Photodynamic therapy for treatment of usual-type vulvar intraepithelial neoplasia: a case report and literature review

Ruina Zhang and Li Wang

Abstract
Vulvar intraepithelial neoplasia (VIN) is a pre-malignant condition of the vulvar skin that is found in 50% to 70% of patients with vulvar squamous cell cancer and is regarded as a precursor of vulvar tumors. Thus far, treatment remains lesion- and patient-specific. Here, we describe a VIN patient who presented with a 15-month history of large lesions in the bilateral labium, associated with human papillomavirus infection. The lesions were inappropriate for surgical excision and laser ablation because of their size; therefore, they were treated with photodynamic therapy and concurrent topical 5-aminolevulinic acid hydrochloride. The patient showed no recurrence throughout 2 years of post-treatment follow-up, and reported only slight pain during treatment. Moreover, no significant side effects or scarring were detected. Thus, we conclude that photodynamic therapy can be a useful alternative treatment for large VIN in the bilateral labium that cannot be excised or ablated.

Keywords
Vulvar intraepithelial neoplasia, photodynamic therapy, aminolevulinic acid, epithelial cells, vulvar squamous cell cancer, human papillomavirus

Date received: 20 February 2019; accepted: 20 June 2019

Introduction
Vulvar intraepithelial neoplasia (VIN) is a non-invasive precursor lesion typically found in 50% to 70% of patients with vulvar squamous cell carcinoma (VSCC).
VIN is divided into two types: human papillomavirus (HPV)-related (classic or usual-type vulvar intraepithelial neoplasia, uVIN), which comprises approximately 80% of VIN cases, and non-HPV-related (differentiated or simplex vulvar intraepithelial neoplasia, dVIN), which comprises approximately 20% of cases. Both Bowen's disease and Bowenoid papulosis are regarded as usual-type VIN. HPV infection is strongly associated with uVIN, and HPV 16 is the most common genotype identified in uVIN, followed by HPV 18, 31, 33, and 45. Lichen sclerosis has been suggested as a precursor of dVIN and HPV-independent VSCC, but an associated carcinogenic mechanism has not yet been clarified. The incidences of both uVIN and dVIN have increased in recent years. VIN can affect women of any age, but most recent studies suggest its occurrence is more common among women <50 years of age. VIN symptoms are non-specific and can include pruritus of the vulva, burning pain, dyspareunia, and abnormal vaginal secretions. VIN lesions are most commonly detected in the perineal body. The most common forms of VIN skin lesions are papules and patches with a clear border and a flat top, many with a diameter of <2 cm. The surface of pathologically changed skin is often red, white, or gray. Hsieh et al. found that 49% of VIN patients had multiple lesions, and 32% had multiple centers of anal, vaginal, and cervical neoplasia. VIN cannot be clinically diagnosed by the naked eye. If the disease is suspected based on the clinical manifestations, biopsy samples should be taken from the suspicious part of the vulva, and pathological examination should be performed for diagnosis.

A variety of treatment methods have been presented for VIN, including surgical excision, topical therapy (5% 5-fluorouracil cream and imiquimod cream), photodynamic therapy (PDT), laser ablation, and ultrasonic surgical aspiration. However, therapeutic options for an individual patient remain dependent on the size and location of the tumor, number of lesions, therapy availability, baseline patient status, cosmetic outcome, and patient preferences. Here, we describe a uVIN patient who had been infected with HPV16 and was admitted to our hospital with large lesions in the bilateral labium. The lesions were inappropriate for surgical excision and laser ablation because of their size; thus, the patient was treated with PDT.

Case report
A 50-year-old woman presented with a 15-month history of white plaques covering the labia majora and was admitted to Beijing Friendship Hospital of the Capital Medical University (Beijing, China) in October 2016. She complained of severe itchiness and slight pain after scratching. Pain and itching occurred intermittently, mainly at night. She had washed the vulva using a Chinese traditional medicine liquid; she had also applied mometasone furoate ointment (Merck & Co., Inc., Kenilworth, NJ, USA) once per day, as prescribed by her local doctor. These drugs initially alleviated the itching, but the lesions slowly enlarged over time. Physical examination of the lesions revealed erosive macerative patches and verrucous papules in the interior of the bilateral labium; the lesions extended throughout the inner part of the labia majora (Figure 1). The patient had a son and a daughter; she reported no history of exposure to arsenic or human papillomavirus (HPV). However, polymerase chain reaction assay of the lesion site revealed that it was HPV16-positive. The patient had no significant family history of any detrimental medical conditions. The results of the routine blood test, urinalysis, liver function test, human immunodeficiency virus and Treponema pallidum hemagglutination
tests, and rapid plasma regain test were all within normal limits or negative. A 4-mm punch skin biopsy of the patient's left labia majora revealed keratinocyte atypia throughout the epidermis (Figure 2). Based on the clinical manifestations and histopathological features, a diagnosis of uVIN was made. PDT was administered because the lesions were improper for surgical excision due to their large size. In addition, 5-aminolevulinic acid hydrochloride (5-ALA; Shanghai Fudan-Zhangjiang Bio-Pharmaceutical Co., Ltd., Shanghai, China) was prepared as a 20% gel. After the lesioned region was washed with 0.9% saline solution, topical 5-ALA solution was applied to the interior of the bilateral labium within a clinically disease-free margin of 1 to 2 cm around the lesions. The affected area was then covered with transparent preservative film for 4 hours to ensure drug penetration. The film was removed and the lesions were then irradiated with $633 \pm 5$ nm red light from a light-emitting diode device (LED-IB; Wuhan Yage Optic and Electronic Technique Co., Ltd., Wuhan, China) at a light intensity of 80 to 100 mW/cm$^2$. The specific laser energy was adjusted in accordance with the patient's tolerance. Irradiation was maintained for 20 minutes for each treatment session, and treatments were administered in 10 sessions at 1-week intervals. The lesions gradually improved after the application of PDT.

Partial improvement of the lesions was observed after four PDT sessions, and a complete therapeutic response was observed after 10 treatment sessions (Figure 3). A histopathological specimen collected after treatment revealed reduced epidermal thickness and replacement of atypical cells with normal keratinocytes (Figure 4). No significant side effects or

Figure 1. Clinical appearance of vulvar lesions before treatment. (a, b) Erosive macerative patches and verrucous papules on the bilateral labium.
Figure 2. Histopathological appearance of vulvar lesions before treatment. (a, b) Histopathological analysis showed pronounced hyperkeratosis and parakeratosis, as well as thickening of the epidermis. Atypical cells and mitosis were observed throughout the epidermis with dermal inflammation. Hematoxylin and eosin (H&E) staining (a, magnification: 20×; b, magnification: 40×).

Figure 3. Clinical appearance of vulvar lesions after treatment. (a) After four sessions: partial response was observed and verruca patches were observed only in some areas. (b) After 10 sessions: complete response (CR) was achieved.
scarring were detected, except for slight pain during treatment. We observed no signs of recurrence of the lesions throughout a 2-year post-treatment follow-up period. Written informed consent was obtained from the patient for publication of this report.

Discussion

The main concern for patients with VIN is the potential for such lesions to progress to cancer of the vulva. An earlier study found that the rate of progression to invasive vulvar cancer in women with untreated high-grade VIN was 9%. Additionally, the risk of progression in treated lesions ranged from 2% to 5% over a period of 1 to 8 years. In such cases, aggressive treatment is necessary, and surgical excision has thus been the standard treatment for the prevention of progression to invasive disease; however, vulvar disfigurement and the loss of sexual function have been observed, especially in patients with larger lesions. Although CO₂ laser ablation may initially appear to be effective, recurrence rates of 12.5% and 41.9% have been reported after 12 and 21 months of follow-up, respectively. Furthermore, the use of imiquimod, a heterolytic imidazoquinoline amide, has shown conflicting therapeutic results.

PDT is a clinically approved, minimally invasive therapeutic procedure that involves treatment with a photosensitizing agent, followed by irradiation at a wavelength that corresponds to the absorbance band of the sensitizer; exogenous ALA or methyl aminolevulinic are not light-sensitive, and comprise pro-drugs that must be converted into protoporphyrin IX to activate the photosensitizers. These photosensitizers then initiate a photochemical reaction after irradiation by a light source, such as blue or red light; the photochemical reaction culminates in the generation of a highly reactive singlet oxygen product, which can cause significant toxicity resulting in cell death via apoptosis or necrosis. Previous studies have shown that protoporphyrin IX permeates the basal layer of the epidermis.

PDT is an effective alternative and safe treatment for VIN that preserves normal anatomy and sexual function without therapeutic impairment. A number of studies have shown the use of PDT as an effective, conservative treatment for women with VIN (Table 1). Those studies indicate that there remains no unified standard for PDT treatment of VIN; moreover, the studies have differed in methodology, such as the type of photosensitizer, route of administration of the photosensitizer, type and wavelength of the light source, energy of light source, and the number of treatments. The definition of the treatment response has also differed among studies. Hence, larger-scale, randomized, controlled trials are needed.

The cosmetic outcome after PDT is typically superior to that of other standard therapies. PDT can be easily repeated if necessary and is generally popular among patients. This treatment option is particularly appropriate for poorly healing sites, for patients with large and multiple lesions,

Figure 4. Epidermal thickness was reduced after treatment. Atypical BD cells were replaced by normal keratinocytes. Some lymphocytes and melanocytes were observed in the shallow layer of the dermis. Hematoxylin and eosin (H&E) staining (magnification: 20×).
## Table 1. PDT for the treatment of vulvar intraepithelial neoplasia.

| Source          | No. of patients | PSZ             | Light source       | Energy        | Result                                                                 |
|-----------------|-----------------|-----------------|--------------------|---------------|------------------------------------------------------------------------|
| Choi et al.17   | 15              | 5-ALA           | 630 nm red light   | 150 J/cm²     | CR rate was 80% (12/15) at the 3-month follow-up and 71.4% (10/14) at the 1-year follow-up. |
| 2015            |                 |                 |                    |               |                                                                        |
| Zawislak et al.18| 25              | Bio-adhesive     | Non-laser light    | —             | 52% of patients had a symptomatic response with pathology restored in 38% of lesions at 6 weeks. |
| 2009            |                 | patch (5-ALA)   |                    |               |                                                                        |
| Campbell et al.19| 6               | mTHPC           | 652 nm diode laser | —             | Two patients had recurrent disease, one patient had an area at a new site at 6 months. There was no recurrence in all patients at 2 years. |
| 2004            |                 |                 |                    |               |                                                                        |
| Abdel-Hady et al.20| 32             | 5-ALA           | 630 nm red light   | 50 J/cm² (10 patients) 100 J/cm² (22 patients) | Two of 10 women (20%) showed short-term response at 50 J/cm². Eight of 22 women (36.36%) had normal histology at 12 weeks at 100 J/cm². |
| 2001            |                 |                 |                    |               |                                                                        |
| Fehr et al.21   | 15              | 5-ALA           | 635 nm laser light | 120 J/cm²     | 11 of 15 patients were free of VIN III as determined by biopsy at 8 weeks. Three recurrences were observed at 5, 6, and 7 months. |
| 2001            |                 |                 |                    |               |                                                                        |
| Hillemanns et al.22| 25              | 5-ALA           | 635 nm laser light | 100 J/cm²     | 52% of patients with 27 VIN lesions achieved a complete histological response. |
| 2000            |                 |                 |                    |               |                                                                        |
| Kurwa et al.23  | 6               | 5-ALA           | 580–740 nm         | 150 J/cm²     | All patients had clinically evident persistent VIN III at 1-month. Five patients underwent surgical treatment and one is regularly reviewed. |
| 2000            |                 |                 | broad-band light   |               |                                                                        |
| Martin-Hirsch et al.24| 18          | 5-ALA           | 630 nm non-laser source | 50 J/cm² (10 patients) 100 J/cm² (8 patients) | 89% of patients reported symptom relief. Nine of 10 developed local recurrence at 1 to 2 years. |
| 1998            |                 |                 |                    |               |                                                                        |

PSZ, photosensitizer; CR, complete response; 5-ALA, 5-aminolevulinic acid; mTHPC, meta-tetra (hydroxyphenyl) chlorin.
and patients with comorbidities. The main disadvantage of PDT is that it can be painful, and early termination of the treatment due to poor tolerability may reduce its therapeutic efficacy. However, our patient reported only slight pain and did not require analgesia. The dose of ALA and energy we used were moderate, and we presume that the patient may have a high tolerance for pain. Based on our clinical experience, other disadvantages of PDT include its lack of availability for some patients, the requirement for extended photosensitizer incubation, the potential for development of erythema and erosions due to PDT, the risk of local recurrence, and the risk of progression to SCC if PDT is ineffective. In our case, the patient showed complete clinical and histological clearance after 10 PDT sessions, with slight burning as a side effect, and no recurrence within 2 years of post-treatment follow-up. However, although cosmetic outcomes of PDT appear to be favorable, longer-term follow-up data are needed to confirm the results in this case. Therefore, we will continue follow-up with the current patient.

**Declaration of conflicting interest**

The authors declare that there is no conflict of interest.

**Funding**

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

**ORCID iD**

Ruina Zhang https://orcid.org/0000-0002-2054-4641

**References**

1. Tosti G, Iacobone AD, Preti EP, et al. The role of photodynamic therapy in the treatment of vulvar intraepithelial neoplasia. *Biomedicines* 2018; 6: E13.

2. Sideri M, Jones RW, Wilkinson EJ, et al. Squamous vulvar intraepithelial neoplasia: 2004 modified terminology. ISSVD vulvar oncology subcommittee. *J Reproductive Med* 2005; 50: 807–810.

3. Soergel P and Hillemanns P. Photodynamic therapy for intraepithelial neoplasia of the lower genital tract. *Photodiagnosis Photodyn Ther* 2010; 7: 10–14.

4. De Sanjose S, Alemany L, Ordi J, et al. Worldwide human papillomavirus genotype attribution in over 2000 cases of intraepithelial and invasive lesions of the vulva. *Eur J Cancer* 2013; 49: 3450–3461.

5. Kaushik S, Pepas L, Nordin A, et al. Surgical interventions for high-grade vulva intraepithelial neoplasia. *Cochrane Database Syst Rev* 2014; 4: CD0007928.

6. Hu J, Shan XM, Zhu LR. Advances in vulva intraepithelial neoplasia. *Chin J Clin Obstet Gynecol* 2013; 14: 186–189. (in Chinese)

7. Hsieh MY and Kuo HW. The simplex (differentiated) variant of vulvar intraepithelial neoplasia. *Dermatol Surg* 2004; 30: 948–951.

8. van Seters M, van Beurden M and de Craen AJ. Is the assumed natural history of vulvar intraepithelial neoplasia III based on enough evidence? A systematic review of 3322 published patients. *Gynecol Oncol* 2005; 97: 645–651.

9. Jones RW. Vulval intraepithelial neoplasia: current perspectives. *Eur J Gynaecol Oncol* 2001; 22: 393–402.

10. Wallbillich JJ, Rhodes HE, Milbourne AM, et al. Vulvar intraepithelial neoplasia (VIN 2/3): comparing clinical outcomes and evaluating risk factors for recurrence. *Gynecol Oncol* 2012; 127: 312–315.

11. Savoca S, Nardo LG, Rosano TF, et al. CO₂ laser vaporization as primary therapy for human papillomavirus lesions. A prospective observational study. *Acta Obstet Gynecol Scand* 2001; 80: 1121–1124.

12. van Esch EM, Dam, MC, Osse ME, et al. Clinical characteristics associated with development of recurrence and progression in usual-type vulvar intraepithelial neoplasia. *Int J Gynecol Cancer* 2013; 23: 1476–1483.
et al. Imiquimod cream and CO₂ laser vaporization in vulvar intraepithelial neoplasia (VIN) 2/3 treatment. *Eur J Gynaecol Oncol* 2017; 38: 368–371.

14. Kennedy JC, Pottier RH, Pross DC. Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience. *J Photochem Photobiol B* 1990; 6: 143–148.

15. Morton CA, Brown SB, Collins S, et al. Guidelines for topical photodynamic therapy: report of a workshop of the British Photodermatology Group. *Br J Dermatol* 2002; 146: 552–567.

16. Westers-Attema A, Lohman BG, van den Heijkant F. Photodynamic therapy in Bowen’s disease: influence of histological features and clinical characteristics on its success. *Dermatology* 2015; 230: 55–61.

17. Choi MC, Kim MS, Lee GH, et al. Photodynamic therapy for premalignant lesions of the vulva and vagina: a long-term follow-up study. *Lasers Surg Med* 2015; 47: 566–570.

18. Zawislak A, Donnelly RF, McCluggage WG, et al. Clinical and immunohistochemical assessment of vulval intraepithelial neoplasia following photodynamic therapy using a novel bioadhesive patch-type system loaded with 5-aminolevulinic acid. *Photodiagnosis Photodyn Ther* 2009; 6: 28–40.

19. Campbell SM, Gould DJ, Salter L, et al. Photodynamic therapy using meta-tetrahydroxyphenylchlorin (Foscan) for the treatment of vulval intraepithelial neoplasia. *Br J Dermatol* 2004; 151: 1076–1080.

20. Abdel-Hady ES, Martin-Hirsch P, Duggan-Keen M, et al. Immunological and viral factors associated with the response of vulval intraepithelial neoplasia to photodynamic therapy. *Cancer Res* 2001; 61: 192–196.

21. Fehr MK, Hornung R, Schwarz VA, et al. Photodynamic therapy of vulvar intraepithelial neoplasia III using topically applied 5-aminolevulinic acid. *Gynecol Oncol* 2001; 80: 62–66.

22. Hillemanns P, Untch M, Dannecker C, et al. Photodynamic therapy of vulvar intraepithelial neoplasia using 5-aminolevulinic acid. *Int J Cancer* 2000; 85: 649–653.

23. Kurwa HA, Barlow RJ and Neill S. Single-episode photodynamic therapy and vulval intraepithelial neoplasia type III resistant to conventional therapy. *Br J Dermatol* 2000; 143: 1040–1042.

24. Martin-Hirsch PL, Whitehurst C, Buckley CH, et al. Photodynamic treatment for lower genital tract intraepithelial neoplasia. *Lancet* 1998; 351: 1403.

25. Morton CA. The emerging role of 5-ALA-PDT in dermatology: is PDT superior to standard treatments? *J Dermatolog Treat* 2002; 13(Suppl 1): S25–S29.

26. Moseley H, Ibbotson S, Woods J, et al. Clinical and research applications of photodynamic therapy in dermatology: experience of the Scottish PDT Centre. *Lasers Surg Med* 2006; 38: 403–416.

27. Ang JM, Riaz IB Kamal MU, et al. Photodynamic therapy and pain: a systematic review. *Photodiagnosis Photodyn Ther* 2017; 19: 308–344.