Frequency of Tumor Diathesis in Smears from Women with Squamous Cell Carcinoma of the Cervix

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OBJECTIVE: To determine the prevalence of tumor diathesis (TD) in cervicovaginal smears from patients with squamous cell carcinoma (SQC).

STUDY DESIGN: We reviewed all the cervical smears obtained no more than one year before a biopsy diagnosis of SQC. Patients who underwent irradiation to the cervix before the smear was taken were excluded from the analysis. The smears were rescreened by both authors, and the presence and extent of TD were recorded.

RESULTS: Twenty-eight smears from 19 patients with SQC fulfilled the study criteria. TD was seen in 15 of the 28 smears (54%). There was a positive correlation between the presence of TD and the depth of invasion.

CONCLUSION: Although an important criterion of malignancy, TD is absent from some cases of SQC, particularly those that invade < 5 mm. A definite distinction between an intraepithelial lesion and a shallow invasive cancer may not be possible on cervicovaginal smears.
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Keywords: carcinoma, squamous cell; cervix neoplasms; diathesis; vaginal smears; cervical smears.

Tumor diathesis (TD), defined as a "granular, proteinaceous precipitate . . . observed in the spaces between cells and overlying cells,"[5] has been recognized as a hallmark of invasive cancer of the cervix for many years. Because TD is usually absent from women with intraepithelial lesions,[3,5] it can be a helpful diagnostic criterion for discriminating intraepithelial from invasive lesions.

When present in association with large numbers of abnormal squamous cells, TD is a very reliable indicator of malignancy....

It has been recognized that this granular material is not specific to invasive cancer and can be seen in a variety of benign conditions, such as in patients with a stenotic os and pyometra.[5] By itself, therefore, it cannot be relied on to render a diagnosis of malignancy. Conversely, some smears from women with invasive cancer lack TD. To our knowledge, there have been no published reports that evaluate the frequency of TD in invasive cancer.

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Materials and Methods

The surgical pathology records of Brigham and Women's Hospital were searched for all cases of invasive carcinoma of the cervix accessioned between January 1, 1990, and December 31, 1992. Only cases of squamous cell carcinoma (SQC) were included; all other types of cervical cancer were excluded. The cytology records of these patients were then searched for all cervical smears obtained no more than one year prior to the biopsy diagnosis of invasive SQC. Smears obtained after irradiation to the cervix or biopsy were excluded from the study.

Although it is disappointing to recognize that TD is neither entirely specific to nor highly sensitive for the diagnosis of invasive cancer, it is still an important criterion of malignancy.

The smears were rescreened by both authors using a mechanical stage, and the presence, extent and location (endocervical vs. exocervical) of 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, even if present in abundance.

Table I *Original Cytologic Diagnoses in 28 Smears from 19 Patients with Invasive SQC*

Diagnosis	No.
Within normal limits	0
Atypical squamous cells of undetermined significance	4[a]
Low grade squamous intraepithelial lesion	0
HSIL	12[b]
Suspicious for carcinoma	5
Positive for carcinoma	7

[a]On review, two of these cases were reclassified as HSIL.
[b]Two cases included a comment that an invasive cancer could not be excluded.

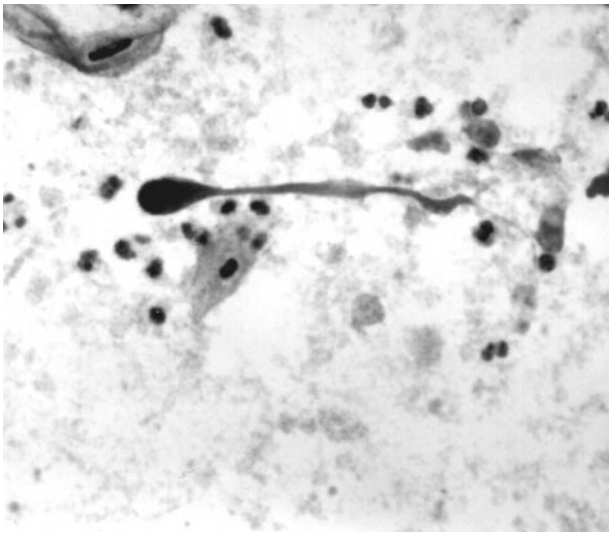

Figure 1 SQC with TD. The granular precipitate seen here most likely represents old blood from prior tumor-related hemorrhage. This precipitate is often thick and can obscure cellular detail. A solitary malignant squamous cell, shaped like a tadpole, is present (Papanicolaou stain, 2 380).

Results

Twenty-eight smears from 19 patients with SQC met the study criteria. Fourteen patients had 1 smear each, 3 patients had 2 smears, 1 had 3 smears, and 1 had 5 smears. The mean age was 45 years (range, 25–79). Six patients (32%) were younger than 35. Samples were taken from the endocervix and exocervix in all cases. In 27 cases both samples were placed on the same slide, and in one case they were placed on two slides. Seven smears (25%) were obtained on the same day as the cervical biopsies. In addition to invasive SQC, histopathologic examination showed a high grade squamous intraepithelial lesion (HSIL) in 14 of 19 patients (74%). Ten women were treated with hysterectomy and six with irradiation; in three the type of treatment was unknown.

The original cytologic diagnoses are displayed in Table I. None of the smears was unsatisfactory for evaluation. Twelve cases were diagnosed as HSIL, and 12 were reported as either suspicious or positive for SQC. Four contained atypical cells of undetermined significance. Of these, two smears (both from the same patient) were reclassified after review as HSIL.

TD was identified on 15 of the 28 smears (54%). Twelve of the 19 patients (63%) had TD on one or more smears. None of the five smears obtained

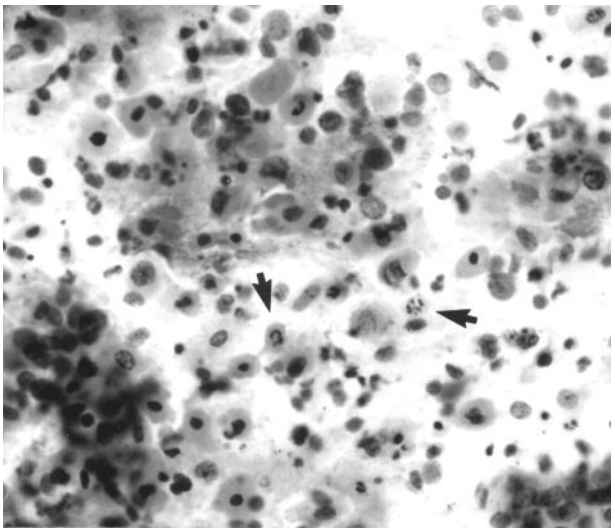

Figure 2 SQC with TD. In some cases of TD, the granular precipitate was accompanied by nuclear fragments, cells with karyorrhexis (arrows) and anucleate cytoplasmic fragments (Papanicolaou stain, 2 380).

from one patient who was pregnant showed TD; her SQC invaded to a depth of < 5 mm. TD covered < 25% of the slide surface on 7 smears, 25–50% on 5 and > 50% on 3. The distribution of TD was predominantly exocervical on 7 smears, predominantly endocervical on 3, equally distributed on 3 and indeterminate on 2.

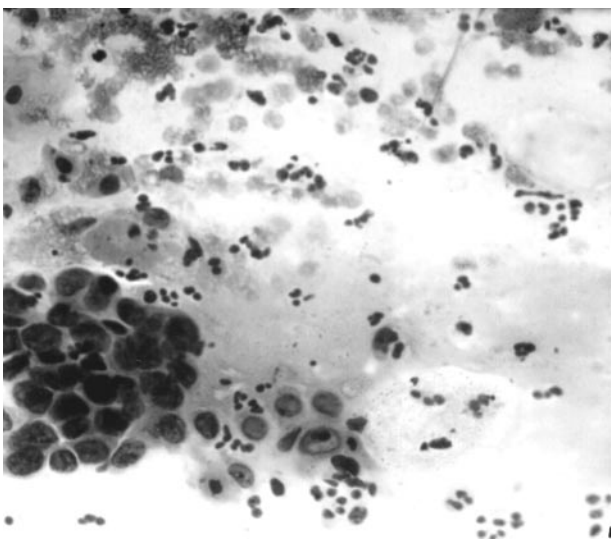

Figure 3 SQC with TD. In a small number of cases, the TD appeared as a watery (serous) proteinaceous fluid in addition to a granular precipitate (Papanicolaou stain, 2 380).

TD consisted of a finely granular precipitate resembling hemolyzed blood in all cases (Figure 1). It varied in thickness from area to area. In very thick areas it showed linear cracks, possibly caused by fixation. In addition, necrosis, in the form of extracellular nuclear fragments, intact cells with karyorrhexis and/or anucleate cytoplasmic fragments of varying sizes, was seen in eight smears (Figure 2). In a small number of cases, TD had a watery appearance in some parts of the smear (Figure 3) and a granular appearance in other areas. Red blood cells and neutrophils were abundant in most cases.

A diagnosis of HSIL does not preclude the possibility that the patient has SQC.

The depth of invasion by SQC was < 5 mm in seven patients and ≥ 5 mm in four. The depth of invasion was unknown in eight patients, most commonly because they had been treated with radiation therapy rather than hysterectomy, and the depth of invasion could not be assessed from the biopsies alone. The relationship between the presence of TD and the depth of invasion is shown in Table II. There was a significant correlation between the depth of invasion and frequency with which TD was found ($P = .05$, Fisher's exact test).

Discussion

The presence of TD in the background of cervical smears has long been accepted as a pattern associated with invasive cancer.[5] Patten has credited von Haam[7] as the first to stress that the background of a smear is a clue to the diagnosis of malignancy.[5] Although von Haam did not use the term *tumor diathesis* he noted that malignant cells were rarely found in smears that lacked a "hemorrhagic exudate,"

Table II *Correlation Between Depth of Invasion by Tumor and Presence of TD on Smears from Patients with Invasive SQC*

Depth of invasion	No. of smears	No. (%) with TD
< 5 mm	14	4 (28)
≥ 5 mm	6	5 (83)
Unknown	8	6 (75)
Total	28	15 (54)

neutrophils and "basal cells with karyorrhexis."

When we embarked on this study we noted that there was some variation in the definition of TD. In particular, we found that some cytologists describe it principally as a granular precipitate,[5] whereas others illustrate it as blood admixed with necrotic cells (as would be obtained from a necrotic tumor by fine needle aspiration).[1] We think that both patterns are associated with invasive SQC, one representing old hemorrhage and the other representing tissue necrosis, and that the patterns may coexist. Indeed, Papanicolaou himself described "old fibrinated blood" as a criterion of malignancy in its own right.[4] In this study, necrosis, always accompanied by a granular, "fibrinated" background, was seen in only eight cases (29%); an additional seven cases showed a granular background only, without necrosis.

The burden of excluding SQC rests with the practitioner who performs the colposcopic examination and takes the appropriate number of biopsies.

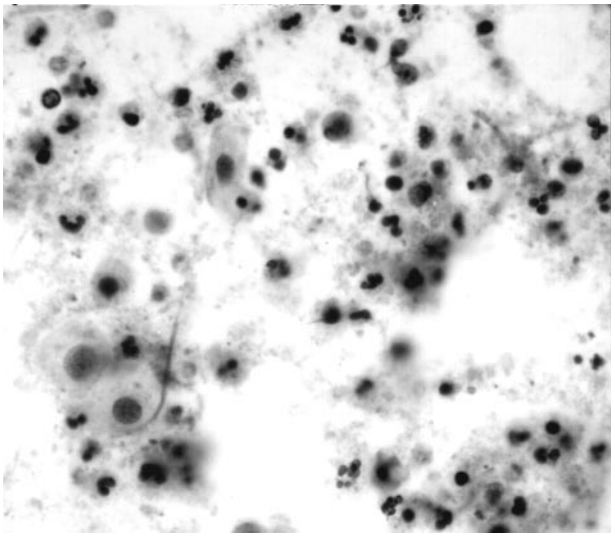

Figure 4 Atrophy with inflammation (atrophic vaginitis). This smear has an abundant, granular precipitate admixed with neutrophils that mimics TD. As in Figure 1, this precipitate can be thick and obscure cellular detail (Papanicolaou stain, 2 380).

Even with this rather liberal definition of TD, we were surprised to discover that it was absent from many cases of invasive SQC, particularly those with relatively shallow stromal invasion. The implication of this is obvious: many smears from patients with invasive cancer will be diagnosed as less than SQC, commonly as HSIL, especially those in whom the tumor invades <5 mm in depth. This study, therefore, reinforced what has long been recognized: a diagnosis of HSIL does not preclude the possibility that the patient has SQC. The burden of excluding SQC rests with the practitioner who performs the colposcopic examination and takes the appropriate number of biopsies.

The pattern of TD is mimicked by some benign conditions. To our knowledge, the specificity of this pattern has not been addressed systematically, but anecdotal reports suggest that smears from women with pyometra[5] and especially atrophic vaginitis[2] may contain a granular precipitate that is indistinguishable from TD (Figure 4). We agree with others that a granular precipitate without abnormal cells is by no means diagnostic of SQC.[6] Other investigators have noted that smears from patients with SQC may contain TD and no abnormal cells whatsoever[2]; we did not encounter such cases in our study.

The granularity of TD bears a superficial resemblance to the shift in vaginal flora due to a predominance of coccobacilli. This shift in flora was seen in a small number of cases from this study but was easily distinguished from TD. Coccobacilli are of more uniform size than the grains of TD and are frequently associated with "clue" cells.

Although it is disappointing to recognize that TD is neither entirely specific to 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.

Acknowledgments

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