

Small cell carcinoma arising from a mature cystic teratoma of the ovary: A case report*

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ABSTRACT

Malignant transformation of a mature cystic teratoma (MCT) or dermoid cyst in the ovary occurs only 1 to 2% of cases of MCTs. Only 6 cases of small cell carcinoma arising from a MCT have been reported.¹⁻⁶

The patient is a 36 year-old G2P2(2002) who presented with an enlarging abdominal mass and right lower quadrant pain. She was diagnosed with a dermoid cyst four years prior to admission, but no surgical intervention was done. On admission, ultrasound revealed multiple pelvo-abdominal masses consistent with dermoid cysts. The patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy, peritoneal fluid cytology, bilateral pelvic lymph node dissection, excision of enlarged paraaortic lymph nodes and infracolic omentectomy. Histopathology revealed a small cell carcinoma arising from a MCT in the left ovary consistent with a Stage IIIA1ii tumor. She underwent chemotherapy with 4 cycles of Etoposide-Cisplatin and has no evidence of disease 3 months after treatment.

Keywords: dermoid cyst, mature cystic teratoma, ovary, small cell carcinoma

INTRODUCTION

Ovarian mature cystic teratoma (MCT), accounting for 27-44% of all ovarian tumors, is a cystic or solid tumor that is composed of mature, adult type tissues. Malignant transformation occurs in 1 to 2% of MCTs. Squamous cell carcinomas account for more than 80% to 90% of malignant transformations. This is followed less frequently by adenocarcinomas in 6.8% and other even rarer malignancies such as choriocarcinomas, leiomyosarcomas, and malignant melanomas.^{2,3} Only 6 cases of small cell carcinoma arising from a MCT have been reported in literature. So far, this is the first case that has been reported in the Philippines. A 15-year review of histopathologic reports revealed that this also the first case of small cell carcinoma arising from a MCT diagnosed in our institution.

CASE REPORT

This is a case of a 36 year-old, G2P2 (2-0-0-2), who presented with an enlarging mass in the abdomen with associated intermittent right lower quadrant pain.

Four years PTA, during an abdominal ultrasound for liver monitoring for Hepatitis B, an incidental finding

of a dermoid cyst was noted. The patient was advised to undergo surgery but she refused due to financial constraints.

One year 7 months PTA, a pelvic ultrasound done during the 6th week of her 2nd pregnancy revealed that both ovaries were enlarged with features suggestive of dermoid cysts. The patient was again advised to undergo surgery but still she refused due to financial constraints. 11 months PTA, she gave birth to a term baby by normal spontaneous delivery with no complications.

Four months PTA, the patient palpated an enlarging abdominal mass at the right upper quadrant approximately 5 cms, non tender, movable, with no other associated signs and symptoms. An ultrasound revealed a right ovarian cyst, 8.1 x 7.9 x 6.6 cm, consistent with a dermoid cyst. A complex abdominal mass measuring 10.7 x 10.3 x 9.5cms was seen, anterior to the right ovarian cyst, suggestive of a gastrointestinal versus an ovarian pathology. She was again advised surgery but she refused.

One month PTA, she had abdominal pain 5/10 in severity, pricking, non-radiating, aggravated by moving and relieved by rest, and the abdominal mass increased in size to 8 cm. An ultrasound revealed the following: (a) large pelvo- abdominal mass superior to the uterus measuring 19.24 x 19 x 11cm and a larger mass more lateral measuring 13.3 x 13.6 x 13.8 cm consistent with dermoid cysta (b) another cystic structure medial to the mass measuring 5.79 x 5.06 x 4.56cm probably mixed type dermoid. Tumor markers were elevated CA 19-9 = 114.20 u/ml (Normal Value: 0 – 39 U/ml) and CA 125 = 282.10 u/ml (Normal Value: 0 – 35 U/ml).

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One week PTA, the right lower quadrant pain progressed to 7/10, with radiation to the lumbosacral area and with associated increase in abdominal mass size. Patient eventually consented to surgery and was admitted.

The patient's menstrual, gynecologic and past medical history are unremarkable. She is a G2P2 (2-0-0-2), both delivered by normal spontaneous delivery. There is a known family history of hypertension on the paternal side. Her brother was recently diagnosed with a malignant brain tumor.

Pertinent physical examination findings revealed a globular abdomen with a firm, non-tender, movable pelvo-abdominal mass more on the left, approximately 25 x 21 cm. Speculum exam showed a smooth midline cervix with no lesions. On internal examination, the cervix was firm, midline, closed, the uterus was small, with a palpable abdominopelvic mass more on the left.

On admission, she was diagnosed as a case of Ovarian new growth, bilateral, probably dermoid cysts R/O malignancy. She underwent surgery and intraoperatively, ascetic fluid approximately 300cc was noted. The left ovary was transformed into a large 21 x 14 x 12 cm solid and cystic mass, with smooth external capsule. Cut section revealed multiple lobules containing serosanguinous fluid, sebum, hair strands, cartilage, with noted whitish solid to necrotic areas. The left fallopian tube was dilated and stretched out over the left ovary measuring 8 x 1 x 1 cm. The right ovary was cystically enlarged with smooth capsule measuring 6 x 6 cm and on cut section revealed smooth inner capsule, sebum and hair strands. The uterus, cervix and the right fallopian tube were grossly normal. An enlarged paraaortic lymph node was noted 5cm above the bifurcation of the aorta measuring 3.5 x 2.5 x 1.5 cm. The patient underwent total hysterectomy with bilateral salpingo-oophorectomy, peritoneal fluid cytology, bilateral pelvic lymph node dissection, excision of the enlarged paraaortic node and infracolic omentectomy.

The histopathologic report revealed: left ovary positive for small cell carcinoma arising in a MCT, infiltrating to involve the left fallopian tube, with lymphovascular invasion. One out of 23 pelvic lymph nodes (size 8 mm) and 2 out of 2 paraaortic lymph nodes (size 20mm) were positive for tumor. The right ovary showed findings consistent with a MCT. The histopathologic findings are consistent with a small cell carcinoma arising from a MCT of the ovary, Stage IIIA1ii (2014 FIGO Staging) or Stage IIIC (1988 FIGO staging). The patient had an unremarkable post-operative course.

Microscopic features of the left ovary revealed the cystic portion is lined by mature stratified squamous epithelium. The wall of the cyst contained mature elements consisting of cartilage, sebaceous glands and hair follicles. The solid portion showed a monotonous population of

small tumor cells with oval to round hyperchromatic nuclei (many cells demonstrate a salt-and-pepper nuclear appearance) and islands separated by thin fibrous strands. Mitotic activity was brisk and areas of tumor necrosis are also noted. The findings were consistent with a small cell carcinoma arising from a MCT. Microscopic features of the right ovary revealed a cyst lined by mature stratified squamous epithelium with mature elements consisting of sebaceous glands, sweat glands and smooth muscle consistent with a MCT.

The specimens were submitted for immunohistochemical staining revealing a positive neuron specific enolase (NSE) and synaptophysin, and a weak positive chromogranin A indicating a neuroendocrine carcinoma; negative leukocyte common antigen (LCA), a marker for lymphoma; and negative CAM 5.2, a variable marker for small cell carcinoma.

The patient underwent 4 cycles of chemotherapy with Etoposide-Cisplatin and has no evidence of disease for 15 months after treatment.

CASE DISCUSSION

MCTs account for 10-20% of all ovarian tumors and is commonly seen in the second and third decades of life. About 1- 2% of MCTs undergo malignant transformation. Risk factors for malignant transformation of MCT are elevated CA-125 levels, older age (mean 43 years (range 27-67 years) compared to a mean of 36.5 years in patients with benign teratomas), large tumor masses(>11.4 cm), and postmenopausal status.⁷ The majority of malignant transformations are squamous cell carcinomas and transformation into small cell carcinoma, as presented in this case, is very rare.

So far, only 6 cases of small cell carcinoma arising in a MCT of the ovary have been reported. The youngest reported case was 22 years old while the oldest was 68 years old, with a mean age of 42 years old. All the cases presented with a palpable abdominal mass and/or abdominal pain. One case, however, presented with abdominal distention with supraclavicular lymph node enlargement at the time of diagnosis.⁴ The size of the ovarian masses ranged from 12 to 28 cm in size. Two cases were diagnosed at Stage IA, while 4 cases were diagnosed at stages III and IV, thus, majority are diagnosed in the late stages. Our patient was 36 years old, presented with abdominal pain and an abdominal mass measuring 21 cm, and was Stage IIIA1ii at diagnosis.

The course of the disease is unpredictable. One case presented with only 1 month history of abdominal pain and was Stage IIIC upon diagnosis.¹ Another case had an 18 month history of abdominal distention and was already Stage IV at the time of diagnosis.⁴ In contrast, one

case was diagnosed to have a dermoid cyst for 24 years before surgery but was only diagnosed to be Stage IA.² Our patient presented with a 4 year history of dermoid cyst and was Stage IIIA1ii. Thus, the disease could behave aggressively or follow an indolent course. This suggests that the behavior of the disease may follow an indolent course during its stages as a dermoid cyst and become aggressive at the onset of malignant transformation from a MCT.

In contrast to small cell carcinoma arising from a MCT, cases of primary small cell carcinoma of the ovary have been described in literature. Primary small cell carcinomas of the ovaries occur more commonly than those arising from an MCT with more than 300 cases reported so far. These tumors have been subclassified into pulmonary and hypercalcemic subtypes. These two subtypes have characteristic pathologic, ultrastructural, flow cytometric and immunohistochemical features. Attempts at distinguishing between ovarian small-cell carcinoma of the hypercalcemic type and pulmonary type utilizes clinical information including age, serum calcium levels, and whether the tumor is unilateral or bilateral.¹

The hypercalcemic type occurs in young women with a mean age of diagnosis of 23 years (SD 9.8) while the pulmonary type has a mean age of diagnosis of 48 years (SD 17.1).⁸ In two-thirds of cases, the hypercalcemic type of tumor is associated with hypercalcemia with only 2.5% showing symptoms of hypercalcemia such as polyuria and polydipsia. The hypercalcemic type of small cell carcinoma has been unilateral almost always without exception, while the pulmonary type are bilateral in 55% of cases.⁴ Elevation of CA-125 is seen in 80% in both types, while CA 19-9 was elevated in 25% of hypercalcemic types and 37.5% of pulmonary types.⁸

Microscopically, the hypercalcemic type is composed of diffuse sheets of small, closely packed round cells with scant cytoplasm, small hyperchromatic nuclei with irregular chromatin clumps, and small but identifiable nuclei. The pulmonary type show sheets and nests of small medium size round/spindle cells with hyperchromatic nuclei, fine regular chromatin (not clumped), inconspicuous nuclei and minimal cytoplasm.¹⁰ It was difficult to determine whether the specimen submitted for this case was of the hypercalcemic or pulmonary type based on the microscopic picture alone because of the similarity in microscopic appearance between the two entities.

On immunostaining, the pulmonary type has been positive for neuron specific enolase (NSE) in 85.7% of cases and positivity for NSE has not been reported in hypercalcemic cases. The hypercalcemic types are rarely positive for chromogranin A but are positive for vimentin in more than half of cases. On the other hand, pulmonary types are positive for chromogranin

A in about half of cases and are negative for vimentin.⁹ For this case, immunostaining was positive for neuron specific enolase (NSE) and synaptophysin, and weak positive chromogranin A.

All cases of small cell carcinoma arising from an MCT reported are pulmonary types except for one case which is mixed hypercalcemic and pulmonary type. In this case, serum calcium levels were not taken preoperatively because the diagnosis was unexpected. Postoperative serum calcium levels were normal but this decline to normal immediately after surgical resection of the tumor. Microscopically it was difficult to distinguish whether the tumor was of the hypercalcemic or pulmonary type. The age of the patient, lack of symptoms of hypercalcemia, bilaterally of the tumor, and positive immunostaining for NSE and chromogranin A highly favors a pulmonary type of tumor. However, vimentin staining should be done to confirm the diagnosis.

The importance of distinguishing between a hypercalcemic type and a pulmonary type of small cell carcinoma has a bearing on the chemotherapeutic regimens that can be used in the management of these patients. Both entities have very poor prognosis and are usually treated with surgery followed by chemotherapy. Hypercalcemic types have been found to have improved survival after chemotherapy with etoposide, cisplatin, carboplatin and vinca alkaloids. While the treatment of the pulmonary type is usually patterned from the treatment of primary small cell carcinoma of the lung. Chemotherapeutic agents like etoposide, platinum agents, and anthracyclines such as doxorubicin has been found to improve survival.

Because of the rarity of small cell carcinoma arising in a MCT the treatment of these types of tumors is not well defined and has been patterned to primary small cell carcinoma of the ovary. In all the cases, all patients underwent surgery followed by chemotherapy.

Chemotherapy has been given to all reported cases of small cell carcinoma arising in a MCT and was not omitted even in Stage IA cases. Chemotherapeutic agents used were Etoposide-Carboplatin, Bleomycin-Etoposide-Cisplatin, and Cisplatin-Doxorubicin-Cyclophosphamide. No case was given postoperative radiotherapy. The patient in this case underwent 4 cycles of Etoposide-Cisplatin and has no evidence of disease for 15 months.

The prognosis of small cell carcinoma arising from a MCT is still unclear, although the prognosis is definitely worse than squamous cell carcinoma arising from a MCT. Cases of small cell carcinoma arising from a MCT reported in literature have survived for 10-84 months after treatment. There are no available five-year survival rates for small cell carcinoma arising from a MCT. The only available data pertains to the five-year survival rates of patients with

malignant transformation of MCT, in general, which are 95% (Stage I), 80% (Stage II) and 0% (Stage III and IV). The single most important prognosticator in patient survival in malignant transformation of a MCT is confinement of the neoplasm within the ovarian tunica.³

SUMMARY

A rare case of a 36-year-old G2P2 (2-0-0-2) diagnosed with small cell carcinoma arising from a MCT of the ovary was presented. She underwent total abdominal

hysterectomy with bilateral salpingo-oophorectomy, peritoneal fluid cytology, bilateral pelvic lymph node dissection, excision of enlarged paraaortic nodes and infracolic omentectomy followed by 4 cycles of Etoposide-Cisplatin. The patient has no evidence of disease 15 months after treatment.

Due to the rarity of this condition, there is still no established treatment regimen for this disease and prognosis remains uncertain. It is therefore recommended to report cases with this condition so as to be able to establish the appropriate treatment regimen.

Table 1. Ultrasounds

Date	Comments	Impression
June 14, 2015	<p>Within the uterus is a well decidualized gestational sac with a yolk sac and an embryo with cardiac activity of 98 bpm noted at the time of scan.</p> <p>The right ovary is cystically enlarged to 6.8x6.8x6.2cm unilocular, thick walled with smooth internal borders, containing hyperechoic lines and dots suggestive of dermoid cyst. Within the left ovary are two cystic structures (1) unilocular, thick-walled with smooth internal borders, containing low level echoes and hyperechoic region, measuring 4.1cm x 3.8 x 4.4cms and (2) unilocular, thick-walled with crenated internal borders suggestive of corpus luteum</p>	<p>Pregnancy uterine 6 weeks and 1 day age of gestation by crown-lump length, live, singleton. Subchorionic hemorrhage, inferior pole, as described ovarion cyst, consider dermoid, bilateral. Corpus luteum in the left.</p> <p>EDC by ultrasound: February 16, 2016</p>
July 8, 2015	<p>Within the uterus is a well decidualized gestational sac with a yolk sac and an embryo with cardiac activity noted at the time of scan.</p> <p>Previously seen ovarian cyst at right and left adnexa are still evident measuring 4.6 x 4.6 cms and 4.1 x 4.1 cms, respectively.</p>	<p>Pregnancy uterine 7 weeks and 6 days age of gestation by crown-lump length, live, singleton. Previously seen ovarian cysts are still evident in this scan.</p> <p>EDC by ultrasound: February 18, 2016</p>
September 15, 2016	<p>Right ovary: posterolateral to the uterus is a cystic structure, unilocular, thick-walled with smooth internal borders, measuring 8.1 x 7.9 x 6.6 cms and demonstrating hyperechoic lines and dots, sonologic features compatible with dermoid cyst.</p> <p>Left ovary: not visualized</p> <p>A complex mass measuring 10.7 x 10.3 x 9.5 cms is noted at right abdominal area, anterior to the right ovarian cyst, suggestive of GI pathology, but cannot totally rule out ovarian pathology.</p> <p>Fluid in the cul-de-sac present</p>	<p>Normal sized anteverted uterus with thin endometrium. Ovarian cyst, right, consider dermoid cyst. Non-visualized left ovary. Complex abdominal mass, to consider gastrointestinal pathology but cannot totally rule out ovarian pathology.</p>
December 15, 2016	<p>There is a large intra-peritoneal complex mass on the right measuring 18.0 x 14.0 cm.</p> <p>Moderate ascites noted</p> <p>Cul de sac is clear.</p>	<p>Large right complex intraperitoneal mass associated with moderate ascites. A malignant ovarian teratoma is a possibility. Normal liver, CBD, gallbladder, pancreas, kidneys, uterus and urinary bladder</p>

Table 2. Hispathology

Date and exam		
January 11, 2017 Histopathology (Surgical pathology cancer case summary)	Histopathologic Diagnosis	Total hysterectomy specimen with bilateral salpingo-oophorectomy Left ovary: small cell carcinoma arising in a mature cystic teratoma, infiltrating to involve the left fallopian tube Tumor size: 12.5 x 7.5 cm Lymph-vascular invasion: present Lymph nodes: two out of two (2/2): Positive for tumor (para-aortic) One out of ten (1/10): Positive for tumor (left pelvic) Pathologic staging: pT2aN1b
	Specimen	Uterus with cervix, bilateral fallopian tubes, bilateral ovaries, omentum
	Procedure	Total hysterectomy with bilateral salpingo-oophorectomy, bilateral lymph node biopsy, peritoneal fluid cytology
	Lymph Node Sampling	Performed: Para-aortic and bilateral pelvic nodes
	Specimen integrity	Right ovary: Capsule is intact Right ovary: Capsule is intact
	Primary Tumor Site	Left ovary
	Ovarian Surface involvement	Present
	Tumor size	Left ovary: 12.5 x 7 x 5 cm
	Histologic type	Small cell carcinoma arising in a mature cystic teratoma
January 11, 2017 Cytopathology	Physical description	Peritoneal fluid submitted Volume: 62.5 ml Color: yellow Appearance: Turbid
	Microscopic description	Smears: Moderate proteinaceous material Some erythrocytes Many lymphocytes Occasional neutrophils Some reactive mesothelial cells No malignant cells Cell blocks: Moderate proteinaceous material Few erythrocytes Some lymphocytes Some neutrophils Some macrophages No malignant cells
	Cytopathologic Diagnosis	Peritoneal fluid cytology (smears and cell blocks) -Moderate acute and chronic inflammation -Negative for malignant cells

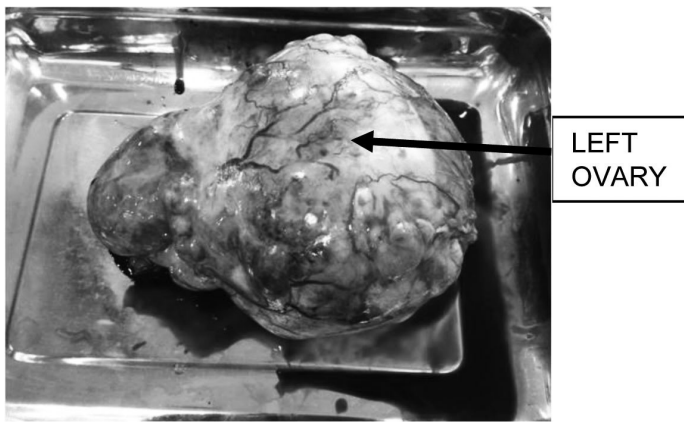


Figure 1. The left ovary is enlarged with nodular external surface, with stretched out blood vessels. No area of defect seen grossly.



Figure 2. The uterus is previously sectioned anteriorly from the fundus to cervix and grossly unremarkable. The right ovary is transformed into a cyst. The left ovary is transformed into a complex cyst with intact capsule previously sectioned, showing hair, sebum and fat. Soft, solid gray white areas are noted with cystic degeneration necrosis and hemorrhage.

It is unknown if and when a MCT will undergo malignant transformation. Preoperatively, a high index of suspicion for possible malignant transformation should be considered in cases with elevated CA-125 levels, older age (> 2 years old), large tumor masses(>11.4 cm), and postmenopausal status. Although majority of MCTs are benign, the possibility of malignant transformation should always be kept in mind to ensure careful gross and histologic examination of the entire neoplasm, especially the solid areas, so that a concomitant malignancy will not be overlooked. Patients should also be convinced more

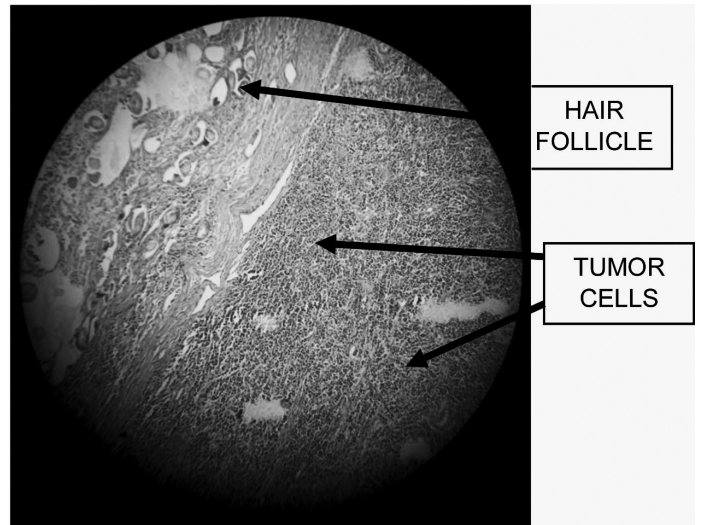


Figure 3. Photomicrograph at 100x shows hair follicles infiltrated by tumor cells from the right.

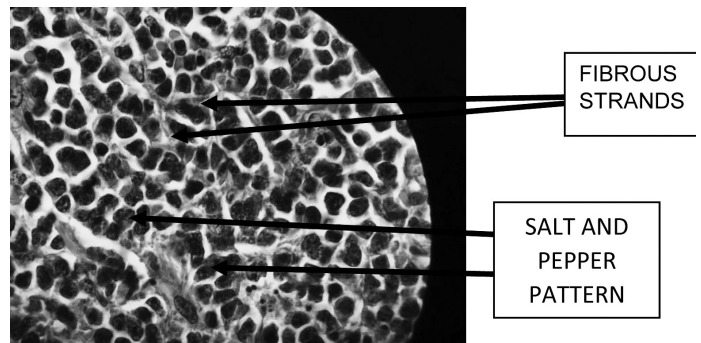


Figure 4. Photomicrographs at oil immersion shows tumor cells that are relatively small with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin (salt and pepper pattern) with inconspicuous nucleoli.

aggressively regarding early surgical treatment of MCTs to avoid encountering the ominous and unpredictable malignant transformation.

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