Does vaginal intraepithelial neoplasia have the same evolution as cervical intraepithelial neoplasia?

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Summary

Background: Vaginal intraepithelial neoplasia is a little known disease which could be related to risk factors different from simple HPV infections. *Objective*: To ascertain wheter vaginal lesions have a natural history similar to cervical lesions. *Materials & Methods*: A retrospective study to identify patients with vaginal lesions and synchronous cervical lesions through biopsy. The rate of mild cervical lesions (koilocytosis, warts, CIN I with and without koilocytosis) was compared with the rate of severe cervical lesions (CIN II and III, cervical carcinoma) in patients with mild vaginal lesions (warts and koilocytosis, and low-grade VAIN) and in patients with severe vaginal lesions (high-grade VAIN). Using koilocytosis as a marker, the rate of "active" cervical lesions was compared with the rate of "non active" cervical lesions in patients with "active" versus "non active" vaginal lesions. Finally, the rates of mild and severe cervical lesions were compared among each group of VAIN (low-grade, high-grade, with or without koilocytosis). *Results*: In patients with mild vaginal lesions, mild cervical lesions were significantly more frequent than severe cervical lesions. In patients with "active" vaginal lesions the rate of "active" cervical lesions was significantly higher than "non active" cervical lesions. The differences in rates of mild cervical lesions and severe cervical lesions among patients with high-grade VAIN and low-grade VAIN (with and without koilocytosis) were not significant. *Conclusion*: These data suggest that CIN and VAIN may have some common features in certain cases, i.e., if an HPV infection is proved.

Key words: VAIN; Koilocytosis; CIN.

Introduction

Vaginal intraepithelial neoplasia (VAIN) is a rare and little known disease which could be related to risk factors different from simple HPV infections [1-3]. Such behavior may reflect the intrinsic resistance of vaginal epithelium to HPV infection, leading to the rarity of VAIN developing. In two recent studies [4, 5], the presence of HPV, DNA has been reported to be integrated in the squamous cells of vaginal and vulvar lesions in some patients who had previously been treated for cervical dysplasia or squamous cervical carcinoma. Such studies suggest that multicentric cancerogenesis in the lower genital tract related to HPV infection may occur in a very similar way.

Under this hypothesis, we can research the features of syncronous HPV-related cervical lesions in patients with vaginal lesions to prove that the more severe the lesion in the cervix is, the more severe the lesion in the vagina is.

Materials and Methods

A retrospective study was carried out from 1999 to 2004. Out of 2,854 patients who had undergone colposcopy with vaginoscopy as follow-up because of a previous cervical dysplasia or an abnormal pap test, 240 directed vaginal biopsies were performed which turned out to be positive for viral infection with or without dysplasia. Colposcopic exams were performed after treatment for cervical-vaginal infection or estroprogestin treatment for postmenopausal dystrophy when necessary.

Vaginal biopsies were performed in abnormal colposcopic areas (i.e., lugol-negative areas as well). At the same time as the vaginal biopsies, cervical biopsies were taken if abnormal areas were seen. The worse colposcopic areas of both vaginal and cervical abnormal patterns were the preferred biopsy sites. In some cases multiple biopsies were taken. Vaginal specimens were distinguished according to the histologic criteria [6]: warts, koilocytosis, low-grade VAIN (VAIN I) with koilocytosis, low-grade VAIN without koilocytosis, high-grade VAIN (VAIN II and III) with koilocytosis, high-grade VAIN without koilocytosis. Cervical specimens were distinguished as cervical koilocytosis, low-grade CIN (CIN I, with and without koilocytosis), high-grade CIN (CIN II and III with and without koilocytosis) and cervical carcinoma. As reported for the cervix [7] koilocytosis was taken as a marker of "active" replication of HPV, and this feature was used to label cervical and vaginal lesions with an "active" production of viral particles.

Among all the vaginal lesions, patients with a previous total hysterectomy (13 cases), in which syncronous cervical lesions could not be assessed, were excluded. The remaining cases were assessed in the following way. First, the rate of mild cervical lesions (koilocytosis, warts, CIN I with and without koilocytosis) was compared with the rate of severe cervical lesions (CIN II and III, cervical carcinoma) in patients with vaginal warts and koilocytosis, patients with low-grade VAIN, and patients with high-grade VAIN. Second, the rate of "active" cervical lesions was compared with the rate of "non active" cervical lesions in patients with "active" and "non active" vaginal lesions. Third, the rate of mild cervical lesions and severe cervical lesions was compared in each group of VAIN.

Revised manuscript accepted for publication September 24, 2007

Statistical analysis was performed using the chi-square test and the Fisher's exact test, when indicated. To check the differences in age among the groups the Tukey-Kramer test was applied. A level of $\alpha \leq 0.05$ was determined as significant.

Results

After exclusion of the above-mentioned 13 cases, the remaining 227 vaginal lesions were divided in the following way: 93 koilocytosis (mean age 36.9, range 19-71), 16 warts (mean age 31.4, range 19-42), 56 low-grade VAIN with koilocytosis (mean age 34.8, range 25-62), 17 low-grade VAIN without koilocytosis (mean age 35.2, range 28-72), 19 high-grade VAIN with koilocytosis (mean age 32.6, range 21-46), 26 high-grade VAIN without koilocytosis (mean age 39.2 range 19-77). The mean ages of the subgroups of patients were not significantly different.

In patients with vaginal koilocytosis and warts, the rate of mild cervical lesions was 53.2% (58/109) and the rate of severe cervical lesions was 21.1% (23/109). This difference was significant ($p = 0.001$). In patients with low-grade VAIN (with and without koilocytosis), the rate of mild cervical lesions was 61.1% (44/73) and the rate of severe cervical lesions was 33.3% (14/73). This difference was also significant ($p = 0.001$). In patients with high-grade VAIN (with and without koilocytosis), the rate of mild cervical lesions was 42.2% (19/45) and the rate of severe cervical lesions was 44.4% (20/45), with no significant difference. Overall, an odds ratio (OR) of 2.592 (95% C.I. 1.29-5.22, $p = 0.011$) may be calculated for a severe cervical lesion in patients with vaginal dysplasia without koilocytosis.

In patients with "active" vaginal lesions (koilocytosis, warts, low-grade and high-grade VAIN with koilocytosis) the rate of "active" cervical lesions (warts, koilocytosis, low-grade and high-grade CIN with koilocytosis) was significantly higher than "non active" cervical lesions (107/184 vs 35/184, $p < 0.001$). This significance was not reached in patients without signs of "active" vaginal lesions ("active" cervical lesions: 14/43; "non active" cervical lesions 23/43; $p = 0.297$). Overall, an OR of 4.896 (95% C.I. 2.42-9.89; $p < 0.001$) may be calculated for a "non active" cervical lesion in a patient with a "non active" vaginal lesion and an OR of 2.88 (95% C.I. 1.43-5.81; $p = 0.004$) for an "active" cervical lesion in a patient with an "active" vaginal lesion. The differences of rates of mild severe cervical lesions among patients with high-grade VAIN and low-grade VAIN (with and without koilocytosis) were not significant. Just the rate of severe cervical lesions was significantly higher in patients with high-grade VAIN without koilocytosis as compared to patients with low-grade VAIN with koilocytosis (57.7% vs 21.4%, $p = 0.047$).

Discussion

The aim of this study was to ascertain if cervical and vaginal lesions which are HPV-related may have the same features, leading to the conclusion that VAIN may have a similar behavior as CIN. So far, a study on the natural history of VAIN (without any treatment) has been reported only by Aho *et al*. [8]. Their study on only a few cases reported a 9% invasion in six to nine years without a clear relationship with the grade of VAIN. Our results seem to suggest some common features of vaginal and cervical lesions in relation to the presence of koilocytosis and the severity of the dysplasia. However, the grade of VAIN may not be strongly linked with the severity of the cervical lesions, suggesting a different evolution in some cases. Such results are similar to those reported by Aho *et al*. [8], and may perhaps be related to the fact that VAIN is not a homogeneous entity, due to HPV infection, as is CIN. Therefore, the absence of koilocytosis may be a marker of worse prognosis. A diagnosis of koilocytosis is hardly reproducible [9], so that this method may be questionable as a reliable marker of "active" HPV infection. However, the presence of koilocytosis is an indication of infection with the production of a high number of viral copies [10], typically "active" infections, and it marks cervical lesions with a good prognosis [9]. This could explain why koilocytosis seems to be an unusual indication for both high-grade CIN and VAIN, where the viral DNA could be integrated and the infection could be "non active" (or "latent") [4-5, 11-13]. As shown in the cervix [11, 12], a latent infection is more dangerous than an active one and might lead to a worse prognosis of VAIN. Moreover, as the natural history of VAIN is not well defined we are not able to give any prognostic value to each vaginal dysplasia, especially where it is not clearly related to an HPV infection, which women can recover from. Thus the presence of koilocytosis could be encouraging even from this point of view.

An aspect of this work, which could be criticized, is that the sample size we have examined does not allow a strong statistical power. Consequently, the reported data are interesting if they are considered together with those by Vinokurova *et al*. [4] and by Hampl *et al*. [5], who provide a cytogenetic model of carcinogenesis HPV related to the female genital tract, but are inconclusive in weighing each risk factor for VAIN.

Conclusion

It seems that synchronous vaginal and cervical lesions have some common features that let us consider a common natural history from a synchronous HPV infection in some cases. Additionally, patients with VAIN and without koilocytosis have an OR of 2.6 to be affected by a severe cervical lesion (including a cervical cancer) at the same time without a relationship with the grade of VAIN. These data confirm those reported by Hampl *et al*. [5] and let us consider koilocytosis associated with vaginal dysplasia as a favorable prognostic factor as it is for CIN.

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