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Review article

An ovarian mature cystic teratoma evolving in squamous cell carcinoma: A case report and review of the literature

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ABSTRACT

Mature cystic teratomas (MCT), also known as dermoid cysts, are the most common ovarian germ cell tumors and the most common ovarian neoplasms in patients younger than 20 years. Malignant transformation (MT) is a rare complication of MCTs which may occur in 1–2% of the cases. Squamous cell carcinoma (SCC) is the most frequent histology arising from MCTs and its appearance depends on diverse risk factors such as patient's age, the size of the tumor and levels of serum tumor markers. Diagnosis and treatment constitute a big challenge due to the rarity and the aggressive course of this entity. Adjuvant chemotherapy has a leading role in the treatment of MCT-arising SCC, while the use of radiotherapy or chemoradiation is still under consideration. Herein, we report a case of a post-menopausal woman, presenting with mild symptoms and a large pelvic mass deriving from the left ovary occurring as dermoid cyst. Simultaneously, we review the literature stressing out the prognostic factors and the treatment options for MCT arising SCC according to traditional and new therapy-strategies.

Contents

1. Introduction

Mature cystic teratoma (MCT), also known as dermoid cyst is the most common ovarian germ cell tumor, comprising 10–20% of all ovarian tumors (Berek, 2005). It may occur at any age, with highest incidence during the reproductive period. The clinical course of MCT is typically indolent, and its prognosis depends on age, stage and optimal cytoreduction. However, it can be complicated by a malignant transformation with squamous cell carcinoma (SCC) accounting for 80–90% of the transformed histology (Hackethal et al., 2008). Malignant transformation confers a significantly worse prognosis compared to epithelial ovarian cancer (Avcı et al., 2012). Only 1–2% of the SCC cases can be diagnosed preoperatively (Berek, 2005; Comerci et al., 1994). Several risk factors and clinical features have been associated to MCT transformation into SCC, including patient age, tumor size, ultrasound characteristics, sonar tumor vessel wave form, computed tomography, and levels of SCC and CA125 tumor markers. Due to the scarcity of literature, adjuvant treatment has yet to be defined. Herein, we report a case of SCC arising from dermoid cysts, including a short review of the literature.

2. Case-report

A 54-year-old woman presented in the gynaecological department with mild abdominal pain, loss of appetite, afternoon low grade fever and substantial loss of weight during the last 2 months. She was

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postmenopausal, gravida 1, para 1. Her medical and family history was insignificant. She was receiving medication for hypertension and she was a 30 py smoker.

On clinical examination her performance status according to ECOG scale was 2. She had a significant abdominal distention, with a mass extending from Douglass space to epigastric region. The mass was palpable, mobile and repelled the rectum. Pap-smear and intrauterine prevention biopsy with device of negative pressure were taken. Admission to the clinic was decided for further examination.

Vital signs were normal except for sinus tachycardia attributed to a grade 3 anemia (hemoglobin 7,8 g%). Serum levels of tumor marker antigens were CA-125: 37,5 (normal range < 35), CA15-3: 32,6 (<28) and CA19-9: 63,5 (<34). Other blood and urine investigations were within normal values. The Pap-smear was negative for malignant cells and the intrauterine biopsy revealed hyperplastic, inflammatory type lesions and groups of sizable glandular cells.

Pelvic magnetic resonance imaging showed a mixed-tissue mass (18X22X12cm) deriving from the left ovary, which repelled adjacent structures with features suggestive of germ cell tumor. There were no signs of enlarged lymph nodes or tumor implants in the pelvis or abdomen. Mammography, colonoscopy and computed tomography of the chest were insignificant.

The patient signed an informed consent and exploratory laparotomy was performed. Interestingly, a huge left-sided ovarian tumor with adhesion to omentum and small intestine, occupying the whole abdomen up to the liver was found. The mass was removed and sent for frozen section, which showed malignant tissues in a mature cystic teratoma. The cytology of peritoneal washings was negative for malignancy, although ample cellularity was present. She underwent a total abdominal hysterectomy with bilateral oophorectomy, omentectomy, pelvic and paraaortic lymphadenectomy.

Macroscopically the tumor measured 28,5 × 18 × 10 cm with uneven surface, consisted by yellowish liquid, sebum and hair, including sections of compact tissue. Histopathologic examination showed invasive squamous cell carcinoma arising in a mature cystic teratoma with cleavage of the outer surface of the ovary from the neoplasm and extensive necrosis (Figs. 1–4). The omentum was infiltrated by the tumor, while the rest structures and lymph nodes were free of disease.

The disease was classified as stage IIIc according to FIGO classification (Berek, 2005). Although current literature is scarce and no strong evidence guidelines over the adjuvant treatment of transformed disease exist, the SCC component mandated further treatment. Adjuvant chemotherapy based on paclitaxel, ifosfamide and cisplatin (TIP) for 4 cycles was planned to be offered to the patient.

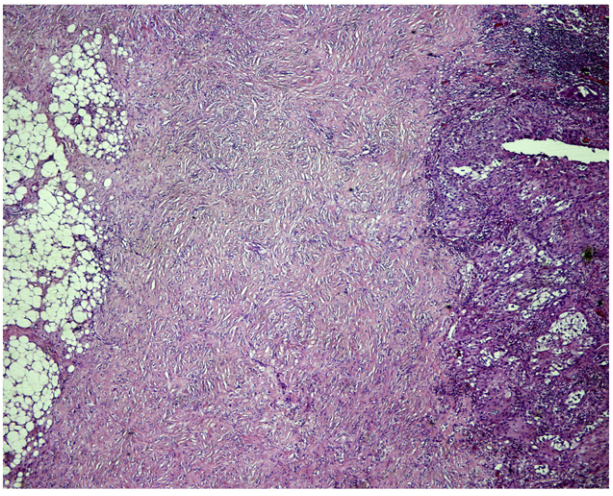

Fig. 1. Photomicrophotograph showing squamous cell carcinoma (right side) arising in a teratoma. On the left side we can see benign mesodermal elements of the teratoma (fatty tissue).

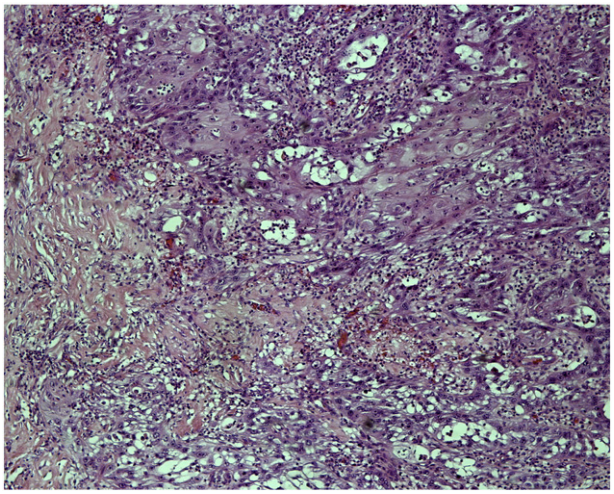

Fig. 2. Photomicrophotograph showing squamous cell carcinoma.

Due to delayed recovery and financial issues hindering her admission the patient was subsequently admitted to start chemotherapy in the ward with a 4-month delay. On the admission, her PS was 4 and she complained of diffuse abdominal distention, pain, fever, vomiting and substantial loss of weight. Labs were consistent with a gr3 anemia, high white blood cells and LDH and electrolyte disorders. CT scan of the abdomen revealed bowel obstruction due to diffuse peritoneal nodules suggestive of disease relapse. She was offered an optimal debulking surgery of the relapsed sites which were histologically proved to be a squamous cell carcinoma recurrence.

Soon after her recovery her PS has improved to 2 and the patient was offered first line chemotherapy based on carboplatin AUC5 and paclitaxel 175 mg/m^2 intravenously on day1 every 21 days, for 8 cycles. At completion of chemotherapy, no disease was detected with abdominal CT scan and a close follow-up was suggested. Unfortunately, 6 weeks after the completion of chemotherapy the patient was admitted to our department due to recurrent vomiting and abdominal pain. Imaging methods did not reveal bowel obstruction or findings suggestive of disease relapse. Due to progressive clinical deterioration exploratory laparotomy was performed. Multiple adhesions to small intestine, occupying the whole abdomen up to the liver and the great curvature of the stomach were found and removed.

Histological examination reported many abdominal sites invaded by squamous cell carcinoma.

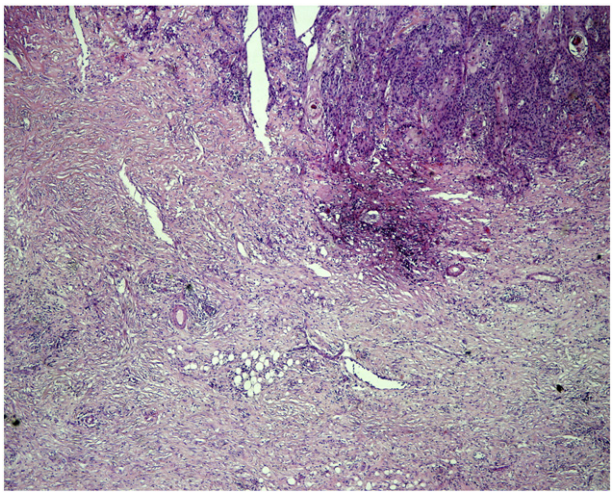

Fig. 3. Photomicrophotograph showing squamous cell carcinoma arising in a teratoma.

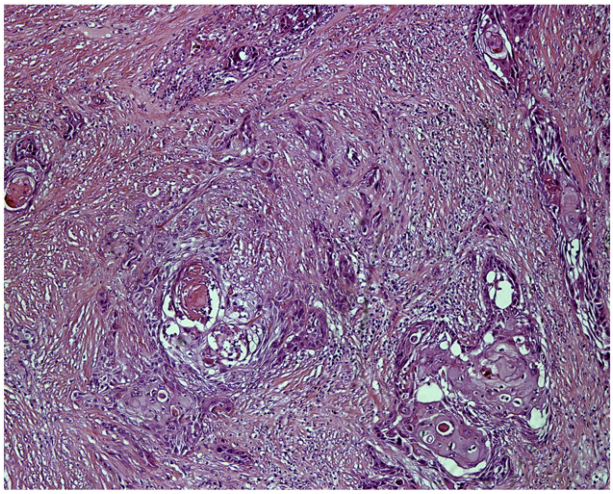

Fig. 4. Photomicrophotograph showing well differentiated squamous cell carcinoma.

Postoperatively, the PS of the patient has improved to 2 and she was offered 2nd line chemotherapy based on gemcitabine 800 mg/m^2 on days 1 and 8 in a 21-day cycle. Unfortunately, after the completion of the first cycle of chemotherapy, the patient was admitted with symptoms consistent with bowel obstruction. She passed away of disease related sepsis 17 months after the diagnosis.

3. Discussion

Mature cystic teratomas (MCT), also known as dermoid cysts, are the most common ovarian germ cell tumors and the most common ovarian neoplasms in patients younger than 20 years. The incidence of MCTs is estimated to be 1.2–14.2 cases per 100.000 people per year (Hackethal et al., 2008). They account for about 10–20% of all ovarian tumors and appear bilaterally in 10–17% of the cases (Hackethal et al., 2008; Comerci et al., 1994). MCTs arise from the primordial germ cells, thus, they might consist of multiple cell types derived from one or more of the 3 germ layers (ectoderm, mesoderm, endoderm) (Hackethal et al., 2008).

MCTs usually remain asymptomatic or cause minimal symptoms (Hackethal et al., 2008). The most common signs and symptoms include increase of the abdominal girth, abdominal pain and distention, palpable abdominal or pelvic mass (Hackethal et al., 2008). In case of invasion of tumor to adjacent structures, gastrointestinal or urinary symptoms may be present. Other symptoms are menorrhagia, fever, cachexia. Regrettably, the patient of the study complained of abdominal pain, loss of appetite, loss of weight and fever.

A rare complication of MCTs is the malignant transformation (MT), which may occur in about 1–2% of the cases (Avcı et al., 2012). Malignant components may evolve from any of the three germ layers, resulting to different histological tumor types (Rim et al., 2006). However, the most common type of malignant transformation consists of squamous cell carcinoma, arising from the ectoderm, which accounts for >80% of the cases (Hackethal et al., 2008; Rim et al., 2006). Less frequent histologies include carcinoid tumors or adenocarcinomas (Hackethal et al., 2008).

Diagnosis of malignant transformation of MCTs poses difficulties to clinicians. It is commonly accepted that all ovarian tumors should be considered as potentially malignant, until proven otherwise (Hackethal et al., 2008). In order to detect the malignant transformation of MCTs, there are some risk factors that contribute to the transformation, such as the patient age, the size of tumor, the serum tumor markers and the imaging characteristics of the tumor (Hackethal et al., 2008).

The age of the patient is a risk factor for malignancy, as SCC in MTC typically occurs in postmenopausal women (Hackethal et al., 2008; Rim et al., 2006). Although 80% of MCTs are diagnosed during reproductive age, malignant transformation is typically detected during postmenopausal age (Hackethal et al., 2008; Rim et al., 2006). According to Chen et al., the mean age at diagnosis was 55 ± 14.4 years and 66.8% of patients were at least 50 years old at time of diagnosis (Kikkawa et al., 1997). Furthermore, Hackethal et al. reported a mean age at diagnosis of 55 years (Hackethal et al., 2008), whereas Chiang et al. reported a mean age of 41.7 years.

Given that MCTs with SCC are usually larger than benign tumors possibly due to the presence of additional areas of necrosis or hemorrhage, tumor size is a potential indicator of malignant transformation of MCT (Hackethal et al., 2008). According to Kikkawa et al., tumors with diameter larger than 9.9 cm or tumors demonstrating rapid growth may be associated with an increased risk for malignant transformation (Kikkawa et al., 1997). Moreover, Chen et al. reported that 78.7% of MCTs with SCC are larger than 10 cm, with a mean size of 13.8 cm. In our case the tumor measured 28.5 × 18 × 10 cm.

Another risk factor for malignant transformation of MCTs is the level of serum tumor markers. Certain tumor markers (SCC antigen, CA125, CA19-9 and CEA) may be increased in patients with SCC (Hackethal et al., 2008), however, the levels of these markers are not associated with the tumor size or FIGO stage. Interestingly, preoperative concentrations of SCC antigen and CA125 are associated with adverse outcomes (Hackethal et al., 2008). For instance, Chen et al. reported that patients with increased SCC and CA125 markers had a worse 5-year survival rate, compared to those with normal values. It is also suggested that a high CA125 is a more reliable prognostic marker than SCC. Other potentially prognostic markers studied include the tissue polypeptide antigen and the macrophage colony-stimulating factor (Hackethal et al., 2008). A study, also, showed that elevated serum calcium levels might be a marker of SCC presence (Ribeiro et al., 1988). In our case, CA-125 antigen was 37.5 (normal values <35) and SCC antigen was not measured due to technical impossibilities of routine clinical practice.

Certain imaging features of the tumor may contribute to the diagnosis of malignant transformation. The use of transvaginal -Doppler- Ultrasound for the measurement of the blood flow resistance in the intratumoral vessel may be an accurate method to distinguish benign from malignant MCTs. Interestingly, Emoto et al. reported that the Doppler detection method was a more useful indicator than serum SCC antigen levels (Emoto et al., 2000). Concerning the clinical use of magnetic resonance imaging in SCC diagnosis, the presence of a solid component that extends transmurally and invades the adjacent structures is highly suggestive of malignancy (Park et al., 2007). Regarding the clinical use of CT in diagnosis of SCC, the formation of an obtuse angle between the border of the soft tissue component and the cyst wall is a sign of malignancy (Mori et al., 2003).

The prognosis of these tumors is poor and depends on the stage of the disease (Hackethal et al., 2008; Avcı et al., 2012). Chen et al. reported that the 5-year survival rate for all stages was 48.4%, whereas the 5-year survival rates for stages I, II, III and IV were 75.7, 33.8, 20.6 and 0% respectively. Furthermore, Hackethal et al. reported that there is an important prognostic difference between stage I disease and all other tumor stages. Other factors that may have an impact on prognosis are capsular invasion, ascites, rupture or spillage, adhesions and vascular space invasion.

Several medical groups investigated the role of adjuvant treatment on the clinical course of the disease, however, the rarity of this entity has precluded patients from participating in large randomized phase III trials. No treatment guidelines have therefore been established. Nonetheless, it is commonly accepted that treatment must be tailored to the transformed histology (Singh et al., 1988).

There is evidence that cisplatin is active against gynaecological SCC, and is the most studied among alkylating agents. In a case series of patients with SCC arising from MCT, 13 patients received cisplatin-based chemotherapy. Ten out of 13 women received the POMB regimen

(comprised of cisplatin, vincristine, mitomycin-c, bleomycin), 2 received PF (cisplatin,5-fluorouracil) and 1 POB (cisplatin, vincristine, bleomycin). Whole pelvic radiotherapy was given individually based on the tumor location. The median disease free interval was 56.4 months (range 7–137 months). Notably, the 2-year disease-free survival (DFS) was 30% for FIGO stage III disease (3/10). Authors advocated multimodality treatment based on optimal cytoreduction, cisplatin-based adjuvant chemotherapy and radiotherapy for disease located into the pelvis (Tseng et al., 1996).

The role of chemotherapy based on alkylating agents has been stressed in a study of 119 patients. Overall survival of patients with teratoma-related SCC had improved to 57.1 months (SD 9.0; 95% CI 39.5–74.8) when alkylating agents were administered compared to 25.2 months for those who received non-alkylating regimens. Other agents offered to the patients of this study included taxanes, anthracyclines, antimetabolites, vinca alkaloids which are known to be active in squamous cell tumors (Hackethal et al., 2008). In the same study, no benefit from radiotherapy has been proven (Hackethal et al., 2008).

In a case series of 17 patients with SCC arising in MCT of the ovary, the impact of adjuvant chemotherapy with the addition or not of radiotherapy on survival was retrospectively studied. Six out of 17 patients (35%) received adjuvant chemotherapy and 4 (23%) chemoradiotherapy. Although no conclusions were extracted since the median survival was not reached, authors advocated the use of concurrent platinum-based chemoradiotherapy (with external pelvic radiation) for low stage disease (FIGO stages IA-IIB) (Dos Santos et al., 2007).

It is therefore extrapolated that adjuvant chemotherapy has a significant though not clearly defined, role in the treatment of MCT-arising SCC. Despite the multimodal treatment, high recurrence rates are still reported.

Advances in chemotherapy may result in better disease outcome. Thus, it was decided to treat the patient of the study with a highly active chemotherapy regimen based on cisplatin-ifosfamide-paclitaxel, which has proved to be efficient in tumors of squamous histology (Zanetta et al., 1998). Particularly, the TIP combination conferred 84% response rate (RR) with 16% complete response (CR) in patients with stage IB2-IVA cervical cancer in the neoadjuvant setting (Zanetta et al., 1998).

There is evidence that TIP is a highly active regimen associated though with substantial toxicity, mainly bone marrow suppression and neutropenic fever.

Patients with a less than optimal performance status are candidates to receive a platinum based chemotherapy doublet. There is strong evidence that the addition of taxanes to platinum is associated with increased activity, a phenomenon that can be partly attributed to synergistic effect between these agents. There are several reports in literature on the combination of carboplatin-paclitaxel regimen in squamous-cell transformed carcinomas of MCT (Patni, 2014).

The short interval between the completion of chemotherapy and disease progression in the patient of the study, make us speculate on the chemoresistance and the high proliferation rate of the disease.

SCC arising from MCT is therefore a rare, albeit potentially lethal disease that warrants aggressive multimodal treatment approach. The scarcity of literature mandates that clinicians share their experience in diagnosing and treating this disease.

4. Conclusion

Although preoperative diagnosis of MCT-SCC is challenging, radiologic and laboratory findings in addition to essential risk factors should guide the necessary surgical procedure. However, due to the poor prognosis and high rates of recurrence of this disease chemotherapy still plays a pivotal role. More evidence for the management of MCT-SCC by large, multicenter studies is required.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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