Title: Nabothian cyst content: A potential pitfall for the diagnosis of invasive cancer on Pap test cytology.

Authors: Barrigón A, Ziadi S, Jacot-Guillarmod M, Da Silva S, Dumont M, Raineri I, Bongiovanni M

Journal: Diagnostic cytopathology

Year: 2019 Feb

Issue: 47

Volume: 2

Pages: 127-129

DOI: 10.1002/dc.24098
Nabothian cyst content: a potential pitfall for the diagnosis of invasive cancer on Pap test cytology.

A. Barrigón, MD; S. Ziadi, MD; Jacot-Guillarmod Martine, MD; S. Da Silva, CT; M. Dumont, CT; I. Raineri, MD; M. Bongiovanni, MD

1Service of Clinical Pathology, Lausanne University Hospital, Institute of Pathology, Lausanne, Switzerland.
2Department of Obstetrics and Gynecology, Lausanne University Hospital, Lausanne, Switzerland.
3Institute for Clinical Pathology, Medica, Zurich, Switzerland.

Correspondence
Massimo Bongiovanni, MD
Service of Clinical Pathology, Lausanne University Hospital, Institute of Pathology
Rue du Bugnon 25
CH-1011, Lausanne, Switzerland
Tel.: ++41 21 314 72 02;
Fax: +41 21 314 72 05;
e-mail: massimo.bongiovanni@chuv.ch

Financial disclosure
The authors have no affiliation and no personal relationships with any companies or products mentioned in this article.
ABSTRACT

Nabothian cysts are common, benign findings of the squamocolumnar junction of the adult cervix. These cysts are filled with mucus and can also contain proteinaceous material, neutrophils or neutrophil debris. Nabothian cysts can be broken by the spatula during smear taking, may stick to the brush and be smeared onto slides in conventional cytology or dissolved in the preserving solution for LBC preparations. The granular content of Nabothian cysts may be mistaken for the tumor diathesis (TD) pattern associated with invasive carcinoma.

In the case described, the patient presented a high-grade squamous intraepithelial lesion (H-SIL) associated with granular material (Nabothian cyst content) that we considered erroneously on liquid-based cytology to be TD-like material, thus, raising the suspicion of invasive carcinoma. To the best of our knowledge, this is the first report showing that Nabothian cyst content may present a potential pitfall in the diagnosis of invasive carcinoma on liquid-based cytology.

Keywords: Nabothian cyst, tumor diathesis, liquid-based cytology, cervical cancer.
INTRODUCTION

Cervical cancer screening in Switzerland is performed on an opportunistic basis, primarily using cytology by conventional smears (CS) and/or liquid-based cytology (LBC). The employment of cytology as a screening tool is certainly justified, as Switzerland has one of the lowest mortality rates for cervical cancer worldwide (1.7/100,000; National Institute for Cancer Epidemiology and Registration; http://www.nicer.org/en/statistics-atlas/cancer-mortality, accessed on June 21, 2018). High standards of cytology have to be maintained and a low false positive rate is essential, as positive cytology results cause anxiety and possibly unnecessary colposcopy examinations. Different quality control measures are suggested for cervical cytology, one of which is cyto-histological correlation of positive and/or discordant cases.1

Nabothian cysts (also called mucinous retention cysts or epithelial cysts) are frequent at the squamocolumnar junction (SCJ), an anatomical point of the cervix that is the target of brush sampling during cervical screening cytology. Inspissated mucus contained inside these cysts may exhibit a granular character or can be filled with granulocyte fragments, resembling tumor diathesis (TD), a key cytological feature of frankly invasive carcinoma.2 Moreover, necrotic debris in glands colonized by high-grade squamous intraepithelial lesions (H-SIL), may also mimic TD.

We report here, for the first time, an intriguing case that came to our attention during a discussion about potential mimickers of TD-like material in the Papanicolaou test (PAP test) cytology.

CASE HISTORY

A 32-year-old woman had been followed for several years due to a history of cervical dysplasia. On the last routine Pap test smear, atypical squamous cells consistent with H-SIL were identified along with TD-like material, thus suggesting invasive carcinoma. On cervical biopsies, areas containing typical low-grade squamous intraepithelial lesion (L-SIL) and H-SIL were diagnosed, but no invasive carcinoma. The subsequent conisation showed cellular morphological alterations consistent with koilocytosis associated with H-SIL, and H-SIL
colonizing cervical glands, next to abundant Nabothian cysts. Stromal invasion was not revealed on multiple levels. The final histopathological diagnosis was H-SIL.

MATERIAL AND METHODS

The cytologic smear, biopsy and conisation of the patient were collected from our archives, for cyto-histological correlation. The cytologic smear was prepared by LBC using ThinPrep (Hologic, Cham, Switzerland) according to standard procedures and the slide was stained with Papanicolaou staining. The biopsy and the conisation, performed by loop electrosurgical excision procedure (LEEP) one month after biopsy, were formalin-fixed, paraffin-embedded and examined at multiple deeper level sections.

RESULTS

The Pap test slide was evaluated in the cytopathology department by two cytotechnicians, one in training, and two cytopathologists, one in training. The cytological slide showed atypical squamous cells with nuclear hyperchromasia, high nuclear/cytoplasmic ratio, irregular nuclear membranes and raisinoid nuclei with focal grooves (Figure 1A). Focally, a dirty background with cellular debris, fibrin, neutrophils, necrotic-like material and degenerated cells was present and deemed consistent with TD-like material (Figure 1B). Beside this dirty, focally present background, only few isolated granulocytes where scattered through the entire slide which might be associated with inflammation. The cytological diagnosis was H-SIL with suspicious features of invasive carcinoma. The biopsy confirmed the HSIL lesion, without signs of invasion. Histological examination of the entire conisation specimen showed three foci of H-SIL colonizing cervical glands, Figure 1C (square and inset) next to abundant Nabothian cysts. Some of these were filled with inspissated mucus, containing neutrophils and necrotic-like material, features reminiscent of the cytological finding of TD (Figure 1C and 1D). Infiltration was excluded by performing three to six additional levels on all paraffin blocks; thus, allowing the final histopathological diagnosis of HSIL. It has to be mentioned that a focus
of moderate dysplasia (H-SIL) extended focally into one lateral margin. Still, the patient was
followed with 3 Pap tests in the following two years, and all returned negative for
intraepithelial lesion. These follow–up data confirm that the lesion was totally resected by
LEEP and no foci of invasion were left behind. No inflammation was identified on the slides,
so that the scattered neutrophils observed on the Pap smear could be ascribed to the cystic
content that was partly dispersed during the LBC slide preparation.
DISCUSSION

Nabothian cysts are common, benign findings of the SCJ of the adult cervix. These cysts can grow, appear superficially and are easily recognized during colposcopy examination. Reported complications of Nabothian cysts are hematometra, abnormal uterine bleeding, especially in the case of giant cysts, obstruction of labor passage and rectal compression. In addition, false positive uptake of iodine-131 in the uterus during whole body scans has been reported. In practice, superficially located Nabothian cysts can be broken by the spatula during smear taking, the mucoid content may stick to the brush and be smeared onto slides in conventional cytology or dissolved in the preserving solution for LBC preparations. In LBC, mucus is rarely present, as it is removed by the preserving solutions and centrifugation prior to slide preparation. Occasionally, mucus contained in Nabothian cysts can be permeated by neutrophils, the granular appearance of which may be visible on LBC slides. It is a well-known phenomenon that Nabothian cyst content can be detected on conventional Pap smears, and that it may be mistaken for the TD pattern associated with invasive carcinoma. In our case, we considered the granular material observed on LBC to be TD-like material, thus, raising the suspicion of invasive carcinoma. To the best of our knowledge, this is the first report showing that Nabothian cyst content may present a potential pitfall in the diagnosis of invasive carcinoma on LBC.

TD may present as a granular precipitate or as blood admixed with necrotic cells. The presence of TD in the background of cervical smears has long been accepted as a pattern associated with invasive cancer. Indeed, von Haam stressed in 1954 the importance of the background of a smear as a clue in the diagnosis of malignancy. However, it is also well know that invasive cervical cancers often do not exhibit TD on the corresponding Pap test slide, pointing to the low sensitivity of TD in the diagnosis of cancer. TD is also not entirely specific to the diagnosis of invasive cancer as several benign conditions, such us pyometra and atrophic vaginitis can mimic TD. In Inflammation or cervicitis, abundant neutrophils and necrotic-like material can be present usually accompanied by an overgrowth of bacteria. A granular precipitate on the cervical smear, indistinguishable from TD, may be exhibited, especially in atrophic vaginitis. Still, when present in association with 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.
Our case was confounded by the fact that the patient was young and had a history of H-SIL. The presence of granular, necrotic-like material admixed with abundant neutrophils resembled tumor diathesis, which in the context of H-SIL cells was interpreted as a possible sign of early infiltration. Moreover, necrosis seen in the background of H-SIL can also occur due to H-SIL colonizing glandular crypts; although, in the present case there clearly is a benign pathology, that produced granular material mimicking tumour diathesis.

**Conclusion**

Our report illustrates for the first time that benign conditions can mimic tumor diathesis also on LBC. CTs and MDs have to be made aware of this pitfall to avoid misinterpreting this benign finding as an invasive carcinoma.
Figure legends

**Figure 1A and 1B.** Cervical cancer screening cytology processed with liquid-based cytology (LBC). (A) Some aggregates of cells showed nuclear hyperchromasia, high nuclear/cytoplasmic ratio and raisinoid nuclei with focal grooves consistent with a high-grade squamous intraepithelial lesion (H-SIL). (B) On a different area of the slide, two foci of granular, dirty material with cellular debris, fibrin, necrosis and degenerated cells, were seen in the background and were consistent with tumor diathesis, a key cytological feature of invasive carcinoma.

**Figure 1C and 1D.** (C) The subsequent conisation showed foci of H-SIL colonising cervical glands (square and inset) next to abundant Nabothian cysts (*). One of these was filled with inspissated mucus ($\text{§}$ and corresponding figure D), morphologically resembling the cytological findings and mimicking tumor diathesis. Histology did not reveal invasion and the final diagnosis was H-SIL.
REFERENCES


