ABNORMAL PAP SMEAR (ABNORMAL CERVICAL CYTOLOGIC FINDINGS)

Kathleen Dor

Cervical cytology screening has significantly decreased rates of mortality from cervical cancer; however, 400 women die each year in the United States from cervical cancer, mostly as a result of inadequate screening.

Cervical cytology results are classified according to the Bethesda 2001 system (Box 1), which describes the categories of epithelial cell abnormalities. Histologic diagnoses of abnormalities are reported as cervical intraepithelial neoplasia (CIN) grades 1-3.

The glandular cell abnormalities are reported under the following categories: atypical glandular cells (AGC), subcategorized as endocervical, endometrial, or glandular not otherwise specified; AGC, favor neoplastic; endocervical adenocarcinoma in situ; and adenocarcinoma. Also noted are the presence of organisms, including *Trichomonas vaginalis* and fungal organisms morphologically consistent with *Candida* species; shift in flora suggestive of bacterial vaginosis; the presence of bacteria morphologically consistent with *Actinomyces* species; and cellular changes consistent with herpes simplex virus. Other findings that are noted include reactive cellular changes associated with inflammation, radiation, presence of intrauterine device, glandular cell status post hysterectomy, and atrophy.

In 2003, the U.S. Preventive Services Task Force recommended that all women be screened for cervical cancer with a cervical cytologic work up beginning at age 21 or 3 years after sexual activity begins, whichever occurs first. Screening then should be performed at least every 3 years. Women who are older than 65 years need not undergo routine screening for cervical cancer if they have had appropriate screening and normal Pap smear results in the past. In addition, women who have had a total hysterectomy for a benign reason should not undergo screening for cervical cancer.

Most cases of cervical cancer are associated with infection with high risk types of human papillomavirus (HPV) which are types 16, 18, 31, 33, 45, 51, 52, 56, 58, 5, 68, 73, and 82. HPV testing is used as an adjunct to the cervical cytologic work up in women aged 30 years and older, as well as in cases of atypical squamous cells of undetermined significance (ASC-US) to determine whether a colposcopy should be performed.

Other risk factors for cervical cancer include cigarette smoking, immunocompromised status (e.g., human immunodeficiency virus [HIV] infection), early age at onset of sexual activity, multiple sexual partners, and sexual activity with male partners at high risk for sexually transmitted diseases.
Medications That May Increase the Risk for Cervical Cancer

- Corticosteroids (long term use)
- Diethylstilbestrol (exposure while in utero)
- Immunosuppressants used in organ transplantation
- Oral contraceptives (long term use)

Causes of Abnormal Cervical Cytologic Findings

- Causes of ASC-US include atrophy, infection, inflammation, cervical dysplasia, and cervical cancer.
- Invasive cervical cancer is present in 0.1% to 0.2% of women with ASC-US and in 1% to 2% of women with high grade squamous intraepithelial lesions (HSIL). About 5% to 10% of women with AGC have adenocarcinoma in situ or adenocarcinoma.
• About 5% of women with ASC US, 24% to 94% of women with atypical squamous cells with high grade intraepithelial lesion (ASC H), 15% to 30% of women with low grade squamous intraepithelial lesions (LSIL), 75% of women with HSIL, and up to 50% of women with AGC have moderate to severe cervical dysplasia.

**Key Historical Features**

**✓ Gynecologic history**
- History of sexually transmitted diseases
- Prior Pap smear abnormalities, positive results of HPV testing, abnormal findings in prior colposcopies, and treatment for abnormalities
- Frequency of prior Pap smears and date of last Pap smear
- Last normal menstrual period

**✓ Sexual history**
- Number of sexual partners
- Age at onset of sexual activity
- Sexual activity with partners at high risk of sexually transmitted diseases

**✓ Obstetric history (early childbearing may increase the risk of cervical cancer)**

**✓ Associated symptoms**
- Abnormal vaginal bleeding
- Postcoital bleeding
- Pelvic pain
- Vaginal discharge
- Foul vaginal odor
- Dyspareunia
- Dysuria
- Urinary frequency

**✓ Menopausal status**

**✓ Medical history**
- HIV infection
- Organ transplantation
- Lymphoproliferative disorders

**✓ Medication use, especially oral contraceptives or immunosuppressants**
✓ Social history
  • Tobacco use
  • Alcohol use
  • Recreational drug use

Key Physical Findings
✓ External genital examination to evaluate for erythema (sign of infection with *Trichomonas* or *Candida* organisms) or ulcerative lesions, which may indicate herpes infection
✓ Speculum examination to evaluate for discharge, bleeding, or vaginal lesions (the vagina may appear erythematous with *Trichomonas* or *Candida* infection) and to evaluate the cervix for masses, erosions, ulcers, friability, or bleeding
✓ Bimanual examination to evaluate for any uterine or adnexal masses or tenderness
✓ Rectovaginal examination to evaluate for any masses or tenderness

Suggested Work-Up

The Bethesda 2001 classification system was used to create the American Society for Colposcopy and Cervical Pathology Consensus Guidelines in 2001 to distinguish women at risk for significant cervical disease from those with mild or no disease. The American College of Obstetrics and Gynecology also published guidelines for the management of abnormal Pap smears/cervical cytologic findings (Figs. 11 to 15). The guidelines involve substantial use of HPV DNA testing and colposcopy. Other testing used includes endocervical sampling, biopsy, and excisional procedures.

In pregnant women, endocervical sampling is not indicated and biopsies should be performed only for visible lesions that appear to be CIN grade 3, adenocarcinoma in situ, or cancer. In addition, excisional procedures should be considered in pregnant women only if a lesion discovered at colposcopy appears to be invasive cancer.

The following are recommendations for evaluation that are based upon cervical cytologic results. Algorithms are provided in Figures 11 to 15.

**ASC US**

If HPV testing is positive, colposcopy should be performed with consideration of endocervical sampling with a brush or curette; if finding is negative, then the Pap smear should be repeated in 1 year.

If HPV test result is negative, then a Pap smear should be repeated in 1 year; if HPV testing is not
performed, other options include immediate colposcopy or repeat Pap smear at 6 and 12 months

If the patient is immunocompromised, then colposcopy should be performed immediately

In adolescents with ASC US who are HPV positive, Pap smears may be repeated at 6 and 12 months or HPV testing may be undertaken at 12 months instead of immediate colposcopy, since clearance rate of HPV is high

### ASC H
Colposcopy should be performed with consideration of endocervical sampling

### LSIL
Colposcopy should be performed with consideration of endocervical sampling

In adolescents with LSIL, Pap smears may be repeated at 6 and 12 months or HPV testing may be repeated at 12 months instead of immediate colposcopy, since the clearance rate of HPV is high

### HSIL
Colposcopy with endocervical sampling and biopsy should be performed. If the colposcopic finding is negative or inconclusive, then an excision should be performed

### AGC
Colposcopy and endocervical sampling should be performed

Endometrial sampling should be performed if the patient is older than 35 years or is at risk for endometrial cancer (abnormal bleeding, obesity, or oligomenorrhea)

Figure 1 outlines the management of AGC based on initial cytology results.

**AGC, favor neoplasia, or adenocarcinoma in situ**
If the previously described work up for AGC does not show invasive disease, then a diagnostic excisional procedure should be performed (cold knife conization is preferred)
Atypical squamous cells: cannot exclude high-grade squamous intraepithelial lesion (ASC-H) present

Benign endometrial cells (BEC) present

See BEC algorithm and annotations (boxes 2-6)

Atypical squamous cells of undetermined significance (ASCUS) present

See ASC-US algorithm and annotations (boxes 7-19)

Atypical squamous cells: cannot exclude high-grade squamous intraepithelial lesion (ASC-H) present

Colposcopy

Atypical glandular cells (AGC) present

See AGC algorithm and annotations (boxes 22-39)

Low-grade squamous intraepithelial lesion (LSIL) present

Colposcopy

High-grade squamous intraepithelial lesion (HSIL) present

Colposcopy with biopsy and/or loop electrosurgical excision (LEEP)

Adenocarcinoma in situ (AIS), squamous cell carcinoma or other malignant cells present

Out of guideline • Refer to GYN or GYN oncology

Exclusions (see Introduction): • Pregnancy • HIV and other immunosuppressed conditions

HPV DNA testing positive without abnormal cytology

Out of guideline

Abnormal cervical cytology in adolescents present

See abnormal cervical cytology in adolescents algorithm and annotations (boxes 47-52)

Figure 1-1. Initial management of abnormal cervical cytology (Pap smear) and human papillomavirus testing. Algorithm for initial abnormal cytologic result. Box numbers refer to algorithm boxes in Figure 1-1 to 1-5.
Additional Work-Up

Test for HIV infection In patients at risk

*Chlamydia* and gonorrhea cultures or a nucleic acid amplification test In patients at risk

Urine pregnancy test Should be performed before an invasive procedure if the patient may be pregnant

Wet mount evaluation To evaluate for *Candida* infection, bacterial vaginosis, or *Trichomonas* infection if any of these conditions is suspected

Figure 1-2. Initial management of abnormal cervical cytology (Pap smear) and human papillomavirus testing. Algorithm for benign endometrial cells (BEC)
Atypical squamous cells of undetermined significance (ASCUS) present

Can HPV DNA test be performed?

Perform test

Colposcopy

Treat and repeat cytology

Infection present?

Repeat cytology one week after completion of therapy

Atrophy present?

Treat

Repeat cytology at 6 and 12 months or do colposcopy

Is patient postmenopausal?

Repeat cytology at 12 months or do colposcopy

Atrophy present?

Repeat cytology at 12 months

Infection present?

Repeat cytology at 6 and 12 months or do colposcopy

ASCUS with high-risk HPV DNA positive?

Repeat cytology at 6 and 12 months or do colposcopy

ASCUS present?

Treat and repeat cytology

Can HPV DNA test be performed?

Perform test

Colposcopy

No

Re" Figure 3, nidia renent of abnorma cervica cyo ogy (Pap smear) and human papi omavirus testing. A gorithm for atypica squamous ce s of undetermined significance (ASC-U).
Figure 1-4. Initial management of abnormal cervical cytologic findings (Pap smear) and human papillomavirus testing. Algorithm for atypical glandular cells (AGC).
Figure 1-5. Initial management of abnormal cervical cytologic findings (Pap smear) and human papillomavirus testing. Algorithm for abnormal cervical cytologic findings in adolescents (younger than 21 years).

FURTHER READING