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Successful Treatment of Primary Vulvar Extra Mammary Paget Disease with Topical Imiquimod Cream- Report of Three Cases

Rama Padma Namuduri[1]*; Lim Yong Kuei[1]; Yeo Yen Ching[2]; Gudi Mihir Ananta[2]

[1]Department of Obstetrics and Gynecology, KK Women's and Children's Hospital (KKH), Singapore.

[2]Consultant Histopathology, Department of Pathology and Laboratory Medicine, KK Women's and Children's Hospital, Singapore.

***Corresponding Author(s): Rama Padma Namuduri**

Department of Gynecological oncology, KK Women's and Children's Hospital, 100 Bukit Timah Road, 229899 Singapore.

Tel: +65-6394-1747, Fax: +65-6291 8135;

Email: rama.padmavathi@kkh.com.sg

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Abstract

Extramammary Paget Disease (EMPD) is a rare cutaneous neoplasm that most frequently affects the vulva. Wide local excision remains the preferred treatment, which may need vulvar reconstruction. However, it is associated with high recurrence rates. Frequently women with Paget's disease of the vulva who are elderly with associated co-morbidities and are not suitable for surgery. Literature have shown clinical responses to imiquimod in patients with EMPD both primary and recurrent. We presented 3 cases of successful treatment of vulvar primary EMPD treated with 5% imiquimod.

Introduction

Vulvar EMPD accounting for approximately 1% of all vulvar neoplasms generally presents between the ages of 50 and 80 years [1]. EMPD lesions of the vulva clinically present as well demarcated itchy erythematous plaques with scaly and erosive surface and commonly mistaken for eczematous diseases.

EMPD is associated with underlying malignancy in at least 17% to 30% of cases, so a thorough investigation to rule out malignancy is important [2].

The standard treatment of EMPD vulva is wide local excision with clear margins. Other recommended treatments are Moh's micrographic surgery, laser ablation, photodynamic therapy, radiotherapy as well as topical 5 -fluorouracil and 5% imiquimod [3].

A number of case reports, retrospective case series, and one observational study have shown topical 5% Imiquimod has been shown as a safe and effective treatment option for both primary and recurrent extramammary Paget's disease (Table 1).

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Table 1: Case reports/series of extramammary Paget disease treated by imiquimod.

Author (year)	No. of cases	Disease	Treatment duration (weeks)	Outcome (CR: Complete Remission; PR: Partial Remission)	Adverse Events
Wang (2003)	1	Recurrent vulva	7	CR	Local irritation
Geisler (2008)	1	Recurrent vulva	-	CR	-
Hatch (2008)	2	Recurrent vulva	20-24	CR	Pain, erosion, ulceration
Bertozzi (2009)	1	Recurrent vulva	8	CR	Local itching
Sendagorta (2010)	3	Primary vulva	6	CR	Local irritaion
Tongue (2010)	1	Recurrent vulva	18	CR	erosion
Feldmeyer (2011)	1	Primary vulva	18	CR	Intense inflammation
Anton (2011)	1	primary	16	CR	Fever, erosion, burning
Matin (2011)	1	primary	8	Disease progressed	Pruritus, tenderness
Hiraldo-Gamero (2011)	1	primary	16	CR	erosion
Toledo (2012)	1	primary	16	PR	Mild irritation, burning, erosion
Cooper (2012)	1	recurrent	-	PR	-
Wagner (2012)	1	primary	6	CR	Erythema, burning
Baiocchi (2012)	4	Primary (1), recurrent (5)	-	3 CR, 1 disease progressed	-
Sanderson (2013)	6	Primary (5), recurrent (1)	2 to 4	3 CR, 2 PR	Irritation (3), erythema (1)
Choi (2013)	10	Primary (surgery + adjuvant imiquimod)	-	10 CR	-
Luyten (2014)	21	Primary (5), recurrent (16)	4 to 28	11 CR, 6 PR	Local reaction (1)
Marchitelli (2014)	10	Primary (7), recurrent (3)	-	9 CR, 1 PR	Moderate irritation (10)
Frances (2014)	1	Primary (with tazarotene treatment)	8	CR	-
Dogan (2016)	1	Primary (surgery+ adjuvant)	12	CR	erythema
Cowan (2016)	8	Recurrent vulva after WLE	12	6/8 had complete clinical and histologic response at 12 weeks, 1/8 had complete clinical but no histologic response	Headache, influenza-like symptoms, myalgia and intolerable local side effects
Liau (2016)	3	Vulvar EMPD (two with previous laser vulvectomy and WLE)	22 to 100 months	2/3 CR, 1/3 PR	Erythema, pain, swelling, atrophy
Apalla (2018)	1	Genital and perianal EMPD	6	CR	Burning/ stinging sensation
Sawada (2018)	5	Primary and recurrent genital EMPD	16 for 4 patients, 1 for 1 patient	3/5 CR, 2/5 PR	Local irritation
Total	86				

Methods

We present 3 patients with primary vulvar EMPD with complete resolution of their disease confirmed by histology after using 5% imiquimod cream. This is a retrospective study.

Case Report 1

A 72-year-old Chinese woman was referred to vulvar clinic for long standing itchy and erythematous rash resistant to topical steroids. Physical examination revealed a 6 cm erythematous plaque on the bilateral labia majora extending to mons pubis. The lesion was diagnosed as vulvar eczema by her primary care physician and treated with topical steroids without any improvement. A 4 mm deep Keyes punch biopsy was taken in the vulva clinic revealed nests of carcinomatous cells within the epidermis with vesicular nuclei, distinct nucleoli, and abundant clear staining cytoplasm without dermal invasion. Immunohistochemically stain was negative for S100 protein while strongly positive for cytokeratin 7. A diagnosis of vulvar Paget's disease was made. The further gynaecological examination and total body skin examination were normal. Mammogram, computerized tomography scan (CT scan) of the pelvis and abdomen were performed. These studies were normal. As patient refused any kind of surgical treatment, she was offered topical application of 5% imiquimod cream.

Imiquimod 5% cream was applied to the vulvar lesion, three times a week before bedtime for 16 weeks and once a week intermittently for another 10 weeks. The therapy was well toler-

ated with only mild local erythema, which required no further therapy. Her lesion showed significant regression clinically. We performed multiple biopsies 6 months after clinical improvement which showed focal hyperkeratosis and hyper granulosis. No recurrence has been noticed after 5 years of follow up. (Figure 1A,B,C,D).

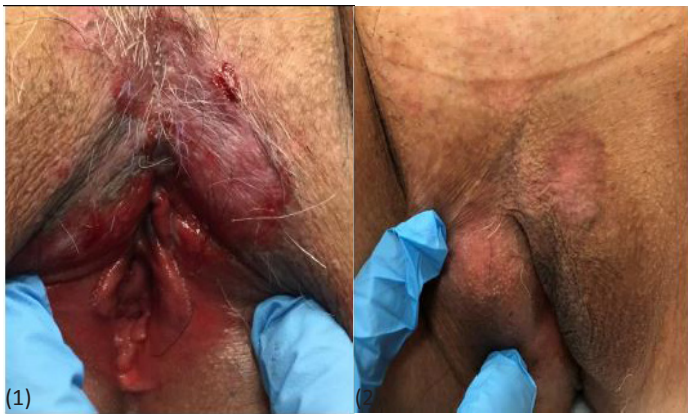

Figure 1A: (1) EMPD vulva Before treatment with 5% Imiquimod. **(2)** EMPD Vulva After treatment with 5% Imiquimod.

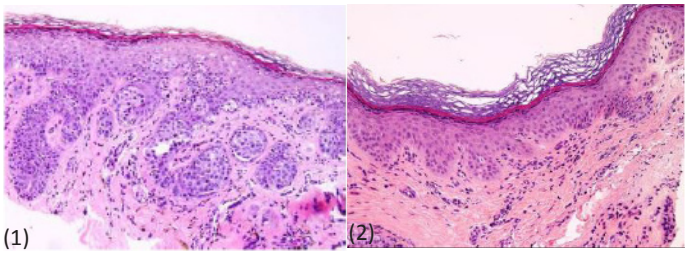

Figure 1B: (1) H &E 200x Paget's cells in the epidermis and dermis- Before treatment. **(2)** No Paget's seen H&E 200x. After treatment.

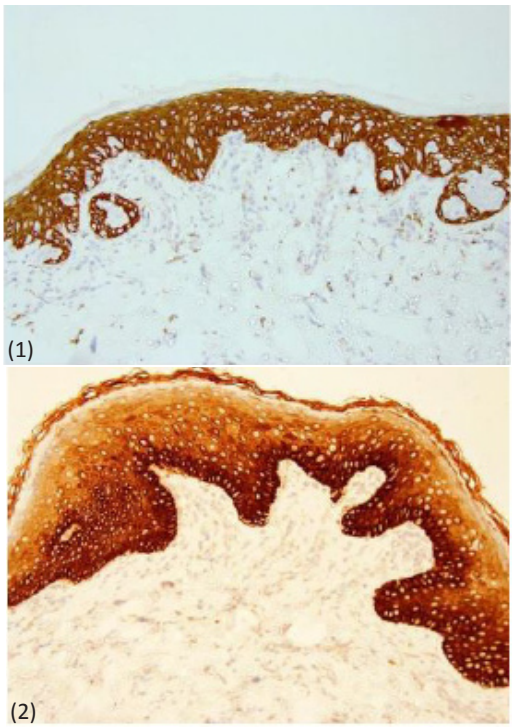

Figure 1C: (1) Staining for CK 5/6 shows negative staining in Paget's cells 200x Before treatment.
(2) Staining for CK 5/6 shows uniform block staining in the epidermis confirming absence of Paget's cells 200 x After treatment.

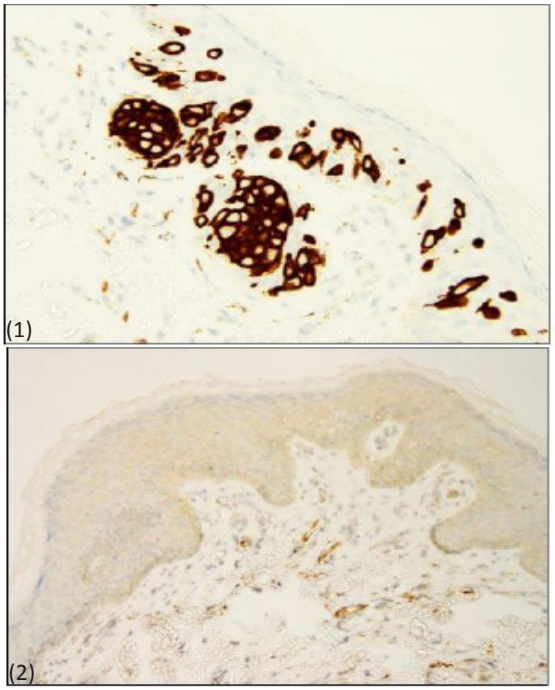

Figure 1D: (1) Staining for CK 7 highlights the Paget's cells in the epidermis 200x. Before treatment. **(2)** Staining for Ck5/6 shows negative staining in Paget's cells 200x After treatment.

Case Report 2

An 80-year-old Chinese woman was referred to our centre with the histological diagnosis of non-invasive EMPD vulva and perineum for further management. Histology showed EMPD with strong positivity for cytokeratin [7]. Physical examination revealed bilateral vulvar erythematous plaque extending to perineum.

Total body skin examination, gynaecological examination, a transvaginal ultrasound, and a computer tomography (CT scan) of the pelvis abdomen, cystoscopy and colonoscopy and mammogram were performed and the studies were normal.

After discussion with patient we planned a wide local excision. While waiting for surgery she was given 5% imiquimod to apply thrice a week. During follow up patient reported improvement of symptoms. We also noted clinical improvement. After completing 12 weeks of application of imiquimod the patient underwent surgical resection as planned in the form of a wide local excision with primary closure with v-y flaps. Histology shows no residual Paget's disease despite all tissue has been submitted for histological assessment (Figure 2A & B).

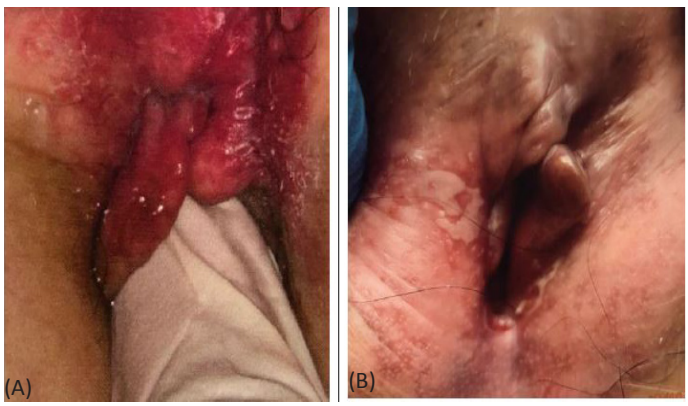

Figure 2: (A) Before treatment. **(B)** After treatment

Case Report 3

A 72-year-old Chinese woman presented with a itchy and erythematous plaque on vulva involving right labia majora of the vulva extending to perineum (Figure 3). Keyes punch biopsy of the vulva confirmed non-invasive EMPD which was positive for CK7 and Negative for CK 20. The total body skin examination and gynaecological examination were normal. A bilateral breast mammogram, Computer Tomography (CT) of the thorax and abdomen, pelvis and colonoscopy were performed and were normal.

After counselling her for Options of wide excision versus 5% imiquimod, patient opted for Imiquimod. Topical therapy with imiquimod 5% cream thrice weekly was applied for 18 weeks. She was given half strength betamethasone cream for mild irritative symptoms after using Imiquimod cream We noted marked clinical improvement of her condition (Figure 3). We have performed multiple systematic biopsies of perineum and vulva one month after stopping imiquimod. Histology showed complete resolution of the EMPD. 5 years after treatment, she has no recurrence.

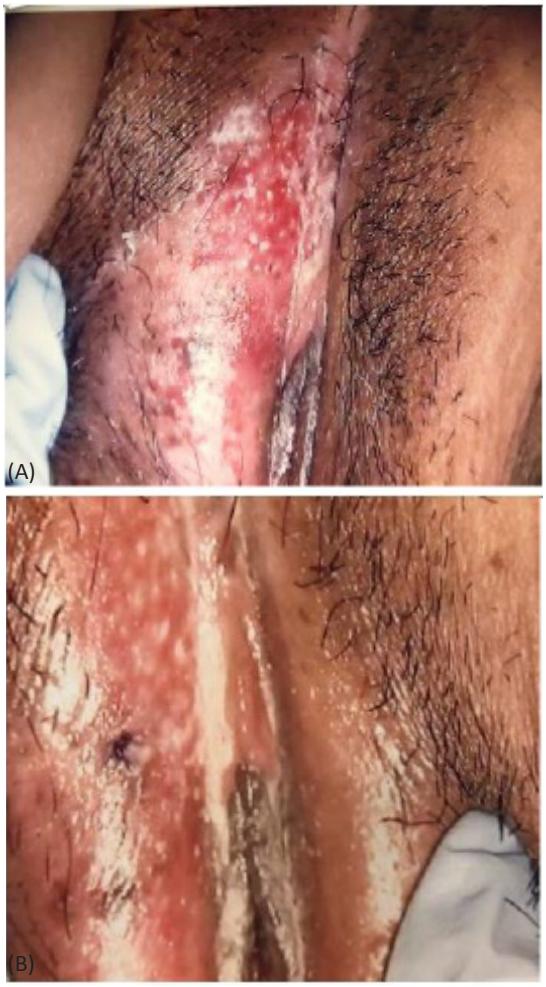

Figure 3: **(A)** Before treatment. **(B)** After treatment

Discussion

The first reported successful treatment of vulva EMPD was by Wang et al, in 2003 [4].

Vulvar surgeries can be associated with significant psychosocial morbidity and decreased quality of life. Up to 30% to 60% recurrences are noted after surgery independent of margin status [5].

Hendi et al reported 16% recurrence rate following Moh's micrographic surgery [6].

Radiation therapy is recommended for those patients with invasive EMPD and surgically unfit. It is associated late onset side effects with up to 70% recurrence rates [7].

Topical Imiquimod 5% cream which is an immune response modifier has been shown as a safe and effective treatment option for extramammary Paget's disease with favourable results. Imiquimod is a topically applied imidazoquinolinone immunomodulator that binds to the toll-like receptor 7 and locally induces the production of proinflammatory chemokines and cytokines. Currently, there are no guidelines for topical 5% imiquimod treatment for EMPD. We made thorough investigation to rule out underlying malignancy and ruled out invasion prior to initiating treatment with 5% Imiquimod [8].

Recommend topical therapy with imiquimod at least 3 times each week for a minimum of 8 weeks, and as long as 16 weeks. The total treatment duration varied from 6 to 24 weeks [9,10]

In our cases the treatment duration ranged from 12-26 weeks.

Luyten et al. Reported complete response in 11 out of 21 (52.4%) cases. Cowan et al. [11] Reported complete response in 6 out of 8 cases (75%). We achieved a complete response in all 3 cases [12].

Studies reported various local and systemic side effects of 5% imiquimod (Table 1).

We have mild local irritation noted in one patient and managed with topical steroid cream.

It is important to rule out invasive disease by multiple biopsies of most suspicious areas of EMPD before any conservative treatment. A long term follows up is mandatory for all these patients to detect local recurrences.

The length of follow up since post treatment biopsy is once in 3 -6 months for 2 years and once in an year later.

Conclusion

Imiquimod therapy may be an alternative for extramammary Paget's disease in selected cases. A long term follow up is needed.

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