Case Reports in Women's Health 37 (2023) e00478

Contents lists available at ScienceDirect

Case Reports in Women's Health

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

Vulvovaginal erosive lichen planus refractory to topical therapies: What's next? A case report

Madeline K. Young, Katherine G. Holder, Teresa E. Baker, Robert P. Kauffman *

Department of Obstetrics and Gynecology, Texas Tech University Health Science Center School of Medicine, 1400 S. Coulter Drive, Amarillo, TX 79106, USA

ARTICLE INFO

Keywords:
Erosive lichen planus
Vulvovaginal disease
Mycophenolate
Cyclosporin
Case report

ABSTRACT

A 60-year-old woman was referred for progressive and severe vulvovaginal pain characterized by erosions and Wickham's stria for the past 7 months. Her condition had not responded to oral fluconazole, topical estrogen cream, and topical clobetasol cream. Vulvar and vaginal biopsies were obtained under general anesthesia to verify the diagnosis of erosive lichen planus given the failed response to ultrapotent topical steroids. Tacrolimus cream was added but not tolerated. Oral and cutaneous lesions of lichen planus also developed. In the absence of evidence-based guidelines, three different systemic treatments were administered sequentially (hydroxychloroquine, mycophenolate, and finally cyclosporin) before a satisfactory, well-tolerated, and sustained clinical response was obtained. Topical betamethasone ointment in a taper was continued to assist in sustaining a vulvovaginal response after cyclosporin was discontinued.

1. Introduction

Lichen planus (LP) is an inflammatory dermatologic condition that typically presents as painful, polygonal, violaceous flat-topped papules and plaques with white streaks known as Wickham striae. This condition has a variety of morphologic presentations. [1] The lifetime incidence is reported to be between 0.5% and 1%. [2] LP lesions can occur on any mucosal or skin surface, including the nail beds. Vulvovaginal LP is an uncommon variant of the disease that involves the vulva and vagina and tends to affect primarily perimenopausal and postmenopausal women in the 6th decade of life. [2] Vulvovaginal LP is a chronic disease characterized by periods of exacerbation and remission with genital irritation, itching, burning, soreness, dyspareunia, and serosanguinous or purulent vulvovaginal discharge as the most prominent symptoms. [2,3] Diagnostic delay may permit lesions to progress to vaginal adhesions, stenosis, or obliteration, making early identification and intervention crucial. [4]

Women with vulvovaginal LP frequently present to gynecologists or primary care physicians who may be unaware of the disease entity and approach to treatment. Indeed, the majority of papers addressing this disease will be found in the dermatologic literature. High-quality studies and robust treatment guidelines for vulvovaginal lichen planus are lacking. [5,6] When topical potent corticosteroids and other topical therapies fail to elicit a remission, evidence-based treatment algorithms are needed.

2. Case Presentation

A 60-year-old postmenopausal woman with progressive and unrelenting vulvar pain of 7 months' duration was referred to a university gynecology clinic for a second opinion. She had diffuse vulvar and vaginal pain exacerbated by touching, sitting, and sexual intercourse. She also complained of dysuria and a non-bloody, malodorous vaginal discharge. Inability to have intercourse created significant marital distress. Medical comorbidities included well controlled type II diabetes mellitus and primary hypertension treated with insulin glargine, empagliflozin, and losartan. No history of an autoimmune condition was elicited.

Prior to referral, her vulvovaginal disease was unresponsive to oral fluconazole, topical vaginal estradiol cream, and topical clobetasol 0.05% cream applied twice daily. Oral analgesics (non-steroidal anti-inflammatory drugs and tramadol) provided minimal pain relief.

At consultation, the patient was standing in the examination room as sitting was painful. Vulvar exam revealed diffuse erythema with plaque-like lesions and lacy, reticular epithelium, resembling Wickham striae (Fig. 1). Exquisitely painful erosive lesions covered the clitoris and

* Corresponding author.
E-mail addresses: madeline.k.young@ttuhsc.edu (M.K. Young), kate.holder@ttuhsc.edu (K.G. Holder), teresa.baker@ttuhsc.edu (T.E. Baker), robert.kauffman@ttuhsc.edu (R.P. Kauffman).

https://doi.org/10.1016/j.crwh.2023.e00478
Received 10 December 2022; Received in revised form 30 December 2022; Accepted 2 January 2023
Available online 3 January 2023

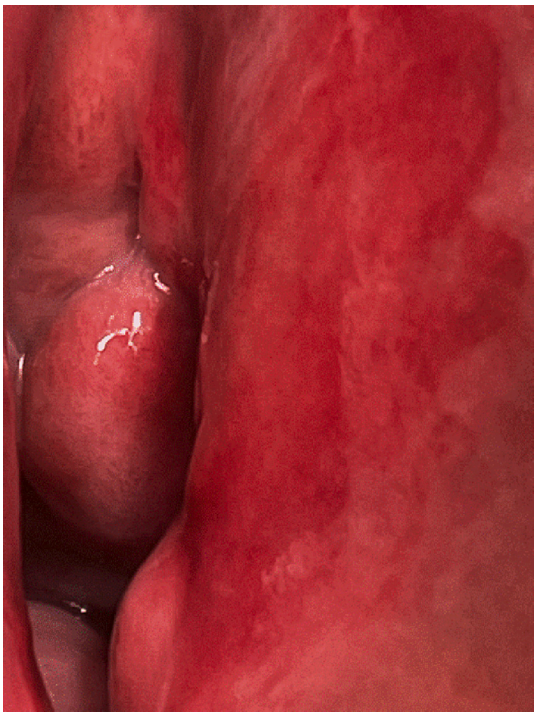

Fig. 1. Gross exam of the left labia showing diffuse erythema with lacy, reticular epithelium (Wickham striae).

periclitoral dermis (Fig. 2). Vaginal speculum examination was aborted due to patient intolerance. No cutaneous, gingival, or other mucosal lesions were noted on careful examination.

An assessment for desmoglein 1 and 3 antibodies was negative, suggesting that this presentation was unlikely to be an autoimmune blistering disorder of the skin or mucous membranes such as pemphigus vulgaris. There is an established correlation between lichen planus and hepatitis C infection, and therefore a hepatitis panel was performed; it returned as negative. [6]

Given her failure to respond to a course of ultrapotent topical corticosteroids combined with the need to rule out malignancy and to arrive at an accurate diagnosis, she was placed under general anesthesia to obtain biopsy specimens and for adequate examination of the vaginal and perianal mucosa (which were precluded by pain in the office setting). At surgery, multiple erythematous lesions measuring 1–3 cm were present in the vagina (Fig. 3). Vaginal and vulvar histology revealed lichenoid infiltration of the subepithelial component with erosive changes, consistent with LP (Fig. 4). There was no evidence of atypical features or malignancy. Immunofluorescent stains were negative.

Her postoperative course is summarized in Fig. 5. Clobetasol 0.05% was continued in ointment form. Ointment was selected due to the absence of alcohol which exacerbates burning. In addition, she was instructed to administer tacrolimus 0.1% ointment twice daily to the vulva, and hydrocortisone vaginal suppositories 25 mg twice daily were prescribed to treat vaginal lesions. The patient reported that tacrolimus 0.1% and 0.03% formulations both caused severe, transient burning despite pretreatment with lidocaine 5% ointment. At one month, the vulvar erythema had diminished slightly but erosive lesions, especially surrounding the clitoris, were still present. She still had difficulty sitting for long durations. Additionally, there was a new lichenoid lesion appearing on the right calf.

In an effort to effect rapid relief in this distressed woman, a course of oral prednisone 60 mg once daily for 6 weeks was initiated She noticed rapid and substantial improvement in vulvovaginal pain, and the erosive lesions on the vulva and vagina had completely resolved. As expected, diabetic glycemic excursions occurred on prednisone and were managed with insulin adjustments.

At completion of systemic steroids, the disease-modifying antirheumatic drug (DMARD) hydroxychloroquine 200 mg orally twice daily was prescribed in addition to twice daily topical application of augmented betamethasone dipropionate 0.05% ointment. The change in topical steroid ointment was at patient request. The choice to begin

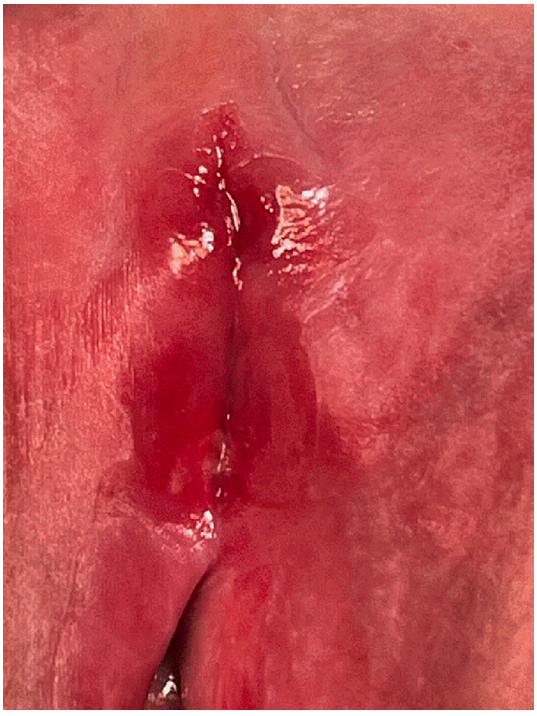

Fig. 2. Gross exam of clitoris showing erosive lesions covering the clitoris and peri-clitoral dermis.

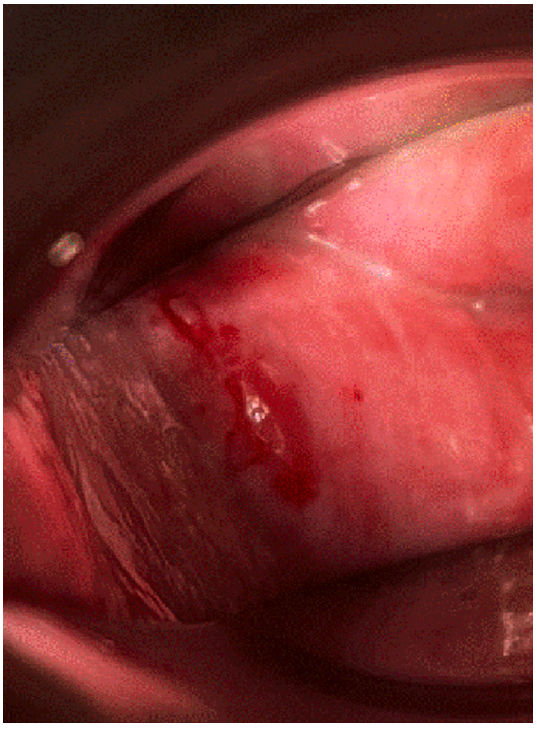

Fig. 3. Speculum exam showing the vaginal sidewall with an erythematous lesion with Wickham striae.

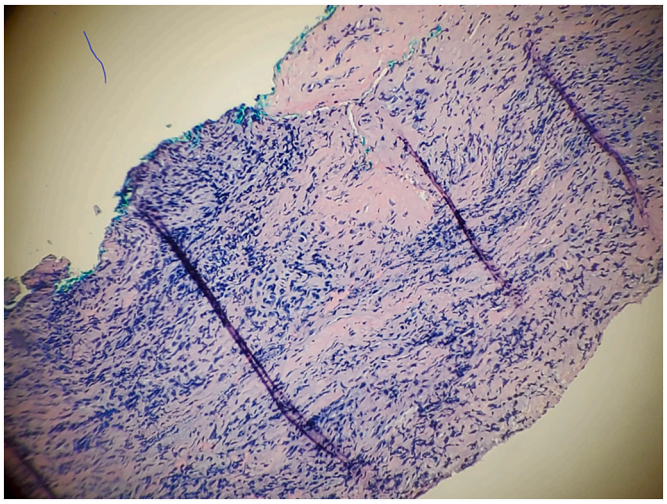

Fig. 4. Right introitus histology showing denuded epithelium with prominent lymphocytic subdermal infiltrate (lichenoid changes).

hydroxychloroquine was based on mutual decision making with lower potential for side-effects compared with other systemic therapies. Methotrexate was considered but her interleukin-6 level was elevated at 12.50 pg/mL, suggesting that she would be a suboptimal candidate for this therapy. [6,7] A "flare" of LP was treated with a 5-day burst of oral prednisolone 60 mg, with rapid response. New-onset oral lesions consistent with oral LP were treated successfully with triamcinolone paste. After 3 months of hydroxychloroquine treatment, the patient had a suboptimal response and treatment was terminated. Mycophenolate mofetil, an inhibitor of B and T lymphocyte proliferation, 500 mg twice daily was prescribed in addition to continuing betamethasone dipropionate 0.05% ointment twice daily. Mycophenolate was increased to 1000 mg twice daily after one week and then increased again to 1000 mg three times daily one week later due to inadequate response to lower dosages. The patient experienced only mild gastrointestinal upset and dyspepsia. Her peripheral white blood cell count remained $\geq$6500/mL. The patient has reported substantial improvement in vulvar pain with resolution of all lesions and erosions in the vagina and vulva. Unfortunately, 6 weeks into therapy, she developed bothersome lower extremity muscle pain, an established side-effect of mycophenolate, that resolved rapidly with drug discontinuation. [8]

As her vulvar pain and erythema worsened to a moderate degree with discontinuation of mycophenolate (despite continued use of betamethasone ointment), cyclosporin, an inhibitor of T-cell lymphocytes, at 3 mg/kg/d (150 mg twice daily) was initiated. Cyclosporin was well tolerated and afforded complete resolution of symptoms. At 3 months, she was given a trial off cyclosporin while continuing topical betamethasone ointment 0.05% in a taper, and her remission was sustained. Her oral and cutaneous lesions also resolved.

3. Discussion

Vulvar LP was first described by Hunt et al. in 1936. Genital subtypes of LP can be categorized into three main subtypes: erosive, classic, and hypertrophic. The erosive subtype is the most prevalent of these and usually exhibits a raw, erosive inflammatory pattern of lesions that are often a local manifestation of widespread disease [2,3,9,10]. The differential diagnosis of vulvar LP includes lichen sclerosis, autoimmune blistering disorders, herpes zoster, and non-HPV-associated vulvar intraepithelial neoplasms and squamous cell carcinoma. Although the diagnosis may be suggested by clinical presentation, biopsy or antibody studies are necessary to differentiate ambiguous clinical cases. [11] In this case, desmoglein 1 and 3 antibody markers for autoimmune bullous disorders were negative, but case history and gross appearance could not rule out malignancy, including squamous cell carcinoma. Non-HPV vulvar neoplasia has been reported in association with vulvovaginal LP. [12] Lichenoid drug eruptions have been reported after administration of many drugs, and careful review of patient medications is warranted. In this case, lichenoid drug reaction could be eliminated since her initial disease was limited to the vulva and vagina, and drug-induced eruptions are typically distributed over the trunk and extremities. [1,13]

Like many patients suffering from vulvovaginal LP, this patient went undiagnosed and undertreated, which led to significant distress as her symptoms worsened. Most patients with isolated vulvovaginal LP present initially to primary care physicians or gynecologists and are frequently treated with vaginal estrogen for presumed genitourinary syndrome of menopause (GSM) and/or antimicrobials for an infectious vaginitis before the correct diagnosis is established. No diagnostic criteria currently exist for vulvovaginal LP, but the most common findings are well-demarcated erosions or erythematous areas at the vulva or vagina (96%), symptoms of pain or burning (92%), and scarring or loss of architecture (88%). [14,15] In cases where a diagnosis is unclear, fail to respond to treatment, or there is suspicion for malignancy, providers should obtain a biopsy from the edge of an erosion to ensure intact epithelium is present. Positive biopsies show classic lichenoid features (band-like lymphocytic infiltrate), basal layer damage, and absent subepithelial sclerosis. [1,9,14,16] Accurate and timely diagnosis of vulvovaginal LP requires a high level of clinical suspicion and collaboration between specialties, including dentists (for oral or gingival lesions), dermatologists, and gynecologists.

Once the diagnosis of LP is established, the clinical challenge of treatment begins. LP is a chronic disease with a cyclic pattern of lesion exacerbation. The goals of treatment for vulvovaginal LP should center around symptom reduction, scar minimization, improving sexual function, and enhancing overall quality of life.

Traditionally, first-line treatment includes application of an ultra-high potency topical steroid and topical calcineurin inhibitors such as tacrolimus ointment at 0.03% or 0.1%. Approximately two-thirds of those suffering with vulvovaginal LP respond to these regimens. There is considerable experience with commercially available hydrocortisone suppositories 25 mg for vaginal involvement. [4,9]. Because of the rarity of vulvovaginal LP, no adequately powered randomized controlled trials exist to guide therapy when topical steroids fail. [6,9] When topical therapies fail to provide an adequate response for vulvovaginal LP, systemic steroids or immunosuppressant agents should be initiated, but there is noticeably less evidence available to guide selection. [6]

Systemic steroids are beneficial in widespread disease or when topical treatments fail. In this case, systemic steroids (prednisone 60 mg daily for 6 weeks) effected a good response, but well-established side-effects associated with prolonged systemic corticosteroids preclude long-term use. Following remission, short bursts of corticosteroids can be administered at the onset of new recurrences.

The optimal long-term systemic therapy for LP is unclear. [3,6,9,10,17] In this case, hydroxychloroquine was initially elected because of relatively low toxicity and low-moderate adverse event rate, the most common being gastrointestinal distress. Evidence for hydroxychloroquine effectiveness in LP has been found in small case series. [6,18] No appreciable response to hydroxychloroquine was observed in this case at 3 months, hence, mycophenolate, a drug with an established record in treatment of cutaneous inflammatory diseases, was substituted. Mycophenolate has been used successfully in small case series of LP. [19,20] Unfortunately, a somewhat unusual adverse event (myalgias) precluded long-term use in this case despite a satisfactory improvement in vulvovaginal symptomatology. Cyclosporin, a member of the calcineurin inhibitor family (like tacrolimus) and immunomodulator of T-cells, was introduced after mycophenolate. The patient's remission was sustained with cyclosporin and it was well tolerated. Again, there is a reassuring small case series with cyclosporin. [21] In a retrospective study from a single institution, methotrexate at various

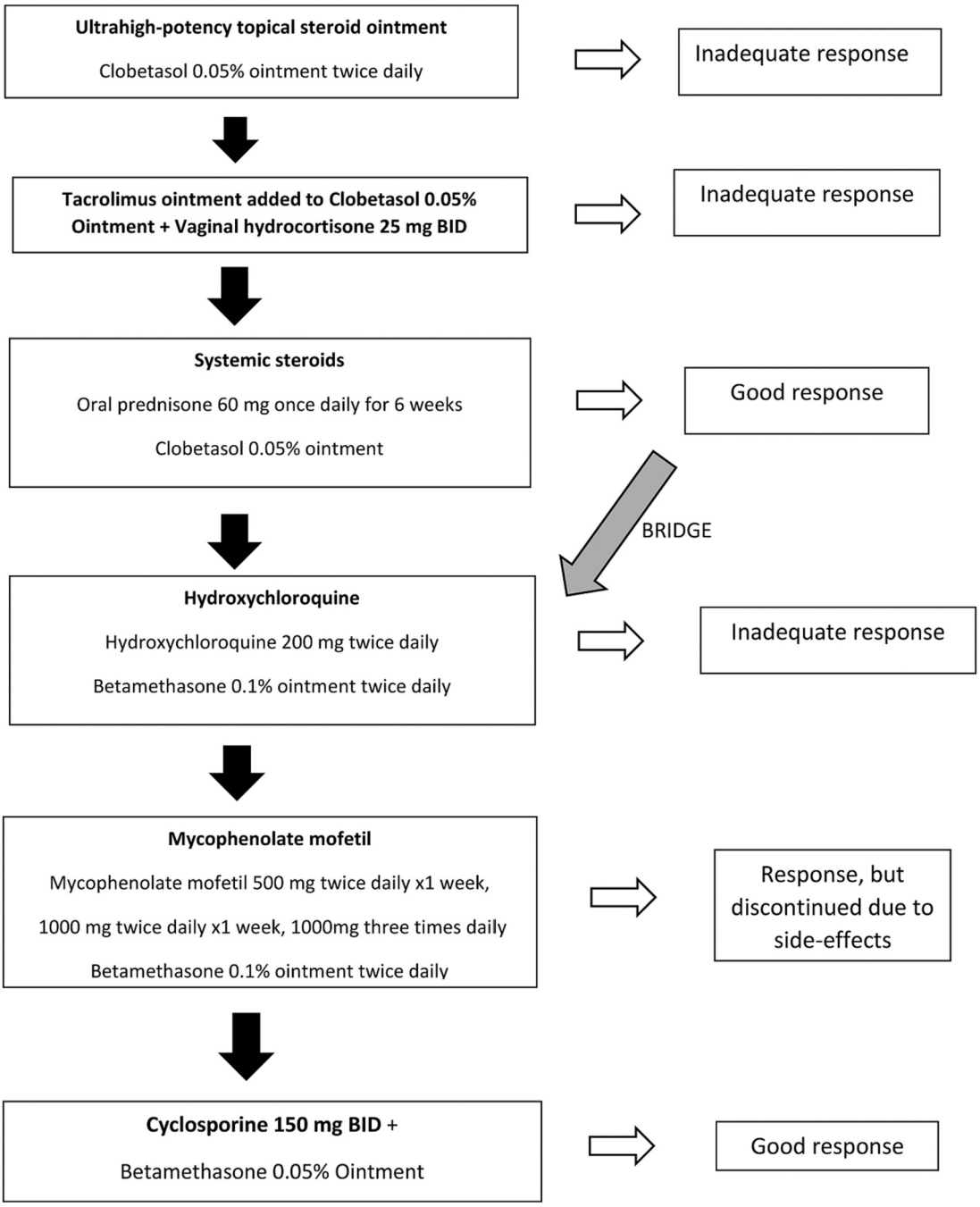

Fig. 5. Summary of treatments required for remission. Figure by K. Holder and R. Kauffman.

doses (7.5–20 mg/week) was reported to be efficacious in the treatment of vulvar LP in 19 of 27 patients. [22] Methotrexate may be less effective when IL-6 levels are elevated—at least for oral lesions. [7,23] As with all immunosuppressant drugs, side-effects, particularly gastrointestinal distress and fatigue, may preclude compliance with methotrexate. [22] From scattered relatively low-quality evidence, it is clear that multi-centered well-designed trials are needed in the future to assist treatment choices.

Single case reports or small case series support utilization of a host of other medications for treatment of LP, including oral retinoids, dapsone, antifungals, topical vitamin D derivatives, azathioprine, sulfasalazine, thalidomide, cyclophosphamide, and various biologics, such as etanercept and adalimumab. [6,9,10]. The optimal dosage and duration of use are not known but prolonged utilization may be mandated by disease recurrence. [6,9] JAK inhibitors are under current investigation and have shown benefit in early studies. [17]

In rare cases, surgery may be required to reconstruct vulvovaginal anatomy and restore sexual function. [24] Vaginal dilators may prevent vaginal stenosis and adhesion formation but may be difficult to tolerate with active disease. [24] Lastly, behavioral interventions to prevent scratching can arrest lichenification and excoriation of lesions. These may include sedating antihistamines and low-dose tricyclic antidepressants. [24] Psychological stress management also has a role in the therapeutic milieu. [25]

In conclusion, finding an appropriate treatment regimen for patients with vulvovaginal LP unresponsive to topical ultrapotent corticosteroids and calcineurin inhibitors is challenging and requires joint decision-making and a willingness to try a spectrum of treatment options with

careful observation for toxicity and side-effects. Management of such cases highlights the need for high-quality evidence-based studies. Multidisciplinary consultation may be wise in the absence of a satisfactory response.

Contributors

Madeline K. Young provided background research and revised the article critically for important intellectual content.

Katherine G. Holder provided background research and revised the article critically for important intellectual content.

Teresa E. Baker was involved in the care of the patient.

Robert P. Kauffman was involved in patient care, participated in the conception of the manuscript, acquired and interpreted results, and drafted the manuscript.

All authors approved the final submitted manuscript.

Funding

No funding from an external source supported the publication of this case report.

Patient consent

The patient has given consent for publication of her case and inclusion of the images.

Provenance and peer review

This case report was not commissioned and was peer reviewed.

Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

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