Fallopian tube malignant mixed müllerian tumor (carcinosarcoma): a case report with immunohistochemical profiling

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Summary

We report a case of malignant mixed müllerian tumor (MMMT) (carcinosarcoma) of the right fallopian tube in a 69-year-old woman presenting with abdominal pain and an adnexal mass. The patient underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, received adjuvant chemotherapy and is without evidence of disease 12 months postoperatively. The tumor involved the fallopian tube and was composed of in situ and invasive high-grade serous and undifferentiated carcinoma, leiomyosarcoma, rhabdomyosarcoma and undifferentiated sarcoma. Immunohistochemically, the epithelial and mesenchymal cells expressed CD56, Leu-7 and p53. The epithelial elements expressed nuclear WT1 and calretinin while the mesenchymal cells showed negative nuclear and strong cytoplasmic staining. HBME was observed focally in carcinoma. The expression of mesothelial-associated antigens WT1, calretinin and HBME in MMMT likely reflects the common embryologic derivation of the mesothelium and urogenital ridge. Loss of nuclear WT1 expression in the mesenchymal component may be involved in MMMT tumorigenesis.

Key words: Fallopian tube; Carcinosarcoma; Malignant mixed müllerian tumor (MMMT); Immunohistochemistry; WT1.

Introduction

Malignant mixed müllerian tumors (MMMT)/carcinosarcomas of the female genital tract are uncommon, but clinically highly aggressive neoplasms with biphasic histology of carcinomatous and sarcomatous elements [1]. Fallopian tube carcinosarcoma is extremely rare, with only about 70 cases previously reported in the international literature [2]. We present a case of fallopian tube MMMT, describe its immunophenotypical characteristics with respect to tumor genesis, and review the literature.

Case Report

A 69-year old, gravida 4, para 2, postmenopausal Greek woman presented with right lower quadrant abdominal pain. Her past medical, surgical and family history was unremarkable. Gynecologic examination revealed a right adnexal mass, but was otherwise unremarkable, findings confirmed by computed tomography (CT) and ultrasound (US) examination. Preoperative chest X-ray and CT, intravenous urography, colonoscopy and urethrocystoscopy were normal. On exploratory laparotomy, the right fallopian tube was markedly distended. Frozen section examination confirmed malignancy and the patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy, and omentectomy.

Pathology

On gross examination, a solid and cystic tumor mass measuring 12.4 x 8.5 x 4 cm, and covered by purple serosa bearing adhesions was identified in a progressively distended tortuous fallopian tube measuring 0.8-2.2 cm in diameter. The cut surface was solid and cystic, tannish-white with necrotic foci and the consistency elastic to soft-friable. The right ovary and uterus with attached left adnexa showed no macroscopic abnormalities.

The specimen was examined histologically and the tumor was submitted to immunohistochemical examination. Immunohistochemical evaluation was conducted on formalin-fixed, paraffin-embedded 4 μm tissue sections, that were dewaxed, rehydrated and incubated in 1% H_2O_2 for 15 min. The following primary antibodies were used: CK8/18, AE1, AE3, EMA, CEA, ER, PR, vimentin, SMA, MSA, desmin, myogenin, myoD1, S100, MART-1, HMB-45, Leu-7, CD56, synaptophysin, chromogranin, HBME, WT1, calretinin, CD34, CD31, CD10, P53, c-kit, and c-erbB2. Immunoreactivity was detected with the Envision detection system (DAKO).

Results

On histologic examination, the fallopian tube epithelium adjacent to the tumor displayed areas of transformation to serous carcinoma in situ, evolving to high-grade serous carcinoma that comprised the bulk of the mass. Scattered among the epithelial elements or forming nodular aggregates were medium to large sized spindle cells and large pleomorphic neoplastic cells with abundant rounded or elongated eosinophilic or multivacuolated cytoplasm, reminiscent of mesenchymal differentiation. The tumor infiltrated the wall of the tube, focally involving the serosal surface.

Immunohistochemical results are shown in Table 1. Briefly, the epithelial elements were positive for AE3, CK8/18, EMA, CEA, vimentin, diffusely positive for WT1 (nuclear only), calretinin and focally for HBME. The mesenchymal elements were diffusely positive for vimentin and HHF-35, variably positive for SMA,

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Table 1. — *Results of immunohistochemical reactions in the tumor elements.*

Ab	Epithelial element	Mesenchymal element		
		Spindle cells	Eosinophilic cells	Multivacuolated cells
CK8/18	Diffuse, 3+	–	–	Rare cells, 3+
AE1	–	–	–	–
AE3	Diffuse, 3+	Variable, cy 1+ Variable, nu 3+	Variable, cy 1+	Variable, cy 1+
EMA	Variable, 3+	–	–	Variable, 2+
CEA	Focal, 2+	Focal, 2+	–	–
Vimentin	Variable, 3+, (nu+cy)	Diffuse, 3+	Diffuse, 3+	Variable, 3+
SMA	–	Variable, 3+	Diffuse, 3+	Diffuse, 3+
HHF-35	–	Variable, 2+	Diffuse, 3+	Diffuse, 3+
Leu-7	Focal, 3+	Focal, 3+	–	–
myogenin	–	Variable 2+	Variable 1+	Variable 1+
Myo-D1	–	Variable 1+	Variable 1+	Variable 1+
CD56	Focal, me 3+ Variable, nu 2+	Variable, 2+	Diffuse, 3+	Diffuse, 3+
HBME	Bn: - Mg:Focal,3+ (me+cy)	–	–	–
WT1	Bn: diffuse, nu 3+ Mg: diffuse, nu 3+	Diffuse, cy 2+	Diffuse, cy 3+	Diffuse, cy 3+
Calretinin	Benign:focal 2+ (nu+cy) Mg: diffuse, nu 2+	Variable, cy 2+	Diffuse, cy 2+	Diffuse, cy 2+
p53	Diffuse, 3+	Diffuse, 3+	Variable, 2+	Focal, 1+

Bn: benign, Cy: cytoplasmic, me: membranous, Mg: malignant, nu: nuclear.
Immunohistochemical reactions for ER, PR, S-100, MART-1, HMB-45, synaptophysin, chromogranin, CD34, CD31, c-kit, and c-erbB2 were negative.

desmin, myogenin, myoD1, WT1 (cytoplasmic only) and calretinin. Both components were positive for p53, CD56 and Leu-7, and negative for synaptophysin, chromogranin, S-100 protein, HMB-45, MART-1, CD31, CD34, ER, PR, c-erb-B2 and c-kit.

Histologic examination of the uterus, ovaries, contralateral fallopian tube and omentum was negative for tumor. A diagnosis of primary fallopian tube heterologous MMMT with serous carcinoma, rhabdomyosarcoma and leiomyosarcoma was rendered. The peritoneal washings were negative for malignant cells. The patient, staged as pT1c NX M0, underwent postoperative chemotherapy consisting of six courses of adriablastine (40 mg/m^2), paclitaxel (175 mg/m^2) and cisplatin (75 mg/m^2) and remains well with no evidence of disease as evidenced by CT scans of the chest, abdomen and pelvis, and abdominal US 12 months postoperatively.

Discussion

A case of MMMT of the fallopian tube with leiomyosarcomatous and rhabdomyosarcomatous differentiation has been described. The expression of the neuroendocrine markers CD56 and Leu-7 in both the epithelial and mesenchymal components of the tumor is suggestive but not certain evidence of neuroendocrine/neuroectodermal differentiation, since the more definitive neuroendocrine markers, synaptophysin and chromogranin were negative. CD56 is expressed in several neuroendocrine/neuroectodermal derived tumors, and various carcinomas [3], but to the best of our knowledge, it has not been identified in MMMT. Leu-7 expression has been reported in MMMT and neuroendocrine differentiation, identified in 17% of MMMTs, has been associated with more aggressive behavior [4]. The absence of the melanocytic markers (S-100 protein, HMB-45, MART-1) excluded melanocytic differentiation [5].

The mesenchymal elements consisted of undifferentiated medium sized ovoid to spindle mesenchymal cells among which aggregates of large rounded or tadpole-shaped eosinophilic cells resembling rhabdomyoblasts and large multivacuolated cells resembling lipoblasts were noted. The mesenchymal elements including eosinophilic and multivacuolated cells expressed vimentin and HHF-35 and variably SMA, myogenin and myoD1, but were negative for S-100 protein, as previously reported by others [6], a phenotype indicative of myogenous and against liposarcomatous or neurogenous differentiation. No morphologic features of immature germ cell elements were observed to suggest an immature teratoma.

The histogenesis of carcinosarcomas has been a matter of speculation and debate. Uterine MMMTs are currently considered as metaplastic carcinomas [7] because of the expression of epithelial markers such as keratins and EMA by the mesencymal component. In line with this concept is the coexpression of keratins CK8/18, EMA and CEA along with vimentin, SMA, HHF-35 and desmin observed in the multivacuolated cells of this case. Furthermore, the identification of the same mutations in the TP53 tumor suppressor gene in both epithelial and mesenchymal elements implies a common derivation from a multipotent stem cell of the müllerian system differentiating towards the epithelium and mesenchyme [8,

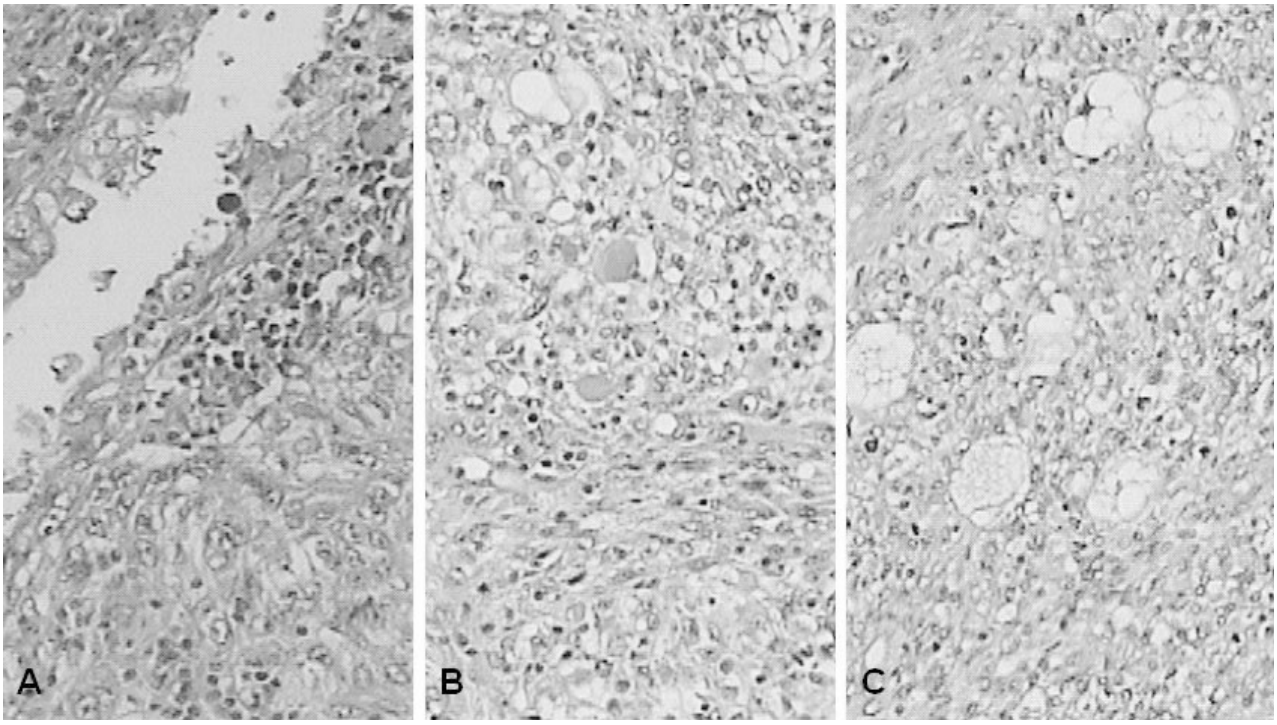

Figure 1. — A) In situ and invasive carcinoma of the fallopian tube. B) C) spindle cells and large pleomorphic neoplastic cells with abundant rounded or elongated eosinophilic cytoplasm resembling rhabdomyoblasts B) or multivacuolated cytoplasm resembling lipoblasts C).

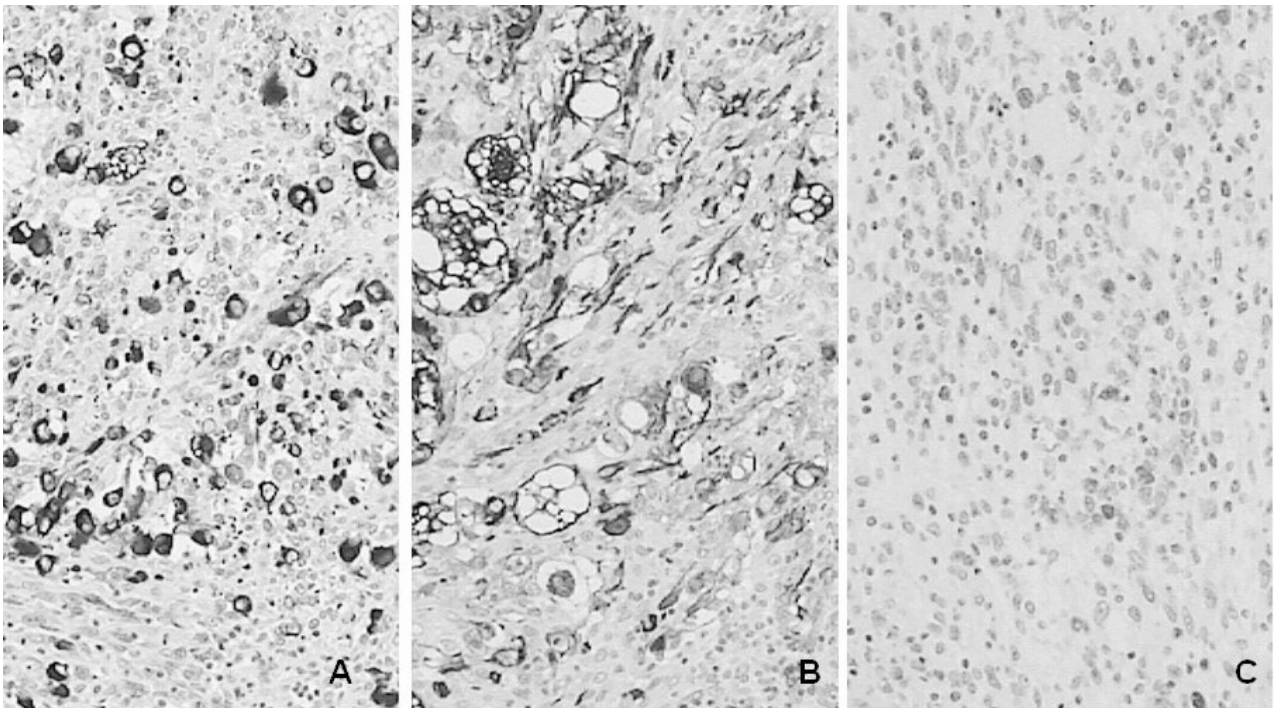

Figure 2. — A) Strong SMA staining of the eosinophilic and multivacuolated cells. B) Strong desmin staining of the eosinophilic and multivacuolated cells. C) Weak to moderate myogenin staining of the spindle cells.

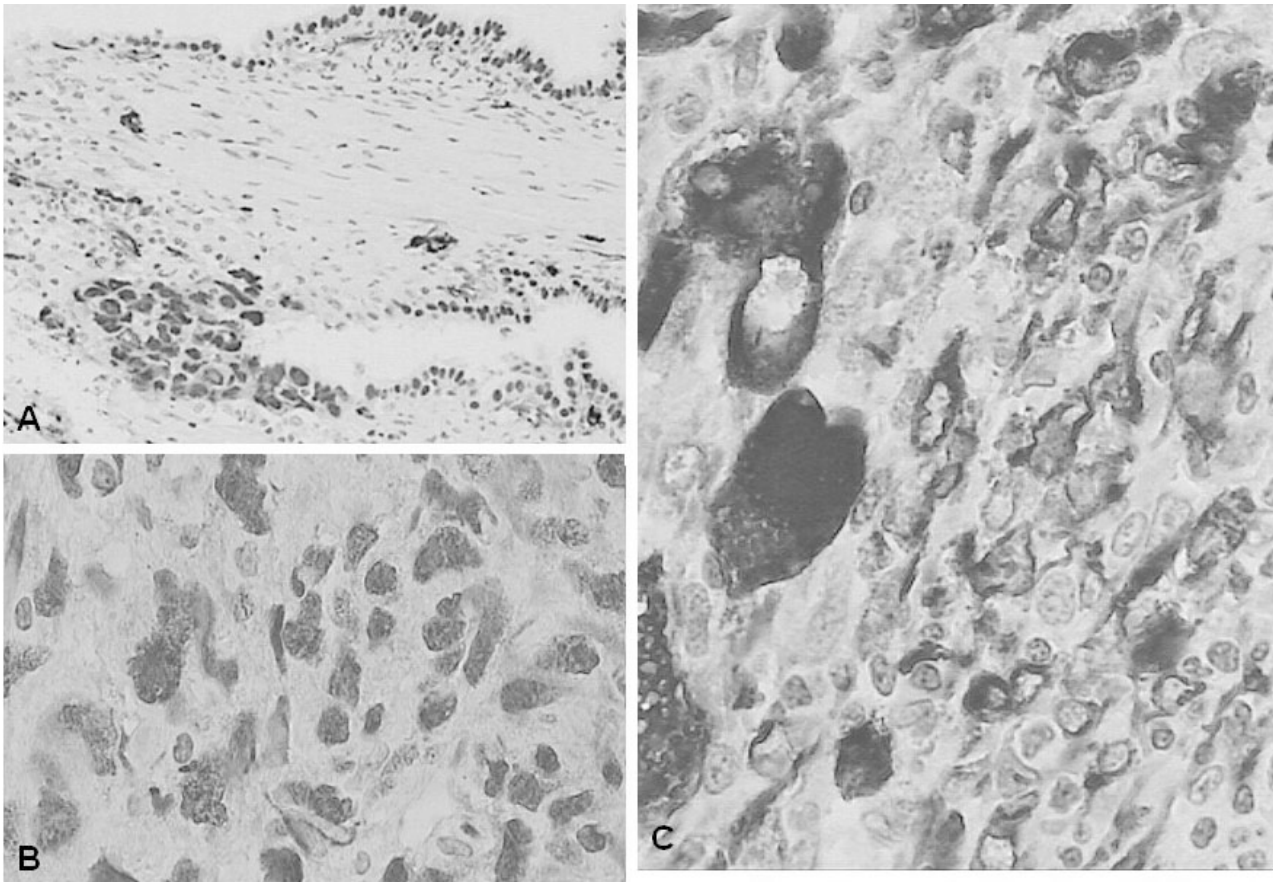

Figure 3. — A) Nuclear WT1 staining of the benign tubal epithelium and the in situ carcinoma, B) Nuclear only WT1 staining of the invasive carcinoma, C) Cytoplasmic only WT1 staining of the sarcomatous component.

9]. Strong overexpression of p53 protein was observed in both mesenchymal and epithelial cells in this case, including carcinoma in situ, suggesting involvement of p53 mutations early in carcinogenesis.

Given the common embryologic origin of the urogenital ridge and mesothelium from coelomic epithelium we investigated the expression of mesothelial markers such as WT1 (Wilms' tumor gene), calretinin and HBME in this neoplasm. WT1 protein, the product of WTI suppressor gene, is important in the development of the organs of the genitourinary system and mesothelium [10]. WT1 protein has been localized in the nuclei of malignant mesothelioma [11], and carcinoma of the ovaries, fallopian tube and uterus, mostly of serous type [12]. Cytoplasmic localization of WT1 has been reported and is thought to represent cross reactivity with an epitope unrelated to WT1 [13]. We noted diffuse, nuclear only, expression of WT1 in the epithelial component of the tumor in striking contrast to diffuse, cytoplasmic only, expression in the sarcomatous component. An analogous observation was made for the p27 tumor suppressor protein in malignant peripheral nerve sheath tumors [14], where the cytoplasmic accumulation and nuclear absence of p27 was later related to disruption of p27 nuclear transport [15]. Whether disruption of nuclear transport of WT1 is responsible for the cytoplasmic localization of the protein needs further investigation. If this is true, then WT1 involvement in MMMT carcinogenesis is a likely event following *p53* mutations. Involvement of c-erbB2 and KIT in carcinogenesis of this tumor is less likely, since these proteins were not detected immunohistochemically.

Conclusion

We have presented a case of early-stage fallopian tube MMMT, consisting of high-grade serous and undifferentiated carcinoma, rhabdomyosarcoma, leiomyosarcoma and undifferentiated sarcoma. The expression of mesothelial-associated markers is in line with derivation of this tumor type from the coelomic epithelium although the distinct nuclear loss and cytoplasmic accumulation of WT1 in the sarcomatous component suggests possible involvement of this tumor suppressor gene in MMMT tumorigenesis.

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