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1 **Nabothian cyst content: a potential pitfall for the diagnosis of invasive cancer on Pap test**  
2 **cytology.**

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30 **ABSTRACT**

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

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

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

## 46 INTRODUCTION

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48 Cervical cancer screening in Switzerland is performed on an opportunistic basis, primarily  
49 using cytology by conventional smears (CS) and/or liquid-based cytology (LBC). The  
50 employment of cytology as a screening tool is certainly justified, as Switzerland has one of the  
51 lowest mortality rates for cervical cancer worldwide (1,7/100.000; National Institute for  
52 Cancer Epidemiology and Registration; [http://www.nicer.org/en/statistics-atlas/cancer-](http://www.nicer.org/en/statistics-atlas/cancer-mortality)  
53 [mortality](http://www.nicer.org/en/statistics-atlas/cancer-mortality), accessed on June 21, 2018). High standards of cytology have to be maintained and  
54 a low false positive rate is essential, as positive cytology results cause anxiety and possibly  
55 unnecessary colposcopy examinations. Different quality control measures are suggested for  
56 cervical cytology, one of which is cyto-histological correlation of positive and/or discordant  
57 cases.<sup>1</sup>

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

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

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## 70 CASE HISTORY

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72 A 32-year-old woman had been followed for several years due to a history of cervical  
73 dysplasia. On the last routine Pap test smear, atypical squamous cells consistent with H-SIL  
74 were identified along with TD-like material, thus suggesting invasive carcinoma. On cervical  
75 biopsies, areas containing typical low-grade squamous intraepithelial lesion (L-SIL) and H-SIL  
76 were diagnosed, but no invasive carcinoma. The subsequent conisation showed cellular  
77 morphological alterations consistent with koilocytosis associated with H-SIL, and H-SIL

78 colonizing cervical glands, next to abundant Nabothian cysts. Stromal invasion was not  
79 revealed on multiple levels. The final histopathological diagnosis was H-SIL.

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### 83 **MATERIAL AND METHODS**

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

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### 93 **RESULTS**

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95 The Pap test slide was evaluated in the cytopathology department by two cytotechnicians,  
96 one in training, and two cytopathologists, one in training. The cytological slide showed atypical  
97 squamous cells with nuclear hyperchromasia, high nuclear/cytoplasmic ratio, irregular nuclear  
98 membranes and raisinoid nuclei with focal grooves (Figure 1A). Focally, a dirty background  
99 with cellular debris, fibrin, neutrophils, necrotic-like material and degenerated cells was  
100 present and deemed consistent with TD-like material (Figure 1B). Beside this dirty, focally  
101 present background, only few isolated granulocytes were scattered through the entire slide  
102 which might be associated with inflammation. The cytological diagnosis was H-SIL with  
103 suspicious features of invasive carcinoma. The biopsy confirmed the HSIL lesion, without signs  
104 of invasion. Histological examination of the entire conisation specimen showed three foci of  
105 H-SIL colonizing cervical glands, Figure 1C (square and inset) next to abundant Nabothian  
106 cysts. Some of these were filled with inspissated mucus, containing neutrophils and necrotic-  
107 like material, features reminiscent of the cytological finding of TD (Figure 1C and 1D).  
108 Infiltration was excluded by performing three to six additional levels on all paraffin blocks;  
109 thus, allowing the final histopathological diagnosis of HSIL. It has to be mentioned that a focus

110 of moderate dysplasia (H-SIL) extended focally into one lateral margin. Still, the patient was  
111 followed with 3 Pap tests in the following two years, and all returned negative for  
112 intraepithelial lesion. These follow-up data confirm that the lesion was totally resected by  
113 LEEP and no foci of invasion were left behind. No inflammation was identified on the slides,  
114 so that the scattered neutrophils observed on the Pap smear could be ascribed to the cystic  
115 content that was partly dispersed during the LBC slide preparation.

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**119 DISCUSSION**

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121 Nabothian cysts are common, benign findings of the SCJ of the adult cervix. These cysts can  
122 grow, appear superficially and are easily recognized during colposcopy examination. Reported  
123 complications of Nabothian cysts are hematometra, abnormal uterine bleeding, especially in  
124 the case of giant cysts, obstruction of labor passage and rectal compression. In addition, false  
125 positive uptake of iodine-131 in the uterus during whole body scans has been reported.<sup>3-9</sup> In  
126 practice, superficially located Nabothian cysts can be broken by the spatula during smear  
127 taking, the mucoid content may stick to the brush and be smeared onto slides in conventional  
128 cytology or dissolved in the preserving solution for LBC preparations. In LBC, mucus is rarely  
129 present, as it is removed by the preserving solutions and centrifugation prior to slide  
130 preparation. Occasionally, mucus contained in Nabothian cysts can be permeated by  
131 neutrophils, the granular appearance of which may be visible on LBC slides. It is a well-known  
132 phenomenon that Nabothian cyst content can be detected on conventional Pap smears, and  
133 that it may be mistaken for the TD pattern associated with invasive carcinoma.<sup>10</sup> In our case,  
134 we considered the granular material observed on LBC to be TD-like material, thus, raising the  
135 suspicion of invasive carcinoma. To the best of our knowledge, this is the first report showing  
136 that Nabothian cyst content may present a potential pitfall in the diagnosis of invasive  
137 carcinoma on LBC.

138 TD may present as a granular precipitate or as blood admixed with necrotic cells.<sup>11,12</sup> The  
139 presence of TD in the background of cervical smears has long been accepted as a pattern  
140 associated with invasive cancer.<sup>13</sup> Indeed, von Haam stressed in 1954 the importance of the  
141 background of a smear as a clue in the diagnosis of malignancy.<sup>14</sup> However, it is also well know  
142 that invasive cervical cancers often do not exhibit TD on the corresponding Pap test slide,  
143 pointing to the low sensitivity of TD in the diagnosis of cancer. TD is also not entirely specific  
144 to the diagnosis of invasive cancer as several benign conditions, such us pyometra and  
145 atrophic vaginitis can mimic TD. In Inflammation or cervicitis, abundant neutrophils and  
146 necrotic-like material can be present usually accompanied by an overgrowth of bacteria. A  
147 granular precipitate on the cervical smear, indistinguishable from TD,<sup>15</sup> may be exhibited,  
148 especially in atrophic vaginitis. Still, when present in association with abnormal squamous  
149 cells, TD is a very reliable indicator of malignancy, especially in young women, in whom the  
150 possibility of atrophic vaginitis can be excluded.

151 Our case was confounded by the fact that the patient was young and had a history of H-  
152 SIL. The presence of granular, necrotic-like material admixed with abundant neutrophils  
153 resembled tumor diathesis, which in the context of H-SIL cells was interpreted as a possible  
154 sign of early infiltration. Moreover, necrosis seen in the background of H-SIL can also occur  
155 due to H-SIL colonizing glandular crypts;<sup>16</sup> although, in the present case there clearly is a  
156 benign pathology, that produced granular material mimicking tumour diathesis.

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### 159 **Conclusion**

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

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166 **Figure legends**

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

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

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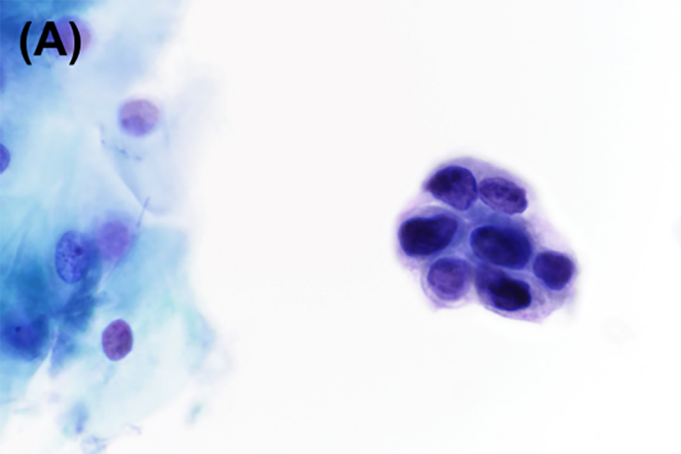
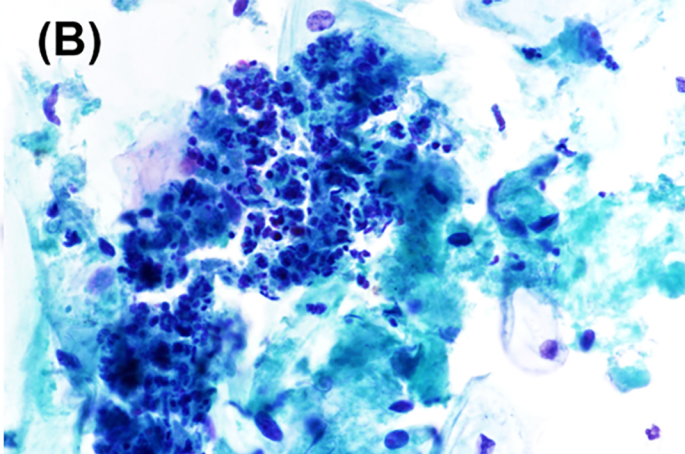
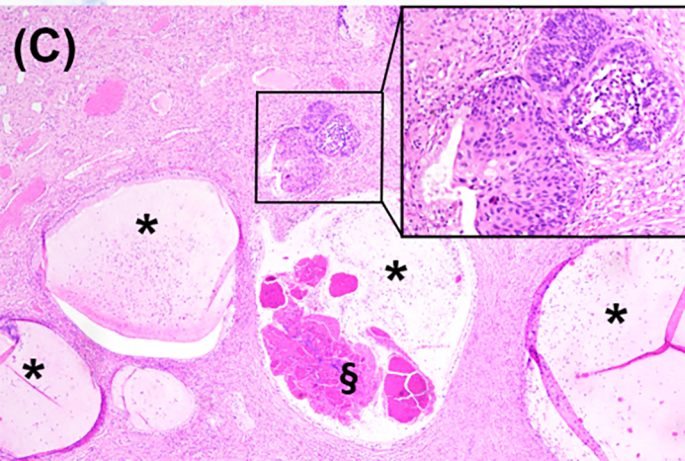
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**(A)****(B)****(C)****(D)**