Can Acid Phosphatase Reduce Pap Test False-Negative Readings?

A quest to reduce false-negative readings of Pap tests has been under way since its introduction almost 30 years ago. Unfortunately, the insufficient sensitivity is still a deterrent heritage for the world’s most used cancer screening assay (1). Therefore, we would like to share an observation that opens a new opportunity and encourages old hopes.

Looking for new applications of image analysis in clinical pathology, we found high activity of acid phosphatase in dysplastic cervical cells. Acid phosphatase is a lysosomal enzyme that has never been shown in cervical epithelial cells. A Medline search produced no evidence from 1962 to the present.

Following this observation, we conducted a pilot study on 30 specimens from patients with a clinical diagnosis of cervical dysplasia and from control subjects. Cervical acid phosphatase (CAP) activity was visualized with a simultaneous azo-dye-coupling reaction by use of the naphthol AS-BI Phosphate/Fast Garnet GBC system. Enzyme activity was presented as a distinct brown–red granular intracellular deposit (Fig. 1). This final reaction product was amenable for visual and image analysis-assisted evaluation. On normal cervical smears, the majority of cells were negative. Only a few cells were low positive, with a small number of fine granule scattered in the cytoplasm. On specimens described as dysplastic, high activity of CAP was found in atypical cells. A cytopathologist, blinded to CAP activity, estimated the degree of dysplasia (cervical intraepithelial neoplasia [CIN] classification) on Pap-stained smears. When results were compared, we found a gradual increase of CAP activity proportional to the CIN degree of dysplasia. Malignant cells were highly positive in two cases of invasive cervical carcinoma.

Next, we tried double staining. When Pap smears were prestained with CAP, the brown–red deposit held up to the following Pap staining, and a new (CAP) contrast appeared in cervical cells. This contrast was an important signal for the screener to stop and, more thoroughly, to examine the cell with a “brown–red flag.” This was a cognitive switch to turn on the screener’s attention and a sufficient impetus to disrupt the monotony of conventional Pap test readings.

Could one lysosomal enzyme, largely neglected in cervical smear diagnosis, prove to be a helpful hint for cervical cancer screening, prescreening, or the recently recommended rapid rescreening procedures (2)? Could CAP reduce the false-negative readings?

We are investigating CAP in two directions: 1) to make the marker (intracellular deposit) amenable for image analysis, and 2) to develop a double CAP-Pap staining procedure (3,4). Regardless of the future of this development, evidence exists that cervical cells express acid phosphatase activity, and that the amount of this activity increases with the degree of dysplasia.

This information should be shared with your audience. It may initiate collaborative efforts to elucidate our findings and to implement this idea for the benefit of thousands of women.

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References

Notes
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