Case 32-2003 — a 37-Year-Old Woman With Atypical Squamous Cells on a Papanicolaou Smear

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Case 32-2003: A 37-Year-Old Woman with Atypical Squamous Cells on a Papanicolaou Smear

Annekathryn Goodman, M.D., and David C. Wilbur, M.D.

PRESENTATION OF CASE

A 37-year-old woman was referred to the colposcopy clinic because of two Papanicolaou smears showing atypical squamous cells of undetermined significance (ASC-US).

One and two years previously, the patient had had Papanicolaou smears that were reported to be normal. Six months before referral, a routine pelvic examination revealed no abnormalities. A Papanicolaou smear at that time was interpreted as revealing ASC-US. The patient was reexamined three months later, and another Papanicolaou smear was again interpreted as showing ASC-US.

The patient (gravida 5, para 4) had had one spontaneous first-trimester abortion. She was a native of El Salvador but had resided in the United States for several years. She reported having a long-standing monogamous sexual relationship. The result of a skin test for tuberculosis with purified protein derivative, performed in the past, was positive; a chest radiograph at that time was normal. She received isoniazid for one year. Two years earlier, during her most recent pregnancy, tests for human immunodeficiency virus infection, syphilis, gonorrhea, and chlamydia had all been negative.

A general physical examination revealed no abnormalities. On pelvic examination, there were no vulvar, vaginal, or cervical lesions. Colposcopic examination revealed a cervical ectropion involving the greater part of the exocervix. The transformation zone was examined visually in its entirety and appeared normal. A repeated Papanicolaou test was performed and reportedly showed no abnormalities. Endocervical curettage was performed, and pathological examination of the specimen disclosed normal endocervical epithelium.

A diagnostic test was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Annekathryn Goodman: This patient had two abnormal Papanicolaou smears, and in both the abnormality of the squamous cells was described as being of unknown significance. The appropriate management in such cases has been an area of controversy, but recent developments may simplify the approach.

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Cervical cancer is one of the leading causes of cancer-related death in women.[1] However, there is epidemiologic evidence that the rates of cervical cancer have fallen in all areas where screening programs have been instituted.[2] The Papanicolaou ("Pap") test, a cytologic evaluation of exfoliated epithelial cells from the lower genital tract, is the gold standard for cervical cancer screening.[3] The Papanicolaou test is effective because cervical neoplasia has a long preinvasive phase before the development of invasive disease; cytologic examination can detect these preinvasive lesions, which can then be eradicated.[4]

This patient's Papanicolaou smears were interpreted as showing ASC-US, indicating that the cytopathologist saw an abnormality in the squamous cells that did not fulfill the criteria for dysplasia but that were not readily categorized as reactive changes.[5] ASC-US may be the finding in as many as 10 percent of all Papanicolaou smears.[6] The majority of women with ASC-US do not have a clinically significant lesion; the abnormalities in the cells are instead due to artifact, inflammation, or estrogen deficiency. However, about 20 percent of women with ASC-US on a Papanicolaou smear are subsequently found to have a dysplastic lesion on cervical biopsy (Table 1).[7] Thus, the ASC-US finding presents practitioners with a challenge in determining how to proceed with further evaluation.

In a patient with suspected cervical squamous-cell dysplasia, the next step after the Papanicolaou test is colposcopic examination of the cervix and biopsy of suspicious areas in order to confirm or rule out a diagnosis of dysplasia and, if dysplasia is present, to determine its grade. The decision to refer a woman such as the patient under discussion for colposcopy is based on two separate assessments: the nature of the abnormality on the Papanicolaou smear and the presence or absence of risk factors for cervical neoplasia in her history. All women with Papanicolaou smears showing clear-cut dysplasia (classified by the cytopathologist as a low-grade or high-grade squamous intraepithelial lesion) should be referred for colposcopy and directed cervical biopsy. However, there has been uncertainty about which women with ASC-US on smears should be evaluated by colposcopy. In practice, women referred for colposcopy have been those who have one Papanicolaou smear showing ASC-US and any risk factor for cervical neoplasia (multiple sexual partners, a history of sexually transmitted diseases, high-risk human papillomavirus [HPV] infection, a previous history of a malignant or premalignant condition of the lower genital tract, or immunodeficiency[8]) and those who have two sequential Papanicolaou smears showing ASC-US and no risk factors.

Referring too many patients for colposcopy, however, has disadvantages both for patients and for society in general. First, colposcopy is expensive. With the addition of a biopsy, a visit can cost several hundred dollars. Each year in the United States, approximately 50 to 60 million women undergo Papanicolaou testing; if 10 percent of them have smears that show ASC-US, and if all of those women are referred for colposcopy, the added cost to the health care system will be large. There are also hidden costs for the patients and society, given that the patient may need to take time away from work or pay for child care and given that the possibility of cancer can cause emotional distress. Since most women with ASC-US do not have a clinically significant lesion, great efforts have been made in the past decade to find another test to help determine whether referral for colposcopy or close follow-up is the best option in a given case.

According to this patient's history, she did not have any risk factors for cervical neoplasia. After a Papanicolaou test yielded a smear showing ASC-US, she underwent another examination and a second Papanicolaou test three months later. After the second Papanicolaou smear was interpreted as showing ASC-US, she was referred to me for colposcopy, according to the standard of practice. I saw no abnormalities of the cervix and therefore obtained another Papanicolaou smear and performed endocervical curettage in an effort to detect endocervical abnormalities that might account for the atypical findings on the previous Papanicolaou smears. I also requested tests for high-risk types of HPV, which were the diagnostic tests in this case.

Table 1. Histologic Findings on Examination of Biopsy Specimens from Women Whose Papanicolaou Smears Showed Atypical Squamous Cells of Undetermined Significance.*

Histologic Finding	No. of Patients (%)
Normal	783 (80.5)
Cervical intraepithelial neoplasia	
Grade 1	125 (12.8)
Grade 2	64 (6.6)
Invasive cancer	1 (0.1)
Total	973 (100.0)

* The data are from Manos et al.[7]

PATHOLOGICAL DISCUSSION

Dr. David C. Wilbur: Some of the squamous cells in this patient's cervical cytologic smear showed alterations in the nuclei consisting of enlargement, slight hyperchromasia, and irregularities of the nuclear envelope (Fig. 1). For this reason, the interpretation was "atypical squamous cells" of the "undetermined significance" subtype (so-called ASC-US).

As Dr. Goodman has said, a specimen for which the cytologic results are equivocal is described as having atypical squamous cells: there are cytologic abnormalities, but they are not sufficient for an outright diagnosis of either low-grade or high-grade

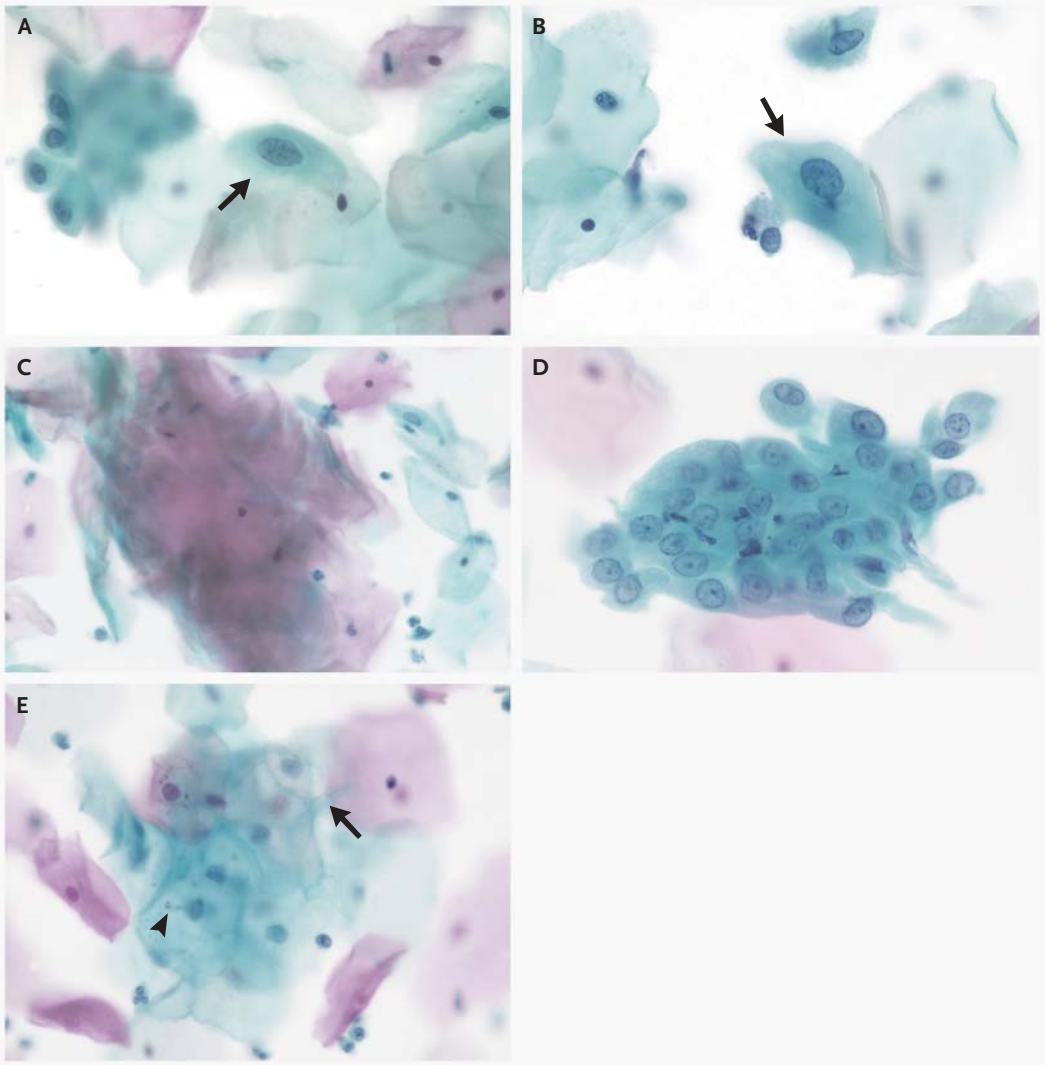


Figure 1. Cervical Specimen Showing Features of Atypical Squamous Cells of Undetermined Significance (Papanicolaou Stain, ×600).

Panel A shows an individual squamous cell with an enlarged nucleus (arrow). Panel B shows a squamous cell with an enlarged nucleus with hyperchromasia and mild irregularity of the nuclear envelope (arrow). Panel C shows a plaque of hyperkeratotic cells indicative of abnormal hypermaturation of the squamous epithelium. Panel D shows a group of reactive cells with infiltration by inflammatory cells and prominent nucleoli. Panel E shows a group of cells with evidence of hypermaturation with keratohyaline granule formation (arrowhead) and perinuclear clearing (arrow), which is suggestive but not diagnostic of human papillomavirus infection. Taken together, these features suggest but do not confirm the presence of a low-grade squamous intraepithelial lesion, but the suggestion of that lesion warrants additional studies; hence, the interpretation of ASC-US was rendered.

dysplasia. The category is divided into two subtypes: one is ASC-US, and the other is a subtype suggestive of high-grade squamous dysplasia (Table 2).[5] This patient, like 95 percent of patients with atypical squamous cells, had cells that were categorized as the ASC-US subtype.

Some patients with atypical squamous cells have dysplastic lesions, whereas some have non-neoplastic conditions with morphologic features on the Papanicolaou smear that overlap with those of dysplastic lesions. The changes in the squamous cells may be quite varied, and interobserver and intraobserver reproducibility in the interpretation of these specimens is poor. Conditions that mimic dysplasias include reactive cellular changes due to tissue damage caused by infection, trauma, or radiation; physiological changes secondary to hormone use and menopausal status; and a wide variety of artifacts resulting from the preparation of the specimen. Fortunately, the latter are minimized by new, liquid-based preparation methods that virtually eliminate air-drying, smearing, and fixation effects. The clinically important entities that may be characterized by atypical squamous cells are true dysplasias and even, in rare instances, invasive carcinomas. The problem, as in this case, is that morphologic features alone do not allow us to predict the risk of such lesions in an individual patient.

Findings of atypical squamous cells typically constitute between 3 and 5 percent of a cytology laboratory's cases. However, indiscriminate use of this designation may increase the percentage to as high as 10 to 15 percent in some laboratories. Dysplasia is found on follow-up biopsy in anywhere from 10 percent to as many as 50 percent of the cases, an indication of the wide range of interpretive differences among cytologists. High-grade lesions (cervical intraepithelial neoplasia, grade 2 or 3) typically constitute 20 to 30 percent of the total.[9] Therefore, for quality-assurance purposes, it is important for each laboratory to monitor the ratio of findings of atypical squamous cells to dysplasia, which should be in the range of 2:1 to 3:1.[10]

Recently, testing for HPV infection has emerged as an important tool in the management of cases in which atypical cells have been found on the Papanicolaou smear. HPV infection is associated with virtually all invasive carcinomas of the cervix, both squamous and glandular, as well as with their precursor dysplastic lesions. Therefore, the presence or absence of HPV should be useful in deciding which cases of atypical squamous cells require triage to colposcopy and which do not.

HPV can be broadly classified into two groups, one associated with cutaneous infections such as the common wart and the other associated with infections and neoplasms of the genital tract. The latter group is further subdivided into low-risk and high-risk types. The former generally cause external genital warts and condyloma, whereas the latter are predominantly (though not exclusively) responsible for cervical neoplasia. Of the high-risk types, the most common are HPV types 16, 18, 31, 33, 35, and 45, which together account for about 85 percent of those detected in cervical-cancer specimens. A variety of other, less prevalent types are responsible for disease in the remaining small percentage of cases. There are geographic variations in the minor, less prevalent viral types associated with cancer; however, in all locations studied, HPV type 16 (HPV-16) and the types related to it predominate.[11]

High-risk HPV infection of the cervical epithelium occurs in two forms, with distinct morphologic features and different associated risks of neoplasia (Fig. 2 and 3). Many people in the general population are infected with HPV; the prevalence is as high as 10 to 15 percent in the younger, more sexually active population. In acute infections, a complete copy of the HPV viral DNA is present as an episome within the host cell, and the virus is capable of completing its life cycle, producing new, infectious viral particles. In the majority of cases, the infection is transient and results either in no demonstrable cytologic changes or in the cytologic changes associated with a productive viral infection. The presence of complete viral particles within the cell may cause a characteristic perinuclear clearing known as koilocytosis (Fig. 4A and 4B), which is the hallmark of the diagnosis of a low-grade squamous intraepi-

Table 2. Classification of Squamous-Cell Abnormalities of the Uterine Cervix.*

Cytologic Interpretation (Papanicolaou smear)	Pathological Interpretation (Biopsy)
Atypical squamous cells	Variable
Undetermined significance (ASC-US)	
Possible high-grade dysplasia (ASC-H)	
Low-grade squamous epithelial lesion	Cervical intraepithelial neoplasia, grade 1
High-grade squamous epithelial lesion	Cervical intraepithelial neoplasia, grade 2 or 3

* The information is from Solomon et al.[5]

thelial lesion on Papanicolaou smears and corresponds to the histologic lesion on biopsy specimens classified as cervical intraepithelial neoplasia, grade 1. This lesion by itself is not associated with an increased risk of cervical neoplasia.

In a small minority of HPV-infected patients, the circular viral genome is integrated into the host-cell DNA, producing high-grade dysplasia, which can progress to invasive carcinoma (Fig. 3). During the integration process, the viral DNA is disrupted in the region of the E2 gene, which is responsible for controlling transcription of other viral genes. The oncogenic genes E6 and E7, which encode proteins that bind to and inactivate the products of important host-cell tumor-suppressor genes, are preserved. Because of the loss of other viral genes during integration, the viral life cycle is not completed, and new virus particles are not produced. The cells of high-grade dysplasia (interpreted as high-grade squamous intraepithelial lesions on the Papanicolaou smear and typically reflected in biopsy findings of cervical intraepithelial neoplasia, grade 2 or 3, or invasive carcinoma) therefore do not show koilocytosis and are primitive and undifferentiated in appearance (Fig. 4C and 4D). It has been estimated that high-grade dysplasia may progress to invasive cancer in as many as 60 percent of cases if left untreated.

Given the central role of HPV in cervical carcinogenesis, testing for the presence of this virus can be an appropriate and cost-effective test to determine whether or not a patient with ASC-US, such as the patient in this case, may harbor high-grade dysplasia. There are several ways to test for the presence of HPV in clinical specimens. The most commonly

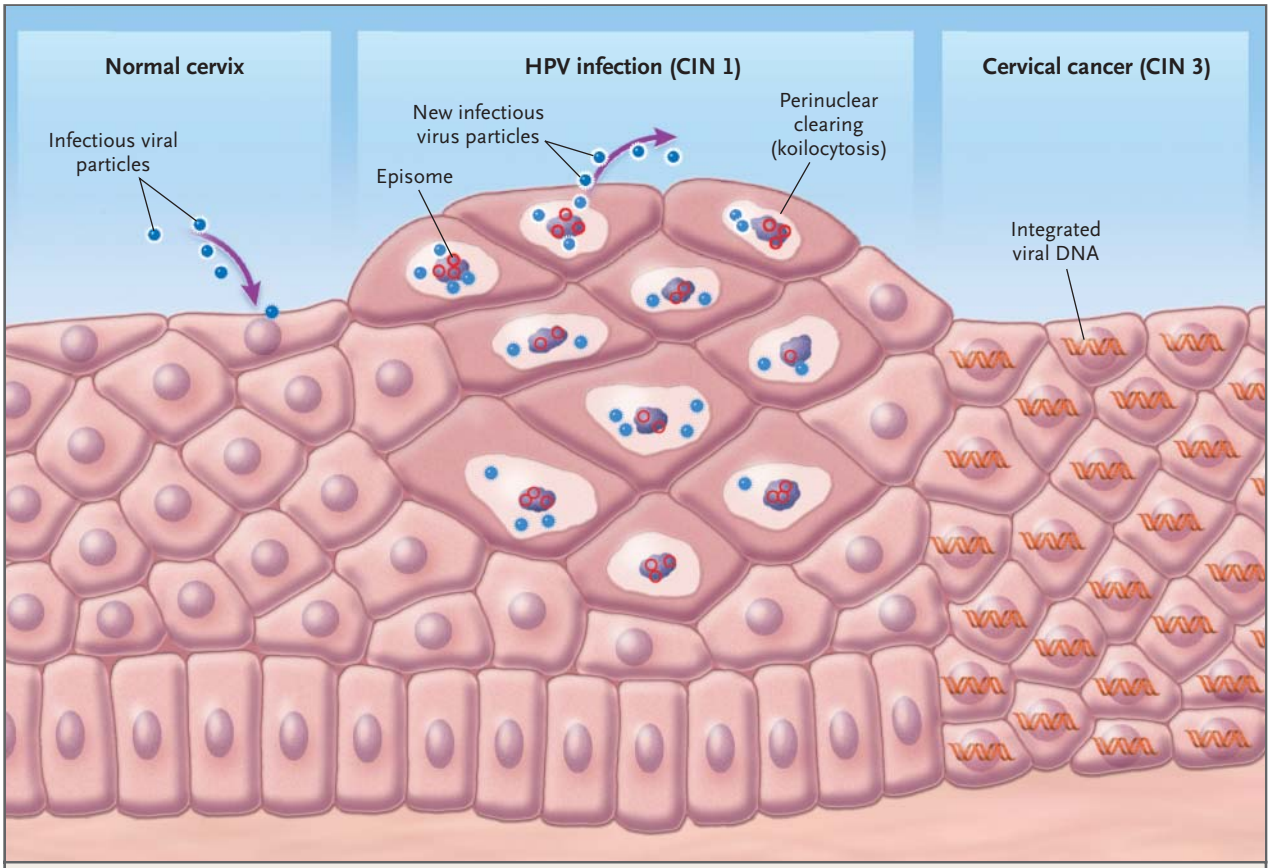


Figure 2. Spectrum of Changes in Cervical Squamous Epithelium Caused by Human Papillomavirus (HPV) Infection.

The left side of the figure shows normal cervical squamous epithelium. When HPV infection occurs (center), the virus exists in the cell nucleus as a circular episome. If the viral genome is intact, new infectious viral particles can be produced; their presence in the cell is indicated by perinuclear clearing, or koilocytosis. In cervical cancer (right), oncogenic portions of HPV DNA become integrated into the host's DNA, with disruption of the *E2* regulatory region and loss of other genes needed to form a complete virus. The cells are undifferentiated and do not show koilocytosis. CIN 1 and CIN 3 denote cervical intraepithelial neoplasia, grades 1 and 3, respectively.

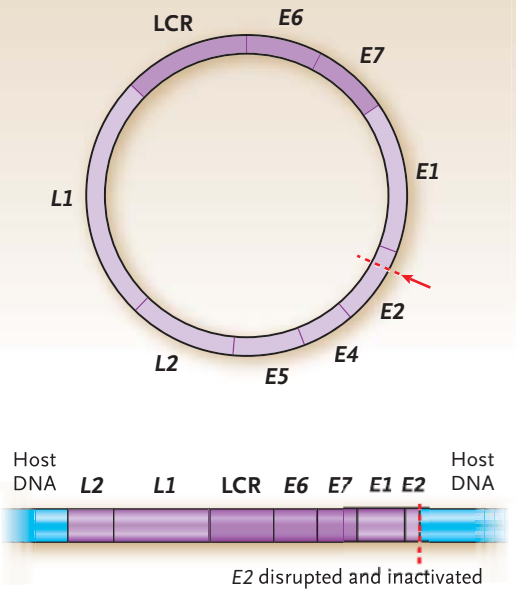


Figure 3. Genome of the Human Papillomavirus.

The circular human papillomavirus (HPV) genome (top) contains early genes (*E1, E2,* and *E4* through *E7*), which are involved in DNA replication, transcriptional regulation, and cellular transformation; late genes (*L1* and *L2*), which encode capsid proteins; and a long control region (LCR). *E6* and *E7* are oncogenic and are always conserved in cervical cancers, as is *LCR*. When the viral DNA is integrated with host DNA (bottom), the *E2* regulatory region is disrupted (arrow), leaving *E6* and *E7* unregulated. Other genes required to complete the formation of a viral particle are lost, and infectious virus is not produced.

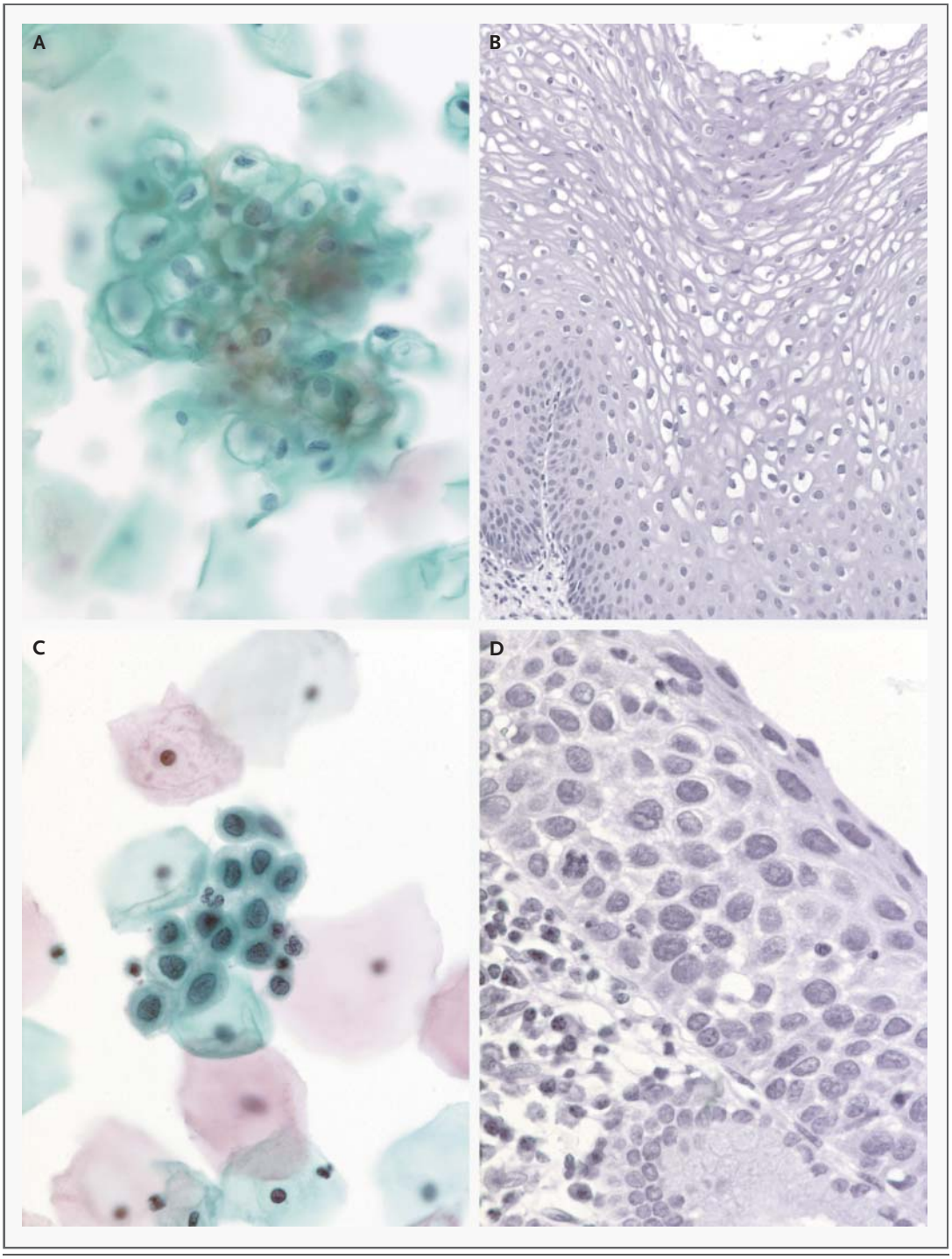
Figure 4 (facing page). Morphologic Manifestations of Various Forms of Human Papillomavirus Infection of the Cervical Squamous Epithelium (from Other Patients).

A Papanicolaou smear (Panel A) shows perinuclear clearing in the squamous cells, known as koilocytosis, which is the morphologic manifestation of productive HPV infection; it is the hallmark of a low-grade squamous intraepithelial lesion (Papanicolaou stain, ×400). A cervical-biopsy specimen from a patient with a low-grade squamous intraepithelial lesion (Panel B) shows histologic changes classified as cervical intraepithelial neoplasia, grade 1, which is characterized by cells with perinuclear vacuolization, corresponding to the koilocytosis seen on the Papanicolaou smear (hematoxylin and eosin, ×200). Integration of high-risk HPV types into the cellular genome can produce high-grade squamous dysplasia (i.e., a high-grade squamous intraepithelial lesion) (Panel C), in which the cells have primitive, undifferentiated features (Papanicolaou stain, ×400). A biopsy specimen from a patient with a high-grade squamous intraepithelial lesion on a Papanicolaou smear (Panel D) shows cervical intraepithelial neoplasia, grade 3; primitive cells are present from the basal layer to the surface (hematoxylin and eosin, ×400). Although cervical intraepithelial neoplasia, grade 3, always contains a portion of the HPV DNA, the lesion does not produce complete viral particles.

used method, which thus far has formed the basis for all major U.S. studies of management according to the presence or absence of HPV, is the so-called hybrid-capture method (Hybrid Capture II HPV Test, Digene). There are separate tests for low-risk and high-risk viral types. At present, management algorithms include only the test for high-risk types. The high-risk HPV test contains a cocktail of whole genomic RNA probes that detect the most prevalent oncogenic types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68); a small number of less prevalent types are not included. Cross-reactivity of some of the probes with low-risk viral types has been reported; hence the theoretical sensitivity and specificity are not 100 percent. The probes bind complementary DNA liberated from cells in a specimen, and the RNA–DNA complexes (hybrids) are detected with the use of an enzyme-linked chemiluminescent assay (hence the name "hybrid capture").

The test can be performed on the residual cells present in a liquid-based cytologic specimen, in what is known as "reflex" testing. The test can also be performed with a specimen obtained with a cervical brush rinsed in transport medium specifically for the HPV test alone. The Hybrid Capture II HPV Test detects high-risk HPV in a highly sensitive manner, resulting in a very high negative predictive value for the detection of high-grade dysplasia. However, it is important to recognize that the large pool of patients who have transient viral infections without having high-grade dysplasia makes the specificity of the test low (i.e., makes the positive predictive value low).

Other tests available for the detection of high-risk HPV types are techniques based on the polymerase chain reaction and in situ hybridization. These tests theoretically have a very high sensitivity for viral detection and may also have the advantage of allowing specific viral typing. In situ hybridization combines the advantages of viral detection with simultaneous visualization of cellular morphologic features — a potential advantage for improving the specificity of the test for the detection of HPV-positive



cases of high-grade squamous intraepithelial lesions.

In addition to guiding management, HPV testing can also be useful in the laboratory for determining whether the designation of atypical squamous cells is being used properly.[12] In addition to correlating such interpretations with the findings on follow-up biopsy specimens, laboratories can now determine the proportion of cases associated with high-risk HPV infection. It has been suggest-

ed that about 50 percent of patients whose smears are categorized as showing atypical squamous cells should be positive for HPV.

In the case under discussion, we tested a liquid-based cytologic specimen with the Hybrid Capture II HPV Test. The test was negative for the presence of high-risk HPV infections.

DISCUSSION OF MANAGEMENT

Dr. Goodman: A recent national study, sponsored by the National Cancer Institute, known as the ASCUS–LSIL Triage Study (where LSIL denotes low-grade squamous intraepithelial lesion), has provided information that is useful in determining the role of HPV testing in the care of patients with a Papanicolaou smear showing ASC-US. In this study, 3488 women with ASC-US on a single Papanicolaou smear were randomly assigned to one of three options: immediate colposcopy, HPV testing with the Hybrid Capture II HPV Test, or a repeated Papanicolaou test.[9] Patients in whom HPV was detected by the Hybrid Capture II HPV Test and patients with a high-grade squamous intraepithelial lesion on the repeated Papanicolaou test were referred for colposcopy. All the patients underwent colposcopy at the end of the trial, with a repeated Papanicolaou test and biopsy of any suspicious areas.

HPV testing detected 92.4 percent of cases of cervical intraepithelial neoplasia, grade 3, whereas examination of the repeated Papanicolaou test, with high-grade squamous intraepithelial lesion used as the threshold for referral, detected only 54.6 percent. Fifty-six percent of the women who underwent HPV testing were referred for colposcopy, as compared with 12.3 percent of the women in the group assigned to a repeated Papanicolaou test. When the threshold for referral for colposcopy on the basis of a repeated Papanicolaou test was changed to any abnormal finding (ASC-US or higher, as is the current standard of practice), the sensitivity for the detection of cervical intraepithelial neoplasia, grade 3, increased to 95.4 percent but required two office visits and was associated with a referral rate for colposcopy of 67.1 percent. Thus, reflex HPV testing provides essentially equivalent sensitivity and slightly better specificity than a repeated Papanicolaou smear for detecting cervical intraepithelial neoplasia, grade 3, and eliminates the need for repeated Papanicolaou testing.[9]

These data have led to the recommendation by the American Society for Colposcopy and Cervical Pathology that all women with Papanicolaou smears showing ASC-US should undergo HPV testing. Those whose tests are positive for high-risk HPV should then be referred for colposcopy. Those whose tests are negative should undergo repeated Papanicolaou testing in one year. Patients who have high-risk HPV and whose colposcopic evaluation shows no abnormalities should undergo repeated Papanicolaou testing at 6 and 12 months. Repeating the HPV testing after 12 months should also be considered for these patients, since persons with persistent HPV infections are at higher risk for the development of cervical neoplasia in the future than those with transient infections.[13,14] This test will help determine the course of management more effectively than the Papanicolaou test alone and help reduce unnecessary testing in women whose HPV tests are negative.

At present, the only indication for HPV testing is a Papanicolaou smear showing ASC-US. However, the Food and Drug Administration recently approved HPV testing in conjunction with Papanicolaou testing for primary screening in women older than 30 years of age. Although infection with a high-risk type of HPV is a necessary condition for the development of lower genital tract cancer, it is clearly not sufficient, since more than 90 percent of HPV infections resolve completely within two years without the identification of clinically significant lesions.[15] Thus, testing as part of primary screening in young patients may increase the frequency of detection of transient infections.

The patient under discussion had a negative test for HPV and is therefore at low risk for the development of cervical neoplasia. She was referred back to her primary care physician and will need no more than a routine yearly Papanicolaou test.

A Physician: The number of sexual partners that put a woman at risk for HPV-related disease has been variably defined as two to five or more. What do you consider to be an indicator of high risk?

Dr. Goodman: Exposure to multiple sexual partners is an indirect measure of risk, since the probability of contact with a high-risk HPV subtype increases with additional exposures. However, if the only sexual contact a woman has had is with a partner who harbors a high-risk HPV subtype, she is at risk. Once HPV testing becomes routine for the evaluation of Papanicolaou smears showing ASC-US, it will be clinically irrelevant to determine the number of sexual partners a woman has had.

A Physician: Will the HPV test be performed rou-

tinely when cases are interpreted as ASC-US in your laboratory, or will it have to be specifically requested?

Dr. Wilbur: We have decided not to perform the test routinely unless it is specifically requested. Many of the Papanicolaou smears we examine were obtained from patients who are referred to our clinics for the evaluation of known abnormalities, so their HPV status may already be known or they may already have been referred for a colposcopic examination. Because our laboratory personnel will have no way of knowing the patient's status, we believe that reflex testing would result in unnecessary tests, and therefore we require a physician's order. In a typical population undergoing primary screening, automatic HPV testing when an ASC-US result is found makes sense.

A Physician: What is the status of the HPV vaccine?

Dr. Goodman: Koutsky and colleagues reported a prospective trial involving 1533 women 16 to 23 years of age who were randomly assigned to receive three doses of HPV-16 vaccine or a placebo.[16] The goal of this study was to determine whether HPV-16 vaccine reduced the incidence of persistent infection, which was defined as the detection of HPV-16 DNA on two or more occasions. There was a reduction in persistent HPV-16 infections in the vaccinated group at 14.7 months. However, given that the majority of HPV-16 infections resolve naturally by 40 months, it will be interesting to see whether this difference persists as the study matures. The duration of the protection conferred will also need to be determined. This vaccine is aimed only at HPV-16, which accounts for only 40 percent of cancers, and it is not yet ready for widespread marketing and use. Other vaccines are in development and testing.

A Physician: I have a patient in her early 40s whose Papanicolaou smears over the years have shown ASC-US. She has had multiple colposcopic examinations followed by biopsies, which showed no abnormalities, and has had negative tests for high-risk HPV. At what point can we be certain that these Papanicolaou-smear findings do not represent high-grade dysplasia?

Dr. Goodman: If the cytologic abnormalities are confined to the squamous cells, if the HPV testing is negative, and if colposcopic examinations show no abnormalities, I do not believe she is at risk for high-grade squamous dysplasia. Repetitively atypical Papanicolaou smears in the absence of dysplasia or HPV infection usually suggest chronic irritation or trauma. Yearly follow-up with Papanicolaou testing is sufficient.

A Physician: I have an 80-year-old patient who has had two sexual partners in her lifetime and who has not been sexually active for 20 years. This year, her Papanicolaou smear showed a high-grade squamous intraepithelial lesion. The findings on a colposcopic examination and examination of a cervical-biopsy specimen were normal. Is there a role for HPV testing?

Dr. Goodman: This patient has a highly abnormal Papanicolaou smear with clear evidence of dysplasia. HPV testing in this setting is not indicated. She may have a lesion in her upper endocervix that is not apparent on colposcopy. A cervical cone biopsy would be an appropriate next step. It also will be important to evaluate her vagina and vulva carefully for other possible sources of the dysplastic cells.

PATHOLOGICAL DIAGNOSIS

Atypical squamous cells of unknown significance (on the Papanicolaou smear), with a negative test for high-risk human papillomavirus.

The patient is currently not at increased risk for cervical cancer.

REFERENCES

1. American Cancer Society home page. (Accessed September 19, 2003, at http://www.cancer.org.)
2. National Cancer Institute. SEER cancer statistics review, 1973-1998. (Accessed September 19, 2003, at http://www.seer.cancer.gov/csr/1973_1998/.)
3. Papanicolaou GN, Traut HF. The diagnostic value of vaginal smears in carcinoma of the uterus. Am J Obstet Gynecol 1941;42:193-205.
4. Holowaty P, Miller AB, Rohan T, To T. Natural history of dysplasia of the uterine cervix. J Natl Cancer Inst 1999;91:252-8.
5. Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA 2002;287:2114-9.
6. Kurman RJ, Henson DE, Herbst AL, Noller KL, Schiffman MH. Interim guidelines for management of abnormal cytology: the 1992 National Cancer Institute Workshop. JAMA 1994;271:1866-9.
7. Manos MM, Kinney WK, Hurley LB, et al. Identifying women with cervical neoplasia: using human papillomavirus DNA testing for equivocal Papanicolaou results. JAMA 1999;281:1605-10.
8. IARC monographs on the evaluation of carcinogenic risks to humans. Vol. 64. Human papillomaviruses. Lyons, France: International Agency for Research on Cancer, 1995.
9. ASCUS-LSIL Triage Study (ALTS) Group. Results of a randomized trial on the management of cytology interpretations of atypical squamous cells of undetermined significance. Am J Obstet Gynecol 2003;188:1383-92.
10. Kurman R, Solomon D. The Bethesda System for reporting cervical/vaginal cytologic diagnoses: definitions, criteria, and explan-

atory notes for terminology and specimen adequacy. New York: Springer-Verlag, 1994:34.
11. Muñoz N, Bosch FX, de Sanjosé S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med 2003;348:518-27.
12. Sherman ME, Schiffman M, Cox JT. Effects of age and human papilloma viral load on colposcopy triage: data from the randomized Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study (ALTS). J Natl Cancer Inst 2002;94:102-7.
13. Davey DD, Austin RM, Birdsong G, et al. ASCCP patient management guidelines: Pap test specimen adequacy and quality indicators. Am J Clin Pathol 2002;118:714-8.
14. Wright TC Jr, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ. 2001 Consensus guidelines for the management of women with cervical cytological abnormalities. JAMA 2002;287:2120-9.
15. Woodman CB, Collins S, Winter H, et al. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. Lancet 2001;357:1831-6.
16. Koutsky LA, Ault KA, Wheeler CM, et al. A controlled trial of a human papillomavirus type 16 vaccine. N Engl J Med 2002;347:1645-51.