Lipschütz ulcers after AstraZeneca COVID-19 vaccination☆

Dear Editor,

Acute vulvar aphthous ulceration or Lipschütz ulcer is a rare non-sexually acquired condition which is characterized by the sudden onset of painful genital ulcers. It doesn't have a clear etiology; therefore, its diagnosis is challenging. The usual course is self-resolution without relapses and scarring. There have been six cases reported following COVID-19 vaccination.[1,2]

Case Report

A 27-year-old healthy, sexually active woman received her third dose of the COVID-19 vaccine, the first two were Pfizer-BioNTech and this one was AstraZeneca (Vaxzevria) vaccine. She complained of acute onset of burning pain in labia majora and swelling 24 hours after receiving the vaccine, accompanied by fever and body aches. Physical examination revealed multiple millimetric, shallow, purple-red, painful ulcerations in labia majora, labia minora, and vaginal introitus (Fig. 1). The patient had no previous history of genital ulcers. Oral mucosa and oropharynx were clear. At 24 hours follow up she reported worsening symptoms complaining of difficulty sitting down. Upon examination, the patient had more ulcerations with yellow and gray covering with surrounding erythema and edema, some with the purulent center. A biopsy of one ulcer was taken and tissue PCR for Herpes Simplex Virus (HSV) 1/2, Varicella-Zoster Virus (VZV), and cytomegalovirus was negative, as well as serologic IgG and IgM for HSV 1/2 and VZV. HIV serology was not reactive, genital swab culture, VDRL, COVID antigen test, and antinuclear antibodies were all negative. The biopsy showed epithelium ulceration, spongiosis, and dense inflammatory infiltrate of lymphocytes and histiocytes, there was no trace of vasculitis or viral infection (Fig. 2). The patient was diagnosed with vulvar aphthous ulcers. She was treated with hydrocortisone 1% and pain control. Ulcers resolved within 9 days. At the 6 month follow-up, she had not presented a recurrence of the lesions.

Discussion

Although the exact etiology of Lipschütz ulcer remains unclear, it likely involves an immunologic response to an infection or other source of inflammation. Most cases are idiopathic with a negative infectious workup.[1] There are six case reports of vulvar aphthous ulcers following COVID-19 vaccination, four after Pfizer-BioNTech and one after AstraZeneca.[1,2] This is the second one reported in the literature after the AstraZeneca vaccination. The diagnosis was challenging since the patient was sexually active. Sexually transmitted diseases were tested for and excluded. After discarding infectious diseases, the main differential diagnosis was Behçet syndrome, however, the biopsy did not show signs of vasculitis.[3] Lipschütz's ulcers were firstly attributed to virgin women, and later to patients with an absence of sexual contact in the previous three months. However, in a study conducted in Brazil, 86 out of 98 patients were diag-

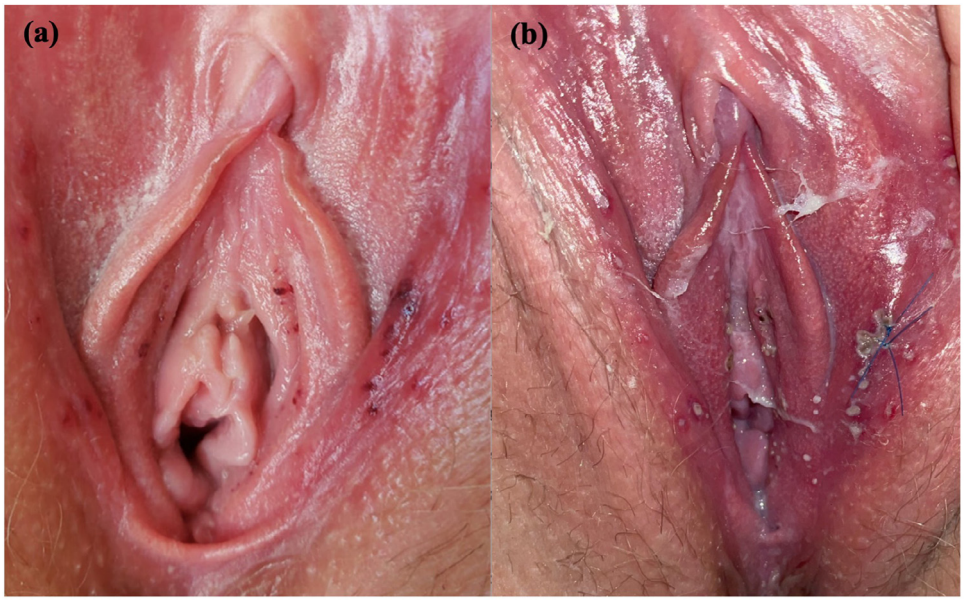

Figure 1 Progression of vulvar aphthosis. (A) Initial clinical presentation, with millimetric, shallow, purple-red, ulcerations, (B) Day 1 follow-up. Labia majora and minora with edema and erythema. Ulcerations with purulent center

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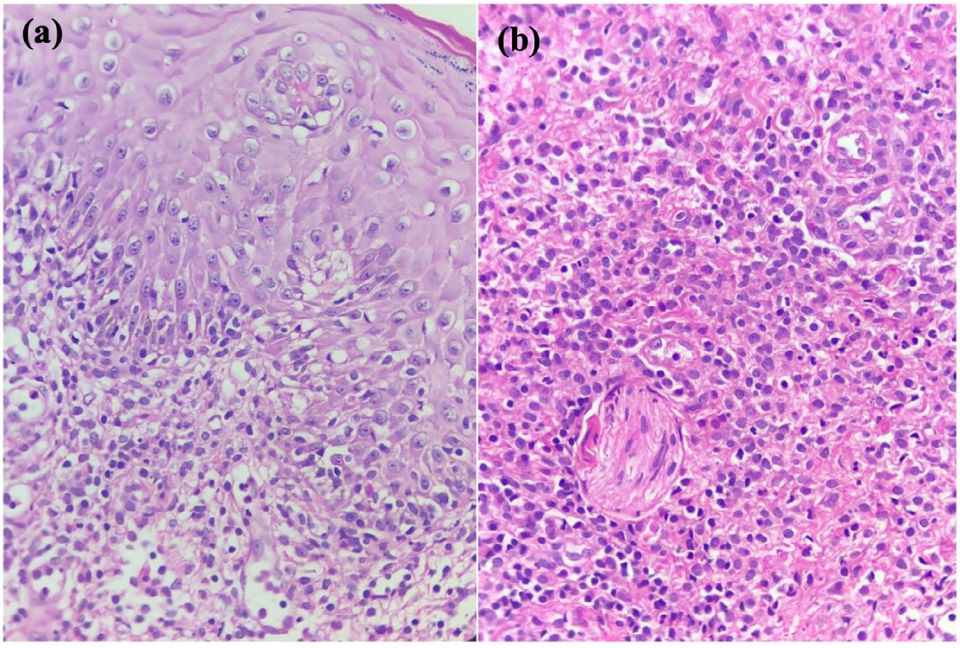

Figure 2 Biopsy of one ulcer stained with Hematoxylin & eosin, 40x. (A) Vulvar mucosa ulceration and spongiosis. (B) Dense mixed inflammatory infiltrate of lymphocytes, histiocytes, and scarce monocytes in all the stroma

nosed with Lipschütz ulcers when expanding criteria to any age and sexual activity.[4] Another retrospective analysis of 33 cases found that 84.8% of the patients had had their sexual debut.[5]

Several cutaneous reactions to the COVID-19 vaccination have been reported. This case demonstrates a potential association between this vaccine and the development of a vulvar aphthous ulcer. Clinicians, especially dermatologists, gynecologists and pediatricians should be aware of the possible risk of this disease after COVID-19 vaccination.

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Authors' contributions

Maria Bracho-Borro: Writing of the manuscript or critical review of important intellectual content; effective participation in the research guidance; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature.

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Mario Magaña: Data collection, analysis, and interpretation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases.

Conflicts of interest

None declared.

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Longitudinal melanonychia: a rare presentation of Bowen's disease☆

Dear Editor,

A 64-year-old female patient has complained of darkening and deformity of the nail of the third left finger for two years. On examination, onychodystrophy, slight subungual thickening, and irregularly pigmented longitudinal melanonychia (LM) measuring 3 mm were observed (Fig. 1A). Dermoscopy of the nail plate showed irregular longitudinal lines with a variety of colors (light and dark brown, black and gray), and hyperkeratosis located centrally on the free edge of the nail plate (Fig. 1A). Intraoperative dermoscopy of the nail bed and matrix showed slightly irregular and variable pigmentation ranging from black to brown (Fig. 1B); absence of Hutchinson's sign and dermoscopic signs of viral verruca. An excisional biopsy of the nail bed was performed with a margin of 2 mm and healing by secondary intention was chosen. Histopathological examination showed intraepithelial proliferation of atypical keratinocytes with loss of polarity (Fig. 2A), and nail plate with focal hyperkeratosis. Immunohistochemistry was positive for AE1/AE3 (pan-cytokeratin; Fig. 2B), and negative for HMB45 and S100 protein, disclosing the epithelial and non-melanocytic nature of the dysplastic cells, compatible with Bowen's disease (BD).

Ungueal BD, or squamous cell carcinoma (SCC) *in situ*, has a variable record of its frequency, possibly due to failure in its recognition or underreporting. On the other hand, SCC is the most common neoplasm of the nail apparatus, often with late diagnosis. Typically, ungueal BD presents as subungual hyperkeratosis or a verrucous lesion of the nail plate or bed; with periungual erythema and paronychia associated with crusts, ulcerations, or fissures, onychocryptosis, and/or nail dystrophy, and rarely with LM.[1] It occurs most often in middle-aged men between 50 and 69 years of age. It is usually asymptomatic and grows slowly for years or decades before developing into an invasive SCC. Exposure to ultraviolet radiation and arsenic, immunosuppression, and human papillomavirus (HPV) infection are considered risk factors.[2,3] Associations, particularly with HPV-56,[4] seborrheic keratosis and solar lentigo are suggested causes for pigmented BD.[5] Of 1712 analyzed BD cases, only 90 cases (5.25%) were pigmented BD. Of these, 29% occurred in sites not exposed to the sun, such as genital and intertriginous regions, indicating that other factors, in addition to ultraviolet radiation, may influence the pathogenesis of pigmented BD. In that series, the majority occurred in patients with phototypes I–III in sun-exposed areas, and only 19% in those with phototypes IV–VI, who were more likely to have pigmented BD in non exposed areas.[5]

Exogenous pigment deposits (dirt, tobacco), blood, and melanin are frequent causes nail plate and nail bed pigmentation, and melanocytic activation and benign melanocytic nevi are the most common causes of LM in adults and children, respectively. However, about 2/3 of ungueal melanomas present clinically as LM.[2]

Some clinical criteria should raise the index of suspicion of melanoma in acquired LM in adults: the presence of heterogeneous pigmentation in bands or lines of variable colors, fissures or clefts in the nail plate, especially in the distal region (triangular shape), the sudden appearance of nail plate pigmentation, and blurring of the nail fold edges.[2,3] In nail plate dermoscopy, the main criteria for suspicion are i) nail dystrophy; ii) Presence of gray or black color together with irregular brown pigmentation, iii) Granular pigmentation; iv) And/or involvement of more than 2/3 of the nail plate.[6]

Digital pigmented BD mimics melanoma and may show a chaotic pattern on dermoscopy: atypical parallel pattern of grooves and ridges, and a chaotic pattern with segmental radial lines suggestive of melanoma, associated with other dermoscopic characteristics suggestive of BD, such as squamous surface and linear arrangement of dotted vessels.[7]

LM dermoscopy is limited to the observation of the distribution of pigment deposited in the nail plate, and the underlying lesions can be misinterpreted, which is why intraoperative dermoscopy becomes relevant. Hirata et al. defined four patterns of intraoperative dermoscopy of the nail matrix and nail bed in LM: regular gray, regular brown, regular brown with globules or spots, and irregular pattern.[8] The irregular pattern was considered the most frequently associated with melanoma,[9] as seen in the present case.

Among dermoscopy findings, hyperkeratosis located on the free edge of the nail plate was the criterion significantly associated with subungual SCC.[10] In onychomatricoma, however, the criteria of non-parallel or diffuse edges of nail lesions seem to favor the diagnosis of subungual SCC, among other less specific ones, such as splinter hemorrhages, parallel longitudinal white lines, and nail thickening.[10]

Despite the clinical and dermoscopic findings of the nail plate, and intraoperative dermoscopic findings of the nail bed and matrix raising the suspicion of melanoma, histopathological evaluation did not show proliferation of atypical melanocytes, confirmed by negative immunohistochemistry for HMB45 and S100 protein. Positive immunohistochemistry for AE1/AE3, an antibody against human epidermal keratins, therefore, a marker of normal epithelial cells, carcinomas, and other tumors with epithe-

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