PRE - INVASIVE DISEASES OF VULVA

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Introduction

Pre - invasive diseases of the vulva include various histological entities, mainly the squamous, glandular and pigmented lesions. Squamous vulvar intraepithelial neoplasia is by far the most frequently recognized pre-invasive vulvar condition. Paget's disease of the vulva and melanoma in situ are both rare pre-invasive pathologies with a significant risk of invasion (1).

Vulvar Intraepithelial Neoplasia

Classification

The terminology for vulvar precancer has evolved throughout time. Terms such as Bowen's disease, erythroplasia of Queyrat, carcinoma simplex, Bowenoid papulosis, Bowenoid dysplasia, hyperplastic dystrophy with atypia and condylomatous dysplasia, dysplasia, or carcinoma in situ should no longer be used (2).

The Vulvar Intraepithelial Neoplasia (VIN) with its 1-3 grading system was introduced in 1986 by the International Society for the Study of Vulvovaginal Disease (ISSVD) as first attempt to stratify scientifically VIN. In 2004, the ISSVD reviewed this VIN classification. The term VIN 1 was no longer used, as it was not considered as premalignant and was referred to as condyloma acuminata or flat condyloma or HPV infection. The high - grade VIN lesions were subclassified into two main categories: the most common HPV-related VIN usual type (uVIN) and the less common (2-10%) non-HPV-related VIN differentiated type (dVIN). The latter is associated with vulvar dermatoses mainly lichen sclerosus. Rare cases that do not fit into these categories are termed 'unclassified' (3).

Two other pathological classification systems are in use. The World Health Organisation (WHO) still grades uVIN into three grades. In 2012, the Lower Anogenital Squamous Terminology Standardization (The LAST Project) gives a new terminology to all the HPV-related lesions and divides them into two grades: the low-grade squamous intraepithelial lesion (LSIL, including infection) and the high-grade squamous intraepithelial lesion (HSIL) (4).

Epidemiology and Risk Factors

In the last couple of decades, the incidence of VIN has increased significantly and the average age-adjusted incidence has also increased by a factor of 1.97 to 3.5% per year (5). Meanwhile, the mean age at diagnosis has decreased, with a first major peak reported between 40 and 44 years of age, and a second significant peak in women older than 55 (6,7).

The increase of uVIN among younger patients is mainly due to the infection of high risk HPV 16 (77.3%), HPV 33 (10.6%) and HPV 18 (2.5%) (8). Other risk factors such as cigarette smoking, immunodeficiency, immunosuppression and long-term use of oral contraceptives result in a doubling or tripling of the risk for high grade squamous intraepithelial lesions (2).

The dVIN occurs commonly in elderly women with a median age of 67 (6), and is generally associated with vulvar dermatoses like lichen sclerosus chronicus.

Table 1. Classification of Vulvar Intraepithelial Neoplasia

ISSVD 1986 / WHO 2003	ISSVD 2004	LAST 2012
VIN 1	Flat condyloma, HPV infection	LSIL
VIN 2 VIN 3	VIN, usual type a. warty type b. basaloid type c. mixed type	HSIL
Differentiated VIN	VIN, differentiated type	

Although the majority of vulvar squamous cell carcinoma (SCC) is not HPV-associated, dVIN accounts for only 2-10% of all reported VIN. The possible explanations for dVIN's low prevalence are that it is a transient lesion that rapidly progresses into invasive carcinoma and/or that it is an underdiagnosed or an underreported lesion due to the difficult histopathological interpretation (9).

Vulvar Oncogenesis

A part of the carcinogenesis for the uVIN is superimposable to that of the cervical carcinogenesis. After the viral DNA integrates in human host-cells, E6 and E7 oncoproteins are overexpressed. From there on, degradation of the tumor suppressor protein p53, and inactivation of the retinoblastoma tumor suppressor gene are induced, leading to escape from programmed cell death, with overexpression of the cell cycle-related marker p16 (2).

The knowledge on the HPV-independent pathway of the dVIN is still limited, but appears to be related to chronic oxidative genetic damages. Genetic mutations in the tumor suppressor genes TP53, PTEN and CDKN2A have frequently been detected. In addition, epigenetic alterations such as hypermethylation of the promoters of O-6-methylguanine-DNA (MGMT), Ras-association domain family 2A (RASSF2A), or thrombospondin-1 (TSP-1) have been described, suggesting that the alteration of these genes contributes to vulvar carcinogenesis (10).

Clinical Features

VIN is asymptomatic in about 50% of cases. When symptomatic, the main complaints include itching, pain and dyspareunia. The diagnosis is made during visual and colposcopic examination where routine application of acetic acid is discouraged as acetowhitening alone is not specific on the vulvar skin. Biopsy is the most important step for diagnosis. A single punch biopsy is considered adequate, however it may not be representative of the whole lesion, which may contain an occult invasive carcinoma in about 23% (11).

uVIN lesions are usually elevated, sharply defined white or erythematous papules/macules that may show a verrucous pattern. Approximately 10 to 15% of the lesions are pigmented. The surrounding skin or mucosa is usually normal. A local decrease in immunity to HPV infection is often associated with multifocality and multicentricity, where usually the same type of HPV is involved throughout the lesions (12).

dVIN lesions appear to have a less specific visual presentation and can be seen as focal discoloration, ill-defined white plaques, or discrete elevated nodules (12,13). They tend to be unifocal and unicentric and should be suspected when they exhibit treatment-resistance. They are mainly seen in older women with dermatosis such as lichen sclerosus, with a long-lasting history of itching, soreness, pain, burning, dyspareunia, dryness or bleeding (12). The dVIN is sometimes difficult to be distinguished from the associated dermatosis. Indeed, from the biopsies performed, only a minority will show dVIN. Concomitant intraepithelial neoplasia of the lower genital tract is rare in women with dVIN compared to uVIN (2.9% vs. 41.2%) (6).

Histopathological Features

The essential histological feature of VIN is a proliferation with atypical basal cells, associated with architectural changes of hyperkeratosis and/or parakeratosis, acanthosis and a dermal lymphocytic infiltrate.

VIN, Usual Type

The proliferation of atypical basaloid cells begins in the basal layer and involves partial to full thickness of the squamous epithelium. These dysplastic squamous cells resemble basal cells with scant basophilic cytoplasm and hyperchromatic large nuclei. Atypical mitosis and apoptotic bodies are common but nucleoli are rare. Towards the surface, these cells may mature and may develop abundant eosinophilic cytoplasm in dyskeratotic cells. Cytological signs of HPV-infection (koilocytotic changes, multinucleation, coarse granules) and acanthosis are common (12). uVIN may involve the skin appendages in more than 50% of the cases (14), resulting sometimes in difficulties to exclude early invasion. Two subtypes of uVIN have been described: the warty (condylomatous) and the basaloid (undifferentiated) types, but these are merely variants of the VIN usual type as they are part of a spectrum with often overlapping morphologies (12). The Pagetoid VIN is a rare variant of uVIN, where the atypical squamous cells present a pale cytoplasm and are isolated or grouped in clusters, resembling extramammary Paget's disease (EMPD) (12).

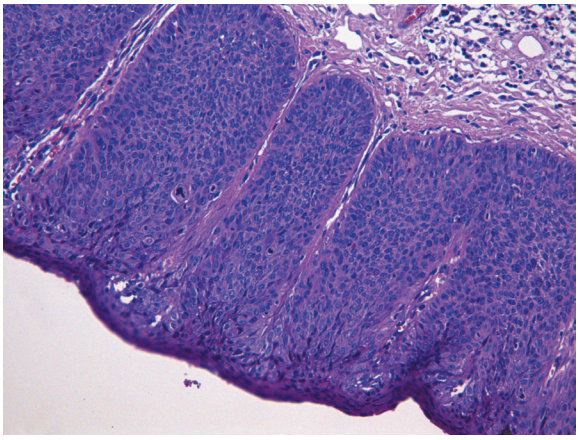

Figure 1. uVIN with proliferation of atypical basaloid cells beginning in the basal layer and involving full thickness of the squamous epithelium (H&E).

VIN, Differentiated Type

The characteristics of dVIN are much more subtle. The key features of dVIN are the basal nuclear atypia with premature maturation above them (12).

Recently van den Einden et al. (9) demonstrated that agreement between pathologists in the diagnosis of dVIN is low and extremely difficult, and thus often misdiagnosed as benign dermatosis. According to a panel of pathologists, consensus may be reached on characteristic histological features for the diagnosis of dVIN. Five histological criteria proved to be the most useful in this diagnosis : atypical mitosis in the basal layer, basal cell atypia, dyskeratosis, prominent nucleoli, and elongation and anastomosis of the rete ridges. In contrast to uVIN, dVIN is not frequently diagnosed as an isolated lesion and may occur synchronously in the skin adjacent to invasive cancer or benign dermatosis such as lichen simplex chronicus (12).

Another major problem is the difficulty to differentiate dVIN from early invasive SCC when separated small cellular nests invade the dermis, especially when the biopsies are superficial. In these circumstances, one must keep in mind the invasiveness criteria: small irregular nests of highly differentiated squamous cells or individual strongly atypical cells with prominent nucleoli and/or a desmoplastic reaction around the invasive nests (9).

Ancillary Studies

When contradictory histopathological features are present, one can rely on the p53 and p16 immunochemistry.

Diffuse and intense nuclear and cytoplasmic p16 staining typically correlates with high-risk HPV infection. Focal and weak positivity is nonspecific and supports the presence of wart. The main difference between condyloma and uVIN is the degree in basal atypia, which is less in the condyloma compared to the uVIN. p16 immunostaining is characteristically negative in dVIN as molecular studies have failed to demonstrate the presence of HPV DNA in the epithelium.

Ninety percents of dVIN show a high p53 positivity in the basal layer with suprabasal extension (12).

Ki67/MIB1 has been reported to help for distinction between dVIN and normal vulvar epidermis (9,12), as the basal cell layer of dVIN shows a higher proliferation index than the normal vulvar dermis.

The differential diagnosis between dVIN and dermatosis remains complex because the p53 expression is of little value. Lichen sclerosus and lichen simplex seem to frequently show the same basal cell positivity in the same pattern as dVIN (13), and seems to be associated with ischemic stress.

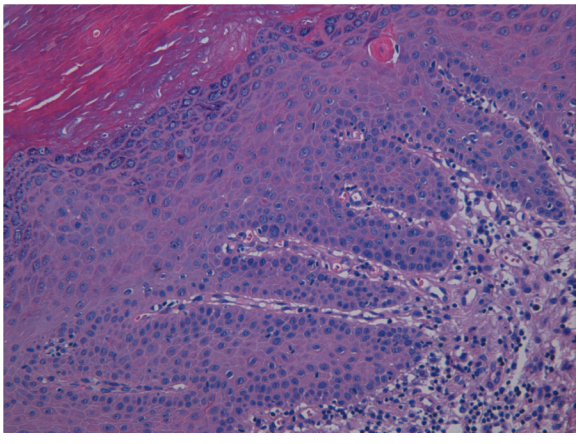

Figure 2. dVIN with atypical mitosis in the basal layer, basal cell atypia, dyskeratosis, prominent nucleoli, and elongation and anastomosis of the rete ridges (H&E).

Treatment

The ideal treatment aims to completely remove the lesion, relieve symptoms, prevent development of vulvar SCC and preserve normal vulvar anatomy and function.

VIN, Usual Type

The increasing incidence of uVIN in younger women and the lower progression rate tend to indicate a conservative management, as extensive surgery may affect the body image and the organ's function. There are few high quality data to guide the choice of treatment and no standard recommendations have been published (15). Therefore, VIN therapy should be individualized. Women who have a worrisome lesion with possibly invasive disease (eg.: raised, ulcerated or with irregular border) or who have clinically significant risk factors for invasive disease (eg.: previous VIN or SCC, immunosuppression, tobacco use, ≥45 years), need surgical resection. Women without such lesion's characteristics or risk factors even with extended lesion can benefit of ablative or topical treatment.

1. Surgical Procedures

Local excision, can be performed with cold knife, electrosurgery (LEEP) or laser CO2. These interventions seem to be similarly effective (13).

One important advantage of surgical excision, is that it provides both a treatment and a diagnostic specimen (about 23% of women with VIN on initial biopsy present an occult invasive carcinoma) (11). Appropriate management is to obtain a 5-mm macroscopically disease-free peripheral margin, with a disease-free depth of 1 mm in hairless to 4 mm in pilous areas (13). Recently, Ioffe et al. demonstrated that positive margins do not predict development of invasive disease (16), although they are known to predict recurrence. Therefore surgeons should aim to obtain clear margins whenever possible but also respect the organ function, taking into account the quality of life (QOL) of these patients. In circumstances of positive margins, close follow-up or alternatively adjuvant topical treatment may be proposed. The latter being evaluated in ongoing studies

(7). The recurrence rate after excision is estimated at 20% to 46%; the estimated mean time to recurrence being 22 to 44 months. Multifocal disease seems to be correlated with a higher recurrence rate (13).

Many consider that CO2 laser therapy is the treatment of choice in the management of VIN, particularly for those who have multifocal or multicentric disease or for those with lesions of the clitoris, the urethra or the anus. It is especially useful in mucous areas. A single laser therapy session is generally sufficient for treatment in about 75 to 80 % of patients (17) and may result in good cosmetic results when practiced by experienced hands. However, coexistence of invasive carcinoma needs to be ruled out by multiple biopsies of the thickest part of the lesion prior to the laser therapy (13,17). The complete response rate reported, is almost 75% in the largest series compared to 100% in vulvectomy and imiquimod cream, with a recurrence rate of 30% (13,17). Lower recurrence-free survival reported in laser-vaporized lesions compared to surgical excision may be due to the multifocal and multicentric lesions (51,3% vs 91% at 5-years' interval) (18).

2. Medical Treatment

Most studies on medical treatment of uVIN lack an adequate number of patients, uniform inclusion criteria, comparison groups, and adequate follow-up. Therefore, no conclusions about the therapies proposed can be drawn and further trials to investigate efficacy and safety are needed.

Imiquimod

It has been hypothesized that the high recurrence rate following surgical therapies is due to failure to remove the reservoir of high risk-HPV types present in the adjacent vulvar skin. Imiquimod is an immune response modifying drug, which could have the ability to generate HPV-specific cell-mediated immunity and potentially induce regression of VIN lesions.

In daily practice, a thin layer of imiquimod 5% cream is applied on the target lesion and remains overnight 2 to 3 times a week for a period of 12 to maximum 16 weeks. However, in about 46% of patients treated with imiquimod, important side effects, mainly presenting as intense local inflammatory reaction, may require temporary withdrawal of treatment (19). For better tolerance, one can suggest an escalating dose regimen starting with an application once a week for 2 weeks, then twice a week for 2 weeks followed by application 3 times a week. Patients must be monitored for efficacy, side effects and symptoms.

In a recent large prospective, randomized, double-blinded and placebo-controlled study (20), Terlou et al. report a 35% complete and a 46% partial response after imiquimod application. After about 7 years of median follow-up, they demonstrated that VIN only recurred in one of the complete responders, suggesting a long term effect from imiquimod (21). Accordingly, a meta-analysis of randomized controlled studies, demonstrated a complete response of 58% to 38% of patients at 6 months and 12 months of treatment respectively (15). Overall, imiquimod seems to offer important benefits: the avoidance of surgery, a lower recurrence rate for complete responders and could be relevant in heavy smokers or immunocompromized patients.

3. Investigational Therapies

Therapeutic Vaccination

There have been preliminary investigations regarding treatment of women with established VIN who benefit from HPV vaccines designed to trigger a cellular immune response. In this context, Kenter et al., demonstrated that vaccination with synthetic long peptides presenting the two oncoproteins E6 and E7 of HPV-16 is effective. He reported a partial response of 32% (95%CI,13-57) with a complete response of 47% (95%CI,24-71) over a period of 24 months. However, the costs for the development of vaccines are high, and at the moment, the focus is on preventive vaccines rather than therapeutic vaccination (7).

Cidofovir

Cidofovir is a nucleoside analogue with antiviral properties. In a randomized, open-label, phase 2 trial, a complete response has been achieved in 46% (90% CI,37.0–55.3) with 87% of patients adherent to the treatment regimen after 6 weeks. Adverse events grade 3 or higher were reported in 37% and were mainly pain in the vulva, pruritus, fatigue, and headache. Cidofovir seems to be better tolerated than imiquimod and could be reserved for patients in whom imiquimod is inefficacious (19). However, cidofovir should be used with careful biological monitoring, as cases of patients presenting acute renal failure during topical treatment are reported, especially when prior renal insufficiency was present or when the skin is abrasive.

Photodynamic Therapy (PDT)

PDT is based on a photochemical reaction induced by a combination of an oncophilic photosensitizing agent and light. A clearance rate of 40 to 60% with similar rate of recurrence compared to laser vaporization and excision has been published, but more trials are needed to confirm efficacy and safety (13).

4. Special Patient Populations

Immunocompromized Patients

Treatment failure, recurrence (60-80%) and progression to SCC are more likely in immunocompromized women. There are no treatment consensus guidelines in this group of women and current treatment strategies are not effective in clearing anogenital HPV-infection. Recently,

cidofovir showed a 51% efficacy in the treatment of uVIN with acceptable toxicity in HIV patients with short follow-up (22).

Pregnant Patients

Treatment options seems to fall into two categories: observation or surgical management. Spontaneous regression has been described, particularly in women who were asymptomatic and younger than 35 years of age with multifocal lesions (12). The expectative approach may be only considered when invasive carcinoma has been ruled out after biopsy. When surgical therapy is proposed, either local excision or ablative therapy as in non-pregnant patients can be performed (23).

Medical therapy as topical imiquimod is classified as a category C drug by the US Food and Drug Administration (FDA) and should only be used if the presumed benefit justifies the potential teratogenic risk. Neither the safety nor the efficacy of the use of imiquimod during pregnancy are clearly established (24). 5-Fluorouracil is a category D drug and therefore contraindicated during pregnancy.

VIN, Differentiated Type

As dVIN is associated with a high risk of developing invasive disease, surgical excision is the treatment of choice and medical therapies should be avoided (25). Resection can be performed with cold knife, LEEP and laser CO2. Wide local excision is the preferred procedure. However, when multifocal or large and confluent lesions are present with no suspicion of invasion, a vulvectomy (simple or skinning) is the choice to make.

Prognosis

If left untreated, VIN may persist, progress or regress. In a systematic review, 9% of women with VIN (not treated or treated with residual macroscopic disease), developed invasive vulvar carcinoma over a one to eight year period. Half of these patients had previous radiation therapy of the genital area, and one patient (1/8) was immunosuppressed (12). Amongst 13 other studies, a complete spontaneous regression in a total of 41 patients was reported. All were younger than 35 years of age with multifocal lesions and 17 women were pregnant (12). It seems that dVIN has a significantly higher risk for progression to SCC than uVIN (5.7 vs 33%), with a shorter time to progression for dVIN (26).

Follow-Up

The risk factors for VIN recurrence after treatment include immunosuppression (tobacco use), multifocal and multicentric disease, large lesion size or a surgical specimen with positive margins (27). The recurrence rate after prolonged follow-up is estimated at 30% of all women with VIN, all treatment confounded (27). Because of the high risk of recurrence and risk of progression to invasive carcinoma, long-term surveillance is mandatory. There is no consensus about the duration or the frequency of the follow-up. The ACOG for example, recommends a post therapy visit at 6 and 12 months, and then annually. Patients should be encouraged to stop smoking (27); cervical cytology or HPV DNA screening should be proposed annually in uVIN patients because of the high risk of the presence of multicentric intraepithelial lesions.

Primary Prevention

It has been demonstrated that sustained protection from uVIN can be obtained with a prophylactic HPV vaccine. In a recent randomized study, it has been shown that in the HPV-naive population, the 9-valent HPV (9vHPV) vaccine efficacy against HPV-31, 33, 45 and 58 related VIN was 96.7% (95% CI,80.9 -99.8%) and that the incidence of diseases related to HPV- 6, 11, 16, and 18 were similar in the two vaccine groups. Studies of the quadrivalent HPV vaccine have not shown any evidence of waning immunity in long-term cohorts. However long-term follow-up of the 9vHPV vaccine is needed before drawing the same conclusion (28).

Vulvar Paget's Disease

Paget's disease of the vulva refers to mucinous intraepithelial carcinoma affecting glandular cutaneous cells in the vulvar region. The exact incidence of Extramammary Paget's Disease (EMPD) is unknown, but it is estimated to be 1 to 6% of all cases of Paget's disease. Vulvar EMPD affects mainly Caucasian postmenopausal women (1) and can be considered as an indolent chronic disease. Prognosis is very favorable with an estimated 5-year survival of 85%. The lesions typically present as multifocal erythematous-white plaques and are often accompanied by pruritus or pain. Because of its non-specific clinical findings and the rarity of vulvar Paget's disease, the diagnosis is often delayed. When there is no response to standard therapy within a short time frame, biopsy is warranted (29). Vulvar EMPD can be classified into primary or secondary based on the site of origin of the neoplasm. Most women present with primary or cutaneous vulvar EMPD and is defined as an intraepithelial mucinous adenocarcinoma originating from the skin (epidermis or underlying apocrine sweat gland). Primary EMPD, can be further subdivided into a primary intraepithelial cutaneous form with or without invasion on one hand and, an intraepithelial cutaneous Paget's disease as a manifestation of underlying adenocarcima of skin appendages on the other hand. About 5% are secondary vulvar EMPD and are due to spread to the skin of an underlying adenocarcinoma, most commonly of urothelial, ano-rectal or cervical origin (30). The recurrence rate of EMPD is estimated to be as high as 34%, at a median time interval of three years, with 12% having invasive Paget's disease of the vulva and 4% vulval adenocarcinoma (1).

Histopathological Features

Microscopically, EMPD consists of large nests or small clusters of large intraepidermal cells with atypical vesicular nuclei, prominent nucleoli and abundant pale-staining mucin cytoplasm. They usually are most numerous within the basal layers and most commonly extend to the skin appendages structures. EMPD subtypes may present morphologically in a similar way, and may also mimic other pre-invasive diseases of the vulva. In such cases immunochemistry helps to establish the final diagnosis. The neoplastic cells of primary vulvar EMPD are typically immunoreactive for CK7, CAM5.2, CEA, EMA and BerEP4 (31). The immunoreactive profile is useful to differentiate EMPD from malignant melanoma in situ, Pagetoid VIN and VIN with mucinous differentiation, which are generally negative for these markers. The addition of p63 staining in the panel of markers seems to be useful to differentiate Pagetoid VIN from EMPD since it is completely negative in the atypical cells of EMPD conversely to the neoplastic cells of Pagetoid Squamous Cell Carcinoma In Situ (SCCIS) (32). Secondary vulvar EMPD from the colorectum or urinary bladder exhibits the immunophenotype of the primary adenocarcinoma. Thus immunoreactive for CK20, CDX2, MUC2, when the origin is colorectal; and immunoreactive for CK20, CK7 with uroplakin-III when the urothelium is the primary neoplasm (31). Overexpression of the Her-2 neu protein has been found in about 38% of vulvar EMPD (33).

Treatment

Standard of care for EMPD is surgical treatment, although there is a wide variation in the recommended radicality (1). EMPD is often multifocal and typically has a larger extent of microscopic disease than that of the visible lesion, leading to frequent positive resection margins and high rates of local failures. Intra-operative frozen section evaluation of the surgical margins have not shown to be helpful in reducing the recurrence rate (29). Furthermore, local recurrences occur even after extensive surgeries with negative margins and have been recorded in skin grafts performed for reconstructive purposes. Two theories could explain this phenomenon: 1. a well vascularized wound may allow existing Paget cells to survive the wound healing inflammatory process; 2. surgeries with reconstruction involve generally large resections for widespread disease, which are more likely to persist (29). In the past decade, there has been a shift towards a more conservative surgical approach, a wide excision with a 2 cm negative peripheric margin (34) and a 4-6 mm depth to include the pilosebaceous units and skin adnexal structures, is considered adequate (35). As resection is also the standard of care for recurrences, multiple surgeries lead to anatomical and functional mutilation. In order to decrease the morbidity, alternative treatments such as radiotherapy, CO2 laser ablation, topical imiquimod, photodynamic therapy and targeted therapy have been proposed. However, based on the current available literature, no recommendations regarding treatment modalities can be made, as none of the treatment options (including surgery) are clearly evidencebased (1).

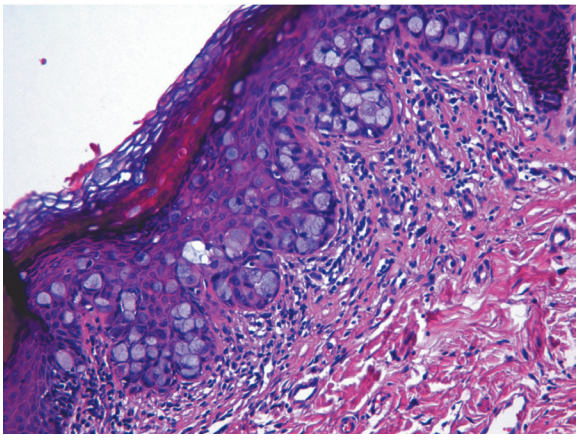

Figure 3. EMPD with infiltration by nests of large intraepidermal cells with atypical vesicular nuclei, prominent nucleoli and abundant pale-staining mucin cytoplasm (H&E).

Radiotherapy has been proposed as exclusive treatment or complementary to surgery. It is mainly considered in aged patients, in patients with severe comorbidities or refusing to undergo further surgery or in patients with uretral or anal involvement that would require extensive surgery for complete resection. Although the optimal radiation field as well as the optimal radiation dose for EMPD is still unclear, disease control in the setting of curative intent has been estimated at 82% at 5 years, with local recurrences mainly outside of the radiation field (36).

CO2 ablation has been used with the purpose of preserving vulvar anatomy but it has the inconvenience of being very painfull, and has a higher incidence (about 67%) of local recurrences compared to the other treatment modalities (34).

Topical imiquimod 5% cream seems to be effective, with minimal treatment-associated morbidity. It may induce complete responses in primary and recurrent vulvar EMPD. The optimal median treatment time seems to be 4 months with an initial treatment frequency to be 3 to 4 times a week (37). However failures and appearance of stromal invasion under treatment are reported in up to 22% of cases (34).

Photodynamic therapy (PDT) is considered to be a feasible and well tolerated treatment, that can be performed in an outpatient setting, and may offer potential clinical benefit in terms of quality of life. Even if it is not considered curative, it is believed to

result in excellent control of symptoms (in about 61.5% of patients), with partial response observed in 87.5% of patients with very extensive lesions. The risk for progression to invasive disease seems to be very low. Once an underlying carcinoma has been ruled out, it is mainly indicated in patients with recurrent disease, or for those who are not fit for surgical procedure or would require very extensive destructive surgery (34).

Targeted therapy with trastuzumab has been reported in selected cases of vulvar EMPD showing Her-2/neu overexpression (33).

Overall, long-term surveillance is recommended, as recurrences are common and can be observed many years after initial treatment (29).

Melanoma In Situ of The Vulva

Vulvar melanoma in situ (MIS) is rare and appears to progress slowly, but definitely to invasive melanoma (38). When properly diagnosed and accurately treated, it is associated with an excellent prognosis. In pigmented lesions, the ABCDE scheme should be applied to diagnose melanoma. ABCDE stands for Asymmetry, indistinct Borders, Color variation, large Diameter (> 6mm), Evolution of color change, shape or symptoms. Eight to 29% of vulvar MIS are found to have invasive foci (39). Therefore, all suspicious pigmented lesions should undergo histopathological evaluation. Small lesions should be completely excized and when confluant areas are present, punch biopsy is acceptable in the thickest region as long as the entire lesion is excised later on. To date, the standard treatment is surgical excision with clear margins, but no optimal required width of surgical margin is defined. The 5-mm accepted margin based on the National Institutes of Health Consensus of 1992 seems to be inadequate. A recent prospective study of 1120 melanoma in situs recommends a standard surgical excision margin of 9 mm based on their 97% clearance and 0.3% local recurrence. This correlates with the more recent expert opinion of the 2011 AAD Guidelines which recommend a 5- to 10-mm margin. Another surgical alternative, is the Mohs micrographic surgery (intra-operative frozen section analysis of margins) which obtains a complete histological margin control and a same low recurrence rate (39). There is a paucity of data regarding the use of topical agents for the treatment of vulvar MIS. However, there have been a growing number of reports suggesting that imiquimod can be an effective alternative treatment for MIS. In a recent retrospective study of a cohort of 22 patients, a 95% complete clinical response rate was achieved (38), supporting the use of topical imiquimod as an alternative or a complementary treatment to surgery. The degree of inflammation around the site of disease seems to be a reliable predictor of outcome and statistically significantly associated with the histopathologic clearance. Still, the clinical treatment protocol for topical imiquimod is not standardized, and larger studies need to be performed with longer follow-up.

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