CA125 Expression in the Tissue of Uterine Leiomyosarcoma

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ABSTRACT: **Background:** Elevated serum levels of the epithelial marker CA125 are occasionally observed in leiomyosarcoma (LMS) patients.

Objectives: To assess the immunohistochemical expression of this marker in the tissue of LMS.

Methods: The consecutive unselected records of all patients with LMS diagnosed during the period 1995–2012 were located and abstracted. After verification of the diagnosis, 4 µm unstained slides were prepared from each case for immunohistochemical staining for CA125. Sections of ovarian carcinoma known to express CA125 were used as positive controls.

Results: We located 17 LMS patients from the period under study. Bleeding was the presenting symptom in 9 patients; the diagnosis was established prior to treatment in 11 patients. The tumor was in an advanced stage in 6 patients, and in 7 unstaged patients it was grossly confined to the uterus. Ten patients died within 14 months after the diagnosis. Serum CA125 levels prior to treatment were assessed in only 8 patients and were above normal limits (› 35 U/ml) in 3 of them. Two of the three with elevated serum levels were in stage III, and the third was an unstaged apparent stage I patient. None of the LMS tissue specimens demonstrated immunohistochemical expression of CA125.

Conclusions: CA125 was not immunohistochemically expressed in the tissue of any LMS tumors examined by us. The origin of elevated serum CA125 in some of these tumors is therefore not in its tissue and remains unknown.

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KEY WORDS: CA125 immunohistochemical expression, uterine leiomyosarcoma, uterine leiomyosarcoma tissue, serum CA125 levels

Leiomyosarcoma (LMS) is an extremely rare but highly malignant uterine tumor that accounts for only 1%–2% of uterine malignancies. However, since the exclusion of carcinosarcoma, which has been reclassified as a poorly differentiated metaplastic form of endometrial carcinoma [1,2], LMS has become the most common subtype of uterine sarcoma [3].

Immunohistochemical studies have shown that uterine LMS usually expresses smooth muscle markers and may also express estrogen, progesterone and androgen receptors as well as c-KIT and Ki67, and occasionally overexpresses p53 [4,5]. CD10 has been found to be expressed in some [4,5] but not all [6] studies. However, although LMS is not of epithelial origin, its tissue may also express epithelial markers [7]. Elevated serum levels of the epithelial marker CA125 in LMS have been previously reported as well [8-10]. The purpose of the present study was to assess the immunohistochemical expression of the epithelial marker CA125 in the tissue of LMS.

MATERIALS AND METHODS

The consecutive unselected records of all patients with LMS diagnosed during the period 1995–2012 were located, and the clinical data, including serum CA125 levels when available, were abstracted.

Formalin-fixed paraffin-embedded tissue blocks of the LMS hysterectomy specimens of these patients were examined. Hematoxylin-eosin staining of 6 µm sections from the tumor tissue blocks were newly performed and reviewed by a senior pathologist (L.S.) in order to verify the diagnosis.

Immunohistochemistry was performed on additional 4 µm sections from each case. Anti-CA125, clone ZY-OV5 (Zymed Laboratories Inc. San Francisco, CA, USA) diluted 1:100 was used as a primary antibody. The staining included a retrieval process with CC1 solution for 64 minutes and detection by Ultra View Universal DAB Detection Kit (Ventana, Tucson, AZ, USA). The staining was performed on the Ventana Benchmark-Ultra automatic system. Sections of ovarian carcinoma known to express CA125 were used as positive controls.

RESULTS

We located the records of 17 LMS patients from the period under study. Selected characteristics of these patients are presented in Table 1. Only two patients were younger than 50 years and only two were nulliparous. Post-menopausal or irregular bleeding was the presenting symptom in nine patients. The diagnosis was established prior to the primary treatment in 11 patients (in 8 of them by curettage, endometrial biopsy or hysteroscopic biopsy). The tumor was in an advanced stage in six patients, and in seven unstaged patients it was grossly confined to the uterus (apparent

*The first two authors contributed equally to this study

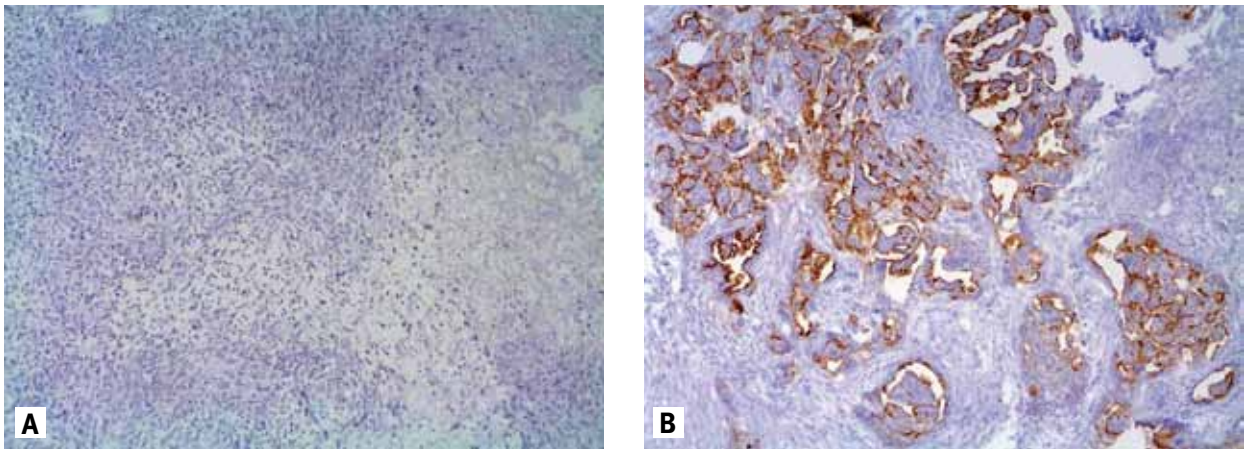
Table 1. Selected characteristics of the leiomyosarcoma patients

Patient #	Age	Presenting symptom	Diagnosis by	Primary treatment	Stage	Adjuvant therapy	Status (months)	Serum CA125 (U/ml)
1	49	PMB	Curettage	Chemo	IV	–	LTFU (2)	–
2	58	PMB	End Bx	TAH & BSO	App I	–	Died (14)	–
3	54	PMB	Curettage	TAH & BSO	I	Chemo+Rt	Alive (87)	–
4	51	Pain, mass	Post-op	TAH & BSO	App I	–	Died (94)	38
5	58	Pulm. emb.	Mass Bx	Chemo	III	–	Died (4)	–
6	47	Myoma, Bl	Post-op	TAH & BSO	App I	Chemo	Alive (34)	–
7	65	PMB	End Bx	TAH & BSO	I	Chemo+Rt	Alive (14)	14.9
8	71	Pain, mass	Expl lap	Bx only	III	–	Died (2)	97
9	52	PMB	Curettage	TAH & BSO	I	Chemo+Rt	Died (13)	27
10	55	Pain	Post-op	TAH & BSO	III	Chemo	Died (9)	199
11	56	Fever	Lung Bx	TAH & BSO	IV	Refuses	Alive (3)	12
12	80	PMB	End Bx	TAH & BSO	I	Rt	Alive (5)	17
13	45	Myoma, Bl	Curettage	TAH & BSO	App I	Chemo+Rt	Alive (31)	–
14	78	PMB	Curettage	TAH & BSO	App I	–	Died (1)*	–
15	62	Pain, mass	Post-op	TAH & BSO	App I	Chemo+Rt	Alive (21)	–
16	61	Pain, mass	Post-op	TAH & BSO	Appl	Chemo+Rt	Alive (25)	–
17	51	Myoma, Bl	Post-op	TAH & BSO	III	Chemo	Alive (4)	8

*Operative death

PMB = postmenopausal bleeding, Chemo = chemotherapy, LTFU = lost to follow-up, End = endometrial, Bx = biopsy, TAH & BSO = total abdominal hysterectomy & bilateral salpingo-oophorectomy, App = apparent, Rt = radiotherapy, Pulm emb = pulmonary embolism, Bl = bleeding, Expl lap = exploratory laparotomy

Figure 1. CA125 immunohistochemical staining of leiomyosarcoma and ovarian serous cystadenocarcinoma



[A] No CA125 staining of leiomyosarcoma

[B] Intense staining of ovarian cystadenocarcinoma

stage I). Adjuvant chemotherapy consisting of doxorubicin and ifosfamide, with and without radiotherapy, was given to 10 patients. Ten patients died within 14 months after the diagnosis. Serum CA125 levels prior to definitive treatment were assessed in only 8 patients (patients # 4,7-12,17) and were above normal limits (> 35 U/ml) in 3 of them (patient # 4,8,10). Two of those with elevated serum levels were in stage III and one was an unstaged apparent stage I patient.

In none of the LMS tissue specimens was immunohistochemical expression of CA125 observed [Figure 1].

DISCUSSION

A PubMed search revealed only three previous studies dealing with CA125 assessment in uterine LMS [8-10]. Two studies compared preoperative serum levels of CA125 in patients with

uterine LMS to those in patients with uterine leiomyoma and arrived at opposite conclusions. In one of these two studies [8] the preoperative serum CA125 levels were significantly higher in 42 uterine LMS patients than in 84 uterine leiomyoma patients, and there was a significant difference in the distribution of preoperative serum CA125 between early-stage and advanced-stage uterine LMS. In contrast, the authors of the second study [9], which consisted of 26 patients with LMS and 2382 with uterine myomas, noted that serum CA 125 levels cannot be used to distinguish between the two tumors and that the preoperative serum CA125 level did not predict the extent of the disease. Tissue expression of CA125 was not assessed in either of these two studies. In only one older study were serum levels as well as tissue expression of CA125 assessed [10]. This study of various uterine sarcomas included only 7 specimens of LMS and, as in our 17 specimens, in none of them was CA125 expressed in the tumor tissue. However, in five of them the serum CA125 level was above normal limits. The authors suggested that the origin of the elevated serum CA125 in some of these tumors is not in its tissue but is likely due to some irritation of epithelial surfaces caused by LMS tumor cells. In the present study the serum level of CA125 was available in only eight LMS patients prior to definitive treatment and was found to be elevated in three of them. Two of these were patients with advanced stage disease, and one was a patient with an unstaged tumor apparently confined to the uterus. Microscopic LMS involvement of epithelial tissues in the latter patient cannot be ruled out. With regard to the association between elevated CA125 serum levels and extent of disease, the number of patients with a known serum level in our study was too small for a meaningful analysis.

Although LMS is not of epithelial origin, some epithelial markers have been shown to be expressed in LMS. In one study [7], which included 20 uterine specimens of LMS, the epithelial markers cytokeratin and epithelial membrane antigen were found to be expressed in 30% and 50% of the tumor tissue specimens respectively. The authors considered this an "aberrant" expression.

The epithelial marker CA125, which is used in the diagnosis and follow-up of epithelial ovarian cancer, is the mucin MUC16. Mucins are high molecular weight glycoproteins widely expressed by epithelial cells of the gastrointestinal, respiratory and urinogenital tracts, and have multiple implications in cancer development [11-13]. While serum levels of CA125 have been shown to be occasionally elevated in uterine LMS, this epithelial marker is not expected to be found in its tissue, as indeed observed in our study. While our study may not be of clinical value it poses a challenging question with regard to the origin of elevated serum CA125 levels in some of these tumors.

In conclusion, we found that the epithelial marker CA125 was not immunohistochemically expressed in any of the tissue specimens of uterine LMS that we examined. The origin of elevated serum CA125 levels in some of these tumors remains obscure.

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"I wanted to change the world. But I have found that the only thing one can be sure of changing is oneself"

Aldous Huxley (1894-1963), English writer best known for his novel *Brave New World*, set in a dystopian London. A humanist, pacifist and satirist, he was deeply concerned about misuse of the mass media and increasingly sophisticated technology. He was widely acknowledged as one of the preeminent intellectuals of his time