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Management of multicentric lesions of the lower genital tract

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Abstract

Objectives: To report management and outcome of multicentric lesions of the lower genital tract. To define risk factors of recurrence.
Study design: Retrospective review of multicentric dysplasias treated in our colposcopic clinic between 1996 and 2003. Multicentric dysplasias included CIN with VAIN and/or VIN. After primary treatment, follow-up was colposcopic, cytologic and virologic.
Results: Forty-four patients presented multicentric lesions out of 998 patients referred for CIN (4.4%). The average age was 36.8 years. Immunologic disorders were present in 20.4%. Ninety-one percent had cervicovaginal or cervicovulvar lesions, only 9% had three sites of genital dysplasia. 53.3% of lesions were concomitant. 79.5% of CIN were high grade, 62.5% of VAIN low grade and 62.5% of VIN high grade. Therapeutic modalities were as follows: conization for CIN (70.4%), CO2 laser for VAIN (33.3%) and surgery for VIN (41.7%). Forty patients were followed and had at least one post-treatment cytologic control; 55% of them had residual disease. Out of the 23 patients with at least two negative controls after treatment, 43.5% presented recurrence. Risk of recurrence was not statistically bound to such parameters as tabagism, immunologic disorder, high grade lesions, non-surgical treatment, and persistence of HPV infection after treatment.
Conclusion: Multicentric dysplasias are associated with high rate of residual lesion and recurrence. Management of these lesions require long term follow-up.

Keywords: Human papillomavirus test; Cervical intraepithelial neoplasia; Vaginal intraepithelial neoplasia; Vulvar intraepithelial neoplasia; Recurrence

1. Introduction

The most common site of genital intraepithelial neoplasia is the cervix (CIN) (36.4/100,000) [1]. Vulvar and vaginal intraepithelial neoplasias (VAIN and VIN) are less frequent [2,3]. The role of high risk types of HPV (16, 18, 33 HPV types) in the pathogenesis of genital tract neoplasia is today well-documented. Multicentricity is defined by intra epithelial lesions of two or three sites (cervix, vagina, and vulva). It could be explained by the HPV infection of the whole lower genital tract [4–7]. Genital intraepithelial neoplasia screening is focused on the cervix. That's the reason why diagnosis of multicentric lesions is still a challenge. The problem is also therapeutic: patients with multicentric disease have a significantly higher rate of recurrence than patients with unicentric disease [8–10]. Patients with multicentric lesions of the lower genital tract were included in a retrospective study. Our aims were to describe the clinical pictures, present the different managements and results, then to define risk factors of recurrence.

Abbreviations: HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; VAIN, vaginal intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia; LEEP, loop electrosurgical excision procedure; 5 FU, 5 fluoro-uracil

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2. Methods

From January 1996 to December 2003, 998 patients were referred in our colposcopic clinic for CIN.

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All these patients had a colposcopic examination with application of 3% acetic acid and Schiller's test. A complete assessment of cervix, vagina and vulva was carried out. Colposcopy-directed biopsies were performed. Slides were reviewed by a single pathologist who graded the lesions according to the Bethesda classification. Prior to colposcopy, the patients underwent HPV-DNA testing (Hybrid Capture 2 test). Cells for HPV DNA analysis were collected from the endocervix and the transformation zone with a sterile conical brush (Cervical Sampler TM, Digene). The Hybrid Capture 2 test is considered as "high oncogenic risk" if positive for 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 HPV types; and as "low oncogenic risk" if positive to the 6, 11, 42, 43 and 44 HPV types. The test is considered negative in the absence of virus.

Multicentric disease included CIN coexisting with VAIN and/or VIN. Lesions could be concomitant or not. Proved by histology, low grade, high grade and microinvasive lesions were included. We excluded invasive lesions, condylomatous lesions and perianal dysplasias. Multicentric lesions were divided into three groups: CIN + VAIN (group 1), CIN + VIN (group 2), and CIN + VAIN + VIN (group 3). For each patient following data were noted: age, gravidity, parity, immunosuppression, tobacco. Different therapeutic modalities were used: surgery (LEEP, hysterectomy, surgical excision) or non-surgical procedures (CO2 laser, cryotherapy, and 5 fluoro-uracil local application). *Conization* was performed under colposcopic control by the same senior surgeon using loop electrosurgical excision procedure (LEEP). Most procedures were performed with a 20 mm loop. A 5 mm cautery ball was used to achieve hemostasis. All specimens were marked for orientation with a delayed absorbable suture at the 12 o'clock position. When *hysterectomy* was indicated, surgical procedure was performed by vaginal route. *Surgical excision* of vulvar or vaginal lesions was performed under colposcopic control. *CO2 laser* was applicated with a power density of 600–1500 W/cm^2 with a 2–3 mm spot size and a power setting of 10–15 W. The lesions were vaporized to a depth of 2–4 mm and up to 2 mm around the lesions. Treatment by *5 fluoro*-uracil (Efudix) for vulvar lesions consisted of a single application at night (5 g/day) for 5 consecutive days per week during 4 weeks. Some patients had no treatment and underwent close observation. Surgical treatments were indicated for high grade lesions and non-surgical procedures or close follow-up for low grade lesions.

Follow-up consisted of an examination at 3 months, 6 months after treatment and every year. At each visit, a complete colposcopic exam was performed, with cervical smear and directed biopsies if necessary. A post-treatment HPV-DNA testing was performed by Hybrid Capture 2 test at each visit. The post-treatment HPV test was considered as positive in case of persistent HPV infection. In this study, residual disease was defined as a persistent histological lesion after primary treatment. Recurrence was defined by histological lesion occurring after at least two negative post-treatment controls.

2.1. Statistical analysis

In order to define risk factors of recurrence, we defined potential risk factors for recurrence: age, immunologic status, tobacco (more than 20 cigarettes per day), histological grade of initial lesion, method of treatment (surgical versus non-surgical procedures), post-treatment HPV testing.

Due to the small size of sample, data were analysed using a univariate analysis. Comparisons of means have been performed with the Wilcoxon test. Comparisons of frequencies have been performed using the Chi-square test, or the Fisher exact test if necessary. Significance level has been set to 0.05 and statistical analysis has been realized with the SAS software.

3. Results

From January 1996 to December 2003, 998 patients were referred to our colposcopic clinic for CIN. Out of 998 patients, 44 presented multicentric lesions (4.4%).

3.1. Demographic data

For these 44 patients, the average age was 36.8 years (range 17–72 years). Median of gravidity and parity was, respectively, 2.06 (range 0–6) and 1.65 (range 0–6). Immunologic disorders were present for nine patients: immunosuppressive treatment after organ transplant ($n = 3$),

Table 1
Site of genital lesions

	Initial lesions ($n = 44$) n (%)	Residual lesions ($n = 22$) n (%)	Recurrent lesions ($n = 10$) n (%)
CIN + VAIN	20/44 (45.5)	3/22 (13.6)	1/10 (10)
CIN + VIN	20/44 (45.5)	2/22 (9.1)	1/10 (10)
CIN + VIN + VAIN	4/44 (9)	0/22 (0)	1/10 (10)
CIN	–	14/22 (63.6)	6/10 (60)
VIN	–	3/22 (13.6)	0/10 (0)
VAIN	–	0/22 (0)	1/10 (10)