PRE INVASIVE DISEASES OF THE VAGINA

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Introduction

Pre-invasive diseases of the vagina are the precursor states of vaginal cancers.

Vaginal cancer is a rare condition with 15,000 cases per year worldwide (1). It is 35 times and 2 times less frequent than cervical or vulvar cancer respectively. Histologic subtypes of primary vaginal cancer include squamous cell carcinoma (83.4%), adenocarcinoma (9.3%), and melanoma (2.6%). These three histologic subtypes together represent 95.3% of vaginal cancers (2) and all have pre-invasive forms. VaIN typically refers to precancer of squamous type. VGIN refers to glandular type precancer (3). Melanoma in situ, as in other locations, represents preinvasive melanoma.

Incidence of vaginal intraepithelial neoplasia is estimated to be as low as 0.2 to 0.3 cases per 100,000 women in the United States but is known to be increasing. Taking into account all grades of VaIN, 78% regress, 13% persist, and 9% progress to invasion (4). Median age of women with VaIN of any grade is 50 years (5).

Due to this low incidence, all available statistics, especially relative to treatment responses, are of limited value due to a short series effect.

Histology, Etiology, Risk Factors

The three vaginal preinvasive histological subtypes are discussed separately.

VaIN is defined by the presence of intraepithelial squamous atypical cells together with architectural atypia without invasion. Histologically, it is stratified according to the depth of epithelial involvement: VaIN 1,2 and 3 represent, respectively, involvement of lower third, two lower thirds, and extent to the upper third of the epithelium. Currently, a binary stratification is being proposed with low-grade VaIN relating to VaIN 1 and high-grade VaIN gathering VaIN 2/3 (6, 7).

Seventy percents of vaginal cancers are attributable to hr-HPV, of which HPV 16/18 represent 93% (1). Prevalence of HPV DNA, detected by PCR or hybrid capture is 98.5% in VaIN 1, and 92.6% in VaIN 2/3. Relatively high sensitivity to oncogenic effect of HPV on the cervix, compared to vagina, is explained by the easy access of HPV to baseline stem cells at the level of the squamo-columnar junction (SCJ) (8).

In addition to hr-HPV, previous radiation, immunosuppression or immunodepression, *in utero* DES exposure, smoking habits have been identified as risk factors for VaIN. The independent causative effect of previous radiation therapy is not clear, as it has often been administered for previous cervical cancer, a condition that represents in itself a risk factor for VaIN. Immunosuppression following organ grafts, or immunodepression related to active VIH-disease are also known to increase VaIN incidence. Not surprisingly, VaIN patients share other risk factors with those having cervical carcinoma: early onset of sexual life, multiple sexual partners, low socio-economic status, tobacco abuse (5, 9).

Adenocarcinoma

Precursors of vaginal adenocarcinoma are described especially when atypical lesions develop within foci of vaginal adenosis following tuboendometrial or intestinal metaplasia (3). This condition is at high risk for the development of Clear Cell Adenocarcinoma (CCA) and is known to be promoted by the *in utero* DES exposure, particularly during the first trimester of pregnancy. High Risk HPV is not recognized as a causal agent (10). Median age at the time of diagnosis of DES related vaginal adenocarcinoma is 19 (range 7-48) although a second peak of incidence over 40 justifies lifetime follow-up (11). Cases of CCA are also reported in DES-non exposed women mainly in the postmenopausal period.

Vaginal adenocarcinoma may also derive from Wolffian remnants, periurethral glands, or develop in foci of endometriosis (6). As these lesions arise underneath the vaginal mucosa, preinvasive states, if they exist, might be not detectable.

Melanoma

In situ melanoma of the vagina is the pre-invasive state of an extremely rare cancer. Mucosal melanoma is rare (1% of all melanomas), mucosal vulvo-vaginal melanoma are only 18% of them, and, finally, vaginal melanoma is only

3% of those arising in the female urogenital tract (12). Clinical diagnosis and histology may be a trap, especially in the relatively frequent non pigmented variety, so immuno-histochemistery is mandatory.

Diagnosis

VaIN is asymptomatic. Diagnosis most often results from a colposcopic investigation for abnormal cytology. This can occur whether the cervix is present or not. In case the cervix is in place, VaIN is most of the time an extension of a synchronous CIN to the vaginal fornices, or is the expression of a multifocal dysplasia. In other situations, the vaginal lesion is isolated. If the whole vagina has not been cautiously examined in the presence of normal cervix and abnormal smear, diagnosis of VaIN may be made at the time of a secondary vaginoscopy, occasionally performed after a negative cone biopsy. In 50 to 90% of cases, VaIN is often diagnosed in patients with present or previous, invasive or pre-invasive cervical or vulvar disease (13, 14, 15). Patients who have been treated for cervical lesions are at significant risk of developing further VaIN. In a series of 94 women who underwent hysterectomy after diagnosis of CIN2+ and without history of VaIN, 7.4% developped VaIN2+ within mean follow-up of 64 months (15). Furthermore, risk is especially high after hysterectomy for cervical cancer, showing a 15% rate of VaIN in a series of 147 women (16).

On the contrary, cytological screening of VaIN after hysterectomy for benign disease doesn't seem to be beneficial. The prevalence ratios for ASC, LSIL, and HSIL/SCC are respectively 0.14, 0.08, and 0.13, in women with previous hysterectomy versus those without. This indicates an approximately ten times lower risk of having abnormal pap smear after hysterectomy for benign condition (17).

Vaginal cytology poorly correlates with the histological grade of the vaginal dysplasia. In the series of Gunderson, ASCUS or ASCH cytology resulted in 60% of HG VaIN, LG cytology in 53%, and HG or AGC cytology in 89%. For that reason, vaginal colposcopy with biopsy is recommended for any abnormal vaginal cytology (5).

Diagnosis depends on biopsy directed under colposcopy. Colposcopy of the vagina is a timely procedure necessitating a thorough inspection of the vaginal mucosa. For postmenopausal or breastfeeding patients, local estrogen application for 2 to 3 weeks prior to the examination improves the demarcation of the normal and the atypical epithelium (18). Infection should also be adequately treated prior to the vaginoscopy. The vaginal colposcopy is best conducted from the upper vaginal third to the lower third. Initial inspection may reveal elevated, rugous or papillary epithelium, leucoplakia, erosion or ulceration and raise suspicion. If any abnormal vascular pattern is suspected, green filter may help at this stage. After application of 3 to 5% acetic acid, punctation or mosaic pattern may develop and guide the confirmation biopsy. Lugol's solution significantly eases the distinction between normal and pathological tissues. Classically high grade VaIN are iodine negative and well demarked multifocal lesions (6). If the vaginal colposcopy cannot be adequately performed due to stenosis, pain or previous local radiation, an examination under anesthesia is recommended.

Since some lesions might be difficult to detect visually, vaginal colposcopy should systematically be associated to a vaginal bi-manual palpation. This allows detection of some thickened or stiff suspicious areas. This is especially important in DES-*in utero* exposed patients, for early detection of CCA (11). On another hand, glandular cysts can develop in areas of adenosis, and mimic tumors: puncturing these cysts produces clear mucus and allow diagnosis of this benign condition (6).

There is no specific description of melanoma in situ. So, detailed conditions of its diagnosis are not available.

Management

Treatment decision for a preinvasive vaginal condition is predominantly based on VaIN grade and its focality (uni vs multifocal). A careful vaginal colposcopy and biopsies for histological confirmation are therefore prerequisites to an individualized management decision.

Data from the literature report VaIN progression to cancer in 0 to 5% of cases. Quite surprisingly, but maybe due to the rarity of the disease, rate of persistent or recurrent VaIN does not differ significantly with treatment or by grade: overall (11%), without treatment (VaIN 1: 15% - VaIN 2, 3: 7%) and with treatment (VaIN 1:13% - VaIN 2,3: 5%) (19).

Low grade VaIN are typically multifocal, varying in terms of localisation and/or colposcopic appearance. In a recent retrospective analysis, Gunderson reports that patients treated for VaIN1 present a recurrence/progression rate of 73% compared to 53 % for untreated patient (5). These data do not support upfront treatment for low grade VaIN, and favor observation in most cases.

It might be advisable to treat VaIN 1 in cases of unifocal VaIN1 or in cases of persistent lesions over 1 or 2 years, especially when adequate follow-up will not be possible. This depends on individual circumstances and preferences, and is expected to lighten the follow up.

High grade VaIN (ie VaIN2 and 3) must be treated. VaIN 3 has a reported rate of progression to invasion of 3% and may mask a microinvasion process (20). In the series of Hoffman, 9 of 32 cases of vaginectomy for VaIN 3 had foci of invasive carcinoma (21).

Available treatment modalities are medical, surgical, radiotherapeutic, and photodynamic.

Medical Treatments

Medical management comprises three main modalities: topical tricholoroacetic acid, 5-fluorouracil and 5% imiquimod. All 3 treatment modalities have a good success rate for disease clearance with low rates of progression to cancer. Other medical options are mainly under investigation.

- Trichloroacetic acid (TCA): TCA applied topically to the lesion, from one to three times per week to once each two to three weeks. Duration should not exceed two to three months, depending on the number of applications, mucosal tolerance, and response. At a concentration of 50 to 85% acts as a caustic agent inducing a burning effect. TCA is well tolerated when applied in the upper vagina, but causes transient pain in the lower third of the vagina. Local estrogen may be useful to better delineate the lesions from an atrophic background and to favour a quicker resolution of the ulcerative effect of TCA. It is best indicated as a first line treatment when lesions are unique or in limited number. Few studies reported results with 50% TCA. In a recent review, 100% clearance has been reported on low grade VaIN, and 53% on high grade VaIN (22).
- 5-Fluorouracil (5-FU) is a chemotherapeutic agent used as a 5% cream for vaginal self application. Its use for vaginal lesion is off-licence. Usual dosage is 2 gr, with several treatment schedules varying from twice a day for five days to one month, to once weekly for ten weeks. Well tolerated at the time of application, its long term use often results in vaginal or vulvar burning; the latter can be prevented by the local application of zinc paste. 5-FU use can also result in chronic ulcers occurring mainly when treatment period exceeds 10 weeks. Areas of columnar metaplasia, resulting in adenosis, may also develop after 5-FU treatment (4). Topical 5-FU is best indicated when extensive or multiple vaginal lesions are present. Due to its side effects, this should not be a first line treatment, but might be considered for recurrences, and / or in patients for which surgery or irradiation are not indicated. Recurrence rate after first treatment ranges from 7 to 59% and cure rates from 45 to 100% (4).
- Imiquimod acts topically on inflammatory/ immune response mediation, by improving cytokins action, particularly interferon alpha. Its use for vaginal lesions is off-licence. It is a self-applied treatment either digitally or using applicators or adeps solidus suppositories. Suggested dosage is 6.25 mg per application one to three times per week, for up to 16 weeks. Treatment may be started carefully and frequency adapted to tolerance and response. Inflammatory side effects are frequent but rarely lead patient to give up. Systemic side effects, especially fever or flu symptoms are more frequent than when applied on the vulva, maybe as a consequence of better vaginal absorption. It is indicated in the presence of multifocal lesions, and may be part of a multisite treatment, especially when concomitant vulvar lesions are present. Few cases of HG VaIN treatment with imiquimod have been reported, resulting in a total of 5 complete response, 2 regressions to VaIN 1, and 2 persistences, in two studies cumulating 9 patients (23, 24). One series reported results of VaIN 1 treatment with Imiquimod in 42 young patients, of which 36 (86%) completely responded and 2 of 26 available for follow up (8%) recurred (25).

Other Medical Treatments

- Cidofovir, an anti-viral agent is mainly used for treatment of recurrent respiratory papillomatosis, and has also been applied on intraepithelial neoplasia of the vulva and the cervix. On the vulva, complete, partial and no response occurred in respectively 4, 3, and 3 cases out of 10 (26). On the cervix, Cidofovir was applied locally previously to planned conisation, and 14 of 23 cones were free of CIN (60.8%) (27).
- Therapeutic vaccine: Vaccine expressed HPV 16-18 oncoproteins E6 and E7 have been tested on vulvar and vaginal intraepithelial neoplasia. Of 12 subjects, 1 (8%) showed complete response, and five (42%) showed a reduction of the lesion greater diameter of at least 50%. The only one case of VaIN included in this series was the only CR case (28).
- Poly-gamma-glutamic Acid: 12 patients with histologically proven VaIN (7 VaIN 1, 2 VaIN 2, 3 VaIN 3) were treated with this natural polymer reported as having an antitumor activity. Cytological regression was observed in 50%, and viral load reduction in 58.3%. Unfortunately, histological response was not documented in this series (29).

Surgical Treatments

CO2 LASER Ablation

CO2 LASER ablation consists in eliminating a lugol identified vaginal lesion down to the underlying stroma by vaporisation under local, regional or general anaesthesia. A 3mm perilesional margin should be respected (30). One and a half mm depth of treatment seems accurate to destroy VaIN (4, 30). Thermal damage to the underlying tissue is limited and allows rapid healing. Recurrence after first treatment goes from 10 to 67%, and success rates go from 50 to 100%, depending on the published series. Vaporisation may be repeated, leading to increasing success rate from 70.8 to 79.2% (30). This treatment is mainly indicated on multifocal lesions, for example after topical treatment failure, but also as part of a surgical resection procedure, for treating minor or peripheral lesions, in an attempt to limit resection

extension. It is especially indicated in young patients for whom vaginal disease is associated with cervical and or vulvar lesions that might be treated in the same time. LASER ablation is not recommended for treating lesions in the vaginal vault fornices, because limited access to this location limits both biopsy effectiveness in its goal of ruling out invasion, and the LASER therapeutic effect itself. Moreover, underlying structures are at high risk of damage (30).

Cavitational Ultrasonic Surgical Aspiration (CUSA)

CUSA consists in applying the handpiece of an ultrasonic surgical aspirator, in the same operative conditions than applied for LASER ablation. Recommanded depth (2mm) and margins (5mm) are within the same range. One study reports a comparison between LASER ablation and CUSA. In this series, vulvar and vaginal lesions were collected, and only half of the lesions were vaginal, which reduces interest of comparison for the present purpose. No difference was noticed in efficacy (no recurrence, cure rate of 75%). Difference in adverse effect, especially pain, did not reach statistical significance (31). Recurrence rate close to 20% and cure rate of 74% are cited (4). Indications and limitations should be similar to those for LASER ablation.

Surgical Excision

Excision of VaIN is favored when risk of invasion has not been reasonably discarted, or when ablative methods are not indicated, especially in deep recesses of the vaginal vault after hysterectomy. In some reports, invasive lesions have been diagnosed in up to 30% of specimen (32). Cold knife or C02 LASER vaginal excision may be conducted. Cold knife has the advantage to be worldwidely available and applicable for all type of lesions while LASER CO2 resection, on the other hand, allows a better control of the depth of resection and a better perioperative pain control and sexual function preservation (32). A recent series comprising 23 patients treated with C02 LASER vaginal excision followed up for 12 months or more describes 87% cure rate with low incidence of adverse side effects (32). Comparison of respective effectiveness between different techniques is not reliable, due to the limited size of studied populations and technique variations.

The extent of vaginal excision varies from focal to total vaginectomy, and the extent of resection is certainly the main factor conditioning secondary effects. Estrogen preparation may be useful in distinguishing normal from atypical tissue and in facilitating the dissection and the healing processes. Focal vaginectomy may be a simple procedure while total vaginectomy may be challenging, mutilating, and may lead to significant blood loss, post-operative hazards, and pain. Vaginal reconstruction is not always possible. Peroperative cystotomy, and per- or post-operative haemorrhage are the most frequent and significant complications of vaginectomy (20, 33). Any needed skin graft is at risk of recurrent disease and should be followed up carefully.

Radiation Therapy

Low or high dose rate brachytherapy are appropriate treatment approaches when (multiple) failures have occurred, for extensive disease especially in elderly patients, when surgical procedure is contra-indicated and sexual activity is not a concern. Fibrosis, narrowing and shortening of the vagina, atrophic and dystrophic changes of the epithelium, may lead to sexual and follow up difficulties. Bladder and bowel may be affected; menopause may also occur. Success rates range from 30 to 100% (20). In a recent series of 34 patients treated exclusively by brachytherapy, a mean dose of 40 Gy was delivered in 8 fractions, resulting in 88.2% success rate at 48 months. 2 recurrences, and 2 persistent diseases requiring a second line therapy. Seven patients had grade 1/2 acute urinary and rectal complications. 15 patients experienced late toxicity, predominantly vaginal mucosal reaction in 12 patients. Two of them suffered grade 3 vaginal stricture and permanent dyspareunia (34).

Photodynamic Therapy

This treatment consists in selective photosensitization of tumor tissue by means of a topical or systemic photosensitizer, which is then activated by a light of specific wavelength, to produce selective tumor necrosis, via a non-free radical oxidative process. In a series of 15 patients with either HG VIN or VaIN, or Paget's disease, 2 had VaIN 2, and 3 VaIN 3. Photosensitizer was an hematoporphyrin derivative. Of these five, at 12 months after treatment, 2 had complete response and 2 were in recurrence. The fifth case, which did not respond at 3 months, was once again treated with PTD but using 5-aminolevulinic acid as photosensitizer, and responded (35).

Conservative Management

High grade VaIN is not a short term life threatening condition. As a result, a series of medical conditions may result in delaying treatment. One may give up treatment in any case in which co-morbidity with a poor prognosis is present.

In some selected cases of healthy women, conservative management may also be considered. The lesion should have been documented by biopsies under colposcopy, and pelvic examination. Any risk of invasion has to be thoroughly excluded. If there is no history of genital cancer, if the patient is not immunosuppressed, if the lesion is unifocal, and less than 2-cm in diameter, conservative management may be discussed with the patient, considering the different treatment options and their expected effects and results (36).

Management of Melanoma in Situ and Other Rare Conditions

Preinvasive melanoma and other histological rarities, such as vaginal tubulovillous adenoma are so exceptional that complete excision of the lesion is recommanded to allow adequate histological and immuno-histological evaluation.

Management of epithelial disorders related to vaginal adenosis, whether they occur in DES *in utero*-exposed patients or not, should be individualized. Extensive ablative treatments on large metaplastic areas mimicking dysplastic changes should be avoided. Diagnosis may be difficult, due to the extent of adenosis and / or metaplastic changes, vaginal anatomy (cervical collar, etc), glandular hyperplasia due to oral contraceptive use, and patches of bleeding (6). VaIN 1, especially in this condition, has to be managed conservatively. Higher grade VaIN should be diagnosed and treated the same way as for non DES-exposed women. There is no reason to consider HG VaIN prognosis different from what it is in general population. Regarding CIN, it has been described that HG CIN and cervical cancer prevalence is respectively two and three-fold higher in DES *in utero*-exposed women (37), suggesting that a higher risk could be present for HG VaIN and resulting vaginal cancer. In situ clear cell adenocarcinoma doesn't seem to be described. On another hand, any biopsy on vaginal adenosis reporting tuboendometrial epithelium should be considered with great caution and resected. This is due to the fact that this epithelium is frequently observed, mainly with foci of atypia, immediately adjacent to the clear cell adenocarcinoma, this observation suggesting a role of precursor (38). Even if CCA due to DES exposure is rare, and getting rarer, it should be kept in mind that it can occur in post menopausal women, after DES exposure or not, and that vaginosis may also be present in some inflammatory conditions resulting in vaginal ulceration, such as Stevens-Johnson syndrome, LASER ablation, and 5-FU topical treatment (6).

Special Conditions

VaIN in HIV-Positive Patients

Women with HIV infection are at increased risk for anogenital HPV-related lesions, including intraepithelial neoplasias. In HIV-positive women, HPV infection, low CD4 T lymphocyte count and a history of frequent drug injections are significant risk factors (39). Incidence and severity of premalignant and malignant diseases of the cervix, vagina and vulva correlate with worsening immunodepression. Thus, HIV-positive patients should be carefully followed up: vulvar and cervico-vaginal examination is to be performed at any occasion of a pelvic exam. Especially, immunosuppressed women with CD4 cell count under 200/mm^3, or with a viral load of 500 copies or more / ml, should be examined every six months. Regarding treatment, no specific recommendations have been formulated, and treatment options are the same as for general population. On another hand, risk of recurrence after treatment, or risk of associated cervical, vulvar, and anal lesions are increased. Highly active antiretroviral therapy seems to reduce both incidence and recurrence of VIN. It should be the case for VaIN too, leading to the recommended use of this treatment for HIV-infected women with VaIN.

Pregnant Patients

During pregnancy, the main precaution is to rule out invasion, by appropriate biopsy despite the increased risk of bleeding due to the gestational status. There is no indication to treat any VaIN confirmed by biopsy during pregnancy. If ever, pregnancy is not a contra-indication to TCA use. A new examination, with biopsies, should be performed 6 to 9 weeks after delivery. If patient is still breast feeding, preliminary estrogen administration for 3 weeks will optimise colposcopy. Women feeling conflicted between this treatment and potential effect on breast feeding should be informed and reassured (40).

Follow Up

Follow up of patients who suffer VaIN must be planned on the long term.

In patients who have benefited from medical or surgical treatment, persistence, recurrence, or progression of persistent disease occur in 31% of VaIN 3, and 57 % of VaIN 2. In a published series, the data were collected on a mean follow up period of 18 months, suggesting that the follow up should be particularly cautious during the first two years following treatment (5). However, long term follow up is recommended, as it is for CIN: this is due to the common HPV aetiology, and to the fact that most VaINs have been found coexistent to CIN (4).

Vaginal cytology should be performed every 6 months for one to two years, and then yearly.

Value of hr-HPV detection based follow-up is promising, with a sensitivity of 90% and specificity of 78% (41).

As long as follow-up recommendations will be mainly based on cytology preferably to hr-HPV detection, and knowing the poor sensitivity of cytology, the place of vaginoscopy in the follow up may be questioned. There is no present recommendation about its use, but one could consider potential benefit of colposcopy during the first one or two years of follow up.

Follow up of DES *in utero*-exposed patients should take into account the biphasic shape of CCA incidence, indicating that new cases could occur in post-menopausal years, and not only in DES exposed patients (6).

Prevention

Prevention against VaIN should rely on anti-hr-HPV vaccines.

HPV-008 phase III study GSK internal data indicate that bivalent anti-HPV 16-18 vaccine is 80% effective in preventing HPV 16/18 VIN1+/VaIN1+, and 71.6% effective in preventing HPV 16/18 VIN2+/VaIN 2+.

Quadrivalent anti-HPV 6-11-16-18 vaccine demonstrated 100% efficacy in preventing HPV 16/18 induced VIN2+/VaIN 2+ (42).

In the near future, optimized prevention will be available: nonavalent anti-HPV 6-11-16-18-31-33-45-52-58 demonstrated the same efficacy as quadrivalent vaccine, in preventing HPV 16-18 related VIN2+/VaIN2+, but it also demonstrated 100% efficacy in preventing these conditions when related to HPV 31-33-45-52-58 (43).

Example

The figures presented here illustrate the case of a 37 years old woman, who underwent, in february 2012, a conization for a CIN 2 lesion, with positive endocervical magin. In July 2012, a vaginal hysterectomy was performed, with a final diagnosis of residual CIN 3, without certainty regarding the status of the pericervical margin on the final protocol.

She was referred for vaginal exploration, because a cytology sampled in September 2014, concluded to ASC-H.

On 15th October 2014, colposcopy showed a grade II atypical transformation zone developed on the right side of the vaginal vault, on an area of 2 by 4 centimeters, (Figures 1 to 3).

Colposcopy guided biopsy showed marked epithelial changes throughout the epithelium. Immuno-stainings for p16, Ki67 (both illustrated with histology, figure 4), PAV, and anti-involucrin corroborated histologic pattern of a VaIN 3.

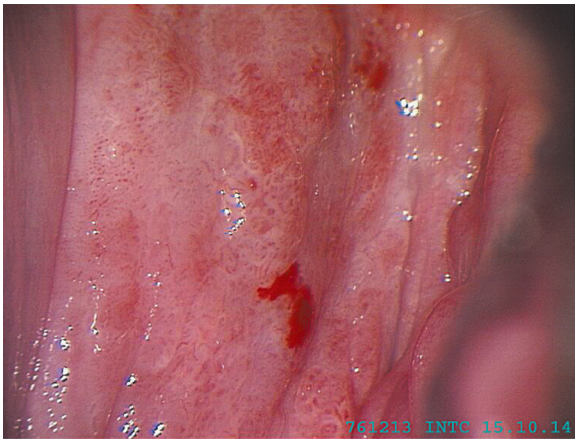

Figure 2. Vaginal colposcopy with 3% acetic acid. Dense and irregular acetowhitening, abnormal vascular pattern showing irregular vessels and punctation. Fragile epithelium may bleed.

On 12th January 2015, she underwent a partial CO2 LASER colpectomy. Histology confirmed a VaIN 3, focally reaching resection margins in three places. No complementary treatment was suggested, and follow up was initiated. Post-operative period was comfortable and uneventful, apart from appearance of a granuloma on the vaginal vault, which disappeared after TCA application.

On 11th June 2015, five months after colpectomy, vaginal colposcopy appeared negative, with grossly normal vaginal epithelium, no acetowhitening, and homogenous iodine positivity, as illustrated on figure 5. Liquid based Cytology (ThinPrep°) and hr-HPV detection by PCR (Abbott Real Time HR HPV°) were negative.

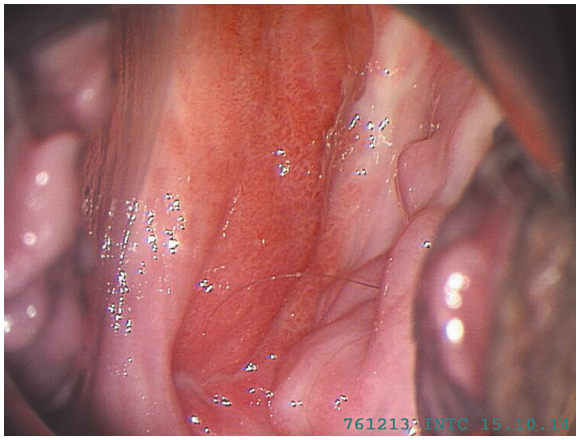

Figure 1. Vaginal colposcopy without preparation. Large antero-lateral area of irregular epithelium with marked congestion of the stroma.

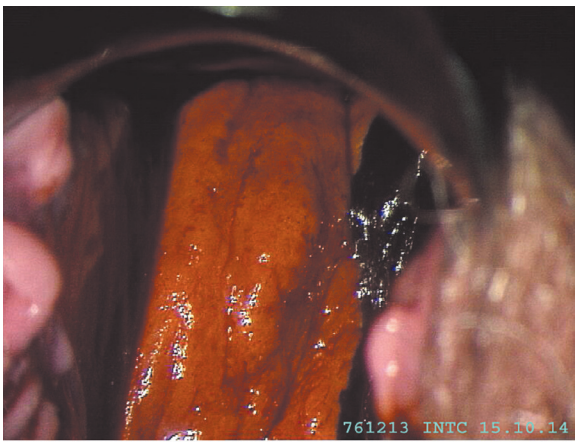

Figure 3. Vaginal colposcopy with 5% Lugol. The same area, showing frank iodine negativity with sharp borders.

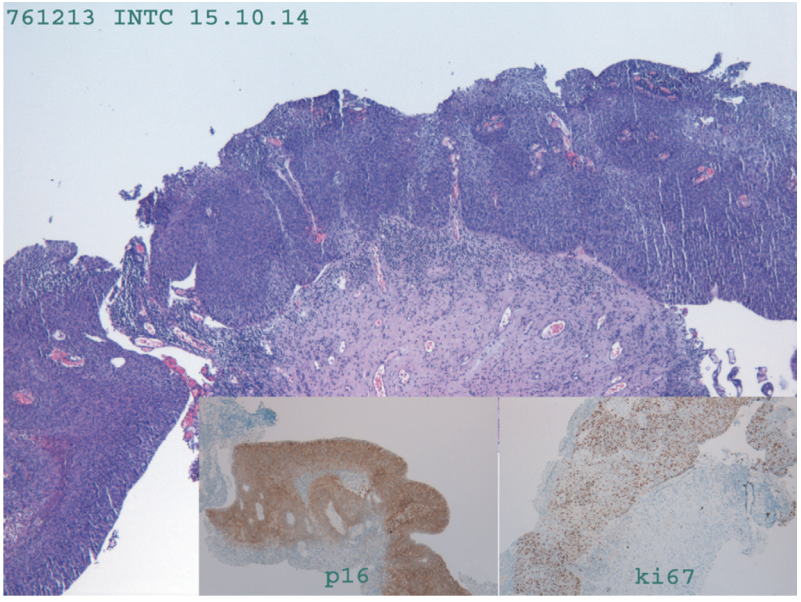

Figure 4. Same patient as fig 1 to 3. Microscopic feature of classic HG VaIN. Full-thickness atypia with absence of maturation. Intense Immuno-histological stainings for p16, indicating hr-HPV activity, positive on the whole height, and Ki67, indicating mitotic activity, positive in the two lower thirds.

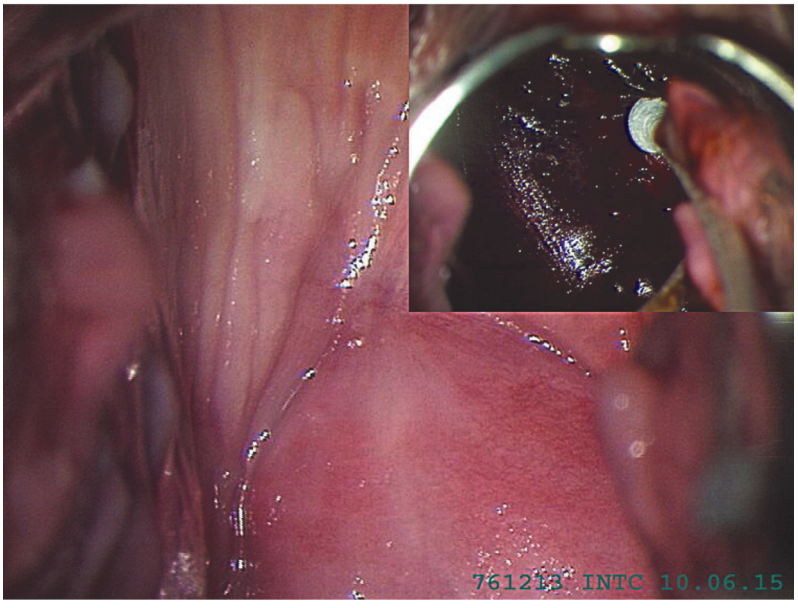

Figure 5. Same patient as in figures 1 to 3. Colposcopy of the vagina recovered to normal (no acetowhitening, no lugol staining defect), 5 months after LASER partial colpectomy. Negative cytology and hr-HPV PCR.

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