Epidemiological aspects of Vaginal Intraepithelial Neoplasia (VAIN)

D. MINUCCI - A. CINEL E. INSACCO - M. OSELLADORE

Summary: In order to evaluate the natural history of Vaginal Intraepithelial Neoplasia (VAIN), its epidemiological characteristics and the risk of its evolving into Invasive Carcinoma, we studied direct vaginal biopsies from 376 outpatients, we ascertained the predominant disease site and investigated whether the lesions (uni or multicentric) were only vaginal, were present at both the cervix and the vagina or were an extension of cervical lesions (DES-like areas). Moreover, in cervical and vaginal biopsies from 265 patients, we compared the severity of intraepithelial neoplasia of the vagina and cervix.

In our series, vaginal lesions accounted for over half (52.6%) of the alterations attributable to HPV infection, while VAIN accounted for 46.5%; in 84.8% of cases, VAIN was associated with HPV. In 49.8% of cases, biopsies were from the upper third of the vagina and in 74.8% the pathological areas involved both the cervix and the vagina.

The DES-like zone accounted for 7.9% of cases, vaginal wall involvement being limited to the upper third. Finally, the comparison of histological findings, in the 265 patients, confirmed that in 69.8% cases vaginal and cervical lesions were of the same grade; in 18.8% vaginal lesions were more severe than cervical lesions.

In our study a higher number of vaginal biopsies were taken than in previous years, and it is difficult to establish whether this depends on improved diagnostic methods or on changes in epithemiological factors, such as the reported increase in the incidence of HPV lesions. A systemic search for lesions and a study on their evolution are therefore required to clarify this aspect.

Key words: Vaginal intraepithelial neoplasia; Epidemiology.

INTRODUCTION

As yet little is known about the natural history of preinvasive vaginal lesions. Although squamous carcinoma of the vagina is rare, accounting for only 1 to 4% of all malignant diseases of the lower genital tract ([1]), the increasingly widespread application of improved cytological and colposcopic screening techniques has resulted in the identification of greater number of cases of vaginal intra-epithelial neoplasia (VAIN), whether single or associated with cervical (CIN) or vulvar lesions.

In 1959, Cromer and Newman ([2]) proposed the "organ system" concept for the perianal area, the vulva, the vagina and the uterine cervix in the study of the neoplastic potential of the genital tract, and in 1960 Marcus ([3]) formulated a similar concept. The few data available in literature, however, suggest that there is an important difference between the neopla-

Received 5-5-1994 from the
Dept. of Obstetrics and Gynecology
University of Padua (Italy)

Revised manuscript accepted for publication 20-6-1994.

stic potential in the vagina and that in the uterine cervix.

Cromer and Cutler (1974) were among the first authors to report on preinvasive vaginal lesions, findings that they accounted for 0.4% of all lesions of the genital tract ([4]).

Notwithstanding the lack of accurate data on the incidence of VAIN, and although these lesions are more frequent in women with a history positive for neoplastic intraepithelial or invasive cervical lesions ([5, 6, 7]), the incidence of carcinoma in situ in the vagina appears to be much lower than in the cervix: 0.2 and 36.4× 100,000 women respectively ([8]). Moreover, VAIN is found in older age groups than CIN ([9, 10, 11]), and this finding is in agreement with the observation that the mean age of subjects in the general population when invasive vaginal carcinoma is diagnosed, is about 10 years higher than that at diagnosis of cervical carcinoma ([12]).

The systematic detection of vaginal lesions (already undertaken for lesions of the cervix), would enable us to improve our understanding of their epidemiological characteristics and natural history, and this would in turn contribute to a better definition of the nature of the disease and its risk of evolution.

We therefore evaluated a series of women who referred to the Outpatients' Gynecological, Oncological and Cytodiagnostics Service of the Gynecologic and Obstetric Clinic of Padua University, where colposcopy is routinely extended to include the vaginal walls.

MATERIALS AND METHODS

Our series consisted of 376 patients who were referred to our Service from January 1983 to December 1990. All these patients underwent direct biopsies of the vagina indicated by a previous colpocytological and/or colposcopic evaluations (total: 426 samples). Fifty-nine had previous laparohysterectomy, 14 for benign and 45 for malignant disease.

The histological findings from the vaginal biopsies were classified on the basis of the histopathological criteria set out by Blaustein ([13]), as follows:

- cellular alterations associated with papilloma virus infection (HPV);
- Grade I intraepithelial vaginal neoplasias (VAIN I);
- Grade II intraepithelial vaginal neoplasias (VAIN II);
- Grade III intraepithelial vaginal neoplasias (VAIN III);
- invasive squamous carcinoma.

We ascertained the predominant site of the pathological areas by sub-dividing localizations into upper, mid and lower third lesions of the vaginal walls, and also by evaluating which lesions (multicentric or unicentric) were in an exclusively vaginal site and which, on the other hand, were present at both the cervix and the vagina, paying particular attention to vaginal lesions that at colposcopic examination appeared to be an extention of cervical lesions (DES-like areas).

We then evaluated the number of vaginal biopsies made annually with respect to those of the cervix and the incidence of vaginal lesions with respect to cervical lesions.

Moreover, in 265 patients from whom biopsies were taken both in the cervix and the vagina, we evaluated the severity of the intraepithelial neoplastic vaginal and cervical lesions, and ascertained whether they were associated with HPV infection.

To do this, we grouped our series following the Bethesda system ([14]), classifying squamous intraepithelial lesions (SIL) as low-grade or high-grade.

This classification, although cytological, is useful because it correlates cytological and histological findings using a diagnostic terminology equivalent to histopathological terminology, thus allowing an evaluation of the evolutive potential of intraepithelial lesions and, consequently, their prognosis.

RESULTS

In 1982 the percentage of vaginal biopsies, with respect to the percentage of cervical biopsies, was 11.8%; while in our histological series from 1983 to 1990 was it 27.4%. During this period we systematically used vaginal colposcopy and the VAIN/CIN ratio was 18.7%.

Table 1. – *Distribution of the histologic reports in the 426 biopsies of vagina.*

	No.	%
HPV	224	52.6
VAIN I	15	3.5
VAIN I+HPV	73	17.1
VAIN II	5	1.2
VAIN II+HPV	51	12.0
VAIN III	10	2.3
VAIN III+HPV	44	10.2
Inv. carcinoma	4	0.9
Tot.	426	

In our series of 376 women (total no. of biopsies 426), vaginal lesions (Table 1) accounted for over half (52.6%) of the alterations that could be referred to HPV infection, while vaginal intraepithelial neoplastic lesions (VAIN) accounted for 46.5%.

Of patients with VAIN, 44.5% (88/198) had grade I lesions, while 28.2% (56/198) had grade II lesions and 27.3% (54/198) had grade III lesions (Table 2).

In 84.8% of cases VAIN lesions were associated with HPV; this association (Table 3) ranged from 83.0% for grade I lesions to 81.5% for grade III lesions, reaching a maximum in grade II lesions: 91.0%.

The incidence of VAIN and HPV lesions were both higher in the 21 to 40 year age group (Fig. 1).

We also found four cases of invasive squamous carcinoma, in the vaginal vault, all in patients who underwent hysterectomy for cervical carcinoma, an operation

Table 2. – *Distribution of reports in relation to the histological grade and its association with HPV in the colposcopically directed biopsies.*

	No.	%
VAIN I	15	7.6
VAIN I+HPV	73	36.9
VAIN II	5	2.5
VAIN II+HPV	51	25.7
VAIN III	10	5.1
VAIN III+HPV	44	22.2
Tot.	198	

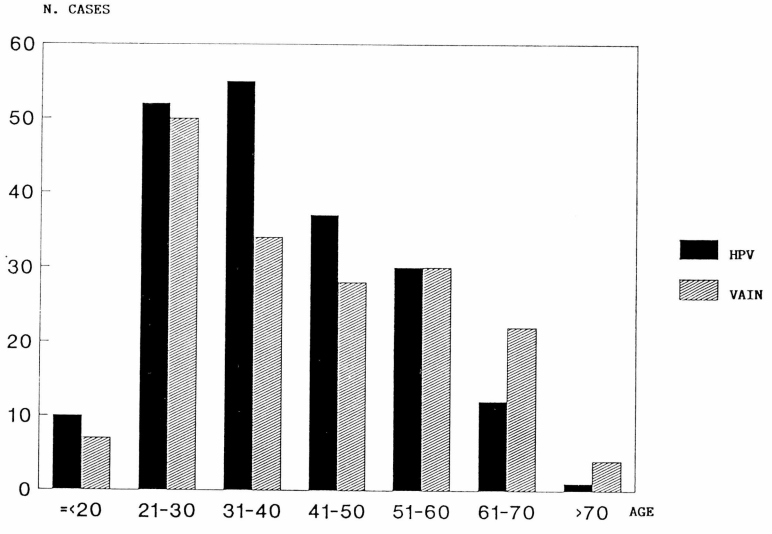

Fig. 1. — Age and vaginal lesions.

Table 3. – *Percentage of HPV lesions in the different grade of VAIN.*

	No.	with HPV	
		No.	%
VAIN I	88	73	83.0
VAIN II	56	51	91.0
VAIN III	54	44	81.5
Tot.	198	168	84.8

performed respectively 7 months, 20 months, 3 years and 7 years earlier.

Although most VAIN and HPV lesions (Table 4) were found in non-hysterectomized patients (317/376 cases), 8/175 (4.6%) cases of VAIN presented in patients who had undergone hysterectomy for benign disease, and of these five were high-grade lesions according to the Bethesda System (VAIN II - VAIN III). The incidence of VAIN lesions in patients hysterectomized for malignant disease was, however, 18.3% (32/175), and 16 of these patients had high grade lesions.

Forty-four patients (11.7%) underwent multiple vaginal biopsies because diseased areas with different characteristics were observed during colposcopy.

In 212 cases (49.8%) biopsies were taken from the upper third of the vagina, 195 (45.8%) at the mid third and in 19 (4.4%) the lower third (Table 5). In the patients from whom multiple biopsies were taken (Table 6), at colposcopy the lesions appeared multifocal, involving both the cervix and vagina (281 cases, 74.8%) or more than one area of the vagina (95 cases, 25.2%): 62 of the latter group had colposcopically different lesions, while 33 appeared the same.

When colposcopically evidenced lesions were considered, the diseased areas extending from the cervix to the vagina

Table 5. – *Site of vaginal lesions.*

Site	No.	%
Upper third	212	49.8
Mid third	195	45.8
Lower third	19	4.4
Tot.	426	

Table 6. – *Localization of colposcopical multifocal lesions in our series.*

		No.	%
Vaginal and cervical lesions		281	74.8
Only vaginal lesions	/ different findings	62	16.5
	\ same findings	33	8.7
	Total	376	

Table 4. – *Distribution of vaginal lesions in 376 patients with or without previous hysterectomy.*

	No hysterect. women		Hysterect. for Benign disease		Malign disease		Tot.
	No.	%	No.	%	No.	%	
HPV	182	48.4	6	1.5	9	2.3	197
VAIN I	8	2.1	1	0.2	6	1.5	15
VAIN I+HPV	50	13.2	2	0.5	10	2.6	62
VAIN II	2	0.5	1	0.2	1	0.2	4
VAIN II+HPV	45	12.0	2	0.5	3	0.7	50
VAIN III	2	0.5	–	–	3	0.7	5
VAIN III+HPV	28	7.4	2	0.5	9	2.3	39
INV. CARCINOMA	–	–	–	–	4	1.0	4
	317		14		45		376

Table 7. – *Comparison between cervical and vaginal histological findings in 265 patients according to the cytological criteria of the Bethesda System.*

	CERVIX			
	Negative and/or minor lesions	Low-grade SIL	High-grade SIL	Total
VAGINA				
Low-grade	16	**160**	30	206
SIL	6.0%	**60.0%**	11.4%	77.8%
High-grade	3	31	**25**	59
SIL	1.1%	11.7%	**9.4%**	22.2%
Total	19	191	55	265

(DES-like areas) accountfor 7.9% and in all cases vaginal wall involvement was limited to the upper third.

Finally, in 265 patients who underwent biopsy of the cervix and the vagina (70.4%) a comparison of histological findings, on the basis of the cytological Bethesda System, showed (Table 7) that: in 185 patients (69.8%) vaginal and cervical lesions were of the same grade; in 30 cases (11.4%) vaginal were less severe than cervical lesions; in 50 cases (18.8%) vaginal were more severe than cervical lesions.

The mean age of patients with intraepithelial vaginal lesions was 39.8 years (range 17 to 82 years) an age greater than that of the group with intraepithelial cervical neoplasia, which was 34.3 years ([15]).

DISCUSSION

Systematic colposcopy of the vaginal walls as well as the cervix during the period 1983 through 1990, enabled us to observe a high number of lesions: during this period, the percentage of vaginal biopsies was 27.4 in our histology unit, significantly higher than in previous years, when the examination was usually limited to the cervix, particularly when lesions were found in this area (11.8% in 1982).

How far the ratio increases depends on improved diagnostic methods and how far on changes in epidemiological factors, such as the reported increase in the incidence of HPV lesions ([16]), cannot be reliably ascertained on the basis of our findings or the few data available in literature.

This aspect is however still an interesting end-point for research as it would provide a better understanding of the carcinogenesis of epithelial squamous tumors of the female genitalia, also in view of the fact that increased incidence of "at risk" epithelial lesions, such as HPV-linked lesions and the so-called neoplastic intraepithelial lesions, does not at present seem to be confirmed in to our series; nor is a parallel increase reported in literature for the primary invasive forms.

The total number of higher-grade intraepithelial neoplasias was 54 (14.3%) against no cases of invasive, clearly primary, neoplasia.

The 20 to 40 year age group appears to have the highest incidence of cervical involvement but, importantly, when the lesions are considered separately, the percentages of VAIN II and III seem similar in the different age groups, while viral lesions are more common in women of 20 to 40 years of age.

This almost homogeneous distribution of high-grade lesions in the different age groups and the low percentage of invasive carcinomas, also found in women hysterectomized for cervical carcinoma may

indicate the slow evolution of these lesions in the vaginal tissue.

However, as already reported in the literature, we found a considerable age difference (12 years) between subjects with intra-epithelial and those with invasive forms. This difference is clearly of a greater statistical significance than that observed in cervical cases.

In almost all cases, moreover, the lesions were located in the upper and mid third of the vagina (49.8% and 45.8% respectively), and in 265 cases biopsies of the cervix were also taken.

These data appear to confirm the theory of Cromer and Newman ([8]) on the "organ system"; but findings indicate that they may depend more on a common susceptibility to noxae, as occurs in viral conditions, than on a common evolutive potential of the lesions.

The different embryologic origins of the vaginal epithelium, with borders varying from case to case, is probably one of the factors underlying the differences in the incidence and, above all, the evolution of the lesions observed.

The instability of the metaplastic squamous epithelium appears to be a ground favoring carcinogenesis: so much so that the invasive forms we encountered were all secondary to cervical neoplasias and localized in the vaginal vault. Likewise, most high-grade lesions in patients hysterectomized for malignant neoplasias were localized at the upper third of the vagina.

Coppleson observed "Mullerian" epithelia in the upper third of the vagina in 5-6% of women, and this findings, once attributed mainly to a DES effect, appears to be much more widespread than once believed ([17]).

In 7.9% of our patients, vaginal lesions were a continuation of cervical neoplasia.

Our findings therefore raise many issues having an important impact on clinical practice too, above all regarding the determination of the risk of preneoplastic and neoplastic intraepithelial lesions.

Probably a systemic search for lesions and the observation of their evolution will yield further information on this aspect.

REFERENCES

1) Di Saia P. J., Morrow C. P., Townsend D. E.: "Synopsis of Gynecologic Oncology", New York, John Wiley and Sons, 1975, p. 203.
2) Newman W., Cromer J. K.: *Surg. Gyn. and Obst.,* 1959, *108,* 273.
3) Marcus S. L.: "Multiple squamous cell carcinoma involving the cervix, vagina and vulva: the theory of multicentric origin". *Am. J. Obst. Gynecol.,* 1960, *80,* 802.
4) Oliver Joseph A. Jr.: "Severe dysplasia and carcinoma in situ of the vagina". *Am. J. Obst. Gyn.,* 1979, *134,* 133.
5) Petrilli E. S., Towsend D. E., Morrow C. P., Nakao C. Y.: "Vaginal intraepithelial neoplasia: biologic aspects and treatment with 5-Fluorouracil and the Carbon Dioxide Laser". *Am. J. Obst. Gyn.,* 1980, *138,* 321.
6) Fu and Regan: "Pathology of the uterine cervix, vagina and vulva". Bennington Ed., 1989.
7) Nwabinelli N. J., Monaghan J. M.: "Vaginal epithelial abnormalities in patients with CIN: clinical and pathological features and management". *Br. J. Obst. Gyn.,* 1991, *98,* 25.
8) Cramer D. W., Cutler S. J.: "Incidence and histopathology of malignancies of the female genital organs in the Unites States". *Am. J. Obst. Gyn.,* 1974, *118,* 443.
9) Gelhoed G. W., Henson D. E., Taylor P. T., Ketcham A. S.: "Carcinoma in situ of the vagina following treatment for carcinoma of the cervix: a distinctive clinical entity". *Am. J. Obst. Gyn.,* 1976, *124,* 510.
10) Lee R. A., Symmonds R. E.: "Recurrent carcinoma in situ of the vagina in patients previously treated for in situ carcinoma of the cervix". *Obst. Gyn.,* 1976, *48,* 61.
11) Aho M., Vesterinen E., Meyer B., Purola E., Paavonen J.: "Natural history of vaginal intraepithelial neoplasia". *Cancer,* 1991, *68,* 195.
12) Herman J. M., Homesly H. D., Dignan M. B.: "Is hysterectomy a risk factor for vaginal cancer?". *Jama,* 1986, *256,* 601.

13) Blaustein A., Sedlei A.: "Disease of the vagina". Blaustein A. ed. Pathology of female genital tract 1977, ed. 2, Berlin, Springer Verlag, 81-86.
14) The Bethesda System for reporting cervical/vaginal cytologic diagnosis. Developed and approved at the National Cancer Institute Workshop, Bethesda, Maryland, U.S.A., December 12-13, 1988. *Acta Cytol., 1989, 33,* 567.
15) Minucci D., Cinel A., Insacco E.: "Treatment with diathermic loop of CIN and HPV lesions: follow-up of 130 cases". *Eur. J. Gyn. Oncol.,* 1991, *XII,* 5.
16) Fuji T., Crum C. P., Winkles B., Fu Y. S., Richard R. M.: "Human papilloma virus infection and vaginal intraepithelial neoplasia. Histopathology and DNA content". *Obst. Gyn.,* 1984, *63,* 99.
17) Copplesson M., Pixley E., Reid B.: In: "Colposcopy". 1986, Thomas C. Ed.

Address reprint requests to:
D. MINUCCI
Via Pannonio, 8
35100 Padova (Italy)