2013년 8월
석사학위논문

고위험군 인유두종 바이러스 감염 환자에서의 자궁경부 편평상피 병변의 진단 보조인자로서의 p16과 Ki-67의 효율성

조 선 대 학 교 대 학 원

의 학 과

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Efficacy of p16 and Ki-67 immunostaining in the detection of squamous intraepithelial lesion in high risk HPV group

2013년 8월 23일

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이 논문을 의학석사학위신청 논문으로 제출함.

2013년 4월

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2013년 5월

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초 록

고위험군 인유두종 바이러스 감염 환자에서의 자궁경부 편평상피 병변의 진단 보조인자로서의 p16과 Ki-67의 효율성

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배경: 자궁경부 편평상피 병변을 위축성 변화 또는 비정형 편평상피의 화생과 감별진단을 하는데 있어서 p16과 Ki-67 면역화학염색이 보조적인 방법으로 사용되어져 왔다. 본 연구의 목적은 자궁경부 생검의 정확한 진단에 위의 두가지 면역화학염색 인자의 효율성을 평가하고 또한 인유두종 바이러스 감염 상태와의 상관성을 알아보고자 하였다. **방법**: 각각 인유두종 바이러스 검사를 시행한 123명 환자의 자궁경부 생검 조직을 이용하여 p16과 Ki-67 면역화학염색을 시행하였다. 헤마토실린 및 에오신(H&E) 염색을 한 슬라이드, p16 그리고 Ki-67 염색 슬라이드를 판독하였다. **결과**: 고위험군 인유두종 바이러스에 감염된 상태에서 편평상피 병변의 등급이 높을수록 p16과 Ki-67의 양성도가 증가하였다. H&E 슬라이드 판독 결과 각각 CIN 2 와 CIN 3로 진단되었던 3개의 경우에서 p16 면역염색에서 음성 소견, Ki-67에서 매우 드물게 염색되는 결과를 보였으며 이는 다시 비정형 편평상피 화생으로 진단되었다. 인유두종 바이러스에 음성인 28명의 환자 중 2명의 환자에서 p16 음성인 소견이 나타났으나 조직학적 소견으로 고등급 자궁경부 편평상피병변과 편평상피암종의 기준을 만족하였다. 이들은 각각 CIN 2과 편평상피종양으로 진단되었다. **결론**: 고위험 인유두종 바이러스에 감염된 그룹에서 p16과 Ki-67 면역화학염색에 미만성으로 강하게 동시에 염색이 되어 실제로 CIN 2, CIN 3 그리고 편평상피암종을 나타냈다. 그러므로 p16과 Ki-67의 면역염색이 자궁경부 편평상피병변을 정확하게 진단하는데 많은 도움을 주는 표지자로서 효율성이 증명되었으나 고위험군 인유두종 바이러스 감염 상태가 아닌 그룹에서는 이러한 면역염색 결과를 진단에 적용하는데 있어서 엄격한 고려가 필요하다고 판단된다.

I. Introduction

Cervical cancer represents the second most common cancer both incidence and mortality in women worldwide, with an increased incidence in low resource countries.[1] Virtually all cervical cancers are caused by persistent infections with high risk-human papilloma virus (HR-HPV) types which may cause cervical intraepithelial neoplasia (CIN) and squamous cell carcinoma (SCC).[2] Cervical biopsy, used in conjunction with Pap cytology testing, HPV DNA testing, and colposcopy, has an important role in the evaluation and management of women with cervical dysplastic lesions, which is crucial for the prevention and early detection of cervical cancer.[3] But there can be a misinterpretation of histologic changes in association with various situations such as atrophy, immature metaplasia, transitional metaplasia, repair or inflammatory atypia, inadequate sample size and tissue artifact, which may eventually cause an interobserver variation and a poor intraobserver reproducibility.[4-6] Recently, several biomarkers have been evaluated for their potential to improve the diagnostic consistency and accuracy of cervical biopsy interpretation.[6,7] Many of such studies[8,9] and other studies[10,11] endorse the use of p16 and Ki-67 immunostains and more recently, ProExC immunostain[11-13] as very useful adjunct techniques to confirm a diagnosis of CIN 2/3 and to distinguish it from its mimics. With regard to p16, it has been shown that almost 100% of CIN 2/3 and SCC associated with HR-HPV express high levels of p16, whereas nondysplastic cervical epithelium of low-grade CIN associated with low-risk HPV (LR-HPV) types does not express p16. To improve the diagnostic accuracy, other markers including Ki-67 have been used along with p16 in a histological assessment of CIN and SCC of the uterine cervix.[5,15] Similar to p16, Ki-67 is overexpressed in CIN 2/3, SCC.[16]

Given the above knowledge, we investigated the efficacy of immuno-histochemical stain for p16 and Ki-67 in the pathological assessment of uterine cervical biopsy samples with viral and histopathological correlation.

II. Materials and Methods

A. Materials

The pathology data program of Chosun university hospital was searched for final report including the terms low grade squamous intraepithelial lesion (LSIL), high grade squamous intraepithelial lesion (HSIL) and squamous cell carcinoma of all gynecologic specimen during January 2012 to March 2013. We selected a total of 123 specimens with the following pathologic diagnoses: LSIL, HPV, 32 cases; LSIL, CIN 1, 27 cases; HSIL, CIN 2, 19 cases; HSIL, CIN 3, 30 cases; SCC, 15 cases. The patients had undergone either cervico-vaginal smear and HPV DNA test. By reviewing the medical records of the medical records and pathologic reports of the selected patients, we confirmed the patients age, underlying disease, other tumor history, cytologic diagnosis and HPV infected status.

B. Methods

1. HPV DNA testing and genotyping

HPV DNA test for HR-HPV was achieved by polymerase chain reaction-based HPV genotyping assay (HPV 9G DNA chip, Fammed Co., Ltd.). DNA chip can detect 28 HPV genotypes (14 HR-HPVs: 16, 18, 31, 33, 39, 45, 51, 52, 54, 56, 58, 59, 66 and 68; and 7 LR-HPVs: 6, 11, 34, 40, 42, 43 and 44). The HPV genotyping were classified as HR-HPV or LR-HPV according to the scheme proposed by Dunne et al.[17]

2. Immunohistochemical studies

For the investigation, 3 μm-thick serial sections were prepared from representative formalin-fixed, paraffin-embedded tissue blocks and mounted on positively charged glass slides for the immunohistochemical studies. Immunostaining were performed by autostainer using an Ventana BenchMark XT instrument (Ventana Medical System, Tucson, AZ, USA). The primary antibodies were p16 (1:100, mouse monoclonal antibody, clone E6H4, Ventana Medical System, Tucson, AZ, USA) and Ki-67 (1:50, mouse monoclonal antibody, clone MM1, Novocastra, Newcastle, UK). Primary antibodies and enzyme complexes were visualized by a brown 3,3'-diaminobenzidine and abbreviation (DAB) reaction and the slides were counterstained with Mayer's hematoxylin.

3. Immunohistochemical interpretation

The interpretation of p16 is positive with observed in nuclear or nuclear and cytoplasmic, strong and continuous staining beginning from basal cell layer of epithelium in contrast of either focal and sporadic pattern or completely negative. The scoring of p16 classified in four groups as 0 (basal), 1 (parabasal) (Fig. 1A), 2 (intermediate) (Fig. 1C) and 3 (superficial) (Fig. 1E). The expression of Ki-67 was also categorized into four groups based on the distribution and proportions of nuclear staining positive cells. score 0, <10% of the cells, restricted to the parabasal cell layers; score 1, 10 to <30% of the cells, restricted to the lower third of the epithelium (Fig. 1B); score 2, 30 to <70% of the cells, reaching the upper third of the epithelium (Fig. 1D); score 3, 70% or more of the epithelial cells including full thickness expression of Ki-67 (Fig. 1F).[18]

4. Evaluation of the slides

Two observers evaluated the hematoxylin and eosin (H&E)-stained slides, and then made a initial diagnosis based on the only histological features on his or her own criteria. These diagnoses include normal, benign lesions such as squamous metaplasia or LSIL with viral cytopathic change (HPV effect) and precancerous lesion such as CIN 1, CIN 2 and CIN 3 and malignant lesion - SCC. Then, each observers had second look of H&E slide included p16 and Ki-67. Then, the diagnosis was revised and then, the consensus diagnosis was reached. The whole slides were reviewed independently by two observers, who were blinded to all the clinicopathologic information.

5. Statistical analysis

SPSS ver. 12.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Multivariate analysis was performed using hit ratio between initial diagnosis and revised diagnosis then these value compared with the HPV infected status: HR-HPV and nonHR-HPV. P-value less than 0.05 was considered statistically significant. The correlation between initial diagnosis and revised diagnosis were evaluated by Pearson's correlation coefficient.

III. Results

A. Expression of p16 and Ki-67 in HR-HPV

Using PCR based HPV genotyping assay, high risk HPV genotypes were detected in 62% (76/123). In the 12 cases of benign lesion - normal or squamous metaplasia, all of them are p16 negative. Of the 4 cases out of 9 cases LSIL with viral cytopathic change showed 1 score in p16 staining. All of the 7 cases of CIN 1 lesions showed a p16 expression score of 1, but 13 cases of CIN 2 lesions showed a p16 expression score of 2. In addition there were 25 cases out of 25 cases CIN 3 and 10 cases of all SCC cases showed expression of score3 (Table 1).

Twelve cases were diagnosed as benign lesion - normal or squamous metaplasia, only one case showed Ki-67 expression score of 1. Of the 3 cases out of 9 cases LSIL with viral cytopathic change showed score of 1 in Ki-67 staining. 6 cases of the 7 cases of CIN 1 lesions showed a Ki-67 expression score of 1, but 10 cases out of 13 cases CIN 2 lesions showed a Ki-67 expression score of 2. In addition there were 24 cases out of 25 cases CIN 3 and 10 cases of all SCC cases showed expression of score 3 (Table 2).

B. Expression of p16 and Ki-67 in nonHR-HPV

HPV genotyping assay detected in 38%(47/123) cases of non-high risk HPV genotypes. In the 14 cases out of 15 cases benign lesion - normal or squamous metaplasia, except 1 case of score 2 showed expression score 0. Of the 9 cases out of 11 cases LSIL with viral cytopathic change showed 0 score in p16 staining and the rest 2 cases are score 1. In the 4 cases out of 6 cases CIN 1,

except 2 case of score 0 showed expression score 1 and CIN 2 lesions showed one case p16 score 0 and four cases p16 score 2. But, there were 6 cases out of 6 cases CIN 3 showed expression of score3. Among 4 cases of SCC lesions, one patient showed completely loss in p16 staining exceptionally (Table 3).

Of the 14 cases out of 15 cases benign lesions showed score of 0 in Ki-67 staining. 6 cases of the 11 cases of LSIL with viral cytopathic change showed a Ki-67 expression score of 1, but only 3 cases out of 6 cases CIN 1 lesions showed a Ki-67 expression score of 1. 4 cases of CIN 3 lesions except 1 case showed of score 2. Similarly, 5 cases of CIN 3 lesions except 1 case showed of score 3. And 4 cases of all SCC cases showed expression of score 3 (Table 4).

C. Efficacy of p16 and Ki-67 in according to HPV genotypes

There were 3 cases of atypical squamous metaplasia (n=3) with previously CIN 2 (n=1) / CIN 3 (n=2) with H&E showed loss of p16 and rare Ki-67 index. And we found a discordance in nonHR-HPV group. Completely negative in p16 stain cases (n=2) in nonHR-HPV group, they were fulfilled of high grade CIN pathologic criteria even carcinoma features in H&E slides. So they were each diagnosed finally in CIN 2 and squamous cell carcinoma based on histopathologic findings.

The positivity of p16 and Ki-67 increased with the severity of cervical lesion in both HR-HPV and nonHR-HPV groups. Following a review of the immunostained slides for p16 and Ki-67, we reviewed the first diagnosis. In nonHR-HPV group, frequency of diagnostic revision was higher than in HR-HPV group (Table 5, 6). There were significant differences in the hit ratios between the HR-HPV and nonHR-HPV groups ($p<0.05$).

IV. Discussion

Diagnostic interpretation of dysplasia in the cervix is usually approached followed, hypercellularity, significant atypia, mitotic figures and disorientation involving more than from parabasal to upper layers. However, unusual histologic features - mildly increased cellularity, absence mitotic figures and questionable atypia can be observed in the lesion. In daily practical field, the accurate diagnosis of cervical dysplastic lesions results is variable by these several factors between interobserver and intraobserver.

Immunostain can improve the diagnostic reproducibility and accuracy of the CIN lesion. Previous study have shown that p16 and Ki-67 are coexpressed in virtually 100% of cases of high grade squamous and glandular lesions, and these markers are rarely coexpressed in normal or benign lesions of cervical epithelial lesion.[19,20,21-23] Immunohistocemical staining for p16 is investigated in cervical pathology as a marker for HPV-transformed lesion and it has demonstrated in many studies that p16 showing diffuse and continuous staining beginning in the basal and parabasal cell layers.[7,24,25] Based on the concept that HPV-mediated transformation in triggered by dysregulated expression of the viral oncogene E6 and E7 in basal and parabasal cells, p16 immuno-histochemistry was hypothesized to distinguish between transforming and nontransforming HPV infections, and only the diffuse p16 expression pattern was defined as hallmark of HPV-dependent transfomation and thus considered as p16 positive.[24,26,27]

Ki-67 is detected by the MIB-1 monoclonal antibody and is a nuclear protein that is associated with RNA transcription and cell cycle progression.[28] Similar to $p16^{INK4a}$, Ki-67 is overexpressed in CIN 2/3, SCC, adenocarcinoma in situ, and adenocarcinoma.[16] However, in contrast with $p16^{INK4a}$, Ki-67 is also overexpressed in the basal cells of normal squamous mucosa and in benign

proliferative lesions, including basal cell hyperplasia of the squamous mucosa.[20] So combination of p16 and Ki-67 is recommended for specificity in distinguishing CIN from its mimickers rather than using each immunostaining markers alone.[11]

While reviewing of previous articles, we had found that these immunostaining markers applied in selective HR-HPV group and high grade dysplastic lesion.[23,24] Thus, in this study we investigated to evaluate the efficacy of these immunostaining markers in accurate interpretation of cervical biopsy in comparison between HR-HPV or nonHR-HPV groups. The p16 and Ki-67 showed that diffuse and strong staining CIN 3 and SCC in both HR-HPV and nonHR-HPV groups. All CIN 3/SCC cases in HR-HPV group were p16 score 3. The obvious expression of p16 has been linked to high-risk HPV infection, which we also found in our study. We also found 3 cases of atypical squamous metaplasia (n=3) with previously CIN 2 (n=1) / CIN 3 (n=2) with H&E showed loss of p16 and low Ki-67 index in both HR-HPV and nonHR-HPV. But, several cases in nonHR-HPV groups have shown that discordancy in H&E and immunohistochemical findings. We found unusual three cases that showed unexpected immunostaining result of p16 out of 47 nonHR-HPV infected patients. The first cases showed p16-negative (Fig. 2D) and Ki-67 score of 3 (Fig. 2F) with consistent with invasive SCC histopathologic feature (Fig. 2B). So final diagnosis was SCC. The patient had radiation therapy and chemotheraputic regimen 2 times but she expired due to pancytopenia and multiple metastatic nodular progression in 9 months later. Next cases initial diagnosis was HSIL, CIN 2 with p16-negative and Ki-67 score of 1 in this case the first diagnosis was not revised. This case was finally confirmed in hysterectomy specimen in 3 weeks later. We found that the clinicopathologic identification limited on H&E stain. The last case, showed abnormal overexpression in both markers but had no dysplastic lesion but only observed with atypical squamous metaplasia. In 12 month later, she had rebiopsy in

uterine cervix and diagnosed in chronic cervicitis. It is currently unknown what causes true-negative p16 immunostaining in CIN 3 or SCC in nonHR-HPV group. In nonHR-HPV group, frequency of diagnostic revision was higher than in HR-HPV group (Table 5, 6). There were significant differences in the hit ratios between the HR-HPV and nonHR-HPV groups ($p<0.05$).

V. Conclusion

In conclusion, simultaneously diffuse and strong overexpression of p16 and Ki-67 virtually implication of CIN 3 and SCC in HR-HPV group. Both markers are efficient in advancing the diagnostic accuracy of cervical biopsy, but application in daily sign-out processing of a immunostain findings should be discreetly considered in nonHR-HPV group.

This is a pilot study with a small number of cases, but we hope that pathologist should be aware of that unusual immunostain result of nonHR-HPV groups imply factors other than high risk HPV infection to negative p16 staining CIN 3 or SCC. In the future, new immunostaining markers or other methods which are could be applicable in nonHR-HPV group are needed to be assessed for reproducible diagnosis of cervix.

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Table 1. The p16 expression in HR-HPV according to the final diagnosis

Final Dx	No. of cases	Score of p16			
		0	1	2	3
Reactive atypia	12	12			
LSIL, viral change	9	5	4		
CIN 1	7		7		
CIN 2	13			13	
CIN 3	25				25
SCC	10				10
Total	76	17	11	13	35

HR-HPV, high risk human papilloma virus; LSIL, low-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia; SCC, squamous cell carcinoma

Table 2. The Ki-67 expression in HR-HPV according to the final diagnosis

Final Dx	No. of cases	Score of Ki-67			
		0	1	2	3
Reactive atypia	12	11	1		
LSIL, viral change	9	6	3		
CIN 1	7		6	1	
CIN 2	13		3	10	
CIN 3	25			1	24
SCC	10				10
Total	76	17	13	12	34

HR-HPV, high risk human papilloma virus; LSIL, low-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia; SCC, squamous cell carcinoma

Table 3. The p16 expression in nonHR-HPV according to the final diagnosis

Final Dx	No. of cases	Score of p16			
		0	1	2	3
Reactive atypia	15	14		1	
LSIL, viral change	11	9	2		
CIN 1	6	2	4		
CIN 2	5	1		4	
CIN 3	6				6
SCC	4	1			3
Total	47	27	6	5	9

nonHR-HPV, non-high risk human papilloma virus; LSIL, low-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia; SCC, squamous cell carcinoma

Table 4. The Ki-67 expression in nonHR-HPV according to the final diagnosis

Final Dx	No. of cases	Score of Ki-67			
		0	1	2	3
Reactive atypia	15	14		1	
LSIL, viral change	11	5	6		
CIN 1	6	1	3	1	1
CIN 2	5		1	4	
CIN 3	6			1	5
SCC	4				4
Total	47	20	10	7	10

nonHR-HPV, non-high risk human papilloma virus; LSIL, low-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia; SCC, squamous cell carcinoma

Table 5. Distribution of first and final diagnosis in HR-HPV group

Final Dx	First(%)	Final(%)	Difference(%)
Reactive atypia	0(0.00)	12(15.79)	15.79
LSIL, viral change	17(22.37)	9(11.84)	-10.53
CIN 1	15(19.74)	7(9.21)	-10.53
CIN 2	13(17.11)	13(17.11)	0.00
CIN 3	19(25.00)	25(32.89)	7.89
SCC	12(15.79)	10(13.16)	-2.63
Total	76(1)	76(1)	0.00

HR-HPV, high risk human papilloma virus; LSIL, low-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia; SCC, squamous cell carcinoma

Table 6. Distribution of first and final diagnosis in nonHR-HPV group

Final Dx	First(%)	Final(%)	Difference (%)
Reactive atypia	0(0.00)	15(31.92)	31.92
LSIL, viral change	16(34.04)	11(23.40)	-10.64
CIN 1	12(25.53)	6(12.77)	-12.77
CIN 2	5(10.64)	5(10.64)	0.00
CIN 3	10(21.28)	6(12.77)	-8.51
SCC	4(8.51)	4(8.51)	0.00
Total	47(1)	47(1)	0.00

HR-HPV, high risk human papilloma virus; LSIL, low-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia; SCC, squamous cell carcinoma

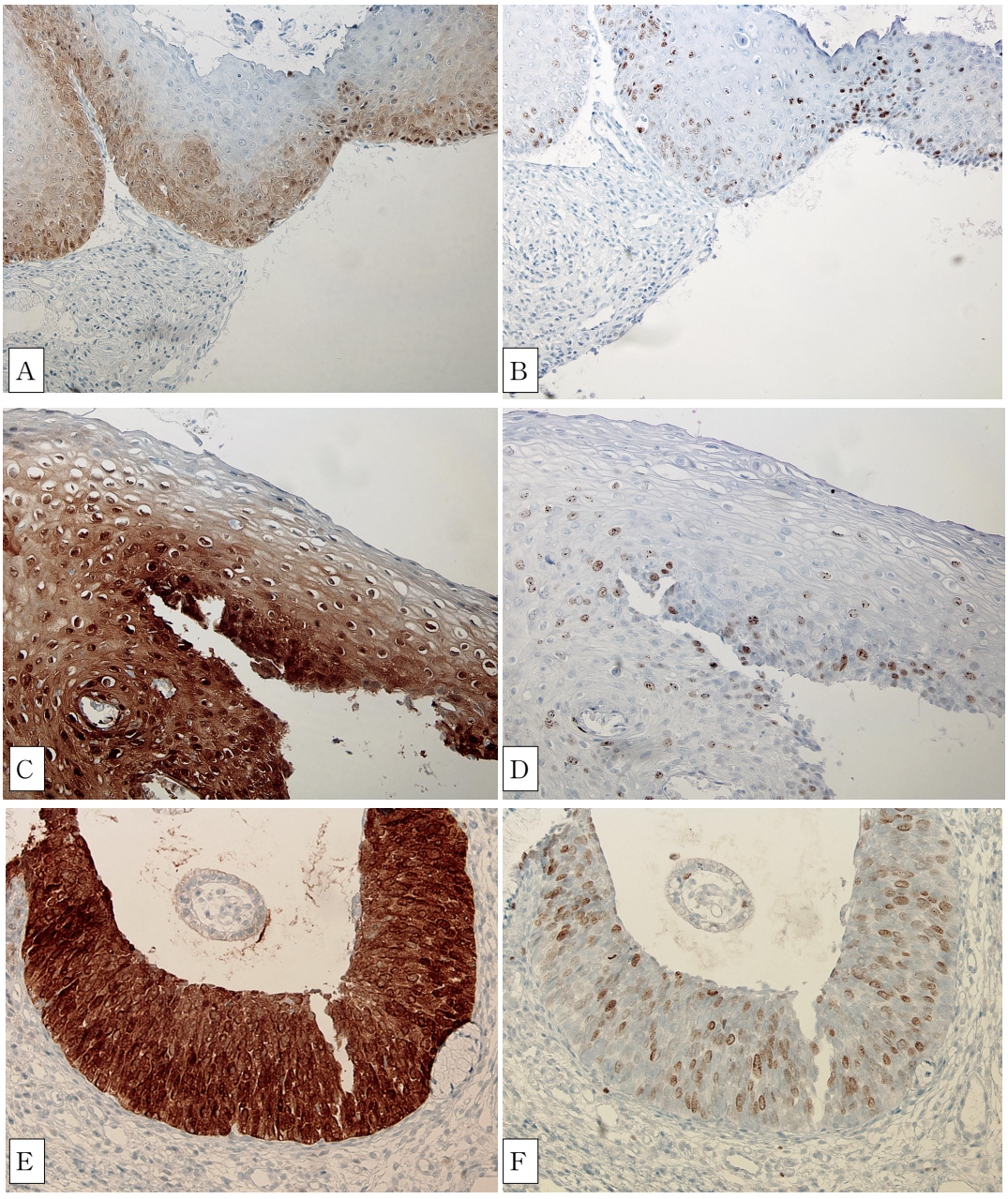

Fig. 1.

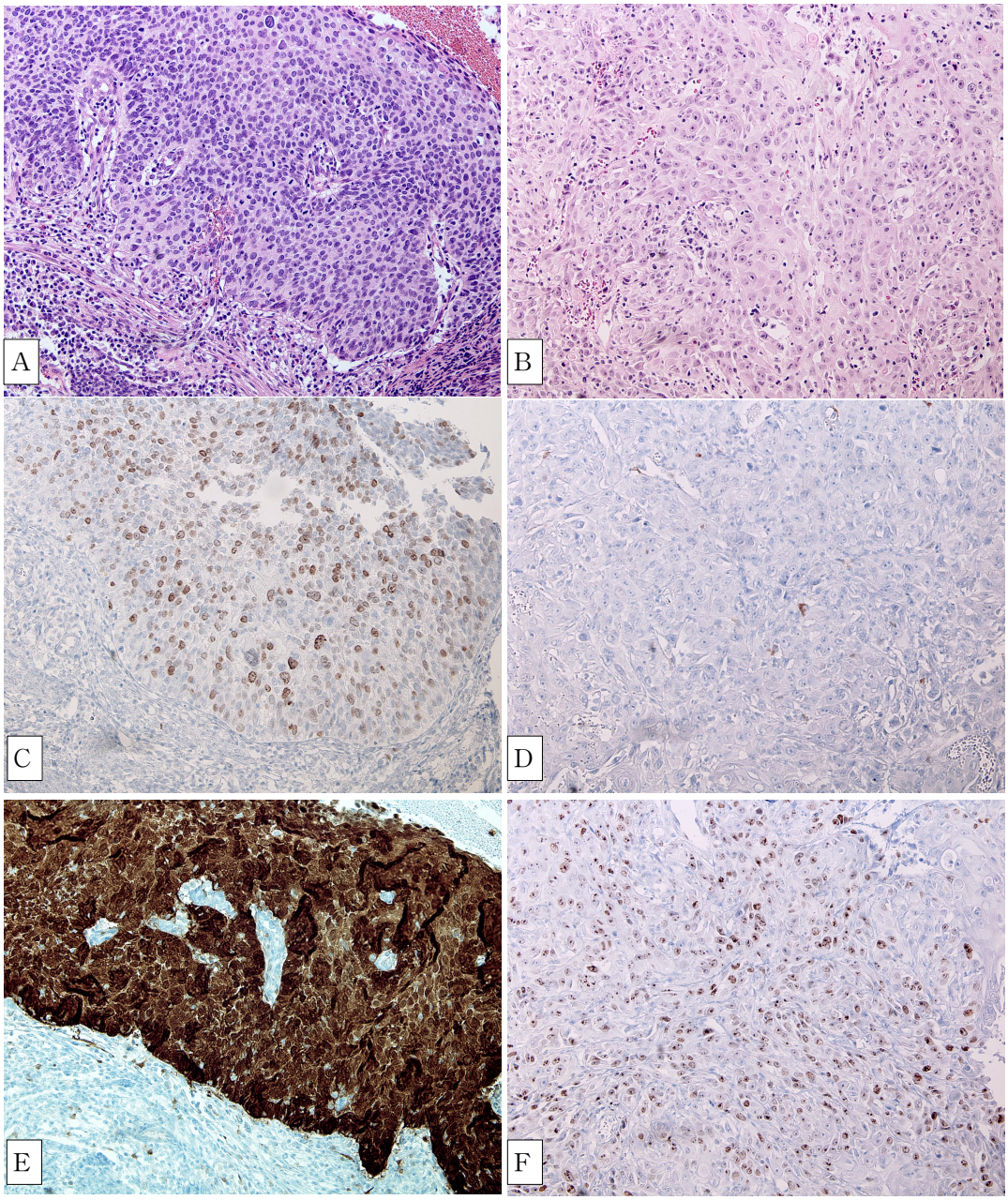

Fig. 2.