Clinical Significance of Hyperkeratosis on Otherwise Normal Papanicolaou Smears

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Background. Although hyperkeratosis is a common cytological finding on Papanicolaou smear, its clinical significance is unclear.

Methods. A profile of patients with hyperkeratosis was constructed by comparing them to an age-matched control population having normal Papanicolaou smears. The clinical significance of hyperkeratosis was evaluated and appropriate follow-up studies were recommended.

Results. Of 2198 Papanicolaou smears done in the University of Kansas Family Practice Department between October 1, 1988, and October 31, 1989, there were 184 diagnoses of hyperkeratosis from smears on which no other pathological findings were noted. Charts of 183 of these patients with hyperkeratosis were reviewed and compared with an age-matched control population having normal Papanicolaou smears. Patients with hyperkeratosis had a statistically higher incidence of infections with *Gardnerella vaginalis*, but a lower incidence of infections with *Chlamydia trachomatis*. Diaphragm use was more prevalent in the group with hyperkeratosis. The incidence of inflammation on Papanicolaou smear was similar between the two groups. Of the patients with hyperkeratosis, colposcopic examination had been performed on 48% (88 of 183), of which 28% (25 of 88) had evidence of human papillomavirus or dysplasia.

Conclusions. Review of the data obtained suggests that follow-up colposcopy, including endocervical curettage, be performed on all patients with hyperkeratosis in order to screen for accompanying pathological conditions that may necessitate treatment.

Key words. Cytology; keratosis; papillomavirus.
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Hyperkeratosis is histologically recognized by the presence of polygonal, lightly staining, anucleate cells, which are often folded over each other or arranged in layers covering surface epithelium (Figures 1 and 2).[1] It is thought to occur as a protective response to trauma—both physical and chemical—inflammation, and uterine descensus.[2] Hyperkeratosis may appear clinically as white cervical plaques (leukoplakia) and is not an infrequent finding on the Papanicolaou smear. It often occurs in patients who were exposed to diethylstilbestrol in utero.[3]

According to published literature, hyperkeratosis alone has not been attributed to the development of cervical dysplasia, yet increased keratinization is often noted as a characteristic of dysplastic lesions.[1,4] Reagan and Hamonic[4] observed hyperkeratosis in 44 of 100 patients presenting with cervical dysplasia. Hyperkeratosis is also a histological feature of the surface epithelium of condyloma acuminatum.[5] The significance of finding hyperkeratosis without other pathological findings on the Papanicolaou smear is unclear, and a standard for follow-up is lacking. Many researchers agree that while hyperkeratosis in itself is a benign condition, it may hide an underlying disease process and should, therefore, be routinely followed up with biopsy.[2,6,7] However, in two recently reported studies, investigators concluded that sufficient evidence is lacking to support this approach.[1,8]

The purpose of the present study was twofold: (1) to identify common characteristics or predisposing factors in patients with hyperkeratosis, and (2) to determine the clinical significance and appropriate follow-up of hyperkeratosis when it appears as the sole diagnosis on the Papanicolaou smear.

Methods

This retrospective study spanned the period from October 1, 1988, through May 31, 1990. The study sample

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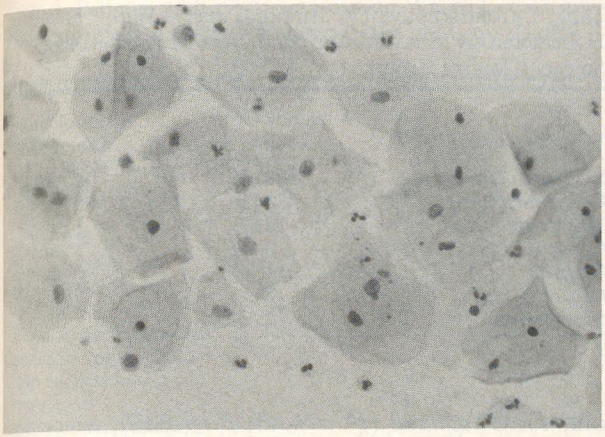

Figure 1. Normal Papanicolaou smear. Note that the squamous cells have normal nuclei.

was obtained from patients whose Papanicolaou smears were done in the University of Kansas Department of Family Practice between October 1, 1988, and October 31, 1989. Only charts of patients whose Papanicolaou smears showed hyperkeratosis without other pathological diagnoses were selected for review. Hyperkeratosis was reported by the pathologist when 10 or more anucleated squamous cells were identified on the smear. Diagnoses that met exclusion criteria for pathology included condyloma, atypical squamous cells, dysplasia of any degree, and carcinoma.

Charts were reviewed, and selected data were recorded. Demographic information included age, race, gravidity, parity, and number of abortions, both therapeutic and spontaneous. Gynecologic history included the type of active contraception used by the patient, whether the patient had had a hysterectomy, whether the patient was menopausal, and if menopausal, whether she used hormone replacement therapy. The presence of any gynecologic infections noted from the time of the initial Papanicolaou smear through the follow-up period, and whether these had been treated, was recorded. Data obtained from the initial Papanicolaou smear included the presence and degree of inflammation, and the presence of squamous metaplasia and repair. The University of Kansas Department of Pathology routinely reports any of these findings if noted on the smear.

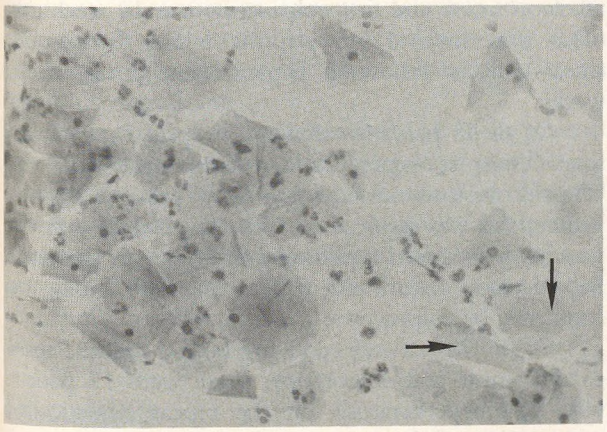

Figure 2. Papanicolaou smear with evidence of hyperkeratosis. Arrows show representative anucleated squamous cells. Regions of hyperkeratosis would stain orange. There is also evidence of inflammation indicated by the presence of white blood cells.

Data from follow-up studies on each patient were collected through May 31, 1990. Information about any colposcopic examinations and additional Papanicolaou smears, as well as the time between the initial Papanicolaou smear and follow-up studies, was recorded. Any resident or staff physician may have done the Papanicolaou smears, but all colposcopic examinations were carried out by one of five family practice staff physicians who were trained in colposcopy. Patients may have had a colposcopic examination alone or in combination with cervical biopsy, endocervical curettage (ECC), or vaginal biopsy. Results considered to be pathological on biopsy included dysplasia of any degree and evidence of human papillomavirus (HPV) infection, including condyloma, koilocytic changes, and dyskeratosis. Cervicitis reported on biopsy was noted, but not considered to be evidence of significant pathology.

In addition to the sample population, a control group of 183 patients was selected. This sample was age-matched and included patients who had normal Papanicolaou smears (without hyperkeratosis or any of the above-mentioned pathologic diagnoses) that were performed during the same period. Demographic and gynecologic data as well as information recorded from the Papanicolaou smear regarding inflammation, squamous metaplasia, and repair were collected on these patients.

Results

During the study period, 2198 Papanicolaou smears were carried out in the University of Kansas Department of Family Practice. Of these, 184 (8.4%) resulted in reports of hyperkeratosis without any other pathologic finding. Subsequent analyses were done on 183 charts (one chart could not be located) of study patients and 183 charts of age-matched controls.

The demographic data of patients are presented in Tables 1 and 2. The study sample and the control group were comparable in regard to age, race, gravidity, parity,

Table 1. Demographic Comparisons Between Patients with Hyperkeratosis (Study Group) and Normal Papanicolaou Smear (Control Group)

Variable	Study Group Mean (SD)	Control Group Mean (SD)	*P* Value
Age	36.3 (14.1)	36.2 (14.1)	.97
Gravidity	2.2 (2.2)	1.8 (2.2)	.06
Parity	1.7 (1.9)	1.4 (1.5)	.13
Therapeutic abortion	0.2 (0.5)	.15 (0.6)	.58
Spontaneous abortion	0.2 (0.6)	.16 (0.5)	.29

number of therapeutic and spontaneous abortions, menopausal status, and incidence of hysterectomy.

Forms of contraception used by women in the sample are reported in Table 3. Patients reporting "no active contraception" included patients not using any form of birth control or those who had undergone a sterilization procedure. Data were missing in 12 of the charts for patients with hyperkeratosis and in 14 of the charts for the control group. Eleven patients reported using "other" forms of active contraception, including the sponge and injectable medroxyprogesterone acetate. The choice of contraception in the two groups was found to be statistically significant ($\chi^2 = 27.06$; $P = .0001$). The study population had a significantly higher number of diaphragm users than the control group, whereas the control group included a significantly higher number of women using oral contraceptives.

Types of gynecologic infections noted from the patient charts included *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Gardnerella vaginalis*, *Trichomonas vaginalis*, and yeast. A total of 100 infections were recorded in 88 patients. No patient was found to be infected with herpes simplex virus. The percentage of study patients with gynecologic infections at the time of the initial Papanicolaou smear was 26%. Infection was found in 19% of the control population. Statistically significant differences between the groups, by chi-square analysis, were found

Table 2. Demographic Comparisons Between Patients with Hyperkeratosis (Study Group) and Normal Papanicolaou Smear (Control Group)

Variable	Study Group No. (%)	Control Group No. (%)	*P* Value
Race			.39
White	119 (65)	126 (69)	
Black	54 (30)	52 (28)	
Other	10 (5)	5 (3)	
Menopause			.89
No	144 (79)	146 (80)	
Yes (no hormone)	27 (15)	24 (13)	
Yes (hormone)	12 (6)	13 (7)	
Hysterectomy			.74
No	163 (89)	161 (88)	
Yes	20 (11)	22 (12)	

Table 3. Contraceptive Use Among Patients With Hyperkeratosis (Study Group) and Normal Papanicolaou Smears (Control Group)

Type of Contraceptive	Study Group Count (%)	Control Group Count (%)
No active contraceptive	108 (59)	91 (50)
Oral contraceptives	30 (16)	58 (32)
Diaphragm	12 (7)	1 (<1)
Condom	8 (4)	5 (3)
Pregnant	11 (6)	5 (3)
Other	2 (1)	9 (5)
Missing data	12 (7)	14 (8)

only for *G vaginalis* ($\chi^2 = 4.43$; $P = .035$), which was more prevalent in the study group, and *C trachomatis* ($\chi^2 = 4.58$; $P = .03$), which was found more often in the control group.

Papanicolaou smear findings that were noted included inflammation, squamous metaplasia, and repair. The occurrence of inflammation was similar in the two groups: 34% in the study group and 29% in the control group. Within the study group, Papanicolaou smears of 40 (22%) patients showed squamous metaplasia and 4 (2%) showed repair. There were no significant differences noted for the control population.

Sixty-four of the patients in the study group received no follow-up procedure, 31 had only a repeat Papanicolaou smear, 34 had both a repeat Papanicolaou smear and a second colposcopy performed, and 54 had only a follow-up colposcopy performed. Patients in whom a repeat Papanicolaou smear was done only after treatment of a pathological lesion, which had been diagnosed by colposcopy, were classified as being in the "colposcopy" group. The mean time interval between the initial Papanicolaou smear and first colposcopy was 12 weeks; the mean time interval between the initial Papanicolaou smear and the follow-up Papanicolaou smear was 32 weeks.

Of all 65 patients receiving a repeat Papanicolaou smear (sum of "repeat Papanicolaou smear only" and "Papanicolaou smear and colposcopy" groups), their hyperkeratosis was resolved in 75%. There were only two patients who had a pathological finding on the repeat Papanicolaou smear, and in both cases the finding was confirmed by colposcopy.

Of the 34 patients receiving both a repeat Papanicolaou smear and colposcopy, there were 12 patients who had hyperkeratosis on the repeat Papanicolaou smear: nine of those women had normal colposcopic examination findings and three had abnormal findings. Twenty-two repeat Papanicolaou smears were normal: 19 of those patients had normal colposcopic examination findings and three had abnormal findings.

Table 4. Patients with Hyperkeratosis on Whom Colposcopy was Performed; Results of Endocervical Curettage, Vaginal Biopsies, and Cervical Biopsies

Finding*	Count	Percent of Total
Endocervical curettage (ECC)		
No ECC	36	41
Negative	50	57
Dysplasia	2	2
Vaginal biopsy		
No vaginal biopsy	76	86
Negative	8	9
Human papillomavirus	4	5
Cervical biopsy		
No cervical biopsy	33	38
Negative†	35	39
Human papillomavirus	16	19
Dysplasia	4	4

*One patient had pathological findings at more than one site.
†Cervicitis was reported on 17 biopsies, but the specimens were considered to be negative for significant pathological diagnosis.

Colposcopy, including any combination of ECC, cervical biopsy, and vaginal biopsy, was performed on 88 (48%) patients in the study group (Table 4). One patient had pathologic findings on more than one tissue type; the remainder had pathologic findings reported on only one. Two of the patients were found to have dysplasia after undergoing ECC, yet they had no pathologic findings at either of the other sampling sites. Pathological findings were found in a total of 25 patients (28% of the patients undergoing colposcopy), of which 19 had HPV, 5 had dysplasia, and 1 had both. All six dysplastic specimens were classified as mild. Thus, of the 183 patients presenting with hyperkeratosis, pathological findings were demonstrated in 14% (11% with HPV and 3% with dysplasia). Chi-square analysis, analysis of variance, and *t* tests were used to determine whether any of the previously described variables predicted pathology in the patients with hyperkeratosis. None were found to be statistically significant.

In the group with hyperkeratosis, 14 of the patients received additional follow-up beyond one repeat Papanicolaou smear and one colposcopic examination. The one patient who had persistent hyperkeratosis on Papanicolaou smear, but no demonstrable pathological conditions even on second colposcopic examination, used a diaphragm for contraception.

Discussion

The results of our study were compared with the results from a similarly designed study done by Andrews and Miyazawa.[1] They reviewed charts of patients who had hyperkeratosis and an otherwise normal Papanicolaou smear, all of whom were referred for colposcopy. The results of colposcopic examinations and biopsies showed that 3.5% of patients in the Andrews study had dysplasia and 22% had HPV. These figures correspond to our findings of 3% and 11%, respectively. Their conclusion was that hyperkeratosis was not associated with increased incidence of dysplasia. They further suggested that colposcopy need not be routinely carried out in patients with hyperkeratosis with an otherwise normal Papanicolaou smear.

Recently, Cecchini et al reported pathological findings in only 7.1% of 1073 cytologically negative women who were self-referred for colposcopy.[8] Human papillomavirus was the diagnosis in 6.3%, whereas 3.6% had cervical intraepithelial neoplasia of grade 2 or 3 or infiltrating cancer (one patient). Their rate of detection for HPV in patients with hyperkeratosis as the sole diagnosis was very low in those patients who were 40 years of age or older, but was 14.7% in the group younger than 40 years.

Although hyperkeratosis does not seem to be a predictor of dysplasia, it appears to be associated with an increased incidence of HPV. Because of mounting evidence that HPV infection is associated with cervical and other genital cancers, we think that colposcopy should be carried out in all patients whose Papanicolaou smears show hyperkeratosis as the sole finding. Furthermore, the colposcopic examination should include an ECC in all cases; two of our patients had pathological findings demonstrated on ECC alone.

Compared with age-matched controls, the patients with hyperkeratosis had a statistically higher incidence of *Gardnerella* and a lower incidence of chlamydial infections. The two groups also differed in contraceptive methods; diaphragm use was more prevalent in the patients with hyperkeratosis. These differences, however, did not predict significant differences in pathological findings within the study group. Finally, a significant difference in the occurrence of inflammation was not shown between the study and control groups. Therefore, in this study, unlike in previously reported studies, inflammation was not seen to be a discriminating characteristic for the patients with hyperkeratosis. A prospective study is underway to determine the effect of treatment of any inflammation or infection on a follow-up Papanicolaou smear and colposcopic examination done concurrently.

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