Vulvar intraepithelial neoplasia

Epidemiological and clinical study of 45 cases

D. MINUCCI - A. CINEL - B. DE MATTEIS - G. LIBERO ONNIS
E. INSACCO - C. OUEDRAOGO

Summary: We observed 45 cases of Vulvar Intraepithelial Neoplasia (VIN) histologically diagnosed which came to our observation between 1986 and 1991.

The average age of the patients and the grade of the VIN lesions were evaluated.

We also examined the eventual association with Papillomavirus infection, with non-neoplastic epithelial disorders in the adjacent areas and with intraepithelial neoplasias of the cervix and/or the vagina (CIN and/or VAIN).

These data were studied in relation to the vulvoscopic pictures and symptomatology presented by the patients at the moment of diagnosis.

Intraepithelial neoplastic lesions of the squamous epithelium of the vulva are morphologically similar to those of the uterine cervix and the vagina (CIN and VAIN) ([1]).

Their biological behaviour is, however, very different: they have a greater evolutive tendency towards invasive forms at the cervical level than at the vaginal (at least in respect to the third lower) and vulvar levels.

From the results reported in recent studies it would appear that there has been an increase in the incidence of Vulvar Intraepithelial Neoplasia in vulvar invasive and pre-invasive neoplastic pathology: 18% in the year 1935-1950, 33% in 1951-1965 and 47% in 1935-1972 ([2]); also, according to other Authors ([3]), the incidence of Vulvar Intraepithelial Neoplasia has increased with respect to invasive carcinoma, passing from 21% in the years 1936-1950, to 47% in 1966-1972 and 57% in 1973-1976.

The epidemiological characteristics of the lesion also seem to have varied; whereas it was once diagnosed in women in higher age groups (about 60 years of age) ([4, 5, 6, 7]), today it is more commonly found in younger women (about 40 years) ([3]) and especially coinciding with the presence of viral aetiological agents (particularly the Papillomavirus) which could act as cofactors in carcinogenesis ([8]).

The aim of our study has been to assess our case records above all from the epidemiological, clinical and histopathological points of view, also in relation to the presence of intraepithelial neoplastic lesions at the level of the uterine cervix and/or the vagina.

Service of Oncologic Gynaecology and Cytodiagnostics
Institute of Gynaecology
University of Padua

MATERIALS AND METHODS

We examined 45 cases of Vulvar Intraepithelial Neoplasia (VIN) which came to our attention between 1986 and 1991, histopathologically diagnosed among 214 cases of benign or non-invasive neoplastic vulvar pathology.

These patients, who attended the Service of Oncologic Gynaecology and Cytodiagnostics, Institute of Gynaecology, University of Padua, were submitted to vulvoscopic examination and vulvar biopsy specimens were taken. Colposcopy, cytological specimens and eventually cervicovaginal biopsy were also taken.

We divided the histopathological reports on the 214 vulvar biopsies into Papillomavirus infections (HPV), VIN lesion (I, II, III), Paget's disease, non-neoplastic epithelial disorders (squamous cell hyperplasia, lichen sclerosus); in a group classed as " other benign vulvar pathologies" we included cases of cutaneous naevus, angioma, lentigo simplex, papillate hydroadenoma and sebocystoma.

We assessed the incidence of VIN lesions in the vulvar pathology considered and the macroscopic aspect especially with relation to the extent of the lesions. We assessed the mean age of our patients and the symptomatology presented at the time of diagnosis.

Finally we highlighted the association of Vulvar Intraepithelial Neoplasia with HPV infection, with non-neoplastic epithelial disorders and with CIN and/or VAIN.

The VIN diagnosis was reached histologically following the criteria proposed by the ISSVD in 1986 (9).

HPV infection was diagnosed on the basis of the epithelial and stromal alterations found during the histologic examination.

RESULTS

Out of the 214 vulvar biopsies performed for diagnostic purposes in the years 1986-1991, VIN was diagnosed in 45 cases (21.02% of the total) (Table 1).

The age of the patients suffering from VIN was between 20 and 78 years (mean age 48.97).

Of the 45 cases considered in our research, 23 were diagnosed as VIN I (51.1%), 13 as VIN II (28.8%), 6 as VIN III (13.3%), while there were 3 cases of Paget's disease (6.6%); the mean age of the patients with VIN I was 44.64 years, with VIN II 46.53 years, with VIN III 66.0 years and with Paget's disease 52.6 yearse (Table 2).

Table 1. — *Distribution of the cases series according to benign and pre-invasive vulvar pathology.*

	No. cases	%
HPV infection	82	38.3
Non-neoplastic epithelial disorders	63	29.4
VIN I	23	10.7
VIN II	13	6.0
VIN III	6	2.8
Paget's disease	3	1.4
Other-benign vulvar pathology	24	11.2
Total	214	100.0

In VIN lesions, HPV infection was found in 23 cases (51.1%), involving especially the youngest patients; about 73% of the patients were younger than 45 years and it should be noted that the mean age of the patients with VIN and HPV was about 20 years lower than that of patients with VIN lesions alone (39.77 as against 59.04 years) (Tables 3, 4, 5).

The simultaneous presence of Intraepithelial Neoplasia of the Cervix or of the

Table 2. — *Mean age of patients suffering from vulvar intraepithelial neoplasia.*

	VIN I	VIN II	VIN III	Paget's dis.
No. of cases	23	13	6	3
Mean age	44.64	46.53	66.0	52.6

Table 3. — *VIN-HPV association and respective* mean ages.

	No. cases	Without HPV	Mean age age	With HPV	Mean age
VIN I	23	11	52.23	12	36.08
VIN II	13	5	60.04	8	38.04
VIN III	6	3	72.33	3	59.66
Paget's dis.	3	3	52.60		
Total	45	22		23	

Table 4. — *Comparison of mean ages of patients suffering from VIN with and without HPV infection.*

	VIN, I II, III	
	With HPV	Without HPV
Mean age	39.77	59.04

Table 5. — *Distribution of HPV infection in patients suffering from VIN according to age group.*

Age group	No. cases	%
20-30	9	39.1
31-40	5	21.7
41-50	3	13.0
51-60	2	8.6
61-70	3	13.0
71-80	1	4.3
Total	23	100.0

Vagina was found in 10 cases (22.22%); no cases showed the presence of invasive of the lower genital tract (Table 6).

At the time of diagnosis, 23 patients were symptomless and 22 patients presented the following symptoms: 13 cases of pruritus (28.8%), 6 of burning sensation (13.3%), two of pain (4.4%) and one case of dyspaurenia (2.2%) (Table 7).

The vulvoscopic examination at the time of the biopsy showed white areas in 27 cases (60%), condylomatous-like areas in 8 cases (17.7%), red areas in 4 cases (8.8%), areas of erosion in 4 cases (8.8%), an ulcerated area in one case (2.2%) (Table 8).

VIN associated with non-neoplastic epithelial disorders were observed in 14 patients (31.1%): these were 12 cases of squamous cell hyperplasia and 2 cases of lichen sclerosus; in this group two patients suffering from VIN II and one from VIN III resulted also infected with HPV (Table 9). The mean age of these patients was 55.92, which was higher than that of patients with VIN associated with HPV (39.77 years) and lower than the mean age of patients with VIN alone (60 years) (Table 10).

Squamous cell hyperplasia was found more frequently in association with VIN (12 cases) than lichen sclerosus (2 cases); furthermore, the former is associated also with cases of VIN III, whereas lichen sclerosus is associated only with VIN I (Table 9).

DISCUSSION

The analysis of the data available shows that the most frequent histological diagnosis in the 45 biopsies considered was VIN I (51.1% of cases). It may also be noted that the mean age of the patients affected tends to increase with the degree of VIN, being 44.64 years for VIN I and 66.0 years for VIN III.

The long interval we found between VIN I and VIN III might suggest the hypothesis of a long natural hystory of VIN, much longer than that found for

Table 6. — *VIN: association with Cin or Vain.*

	No. cases	CIN I	II	III	VAN I	II	III
VIN I	8	5	1	1	1	–	–
VIN II	2	2	–	–	–	–	–
VIN III	–	–	–	–	–	–	–
Paget's disease	–	–	–	–	–	–	–
Total	10	7	1	1	1	–	–

Table 7. — *Symptomatology reported by patients suffering from VIN.*

	No. cases	%
Pruritus	13	28.8
Burning	6	13.3
Pain	2	4.4
Dyspaurenia	1	2.2
Asymptomatic	23	51.1
Total	45	100.0

Table 8. — *Findings of the vulvoscopic examination at the time of biopsy.*

	No. cases	VIN I	II	III	Paget's dis.
White areas	28	16	8		3
Condylomatosis like-lesions	8	4	3	1	
Red areas	4	1		3	
Areas of erosion	4	2	2		
Areas of hyperpigmentation	1			1	
Ulcerated areas	1			1	
Total	45	23	13	6	3

CIN but suggests also the problem of the real nature of lesions denominated VIN at various grades; in the vulva, also, particularly in relation with VIN I it's very difficult an exact differential diagnosis among VIN and other lesions as those by HPV [1]. Differences in the mean age are also found in the patients who also presented HPV infection (39.77 years) in comparison with others, without HPV infection (59.04 years): the patients with vulvar HPV infection are struck by VIN at a much younger age than those not infected; this fact, supported by other Authors [3, 10], seems to support the hypotesis that the Papillomavirus may play some part in the genesis of Vulvar Intraepithelial Neoplasia, as has already been proposed for Intraepithelial Neoplasia of the Uterine Cervix, or the Papilloma virus infection may play the role of reveling, by means of itself symptoms also other lesions as VIN.

Many Authors [1, 3, 4] report the presence of simultaneous or previous CIN and/or VAIN in 20-25% of cases. In the cases we studied, the simultaneous presence of CIN or VAIN was found in about 23% of cases; moreover, these patients had HPV infection at both vulvar and cervicovaginal level. It might be supposed that the whole genital tract is subject to the same pathogenic noxae; the greater frequency of CIN with respect to VIN, found in the literature, would be due to the different type of cells present in the Transformation Zone [1].

The symptomatology reported by the patients, present in 49.9% of cases, is non-specific, absolutely similar to that presented by patients suffering from non-neoplastic epithelial disorders, therefore non pathognomonic.

The vulvoscopic examination revealed white areas in about 60% of cases while other pictures were less frequent. In 8 cases the vulvoscopic examination revealed condylomatous lesions; in fact, the histopathological examination showed that these patients were suffering from VIN and Papillomavirus infections.

It may also be noted that the patients suffering from lichen sclerosus presented VIN I histologic pictures, while those with squamous cell hyperplasia also presented VIN II and VIN III pictures, confirming the findings in literature [1, 11]

Table 9. — *Contemporary presence of non-neoplastic epithelial disorders in areas adjacent to vulvar intraepithelial neoplasia.*

	VIN I		VIN II		VIN III	
	w/o HPV	HPV	w/o HPV	HPV	w/o HPV	HPV
Squamous cell hyperplasia	5	–	4	2	–	1
Lichen sclerosus	2	–	–	–	–	–
Total	7	–	4	2	–	1

HPV: Papillomavirus infection.
w/o HPV: Without Papillomavirus infection.

Table 10. — *Comparison of mean ages of patients suffering from VIN and patients suffering from VIN and non-neoplastic epithelial disorders.*

	Vin and non-neoplastic epithelial disorders	VIN+HPV	VIN alone
Mean age	55.92	39.77	60.0

which consider squamous cell hyperplasia a lesion with a greater risk as regards the development of pre-invasive and invasive lesions of the vulva; the mean age of the patients with VIN and non-neoplastic epithelial disorders is much higher than that of patients with VIN and VIN with HPV; this observation agrees with the fact that these lesions are much more frequent in higher age groups, as pointed out by other Authors ([11]).

Despite the increased incidence of VIN found by many Authors ([2, 10, 12]), there has been no reduction in the incidence of invasive carcinoma of the vulva ([8]); besides, there is no screening of the population for VIN and, at least in our cases, there appears to be a long natural history in VIN lesions (the interval we found between VIN I and VIN III is about 20 years).

However, some doubts still remain: are VIN and invasive carcinoma of the vulva different phases of one disease or two different pathologies with different biological behaviour, indicating that the Vulvar Intraepithelial Neoplasia is not necessarily a lesion at high risk for evolving towards invasive forms? ([8]). In a number of recent case records it has been observed that the age of major incidence of VIN is around 40 years ([4]), much lower than the age of major incidence of invasive carcinoma of the vulva, which is around 65-70 years ([13]): the interval of latency between intraepithelial neoplasia and the invasive form would therefore be 25-30 years. In the opinion of some Authors ([13, 14, 16]), this interval should be shorter, considering that at the level of the uterine cervix it is around 5-15 years ([15]); basing their hypothesis on this epidemiological finding, these Authors maintain that VIN is a preinvasive lesion only in older women, while in younger women it would in many cases represent a condition related to the Papillomavirus infection (this infection is, indeed, much more frequent among young coomen) and its biological behaviour could be different, with a very low incidence of evolution towards more serious lesions ([2, 3]).

Besides, in the opinion of other Authors, since the biological characteristics of the epithelia covering the vulva and the cervix are different, the interval of latency between carcinoma in situ and invasive lesions would not necessarily be similar in the two epithelia ([15]).

An answer to all this hypothesis, which are based only on epidemiological findings, might be found in perspective studies which are generally not carried out, since today are no scientific assumption to justify the non-treatment of the most serious forms of Vulvar Intraepithelial Neoplasia.

However, in our cases the mean age of the patients suffering from VIN, and especially from VIN III, was much higher than that reported by other Authors ([2, 4, 6, 8, 10]): this may be due to a real epidemiological diversity in our sample or to more restrictive criteria applied in diagnosing VIN; however, in agreement with the most recent literature ([2, 4, 14, 16]), also in our cases, HPV infection was most frequently diagnosed in younger women.

REFERENCE

1) Prat J: "Pathology of Vulvar Intraepithelial Lesions and early invasive carcinoma". *Human Pathology,* 1991, *22 (9),* 877.
2) Japaze H., Rafael G. B., Woodruff J. D.: "Primary Vulvar Neoplasia: a review of in situ and invasive carcinoma 19351-1972". *Obst. Gyn.,* 1977, *49,* 404.
3) Woodruff M. D., Julian E., Puray M. *et al.*: "The contemporary challenge of carcinoma in situ of the vulva". *Am. J. Obst. Gyn.,* 1973, *115,* 830.
4) Friedrich E. G., Wilkinson E. J., Fu Y. S.: "Carcinoma in situ of the vulva: a continuing challenge". *Am. J. Obst. Gyn.,* 1980, *136,* 830.
5) Bernstein S. G., Kovacs B. R., Townsend D. E. *et al.: "Vulvar carcinoma in situ". Obst. Gyn.,* 1983, *61,* 304.
6) Caglar H., Tamer S. *et al.:* "Vulvar intraepithelial neoplasia". *Obst. Gyn.,* 1982, *60,* 346.

7) Dean R. E., Taylor E. S., Weisbrod D. M. *et al.:* "The treatment of premalignant and malignant lesions of the vulva". *Am. J. Obst. Gyn.,* 1974, *119,* 59.
8) Husseinzadeh N., Newman N. J., Wesseler T.: "Vulvar Intraepithelial Neoplasia: a clinico-pathological study of carcinoma in situ of the vulva". *Gyn. Oncol.,* 1989, *33,* 157.
9) Wilkinson E. J., Knabe B., Linch P. J.: "Report of the ISSVD terminology committee". *J. Reprod. Med.,* 1986, *31,* 973.
10) Crum C. P., Liskow A., Petra S. P., Keng W. C. *et al:* "Vulvar Intraepithelial Neoplasia (severe atypia and carcinoma in situ): a clinico-pathological analysis of 41 cases". *Cancer,* 1984, *54,* 1429.
11) Zarcone R., Cardone G., Voto I., Palumbo S., Cardone A.: "Distrofie e VIN". *Minerva Ginecologica,* 1991, *43,* 43.
12) Hilliard G. D., Massey F. M., O'Toole R. V.: "Vulvar neoplasia in the young". *Am. J. Obst. Gyn.,* 1979, *135,* 185.
13) Woodruff M. D.: "Carcinoma in situ of the vulva". *Clin. Obst. and Gyn.,* 1989, *28,* 230.
14) Barbero M., Micheletti L., Preti M., Cavanna L., Boselli F., Garutti G., Zanotto Valentino M. G., Nicolaci P., Ghiringhello B., Borgno G.: "Vulvar Intraepithelial Neoplasia. A clinicopathologic study of 60 cases". *J. of Reprod. Med.,* 1990, *35 (11),* 1023.
15) Ferenczy A., Winkler B.: "Cervical Intraepithelial Neoplasia and condyloma". In: Pathology of the female genital tract. Ed. 3rd Kurman R. J., New York, Springer-Verlag. Ed. Blaustein's, 1987, 177-217.
16) Park J. S., Ronald W. J., Mc Nean M. R.: "Possible etiologic heterogeneity of vulvar intraepithelial neoplasia". *Cancer,* 1991, *67 (3),* 1599.

Address reprint requests to:
A. CINEL
Via M. Ravel, 2
35100 Padova (Italy)