Vulvar Carcinoma in a 12-Year-Old Girl With Vertically Acquired Human Immunodeficiency Virus Infection

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ABSTRACT. We report the first case of a girl with vertically acquired human immunodeficiency virus (HIV) infection, who developed invasive squamous cell carcinoma of the vulva at 12 years of age. Lesions resembling Bowenoid papulosis covered the perianal area as well. She underwent a nonmutating surgical excision of the infiltrating lesion. More than 3 years later, her clinical condition is excellent, although dysplastic, noninfiltrating multifocal lesions persist. This case highlights the need to perform careful periodic genital examinations in all HIV-infected children and adolescents born to HIV-positive mothers. Pediatrics 2000;106(4).

ABBREVIATIONS. HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; SCC, squamous cell carcinoma; CIS, carcinoma in situ; HPV, human papillomavirus; VIN, vulvar intraepithelial neoplasia.

Findings of the European Collaborative Study and the French Perinatal Study show that 50% of HIV-infected children live >9 years. Combination therapy has further decreased the progression rate, and by 6 years of age >90% of these children are still alive, as reported by the Pediatric European Network Treatment AIDS; the disease spectrum in these long-term survivors is not yet well established.

In adult patients, invasive cervical cancer has been an acquired immunodeficiency syndrome (AIDS)-defining condition since 1993; interestingly, a higher risk has been demonstrated in Europe, but not in the United States, Africa, and Australia. HIV-infected women may also be at higher risk for developing vulvar cancer, because this carcinoma is more common in immunosuppressed patients than in immunocompetent controls. Over the last few years, invasive vulvar carcinoma has been reported in 4 women (>25 years old) with HIV infection. We describe the case of a 12-year-old girl with vertically acquired HIV infection who developed an invasive squamous cell carcinoma (SCC) of the vulva.

CASE REPORT

A white female, born in November 1983 to an HIV-positive drug-user mother, was completely asymptomatic at birth and her growth was normal. HIV infection was diagnosed in 1985 by HIV isolation from peripheral blood mononuclear cells and persistence of HIV-specific antibodies.

At 5 years of age, she was referred to our Pediatrics Department and has since been followed-up regularly every 3 months with clinical and laboratory investigations. Until June 1996 (151 months of age), her clinical history was negative except for diffuse lymphadenopathy; she never developed any symptoms. According to the classification of the Centers for Disease Control and Prevention, she was considered to be in the A category (mild symptoms). Until June 1994 (127 months of age), the total CD4 count was always above 400 cells/mm³ (>20%), and antiretroviral therapy was initiated only in March 1996 (148 months of age). CD4 cell counts, viral load, and antiretroviral therapy are reported in Fig 1 (fluctuations are attributable to poor compliance).

In February 1996, she had her first menstrual period, but she never underwent a gynecologic examination. In July 1996, she complained of mild vulvar discomfort related to a mass on the left side of the vulva. Physical examination revealed a vegetating neoplasia (3 cm in diameter), which involved the left labia majora and minora, and a smaller vegetating neof ormation over the prepuce of the clitoris. The upper-right hemivulva and the anal area were covered by lesions resembling Bowenoid papulosis; the left inguinal lymph nodes were slightly enlarged. A biopsy of the vegetating mass revealed SCC. Psychological services provided by our department for all HIV-infected children and adolescents did not reveal evidence of sexual abuse, but we cannot rule it out completely.

Surgical treatment personalized to the patient’s young age involved radical resection of the infiltrating lesion. If consisted of a left hemivulvectomy, partial resection of the right hemivulva, amputation of the clitoris, and bilateral inguinal lymphadenectomy. Histologic examination disclosed a well-differentiated SCC with a very high mitotic index in the vegetating mass, a carcinoma in situ (CIS) in the surrounding area of the left hemivulva, and an infiltrating SCC (1–2 mm) in the right hemivulva; all inguinal lymph nodes were negative for metastases. The patient was, therefore, classified as stage II (T2 N0 M0). The postoperative period was uneventful except for hyperpyrexia for 3 days, which resolved after high-dose antibacterial and antifungal therapy, and the patient was discharged 10 days after surgery.

Human papillomavirus (HPV) type 16 DNA sequences were found in the SCC and CIS samples by means of polymerase chain reaction under stringent conditions with type-specific primers and H16L1 and H16R3 (Censet SA, Paris, France), which amplify a 323-base pair fragment in the E6 open-reading frame (nucleotide positions 201–523). HPV 16 is one of the >80 types identified to date and is the most commonly associated with cervical, vulvar, and anal carcinomas.

Gynecologic follow-up visits were performed every 4 months. In November 1996, perineal and vulvar biopsies revealed CIS and koilocytosis of the epithelium. HPV 16 sequences were detected in vaginal, vulvar, and perianal exfoliated cells. Laser vaporization was performed on the residual right major labium, followed by...
local applications of interferon-β for 2 months. Laser vaporization was not successful and was discontinued. Topical interferon-β therapy obtained some macroscopic improvement and, to date, has been repeated for a total of 4 cycles. In April 1997, anoscopy and rectoscopy disclosed a normal macroscopic appearance; histologic examinations showed chronic inflammation of the mucosa, CIS of the perianal area, and CIS of the right labium; the residual vulva showed a bowenoid aspect, cytologically diagnosed as vulvar intraepithelial neoplasia grade 3 (VIN 3). A biopsy confirmed the cytologic diagnosis. The term VIN indicates a proliferative intraepithelial squamous lesion displaying abnormal maturation, nuclear enlargement, and atypia; grading depends on the extent of epithelium replacement by abnormal cells. VIN is found adjacent to invasive carcinoma in 25% of cases; in younger women this figure can reach 80%.12

In November 1997 (168 months of age), a Papanicolaou smear showed low-grade squamous intraepithelial lesion; all subsequent follow-up visits showed the persistence of VIN 2 through 3 and CIS of the perineum and of HPV 16 infection. The multifocal intraepithelial lesions have been managed so far only with strict clinical and cytological follow-up and periodic biopsies. The last follow-up visit was in February 2000 (195 months of age), 3 years after surgery. At this writing, the patient’s overall clinical condition is excellent; she has not developed any HIV-related symptoms or opportunistic infections, and her growth is normal.

DISCUSSION

Invasive SCC of the vulva is an uncommon disease that develops in older women and is rarely observed in women younger than 30 years of age.13 Women who are immunosuppressed because of HIV infection have a high prevalence of multicentric lower genital tract intraepithelial neoplasia and HPV infection and respond poorly to conventional treatment. An aggressive course also characterized 2 of the 4 cases of invasive vulvar carcinoma described in HIV-infected women; they died 9 and 11 months after diagnosis, respectively, attributable to tumor progression.7–9

Our patient acquired HIV infection vertically from her mother; however, she never lived with her mother, whose gynecologic history is not available. The patient has never had sexual intercourse. Regardless of her HIV infection status, she is the youngest person with invasive vulvar carcinoma described to date. The 4 reported cases of HIV-related invasive vulvar carcinoma7–9 have some important characteristics in common: moderate immunosuppression (CD4+ range: 302–735 cells/mm3), a previous history of VIN, the presence of HPV sequences, and an aggressive course in the 2 patients under 35 years of age. Unlike these cases, our patient acquired both HIV and HPV infections through a nonsexual route; however, although vertical transmission of HIV was documented, it is the only likely explanation for HPV at present. Although the predominant mode of HPV transmission is through sexual contact, vertical transmission is another (and indeed highly debated) mode of infection.

Despite her young age and the multicentric squamous neoplasia (vulva, perineum, and perianal region), our patient is showing a stable clinical course. The bowenoid lesions were present when the invasive lesion was diagnosed and treated and, to date, have been managed by a conservative, observational approach; indeed, at >3 years of follow-up, progression to invasion has not occurred at any site. This good short-term outcome might be related to her condition before development of the vulvar carcinoma, which typified a long-term survivor as well.

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Fig 1. Plasma HIV-1 RNA (expressed as log10) and CD4+ cell counts in sequential samples (girl's age is indicated at the bottom); arrows refer to the time of antiretroviral therapy and appearance of the symptoms related to the vulvar carcinoma. ddI indicates didanosine; 3TC, lamivudine; ZDV, zidovudine; INV, indinavir; D4t, stavudine; RTV, ritonavir; ABC, abacavir; NFV, nelfinavir.
as her moderate response to antiretroviral therapy (despite some problems of compliance) with no intercurrent opportunistic infections.

These considerations suggest that a delay in the progression of HIV disease might be associated with a slower progression of the SCC. Because of her young age, the surgical approach was conservative and nonaggressive. The present stability of her clinical condition, in contrast with her high viral load levels and low CD4 counts, now poses the problem of how to manage the large areas of VIN 3: will a strict follow-up be sufficient, or, alternatively, is a more aggressive approach needed?

With improved management and longer survival of children with vertically acquired HIV infection, the incidence of malignancies in adolescents with AIDS will possibly increase, and the spectrum of HIV disease in such patients will become more similar to that of adult cases.

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