Gynecologic Oncology Reports 55 (2024) 101511

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Non-surgical management of recurrent Paget's disease of the vulva: A case report

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ARTICLE INFO

Keywords:
Paget disease of the vulva
Imiquimod
Silver sulfadiazine

ABSTRACT

Paget's Disease of the Vulva is a relatively rare condition with a high rate of recurrence. Extensive work-up and treatment is warranted as lesions have the capacity to become invasive and can be associated with underlying malignancy. First line therapy includes surgical resection. For those that are not surgical candidates or who do not desire surgical intervention, non-surgical management options include topical therapy with imiquimod. Unfortunately, irritating side effects often results in poor treatment compliance and premature discontinuation limiting efficacy. Here we present a unique case of extensive, recurrent vulvar Paget's disease with excellent response to a combination therapy of imiquimod and Silver Sulfadiazine. To the best of our knowledge, this is the first documented case illustrating the utility of non-surgical management with combination therapy with topical imiquimod and Silver Sulfadiazine for treatment in patients who do not desire surgical intervention.

1. Introduction

Paget's Disease of the Vulva (PDV) is a relatively rare condition, with invasive disease occurring at 0.36 per 100,000-person years in the United States (Kilts et al., 2020). PDV is an intraepithelial adenocarcinoma, characterized by large pleomorphic cells with abundant, pale cytoplasm (Van Der Linden et al., 2016). While the majority of cases are benign and remain localized to the vulva, invasive disease is associated with underlying malignancies and high rates of recurrence (Kilts et al., 2020; Van Der Linden et al., 2016). First line therapy includes surgical resection, however, imiquimod has been shown to be an effective topical therapy for patients who desire non-surgical management or are not a candidate for surgical resection (Bubna, 2015; Ishizuki and Nakamura, 2021).

Imiquimod is an imidazoquinolinone immunomodulator whose mechanism of action includes agonistic effects on toll like receptors, which trigger cytokine expression and other inflammatory markers, resulting in a promotion of apoptosis and inhibition of angiogenesis (Bubna, 2015; Wagstaff and Perry, 2007). It is FDA approved for the treatment of actinic keratosis, basal cell carcinoma, and external anogenital warts (Wagstaff and Perry, 2007). However, it's unique activation of the immune system has proven useful in various cutaneous premalignant and malignant conditions (Bubna, 2015). The most common side effects include local inflammatory effects, such as burning and pain. The side effects associated with imiquimod therapy are often managed with the concurrent use of emollients.

Conservative management with imiquimod topical therapy is often challenging due to local side effects which has limited the applicability, patient compliance, and use of this potentially active agent as patients frequently discontinue therapy due to toxicity before the full effect has been reached. Here we describe the unique use of silver sulfadiazine combined with imiquimod to ameliorate side effects to achieve complete clinical resolution.

2. Case

The patient is a 77-year-old female who initially presented in 2000 and underwent vulvectomy with bilateral skin grafts. Four separate recurrences of disease occurred between 2001–2007, of which were resected or managed with laser ablation. She underwent subsequent topical treatment with Fluorouracil cream. Additional recurrence occurred in 2012, when the patient presented with vulvar erosions and ulcerations. A biopsy once more showed recurrent and persistent PDV. In 2014, the decision was made to proceed with total radical vulvectomy and perianal skin resection with concurrent reconstruction with fascial cutaneous advancement flaps. Pathology showed no evidence of invasive disease, but the margins were positive. Management with clinical follow up every 6 months was recommended, and the patient was closely

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https://doi.org/10.1016/j.gore.2024.101511
Received 28 July 2024; Received in revised form 9 September 2024; Accepted 15 September 2024
Available online 16 September 2024

followed. In 2016, the patient once more reported a new vulvar lesion, however, the exam in the office was negative per documentation. She was recommended for follow up with her gynecologist as needed.

In mid 2021, the patient's gynecologist recommended follow-up with gynecology oncology. However, the patient was lost to follow up due to the COVID-19 pandemic and fear of discomfort associated with prior procedures. Given ongoing worsening symptoms, she represented in early 2022 for evaluation. At this time, a recommendation was made for additional local excision of perianal and gluteal disease and possible reconstruction with plastic surgery. The patient was understandably reluctant to proceed with surgery and desired to pursue non-surgical management options. She then sought a second opinion.

To better document the extent of disease, she underwent an exam under anesthesia with bilateral mapping biopsies late 2022. At this time pathology was again positive for extramammary Paget's disease. Given extensive disease presentation, surgical treatment options with resection would certainly require skin flaps or grafting to close the defects. Alternatives to surgical management included imiquimod. Following discussion, the patient declined intervention and desired to proceed with imiquimod. Imiquimod was dosed Monday, Wednesday, and Friday for 8 h to the entire vulva each night and washed of in the morning. Treatment course with imiquimod proceeded for 16 weeks and follow up after 2 months of treatment.

After the initial 2 months of treatment there was a minimal response. Additionally, despite the use of emollients on treatment and non-treatment days, she experienced severe discomfort and excoriations. The decision was made to proceed with a 1 week of treatment break and the addition of silver sulfadiazine for soothing side effects of imiquimod. Silver sulfadiazine greatly improved adverse side effects from imiquimod, and exam was much improved from prior (Figs. 1-3).

As an aside, she originally had an appointment with plastic surgery scheduled to discuss reconstructive options at the time of surgical resection, however the decision was made to defer surgery as she has had a great response to imiquimod/silver sulfadiazine. Decision was made to continue imiquimod with silver sulfadiazine for a second (maintenance) course. She completed two 16 week courses for a total of 32 weeks of Imiquimod, 24 of which were combined with silver sulfadiazine). Complete clinical response occurred after the first 16 weeks of treatment. She remains free from Paget's disease, now 1 year after completion of her last course of imiquimod/silver sulfadiazine and continues close follow-up every 3–6 months.

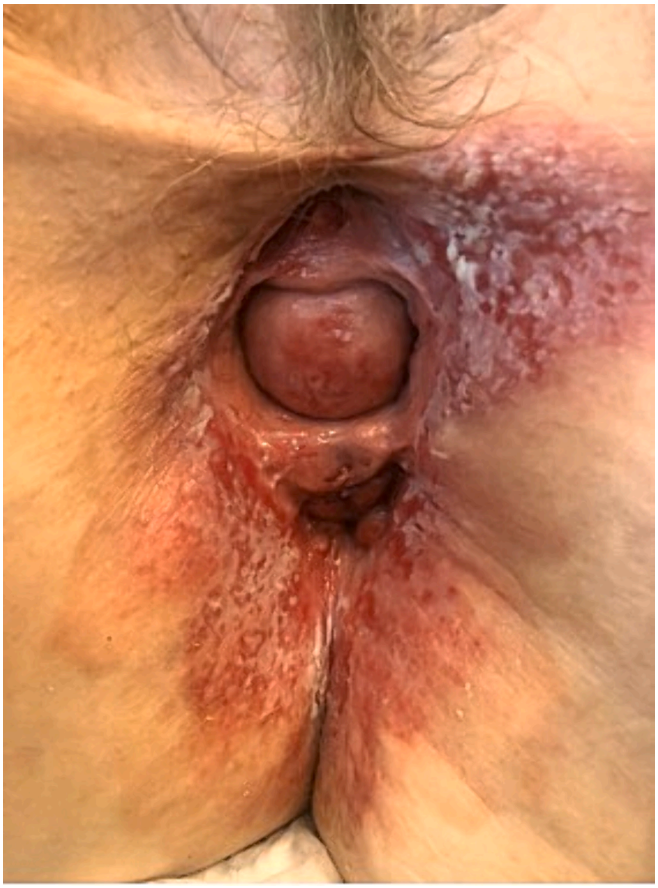

Fig. 1. Clinical exam at re-presentation in 2022, prior to imiquimod treatment.

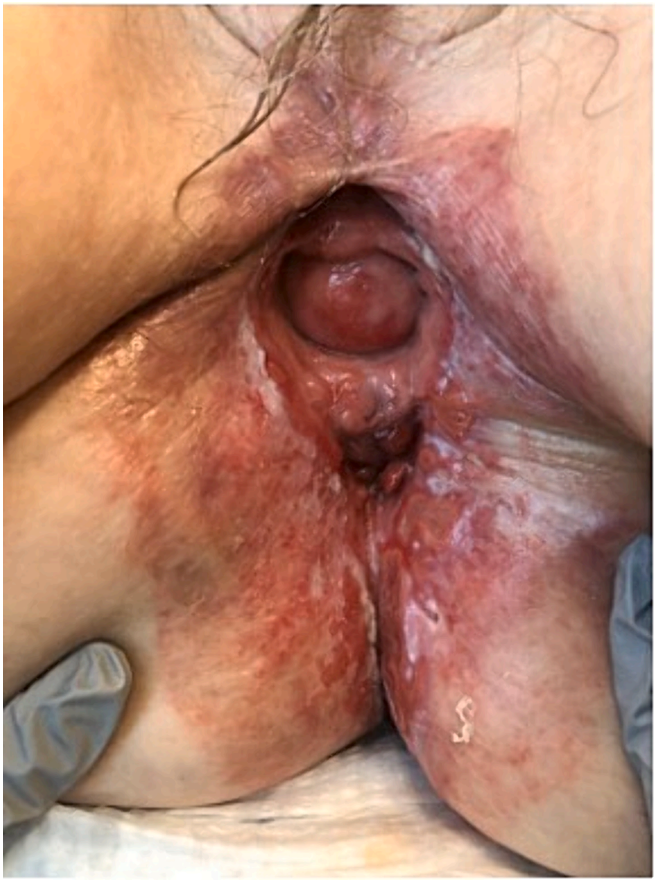

Fig. 2. Clinical exam after 2 months of treatment of imiquimod and emollient.

3. Discussion

Extramammary Paget's disease is rare, with invasive PDV making up 1–2 % of all vulvar carcinomas (Van Der Linden et al., 2016). Wide local excision is considered as the gold standard, however, alternative therapies such as radiotherapy, imiquimod, and photodynamic therapy are often utilized (Ishizuki and Nakamura, 2021). As evidenced by this patient's clinical course, PDV has a very high rate of recurrence after surgical management, ranging from 34-56 % (Van Der Linden et al., 2016). Additionally, even with surgical resection, margins are positive in 52.7 % of cases (Nasioudis et al., 2020). Mohs microscopic surgery, a technique that allows tumors to be removed to microscopically negative margins and as much normal tissue to be preserved as possible, has been shown to reduce the recurrence rate compared to surgical interventions (Hendi et al., 2004). Imiquimod has also been suggested as an especially useful treatment for patients that experience recurrence after surgical resection (Ishizuki and Nakamura, 2021). Here, imiquimod is an appropriate treatment choice given the extent of disease, low likelihood of a complete resection to negative margins, and our patient's desire for non-surgical management.

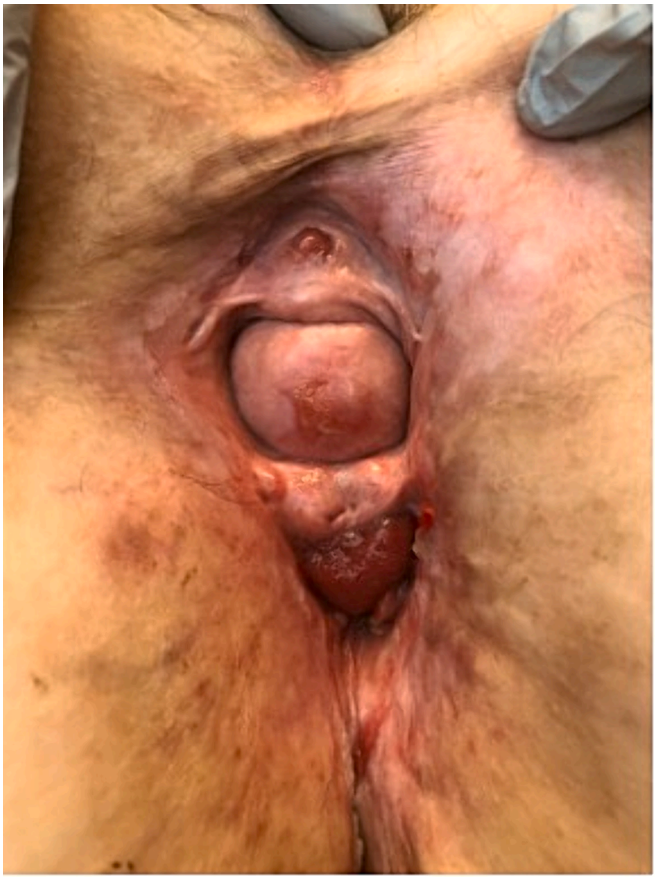

Fig. 3. Clinical exam 2 months after the addition of Silvadene (4 months imiquimod).

Imiquimod is FDA approved for various dermatologic conditions, such as actinic keratosis and basal cell carcinoma. However, there is strong evidence in the literature for its off-label use in extramammary Paget disease, including PDV. A prospective pilot study (Cowan et al., 2016) and The Paget Trial (Van Der Linden et al., 2022), a multicenter clinical study, have demonstrated a 75 % and 82.6 % response rate, respectively, in patients with a standardized treatment schedule of 5 % imiquimod. To date, various retrospective chart reviews, systematic reviews, and case reports have cited similar rates of treatment response (Mayo-Martínez et al., 2023; Dogan et al., 2017). Out of 233 patients, Mayo-Martinez et al. (Mayo-Martínez et al., 2023) systematic review reported a 48 % complete clinical response rate in patients who used imiquimod alone or as adjuvant therapy. While imiquimod is considered a safe, conservative treatment, it is not without side-effects. The most common side-effects include local skin reactions, such as erythema, excoriations, erosions, and edema, however, more severe, systemic adverse effects have also been reported (Wagstaff and Perry, 2007). In a study by Leong et al. (Leong et al., 2023) exploring patients' perspective and tolerability of imiquimod; 88 % of respondents reported experiencing local side-effects. While considered safe, it is not uncommon for these side effects to reduce tolerability of imiquimod and cause patients to reduce dosage or completely cease treatment. Premature cessation of imiquimod treatment due to side effects has been reported to be 7 %, 15 % and up to 38 % in the literature (Mayo-Martínez et al., 2023; Dogan et al., 2017; Leong et al., 2023). Side-effects of imiquimod therapy in patients with PDV are often managed with the concurrent use of emollients. However, as demonstrated in the present case, emollients do not always manage side-effects adequately.

Silver sulfadiazine (Silvadene®) is a topical antimicrobial that has traditionally been used as the gold standard for the management of burn wounds (Atiyeh et al., 2007). Interestingly, there is strong evidence that silver sulfadiazine can be used as a preventative and therapeutic treatment for radiation induced acute dermatitis (Hemati et al., 2012). In a randomized control trial by Hemati et al. (Hemati et al., 2012), silver sulfadiazine was shown to reduce the severity of dermatitis and degree of skin injury during the course of radiotherapy. While the exact mechanism of how silver sulfadiazine accomplishes this is unknown, Hemati et al. (Hemati et al., 2012) attributed its anti-inflammatory and barrier enhancing activity as a factor. There have also been case reports illustrating how silver sulfadiazine in a lidocaine solution has been used to alleviate painful skin lesions in patients receiving chemotherapy, including a patient being treated for vulvar carcinoma with carboplatin and 5-fluorocil (Meeuse et al., 2007).

While previous literature has suggested that silver sulfadiazine can be used to alleviate painful skin reactions due to radiation therapy and chemotherapy, to our knowledge, it has not been used previously as a complimentary treatment of PDV. Thus, the current case illustrates the unique combination of silver sulfadiazine and imiquimod to treat PDV. The mechanism for how silver sulfadiazine alleviates local skin reactions caused by irritative therapies, including imiquimod, continues to be unknown. Its combined anti-inflammatory and anti-microbial properties may provide enhanced skin barrier protection and allow patient to successfully continue to treat imiquimod.

4. Conclusion

Extramammary Paget disease of the vulva, while rare, has a high rate of recurrence. While topical imiquimod has been proven to be an effective treatment, patients often experience uncomfortable side-effects which limits the utilization of the potentially very effective therapy. The current case highlights the unique combination of silver sulfadiazine and imiquimod for the treatment of PDV and the potential to manage this disease conservatively, without aggressive radical life altering surgery. Thus, clinicians should consider the addition of silver sulfadiazine for patients being treated for PDV who experience irritative, debilitating effects due to imiquimod.

5. Author contributions statement

All authors contributed to the manuscript. Dr. Backes developed the key concept, supervised data collection, writing, and provided editing. Dr. Kennedy gathered patient information and assembled the description of the patient's course. Dr. Kennedy and Ms. Coffey-Noriega drafted and revised the manuscript. All authors read, edited and approved of the final manuscript.

CRediT authorship contribution statement

Emily Coffey-Noriega: Writing – review & editing, Writing – original draft. **Hannah Kennedy:** Writing – review & editing, Writing – original draft. **Floor J. Backes:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Floor Backes: Advisory boards/consulting: Merck, Eisai, ImmunoGen, AstraZeneca, EMD Serono, BioNTech, Daiichi Sankyo. Research funding: Merck, Eisai, ImmunoGen, AstraZeneca, Tempus, Natera.

References

Atiyeh, B.S., Costagliola, M., Hayek, S.N., Dibo, S.A., 2007. Effect of silver on burn wound infection control and healing: review of the literature. Burns 33 (2), 139–148.
Bubna, A.K., 2015. Imiquimod - Its role in the treatment of cutaneous malignancies. Indian J. Pharmacol. 47 (4), 354–359.

Cowan, R.A., Black, D.R., Hoang, L.N., Park, K.J., Soslow, R.A., Backes, F.J., et al., 2016. A pilot study of topical imiquimod therapy for the treatment of recurrent extramammary Paget's disease. Gynecol. Oncol. 142 (1), 139–143.
Dogan, A., Hilal, Z., Krentel, H., Cetin, C., Hefler, L.A., Grimm, C., et al., 2017. Paget's disease of the vulva treated with imiquimod: case report and systematic review of the literature. Gynecol. Obstet. Invest. 82 (1), 1–7.
Hemati, S., Asnaashari, O., Sarvizadeh, M., Motlagh, B.N., Akbari, M., Tajvidi, M., et al., 2012. Topical silver sulfadiazine for the prevention of acute dermatitis during irradiation for breast cancer. Support Care Cancer 20 (8), 1613–1618.
Hendi, A., Brodland, D.G., Zitelli, J.A., 2004. Extramammary Paget's disease: surgical treatment with Mohs micrographic surgery. J. Am. Acad. Dermatol. 51 (5), 767–773.
Ishizuki, S., Nakamura, Y., 2021. Extramammary paget's disease: diagnosis, pathogenesis, and treatment with focus on recent developments. Curr Oncol. 28 (4), 2969–2986.
Kilts, T.P., Long, B., Glasgow, A.E., Bakkum-Gamez, J.N., Habermann, E.B., Cliby, W.A., 2020. Invasive vulvar extramammary Paget's disease in the United States. Gynecol. Oncol. 157 (3), 649–655.
Leong, J.Y., Shumaker, A., D'mello, D., Jones, E.K., Chung, P.H., 2023. Patient's experience with imiquimod for extramammary paget disease. Dermatol. Surg. 49 (7), 706–707.
Mayo-Martínez, F., Moro, R., Millán-Esteban, D., Ríos-Viñuela, E., Bautista, I.J., Nagore, E., et al., 2023. Topical imiquimod in primary cutaneous extramammary paget's disease: a systematic review. Cancers 15 (23), 5665.
Meeuse, J.J., Reyners, A.K.L., Wymenga, A.N.M., 2007. Topical lidocaine in silver sulfadiazine cream on painful, cancer, or treatment-related skin lesions. J. Pain Symptom Manage. 34 (3), 223–225.
Nasioudis, D., Bhadra, M., Ko, E.M., 2020. Extramammary paget disease of the vulva: Management and prognosis. Gynecol. Oncol. 157 (1), 146–150.
Van Der Linden, M., Meeuwis, K.A.P., Bulten, J., Bosse, T., Van Poelgeest, M.I.E., De Hullu, J.A., 2016. Paget disease of the vulva. Crit. Rev. Oncol. Hematol. 101, 60–74.
Van Der Linden, M., Van Hees, C.L., Van Beurden, M., Bulten, J., Van Dorst, E.B., Esajas, M.D., et al., 2022. The Paget Trial: topical 5% imiquimod cream for noninvasive vulvar Paget disease. Am. J. Obstet. Gynecol. 227 (2), 250.e1–250.e8.
Wagstaff, A.J., Perry, C.M., 2007. Topical imiquimod: a review of its use in the management of anogenital warts, actinic keratoses, basal cell carcinoma and other skin lesions. Drugs 67 (15), 2187–2210.