that in 148 patients with FIGO Stage III or IV ovarian cancer, 7 had cervical metastatic deposits which showed the presence of adenocarcinoma rather than SCC. These patients had associated malignant ascites, retroperitoneal lymph node involvement, and significant peritoneal carcinomatosis[6] which was not evident in the presented case. This suggests a shift in the diagnosis away from a primary ovarian cancer and leading more toward a cervical origin.

Ovarian tumor of early stage is often detected accidentally during physical examination or postoperative pathological examination, while palpable mass, bloating and abdominal pain are often present in an advanced stage. In the presented case, there was a 1-year history of palpable pelviabdominal mass and abdominal pain. The risk of malignancy is related to age and is substantially greater in postmenopausal women, the highest incidence being in the fifth and sixth decades of life.[7] A study conducted by Wang *et al.* stated that the complications associated with cystic teratoma cases include torsion (16%), malignant degeneration (2%), rupture into adjacent organs (1%–2%), and infection (1%).[8]

The measurement of serum tumor markers and imaging are two important elements in differentiating malignant

from benign ovarian tumors. Metastatic workups were requested and done in the presented case. Tumor markers such as CA-125 and alpha-fetoprotein and transvaginal ultrasound were also done which gave the picture of a benign tumor more than a malignant one. The patient's case, however, intraoperatively, showed gross malignancy on the cervix, lower uterine segment, ovary, and cul-de-sac. There were no workups for cervical cancer done, like cervical punch biopsy, which could have changed the approach of treatment and management of the patient's condition.

A possible approach to this case involves the molecular aspect of the said diseases. Newer research and studies discussed that the protein p16INK4a (henceforth referred to as p16) is a cellular protein involved in cell cycle regulation, and its expression is tightly controlled in normal cells. In normal nondysplastic cells, p16 protein is expressed at a very low level and is almost undetectable by immunohistochemistry. It may be considered a surrogate marker for the activated oncogene expression of HR-HPV in dysplastic cervical cells.[9]

A study by Izadi-Mood *et al.* findings showed that the expression of p16 increases from normal in invasive squamous carcinoma in the uterine cervix emphasizing that it might be a useful marker for predicting the risk of developing cervical cancer in women.[10] In correlation to the case, the expression of p16 in the ovarian mass points to a primary cervical cancer rather than ovarian cancer. However, the absence of the said protein does not rule out primary cervical cancer entirely.

Hall *et al*. (2008) performed a study on longitudinal clinical samples in a cohort of patients with histologically proven epithelial dysplasia. They found that p16 promoter methylation occurred in 26% of the cases followed by transformation in SCC, and in only 1% of those that did not develop SCC, concluding that p16 promoter methylation can be a reliable predictor of malignant transformation.

Summary

To conclude, the detection of cervical carcinoma in a setting of a pelviabdominal mass with normal preoperative cervical findings poses a difficulty. A routine Pap smear is highly recommended to screen for cervical cancer. This, however, is not accurate 100% of the time.

SCC of the cervix rarely metastasize to the ovaries and the endophytic type usually presents with a barrel-shaped cervix. Because of its unusual presentation, it is often diagnosed late and is already in its advanced stages. It is therefore fitting to be vigilant in doing routine gynecologic examinations to recognize the slightest abnormalities which will assist in pointing to the right diagnosis. Concurrent chemotherapy and radiotherapy is the cornerstone treatment for this cancer.

Ovarian SCC rarely metastasizes to the cervix with only a very few reported cases and mostly are adenocarcinomas. This tumor is usually in its advanced stage already as well. Adequate sampling is essential in these ovarian tumors to establish their teratomatous origin and to avoid an erroneous diagnosis.

Hysterectomy and platinum-based chemotherapy are associated with better survival for this type of ovarian tumor. Early detection and complete surgical removal of the entire tumor, in accordance with oncosurgical treatment principles, is essential, following which complete cytoreduction can further improve the outcome in these patients.

For the present study, an immunochemistry staining using p16 is recommended to increase the certainty of the SCC of the cervix as the primary tumor. Platinum-based chemotherapy, nutritional build-up, and regular follow-up could have been beneficial to the patient. However, due to the poor prognosis of this case, there is no certainty of increasing the chances of survival and improving the quality of life even with the recommended treatments.

With the advancement of science and technology, the expression of p16 in the cervix can help in predicting the risk of cervical cancer even in women with normal pap smear results. It is also beneficial for the general population to have anti-HPV vaccination to help decrease the risk of cervical cancer.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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