

Utility of CD10 in Distinguishing between Endometrial Stromal Sarcoma and Uterine Smooth Muscle Tumors: An Immunohistochemical Comparison of 34 Cases

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Endometrial stromal sarcoma (ESS), uterine cellular leiomyoma (UCL), and uterine leiomyosarcoma (ULS) are composed mainly of spindle cells that express similar antigens such as desmin, smooth muscle actin (SMA), and muscle-specific actin (MSA). The differential diagnosis of an ESS versus a uterine smooth muscle tumor or an extrauterine spindle cell sarcoma can be problematic based solely on clinical presentation, histologic assessment, or routine immunohistochemistry. Recently, we reported that normal endometrium, but not myometrium, as well as five cases of ESS, were positive for CD10. We now report the results of CD10 immunohistochemistry in an additional 11 cases of ESS (total 16 cases), 10 cases of UCL, and nine cases of ULS. CD10 immunoreactivity was detected in 16 of 16 cases of ESS (100%) as compared to only 2 of 10 cases of UCL (20%) and none of nine cases of ULS (0%). We compared the utility of CD10 immunoreactivity with that of desmin, SMA, MSA, estrogen receptor (ER), and inhibin in these tumors. Although the majority of cases of UCL and ULS were positive for SMA, MSA, and desmin, a substantial portion of cases of ESS were also positive for SMA, MSA, and desmin. We conclude that in combination with SMA, MSA, and desmin, CD10 is a useful immunohistochemical marker in the differential diagnosis of ESS versus UCL or ULS.

KEY WORDS: CD10, Endometrial stromal sarcoma, Immunohistochemistry, Uterine cellular leiomyoma, Uterine leiomyosarcoma.

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Endometrial stromal sarcomas (ESSs) account for 0.2 to 1.5% of all uterine malignancies (1) and <10% of cases of uterine sarcomas (2). ESS is usually composed of uniform cells intimately associated with prominent arterioles, closely recapitulating proliferative endometrial stroma. ESS may be confused with uterine cellular leiomyoma (UCL), uterine leiomyosarcoma (ULS), or other sarcomas, in particular, when ESS is associated with myxoid, epithelioid, and fibrous changes (3); has high histologic grade (4); and metastasizes to extrauterine sites (5). The immunohistochemical profile of ESS may have similarities to UCL and ULS, with expression of muscle-specific actin (MSA), smooth muscle actin (SMA), and desmin, particularly in cases of ESS showing smooth muscle differentiation (6–8). Other immunohistochemical markers, including cytokeratin and estrogen receptors, have also been described in both neoplasms (8–11). The lack of a unique immunohistochemical profile for ESS further hampers diagnostic efforts. Cytogenetic studies have not shown consistent chromosomal abnormalities and thus, their utility in the diagnosis of ESS is limited (5, 12).

The common acute lymphoblastic leukemia antigen (CALLA or CD10) was originally found to be expressed on the cell surface of most cases of acute lymphoblastic leukemia (13, 14), and was soon found in many other types of leukemias, as well as lymphomas and nonhematopoietic neoplasms (15, 16). CD10 functions as a cell surface enzyme that acts to reduce cellular response to peptide hormones by regulating local peptide concentration (17). Thus, many hormone-sensitive and peptide-sensitive cells and their corresponding neoplasms express CD10 antigen (18–21), including normal endometrial stroma and ESS (22–24).

In this study, we examined the utility of CD10 paraffin immunohistochemistry and other muscle-specific immunohistochemical markers for differentiating primary or metastatic ESS from UCL and ULS.

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MATERIALS AND METHODS

Case Selection

The files of the City of Hope National Medical Center Division of Pathology were searched from 1989 to 1999 for the diagnosis of primary or metastatic ESS, UCL, and ULS. Sixteen cases of ESS (including five previously reported cases; 24), 10 cases of UCL, and eight cases of ULS were identified (Table 1). Of the 16 ESS cases, seven were primary, eight were metastatic, and one (Case 14) was a case of primary extrauterine ESS arising from endometriosis. Of the eight ULS cases, four were primary, and four were metastatic. All metastatic cases had a previous history of ESS or ULS. The age range for ESS was 36 to 74 years old (mean age, 51 years), for UCL, it was 31 to 58 years old (mean age, 47 years), and for ULS, it was 40 to 85 years old (mean age, 57 years). The diagnoses of ESS, UCL, and ULS (Table 1) were made by consensus of three of the authors (DAA, LMW, and KLC) based solely on previously established morphologic criteria (25–28), without access to results of immunohistochemical analysis.

Immunohistochemistry

All tissues were fixed in 10% neutral buffered formalin and embedded in paraffin. The antibodies used in this study are listed in Table 2. Paraffin section immunohistochemical studies were performed using the avidin-biotin complex technique, augmented by heat-induced epitope retrieval (HIER) methodology and/or enzyme digestion (29, 30). Immunohistochemical staining was performed on an automated immunohistochemical stainer (TechMate 1000, Ventana Medical System, Tucson, AZ). Briefly, deparaffinized 5- μ m sections were rehydrated through a xylene and graded alcohol series. For CD10, desmin, smooth muscle actin, estrogen receptor, and inhibin, the slides were rinsed with tap water for 5 minutes and steamed in 1 mM EDTA buffer (pH 8.0) in a household food steamer (HH90, Black and Decker, Shelton, CT) for 20 minutes at 100°C. For inhibin, the slides were also digested with trypsin (provided by vendor) for 10 minutes. For muscle-specific actin, the slides were digested with trypsin, without HIER. All staining procedures were then carried out on the automated

TABLE 1. Clinical and Immunohistochemical Features of ESS, UCL, and ULS

	Case Number	Age	Site	CD 10	Desmin	SMA	MSA	Inhibin	ER
ESS	1	40	Endometrium	+	+	+	–	–	+
	2	47	Endometrium	+	+	+	+	–	+
	3	47	Endometrium	+	–	+	–	–	+
	4	53	Endometrium	+	+	–	–	–	+
	5	48	Endometrium	+	–	+	+	–	–
	6	57	Endometrium	+	+	+	+	–	+
	7	41	Endometrium	+	+	–	–	–	+
	8	55	Pelvic	+	–	–	–	–	–
	9	74	Abdomen	+	–	+	+	–	–
	10	56	Abdomen	+	+	–	+	–	–
	11	62	Abdomen	+	–	–	–	–	+
	12	50	Bladder	+	–	–	–	–	+
	13	42	Lung	+	–	+	+	–	+
	14	36	Omentum	+	+	–	–	–	+
	15	46	Pelvic	+	–	–	–	–	+
UCL	16	65	Peritoneum	+	+	–	–	–	+
	17	42	Uterus	+	+	+	+	–	+
	18	50	Uterus	+	+	+	+	–	+
	19	77	Uterus	–	+	+	+	–	+
	20	33	Uterus	–	+	+	+	–	+
	21	42	Uterus	–	+	+	+	–	+
	22	40	Uterus	–	+	+	+	–	+
	23	31	Uterus	–	+	+	+	–	+
	24	40	Uterus	–	+	+	+	–	+
	25	54	Uterus	–	+	+	+	–	+
ULS	26	58	Uterus	–	+	+	+	–	+
	27	61	Uterus	–	+	+	+	–	–
	28	73	Uterus	–	+	+	+	–	–
	29	40	Uterus	–	+	+	+	–	+
	30	52	Uterus	–	+	+	+	–	+
	31	54	Abdomen	–	+	+	–	–	+
	32	47	Colon	–	–	+	+	–	–
	33	44	Pelvic	–	+	+	–	–	–
	34	85	Pelvic	–	+	+	+	–	+

ESS, endometrial stromal sarcoma; UCL, uterine cellular leiomyoma; ULS, uterine leiomyosarcoma; SMA, α -smooth muscle actin; MSA, muscle-specific actin; ER, estrogen receptor.

TABLE 2. Antibodies Used in Immunohistochemical Studies

Antibody Clones	Specificity	Dilution	Antigen Retrieval ^a	Source
HHF35	MSA	1:50	Enzyme	Accurate Chemical & Scientific Corporation, Westbury, NY
56C6	CD10	1:10	HIER	Novocastra, Burlingame, CA
D33	Desmin	1:2	HIER	Ventana Medical System, Inc., Tucson, AZ
ER1D5	ER	1:100	HIER	Immunotech, Inc., Westbrook, ME
RI	Inhibin	1:4	HIER & enzyme	Serotec Ltd., Oxford, England
Asm-1	SMA	Undiluted	HIER	Ventana Medical System, Inc., Tucson, AZ

HIER, heat-induced epitope retrieval; ER, estrogen receptor; SMA, α -smooth muscle actin; MSA, muscle-specific actin.

^a See Materials and Methods.

stainer as previously described (24). Cytoplasmic and membranous immunostaining were evaluated.

RESULTS

General Features

The hematoxylin and eosin (H&E) sections of ESS typically showed uniform tumor cells whorled around arterioles (Fig. 1A). Cases of UCL were characterized by densely cellular fascicles of smooth muscle with little intervening collagen, fewer than five mitotic figures per 10 high-power field, and little or no cytologic atypia (28, 31). Cases of ULS

were highly cellular tumors composed predominantly of intersecting bundles of large spindled cells with markedly atypical nuclei, increased mitotic figures, and frequent atypical mitotic figures (Fig. 1C).

Immunohistochemical Results

The results of immunohistochemical studies are summarized in Table 1. The majority of cases of ESS were CD10⁺, ER^{-/+}, SMA^{-/+}, and MSA^{-/+}, whereas the majority of cases of UCL and ULS were CD10⁻, ER^{-/+}, SMA⁺, and MSA⁺.

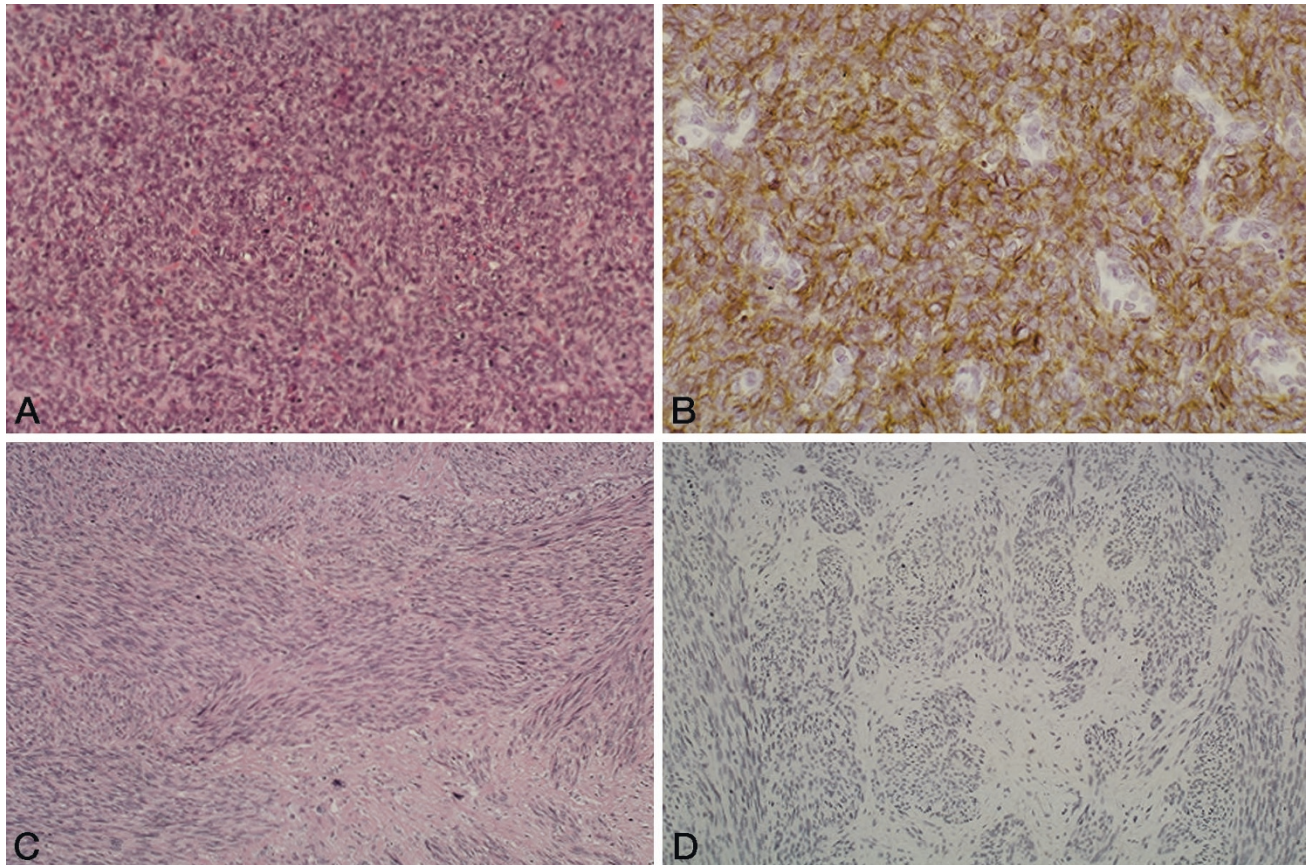


FIGURE 1. Endometrial stromal sarcoma (Case 9) shows uniformly sized tumor cells whorling around arterioles on hematoxylin and eosin (H&E) section (A). Tumor cells are diffusely positive for CD10 by immunohistochemistry, whereas the periaarteriolar cells are negative (B). Uterine leiomyosarcoma (Case 30) shows intersecting bundles of spindled cells with nuclear atypia and atypical mitotic figures on H&E section (C). Tumor cells are negative for CD10 by immunohistochemistry (D).

CD10 in ESS

All 16 cases of ESS (100%) were positive for CD10. The tumor cells usually showed diffusely membranous and cytoplasmic CD10 positivity, whereas the periarterial cells were negative (Fig. 1B). We observed no difference in CD10 staining quantity or intensity among cases of primary, metastatic, or extrauterine ESS. Within any given case, the staining intensity varied, with some tumor cells staining darker than other tumor cells (Fig. 2A). Cases of ESS with myxoid features (Fig. 2B) or with a prominent spindle cell component were also diffusely CD10 positive (Fig. 2C). Many CD10-positive tumor cells coexpressed SMA, MSA, desmin, and ER.

CD10 in UCL

Two of 10 cases of UCL showed focal (<5%) CD10-positivity. The CD10-positive cells were characterized by round or ovoid shape with inconspicuous cytoplasm and were intimately associated with blood vessels (Fig. 3, A-B) on H&E sections. Typical smooth muscle cells with elongated nuclei were CD10-negative. The interface between the CD10-positive areas and the CD10-negative areas was not well demarcated.

CD10 in ULS

All eight cases of ULS did not stain for CD10 (0%) (Fig. 1D).

Expression of SMA, MSA, Desmin, ER, and Inhibin in ESS, UCL, and ULS

The immunohistochemistry results of SMA, MSA, desmin, ER, and inhibin in ESS, UCL, and ULS are also summarized in Table 1. SMA, MSA, and desmin immunoreactivities were seen in both conventional areas of ESS and areas of ESS showing smooth muscle differentiation. All 10 cases of UCL (100%) and all eight cases of ULS (100%) expressed SMA in almost all tumor cells. In contrast, only 7/16 (44%) ESS cases expressed SMA. Staining was seen diffusely throughout the tumor. MSA was positive in all 10 cases of UCL (100%), 6/8 cases of ULS (75%), and 6/16 cases of ESS (37%). MSA staining was seen in the majority of tumor cells. Desmin was positive in all 10 cases of UCL (100%), 7/8 cases of ULS (87%), and 8/16 cases of ESS (50%). Although the majority of cases of ESS, UCL, and ULS showed cytoplasmic desmin positivity, some cases of ESS showed perinuclear dot-like (Golgi pattern) desmin positivity. ER was positive in all 10 cases of UCL (100%), 4/8 cases of ULS (50%), and 12 of 16 cases of ESS (75%). All 34 cases of ESS, UCL, and ULS were negative for inhibin.

DISCUSSION

Endometrial stromal tumors and uterine smooth muscle tumors represent two major types of uterine mesenchymal tumors. The necessity of distinguishing between the two tumor types often arises in surgical pathology practice. The distinction between endometrial stromal tumors and highly cellular leiomyomas and other cellular spindle cell tumors is important for several reasons (26, 32). First, highly cellular leiomyomas can be confused with an endometrial stromal nodule when the former is well circumscribed or with an ESS when the borders of a leiomyoma are irregular (33). It is crucial to differentiate a highly cellular leiomyoma from an ESS because the former always follows a benign clinical course, and the latter is capable of behaving aggressively. Second, cases of metastatic ESS or primary extrauterine ESS should be recognized and separated from other spindled cell tumors because the majority of cases of ESS are ER positive and can be treated with antiestrogen therapy.

In most circumstances, it is not difficult to separate ESS from uterine smooth muscle tumors by routine histologic examination. However, the most difficult differential diagnoses lie between endometrial stromal tumors, highly cellular leiomyomas, and leiomyosarcoma. Immunohistochemistry is not useful in this differential diagnosis for several reasons: there are no endometrial stroma-specific immunohistochemical markers; both endometrium and myometrium derive from the Müllerian duct embryonically and therefore often express identical antigens; and the endometrial stromal cells have myofibroblastic qualities with a potential for differentiation into fully developed smooth muscle cells (34–36). Therefore, endometrial stromal tumors that arise in the endometrial stroma may express muscle-related antigens and vimentin (6, 7, 37).

SMA, MSA, and vimentin were shown by many researchers to have little reliability in differentiating endometrial stromal neoplasms from uterine smooth-muscle tumors. However, there appeared to be conflicting results regarding the discriminatory value of desmin for this differential diagnosis. Oliva *et al.* demonstrated that all highly uterine cellular leiomyomas were positive for desmin, whereas endometrial stromal nodules and ESSs were negative (38). In contrast, Farhood *et al.* (8) found that 7 of 23 ESSs were positive for desmin, including three focally positive (<30% cells), three diffusely positive (30 to 70% cells), and one with generalized positivity (>70% cells). In addition, after studying 10 cases of normal endometrial stromal cells of proliferative or secretory phases and 14 cases of endometrial stromal neoplasms (12 ESSs and two stromal nodules), Franquemont *et al.* (6)

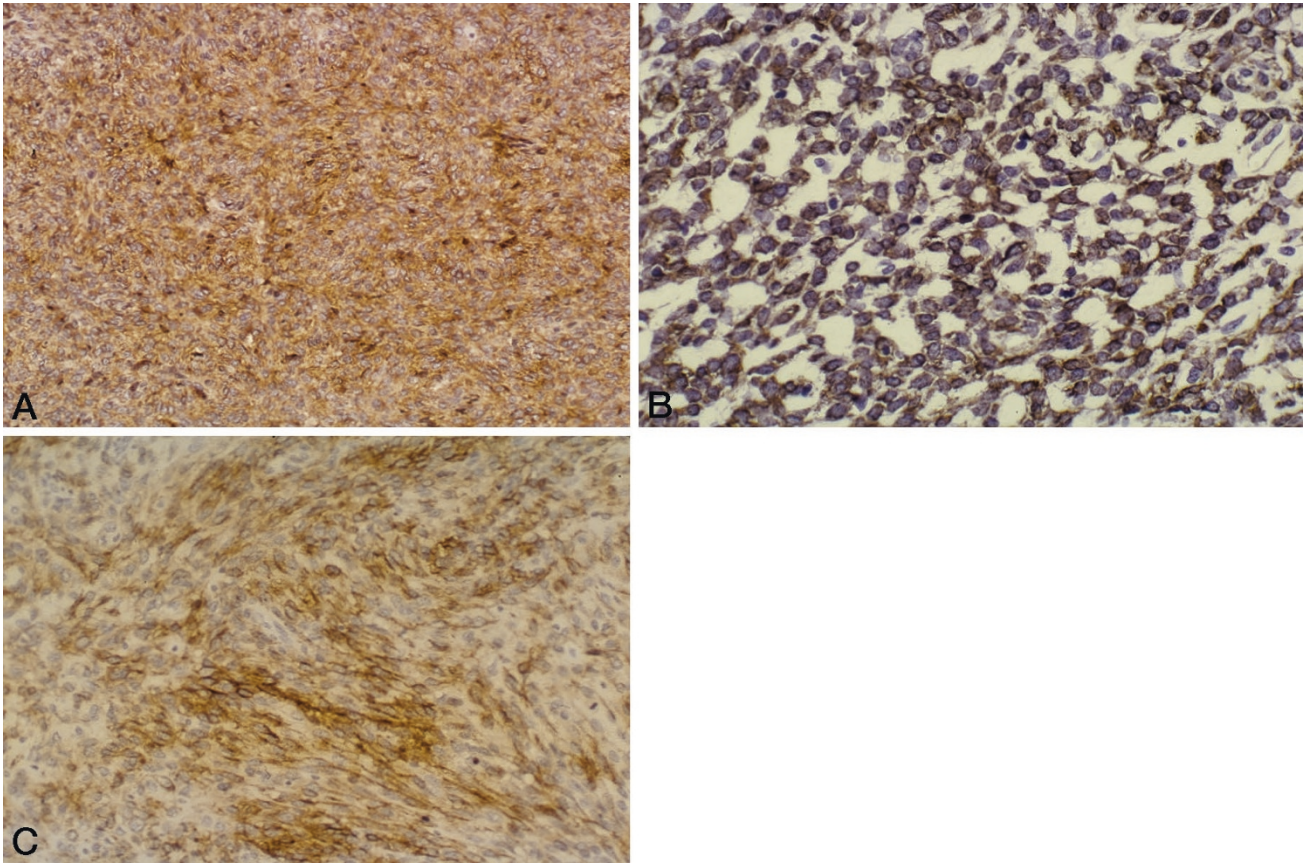


FIGURE 2. Diffuse CD10 immunoreactivity is seen in different histologic variants of ESS: (A) classical (Case 5), (B) myxoid (Case 7), and (C) with prominent spindle cell (Case 1). Note the staining intensity varies between tumor cells in (A).

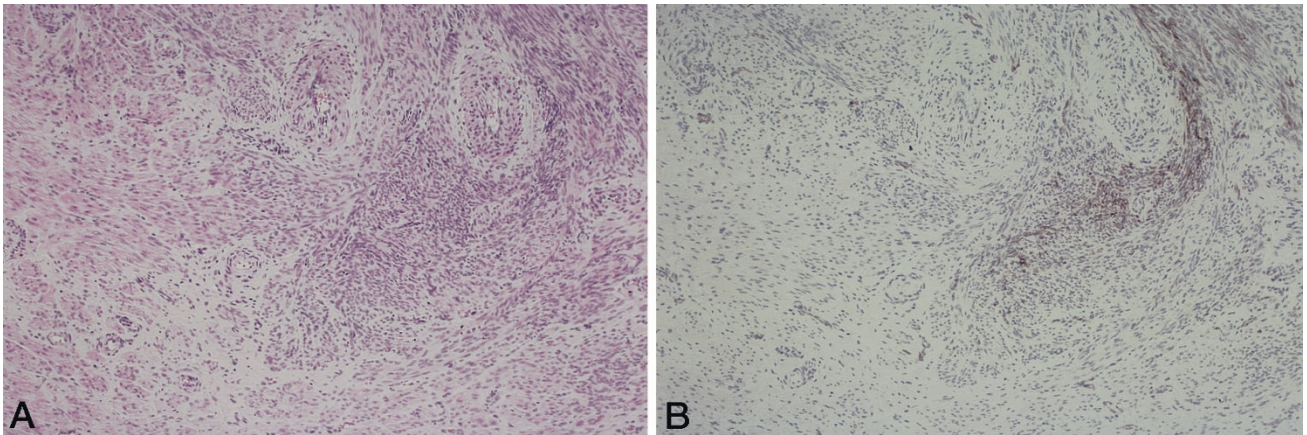


FIGURE 3. Uterine cellular leiomyoma (Case 18) shows intersecting fascicles of smooth muscle cells on hematoxylin and eosin section (A) and focal CD10-positive round, ovoid or spindled cells intimately associated with vessels (B). Both (A) and (B) were photographed from the same field.

identified desmin positivity in nine cases of normal endometrial stromal cells (eight with rare cells staining and one with diffuse staining) and nine cases of endometrial stromal neoplasms (seven ESSs and two stromal nodules). Three of the seven desmin-positive ESSs showed scattered positive cells, whereas four were diffusely positive. Our results also indicate that SMA, MSA, and vimentin were not reliable markers for differentiating ESS from a uterine cellular leiomyoma or uterine

leiomyosarcoma. In addition, desmin reactivity in our study did not have high discriminatory value between ESS from UCL or ULS. The different immunohistochemistry staining results may be the result of case selection (some cases may have had more myxoid or epithelioid changes) or the use of different antibody clones. The staining differences among the tumor types were not apparent after use of antigen-retrieval immunohistochemistry methods, which were not used in the three cited reports.

The value of ER and cytokeratins in the differential diagnosis of ESS *versus* uterine smooth muscle tumor is limited, because both ESSs and uterine smooth muscle tumors are usually ER positive and occasionally cytokeratin positive (8, 10, 11). Inhibin was positive only in cases of ESS with sex-cord-like elements, which can be found in 15 to 60% of ESS (39). In the current study, none of 16 cases of ESS showed sex-cord-like elements. For cases of ESS without sex-cord-like elements, inhibin immunohistochemistry does not provide useful information.

Imai *et al.* (23) demonstrated CD10-positivity in human endometrial stromal cells and decidual cells, as well as stromal cells of endometriosis and adenomyosis by indirect immunofluorescence staining (40). There have been no follow-up studies on this topic since his two studies. In the current study, we investigated CD10 expression in 16 cases of ESS, 10 cases of UCL, and eight cases of ULS. All 16 cases of ESS were diffusely positive for CD10, whereas all eight cases of ULS and 8 of 10 cases of UCL did not stain for CD10. The two CD10-positive UCLs showed focal scanty positive cells (<5%). As outlined earlier, the vast majority of our UCL and ULS cases and over one third of our ESS cases were positive for SMA, MSA, and desmin. These observations indicate that CD10 protein expression is a relatively specific endometrial stromal marker in the uterus and can be used in differentiating endometrial stromal tumors from uterine smooth muscle tumors.

In the current study, we found that 2 of 10 cases of UCL had scattered clusters of CD10-positive round or ovoid cells with inconspicuous cytoplasm (morphologically different from nearby smooth muscle cells), suggesting endometrial stromal differentiation. The interface between the smooth muscle cells and CD10-positive cells in the two cases was vague, and the volume of CD10-positive cells was small. This is in contrast to the morphologic features of a "mixed endometrial stromal and smooth muscle tumor of the uterus," which is an endometrial stromal tumor with a prominent (>30%) component of smooth muscle differentiation. In the latter tumor, both components are usually well demarcated from one another. Whether CD10-positive cells in our two UCL cases truly represent a tumor with stromal differentiation or entrapped normal endometrial stroma or gland-poor adenomyosis cannot be determined. However, we did not observe adenomyosis elsewhere in the two CD10-positive UCL cases.

The major clinicopathologic application of CD10 immunoreactivity has been in the diagnosis of precursor B-cell leukemia, follicular lymphoma, and Burkitt-type lymphoma. CD10 paraffin immunohistochemistry is also useful in the differentiating of renal cell carcinoma (where it is often positive)

from other carcinomas (where it is often negative; 24). Spindle myoepithelial cells of the breast (41) and spindle stromal cells of the bone marrow (42) have also been found to be CD10 positive. We previously found that vast majority of cases of low-grade spindle cell sarcomas resembling ESS, such as gastrointestinal stromal tumor, fibrosarcoma, synovial sarcoma, leiomyosarcoma, and schwannoma, were negative for CD10. Only some cases of high-grade peripheral nerve sheath tumor, rhabdomyosarcoma, and leiomyosarcoma with marked pleomorphic features, and some cases of epithelioid sarcoma, were CD10 positive (24).

In summary, we found that diffuse CD10 immunoreactivity is a very useful positive predictive marker for ESS. In particular, CD10 detection is useful in differentiating ESS from UCL and ULS, although rare cases of UCL may show focal CD10 immunoreactivity. The study of more cases of ESS and various types of uterine smooth muscle tumors will be helpful to confirm the utility of CD10 antibody in the differential diagnosis of these tumor types.

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