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Monoclonal Anti-Stathmin-1 and Anti-HSP27 are Reliable Biomarkers for Identification of Cervical Intraepithelial Neoplasia and Cervical Squamous Carcinoma

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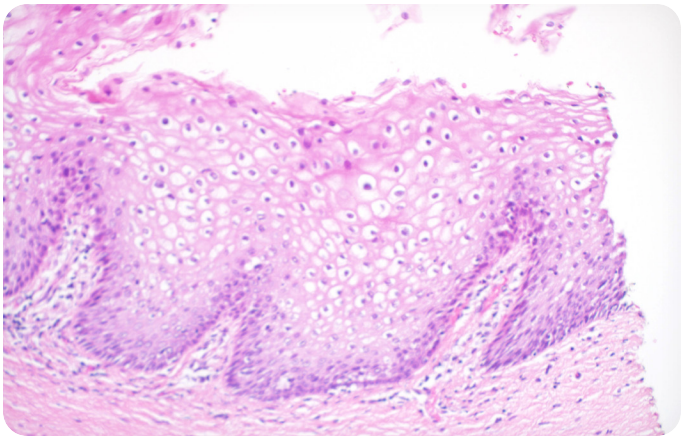

Fig. 1a CIN I

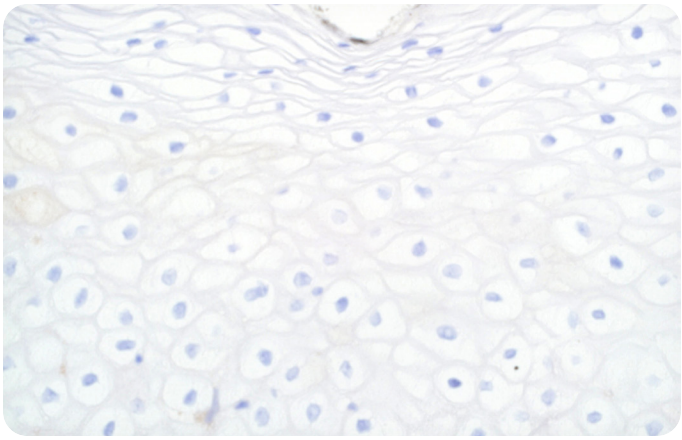

Fig. 1b Stathmin-1 is negative for CIN I.

Introduction

Distinction of high-grade squamous intraepithelial lesion (HGSIL, CIN II/III) from low-grade intraepithelial lesion (LGSIL, CIN I) is very important because of the differences in treatment.1-3 CIN I will progress to invasive carcinoma in <1% of cases and is typically managed with Papanicolaou smear follow-up.[1] CIN II/III has 5% to 20% risk of progression to invasive carcinoma and is usually treated with an excisional procedure.[2] Cervical adenocarcinoma *in situ* has an approximate 30% risk of progression to invasive adenocarcinoma.[3] p16 immunohistochemical (IHC) staining has been used as a reliable and sensitive biomarker to identify cervical intraepithelial neoplasia (CIN) and cervical squamous carcinoma (CSC). However, the specificity of p16 for CIN and CSC is limited, thus providing a need for additional complementary biomarkers that allow for more accurate detection of CIN and CSC by the laboratory.

Design

Cervical biopsy specimens of 29 cases of CIN I, 27 cases of CIN II, 33 cases of CIN III, and 4 cases of CSC were evaluated by IHC. One full section from each case was stained with monoclonal anti-stathmin, monoclonal anti-heat shock protein 27 (HSP27) and monoclonal anti-p16. Staining intensity was scored as 0 (negative), 1-2 (weak), 3 (moderate), 4 (strong); the labeling extent was tabulated as 0 (less than 5% positive cells), 1-2 (5-25% positive cells), 3 (26-75% positive cells), and 4 (greater than 75% positive cells).

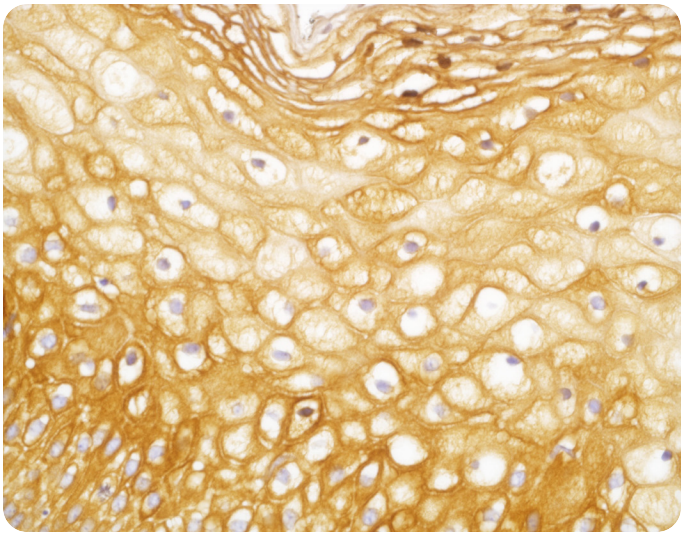

Fig. 1c HSP27 is positive in CIN I.

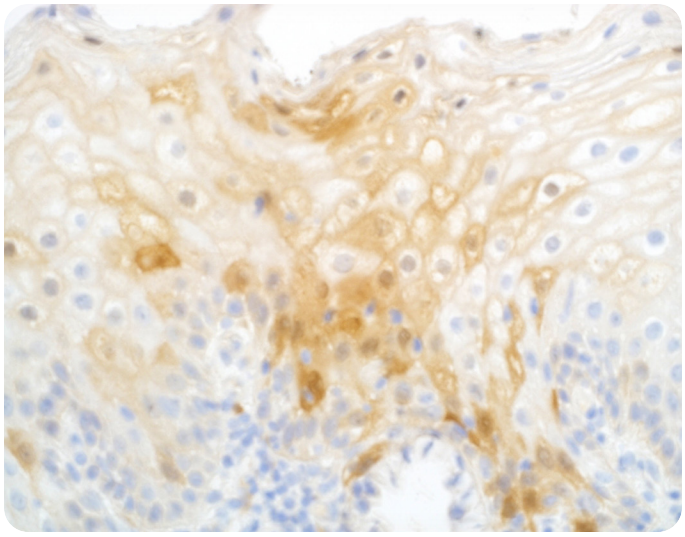

Fig. 1d p16 expression is seen in CIN I.

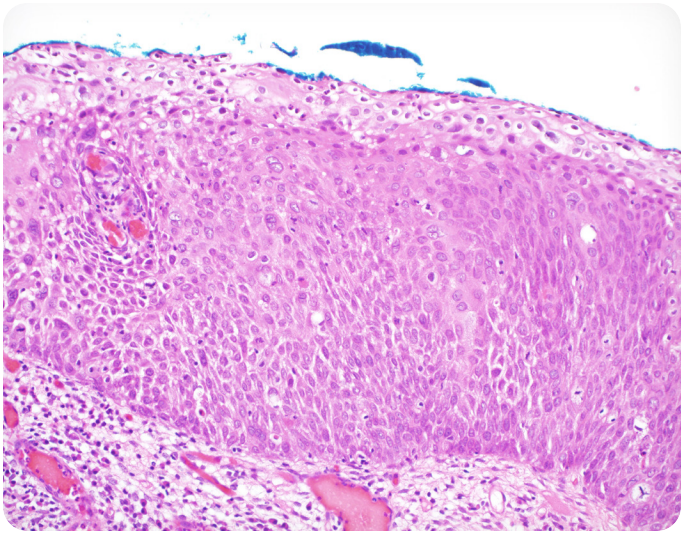

Fig. 2a CIN II

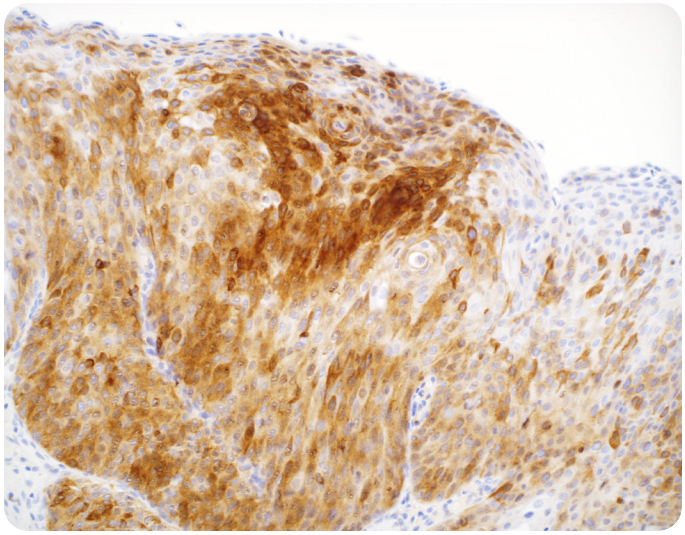

Fig. 2b Stathmin-1 is detected in CIN II by IHC.

Results

As shown in the table and figures, none of 29 cases of CIN I (Fig. 1a) was stained using anti-stathmin (0/29, 0%; Fig. 1b); HSP27 was expressed in 9 cases (9/29, 31%; Fig. 1c); 13 cases were positive for p16 (13/29, 45%; Fig.1d). Of 27 cases of CIN II (Fig. 2a), 11 cases (11/27, 41%) were positive for stathmin (Fig. 2b); 25 cases expressed HSP27 (25/27, 93%; Fig. 2c); 20 cases (20/27, 74%) displayed staining using anti-p16 (Fig. 2d). Of 33 cases of CIN III (Fig. 3a), 28 (28/33, 84.8%) demonstrated stathmin expression (Fig. 3b); 33 cases (33/33, 100%) were positive for HSP27 (Fig. 3c); 32 cases (32/33, 97%) displayed positivity for p16 (Fig. 3d). All 4 cases of CSC (4/4, 100%) showed positive expression of stathmin, HSP27 and p16 in neoplastic cells.

Table 1

Immunohistochemical expression of Stathmin-1, HSP27 and p16 in cervical specimens			
	Stathmin-1 (SP49)	**HSP27 (G3.1)**	**p16 (G175-405)**
CIN I	0/29 (0%)	9/29 (31%)	13/29 (45%)
CIN II	11/27 (41%)	25/27 (93%)	20/27 (74%)
CIN III	28/33 (85%)	33/33 (100%)	32/33 (97%)
CSC	4/4 (100%)	4/4 (100%)	4/4 (100%)

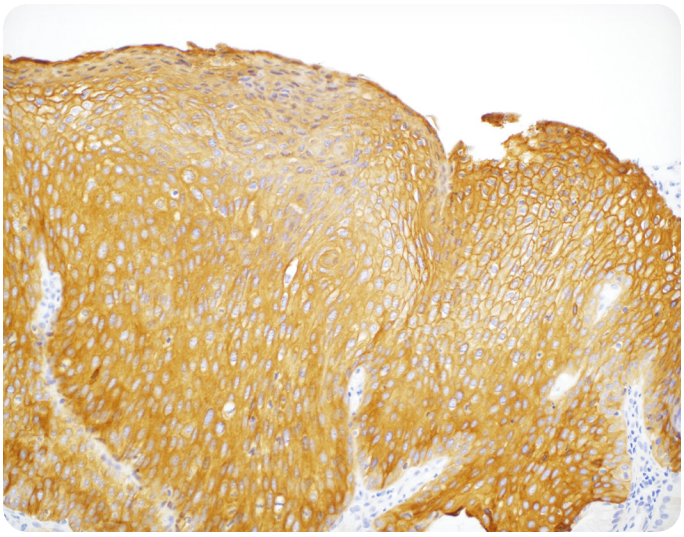

Fig. 2c HSP27 highlights CIN II.

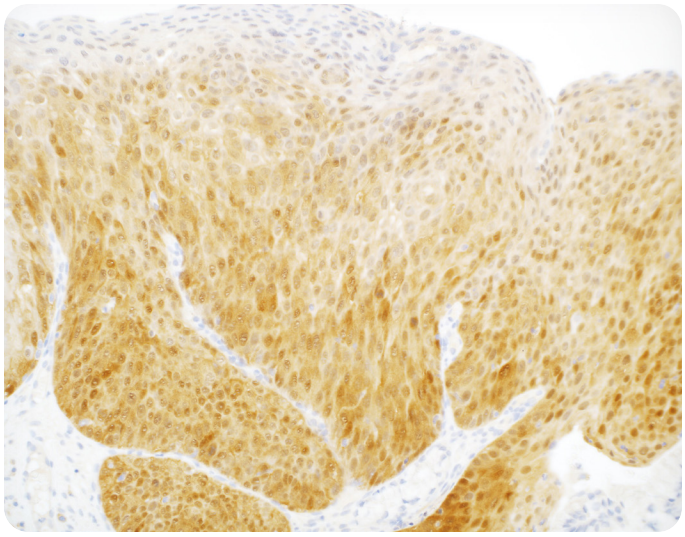

Fig. 2d p16 is positive for CIN II.

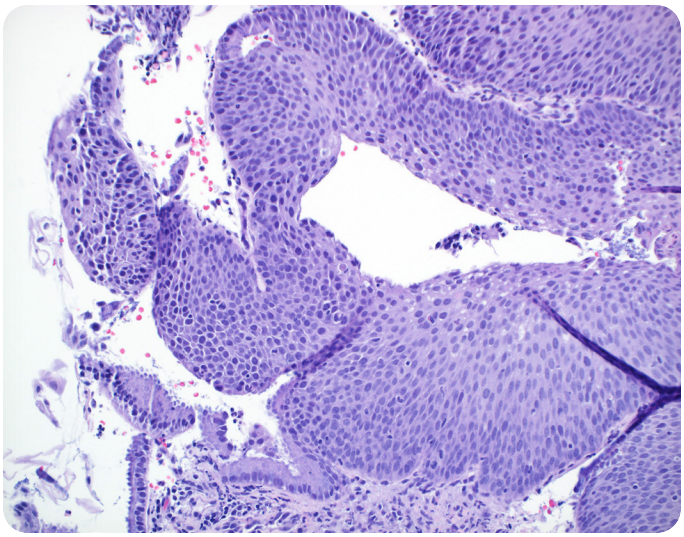

Fig. 3a CIN III

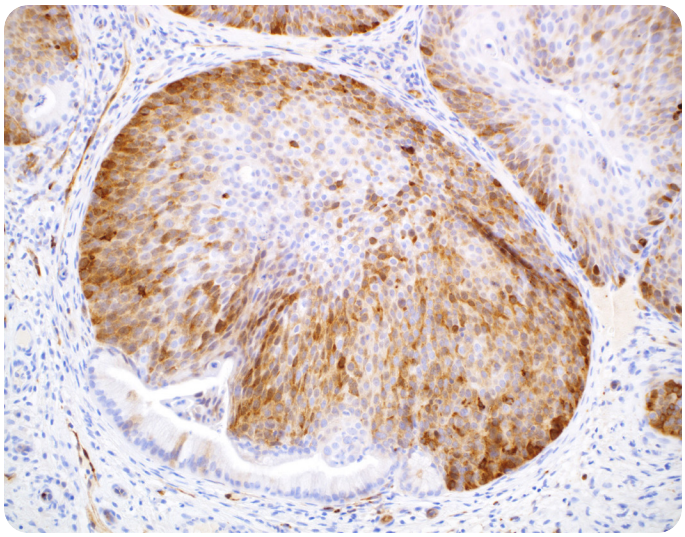

Fig. 3b Stathmin-1 stains CIN III.

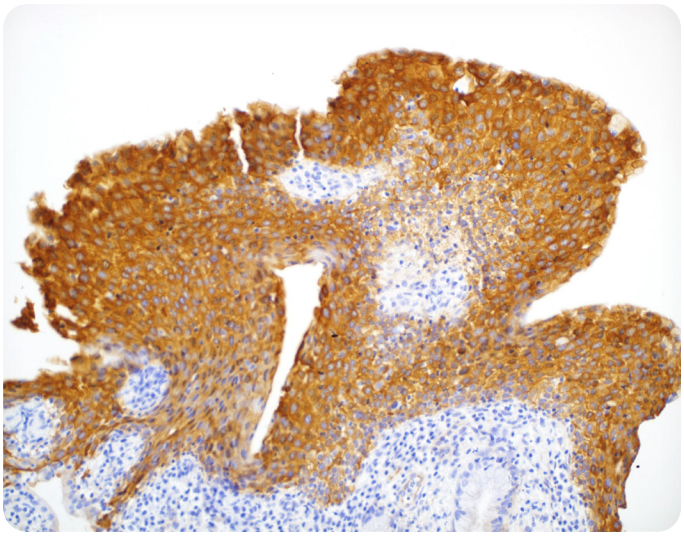

Fig. 3c HSP27 is expressed in CIN III.

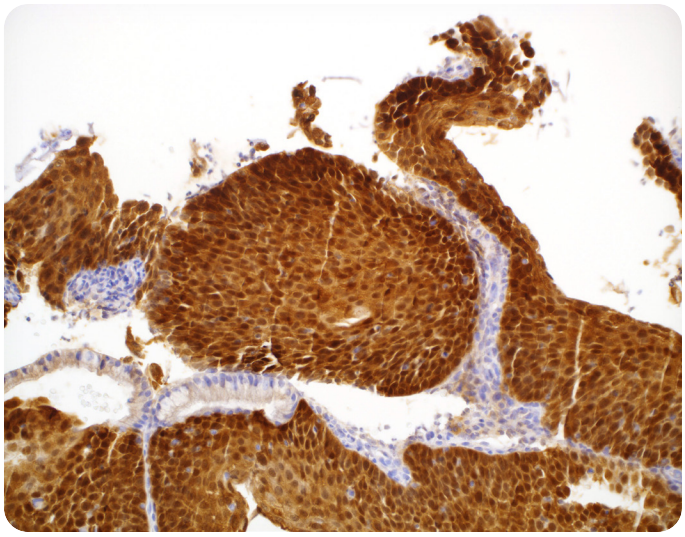

Fig. 3d p16 antibody detects CIN III.

Conclusion

Ancillary biomarkers are helpful in differentiating CIN, especially low-grade CIN, from benign cervical lesions, such as immature cervical metaplasia, chronic cervicitis, and atrophic cervical epithelium. Anti-p16, mostly combined with anti-Ki-67, has been widely used in IHC detection of CIN, especially high-grade CIN. However, the specificity of anti-p16 is limited by the high prevalence of carcinogenic HPVs across the entire spectrum of CIN. Stathmin-1 is a microtubule-stabilizing phosphoprotein and regulates cell cycle progression and is essential for cell division and proliferation. In this study we have demonstrated that anti-stathmin-1 did not detect CIN I, but p16 was positive in 45% (13/29), indicating that stathmin-1 is more specific for distinguishing low-grade CIN from high-grade CIN. HSP27 has been known to be related to HPV infection and this study also displayed its potential for improved specificity in differentiating low-grade CIN from high-grade CIN. Anti-HSP27 provided comparable detection for high-grade CIN and CSC as compared to anti-p16. In conclusion, monoclonal antibodies against stathmin-1 and HSP27 are reliable antibodies that complement anti-p16 in the identification of cervical intraepithelial neoplasia and cervical squamous carcinoma.

Reference

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3. DeSimone CP, et al. J Reprod Med 2011;56:376.

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