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A rare case and literature review of bullous pemphigoid appearing in the setting of lichen sclerosus: a dermatopathological conundrum and what to expect

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Abstract

Co-occurrence of blisters in patients with lichen sclerosus (LS) can raise the question of whether they represent a bullous variant of LS or a concomitant autoimmune disorder. We report a rare case of bullous pemphigoid (BP) occurring on previous LS lesions. To the best of our knowledge, this is also the first BP180-negative case reported in literature. Here, we propose alternative mechanisms, independent of BP autoantibodies, that may lead to development of BP on skin affected by LS. In addition, we provide a literature review that explores the underlying pathophysiology and offers practical treatment insights, equipping clinicians with valuable guidance for similar complex cases.

Keywords: autoimmune diseases, BP180 antigen, bullous pemphigoid, lichen sclerosus, dermatopathology

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Introduction

Blisters occurring on lichen sclerosus (LS) lesions are often initially considered a bullous variant of LS. However, clinicians should remain vigilant for other potential autoimmune conditions, particularly bullous pemphigoid (BP). Differential diagnoses to consider include lichen planus pemphigoides, cicatricial BP, bullous scleroderma, bullous lichen planus, and circumscribed lymphangioma. Comprehensive diagnostics, including histopathology and direct immunofluorescence (DIF) testing, are crucial for distinguishing between these conditions and ruling out alternative diagnoses.

Case report

A 69-year-old woman presented to our dermatology clinic with a 10-month history of sclerotic plaques on her back, breasts, thighs, and genital and perianal regions, accompanied by itching and pain. After 9 months, she reported blistering on these sclerotic plaques. Her medical history was significant only for hypertension, managed with bisoprolol and enalapril, and she denied any history of trauma. Physical examination revealed reddish-white indurated plaques with follicular plugging, measuring approximately 25 × 20 cm, symmetrically distributed over the proximal thighs, with multiple erosions and crusts. No new blisters were observed. Similar plaques were found on the abdomen, lower back, anogenital area, and breasts, although without erosions (Fig. 1a, b).

Biopsies were taken from an indurated plaque with erosion. Histopathology showed hyperkeratosis, interface dermatitis, and flattened rete ridges in the epidermis. In the dermis, there was hyalinosis in the papillary and upper reticular layers, along with focal infiltrates of lymphocytes and some eosinophils (Fig. 2a). A subepidermal cleft was also noted (Fig. 2b). DIF from perilesional

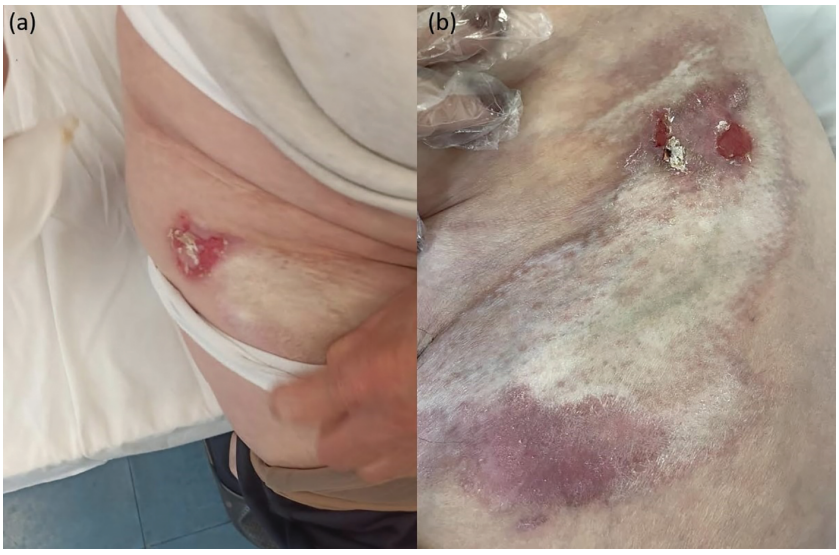

Figure 1 | (a, b) Reddish and whitish indurated plaques with follicular plugging and solitary erosions with hyperkeratosis and crusts.

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skin demonstrated linear deposition of immunoglobulin (Ig) G and complement component (C) 3 along the basement membrane zone (Fig. 2c). Based on these histopathological and DIF findings, a diagnosis of localized BP superimposed on LS was established.

Further testing with indirect immunofluorescence (IIF) was negative. Enzyme-linked immunosorbent assay (ELISA) showed no elevated levels of antibodies to BP180, BP230, desmoglein 1, desmoglein 3, envoplakin, or type VII collagen. Routine laboratory tests were within normal limits. Treatment with methotrexate 15 mg weekly and topical 0.05% clobetasol propionate ointment was initiated. A positive clinical response was observed after only four doses of methotrexate, with no new blister formation throughout follow-up.

Discussion

LS is a chronic inflammatory disorder that usually affects the skin of the anogenital area, but it can also affect any other body region. Multiple etiopathological theories have been suggested, primarily, genetic background combined with triggering factors (1, 2). In the latest review by De Luca et al., pathogenesis involved immune-mediated T helper (Th) 1-specific interferon (IFN) γ-induced phenotype and infiltrate (3). They also highlighted distinct expression of tissue remodeling–associated genes as well as microRNAs, oxidative stress with lipid and DNA peroxidation providing an enabling microenvironment for autoimmunity, carcinogenesis along with abnormal fibroblast growth, and collagen synthesis leading to hyalinization and sclerosis of the dermis (1, 3). Finally, circulating IgG autoantibodies against extracellular matrix protein 1 and hemidesmosome have been mentioned as potential contributors to progression of LS or simply representing an epiphenomenon (1–3). The role of hormonal factors has also been considered, among them hypoestrogenism, due to the typical onset of LS before puberty and after menopause. Certain medications may also trigger LS, such as immunotherapy and antiarrhythmics, and even infections (3).

Some authors have searched for autoimmune factors. In a study by Meyrick Thomas et al. (4), based on 350 female patients with LS, 21.5% had at least one autoimmune-related disease, and 42% had elevated titers of up to three different autoantibodies. Other studies concluded that LS patients had elevated odds of developing alopecia areata, lichen planus, and atopic dermatitis as well as psoriasis, hypertension, diabetes mellitus, obesity, dyslipidemia, and even genital warts (5).

As of May 2024, only five cases have been reported of localized BP coexisting with LSA (2, 6–9, Table 1). All the patients were female, age range 66 to 77 years old, with blisters appearing on top of sclerotic plaques.

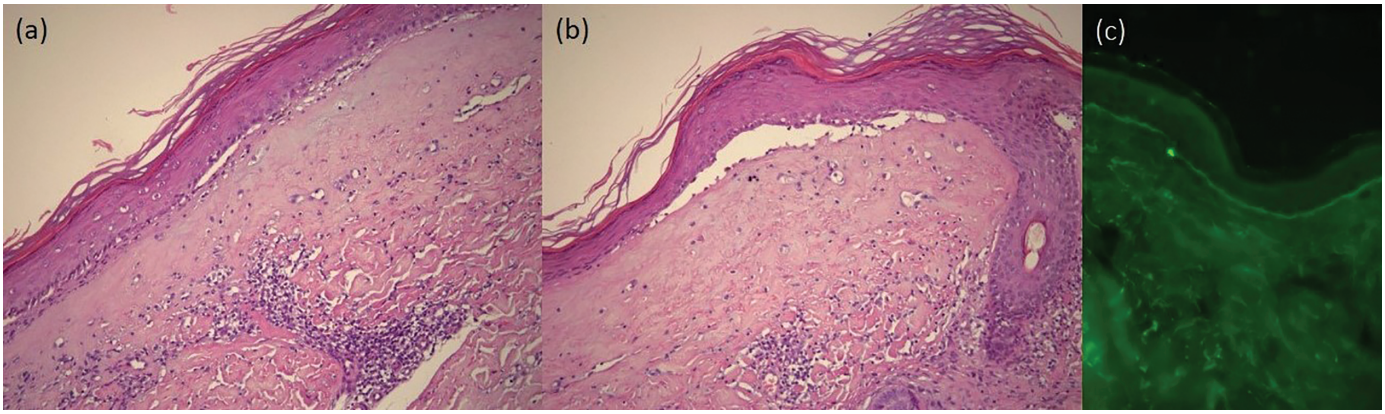

Figure 2 | (a, b) Interface dermatitis and flattened rete ridges in the epidermis. Dermal hyalinosis with focal lymphocytic and eosinophilic infiltrate. A subepidermal cleft is also present (hematoxylin and eosin, ×400); (c) linear deposition of immunoglobulin G and complement component C3 along the basement membrane zone (direct immunofluorescence).

Table 1 | Comparative overview of clinical, laboratory, and microscopic characteristics of cases reported in the literature, including the present case, of patients with coexisting lichen sclerosus and bullous pemphigoid.

Case	Age	Sex	BP lesion localization	LS history prior to BP diagnosis	ELISA test	DIF test (linear deposits in basal membrane zone)	Therapy	Response to therapy
Leonard N, et al. (2008) (6)	74	F	Vulva, abdomen	—	Not done	IgG, C3	Prednisolone, 0.5 mg/kg, azathioprine, local corticosteroids, tacrolimus	Partial
Walsh ML, et al. (2012) (1)	74	F	Vulva, gluteus	10 years	Not done	IgG, C3	Prednisolone, 0.5 mg/kg	Complete
Yoshifuku A, et al. (2018) (7)	66	F	Vulva, anogenital region, body, extremities	12 years	BP180+	IgG	Prednisone, 30 mg daily	Complete
Maglie R, et al. (2022) (8)	77	F	Forearms	25 years	BP180+	IgG, C3	Methotrexate, 15 mg weekly, prednisone 5 mg daily	Complete
Boeijink N, et al. (2023) (9)	72	F	Vulva, anogenital region	—	BP180+	IgG, C3	Local corticosteroids	Partial
Orlic et al.	69	F	Thighs	9 months	Negative	IgG, C3c	Methotrexate, 15 mg weekly, local corticosteroids	Complete

BP = bullous pemphigoid, DIF = direct immunofluorescence, ELISA = enzyme-linked immunosorbent assay, F = female, LS = lichen sclerosus, Ig = immunoglobulin, C3 = complement component 3.

DIF is considered the gold standard for BP (10). Only three cases reported an ELISA panel test: all were BP180-positive and none were positive for BP230. Our case was negative for both. Non-collagenous extracellular domain (NC16A) is the major pathogenic epitope in BP, especially in BP180-positive patients (10). However, patients with the non-NC16A regions are not recognized in commercial ELISA panels (11). Keller et al. (10) concluded that the use of ELISA for BP is inadequate because a standalone test with sensitivity for BP180 alone was only 54%, BP230 alone yielded 48% sensitivity, and a combination of BP180 and BP230 showed 66% sensitivity.

Regarding BP autoantibodies in LS patients, Baldo et al. found that 43% of patients (6/14) with LS have the NC16A domain of BP180 as the target for circulating T-cells, whereas none in the smaller control group did (12). Our case is the only BP180-negative case that actually developed bullae with a positive DIF. This could imply that autoantibodies do not correlate with the clinical picture. In previous cases, duration of LS before the occurrence of bullae was over 10 years, and thus plenty of time for autoantibodies to form. In our case it took only 9 months. Another possibility is that bullae are induced by different factors and/or autoantibodies outside of domains tested with the BP/ELISA panel. It is known that BP might appear on skin sites damaged by physical factors: injections, radiation, burns, or surgery (2, 8). Interestingly, it has been theorized that blisters can occur on normal skin due to epitope dissemination (2).

Conclusions

To differentiate between various causes of blisters in LS patients, a detailed history should be obtained. Not performing the DIF test might lead to misdiagnosis. An ELISA panel should be used in combination as a supportive diagnostic tool instead of a standalone test. With our case being BP180-negative, we can potentially theorize about other potential mechanisms outside of BP autoantibodies that could still lead to BP superimposed on LS lesions. We hope that this case motivates larger studies of pathophysiological mechanisms for this diagnosis.

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