Malignant mixed Müllerian tumor of the fallopian tube: Case report and literature review

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Received April 19, 2021; Accepted May 19, 2021

DOI: 10.3892/etm.2021.11100

Abstract. Carcinosarcoma, also known as malignant mixed Müllerian tumor (MMMT), includes both malignant epithelial and mesenchymal elements. While the endometrium is the most frequent known site for carcinosarcomas, their development in the fallopian tube is rare condition, only accounting for 0.1 to 0.5% among all gynecological malignancies. Fallopian tube MMMT is associated with an aggressive progression. A total of 94 previous case reports were reviewed and divided, after applying the exclusion criteria, into 2 groups: No evidence of disease (NED) Group including 33 patients reported to be without any residual disease at the end of the follow-up period; death of disease (DOD) Group including 51 patients who died due to the progression of fallopian carcinosarcoma or its complications. The gathered data were statistically analyzed together with a case from our clinical experience: a 65-year-old postmenopausal patient with a final histological diagnosis of fallopian carcinosarcoma staged FIGO IC2, synchronous with a serous endometrial intraepithelial carcinoma. Patient age between 41 and 60 years, symptoms at presentation and computed tomography (CT)/magnetic resonance imaging (MRI) tumor evidence are prognostic factors ($P<0.05$). Omentectomy [odds ratio (OR)=0.3545] and pelvic lymphadenectomy (OR=0.3732) were found to be significant factors for survival ($P<0.05$). Fimbrial localization of the tumor is a negative prognosis factor (OR=4.263), as well as the heterologous type of tumor (OR=2.880). Chemotherapy was found to improve survival (OR=0.2679) while radiotherapy had no influence on patient prognosis. Reporting these rare cases could be essential for obtaining more precise information regarding the treatment and prognosis of patients with MMMT of the fallopian tube, in order to improve patient survival and quality of life.

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Key words: fallopian tube, carcinosarcoma, surgery, chemotherapy, omentectomy, lymphadenectomy

Introduction

Malignant mixed Müllerian tumors (MMMT), widely known as carcinosarcomas, are extremely rare and highly malignant neoplasms when diagnosed in the female genital tract (1). Field literature recognizes the uterus, cervix and ovary as the most common primary sites of these malignancies (2). While the endometrium is the most frequent known site for carcinosarcomas, their development in the fallopian tube is a rare condition, only accounting for 0.1 to 0.5% among all gynecological malignancies (3,4). Usually fallopian carcinosarcomas develop in the fifth to sixth decade in postmenopausal women, and the preoperative non-specific aspects and multiple similarities to hydrosalpinx, ovarian malignancies or tuboovarian abscess lead in most cases to a misdiagnosis. Symptomatology has no specific elements; the presenting symptom being usually abdominal pain mostly in the hypogastric area, followed by abnormal vaginal bleeding or abdominal distension, and exceptionally with an acute clinical picture (5,6). Due to all the mentioned elements, a diagnosis of certitude is extremely difficult to confirm, often being verified only by the final histology result, but in some cases cervical cytology or endometrial curettage may guide the specialist (7).

Regarding the histological features, MMMTs integrate both stromal and epithelial, carcinomatous and sarcomatous elements, typically high grade, with a significantly aggressive progress and a poor patient prognosis. In addition, this type of tumor usually metastasizes and disseminates rapidly among the pelvic organs in approximately 60% of the cases, but also to the peritoneum, paraaortic lymphatic nodes, even distant metastasis to the lungs, liver or bones (8,9).

The present article presents one case of fallopian MMMT with heterologous elements synchronous with an endometrial serous carcinoma surgically operated on in the First Obstetrics and Gynecology Clinic, 'George Emil Palade' University of Medicine, Pharmacy, Science, and Technology, Târgu Mureș,

Romania. In addition, a meta-analysis of the medical literature was performed in order to find correlations between the patient medical data and prognosis.

Patients and methods

A synchronous fallopian MMMT together with an early-stage endometrial serous carcinoma is further described. Moreover, the present study incorporates all the data found in field literature regarding MMMTs, statistically analyzed in order to identify potential associations between specific characteristics and the described management of each patient and the post-treatment survival. The data available in English literature was found through Medline search, using the following keywords: 'fallopian carcinosarcoma', 'tubal carcinosarcoma' and 'fallopian malignant mixed tumor'.

During the Medline search, 94 patients were reported between 1902 and 2019. Ten cases were excluded because the patients were lost to follow-up, or because of the lack of reported information. Finally, 84 cases presented in Table I (4,5,7,8,10-69), together with the one case surgically operated on by our team were included in the present analysis. The reported cases were divided into 2 groups according to patient outcome at the end of the follow-up period in each case: No Evidence of Disease (NED) group including 33 patients reported to be without any residual disease at the end of the follow-up period; death of disease (DOD) group including 51 patients who died due to the progression of fallopian carcinosarcoma or its complications. The collected data concerned the patient age at diagnosis, signs and symptoms at presentation, imaging findings, the accuracy of the first diagnosis, surgical, histological and oncological aspects.

Statistical analysis. Data were gathered from the previously reported cases in the literature and processed using Microsoft Excel. For the statistical analysis, the GraphPad InStat software (GraphPad Software, Inc.) was used, made available by 'George Emil Palade' University of Medicine, Pharmacy, Science, and Technology of Târgu Mureș, Romania. Quantitative variables were revealed as mean and median, qualitative and categorical variables being expressed as integer and percentage values. For all variable groups the normality of distribution was evaluated by applying Kolmogonov-Smirnov test. Quantitative analysis was performed using the Student's t-test for groups with Gaussian distribution of values and Mann-Whitney test for groups with abnormal distribution. Inferential statistics consisting in odds ratio (OR) calculations for mentioned pre-treatment, surgical, histopathological and oncological data was conducted with Fisher's exact test, this offering a higher accuracy. The level of statistical significance was established at a P-value of 0.05, with a 95% confidence interval for all the investigated parameters.

Case report

Clinical and paraclinical findings. A female patient aged 65, primigravidae, primiparous presented with a moderate lower abdomen discomfort and a light atypical vaginal bleeding for 2 weeks. The patient was postmenopausal from the age of 50, this being the first bleeding episode. At the clinical gynecologic exam, no vaginal or cervical macroscopic pathologies were detected, but abdominal palpation revealed a moderate sensitivity in the hypogastric area, accentuated in both iliac fossa. Transvaginal ultrasonography uncovered images suggesting a bilateral hydrosalpinx of 92x33 mm on the right side and 45x12 mm on the left side, also showing an intracavitary image pleading for a large endometrial polyp of 19x23 mm. These ultrasonography findings did not raise any suspicions or the necessity of substantial imagistic explorations, due to the absence of criteria which could indicate a neoplastic disease. After appropriate counseling and considering the patient age and associated medical conditions, the patient was scheduled for an operative hysteroscopy followed by laparoscopy and histopathological exam.

Intraoperative appearance. On October 2019, the patient was admitted to the First Obstetrics and Gynecology Clinic, Targu Mures Emergency Clinical County Hospital, Romania, for a combined hysteroscopic and laparoscopic approach. Under general anesthesia, a diagnostic hysteroscopy was performed, which revealed an atrophic endometrium with permeable tubal ostia together with an endometrial tumor suggesting a polyp. Thus, a hysteroscopic polypectomy was performed and the specimen was sent for histopathological examination.

During the laparoscopic phase, extended perianexial adhesions on the left side were found and an atrophic uterus and ovaries. Both fallopian tubes were enlarged and tumoral, similar to a hydrosalpinx with thick walls, sinuous, measuring 7x2x3 cm on the left side and 8x7x4 cm on the right side, without noticeable vegetation on the tubal surface but with mixed content, both fluid and cerebroid, expelled through the pavilion. A bilateral adnexectomy was performed and the specimen was carefully extracted through a mini laparotomy in the left iliac fossa and sent for frozen section, which confirmed malignancy. Subsequently, a laparotomy approach was chosen and a total hysterectomy, pelvic and paraaortic lymphadenectomy, appendectomy, total omentectomy were performed, without intraoperative complications and with no residual disease in the abdomen. Her postoperative recovery was uneventful under antibiotic prophylaxis and anticoagulant treatment. The patient was discharged on the 7th postoperative day. After surgery and the final pathology result, the patient completed 6 cycles of systemic chemotherapy with carboplatin and paclitaxel and has NED.

Histopathological examination. Macroscopic and microscopic features of the two excised fallopian tubes are presented in Figs. 1 and 2. The right fallopian tube measured 110x45 mm, exhibited an increase in volume and dilated on the entire length, presenting a ruptured serosa in several portions and a friable white tumoral mass which filled and enlarged the lumen in all performed sections, with many necrotic associated with hemorrhagic areas. The left fallopian tube measured 50x15 mm, with dilated portions and the examined sections unveiling a white vegetant tumoral mass extended in the entire length of the organ.

Microscopically, in both fallopian tubes, the same type of infiltrative tumor was found, with mixed aspect: an epithelial component of high-grade serous carcinoma associated with heterologous elements, such as chondrosarcoma, liposarcoma and undifferentiated sarcoma, with

Table I. Previously reported cases of fallopian MMMT.

Patient no.	Author (Refs.)	Year of report	Age of patients (years)	FIGO stage	Outcome
1	Motta (10)	1926	14	IV	DOD
2	Zacho (11)	1933	N/D	IIIC	DOD
3	Platz (12)	1940	58	IV	DOD
4	Bochner (13)	1961	58	N/D	DOD
5	Williams and Woodruff (14)	1963	35	IV	DOD
6	Malnasy and Gaal (15)	1963	45	IIB	DOD
7	McQueeney *et al* (16)	1964	69	IIB	DOD
8	De Queiroz and Roth (17)	1970	64	IIIC	DOD
9	Wu *et al* (18)	1973	57	IA	NED
10	Acosta *et al* (19)	1974	46	IIB	DOD
11	Acosta *et al* (19)	1974	62	IV	DOD
12	Acosta *et al* (19)	1974	48	IC	DOD
13	Aggarwal *et al* (20)	1976	50	IIIC	DOD
14	Manes and Taylor (21)	1976	76	IA	DOD
15	Manes and Taylor (21)	1976	74	IA	DOD
16	Manes and Taylor (21)	1976	47	IA	NED
17	Manes and Taylor (21)	1976	58	IA	NED
18	Henderson *et al* (22)	1977	62	IIB	DOD
19	Jain (23)	1977	52	IA	NED
20	Oka *et al* (24)	1978	57	IA	NED
21	Hanjani *et al* (25)	1980	62	IV	DOD
22	Viniker *et al* (26)	1980	63	IA	NED
23	Holst and Erichsen (27)	1981	65	IIIC	NED
24	O'Toole *et al* (28)	1982	71	IV	DOD
25	Egorov (29)	1982	53	N/D	DOD
26	Kahanpää *et al* (30)	1983	65	III	NED
27	Deppe *et al* (31)	1984	68	IIIB	NED
28	Punnonen *et al* (32)	1985	68	IIIC	DOD
29	Buchino and Buchino (33)	1987	61	IIIC	DOD
30	Yabushita *et al* (34)	1987	53	IIA	NED
31	Chen and Wolk (35)	1988	56	IC	DOD
32	Muntz *et al* (36)	1989	57	IIIC	DOD
33	Muntz *et al* (36)	1989	60	IIIA	DOD
34	Muntz *et al* (36)	1989	61	IV	DOD
35	Axelrod *et al* (37)	1989	62	IIIC	NED
36	Kinoshita *et al* (38)	1989	79	IC	NED
37	van Dijk *et al* (39)	1990	45	IIA	DOD
38	van Dijk *et al* (39)	1990	67	IIIB	DOD
39	Seraj *et al* (40)	1990	62	IIIC	DOD
40	Seraj *et al* (40)	1990	53	IIIC	DOD
41	Liang *et al* (41)	1990	63	IIIC	DOD
42	Chang *et al* (42)	1991	66	III	DOD
43	Chiou *et al* (43)	1991	63	IIIC	DOD
44	Imachi *et al* (5)	1992	60	IIIC	DOD
45	Imachi *et al* (5)	1992	67	IV	DOD
46	Moore *et al* (44)	1992	66	IIIC	DOD
47	Carlson *et al* (45)	1993	72	IIIC	DOD
48	Carlson *et al* (45)	1993	56	IIIC	NED
49	Carlson *et al* (45)	1993	60	IB	NED
50	Carlson *et al* (45)	1993	44	IA	NED
51	Carlson *et al* (45)	1993	59	IIIB	NED
52	Weber *et al* (46)	1993	74	IIA	NED

Table I. Continued.

Patient no.	Author (Refs.)	Year of report	Age of patients (years)	FIGO stage	Outcome
53	Zorlu *et al* (47)	1994	38	III	DOD
54	Horn *et al* (48)	1996	62	IIIB	DOD
55	Horn *et al* (48)	1996	64	IIB	DOD
56	Horn *et al* (48)	1996	69	IIIC	DOD
57	Horn *et al* (48)	1996	71	IV	DOD
58	Ebert *et al* (49)	1998	70	IA	NED
59	Maitra *et al* (50)	2004	29	IIIA	DOD
60	Moustafa *et al* (51)	2004	75	IIA	DOD
61	Humble and Carter (52)	2004	63	IIIC	DOD
62	Lim *et al* (53)	2004	57	IA	NED
63	Gagner and Mittal (54)	2005	77	IV	DOD
64	Kuroda *et al* (55)	2005	65	IIB	DOD
65	Das *et al* (56)	2005	49	III	NED
66	Das *et al* (56)	2005	80	IIB	DOD
67	Hudelist *et al* (57)	2006	57	IIB	NED
68	Kuroda *et al* (58)	2007	77	IIIC	DOD
70	Kawaguchi *et al* (59)	2008	69	IC	NED
71	Kourea *et al* (60)	2008	72	IIIC	NED
72	Piura *et al* (61)	2009	46	IIIC	NED
73	Shen *et al* (8)	2010	58	III	DOD
74	Malhotra *et al* (62)	2012	60	IIIC	DOD
75	Watanabe *et al* (7)	2012	53	IIIC	NED
76	Tsai *et al* (63)	2012	57	IIIA	NED
77	Gupta and Jenison (64)	2011	74	IIIC	DOD
78	Takemoto *et al* (65)	2015	56	IIIC	DOD
79	Narin *et al* (66)	2015	68	IIA	NED
80	Vale-Fernandes *et al* (67)	2015	57	IIA	NED
81	Ji *et al* (4)	2015	60	IIIC	NED
82	Monsalve *et al* (68)	2015	71	III	NED
83	Zhang *et al* (1)	2018	70	IIIB	NED
84	Bécsi *et al* (69)	2019	70	IIIB	NED

MMMT, malignant mixed Müllerian tumors; NED, no evidence of disease; DOD, death of disease; N/D, not determined.

extended areas of necrosis and hemorrhage. In the tubal epithelium, multiple serous intraepithelial carcinoma zones with an increased mitotic index were observed. In the right tube, the tumor was found to infiltrate the entire wall, and tumoral cells were found on the serosa. In the left tube, the tumor infiltrated only the muscular wall. The microscopic examination revealed lymphovascular emboli but without tumoral invasion in the ovaries and without metastases in all the 58 pelvic and paraaortic removed lymph nodes. The omentum and appendix were tumor-free.

Regarding the uterus, the endometrial mass appeared as a polypoid lesion with predominant atrophic glands, but with serous endometrial intraepithelial carcinoma features on the surface, with no invasion. The microscopic aspect is presented in Fig. 3. The final histological diagnosis was bilateral tubal carcinosarcoma (MMMT) and synchronous serous endometrial intraepithelial carcinoma, FIGO stage IC2 and pTNM stage pT1c2.

Results

The pre-treatment assessment of the cases previously reported in the literature (4,5,7,8,10-69) is presented in Table II. The mean age was not significantly different in the study groups. Regarding the patients' repartition by decades, the age interval 41-60 years was a statistically significant protective factor towards death (OR=0.3684, P=0.0419). Patients' age <40 years and 61-80 years represented a higher risk for a negative outcome, although the results were not statistically significant. Regarding the symptoms, the abdominal distention reported in the died of disease (DOD) group was confirmed to be the only one directly affecting prognosis and could be considered a risk factor for death with an OR=3.955 (P=0.0226). In addition, ascites was found to influence the outcome, being present in 17.6% of the patients included in the DOD group, but the calculated P-value for its OR was above the level of statistical significance. Tumor evidence on imaging could better

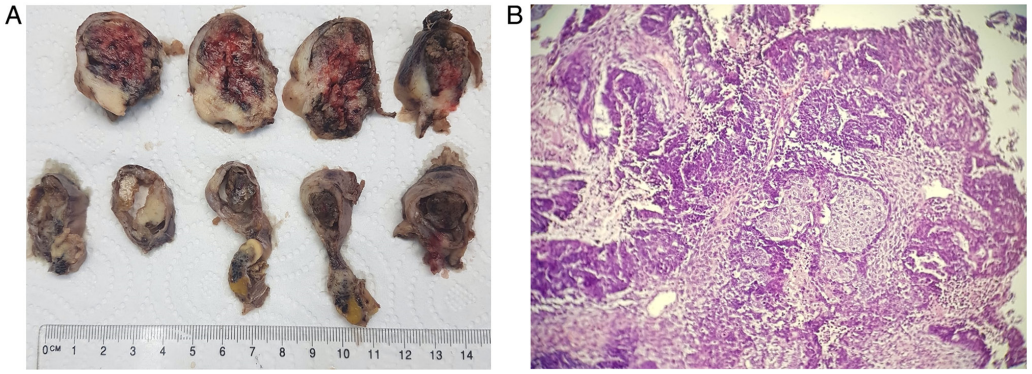

Figure 1. Right fallopian tube: (A) macroscopic and (B) microscopic features in hematoxylin and eosin staining.

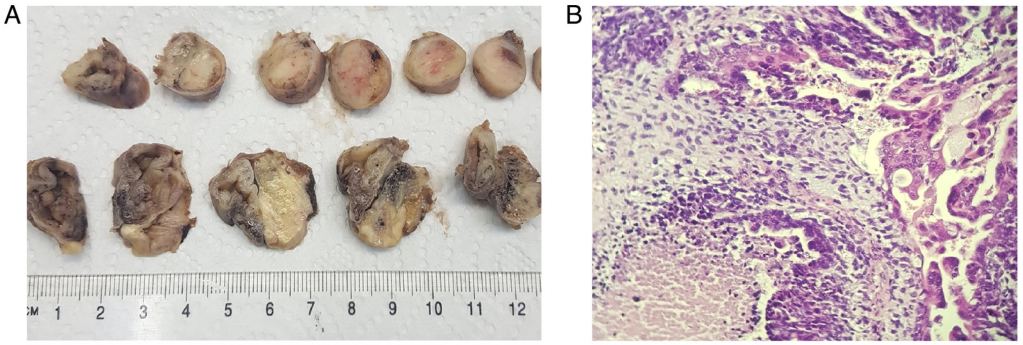

Figure 2. Left fallopian tube: (A) macroscopic and (B) microscopic features in hematoxylin and eosin staining.

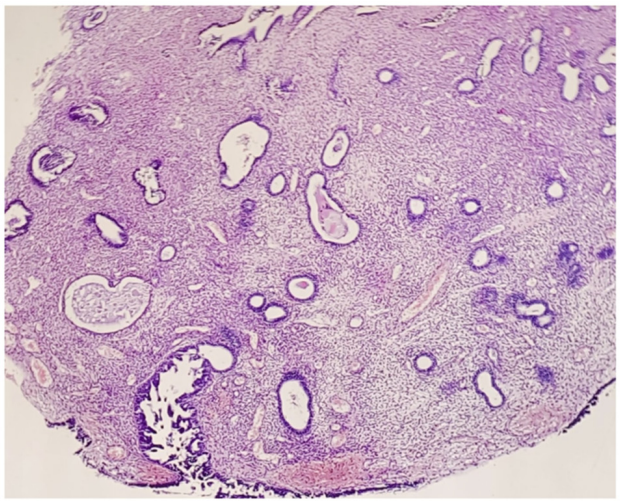

Figure 3. Endometrial polyp with '*in situ*' serous carcinoma features; hematoxylin and eosin staining.

guide treatment, prolonging the life of patients (OR=0.2500, P=0.0216). Cancer antigen (CA)125 level was not shown to be a statistically significant prognostic factor, but the published data when performed by routine in patients with suspicious tubal malignancies were poor. The accuracy of the initial diagnosis was low due to the multiple non-specific elements of the disease as previously mentioned, more frequent patients being diagnosed with ovarian or pelvic tumor, followed by hydrosalpinx in both the NED and DOD groups. None of the initial misdiagnoses affected prognosis from the statistical perspective.

In Table III, the surgical management and pathology reports are shown. Concerning the surgical treatment, a total hysterectomy and bilateral salpingo-oophorectomy were performed for most of the patients. Omentectomy proved to be a statistically significant protective factor, increasing the survival (OR=0.3545, P=0.0269). Similar data were found regarding pelvic lymphadenectomy, performed more frequent in the NED group (42.4%), with an OR=0.3732 and P=0.05. The need for bowel resection in fallopian MMMT patients could highly predispose to a poor prognosis, but the calculated chance rates (OR=7.925) were not statistically significant. Other surgical procedures, such as appendectomy, paraaortic lymphadenectomy, peritonectomy or metastases resection did not present statistical importance in the patient evolution.

The presence of extragenital metastases proved to be risk factors for death, especially involving the lymph nodes (OR=3.055, P=0.0491), bowel (OR=4.263, P=0.05) or distant organs and tissues (OR=14.976, P=0.0103). Although omentectomy has been proven to be a protective factor, the evidence of omentum metastases was not highly reported in the reviewed articles, thus the OR for this parameter (OR=2.026) was not statistically significant. FIGO staging was another important aspect searched in previous reports. FIGO stage I can be considered a positive prognosis factor, the results fitting into protective factor intervals towards death (OR=0.1309, P=0.0007). Patients with FIGO staged IIIC (OR=2.567, P=0.05) and IV (OR=14.976, P=0.0103) were more susceptible to negative post-treatment outcomes.

Table II. Pre-treatment evaluation in the field literature.

Features	No evidence of disease (NED) group (n=33), n (%)	Death of disease (DOD) group (n=51), n (%)	Odds ratio (OR)	P-value
Age of the patients (years)				
<40	0 (0)	3 (5.9)	4.8350	NS
41-60	19 (57.6)	17 (33.3)	0.3684	**0.0419**
61-80	14 (42.4)	31 (60.8)	2.1040	NS
Mean age	60.27	61.25	-	NS
Signs and symptoms				
Atypical vaginal bleeding	16 (48.5)	21 (41.2)	0.7438	NS
Pelvic mass	10 (30.3)	12 (23.5)	0.7077	NS
Abdominal pain	13 (39.4)	25 (49.0)	1.4790	NS
Abdominal distention	4 (12.1)	18 (35.3)	3.9550	**0.0226**
Fever	1 (3.0)	2 (3.9)	1.3060	NS
Ascites	2 (6.0)	9 (17.6)	3.3210	NS
Other pre-treatment findings				
CT/RMN tumor evidence	10 (30.3)	5 (9.8)	0.2500	**0.0216**
CA125				
Normal	3 (9.1)	1 (2.0)	0.2000	NS
Elevated (>35 U/ml)	4 (12.1)	4 (7.8)	0.6170	NS
No evidence	25 (75.8)	48 (94.1)	-	-
Accuracy of first diagnosis				
Accurate diagnosis	1 (3.0)	3 (5.9)	2.0000	NS
Ovarian tumor	8 (24.2)	8 (15.7)	0.5814	NS
Pelvic tumor	4 (12.1)	6 (11.8)	0.9667	NS
Hydrosalpinx	3 (9.1)	1 (2.0)	0.2000	NS
Uterine tumor	1 (3.0)	1 (2.0)	0.6400	NS

CT/MRI, computed tomography/magnetic resonance imaging; CA, cancer antigen. NS, not significant (P>0.05). Significant P-values (P<0.05) are presented in bold print.

The histologic features were also analyzed, depending on the existing evidence in the reviewed articles. Despite the lack of existing data regarding the tumor localization in different segments of the fallopian tube, an intraluminal development of the tumor could be a protective factor in relation to death (OR=0.0636), while fimbrial localization is more probable to be a risk factor (OR=4.263), but none of the parameters presented statistical significance. Analyzing the histological type of the MMMT, homologous type was a protective factor for death (OR=0.3472) while heterologous type could be considered a risk factor (OR=2.880), both parameters being extremely significant (P=0.0247). Due to insufficient evidence concerning the heterologous-specific elements, the obtained results are not of statistical importance.

Oncological approach and patient follow-up data are presented in Table IV. In the NED group, the majority of patients (72.7%) received systemic chemotherapy, the statistical analysis results confirming that chemotherapy administration is a very significant protective factor against death, with an OR=0.2679 and P=0.0070, while the absence of chemotherapy in the treatment of fallopian MMMT is an uncontestable risk factor (OR=3.733). Regarding the chemotherapy agents reported, the only regimen with a statistical positive impact on the survival of patients was carboplatin + paclitaxel (OR=0.2857, P=0.0293). The necessity of using multiple therapeutic lines during the treatment may suggest a negative outcome (OR=2.1330, OR=2.2140), but without statistical significance. Concerning radiotherapy, the evidence gathered from the literature did not suggest any significant involvement in disease progression from a statistical perspective.

Regarding the follow-up period, after eliminating the outlier values, the average was 33.40 months in the NED group and 13.19 months in the DOD group, the differences being statistically significant (P<0.0001). The median survival was 29 months in the NED and 8 months in the DOD group. The follow-up period depending on FIGO stage also presented several differences between the two groups. For stages I (A-C) and III (A-B), there were no statistically significant differences regarding the average follow-up period in the NED and DOD group. For FIGO stage II (A-B), the average follow-up was 29 months in the NED and 11.33 months in the DOD group, differences being statistically significant (P=0.0256). For stage IIIC, the average follow-up was significantly higher in the NED (31.75 months) than in the DOD group (12.13 months) (P=0.0034). It is also notable that were no FIGO stage IV patients in the NED group.

Table III. Surgical management of fallopian MMMT.

Feature	No evidence of disease (NED) group (n=33), n (%)	Death of disease (DOD) group (n=51), n (%)	Odds ratio (OR)	P-value
Surgical procedure				
Hysterectomy	32 (96.9)	42 (82.4)	0.1458	NS
Bilat. salpingo-oophorectomy	32 (96.9)	47 (92.2)	0.3672	NS
Omentectomy	20 (60.6)	18 (35.3)	0.3545	**0.0269**
Appendectomy	7 (21.2)	8 (15.7)	0.6910	NS
Pelvic lymphadenectomy	14 (42.4)	11 (21.6)	0.3732	**0.0500**
Paraaortic lymphadenectomy	6 (18.2)	7 (13.7)	0.7159	NS
Peritonectomy	1 (3.0)	2 (3.9)	1.3060	NS
Bowel resection	0 (0)	5 (9.8)	7.9250	NS
Metastases resection	5 (15.2)	6 (11.8)	0.7467	NS
Presence of extragenital metastases				
Omentum	7 (21.2)	18 (35.3)	2.0260	NS
Appendix	2 (6.1)	2 (3.9)	0.6327	NS
Lymph nodes	5 (15.2)	18 (35.3)	3.0550	**0.0491**
Peritoneum	7 (21.2)	17 (33.3)	2.0000	NS
Bowel	2 (6.1)	11 (21.6)	4.2630	**0.0500**
Distant	0 (0)	9 (17.6)	14.9760	**0.0103**
FIGO staging				
I (A-C)	13 (39.4)	4 (7.8)	0.1309	**0.0007**
II (A-B)	6 (18.2)	8 (16.7)	0.8372	NS
III (A-B)	6 (18.2)	7 (13.7)	0.7159	NS
IIIC	8 (24.2)	23 (45.1)	2.5670	**0.0500**
IV	0 (0)	9 (17.7)	14.9760	**0.0103**
Tumor localization				
Intraluminal	16 (48.5)	14 (27.4)	0.0636	NS
Fimbria	2 (6.1)	11 (21.6)	4.2630	NS
No evidence	15 (45.4)	26 (51.0)	-	-
Histological type				
Homologous	18 (54.5)	15 (29.4)	0.3472	**0.0247**
Heterologous	15 (45.5)	36 (70.6)	2.8800	**0.0247**
Chondrosarcoma	13 (39.4)	26 (51.0)	1.6000	NS
Rhabdomyosarcoma	4 (12.1)	12 (23.5)	2.2231	NS
Osteosarcoma	2 (6.1)	1 (2)	0.3100	NS
Liposarcoma, angiosarcoma	4 (12.1)	0 (0)	0.0636	**0.0212**

MMMT, malignant mixed Müllerian tumors; NS, not significant (P>0.05). Significant P-values (P<0.05) are presented in bold print.

Fig. 4 presents the Kaplan-Meier survival analysis and survival rates at different checkpoints. The survival rate was 0.9879 at 1 month of follow-up, 0.8049 at 6 months, 0.4657 at 2 years, while at 5 years of follow-up it was 0.2865.

MMMT accounts for about 2.4% of all fallopian tube malignancies, and only 4% from this histologic type develop in the fallopian tube as a primary tumor. The rarity of fallopian MMMTs could be correlated with the reduced cyclical activity and lower hormonal responsiveness of the tubal stroma, as compared with endometrial stroma where these tumors occur almost 10 times more frequently (16). These tumors are associated with high invasiveness and poor patient prognosis, especially if the diagnosis is delayed. Due to the extremely low incidence of fallopian carcinosarcoma, clinical protocols for these tumors are not clearly established (22,70).

Discussion

Previously published literature reviews (Table I) (4,5,7,8,10-69) have revealed that the average age of the 85 patients was 59.7 years. Regarding the symptomatology at presentation, our results are in accordance with previous reports by reporting atypical vaginal bleeding and pelvic pain or discomfort, although there is no relevant evidence for which these symptoms may be correlated with prognosis. MMMTs can present, although rarely, as acute abdomen, cases in which are associated

Table IV. Oncological approach and follow-up.

Treatment approach	No evidence of disease (NED) group (n=33), n (%)	Death of disease (DOD) group (n=51), n (%)	Odds ratio (OR)	P-value
Chemotherapy				
Received	24 (72.7)	20 (39.2)	0.2679	**0.0070**
Not received	9 (27.3)	28 (54.9)	3.7330	**0.0070**
No evidence	0 (0)	3 (5.9)	-	-
First-line chemotherapy agents				
Carboplatin+paclitaxel	11 (45.8)	6 (30.0)	0.2857	**0.0293**
Cisplatin+doxorubicin+cyclophosphamide	7 (29.2)	8 (40.0)	0.7429	NS
Cyclophosphamide+vincristine+doxorubicin	2 (8.3)	1 (5.0)	0.3298	NS
Vincristine+actynomicin D+cyclophosphamide	1 (4.2)	2 (10.0)	2.1330	NS
Unknown agents	3 (12.5)	3 (15.0)	-	-
Multiple therapeutic lines	2 (8.3)	6 (30.0)	2.2140	NS
Radiotherapy				
Received	12 (36.4)	16 (31.4)	0.8750	NS
Not received	21 (63.6)	32 (62.7)	1.1430	NS
No evidence	0 (0)	3 (5.9)	-	-
Follow-up (months)				
Average	33.40	13.19	-	**<0.0001**
Median	29	8		
FIGO stage				
Stage I (A-C)	46.53	26	-	NS
Stage II (A-B)	29	11.33	-	**0.0256**
Stage III (A-B)	40.17	29.42	-	NS
Stage IIIC	31.75	12.13	-	**0.0034**
Stage IV	-	18.5	-	-

NS, not significant (P>0.05). Significant P-values (P<0.05) are presented in bold print.

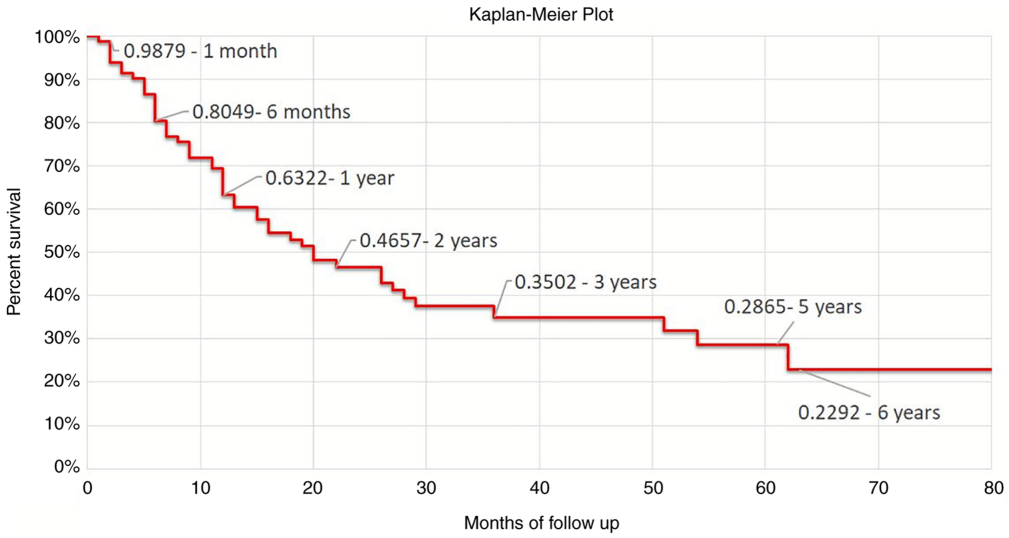

Figure 4. Kaplan-Meier survival plot at different checkpoints.

with torsion or rupture, leading to hemoperitoneum (64,66). Due to the common symptoms of MMMTs, rarity and localization, an initial definitive diagnosis is very difficult to achieve and prove, in the majority of cases remaining uncertain

until the histological examination is performed; the most frequent preoperative and intraoperative diagnosis is related to an ovarian tumor, underlining its inaccuracy (67). Concerning imaging examination, MRI is more sensitive compared to CT to distinguish various tumor characteristics that may facilitate the preoperative diagnosis and further treatment, although imaging reports of carcinosarcoma of the fallopian tube are limited, as well as the role of CA125 (71).

Despite the lack of therapeutic protocols for fallopian MMMTs and the small number of reported cases, the strategy involves a primary surgical procedure aimed to resect all visible tumors, followed by oncological treatment intensely debated in the past decades (72). For proper staging, ascites or peritoneal washings must be collected for cytological examinations, followed by a thorough exploration of all peritoneal surfaces; a total hysterectomy and bilateral salpingo-oophorectomy must be performed, together with omentectomy, lymphadenectomy and peritoneal biopsies, depending on the intraoperative findings, achieving a maximal cytoreduction when possible (48,73). As already demonstrated, omentectomy could be an important positive prognostic factor, together with pelvic lymphadenectomy, but the extent of surgery might be variable and sometimes demanding because of pelvic modified anatomy, requiring a retroperitoneal dissection (74). Regarding the possible metastatic sites, the most frequent are the contralateral tube, ovaries, uterus, but also the peritoneal surface, emphasizing that pelvic and paraaortic lymphatic nodes are not often involved, while distant metastasis is extremely rare (63), but our meta-analysis has confirmed that omentum, lymph node and distant metastases in fallopian MMMTs are often described. Sometimes, when the fallopian tumor invades other pelvic organs, different types of exenterative procedure must be performed, but these situations are rare (75).

A proper staging concerning fallopian carcinosarcomas is essential to adopt a therapeutic strategy, the survival rates being directly dependent on this parameter. As the results of the meta-analysis demonstrated, FIGO stage I presented the best survival outcomes, while FIGO stages IIIC and IV were prone to death due to disease. The prognosis of a primary fallopian tube malignancy is usually poor and depends rather on staging than on histological criteria, such as tumor type or grade (76).

Previous histological macroscopic descriptions of the tumor were similar with the present case report, revealing a dilated lumen of the tube containing polypoid or infiltrative grey or white colored mass, more frequent with necrosis and hemorrhage areas (69). Microscopically two mentioned components of the MMMT were often reported-a serous carcinoma with high-grade malignancy associated with a neoplastic proliferation of the conjunctive tissue, the presence of chondrosarcoma detected in about 50% of cases (38,60). The current meta-analysis has shown that a fimbrial localization of the tumor could predispose to a more aggressive tumor evolution, an issue explained by the fact that intraluminal fluid can be discharged through the uterus in the case of fimbrial atresia. But when the end of the fimbria remains open or the tumor develops at this level, it is more likely for tumor cells to be implanted into the abdominal cavity, situations in which the prognosis is poor (77). The histological type is also known to be a prognostic factor in many gynecological malignancies. Current meta-analysis results reporting that the heterologous type of fallopian carcinosarcoma could negatively affect survival and, by contrary, homologous MMMTs are thought to be associated with a better prognosis (78).

Systemic chemotherapy significantly improves survival, especially associated with an optimal cytoreductive surgery, as mentioned before. Over the past several decades, multiple regimens have been tried, demonstrating that adjuvant chemotherapy containing platinum agents is the most effective treatment for fallopian carcinosarcomas (79). GOG Study analyzed the association between ifosfamide and cisplatin, confirming no survival advantage, with the cost of increased toxicity (80). Currently, the combination of paclitaxel and carboplatin has been intensely studied and gained popularity in a great variety of gynecological malignant diseases, due to its important activity, acceptable toxicity and ease of administration; the results of current meta-analysis have also revealed that patients who received this drug combination exhibit better survival outcomes (59). Radiotherapy has no influence on prognosis and no benefit on survival (25,54,57,65,81).

To date, the few reported fallopian MMMTs emphasize its extremely low incidence and its high malignancy, fulminant progression, and high incidence of local and distant metastases, all associated with poor survival outcomes. As an early definite diagnosis is extremely difficult to achieve even with high performance imaging examinations, most of the cases are finally diagnosed after histological evaluation. Fallopian MMMTs should be considered as a differential diagnosis in all postmenopausal patients who present with a pelvic mass, vaginal bleeding, abdominal pain or distension and with no other significant findings. Due to the non-specific presentation, symptomatology and low incidence of this neoplasia, the success of conducting large randomized trials in order to improve diagnosis accuracy, treatment options and establish international therapeutic protocols is limited. Reporting this rare pathology could be essential for obtaining more precise information regarding the diagnostic methods, targeted treatment and prognosis, in order to improve the survival and quality of life in patients with MMMTs.

Acknowledgements

Not applicable.

Funding

No funding was received to complete the present literature research.

Availability of data and materials

Data was gathered from previously published reports and collected into a database. The dataset used and analyzed during the current study is available from the corresponding author on reasonable request, all the results being included in this article.

Authors' contributions

ALC conceived, directed the project and prepared the manuscript. MEC was the leading surgeon for the surgical procedure

described in our case report. AAM and NB supervised the work and revised the article. SM prepared and histologically analyzed the specimens. ALC, MG, SLK, AF and MS are part of the surgical team since 2016 and collected data from previously published articles. MG, SLK and MS were involved in designing and drafting the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable. Yet, informed consent was obtained for publication of the patient's data.

Patient consent for publication

The patient provided written informed consent for the scientific publication of any associated data and accompanying images.

Competing interests

Authors declare no competing interests relevant to this article.

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