Secondary malignancies in ovarian dermoid cyst

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ABSTRACT

الأهداف: استعراض خبراتنا المحلية في الأورام الخبيثة الناجمة عن التيراتوما الناضجة وهي من الأمراض النادرة في المبيض. ووصف طريقة المعالجة التي تتعلق بهذا المرض الغير الشائع.

الطريقة: تمت مراجعة بيانات لفريق سيدني للأورام – قسم أمراض النساء – في مستشفى الأمير الفريد الملكي وليفربول، خلال الفترة مابين 1987م وحتى 2007م. تمت دراسة وتحليل بيانات المرضى بأثر رجعي.

النتائج: تم تحديد 11 حالة من كيس درموید في المبيض مع تكون ورم ثانوي خبيث. ستة من أصل إحدى عشر (54.5%) من الحالات كانت ورم كارسينويد، 4/11 (36%) سرطان الخلايا القشرية، حالة واحدة (9%) من سرطان النسيج المتنقل. متوسط العمر للحالات كان 47 عام (المدى من 28–74). سجلت حالات المرحلة الأولى والثانية من المرض في 8/11 (73%)، بينما حالات المرحلة الثالثة والرابعة .(27%) 3/11 المعالجة المبدئية تراوحت ما بين إزالة الكيس من المبيض إلى استئصال الرحم، المبيضين وقناتي فالوب أو إزالة ما يمكن إزالته من الورم. جميع المريضات في المرحلة الأولى من المرض بقين على قيد الحياة لأكثر من خمسة أعوام (100%). الناجيات في المرحلة الثالثة والرابعة من المرض بقين على قيد الحياة لمدة تتراوح ما بين شهرين ونصف وحتى 18 شهراً، بمتوسط 8 أشهر.

خاتمة: يعتبر ورم كارسينويد هو الأكثر شيوعاً، وفرص النجاة منه تعتمد بشكل أساسي على مرحله الورم والجراحة المثلى لإزالته، ومع ذلك يجب إجراء دراسات عديدة لمعرفة ما إذا كان هنالك عوامل أخرا تؤثر على معدل النجاة.

Objectives: To review our local experience with mature cystic ovarian teratoma, and describe our treatment modality regarding this uncommon condition.

Methods: The databases of the Sydney Gynecologic Oncology Group at Royal Prince Alfred and Liverpool Hospital, Sydney, Australia, were reviewed from 1987 to 2007. A retrospective chart review, and analysis of patient's data were conducted.

Results: Eleven cases of ovarian dermoid cyst with secondary malignancy were identified. Six out of eleven (54.5%) of the cases were carcinoid tumor, 4/11 (36%) squamous cell cancer, and one case (9%) transitional cell carcinoma. The median age of cases was 47 years (range of 28-74). Stage I-II was recorded in 8/11 (73%) of the cases, while stage III-IV was found in 3/11 (27%). The initial treatment ranged from unilateral cystectomy to hysterectomy, and bilateral salpingo-oophrectomy, and debulking surgery. All patients with stage I disease showed more than 5 years survival (100%). The survival for late staged disease (III-IV) ranged from 2.5 months to 18 months with an average of 8 months.

Conclusions: Carcinoid tumor is the most common malignancy noticed. Survival is related mainly to tumor stage, and optimal debulking procedure. However, further studies are needed to study the effect of other factors on survival.

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Benign ovarian dermoid cysts (mature cystic teratomas) account for 20% of all ovarian tumors, and more than 95% of all ovarian teratomas, and is almost invariably benign.[1] They are bilateral in 12% of cases, and are the most common ovarian tumor in the second, and third decades of life. They contain mature tissue of all cell layers, ectodermal, mesodermal, and endodermal origin.[2] The characteristic macroscopic appearance of benign cystic teratomas is a multicystic mass that contains hair, teeth, or skin mixed into sebaceous, thick, sticky, and often foul-smelling material. Symptoms depend upon the size of the mass. Torsion is not rare. Rupture of dermoid cysts with spillage of sebaceous material into the abdominal cavity can occur, but it is uncommon. These tumors have a characteristic ultrasound appearance, which allows reasonably accurate noninvasive diagnosis in many cases.[3] A solid prominence (for example, Rokitansky's protuberance) is at the junction between the teratoma, and normal ovarian tissue.[4] The greatest cellular variety is found in this area, which should therefore be examined carefully by the pathologist to exclude malignant components. Cystectomy is suggested in order to make a definitive diagnosis, preserve ovarian tissue, and avoid potential complications or development of malignant components. Approximately 1% of mature cystic teratomas have malignant somatic-type tissue elements. Although any of the components of a mature cystic teratoma may undergo malignant degeneration, squamous cell carcinoma is the most common secondary tumor.[5] Other malignant tissues include basal cell carcinoma, melanoma, adenocarcinoma, sarcoma, neuroectodermal tumor, and thyroid cancer. When malignant transformation has occurred within a teratoma, treatment must be tailored to the transformed histology. Ovarian carcinoid tumors are rare.[6] Such tumors are malignant in fewer than 5% of cases. Risk factors for malignancy in a mature cystic teratoma include age over 45 years, tumor diameter greater than 10 cm, rapid growth, and findings on imaging (for example, low resistance intra-tumor flow on Doppler).[5] The purpose of this study was to describe our local experience regarding this uncommon condition.

Methods. The database of the Sydney Gynecological Oncology Group of Royal Prince Alfred and Liverpool Hospital, Sydney, Australia, was reviewed from 1987 to 2007. Patient records were reviewed, and a systematic

Table 1 - Patient characteristics of 11 cases.

Patients numbers	Age (Years)	Presenting symptoms	Menopause	Bilateral	Size (cm)	Primary surgery	Final histopathology	Stage	Further treatment	Overall survival
1	73	Pain	Post	Unilateral	7	BSO	SCC	4	Surg debulking, chemotherapy	18 months
2	28	Mass	Pre	Unilateral	13	LSO	Trabecular carcinoid	1	None	>5 years
3	37	Mass	Pre	Unilateral	5	Rt ovarian cystectomy	Trabecular carcinoid	1	RSO	>5 years
4	48	Bleeding, mass	Pre	Unilateral	9	TAH BSO omentectomy	Trabecular carcinoid	1	None	>5 years
5	61	Pain	Post	Unilateral	13	TAH BSO	SCC	1	None	>5 years
6	39	Pain	Pre	Unilateral	12	LSO Omental biopsy, left pelvic lymph node	Carcinoid, mets appendex, lymphnodes	3	Chemotherapy	6 months
7	51	Pain, bleeding	Pre	Unilateral	7	TAH BSO lymph nodes	SCC	1	None	>5 years
8	45	Pain, bleeding	Pre	Unilateral	8	LSO	TCC	1	Surg staging	>5 years
9	32	Pain	Pre	Unilateral	10	Rt ovarian cystectomy	Trabecular carcinoid	1	RSO	>5 years
10	35	Accidental pregnancy 11 weeks	Pre	Unilateral	8	C/S RSO	Carcinoid mixed	1	None	>5 years
11	74	Mass	Post	Unilateral	15	TAH BSO debulking	SCC	3	HDU admission, palliative care	2.5 months

SCC - squamous cell carcinoma, TCC - transitional cell carcinoma, Rt - right, LSO - left salpingo-oophorectomy, BSO - bilateral salpingo-oophorectomy, HDU - high dependency unit, RSO - right salpingo-oophorectomy, TAH - total abdominal hysterectomy, C/S - cesarean section

Table 2 - Tumor characteristics in 11 patients with mature cystic ovarian teratoma.

Tumor characteristic	n	(%)
Type cancer		
Carcinoid	6	(54.5)
Squamous cell	4	(36.4)
Transitional cell	1	(9.1)
Size ovarian mass		
<5 cm	0	(0)
≥5-10 cm	6	(54.5)
≥10 cm	5	(45.5)
Bilaterally		
Unilateral	11	(100)
Bilateral	0	(0)

Table 3 - Treatment options provided in 11 patients with mature cystic ovarian teratoma.

Treatment	n	(%)
Cystectomy	2	(18.2)
Oophorectomy	5	(45.5)
TAHBSO staging ± nodes	3	(27.3)
Debulking	1	(9.1)
Definite treatment		
Nill	5	(45.5)
Oophorectomy	2	(18.1)
TAH staging	1	(9.1)
Chemotherapy	2	(18.1)
Palliative	1	(9.1)

TAH - total abdominal hysterectomy, BSO - bilateral salpingo-oophorectomy

search was made through the pathology records for patients reported as having secondary malignant transformation within a dermoid cyst. Data abstracted included patient characteristics, tumor characteristics, modality of treatment offered, and outcome data of recurrence and survival. Patient's characteristics were age, menopausal state, and the main presenting symptoms at the time of diagnosis. Tumor characteristics included tumor size, extent of tumor spread, and the final histopathology detected. Patients were included for analysis if complete data was available for analysis and at least the Sydney Gynecologic Oncology Group undertook a component of their treatment. A retrospective chart review, and analyses of patient's data were conducted. Approval from the local ethical board was not required as this research was a clinical audit supported by the head of department of Sydney Gynecologic Oncology Group.

Table 4 - Survival in relation to clinical stage (N=11).

Stage	n	(%)	Survival	
			≤5 years	>5 years
I	8	(72.7)	0/8	8/8
II	0	(0)	0/0	0/0
III	2	(18.2)	2/2	0/2
IV	1	(9.1)	1/1	0/1

Results. As shown in **Table 1**, only 11 cases of secondary malignant changes within a dermoid cyst were identified in the last 20 years; with an average one case every other year. The median age of cases reported was 47 years with a range of 28 - 74 years. Of the 11 cases, 6 patients (54.5%) were 40 years of age or older. However, only 3 cases (27%) were postmenopausal. More than half of the cases 6/11 (54.5%) presented with abdominal pain, 4/11 (36%) with mass, 3/11 (27%) abnormal vaginal bleeding, and one case discovered incidentally during routine antenatal ultrasound at 11 weeks pregnancy and underwent surgery with unilateral salpingo-oophorectomy at second trimester with final report showed mixed type carcinoid cancer. **Table 2** showed the final histopathology of the dermoid cysts. For non-carcinoid type of cancer, squamous cell cancer formed 4/5 (80%) of total cases of malignancy within dermoid cyst. The median size of ovarian mass was 9.6 cm (average 5-15 cm). **Table 3** shows the treatment modalities provided for our patients, it shows also that only one third of cases received proper staging, and management initially. **Table 4** shows the survival rate ranged from 2.5 months to 18 months with an average of 8 months. Regardless of the type of neoplasia and tumor size, the extent of the disease and patients age were the major features dictating the survival in patients with secondary malignancies of mature cystic teratoma of the ovary.

Discussion. Malignant transformation within a mature cystic teratoma occurs in less than 2% of cases[1,7] with the most common malignancy being a squamous cell carcinoma.[5,8] Other reported malignancies include adenocarcinoma, adenosquamous carcinoma, sarcomas, carcinoid, melanomas, meningioma, malignant germ cell neoplasms, and others have also been reported.[9-13] Our study showed that carcinoid tumor was found in more than half of cases 56%, while squamous cell carcinoma was found in 36% of cases. Primary ovarian carcinoid tumors are usually unilateral, localized to the ovary, and composed of gastrointestinal or respiratory epithelium within a mature cystic teratoma. Carcinoid tumors metastatic to the ovary are even rarer; they tend to be bilateral, and arise from

primary ileal carcinoid tumors.[14] Since mature cystic teratoma is a common ovarian neoplasm, and is still increasingly diagnosed as an Incidental finding in spite of the availability of advanced imaging techniques, there has been growing emphasis on preoperative risk assessment of these tumors in order to optimize the surgical management. Risk factors for suspicion of malignancy within a dermoid cyst include patient age, and tumor size, and to a lesser extent imaging characteristics, and serum tumor markers. Secondary malignant changes within mature cystic teratoma have been observed in elderly patients, although it has been reported in patients as young as 19 years old.[15] The median age at diagnosis in our study was 47 years, which is consistent with the previously reported range of 45-60.[16]

Stamp et al[17] suggested that a possibility of malignancy should always be considered in patients who present with an ovarian dermoid cyst at an older than average age; therefore, it is important to maintain a higher suspicion of malignancy in mature cystic teratoma occurring in patients over the age of 45 years.[18] Although ovarian mature cystic teratoma presents in a wide range of sizes; the larger the tumor size is, the higher risk of malignant changes to be present. In our study, the average tumor diameter was 9.6 cm, and 45% of our cases presented with tumor size more than 10 cm. Several studies reported that a tumor diameter of >9.9 cm was 86% sensitive for malignancy.[18,19] In general, a tumor size more than 10 cm, or a rapidly growing tumor should raise the index of suspicion for malignancy. Due to its rarity, the ideal management of malignant transformation arising from a mature cystic teratoma of the ovary is not established in the literature. When preoperative suspicion of malignancy is present, laparotomy and frozen-section is recommended to prevent inadvertent upstaging by intraperitoneal rupture during laparoscopic removal.[20,21] Complete tumor excision, and proper staging are crucial to prognosis, and treatment planning, and should be performed at the initial surgery or as soon as possible after pathologic diagnosis.[21] In our study, only 4/11 (36%) of patients underwent proper initial surgical staging, this is related to some limitation factors for extensive surgery such as, patient's age, and desire to have children. Kurtz et al[22] suggested that regimens designed for the squamous cell neoplasias (cervical or head, and neck cancer) are likely to be more adapted for treating squamous cell cancers arising from ovarian mature cystic teratomas. In our study, only 3 cases of secondary squamous cell carcinoma arising from dermoid cyst were identified; all of them received proper surgical staging and debulking procedures. However, only one of them received adjuvant chemotherapy, and one received palliative care after prolonged stay in the intensive care unit and died 10 weeks after diagnosis. There is no consensus on the role of chemotherapy, and type, and regimes of chemotherapy that are successful in these cases. Kurtz et al[22] reported a case of a stage IIIb, squamous cell carcinoma arising from a left ovarian teratoma extending to the sigmoid colon in a 34-year-old women. The patient underwent debulking surgery, and both adjuvant chemotherapy, and radiotherapy was undertaken. Four additional chemotherapy courses were administered. No signs of recurrent malignancy were found. The patient is disease free 19 months since diagnosis. Ayhan et al[23] presented their experience with 3 cases of squamous cell carcinoma arising in the dermoid cyst. The authors concluded that although chemotherapy, and radiotherapy did not appear to improve survival in cases described in the literature, they believed that survival might be improved with a combination of chemotherapy and radiation. Radiation therapy has been delivered post-operatively for residual pelvic disease or as adjuvant therapy. The literature review has suggested that platinum-based chemotherapy with pelvic radiation may be a reasonable adjuvant therapy for early-stage disease.[1] In our study, no patient received adjuvant radiotherapy, and only 2 cases received adjuvant chemotherapy for stage III-IV cancer; one squamous cell cancer, and the other carcinoid tumor of ovary with metastasis to appendex, and pelvic lymph nodes. For young patients with intact stage IA disease, and fertility considerations, conservative treatment with unilateral salpingo-oopherectomy, surgical staging, and close follow up has been proposed. Hackethal et al,[24] reported patients with the International Federation of Gynecology and Obstetrics (FIGO) stage IA tumors had better survival than those with more advanced disease. In our study, 100% 5-years survival was noted for 8 patients with presumed stage IA cancer. Irrespective of the tumor type, and the size of the cyst, the prognosis was good if the tumor was limited to one ovary with an intact capsule, and without any tumor on the external surface (FIGO stage IA). If the tumor extended outside the capsule, the prognosis was poor. For squamous cell carcinoma arising from a mature cystic teratoma, survival varies markedly for stage I patients (76.9%), versus stage II-IV patients (11.1%), $p<0.001$.[25] Our study showed the survival for advanced stage disease from 10 weeks to 18 months with an average of 8 months. Further studies are needed to study the effect of other factors on survival in the management of patients with secondary malignancies within mature cystic teratoma. These factors can include cyst wall invasion, ascites, spontaneous, or accidental rupture, adhesions, tumor grade, and vascular invasion. Our study has some limitations related to the rarity of the disease; the limited

number of cases, and the lack of proper staging at the time of primary surgery.

In conclusion, secondary malignancies arising from mature cystic ovarian teratoma are rare, carcinoid tumor is the most common malignancy noticed in our study of more than 50% of cases. It is difficult to predict the presence of secondary malignancies within the dermoid cyst preoperatively. However, we recommend maintaining a higher suspicion of malignancy in managing dermoid cysts occurring in patients over the age of 45 years, especially when the size of tumor is more than 10 cm or rapidly growing tumors. Management of such cases should include laparotomy, and frozen-section with complete tumor excision, and proper staging. Survival is related mainly to tumor stage, and optimal debulking procedures.

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