

Rapidly progressive high-grade cervical intraepithelial neoplasia in a Hodgkin lymphoma patient. A case report

Abstract

The progressive behavior of human papillomavirus (HPV) associated neoplasia in immunosuppressed patients has been clearly demonstrated. Hodgkin's disease and its treatment render a patient highly susceptible to persistent HPV and its consequences, thus requiring a more aggressive treatment and a closer follow-up protocol. We present the case of a 41-years old patient diagnosed with nodular sclerosing Hodgkin lymphoma receiving radiochemotherapy regimen. After having completed the oncologic therapy the patient was addressed to our clinic presenting abnormal uterine bleeding; a HPV 16-positive high-grade cervical intraepithelial neoplasia diagnosis was established. We obtained persistent disease after conservative treatment which finally leads us to performing a total hysterectomy. We observed a rapidly progressive course of high-grade HPV-induced neoplasia in a case of Hodgkin's disease patient which may represent an accelerated version of untreated neoplasia in the immunocompetent. Screening and prompt treatment are of utmost importance in this group at risk.

Keywords: lymphoma, human papillomavirus, cervical neoplasia

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Introduction

Lower genital neoplasia occurs more frequently in immunosuppressed women than in the general population^(1,2). The most likely mechanism for this association is the inability of the immunocompromised patients to clear human papillomavirus (HPV), increasing susceptibility to HPV and oncogenicity. In human immunodeficiency virus (HIV)-infected women, the prevalence of cervical HPV infection ranged from two to four times greater than the one observed in HIV-uninfected control women⁽³⁾; furthermore, in the United States, the RR for invasive cervical cancer in women HIV positive/acquired immunodeficiency syndrome compared to the women in the general population is 5.4 (95% CI= 3.9 to 7.2)⁽⁴⁾.

There is also increasing evidence that the incidence of cervical intraepithelial neoplasia (CIN) is higher in female renal transplants recipients⁽⁵⁾, in those taking immunosuppressive drugs, especially cyclophosphamide and in women with systemic lupus erythematosus^(6,7). The role of immunosuppression as a risk factor for the development of HPV-induced lesions in patients with Hodgkin's disease has also been a subject of interest, as it is widely known the association between lymphomas and the risk of second malignancies, especially acute myeloid leukaemia⁽⁸⁾.

Case Report

We present the case of a 41-years old patient, gravida 3, para 0, abortus 3 who was diagnosed with nodular sclerosing Hodgkin's disease stage II A (The Ann Arbor Staging System). The patient obstetrical history revealed 3 first-trimester spontaneous abortions (i.e. at the ages 24-30 years old) for which the patient performed no medical investigation. From the family history we emphasize one case of fatal Hodgkin lymphoma in a first degree relative (i.e. father).

After a complete evaluation, the patient received chemotherapy followed by thoracic radiotherapy. The chemotherapy regimen included doxorubicin, bleomycin, vinblastine and dacarbazine. During the follow-up protocol (comprising of complete blood count, erythrocyte sedimentation rate, chemistry studies, computed tomography scan of the chest, abdomen and pelvis and positron emission tomography scan), the patient was declared to be in remission.

Four years after having completed the oncologic therapy, the patient was referred to our clinic presenting abnormal uterine bleeding. An initial evaluation was performed including clinical examination, transvaginal ultrasound, Pap examination (liquid based cytology) and a HPV test. The results revealed high-grade squamous intraepithelial lesion (HSIL, Bethesda System Termi-

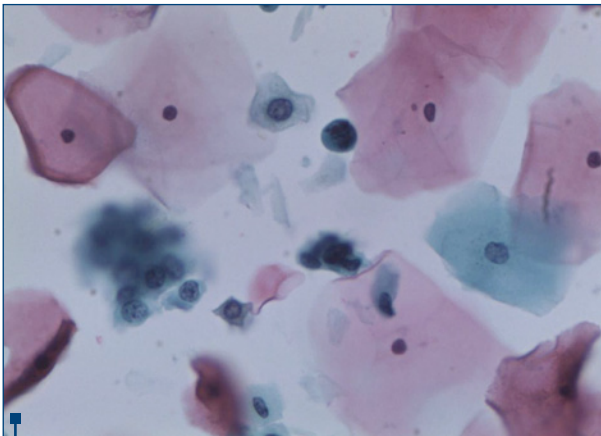


Figure 1. HSIL cytology report

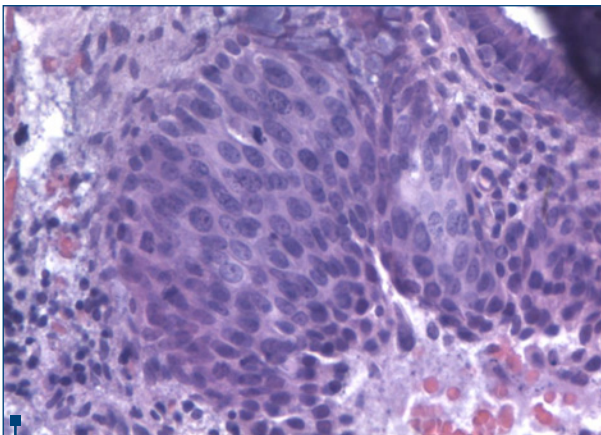


Figure 2. High-grade cervical intraepithelial neoplasia (LEEP specimen)

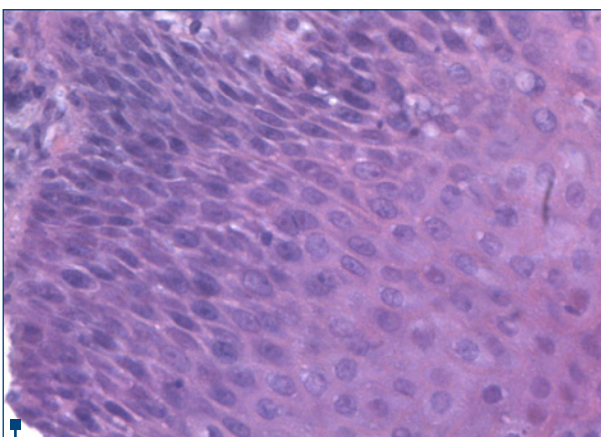


Figure 3. Low-grade cervical intraepithelial neoplasia (hysterectomy specimen)

nology) and cervical HPV 16 positive (Figure 1). We decided to use the “see and treat” approach (without prior colpo-biopsy confirmation of a high grade lesion): we performed a loop electrosurgical excision of the transformation zone (LEEP). Nevertheless, colposcopy was

realized prior to the intervention to tailor the excision to the size of the lesion and the limits of the transformation zone. An informed consent according to the World Medical Association Declaration of Helsinki regarding both colposcopy and LEEP procedure was obtained. The LEEP specimen was removed, formalin fixed and sent for histologic evaluation in the Department of Pathology of our hospital where it was paraffin embedded and the slides obtained hematoxylin-eosin stained. Diagnosis of dysplasia was made according to the World Health Organization Classification of Tumors: benign (including cervicitis, cervical papilloma, flat/exophytic condyloma), CIN1/2/3, microinvasive carcinoma and the surgical status of the margins was also described⁽⁹⁾. The histological result of the specimen obtained was CIN3 with immunohistological staining confirmation of the diagnosis: ki67, p16 and p63 positive.

The follow-up after LEEP was uneventful, the patient recovered well without any complications. Yet, the Pap smear obtained 6 months after the procedure revealed a HSIL result. Colposcopy was performed and showed a densely aceto-white lesion on the posterior cervical lip with coarse punctation and mosaic vessels and with the corresponding yellow color following application of Lugol’s iodine solution.

In consequence, a re-excision (i.e. LEEP conization) was performed in the operating theater under general intravenous anesthesia and the pathological final diagnosis reported high-grade cervical intraepithelial neoplasia with both exocervical and endocervical involvement (Figure 2).

The same follow-up protocol was used and again at the 6 months post-procedure evaluation we performed a Pap test and also an HPV test. The results proved to show persistent cervical dysplasia: HSIL Pap report and HPV 16 positive.

Having discussed with the patient about the possible further therapeutic approaches in this case, she expressed her firm desire for a radical treatment consisting of total hysterectomy although her childbearing had not been completed. The patient signed an informed consent and a total abdominal hysterectomy was performed under spinal anesthesia. The pathological examination of the specimens (uterus and cervix) revealed low-grade cervical intraepithelial neoplasia with koilocytes and frequent mitoses in the lower third of the epithelial layer and no glandular involvement (Figure 3). The patient made an uneventful recovery and was discharged home on the third post-operative day.

The patient was offered follow-up cytology every 6 months after hysterectomy together with a thorough clinical examination; up until the present moment two tests were obtained showing normal/negative reports. The patient also continues with the oncologic yearly follow-up protocol.

Discussion

The association between Hodgkin lymphoma and CIN has been stated in clinical studies published more

than 20 years ago^(10,11). Sillman et al. found that in more than half of the immunosuppressed patients the cervical neoplasia was unusually aggressive and in one case, progressed to invasive cancer in spite of multiple surgical interventions. Katz et al.⁽¹⁰⁾ showed that 45.9% of the 85 women with Hodgkin's lymphoma who had a gynecologic examination showed evidence of condyloma, dysplasia or carcinoma of the cervix or anogenital region.

According to a number of studies^(8,3), immunosuppressed individuals have an increased incidence of both viral infections and malignant disease. Furthermore, we now know that HPV have evolved immune evasion strategies that allow them to cause persistent lesions⁽¹²⁾. These viruses activate the cell cycle as the infected epithelial cell differentiates in order to create a replication competent environment that allows viral genome amplification and packaging into infectious particles. This is mediated by the viral E6, E7 and E5 proteins. In cases of immunosuppressive status, HPV infections are significantly more likely to be persistent and the prevalence and severity of HPV-associated lesions, including CIN is higher⁽³⁾. The risk for developing both HPV infections and CIN increases as immunosuppression levels increases⁽¹³⁾.

The increased prevalence of CIN in lymphoma patients is in agreement with the increase in other malignancies seen in these patients⁽⁸⁾. Patients receiving chemotherapy tend to have more extensive disease so that the apparent association between CIN and chemotherapy may be due to the immunosuppressive effects of the disease rather than the effects of chemotherapy.

In our case, the patient was found to be HPV 16 positive. It is well known that HPV 16 is likely to persist and to cause neoplastic progression when it persists, marking it a remarkably powerful human carcinogen⁽¹⁴⁾. The low level presentation of viral antigens, in conjunction with active immune evasion strategies and the absence of inflammation, is thought to favor immune tolerance rather than an effector T cell response able to clear disease⁽¹²⁾. Immunosuppression due to the lymphoid malignancy and also chemotherapy may enhance this immune tolerance and thus lead to HPV persistence and development of cervical neoplasia. Nonetheless, other factors including age at first sexual intercourse, the number of lifetime sexual partners, smoking and genetic factors are likely to be implicated⁽¹⁴⁾.

We cannot predict what prognosis would the high-grade cervical dysplastic lesion have in our patient should we have chosen a third conservative therapeutic approach. We intend to discontinue cytology screening following three documented, consecutive, satisfactory normal/negative vaginal cytology tests and no abnormal/positive cytology tests achieved within an 18- to 24-month period following hysterectomy, as The American Cancer Society recommends⁽¹⁵⁾.

Conclusions

Taking into account the increased potential of high-risk HPV persistence and HPV-induced cervical neoplastic lesions in immunosuppressed patients, including lymphoid malignancies, we emphasize the need for a close investigation and prompt therapy in these groups at risk. ■

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