CASE RECORDS *of the* MASSACHUSETTS GENERAL HOSPITAL

Case 10-2009: A 23-Year-Old Woman with an Abnormal Papanicolaou Smear

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PRESENTATION OF CASE

Dr. Naana Afua Jumah (Student, Harvard Medical School): A 23-year-old woman was seen in the gynecology clinic of this hospital because of a high-grade squamous intra-epithelial lesion seen on pathological examination of a Papanicolaou (Pap) smear.

Four weeks earlier, the patient had come to the adolescent and young adult medicine clinic of this hospital to establish care and to receive counseling regarding oral contraception, screening for sexually transmitted infections, and vaccination for the human papillomavirus (HPV).

Menarche had occurred at the age of 13 years, and menses had been monthly and regular. She had been sexually active since the age of 21 and had had 18 male partners, most of whom had had other sexual partners, and she had no history of sexually transmitted infections or pelvic infections. She had used oral contraceptives for 3 months, when she first became sexually active, and reported consistent condom use for both contraception and protection against sexually transmitted infections, except on three occasions. Physical and gynecologic examination 20 months earlier had been normal; the Pap smear was normal, with endocervical cells present. Testing of cervical secretions for gonorrhea and chlamydia were negative. Five months later, a viral culture of a genital specimen and serologic tests for herpes simplex virus (HSV) type 1 and type 2 IgG and IgM antibodies were reportedly negative. Three months before this evaluation, she had been seen in the emergency department of this hospital for a possible accidental overdose of acetaminophen, which she had been taking for dental pain. The blood acetaminophen level was 25.9 mg per liter (reference range, 10 to 25; toxic level, >120); the level 3 hours later was normal. She was instructed on proper dosing of the drug and discharged. She had had multiple atypical nevi, and one of two previous excisions had report-edly shown dysplastic changes. She had had an adenoidectomy at the age of 10 years. The patient worked in an office and lived with roommates. She had been without health insurance since graduating from college 1 year earlier. She drank 5 to 10 alcoholic beverages 2 to 3 days per week, including during sexual activity, and reported several episodes of blackouts while drinking; she had smoked marijuana on a few occasions in the past and did not smoke tobacco. Her mother had a his-tory of vitiligo and alcohol abuse; her father and two sisters had irregular nevi. There was no family history of coagulopathy or gynecologic cancer. She was allergic to

codeine. Her only medication was lorazepam, as needed for anxiety during airplane flights.

On examination, she appeared well. The vital signs were normal; the weight was 60.2 kg, the height 162 cm, and the body-mass index (the weight in kilograms divided by the square of the height in meters) 23.0. The tonsils were enlarged. There were multiple nevi on the trunk, arms, and legs (one over the right scapula was 3 mm in diameter with irregular borders, and one in the left inguinal region was 4 to 5 mm with color variation). Sexual development was Tanner stage 5 (fully mature), with normal external genitalia. The cervix was friable and tender to palpation; the uterus was midline, retroverted, and antiflexed; and the ovaries were normal. The remainder of the examination was normal. Laboratory testing included a complete blood count; measurement of electrolyte and cholesterol levels; tests of renal, liver, and thyroid function; testing for syphilis and the human immunodeficiency virus; cervical screening for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*; and a liquid-based Pap smear. The patient was counseled about her level of alcohol consumption. The first dose of HPV vaccine was administered, and a prescription for oral contraceptives was written. Follow-up for the second vaccination in the series and for management of the oral contraceptives was scheduled. She was referred to the dermatology clinic.

The next week, review of the Pap smear revealed a high-grade squamous intraepithelial lesion. All other laboratory-test results were normal, and tests for infectious diseases were negative.

Three weeks later, she was seen in the colposcopy clinic. The results of a pelvic examination were unchanged from the previous examination. Colposcopic examination, performed after application of 3% acetic acid, revealed the entire squamocolumnar junction with an area of aceto-white change with punctation between the 9 o'clock and 12 o'clock positions. A biopsy specimen of the lesion was obtained, and endocervical curettage was performed. Pathological examination revealed moderate-to-severe squamous dysplasia with koilocytosis. Review of the endocervical-curettage specimen revealed highly atypical glandular epithelium. Testing for gonorrhea and chlamydia was negative.

Four weeks later, the patient was seen in the gynecology oncology clinic of this hospital. A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Mark A. Goldstein: On her first visit to our clinic, this young woman, who had had many sexual partners since becoming sexually active 2 years earlier, was found to have a high-grade intraepithelial lesion, a precursor of cervical cancer. This process is invariably associated with infection with certain types of HPV, estimated to be the most common sexually transmitted infection in 15-to-24-year-old persons in the United States. Infection is most frequent in sexually active women under the age of 25 years, like this patient.[1]

RISK FACTORS FOR HPV INFECTION

Adolescents and young adults such as this patient are at higher risk for sexually transmitted infections, including HPV, than older persons, because of both behavioral and biologic factors. Young persons are more likely to engage in high-risk behaviors, including unprotected intercourse, multiple sexual partners, and substance abuse in association with sexual acts, all of which this patient had done. In women, having sex during menses, having early coitarche, and being subject to coercive sex are also important risk factors; using alcohol, tobacco, marijuana, or oral contraceptives and having a new partner, especially if he is known for less than 8 months before initiation of sexual activity, are predictive of an incident HPV infection.[2-5] This patient used oral contraceptives and acknowledged using alcohol and marijuana, including during sex. Other risk factors may include inadequate knowledge of the risks of sexually transmitted infections and lack of access to appropriate medical care; this patient had been without health insurance since leaving college.

Biologic risk factors in young people include the more frequent presence of cervical ectopy and a larger transformation zone than in older women, inadequate production of cervical mucus, and increased susceptibility to trauma during intercourse. The presence of another sexually transmitted infection, such as vulvar warts or HSV infection, is an additional biologic risk factor for HPV infection in this age group.[3] This patient had cervical ectopy but did not have other sexually transmitted infections.

Several studies have addressed the incidence of HPV infection in sexually active women in this patient's age group. The studies show cumulative

incidences of HPV infection during periods of 12 to 24 months of about 40% among those who had vaginal intercourse[2,4,5]; 50 to 80% of sexually active teenage girls and young women test positive for HPV.[6,7] Consistent use of condoms reduces but does not eliminate the risk of cervical and vulvovaginal HPV infection.[5] The risk is increased if the male partner has had multiple other partners or if his sexual history is not known.[8] This patient had multiple new sexual partners during a short time and reported that on at least three occasions she failed to use condoms. We can thus assume that she was at high risk for an incident HPV infection.

Most HPV infections in female adolescents and young adults are transient and have little long-term clinical significance; 70% of women clear the infection within 1 year and more than 90% in 2 years.[2,3,7] Risk factors for persistent infection include infection with multiple strains, as well as immunocompromise.[9] Persistent infection is associated with abnormal cervical cytology, and more than 90% of patients with low-grade squamous intraepithelial lesions,[5] high-grade squamous intraepithelial lesions, or adenocarcinoma in situ are positive for high-risk HPV.[10]

Current guidelines recommend initiation of cervical-cancer screening within 3 years after first intercourse or by the age of 21 years, whichever occurs first.[11] Cervical screening may be performed earlier than stated in the guidelines if follow-up of the patient is unpredictable, the patient is immunocompromised, or there is concern that the patient may not have reported sexual abuse or sexual intercourse. This patient reported that her first vaginal sexual intercourse occurred when she was 21 years of age, and 7 months later she had her first Pap smear at her college health service. The specimen was adequate, endocervical cells were present, and it was negative for intraepithelial lesions and cancer. Her medical insurance lapsed, and she had no routine medical care after college graduation, resulting in a delay of cervical cytologic screening and of the initiation of the HPV vaccine. At the first visit to our clinic, 20 months after the initial negative cervical cytologic test, she reported multiple sexual partners and other high-risk sexual behaviors. The HPV vaccine was initiated, she was screened for sexually transmitted infections, and liquid-based cervical-cancer screening was performed in accordance with the published guidelines for adolescents and young adults (Table 1).[11-13]
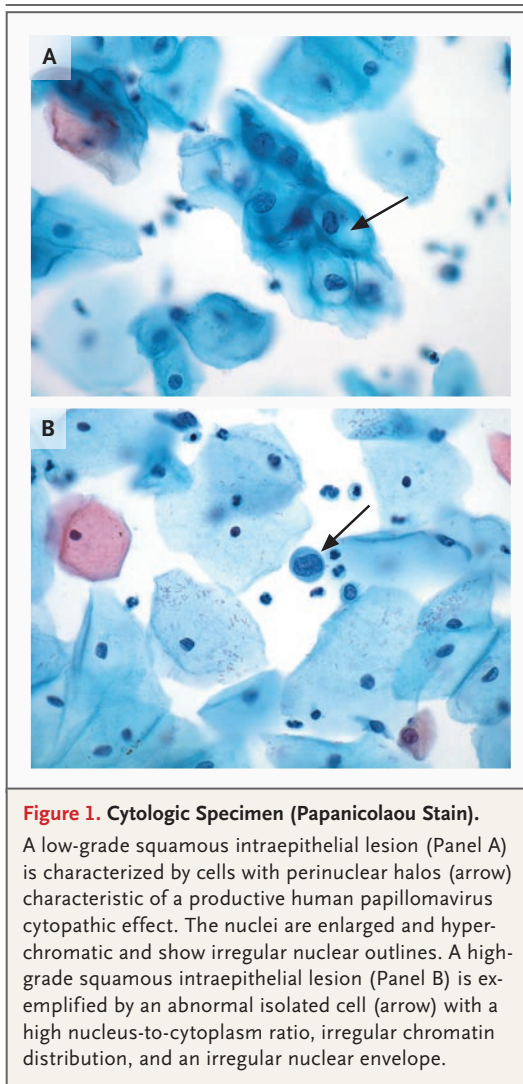
PATHOLOGICAL DISCUSSION

Dr. David C. Wilbur: A specimen from a liquid-based Pap test was obtained, and the slide was initially screened by a computerized scanning device, as is routine in the cytopathology laboratory at this hospital. The scanning device flagged the specimen as requiring manual review, which was performed by a cytotechnologist. Abnormal cells were identified, and the slide was then referred to the cytopathologist. The specimen contained a mixture of types of abnormal cells, ranging from those of a low-grade to those of a high-grade squamous intraepithelial lesion. Koilocytes (Fig. 1A), which are cells with the classic features of a productive viral infection, were in-

Table 1. Cervical-Cancer Screening Guidelines for Adolescents and Adults Younger Than 30 Years of Age.*			
Variable	ACOG	ACS	USPSTF
Age to begin screening	Within 3 yr after first vaginal intercourse but no later than 21 yr of age	Same as ACOG	Same as ACOG
Screening method	Conventional or liquid-based cytologic test	Same as ACOG	No specific recommendation
Frequency of screening with conventional Papanicolaou test	Annual	Annual	"No direct evidence that annual screening achieves better outcomes than screening every 3 years"
Frequency of screening with liquid-based cytologic test	Annual	Every 2 yr	Insufficient evidence

* ACOG denotes American College of Obstetricians and Gynecologists,[11] ACS American Cancer Society,[12] and USPSTF U.S. Preventive Services Task Force.[13]

Figure 1. Cytologic Specimen (Papanicolaou Stain).

A low-grade squamous intraepithelial lesion (Panel A) is characterized by cells with perinuclear halos (arrow) characteristic of a productive human papillomavirus cytopathic effect. The nuclei are enlarged and hyperchromatic and show irregular nuclear outlines. A high-grade squamous intraepithelial lesion (Panel B) is exemplified by an abnormal isolated cell (arrow) with a high nucleus-to-cytoplasm ratio, irregular chromatin distribution, and an irregular nuclear envelope.

dicative of the presence of low-grade squamous intraepithelial lesions. These cells are representative of a transient infection with HPV. However, coexisting with the koilocytes were cells representative of a high-grade squamous intraepithelial lesion, which is a true neoplastic precursor lesion capable of progression to invasive carcinoma (Fig. 1B). These cells are primitive in that they lack differentiation and have a high nucleus-to-cytoplasm ratio and a hyperchromatic nucleus with an irregular distribution of chromatin. The presence of a high-grade squamous intraepithelial lesion typically correlates with the presence of severe dysplasia or carcinoma in situ, known as grade 3 cervical intraepithelial neoplasia (CIN 3) on biopsy specimens.

DISCUSSION OF MANAGEMENT

Dr. Goldstein: The patient's second cervical cytologic test, 2¼ years after her first intercourse, indicated the presence of a high-grade squamous intraepithelial lesion. Although the majority of low-grade squamous intraepithelial lesions regress,[14] high-grade squamous intraepithelial lesions are likely to persist or progress, so that follow-up was indicated.[15] Tests for human immunodeficiency virus were negative, and we referred the patient for colposcopy in accordance with recent consensus guidelines.[16]

Dr. Annekathryn Goodman: To determine the best treatment for this patient, an understanding of the natural history of cervical neoplasia is crucial. Persistent infection with HPV is strongly linked to the development of high-grade squamous intraepithelial lesions, which this patient already has, as well as invasive cancer. Although the time of progression from persistent HPV infection to high-grade squamous intraepithelial lesions has been thought to be 5 to 15 years, on the basis of cross-sectional studies,[17] recent longitudinal studies of newly infected patients suggest that the interval may be much shorter, with cumulative 36-month progression rates to grade 2 or 3 CIN (CIN 2/3) from 7 to 20%, with the highest rates reported for HPV type 16 (HPV-16).[7,18-20] Thus, this patient's diagnosis of high-grade squamous intraepithelial lesions within 2 years after becoming sexually active may not be as unusual as we might have thought.

What is the likelihood that this patient's high-grade squamous intraepithelial lesions will progress to invasive cancer? Invasive cervical cancer is rare in adolescents and young women aged 13 to 20 years[7,21]; however, few data exist on the natural history of high-grade cervical lesions in adolescents. Two retrospective studies estimated a likelihood of progression from CIN 3 to invasive cancer ranging from 2 to 12%.[22,23] The median age of women with invasive cancer is typically 10 years higher than that of women with CIN 3.[7] Thus, although high-grade squamous intraepithelial lesions in adolescents and young women is unlikely to regress, it does not appear to progress rapidly to invasive cancer.

The 2006 consensus guidelines recommend colposcopic evaluation of patients with high-grade Pap smears, along with biopsy and endocervical curettage.[16] Adolescents with high-grade

squamous intraepithelial lesions are also immediately evaluated by colposcopy. Because of the low risk of invasive cancer in this population, diagnostic excisional procedures are avoided in adolescents, unless high-grade squamous intraepithelial lesions persist for a total of 24 months.

In this patient, I performed a colposcopic examination and applied acetic acid to distinguish normal from abnormal cervical epithelium and assess the extent of the high-grade dysplasia.[24] The normal, glycogenated epithelium, which has cells that have tiny nuclei and abundant cytoplasm, is not affected by this fixative, whereas dysplastic epithelial cells, which have larger nuclei and scant cytoplasm, become opaque and appear white (aceto-white) on examination. In this patient, a white area was evident, from which I took a biopsy specimen; I also performed an endocervical curettage.

Dr. Wilbur: Colposcopic biopsy showed evidence of a high-grade squamous dysplasia, predominantly CIN 2 but with focal areas indicative of CIN 3 (Fig. 2A). As predicted by examination of the cytologic specimen, evidence of a productive viral infection in the form of koilocytotic change was also noted (Fig. 2B). In addition, the endocervical curettage revealed an area of atypical endocervical epithelium (Fig. 2C). Although a number of endocervical reactive processes may have similar features, such changes raise the possibility of endocervical neoplasia and must therefore be further investigated. Adenocarcinoma in situ is also associated with HPV. It is rarer than squamous dysplasia but has increased in incidence during the past 20 years, most likely because of better detection but also perhaps in association with increasing use of hormonal contraception.

Dr. Goodman: The consensus guidelines recommend excision or ablation of carcinoma in situ and adenocarcinoma in situ at all ages. In adolescents and young adults who have solitary CIN 3 lesions that are confined to the exocervix, observation every 6 months for up to 2 years is appropriate. A lesion that extends into the cervical canal, is multifocal, or contains adenocarcinoma in situ, as this one does, should be excised (there are no accepted nonsurgical therapies for adenocarcinoma in situ). Therefore, I performed a cervical loop electrosurgical excision procedure (LEEP) to excise the high-grade lesions involving both the exocervix and endocervix.
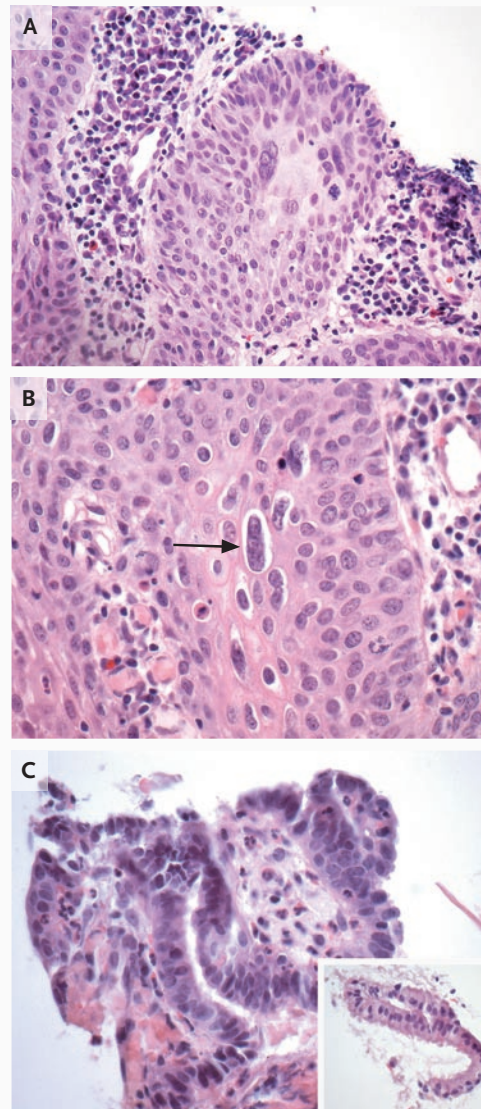

Figure 2. Cervical-Biopsy Specimen (Hematoxylin and Eosin).

This specimen shows high-grade dysplasia with immaturity of the basal squamous cells extending into the midportion of the epithelium (Panel A). In addition to the maturation abnormality, another area of the epithelium (Panel B) shows atypical cells with perinuclear halos, nuclear enlargement, and multinucleation, known as koilocytosis (arrow). These changes are indicative of the viral cytopathic effect associated with human papillomavirus infection. Atypical endocervical epithelium was also present in the cervical-biopsy specimen (Panel C). The epithelium is pseudostratified and shows enlarged nuclei with hyperchromasia. This appearance is in contrast to normal simple endocervical epithelium (inset).
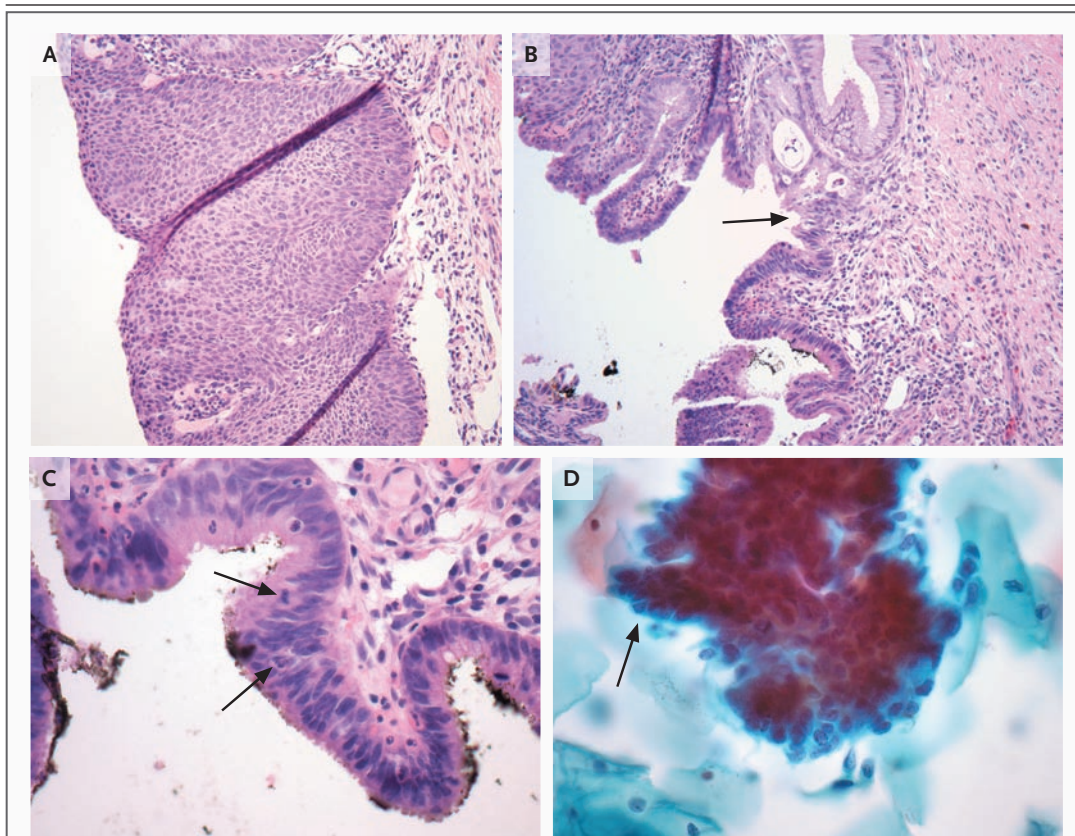
Figure 3. Specimen from a Loop Electrosurgical Excision Procedure.

In a lesion identified as grade 3 cervical intraepithelial neoplasia (Panel A, hematoxylin and eosin), an abnormality of maturation of squamous cells is noted to ascend to involve near full thickness. No koilocytosis is present in this lesion, since these cells are indicative of a neoplastic, not infectious, process, and viral particles are not produced. Endocervical adenocarcinoma in situ (Panel B, hematoxylin and eosin) is present adjacent to normal endocervical epithelium. The arrow points to the junction between adenocarcinoma in situ and normal-appearing cells. At higher magnification (Panel C, hematoxylin and eosin), the typical features of endocervical adenocarcinoma in situ are shown, including nuclear pseudostratification, enlargement, and hyperchromasia. Mitotic figures are prominent (arrows). A hyperchromatic, crowded group of cells from the patient's original Papanicolaou test (Panel D, Papanicolaou stain) has features that may be seen in both high-grade squamous lesions and endocervical lesions. A vague columnar appearance is present at one margin (arrow), suggesting an origin from endocervical cells, although the rest of the group has a more syncytial appearance, a feature suggestive of high-grade squamous intraepithelial lesions.

Dr. Wilbur: The LEEP produced the following three specimens: portions of exocervix and endocervix and an endocervical curettage. All the disease identified was in the exocervical specimen. One CIN 3 lesion (equivalent to severe dysplasia or carcinoma in situ) had an abnormality of maturation involving full or near full thickness (Fig. 3A) and numerous mitoses in the upper levels of the epithelium. This process extended to the exocervical resection margin. In addition, multiple foci of endocervical adenocarcinoma in situ were present. In the lesion, pseudostratified epithelium abutted normal simple endocervical cells (Fig. 3B). The initial endocervical curettage specimen did not show the pseudostratified epithelium with mitotic activity (Fig. 3C). These changes are indicative of endocervical adenocarcinoma in situ, since no evidence of stromal invasion is noted in the specimen.

In retrospect, the original cervical cytologic specimen showed very subtle changes suggestive of the presence of an endocervical lesion (Fig. 3D). The Pap test was originally designed to detect the far more common squamous lesions, and its sensitivity for glandular lesions is generally thought to be less than 50%. Glandular lesions, which often reside high in the endocervical canal and deep in the endocervical crypts, may not

produce cells for examination, and when they do, the features may be difficult to differentiate from squamous dysplasias and from reactive conditions.

Dr. Goodman: The rate of treatment failure after LEEP ranges from 1 to 25% depending on the size of the lesion, whether it is multifocal, and whether the cervical margins are negative. The majority of recurrences occur within 2 years. In general, for a patient with an excision with negative margins, Pap smear and colposcopy are performed at 6-month intervals; after two normal Pap smears, the patient can return to routine screening. The consensus guidelines state that yearly screening after two consecutive repeat cytologic examinations are negative must be continued for 20 years.[16] In this patient, with positive exocervical resection margins and negative endocervical margins, I performed a repeat LEEP with endocervical curettage 3 months later; the specimen showed no evidence of dysplasia.

Dr. Marcela G. del Carmen: This patient had received one dose of quadrivalent HPV vaccine before the diagnosis of high-grade squamous intraepithelial lesions. Should she continue with the vaccination program? Two vaccines are currently available[25-28]: a bivalent vaccine containing HPV-16 and HPV-18, which are associated with most cases of cervical cancer (approved in Europe and Australia and submitted to the Food and Drug Administration [FDA] for approval in the United States), and a quadrivalent vaccine containing HPV-6 and HPV-11 (associated with genital warts) and HPV-16 and HPV-18 (approved by the FDA for use in girls and women aged 9 to 26 years).[29] Both vaccines provided more than 90% protection against incident infection by the relevant HPV strains in clinical trials[30-32] and had more than 90% efficacy for prevention of CIN 2 or higher lesions in women who were HPV-negative at the end of the vaccination program.[33-36] The efficacy of the quadrivalent vaccine was assessed in subjects who were enrolled regardless of baseline HPV status. In the 21% of subjects who had evidence of infection with HPV-16 or HPV-18, the vaccine did not appear to alter the risk of the development of CIN.[34-36] Nonetheless, for this patient, the benefit of vaccination would include protection against the development of new HPV infection with other high-risk strains, as well as against genital warts.

Although HPV vaccination will be important in the prevention of cervical cancer, it will not replace the continued need to participate in other preventive strategies, the most important of which may be continued cytologic screening for cervical cancer. In this patient, completion of vaccination with the quadrivalent vaccine would be appropriate, despite the likelihood that she is already infected with at least one of the four HPV types in the vaccine.

Dr. Nancy Lee Harris (Pathology): Dr. Goldstein, can you tell us what has happened to this patient?

Dr. Goldstein: The patient completed the series of three HPV vaccinations. On repeat colposcopy 6 months after the second LEEP, there was no gross abnormality of the cervix. Pap smear and endocervical curettage disclosed atypical squamous cells; for this reason, HPV testing was performed, and it was negative for all the high-risk strains. She will follow up in 2 months in the gynecology clinic.

Dr. Goodman: It is reassuring that, even though this patient had a clinically significant cervical lesion that was due to HPV infection, she eventually cleared the HPV infection. As long as she is sexually active, she can develop a new HPV infection that is not covered by the vaccine, so annual Pap smears are still essential. We do not know why a high-grade lesion developed in this patient, which occurs in less than 1% of all adolescent girls and young women.

ANATOMICAL DIAGNOSES

CIN 3 (severe dysplasia or carcinoma in situ) of the uterine cervix.

Endocervical adenocarcinoma in situ.

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