Malignant mixed mullerian tumor of the ovary: report of four cases

G. A. Melilli, L. Nappi, C. Carriero, M. Lapresa, V. Loizzi, F. Caradonna M. Quaranta, G. Putignano

Gynecology Oncology Unit, University of Bari, Bari (Italy)

Summary

Introduction: Malignant mixed mullerian tumor (MMMT) of the ovary is an extremely rare gynaecologic neoplasm that represents 1% of the malignances of this organ. Stage I disease is rare because it is asymptomatic in early stage. We describe four cases.

Case reports: In the Department of Obstetrics and Gynecology of the University of Bari four cases of MMMT of the ovary were diagnosed. Three patients were in stage IIIC and one of them was a homologous MMMT; the fourth patient was affected by a heterologous stage IV MMMT. All women were treated with surgery and chemotherapy. Two patients are alive 14 and 12 months after diagnosis. The other two died after 37 months and one month, respectively.

Conclusions: The malignant mixed mullerian tumor (MMMT) of the ovary is a particularly aggressive tumor, especially in advanced stages. The survival rate is very low in spite of surgery, chemotherapy and radiotherapy. The optimal treatment for this neoplasm is unknown because of its rarity. Our experience, when considering survival, seems to confirm the use of cisplatin and ifosfamide and to give new horizons to taxol.

Key words: Ovarian cancer; Ovarian MMMT.

Introduction

Malignant mixed mullerian tumor (MMMT) of the ovary is an extremely rare gynaecologic neoplasm. It represents less than 1% of all malignances of this organ [1]. It is also particularly aggressive especially in advanced stages which are the majority of cases. The causes of this disease seem to generally be the same as those of common epithelial ovarian malignancies.

The most reliable histopathogenetic theory is that both the epithelial and stromal component, which are intimately associated, come from mullerian tissue.

Though aggressive surgery is generally felt to be indicated for this tumor, and because of the rarity, there is no uniform opinion about adjuvant therapy.

The survival rate is very low; at 12 months it varies between 23 and 64%, in spite of surgery, chemotherapy and radiotherapy treatment.

Prognosis depends on stage, residual tumor at surgery and is largely independent of histology, tumor grade and characteristics of the epithelial component.

We report four patients with this rare neoplasm admitted to our Unit and and the treatment we followed. All patients were staged according to FIGO classification of ovarian carcinoma and underwent surgical therapy and chemotherapy.

Case Report

Case 1

C.S., a 64-year-old Caucasian, G4P3, was referred to our Unit after THA/BSO and omentectomy with no residual intra-abdominal tumor at the end surgery; no mention of nodal status and Ca125 titer was given. Histologic examination showed a heterologous MMMT of the ovary with focal areas of condrosarcomatous differentiation. A total-body CT scan showed node enlargement in the left axilla (positive to histology), metastatic nodularity located in the IV hepatic segment and midline at the anterior pelvic wall. Ca 125 and Ca 72.4 were 244 and 59 UI/ml, respectively. According to FIGO criteria she was stage IV.

The patient received six courses of chemotherapy containing: mesna, ifosfamide, carboplatin and cisplatin. At the end of chemotherapy a total body CT scan, bipedal lymphography, serum level of tumoral markers and second-look laparotomy (including pelvic and lombo-aortic (L-A) lymphoadenectomy) did not show any evidence of residual disease.

She was submitted to six courses of taxol and was free of disease 22 months [R1] after diagnosis when ascites and a pelvic mass of 7 cm developed with Ca 125 levels within normal range. She was submitted to three courses of taxol and the CT scan showed disappearance of the mass. The patient died 37 months after diagnosis due to large bowel obstruction and disseminated disease.

Case 2

D.P., 55 years old, para 9/1/1/7, affected by chronic renal insufficiency and submitted to dialysis, was admitted to our Unit with a diagnosis of ovarian carcinoma with ascites in Stage IIIC. Ca 125 was 3,224 U/ml. She was treated with TAH&BSO and omentectomy; residual tumor was >2 cm in the paracolic and Douglas sites. Histologic examination showed a homologous MMMT, with positive peritoneal fluid, and negative pelvic lymph nodes. Immunohistochemistry was positive for CK Pool (+++) in the epithelial component and for vimentin (+++) in the sarcomatous component. The patient received five cycles of taxol and 14 months after diagnosis presented partial response with a Ca 125 titer off-limits.

Case 3

D.D., 61 years old, para 4/0/1/4, was admitted to our Unit with diagnosis of Stage IIIC ovarian carcinoma with ascites. Titers of Ca 125 and Ca 72.4 were respectively 1,056 and 13

Revised manuscript accepted for publication June 22, 2000

U/ml. The patient was treated with TAH&BSO, omentectomy, sigmoid resection, appendectomy and peritoneal debulking; residual tumor was >2 cm.

Histologic examination showed a heterologus MMMT and peritoneal fluid was suspicious. She received six courses of chemotherapy based on cisplatin, ifosfamide, mesna and epiadriamicin. The Ca 125 level was in range after the second course. The patient was free of disease 12 months after diagnosis.

Case 4

D.L., 59 years old, para 5/0/1/5, was admitted to our Unit with a diagnosis of ovarian carcinoma. Ca 125 level was 294 U/ml. She was treated with a suboptimal cyto-reduction. Residual tumor was >2 cm (omentum 20x15 cm, right iliac pit 6x8 cm, hepatic mass of 10 cm). Cytologic examination showed suspicious peritoneal fluid and negative pleural fluid. Histology was heterologous MMMT. The patient received one course of chemotherapy based on carboplatin, ifosfamide, cisplatin and mesna. She died 40 days after diagnosis due to rapid progression of disease.

Discussion and Conclusion

MMMT of the ovary is a particularly aggressive neoplasm that represents 1% of all ovarian malignancies [1].

Our data are in accordance with the literature, where MMMT generally arises in postmenopausal, nulliparous women with the highest incidence rate in the sixth decade. The most frequently encountered symptoms were the presence of an abdominal mass, pain or ascites; there was no vaginal bleeding.

Stage I disease is rare because, in general, it is asymptomatic in early stages, thus surgical therapy is associated with chemotherapy and/or radiotherapy.

Terada *et al.* found in 10% of cases the neoplasm to be bilateral and in 80% of cases metastasis, which after autoptic examination presented this distribution: serosa surface (5 patients), liver (3 patients), diaphgram (3 patient), peri-aortic lymphnodes (4 patients), soft pelvic tissue (3 patients), omentum (2 patients), spleen (1 patient), pancreas (1 patient), bladder (1 patient) [2].

Because of its rarity, the literature is very poor and there is no uniform opinion about treatment. Thus, the optimal treatment for this tumor is unknown.

Aggressive surgery with optimal cyto-reduction is very important in MMMT.

Radiotherapy does not seem to be superior to chemotherapy, having a referred mean survival time varying between 6 and 16 months [3].

In a GOG study Morrow *et al.* reported 3 CR plus 1 PR on 13 patients with measurable disease, using different chemotherapy regimens based on VAC (vincristine, adriamycin and cyclophosphamide) plus radiotherapy, doxorubicin plus cyclophosphamide or alkeran [1].

Carlon *et al.* treated 12 patients with a VAC regimen plus radiotherapy. Five patients out of 12 showed CR and a single patient, unstaged and without residual tumor at surgery, survived with NED 5 years after diagnosis [4].

In a GOG study single agent chemotherapy based on doxorubicin did not show any significant activity. Higher response rates of 50-70% have been reported for cisplatinum-based regimens [5].

Moore reported a median survival of 21 months for a group of patients treated with antracycline containing chemotherapy (VAC-CYVADIC-PAC) [6].

In spite of surgery, chemotherapy and/or radiotherapy the survival rate of MMMT is very low.

In a study of 22 patients only four survived from 3 to 13 years and this data was associated with stage I or II and with a purely homologous stromal pattern [7].

However, survival associated to the presence or absence of heterologous elements has not been confirmed by all authors.

The prognosis of MMT seems to depend on stage, residual tumor at surgery; it is largely independent of histology, tumor grade and characteristics of an epithelial component.

Our data in comparison to survival, seems to confirm the use of cisplatin and ifosfamide [5, 8] and to give new horizons to taxol.

Table 1.

Patient age	Stage Histotype	Ca125 Ca72.4	Surgery	Resid. Tumor	Chemotherapy 1° line	IInd look	RI	Chemotherapy 2nd line	RI/ months	Dead/Alive Survival
1	IV	+	THA/BSO	>2 cm	carboplatin	negative		Taxol	22	D
64	hetero	+	omentectomy		ifosfamide cisplatin mesna					37 mo
2	IIIC	+	THA/BSO	>2 cm	taxol	—				A
55	homol	–	omentectomy							14 mo
3	IIIC	+	THA/BSO	>2 cm	cisplatin	—				A
61	hetero	–	omentectomy appendectomy sigmoid res.		ifosfamide epiadriamicin mesna					12 mo
4	IIIC	+	suboptimal	>2 cm	carboplatin	—				D
59	hetero	–	cyto-reduction		ifosfamide cisplatin mesna					1 mo

References

[1] Morrow C. P., D'Ablaing G., Blady L. W.: "A clinical and pathologic study of 30 cases of malignant mixed mullerian epithelial and mesenchymal ovarian tumors. A Gynecologic Oncology Group Study". *Gynecol. Oncol.*, 1994, *18*, 278.

[2] Terada K. Y., Yohnson T. L., Hopkins M.: "Clinicopathologic features of ovarian mixed mesodermal tumors and carcinosarcomas". *Gynecol. Oncol.*, 1989, *32*, 228.

[3] Ostor A. G.: "Sarcoma degli organi molli anatomia patologica". In: "Surgical Gynecologic Oncology". Ed. Burghardi F. Theme, 1994, 397.

[4] Carlon J. A., Edwards C., Wharton J. T.: "Mixed mesodermal sarcoma of ovary: treatment with combination radiation therapy and chemotherapy". *Cancer*, 1983, *52*, 1473.

[5] Plaxe S. C.: "Clinical features of advanced ovarian mixed mesodermal tumors and treatment with doxorubicin and cisplatinum based chemotherapy". *Gynecol. Oncol.*, 1990, *37*, 244.

[6] Moore M., Fine S., Sturgeon J.: "Malignant mixed mesodermal tumors (MMMT) of the ovary. The Princess Margaret Hospital (PMH) experience". *J. Clin. Oncol.*, 1986, *5*, 114.

[7] Dictor M.: "Mixed mesodermal tumor of the ovary: a report of 22 cases". *Obstet. Gynecol.*, 1985, *65*, 720.

[8] Patsner B., Greenberg S.: "Mesna, Doxorubicin, Ifosfamide and Dacarbazine chemotherapy for ovarian mixed mullerian sarcoma: report of four cases". *Gynecol. Oncol.*, 1995, *58*, 386.

Address reprint requests to:
GIOVANNI ANTONIO MELILLI, M.D.
Via Faenza, 58
70019 Triggiano (Bari) Italy