Benign glandular and squamous metaplastic-like cells seen in vaginal Pap smears of post hysterectomy patients: incidence and patient profile

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Summary

We have observed benign glandular cells and squamous metaplastic-like cells in vaginal Pap smears of post hysterectomy patients (PHP). Vaginal Pap smears from 1,547 PHP were retrieved. In 2% of these smears (Group A) glandular cells were observed, with the majority of the smears revealing squamous metaplastic-like cells (47%). Mucinous endocervical columnar-like cells were seen in 9% of the cases, glandular cells not resembling endocervical cells in 13%, and a combination of the former two categories in 31%. Group A patients were compared with other PHP without these cells in their vaginal smears (Group B). Several clinical and surgical parameters were evaluated. A distinctive clinical profile was not identified for either group of patients (A or B). Of patients in group A 49.8% had a history of a previous gynecologic malignancy (Group B: 19%). Based on our study, we postulate that in the absence of a clinically identifiable source of these cells, the most likely source of origin is probably vaginal adenosis not associated with DES exposure in utero or a metaplastic phenomenon perhaps related to therapy. These cells do not seem to be related to imminent neoplasia or dysplasia.

Key words: Post hysterectomy; Metaplastic-like cells; Glandular cells.

Introduction

The presence of benign glandular cells as well as of cells resembling metaplastic squamous epithelium in vaginal Pap smears of post hysterectomy patients (PHP) can be of concern to the pathologist [1]. There are reported cases in which the origin of these cells can be identified, for example, vaginal prolapse of a fallopian tube [2], vaginal endometriosis [2-5], and a rectovaginal fistula [2], among others [6]. In a number of cases, however, the exact source of these cells remains unknown. In some cases the PHP have a history of carcinoma (particularly a gynecologic malignancy) [1] and the presence of these cells may raise the question of a recurrent malignancy. It is important to avoid misinterpretation and over-stating these findings as evidence of malignancy. Considering the potential clinical significance of these findings, we decided to determine the incidence and the clinical profile of these PHP.

Materials and Methods

We retrieved 9,393 otherwise negative Papanicolaou stained vaginal smears examined at our institution (Hutzel Hospital/Detroit Medical Center, Detroit, MI) during 1992. Of these, 1,547 smears originating from PHP were identified. Benign glandular cells as well as cells resembling metaplastic squamous cells were seen in 44 of the smears. Twelve of these cases were excluded from the study because of a history of supracervical hysterectomy (therefore a cervix was still present in each case). The remaining 32 smears were examined by two of the authors (NR, LS) and divided into four categories (based on the type of the cell identified) as follows: I) squamous metaplastic-like cells (SMLC), II) mucinous endocervical columnar-like glandular cells (ENLC), III) glandular cells not resembling mucinous endocervical (columnar) epithelium (GLC), and IV) combinations of two of the previously described categories. Also noted was the type of background seen in each case, the method of collection and the adequacy of the Pap smears. The following criteria were evaluated in all of the PHP: age, type of hysterectomy (abdominal or vaginal), and number of years after surgery. Also identified was any previous history of endometriosis, DES (diethylstilbestrol) exposure in utero, gynecologic malignancy, malignancy of any other type, radiation, chemotherapy, and hormonal therapy (that was received during the time the smear was collected).

Results

Of the 32 cases examined (2% of all PHP evaluated), 15 were categorized as I (SMLC), three as II (ENLC), four as III (GLC), and ten as IV (combinations of two of the other categories) [7]. All the smears examined were satisfactory for evaluation. The smear background associated with a large majority of the cases showed evidence of cellular maturation as well as varying degrees of mild to moderate acute inflammation. Three of the smears with the previously described background contained microorganisms (table 1). One category I smear had an atrophic background and one category IV smear had a reparative background.

Cytologic Description

The metaplastic-like cells observed in category I smears were arranged in sheets and rarely in syncytia,

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features highly reminiscent of squamous metaplastic cells seen in the endocervix (figure 1). Individual cells were round to polygonal with the majority of cells having well defined cytoplasmic borders. The cytoplasm was dense and cyanophilic; the nuclear to cytoplasmic (N:C) ratio was relatively high. The nuclei were hypochromatic with finely granular chromatin and rare prominent nucleoli (figure 2). The endocervical columnar-like cells identified in three category II smears were arranged in honeycomb-like sheets. The cell borders were clearly defined. The cytoplasm was finely vacuolated and rather abundant; the N:C ratio was low (figure 3). The nuclei were benign appearing with hypochromasia, finely granular chromatin and regular nuclear membrane (figure 4). Category III smears revealed glandular cells that did not have features similar to mucinous endocervical (columnar) cells. One patient had a group of tightly cohesive small cells resembling endometrial epithelial cells (figure 5). Individual cells were hyperchromatic and occasionally smudged, without recognizable amounts of cytoplasm. The possibilities raised in the differential diagnosis of the latter case included endometriosis and endometrial adenocarcinoma. However, the background and absence of malignant features excluded both the above-mentioned possibilities. The other three cases exhibited columnar cells with combined features of endometrial cells and tubal epithelial cells (figures 6, 7). The combination of cell types seen in category IV smears consisted exclusively of endocervical-like and metaplastic-like type cells; the cells exhibited cytological features similar to those identified in the cells of smears categorized as I and II. When data from the PHP with benign glandular and metaplastic-like cells in their vaginal smears (Group A patients) were compared with data from PHP that lacked such findings in their vaginal smears (Group B patients) the following results were obtained (table 2).

Comparison of the data obtained from both groups of PHP failed to reveal any difference between the methods of collection of the vaginal samples, the type of surgery the patients underwent or any previous history of endometriosis, DES exposure in utero, radiation, chemotherapy, and hormonal therapy. Thirty-one percent of the Group A patients still had one or both of their ovaries in

Table 1. — *Smear background.*

Background	Category I	Category II	Category III	Category IV
Repair	0	0	0	1
Maturation and inflammation	14 (1 t*)	3	4 (1C**)	9 (1C**)
Atrophy	1	0	0	0

*Trichomonas; **Candida.

Table 2. — *Clinical profile of patients.*

Criteria evaluated Average age (years)	Group A patients 58 (range 32 - 81)	Group B patients 53 (range 37 - 72)
Average number of years post hysterectomy	8.0	11.0
Status post abdominal hysterectomy (%)	85.0	85.0
History of endometriosis	0	0
History of DES exposure in utero	0	0
History of gynecologic malignancy* (%)	49.8	19.0
History of malignancy** (%)	0	1.12
History of radiation / chemotherapy (%)	4.0/7.0	3.6/6.5
History of hormonal therapy	20.0	21.6
Method of collection - vaginal scraping (%)	87.0	87.0
Method of collection - cell sweep (%)	13.0	13.0

*Includes uterus, ovaries, cervix, vagina and vulva; ** Excluding gynecologic.

Table 3. — *Comparison of Gynecologic malignancies in patient history.*

Post hysterectomy patients	MMMT* (%)	Endometrial carcinoma (%)	Cervical carcinoma (%)	Ovarian carcinoma (%)	Endometrial stromal sarcoma (%)
Group A patients (Total = 32)	6.2	9.3	12.5	21.8	0
Group B patients (Total = 1503)	0	6.3	7.5	4.8	0.4

*Malignant mixed mullerian tumor of the uterus.

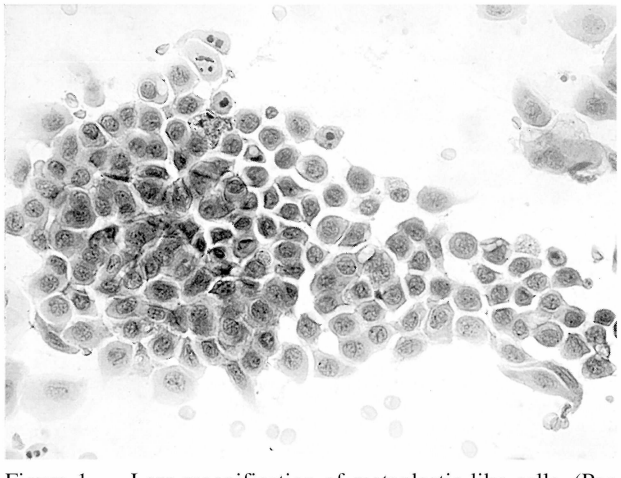

Figure 1. — Low magnification of metaplastic-like cells. (Pap stain, x 100).

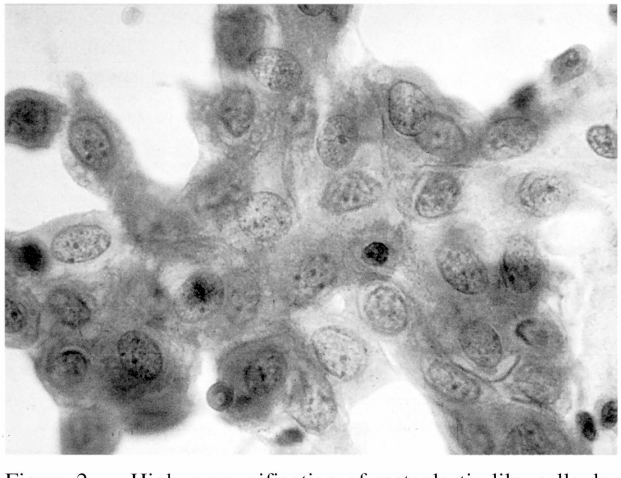

Figure 2. — Higher magnification of metaplastic-like cells demonstrating a relatively high N:C ratio and dense cytoplasm. (Pap stain, x 1000).

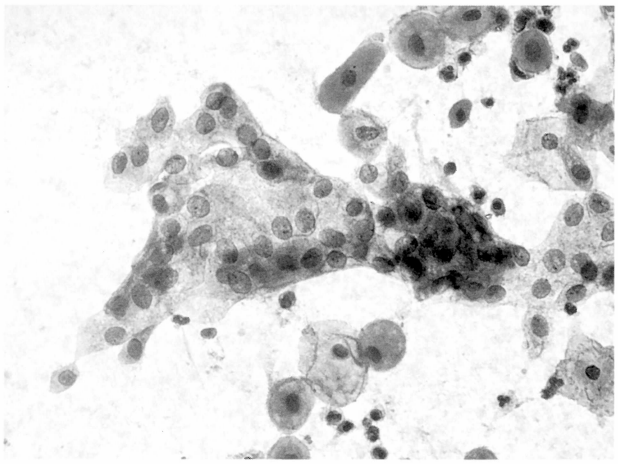

Figure 3. — Low power view of endocervical-like cells observed in the vaginal smear of a post hysterectomy patient. A honeycomb-like arrangement is seen. (Pap stain, x 100).

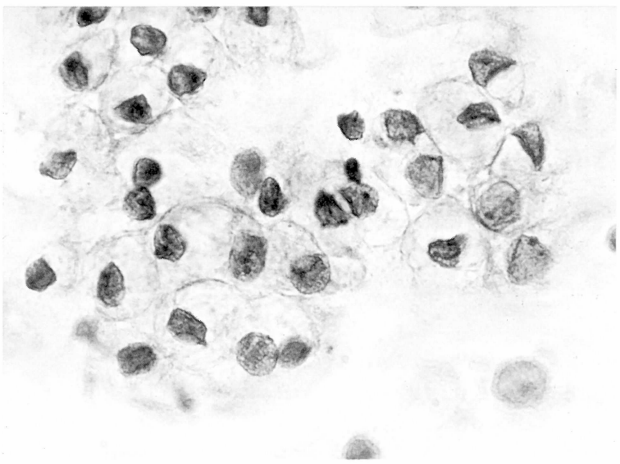

Figure 4. — Vaginal smear of a post hysterectomy patient containing benign mucin producing glandular cells. Morphologic features are similar to a case of vaginal adenosis not related to DES exposure in utero shown in figure 8. (Pap stain, x 1000).

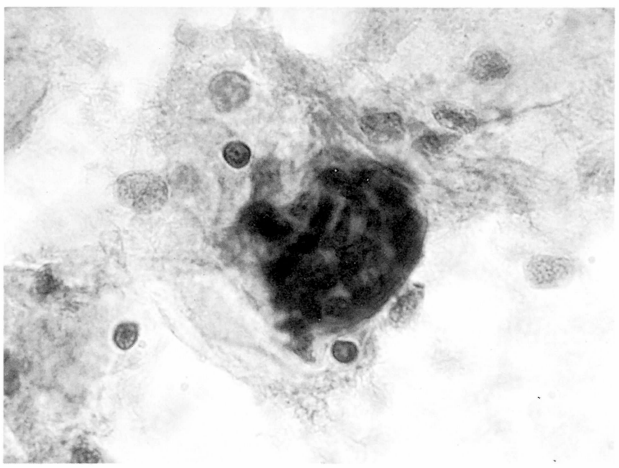

Figure 5. — Vaginal smear containing one cohesive group of endometrial-like cells. The patient had no history of endometriosis or adenocarcinoma. (Pap stain, x 1000).

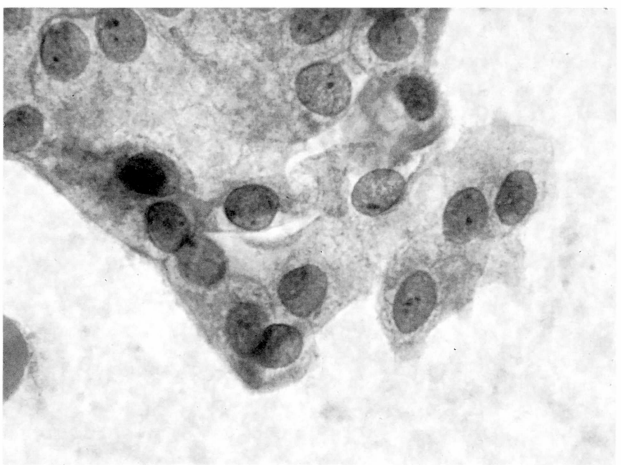

Figure 6. — An example of glandular cells (Type III). (Pap stain, x 1000).

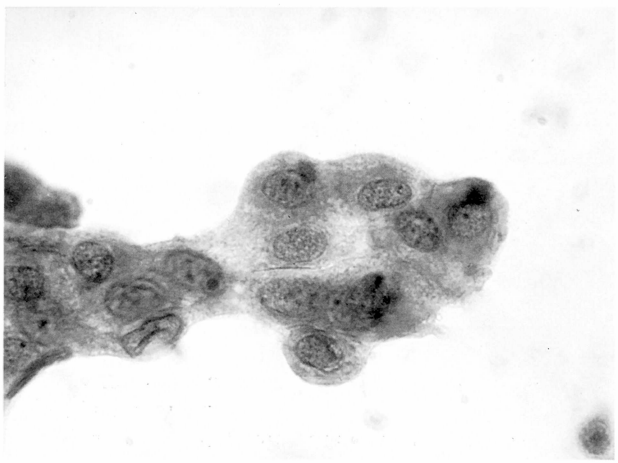

Figure 7. — Note the attempted gland formation in a group of Type III cells. (Pap stain, x 1000).

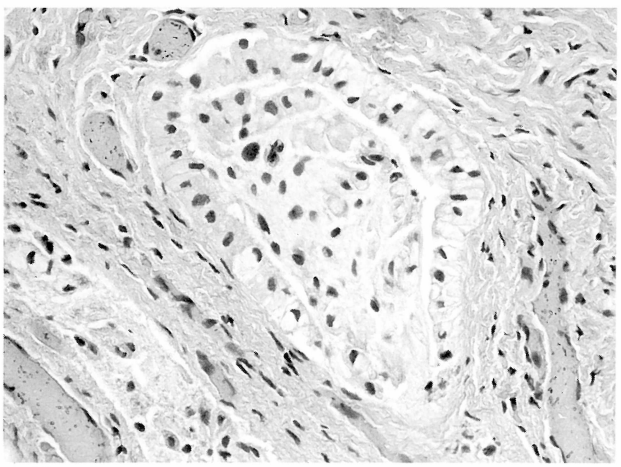

Figure 8. — Higher magnification demonstrating benign mucin producing glands in a case of vaginal adenosis not related to DES exposure in utero. (H&E, x 100).

place. A history of malignancy other than that of the reproductive tract was only identified in Group B patients. The types of carcinoma identified in the latter population were: breast (11 cases), lung (1 case), colon (2 cases), and urinary bladder (2 cases). In both groups of PHP there were patients with a history of gynecologic malignancy. However, the percentage of patients with these malignancies was higher in Group A (table 3).

There was little difference in the average age of the patients in both groups and in the number of years after surgery. Follow-up clinical information from Group A patients revealed that as a result of the findings reported by our laboratory to the clinicians, 22% of all the patients underwent colposcopic examination as an immediate follow-up procedure. However, less than half of those colposcoped (42%) underwent biopsy procedures, the latter only performed when a lesion was detected on colposcopy. In all cases, the biopsies failed to reveal evidence of malignancy or to clarify the origin of the benign glandular cells and/or the metaplastic-like cells. All Group A patients who were not colposcoped were followed-up by a subsequent vaginal smear within 6 months. Two of the patients in Group A had previous smears with metaplastic-like cells observed; their follow-up smears (included in our study) revealed metaplastic-like cells in both cases. None of the Group A patients with a history of malignancy had evidence of recurrence (as evaluated at the time that this manuscript was completed).

Discussion

In our PHP population, the incidence of benign glandular cells and/or metaplastic-like cells in vaginal smears was 2%. We were able to categorize these cells as squamous metaplastic-like only (46.9%), endocervical columnar-like only (9.3%), glandular cells not resembling endocervical (columnar) mucinous epithelium (12.5%) and as combinations of the previously described groups (31.3%). While the majority of the glandular cells seen resembled endocervical (mucinous) columnar cells, in our category III smears three cases exhibited cytological features reminiscent of tubal epithelium (although they lacked cilia) and one case exhibited features resembling endometrial epithelial cells. We noticed that the types of cells observed in this study were similar to the types of cells described in the literature such as those commonly seen in cases of patients with vaginal adenosis (figure 8) not associated with DES exposure in utero (N-DES-EXP). According to the literature, vaginal adenosis N-DES-EXP is characterized in the majority of cases by mucinous columnar cells resembling endocervical-type glandular epithelium, but tuboendometrial-type glands can also be observed [9, 10]. Vaginal adenosis is known to undergo involution, at which time squamous metaplasia (the process by which involution of the glands is attained) occurs [9, 10]. The incidence of vaginal adenosis N-DES-EXP has been described in the literature to vary from 0 to 40.8% [9] and to affect women between the ages of 25 to 62 years (median 39 years) [10]. Although in clinically suspected cases of adenosis colposcopic examination usually results in the identification of gross mucosal lesions, sometimes clinical evaluation fails to reveal any mucosal abnormalities. It appears that vaginal adenosis is identified in a more accurate manner in autopsy studies, probably related to the extensive sampling of the vaginal mucosal tissue that is usually performed in those types of studies [10-12].

The presence of the various types of cells we observed in the vaginal smears of PHP can be attributed to different etiologies [13]. Vaginal adenosis N-DES-EXP is perhaps the most likely origin of these cells in cases in which the specific source can not be identified by any practical and accepted medical means. If the process of involution exemplifies the natural history of vaginal adenosis, then it is possible that foci of adenosis undergoing involution might be clinically silent. This might explain why when PHP with unexpected benign glandular cells and/or metaplastic-like cells in their vaginal smears are colposcoped, there are no gross vaginal mucosal lesions detected in the majority of cases [13]. The presence of a large percentage (78%) of squamous metaplastic-like cells in the smears we examined will then favor lesions of vaginal adenosis undergoing involution that, although clinically asymptomatic and most probably undetectable, manifest themselves at the microscopic level in the vaginal Pap smears. Depending on how long the process of involution will take might probably determine the types of cells that will eventually be detected in subsequent vaginal Pap smears. Six percent of Group A patients had a history of having similar findings in previous smears. In our study less than half of the patients colposcoped had glandular cells in their smears and of those, only one was biopsied.

Only 6% of the cases exhibited a background different from that of the majority (table 1). One category I smear had an atrophic background and the other (a category IV) had a reparative background.

A specific patient profile was not evident from this study. The average age of the patients in Group A was 58 years, an average of 5 years older than those in Group B. The percentage of patients with a history of gynecologic malignancy, however, was larger in Group A patients (49.8%) than in Group B (19%). PHP with a history of gynecologic malignancy undergo closer clinical scrutiny and systematic follow-up studies; the presence of a larger population of patients with these particular characteristics may be coincidental. Bewtra [13], who in her study examined a population of PHP in a manner similar to our study, also noted the higher number of PHP with a previous history of gynecologic malignancies and raised the same concern. Our institution (Hutzel Hospital) has a large Gynecologic Oncology Service that consistently contributes a significant number of smears to our department, probably increasing our chances of including patients from their service in our study. Only group B patients showed a history of malignancy not related to the reproductive tract, but in a very small percentage of cases (1.12%). None of the other criteria evaluated in both

populations of PHP revealed any particular trend. Therefore we conclude that the method of collection of the Pap smear, the type of hysterectomy the patients underwent, as well as the number of years post-surgery did not appear to be important factors in any of the groups of PHP examined; they also failed to define a specific patient profile for either group of patients (A or B). Also of no significance was a history of endometriosis, DES exposure in utero, radiation, chemotherapy, and hormonal (estrogenic) therapy.

Bewtra [13] examined nine cases of columnar cells in vaginal smears of PHP. Although we examined approximately four times as many cases, some of the major findings of her study were in agreement with what we observed. In her study, the author identified three populations of benign cells in the vaginal smears of PHP. In her assessment of those cells Bewtra identified the fact that in one group the glandular cells resembled mucinous endocervical cells and goblet cells. We did not find glandular cells resembling globet cells in our study, but 40.6% of all of our smears showed glandular cells that exhibited cytological features resembling those of glandular cells of endocervical (columnar) origin. The second group of the cells that she described as being the most frequent group resembled reparative squamous or columnar cells. In our study the largest category of cells were those that resemble metaplastic squamous epithelium. A third group of cells identified by Bewtra was thought to represent exfoliated parabasal and basal cells resembling glandular-type cells; the latter was the least common type of cells she encountered. In our study the smallest group of cells (Category III) did not resemble the types of cells reported by her, but resembled both tubular and endometrial-type glandular epithelium. There are differences in the cytological features of the types of glandular cells identified in the vaginal smears of PHP between both studies. There are also disagreements as to what may be the origin of these cells, with Bewtra favoring goblet cell metaplasia of the vaginal epithelium and exfoliated atrophic squamous cells mimicking reparative columnar cells as the possible source. It is important, however, to emphasize that both studies highlight the presence of three different major groups of benign cells as well as the importance of avoiding misinterpretation of the process as malignant. Both studies also show that the findings are more common in women with a previous history of gynecologic malignancies and that there does not appear to be a particular patient profile associated with these findings.

A study by Koike *et al.* [14] points out the presence of goblet cell metaplasia in the vagina of postmenopausal patients. None of our cases had glandular cells with an associated atrophic background. We acknowledge the fact that the process of goblet cell metaplasia of the atrophic vaginal epithelium can be a source of glandular-type cells (and also probably of metaplastic squamous cells) that can eventually be detected in the vaginal smears of PHP. We do share the concern of Koike *et al.* that it is possible that glandular cells resembling endocervical-type epithelium which originate in places other than the endocervix may be used by the cytologist as evidence of the adequacy of the smear when the cervix is still present.

Recent papers have addressed issues related to different aspects of glandular cells in cervical smears [15-18]. The study by Ponder *et al.* [15] examined a series of 15 cases with glandular cells in post-hysterectomized patients. The cells were comprised mostly of cuboidal and goblet-like cells. Thirteen percent of patients in this series however developed vaginal intraepithelial neoplasia (VAIN). Our study with a larger number of cases, was aimed at evaluating the incidence and clinical profile of these patients. None of our patients had developed dysplasia or neoplasia at the last follow-up.

Conclusion

The incidence of benign glandular cells as well as of cells resembling metaplastic squamous epithelium in negative vaginal Pap smears of PHP in our population was 2%. We did not identify any distinctive clinical profile for these patients. We believe that our finding is truly representative of the incidence of this phenomena and acknowledge the possibility that patients with a past history of gynecologic malignancies may be over-represented in our population. It is possible that the latter may also hold true for studies similar to ours because gynecologic oncology patients (largely post hysterectomy as the result of their treatment) tend to be followed-up more carefully and in a more systematic manner. There was no specific method of sample collection associated with the detection of these cells in vaginal Pap smears. We postulate that if the source of benign glandular cells and squamous metaplastic-like cells in PHP can not be identified after extensive clinical and pathological evaluations, the most likely source of origin is vaginal adenosis not associated with DES exposure in utero, or a metaplastic phenomenon perhaps related to therapy [19-22]. These cells however do not appear to be related to imminent neoplasia or dysplasia.

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