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Case Report

Appendix invasion of squamous cell carcinoma arising from ovarian mature cystic teratoma and resistant to combination chemotherapy with docetaxel and oxaliplatin: a case report

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Summary

Ovarian squamous cell carcinoma arising from mature cystic teratoma is extremely rare. Our study adds to our understanding of this rare but ominous tumor. Herein we report a case of squamous cell carcinoma in a mature cystic teratoma of the right ovary in a 56-year-old woman presenting with pelvic mass and abdominal pain. Histopathological examination after exploratory laparoscopy revealed squamous cell carcinoma arising from an ovarian mature cystic teratoma with appendix invaded. The patient subsequently underwent complete debulking surgery. Unfortunately, the tumour was refractory to combined chemotherapy with docetaxel and oxaliplatin, the patient refused further treatment and passed away six months after the operation.

Key words: Chemotherapy; Mature cystic teratoma; Ovary; Squamous cell carcinoma.

Introduction

Mature cystic teratoma (MCT) is very common in premenopausal women, occurring bilaterally in 10–17% of patients [1]. MCT may consist of immature or mature tissues arising from the 3 germ cell layers. Most women with MCT are asymptomatic but mass compression effect can lead to pain and abdominal distension. The complications of MCT include torsion, rupture, and malignant transformation. Various tissue components of MCT can generate malignant transformation, typically in post-menopausal women. The reported incidence of malignant transformation of MCT is 0.17–2% [2]. More than 80% of malignant transformations are squamous cell carcinomas (SCC) derived from the ectoderm; the rest are carcinoid tumors or adenocarcinomas [1]. Few case reports on this subject have been published because of the low incidence of malignant transformation of MCT.

Herein we report a case of a 56-year-old woman with SCC transformation from an MCT and appendix metastasis. Following debulking surgery, her tumour developed resistance to combination chemotherapy with docetaxel and oxaliplatin. We incorporate a review of relevant literature on diagnosis, possible risk factors, prognosis and interventions for MCT.

Case Report

A 56-year-old multiparous patient was admitted with an abdominopelvic mass and abdominal pain. She had undergone hysterectomy for uterine leiomyoma 14 years previously. Pelvic examination suggested an extensive immobile pelvic mass with a regular boundary filling the pelvic cavity, extending from the vaginal stump up to the umbilicus. Ultrasound showed a 10.6 × 10.5 × 10.2 cm cystic mass with solid components on top of vaginal stump, and an absence of ascites (Figure 1a). Tumor marker profiling revealed: Cancer Antigen 125 (CA 125): 21.8 U/ml (normal: 1.9-35 U/ml), CA 19-9: 14.6 U/ml (normal: 0-33 U/ml), CA 153: 11.2U/ml (normal: 0-53 U/ml), alpha-fetoprotein (AFP): 4.2 ng/ml (normal:0-7 ng/ml), and Carcinoembryonic Antigen (CEA): 2.4 ng/ml (normal: 0-5 ng/ml). No evidence of neoplasia or dysplasia was observed in cervical smears. HPV testing was negative for high-risk serotypes. Computed tomography (CT) scanning was not performed prior to surgery.

The patient underwent exploratory laparoscopy to remove the ovarian mass. Omentum majus was adherent to the peritoneum of the anterior abdominal wall. A pelvic mass with an intact capsule was identified, with adhesiotomy indicating it arose from the right ovary. The right fallopian tube was maroon in color, thickened and edematous, crawling on the surface of the mass (Figure 2a). The tumor also showed extensive adhesions to the appendix (Figure 2b). Laparoscopic bilateral salpingooophorectomy and appendectomy were performed. No remaining macro metastases were evident in the abdominal cavity. Gross examination of the excised ovarian mass showed a solid-cystic mass measured 10 × 7 × 6 cm with a wall ranging from 0.2 to 2.0 cm. The cyst was filled with hair, sebum and amorphous debris. Given that the mass was judged to be an

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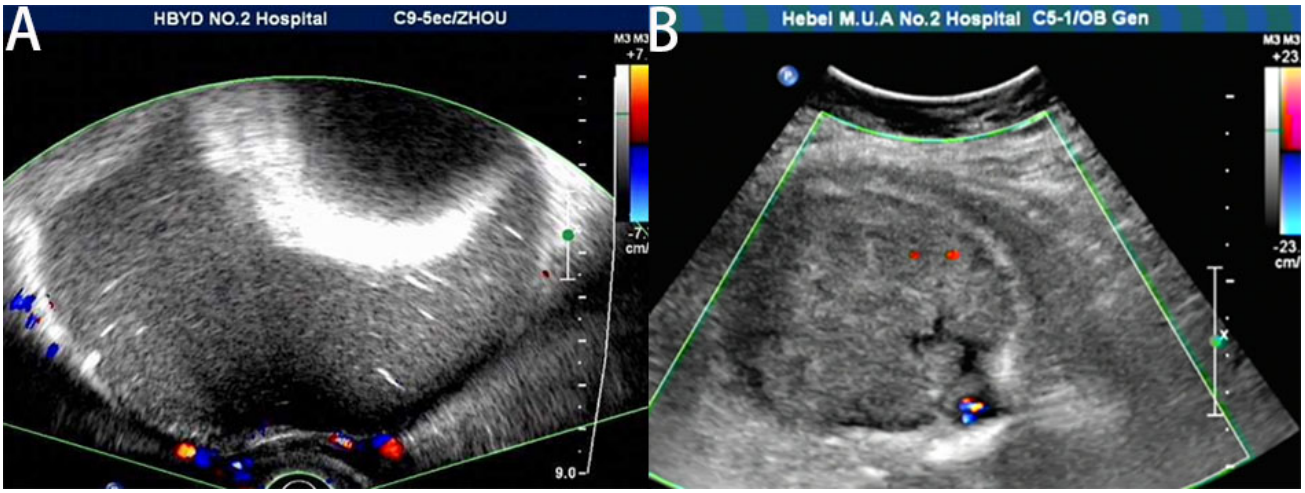

Figure 1. — Ultrasound of the pelvic mass before surgery. (A), and after 2 courses of chemotherapy with docetaxel and oxaliplatin (B). The arrows indicate the margin of the mass.

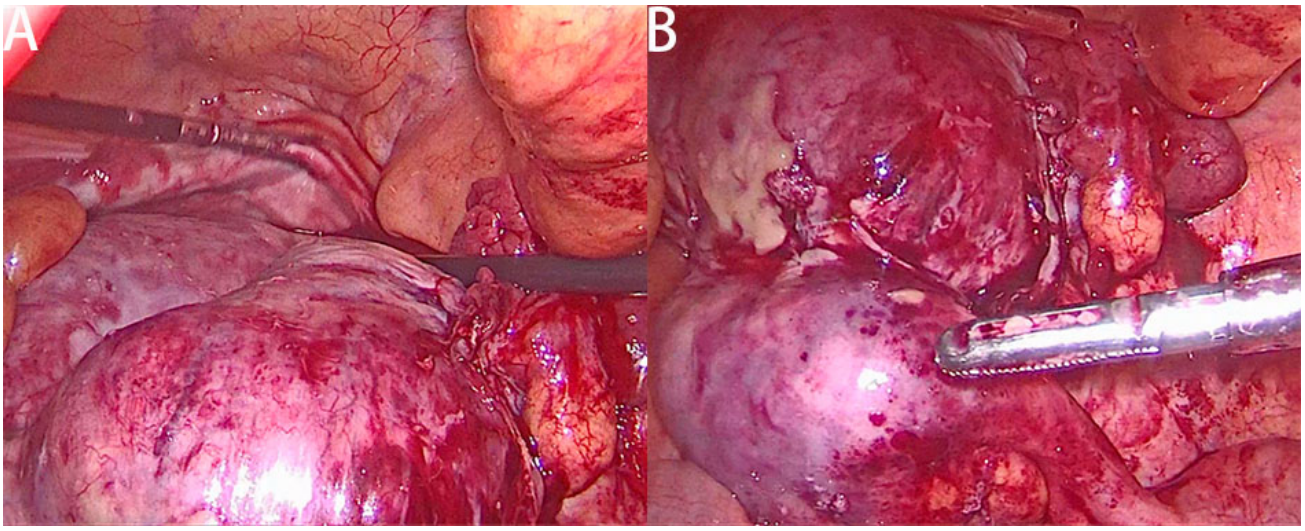

Figure 2. — Laparoscopic exploring of pelvic mass. (A) and appendix (B).

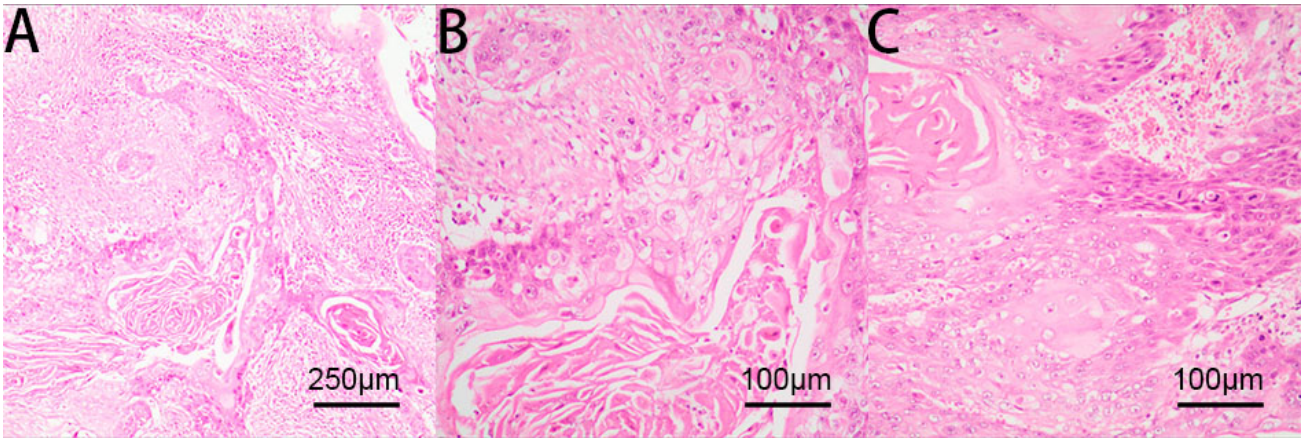

Figure 3. — SCC with keratinization and cystic formation. (A) Macroscopic (H&E × 40) and (B) microscopic (H&E × 100) pathologic findings. (C) invaded appendix (H&E × 100).

MCT, no frozen sections were prepared. The appendix was inflamed.

Histopathological examination revealed SCC arising in an MCT of the right ovary. Moderately differentiated SCC cells were arranged in solid bands or nests. In some areas, squamous epithelial differentiation features such as single cell keratosis, intercellular bridge and keratobead can be seen. The nucleus was large and deeply stained, nucleoli can be seen, and mitosis image was easy to see. (Figure 3a, b). The tumour had invaded the appendix (Figure 3c), but the right fallopian tube was not infiltrated.

In accordance to these findings, the patient was diagnosed with FIGO stage IIIC ovarian cancer [3]. After 7 days post-operative recovery, a CT scan showed no metastases to post peritoneal lymph nodes. The patient subsequently underwent optimal debulking surgery, including pelvic and para-aortic lymphadenectomy in the obturator, internal, external and common iliac area, presacral space and extending to the level of inferior mesenteric arteries, omentectomy, and multiple peritoneal biopsy of adhesions in the pelvic and abdominal cavity until there was no visible lesion remaining. Histopathological analysis revealed no viable tumour cells in any peritoneal biopsy samples or lymph nodes. The patient received 4-weekly intervals of dose-dense combined chemotherapy with docetaxel (80 mg/mm^2 on day 1) and oxaliplatin (130 mg/mm^2 on day 1) at 28 days after surgery. Her baseline tumor marker profile prior to chemotherapy was: CA 125: 44.7 U/mL (normal: 1.9-35 U/ml), CA 19-9: 13.6 U/ml (normal: 0-33 U/ml), CA 153: 6.6 U/ml (normal: 0-53 U/ml), AFP: 2.0 ng/ml (normal: 0-7 ng/ml), and CEA: 2.7 ng/ml (normal: 0-5 ng/ml). The patient complained mild nausea and vomiting. Blood cell count, liver function and kidney function were roughly within normal range. Prior to the third round of chemotherapy, ultrasound revealed a recurrent mass in the right side of the pelvis, measuring 4.86 $\times$ 4.37 $\times$ 4.08 cm (Figure 1b). However, serum tumor maker levels remained within normal range. Four weeks later, the mass had grown rapidly to measure 8.62 $\times$ 6.8 $\times$ 6.77 cm. Serum tumor maker levels remained within normal range, but SCC antigen level was significantly increased (17.4 ng/ml, normal: 0-1.5 ng/ml). Given that the tumour had become refractory to combination chemotherapy with docetaxel and oxaliplatin, a weekly irinotecan monotherapy protocol was proposed. However, further treatment was declined and the patient was given palliative care, passing away six months after the operation.

Discussion

Diagnosis of MCT is relatively easy pre-operatively, but SCC in MCT does not possess any specific diagnostic features [4]. SCC arising in MCT mainly affects post-menopausal women [5], with a median age of diagnosis being 52 years, but can occur rarely in young patients (range 29-89 years) [6]. Patient age and large tumor size have been reported as positive predictors of malignant transformation [7]. Concentrations of several tumor serum markers (CEA, CA 125, CA 19-9, SCC antigen) are elevated frequently. However, there is no correlation between concentrations of tumor markers and FIGO stage [1]. In a largest study of SCC-MCT patients, CEA was reportedly the best screening biomarker, whereas age and tumor size were better markers than CA 125 or CA19-9. The optimal cut-off values for age and tumor size were 45 years and 99 mm, respectively [8]. The combination of patient's age (under 40 years old) and serum SCC level (under 2.5 ng/ml) were reported as a suitable approach for differential diagnosis between MCT and malignant transformation [9]. Thus far, patient age, tumor size, stage, tumor markers, imaging characteristics, rupture, tumor dissemination, ascites, adhesion, growth pattern, cyst-wall invasion, vascular invasion, and tumor type have all been suggested as risk factors for malignancy arising from MCT [10-12]. In our case, advanced age (56 years), tumor size (10 $\times$ 7 $\times$ 6 cm), solid component of the cyst, and invasion into the appendix were all suggestive of malignancy.

In most patients, malignant transformation is confirmed only by postoperative histopathological analysis. In one study, the sensitivity and positive predictive value of intraoperative frozen section pathological examination for the detection of malignancy in ovarian teratomas was 80% and 100%, respectively [7]. In our case, frozen sections were not analyzed during the first operation because the tumor marker profile was within normal range and the differences of gross appearance between MCT with SCC transformation and benign MCT were hard to determine. The patient had to undergo a subsequent extra round of cytoreductive surgery. Thus, we suggest perioperative frozen section analysis should be performed in all cases with risk factors.

Early stage and optimal debulking surgery are reported to be good prognostic factors [1]. In our case, the FIGO IIIc staging hinted at a bad prognosis even with optimal debulking surgery, emphasizing the severity of advanced stage SCC transformation in MCT.

To date, there is no consensus for treatment because of the rarity of the event. Debulking surgery is a key point of intervention in advanced stage cases (greater than FIGO Ia) [13], but currently there is no acknowledged first-line adjuvant therapy for SCC transformation in MCT. The recommend first line chemotherapy for epithelial ovarian cancer and for ovarian germ cell tumor is paclitaxel/carboplatin (TC) and bleomycin/ etoposide/ cisplatin (BEP), respectively [14]. Systematic review has indicated that chemotherapy can improve survival in patients with advanced stage SCC transformation in MCT, and chemotherapy with platinum gave better prognosis compared with other drugs [2]. Moreover, radiotherapy and chemoradiotherapy did not improve survival. To our knowledge, this is the first case reporting the use of docetaxel and oxaliplatin in an SCC transformation in MCT. Others have reported a case of pure ovarian SCC that was resistant to combined chemotherapy with paclitaxel and carboplatin but markedly responsive to monotherapy with weekly irinote-

can [15]. This monotherapy was not possible in our current study, but we look forward to future studies to determine whether monotherapy with weekly irinotecan would work in ovarian SCC transformation in MCT.

In summary, although preoperative diagnosis of SCC transformation in MCT is challenging, an awareness of its risk factors before surgery is critical, since management and prognosis are highly different between benign teratomas and malignant transformation in MCT. Perioperative frozen section analysis is recommended for all suspicious cases. Effective adjuvant chemotherapy for patients with advanced stage disease still demands further research.

Ethics approval and consent to participate

The ethics committee of the second hospital of Hebei medical university approved the study. The husband of the patient gave consent to publish individual data.

Authors' contributions

YNL gathered the information of the case and drafted the manuscript. DGW and WCZ managed the patient and participated in the operation. XDL and XHH performed the surgeries and were in charge of the case. YBL gave critical revision of the manuscript.

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Conflict of Interest

None declared.

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References

[1] Hackethal A., Brueggmann D., Bohlmann M.K., Franke F.E., Tinneberg H.R., Münstedt K.: "Squamous-cell carcinoma in mature cystic teratoma of the ovary: systematic review and analysis of published data". *Lancet Oncol.,* 2008, *9*, 1173.

[2] Li C., Zhang Q., Zhang S., Dong R., Sun C., Qiu C., *et al.*: "Squamous cell carcinoma transformation in mature cystic teratoma of the ovary: a systematic review". *BMC Cancer,* 2019, *19*, 217.

[3] Prat J., Belhadj H., Berek J., Bermudez A., Bhatla N., Cain J., *et al.*: "Abridged republication of FIGO's staging classification for cancer of the ovary, fallopian tube, and peritoneum". *Eur. J. Gynaecol. Oncol.,* 2015, *36*, 367.

[4] Saba L., Guerriero S., Sulcis R., Virgilio B., Melis G., Mallarini G.: "Mature and immature ovarian teratomas: CT, US and MR imaging characteristics". *Eur. J. Radiol.,* 2009, *72*, 454.

[5] Feng X., Xu L.: "Rare case of squamous cell carcinoma arising in a recurrent ovarian mature cystic teratoma of a young woman: A case report and review of the literature". *Medicine (Baltimore),* 2018, *97*, e10802.

[6] Chiang A.J., Chen M.Y., Weng C.S., Lin H., Lu C.H., Wang P.H., *et al.*: "Malignant transformation of ovarian mature cystic teratoma into squamous cell carcinoma: a Taiwanese Gynecologic Oncology Group (TGOG) study". *J. Gynecol. Oncol.,* 2017, *28*, e69.

[7] Desouki M.M., Fadare O., Chamberlain B.K., Shakir N., Kanbour-Shakir A.: "Malignancy associated with ovarian teratomas: frequency, histotypes, and diagnostic accuracy of intraoperative consultation". *Ann. Diagn. Pathol.,* 2015, *19*, 103.

[8] Kikkawa F., Nawa A., Tamakoshi K., Ishikawa H., Kuzuya K., Suganuma N., *et al.*: "Diagnosis of squamous cell carcinoma arising from mature cystic teratoma of the ovary". *Cancer,* 1998, *82*, 2249.

[9] Mori Y., Nishii H., Takabe K., Shinozaki H., Matsumoto N., Suzuki K., *et al.*: "Preoperative diagnosis of malignant transformation arising from mature cystic teratoma of the ovary". *Gynecol. Oncol.,* 2003, *90*, 338.

[10] Paliogiannis P., Cossu A., Capobianco G., Sini M.C., Palomba G., Virdis G., *et al.*: "Squamous cell carcinoma arising in mature cystic teratoma of the ovary: report of two cases with molecular analysis". *Eur. J. Gynaecol. Oncol.,* 2014, *35*, 72.

[11] Choi E.J., Koo Y.J., Jeon J.H., Kim T.J., Lee K.H., Lim K.T.: "Clinical experience in ovarian squamous cell carcinoma arising from mature cystic teratoma: A rare entity". *Obstet. Gynecol. Sci.,* 2014, *57*, 274.

[12] Balık G., Ustüner I., Bedir R., Ural U.M., Kağıtçı M., Güven E.S.: "Appendix and uterus metastasis of squamous cell carcinoma arising from mature cystic teratoma of the ovary". *Case Rep. Obstet. Gynecol.,* 2013, *2013*, 474891.

[13] Armstrong D.K., Alvarez R.D., Bakkum-Gamez J.N., Barroilhet L., Behbakht K., Berchuck A., *et al.*: "NCCN Guidelines Insights: Ovarian Cancer, Version 1.2019". *J. Natl. Compr. Canc. Netw.,* 2019, *17*, 896.

[14] Simone C.G., Markham M.J., Dizon D.S.: "Chemotherapy in ovarian germ cell tumors: A systematic review". *Gynecol. Oncol.,* 2016, *141*, 602.

[15] Nakamura Y., Kamei T., Shinagawa M., Sakamoto Y., Miwa I.: "Case of pure ovarian squamous cell carcinoma resistant to combination chemotherapy with paclitaxel and carboplatin but responsive to monotherapy with weekly irinotecan". *J. Obstet. Gynaecol. Res.,* 2015, *41*, 809.

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