

## Original Article

### Frequency of Tumor Diathesis in Pap Smears of Women with Carcinoma of Uterine Cervix in Women Hospital (1995- 2003)

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#### ABSTRACT

**Background & Objectives:** Tumor diathesis (TD) is defined as granular proteinaceous precipitates on slide surface of cytologic smears. It is found in the background of smears of invasive carcinoma but not in all cases. The aim of present study was to determine the prevalence of TD in cervicovaginal smears from patients with uterine cervix carcinoma.

**Methods:** Cytological smears and histological slides from the Department of Pathology, Women Hospital, Tehran, Iran, of forty six patients histologically confirmed carcinoma of uterine cervix from 1995 to 2003 were reviewed for presence of TD, red blood cells, and neutrophils on cytological smears as well as depth of invasion, histologic types and grade of differentiation of tumor.

**Results:** TD was detected in 28 of the 46 smears (60.9%); in 18 patients with squamous cell carcinoma (62.1%), 7 adenocarcinoma (58.3%), 2 adenosquamous carcinoma (66.7%) and one endometrial carcinoma which involved uterine cervix. TD was seen in 4 (33.3%) uterine cervix carcinoma with 5mm depth of invasion and 17 (65.4%) uterine cervix carcinoma with  $\geq 5$ mm depth of invasion. There was a positive correlation between the presence of TD and the depth of invasion. Although an important criterion of malignancy, TD, was absent in some cases of carcinoma, particularly those that had  $< 5$ mm depth of invasion.

**Conclusion:** Increasing in depth of invasion and decreasing in differentiation of the tumor were associated with increasing in frequency of TD in cytological smears. A definite distinction between an intraepithelial lesion and a shallow invasive cancer may not be possible on cervicovaginal smears.

**Keywords:** Cervical Smear, Cervical Cancer, Tumor Diathesis, Thin Prep

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## Introduction

**T**umor diathesis (TD), defined as a “granular, proteinaceous precipitate observed in the spaces between cells and overlying cells” has been recognized as a hallmark of invasive cancer of the cervix for numerous years (1). Since TD is frequently absent from women with intraepithelial lesions, it can be a helpful diagnostic criterion for discerning intraepithelial from invasive lesions. The cytological diagnosis of invasive squamous cell carcinoma (SCC) is often more difficult than that of precursor lesions, because the preparations may contain necrotic material, blood and debris obscuring the often poorly preserved cancer cells.

The term TD has been applied to such features, which are an indication of necrosis of the surface of invasive tumor. Not all invasive cancers illustrate TD, mainly those in early stages without surface necrosis. In such instances, the cell samples may be difficult to interpret as invasive tumor. It has been recognized that this granular material is not specific to invasive cancer and can be seen in a selection of benign situation, for example in patients with a stenotic os and pyometra (1). Cervicovaginal samples from postmenopausal women with marked atrophy/atrophic vaginitis can be difficult to interpret with confidence, particularly in the presence of a granular background. The granular material in the slide background, reported to be derived from degenerative parabasal cells, can also be confused with a tumor diathesis (2). Certain types of neoplasm are less commonly associated with TD. Smear from patients with keratinizing SCC are more likely to lack the TD than nonkeratinizing SCC (3).

Smears of adenocarcinoma are often associated with dense inflammatory and fresh blood exudates and less often there is a recognizable tumor diathesis (4, 5).

Use of liquid-based cytology continues to increase in the world. Other than despite the increasing utilization of this test, limited data exist regarding the cytomorphologic features &

patterns of invasive cancer (6). The cytologic features of SCC in liquid-based cytology specimens are similar to those in conventional smears. Some authors noted, however, that a diathesis was common and that the cellularity of these specimens appeared decreased (7). In Selvaggi *et al.* study to evaluate the background features on ThinPrep1 slide preparations from endometrial carcinomas, the improvement in the quality of the slide with the ThinPrep1 process addressed many of the limitations of the conventional smear method. The number of slides limited by blood, inflammation, and air-drying artifact is greatly reduced with the use of the ThinPrep1 method. Cellular detection, architectural preservation, and morphologic cellular detail are enhanced. Nonetheless the presence of a classic tumor diathesis on Pap tests from women with endometrial carcinoma is dependent on the histologic type and grade of the tumor and the extent of the disease process (8).

The purpose of this study was to describe the background features of in cervicovaginal smears from 46 patients with uterine cervix carcinoma diagnosed on conventional smears.

## Materials and Methods

All pathological reports of invasive carcinoma of the uterine cervix were selected from Pathology Department of Women’s Hospital, a referral gynecological hospital in Tehran between 1995 and 2003. Then the cytological reports of these patients were searched for all cervical smears obtained no more than one year prior to the biopsy diagnosis of invasive carcinoma. The smears that were got after radiation to the cervix or biopsy were excluded from the study. Then all of smears were rescreened by authors to find the presence and extent of tumor diathesis (TD) was noted for each smear. TD was defined as a granular precipitate that was either eosinophilic or cyanophilic. The presence of necrosis, in the form of nuclear fragments, cells with karyorrhexis or anucleate cytoplasmic fragments of varying sizes, was

noted but not required. Intact red blood cells and neutrophils alone were not considered indicative of TD, but they could be considered separately along with TD. Histological slides of uterine cervix carcinoma were reexamined for histological typing, differentiation of the tumor and measuring the depth of invasion. Assessment the depth of invasion was performed only on hysterectomy or cone biopsy specimens and other biopsy specimens were excluded from the study. For assessment the depth of invasion, the current FIGO staging method was used, that recommends the measurement be made from the base of epithelium where invasion occurs to the deepest point of carcinoma in a vertical line (9).

The gathered data was evaluated by Statistical Package for Social Sciences v 18.0 (SPSS Inc., Chicago, IL, USA) software.

## Results

Forty six conventional cervical smears from 46 patients with cervical carcinoma were found according to the study criteria. The mean age was 50 years (rang 26-73), samples were taken from the endocervix and exocervix (by Ayre spatula and endocervical brush) in all cases and both samples were placed on the same slide.

Tumor diathesis (TD) was identified on 28 of the 46 smears (60.9%). TD enclosed < 25% of the slide area on 8 smears, 25-50% on 11 smears and > 50% on 9 smears.

TD consisted of a finely granular precipitate resembling hemolyzed blood in all cases. It was varied in thickness in different regions on smears surface. Red blood cells (RBCs) were found on 16 of 46 smears (34.8%). RBCs covered < 50% of the slide on 8 smears and > 50% on the other 8 smears. Neutrophils enclosed < 25% of the slide surface on 23 smears, 25-50% on 13 and > 50% on 10 smears.

The original histological diagnosis were 29 SCC (11 keratinizing squamous cell carcinoma (SCC), 17 large cell nonkeratinizing SCC and 1 small cell carcinoma), 12 adenocarcinoma (3

well differentiated, 3 moderately differentiated and 6 poorly differentiated adenocarcinoma), 3 adenosquamous carcinoma and 2 cases of endometrial carcinoma which extended to the cervix.

TD was identified on 18 of the 29 SCC (62.1%), 7 of the 12 adenocarcinoma (58.3%), 2 of the 3 adenosquamous carcinoma (66.7%) and 1 of the 2 endometrial carcinoma with extension to the cervix (50%). TD was found on 6 of the 11 keratinizing SCC (54.5%), 11 of the 17 large cell nonkeratinizing SCC (64.7%) and 1 of the 1 small cell carcinoma.

Moreover, TD was identified in 1 out of 3 well differentiated adenocarcinoma and on 6 of the 6 poorly differentiated adenocarcinoma. None of 3 patients with moderately differentiated carcinoma showed TD in their smears. The depth of invasion was < 5mm in 12 and  $\geq$  5mm in 26 patients and could not be assessed in 8 patients from the biopsies alone.

The depth of invasion in SCC was < 5mm in 9 patients and  $\geq$  5mm in 15 patients. Five patients had just biopsy, therefore excluded from this part of the study. The TD was found on 3 of the 9 SCC with depth of invasion < 5mm (33.3%) and on 10 of the 15 SCC with depth of invasion  $\geq$  5mm (66.7%). Red blood cells were identified on 12 of the 26 SCC smears (41.4%).

The depth of invasion in adenocarcinoma was < 5mm in 1 patient and  $\geq$  5mm in 9 patients. Two patients had just biopsy, consequently they were excluded. The TD was not seen in those patients with depth of invasion < 5mm but was identified on 6 of the 9 adenocarcinoma with depth of invasion  $\geq$  5 mm (66.7%).

Red blood cells were seen on 4 of the 12 adenocarcinoma smears (33.3%).

## Discussion

Tumor diathesis, characterized by the presence of a granular, proteinaceous precipitate between, admixed or overlying cells, is often seen in association with invasive squamous cell carcinoma

(SCC) of the cervix on conventional smears and more recently on liquid – based preparation (8). Incorporated are the presence of fresh/crenate red blood cells, acute inflammatory cells, apoptotic bodies, and granular debris. The presence of tumor diathesis (TD) in the background of cervical smears has long been accepted as a pattern associated with invasive cancer. Pattern has qualified by Von Haam as the first to stress that the background of a smear is a clue to the diagnosis of malignancy (1). Although, TD is the hallmark of invasive carcinoma of cervix on cytological smears, but there has been just a few studies about it. According to literature review, there has been just one published report which evaluated the frequency of TD in SCC on conventional smear, although, recent studies on liquid–based preparation were performed to show the utilization of this new test (1). The ThinPrep Pap test was approved in 1996 by the Food and Drug Administration. It improves specimen adequacy, resulting in the cytologic diagnosis of significantly more cervical abnormalities than the conventional smear technique (10). In individual study, there was a trend for increased detection of the ThinPrep Pap test in detecting invasive/in situ cervical adenocarcinoma (17.2% vs. 7.0%) and their findings propose that this system can facilitate a more directed approach to the evaluation of cervical and endometrial adenocarcinomas (10).

We noted that there were some variations in the definition of TD. Some cytologists describe it principally as a granular precipitate; while others demonstrate it as blood admixed with necrotic cells (1). We defined TD as granular proteinaceous precipitate. WBCs and RBCs were considered separately along with TD. Although, both patterns are associated with invasive carcinoma, one representing old hemorrhage and the other representing tissue necrosis, and both patterns may coexist. Indeed, papanicolaou himself described old fibrinated blood as a criterion of malignancy in its own right (1).

In this study, necrosis, accompanied by a granular, fibrinated background, was seen in 26 cases. The pattern of TD is mimicked by some benign conditions. The specificity of this pattern has not been addressed systematically, but some reports suggest that smears from women with pyometra and especially atrophic vaginitis may contain a granular precipitate that is indistinguishable from TD (2). We agree with others that a granular precipitate without abnormal cells is by no means diagnostic of carcinoma.

Other investigators have noted that smears from patients with carcinoma may contain TD and no abnormal cells whatsoever; we did not encounter such cases in our study.

Even with this rather liberal definition of TD, we were surprised to discover that it was absent from some cases, particularly those with relatively shallow stromal invasion such as microinvasive carcinoma. The implication of this is obvious: many smears from patients with invasive cancer will be diagnosed as less than carcinoma, commonly as high grade intraepithelial lesion, especially those in whom the tumor invades < 5 mm in depth. This study, therefore, reinforced what has long been recognized: diagnoses of high grade intraepithelial lesion does not preclude the possibility that the patient has carcinoma. The burden of excluding carcinoma rests with the practitioner who performs the colposcopic examination and takes the appropriate number of biopsies. In our study, frequency of TD in adenocarcinoma was 58.3% but it was reported by two studies 25% and 30.8% respectively (11). This difference is probably due to the grade of differentiation and the depth of invasion. Most cases in our study were poorly differentiated adenocarcinoma and had depth of invasion > 5mm. But in those studies most cases were microinvasive carcinoma with depth of invasion < 5mm (4, 11). We noted that frequency of TD in large cell nonkeratinizing SCC and small cell carcinoma is more than keratinizing SCC. We think that may be due to different of differentiation

in these tumors. It reinforced what has been recognized: TD was present in the majority of smears from large cell nonkeratinizing and is more pronounced than in keratinizing SCC. TD is almost always present in small cell carcinoma (3).

### Conclusion

Increasing in depth of invasion and decreasing in differentiation of the tumor are associated with increasing in frequency of TD in Pap smears. Although it is disappointing to recognize that TD is neither entirely specific nor highly sensitive for the diagnosis of invasive cancer, it is still an important criterion of malignancy. When present in association with large numbers of abnormal squamous cells, TD is a very reliable indicator of malignancy, especially in young women, in whom the possibility of atrophic vaginitis can be excluded.

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