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Malignant mixed Mullerian tumor of the ovary with two cases and review of the literature

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Abstract
Introduction Malignant mixed Müllerian tumor (MMMT) of the ovary is a rare and highly aggressive tumor. It accounts <1% of all ovarian carcinomas. It is characterized by the presence of both carcinomatous and sarcomatous components and tends to occur in low parity postmenopausal woman. These are mixed, mostly monoclonal tumors, and the predominance of the stromal component aggravates the prognosis. The staging system for ovarian and primary peritoneal cancer is also used for MMMT. After complete surgical staging, patient with stage II–IV at the time of surgery should have postoperative chemotherapy. Chemotherapy can be considered for stage I MMMT. Its optimal treatment is debatable. Taxane and platinum combination is standard for the epithelial ovarian carcinoma. There is very limited literature reporting this combination therapy in ovarian MMMTs.
Case 1 and Case 2 We presented two cases of stage III primary ovarian MMMT. The patients were treated with the taxane/platin combination, without adverse events following surgery, and remained in clinical remission in Case 1 at follow-up. Case 2 has progressed after first line taxane/platin regimen and treated like epithelial ovarian carcinoma. Case 1 was in complete remission in the follow-up visit 2 years later. Case 2 died 14 months later after the tumor was initially diagnosed.
Conclusion Predominating carcinomatous or sarcomatous component should be taken into consideration in predicting the response and planning the chemotherapy protocol.

Keywords Mixed müllerian · Ovarian neoplasms · Chemotherapy

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Introduction

Malignant mixed Müllerian tumor (MMMT) of the ovary is a rare tumor, constituting <1% of all primary ovarian tumors [1]. MMMT is a highly aggressive and rapidly progressive tumor with a poor long-term prognosis. The median survival of patients with MMMT is around 8–16 months, and more than 70% of patient die when the disease at 1 year despite the treatment [2–4]. Histologically, the tumors include malignant epithelial and sarcomatous elements. MMMT of the ovary has been classified according to the origin of the mesenchymal tissue: homologous versus heterologous [2]. The optimal treatment for ovarian MMMT is also debatable partly though the histogenesis of MMMT is controversial [3]. Due to the aggressive nature of this tumor, systemic chemotherapy is usually recommended. However, there is a few consensus about the optimal combination chemotherapy for the ovarian MMMT as a result of its rare occurence [2]. Debulking surgery followed by chemotherapy is the treatment of choice for this type of malignancy. However, studies supporting this approach are extremely limited [5, 6].

We report two cases of ovarian MMMT treated with a combination of platin and taxane therapy following surgery.

Case report

Case 1

A 65-year-old woman was admitted to our hospital due to abdominal pain for 1 month. She was gravida 5, para 5, and postmenopausal since 53 years of age, with no history of hormone therapy or major systemic disease. Physical

examination revealed a pelvic mass and abdominal tenderness. A laboratory evaluation revealed high serum levels of carbohydrate antigen (CA) 125.

The patients underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. A histopathological examination demonstrated MMMT of the ovary and staged as stage IIIC. Following surgery, an adjuvant combination chemotherapy regimen, consisting of carboplatin and paclitaxel for six cycles was initiated. Chemotherapy was administered as follows: carboplatin 5AUC on day 1 and paclitaxel 175 mg/m^2 on day 1 of each cycle, every 3 weeks for six cycles. The patient tolerated chemotherapy well without any significant adverse events. The patient was in complete remission in the follow-up visit 2 years later. The patient was followed with serum tumor marker CA 125 and imaging studies, i.e., computed tomography. CA-125 level decreased to the normal range after the first chemotherapy cycle. Follow-up after completion of therapy showed no increase in the tumor marker, and CT scans showed complete remission.

Case 2

A 51-year-old woman was admitted to our hospital due to abdominal pain for 2 months. She was gravida 0, para 0, and postmenopausal since 45 years of age, with no history of hormone therapy or major systemic disease. A laboratory evaluation revealed high serum levels of carbohydrate antigen (CA) 125.

The patients underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy. A histopathological examination demonstrated MMMT of the ovary and staged as stage IIIA. Following surgery, an adjuvant combination chemotherapy regimen, consisting of carboplatin 5AUC and docetaxel for six cycles was initiated. Chemotherapy was administered as follows: carboplatin 5AUC on day 1 and docitaxel 75 mg/m^2 on day 1, of each cycle every 3 weeks for six cycles. The patient tolerated chemotherapy well without any significant adverse events. The patient was followed with serum tumor marker CA125 and imaging studies, i.e., computed tomography. Follow-up after 4 months from therapy increase in the tumor marker (CA125) was observed and CT scans showed metastatic disease at lung and liver. Lyposomal doxorubicin 50 mg/m^2 on day 1 and gemcitabine 1 g/m^2 on day 1 and 8 chemotherapy regimen were given to the patient. Progressive disease was found after four cycles. Weekly paclitaxel was administered to patient for 2 months. The disease progressed after 2 months. Topotecan 1.5 mg/m^2 for 5 days was given only for one cycle. She died 14 months later after the tumor was initially diagnosed.

Discussion

Primary ovarian MMMT (MMMT: also termed carcinosarcoma) is a rare malignant tumor and is associated with a poor prognosis. Patients usually have advanced disease at the time of diagnosis, approximately 70% of the cases present as stage III or IV disease and die of the tumor shortly after the diagnosis [4, 7] like our Case 2.

Histologically, the tumors include malignant epithelial and sarcomatous elements. MMMT of the ovary has been classified according to the origin of the mesenchymal tissue: homologous versus heterologous. Homologous MMMT or carcinosarcoma contains malignant stromal elements native to the ovary such as spindle cells. The heterologous MMMT has sarcomatous tissue not found in the ovary such as bone or cartilage [2].

Although there have been many histological studies, the histogenesis of carcinosarcomas is still unknown. Meyer described three possibilities for the coexistence of carcinomatous and sarcomatous elements in carcinosarcoma: (1) a collision tumor, which is a mixture of two histologically distinct malignant cell populations that have arisen in separate primer sites, such as endometrium and stroma; (2) a combination tumor, which is composed of both histologic elements of common stem cell origin or of transformed elements from the original cell to another cell type; and (3) a composition tumor, which is an endometrial carcinoma with reactive atypical stroma. More recently, few studies have described the close relationship of MMMT with endometrial adenocarcinoma. Most tissue culture studies have supported the theory of single stem cell origin; however, some immunohistological studies have speculated on the presence of common ancestor cells. All these theories have tested the combination theory [8].

The role of surgical cytoreduction for ovarian MMMT is controversial. Although Muntz et al. reported that optimal cytoreduction was associated with statistically significantly improved survival [3], other studies failed to show this improvement in survival [10, 11]. For treatment of ovarian MMMT, total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and removal of all tumor burdens can be performed as done in epithelial tumors. Systemic chemotherapy is usually recommended even for optimally resected tumors due to the aggressive nature [12].

These tumors arise from Müllerian epithelium with subsequent divergent differentiation to the stromal-like sarcomatous elements suggesting that primary ovarian MMMTs can be treated like epithelial ovarian carcinomas [3]. Meanwhile, ovarian MMMTs and ovarian epithelial tumors have similar clinical presentation and tumor origin. These facts suggest that MMMTs can be treated with the chemotherapeutic agents used for epithelial ovarian cancer

Table 1 The studies of platinum-based chemotherapy for ovarian MMMT

Author	Number of cases	Mean age (years)	Mean survival (month)
Anderson et al. [16]	10	62.3[a]	14
Bicher et al. [4]	36	59	18
Muntz et al. [3]	27	63	23
Le et al. [17]	36	67.5	36[b]
Helstrom et al. [15]	36	64	Homologous:21.6
			Heterologous:14.7
Sit et al. [2]	13	TC:56.9	19
		IP:69	23
Duska et al. [6]	28	66	27.1
Mok et al. [12]	10	57.5	46

TC taxane/carboplatin, *IP* ifosfamid/cisplatin

[a] Mean age

[b] The patients received cytotoxic combination chemotherapy

[12]. However, the Gynecology Oncology Group (GOG) classifies MMMT of the ovary in the category of soft tissue sarcomas [9], while other authors suggest that MMMT represents very poorly differentiated (anaplastic) epithelial tumors [3]. The recent studies suggest that platinum-based therapy is a good choice for MMMT of ovary [3, 6, 11, 12]. Our two cases were treated like epithelial ovarian carcinomas. However, there is no consensus on the optimal combination chemotherapy because of the rarity of the disease. A variety of chemotherapy regimens have been reported in the literature with response rates ranging from 27 to 100%, consisting of adriamycin, dacarbazine, and cisplatin [9, 10, 13, 14]. The GOG has studied combination therapy with VAC (vincristine, adriamycin, cisplatin) and ifosfamide/mesna in two small series. Rates of response for VAC and ifosfamide/mesna were 16.7 and 20%, respectively [7, 9]. Platinum-based combination chemotherapy after optimal cytoreductive surgery may be effective in the treatment of ovarian MMMT (Table 1) [12]. Response rates range from 65 to 80% with the different platinum-based chemotherapy regimen. However, platinum-based combination chemotherapy is associated with increased toxicity [1, 4, 6, 10, 11, 16, 17].

Paclitaxel/platinum-based chemotherapy has emerged as the first-line chemotherapy for the treatment of advanced epithelial ovarian carcinoma [2, 5]. In an effort to reduce toxicity, the combination of paclitaxel/carboplatin was found by the GOG to have comparable activity to cisplatin/paclitaxel but with less toxicity [2]. Duska et al. [6] have reported their retrospective study of 28 patients with MMMT and 57% of these patients achieved a complete response with the combination of paclitaxel and carboplatin. The mean survival was 27.1 months. On the other hand, Sit et al. [2] have reported a mean survival of 19 months with the same combination. There are several reports regarding platinum-based chemotherapy activity against MMMT of the ovary. Combination regimens including cisplatin have been shown to have a total response rate ranging from 70 to 100% and a median survival of 16–18 months [4, 10, 13, 14, 16, 18].

Ifosfamide has also been studied in MMMT of the ovary and ifosfamide could be used as second line therapy after platinum-based chemotherapy in some reports. Simon et al. reported a patient with MMMT of the ovary who had a suboptimal response to single-agent cisplatin chemotherapy but demonstrated a CR with mesna, ifosfamide, adriamycin, and dacarbazine [19]. A phase II GOG trial, however, observed only a 3.6 and 14.3% partial response in patients with recurrent MMMT of the ovary treated with ifosfamide and mesna after platinum-based chemotherapy [9]. Silasi et al. have compared cisplatin/ifosfamide combination with carboplatin/paclitaxel combination following cytoreductive surgery in their report. Median progression-free interval in the cisplatin and ifosfamide group was 13 months, and median survival was 51 months. Median progression-free interval and median survival were 6 and 36 months, respectively, in carboplatin/paclitaxel group. The difference in survival between the cisplatin and ifosfamide group and the carboplatin and paclitaxel group was not statistically significant ($p = 0.48$), and median survival was 46 months for patients if optimally debulking surgery was performed; however, median survival was 27 months for suboptimally debulking surgery patients in their report [20]. On the other report by Rutledge et al. progression-free interval was improved with the use of ifosfamide/cisplatin versus carboplatin/paclitaxel. The median progression-free interval was 12 months in the carboplatin/paclitaxel group and has not been reached in the ifosphamide/cisplatin group ($p = 0.005$). The overall survival was also significantly improved with the use of ifosfamide/cisplatin ($p = 0.03$). In advanced stage patients, the overall survival was not significantly influenced by type of adjuvant chemotherapy administered ($p = 0.13$) [21].

The most effective therapy is unknown, whereas aggressive surgical cytoreduction combined with adjuvant platinum-based chemotherapy are recommended as the treatment of choice in MMMT of ovary [2, 3, 22]. Although pelvic radiotherapy (RT) has been indicated to reduce local recurrence rate, there are reports against the beneficial effect of RT [23, 24].

Many factors have been evaluated as prognostic indicators for survival of patients with MMMT. Some studies have described prognostic significance to the grade of the carcinomatous components and histological type and proportion of sarcomatous components in the primary tumor and metastatic foci [3, 11, 24]. Residual tumor after

Table 2 The impact of carcinomatous/sarcomatous component in ovarian MMMT [26]

Age	Stage	Treatment	Response to chemotherapy	Carcinomatous component (%)	Sarcomatous component (%)
50	IIIA	PC	Under treatment	80	20
40	IIIA	PI	PR	50	50
60	IIIC	PI	CR	70	30
47	IIIC	PI	CR	20	80
73	IIIC	PI	Progressive disease	60	40
70	IIIC	PI	Progressive disease	35	65
51	IV	PC	PR	70	30
80	IIIB	PC	CR	95	5
60	IIB	PC	PR	85	15

PC paclitaxel/carboplatin, *IP* ifosfamid/cisplatin, *PR* partial response, *CR* complete response

primary surgery, advanced age and stage were the best defined poor prognostic factors [26].

The present case (Case 1) of a stage III primary ovarian MMMT with heterologous origin of epithelial carcinogenesis has been treated with a paclitaxel and carboplatin combination without adverse events following surgery. She remains in clinical remission at follow-up. This case may indicate that paclitaxel and carboplatin regimen can be considered as an active regimen and worthy of further study. Eltabbakh et al. have reported a patient with stage IIIC ovarian MMMT treated with cisplatin/paclitaxel combination. The patient tolerated chemotherapy well, completed the clinical response and remained without disease for 21 months following diagnosis. Paclitaxel and cisplatin may be effective in MMMTs of the ovary for their report [27]. On the other hand in Case 2 taxane/platin combination and lyposomal doxorubicin, gemcitabine, topotecan were given to the patient in other lines like epithelial ovarian carcinoma. Survival was 14 months. First case indicated that paclitaxel and carboplatin regimen can be considered as an active regimen and worthy of further study. But in Case 2, survival rate was 14 months compatible with literature. Some predictive factors can be responsible from different responses in our each patient. Ozguroglu et al. have reported that one of the best predictors to response is the histological pattern. Predominating carcinomatous or sarcomatous component should be taken into consideration in predicting the response and planning the chemotherapy protocol [26] (Table 2). Each patient in this report had different prognosis because of this reason. We think that the ratio of sarcomatous and carcinomatous components in these tumors can be predictor of treatment choice. Kim et al. have reported 11 MMMTs (eight were of endometrial, two were of ovarian, and one of tubal origins) by both electron microscopy (EM) and immunoperoxidase techniques (IPX). Carcinomatous elements were always keratin positive (K+) and were focally positive for vimentin in six tumors. Homologous stromal sarcoma cells were vimentin positive (V+) and in three tumors were focally K+. Ultrastructurally, the epithelial cells were not highly differentiated and the sarcomatous elements generally resembled normal proliferative-phase stromal cells [28]. EM and IPX can be useful to differentiate sarcomatous and carcinomatous components.

The management of ovarian carcinosarcoma is difficult. Consensus is lacking about the most suitable method of treatment for ovarian carcinosarcoma. Several previous studies have found that optimal cytoreduction followed by combination chemotherapy may result in an improved progression-free interval for patients with ovarian carcinosarcoma [3, 13, 29]. Large residuals (>20 mm in greast diameter) tended to predict the prognosis, but no significant correlations were found (p:0,089, log-rank test) in their study was reported by Ariyoshi et al. [29].

In conclusion, these are mixed, mostly monoclonal tumors, and the predominance of the stromal component aggravates the prognosis. The clinical presentation of these tumors is similar to that of epithelial ovarian tumors, although they tend to manifest themselves at later stages of disease. There are no useful biochemical markers: imaging diagnostic methods (ultrasound, computed tomography, magnetic resonance imaging) do not provide specific data. The staging and primary treatment are always surgical. Survival improves when cytoreduction is satisfactory. Chemotherapy (platinum) can prolong survival, but there are no effective second-line treatments. Radiotherapy is of no help. The prognosis of this cancer is always guarded. Genetic and molecular techniques will be very important in advancing our knowledge of tumoral biology. In order to improve therapeutic results, it will be necessary to design multicenter, cooperative studies including larger numbers of patients [25]. Stage of disease remains the most important predictor of survival in ovarian MMMT and in all other neoplasms, with some studies demonstrating a

significant difference in survival between early-stage (I and II) and advanced-stage (III and IV) [29, 30]. In their study, Ariyoshi et al. failed to demonstrate any significant effect of heterologous elements on survival among other studied factors, including histological type of carcinoma, mitotic count, vascular space invasion, ki67 reactivity and p53-positive staining [29, 30]. The stage was significant prognostic factor in ovarian MMMT's [29]. Barakat et al. [11] demonstrated a median survival of 104.8 months in patients with stage I or II disease compared to 9.5 months in patients with stage III or IV disease. In the study which has been reported by Barnholtz-Sloan et al., the median survival of women with early-stage ovarian MMMT was 64 months and for advanced-stage ovarian MMMT was 13 months. Women with advanced-stage ovarian MMMT were at a 60% increased risk of death compared to women with advanced-stage, high grade epithelial ovarian carcinoma [30]. Predominating carcinomatous or sarcomatous component can be predictive factor for the response and planning the chemotherapy protocol [26]. Further series are required for replying some questions about ovarian MMMTs.

Conflict of interest None.

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