BRIEF ARTICLE

Successful Treatment of Lipschütz Ulcer with a JAK Inhibitor, Upadacitinib

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ABSTRACT

Lipschütz ulcer (LU), is a rare non-venereal diagnosis of exclusion. Typically affecting sexually inactive, young women, LU presents with acute pain and edema along with necrotic ulcerations on the vulva, labia minora, or lower vaginal region. The pathogenesis of LU remains unknown. Published cases suggest that LU may heal spontaneously or with supportive and symptomatic treatment focused on pain relief and inflammation reduction using oral or topical steroids. Here, we present a case of persistent LU that required continuous treatment with a janus kinase (JAK) inhibitor, upadacitinib.

INTRODUCTION

Lipschütz ulcer (LU), first documented by Benjamin Lipschütz in the early 20th century, is a perplexing and understudied condition characterized by the sudden onset of painful, “kissing” vulvar ulcers that are often associated with a fibrinous coating.[1] It predominantly affects young females, who may not be sexually active.[2] These lesions are a diagnostic challenge, as their pathogenesis is not well understood due to their unknown etiology. [2]

Historically, LU cases have been linked to infections such as Epstein-Barr virus, cytomegalovirus, mumps, influenza, and less commonly, streptococcal infections.[3–5] However, there has been a notable increase in reported cases globally following the recent pandemic, possibly triggered by the COVID-19 vaccination.[6–8]

Despite this increase in publications on LU, there remains a relative paucity of reported cases, which raises concerns about potential under-diagnosis. This is compounded by the absence of firmly established diagnostic and treatment guidelines. In this paper, we describe the case of a 34-year-old female patient with persistent vulvar ulcers, who was eventually diagnosed with LU and successfully treated with upadacitinib, a selective JAK1 inhibitor.

CASE REPORT

Our patient, a 34-year-old, otherwise healthy female, sought medical attention for vulvar ulcers she had first noticed three months earlier. Her symptoms included dysuria, dyspareunia, suppurative vaginal discharge, and severe pain attributed to the vulvar ulcers. Before the dermatology consultation, the patient had consulted various other specialists, including gynecologists,

urologists, neurologists, and pelvic pain therapists, to determine the etiology of her symptoms. No relevant family history was reported. Of note, the patient reported no prior history of such ulcers or history of any sexually transmitted diseases, including chlamydia, gonorrhea, HIV, trichomoniasis, HPV, and syphilis.

Physical exam revealed broad ulcers on the inner part of her labia, consistent with the classic presentation of "kissing ulcers" accompanied by overlying fibrinous membranes. The patient underwent a comprehensive workup for infectious etiology, revealing a positive HSV-1 and HSV-2 immunoglobulin G (IgG). Despite this localizing finding of herpetic vulvovaginitis, a broad differential diagnosis of other infectious etiologies included LU, Behcet's disease and malignancy.

Following the initial consultation, the patient was prescribed topical clobetasol, lidocaine/prilocaine topical ointment for pain relief, and treatment for herpes simplex of valacyclovir for fourteen days. Of note, the patient had previously tried multiple systemic treatments: doxycycline, cephalexin, fluconazole, ciprofloxacin, and uribel (hyoscyamine/methenamine/phenyl salicylate/sodium phosphate/methylene blue) with no symptomatic relief. Despite completing the fourteen-day course of valacyclovir, the patient did not show any improvement. This prompted a punch biopsy that revealed a vulvar ulcer with suppurative and granulomatous inflammation.

Due to inconclusive biopsy findings, the patient was started on prednisone 40 mg for two weeks while further investigating a broader differential, including Crohn’s disease, vasculitides, pyoderma gangrenosum, sarcoidosis, and pemphigus vulgaris. Antinuclear antibody (ANA), desmoglein antibodies, and rapid plasma reagin (RPR) test results were all negative. During this prednisone course, the patient reported improved dysuria and dyspareunia, corresponding with approximately 80% re-epithelialization after two weeks of treatment. Given the improvement, the patient was advised to taper the steroid course by a 5 mg per day reduction over eight days.

At her one-month follow-up, the patient reported further pain improvement and an enhanced quality of life, was able to sit without discomfort, and reported no longer having pain and bleeding upon urination. Unfortunately, a few days after tapering down to 5 mg of prednisone daily, the patient experienced significant discomfort and noted persistent serosanguineous discharge from her labia. Consequently, as prophylactic antimicrobial agents and the steroid course showed no efficacy, the patient was initiated on a JAK inhibitor, upadacitinib 15 mg extended release once daily, after appropriate screening laboratory testing for tuberculosis (TB) and a lipid panel was performed.

Within a week of starting upadacitinib, the patient reported a significant improvement in all symptoms, and the 7 mm ulcer was noted to shrink to 3 mm on physical examination. The patient was counseled to remain on upadacitinib for 6 months before discontinuation to ensure symptomatic relief and completely neutralize the underlying inflammatory pathway of the ulcers.

Upadacitinib was then discontinued due to the patient's desire to plan for pregnancy in the near future. Several weeks later, the patient reported a recurrence of vulvar erythema, which resolved with a course of prednisone taper. No longer requiring medication, the patient currently remains disease and symptom free.

DISCUSSION

LU serves as a broad diagnostic term encompassing rare and mostly unidentified causes of acute genital ulcers. Typically, these lesions are self-limited, resolving without scarring in two to six weeks.[1] While they may be preceded by or associated with acute viral or bacterial infections in some cases, the cause often remains unknown.[2] Treatment strategies may vary based on the etiology of the ulcers, incorporating antibiotics, antivirals, and anti-inflammatory therapies of oral and topical steroids. However, the primary focus remains on supportive wound care, local hygiene, and pain management.[7]

In contrast to the published cases of LU, our case presentation introduces several noteworthy features that broaden both the diagnostic and treatment understanding of this rare condition. Our patient, who is sexually active and 34 years old, challenges the typical demographic profile of non-sexually active, adolescent females associated with LU. This underscores the importance of considering LU in the differential diagnosis for genital ulcers regardless of patient demographics.[2, 7, 9–11]

In addition, despite testing positive for HSV-1 and HSV-2 IgG, our patient's negative results for active herpes simplex virus indicate that the ulcers were not a straightforward manifestation of herpes virus related lesions.[12] Emphasized by the lack of clinical response to the fourteen-day course of valacyclovir, the possibility of herpes simplex as a cause only served as a distraction to the diagnostic process. Furthermore, LU typically resolves within two to six weeks, with most patients experiencing no recurrences if not associated with viral infections or systemic illness. However, our patient's healing process extended over several months, with an unusual recurrence shortly after discontinuing oral steroids.[2]

Most notably, there are no documented cases of LU successfully treated with a JAK inhibitor. Janus kinases play a critical role in the regulation of immune cell function in response to various growth factors and cytokine-mediated signals by the phosphorylation of signal transducers and activators of transcription (STATs).[13] Upadacitinib has become increasingly used for patients with inflammatory and autoimmune conditions that are resistant to conventional treatment.[14,15] Upadacitinib was chosen to due to its selective inhibition of JAK1, decreasing other off-target effects, and increased efficacy to reduce inflammatory responses in multiple different conditions.[15,16]

Despite being approved by the Food and Drug Administration (FDA) for rheumatoid arthritis, psoriatic arthritis, and atopic dermatitis and undergoing clinical trials for other autoimmune conditions, the stigma associated with the boxed warning for JAK inhibitors significantly limits their consideration for off-label uses. Grounded in the preliminary post-marketing safety data findings of tofacitinib, a pan-JAK inhibitor, which showed higher risks of major adverse cardiovascular events (MACE) and cancer with tofacitinib compared to TNF(tumor necrosis factor)-α inhibitors, the FDA mandated an universal warning for all JAK inhibitors due to the similar mechanism of action.[17] However, in order to properly contextualize the MACE risk of JAK inhibitors, it is essential to recognize that while there is a 33% increased risk with JAK inhibitors, certain non-steroidal anti-inflammatory drugs (NSAIDs) can pose up to a 58% increased risk for MACEs.[18,19]

Therefore, despite these concerns, JAK inhibitors should not be disregarded entirely and should be considered for such off-label uses, especially in the treatment of rare diseases like LU that are driven by idiopathic, nonspecific inflammatory pathways.[17] Addressing the hesitancy associated with JAK inhibitors also might have impacted our decision not to discontinue treatment for our patient after the initial three months, leading to another flare.

Our patient's relapse after the initial three months of treatment with upadacitinib raises salient questions: is prolonged JAK inhibitor use warranted in cases where patients have previously failed standard treatment options, such as steroids? Is extended use necessary to prevent subclinical disease progression that may be more resistant to such standard treatments? Certainly, the side effects of prolonged systemic steroids greatly outweigh those of JAK inhibitors. Even short-term use of corticosteroids has side effects that exceed those of JAK inhibitors. [20, 21]

CONCLUSION

Remaining enigmatic on several fronts, this case unveils a new layer of complexity in both the diagnosis and treatment of LU. Our patient's successful treatment with upadacitinib warrants further research to better characterize the pathogenesis and prognosis of this challenging diagnosis.

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