Malignant mixed Müllerian tumor with small cell neuroendocrine differentiation: a case report and review of the literature

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Summary

Introduction: Small cell neuroendocrine differentiation (NE) in malignant mixed Müllerian tumors (MMMTs) is a rare and unusual occurrence with very few previously reported cases. There is no consensus regarding its diagnosis, classification, and optimal treatment options. *Case:* The authors report a patient with endometrial MMMT and NE differentiation who initially received comprehensive surgery followed by adjuvant chemotherapy containing cisplatin and etoposide. She further underwent metastasectomy and received carboplatin and paclitaxel for the relapse. She is still alive 12 months after the diagnosis. The authors performed a review of literature in order to characterize the clinical phenotype. These patients have a very aggressive disease. Median life expectancy seems to be less than a year. *Conclusions:* It is reasonable to perform comprehensive staging surgery followed by adjuvant chemotherapy irrespective to stage of the disease.

Key words: Malignant mixed Müllerian tumor; Small cell neuroendocrine differentiation; Endometrium.

Introduction

Malignant mixed Müllerian tumors (MMMTs) are aggressive biphasic neoplasms histologically composed of both malignant epithelial and mesenchymal components. The epithelial component may be of different Müllerian types, often a high-grade carcinoma such as serous, endometrioid, clear cell or undifferentiated. Whereas the sarcomatous component may be homologous or heterologous depending on whether it is composed of native mesenchymal elements of the Müllerian tract, such as endometrial stroma, fibrous tissue, smooth muscle or other non-native elements such as osteogenic, chondroblastic, lipoblastic or rhabdomyoblastic element [1].

Small cell neuroendocrine (NE) differentiation in MMMTs is quite rare as an epithelial component [2-7]. Herein the authors report a case of homologous endometrial MMMT with small cell carcinoma component with a brief review of the literature.

Case Report

A 67-year-old woman with neglected postmenopausal bleeding admitted to the present clinic with an endometrial biopsy of high-grade endometrial adenocarcinoma. On physical examination, she had an unremarkable cervix with a 16-week in size uterine mass extending to the umbilicus. Transvaginal ultrasound revealed an enlarged uterus with an irregular mass located within the uterine cavity. Bilateral adnexae were normal. An abdominal computed tomography revealed a 15 x 12 x 10 cm in size mass within the endometrial cavity and multiple pelvic-paraaortic lymphadenopathies. No distant metastases were detected.

The patient underwent exploratory laparotomy. The uterus was enlarged with irregular and nodular serosal surface. There were suspicious small peritoneal implants on the serosa of the urinary bladder. Both ovaries were grossly described as atrophic. Inspection of the abdomen and pelvis revealed no other abnormalities. Peritoneal washings from the pouch of Douglas and bilateral para-colic gutters were obtained. A comprehensive staging surgery, including total abdominal hysterectomy with bilateral adnexectomy, infracolic omentectomy, and pelvic-paraaortic lymph node dissection up to the renal vessels, was performed. Biopsy samples were taken from the suspicious peritoneal surfaces. The patient had an uneventful postoperative course.

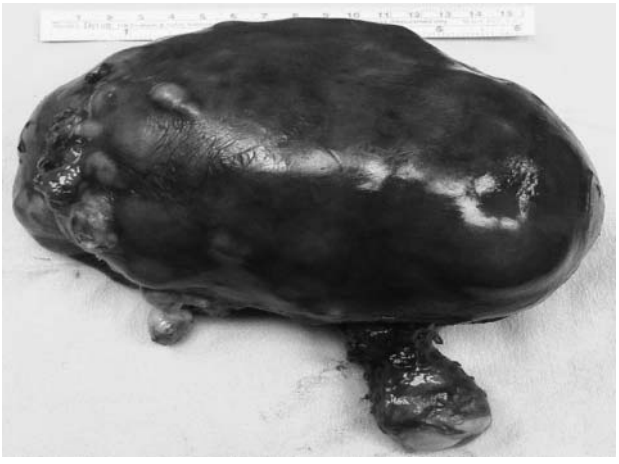

Figure 1. — Macroscopic appearance of the tumor.

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Table 1. — *Clinicopathological features of the patients.*

Reference	Case	Age	Origin	Sarcomatous Component	FIGO Stage	Primary Treatment	Survival Status	Survival (months)
Manivel C. *et al.*, 1986 [2]	1	67	Endometrium	Homologous	3A	Comprehensive staging surgery + Adj Pelvic RT	Died	5
George E. *et al.*, 1991 [3]	2	NR	Endometrium	Homologous	NR	NR	Not individually specified. Reported as "5 out of 6 patients had died within 9 months".	
George E. *et al.*, 1991 [3]	3	NR	Endometrium	Heterologous (chondrosarcoma, rhabdomyosarcoma)	NR	NR		
George E. *et al.*, 1991 [3]	4	NR	Endometrium	Heterologous (rhabdomyosarcoma)	NR	NR		
George E et. al., 1991 [3]	5	NR	Endometrium	Homologous	NR	NR		
George E. *et al.*, 1991 [3]	6	NR	Endometrium	Heterologous (chondrosarcoma)	NR	NR		
George E. *et al.*, 1991 [3]	7	NR	Endometrium	Heterologous (chondrosarcoma)	NR	NR		
George E. *et al.*, 1991 [3]	8	NR	Endometrium	Heterologous (chondrosarcoma, rhabdomyosarcoma)	NR	NR		
George E. *et al.*, 1991 [3]	9	NR	Endometrium	Heterologous (rhabdomyosarcoma)	NR	NR		
van Hoeven K.H. *et al.*, 1995 [4]	10	74	Endometrium	Heterologous (chondrosarcoma, osteosarcoma)	1B	Surgery + RT	Alive (NED)	3
Lim S.C. *et al.*, 1998 [5]	11	69	Adnexa	Homologous	3C	Comprehensive staging surgery + single cycle of cisplatin-doxorubicin, further cycles not given because of the patient's refusal.	Alive (NED)	4
Cokelaere K. *et al.*, 2001 [6]	12	78	Peritoneum	Heterologous (rhabdomyosarcoma)	3C	Resection of tumoral mass. No CT was given, due to poor performance.	Died	1
Ribeiro-Silva A. *et al.*, 2002 [7]	13	71	Cervix	Heterologous (rhabdomyosarcoma)	NR	Neoadjuvant CT + adj hysterectomy.	Alive (NED)	12
Present	14	67	Endometrium	Homologous	3C2	Comprehensive staging surgery + 6 cycles of cisplatin-etoposide. Metastasectomy + 2 cycles of paclitaxel-carboplatin for relapse	Alive	12

ADJ: adjuvant; RT: radiotherapy: NR: not reported; NED: no evident disease; CT: chemotherapy.

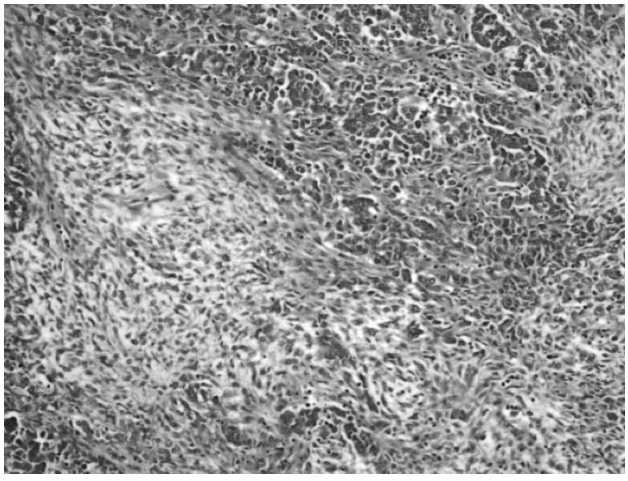

Figure 2. — Histologic appearance of the tumor: A biphasic tumor composed of poorly differentiated malignant glands and sarcomatous elements (*H&E, x10*).

Uterus was 15 × 15 × 15 cm in size on macroscopic examination. The serosal surface was fragile, tense, and nodular (Figure 1). Uterine cavity was filled with a bulky mass, 15 cm in diameter, with a lobulated cut surface and extensive necrosis. The mass showed a deep invasion into the myometrium extending to the outer surface of the serosa. The cervix, ovaries, fallopian tubes, and omentum were grossly unremarkable.

A biphasic tumor containing poorly differentiated malignant glands and sarcomatous elements was detected on microscopic examination (Figure 2). The epithelial component was the predominant element of tumor (Figure 3). It was highly cellular containing solid sheets of small uniform cells with a high nucleocytoplasmic ratio. The tumor cells had small round nuclei and scanty cytoplasm. Extensive tumor necrosis was evident.

On immunohistochemical staining, the epithelial component of the tumor showed diffuse and strong immunoreactivity for synaptophysin and CD 56; and focal positivity for pan-cytokeratin (pan-CK) (Figure 4a-c). Staining with chromogranin A and cytokeratin 7 (CK7) was negative. The mesenchymal component showed immunoreactivity for CD 10 (Figure 5a-b). However, staining for caldesmon and myoglobin were negative. These morphologic and

Table 2. — *Positive immunohistochemical neuroendocrine markers of the patients.*

Reference	Case	Chromogranin A	Leu-7	NSE	Synaptophysin	CD 56
Manivel C. *et al.*, 1986 [2]	1	−	+	+	NR	NR
George E. *et al.*, 1991 [3]	2	+	NA	NA	+	NA
George E. *et al.*, 1991 [3]	3	−	+	+	+	NA
George E. *et al.*, 1991 [3]	4	−	+	+	−	NA
George E. *et al.*, 1991 [3]	5	−	−	−	+	NA
George E. *et al.*, 1991 [3]	6	−	NA	+	+	NA
George E. *et al.*, 1991 [3]	7	−	+	+	+	NA
George E. *et al.*, 1991 [3]	8	+	+	+	−	NA
George E. *et al.*, 1991 [3]	9	+	+	+	−	NA
van Hoeven K.H. *et al.*, 1995 [4]	10	−	−	+	−	NR
Lim S.C. *et al.*, 1998 [5]	11	+	+	+	+	NR
Cokelaere K. *et al.*, 2001 [6]	12	+	+	+	+	NR
Ribeiro-Silva A. *et al.*, 2002 [7]	13	+	NR	NR	NR	NR
Present	14	NA	NA	NA	+	+

NR: not reported; NA: not applied.

immunohistochemical findings were consistent with homologous endometrial MMMT with small cell carcinoma component.

The cytological examination of peritoneal washings was positive for malignant epithelial cells. There were no cervical or omental involvement. Tumor emboli were evident in lymphovascular spaces. Microscopic foci of metastatic carcinoma were seen in the left ovary, pelvic-paraaortic lymph nodes, and serosa of the bladder. Tumoral invasion was also detected within the associated soft tissues of the involved lymph nodes. The post-operative positron emission tomography computed tomography (PET CT) scan revealed no evidence of distant metastasis. Thus, the patient was surgically staged as FIGO IIIC2 disease.

Adjuvant chemotherapy with cisplatin (100 mg/m^2, intravenously on day one) and etoposide (75 mg/m^2, intravenously on days one to three) was commenced. A total of six 28-day cycles were given with no serious adverse events. At the tenth month of follow-up, PET CT scan revealed a three-cm sized mass protruding from the lower pole of the left kidney (SUV max. of 13.8) and a lymphadenopathy 2.5 cm in size located beneath the left renal vein (SUV max. of 21.7). Re-laparotomy was performed. Peritoneal surfaces were unremarkable. Metastatic tumoral foci were completely resected.

The renal metastatic mass was invaded by the sarcomatoid component of the MMMT. Tumoral cells in mass showed immunoreactivity for actin and vimentin. However, HMB-45, chromogranin A, myoglobin, CD 10, CD 56, synaptophysin, and pan-CK were negative. Interestingly, associated lymph node was infiltrated by small cell carcinoma component of the MMMT. Tumoral cells in lymph node were focally positive for pan-CK; diffuse positive for CD 56 and synaptophysin; and negative for CK7, CD 10, caldesmon, chromogranin A, and myoglobin.

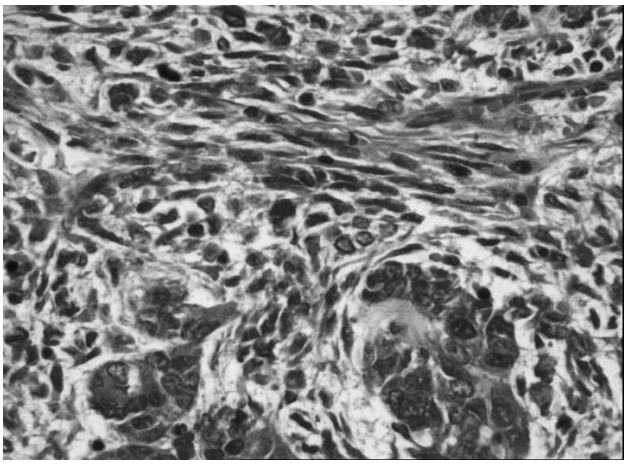

Figure 3. — The epithelial carcinoma (bottom) is admixed with malignant cells that have undergone sarcomatous transformation (top) (*H&E, x20*).

Carboplatin (5AUC) and paclitaxel (175 mg/m^2) regimen was started following the second surgery. The patient received the second cycle of chemotherapy and is still alive 12 months after the first operation.

Discussion

MMMTs are rare, high-grade neoplasms arising from structures that are embryologically related to the Müllerian system along the female genital tract and in peritoneum [1]. Those are more common in uterus than elsewhere, probably because the epithelium and mesenchyme in this site have a common embryologic origin [8].

MMMTs are currently thought to be undifferentiated or metaplastic carcinomas rather than sarcomas [1]. They contain malignant endometrial glands admixed with sarcomatous elements with the dominant element often being the epithelial component yet distinct from endometrial carcinoma [9]. The lack of difference in antigen expression profile between the epithelial and the sarcomatous components supports that the histogenesis of this tumor is probably from a single pluripotential malignant clone with distinct histological differentiation [10, 11]. The carcinomatous component is usually serous (2/3 of cases) or endometrioid (1/3). However, it may rarely be clear cell, mucinous, squamous cell carcinoma, or others [8]. Up to 80% of patients have grade III disease [12]. Median survival is inferior in comparison to endometrial cancer (18 vs 36 months, respectively) [13].

NE differentiation in tumors arising from genital tract is uncommon and little is known. The 1997 College of American Pathologists Workshop proposed a classification system for NE tumors of the cervix, which includes typical carcinoid tumor, atypical carcinoid tumor, large cell NE carcinoma, and small cell NE carcinoma. However, tumors of the endometrium and ovaries were not addressed [14].

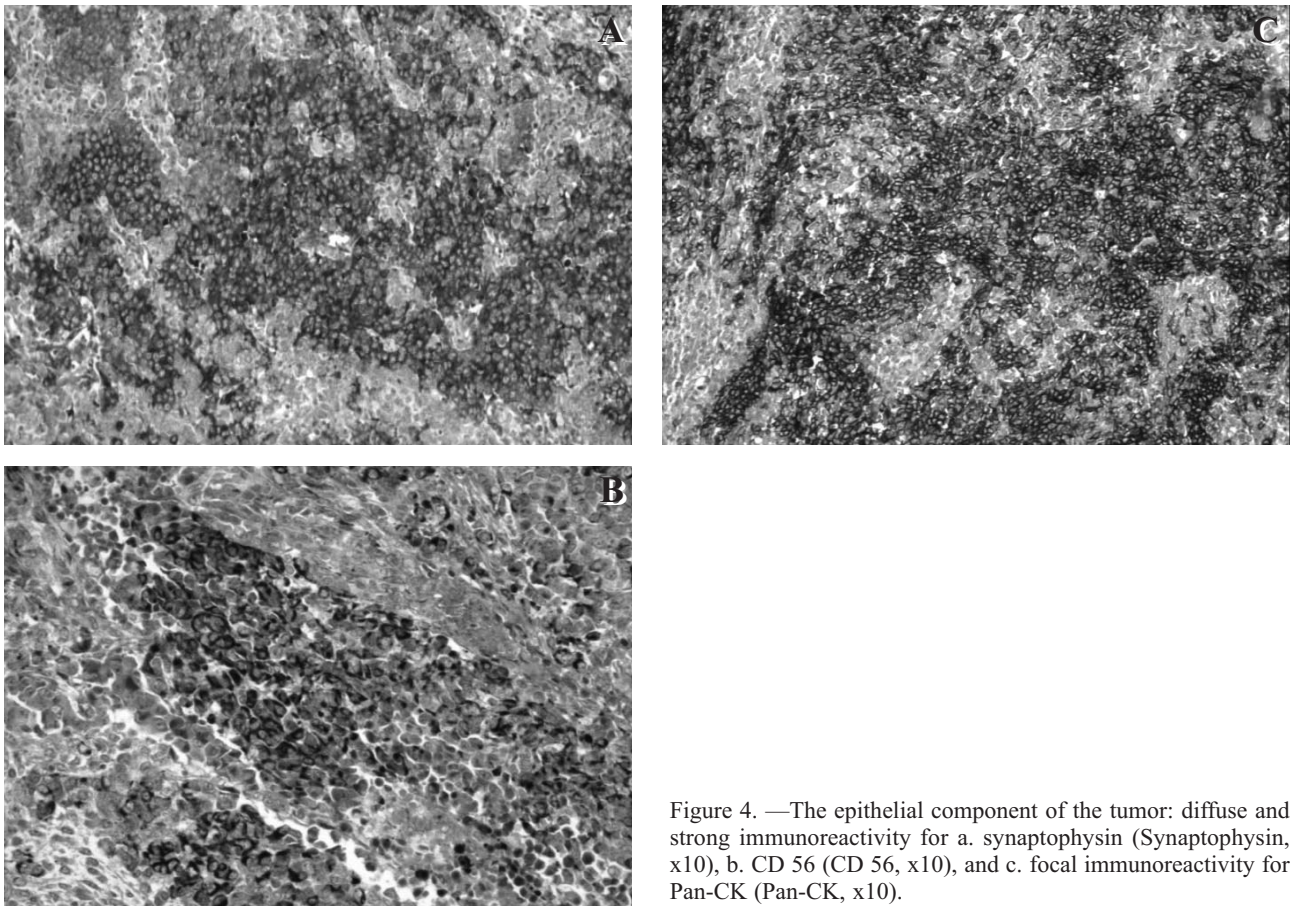

Figure 4. —The epithelial component of the tumor: diffuse and strong immunoreactivity for a. synaptophysin (Synaptophysin, x10), b. CD 56 (CD 56, x10), and c. focal immunoreactivity for Pan-CK (Pan-CK, x10).

The 2003 World Health Organization (WHO) histological classification of tumors of the uterine corpus recognizes small cell carcinoma of the endometrium as a distinct type of epithelial endometrial carcinoma, but it does not even mention any other type of NE differentiation such as MMMT with small cell NE carcinoma component [15].

There are only a few reports addressing NE differentiation in MMMTs [2-7]. Manivel *et al.* first described a case of endometrial MMMT with an extensive small cell NE carcinoma component [2]. George *at al.* reported eight cases of NE differentiation in a total of 47 endometrial MMMTs. Van Hoeven *et al.* reported a case series of the endometrial small cell carcinoma in ten patients. Only one of those was diagnosed as endometrial MMMT with small cell carcinoma component [4].

All 14 previously reported cases of MMMT with NE epithelial component, including the current report, had the small cell type (Table 1). Eleven out of 14 cases were located in the endometrium [2-4]. Other localization sites were the adnexae, mesentery, or cervix [5-7]. Sarcomatous component was homologous in four and heterologous in seven patients. Heterologous differentiation patterns were predominantly in forms of rhabdomyosarcoma and chondrosarcoma. Four out of five patients had a grade III tumor. Most authors place emphasis on the aggressive nature of MMMTs with small cell NE differentiation. Follow-up data were reported for 11 patients. Median follow-up was nine (one to 12) months. Seven out of 11 patients died within the first year of diagnosis. Two out of four so-called alive patients had a follow-up less than six months. Only two patients received radiotherapy. Three out of four patients of those reported to be alive received adjuvant chemotherapy, whereas none of patients lost were given chemotherapy.

The distinctive appearance of small cell NE differentiation necessitates immunohistochemical examination to confirm the diagnosis. NE markers include neuron-specific enolase (NSE), synaptophysin, chromogranin A, leu-7 (CD 57), CD 56, and several neuropeptides. Tumoral cells may be stained in a focal manner. For definitive histopathological diagnosis for small cell NE differentiation, sheet-like growth of small tumor cells, and at least one positive NE marker are required [4,16]. Current report showed prominent NE differentiation including an extensive small cell NE carcinoma component with diffuse and strong positivity for synaptophysin and CD 56. Among the cases, the most commonly observed marker was NSE in 91% of patients (10/11). Other common NE markers were chromogranin A, leu-7, and synaptophysin, observed in 46% (6/13), 80% (8/10), and 67% (8/12) of patients, respectively (Table 2).

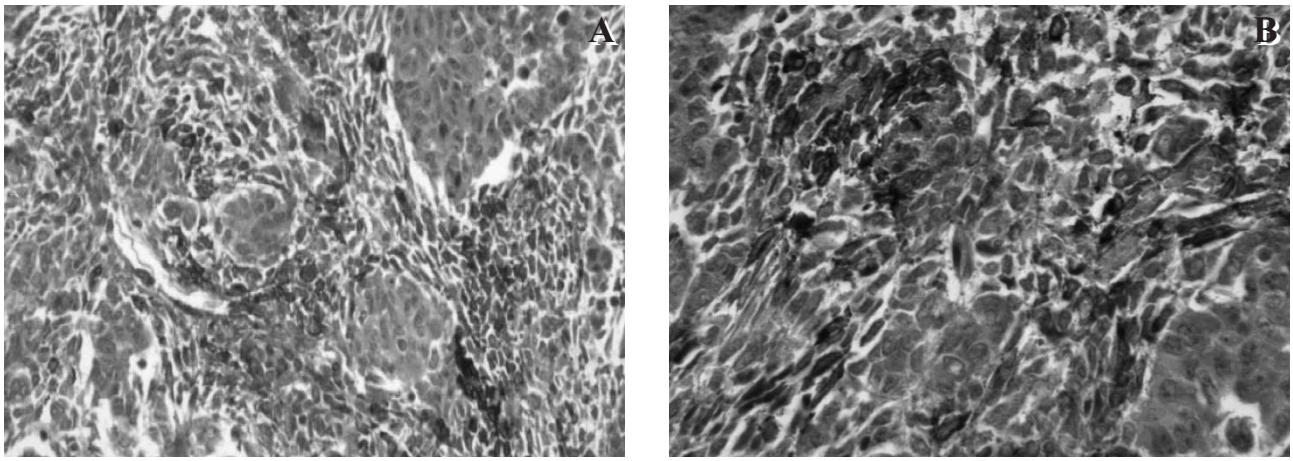

Figure 5. —The mesenchymal component of the tumor: immunoreactivity for CD 10. a. *(CD 10, x10)*, b. *(CD 10, x20)*.

Conclusions

MMMT with NE differentiation is a rare entity. It should be considered during histopathologic examination of endometrial tumors. Most of the patients have a dismal prognosis. Hence, comprehensive staging surgery followed by adjuvant chemotherapy may be mandatory. However, due to scarcity and heterogeneity of clinical data, it is not possible to draw a definite conclusion about the optimal treatment strategy.

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