

Colposcopic patterns of vaginal intraepithelial neoplasia: a focus on low-grade lesions

F. SOPRACORDEVOL¹, N. CLEMENTE², M. BARBERO³, A. AGAROSI⁴, P. CATTANI⁵, P. GARUTTI⁶, M.G. FALLANI⁷, A. PIERALLI⁷, F. BOSELLI⁸, A. FREGA⁹, G. DE PIERO¹, A. DEL FABRO¹, M. BUTTIGNOL¹, A. CIAVATTINI² AND ITALIAN SOCIETY OF COLPOSCOPY AND CERVICO-VAGINAL PATHOLOGY (SICPCV)

¹Gynecological Oncology Unit, Centro di Riferimento Oncologico – National Cancer Institute, Aviano, Italy

²Woman's Health Sciences Department, Gynecologic Section, Polytechnic University of Marche, Ancona, Italy

³Department of Obstetrics and Gynecology, Asti Community Hospital, Asti, Italy

⁴Department of Obstetrics and Gynecology, Clinical Science Institute, L. Sacco Hospital, University of Milan, Milan, Italy

⁵Center for Gynecologic Oncology Prevention, AULSS 20, Verona, Italy

⁶Department of Obstetrics and Gynecology, University Hospital, Ferrara, Italy

⁷Maternal and Child Department, Careggi University Hospital, Firenze, Italy

⁸Department of Gynecological, Obstetric and Pediatric Sciences, Section of Gynecology, University of Modena and Reggio Emilia, Modena, Italy

⁹Department of Surgery, Medicine and Translational Medicine, Sant'Andrea Hospital, Sapienza University of Rome, Roma, Italy

Abstract. – OBJECTIVE: The aim of this study was to evaluate the colposcopic patterns observed in women with a histopathological diagnosis of vaginal intraepithelial neoplasia, with a particular interest in analyzing the colposcopic characteristics of low-grade squamous intraepithelial lesions (LSIL).

PATIENTS AND METHODS: Medical charts and colposcopy records of women diagnosed with vaginal intraepithelial neoplasia from January 1995 to December 2015, were analyzed in a multicenter retrospective case series. The abnormal colposcopic patterns observed in women with vaginal LSIL and vaginal high-grade SIL (HSIL) were compared. The vascular patterns and micropapillary pattern were considered separately.

RESULTS: Regardless the histopathological grading, in women with vaginal SIL, the grade I abnormal colposcopic findings were more frequent than grade II abnormalities. However, a grade I colposcopy was more commonly observed in women with a biopsy diagnosis of LSIL rather than HSIL ($p<0.0001$). Similarly, the micropapillary pattern was more frequently observed in women with LSIL ($p=0.004$), while vascular patterns were observed more frequently in women diagnosed with vaginal HSIL ($p<0.0001$). In women with grade I colposcopy, the meno-

pausal status and a previous hysterectomy appeared to be associated with the diagnosis of vaginal HSIL.

CONCLUSIONS: Grade I abnormal colposcopic findings were more commonly observed in women with vaginal LSIL, as well as the micropapillary pattern. On the other hand, grade II abnormal colposcopy and the presence of vascular patterns were more frequently observed in women with vaginal HSIL.

Key Words:

ValN, Colposcopy, Vaginal dysplasia, Vagina, Colposcopic pictures.

Introduction

Vaginal intraepithelial neoplasia is an unusual human papillomavirus (HPV)-related dysplastic lesion of the vaginal epithelium¹, with an estimated incidence of 0.2-2 per 100,000 women/year^{2,3}. It is currently classified according to the two-tiered classification system introduced with the 2012 revised LAST terminology, with the distinction between low grade and high grade squamous intraepithelial lesions (SIL)⁴. Vaginal SIL is diagno-

sed through the histopathological examination of biopsy specimens obtained during an accurate colposcopic evaluation of vaginal walls in women with an abnormal referral pap smear⁵. Thus, the colposcopy has an essential role in the diagnostic process. However, vaginal colposcopy is quite difficult, and the ability to reliably predict the histology of lesions is a challenge for most of colposcopists⁶, since colposcopic pictures of vaginal SIL are extremely variable and nonspecific⁷. To our knowledge, very few studies analyzed the colposcopic patterns observed in women with a histopathological diagnosis of vaginal SIL⁶⁻⁸, most of them affirming the lack of a clear correlation between colposcopy and histology.

Patients and Methods

This was a retrospective, multicenter observational study sponsored by the Italian Society of Colposcopy and Cervico-Vaginal Pathology (SICPCV). All women with a histopathological diagnosis of vaginal SIL consecutively referred to the institutions involved, from January 1995 to December 2015, were considered. Institutional Review Board approval (CRO IRB n. 17/2013) was properly obtained. These women were diagnosed with vaginal SIL through biopsies of suspicious areas detected on colposcopy after an abnormal referral pap smear. Colposcopic examinations were recorded according to the 2011 revised colposcopic terminology of the International Federation for Cervical Pathology and Colposcopy (IFCPC)⁹. Colposcopies performed before the introduction of the 2011 IFCPC terminology were revised accordingly, through the revision of colposcopic charts and images. The revision of all the colposcopic charts and images was carried out by the same experienced colposcopist (FS) (certified by the SICPCV), avoiding the potential interobserver variability. According to the 2011 IFCPC terminology⁹, we considered the thin acetowhite epithelium, the fine punctuation and the fine mosaic as grade I abnormal colposcopic patterns, while dense acetowhite epithelium, coarse punctuation and coarse mosaic were considered as grade II abnormal patterns. In the 2011 IFCPC terminology, Lugol's non-staining areas were considered as nonspecific colposcopic findings. However, since vaginal SIL may sometimes appear only as a Lugol's non-staining area^{7,8}, for the present study, we have considered the aceto-negative-Lugol's non-staining areas as grade I abnormality. Furthermore, vascular patterns (fine/coarse punctuation and fine/coarse mosaic) and

micropapillary pattern (defined as an acetowhite area with an irregular micropapillary surface) were considered separately. Colposcopic examinations were performed after treatment of cervical/vaginal infection or estrogenic treatment of postmenopausal dystrophy, when necessary (and if not contraindicated). All the colposcopies were performed by staining with a 5% acetic solution and a 3% Lugol's solution (Schiller test). In each case, the biopsy was taken at the site with the worst colposcopic pattern, with the goal of sampling the area most likely to contain high-grade SIL (HSIL) or cancer. In some cases of multifocal or extremely wide lesions, multiple biopsies were performed in the same patient. In these cases, if vaginal LSIL and HSIL coexisted in the same woman, we considered the worst histopathological diagnosis and the related colposcopic pattern of the specific site in which such biopsy had been performed. Histopathological diagnosis on vaginal biopsies was recorded according to the two-tiered classification introduced with the 2012 revised LAST terminology⁴. Biopsies performed before the introduction of the 2012 LAST classification were revised accordingly, through the revision of histopathological samples. All the women considered were diagnosed with vaginal SIL for the first time, so women with previous diagnosis and/or treatments for vaginal SIL were excluded, in order to avoid potential confounders. Similarly, women with a histological diagnosis of invasive vaginal cancer were excluded. Women with an incomplete colposcopic description of the vaginal lesions or in which the colposcopic images were not available, were excluded. Patients were identified by searching the clinical databases of the institutions involved, and the medical records of women fulfilling the study inclusion criteria were analyzed in a retrospective case series.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 22.0 (IBM Corporation, Armonk, NY, USA). χ^2 -testing was used for the statistical evaluation and a p -value <0.05 was considered statistically significant. The K coefficient was used to evaluate the potential correlation between the grade of colposcopic abnormalities and the histopathological grading of vaginal SIL.

Results

466 women diagnosed with vaginal SIL at the institutions involved (from January 1995 to December 2015), and fulfilling the study inclusion/

exclusion criteria, were considered. The mean age of these women was 44.5 years old (SD $\pm$ 13.2, range 18-81 years) and, in particular, 173 women (37.1%) were in post-menopausal status. HIV infection was reported in 14 cases (3%), while data about tobacco use were available only for 263 women, with 82 smokers (31.2%). Seventy-nine women (17%) underwent a prior hysterectomy; in particular, hysterectomy was performed because of CIN or invasive cervical cancer in 64 cases and because of benign conditions (or non HPV-related malignancies) in the remaining 15 cases. In the whole study cohort, 205 women (44%) were diagnosed with vaginal LSIL on biopsy, and 261 (56%) had vaginal HSIL. Grade I abnormal colposcopic patterns were observed in 373 women (80%) while the remaining 93 women (20%) had grade II abnormalities on colposcopy. Hence, an overall higher rate of grade I colposcopic patterns was observed in women with vaginal SIL, regardless the histopathological grading (80% vs. 20%, $p < 0.0001$). Table I shows the colposcopic pictures detected in the women of the study cohort. For this study, we have considered the aceto-negative-Lugol's non-staining areas as a grade I abnormality, and this pattern was observed as unique colposcopic finding in 46 cases (9.9%). More in detail, this pattern was observed in 34 women among the 205 with a biopsy diagnosis of vaginal LSIL (16.6%) and in 12 cases among the 261 with a biopsy diagnosis of vaginal HSIL (4.6%). Thus, the detection of an aceto-negative-Lugol's non-staining area as unique colposcopic finding was more common in women with vaginal LSIL compared to women with vaginal HSIL ($p < 0.0001$). Comparing women with vaginal LSIL and vaginal HSIL, the K coefficient (used to evaluate the potential correlation between the grade of colposcopic abnormalities and the histopathological grading of vaginal SIL), showed a fair correlation ($K=2.1$; SE: 0.03;

95% CI: 0.15-0.28). Considering the 93 women with grade II abnormal colposcopy, a significantly higher rate of vaginal HSIL, compared to vaginal LSIL, emerged (83.9% vs. 16.1%, $p < 0.0001$). Conversely, considering the 373 women with grade I abnormal colposcopy, a similar rate of vaginal LSIL and HSIL was found (50.9% vs. 49.1%, $p=0.7$). Subsequently, the vascular patterns (fine/coarse punctuation and fine/coarse mosaic) have been considered separately. In the whole study cohort, these patterns were found in 57 women (12.2%). More precisely, the vascular patterns were observed in 15 women with vaginal LSIL (7.3%) and in 42 women with a biopsy diagnosis of vaginal HSIL (16.1%). Therefore, the vascular patterns were observed more frequently in women diagnosed with vaginal HSIL ($p=0.006$). Also, the micropapillary pattern was considered separately. In the whole study cohort, these patterns were found in 169 women (36.3%). More precisely, it was found in 87 women among the 205 with a biopsy diagnosis of vaginal LSIL (42.4%) and in 82 women with vaginal HSIL (31.4%). The micropapillary pattern was observed more frequently in women with vaginal LSIL ($p=0.02$). Furthermore, this colposcopic pattern was found more frequently in childbearing age women compared to menopausal women (45.7% vs. 20.2%; $p < 0.0001$). Among the 169 women with the micropapillary pattern, 153 (90.5%) had a grade I abnormal colposcopy, while the remaining 16 (9.5%) had a grade II abnormal colposcopy. Thus, the detection of a micropapillary pattern was more commonly associated with grade I colposcopic pictures (90.5% vs. 9.5%; $p < 0.0001$). Considering the 373 women with a grade I abnormal colposcopy, a micropapillary pattern was observed in 153 cases (41%). In the 93 women with a grade II abnormal colposcopy, this pattern was found in 16 cases (17.2%). Thus, the micropapillary pattern was more commonly observed in women with grade I abnormal colposcopy (41% vs. 17.2%, $p < 0.0001$). Subsequently, we performed a multivariable logistic regression, in order to identify the factors potentially associated with the diagnosis of vaginal HSIL. In the whole study cohort, the presence of grade II abnormal colposcopic findings, the menopausal status, and a previous hysterectomy were significantly associated to histopathological diagnosis of vaginal HSIL (Table II).

Moreover, we performed another multivariable logistic regression considering only the 373 women with grade I abnormal colposcopic findings. Even in this subgroup of women, the menopausal

Table I. Colposcopic pictures in women with histopathological diagnosis of vaginal SIL on biopsy (study cohort No. = 466).

	Vaginal LSIL	Vaginal HSIL
Grade I colposcopic patterns	190 (92.7%)	183 (70.1%)
Grade II colposcopic patterns	15 (7.3%)	78 (29.9%)
Total	205 (100%)	261 (100%)
$\chi^2=35.209$; $p < 0.0001$		

Data are expressed as no. (%)

Table II. Multivariable logistic regression of factors potentially associated with the diagnosis of vaginal HSIL in the whole study cohort (No.= 466).

Characteristics	Adjusted Odds ratio (95% CI)	<i>p</i>
Age (years)	0.98 (0.96-1.01)	0.3
Menopause	2.11 (1.03-4.3)	0.04
Previous hysterectomy	2.38 (1.15-4.93)	0.02
Multiple vaginal lesions	1.33 (0.87-2.04)	0.2
Grade II abnormal colposcopy	4.56 (2.46-8.45)	<0.0001
Papillary pattern	0.88 (0.58-1.35)	0.6
Vascular patterns	1.22 (0.59-2.49)	0.6

Table III. Multivariable logistic regression of factors potentially associated with the diagnosis of vaginal HSIL in women with grade I abnormal colposcopic findings (No. = 373).

Characteristics	Adjusted odds ratio (95% CI)	<i>p</i>
Age (years)	0.98 (0.96-1.01)	0.2
Menopause	2.0 (1.11-4.26)	0.04
Previous hysterectomy	2.1 (0.98-4.63)	0.05
Multiple vaginal lesions	1.14 (0.72-1.79)	0.6
Papillary pattern	0.89 (0.57-1.38)	0.6
Vascular patterns	1.36 (0.63-2.95)	0.4

status and a previous hysterectomy appeared to be associated with the diagnosis of vaginal HSIL (Table III). As a secondary analysis, we focused on the 205 women with a biopsy diagnosis of vaginal LSIL. Among them, grade I abnormal colposcopic findings were detected in 190 women (92.7%), while grade II findings were found in the remaining 15 women (7.3%). Thus, considering only women with vaginal LSIL on biopsy, the grade I abnormal colposcopic patterns were significantly more frequent than grade II (92.7% vs. 7.3%; $p<0.0001$). As previously reported, these 205 women with vaginal LSIL, showed a higher rate of micropapillary pattern and a lower rate of vascular patterns compared to women with vaginal HSIL (42.4% vs. 31.4%, $p=0.02$ and 7.3% vs. 16.1%, $p=0.006$, respectively).

Discussion

The diagnosis of vaginal SIL is essentially a histopathological diagnosis on colposcopy-guided biopsy of vaginal walls. Therefore, in these women, the identification of the proper site for biopsy (with a subsequent correct histopathological diagnosis) is crucial, even because the following management depends on the grade of the lesion⁸. In case of vaginal LSIL, no controversy about treatment options exists and, since a high rate of

spontaneous regression is reported^{10,11}, observation alone with cytology and colposcopy seems to be the better choice^{8,12,13}. On the other side, the vaginal HSIL requires treatment (and a subsequent follow up with pap smear and colposcopy), but the optimal management actually remains a “therapeutic dilemma”¹⁴, and different therapeutic strategies have been proposed, including surgical excisions and ablative procedures³. First of all, the identification of a potential correlation between colposcopy and histology of vaginal intraepithelial lesions is extremely relevant for a correct diagnosis, since it would allow the colposcopist to choose carefully the site for biopsy, and sample the area most likely to contain HSIL. This is particularly true in case of large or multifocal lesions, in which different grades of SIL can coexist; in these cases, a correct identification of vaginal HSIL is necessary for the appropriate management of the patient. However, the identification of a potential correlation between colposcopic findings and histology of vaginal intraepithelial lesions could be extremely important even for the follow-up of women already diagnosed (and eventually treated) for vaginal SIL. Indeed, if a sufficient correlation exists, in women with colposcopic pictures suggestive for vaginal LSIL, a further biopsy could be avoided or postponed, while it should be performed in case of colposcopic pattern suspicious for HSIL. From the present study, some interesting elemen-

ts of correlation between colposcopy and histology of vaginal SIL emerged. In particular, grade I colposcopic findings were more commonly observed in women with vaginal LSIL. Similarly, the presence of micropapillary pattern appeared to be associated with vaginal LSIL, while the vascular patterns were more commonly observed in women with vaginal HSIL, as well as grade II abnormal colposcopic findings. The micropapillary pattern, not specifically considered in the 2011 IFCPC terminology⁹, is quite rare on the cervix but seems to be relatively common on the vaginal epithelium, especially in childbearing-age women⁸. As already reported⁸, the specific significance of this pattern is currently unknown, but it seems to be associated with less severe disease and it could probably be an expression of persistent HPV infection. However, further studies clarifying the specific meaning of this pattern are desirable. Regarding the vascular patterns, a possible explanation of the association with vaginal HSIL was already provided by other authors⁶. They argued that, in the uterine cervix, the vascular patterns can be detected early in the dysplastic process, since the vascular patterns are the result of exaggeration of the vasculature of immature squamous metaplasia in the transformation zone. In contrast, vaginal SIL develops on very mature squamous epithelium, which lacks underlying vascular structure and abnormal vascular patterns, hence developing late in the neoplastic process⁶. Furthermore, it is interesting to observe that women with grade I abnormal colposcopy are more likely to have vaginal HSIL on the biopsy if they are in menopause or had a previous hysterectomy, as pointed out by the multivariable analysis. Therefore, is possible to identify a subgroup of women with grade I abnormal colposcopy without further risk factors for vaginal HSIL (menopause or previous hysterectomy) in which the biopsy could be initially avoided (or, better, deferred if an abnormal cytology on pap smear persists). However, in these women it would be appropriate to evaluate even the traditional risk factors for high-grade vaginal dysplasia (persistent high-risk HPV infection, multiple sexual partners, early stage at sexual debut, smoking, HIV infection, and immunosuppression)⁵. Thus, the opportunity to perform (or defer) the biopsy should be carefully evaluated and tailored to the characteristics of each patient. Moreover, the potential correlation between colposcopy and histopathological grading of vaginal SIL could be extremely useful during the follow-up visits in women already diagnosed (and eventually treated) for vaginal SIL. In these cases, indeed, the detection

of colposcopic patterns evocative for LSIL (grade I colposcopy, micropapillary pattern and absence of vascular patterns) could lead colposcopists to avoid (or defer) biopsy. On the contrary, if during the follow-up assessments a colposcopic pattern evocative for HSIL is found, a biopsy could be useful to detect the presence (or a recurrence) of a vaginal HSIL, especially if further risk factors such as menopause or previous hysterectomy are present¹⁵. In the present case series, we were able to collect data from a large number of patients and, even though the retrospective nature of this study limited the available clinical data to those already collected in the medical charts, to our knowledge, this is the largest cohort of patients with histopathological diagnosis of vaginal SIL in which the colposcopic pictures were extensively evaluated. Unfortunately, due to the retrospective nature of the study, data on colposcopic patterns observed in women with negative biopsy or colpitis were not available. Similarly, data about HPV infection, smoking and sexual habits of patients (considered as traditional risk factors for vaginal HSIL) were not available.

Conclusions

The findings of the present study could be useful for colposcopists to better manage the women with vaginal SIL, both during the diagnostic process and during follow-up. However, considering the substantial heterogeneity of colposcopic findings in women with vaginal SIL, the colposcopic evaluation of these patients should be performed only by trained colposcopists, with particular expertise in the diagnosis and management of vaginal dysplasia.

Conflict of interest

The authors declare no conflicts of interest.

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