Cytology of Vaginal and Uterine Sarcomas

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OBJECTIVE: To retrospectively review, based on cytologic and histopathologic findings, the diagnoses of 13 patients with uterine sarcoma and 1 with vaginal sacoma.

STUDY DESIGN: There were 8 cases of uterine carcinosarcoma (CS), 2 of leiomyosarcoma, 2 of endometrial stromal sarcoma (ESS), 1 of endocervical stromal sarcoma (ECSS) and 1 of malignant fibrous histiocytoma (MFH) of the vagina. The presence of sarcomatous components was retrospectively investigated by microscopic observation of preoperative specimens from the endocervical canal and endometrial cells. Characteristic features of sarcomatous cells were then investigated by cytodiagnostic micrometry of malignant cells.

RESULTS: Of the 14 patients, 1 with low grade ESS and 1 with homologous CS were diagnosed as negative for sarcomatous components. One case of high grade ESS had been overlooked, as were 4 cases of CS. Thus, 7 cases (50%) were diagnosed as positive for sarcomatous cells by preoperative cytologic observation. Based on these findings, 12 of the 14 cases (85.7%) were positive for sarcomatous elements on retrospective reexamination of the specimens.

Careful attention needs to be paid to the detection of small sarcoma cells in order to minimize false negative results on cytodiagnosis....

CONCLUSION: Careful attention should be paid to small sarcomatous cells since cases of ESS or ECSS with such cells show morphologic characteristics similar to those of stromatous cells. Furthermore, careful microscopic observation of an entire specimen is required to avoid misdiagnosis as carcinoma since it is easy to overlook sarcomatous elements in smears with carcinosarcoma if there are only a few sarcomatous cells. (Acta Cytol 2004;48:601–607)

Keywords: sarcoma, vaginal cancer, uterine cancer.

The major type of sarcomatous tumor encountered in the field of gynecology is uterine sarcoma, which is a relatively rare malignancy that arises from the myometrium or mesodermal tissue. Since early diagnosis and preoperative diagnosis are not very easy, many cases are diagnosed only by postoperative histopathology. Sarcomas are classified into

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various histologic types but tend to be highly malignant, with rapid enlargement or distant metastasis, and to have an unfavorable prognosis due to the lack of any well-established treatment, including effective chemotherapy.

There is a tendency to misdiagnose carcinosarcoma as carcinoma since it is easy to overlook the presence of a sarcomatous component when few sarcoma cells are present.

In the present study, we performed a cytopathologic review of 14 cases of primary uterine or vaginal sarcoma encountered over the past 10 years and retrospectively investigated the possibility of preoperatively making a correct diagnosis by cytologic rescreening.

Materials and Methods

We retrospectively investigated 14 patients, including 13 with uterine sarcoma and 1 with vaginal sarcoma, who were treated at our department over a period of approximately 10 years, from October 1990 to December 1999. Although cases of carcinosarcoma were included in this investigation, cases of malignant melanoma were excluded. The 14 patients included 8 cases of carcinosarcoma (CS); 2 of these patients had tumors of the homologous type that were mixed with adenocarcinoma and leiomyosarcoma. The other 6 cases were of the heterologous type, which was understood as a combination of either adenocarcinoma or adenosquamous carcinoma (as the malignant epithelial element) with either chondrosarcoma or osteosarcoma (as the stromal element). In addition to these 8 patients, there were 6 patients with the following types of sarcoma: 2 cases of leiomyosarcoma, 1 each of low and high grade endometrial stromal sarcoma (ESS), 1 of endocervical stromal sarcoma (ECSS) and 1 of malignant fibrous histiocytoma (MFH).

Cervical and endometrial cytodiagnoses were made on all patients using conventional Pap smears prepared using a wooden spatula and screen-brush (Soft Medical Co., Tokyo, Japan) as sampling devices. Tumor cells obtained with the sampling devices were examined by cytodiagnostic micrometry.

The long and short axes of the tumor cells, long and short axes of the nucleus, diameter of the nucleolus and the nuclear/cytoplasmic (N/C) ratio of 150 sarcomatous cells per specimen were measured by a micrometer at 400× magnification. (As many cells as possible were measured if there were < 150 sarcomatous cells in a specimen.) Sarcomatous cells > 50 μm and cells < 25 μm were assessed separately using cervical scrapings and endometrial brushings, respectively, and the mean values were calculated.

Table I *Summary of Clinical Findings*

Case no.	Age (yr)	Chief complaint	Final histologic diagnosis	Main therapy
1	56	AGB+LAP	Adenoca.+LMS	TAH+BSO+LA
2	72	Giant polyp	MFH of vagina	Partial resection
3	45	AGB	Adenoca.+OS+LMS	TAH+BSO+LA
4	48	AGB	Low grade ESS	TAH+LA
5	59	AGB+giant polyp	Adenoca.+ChS	EAH+BSO+LA
6	48	Hypermenorrhea	Adenoca.+LMS	TAH+BSO+LA
7	66	AGB	LMS	TAH+BSO+LA
8	68	LAP+giant polyp	RhS+LMS	EAH+BSO+LA
9	36	Giant polyp	ECSS	TAH+BSO+LA
10	57	AGB	LMS	TAH+BSO+LA
11	50	Hypermenorrhea	High grade ESS	TAH+BSO+LA
12	64	AGB	Adenoca.+ChS	TAH+BSO+LA
13	56	AGB+Polyp	Adenoca.+ChS	Chemotherapy
14	62	AGB	Adenoca.+ChS	TAH+BSO+LA

Adenoca. = adenocarcinoma, LMS = leiomyosarcoma, AGB = abnormal genital bleeding, ChS = chondrosarcoma, LAP = lower abdominal pain, RhS = rhabdomyosarcoma, OS = osteosarcoma, TAH = total abdominal hysterectomy, BSO = bilateral salpingo-oophorectomy, LA = lymphadenectomy, EAH = extended abdominal hysterectomy.

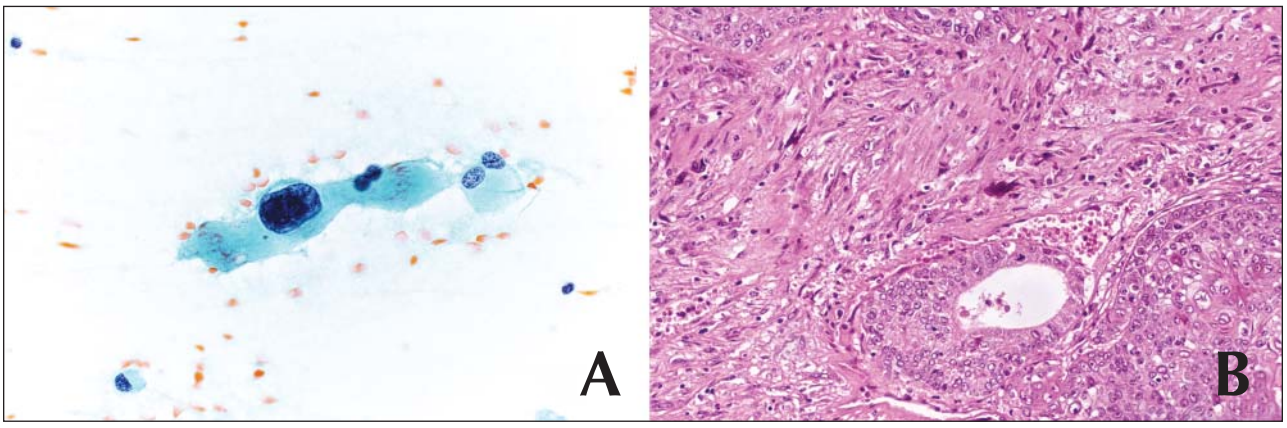

Figure 1 (A) Cytologic and histologic appearance of the sarcomatous component in the homologous type of CS. Cytology shows leiomyosarcoma cells, which have giant atypical nuclei, while (B) histology reveals mixed leiomyosarcoma and adenocarcinoma (Papanicolaou stain; A, ×400; B, ×100).

Results

Clinical Summary

The age distribution of the 14 patients was 36–72 years, and the average was 56.2. Although the major complaints at presentation were mostly abnormal vaginal bleeding or lower abdominal pain, the MFH patient presented with a sensation of vaginal prolapse, and extravaginal protrusion of her tumor was observed. Although a polypoid tumor projecting from the external os of the uterus was also observed in 5 cases, there was no relationship to a specific histology, and the histologic types were diverse. The age, chief complaint, histologic diagnosis and main therapy for each subject are summarized in Table I.

Cytologic and Histologic Findings

Various types of sarcomatous cell were detected. The typical cytologic findings and histologic appearance of both the homologous and heterologous type of CS were seen, as were leiomyosarcoma, high grade ESS, ECS and MFH. Cytologic and histologic appearance of the sarcomatous component in the homologous type of CS is shown in Figure 1A. Cytologic examination detected leiomyosarcoma cells, which had giant atypical nuclei, while histologic examination (Figure 1B) revealed mixed leiomyosarcoma and adenocarcinoma. Figure 2A shows a mixed case of chondrosarcoma plus adenocarcinoma in the heterologous type of CS. Cytologic examination showed syncytial chondrosarcoma

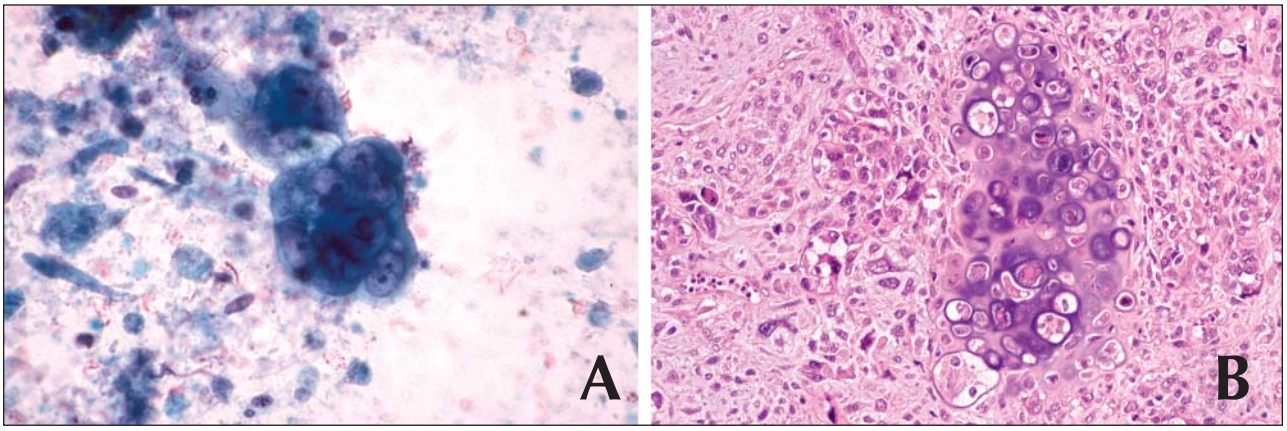

Figure 2 Mixed chondrosarcoma and adenocarcinoma in a case of the heterologous type of CS. (A) Cytologic examination shows syncytial chondrosarcoma cells with conspicuous nucleoli; these are small cells with nuclear chromatin that looks like frosted glass. (B) Histologic appearance of a chondrosarcomatous region (Papanicolaou stain; A, ×400; B, ×100).

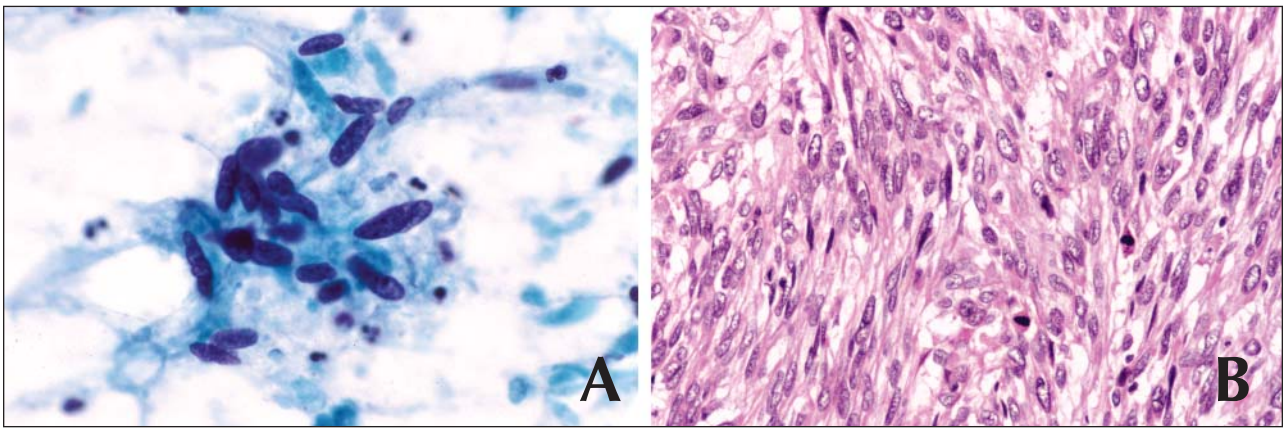

Figure 3 (A) Cytology of leiomyosarcoma; the leiomyosarcoma cells are spindle shaped, with clublike nuclei. (B) Histologic appearance (Papanicolaou stain; A, ×400; B, ×200).

cells with conspicuous nucleoli; these small cells had nuclear chromatin that looked like frosted glass. The histologic appearance (Figure 2B) of a chondrosarcomatous region is also shown. Figure 3A shows the cytologic results in a patient with leiomyosarcoma; the leiomyosarcoma cells are spindle shaped, with clublike nuclei, and their histologic appearance (Figure 3B) is also shown in the figure. Figure 4A displays the cytologic appearance of high grade ESS, which features small, spindle-shaped ESS cells that have round or oval nuclei and conspicuous nucleoli; the histologic appearance is also shown in Figure 4B. Figure 5A shows the cytology of ECS. ECS cells appear as small, irregular or naked nucleus–shaped cells that have round or oval nuclei and relatively conspicuous nucleoli; the histologic appearance of ECS is also shown Figure 5B. Figure 6A shows the cytologic appearance of MFH, in which malignant cells originating in fibroblasts have giant atypical nuclei, while those that originate in histocytes are polykaryocytes. The histologic appearance of MFH (Figure 6B) is also displayed.

Histomorphometry using a micrometer gave the results shown in Table II. Although the maximum number of sarcomatous cells >50 μm in a single specimen was only 70, the mean long axis of these cells was 82.0 μm, and the mean short axis was 15.7 μm. In addition, the mean long axis of the nucleus was 27.5 μm, the mean short axis was 12.0 μm, the nucleolus was 5.3 μm in mean diameter, and the mean N/C ratio was 33.5%. Sarcomatous cells <25

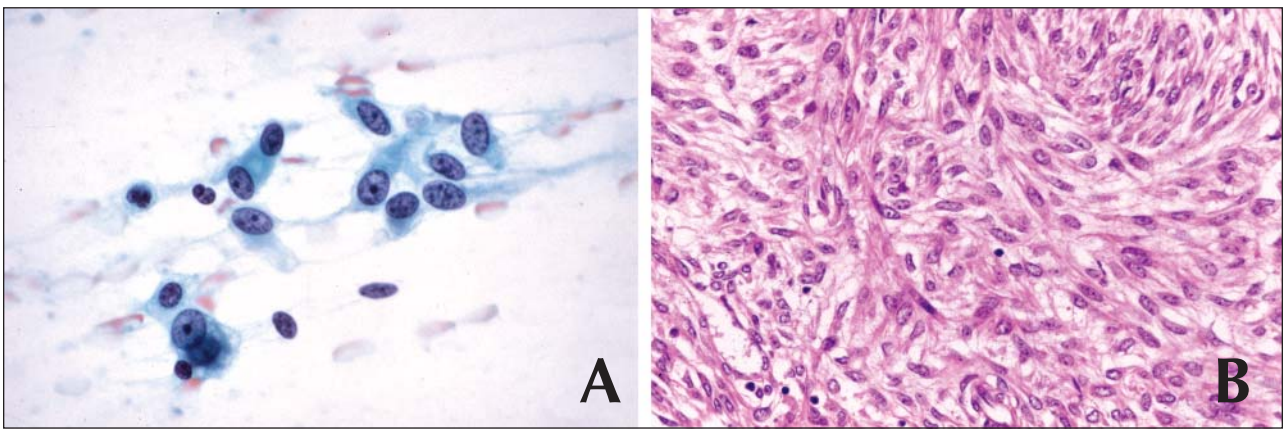

Figure 4 (A) Cytologic appearance of high grade ESS featuring small, spindle-shaped ESS cells that have round or oval nuclei and conspicuous nucleoli. (B) Histologic appearance (Papanicolaou stain; A, ×400; B, ×200).

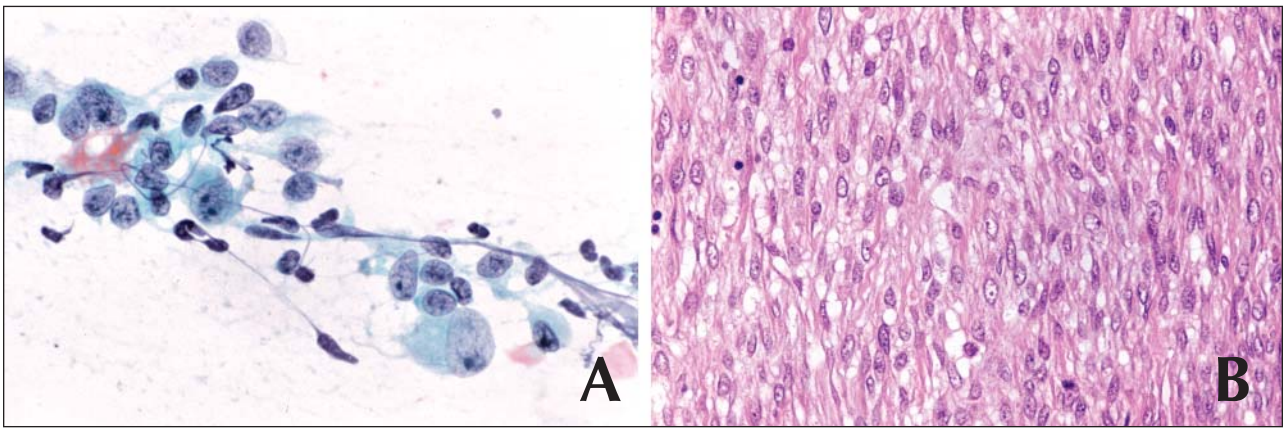

Figure 5 (A) Cytology of ECS. ECS cells appear as small, irregular or naked nucleus–shaped cells that have round or oval nuclei and relatively conspicuous nucleoli. (B) Histologic appearance (Papanicolaou stain; A, ×400; B, ×200).

μm had a long axis of 20.8 μm and a mean short axis of 11.9 μm, which were nearly the same dimensions as those of normal endocervical cells. However, the mean N/C ratio was high (59.1%) since the mean long axis of the nucleus was 12.3 μm and the mean short axis 8.1 μm. Also, a relatively large nucleolus (2.3 μm in mean diameter) was observed in 57.3% of the cells.

The results of our cytologic investigation are summarized in Table III. The patients who were negative for sarcomatous cells on preoperative cytodiagnosis included 1 with low grade ESS and 1 with the homologous type of CS. The patients in whom sarcoma cells were missed at the original preoperative cytodiagnosis included 1 with high grade ESS and 4 with CS. In the other 7 patients (50%), sarcoma cells were detected by preoperative cytodiagnosis. Based on these findings, 12 of 14 patients (85.7%) were positive for sarcomatous elements on retrospective examination of the cytologic specimens.

Discussion

The cytologic appearance of uterine sarcoma was described by Graham,[1] Holmquist[2] and Howden et al[3] before 1980. Later Massoni et al[4] reported that exfoliated leiomyosarcoma cells tended to blend into the background of the smear, and they found very few exfoliated malignant cells in gynecologic smears. The cells exhibited elongated, bipolar cytoplasmtic processes. The nuclei were elongated, cigar shaped and slightly hyperchromatic, while

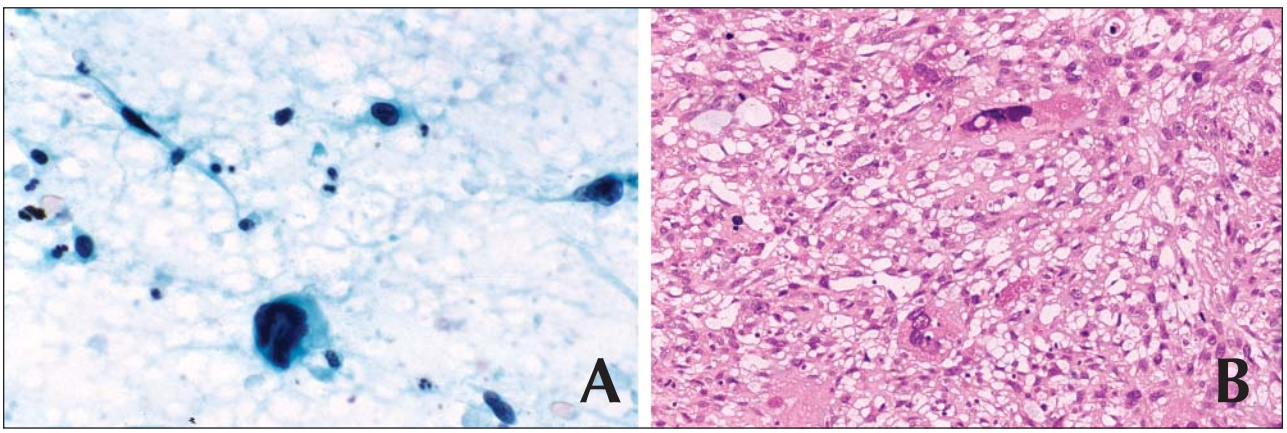

Figure 6 (A) Cytologic appearance of MFH in which malignant cells that originated in fibroblasts have giant atypical nuclei, while those originating in histocytes are polykaryocytes. (B) Histologic appearance (Papanicolaou stain; A, ×300; B, ×100).

the nuclear chromation was coarse and varied in configuration from cell to cell. As regards leiomyosarcoma cells, our findings agreed with those in that report.

Rhabdomyosarcoma cells have round or oval nuclei, thick nuclear borders and single, large nucleoli.[3] The chromatin is finely granular, and the cytoplasm is pale and shows lines. Recognition of the characteristic cytoplasmic cross-striations renders the diagnosis of rhabdomyosarcoma cells unequivocal.

Becker et al[5] reported that ESS cells were mostly small, round, malignant cells with occasional tapered, "comet" forms, distinct nucleoli and associated bleeding. Morimoto et al[6] described ESS cells as similar to normal endometrial stromal cells. In that study, frequent mitoses were characteristic of the cytologic specimens from high grade stromal sarcoma but not of those from low grade sarcoma. Our findings agree with those of Becker et al[5] and Morimoto et al.[6]

There are extremely few reports on the histomorphometry of sarcoma cells. Howdon et al[3] studied cell specimens collected from 6 cases of malignant mixed mesenchymal tumors of the endometrium and reported that the size of the sarcoma cells varied markedly, from 6 to 50 μm. As regards primary uterine sarcoma cells, those originating in ESS or ECS and cells with low differentiation tended to be small, while cells originating in leiomyosarcoma or rhabdomyosarcoma tended to be large. Since we considered that there was a higher probability of missing small sarcoma cells in the specimens than missing large cells, we divided the cells into 2 types, those > 50 μm and those < 25 μm, and we paid close attention to the small sarcoma cells. Those cells had a long axis of 12.3 μm, a short nuclear axis of 8.1 μm and an N/C ratio of 59.1%, although their size was nearly the same as that of normal endocervical cells; in addition, large nucleoli with an average diameter of 2.3 μm were conspicuous in 57.3% (86 of 150) of these cells. Therefore, to avoid missing small sarcoma cells, it appears necessary to pay special attention to cells that are similar in size to normal endocervical cells but that have a high N/C ratio and conspicuous nucleoli.

Table II *Results of Histomorphometry of Sarcomatous Cells*

Cell size (μm)	Mean long axis	Mean short axis	Mean diameter
> 50 μm (n = 70)			
N/C ratio = 33.5%			
Cell size	82.0	15.7	
Nucleus	27.5	12.0	
Nucleolus			5.3 (15/70 cells)
< 25 μm (n = 150)			
N/C ratio = 59.1%			
Cell size	20.8	11.9	
Nucleus	12.3	8.1	
Nucleolus			2.3 (86/150 cells)

Table III *Results of Cytologic Investigation*

Cytology	Findings
Preoperative (n = 14 cases)	Positive: 7 cases Negative: 1 low grade ESS (no. 4), 1 heterologous-type CS (no. 6) Missed: 1 high grade ESS (no. 11), 4 cases of CS (nos. 1, 3, 5, 7)
Retrospective	Positive cases: 12 of 14 (85.7%)

Parker[7] reported that of 6 cases there was 1 positive for sarcoma cells and 1 with suspected sarcoma cells as well as 1 with rhabdomyosarcoma cells in the vaginal and/or cervical smears collected from patients with primary malignant mixed müllerian tumors of the uterus. Massori et al[4] reported that malignant cells were observed in cervicovaginal smears from only 6% of uterine sarcoma patients, and definite sarcomatous elements were observed in 29% of those cases. In the present study, we found that 7 of 14 cases (50%) were positive for sarcomatous elements by preoperative cytodiagnosis. This positive rate was relatively high in comparison with those in earlier reports. The reason for this discrepancy seems to be a difference in the procedure of collecting specimens; i.e., positive cases were diagnosed mostly using endometrial smears, although endocervical smears were also positive at times. Thus, careful attention needs to be paid to the detection of small sarcoma cells in order to minimize false negative results on cytodiagnosis, although ESS and ECSS have small sarcoma cells that show morphologic characteristics similar to those of stromal cells.

Furthermore, there is a tendency to misdiagnose carcinosarcoma as carcinoma since it is easy to overlook the presence of a sarcomatous component when few sarcoma cells are present. To avoid such errors, careful microscopic observation of the entire specimen is always required.

References

1. Graham RM: Cytology of uterine sarcoma and chorionepithe-

lioma. Acta Cytol 1958;2:555–556

2. Holmquist ND: The exfoliative cytology of mixed mesodermal tumors of the uterus. Acta Cytol 1962;6:373–375
3. Howdon WM, Howdon A, Frost JK, Woodruff JD: Cyto- and histopathologic correlation in mixed mesenchymal tumors of the uterus. Am J Obstet Gynec 1964;89:670–679
4. Massoni EA, Hajdu SI: Cytology of primary and metastatic uterine sarcomas. Acta Cytol 1984;28:93–100
5. Becker SN, Wong JY: Detection of endometrial stromal sarcoma in cervicovaginal smears: Report of three cases. Acta Cytol 1981;25:272–276
6. Morimoto N, Ozawa M, Kato Y, Kuramoto H: Diagnostic value of mitotic activity in endometrial stromal sarcoma: Report of two cases. Acta Cytol 1982;26:695–698
7. Parker JE: Cytologic findings associated with primary uterine malignancies of mixed cell types (malignant mixed mullerian tumor). Acta Cytol 1964;8:316–320