Treatment of extramammary Paget disease of the vulva with imiquimod: A retrospective, multicenter study by the German Colposcopy Network

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Background: Extramammary Paget disease (EMPD) is a very rare genital neoplasia associated with a high frequency of local recurrences. Surgical excision is the standard treatment, but results in mutilating procedures in patients with advanced or recurrent disease. Case reports have shown clinical responses to imiquimod in patients with EMPD, but this therapy has not been evaluated systematically.

Objective: The aim of this study was to evaluate imiquimod as local treatment of first-time and recurrent EMPD.

Methods: All cases of biopsy-proven EMPD of the vulva treated within the German Colposcopy Network or other institutions specializing in vulvar diseases in Germany were included in this retrospective analysis.

Results: A total of 21 women with EMPD treated with imiquimod were identified: 11 (52.4%) achieved complete response, 6 (28.6%) achieved partial response, and there were no cases of progressive disease. The dose and duration of imiquimod differed between patients. The mean duration of treatment exceeded 16 weeks in women achieving complete response.

Limitations: EMPD is rare and this retrospective study is limited by the small number of patients identified.

Conclusion: When associated cancers and invasive growth are excluded, imiquimod appears to be a useful treatment option for recurrent EMPD and may avoid extensive mutilating surgical treatment. (J Am Acad Dermatol 2014;70:644-50.)

Key words: clinical response; extramammary Paget disease of the vulva; imiquimod; tissue-sparing surgery; treatment of recurrences.

Extramammary Paget disease (EMPD) is histologically similar to Paget disease of the breast[1,2] and typically affects external genitalia. Primary (cutaneous) EMPD is defined as a noninvasive intraepidermal adenocarcinoma that may spread into neighboring epithelial glandular appendices.[3] Paget disease of the vulva is the most frequent form of EMPD with cutaneous origin.[4]

Abbreviations used:

CR:	complete response
EMPD:	extramammary Paget disease
PR:	partial response

Secondary vulvar EMPD is defined by the involvement of a noncutaneous neoplasia. Cancers most

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frequently leading to secondary EMPD are anal and rectal adenocarcinoma with involvement of the anogenital skin,[3,5-7] followed by carcinoma of the urothelium.[7-9] Differentiating between primary and secondary EMPD is not standardized, however, expression of human epidermal growth factor receptor-2 (HER2) may provide a biomarker for differential diagnosis.[10]

EMPD of the vulva is a rare and hard-to-treat epidermal neoplasia, comprising less than 1% of all vulvar neoplasms.[1] Multimodality treatment involving surgery, chemotherapy, or irradiation may be curative for first-time or recurrent EMPD, however, relapse occurs in 30% or more of patients.[1,11-13]

The immune-stimulator imiquimod, which is highly effective in the treatment of genital warts and vulvar intraepithelial neoplasia associated with human papillomavirus,[14-16] seems to be a promising treatment for EMPD.[12,17-20] However, the role of imiquimod has not been widely studied because of the low incidence of EMPD.[21,22]

Imiquimod promotes an immune response in activating macrophages and other cells by increasing the synthesis of proinflammatory cytokines.[23-26] Imiquimod also induces distinctive apoptosis of transformed epithelial cells.[24,27]

This multicenter study was designed to evaluate imiquimod as local treatment for first-time and recurrent EMPD of the vulva. From a clinical perspective, imiquimod may help to avoid mutilating surgery, radiotherapy, or chemotherapy.

CAPSULE SUMMARY

- Extramammary Paget disease of the vulva is a rare neoplasia associated with a high rate of local recurrence and potentially mutilating surgery.
- Imiquimod produces a high clinical response rate (81%) as a first-line therapy or for recurrent disease.
- Imiquimod appears to allow tissue-sparing surgery.

METHODS

We conducted a retrospective analysis of patients with EMPD of the vulva treated with imiquimod within the German Colposcopy Network or other institutions specializing in vulvar diseases in Germany. The German Colposcopy Network is a network of colposcopy clinics with an interest in scientific research and independent quality assessment.

The local ethics committee of the Ärztekammer Niedersachsen was consulted but formal approval was not necessary because data collection was pseudonymous.

The diagnosis of EMPD of the vulva was confirmed by single or multiple biopsies performed between July 1978 and December 2012. Patients with associated cancers and invasive growth confirmed by colposcopy and biopsy were excluded.

The study end point was best clinical response defined as: complete response (CR) when visible lesions regressed entirely and corresponding biopsy specimens showed no residual disease, partial response (PR) when clinical lesions regressed by 50% or more, stable disease when the lesions regressed by less than 50%, and progressive disease when progression of clinical lesions was observed.

Data collected included patient age, associated cancers, lesion size, previous therapies, and the duration and dosage of imiquimod therapy. Follow-up of patients was performed according to the local protocol of the participating institution and was based on repeated colposcopy examinations with punch biopsy specimens taken when suspicious lesions were identified.

Univariate descriptive analyses were performed to characterize the student population and to compare the proportions of outcomes (CR, PR, progressive disease, or treatment interruption) between different age groups (<50, 50-64, 65-74, and ≥75 years), and between treatment indications (first-time therapy or for recurrent disease). A Fisher exact test was used to make statistical comparisons because of the small numbers in the data set. We assessed the *P* value against the nominal .05 level of significance. The analyses were conducted using statistical software (R, Version 2.15.1, R Project for Statistical Computing, Vienna, Austria). Mean treatment time in weeks and respective therapy outcomes were described; SD was used to describe variability in parameter values.

RESULTS

In total, 85 patients with EMPD of the vulva were identified, of whom 21 received local therapy with imiquimod (Table I and Figs 1 to 4). One case was defined as secondary Paget disease with previous urothelial carcinoma more than 10 years before EMPD was diagnosed, whereas the remaining 20 cases were classified as primary EMPD. The mean age was 66.4 years (range 41-84 years). Imiquimod was given as initial therapy in 6 cases and for recurrent disease in 15 cases. Imiquimod was applied locally 2 or 3 times per week on the area of

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