Cytyc Corporation - Case Presentation Archive - July 2002

ThinPrep® Pap Test™

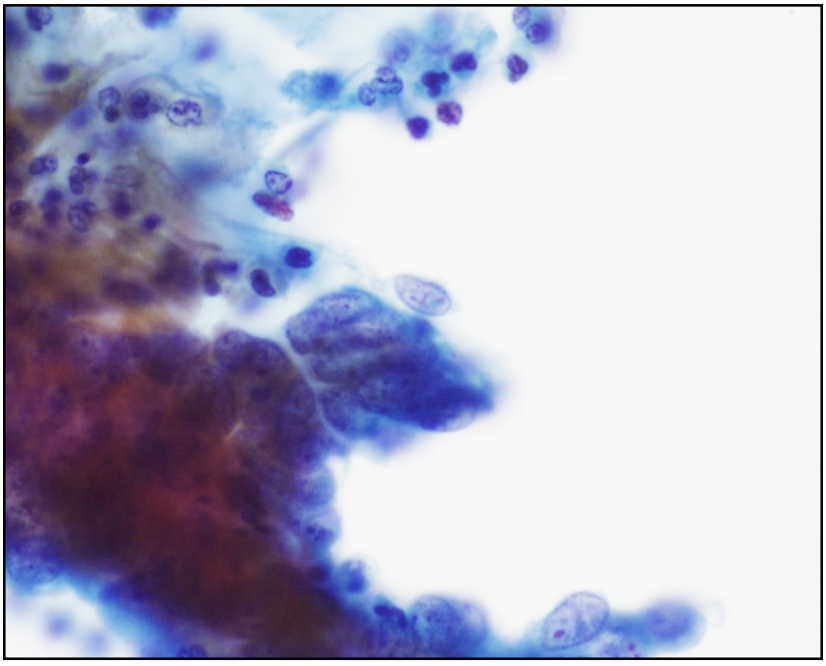
History: 34 Year Old Female

LMP: Day 20

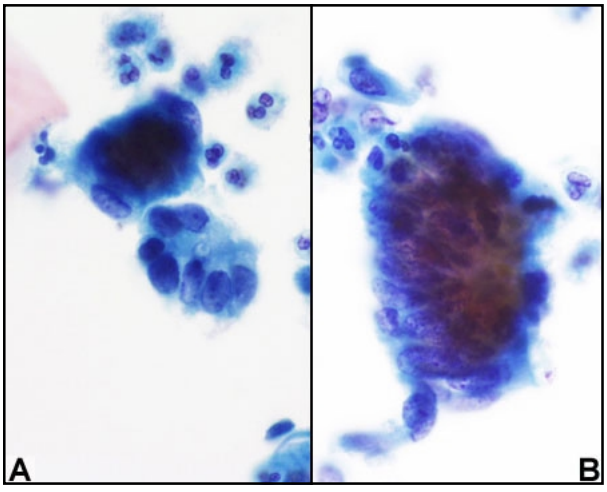
Specimen Type: Cervical/Vaginal

Case provided by Mark Tulecke, M.D. and Gabrielle Trawinski CT (ASCP), Mount Auburn Hospital, Cambridge, Massachusetts.

*The images, analysis and diagnosis for this case study were provided to Cytyc by an independent physician. All conclusions and opinions are those of Mount Auburn Hospital and not Cytyc Corporation.



Slide 1 - 60x



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P/N 85963-001 Rev. A

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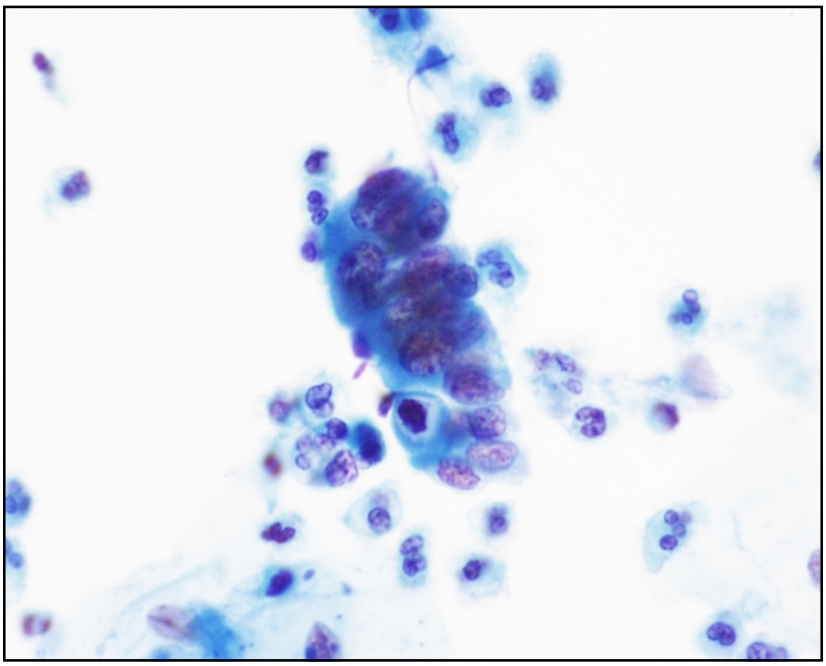

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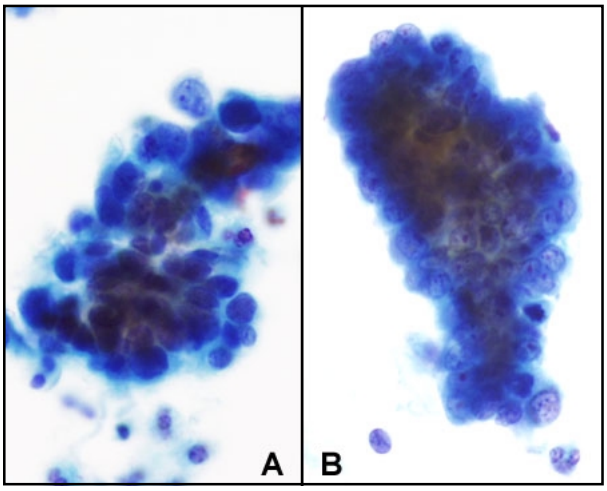

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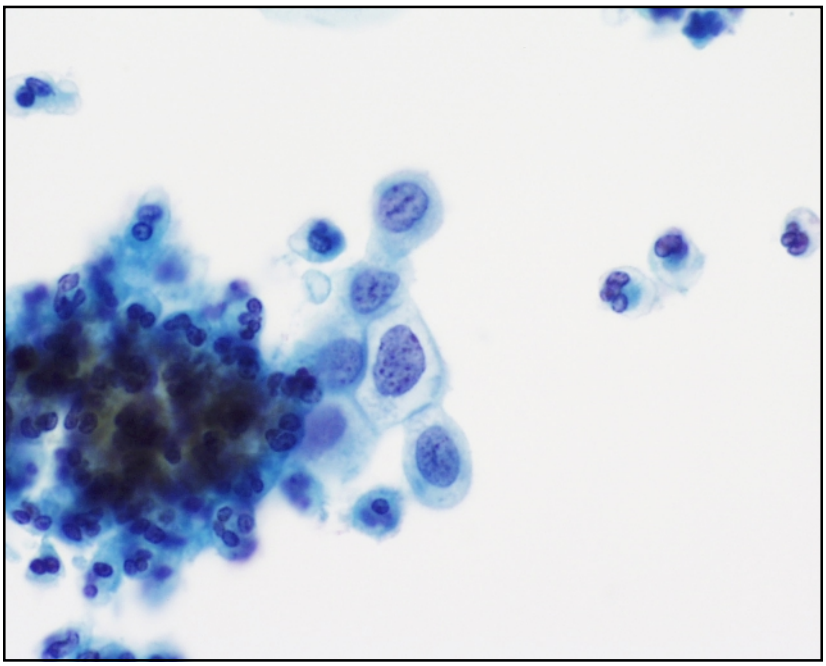

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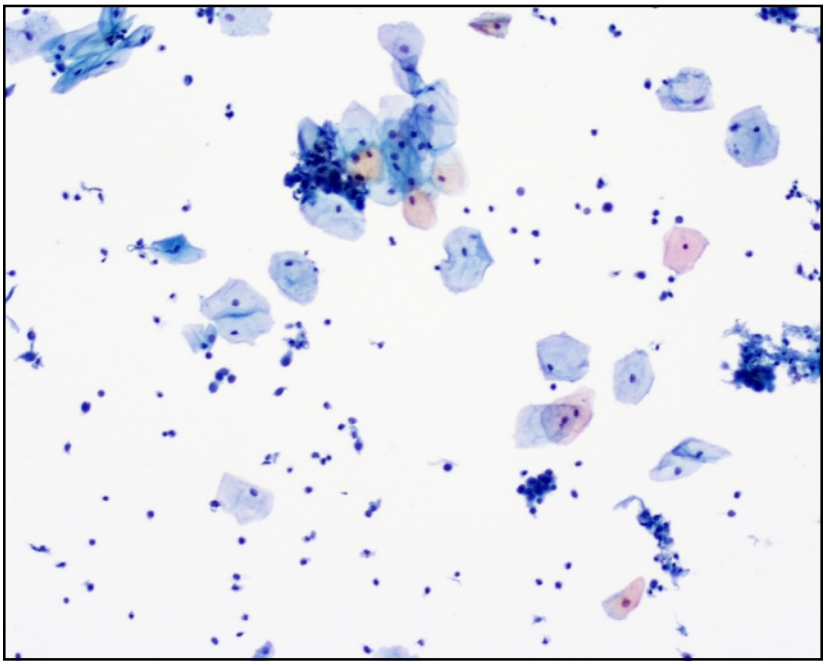

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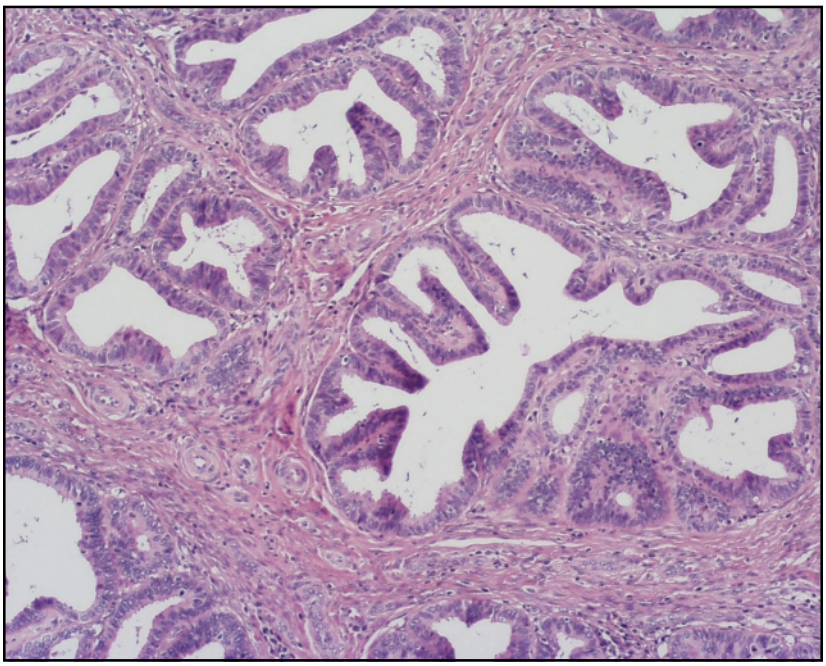

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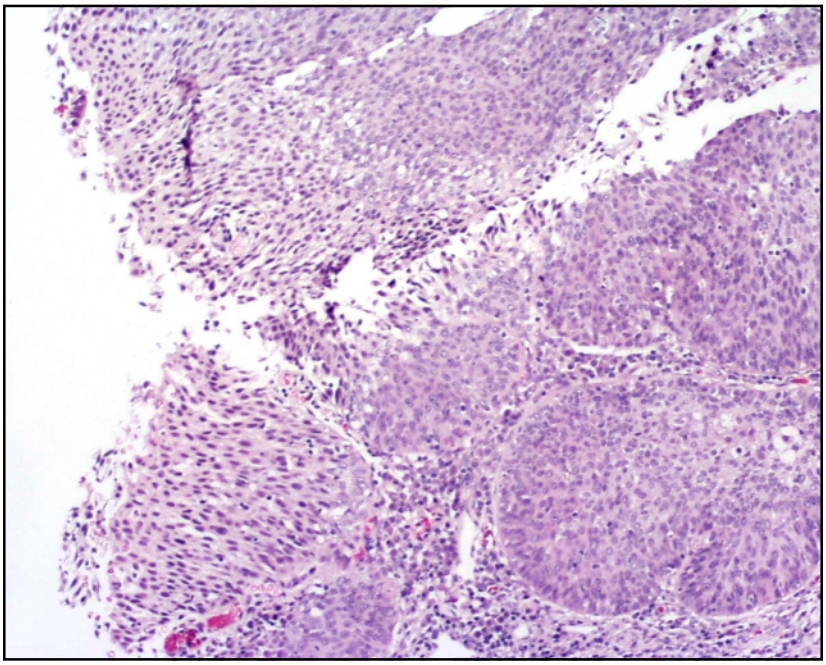

Slide 8 - 10x

Discussion:

Slide 1: Short strip of crowded cells with elongated, hyperchromatic nuclei, high N/C ratio, moderately coarse even chromatin and micronucleoli. There is a suggestion of "feathering" as the elongated nuclei are on the periphery and level with each other.

Slide 2: Cell groups displaying different architectural forms. On the left, a short strip and rosette; On the right, a 3D syncytial type aggregate with a possible gland opening.

Slide 3: A single strip of atypical glandular cells with coarse even chromatin and pseudostratification, falsely appearing to have many layers due to crowding and slight overlap of the nuclei.

Slide 4: Side A shows a loosely cohesive group of cells that are more polygonal and flat than group B. It also is less papillary appearing, has more distinct cytoplasmic borders, central nuclei and more variation in size and chromatin pattern than group B.

Slide 5: Group of flat cells showing polygonal cytoplasm with distinct cell borders, high N/C ratio, coarse evenly distributed chromatin and irregular nuclear membranes.

Slide 6: Overview showing a background of numerous single high N/C ratio cells in the "white" spaces.

Slide 7: Tissue section showing crowded glands with atypical hyperchromatic nuclei.

Slide 8: Tissue section showing high grade squamous intraepithelial lesion invading the gland crypts.

Cytologic Diagnosis: Atypical Glandular Cells of Undetermined Significance.
Small atypical squamous metaplastic cells suspicious for high-grade squamous intraepithelial lesion. Cannot exclude glandular extension of squamous dysplasia. Cervical Cone Biopsy: Adenocarcinoma In-Situ

High grade squamous intraepithelial lesion with the involvement of endocervical glands (CIN III).

Adenocarcinoma In Situ (AIS) occurs when: the epithelial cells and/or glands are lined with abnormal cells, the normal interrelationship of the glands is maintained and when there is no invasion into the stroma.The cell of origin is the same as squamous epithelial lesions, the subcolumnar reserve cell or multipotential cell. The progression from normal endocervical cells to frankly invasive adenocarcinoma are thought to involve 3 intermediate steps: endocervical dyplasia, adenocarcinoma in-situ and microinvasive adenocarcinoma. However, adenocarcinoma may also arise with out a precursor, arising directly from the cells of origin.

AIS was first described histologically as an entity in 1953 by Friedell and McKay. The following criteria that suggests AIS as a precursor to endocervical adenocarcinoma are from their studies and other well established studies:

1) Histologically, AIS resembles carcinoma but without demonstrable invasion of the stroma.

2) Similar morphologic changes occur at the periphery of invasive adenocarcinoma.

3) An in situ lesion can be followed through to its development into an invasive adenocarcinoma.

4) Cytologic features of exfoliated cells from histologically proven in-situ lesions to those found in smears from patients with microinvasive and invasive carcinoma of the same type are similar.

5) The average age of patients with AIS is several years younger than that of patients with invasive cancer suggesting that the in-situ form precedes the development of the invasive form of cancer.

It would be a conclusion to link the factors of frankly invasive endocervical adenocarcinoma to its precursor lesions.

Studies suggest that their may be 2 different factor lines of progression of adenocarcinoma:HPV and hormones. Like squamous lesions, there is a strong association with HPV, particularly HPV 18 for glandular lesions. However, there does not seem to be as strong an association with other squamous factors such as early age of 1st intercourse, sexual activity, or smoking. Like endometrial lesions, there is a strong hormonal association and other endometrial risk factors namely, a more affluent socioeconomic background with significantly more education, nulliparity, overweight, possible hypertension, diabetes and progesterone. The mean age for AIS is 37 but that statistic may be falling.

The frequency of glandular lesions is increasing significantly while the incidence of cervical squamous carcinoma is decreasing. However, precursor glandular lesion frequency is still less than for outspoken adenocarcinoma. Endocervical adenocarcinoma now accounts for up to 1/3 of all invasive cervical cancers.

Studies show that AIS involves some or all of the transformation zone if there is an accompanying squamous abnormality and up to 50% of glandular lesions are associated with an abnormal squamous epithelial lesion. The accompanying squamous abnormality may extend into the gland crypts and replace or partially replace the indigenous cells and take on a similar morphologic appearance (elongated nuclei, false “feathering”, syncytial-like aggregates etc.) possibly due to the same environmental tight constrictions of a gland. This makes an accurate cytological diag-

nosis difficult whereas the histological diagnosis is a little more clear cut as to what is a true glandular lesion and what is squamous with gland involvement. Otherwise, the lesion usually arises contiguous with the squamo-columnar junction. However, as the transformation zone recedes into the endocervical canal with age (usually women over 35), early detection by endocervical scraping and colposcopy becomes more difficult (giving rise to the statistic that glandular precursor lesion frequency is less than adenocarcinoma). Also the deep glands tend to be more involved than the surface, which can affect both cytologic and histologic sampling. The lesions can also be very focal, particularly when in-situ. Unfortunately, these factors give the pap smear a false negative rate as high as 50% in patients with grossly identifiable lesions (as high as 80% if there is no gross lesion). Fortunately, the abnormal endocervical cells that do make it on a slide, are much more accurately detected with improved pap test preparation technology; decreasing false negative rates due to interpretation error.

References:

1) Demay, Richard. The Art and Science of Cytopathology. 1996:127-133

2) McKee, Grace T. Cytopathology.1997:56-57

3) Bibbo,Marluce., MD. Comprehensive Cytopathology.1990:231-249

4) Keebler, Catherine.,Somrak,Theresa. The Manual of Cytotechnology 7th edition. 1993:129-137