Treatment of recurrent vulvar Paget disease with imiquimod cream: a case report and review of the literature

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Abstract

Introduction Extra-mammary Paget disease is one of the rare neoplastic conditions of the skin. The most common site of involvement is the vulva and presents itself with erythematous plaques. Surgery is the most important treatment option. In the recent years, there are publications of the topical use of imiquimod cream in extra-mammary cutaneous Paget disease. We report the case of a woman with recurrent vulvar Paget disease, who underwent successful treatment with imiquimod cream. We also review the reports of other patients with vulvar Paget disease who were treated with topical imiquimod cream.

Case report A 65-year-old woman presented to the Oncology Outpatient Clinic with an itchy lesion in her vulva for 2 years. In the gynecologic examination, a hyperkeratotic erythematous lesion was found starting from the right labium to involve clitoris, with a size of $4 \times 3$ cm. Pathology result was reported as Paget disease. She was operated and wide vulvar excision was performed with a safety margin of 2 cm. Then recurrence two times occurred. Because she refused surgery, imiquimod cream 5% was applied for treatment.

Conclusion Imiquimod cream is an effective and safe therapeutic agent for both primary and recurring vulvar Paget disease.

Keywords Vulva · Paget disease · Recurrence · Imiquimod cream · Treatment

Introduction

Extra-mammary Paget disease is one of the rare neoplasms of the skin. It is thought to originate from intraepidermal apocrine glands or from pluripotent keratinocyte stem cells. It is frequently located in the anogenital region and the lesions are in the form of erythematous or leucoplasic plaques raised from the skin [1, 2]. They have symptoms such as irritation, burning sensation, pain and ulceration. It is frequently confused with candidiasis and dermatitis because of these symptoms [3]. However, lack of response to antifungal treatment and steroids provides for the elimination of these diagnoses. Biopsy must be performed both with the purpose of diagnosis and for differentiating it from other neoplasms. Extra-mammary Paget disease has four clinical forms:

1. restricted primary skin disease located intra-epidermally,
2. primary intra-epidermal disease together with secondary adenocarcinoma under the dermis or in regional lymph nodes,
3. secondary skin disease arising from an underlying adnexial carcinoma and
4. skin disease accompanying an internal cancer [4].

Therefore, breast examination, skin examination, vaginal and rectal examination and lymph node palpation must be performed in extra-mammary Paget disease. Colonoscopy, cystoscopy, pelvic and abdominal ultrasonography must be ordered for the patient [4].

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Case report

The case was 65-year-old and was in natural menopause for 15 years. She applied to the Oncology Outpatient Clinic in July 2007 to Zekai Tahir Burak Women’s Health Training and Research Hospital with an itchy lesion in her vulva for 2 years that did not respond to steroid and anti-fungal treatment. In the gynecologic examination, a hyperkeratotic erythematous lesion was found starting from the right labium to involve clitoris, with a size of 4 × 3 cm. Biopsy from the lesion was performed. The result of the biopsy was Paget disease (Fig. 1a). Staining was positive on the histochemical examinations of the biopsy material with Alcian Blue (Fig. 1b) and CEA and keratin, while staining with S100 was negative. Upon the result of Paget disease from the pathology, other systems were examined. Breast examination, mammography results, skin examination and lymph node palpation results were normal. Colonoscopy, cystoscopy and pelvic and abdominal ultrasonography were performed, and no pathologies could be found. She was operated and wide vulvar excision was performed with a safety margin of 2 cm. Pathological examination gave the result of Paget disease. Since the surgical margin was positive, she was taken for regular close follow-up. 2 months later, she had complaints of itching and had a hyperkeratotic erythematous lesion with a size of 2 × 2 cm in the same region. It was decided that she had recurrent Paget disease and was re-operated. Surgical margins were negative this time. In the control visit, 4 months later, she had again a similar lesion in the same region with a size of 3 × 2 cm. Punch biopsy was performed and recurrent Paget disease was diagnosed in the pathological examination. However, she refused surgery this time. Therefore, treatment with imiquimod cream 5% was recommended. She was informed about the drug therapy and the possible side effects. Her informed consent was obtained.

Treatment with imiquimod cream 5% was administered every day. The cream was administered by thoroughly rubbing onto the lesion and its surroundings. Treatment was stopped for 1 week when skin erosion was observed 3 weeks later. 1 week later, the treatment was started again, this time it was administered every other day. Betametasone was added to the treatment because of skin problems, and it was applied alternatively with imiquimod cream. Clinical remission was achieved 8 weeks later. Treatment was continued for six more weeks. Biopsy was taken from the lesion at the end of the week 14. Pathology result was reported as chronic inflammation (Fig. 2). Follow-up of the patient was continued for 2 years. No evidences of recurrence were observed throughout this period. Disease was reported as negative consistently in the control biopsies.

Discussion

Wide surgical excision is the most important treatment option. However, recurrences between 20 and 60% can be
| Author (year) | Age | Disease       | Dosage                                                                 | Treatment duration (weeks) | Follow-up | Result          | Adverse events     | Steroid usage |
|--------------|-----|---------------|------------------------------------------------------------------------|---------------------------|-----------|-----------------|-------------------|---------------|
| Wang (2003)  | 75  | Recurrent     | Every day: 6 days 2 times a week: 1 week 3 times a week: 5 weeks        | 7                         | 2 weeks   | Cl rem          | Path rem          | Local irritation | Lidokain      |
| Denehy (2008)| 6 Patients | Recurrent | 3 times a week                                                      | 6–16                      | 6 months  | 5 Com rem       | 1 Par rem         |               |               |
| Geisler (2008)| 80 | Recurrent     | Every other day Every day: 4 weeks                                   | 24                        | 4 months  | Cl rem          | Path rem          |               |               |
| Hatch (2008) | 68  | Recurrent     | Every day 2 times: 2 weeks Every day: 5 weeks Every other day          | 20                        | 7 months  | Cl rem          | Path rem          | Pain erosion     | (+)           |
| Challenor (2009)| 48 | Surgical margin (+) | 3 times a week                                                          | 12                        | 4 months  | Follow up       |                  |               |               |
|                | 66  | Surgical margin (+) | 3 times a week                                                          | 12                        | 3 months  | Follow up       |                  |               |               |
| Bertozzi (2009)| 71 | Recurrent     | Every day: 3 weeks Every other day: 3 weeks                            | 8                         |           | Cl rem          | Local itching     |               |               |
| Sendogorta (2009)| 66 | Primer       | Every day: 3 weeks Every other day: 3 weeks                            | 6                         | 26 months | Cl rem          | Path rem          | Local irritation | (+)           |
|                | 58  | Primer       | Every day: 3 weeks Every other day: 3 weeks                            | 6                         | 22 months | Cl rem          | Path rem          |               |               |
|                | 82  | Primer       | Every day: 3 weeks Every other day: 3 weeks                            | 6                         | 20 months | Cl rem          | Path rem          |               |               |

*Cl rem Clinical remission, Path rem Pathological remission, Com rem Complete remission, Par rem Partial remission*
seen after surgical treatment. Such high rates of recurrence can be explained with irregular borders of the lesion, multicentricity and distance of the pathology to the visible lesion [5]. In the recent years, Mohs micrographic technique is the most preferred treatment modality for the cutaneous lesions of the extra-mammary Paget disease [6]. Other treatment options include electro-dessication and curettage, laser, photodynamic treatment with aminolevulinic acid, radiotherapy and topical use of 5-fluorouracil [7–10]. In the recent years, there are publications on the topical use of imiquimod cream in extra-mammary cutaneous Paget disease.

Imiquimod cream 5% is used in external genital condylomas, actinic keratosis and superficial basal cell carcinomas. Its side effects are local irritation, erythema, development of erosion–ulceration, itching and pain. In addition, it can have systemic effects like fever, headache or myalgia [11].

Imiquimod cream shows its effects by binding to the toll-like receptor 7 on the surfaces of macrophages, monocytes and dendritic cells. Proinflammatory chemokines (including interleukin 1, 6, 8 and 10) and cytokines (including interferon, interleukin12, tumor necrosis factor-alpha) are released and T-helper cell type 1 cytokines (including interferon-gamma) are stimulated while T-helper cell type 2 cytokines (including interleukin 4 and 5) are inhibited [12–15].

Direct antineoplastic activity of imiquimod is also thought of. It has been shown that imiquimod promotes the induction of apoptosis in basal cell carcinoma cells [16]. However, how imiquimod cream ensures the tumor eradication in extra-mammary Paget disease has not been explained yet.

Surgical excision of vulvar Paget disease is controversial because of high recurrence rates. Radical vulvectomy has been tried in surgery to decrease the recurrence rate; however, no significant differences were seen between the radical vulvectomy and local excision as regards recurrence [17]. Interestingly, high recurrence rate is not related with the presence of the tumor in the surgical margin. In a study, while recurrence rate was 31% in patients with positive surgical margins, the same was 33% for those with negative surgical margins [17]. In three different studies, while recurrence in patients with positive surgical margins was 25, 33 and 70%, respectively, the same was 13, 21 and 38% in patients with negative surgical margins [18–20]. In a study, it was observed that recurrence occurred in half of the patients with negative surgical margins in the localization of the lesion [21]. It was reported that a decrease in the rate of recurrence up to 50% was observed with the use of frozen section [22]. In the recent years, Mohs micrographic technique is being used by the dermatologists as a standard surgical technique for the cutaneous lesions of extra-mammary Paget disease [23]. Hendi et al. [6] reported a recurrence rate of 16% for the primary disease and 50% in recurrent cases.

Therefore, supporting treatments as alternative to the surgery or for the post-operative period has become the agenda. Use of imiquimod cream in extra-mammary Paget disease is being reported in the recent years. Zampogna [24] used imiquimod cream in 2002 for the first time in the skin lesions of extra-mammary Paget disease. In 2003, scrotal Paget disease was treated by using imiquimod cream [25]. Again in the same year, vulvar Paget disease was treated completely with imiquimod cream for the first time [26]. In a study, which reviewed the use of imiquimod cream in extra-mammary Paget disease, reported that confirmation with biopsy was ensured in six patients out of eight; and complete remission was seen in one patient who did not have a biopsy, and partial remission was present in the other [27]. Imiquimod cream, generally, was used in recurrent cases in vulvar Paget disease [28–31]. In a study in 2009, imiquimod cream was used in two patients whose surgical margins were positive in their pathological specimen after the operation [32]. In a recent study, imiquimod cream was used in three patients with primer vulvar Paget disease [33]. The case reports/series of vulvar Paget disease which was treated by imiquimod are shown in Table 1.

There are differences with regard to dosage and duration in the use of imiquimod cream. There is no consensus for dosage, duration of use and follow up. Topical therapy with imiquimod was used for 3–7 times in a week [28–33]. The duration of using imiquimod ranged from 6 to 24 weeks [28–33]. In Sendagorta’s [33] study patients applied the cream every day for 3 weeks and every other day for 3 weeks and followed up 24 months. Challenger [32] used 3 times per week for 12 week and followed up 4 months. Denely [28] also used 3 times per week for 6–16 months and followed up 6 months. The duration of follow up ranged from 6 to 26 months [28–33].

**Conclusion**

Successful results are obtained with the use of imiquimod cream in both primary and recurring vulvar Paget disease. It can be used as the first line therapy because of the high recurrence rates after surgical excision. However, this would require prospective, randomized studies with large series that imiquimod cream is compared to other modalities of treatment.

**Conflict of interest** None.
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