Two Cases of Vulval Extramammary Paget's Disease Treated with Topical Imiquimod Cream

Dear Editor,

Extramammary Paget's disease (EMPD) is a rare non-invasive intraepithelial adenocarcinoma that occurs on the vulva in around 60% of cases and forms up to 1% of vulvar malignancies.[1] We report two cases of extramammary Paget's disease over the vulva treated with topical imiquimod.

Patient 1: A female in her 40s presented with an itchy, skin-colored to hyperpigmented plaque with overlying whitish deposits over the right labia majora and minora for the past 2 years [Figure 1a]. There was no evidence of oozing or crusting. There was no history suggestive of atopy.

Patient 2: An otherwise healthy woman in her 30s presented with vulvar pruritus for the past 10 years. She had itchy, skin-colored to hyperpigmented plaques with areas of overlying erosions over both labia majora, minora, and introitus for about 3 months [Figure 1b]. She also had dyspareunia and a history of intermittent, mild serosanguinous vaginal discharge. There was no history of atopy.

Skin biopsy of both patients showed small nests of cells in the epidermis showing moderate pleomorphism, abundant clear vacuolar cytoplasm, and vesicular nuclei [Figure 2a]. There was no dermal invasion. The cells showed intracellular mucin on alcian blue stain [Figure 2b], consistent with the diagnosis of extramammary Paget's disease. They were immunopositive for cytokeratin 7 (CK7) and carcinoembryonic antigen (CEA) [Figure 2c].

Figure 1: (a) Skin-colored to hyperpigmented plaque with overlying whitish deposits over the right labia majora and minora (b) Skin-colored to hyperpigmented plaques with areas of overlying erosions over both labia majora, minora, and introitus

Pap smear, high-risk human papillomavirus DNA, stool for occult blood, urine for cytology, mammogram, and contrast-enhanced computed tomography (CECT) of abdomen and pelvis were normal in both patients. CT urography and colonoscopy were normal in patient 2. Patient 1 declined to undergo these tests.

Both patients were treated with overnight application of imiquimod 5% cream thrice a week, with the application extending onto the skin 1 cm beyond the lesion. Both patients experienced severe stinging, burning, and itching initially, which required intermittent stoppage of therapy and treatment with antihistamines. With time, both of them were able to tolerate imiquimod therapy. After 5 months of therapy, there was an excellent response with near complete healing in case 1 and a partial response in case 2 [Figures 3a and b]. Due to partial response in case 2, imiquimod therapy was initiated 5 days a week for 1 month with no further improvement. The patient has been referred to the gynecology department for surgical excision. Case 1 has been planned for a repeat biopsy after complete clinical resolution of the lesion.

Extramammary Paget's disease of the vulva is usually seen in postmenopausal women and presents as an eczematous, erythematous, or lichenified plaque. Primary EMPD occurs without an underlying malignancy, while secondary EMPD, which occurs in up to 10–20% of cases, is due to an associated malignancy in the vulva, breast, rectum, bladder, cervix, or skin.[2] The origin of this malignancy remains controversial, but suggested hypotheses include carcinoma of adnexal stem cells, a sweat gland cancer arising from the intraepidermal part of the gland, and carcinoma derived from the toker cells of mammary-like glands of the vulva.[3]

The clinical differential diagnoses include lichen simplex chronicus, psoriasis, lichen planus, and Bowen's disease, while the histopathological differential diagnoses are pagetoid Bowen's disease and pagetoid melanoma. Paget cells are positive for mucin stain, CK7, CK CAM5.2,

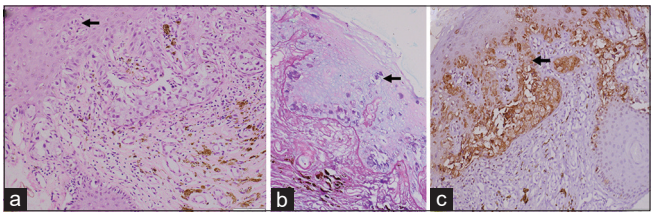

Figure 2: (a) Small nests of cells (black arrow) in the epidermis showing moderate pleomorphism, abundant clear vacuolar cytoplasm, and vesicular nuclei (H&E stain, 200x) (b) Cells showing intracellular mucin (black arrow) (Alcian blue stain, 200x) (c) Paget cells showing immunopositivity to CEA (black arrow) (200x)

Table 1: Various treatment options for extramammary Paget's disease

Modality	Response	Recurrence	Limitations
Surgery	33–70%	58% (overall) Negative margin: 18–38% Positive margin: 46–61%	Skin graft placement has 6.8% risk of physical/sexual dysfunction
Radiotherapy	62–100%	0–35%	Radiation dermatitis. Treatment of recurrence can be challenging due to compromised healing
5-fluorouracil, bleomycin	57–100%	25%	Pain, erosions, allergic contact dermatitis
Photodynamic therapy	14–50%	38–56%	Photosensitivity reaction, burning sensation
Ablative laser	Up to 100%	67%	Very few case reports are available
Imiquimod	52–80%	19%	Majority of studies are retrospective, with small sample size. Varied doses, regimens, and durations of therapy. Erythema, itching, burning, and pain are some of the side effects

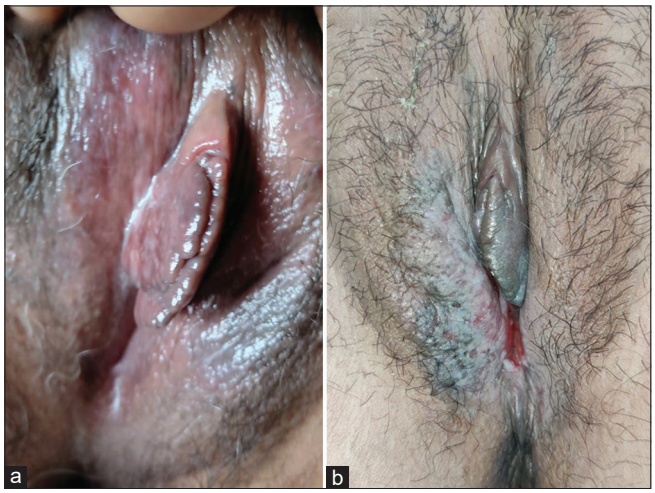

Figure 3: (a) After 5 months of topical imiquimod therapy, there was an excellent response with near complete healing in case 1 (b) After 5 months of topical imiquimod therapy, there was a partial response in case 2

CEA, epithelial membrane antigen, and Ber-EP4/BRST-2/HER-2neu/GCDFP-15 and negative for p63 (positive in Bowen's disease) and S-100 (positive in melanoma).[4]

Surgical excision is the standard treatment and leads to clearance in the majority of patients. However, there is a high recurrence rate after surgical excision, with recurrences reported in 18–38% of cases when there are clear surgical margins as opposed to 46–61% of cases with a positive surgical margin. Excision is usually done with a 1–2 cm margin of clinically unaffected skin, and this can entail significant loss of tissue requiring reconstruction with flaps in some cases. In view of the high recurrence rate despite a negative margin, morbidity related to surgery and physical, psychological, and sexual dysfunction, alternate treatment modalities are often sought. These include radiotherapy, topical imiquimod, 5-fluorouracil, photodynamic therapy, and ablative laser [Table 1].[5] Response rates are almost similar with all modalities and range from 15 to 100%.[5] 5-fluorouracil has been found to be less efficacious in a recent meta-analysis.[6]

Topical imiquimod has been used for 2–52 weeks with a mean duration of therapy of 12.4 weeks and has induced complete remission in 71% (50/70) and partial remission in 16% (11/70) of patients. It was found to induce complete remission in a case with positive margin who had twice undergone surgical excision previously.[7] It has also been used as a neoadjuvant treatment prior to surgery, making the surgery easier by decreasing the size of the lesion.[8] The recurrence rate following imiquimod therapy is 19% which compares well with other modalities, though the majority of studies were retrospective in nature, had small sample sizes, and used varying schedules and durations of therapy.[5]

Imiquimod appears to be a convenient, cheap, and non-invasive alternative/adjuvant to surgical management of EMPD, but patients need to be regularly followed up to look for any recurrence and its management, as EMPD is notorious for its high recurrence rate.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Bhavya Swarnkar, Gouri R. P. Anand, M. Ramam, Neetu Bhari, Shipra Agarwal[1]

Departments of Dermatology and Venereology, [1]Pathology, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence:
Dr. M. Ramam,
Professor, Department of Dermatology and Venereology, All India Institute of Medical Sciences, New Delhi, India.
E-mail: mramam@hotmail.com

References

1. Fanning J, Lambert HC, Hale TM, Morris PC, Schuerch C. Paget's disease of the vulva: Prevalence of associated vulvar adenocarcinoma, invasive Paget's disease, and recurrence after surgical excision. Am J Obstet Gynecol 1999;180:24-7.
2. Shaco-Levy R, Bean SM, Vollmer RT, Papalas JA, Bentley RC, Selim MA, *et al*. Paget disease of the vulva: A histologic study of 56 cases correlating pathologic features and disease course. Int J Gynecol Pathol 2010;29:69-78.
3. Belousova IE, Kazakov DV, Michal M, Suster S. Vulvar toker cells: The long-awaited missing link: A proposal for an origin-based histogenetic classification of extramammary paget disease. Am J Dermatopathol 2006;28:84-6.
4. Goyal T, Varshney A, Solanki R. Co-existence of extramammary Paget's disease and Bowen's disease of vulva. Indian J Dermatol Venereol Leprol 2014;80:530-3.
5. Machida H, Moeini A, Roman LD, Matsuo K. Effects of imiquimod on vulvar Paget's disease: A systematic review of literature. Gynecol Oncol 2015;139:165-71.
6. Snast I, Sharon E, Kaftory R, Noyman Y, Oren-Shabtai M, Lapidoth M, *et al*. Nonsurgical treatments for extramammary paget disease: A systematic review and meta-analysis. Dermatol Basel Switz 2020;236:493-9.
7. Dogan A, Hilal Z, Krentel H, Cetin C, Hefler LA, Grimm C, *et al*. Paget's disease of the vulva treated with imiquimod: Case report and systematic review of the literature. Gynecol Obstet Invest 2017;82:1-7.
8. Toledo F, Silvestre JF, Cuesta L, Ballester I, Latorre N, Monteagudo A, *et al*. Sequential use with imiquimod and surgery in extramammary Paget's disease. Dermatol Ther 2012;25:82-5.

Access this article online

Website: https://journals.lww.com/idoj

Quick Response Code

DOI: 10.4103/idoj.idoj_52_23

How to cite this article: Swarnkar B, Anand GR, Ramam M, Bhari N, Agarwal S. Two cases of vulval extramammary Paget's disease treated with topical imiquimod cream. Indian Dermatol Online J 2024;15:129-31.

Received: 18-Jan-2023. **Revised:** 12-Apr-2023.
Accepted: 12-Apr-2023. **Published:** 17-Oct-2023.