Paget's Disease of the Vulva Treated with Imiquimod: Case Report and Systematic Review of the Literature

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Key Words

Paget's disease · Superficial skin cancer · Vulva · Extramammary Paget's disease · Genital neoplasia

Abstract

Background: Extramammary Paget's disease of the vulva (EPDV) is a rare adenocarcinoma in situ of the vulvar skin and is often resected with involved margins due to its reticular growth pattern. Adjuvant treatment with the immunomodulator imiquimod may be suitable to avoid repeated and mutilating surgery. **Case Presentation:** We present the case of a 73-year-old woman with EPDV, initially treated with surgical resection and re-resection for involved margins. Final histology revealed Paget's disease of the left vulva with 8 cm in the largest diameter and again involved margins. Subsequently, topical therapy with imiquimod 5% cream twice weekly was applied for 3 months. Vulvoscopy and local biopsies confirmed complete remission (CR). Based on a literature search using PubMed and the Cochrane Central Register of Controlled Trials, 21 reports on the therapeutic efficacy of imiquimod in 70 women with EPDV have been published. Pooled rates of CR and partial remission were 71% (50/70)

and 16% (11/70), respectively. There were 4 cases of disease progression under imiquimod and the therapy was generally well tolerated with mild to moderate local reactions in >50% of cases. **Conclusion:** EPDV is a rare genital neoplasia and may be successfully treated with the topical immunomodulator imiquimod. Specifically, adjuvant imiquimod is a feasible and efficacious treatment option for women with involved resection margins after surgery.

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Introduction

Paget's disease was first described in 1874 and extramammary Paget's disease in 1888 [1]. Extramammary Paget's disease of the vulva (EPDV) is a rare form of vulvar superficial skin cancer and accounts for less than 1% of vulvar neoplasias [2]. Histologically, EPDV is a form of intraepidermal adenocarcinoma [3]. Surgical resection is the mainstay of treatment in women with EPDV. However, surgery with the goal of adequate and complete excision of the tumor is challenging due to EPDV's distinct growth pattern with occult intradermal

reticular spread. Therefore, surgical margins are often involved with tumor cells, and this subsequently leads to repeated and mutilating surgery [4, 5]. Specifically, rates of involved margins after primary surgery have been reported in up to 72% of cases [6–8]. On the other hand, the prognosis of women with EPDV is excellent with 5-year disease-specific survival rates of >95% despite local recurrence rates of up to 32% [5, 9]. Of note, involved surgical resection margins are neither associated with recurrence rates nor with overall survival [4, 5]. Based on a systematic literature review of the PubMed library and the Cochrane Clinical Trials Register, no randomized trial in women with EPDV has been published. Thus, no evidence-based treatment recommendations for EPDV are available and there is no consensus regarding the optimal treatment of this rare form of vulvar neoplasia. Apart from surgery, which is generally accepted as the primary treatment of choice [1–6], a wide range of pharmacological and other noninvasive treatments have been reported, among them photodynamic therapy, laser therapy, radiotherapy, topical immunomodulatory treatments, and cytotoxic chemotherapy [1, 4]. The main challenge of treating women with EPDV is to achieve disease control without overtreatment and with a minimization of the associated morbidity from radical and repeated surgery.

Imiquimod is an immunomodulatory agent targeting the toll-like receptor (TLR) 7 as a receptor agonist. TLRs are cell-surface receptors recognizing ligands associated with pathogenic organisms. TLR-7 activates the T-helper cells and increases the production of pro-inflammatory cytokines mainly interferon- α , tumor necrosis factor- α and interleukin-12 [10, 11]. Imiquimod has direct antitumor activity and can induce cell death in various types of human cancer cells [12]. Specifically, imiquimod exerts an inhibitory effect on cell proliferation in a dose- and time-dependent manner by inducing autophagy and apoptosis. In this respect, blocking of autophagy inhibits imiquimod-induced apoptosis, suggesting that autophagy functions as a mechanism which, upon activation, directly leads to apoptosis and cell death of cancer cells [10, 12].

Imiquimod is an established treatment for vulvar condyloma, superficial basal cell carcinoma, and actinic keratosis and has been reported to be efficacious in vulvar, vaginal, and cervical intraepithelial neoplasia [13, 14]. In addition to these indications, imiquimod has also been used to treat women with EPDV. For example, Luyten et al. [15] published a retrospective cohort of women with EPDV treated with imiquimod. They summarized the treatment effects of 5% imiquimod cream in a series of 21

women with EPDV from 8 centers in Germany. In this study, 11 (52%) women achieved a complete response and 6 women (28%) achieved a partial response for a total response rate of 80% (17/21). There was no case of progressive disease in this patient collective. The dose and duration of imiquimod differed widely between patients. The mean duration of treatment exceeded 16 weeks in those women who achieved a complete response.

In another retrospective case series, Sanderson et al. [16] described 6 women with primary and recurrent EPDV treated with imiquimod. Adding 23 cases previously published in the literature, the authors cite clinical resolution rates of 50% for primary disease and 73% for recurrent disease based on 29 documented EPDV cases treated with imiquimod. The authors concluded that imiquimod provides a viable alternative to surgical excision for women with EPDV.

The aim of this study was to perform a systematic literature review on EPDV cases treated with imiquimod and to assess the efficacy of this therapy as an adjuvant to surgical excision in women with involved surgical resection margins. First, we systematically searched the PubMed library and the Cochrane Central Register of Controlled Trials to identify all clinical trials reporting on the safety and efficacy of topical imiquimod in women with EPDV. Then we describe the case of a 73-year-old woman with EPDV, initially treated with surgical resection and re-resection for involved margins. Topical therapy with imiquimod 5% cream twice weekly was successfully applied for 3 months.

Materials and Methods

Literature Review

We performed a systematic literature search of the PubMed library and the Cochrane Central Register of Controlled Trials. There were no time and language limits applied to the search. No citation in the Cochrane Central Register of Controlled Trials was identified using the search term 'Paget's disease of the vulva'. With the search terms 'extramammary Paget's disease' and 'imiquimod' and using the search details: ('Paget disease, extramammary' (MeSH terms) OR ('Paget' (all fields) AND 'disease' (all fields) AND 'extramammary' (all fields)) OR 'extramammary Paget disease' (all fields) OR ('extramammary' (all fields) AND 'Paget's' (all fields) AND 'disease' (all fields)) OR 'extramammary Paget's disease' (all fields)) AND ('imiquimod' (supplementary concept) OR 'imiquimod' (all fields)), we identified 63 PubMed citations. Eligibility criteria for study acceptance were at least one case of EPDV and neoadjuvant, adjuvant, or exclusive treatment with imiquimod. The principle summary measure was the pooled rates of efficacy (complete remission (CR), partial remission (PR), stable disease, and progression (PRO)) and pooled rates of side effects. All 63 abstracts were screened and 24

citations were excluded for not reporting EPDV cases. Thus, 39 articles were retrieved in full and analyzed. In the next step, 18 articles were further excluded for the following reasons: cases were not EPDV but Paget's disease in other locations ($n = 12$); patients already reported in a previous publication ($n = 1$); narrative review without reporting new cases ($n = 3$); extramammary Paget's disease without reporting the exact location ($n = 1$); EPDV, but not treated with imiquimod ($n = 1$). Finally, 20 articles [15–34] and our own case containing data of 70 cases of EPDV treated with imiquimod – including our own case – were extracted and analyzed. From these studies, patients numbers, efficacy rates in terms of CR, PR, stable disease (where available), and progressive disease, the rate of treatment discontinuation, side effects, and length of follow-up were extracted. Figure 1 shows a flow diagram of the search algorithm. Based on the low numbers of patients reported in the literature, no subgroup or sensitivity analyses were performed. Since only retrospective cohort studies have been reported, no assessment of the risk of bias was performed. There was no funding for this systematic review and there was no registration of this study in a study database. Investigators were not contacted to retrieve additional information.

Case Presentation

A 73-year-old Caucasian woman presented with a 3-month history of left vulvar erythema and pruritus not responding to topical creams. The patient had a history of breast cancer of the left breast treated with local excision, adjuvant irradiation of the left breast, and adjuvant chemotherapy 8 years ago. There were no signs and symptoms of recurrent breast cancer. A recent mammogram was normal. Further diagnostic studies, that is, a gynecologic examination, a transvaginal ultrasound, and a CT of the abdomen were performed to rule out invasive or metastatic disease. These studies were normal. She was in otherwise good health. Gynecologic examination revealed an 8 cm by 5 cm erythematous lesion of the left hemivulva without clinically and vulvoscopically visible satellite lesions. A 5-mm punch biopsy was performed and histology confirmed the suspected diagnosis of EPDV. The patient underwent surgical resection in the form of a hemivulvectomy with primary closure. The histological report showed EPDV of 6.9×3.9 cm in size and involved surgical resection margins in 3 locations. Figure 2 shows a microscopic image of the patient's vulvar skin with intradermal Pagetoid cells. Subsequently, re-resection for involved margins was performed. This management was based on the assumption that the local standard of care of Paget's disease of the vulva is complete resection. Therefore, we opted for a second attempt to completely resect the disease. In fact, there was no macroscopic evidence of residual disease after the first surgery and therefore, we assumed that the re-resection specimen would only contain normal tissue thus establishing an R0 status. No biopsies were performed prior to the second surgery. However, final histology of the re-resection specimen showed EPDV of 0.8×0.4 cm in size and again involved margins. Subsequently, topical therapy with imiquimod 5% cream twice weekly was applied for 3 months. No additional local therapy or systemic therapy was applied. The therapy was well tolerated with only moderate local erythema, which required no further therapy. Clinical and vulvoscopic examinations were performed every 4 weeks to rule out clinical disease progression under PRO. Finally, vulvoscopy and multiple local scouting biopsies confirmed CR after 3 months. Four scouting biopsies were performed adjacent to the left lateral wound edge at 2, 3, 4, and

Fig. 1. Flow diagram of the literature search algorithm.

5 o'clock. Afterwards, the patient was then seen every 3 months in the outpatient clinic. At the time of publication, the patient is without recurrence 6 months after the end of therapy.

Literature Review

Based on a systematic literature search of the PubMed library and the Cochrane Central Register of Controlled Trials, we identified 21 articles – including our own case report – containing data of 70 women with EPDV treated with topical imiquimod. Data on disease location, disease status (primary EPDV or recurrent EPDV), study type, toxicity associated with imiquimod, and disease outcomes were extracted and analyzed. Table 1 summarizes these findings. Women with primary EPDV were treated in 42 cases, whereas 28 women had recurrent EPDV. Pooled rates of CR and PR were 71% (50/70) and 16% (11/70), respectively for a clinical benefit rate of 87% (61/70). Stable disease and/or no effect of imiquimod were noted in 3 patients. There were 4 cases of disease PRO under imiquimod. In one of these cases, a newly developed primary cutaneous mucinous carcinoma arose on the background of the EPDV.

The duration of imiquimod treatment varied widely between the reports. We found a mean therapy duration of 12.4 weeks with a range between 2 and 52 weeks of therapy. The treatment intervals also varied, but most authors (>90%) used either a 3 or 2 times per week schedule.

In women with EPDV, imiquimod was generally well tolerated with mild-to-moderate local reactions in >50% of cases. Typical side effects of imiquimod were erythema, burning, erosion, and local tenderness. The only systemic side effects noted among this patient collective were flu-like symptoms in 1 patient, fever in 2 patients, and myalgia/arthritis in 1 patient. Five patients (7% (5/70)) stopped treatment prematurely due to side effects.

Fig. 2. EPDV with microscopic depiction of a vulvar skin sample with Pagetoid cells. Black bar equals 50 μ m.

Adjuvant imiquimod therapy in women with involved margins after excisional surgery was only reported in our case report. The outcome of this case was successful with no evidence of disease after 3 months of adjuvant treatment. Only one other publication reported on the outcome of adjuvant imiquimod in women with involved resection margins after EPDV surgery. Choi et al. [31] reported on 10 patients who all underwent prophylactic adjuvant imiquimod therapy after initial surgery irrespective of margin status. They reported no recurrence during a 6-year follow-up period.

Discussion

In this case report and literature review, we summarize the clinical evidence on the safety and efficacy of 5% imiquimod cream as a topical treatment in women with primary and recurrent EPDV. Based on clinical reports of 70 patients, we found that imiquimod is efficacious with 71% (50/70) of patients achieving a CR. An additional 16% (11/70) achieved a PR for a clinical benefit rate of 87% (61/70). Although efficacious, imiquimod applied to the vulva causes both local and systemic side effects in the form of erythema, erosion, fever, and flu-like symptoms in >50% of patients. However, only a few patients (7%; 5/70) prematurely discontinued the treatment. In our case report, we found that imiquimod can be effectively used as an adjunct treatment after local excisional surgery

with involved surgical resection margins. This is of note, because involved surgical resection margins are a typical feature of EPDV due to its intradermal reticular growth pattern. Thus, we propose that topical imiquimod may be used in these women to avoid repeated and mutilating surgeries. The results of this systematic review might be relevant to health care providers adding a new treatment option for women with this rare disease. Professional societies might officially endorse this treatment option for EPDV, thus making it easier for physicians to use imiquimod as an off-label drug.

Imiquimod is a local immunostimulating agent. Thus, local and regional side effects due to inflammatory processes are expected with this treatment. In randomized trials, the most common side effect of imiquimod is local erythema, which has been reported in up to 42% of patients [35]. Otherwise, it is well tolerated but occasionally can lead to more pronounced unwanted effects such as adenopathy [36], severe eczema [37], vitiligo [38] or meningitis [39]. In women with EPDV, imiquimod was generally well tolerated with mild-to-moderate local reactions in a majority of cases. Typical side effects of imiquimod were erythema, burning, erosion, and local tenderness. Severe side effects as described in the literature did not occur among women with EPDV. The only systemic side effects noted among this patient collective

Table 1. Clinical studies assessing the effects of topical imiquimod in women with EPDV

Author	Year	Disease status, n	Study type	Number of patients	Duration of therapy, weeks	Toxicity, n	Outcomes (CR/PR/PRO)
Luyten et al. [15]	2014	PRI (5), REC (16)	Retrospective cohort; multicenter	21	28, 20, 12, 24, 52, 26, 10, 8, 6, 8, 12, 10, 4, 10, 16, 16, 16, 6, 12, 12	Local reaction (1)	11/6/0; premature discontinuation (2); stable disease (2)
Sanderson et al. [16]	2013	PRI (5), REC (1)	Retrospective cohort	6	2, 2, 2, 4, 4, 4	Irritation (3), erythema (1)	3/2/0; no effect (1); premature discontinuation (3)
Baiocchi et al. [17]	2012	PRI (1), REC (3)	Retrospective cohort	4	–	–	3/0/1
Tonguc et al. [18]	2011	REC	Case report	1	18	–	1/0/0
Bertozzi et al. [19]	2009	REC	Case report	1	7	Local reaction	1/0/0
Marchitelli et al. [20]	2014	PRI (7), REC (3)	Retrospective cohort	10	–	Moderate irritation (10)	9/1/0
Hatch et al. [21]	2008	PRI	Case series	2	–	–	2/0/0
Sendagorta et al. [22]	2010	PRI	Case series	3	16, 16, 16	Moderate irritation, tenderness	3/0/0
Frances et al. [23]	2014	PRI + tazarotene	Case report	1	8	–	1/0/0
Anton et al. [24]	2011	PRI	Case report	1	16	Fever, erosion, burning	1/0/0
Geisler et al. [25]	2008	REC	Case report	1	–	–	0/0/1
Matin et al. [26]	2011	PRI	Case report	1	8	Pruritus, tenderness	0/0/1*
Toledo et al. [27]	2012	PRI**	Case report	1	16	Mild irritation, burning, erosion	0/1/0
Hirald-Gamero et al. [28]	2011	PRI	Case report	1	16	Erosion	1/0/0
Wang et al. [29]	2003	REC	Case report	1	7	Erosion, tenderness, flu-like symptoms	1/0/0
Wagner et al. [30]	2012	PRI	Case report	1	6	Erythema, burning	1/0/0
Choi et al. [31]	2013	PRI (surgery + adjuvant imiquimod)	Retrospective cohort	10	–	–	10/0/0
Cooper et al. [32]	2012	REC (imiquimod + surgery)	Case report	1	–	–	0/1/0
Feldmeyer et al. [33]	2011	PRI	Case report	1	18	Intense inflammation	1/0/0
Misery et al. [34]	2007	PRI	Case report	1	2	Fever, myalgia, arthralgia	0/0/1
Dogan et al. [present case report]	2016	PRI (surgery + adjuvant imiquimod)	Case report	1	12	Erythema	1/0/0
Pooled analysis	–	–	–	70	12.4 (min 2; max 52)	–	50/11/4

REC = Recurrent disease; PRI = primary disease.

* Primary cutaneous mucinous carcinoma arising on the background of an EPDV.

** Imiquimod followed by surgery.

were flu-like symptoms, fever, and myalgia/arthralgia. Only 7% (5/70) of patients stopped imiquimod treatment prematurely due to side effects. Thus, imiquimod in women with EPDV is generally well tolerated. However, patients and physicians using imiquimod in this off-label indication should be aware of the possible rare, but severe side effects of this drug. Based on our own experience and the data reported in the literature we suggest that imiquimod should be applied for 12 weeks using a 2 or 3 days per week schedule.

EPDV is a rare entity characterized by high rates of recurrence and repeated surgical interventions. Thus, it is important to identify effective and well-tolerated conservative treatment strategies. Specifically, EPDV is a disease of elderly women, for whom repeated surgical interventions are problematic. EPDV has an excellent prognosis with 5-year disease-specific survival rates >95% [5, 9]. Therefore, a conservative treatment approach with imiquimod is a reasonable alternative to surgery in selected patients. In our literature review, we identified 70 women treated with imiquimod. This treatment was successful with 71% of the patients achieving a CR. This strong treatment effect is remarkable and consistent across the literature. Based on our case report and the data reported in the literature, we suggest that all women with EPDV and involved surgical resection margins after the initial surgery should be offered a course of topical imiquimod, given that the patient is compliant with close follow-up and willing to tolerate local side effects.

This systematic review has limitations. First, there is a high chance of reporting bias due to the rarity of EPDV. Also, adverse outcomes of therapy attempts with this experimental and off-label treatment may not have been re-

ported, thus inflating success rates and obscuring the true rate of adverse effects.

Based on the efficacy and safety of imiquimod in women with EPDV, future research should focus on establishing the optimal dosage and therapy duration of imiquimod in women with EPDV including a formal phase I dose escalation trial and a phase II safety and efficacy study. This, however, will require a coordinated, multi-institutional effort given the rarity of this disease.

In conclusion, EPDV is a rare vulvar neoplasia and can be successfully treated with imiquimod. Specifically, adjuvant imiquimod is a feasible and efficacious treatment option for women with involved margins after surgery.

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Disclosure Statement

All authors declare that there are no potential conflicts of interest, whether of a financial or other nature.

Authors' Contributions

All authors contributed to the writing process of the manuscript and approved the final version. A.D. and C.B.T. were the principal investigators, wrote the study protocol and manuscript. H.K., C.C., L.A.H. and C.G. worked as co-investigators performed the literature search and were crucially involved in data interpretation. All authors read and approved the final manuscript.

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