Carcinoid tumor arising in a mature cystic teratoma: A case report*

By Katherine Abegail P. Galang, MD and Leo Francis N. Aquilizan, MD, FPOGS

Department of Obstetrics and Gynecology, St. Luke's Medical Center – Quezon City

ABSTRACT

This report will discuss a case of carcinoid tumor arising in a mature cystic teratoma in a 27-year-old single nulligravid, who initially consulted for primary amenorrhea and right lower quadrant pain. Pelvic ultrasound was done and revealed an ovarian cyst on the right, to consider mature cystic teratoma. She underwent right oophorectomy with unremarkable post-operative course. Furthermore, this case report will tackle the diagnosis, definitive management and prognosis of the condition.

Keywords: Mature cystic teratoma, Carcinoid, Malignant Transformation, Nulligravid

INTRODUCTION

Mature cystic teratomas (MCT) are ovarian tumors that are almost always benign in nature; the extremely rare coexistence of malignancy deserves emphasis due to a very small number of published cases especially in young females. This rarity is of high clinical interest and poses a challenging dilemma about the optimal therapeutic strategy especially in women desiring to preserve fertility. Fertility sparing surgical approach may be considered in nulliparous women with favorable pathologic and clinical signs and symptoms. This case report aims to discuss a case of carcinoid tumor arising in a mature cystic teratoma in a 27-year-old single nulligravid patient, its diagnosis, definitive management and prognosis.

CASE PRESENTATION

This is a case of RR, a 27-year-old, single, nulligravid who sought consult for right lower quadrant pain. She is a known asthmatic previously maintained on Salbutamol as needed for acute attacks and with regular pulmonary consult. She underwent recto-anal pull through at birth due to imperforate anus with unremarkable results. She has family history of diabetes and endometrial hyperplasia. She reported previous 6-pack year history of smoking. Since age 14, she undergoes regular gynecologic check-up due to primary amenorrhea. Initial transrectal ultrasound at this time showed an infantile anteverted uterus measuring 2.1x1.7x1.1cm with no myometrial lesion. Endometrium is thin 0.28cm. The cervix is also small measuring 1.4x1.4cm with normal echotexture. The right ovary measures 4.1x3.1cm with a portion containing multiple small follicles <1cm in diameter consistent with polycystic pattern and a round highly echogenic portion measuring 2.0x1.9cm which could be a dermoid component. The left ovary is normal in size and also polycystic looking (Table 1). She was advised annual monitoring with transrectal ultrasound and was prescribed various unrecalled oral-contraceptive pills for her polycystic ovaries. She sought consult in different institutions regarding her amenorrhea and underwent tests such as chromosomal analysis revealing genetically female with complete set of chromosomes. Furthermore, serum chemistries and hormone levels were also requested which revealed normal results. In the interim, she continuously sought opinion from different doctors and remained amenorrheic with no other associated sign and symptom. She denies vaginal spotting, abnormal vaginal discharge, hypogastric pain, nor was she able to appreciate a palpable pelvic mass. There were no changes in urinary and bowel movement either. No weight loss and anorexia experienced. Monitoring of the right ovarian cyst revealed slight interval increase in size from 2.0x1.9cm to 2.9x2.5cm in a span of 10 years. Four months prior to admission, she experienced right lower quadrant pain with visual pain score of 2-3/10 initially; this was noted to increase in intensity to 8-9/10, radiating to the hypogastric area, not associated with menstruation nor food intake. She sought consult and underwent transrectal ultrasound which revealed the following results: small anteverted uterus measuring 3x1.9x1.5cm, with undefined endometrium. The left ovary measured 2.3x2.2x1.9cm with normal echopattern. The right ovary measured 4.2x4.3x3.1cm with a 3.4x3.6x3.2cm well-defined, thick-walled cystic structure with solid nodules within, could be a right ovarian complex mass (Table 1). No tumor

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Table 1. Ultrasonographic imaging requested yearly for monitoring.

May 10, 2001	Transrectal ultrasound: Small, infantile anteverted uterus measuring 2.1x1.7x1.1cm with no myometrial lesion. Endometrium is thin 0.28cm. The cervix is also small measuring 1.4x1.4cm with normal echotexture. The endometrium is thin and intact. The right ovary measures 4.1x3.1cm with a portion containing multiple small follicles <1cm in diameter consistent with polycystic component and a round highly echogenic portion measuring 2.0x1.9cm which could be a dermoid component. The left ovary is normal in size and also with multiple small follicles <1cm in size. No free fuid in cul-de-sac.
August 23, 2003	Transrectal ultrasound: Anteverted small and flat homogenous uterus measuring 1.67x2.32x1.05cm. Thin hypoechoic endometrium with clean borders. The left ovary is average in size (2.07x1.44x1.11) with undeveloped follicles. The right ovary is average in size (2.04x1.66x0.73) with a round hyperechoic foci at the superior pole measuring 1.93x2.25x1.93cm.
April 12, 2004	Transrectal ultrasound: Infantile anteverted uterus measuring 1.86x1.06x1.31cm with thin endometrium 0.14cm, cervix intact and measures 1.11cm. The right ovary is converted into a 2.7x2.7x2.6cm intensely echoic mass with a hypoechoic rim. The left ovary measures 2.55x1.57x1.56cm.
March 29, 2005	Transrectal ultrasound: Infantile Uterus measuring 1.07x1.97x0.73 with thin, intact endometrium measuring 0.23cm. cervix intact 1.31cm. The right ovary measurs 4.1x2.16x2.84cm with a wll delineated hyperechoic refractile echoes measuring 2.5x2.5cm with a thin rim of typical ovarian tissue echoes at one pole, could be dermoid cyst. Left ovary normal. Cul-de-sac unremarkable.
July 9, 2005	Transrectal ultrasound: Retroverted infantile, small, flat, cordlike uterus measuring 2.46x1.98x1.29cm with paper thin endometrium 0.20cm. cervix unremarkable and measures 1.47cm. small flat left ovary measuring 2.23x1.21x1.38cm while right ovary is converted into a small homogeously hyperechoic mass measuring 2.7x2.22x2.54cm, could be a dermoid cyst.
August 4, 2007	Transrectal ultrasound: Small anteverted uterus measuring 2.5x1.8x1.1cm with no myometrial lesion. The endometrium is think at 0.22cm and intact. The right ovary measures 2.4x3.3cm and contains an echogenic structure measuring 2.4x1.7cm, could be a dermoid focus with multiple subcapsular follicle <1cm in size, >12 in numbers, suggestive of polycystic ovaries. The left ovary measures 2.3x1.7cm also contains multiple subcapsular follicle <1cm in size, >12 in number, suggestive of polycystic ovaries. No free fluid in the cul-de-sac.
January 18, 2011	Transrectal ultrasound: Small anteverted uterus measuring 2.9x1.2x1.9cm, with thin endometrium 0.11cm, intact cervix 1.5x1.1cnm the right ovary measures 1.9x1.6cm and is transformed into a cystic structure with hyperfractile echoes measuring 2.9x2.5cm. Normal left ovary measuring 2.9x2.1cm.
January 29, 2013	Transvaginal ultrasound: Small 3x1.9x1.5cm anteverted uterus with undefined endometrium, margin is smooth, endometrial echopattern is homogenous without focal lesions demonstrated. Cervix intact. The right ovary measures 4.2x4.2x3.1cm and showed a 3.4x3.6x3.2cm well-defined, thick walled cystic structure with solid nodules within. No vascularity is noted. The left ovary is normal and measures 2.3x2.2x1.9.

markers were requested at this time. She was advised to continue observation however she opted to have the right ovarian cyst removed. The working impression at this time is ovarian newgrowth, right probably benign possible dermoid cyst. On physical examination during admission, patient was four feet eleven inches tall, weighing 40 kilograms, her BMI is 17.8; she is underweight and her weight is 10 kilos less than the ideal body weight for her height. She had stable vitals signs, soft nontender abdomen. Tanner staging for her breasts and pubic hair is both at stage 4; this is appropriate for age. On digital rectal examination, cervix is short, firm closed, uterus seemed small, and there is a palpable adnexal mass on the right measuring 3x3cm, movable, cystic. The working impression at this time is ovarian newgrowth, right probably benign possible dermoid cyst and the plan is to do right oophorocystectomy possible oophorectomy. Intraoperatively, there was minimal peritoneal fluid noted, the left ovary and both fallopian tubes appeared grossly normal. The right ovary was cystically enlarged to

Table 2. Serum chemistries requested post-operatively done on June 11, 2013.

SGPT	17.87 U/L
SGOT	24.73 U/L
Sodium	138 mmol/L
Potassium	3.87 mmol/L
Chloride	98.6 mmol/L

Table 3. Complete Blood Count prior and after the procedure.

Parameter	June 11, 2013	April 18, 2013
Hemoglobin	134 g/dL	133 g/dL
Hematocrit	0.38	0.37
Red blood cells	4.5	4.39
White blood cells	9.36	9.53
Neutrophils	41.9%	46.98%
Lymphocytes	48.9%,	45%
Platelets	345,000	345,000

Table 3. Tumor markers requested post-operatively done on June 11, 2013.

Ca-125	9.75
AFP	0.89

5x4x6cm, capsule was noted to be smooth and pearl white in color. The uterus was small with smooth serosal surface. She tolerated the procedure well and the estimated blood loss was 200 ml. Postoperatively, she remained stable and with good post-op pain control. She was discharged after 2 days. Grossly, the ovarian newgrowth showed gray-brown rubbery tissue measuring 4.7x3x1.7cm, on cut section it showed a unilocular cyst, thick walled, measuring 3cm containing brown pasty material noted to be sebum along with tufts of hair. Histopathologic report showed the following results: right ovarian new growth, poorly differentiated adenocarcinoma in a mature cystic teratoma rule out carcinoid tumor in a mature cystic teratoma. Serum tumor markers were then requested for surveillance, results showed CA-125 9.57 U/mL and AFP 0.89 IU/mL, both within normal limits (Table 3). The plan at this time was to do monitoring via Whole Abdomen Computed-Tomography Scan for surveillance to be done every 6 months. Initial CT Scan done two months after surgery showed essentially normal abdominal organs, renal cortical cysts bilateral, physiologic cyst, left ovary, normal-sized uterus, blocked vertebrae L4-L5 (Table 5). The patient and her parents then decided to seek second opinion at our institution. On consult in our institution,

Table 4. Histopathologic report and slide review.

April 27, 2013	Right ovarian new growth, poory differentiated adenocarcinoma (0.4cm) in a mature cystic teratoma rule out carcinoid tumor in a teratoma Pelvic cyst: Mesothelial cyst
May 24, 2013	Right Ovarian new growth: Carcinoid tumor in a mature cystic teratoma Immunohistochemical stain results: Mammaglobin equivocal, Ber Ep4 positive, Chromogranin equivocal Pelvic cyst: Mesothelial cyst

Table 5. Whole abdominal CT Scan with intravenous, rectal and oral contrast requested for surveillance.

June 21, 2014	The liver is normal. No intraluminal lesions seen within the normal-sized gallbladder. Pancreas, spleen and adrenal glands normal unremarkable. Both kidneys normal in size; renal parenchymal opacifications at both sides are symmetrical and simultaneous, several simple cyst measuring 0.7 to 0.8cm seen in both kidneys. The urinary bladder is partially filled and unremarkable. The stomach and bowels are not unusual. The appendix is not clearly delineated. The mesentery is not thickened. No enlarged pelvic lymph nodes and ascites detected. The uterus is normal in size and anteverted in configuration. No masses seen in both adnexa. The L4 and L5 vertebral bodies are fused. The included sections of the lower lungs reveal no pulmonary nodules nor effusion.

slide-review was done and showed carcinoid tumor arising in a mature cystic teratoma. Immunohistochemical staining showed the following results: synaptophysin positive, Ber Ep4 positive, mammaglobin and Chromogranin stains equivocal (Table 4). Working impression at this time is a carcinoid tumor, right ovary. The patient was advised to undergo transrectal ultrasound and chest x-ray (Tables 7 and 8) for better visualization of the remaining pelvic organs and for metastatis work-up, respectively, however, she was lost to follow-up for 3 years. In the interim, after more than 1 year after surgery, she remained asymptomatic with no gynecologic complaints, except for persistent amenorrhea. On follow-up check-up, three years after right oophorectomy, she underwent transrectal ultrasound which showed a small cervix with thin endometrium (0.22cm), the right ovary was surgically absent and the left ovary measured 2.8x1.8x2cm with a developing follicle (Table 7). In addition, the following

blood tests were requested which showed normal results: Fasting blood sugar 81, Thyroid stimulating hormone 1.69, T3 1.27, T4 8.51, Progesterone 0.34, Serum Prolactin 19.59, Follicle stimulating hormone 6.63, Luteinizing hormone 4.94, Estradiol 218.2 (Table 9). The plan at this time is to continue with surveillance with abdominal CT scan every 6 months. As of this writing, the patient is asymptomatic, desirous of pregnancy and is planning to undergo in-vitro fertilization.

CASE DISCUSSION

One of the most common benign tumors of the ovary is the mature cystic teratoma (MCT), consisting of tissues from the three germ layers: the ectoderm, endoderm and mesoderm. This accounts for 15-20% of benign tumors of the ovary.[1] This type of ovarian newgrowth occurs unilateral and often diagnosed in young females.[2] A malignant tumor that arise from a mature cystic teratoma is called a teratoma with malignant transformation (TMT), and this occurs in 1-3% of all mature teratomas. TMTs are usually unilateral and are mostly seen in perimenopause and postmenopausal women.[3] Malignant transformation is rarely observed and patients are usually asymptomatic; the most common form of malignant transformation in a mature cystic teratoma is squamous cell carcinoma comprising about 80% followed by adenocarcinoma and carcinoid tumor. Growth of carcinoid within a teratoma represents only 5% of all cases with TMT.[4] Based from online literature search, locally, there have been no published articles discussing about carcinoid tumor arising from a mature cystic teratoma since it is an extremely rare case.

Carcinoid tumors are rare, slow-growing, neuroendocrine malignancies with reported incidence of 1-2 cases per 100,000 individuals, accounting for only 0.3 % of all carcinoid tumors and less than 0.1 % of all ovarian cancers.[5] They typically arise form the intestine, or more rarely from the thymus, bronchus, stomach or pancreas.[6] Occasionally they appear with other teratomas and can be often neglected as part of mature teratomas. Often times, carcinoid tumors are not properly diagnosed until the histopathologic results come out. These malignant tumors are occasionally associated with metastases and are a majority of cases were associated with carcinoid syndrome. Carcinoid tumors predispose an affected patient to experience flushing, wheezing and diarrhea due to the secretion of a wide variety of neurohumoral substances and biogenic amines such as serotonin, histamine, tachykinin, bradykinin, kallikrein, corticotropin, substance P, motilin, and prostaglandins. Normally, systemic exposure does not occur with an intestinal carcinoid until it has metastasized, because of efficient hepatic metabolism of the secreted substances. However, primary ovarian carcinoids can cause these symptoms directly, because their venous drainage by-passes the portal system.[8] In our case, the patient, prior to the procedure was noted to be asymptomatic with no

Table 6. Whole abdominal CT Scan with intravenous and oral contrast requested for surveillance.

June 9, 2015	The liver is normal. No intraluminal lesions seen within the normal-sized gallbladder. Pancreas, spleen and adrenal glands normal unremarkable. Both kidneys normal in size; there is a hypodense, non-enhancing foci at the upper and mid cortex of the right kidney and low cortex of both kidneys. The largest of which measures 0.7x0.7cm is noted at the lower pole of the left kidney. The urinary bladder is partially filled and unremarkable. The stomach and bowels are not unusual. The appendix is not clearly delineated. The mesentery is not thickened. No enlarged pelvic lymph nodes and ascites detected. The uterus is not unusual. No masses seen in both adnexa. The L4 and L5 vertebral bodies are fused.

Table 7. Ultrasonographic imaging requested for surveillance.

February 9, 2016	Transrectal ultrasound: Small anteverted uterus measuring 2.1x2.1x1.1cm with no myometrial lesions, cervix intact measuring 2.5x3x2.2cm, surgically absent right ovary, left ovary normal easuring 2.8x1.8x2cm. No free fluid in cul-de-sac.

Table 8. Chest X-ray requested for surveillance.

February 9, 2016	Clear lungs, heart not enlarged, diaphragm and sulci are intact, bony thorax unremarkable.

Table 9. Serum chemistries requested post-operatively done on June 11, 2013.

Fasting blood sugar	81 mg/dL
Thyroid stimulating hormone	1.69 mmol/L
T3	127 mmol/L
T4	8.51 mmol/L
Progesterone	0.34 mmol/L
Serum Prolactin	19.59 mmol/L
Follicle stimulating hormone	6.63 mmol/L
Luteinizing hormone	4.94 mmol/L
Estradiol	218.2 mmol/L

reported episodes of flushing, wheezing and diarrhea.

MCTs may be diagnosed preoperatively through radiologic findings in ultrasound or CT scan indicated by the presence of fat tissue, hairs, bone and cartilage within the tumor. In addition, imaging findings of carcinoid tumor may be of help in diagnosis however there is no sufficient literature describing the detailed imaging findings of primary carcinoid tumors. In our case, ultrasonographic findings of the right ovary revealed round, well delineated, highly echogenic, cystic, thick walled structure with solid nodules within. In a study of Ting, et.al (2014) entitled *Primary carcinoid tumor of the ovary arising in a mature cystic teratoma: a case report*, the detailed findings of carcinoid tumors using various imaging modalities were discussed and compared showing that vague imaging findings may be expected since the appearance of ovarian carcinoid tumor is not characteristic enough. Based on the study, imaging findings may range from hypervascularity with intensified enhancement on CT, with isoattenuating density and solid part. There could also be miniscule streaks within the solid part and calcification with fat contents. The study concluded that in cases of ovarian tumor with solid component and hypervascularity on CT scan, prompt intraoperative investigation such as frozen section must be done. Similarly, in the study of Outwater et. al on ovarian teratomas imaging characteristics, the imaging appearance of ovarian carcinoid tumors is not well described. Because these are solid tumors, they would be expected to be indistinguishable from solid malignancies, although necrosis is less common in the former. Mucinous carcinoid tumors have higher signal intensity on T2-weighted MR images than do most solid tumors because they contain high-signal-intensity mucin.[9] In this case, ultrasonography was done yearly and nonspecific imaging findings were always noted.

The treatment for ovarian carcinoid tumors is surgical excision and surgical staging is not required.[3] Moreover, the optimal therapeutic management in young patients remains to be a challenge because this condition is commonly observed in postmenopausal women, in whom a more extensive surgical treatment such as hysterectomy and bilateral salpingoophorectomy is a considerable option. However, in a study by Stamatios et. al. (2013) entitled *Mature Ovarian Teratoma with Carcinoid Tumor in a 28-Year-Old Patient*, fertility sparing surgery among women wanting to preserve their genital tract is said to be a reasonable approach. This management is comparable in our case since the patient is a single nulligravid desirous of pregnancy in the future. No concensus has been made yet because of the small number of reported cases, however, there are case reports in young nulliparous and childbearing women with this condition wherein fertility preservation through conservative surgical approach is considered to be more reasonable than prevention of malignancy progression. Other determinants of treatment in these rare cases would include clinical and histopathologic factors. The following are considered unfavorable: cyst wall invasion, intraoperative rupture of the ovarian mass, tumor dissemination, and adhesions.[2] In carcinoid syndrome as previously discussed in this case report, the disease may be an aggressive one due to the large amount of secretion of vasoactive factors from the neuroendocrine cells. This occurs only in 1/3 of the patients with primary ovarian carcinoid tumor.[3] Cardiac involvement is the major cause of death in this condition.[5] In our patient initial working impression is dermoid cyst, right and was managed conservatively by doing oophorectomy. Thereafter, a diagnosis of carcinoid was only made when the histopathologic results came in. Prior to the contemplated procedure, she was clinically asymptomatic. Also, intraoperative findings did not show cyst wall invasion, the right ovary was excised completely with no noted rupture, there were no adhesions and tumor dissemination noted making her a good candidate for fertility sparing surgery and post-operative surveillance may be done.

According to Davis et. al (1996), if the disease is limited to one ovary, the prognosis is excellent in primary ovarian carcinoid tumors and ten year survival rates are approximately 100%. However, if the disease is in advanced stage, five year survival rates are approximately 33%. For our patient, the diseased ovary is unilateral and prognosis is expected to be excellent.

SUMMARY

In conclusion, a carcinoid tumor arising in an MCT is very rare in young nulliparous childbearing patients, especially in those less than 30 years of age, as presented in our case. Furthermore, preoperative identification of TMT is not easy because of its nonspecific radiologic characteristics. Its definitive management remains a challenge but surgical excision either through laparoscopy or laparotomy may be regarded as the first approach. Also since the lesion is unilateral, prognosis is good and is approximately 100% for the next ten years. ■

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