Surgical Treatment of Paget Disease of the Vulva: Prognostic Significance of Stromal Invasion and Surgical Margin Status

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Objective: The aim of the study was to evaluate the risk of recurrence according to the surgical margin status and the presence of invasion or of superficially invasive carcinoma in patients with extramammary Paget disease (EMPD) of the vulva, who underwent elective surgical treatment.

Materials and Methods: We performed a retrospective analysis of 27 patients with first diagnosis of extramammary Paget disease of the vulva, who underwent primary and elective surgical treatment from January 1989 to December 2014. A *p* value of less than .05 was considered statistically significant. Multivariable logistic regression was performed to adjust for confounding factors.

Results: We observed invasive disease in 11 cases, with microinvasion in 8 of them. A positive surgical margin was found in 10 patients. During a median follow-up period of 79.5 months, 8 patients (29.6%) showed a first recurrence after a median (range) time of 4.9 (2.3–7.1) years. No significant differences were observed between patients with recurrence and patients without recurrence with respect to age, number of vulvar sectors involved, bilaterality and multifocality, presence of invasion or microinvasion, and surgical margin status. However, during the follow-up period, the presence of invasion was higher (67% vs 41%) in patients with recurrence compared with patients without recurrence.

Conclusions: The rate of recurrence of the disease after therapy is high. Patients should be subjected to a close and long-term follow-up to identify those who must undergo further treatment, especially if they presented with an invasive or even microinvasive disease. A free margin of no greater than 1 to 2 cm might be the most appropriate surgical choice.

Key Words: extramammary Paget disease, vulva, EMPD, cancer recurrence, surgical margin status

Extramammary Paget disease (EMPD) is an unusual skin neoplasm (adenocarcinoma) with unclear pathogenesis. The most common site of involvement is the vulva. Because of the rarity of the disease, (1%–2% of vulvar malignancies),[1] its true incidence and prevalence remain unknown.[2]

The histopathological diagnosis of EMPD relies on the presence of Paget cells that present in a thickened epidermidis with papillomatosis, elongated dermal rete, and parakeratotic hyperkeratosis.[3] The Paget cells can occur as solitary cells or in groups and nest in the epithelium of squamous mucosa or the adnexa. Their spread can also affect areas of apparently healthy skin and the disease can have margins extending beyond the clinical apparent edges of the lesion.

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The association between EMPD of the vulva and other malignancies has been reported, varying considerably, with a reported range of 4% to 55%.[2]

The management, to date, is not definite, but surgery is the mainstay of treatment for EMPD of the vulva.[3] Because of the extension and multifocality of the lesion, surgical excision can cause significant vulvar mutilation and several complications.

The rate of recurrence of the disease after therapy is high, with a range between 20% and 70%[4–9] and an average rate of 35% and 33% for the intraepithelial and invasive type, respectively.[4] Some predictive factors have been studied without achieving a definitive conclusion. Recent studies, in contrast to previous ones, have reported that there seems to be no correlation between surgical margin status and disease recurrence, which is common regardless of the surgical margins.[6,7,10]

Using data derived from 2 tertiary care oncologic centers, we undertook a retrospective analysis of the risk of recurrence according to the surgical margin status and the presence of superficially invasive carcinoma (≤1 mm, International Federation of Gynecology and Obstetrics [FIGO] stage IA)[11] or frankly invasive carcinoma in patients with first diagnosis of EMPD of the vulva, who underwent primary and elective surgical treatment.

MATERIALS AND METHODS

The medical records of patients with EMPD of the vulva admitted to gynecologic oncologic units at the Department of Gynecologic Oncology, Centro di Riferimento Oncologico-National Cancer Institute Aviano, Italy, and at the Woman's Health Sciences Department, Università Politecnica delle Marche, Ancona, Italy, between January 1, 1989 and December 31, 2014 were retrospectively analyzed in a retrospective case series.

Inclusion criteria were the following: (1) primary EMPD of the vulva histopathologically confirmed, (2) primary and elective surgical treatment, and (3) more than 1 year of follow-up evaluation.

Women who underwent elective or adjuvant radiotherapy (RT), exclusive or adjuvant medical therapy (imiquimod, chemotherapy, or others), or ablative surgical treatment were excluded.

The histopathological diagnosis was confirmed under microscope by conventional hematoxylin and eosin staining: the pathognomonic characteristics of EMPD included large cells with pale, clear cytoplasm and clustered or nested, round hyperchromatic nuclei. Immunohistochemical staining for antibodies, including CK7, CK20, GCDFP-15, CEA, Uroplakin-III, S-100 protein, and HMB45 was performed in case of diagnostic doubt. All the histopathological evaluations of the specimens collected were performed by the same pathologist of our institute (V.C.), with particular expertise in gynecologic-oncologic disease.

Clinical data were retrieved, including age at initial diagnosis, interval from the onset of symptoms to the confirmed diagnosis, location and extent of the disease, association with other vulvar disease, history of a secondary malignancy, characteristics of the surgical procedure, and time to and site of recurrence.

The genital area was divided into 12 sectors to evaluate the numbered location and extent of the disease (mons pubis, clitoral region, right or left labium majora, right or left labium minora,

right or left interlabial sulcus, posterior commissure of labia majora, perineum, perianal, gluteal region).

Patients were followed up at approximately 3-month intervals in the first 2 years and at 6-month intervals in the following years. Recurrence was defined as the reappearance of histopathologically confirmed EMPD at least 6 months after surgery.

Ethics approval for the review of case records was obtained from the Clinical Research Ethics Committee of the Centro di Riferimento Oncologico-National Cancer Institute of Aviano (CRO 2014–30) and a written informed consent for use of personal data was obtained from each woman.

Statistical Analysis

Data were analyzed using the Student *t* test and the Fisher exact test. Continuous parametric variables were expressed as mean (SD); nonparametric variables were expressed as median and range. A *p* value of less than .05 was considered statistically significant. Multivariable logistic regression was performed to adjust for confounding factors identified through the results of the univariable analyses. All of the statistical analyses were performed using MedCalc for Windows Version 12.7.0 (Medcalc, MedCalc Software bvba, 2013, Ostend, Belgium).

RESULTS

Of the 33 patients with histopathologically confirmed primary EMPD, 6 were excluded from the analysis because 2 patients underwent adjuvant RT, 2 underwent elective RT, 1 underwent ablative laser vaporization of the lesion, and 1 underwent adjuvant RT and chemotherapy; no patients underwent immunomodulatory therapy (imiquimod). All 4 patients who underwent elective or adjuvant RT developed a first recurrence of disease after a median (range) time of onset of 1.9 (0.7–3.0) years. The patient who underwent adjuvant RT and chemotherapy had a very aggressive invasive disease and died 3 years after the first diagnosis, after developing distant metastases.

The mean (SD, range) age at diagnosis of the 27 included cases was 66.5 (11.8, 36–88) years. The majority of them (93.3%) were symptomatic at diagnosis and itch was the most common symptom (64.3%). Other symptoms included burning associated to itch (14.3%), burning alone (7.2%), and vulvar pain (14.3%). The mean (range) interval between the onset of symptoms and the histopathological diagnosis was 33.8 (6–48) months.

The majority of the study population (73.7%) presented with erythematous lesions; some patients had erythematous lesions associated with white hyperkeratotic lesions (31.6%). Less common lesions were ulcerations, erosions, nodules, or dystrophic areas. Data related to the number of vulvar sectors involved are available for 24 (88.9%) of the patients. Two or more sectors were involved at the time of biopsy in 20 patients (83.3%); the mean (SD, range) number of sectors involved was 2.9 (1.65, 1–6). The lesion was plurifocal in 50% of cases. In 12 cases, the lesion was unilateral, and in 8 cases (33.3%), clitoral, perineum, and perianal region were simultaneously involved.

In 5 (18.5%) of 27 cases, a vulvar lichen sclerosus was associated, and in 4 patients (14.8%), a high-grade squamous vulvar intraepithelial lesion (high-grade squamous vulvar intraepithelial lesion usual type) was associated.

A total of 25 patients underwent traditional surgery: 5 had a wide local excision, 8 had a simple partial vulvectomy (hemivulvectomy), 9 had a simple total vulvectomy, 1 had a superficial (skinning) total vulvectomy, and 2 had a deep total vulvectomy with inguino-femoral lymphadenectomy. Two patients had a CO_2 laser excision. Eleven patients (40.7%) needed reconstructive plastic surgery (V-Y plasty, transposition flap, rotational flap, skin graft) after the removal of the lesions.

Stromal invasion was present in the following 11 cases: specifically, 8 were superficially invasive carcinoma (FIGO stage IA) with less than 1 mm of invasion and 3 patients had FIGO stage IB lesions.

Table 1 summarizes the surgical procedure and outcomes among the 23 cases with available histopathological data, according to the presence or the absence of invasion and marginal status.

In 12 of 13 patients with negative surgical margin, the clearance of disease was greater than 10.0 mm.

No cases of macroscopic residual disease after surgery were recorded. No lymph node involvement was found in the frankly invasive disease.

Recurrence of Disease

The median (range) duration of follow-up was 79.5 (12–313) months. Recurrence data were available for all patients. Eight patients (29.6%) showed a first recurrence after a median (range) time of onset of 4.9 (2.3–7.1) years. In 1 case, the recurrence even appeared 7 years after the first treatment. Table 2 lists the characteristics of the 8 recurrent cases. The site of recurrence was on the incision area in 5 cases (62.5%). No significant differences were observed between patients with recurrence and ones without recurrence with respect to age at diagnosis ($p = .62$), number of sectors involved at first diagnosis ($p = .61$), bilaterality and multifocality ($p = .72$), presence of invasion or of superficially invasive carcinoma ($p = .62$), and surgical margin status ($p = .95$). Notably, a superficially invasive carcinoma was present in 50%

TABLE 1. The Surgical Outcomes Among the 23 Cases With Available Histological Data, According to the Presence or the Absence of Invasion

	Intraepithelial EMPD	Superficially invasive EMPD (<1.0 mm)	Invasive EMPD
Preoperative biopsy, *n* (%)	15 (65.2)	6 (26.1)	2 (8.7)
Definitive histology, *n* (%)	12 (52.2)	8 (34.8)	3 (13)
Positive surgical margin, *n* (%)	6 (60)	3 (30)	1 (10)
Surgical procedure (23 cases), *n*			
WEC	1	3	0
LE	2	0	0
HE	5	2	1
SVC	5	2	0
DTV	0	0	2

EMPD indicates extramammary Paget disease; WEC, wide excision; LE, laser excision; HE, simple partial vulvectomy (hemivulvectomy); SVC, superficial or simple total vulvectomy; DTV, deep total vulvectomy with inguino-femoral lymphadenectomy.

TABLE 2. Clinical Characteristics of the 8 Recurrent Patients

	Age	Time to recurrence, mo	Initial Treatment	Preoperative biopsy	Definitive histopathology	Incision margin	Recurrence site
Case 1	61	27.77	HE	SIC	SIC	N	Incision area
Case 2	55	85.57	SVC	ND	ND	N	Clitoral area and left interlabial sulcus
Case 3	65	74.20	HE	INT	INT	P	Right paraclitoral area
Case 4	72	32.60	WEC	INT	INT	P	Perineum
Case 5	56	70.40	SVC	SIC	SIC	N	Incision area
Case 6	70	32.53	LE	ND	ND	N	Incision area
Case 7	74	78.43	SVC	SIC	SIC	N	Incision area
Case 8	71	49.07	DTV	INV	INV	P	Incision area

HE indicates simple partial vulvectomy (hemivulvectomy); SIC, superficially invasive EMPD; N, negative; SVC, superficial or simple total vulvectomy; ND, not available data; INT, intraepithelial EMPD; P, positive; WEC, wide excision; LE, laser excision; DTV, deep total vulvectomy with inguino-femoral lymphadenectomy; INV, invasive EMPD.

of patients who recurred but was only present in 29% of patients who did not recur. Moreover, when we included patients with invasion greater than 1 mm (FIGO stage IB), invasion was present in 67% of the patients who recurred versus 41% of patients without recurrence. No cases of distant metastasis were recorded in our series. After multivariable logistic regression analysis of possible risk factors, no statistically significant correlation was identified (see Table 3).

The histopathological examination of the cases treated for recurrence showed an invasive lesion in 4 cases (50%) with the presence of invasion 1 mm or greater in 3 of these 4 cases. No significant difference was observed regarding the rate of invasive lesions between the first definitive histopathological diagnosis (47.8%) and the definitive histopathological diagnosis at recurrence (50%).

Association With Other Malignancies

Among the 33 patients observed in the study period, the following 7 (21.2%) showed the presence of an underlying or distant synchronous malignancy: 1 case of pheochromocytoma and left ovarian cystoadenoma, 4 breast cancers (bilateral in 2 cases), 1 stomach and colorectal cancer, and 1 skin carcinoma. In each of the cases, the course of EMPD, even at recurrence, was apparently not influenced by the presence of the synchronous malignancy.

DISCUSSION

Extramammary Paget disease can be considered a chronic disease with a high probability of relapse, even many years after the initial appearance. Our results derive from an extensive clinicopathological evaluation of patients with EMPD who were all diagnosed, treated, and followed by 2 groups of physicians who collaborated, during the study period, in the treatment of this uncommon condition.

Firstly, our findings indicate a very long time between the onset of symptoms and the histopathological diagnosis of the disease. This may be due to the fact that the clinical signs of EMPD are nonspecific. The majority of our study population presented with pruritic erythematous lesions, resistant to nonspecific topical treatment. Only a few patients had more suspicious signs, with ulcerations, erosions, and nodules. Lesions appeared to be more frequently extensive, not focal, thus conditioning an impression of a benign irritative or infective lesion, more than a neoplasia. Therefore, every extensive, asymmetrical, multifocal, bilateral, erythematous lesion, associated or not with hyperkeratotic areas or superficial erosion, in relatively advanced aged women, that does not regress spontaneously or after a nonspecific therapy has to be suspected of Paget disease and should be biopsied to obtain an early diagnosis to prevent the considerable extension of the disease.

Although the disease was described more than a century ago, to date, there are no treatment guidelines, and the staging system of the vulvar cancer seems to be inadequate to grade the treatment choices of a neoplasia characterized by diffuse superficial extension and limited invasion, frequently less than 1 mm.

Even though there is a high probability of relapse, the risk factors for recurrence are unclear. Extramammary Paget disease

TABLE 3. Multivariable Logistic Regression of Risk Factors of Recurrence Among the 23 of 27 Cases With Available Histological Data

Outcome	Recurrence cases (6 cases)	Nonrecurrence (17 cases)	Adjusted odds ratio (95% CI)	*p*
Age, mean (SD), years[a]	66.5(7.4)	69.0(11.5)	0.96 (0.86–1.08)	.57
Superficially invasive EMPD on preoperative biopsy, n (%)	3 (50)	3 (17.6)	5.84 (0.21–155.44)	.29
Superficially invasive EMPD on definitive histology, n (%)	3 (50)	5 (29.4)	0.81 (0.03–21.25)	.90
Invasion (≤1 and >1 mm) on definitive histology, n (%)	4 (66.6)	7 (41.2)	1.24 (0.04–35.07)	.89
Positive surgical margin, n (%)	3 (50)	7 (41.2)	2.89 (0.24–33.98)	.39
Bilateral disease, n (%)	3 (50)	9 (52.9)	0.31 (0.01–8.56)	.49
No. sectors involved, mean (SD)	2.6(1.8)	3(1.65)	0.68 (0.23–2.00)	.49

[a]At the diagnosis.

EMPD indicates extramammary Paget disease.

of the vulva appears as a slowly progressive disease, which seems to become very aggressive only in cases of profound invasion with a higher risk of distant metastasis and mortality.[12]

Patients treated with deep total vulvectomy, deep partial vulvectomy, and wide local excision have reported a high recurrence rate of 15%, 20%, and 43%, respectively[2]; however, the more radical procedures are associated with mutilating interventions and might not ever be indicated for a relatively indolent malignancy.[4]

Our median follow-up of 6.6 years, among the longest in the published series, has allowed us to identify patients with a higher probability of relapse.

We found a recurrence rate of 29.6%, consistent with previous published data. We focused our attention on invasion and risk of recurrence, and particularly, we analyzed the role of invasion of 1 mm or greater, which seems to be more frequent. In our series, in fact, a superficially invasive carcinoma was observed in 72% of all invasive lesions and in 50% of our recurrent cases.

The presence of a superficially invasive carcinoma was almost double (50% vs 29%) in patients who recurred, in comparison with patients free of disease during the follow-up period, and when we included patients with invasion greater than 1 mm, the presence of invasion was 67% in patients who recurred. Mendivil et al.[13] recently reported a significant association between the presence of invasive disease and patient progression-free survival, according to previous published data.[4,14] Nomura et al.[15] found a significantly higher rate of recurrence in patients with invasive disease in contrast to patients with intraepithelial EMPD but this result refers to a limited number of patients and the significance of microinvasion is not yet defined.

Extramammary Paget disease appears as a slowly progressive disease, which seems to become very aggressive only in rare cases of profound invasion with a higher risk of recurrence, distant metastasis, and mortality.[12]

By analyzing our data, the association between invasion and recurrence risk was not significant. It seems interesting to note that the histopathological characteristics of primary lesions were similar to the recurrence lesions with a rate of invasion of 48% versus 50%, respectively, suggesting a substantially low aggressiveness of disease even when in relapse.

Superficially invasive carcinoma is characterized by a favorable long-term prognosis,[16] but according to our data, it may identify patients who require more accurate controls, because of an increased risk of local relapse but not of metastasis even after a long time. In fact, 1 of our patients with a superficially invasive carcinoma showed a first recurrence of disease 7 years after the first treatment. Therefore, EMPD requires long-term follow-up. Our patients were followed up at approximately 3-month intervals in the first 2 years after diagnosis and treatment and at 6-month intervals in the following years.

According to other authors,[6,7,10] there seems to be no correlation between margin status and disease recurrence after surgery. The lesions are often multifocal and the margins are irregular. Therefore, an involvement of microscopic margins occurs in approximately 40% to 75% of patients who underwent surgery.[6–9]

Recommended margin status for excision should be based on excision of the visible lesion 1 to 2 cm from the margin of the clinically visible lesion. Some surgeons recommended an excision of the visible lesion up to 5 cm, causing a very large tissue loss and the need of extensive plastic reconstruction.[2] Because there seems not to be a relationship between margin status and risk of recurrence, a more conservative 1- to 2-cm margin from the clinically visible lesion might be the most appropriate choice, provided that it excises the entire macroscopic lesion. In our cases, we limited the excision to approximately 1 to 2 cm from the visible lesion without recording any case of macroscopic residual disease after surgery; in almost 90% of our patients, the clearance of disease from the negative surgical margin was greater than 10.0 mm.

The secondary objective of the study was to evaluate the incidence of other associated cancers. The rate of neoplasm observed is similar to that of 2 large case series,[4,17] and it seems to be slightly lower (29.4%) than the largest Italian series, which was recently published[18] (34 patients in a period of 27 years).

The published literature regarding treatment of Paget disease of the vulva is dominated by surgical treatment.[3] In recent years, interest in alternative therapies to surgery, such as an immunomodulatory therapy such as imiquimod, has grown and some case series have been reported.[19–21] Paget disease most commonly occurs in elderly women, and having evidence-based alternative treatments to surgery would be of benefit to these women. The use of imiquimod seems promising; however, no recommendations regarding treatment modality can be made from the current available literature, and women need to be made aware that any treatment including surgery does not have a clear evidence base.[3] Our series included patients who underwent primary and elective surgical treatment. Many of the treated cases had a considerable extension of the disease, with a mean involvement of 3 sectors of the genital area. In these cases of extensive disease, the elective use of imiquimod could be contraindicated, because of its local toxicity. However, the use of imiquimod as an adjuvant therapy could be tested, with treatment scheduling and follow-up investigated in a trial setting.

It is likely that our patients, referred to 2 tertiary care oncologic centers, had more worrisome disease than those usually treated with medical therapy. In these patients, treatment with RT and chemotherapy seemed to be not very useful, with a first recurrence of disease after a median time earlier than surgery. We recognize that there are some study limitations; our study was retrospective and, despite the extensive historical records, data of all patients are not available. However, given the rarity of the disease, 27 patients treated homogeneously and who underwent primary and elective surgery represents a viable population for the study of the factors of recurrence, and some conclusions could be drawn.

Given the slow progression to invasive disease but the high risk of recurrence, we agree with the authors that recommend minimal resection surgery. Moreover, the disease occurs frequently in patients of advanced age in whom it is not always clear the usefulness of some resection interventions. However, the treatment should still be adequate to exclude the presence of profound invasive disease, characterized by a poor prognosis.

CONCLUSIONS

The patients should be treated in dedicated oncologic centers and must be subjected to a close and long-term follow-up to identify those who must undergo further treatment, especially if they presented with an invasive or superficially invasive EMPD at the first diagnosis.

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