Prognostic factors for the development of vaginal intraepithelial neoplasia

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Summary

Objective: To identify risk factors for the appearance of vaginal intraepithelial neoplasia (VAIN). *Material and methods:* A total of 485 women with abnormal cytologies were followed over three years (2003-2006). They underwent cytolology and colposcopy, and testing for human papillomavirus virus (HPV) infection. If the colposcopy was atypical, a biopsy was performed. *Results:* A total of 256 women were treated: 161 by cone biopsy, 103 by LLETZ, 12 by repeat conization, and 44 by total hysterectomy. In eight cases VAIN was diagnosed following hysterectomy. The average age at which VAIN appeared was 49.8 years (age range 39-61). Hysterectomy was indicated in two cases of cervical cancer, four cases of persistent high-grade cervical SIL, and two cases of recurrent high-grade cervical SIL. The mean time for the appearance of VAIN following hysterectomy was 3.8 years (range 1-9 years). Of these eight women, seven had HPV infections at high risk for carcinogenesis. *Conclusions:* Long-term follow-up cytology is necessary for women treated for high-grade SIL, even after hysterectomy, because of the increased risk of a primary vaginal VAIN lesion, especially in women with high-risk HPV infection.

Key words: Vaginal intraepithelial neoplasia; Human papillomavirus; Cervical SIL.

Introduction

Vaginal intraepithelial neoplasia (VAIN) is rare disorder of the lower genital tract in contrast to cervical intraepithelial neoplasia (CIN). VAIN represents only 1% of all intraepithelial neoplasias of the lower genital tract [1, 2]. The etiopathology of both types of lesions, along with that of vulvar intraepithelial neoplasia (VIN), is closely linked to human papillomavirus (HPV) infection [3]. It is known that although the cervix is the site most frequently affected by HPV infection due to the histological characteristics of the epithelium, the infection is multicentric, simultaneously affecting the cervix, the vulva and the vagina, in this order of frequency [4].

As the vagina is less frequently involved, cytology screening to detect vaginal pathology in women who have undergone hysterectomy is less frequently performed than cervical cytology screening. The American College of Obstetricians and Gynecologists recommends periodic follow-up vaginal cytology in women who present risk factors, but without establishing what those risk factors are or at what intervals cytology should be repeated [5].

This prospective study attempts to determine the factors that place women at risk of developing VAIN.

Material and Methods

This was a prospective study carried out between 2003 and 2006 in which 485 women followed for abnormal cytology were followed. In all cases the women underwent colposcopy and genotyping of HPV using a microarray-based method. In cases of atypical colposcopy, a colposcopically guided punch biopsy was also performed.

In this study, the frequency of the appearance of VAIN was analyzed, focusing on those women who required hysterectomy. VAIN was diagnosed cytologically, and the diagnosis was subsequently confirmed by colposcopically directed punch biopsy.

Risk factors for VAIN presented by the women who had undergone hysterectomies were analyzed, with special attention to HPV infection and its different genotypes. Subsequently, the women diagnosed with VAIN and HPV infection were compared with the total sample.

Results

Of the 485 women included in the study, 316 were diagnosed with HPV infection (65%). The most frequent reason for medical consultation was cytological diagnosis of high-grade squamous intraepithelial lesions (SIL) in 200 women (41.1%) followed by low-grade SIL in 160 cases (32.9%). The remaining cytological diagnoses were ASCUS, AGUS, and cases suggestive of carcinoma.

Of the women with a cytological diagnosis of high-grade SIL, 86.5% presented HPV infection as compared with 65% of the women with low-grade SIL.

The most frequently observed colposcopy result was leukoplasia (91 cases), followed by punctation (51 cases).

Colposcopically guided biopsy confirmed the presence of high-grade SIL diagnosed cytologically in 84 women (42%), and cervical cancer in seven cases (3.5%).

In women with low-grade SIL diagnosed cytologically, colposcopically guided biopsy identified low-grade SIL in 53 cases (33.1%), and high-grade SIL in 12 cases (7.5%).

Of the total number of women followed in this study, 256 were treated; 161 by cone biopsy, 103 by LLETZ, 12

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by repeat conization, and 44 by hysterectomy. Some of the women were treated by more than one type of procedure. In 36 of the 44 cases requiring hysterectomy, a previous conization for high-grade SIL had been performed, and the indication for hysterectomy was persistent or recurrent disease. In the eight remaining cases, the indication for hysterectomy was cervical cancer.

Of the 44 women who underwent hysterectomy, eight subsequently presented a vaginal lesion (18%). The indications for hysterectomy were as follows: cervical cancer (2 cases); persistent high-grade SIL following conization, with the lesion being detected within the year following the procedure (4 cases); and recurrent high-grade SIL in which the lesion reappeared more than a year following treatment (2 cases).

The mean age of the women who presented VAIN was 49.8 years (age range 39-57 years).

The average time elapsed between hysterectomy and the appearance of VAIN was 3.8 years (range 1-9 years). In all cases, the diagnosis was made cytologically and subsequently confirmed by colposcopy and guided biopsy, and the colposcopic image was leukoplasia located in the vaginal cupula. The histologic diagnosis of the colposcopically guided biopsy was VAIN I in three cases, VAIN II in one case, and VAIN III in four cases.

Of the eight women with VAIN, seven (87.5%) had HPV infection with a high-risk genotype for carcinogenesis. In three cases it was possible to isolate two different genotypes. The most frequently isolated HPV genotypes were types 51 and 53 (Table 1).

The presence of HPV infection in women with VAIN was similar to that observed in women presenting high-grade cervical SIL (87.5% and 86.5%, respectively).

Treatment of the women with VAIN III was carried out by partial colpectomy of the vaginal cuff. In three cases the lesion was confirmed, and in one case the result was negative.

Table 1. — *HPV genotypes isolated in patients with VAIN.*

Case	HPV genotypes
1	51/56
2	53/35
3	51
4	16
5	53
6	51
7	66/70

No HPV infection was detected in one case.

Table 2. — *Risk factors for the development of VAIN.*

VAIN risk factors
Abnormal cytology*
History of CIN*
History of cervical cancer*
Condylomas
Vaginal radiotherapy*
Inmunosuppression
Low level of education
Low social class

* Risk factors found in the 8 women with VAIN in the study group.

Discussion

VAIN is the least frequent type of intraepithelial neoplasia of the lower genital tract [1]. Although it is possible to diagnose primary VAIN, or to diagnose it in conjunction with cervical intraepithelial neoplasia (CIN) or vulvar intraepithelial neoplasia (VIN), it is usually diagnosed in women who have previously undergone hysterectomy.

In a study analyzing the incidence of VAIN in a given population, 0.6% of all cytologies performed yielded a diagnosis of VAIN [1]. In our study, since the population was selected for abnormal cytology results, the VAIN diagnosis rate was just over 1%.

VAIN diagnoses among women who have undergone hysterectomy correspond to 70% of all VAIN diagnoses [1]. If we consider only women with previous hysterectomies, the incidence of VAIN depends on the indication for hysterectomy. Women with previous hysterectomies for CIN account for 87% of VAIN diagnoses, and women who underwent hysterectomy for benign pathology of the uterus account for 13% of VAIN diagnoses [1].

The percentage of VAIN diagnoses in women with previous hysterectomies for CIN varies between 1% and 6% [6, 7]. In this study, it was slightly over 16.6%. It should be emphasized that we were extremely conservative, performing 12 repeat conizations in cases of persistent CIN III instead of hysterectomy. In this study as well as others, these percentages may be influenced by the number of hysterectomies performed for CIN [6, 7]. Other indications for hysterectomy that lead to higher risk for detection of VAIN in follow-up may be cervical cancer [8], of which there were two cases in our study.

The average age at appearance of VAIN varies between 57 and 58 years in different studies [9, 10]. In this study, it was 49 years (age range 39-57 years).

Several risk factors that may influence the development of VAIN have been described in the literature [10, 11] (Table 2). Among these, a history of hysterectomy for cervical cancer and CIN, vaginal radiotherapy, and HPV infection, especially by high-risk genotypes. In this study, as shown in Table 2, several of these risk factors were present.

The HPV genotypes most frequently involved in VAIN are usually 16 and 18 [3, 11]. In this study, the most frequently isolated genotypes were 51 and 53 (Table 1).

The definitive diagnosis is attained by biopsy, since the initial diagnosis is cytological. VAIN is usually located in the upper third of the vagina [9, 12] and the lesion usually presents as a leukoplasic area [1], which was true in all the cases in this study.

The time elapsed between hysterectomy and the appearance of VAIN varies between one and nine years [1, 9, 13]. In this study, the mean was 3.8 years (range 1-9 years).

The recommended treatment for VAIN is surgical, based on excision or destruction techniques. Excision is recommended because it makes it possible both to confirm the lesion and to rule out the presence of invasive disease [10]. The most frequent complication [10] is

excessive bleeding (10%), which was observed in one case in this study. In 22% of cases [10] histologic study of the vaginal cuff was negative, as found in one case in our study.

In conclusion, it should be stressed that it is important to continue long-term follow-up vaginal cytology for women who have undergone hysterectomy for CIN for a period of at least five years (the average time during which VAIN may appear following hysterectomy). Detection of HPV in these women may be of value in identifying those who are at greater risk of developing VAIN. In our view, women infected with a high-risk HPV genotype should continue to have follow-up cytologies and colposcopies until the infection disappears.

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References

[1] Murta E.F., Neves Junior M.A., Sempionato L.R., Costa M.C., Maluf P.J.: "Vaginal intraepithelial neoplasia: clinical-therapeutic analysis of 33 cases". *Arch. Gynecol. Obstet*., 2005, *272*, 261.

[2] Sillman F.H., Sedlis A., Boyce J.G.: "A review of lower genital intraepithelial neoplasia and the use of topical5-fluorouracil". *Obstet. Gynecol. Surv.,* 1985, *40,* 190.

[3] Barzon L., Pizzighella S., Corti L., Mengoli C., Palu G.: "Vaginal dysplastic lesions in women with hysterectomy and receiving radiotherapy are linked to high-risk human papillomavirus". *J. Med. Virol.,* 2002, *67,* 401.

[4] Ait Menguellet S., Collinet P., Debarge V.H., Nayama M., Vinatier D., Leroy J.L.: "Management of multicentric lesions of the lower tract". *Eur. J. Gynecol. Reprod. Biol*., 2006, May 17 (Epub ahead of print).

[5] American College Obstetricians and Gynecologists Cervical cytology:"Evaluation and management of abnormalities". Washington, American College of Obstetricians and Gynecologists, ACOG Tech. Bull. Aug., 1993, No. 183.

[6] Wade-Evans: "The aetiology and pathology of cancer of the vagina". *Clin. Obstet. Gynecol*., 1976, *3*, 229.

[7] Lee R.A., Symmonds R.E.: "Recurrent carcinoma in situ of the vagina in patients previously treated for in situ carcinoma of the cervix". *Obstet. Gynecol*., 1984, *48*, 61.

[8] Hoffman M.S., Roberts W.S., LaPolla J.P., Sterghos S., Cavanagh D.: "Neoplasia in vaginal cuff epithelial inclusion cysts after hysterectomy". *J. Reprod. Med.,* 1989, *34,* 412.

[9] Kalogirou D., Antoniou G., Karakitsos P., Botsis D., Papadimitriou A., Giannikos L.: "Vaginal intraepithelial neoplasia (VAIN) following hysterectomy in patients treated for carcinoma in situ of the cervix". *Eur. J. Gynaecol. Oncol.,* 1997, *18,* 188.

[10] Indermaur M.D., Martino M.A., Fiorica J.V., Roberts W.S., Hoffman M.S.: "Upper vaginectomy for the treatment of vaginal intraepithelial neoplasia". *Am. J. Obstet. Gynecol*., 2005, *193,* 577.

[11] Frega A., French D., Piazze J., Cerekja A., Vetrano G., Moscarini M.: "Prediction of persistent vaginal intraepithelial neoplasia in previous hysterectomized women by high-risk HPV DNA detection". *Cancer Lett.,* 2006, Oct. 27 (Epub ahead of print).

[12] Indraccolo U., Del Frate E., Cenci S., Ubertosi M., Donati Sarti R., Donati Sarti C., Baldoni A.: "Vaginal intraepithelial neoplasia and human papillomavirus infection: A report of 75 cases". *Minerva Ginecol*., 2006, *58,* 101.

[13] Ruiz-Moreno J.A., García-Gómez R., Vargas-Solano A., Alonso P.: "Vaginal intraepithelial neoplasia. Report of 14 cases". *Int. J. Gynaecol. Obstet.,* 1987, *25*, 359.

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