CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 16-2014: A 46-Year-Old Woman in Botswana with Postcoital Bleeding

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PRESENTATION OF CASE

Dr. Rajesh T. Gandhi (Medicine, MGH): A 46-year-old woman with human immunodeficiency virus (HIV) infection was seen by a clinician in Botswana (working in collaboration with members of a Massachusetts General Hospital [MGH] outreach program) because of postcoital bleeding.

The patient had been generally well until 6 years before presentation, when weight loss and pelvic pain developed and she requested HIV testing at a government clinic. HIV-antibody testing was positive.

Four years 3 months before presentation, the CD4+ T-cell count was 193 cells per cubic millimeter (Table 1), indicating that the patient was eligible for antiretroviral treatment (ART) in Botswana. The white-cell count was 3400 cells per cubic millimeter (reference range, 3900 to 8600), and the blood level of creatinine was 0.41 mg per deciliter (36 μmol per liter; reference range, 0.45 to 0.81 mg per deciliter [40 to 72 μmol per liter]). Two months later, treatment with a combination of tenofovir, emtricitabine, and efavirenz was begun. At a follow-up appointment 1 month later, a gynecologic examination was performed to evaluate vaginal discharge, urinary frequency, and dysuria. Abnormalities were reported, and administration of a 10-day course of amoxicillin was begun. Pathological examination of the specimen obtained during a screening Papanicolaou (Pap) test revealed a low-grade squamous intraepithelial lesion; however, the patient never received this result. Four months after the initiation of ART, the CD4+ T-cell count had improved (Table 1).

One month later (5 months after the initiation of ART), the patient again reported dysuria; a course of nalidixic acid was administered. During the next 18 months, she continued to have recurrent pelvic pain, dysuria, and vaginal discharge. She sought care from traditional healers for these symptoms and postponed reporting the symptoms to her medical caregivers and undergoing a repeat Pap test, since she believed that the traditional therapies would help; the symptoms did not improve. Approximately 13 months before this presentation, the patient reported vaginal pruritus. Speculum examination revealed white patches on the cervix, and a repeat Pap test revealed a high-grade squamous intraepithelial lesion. One month later,

on review of the test results, colposcopic examination with biopsy was scheduled for the next available appointment, which was 14 months later.

Approximately 10 months before this presentation, a small amount of vaginal bleeding reportedly occurred each time the patient had sexual intercourse; the patient was referred for gynecologic evaluation. One month before this presentation, the complete blood count, the creatinine level, and tests of liver function were normal; other results are shown in Table 1. She returned to the HIV clinic for evaluation.

The patient reported no dyspareunia. She had undergone menarche at 15 years of age and first had sexual intercourse after the age of 17 years, and she was gravida 7, para 5. Medications included tenofovir, emtricitabine, and efavirenz; she had no known allergies. She lived in an urban area in Botswana with her five children and their father (who was also receiving ART for HIV infection). She did not smoke, drink alcohol, or use illicit drugs. She was employed periodically in a small shop. There was no family history of cancer.

On examination, the abdomen was soft, without distention, rebound, or palpable masses. On pelvic examination, there were ulcers at the introitus; a malodorous, fungating lesion, 6 cm by 2 cm, on the right lateral vaginal wall, extending from the fornix to the introitus, with minimal bleeding on contact; and a nodular cervix. The remainder of the general examination was normal.

Diagnostic procedures were performed.

Table 1. Laboratory Data.

Variable	Reference Range*	4 Yr 3 Mo before Presentation	3 Yr 9 Mo before Presentation	3 Yr 3 Mo before Presentation	2 Yr 8 Mo before Presentation	1 Yr 8 Mo before Presentation	13 Mo before Presentation	6 Mo before Presentation	1 Mo before Presentation
CD4+ T-cell count (cells/mm^3)	467–1603	193	281	249	308	373	330	352	483
HIV RNA (copies/ml)	<400				<400	<400		<400	<400

* Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at the Botswana clinic are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

DIFFERENTIAL DIAGNOSIS

Dr. Doreen Ramogola-Masire: This 46-year-old HIV-infected woman presented after 10 months of recurrent postcoital bleeding. Other symptoms included intermittent urinary frequency, dysuria, pelvic pain, vaginal discharge, and pruritus. She had had two Pap tests, 3 years apart, with the results showing low-grade and high-grade squamous intraepithelial lesions. She had been receiving treatment for HIV for approximately 4 years, with virologic suppression and good CD4+ T-cell recovery.

Postcoital bleeding is defined as bleeding that occurs during or after sexual intercourse not related to menses, and the differential diagnosis varies with age and menstrual status. Postcoital bleeding typically results from a sur-

face lesion of the lower genital tract, but it may also occur with diseases of the endometrium. Although the majority of conditions associated with postcoital bleeding are benign, it is vital that cancer is considered in patients in this patient's age group (Table 2).

A comprehensive history of the patient and bimanual and speculum examinations of the vulva, vagina, and cervix are essential in determining the underlying cause of postcoital bleeding. Patients can occasionally mistake bleeding from nongynecologic conditions, such as urethral lesions, for vaginal bleeding, and careful examination of the lower urinary tract is mandatory, especially in patients with symptoms of dysuria and urinary frequency. If a lesion of the lower urinary tract or genital tract is not identified, ultrasonographic imaging and possibly endometrial sampling are necessary to rule out endometrial disease.

In this case, there is limited evidence to suggest that the patient had a nongynecologic disease or a benign anogenital condition. The combination of vaginitis (vaginal discharge and pruritus), a malodorous fungating lesion on the vaginal wall, and a nodular cervix is highly suggestive of cancer and should prompt a biopsy of the cervix and vagina.

CANCER OF THE CERVIX AND VAGINA

Cervical cancer is the most common cancer in women in sub-Saharan Africa, especially in those who have HIV infection. Approximately 11% of patients who have cervical cancer present with postcoital bleeding.[1] This patient's history of sequential cytologic tests that revealed low-grade and high-grade squamous intraepithelial lesions, followed by recurrent postcoital bleeding, is suspicious for cervical cancer.

There are no guidelines for screening for vaginal intraepithelial neoplasia, a precancerous condition of the vagina. Often these lesions are incidental findings revealed during colposcopy performed for abnormal cervical cytologic findings. The abnormalities detected by the two Pap tests in this patient may have been due to exfoliated cells from the vagina and the cervix. Therefore, it is important to also examine the vagina when evaluating patients for abnormal cervical cytologic findings.

Although this patient's lesion seems to have developed rapidly, it is possible that a vaginal lesion was missed during earlier examinations, since small vaginal lesions can be obscured by the speculum blades. This possibility, together with the finding of a lesion arising from the vaginal wall, makes the rare diagnosis of

Table 2. Causes of Postcoital Bleeding.

Cause	Benign	Cancerous	Infectious	Other
Lower genital tract epithelial lesions				
Uterine	Polyps, fibroids	Endometrial cancer	Endometritis	
Cervical	Ectropion, endometriosis, polyps, condylomata	Invasive carcinoma, metastasis	Cervicitis	
Vaginal	Polyps, adenosis	Carcinoma, metastasis	Sexually transmitted infections	Atrophy
Vulvar	Condylomata, skin tags	Cancer		
Other				
Urethral	Carbuncle, condylomata	Cancer		
Anorectal	Condylomata, hemorrhoids	Anal carcinoma		
Traumatic				Forceful sexual intercourse, foreign bodies (e.g., vaginal pessaries, intrauterine devices)
Drug-related (e.g., hormonal agents and anticoagulants)				
Systemic disease (e.g., bleeding disorders)				

primary vaginal cancer also likely in this patient.[2]

GENITAL DISEASES RELATED TO HUMAN PAPILLOMAVIRUS

Human papillomavirus (HPV) infections are the most common sexually transmitted disease worldwide, although only a small fraction of infections lead to clinical disease.[3,4] Genital HPV infection is associated with multiple risk factors (Table 3), of which this patient had at least two (multiparity and immunosuppression).

There are more than 130 types of HPV, of which 30 to 40 infect the genital mucosa and are categorized as low-risk or high-risk, depending on their likelihood to facilitate progression to cancer.[5,6] Chronic infection with a high-risk type of HPV is essential for the development of cancer, in conjunction with such cofactors as smoking and immunosuppression. Virtually all cases of cervical cancer and 40% of cases of vaginal cancer are attributed to HPV infection, with HPV types 16 (HPV-16) and 18 (HPV-18) accounting for 60 to 70% of cervical cancers and 75% of vaginal HPV-related cancers.[7]

HIV AND HPV

HIV and HPV are interrelated sexually transmitted diseases that share similar risk factors and probably facilitate each other's acquisition.[8,9] HIV-infected women have a higher prevalence of persistent infection with HPV, especially with high-risk types,[10] than do women without HIV infection, and they have rapid progression to clinical disease[11]; this is mostly likely the case with this patient.

There seem to be conflicting data on the effect of ART on HPV-related disease, but most studies have shown that ART is not associated with a reduction in the rates of cervical cancer.[12,13] This would explain why the disease in this patient (if we assume she had an HPV-related disease) progressed rapidly, despite suppressive ART.

CHALLENGES OF CERVICAL-CANCER SCREENING IN LOW-RESOURCE AREAS

Even if the final diagnosis in this patient is not cervical cancer, this case brings to attention the challenges of cervical-cancer screening in low-resource settings. Organized cytology-based screening has reduced the incidence of invasive cervical cancer in developed countries.[14] This screening requires sophisticated and costly systems to be in place for the timely identification and treatment of precancerous lesions. This patient had two tests; she did not receive the result of the first test, and there was a 14-month gap between the result of the second test and planned evaluation, both of which delayed diagnosis and treatment. Because of these logistic challenges and the high burden of HPV-related diseases of the lower genital tract, other low-cost methods of screening, such as visual inspection of the cervix with acetic acid followed by same-visit treatment with cryotherapy (if the visual inspection was positive), are necessary in certain countries, such as Botswana.[15]

VACCINATION AGAINST HPV IN SUB-SAHARAN AFRICA

Vaccination against HPV-16 and HPV-18 is efficacious in the prevention of invasive cervical cancer.[16,17] Vaccination is also thought to be effective in patients with HIV infection.[18] In the absence of robust secondary screening and treatment programs, vaccination against HPV remains the best long-term strategy to reduce the incidence of cervical cancer and other anogenital cancers.[18] We expect an even greater reduction in the incidence of these cancers when newer HPV vaccines that include five additional oncogenic types (HPV-31, 33, 45, 52, and 58) become available. Although HPV-16 and HPV-18 account for the majority of cervical cancers in sub-Saharan Africa, the proportion of cancers associated with HPV-31, 33, 45, 52, and 58 in this region is higher than the proportion in other parts of the world, making it likely that these future vaccines will result in a large benefit.[19]

Although the majority of women with postcoital bleeding have benign disease, it is important to rule out cancer of the lower genital tract. In a 46-year-old HIV-infected woman with recurrent abnormal Pap smears, timely colposcopic evaluation of the lower genital tract is critical. Had this patient undergone colposcopy, her disease may have been detected earlier, possibly at the precancerous stage. Given the history and examination, I believe the most likely diagnosis is vaginal cancer and that the second most likely diagnosis is cervical cancer.

DR. DOREEN RAMOGOLA-MASIRE'S DIAGNOSIS

Human papillomavirus–related vaginal cancer.

Table 3. Risk Factors for Genital HPV-Related Disease and Progression to Cancer.*

Infectious (persistent infection with high-risk HPV, such as HPV types 16 and 18)
Environmental (e.g., smoking)
Sexual (e.g., young age at sexual debut, multiple partners, and multiparity)
Hormonal
Immunosuppressive (due to HIV or immunosuppressive therapy)

* HIV denotes human immunodeficiency virus, and HPV human papillomavirus.

PATHOLOGICAL DISCUSSION

Dr. Mukendi K.A. Kayembe: The first Pap test, performed 4 years before the patient's presentation, is said to have shown a low-grade squamous intraepithelial lesion; this test result was not available for our review. The second Pap test, performed 1 year before presentation, showed clusters of small cells with a high nucleus-to-cytoplasm ratio, nuclear hyperchromasia, and variation in nuclear size and shape. Some cells had koilocytotic change, a finding consistent with the characteristic cytopathic effects of HPV. These findings are consistent with a diagnosis of a high-grade squamous intraepithelial lesion (Fig. 1A).

Because there was a clinical suspicion for cancer, the patient underwent biopsies of the cervix and the vaginal mass. Specimens of the cervical tissue showed papillary connective-tissue stroma covered by thickened epithelium displaying hyperkeratosis, parakeratosis, and koilocytotic change (Fig. 1B). A small portion of the epithelium showed full-thickness disordered maturation and cytologic abnormalities consisting of an increased nucleus-to-cytoplasm ratio, nuclear hyperchromasia and pleomorphism, and anisokaryosis (Fig. 1C). These findings are consistent with condylomata acuminata associated with a high-grade squamous intraepithelial lesion. Examination of sections of the vaginal mass showed two findings that are diagnostic for invasive squamous-cell carcinoma: the presence in the lamina propria of irregular cords and nests of malignant squamous cells with keratinization in the form of keratin pearls and dyskeratotic keratinocytes (Fig. 1D and 1E). Koilocytotic change was also seen in nonmalignant areas (Fig. 1F). The paraffin blocks of cervical and vaginal tissues were sent to MGH for ancillary tests.

Dr. David C. Wilbur: On receipt of the biopsy specimens, we performed nucleic acid testing that is sensitive for the detection of 14 high-risk types of HPV. The results showed that the two specimens were positive for high-risk HPV, although not the most oncogenic types (HPV-16 and HPV-18).

We also performed an in situ hybridization assay for high-risk HPV and an immunohistochemical assay for the p16 protein. The in situ hybridization test allows for localization of HPV DNA and can also illustrate patterns to distinguish whether the viral DNA is present as an episome (generally seen in benign infections) (Fig. 2A) or is integrated into the host genome (generally seen in precancers and cancers) (Fig. 2B). In the two specimens from this patient, we observed a strong and diffuse staining pattern for p16 (Fig. 2C), which is highly predictive of cellular transformation to precancer or cancer. In contrast, the low-grade lesion in the cervical specimen was negative for p16, showing only a faint blush of brown stain (Fig. 2D). This pattern is characteristic of a nontransformed HPV infection or other non-HPV–associated process. The molecular and immunohistochemical findings support the final diagnoses in this case and are consistent with HPV-associated cellular transformation in the precancerous and cancerous portions of the lesions.

DISCUSSION OF MANAGEMENT

Dr. Anthony H. Russell: This patient's cancer extended lengthwise 6 cm from the vaginal fornix to the vaginal introitus and through the vaginal wall into paravaginal tissues (stage II); it was 2 cm in diameter. Our goals were to maximize the chances of permanent eradication of the cancer and to minimize the effect of treatment on adjacent normal tissues and on the patient's quality of life. Conservative surgery, which is typically performed when small-volume disease is limited to the vaginal wall, was not feasible in this case because of the extent of the disease.

The biologic effect of radiation therapy was augmented by the synchronous administration of systemic cytotoxic chemotherapy. This combined approach results in equivalent or superior cancer control within irradiated target volumes as compared with radiation alone. Lower doses

of radiation may be used with concurrent chemotherapy, which can result in reduced late radiation complications.[20,21] Commonly used chemotherapeutic agents are cisplatin, fluorouracil, and mitomycin C. In this patient, radiation was administered with curative intent, and the tar-

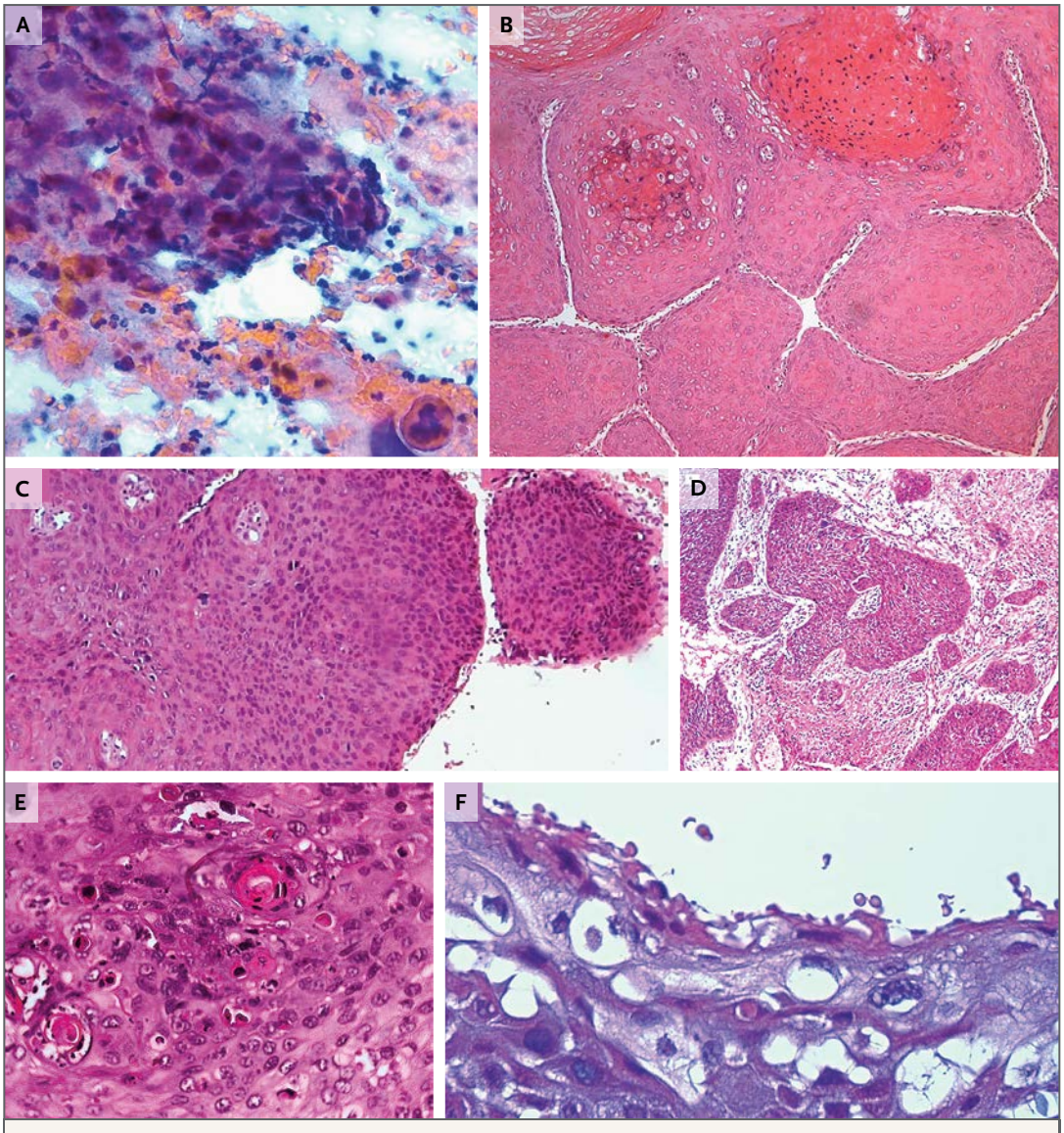

Figure 1. Pathological Examination of a Papanicolaou Smear and Biopsy Specimens of the Cervix and Vagina.

Examination of a Papanicolaou smear obtained 13 months before the patient's presentation shows clusters of squamous cells that are consistent with a high-grade intraepithelial lesion (Panel A, Papanicolaou stain) and squamous cells that have koilocytotic change. Biopsies of the cervix and vagina were performed on presentation. Examination of the cervical specimen shows papillary projections of fibrous tissue covered by squamous epithelium showing hyperkeratosis, parakeratosis, and koilocytotic change (Panel B, hematoxylin and eosin). A portion of the epithelium shows hyperchromatic nuclei (Panel C, hematoxylin and eosin), as well as disordered maturation and other cytologic abnormalities. These findings are consistent with condylomata acuminata of the cervix and a high-grade squamous intraepithelial lesion. The vaginal-biopsy specimen shows irregular cords and nests of malignant squamous cells (Panel D, hematoxylin and eosin) and groups of malignant cells with keratin pearls and dyskeratotic keratinocytes (Panel E, hematoxylin and eosin). The vaginal epithelium shows koilocytotic change (Panel F, hematoxylin and eosin). These findings are diagnostic of an invasive keratinizing squamous-cell carcinoma of the vagina.

gets were the external and internal iliac lymph nodes and the inguinal and femoral lymph nodes (i.e., the entire first-echelon lymphatic drainage systems of both the proximal vagina and the distal vagina). Concurrently, cisplatin was administered intravenously once a week for 5 weeks.

Supplemental intravaginal radiation was administered by brachytherapy with high-activity iridium-192. The intensity of radiation exposure from a point source is inversely proportional to the square of the distance from that source. Steep dose gradients can be accomplished with brachytherapy; that is, when substantial additional doses of radiation are administered to the area of initial tumor involvement, the surrounding organs (which are at risk for late radiation injury) will absorb a smaller dose. Reexamination of this patient after the completion of therapy revealed complete clinical disappearance of the primary cancer.

MANAGEMENT OF HIV

Dr. Scott Dryden-Peterson: The majority of cases of cancer in Botswana arise in HIV-infected persons, and cancers (e.g., vulvar cancer) that are not an acquired immunodeficiency syndrome (AIDS)–defining condition (e.g., Kaposi's sarcoma, non-Hodgkin's lymphoma, and cervical cancer) have become increasingly common. Nearly all these cancers occur despite the long-term administration of ART and successful immune reconstitution, as was true for this patient.[22] Widespread access to ART has been associated with a decrease in the incidence of

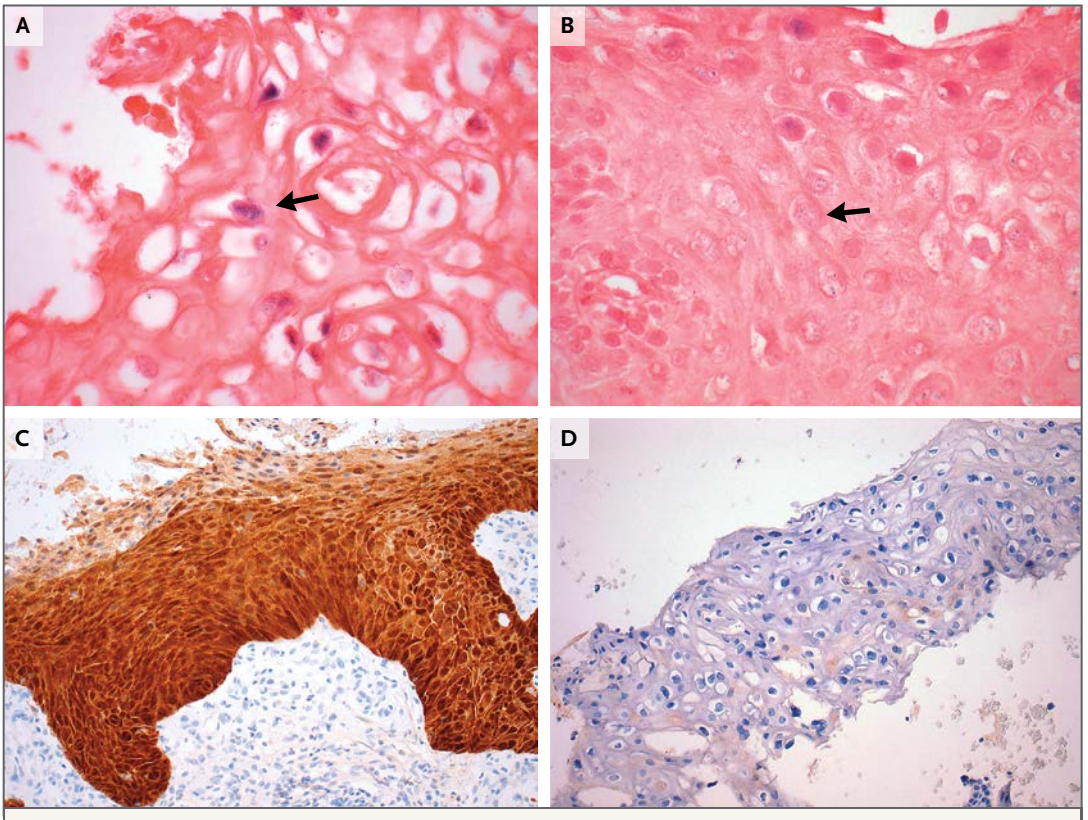

Figure 2. Testing of the Cervical-Biopsy Specimen for Human Papillomavirus (HPV).

An assay for high-risk HPV performed by means of in situ hybridization of the condylomatous area of the cervical-biopsy specimen shows a speckled pattern in the nucleus that is indicative of the presence of viral DNA as an episome (Panel A, arrow; hematoxylin and eosin). In situ hybridization of the area of the high-grade lesion in the cervical-biopsy specimen shows a dotlike pattern in the nucleus that is indicative of the integration of viral DNA into the genome (Panel B, arrow; hematoxylin and eosin). Immunohistochemical analysis shows a strong and diffuse pattern of staining for the p16 protein in the high-grade lesion in the cervical specimen (Panel C, immunoperoxidase) but virtually no staining for p16 in the condylomatous areas (Panel D, immunoperoxidase).

Kaposi's sarcoma. However, the burden of cancer linked to HPV has increased.[23]

The concurrent management of HIV and cancer poses numerous challenges, particularly in the resource-constrained environments where HIV is most prevalent. This patient had virologic suppression of HIV for more than 4 years while she received tenofovir, emtricitabine, and efavirenz, and subsequently, the CD4+ T-cell count recovered, from 193 to 483 cells per cubic millimeter. She adhered well to the therapy, which been associated with an acceptable side-effect profile. However, we should consider whether modification of her HIV treatment would improve the safety or the outcome of treatment with radiation and cisplatin.

Among HIV-infected patients, outcomes associated with oncologic treatment are generally improved with concurrent ART. Continuation or initiation of ART is generally recommended.[24] Although pharmacologic interactions are possible, clinically significant adverse events are uncommon.[25] Among patients undergoing chemoradiation, ART has not been associated with an increased rate of adverse events.[26,27] However, despite concurrent ART, prolonged suppression of CD4+ T-cell counts after chemoradiation is often observed and is occasionally associated with the development of opportunistic infections.[28]

Cisplatin has a low potential for pharmacokinetic interaction with the patient's antiretroviral agents because of its predominantly renal elimination.[29] However, renal tubular dysfunction is a concern with cisplatin,[30] and the administration of cisplatin with potentially nephrotoxic drugs is avoided.[31] Long-term use of tenofovir is associated with an increased risk of renal injury, particularly in the context of concurrent nephrotoxic medications.[32] The use of these drugs together may increase the risk of clinically significant nephropathy.

Options for this patient include the continuation of her current ART (including tenofovir, with careful hydration and monitoring of her renal function), the exchange of tenofovir for an agent such as abacavir (which is associated with a lower risk of renal injury) during chemotherapy, or the administration of carboplatin instead of cisplatin (to reduce the risk of nephropathy). In Botswana, we have generally not stopped tenofovir during chemoradiation because renal injury is infrequently seen and because the alternative agents are associated with increased cost, logistic challenges, and possible adverse effects on adherence to ART.

COLLABORATIVE ONCOLOGY

Dr. Jason A. Efstathiou: In Botswana, limited specialized oncologic services are available in the face of a rising burden of cancer. A collaborative outreach program between doctors at MGH and in Botswana was established in 2011 to build the capacity to deliver quality cancer care in Botswana.[33,34] A goal of the outreach program was the creation of a multidisciplinary tumor board, which involves physicians in Botswana and physicians based at MGH and Harvard Medical School who have expertise in a variety of cancer-related fields. The tumor board discussed this patient's case by telephone-based and Internet-based conferencing and helped to develop the treatment plan. The outreach program also includes on-site training in Botswana and ongoing mentorship, which has assisted with the implementation of brachytherapy services in Botswana, as well as the elimination of a treatment backlog in brachytherapy. The outreach program is an example of a successful partnership between academic medical centers committed to broadening health services and institutions in high-burden countries with limited resources.

Dr. Gandhi: Dr. Dryden-Peterson, what happened with this patient?

Dr. Dryden-Peterson: This patient received chemoradiation followed by intravaginal brachytherapy and had a complete clinical response, with no palpable tumor. No changes were made to her ART and no nephrotoxic effects were detected. Diarrhea and mild vaginal stenosis developed during the course of therapy. One year after completing treatment, she remained in remission, without any pain, and was able to resume normal sexual activity.

ANATOMICAL DIAGNOSES

Condylomata acuminata and a high-grade squamous intraepithelial lesion of the cervix.

Keratinizing squamous-cell carcinoma of the vagina.

High-risk human papillomavirus infection.

Presented at the 2013 Annual Workshop on Advanced Clinical Care–AIDS, Durban, South Africa (organized by Drs. Henry Sunpath, Mahomed-Yunus S. Moosa, Francois Venter, and Rajesh T. Gandhi).

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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