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Review

A review of extramammary paget's disease: Clinical presentation, diagnosis, management and prognosis

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Abstract

Extramammary Paget's Disease (EMPD) is a rare neoplastic lesion, which represents less than 1% of vulvar neoplasms. The lesion generally appears as eczema and the most frequently reported symptom is the itch. Also because of these poor clinical features, there is usually a delay in its diagnosis, based on the typical biopsy histological pattern. It has a good prognosis in absence of malignancy, but can result in a heavy quality of life impairment because of frequent recurrence with necessity of ablative therapies and anxiety for possible cancerization. Rarely EMPD can be invasive or associated to adenocarcinoma or other kinds of cancer. The first choice therapy is the surgical excision, with inguinal lymphadenectomy in case of infiltrative disease. However, many other conservative therapies, including the topical use of antiblastic, immuno-modulating, and hormone-modulating drugs, are used against EMPD even if still off label. After completion of this article, the reader should be able to recall the clinical manifestations of the EMPD, the histological pattern which allows its diagnosis, and to state the options for a treatment, which should be conservative and at the same time as radical as possible.

Keywords: Extramammary Paget's Disease; Vulva; Conservative treatment.

INTRODUCTION AND EPIDEMIOLOGY

Paget's disease is considered to be an intraepithelial adenocarcinoma, whose first case was described by James Paget in 1874 as a breast lesion. Since then, it has been surrounded by controversy, speculation and much interest on the part of surgeons, pathologists and dermatologists. Due to its rare incidence, no clear diagnostic and treatment guidelines are available yet (Siesling et al., 2007). The lesions are primarily found along the "milk line", where the sites of involvement are anywhere apocrine exhibiting that type of glandular secretion in which the free end of the secreting cell is cast off along with the secretory products accumulated therein (e.g., mammary and sweat glands).

A Paget-like lesion identified in another site is called Extramammary Paget's Disease (EMPD), whose first case was described in 1889 by Crocker. EMPD can generate from all areas characterized by a high density of apocrine glands, as the axilla, the anus and perianal region, the vulva in women, the penis and the scrotum in men. Vulvar EMPD accounts for the majority of EMPD

Abbreviations: AIN: Anal intraepithelial neoplasia; **AR**: Androgen receptor; **CEA**: Carcinoembryonic antigen; **CK**: Cytokeratin; **EMPD**: Extramammary Paget's Disease; **ER**: Pstrogen receptor; **ERK**: Extracellular regulated protein kinase; **FAK**: Fokal adhesion kinase; **GCDFP-15**: Gross cystic disease fluid protein 15; **Her2/neu**: Human Epidermal growth factor Receptor 2; **JAK**: Janus kinase; **LH-RH**: Luteinizing-hormone-releasing hormone; **MUC**: mucin; **PIN**: Penile intraepithelial neoplasia; **PR**: Progesterone receptor; **Sp1**: Specificity Protein 1;**Tag-72**: Analysis of a Human Tumor-associated Glycoprotein; **TLR**: Toll-like receptor; **VEGF**: Vascular endothelial growth factor; **VIN**: Vulvar intraepithelial neoplasia; **UPK**: Uroplakin III.

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findings (76%) (Pierie et al., 2003), although vulvar EMPD remains a rare neoplastic finding, representing less than 1% of the vulvar neoplasms (Fanning et al., 1999).

On the other hand, interesting is the case of an EMPD presenting as alopecia neoplastica and described in 2008 by an American team as a poorly circumscribed erythematous plaque with patchy alopecia of the scalp. Histology of this lesion showed pagetoid infiltration of the epidermis by atypical single and nested cells, which resulted to be positive for the markers common to Paget cells (Iwenofu et al., 2008).

Epidemiologically, Paget's disease is essentially a disease of postmenopausal Caucasian women, with a mean age at the diagnosis of about 70 years, as many studies have documented (Banerjee et al., 2005; Shaco-Levy et al., 2010).

The prevalence of invasive disease is reported to occur in 5-25% of patients (Awtrey et al., 2003; Hoffman and Cavanagh, 1997). The average interval between the diagnosis of intraepithelial vulvar EMPD and its sequential progression to invasive carcinoma amounts approximatively to 11 years (Hart and Millman, 1977).

Between 17% and 30% of the patients with EMPD may have an underlying adenocarcinoma (Parker et al., 2000). A higher rate of underlying adenocarcinoma was found in patients with perianal involvement and palpable masses in the vulvar region (Berardi et al., 1988). For example, vulvar EMPD can also be extended to the upper vaginal mucosa and cervix, as in a reported case of an elderly woman who had EMPD associated with vulvar adenocarcinoma and a uterine prolapse (Lloyd et al., 1999). In 10-20% of cases EMPD is associated to coexisting malignancies at other sites, as the breast, the skin basal cells, the rectum, the genitourinary tract and the cervix (Hoffman and Cavanagh, 1997; Parker et al., 2000; Tebes et al., 2002).

About that, a Spanish study suggests a relationship between the site of EMPD and the probability to find an adenocarcinoma of cutaneous adnexal structures or an internal malignancy. More in detail, this study reports that vulvar EMPD was associated with adnexal adenocarcinoma in 4% of cases and with a distant malignancy in 20%, while perianal EMPD was associated with adnexal adenocarcinoma in 7% of cases and with an internal malignancy in 14% (Pascual et al., 2008).

Many studies report cases of EMPD associated with internal malignancies. For example, a recent Korean study has documented an association with gastrointestinal neoplasms, intended as both a gastrointestinal malignancy and a colorectal adenoma. This study also reported that this association with gastrointestinal neoplasm was stronger when a EMPD was found in male patients (Yoon et al., 2008). These results are also supported by an American article, presenting the case of a synchronous primary perianal Paget's disease and a rectal adenocarcinoma (Shi and Argani, 2009).

Moreover, a recent Taiwanese study has reported an unusual case of EMPD of the scrotum associated with hepatocellular carcinoma (HCC). The EMPD was diagnosed one year after the appearance of a scrotal erythematous plaque, and a HCC nineteen months later (Li et al., 2009). Again, an American study reports a rare collision of EMPD and malignant melanoma, by describing the case of a 78 years-old woman with a pigmented vulvar mass, which the biopsy turned out to be a malignant melanoma. Peripheral to the main mass, erythematous and thickened plaques were described, which resulted to be histologically an EMPD (Hill *et al.*, 2008). A Danish study cites the association of EMPD and an underlying prostate carcinoma (Hammer *et al.*, 2008).

In any case, due to the high incidence of coexisting malignancies at other sites, EMPD diagnose should not leave out to take into consideration additional controls as mammography, colonscopy, colposcopy and cervical cytology with Papanicolau staining (Dimitroulas and Settas, 2009; Minicozzi *et al.*, 2010).

Clinical presentation

The most common symptoms are pruritus, burning pain, lump (Lu *et al.*, 2004), and occasionally a painful erosion (Sommer *et al.*, 2006). A visible lesion, typically an erythematous plaque is present in almost all patients (Figures 1A, 1B, 2A, 2B, 2C, 2D, 2E, 3A, 3B, and 3C). The average lesion's dimension is of about 5 cm and the lesion is in the most of cases unilateral with no side prediction. Major labia are the most often involved site, followed by minor labia, clitoris, perineum and the perineal area (Shaco-Levy *et al.*, 2010).

The usual clinical eczematous appearance of the EMPD and other early signs, as localized depigmentation in the genital area, lead often to misdiagnoses (Chen *et al.*, 2001; Yang *et al.*, 2004).

If a mass is palpable, invasive disease or underlying adenocarcinoma are always clinically suspected (Louis-Sylvestre *et al.*, 2001), since many works have described clinical cases in which this association was documented.

As already mentioned, previous studies have stated that the frequency of occurrence of an associated underlying adnexal adenocarcinoma is in the order of 10-30% (Chanda, 1985). About that, some theories suggest that intraepidermal adenocarcinoma cells have metastasized to the overlying surface from the underlying carcinoma, whereas others have suggested that Paget cells infiltrate downwards to develop invasive disease. On the other hand, an American group has lately described a unique case: a primary perineal Paget's disease in collision with a colorectal adenocarcinoma. As just observed, perianal Paget's disease usually represents intraepidermal extension of an invasive carcinoma from an adjacent

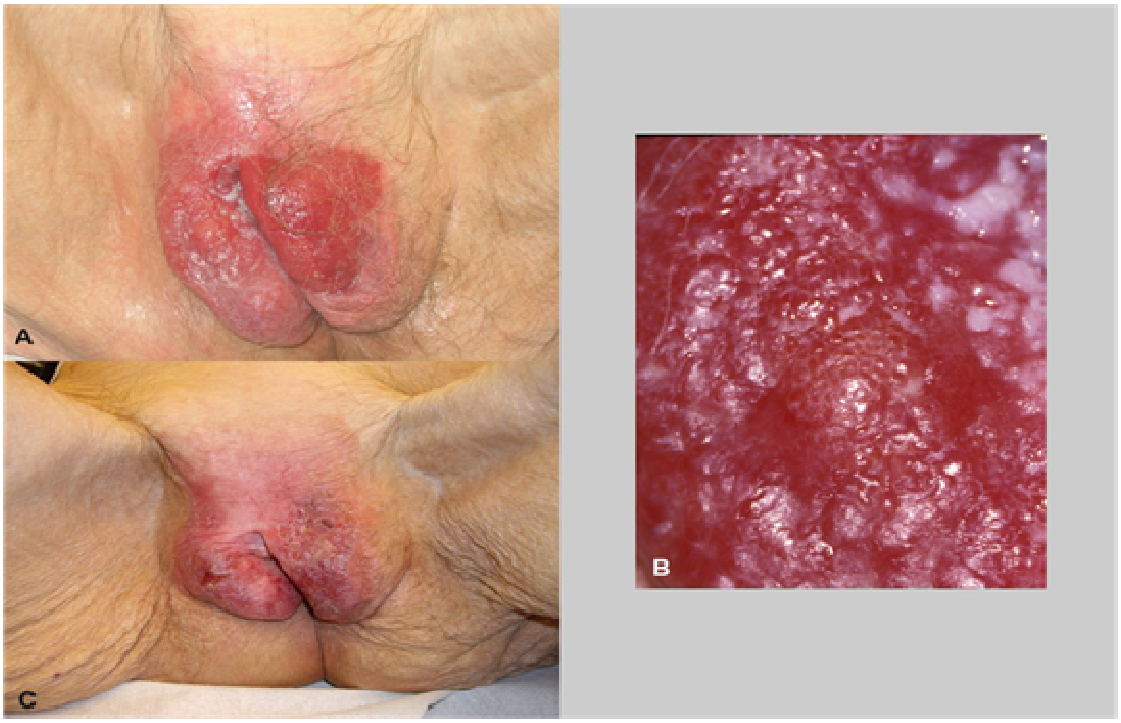

Figure 1. In 1997 at the age of 84 years it was performed an emivulvectomy to this woman because of right vulvar EMPD. At the age of 92 years, the patient presented with local recurrence (Panel A and B), characterized by severe itching. Panel B represents the 15x colposcopic image of the lesion. The relapse was treated with radiation therapy (2006) that leads to remission of disease (Panel C).

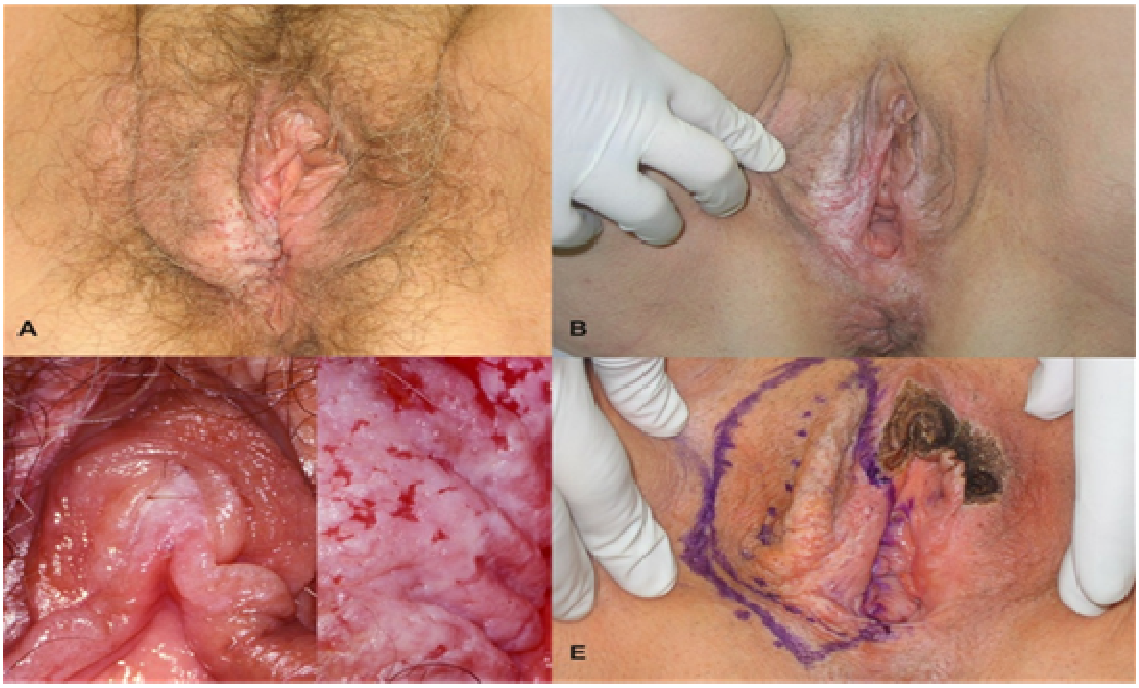

Figure 2. This picture refers to a patient who presented in May 2006, at the age of 70 years, with a history of 5 years intense itching and a lesion located mainly in the right large and small labia (Panels A and B). After biopsy the diagnosis was vulvar EMPD. In June 2006 she underwent surgical resection of the greater lesion and colposcopic-guided carbon dioxide laser vaporization of the satellite lesions (Panels C and D). Panel C and D colposcopic view of the satellite lesions (15x). Panel E view after carbon dioxide laser vaporisation and before surgical excision of greater lesion.

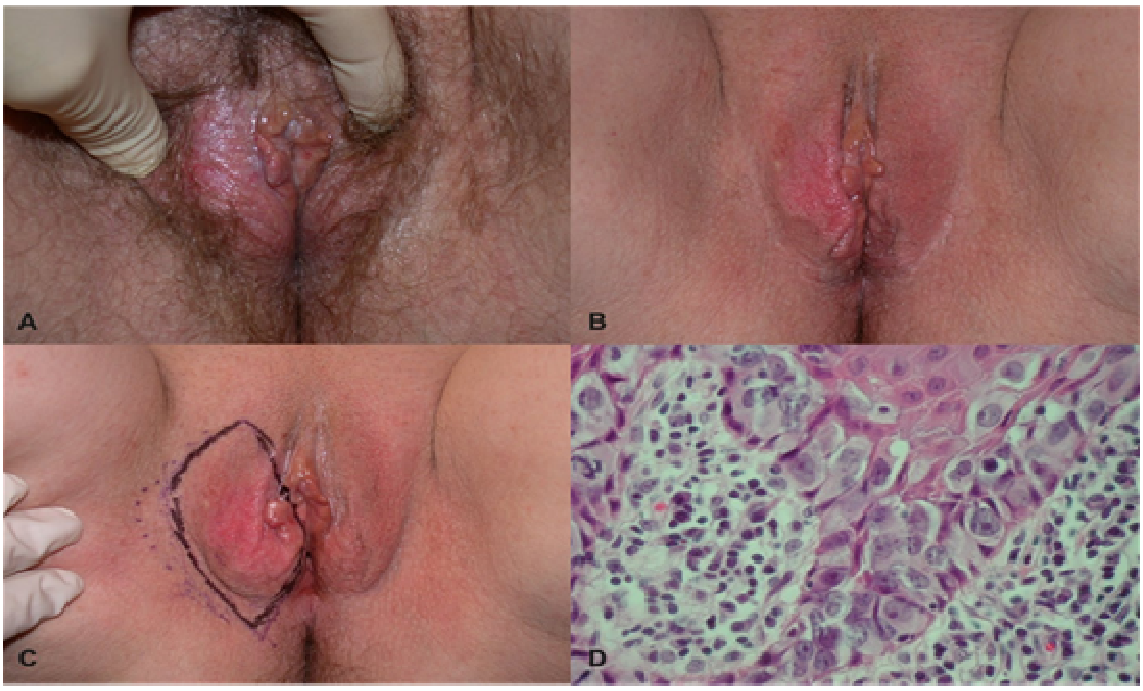

Figure 3. This patient in 2004, aged 63, underwent to surgical resection of a lesion with a diagnosis of Paget microinvasive adenocarcinoma (Panels A, B, and C), which comes to the margins of resection. Then, we performed a second operation with multiple biopsies on the previous scar and carbon dioxide laser vaporisation under colposcopic guidance and currently the women is disease-free. Panel D refers to histological characteristics of Paget's disease. Clonal nests of pale-staining dysplastic cells are located within the epidermis (Panel D). The tumor cells also compress the basal layer of squamous cells in the epidermis (Panel D).

internal organ, but some cases represent primary intraepithelial cutaneous apocrine adenocarcinoma. In this case, immunohistochemical stains demonstrated that the Paget's cells were CK7+/ CK20- (cytokeratines) and Gcdfp+ (gross cystic disease fluid protein), whereas the rectal adenocarcinoma was CK7+(variable)/CK20+/ Gcdfp-. This discordant immunoprofile supported the hypothesis that the Paget's disease in this patient was of cutaneous apocrine origin rather than a pagetoid extension from the patient's nearby rectal adenocarcinoma (Shi and Argani, 2009).

Histology

EMPD is histologically characterized by the presence of Paget cells, that are atypical glandular-type cells, larger than the adjacent keratinocytes and have finely granular amphophilic to basophilic cytoplasm. The cytoplasm is paler than that of adjacent keratinocytes and may be vacuolated and form signet ring cells. The nucleus is typically round or oval with one or more prominent nucleoli. Typically, they are grouped predominantly within the basal and parabasal zone, with fewer cells present superficially (Kurman *et al.*, 2010). Histochemically, some or all of the tumor cells contain acid mucin, as evidenced by their positivity for Mayer mucicarmine and aldheyde fuchsin stains. Immunohistochemically, these mucins are positive for MUC1 and MUC5AC, the latter in striking contrast with Paget disease of the breast (Helm *et al.*, 1992).

Beside the polygonal Paget cells, another cell population was described: in all cases of EMPD, Paget cells were intimately associated with small, flat, mitotically active, compressed keratinocytes, which are also considered integral part of EMPD. This dual cell population is reminiscent of sebaceous glands with mature sebocytes and germinative keratinocytes. Therefore, EMPD could be viewed as a carcinoma of multipotential cells (adnexal stem cells) residing in the infundibulosebaceus unit of the hair follicles and other adnexal structures that differentiate along glandular (sweat gland) lines (Regauer and Beham-Schmid, 2006) (Figure 3D).

The neoplastic lesion is usually accompanied by tissue reactive changes such as hyperkeratosis (thickening of the stratum corneum, often associated with a qualitative abnormality of the keratin), parakeratosis (keratinization characterized by the retention of nuclei in the stratum corneum), epidermal hyperplasia (increased thickness and number of cells) and epidermal acantholysis (loss of intercellular connections resulting in loss of cohesion between keratinocytes). Chronic inflammation with small capillary proliferation is also a

Table 1. Histological differential diagnosis among EMPD types (Wilkinson and Brown classification).

EMPD	Useful Markers
Primary (cutaneous origin)	
A) intraepithelial cutaneous Paget disease of the usual type	**POS**: CK7; GCDFP; CEA;
B) intraepithelial cutaneous Paget disease with invasion	
C) intraepithelial cutaneous Paget disease as a manifestation of underlying adenocarcinoma of skin appendage	**NEG**: CK20; UPK
Secondary (of non-cutaneous origin)	
A) anorectal origin	**POS**: CK20; CEA;
	NEG: CK7; GCDFP; UPK
B) urothelial origin	**POS**: CK7; UPK; CK20;
	NEG: GCDFP15; CEA
C) other origin	Antigen expression depends on primary tumor

common finding. These histological characteristics are believed to have a meaning in the disease course (Shaco-Levy et al., 2008).

Although traditionally considered a single disease process, EMPD represents several distinct entities and have been subclassified by Wilkinson and Brown (2002) into two distinct types, specifically primary (of cutaneous origin) or secondary (of non-cutaneous origin). Each classification has 3 subtypes. The primary is divided into intraepithelial cutaneous Paget disease of the usual type, intraepithelial cutaneous Paget disease with invasion, and intraepithelial cutaneous Paget disease as a manifestation of underlying adenocarcinoma of skin appendage or vulvar glans. The cells are immunoreactive for cytocheratin 7(CK7), gross cystic disease fluid protein 15(GCDFP-15) and carcinoembryonic antigen (CEA), but negative for cytocheratin 20 (CK20) and uroplakin III (UPK). The secondary is divided into Paget disease of anorectal origin, that demonstrates CK20 and CEA immunoreactivity but is usually nonreactive for CK7 and consistently non-immunoreactive for GCDFP-15 and UPK; Paget disease of urothelial origin, that is immunoreactive for CK7, UPK, may express CK20 but non-immunoreactive for GCDFP-15 and CEA, and Paget disease of other origin. (Table 1)

Then, the distinction between these 3 types of Paget-like can be done through detection of CK7, CK20, UPK, CEA and GCDFP-15 (Kurman et al., 2010) and this distinction is essential to avoid potential confusion and unnecessary surgery. In fact, the correct diagnosis has a significant influence on current treatment (Brown and Wilkinson, 2002; Wilkinson and Brown, 2002).

Immunocytochemistry for Tag-72 (identified by monoclonal Antibody B72.3) seems to be as useful as anti-GCDFP-15 in identifying EMPD (Olson et al., 1991).

In the invasive EMPD, Paget cells penetrate the basement membrane and invade the dermis (Wilkinson and Mullins, 1997). The capacity to be invasive has been found in association with reduced expression of E-cadherin and in some cases with abnormal plakoglobin (gamma-catenin) expression (Ellis et al., 2008).

Another useful method for identifying invasive Paget cells is a combination of immunohistochemical staining for MUC1 and MUC5AC. In fact, decrease or loss expression of MUC5AC reveals increasing malignant potential, and consequently an higher tendency of these Paget cells to invasion (Yoshii et al., 2002).

More recent studies have pointed out the role of other markers in predicting the invasive potential of Paget's cells. For example, a concordant higher expression of Fak, Jak, and Erk 1/2 correlates with the grade of malignancy of EMPD (Chen et al., 2008a).

Expression levels of Sp-1 and Vegf are also concordantly higher in invasive Paget cells than those of normal skin (Chen et al., 2008b). Besides, the Yale experience reveals an association among clinical, pathological and outcome data of EMPD with the grade of Her2/neu expression. It was found in this work that Her2/neu expression was higher in patients with invasive disease (71% vs 54%) (Richter et al., 2010). This finding supports the possible therapeutic use of anti Her2/neu antibodies (Trastuzumab).

A more noteworthy difference is met in the Ki67 and Cyclin D1 expression, whose levels are significantly higher in invasive lesions than in situ lesions. Furthermore, the mean of the sum of Ki67 and Cyclin D1 expression scores is significantly higher in invasive lesions (Aoyagi *et al*., 2008).

Aneuploidy appears to be associated with in situ sweat gland adenocarcinoma, invasive carcinoma, and lymphatic invasion. These results suggest that Paget's cells with aneuploid DNA stem-cell lines may be associated with an aggressive biological behavior (Cotton *et al*., 1995).

The differential diagnosis should consider Vulvar Intraepithelial Neoplasia (VIN), Bowen disease, micosis fungoide, istiocitosis (Zampogna *et al*., 2002), melanoma (Kirkham, 1997), sebaceous carcinoma, clear cell papulosis, eccrine porocarcinoma, Merkel cell carcinoma (Table 2).

Table 2. Histological differential diagnosis.

Neoplasm
Extramammary Paget's Disease
Vulvar Intraepithelial Neoplasia / Bowen disease
Micosis fungoide
Istiocitosis
Malignant Melanoma
Sebaceous carcinoma
Clear cell papulosis
Eccrine porocarcinoma
Merkel cell carcinoma
Basalioma

In particular, a case report describes a patient treated for Bowen disease, who discovered just after surgery to be affected by EMPD (Quinn *et al*., 2004). Bowen himself recognized a lot of similarity between the two pathologies (Bowen, 1912) and in his discussion of atypical epithelial proliferations described the presence of clear cells arising in both disorders (Jones *et al*., 1979). A century later, a Japanese team confirms Bowen's suppositions. In fact, they found that primary EMPD and squamous cell carcinoma in situ or Bowen disease arise multifocally from a common cell in the epidermis. They describe a situation in which the histological specimen reveals areas of Bowen and Paget disease sharply separated. Immunohistochemical findings showed CEA to be expressed in areas containing Paget cells, but not in areas affected by Bowen disease, whereas CK7 and CK8 were strongly expressed in both of these areas.

Some authors also stated that it might be impossible to distinguish EMPD and Bowen disease on routine histological examination alone (Park *et al*., 2001). Nowadays it is possible only thank to the immunohistochemical techniques (Nowak *et al*., 1998).

Histological resemblance between Paget disease and VIN was also described. In fact, Mc Cluggage at al documented an atypical histological pattern in a classical VIN finding. The lesion presented a collection of cells throughout the full epithelial thickness containing intra-cytoplasmic mucin, which turned out to be Paget's cells (McCluggage *et al*., 2009).

Another interesting case report shows the possibility to misdiagnose the EMPD for example when simulating a metastatic breast cancer (Ohira *et al*., 2004).

Diagnostic difficulty occurs when pagetoid spread is possible by cells of epithelial, melanocytic, neuroendocrine, lymphoid, Toker cell, and histiocitic differentiation (Kohler *et al*., 1998). Therefore, the differential diagnosis of intraepidermal pagetoid cells is extensive.

Etiopathogenesis

Although EMPD pathological origin remains controversial, improvements in the immunohistochimical techniques allow many hypothesis to be made.

Nadji et al. first reported that CEA is highly expressed in Paget cells, supporting a glandular origin, and they concluded that primary EMPD arises as an intraepidermal adenocarcinoma from apocrine or eccrine sweat gland (Nadji *et al*., 1982).

Mazoujian et al. then proposed more specific evidence for an apocrine gland origin, when they found antibodies to GCDFP-15 reacting with both Paget cells and apocrine gland cells, but not with cells of eccrine glands (Mazoujian *et al*., 1984).

A more recent study asserts that EMPD may be a proliferation of adnexal stem cells residing in the infundibulosebaceous unit of hair follicles and adnexal structures, since they express the citokeratines typical for follicular differentiation (Regauer, 2006).

Actually, even if most reported cases of vulvar sweat gland carcinomas associated with EMPD describe a tumor of apocrine origin, in literature have been described also two cases of vulvar eccrine sweat gland carcinoma associated with Pagetoid extension (Grin *et al*., 2008).

In a substantial proportion of EMPD cases, the immunophenotype is characteristic of apocrine carcinomas: AR (Androgen receptor) positive, ER (estrogen receptor) negative, PR (progesterone receptor) negative (Diaz de Leon *et al*., 2000; Iijima *et al*., 2006) and the concentration of AR seems to be higher than normally (Liegl *et al*., 2005) suggesting a role of these last in the pathogenensis of EMPD.

In the study of Quinn et al. the strong expression of CK7, CEA, and staining of CAM 5.2 found in both the Paget cells and the areas of full-thickness atypia of Bowen disease suggested a common cell of origin (Quinn

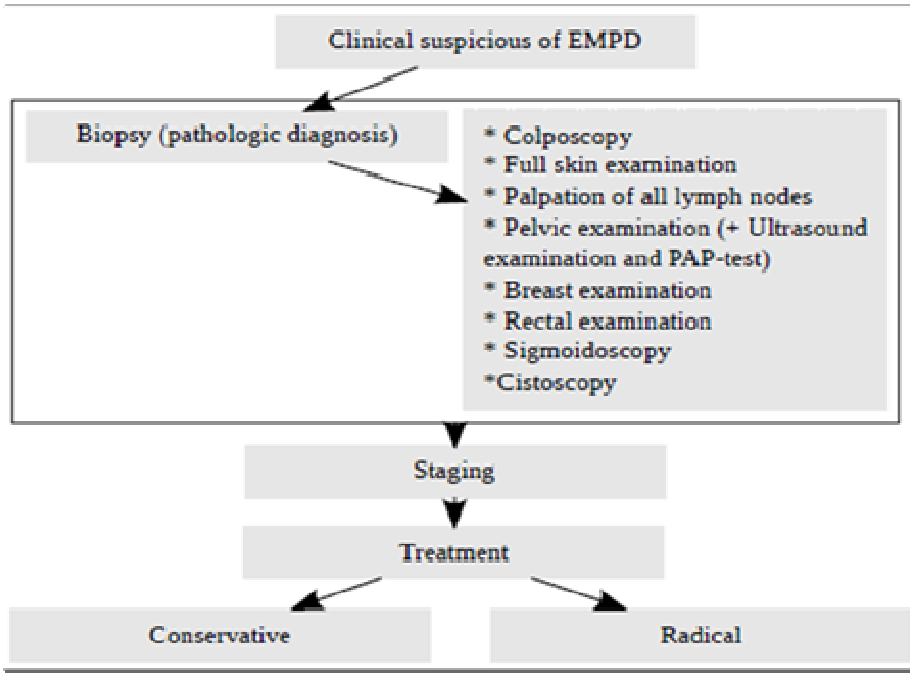

Figure 4. Clinical management of a lesion suspected to be a EMPD location.

et al., 2004). Their hypothesis, according to the theory first put forward by Woodruff (Neilson and Woodruff, 1972), the squamous epithelium and pilar apparatus, including apocrine and eccrine sweat glands, are derived from the pluripotent embryonal germinativum and that EMPD arises from the malignant transformation in situ of a basal stem cell that expresses apocrine gland differentiation.

There could be also a migration of mammary ectopic cells, called Toker cells, from the nipple (Belousova et al., 2006; Di Tommaso et al., 2008; Kuan et al., 2001). In detail, these Toker cells have been regarded, on a morphological, histological and ultrastructural point of view, to be EMPD precursors, although these cells have not been identified as normal component of genital skin. On the other hand, in patients affected by EMPD, Toker cells have been found in association with mammary-like glands of the vulva (Fernandez-Flores, 2008; Willman et al., 2005).

Paget disease then could be viewed either as a carcinoma of multipotential (adnexal stem cells) residing in the infundibulosebaceous unit of the hair follicle or as a sweet gland carcinoma arising from the intraepidermal portion of the glands (acrosyringium) or as a carcinoma derived from the Toker cell of the mammary-like glands of the vulva.

Management

After the correct diagnosis and staging as shown in Figure 4 we could choose the treatment between a variety of possibilities (Table 3), that we will briefly present in the following section.

Surgery

Classical treatment for EMPD is surgery, but since recurrence after surgery is very common, as consequence, it has been debated for long time about vulvectomy, wide local excision, or more conservative treatments.

Some authors propose to perform aggressive surgery for the fear to overlook invasive disease or underlying adenocarcinoma (Feuer et al., 1990), others are in the opinion that aggressive surgery is not always necessary in patients with intraepithelial EMPD (Louis-Sylvestre et al., 2001). Even the actual Korean experience demonstrates that conservative but radical surgery such as Mohs micrographic surgery (MMS) is more effective than wide excision in terms of recurrence and disease free interval (Lee et al., 2009). However, there are no large cohorts evaluating the efficacy of MMS in the management of EMPD. MMS differs from routine excision with histological margin examination by providing intra-operative microscopic evaluation of 100% of the tissue margin. The technique allows for the microscopically guided excision of tumors and preservation of normal tissue. In contrast, routine frozen sections, done without MMS technique of enface sectioning, sample less than 0.1% of the surgical margin and to examine the entire

Table 3. Treatment procedures.

Treatment	Notes
Vulvectomy/emivulvectomy ± groin dissection	Extent of surgery analogous to vulvar cancer treatment
Wide excision	Depending on macroscopic extent of disease, ideally with a 2 to 3 cm margin
Mohs micrographic surgery	It allows for the microscopically guided excision of tumors and preservation of normal tissue
Carbon dioxide laser vaporisation	After invasive disease has been ruled out through multiple biopsies
Photodynamic therapy	5-aminolevulinic acid (ALA), Photofrin
Radiotherapy	Radiation dose needs to be determined individually as there is only limited experience with RT for vulvar EMPD
Chemotherapy	
Antiblastic drugs	5-fluorouracil, cisplatin, mitomycin C, etoposide, epirubicin, vincristine
Immunomodulator drugs	Imiquimod
Hormone therapy	LH-RH analogues
Trastuzumab	Her2/neu

margin of 1 cm of submitted specimen by serial vertical sectioning require about 1500 7-µm thick sections (Hendi et al., 2004). Also a modified MSS technique has been proposed to incorporate histological analysis of the central specimen's depth with the intent of increasing accuracy (O'Connor et al., 2011).

In fact, a lot of studies have found no significant difference in recurrence rate comparing wide local excision and vulvectomy (Berman *et al*., 1989; Chan *et* al., 2004; DiSaia et al., 1979; Hacker et al., 1984; Pierie et al., 2003), and even if the recurrence rate has been found higher in case of wide local excision, this approach has been reported to give a longer survival than a more aggressive treatment that aims to a wide tissue demolition (Parker *et al*., 2000).

In case of underlying adenocarcinoma or of persistent disease the radical vulvectomy is accompanied by inguinal lymphadenectomy, that is suggested in case of lymphatic metastasis (Ewing *et al*., 2004). This approach has generally some common complications, which include lymphedema, sexual dysfunction, and wound infections sometimes requiring an extended hospital stay and a prolonged recovery (Gaarenstroom *et al*., 2003).

Even if limiting wide surgical interventions, such as radical vulvectomy, permits better preservation of sexual function, urinary and fecal continence, vulva anatomy and body image (Broso and Buffetti, 1996), many authors have continued to recommend a tumor-free surgical margin of almost 1 cm from the resection of the tumor to prevent local recurrence (Heaps *et al*., 1990; Murata and Kumano, 2005). Morrow et al. (Morrow *et al*., 1996) suggest a 2-3 cm surgical margin to decrease the risk of local failure. De Hullu et al. (de Hullu *et al*., 2002) speak about a 2 cm one.

Nevertheless, in order to prevent recurrence, some authors propose surgical excision extending beyond the visible clinical lesions with intraoperative frozen sections. Baehrentz et al. demonstrate that free margins give significantly longer recurrence-free survival than dubious ones (Baehrendtz *et al*., 1994; Zhu *et al*., 2007). Even in absence of any palpable mass, some authors recommend an intraoperative frozen section during the superficial vulvectomy, to evaluate disease margins in order to eventually extend the excision. For some authors this kind of approach seems to reduce recurrence of about 50% (Black *et al*., 2007). Application of a modified PAS procedure technique in frozen section analysis of surgical margins of vulvectomy specimen in EMPD has been found to be useful in identifying Paget cells on the margins thought to be free of disease by conventional histological evaluation. The reaction obtained using a microwave procedure takes only 30 seconds (Fishman *et al*., 1998).

Misas et al. proposed the use of fluorescein intravenously in order to visualize disease margins with the use of an ultraviolet light and to eventually suggest an adjunct to surgical management of patients with primary vulvar EMPD (Misas *et al*., 1991).

In particular, Chan et al. suggest that a ≥8 mm pathologic margin clearance leads to a high rate of loco-regional control, while a <8 mm one is an important predictor of local vulvar recurrence (Chan *et al*., 2007). The optimal depth has been proposed by Feuer et al. of at least 5 mm of subcutaneous tissue (Feuer *et al*., 1990).

Also Baker et al. agree that an intraoperative consultation is indicated to ensure that the tissue sampled is adequate for diagnosis, to determine the nature of a disease process, to plan for appropriate ancillary studies, to determine tumor spread, and to assess the margins (Baker and Oliva, 2008).

They also discussed the intraoperative evaluation of lymph nodes including the role of sentinel lymph nodes. Actually, in case of microinvasive EMPD the research of

the sentinel lymph node might reduce the morbidity related to demolitive surgery (Ewing et al., 2004; Fine et al., 1995).

Besides, other authors demonstrated that free margins do not correlate with recurrence, so that large excision beyond the clinical lesion is not useful (Molinie et al., 1993). For example, these data are confirmed also the previous cited multi centric study of Pierie et al. (Pierie et al., 2003). Others have demonstrate that positive margins do not always correlate with recurrence and margin status does not seem to change the natural course of disease (Atrey et al., 2003).

More recently Shako et al have noticed that the presence of Paget cells in the margins does not necessarily predict disease recurrence: the inflammatory and reactive changes evoked within the surgical wound most likely lead to the destruction of the residual tumor cells in those cases (Shaco-Levy et al., 2008)

On the other hand, disease recurrence may, therefore, reflect a larger extent of residual disease not eradicated by the postsurgical inflammatory milieu. In addition, recurrence may also derive from lesions with multicentric origin (Murata and Kumano, 2007).

About microinvasion, Awtrey et al. reported a case in which a clinically unapparent invasive lesion was discovered on re-excision of microscopically persistent vulvar EMPD (Awtrey et al., 2003).

Anyway, because of the rarity of that disease, whether criteria for microinvasive squamous cell carcinoma might be applied to EMPD of the vulva is still unknown (Ewing et al., 2004).

In conclusion, treatment with surgical excision can be complicated by extension of microscopic disease in an irregular manner well beyond the visible margins of the lesion (Black et al., 2007). And an invasive vulvar EMPD may occur in association with microscopically persistent vulvar EMPD, that can remain misrecognized until relapse of the disease.

Lasertherapy and Cryotherapy

Lasertherapy has been introduced to preserve sexual function and vulvar anatomy after preclusion of invasive disease by biopsy. For vulvar and scrotal EMPD may become a useful therapeutic modality in the future, because it is relatively easy to perform and allows for extension of the surgical field without excessive loss of tissue (Weese et al., 1993). Although laser therapy allows a more conservative approach to EMPD, recurrence rate is high for both laser alone and limited excision plus peripheral laser in comparison with wide excision (Louis-Sylvestre et al., 2001). This is probably due to the fact that laser removes only superficial disease and leaves more microscopic disease than surgery does.

Cryosurgery has also been proven as alternative therapy with a conservative aim (Yang et al., 2004).

Photodynamic therapy

Photodynamic therapy (PDT) is one of most recent modality of therapy, and the reports to date have used 5-aminolevulinic acid 20% (ALA) or Photofrin Photodynamic Therapy (Housel et al., 2010; Tanaka et al., 2009). Its mechanism of action involves three key components: a photosensitizer, light (wavelength appropriate for the photosensitzer), and tissue oxygen. In case of ALA the topical application leads to the biosynthesis and transient accumulation of the endogenous photosensitizer protoporphyrin IX. ALA can diffuse in the skin and be preferentially accumulated in neoplastic cells. When a specific light wavelength is applied to the site, the light will be absorbed, and the energy will be transferred to molecular oxygen producing reactive singlet oxygen capable of causing direct cellular killing (Raspagliesi et al., 2006; Tanaka et al., 2009). Even if there is still no consensus about the treatment protocols with PDT in Paget's disease. Previous studies showed promising results using PDT alone or combined with surgery or carbon dioxide laser vaporisation or Imiquimod (Fukui et al., 2009; Housel et al., 2010; Raspagliesi et al., 2006; Tanaka et al., 2009).

This is a promising surgery-sparing therapeutic option for management of noninvasive EMPD but the follow up time is limited and prospective, randomized clinical trials are necessary to assess the effectiveness of PDT to treat noninvasive EMPD.

Radiotherapy

Radiotherapy is recommended as first choice treatment in selected patients, especially in elderly patients (Moreno-Arias *et al*., 2003), so that the use of aggressive surgical therapeutic regimens, particularly in the case of tumors localized to the skin, must be reassessed, especially given the likelihood of long-term morbidity with such regimens (Abbott and Ahmed, 2006; Luk *et al*., 2003; Yanagi *et al*., 2007).

In these last years, a Korean team has also used radiotherapy as primary approach against scrotal EMPD and this resulted effective for local control of disease (Kim *et al*., 2009).

Radiotherapy can also be combined with chemioterapy in unresectable cases or cases with advanced adenocarcinoma (Yamamoto et al., 2001). Its use should be anyway considered with caution in younger patients, because of the possible risk of a secondary iatrogenic cancer.

Chemotherapy

Antiblastic drugs

The original role of chemotherapy was palliative, just to

obtain the cytoreduction of regionally advanced unresectable EMPD (Voigt et al., 1992), but nowadays, in determinate patients, it has become even a first choice therapy. A low dose 5-fluorouracil/cisplatin (FP) topic regimen has been reported to be effective for many kinds of adenocarcinoma, among which EMPD with systemic nodular metastasis as an adjuvant therapy combined with surgery (Beleznay *et al*., 2009; Kariya *et al*., 2004; Ye *et al*., 2006).

A low dose mitomycin C, etoposide and cisplatin (low dose MEP) regimen has been found effective and safe for invasive vaginal EMPD and may significantly improve postoperative quality of life in patients with invasive vaginal EMPD by avoiding extensive vulvar resection and skin grafting (Watanabe *et al*., 2002).

Docetaxel may be an effective drug for patients with advanced EMPD. The partial response has been reported to persist for more than 12 months, and the major toxicities (neutropenia, alopecia, pitting edema, and facial erythema) to be tolerable (Oguchi *et al*., 2002).

A particular combination of mitomycin C, epirubicin, vincristine, cisplatin and 5-fluorouracil has been successfully used against systemic nodal metastases of EMPD, with tolerable toxicities (anorexia, alopecia, neutro-leukopenia). The use of this therapy decreased the metastatic lymph nodes in size by more than 90% compared to that before chemotherapy, and microscopic examination of the removed lymph nodes revealed replacement of metastatic lesions by fibrous tissue, suggesting a therapeutic effect. (Mochitomi *et al*., 2005; Yamazaki *et al*., 1999).

A combination of mitomycin C, vincristine and cisplatin gave also remission of EMPD with systemic metastases. Unfortunately a similar combination chemotherapeutic regimen, administered to treat a recurrence, failed because the lesions became resistant (Yokoyama *et al*., 1990).

Immunomodulator drugs

Imiquimod belongs to the family of synthetic small nucleotid-like molecules of imidazoquinolinamines. It is an immune response modifier with potent antiviral and antitumor effects, which are mediated by Toll-like receptors (TLR7 and TLR8). Imiquimod targets predominantly TLR7 expressing plasmacytoid dendritic cells and Langerhans cells, with secondary recruitment and activation of other inflammatory cells (Kemény and Nagy, 2010). These cytokines trigger the immune system to recognize the presence of a viral infection or tumor and the associated lesion is ultimately eradicated. That demonstrate the indirect antiviral and antitumor effects of this agent in animal models (Berman et al., 2003; Chuang et al., 2010; Gupta et al., 2004; Qian et al., 2003; Wang et al., 2003).

Moreover, a recent study demonstrates that imiquimod can directly induce autophagy and apoptosis in Basal carcinoma cells, and also shows the cooperation and coordination between these two processes to induce cell death (Huang et al., 2010).

Imiquimod local side effects are vulvar pain and pruritus, erithema, mild to moderate erosion, vesiculation and edema. They are generally tolerated, but in about 20% of patient can be severe. In a recent article the frequency of Imiquimod application was reduced to once a week in order to resolve severe local inflammation. Other systemic side effects, that appear immediately after application or within the next day but resolve spontaneously, are flue-like symptoms, headache, apathy, weariness and muscular ache (Ano, 2009; van Seters *et al*., 2008).

A recent survey has indicated that, since Imiquimod has immune-stimulant properties, it can precipitate autoimmune conditions like eczema, psoriasis and lichenoid conditions; two cases here were reported, where Imiquimod induced florid lichen sclerosus in one patient and lichen planus in another (O'Mahony *et al*., 2010). There is also a recent report of acute renal failure probably caused by Imiquimod 5% cream in a renal transplant patient (Santos-Juanes et al. 2011).

Thus, Imiquimod has been shown to be a safe and effective treatment for a variety of skin conditions (Cecchi *et al*., 2010; Cohen *et al*., 2006; Gupta et al., 2004; Sendagorta *et al*., 2010).

Imiquimod is primary indicated for the treatment of external genital and perianal wart such as vulvar, penile and anal intraepithelial neoplasias (VIN, PIN and AIN) (Mahto *et al*., 2010). However, the drug has been recently approved for the treatment of actinic keratosis and superficial basal cell carcinoma. There is a growing body of evidence for its effectiveness in treating a variety of other skin conditions as Bowen disease (VIN 3), lentigo maligna (Cheikhrouhou *et al*., 2010), keloides, EMPD, and viral papillomatoses (van Seters *et al*., 2008), and even molluscum contagiosum (Lin *et al*., 2010).

Imiquimod 5% cream is a promising agent for the treatment of vulvar neoplastic lesions. In a recent study about VIN, lesion size was significantly reduced by Imiquimod than by placebo, and the Imiquimod grup had a significantly greater histological regression than the placebo one (van Seters *et al*., 2008). In the same way, a Danish study has demonstrated that a three-months daily application of topical Imiquimod, prescribed as an alternative treatment, biopsy confirmed regression of the primary lesion and no recurrence has been noted during a 12-months follow up (Vereecken *et al*., 2007).

Imiquimod has been reported to induce complete responses in primary or recurrent EMPD of the vulva (Bertozzi et al., 2009; Hatch and Davis, 2008; Wagner et al., 2012; Zampogna et al., 2002), and of the scrotum (Berman et al., 2003). As a convenient, self-administered treatment, Imiquimod is well tolerated, is less invasive than surgery, relieves itching and pain, and does not influence health-related quality of life, body image, or sexuality (van Seters et al., 2008).

Recently was also described a successful treatment of a cutaneous hemangioma of infancy with Imiquimod creme 5% (Senchak *et al*., 2010). The use of Imiquimod creme 5% has resulted to be useful even in arsenic-induced cutaneous neoplasms (Lonergan *et al*., 2010).

In case of metastasis the prognosis is not good, because there is poor answer to the treatment (Firoz and Goldberg, 2010).

Although those are promising reports of successful treatment with Imiquimod, the number of cases and the follow-up time are still small. Therefore, randomized controlled trials with long-term follow-up to determine the true safety and efficacy of Imiquimod compared with other therapy modalities for EMPD would be useful.

Androgen-receptors, Estrogen-receptors and Her2/neu

Many studies have described the presence of ARs on Paget cells. In detail, ARs are present in 88% of mammary Paget disease and in 78% of EMPD (Inoguchi *et al*., 2007; Kasashima *et al*., 2010; Liegl *et al*., 2005). This considerations suggest their etiopathogenetical involvement in EMPD, and their possible use as therapeutic targets (Iijima *et al*., 2006). Anyway, ARs antagonists or LH-RH analogues have shown poor responsiveness. Even if they permit a good remission of the lymph nodes metastasis, they seem to be almost inactive against skin and bone locations of disease. Nevertheless, a drug resistance can grow very quickly.

In less than 1% of EMPD cells also ERs have been found, this explains the limited use of estrogen receptors modulator, and aromatase inhibitors against EMPD (Iijima *et al*., 2006).

A hyperexpression of Her2/neu has been observed in 96% of mammary Paget disease cases and in 52% of EMPD, even if not all authors confirm this data (Bianco and Vasef, 2006; Plaza *et al*., 2009). Patients with metastatic cancer and with Her2/neu hyperexpression may be treated with Trastuzumab (Herceptin), a human monoclonal immunoglobulin that binds p185-HER2 with an antiproliferative effect (Brummer *et al*., 2004; Karam *et al*., 2008; Reich *et al*., 2005; Takahagi *et al*., 2009). But its side effect, as cardiotoxicity, practically limit its use.

Prognosis

Prognosis of EMPD is almost always good. Its progression is generally very slow and occurs only in some patients (Tebes et al., 2002). The rare patients with invasive disease or underlying adenocarcinoma have a poorer prognosis (Lu et al., 2004).

The course of EMPD may last 10-15 years without evidence of cancer or metastases. In literature it is reported an overall mortality rate of 26%, and 18% for patients without associated underlying cutaneous adnexal adenocarcinoma and 46% for those with underlying cutaneous adnexal adenocarcinoma (Chanda, 1985). About 12% of patients with EMPD have an associated concurrent underlying internal malignancy, in this cases the prognosis depends upon the stage of the internal malignancy.

Full recovery is possible in patients with purely epidermal disease. Perianal disease, dermal invasion, and lymph node metastasis are poor prognostic indicators. The prognosis decreases substantially with lymphovascular involvement, with a five-year survival rate of 0% in the presence of inguinal lymph node metastases. The average time to recurrence is 2.5 years, with case reports presenting a recurrence even after more than 10 years of follow-up.

Otherwise, recurrence is relatively common. In fact, after surgery relapses are found in 40% of cases, because of the multifocal nature of EMPD and its tendency to extend over the clinically visible borders (Molinie *et al*., 1993).

Status of surgical resection margins, tumor cell DNA ploidy, estrogen receptor expression, and p53 immunoreactivity are not predictive of local recurrence (Crawford *et al*., 1999).

On the other hand, specific histological features were examined, aiming to evaluate their influence on disease course: for example, epidermal acantholysis, resulting from the distruptive effect of tumor cells on adjacent keratinocytes, is correlated with increased recurrence rate and shorter time to recurrence and since it's regarded as an adverse prognostic factor, its presence should be indicated in the pathology report. Marked chronic inflammation and parakeratosis are also associated with increased recurrence rate, while controversial findings are reported about the meaning of stromal invasion on the recurrence rate (Shaco-Levy *et al*., 2008).

For example, a recent study states that on univariate analysis, the presence of nodules in the primary tumour, clinical lymph node swelling, elevated CEA levels, tumor invasion and lymph node metastasis were significant prognostic factors. On multivariate analysis, tumor invasion and elevated serum CEA were the only factors that were significantly associated with reduced survival, in contrast with the results of the previously cited study (Hatta *et al*., 2008).

When EMPD reappears after 6 months from initial treatment it is called recurrent. If the relapse happens within 6 months it is called persistent (Tebes *et al*., 2002).

For this reason, long-term monitoring is recommended, every 3-4 months in the first 3 years from treatment and then every 6 months, with careful examination of any abnormal vulvar lesion (Petkovic et al., 2006). Moreover, any eczematous or thickened area where apocrine glands are normally encountered, which

does not resolve with appropriate therapy should arise the suspicion of EMPD (Banerjee et al., 2005).

Another early sign of EMPD recurrence may be a new white lesions and continuous enlargement of depigmented patches, that should never be dismissed as simple treatment-induced postinflammatory hypopigmentation or another type of hypopigmented lesion without biopsy confirmation (Yang *et al*., 2004). In any case of doubt, biopsy should be performed.

CONCLUSIONS

EMPD is a rare neoplastic lesion, which represents less than 1% of the vulvar neoplasms. The lesion generally appears as eczema and the most frequently reported symptom is the itch. Also because of this poor clinical features, there is usually a delay in its diagnosis.

We can then assert that in patients with no specific cutaneous lesions that are nonrespondent to conventional treatment, EMPD should be considered and skin biopsy should be performed. Moreover, a long-term follow up is needed to investigate the appearance of an adnexal adenocarcinoma or an internal malignancy. In this follow up, full body skin and lymphnodes examination, colonscopy, cystoscopy, Papanicolau staining, pelvic and breast examinations should be performed.

Although the immunohystochemical techniques have improved and the knowledge about histological characteristics of Paget cells permits the detection of a pathognomonic histological pattern of disease, its etiopathogenesis remains partially unclear and the etiopathogenetical hypothesis are a few.

The prognosis is good in the most cases, because of the slow progression and the rarity of metastasis. On the other hand, recurrence after treatment is very common. Sometimes EMPD can be invasive or associated to adenocarcinoma or other kinds of cancer.

The first choice therapy is the surgical excision, with inguinal lymphadenectomy in case of infiltration. But many other conservative therapies may be an optimal treatment against EMPD even if still off label.

Lasertherapy aims to preserve sexual function and vulvar anatomy. Radiotheray is indicated in selected, mostly elder, unresectable patients. The topical use of drugs is accompanied by relative poor side effects. In particular, immunomodulating drugs, such as Imiquimod, and antagonist of hormonal receptors have been proposed.

In conclusion, because of the relative good prognosis of EMPD and its high rate of relapse, independently from the extension of resection out of the visible lesion margins, the ideal treatment should be at the same time radical and conservative, to prevent recurrence while sparing tissue morphology and function.

Anyway, rarity of vulvar EMPD makes research in this area very difficult, and there is still a lot to study in order to reach a quicker diagnosis and a more efficient management. It would be desirable to create an international register in order to monitor the efficacy of therapies and the follow-up. It would be also an interesting opportunity to delineate an optimal management of this rare pathology.

Conflict of interest

The authors declare that they have no potential conflicts of interest relevant to this article. This study had no financial support.

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