CASE REPORT

Extramammary Paget's disease of the scrotum with complete response to imiquimod and photodynamic therapy

Tyler M Bauman, Ilana S Rosman, David M Sheinbein

Division of Dermatology,
Washington University in St
Louis School of Medicine, St
Louis, Missouri, USA

Correspondence to
Dr David M Sheinbein,
sheinbeind@wustl.edu

Accepted 16 February 2018

SUMMARY

Extramammary Paget's disease (EMPD) is a rare intraepithelial neoplasm with an extremely variable clinical course. The objective of this study was to determine if combination imiquimod and photodynamic therapy could induce remission of EMPD. A 69-year-old man with EMPD was treated with topical imiquimod 5% cream at night for 5 days per week for 1 month, followed by 2 months of 5% imiquimod for three nights a week. For the following 6 months, monthly 5-aminolevulinic acid photodynamic therapy was added. After 6 months, imiquimod was discontinued and the patient continued to be treated with quarterly photodynamic therapy. Treatment resulted in significant improvement in the appearance of the lesion, and pathology revealed no evidence of residual disease. The patient has had no clinical signs of disease for >5 years. We conclude that topical imiquimod 5% cream and photodynamic therapy may aid in the treatment of some patients with EMPD.

(2) as a secondary adenocarcinoma with an underlying dermal tumour, (3) as a cutaneous lesion associated with an underlying visceral malignancy or (4) as a skin tumour arising from a secondary adnexal tumour.^{2,3}

The treatments of choice for EMPD include Mohs micrographic surgery or complete surgical excision with wide margins.^{4,5} Alternative treatments include topical 5-fluorouracil and imiquimod, Nd:YAG and photodynamic therapy. Herein, we describe a case of EMPD of the scrotum and inner thigh in a patient with underlying prostate cancer. No excision of the lesion was performed, and treatment with imiquimod and photodynamic therapy induced a complete remission of the adenocarcinoma. To our knowledge, this is the first reported case of complete remission of EMPD with >5 years of follow-up in response to imiquimod and photodynamic therapy.

BACKGROUND

Extramammary Paget's disease (EMPD) is a rare intraepithelial adenocarcinoma that typically presents as an eczematous plaque with symptoms including burning and pruritus. There is a known predilection for apocrine gland-containing areas of the body including the perineum, vulva, scrotum and axilla.¹ EMPD is thought to arise in multiple clinical settings: (1) as a primary cutaneous tumour,

CASE PRESENTATION

A 69-year-old man presented with 6 months of a pruritic erythematous rash on his left scrotum and thigh. He had tried topical antifungals and hydrocortisone cream with no relief of symptoms or decrease in size of the rash. Physical exam revealed a 6.5×5.5 cm erythematous plaque with small erosions in the left inguinal crease and lateral scrotum (figure 1). The patient had no palpable inguinofemoral lymphadenopathy.

Medical history was significant for coronary artery bypass graft for coronary artery disease and hypercholesterolaemia. Patient denied any history of skin cancer. Medications at time of presentation included metoprolol, simvastatin, losartan and hydrocortisone. Family history and review of systems was unremarkable. He was a current smoker at one pack/day of cigarettes.

INVESTIGATIONS

A 4 mm punch biopsy was performed on the lesion; on routine histopathology, there were atypical cells with enlarged, hyperchromatic nuclei and pale cytoplasm within the epidermis (figure 2A). There was no involvement of the dermis. Lesional cells stained positively with cytokeratin-7 (figure 2B), compatible with a diagnosis of EMPD.⁶

Extensive workup for visceral malignancy was performed previously at an outside hospital before referral to our centre. Colonoscopy and cystoscopy

Figure 1 Gross appearance of the scrotum and inguinal region at initial presentation. A 6.5×5.5 cm erythematous plaque with small erosions was concerning for extramammary Paget's disease.

To cite: Bauman TM, Rosman IS, Sheinbein DM. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-221696

Figure 2 Routine histopathology from 4 mm punch biopsy taken from inguinal region. On H&E staining, atypical cells with enlarged, hyperchromatic nuclei and pale cytoplasm were observed within the epidermis (2A; 200 $\times$). Using immunohistochemistry, the lesional cells stained positive for CK7 (2B; 200 $\times$).

were unremarkable. Patient had a serum prostate-specific antigen (PSA) of 4.1 approximately 2 years prior, which prompted a prostate biopsy at that time that showed high-grade prostatic intraepithelial neoplasia. Additional prostate biopsies performed around the time of his original EMPD presentation revealed Gleason 3+3 prostatic adenocarcinoma. This was originally managed conservatively before the patient opted for laparoscopic radical prostatectomy. No adjuvant or salvage therapy was warranted and PSA nadired to 0.1 around 1 month after surgery.

DIFFERENTIAL DIAGNOSIS

- ▶ Eczematous dermatosis;
- ▶ Inverse psoriasis;
- ▶ Intertrigo;
- ▶ Melanoma;
- ▶ Scrotal intraepithelial neoplasia with pagetoid spread;
- ▶ Pagetoid spread of an underlying urothelial carcinoma.

TREATMENT

Surgical and medical treatment options for his EMPD were discussed with the patient after the diagnosis was confirmed. The patient's EMPD was originally treated with topical imiquimod 5% cream at night for 5 days per week for 1 month, and he experienced significant erythema and tenderness at this dosing schedule. For the next 2 months, imiquimod dosing was decreased to 3 days per week. For the following 6 months, the patient was treated with monthly 5-aminolevulinic acid photodynamic therapy with continued application of imiquimod for 3 days per week. After 6 months of this treatment regimen, imiquimod was discontinued and the patient continued to be treated with quarterly photodynamic therapy.

Figure 3 Gross appearance of the scrotum and inguinal region after 11 months (3A) and 18 months (3B) of treatment with imiquimod and 5-aminolevulinic acid photodynamic therapy.

OUTCOME AND FOLLOW-UP

The patient's EMPD responded well to treatment (figure 3). Eleven months after the original diagnosis of EMPD, an additional 4 mm punch biopsy was taken from the periphery of the left scrotal lesion for follow-up. Follow-up biopsies were guided by black light fluorescence approximately 6 hours after application of aminolevulinic acid. Pathology revealed compact hyperkeratosis, mild spongiosis of the epidermis and scattered intraepidermal eosinophils. There was no evidence of residual EMPD. Two subsequent biopsies of the affected area, most recently 20 months after initial diagnosis, also showed no evidence of residual disease. The patient has continued quarterly photodynamic therapy with no evidence of recurrence or symptoms over the previous 6 years.

DISCUSSION

While relatively rare, EMPD follows an extremely variable clinical course, ranging from relatively indolent to aggressive carcinoma. The standard of care for EMPD includes excisional biopsy with wide margins or Mohs micrographic surgery. Despite being standard of care, wide local excision often leads to disfigurement and functional deficits.⁵ Further, both of these interventions are limited in their efficacy, as positive surgical resection margins occur in upwards of 75% of cases of scrotal EMPD, and Mohs micrographic surgery has a reported recurrence rate of 27%.^{4,5} The common presence of vague margins and satellite lesions may contribute to the high rate of recurrence with excision⁷; therefore, topical therapies may provide additional therapeutic benefit for some patients.

Imiquimod is a topical imidazoquinoline that stimulates a Th1- dominant acquired immune response through induction of macrophage-derived cytokines such as tumour necrosis factor alpha, interferon alpha interleukin (IL)-1a and IL-12.⁸ It is thought that these effects are mediated through activation of toll-like receptor 7.⁹ Imiquimod is most commonly used for the treatment of actinic keratosis, superficial and nodular basal cell carcinoma and Bowen's disease/squamous cell carcinoma in situ, though numerous case reports exist for other dermatological conditions, including EMPD.⁹ The response of EMPD to imiquimod is variable, and most current reports have primarily studied vulvar disease.¹⁰ Further, imiquimod is most commonly used as a neoadjuvant or adjuvant treatment along with excision of the lesion. Few reports exist of complete response to imiquimod without any type of prior or concurrent excisional intervention, particularly for scrotal and perianal disease.^{11,12}

In 2010, Ho and Aw reported on a 75-year-old man with primary scrotal EMPD and no underlying visceral malignancy with complete response to imiquimod after 12 months of follow-up.¹¹ Cohen *et al* published both a case report and literature summary in 2006 that included three patients with complete response to imiquimod without prior surgical intervention, with a maximum follow-up of 8 months.¹² Of note, none of the three patients with complete response had an underlying visceral malignancy on extensive workup. More recently, Jing *et al* reported successful treatment of two patients with EMPD with combination imiquimod and photodynamic therapy after these patients were unsuccessfully treated with CO₂ laser.¹³

Herein, we report a patient with EMPD and underlying prostate cancer treated with 5% imiquimod and 5-aminolevulinic acid-based photodynamic therapy. Diagnosis was first confirmed with biopsy and immunohistochemical staining. Extramammary Paget's cells typically demonstrate positive staining for cytokeratin, epithelial membrane antigen, carcinoembryonic

antigen, and gross cystic disease fluid protein, with negative staining for S100.¹⁴ This patient responded well to therapy and has been followed for 6 years with no evidence of EMPD recurrence or symptomology. Aggressive tumour surveillance is necessary in patients with EMPD, particularly when treating with topical therapies. We followed this patient with multiple serial biopsies as well as Wood's lamp examinations with coral red fluorescence. Interestingly, this patient had both EMPD and an underlying visceral malignancy yet still had good response to imiquimod and photodynamic therapy. Given the high mortality of secondary EMPD compared with primary EMPD (48% vs 18%),¹⁵ it is imperative to find alternative treatment modalities for secondary EMPD besides excision of the lesion. We conclude that topical imiquimod 5% cream and photodynamic therapy may aid in the treatment of some patients with secondary EMPD.

Learning points

- Extramammary Paget's disease (EMPD) of the scrotum is relatively rare and is occasionally associated with visceral malignancy.
- Surgery remains standard of care for EMPD but is limited by positive margins and local recurrence.
- Topical imiquimod cream and photodynamic therapy may aid in the treatment of some patients with EMPD.

Contributors TMB was responsible for writing the manuscript and making the figures. ISR was responsible for reading the pathology, acquiring images and reading and editing the final manuscript. DMS saw the patient in clinic, was responsible for the workup and diagnosis, read and edited the final manuscript and oversaw the project.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Mehta NJ, Torno R, Sorra T, *et al.* Extramammary Paget's disease. *South Med J* 2000;93:713–5.
- 2 Chaudhuri SP, Smoller BR. Extramammary Paget's disease: diagnosis and disease pattern. *Cutis* 1992;50:195–6.
- 3 Zampogna JC, Flowers FP, Roth WL, *et al.* Treatment of primary limited cutaneous extramammary Paget's disease with topical imiquimod monotherapy: two case reports. *J Am Acad Dermatol* 2002;47:S229–S235.
- 4 Coldiron BM, Goldsmith BA, Robinson JK. Surgical treatment of extramammary Paget's disease. A report of six cases and a reexamination of Mohs micrographic surgery compared with conventional surgical excision. *Cancer* 1991;67:933–8.
- 5 Zollo JD, Zeitouni NC. The Roswell Park Cancer Institute experience with extramammary Paget's disease. *Br J Dermatol* 2000;142:59–65.
- 6 Berman B, Spencer J, Villa A, *et al.* Successful treatment of extramammary Paget's disease of the scrotum with imiquimod 5% cream. *Clin Exp Dermatol* 2003;28(Suppl 1):36–8.
- 7 Badgwell C, Rosen T. Treatment of limited extent extramammary Paget's disease with 5 percent imiquimod cream. *Dermatol Online J* 2006;12:22.
- 8 Arany I, Tying SK, Stanley MA, *et al.* Enhancement of the innate and cellular immune response in patients with genital warts treated with topical imiquimod cream 5%. *Antiviral Res* 1999;43:55–63.
- 9 Navi D, Huntley A. Imiquimod 5 percent cream and the treatment of cutaneous malignancy. *Dermatol Online J* 2004;10:4.
- 10 Machida H, Moenini A, Roman LD, *et al.* Effects of imiquimod on vulvar Paget's disease: a systematic review of literature. *Gynecol Oncol* 2015;139:165–71.
- 11 Ho SA, Aw DC. Extramammary Paget's disease treated with topical imiquimod 5% cream. *Dermatol Ther* 2010;23:423–7.
- 12 Cohen PR, Schulze KE, Tschen JA, *et al.* Treatment of extramammary Paget disease with topical imiquimod cream: case report and literature review. *South Med J* 2006;99:396–402.
- 13 Jing W, Juan X, Li X, *et al.* Complete remission of two patients with recurrent and wide spread extramammary Paget disease obtained from 5-aminolevulinic acid-based photodynamic therapy and imiquimod combination treatment. *Photodiagnosis Photodyn Ther* 2014;11:434–40.
- 14 Guarner J, Cohen C, DeRose PB. Histogenesis of extramammary and mammary Paget cells. An immunohistochemical study. *Am J Dermatopathol* 1989;11:313–8.
- 15 Chen KCH, Lin YH, Chian HS. Extramammary Paget's disease of the external genitalia: a case report. *JTUA* 2003;14:88–91.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow