More Human Papilloma Virus Shedding With HIV

Vulvar condylomas are multifocal in this population and respond poorly to standard treatments.

BY ELIZABETH MECHCATIE
Senior Writer

BETHESDA, MD. — HIV-infected women have higher rates of human papilloma virus shedding and higher rates of high grade cervical intraepithelial neoplasia, and are diagnosed more frequently with vulvar intraepithelial neoplasia (VIN) than are women who are not infected, Thomas C. Wright Jr., M.D., said at a conference on vulvovaginal diseases.

Women infected with HIV have an increased rate of human papilloma virus (HPV) shedding that is generally estimated at about four times that of HIV-negative women, said Dr. Wright, director of obstetrics, gynecology, and pathology at Columbia University College of Physicians and Surgeons, New York.

Among HPV-infected women, those who are also infected with HIV have more HPV types than do women without HIV. In one study conducted in New York City, 31% of HIV-positive women had more than one HPV type, vs. 9% of HIV-negative women. A total of 16% and 14% had HPV 16 and HPV 18, respectively, in the HIV-positive group vs. 6% and 3%, respectively, in HIV-negative women.

Studies conducted in the 1990s determined that the distribution of HPV types in women without cervical intraepithelial neoplasia (CIN) tend to be the same in those who are HIV positive and those who are HIV negative. But women with biopsy-confirmed CIN 2,3 who are HIV positive "tend to be more heterogenous for high risk [HPV] types" he said.

Types 16 and 18, which tend to be the most common high-risk HPV types in the general population and appear to be more aggressive than other high-risk HPV types, are found in considerable numbers of CIN 2,3 cases in both HIV-infected and uninfected women. However, in HIV-infected women, the other HPV types that can cause cancer "may become a little more pathogenic" as the immune system deteriorates, Dr. Wright noted.

Viral load and CD4 counts have both been found to be markers for patients who shed HPV: The Women's Interagency HIV Study (WIHS) published in 1999 found that HPV was detected more frequently in women with low (under 200) CD4 counts, regardless of their HIV viral load. Similarly, women with a high HIV viral load, even with a higher CD4 count, will have high rates of HPV shedding, Dr. Wright said at the conference, sponsored by the American Society for Colposcopy and Cervical Pathology.

For more than a decade, it has been clear that the prevalence of CIN among HIV-positive women is high, estimated at two to four times higher than among noninfected women. Dr. Wright referred to four large prospective follow-up studies, including one that he and his associates conducted in New York City, which found that the rates of abnormal cytology in HIV-positive women ranged from 30% to 40%, vs. 8% to 20% among HIV-negative women.

In his study, 7% of the HIV-positive women had high-grade CIN (CIN 2,3), vs. 1% of the HIV-negative women. Over a 3-year follow-up, 20% of the HIV-positive women developed biopsy-confirmed CIN, increasing to 30% over 6 years. Predictably, a woman with low CD4 counts is more likely to develop CIN, Dr. Wright said, adding that a woman with low CD4 counts who is followed for 48 months has a 40% chance of developing biopsy-confirmed CIN.

In HIV-infected women, condylomas are very common. Vulvar condylomas in this population are numerous and multifocal, and tend to respond poorly to standard treatments, he said. Although VIN is less common than is CIN, VIN is much more common in HIV-infected women compared with uninfected women.

In a study published this year of 1,778 HIV-infected women and 500 HIV-negative women followed for 8 years, incident condylomas were detected in 23% of HIV-positive women vs. 7% of HIV-negative women.

Seven percent of HIV-positive women had high-grade CIN, vs. 1% of HIV-negative women.

DR. WRIGHT

In the WIHS study published this year, risk factors for condylomas identified among HIV-positive women were cytologic abnormalities, HPV, smoking, no HAART (highly active antiretroviral therapy), and a low CD4 count, Dr. Wright said.

Now that HAART is used so widely, there is much less cervical and vulvar disease in HIV-infected patients, Dr. Wright observed. At one point, a large proportion of the patients he saw at the Columbia colposcopy clinic were HIV positive, but those numbers have markedly dropped now that most are on HAART, which has been shown to reduce the incidence of condylomas.

VIN, however, is clearly an increasing problem in this population, he said. Because women in the HIV clinic are well screened and treated with loop electrosurgical excision procedure when CIN is detected, cervical cancer is less common. In contrast, "we continue to identify vulvar cancers," since screening and treating for VIN lesions is not as thorough.

In a study that followed cervical disease in HIV-positive and HIV-negative women, he and his coinvestigators have found that about 4% of HIV-positive women developed biopsy-confirmed VIN over 60 months vs. less than 1% of HIV-negative women. And, as with cervical disease, the risk was higher with lower CD4 counts, where almost 20% of those with CD4 counts under 200 developed biopsy-confirmed VIN.

In the WIHS study, incident VIN 2,3 was detected in 8% of HIV-positive women during follow-up and 2% of HIV-negative women, "a relatively high attack rate" of 1.52 per 100 person years among HIV-positive women, vs. 0.36 per 100 person years for HIV-negative women. This indicates that about 1% of HIV-positive women will develop biopsy-confirmed VIN every year, Dr. Wright pointed out.

In the WIHS study, the risk of VIN 2,3 was increased in women with cytologic abnormalities and high-risk HPV types. However, HAART use and CD4 counts did not have a significant impact on incidence, so while HAART is effective in reducing condylomas and CIN, "we're not seeing the same dramatic impact of HAART on VIN incidence, in the studies that have been reported."

Based on these findings, Dr. Wright recommended a high level of awareness of vulvar disease in HIV-infected patients, and when an HIV-positive patient is referred with an ASCUS (atypical squamous cells of undetermined significance) and LSIL (low-grade squamous intraepithelial lesions) Pap, "be absolutely certain that you do a very careful inspection of the vulva, and do liberal biopsies" of anything that looks abnormal. ■

Prognosis for Vulvar Paget's Disease Called Excellent

BY ELIZABETH MECHCATIE
Senior Writer

BETHESDA, MD. — Extramammary Paget's disease is most often found in the vulvar area and usually has an excellent prognosis, Peter J. Lynch, M.D., said at a conference on vulvovaginal diseases.

The vulva is the site of about 65% of extramammary Paget's disease (EMPD), which accounts for about 1% of all vulvar malignancies, said Dr. Lynch, emeritus professor and training program director, department of dermatology, University of California, Davis. EMPD is a disease of the elderly, affecting women 55-90 years old, with a mean age of 65. It occurs primarily among whites, although it has been reported increasingly among Asians over the past 4-5 years.

The lesions are primarily found along the "milk line," where the sites of involvement are anywhere apocrine glands are found, including the axillae, breast, and perianal area.

Typically, extramammary Paget's lesions are similar in appearance, with an erythematous plaque that is sharply marginated. The surface of these lesions is often moist and/or crusted, but patients also may have frank erosions, he said. Whiteness in the vulvar area can be due to the absence of melanocytes, or caused by what happens when keratin gets waterlogged, since keratin is highly hydrophilic. Any disease with a buildup of keratin occurring in a wet area will have whitening in some areas, he explained.

While it may be suspected, the correct diagnosis is rarely made clinically, and generally requires a biopsy. Failure to respond to treatments, such as topical steroids and "anticandidals," should prompt a biopsy. Diseases that may look like this condition but are less common include lichen planus and lichen sclerosis, Dr. Lynch said at the conference, sponsored by the American Society for Colposcopy and Cervical Pathology.

Histology, which is distinctive, but not pathognomonic, is characterized by clusters of pale staining cells in the epidermis, with variable extension into the hair follicles and sweat glands. However, the degree of cellular atypia can be "quite variable," he added.

In the vulvar area, 90% of EPMD cases are primary, presenting with only intraepithelial neoplasia, and have an "excellent" prognosis, he said. Primary EPMD arises in the epidermis and does not extend into the surrounding dermis; biopsies show little (1 mm or less) or no invasion, and positive nodes or metastases are rare. (About 15% of patients with primary disease have microscopic invasion, measuring 1 mm or less).

But the prognosis is poor for those with primary disease with a deeper invasion and patients with secondary EPMD. Secondary EPMD arises from within the apocrine gland and grows for a long time, or occurs when the same or similar cells from underlying adenocarcinoma in the genitourinary or GI tract migrate upward.

Historically, the treatment of choice for EPMD has been local excision, but recurrence rates are high: For a patient with primary EPMD, with little (1 mm or less) or no invasion, the recurrence rate after a wide local excision is 35%, Dr. Lynch said.

With invasion or secondary disease, the recurrence rate is 65%, he added, noting that even after a radical vulvectomy, the recurrence rate is about 20%.

Clinical margins are not that helpful because the lesions extend beyond the visible surface. The literature currently calls for 5-cm margins, but even with Mohs micrographic surgery, recurrence rates range from 20% to 30%.

Because patients with primary in situ disease appear to have an extremely low risk of developing an associated underlying malignancy, nonexcisional treatments, such as lasers, radiotherapy, electrosurgery, photodynamic therapy or 5-fluorouracil, can be used when there is no invasion. These approaches can also be used to treat local recurrences, which usually are due to in situ disease, he said. ■