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# A pilot study of topical imiquimod therapy for the treatment of recurrent extramammary Paget's disease

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## HIGHLIGHTS

- Conservative therapy is proposed for recurrent EMPD of the vulva.
- Imiquimod, an anti-tumor immune response modifier, can be used off-label for EMPD.
- Complete clinical and histologic responses are achievable using topical imiquimod.

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## ABSTRACT

*Objective.* The objective of this prospective pilot study was to assess the clinical and histologic effects of topical imiquimod therapy on recurrent extramammary Paget's disease of the vulva.

*Methods.* Patients with biopsy-proven recurrent extramammary Paget's disease presenting to the gynecology outpatient services at two participating institutions were recruited for conservative treatment with 5% imiquimod cream from 2007 to 2011. The topical cream was to be applied 3 times per week for 12 weeks. Punch biopsy and photography were performed at baseline and at the 12-week time point.

*Results.* Eight patients from two institutions were enrolled. Complete clinical and histologic response was achieved in 6 (75%) patients by the 12-week follow-up appointment. Of the two remaining patients, one had a complete clinical response but no significant histologic response; the other patient was removed from the study protocol secondary to intolerable local irritation. Two patients continue to have no evidence of disease after a median follow-up of 35 months. Five are alive with disease. No patients progressed to invasive cancer while receiving therapy.

*Conclusion.* Topical 5% imiquimod cream is a safe and feasible option for women suffering from recurrent extramammary Paget's disease of the vulva, and should be considered as a viable alternative to surgical management. Given the rare nature of this disease, additional multi-institutional prospective studies should be conducted to explore the efficacy of this treatment regime.



## 1. Introduction

Extramammary Paget's disease (EMPD) of the vulva is particularly rare, accounting for approximately 1% of all vulvar neoplasias. The diagnosis is confirmed by the histological identification of unique intraepithelial neoplastic cells showing glandular differentiation [1]. Surgical excision is the standard treatment for EMPD. However, relapse is common. Multiple studies have demonstrated recurrence rates >30%, regardless of whether or not surgical margins were positive for disease at the time of primary excision [2–4]. Many of these patients undergo re-excision. Vulvar surgeries can be associated with significant psychosocial morbidity and decreased quality of life [5]. Given these negative sequelae and the high rate of recurrence, a more conservative approach may be of benefit when there is no evidence of an underlying adenocarcinoma.

Topical therapies including 5-fluorouracil (5-FU), bleomycin, and imiquimod have been used to treat EMPD. Unfortunately, 5-FU and

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**Table 1**
Pre-treatment symptom assessment.

| Symptom | N (%) |
|---|---|
| Visible lesion | 8 (100) |
| Erythema | 6 (75) |
| Pruritus | 5 (63) |
| Burning | 2 (25) |
| Pain | 2 (25) |
| Anal involvement | 1 (13) |
| Bleeding | 0 (0) |
| Clitoral involvement | 0 (0) |
| Discharge | 0 (0) |

bleomycin are associated with poor response rates and toxic side effects [1]. Imiquimod appears to modify the biologic response to the tumor cells, enhancing immune function, and multiple case reports have shown that it confers a complete clinical response in vulvar EMPD [1, 6–8]. However, there are no prospective clinical trials evaluating EMPD and imiquimod therapy [9]. The objective of this prospective pilot study was to assess the clinical and histologic effects of topical imiquimod therapy on recurrent extramammary Paget's disease of the vulva.

## 2. Materials and methods

All patients presenting to the gynecology outpatient services at Memorial Sloan Kettering Cancer Center (MSKCC) and Ohio State University Medical Center (OSUMC), who were 18 years of age or older and diagnosed with biopsy-proven recurrent extramammary Paget's disease, were recruited for study inclusion from 2007 to 2011. Women were excluded if they had a known hypersensitivity to imiquimod, were pregnant or nursing, or if biopsy of the lesion demonstrated an underlying adenocarcinoma or urothelial carcinoma. Approximately 7 patients from MSKCC and 2 patients from OSUMC are diagnosed with EMPD each year. Based on this, the study accrual goal was 20 patients: 5–8 women per year for 3 years. However, the study was closed after 4 years due to poor accrual.

The pre-therapy evaluation included histologic confirmation of recurrent EMPD, a history and physical examination as per standard clinical work-up at the participating site for a vulvar lesion, and a photograph of each lesion. Patients were seen in clinic every 6 weeks during treatment for examination. Compliance with therapy was monitored with a patient diary, in which date and quantification of residual medication was recorded. These data were collected at completion of the study.

In each photograph obtained by the treating physician, millimeter scales were included to ensure spatial standardization. Given the subjective nature of determining "significant" changes in the appearance of these skin lesions, we used a method similar to that employed in a 2006 study evaluating the effects of imiquimod on dysplastic nevi [10]. Clinical response was assessed by comparing pairs of clinical photographs obtained at baseline and study completion. The pairs of photographs were graded as follows:

- Complete response (CR) = reversion to clinically normal-appearing skin.
- Partial response (PR) = 50% or greater reduction in diameter of affected skin.
- Progression of disease (POD) = 50% or greater increase in diameter of affected skin.

The biopsied lesion was the focus of histologic assessment. All biopsies were routinely sectioned and stained (H&E). Primary histologic evaluation entailed quantification of the number of involved areas/$mm^2$ containing Paget's cells. Histologic responses were graded as follows:

- Complete response (CR) = no evidence of Paget's cells;
- Partial response (PR) = ratio of involved areas/$mm^2$ in post-treatment biopsy specimen/pre-treatment biopsy specimen < 50%; and
- Progression of disease (POD) = ratio of involved areas/$mm^2$ in post-treatment biopsy specimen/pre-treatment biopsy specimen > 150%.

Punch biopsy and photography were performed at baseline and 12-week time points. If the lesion was still present after 12 weeks of therapy, the treating physician recommended surgical excision 4 weeks following completion of therapy (week 16). If no lesion was present, or the patient refused surgical excision at week 16, the patient was instructed to return for follow-up exams every 3 months for at least 2 years.

Aldara™ 5% Cream is the brand name for imiquimod, an immune response modifier. Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base. Imiquimod 5% Cream is a Food and Drug Administration (FDA)-approved safe and effective treatment for anogenital warts, superficial basal cell carcinoma, and actinic keratosis [11]. The mechanism of

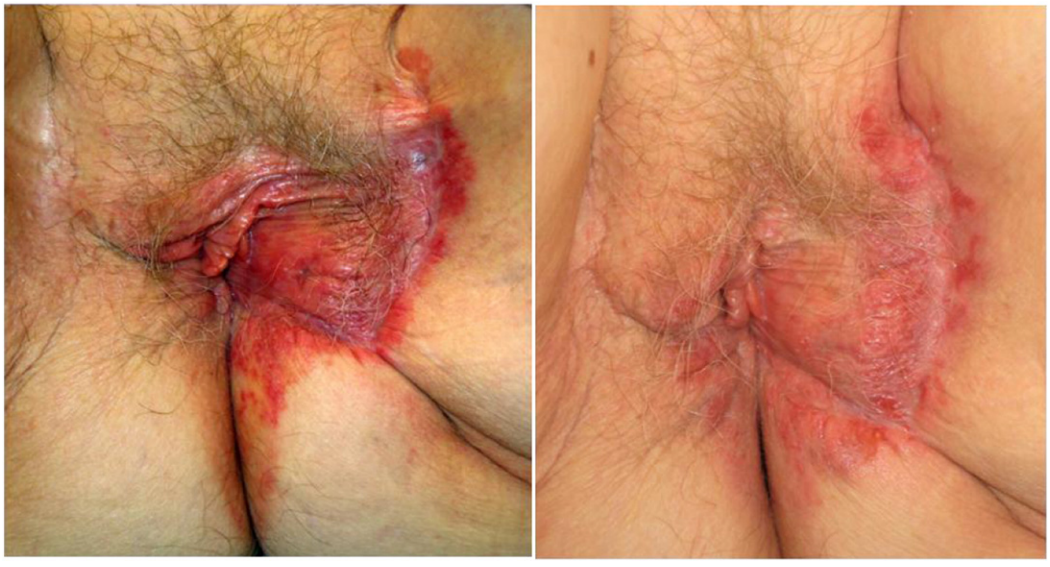

**Fig. 1.** Case 1 baseline photo on the left, post-treatment on the right.