Malignant mixed mullerian tumor of the cervix including components of a rhabdomyosarcoma: case report and literature review

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Summary

Malignant mixed mesodermal tumors (MMMTs) are composed of carcinomatous and sarcomatous components and have an aggressive metastatic potential, resulting in a poor prognosis. MMMTs of gynecologic origin typically arise from either the ovary or the uterus, and MMMTs of the cervix are extremely rare. Due to the rarity of MMMTs arising from the cervix, there is no consensus regarding treatment, prognosis, and outcome; however, aggressive surgical cytoreduction, combined with adjuvant platinum-based chemotherapy and/or radiotherapy, is recommended as the treatment of choice for MMMTs of the cervix. Cervical MMMTs are more often confined to the uterus at the time of diagnosis and frequently have non-glandular epithelial components. For these reasons, MMMTs of the cervix may have a better prognosis compared to the uterine counterparts. A case of an immunohistochemically confirmed primary MMMT of the cervix, including components of a rhabdomyosarcoma, is reported.

Key words: Malignant mixed mesodermal tumor; Cervical cancer; Rhabdomyosarcoma.

Introduction

Approximately 70% to 80% of cervical malignancies are squamous cell carcinomas, 20% to 25% are adenocarcinomas, and the other histologic types include adenosquamous carcinomas, clear cell carcinomas, small cell carcinomas, sarcomas, melanomas, lymphomas, and metastatic tumors [1]. Malignant mixed mesodermal tumors (MMMTs) are composed of carcinomatous and sarcomatous components and have an aggressive metastatic potential, resulting in a poor prognosis. MMMTs of gynecologic origin have generally been identified from either the ovary or the uterus, but have been found only rarely in the cervix [2, 3]. MMMTs arising from the cervix were first described in the literature by Ferriera in 1951 [4], and approximately 50 other cases have been reported in the English literature, including detailed presentations [2]. Due to the rarity of MMMTs of cervical origin, there is also no consensus regarding treatment, prognosis, and outcome, but aggressive surgical cytoreduction combined with adjuvant platinum-based chemotherapy and/or radiotherapy have been recommended as the treatment of choice for MMMTs of the cervix [2, 5-7].

We report a case of an immunohistochemically confirmed primary MMMT of the cervix, including components of a rhabdomyosarcoma.

Revised manuscript accepted for publication November 23, 2009

Case Report

The patient was a 47-year-old gravida 2, para 2, who was referred to our institution with a suspected submucosal myoma. Her main complaint was vaginal bleeding during the previous five days. She denied a history of medication use, other medical problems or surgeries, except a cesarean section, and the family history was also unremarkable. Her menstruation had been profuse and at irregular intervals for ten days, without dysmenorrhea. On pelvic examination, an egg-sized mass with poor mobility was palpable on the cervix and the lower segment of the uterus. A large ulcerated mass was noted, which had projected onto the exocervix after the Pap smear (Figure 1), and a cervical biopsy was performed. Vaginal ultrasound revealed a 4.7 cm solid mass with mixed internal components on the cervix. Magnetic resonance imaging (MRI) showed the presence of a pear-shaped mass (5 x 4 x 5 cm) that was widening the endocervical canal, and a normal-sized uterus and adnexa (Figure 2). There was no abnormal fluid collection or lymph node enlargement in the bilateral pelvic sidewalls and retroperitoneum. The pathologic results of the Pap smear demonstrated some atypical cells suggestive of a malignancy and the biopsy specimen revealed a MMMT.

Chest X-ray, intravenous pyelogram, mammography, duodenoscopy, and colonoscopy were performed and the findings were normal. Tumor markers were within normal limits; serum CA125 was 12.28 IU/ml, carcinoembryogenic antigen was 1.38 ng/ml, and CA19-9 was 16.92 IU/ml. Other hematologic data were also within normal limits.

Based on these results, the patient underwent a radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node dissection. At the time of surgery, a 5 cm tumor mass arising from the endocervix and confined to the endocervical canal was identified. The body of the uterus, the bilateral ovaries, fallopian tubes, and other abdominopelvic organs showed normal gross findings. Microscopically, the tumor consisted of endocervical adenocarcinoma admixed with the stromal (sarcomatous)

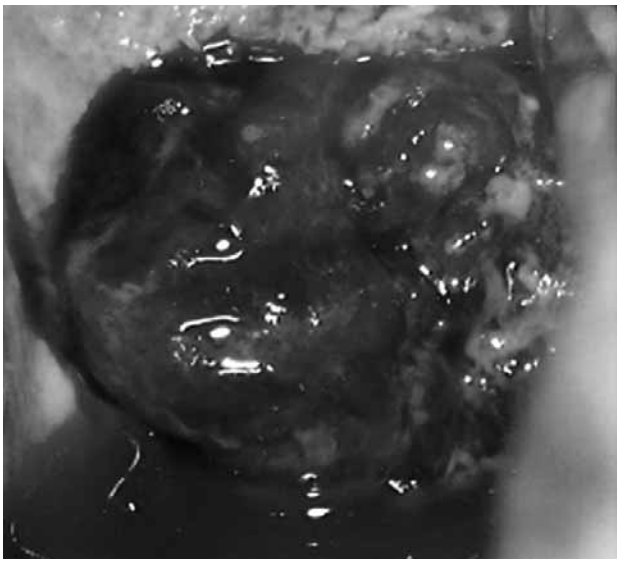

Figure 1. — A 3 cm ulcerated mass that is projected onto the exocervix after the Pap smear.

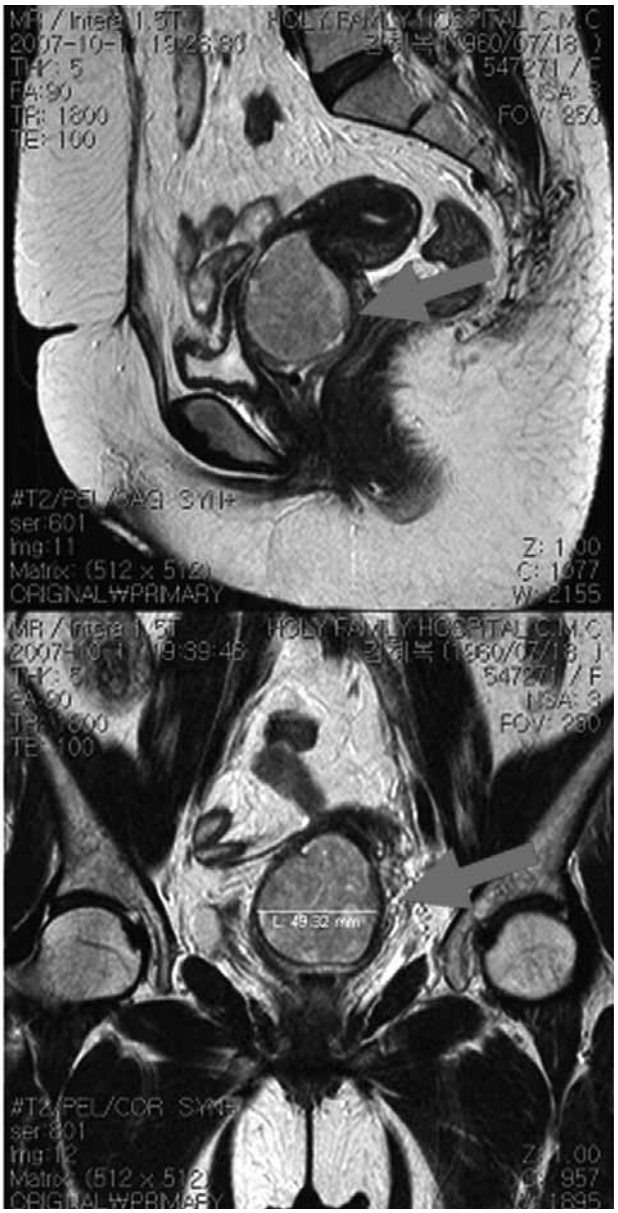

Figure 2. — MRI T2W enhanced, sagittal (A) and coronal (B) views of a pelvic mass (arrow) filling the cervical cavity. The uterus is seen as a normal finding.

elements (Figure 3A). The epithelial adenocarcinoma components were positive to cytokeratin (Figure 3B) and vimentin (Figure 3C). The mesenchymal stromal components were composed of spindle cells showing reactivity to vimentin and smooth muscle actin (Figure 3D). Some cells showing rhabdoid features with reactivity to desmin (Figure 3E) suggested rhabdomyosarcoma components. The mass was diagnosed as MMMT with focal rhabdomyosarcoma components. The depth of invasion of the tumor was 7 mm and there was no malignant cell infiltration of the parametrium, paracolpium, resected margins, and pelvic lymph nodes.

The chemotherapeutic protocol consisted of five days of ifosfamide (1.5 g/m^2 intravenously over 1 h) and cisplatin (20 mg/m^2 over 15 min), followed by mesna (120 mg/m^2 by intravenous bolus, then 1.5 g/m^2/24 h as a continuous infusion). Chemotherapy was repeated three times at three to four week intervals. The patient tolerated the treatment well with only grade 1 or 2 toxicities (alopecia, nausea, and vomiting) without a severe toxic effect (grade 3-4 neutropenia, anemia, thrombocytopenia, severe nausea, and vomiting). She then received external beam radiation therapy (5040 cGY in fractions) and there was no evidence of any side-effects to radiation. She is currently being followed as an outpatient without evidence of a relapse for 20 months.

Discussion

Female genital tract carcinosarcomas, otherwise known as MMMTs, are highly aggressive biphasic neoplasms that exhibit a malignant epithelial component (carcinoma) in conjunction with a malignant stromal component (sarcoma). The sarcomatous element is classified as a homologous tumor, which originates from homogeneous tissue, and the heterologous tumor is composed of foreign materials, such as cartilage, bone, or striated muscle, if it is a uterine MMMT. It is named rhabdomyosarcoma, osteosarcoma, or chondrosarcoma, respectively.

MMMTs have been reported in a variety of anatomic sites. The most common site of occurrence in the female genital tract is the uterine corpus, and primary MMMTs of the uterus account for approximately 2% of all uterine cancers. Ovarian MMMTs are also rare, accounting for approximately 1% of all ovarian cancers [8]. Cervical MMMTs are extremely unusual, so it is difficult to determine the proportion of cervical origin. In a review of the literature, Clement and co-workers [5] reported cervical MMMTs account for < 3% of uterine origin.

In fact, cervical and uterine MMMTs do not differ significantly in their gross appearance (polypoid mass, hemorrhage, necrosis, and invasion). Sometimes, cervical MMMT, are confused with more common uterine

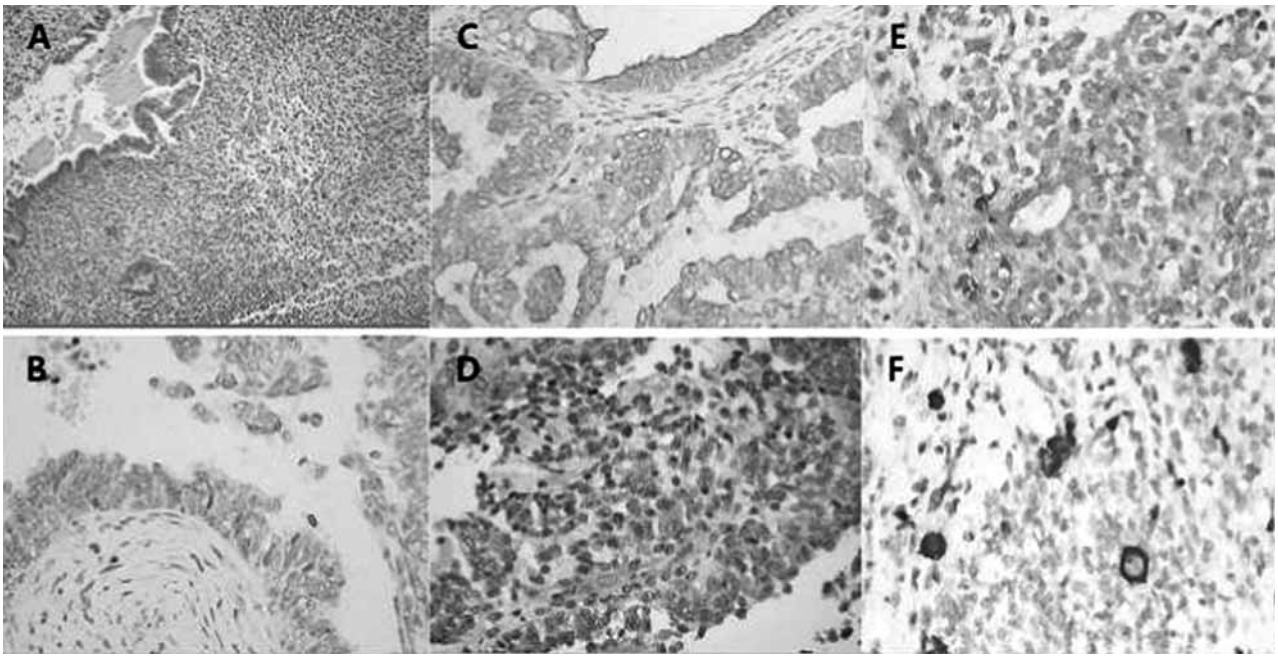

Figure 3. — (A) Microscopic finding showing biphasic components of adenocarcinoma and stromal sarcoma (H&E stain, × 40). (B) Immunohistochemical stain. Positive reaction for cytokeratin in the carcinomatous component, (immunohistochemical stain, × 100). (C) Immunohistochemical stain. Positive reaction for vimentin in the sarcomatous component (immunohistochemical stain, × 100). (D) Stromal cell showing rhabdoid features (H&E stain, ×100). (E) Immunohistochemical stain. Positive reaction for actin in smooth muscle (immunohistochemical stain, × 400). (F) Immunohistochemical stain. Positive reaction for desmin in rhabdoid cells (immunohistochemical stain, × 400).

MMMTs. However, they have striking differences with respect to the carcinomatous component. The carcinomatous component of the cervix includes squamous cell carcinoma, at least focally, but that of the uterus is predominantly a glandular type (endometrioid, serous, or clear cell). Otherwise, the sarcomatous elements resemble each other. In 1998, Clement and co-workers [5] reviewed 30 reported cases of cervical carcinosarcomas and added nine cases of their own. They identified several key features in a large study; specifically, cervical MMMTs are more often confined to the uterus at the time of diagnosis and frequently has a non-glandular epithelial component. For these reasons, cervical MMMTs may have a better prognosis compared to their uterine counterparts [5, 9].

The commonest clinical features are vaginal bleeding, an abnormal Pap smear, and a cervical mass [3, 5, 10, 11]. In our case, the patient sought evaluation at the hospital due to persistent vaginal bleeding. She also had an abnormal Pap cytology and cervical mass, although it was initially thought to be a submucosal myoma. In fact, most patients with cervical cancer visit the hospital with symptoms like postcoital vaginal bleeding. Younger patients tend to manifest symptoms more rapidly than older patients, and receive gynecologic examinations in a more timely fashion in response to abnormal bleeding.

To date, MMMTs within the female reproductive system have been managed with a variety of treatments including local excision, total hysterectomy, pelvic lymph node dissection, radiation, and chemotherapy. In several previous reports, MMMTs of gynecologic origin were treated with cisplatin-based chemotherapy, such as a cisplatin-ifosphamide combination, yielding a high response rate [6, 8, 9, 12]. And some authors have reported the benefits of adjuvant radiotherapy in the treatment of uterine sarcoma, thereby decreasing the pelvic recurrence rate [13]. The origin of the tumor does not influence the clinical course, and there is no evidence to suggest that adjuvant treatment should depend on the primary site (uterus, ovary, and cervix) [14]. For these reasons, treatment of cervical MMMT has been tried with that of the uterus.

Table 1 shows the variable treatments of cervical MMMT and the results. Patients were treated with surgery, local excision, total hysterectomy, radical hysterectomy, pelvic exenteration, and pelvic lymph node dissection, radiation, and chemotherapy according to their condition. Surgery was the initial treatment for most of the patients with early-stage (I or II) disease followed by adjuvant therapy. Patients with advanced stage disease received radiation therapy or chemotherapy as a first-line therapy.

In conclusion, MMMT of the cervix is a rare disease and is associated with a poor prognosis, although it is mostly detected in early stages. Aggressive primary therapy can offer the best chance of cure in patients with early-stage disease.

Table 1. — *Overview of all reported cases of cervical carcinosarcoma*.

Author	No. of patient	Stage	Initial Tx	Result	Reference
Abidi(2008)	1	I	RH+BA+ PLND+RTx	NED for 18 months	11
Rosa Laterza (2007)	2	I	TAH+BSO+PLND+CTx	NED for 48 months	15
		II	RH+BSO+PLND+RTx	DOD after 2 months (Systemic recurrence)	
Maheshwari (2006)	1	I	TAH + BSO	Recur after 2 months (vagina)	2
Sharma (2005)	5	I	RH +PLND+RTx	NED for 35 months	3
		I	RH+ PLND	NED for 42 months	
		I	RH+ PLND	NED for 65 months	
		I	RTx	NED for 28 months	
		IV	RTx	DOD after 5 months	
Wright (2005)	5	I	TAH+BSO+PLND	NED	10
		I	RH+BSO+PLND	Recur	
		I	RH+BSO+CTx+ RTx *	DOD after 5 months*	
		I	Chemoradiation	NED	
		III	RTx	DOD after 4 months	
Iida(2005)	1	I	RH+BSO+PLND+RTx	DOD after 17 months	16
Clement (1998)	9	I	TAH+BSO+PLND+ RTx+CTx	DOD after 13 yrs (due to colon cancer)	5
		I	Local excision	F/U loss	
		I	TAH+BSO	F/U loss	
		I	TAH+BSO+PLND	Recur after 3 yrs (vagina)	
		I	TAH+BSO+PLND+ RTx	NED for 21 months	
		I	TAH+BSO+PLND	NED for 13 months	
		I	TAH+BSO+PLND	Recur after 19 months (pelvic)	
		II	Local excision+ RTx	NED for 16 months	
		NA	Local excision+PLND+CTX+RTX	NED for 15 months	
Mathoulin-Portier (1998)	1	I	TAH+BSO	Recur after 12 months (abdomen)	17
Farley (1997)	1	IV	Local excision+ RTx	DOC after 2 months	18
Manhoff (1995)	1	I	TAH+BSO+RTx	NED for 6 months	19
Rodriguez-Escudero (1988)	1	I	TAH+BSO+PLND	Recur after 6 months (vagina)	20
Young (1988)	1	I	TAH+BSO+PLND+ RTx	F/U loss	21
Miayzawa (1986)	1	I	RH+BSO+PLND+RTx	NED for 30 months	22
Waxman (1983)	1	I	Local resection + Chemoradiation	NED for 9 months	23
Hall-Craggs (1981)	1	I	TAH+BSO	F/U loss	24

NED: no evidence of disease; DOD: dead of disease; F/U: follow-up; NA: not stated; CTx: Chemotherapy; RTx: Radiation therapy; TAH: Total abdominal hysterectomy; RH: Radical hysterectomy; BSO: Both salpingo-oophorectomy; PLND: Pelvic lymph node dissection.
* The patient had an 8 cm in size cervical mass.

Reference

[1] Smith H.O., Tiffany M.F., Qualls C.R.: "The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States: a 24 year population - based study". *Gynecol Oncol*., 2000, *78*, 97.

[2] Maheshwari A., Gupta S., Shet T., Wuntkal R., Tongaonter H.B.: "Diagnostic dilemma in a case of malignant mixed mullerian tumor of the cervix". *World Journal of Surgical Oncology*, 2006, *4*, 36.

[3] Sharma N.K., Sorosky J.I., Bender D., Fletcher M.S., Sood A.K.: "Malignant mixed mullerian tumor (MMMT) of the cervix". *Gynecol. Oncol*., 2005, *97*, 442.

[4] Ferriera H.P.: "A case of mixed mesodermal tumor of the uterine cervix". *J. Obstet. Gynecol. Br. Emp*., 1951, *58*, 446.

[5] Clement P.B., Zubovits J.T., Young R.H., Scully R.E.: "Malignant mullerian mixed tumors of the uterine cervix: a report of nine cases of a neoplasm with morphology often different from its counterpart in the corpus". *Int. J. Gynecol. Pathol*., 1998, *172*, 11.

[6] Wheelock J., Hancock K., Smith K.: "Cisplatin, doxorubicin, and cyclophosphamide (PAC) in the treatment of mixed mesodermal tumor of the ovary". *Cancer Treat. Rep*., 1987, *71*, 1275.

[7] Morrow C., d'Ablaing G., Brady L.W., Blessing J.A., Hreshchyshyn M.M.: "A clinical and pathologic study of 30 cases of malignant mixed mullerian epithelial and mesenchymal ovarian tumors: a Gynecologic Oncology Group study". *Gynecol. Oncol*., 1984, *18*, 278.

[8] Ozguroglu M., Bilici A., Ilvan S., Turna H., Atalay B., Mandel N. *et al*.: "Determining predominating histologic component in malignant mixed müllerian tumors: is it worth it?". *Int. J. Gynecol. Cancer*, 2008, *18*, 809.

[9] Alireza Abidi *et al*.: "Cervical carcinoma: Case report". *J. Reprod Med*., 2008, *53*, 138.

[10] Wright J.D., Rosenblum K., Huettner P.C., Mutch D.G., Radar J.S., Powell M.A. *et. al*.: "Cervical sarcomas: An analysis of incidence and outcome". *Gynecol. Oncol*., 2005, *99*, 348.

[11] Grayson W., Taylor L.F., Cooper K.: "Carcinosarcoma of uterine cervix: a report of eight cases with immunohistochemical analysis and evaluation of human papillomavirus status". *Am. J. Surg. Pathol*., 2001, *25*, 338.

[12] Baker T.R., Piver M.S., Caglar H., Piedmonte M.: "Prospective trial of cisplatin, adriamycin, and dacarbazine in metastatic mixed mesodermal sarcomas of the uterus and ovary". *Am. J. Clin. Oncol*., 1991, *14*, 246.

[13] Knocke T.H., Kucera H.K., Dorfler D., Pokrajac B., Potter R.: "Results of postoperative radiotherapy in the treatment of sarcoma of the corpus uteri". *Cancer*, 1998, *9*, 1972.

[14] Krishnan E., Coleman R.E.: "Malignant mixed mullerian tumors of gynecological origin: chemosensitive but aggressive tumours". *Clin. Oncol*., 1998, *10*, 246.

[15] Laterza R., Seveso A., Zefiro F., Formenti G., Mellana L., Donadello N. *et al*.: "Carcinosarcoma of the uterine cervix: Case report and discussion". *Gynecol Oncol*., 2007, *107*, S98-S100.

[16] Iida T., Yasuda M., Kajiwara H., Minematsu T., Osamura R.J., Itoh J. *et al*.: "Case of uterine cervical carcinoma". *J. Obstet. Gynecol. Res*., 2005, *31*, 404.
[17] Mathoulin-Portier M.P., Penault-Horca F., Labit-Bouvier C., Charafe E., Martin F., Hassoun J., Jacquemier J.: "Malignant mullerian mixed tumor of the uterine cervix with adenoid cystic component". *Int. J. Gynecol Pathol*., 1998, *17*, 91.
[18] John H. Farley, Robert R., Taylor.: "Cervical carcinoma occurring after subtotal hysterectomy, a case report". *Gynecol Oncol*., 1997, *67*, 322.
[19] Manhoff D.T., Schiffman R., Haupt H.M.: "Adenoid cystic carcinoma of uterine cervix with malignant stroma: an usual variant of carcinosaroma?". *Am. J. Surg. Pathol*., 1995, *19*, 229.
[20] Rodriguez-Escudero F.J., Martin Mateos M., Burgos J., Rementeria A., Lujan S.: "Malignant mixed mullerian tumor of the cervix in a 12 year-old girl". *Eur. J. Gynecol. Oncol*., 1988, *9*, 365.
[21] Young N., Damien M., Schwartz P.E., Carter D., Mittal K.R.: "Carcinosarcoma of the uterine cervix initially interpreted as high grade sarcoma". *Hum. Pathol*., 1988, *19*, 605.
[22] Miyazawa K., Hernandez E.: "Cervical carcinosarcoma: A case report". *Gynecol. Oncol*., 1986, *23*, 376.
[23] Waxman M., Waxman J.S., Alinovi V.: "Heterologous malignant mixed mullerian tumor of the cervical stump". *Gynecol. Oncol*., 1983, *16*, 422.
[24] Hall-Craggs M., Toker C., Nedwich A.: "Carcinosarcoma of the uterine cervix: a light and electron microscopic study". *Cancer*, 1981, *48*, 161.

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