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Original Article

PAP smear test in the diagnosis of endometrial carcinoma: How useful is it, what does it indicate ?

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Abstract

Aim: Endometrial carcinoma constitutes the most common gynecological malignancy. Although early diagnosis is important as in all other malignancies, there still exists no screening-imaging modality that can be used effectively in the 517diagnosis of endometrial carcinomas. This study investigated the role of the cervical Papanicolaou (PAP) smear test in the diagnosis of endometrial carcinoma and evaluated the correlation of the results with histological and prognostic data.

Material and Methods: Data obtained from 367 patients who underwent hysterectomy and lymph node dissections due to endometrial carcinoma at Gaziantep University Medical Faculty Hospital between 2010 January-2018 June were retrospectively evaluated. PAP smear results of 75 of these patients, who had undergone cervical PAP smear screening preoperatively (in a 1-36 month period), were evaluated independently by two pathologists. The relationship of the results with diagnosis and prognostic data was investigated.

Results: Of the 75 cases included in the study; 58 were endometrioid endometrial carcinomas, 9 were serous carcinomas, 6 were malignant mixed Mullerian tumours, 1 was clear cell carcinoma, and 1 was adenosquamous carcinoma. Atypical glandular cells were detected in 29 cases (38.6%). While the evaluation of the relationship of positive cases with histological and prognostic data revealed no relationship with histological tumor type or cervical and lymph node involvement, depth of myometrial invasion presented a significant result.

Conclusion: Although rates of endometrial carcinoma detection with PAP smear screening are not very high, they are also not negligible. The detection of an increase in smear positivity rate in correlation with an increase in myometrial invasion depth in our study is quite significant as it represents an important parameter with implications for the surgical procedure.

Keywords: Atypical Glandular Cells; Endometrial Carcinoma; PAP Smear Test.

INTRODUCTION

Endometrial carcinoma is the most commonly encountered gynecological malignancy and comprises 6% of cancers seen in women (1). It has a greater incidence in developed countries, and with variability across regions, approximately 200 000 women are diagnosed every year with endometrial carcinoma (2). Abnormal uterine bleeding is experienced by 90% of the patients and constitutes the most common symptom. While most cases receive an early diagnosis in this way; cases at advanced stages present symptoms such as abdominal tension, pelvic or abdominal pain (3). In spite of being common, there still exists no screening-imaging modality that can be used effectively in the diagnosis of endometrial carcinomas (4). The methods that are mostly utilized for diagnosis include pipelle endometrial sampling or endometrial biopsy with dilatation and curettage (3). Endometrial biopsy performed with hysteroscopic examination is the gold standard method for diagnosis (5).

In this study, the role of the cervical Papanicolaou (PAP) smear test, which is mainly used in the diagnosis of cervical lesions, in the diagnosis of endometrial carcinoma was investigated and the relationship of the results with histological tumor type, invasion depth, and cervical and lymph node involvement was evaluated.

MATERIAL and METHODS

Data obtained from 367 patients who underwent hysterectomy and lymph node dissections due to endometrial carcinoma at Gaziantep University Medical

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Faculty Hospital between 2010 January-2018 June were retrospectively evaluated. PAP smear preparations of 75 of these patients, who had undergone cervical PAP smear tests preoperatively, were included in the study to be re-evaluated. The assessed PAP smear preparations had been prepared using the liquid-based cytology technique.

PAP smear results were evaluated independently by two different pathologists regardless of the initial results that had been reported. In the evaluation, the 2014 Bethesda System (BS) criteria were utilized. Ten cases who had been evaluated independently with different diagnosis were re-examined and diagnosed with consensus. Data associated with the resection material were acquired from tee pathology reports via the information system of our hospital. Where deemed necessary for certain patients, slides belonging to the resection materials were retrieved from the pathology archive and re-evaluated. Data regarding patient age, histological tumor type, invasion depth, cervical and lymph node involvement were recorded. The time between hysterectomy and smear test was also recorded. Cases who had PAP smear screening test results from up to 36 months before the hysterectomy were included in the study.

The study was approved by the Clinical Trials Ethics Committee of Gaziantep University.

The categorical variables were analyzed using the Pearson Chi-Square Test with IBM SPSS® Version 23.0 for Window 7. P values less than 0.05 were accepted as significant.

RESULTS

75 cases of ages ranging between 39 and 79 (mean:56.5) were included in the study. Atypical glandular cells were detected in 29 (38.6%) of the cases. An investigation of PAP smear test results of these cases revealed that 12 had atypical glandular cells (AGC), 4 atypical glandular cells-favor neoplasia (AGC-FN), and 13 adenocarcinoma. (Figure1, 2 and 3). The data has been summarized in table 1.

Table 1. Cytological results according to histological types

		Cytologic Diagnosis			
Histologic type	**(n)**	**Negative**	**AGC**	**AGC-FN**	**Adenoca**
Endometrioid ca	**58**	38	10	2	8
Serous ca	**9**	1	2	2	4
MMMT	**6**	6	0	0	0
Clear cell ca	**1**	0	0	0	1
Adenosquamous ca	**1**	0	0	0	0

The time between the PAP smear test and hysterectomy ranged between 1-12 months (mean:3.8 months) in 93.3% of the cases. The most commonly detected histological type across resection materials was endometrioid endometrial adenocarcinoma, which was detected in 58 cases, while 9 cases manifested serous carcinomas, 6 malignant mixed Mullerian tumours, 1 clear cell carcinoma, and 1 adenosquamous carcinoma. Myometrial invasion was restricted to the inner half in 52 patients, whereas it exceeded the inner half in 23 cases. Cervical involvement was present in 11 cases and absent in 66. No lymph node involvement was observed in 68 cases while 7 manifested lymph node involvement. Correlations between the results and cytologic findings have been presented in Table 2.

Table 2. A statistically significant difference was determined between depth of myometrial invasion and smear positivity (p<0,05). Accordingly, atypical glandular cells are usually not found in patients with invasion restricted to the inner portion of the myometrium

		PAP smear test results		P value
Clinicopathological parameters	**n:75**	**Normal**	**Atypical or malignant cells (%)**	
Histologic Type	n			0.589
Endometrioid	(57)	36 (63.2%)	21 (36.8%)	
Nonendometrioid	(18)	10 (55.6%)	8 (44.4%)	
Myometrial invasion				0,043*
< ½	(52)	36 (69.2%)	16 (30.8%)	
> ½	(23)	10 (43.5%)	13 (56.5%)	
Cervical Involvement				0.319
Negative	(64)	41 (64.1%)	23 (35.9%)	
Positive	(11)	5 (45.5%)	6 (54.5%)	
Lymph Nodel Involvement	(68)	42 (61.8%)	26 (38.2%)	0.811
Negative	(7)	4 (57.1%)	3 (42.9.5%)	
Positive				

While the evaluation of the relationship of abnormal cytologic findings with histological and prognostic data revealed no relationship with the histological tumor type or cervical and lymph node involvement, depth of myometrial invasion represented a significant result (p<0.05).

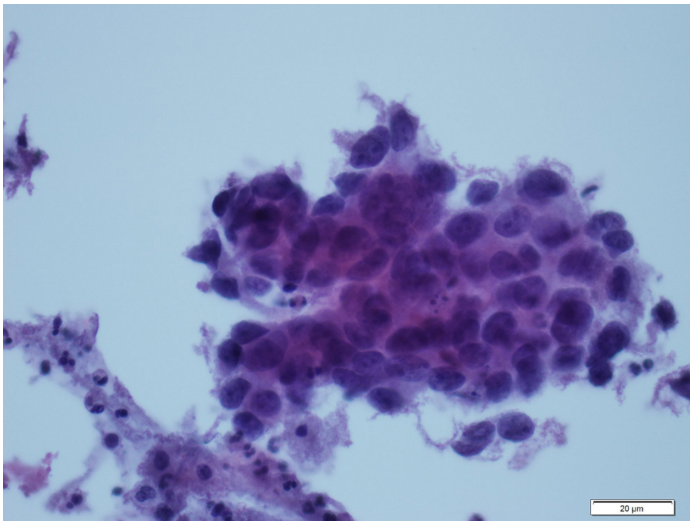

Figure 1. Cytology: Adenocarcinoma (cervical smear by Pap stain, 49-year-old woman). Large cluster of malignant cells with marked enlarged nuclei, coarse chromatin and prominent nucleoli. Histologic diagnosis was endometrioid endometrial carcinoma, Figo Grade II (×400)

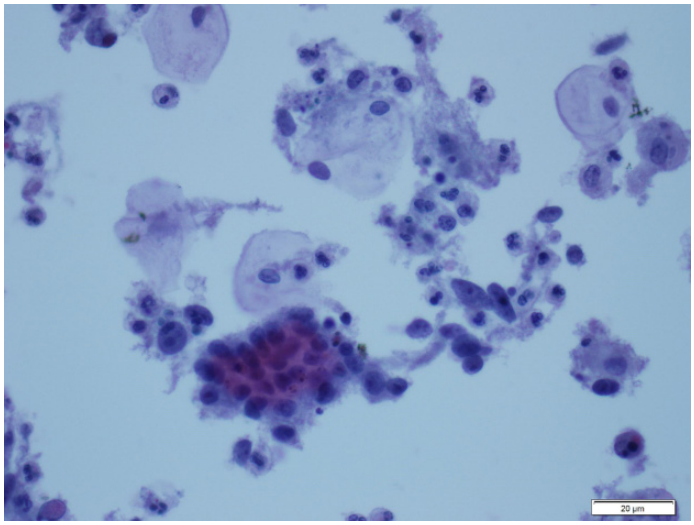

Figure 2. Cytology: Adenocarcinoma (cervical smear by Pap stain, 66 year-old woman). Single and a cluster of malignant cells with marked enlarged nuclei, and prominent nucleoli. Histologic diagnosis was clear cell carcinoma (×400)

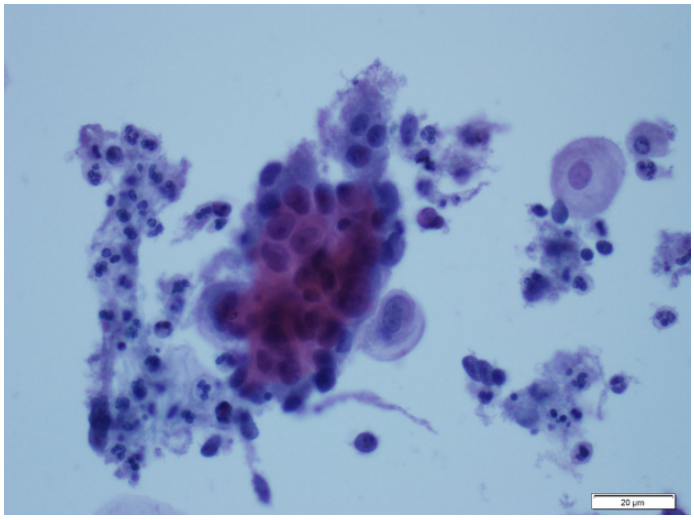

Figure 3. Cytology: Adenocarcinoma (cervical smear by Pap stain, 69-year-old woman). A cluster of malignant cells with marked enlarged nuclei, coarse chromatin, prominent nucleoli. Histologic diagnosis was serous carcinoma (×400)

DISCUSSION

The PAP smear test is a screening test that is used commonly in the diagnosis of cervical cancer and results in a significant decrease in the incidence of cervical cancer due to early diagnosis (6). As opposed to the decreasing incidence of cervical cancer, the incidence of endometrial carcinomas is gradually increasing and it ranks fourth among the most common cancers in females (7).

The Bethesda System (BS) is used to ensure standardization in the reporting of PAP smear tests. The atypical glandular cell (AGC) terminology was adapted to the BS in 2001 and defines cells that manifest changes beyond reactive and regenerative changes but do not bear the characteristics of invasive adenocarcinoma. The incidence of AGC in PAP smear tests varies between 0.12-0.74% across all cervical smears. Such low incidence rates cause difficulties in diagnosis and allow it to be disguised as a benign entity (8). In cervical cytology, normal endometrial cells can also be seen normally during menstruation and at the proliferative phase (9). However, the fact that these cells are seen in women older than 40 years and particularly in postmenopausal women requires further investigation (10,11).

Other terms in the Bethesda System that define glandular cell abnormalities include; Atypical Glandular Cells-Favor Neoplasia (AGC-FN), Endocervical Adenocarcinoma in Situ (EAIS) and Adenocarcinoma (8).

Our aim in this study was to evaluate the role of the PAP smear test and the correlation of its positive results with histological and prognostic data.

Abnormal cytologic findings detected by the PAP smear test in endometrial carcinomas, which range from atypical glandular cell morphology to adenocarcinoma, have been determined at rates that vary between 31.9% and 89.6% in the literature (4). In our series, this rate was 38.6%.

Across PAP smear tests of 76 female patients, Gu and colleagues determined abnormal cytologic findings in 55% of the patients. In this series, in which the number of patients was the most comparable to that in our series, PAP smear tests were performed in a period that preceded hysterectomy by 2-3 months (12). In our series, this time was 3.8 months on average.

In the patient group inspected by Sams and colleagues that included 69 individuals, the positive result rate was 31.9%. In the series reported by Sams and colleagues, the period between smear results and hysterectomy was not stated clearly (13). On the other hand, Zhou J and colleagues reported a positivity rate of 89.6% in their series that involved 67 cases, which is the highest rate of positivity in the literature. Cases in this series were comprised of cases that had been diagnosed within up to a 12-month-long time period after the histopathological diagnosis. In cases investigated in this series, the time period between the smear test and histopathological diagnosis was found to have no relationship to cytologic positivity (abnormal cytology) (14).

Although there are studies in the literature on the importance of AGC detected in the PAP smear test; there are not many studies that investigate its relationship with histopathological and prognostic data (15-17).

The series reported by Zhou J et al., which was the first study in the literature that evaluated multiple parameters, determined a significant relationship between severe cytologic atypia and increases in depth of myometrial invasion, cervical involvement, high histological grade (14).

In their series comprised of 32 cases, Nadaf et al. determined no significant relationship between depth of myometrial invasion and surgical stage, but determined a significant relationship between high tumor nuclear grade

and positive cytologic results. In the mentioned study, they detected cytologic atypia in 23 cases (71.2%) (9).

In a series where Pristauz G and colleagues also evaluated cervical involvement and PAP test results, they found a significant relationship between cervical involvement and positive smear results. They did not evaluate other parameters in this study (18).

In the study conducted by Serdy et al. that involves the largest series in the literature, 385 cases were evaluated along with resection material. They found in this study that positive cytologic findings had a significant relationship with tumor type, increased depth of myometrial invasion, cervical involvement, and presence of lymphovascular invasion (4).

In our study, no relationship with histological tumor type, cervical and lymph node involvement were determined but the depth of myometrial invasion represented a significant result. Among these variables, the absence of the expected potential relationship between cervical involvement and positive cytology in our series was thought to be due to the fact that few cases (11/75) in our series manifested cervical involvement. Similarly, the number of patients in our study that demonstrated lymph node involvement (7/75) was also quite low.

CONCLUSION

In conclusion, while the endometrial carcinoma detection rate in PAP smear tests was not very high in our study (38.6%), it is yet a rate that cannot be disregarded. The detection of an increase in smear positivity rate in correlation with an increase in myometrial invasion depth in our study is worth consideration as it constitutes an important parameter with implications for the treatment management by the surgeon.

The study was presented as an oral presentation at the 8th National Cytopathology Congress.

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