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Multiimmunity Ratio in a Patient with Bullous Pemphigoid and Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis (RA) and bullous pemphigoid (BP) are autoimmune diseases influenced by genetic and environmental factors, with the concept of "shared autoimmune diathesis" suggesting that individuals with one autoimmune condition may be predisposed to developing another. This report describes a 62-year-old female with a 30-year history of untreated RA who presented with a progressive skin eruption initially misdiagnosed as herpes zoster. Over a four-month period, the patient developed pruritic bullous lesions predominantly in flexural areas. Histopathology and direct immunofluorescence confirmed BP by revealing subepidermal blisters with prominent eosinophilic infiltrate and linear IgG deposits along the dermoepidermal junction. Initial management with high-dose prednisone and azathioprine resulted in partial improvement; however, due to persistent lesions, rituximab was introduced, leading to significant clinical improvement. This case highlights the diagnostic challenges and therapeutic complexities encountered when RA and BP coexist, underscoring the potential shared pathophysiological mechanisms underlying autoimmune diathesis. The successful use of rituximab in this patient aligns with current literature advocating for biologic therapy in refractory BP cases, particularly in the context of other autoimmune disorders. These findings emphasize the importance of a multidisciplinary approach—integrating dermatology, rheumatology, and immunology—to ensure timely diagnosis and optimal management, ultimately improving patient outcomes in complex autoimmune presentations.

KEYWORDS: Rheumatoid arthritis, Bullous pemphigoid, Autoimmune diathesis.

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INTRODUCTION

Both rheumatoid arthritis (RA) and bullous pemphigoid (BP) are autoimmune diseases influenced by genetic and environmental factors. The term "shared autoimmune diathesis" describes a cascade in which individuals with one autoimmune disease may be more susceptible to developing other additional autoimmune conditions. This concept highlights the interconnected nature of autoimmune disorders, suggesting that the genetic and environmental factors contributing to one autoimmune disease may increase vulnerability to others.

Bullous pemphigoid (BP) is the most common autoimmune blistering disease, primarily affecting older adults, particularly in the eighth decade of life, with no gender differences. Additionally, cases in children and adolescents are rare. In recent decades, the incidence of BP has increased, which is attributed to the aging population with multiple comorbidities, autoimmunity, and exposure to certain medications that may trigger the disease (1). In the United States, the incidence of BP ranges from 2.4 to 23 cases per million people in the general population each year. However, in individuals over 70 years of age, the number of annual cases may reach between 190 and 312 per million (2).

BP generally presents as multiple tense blisters of varying sizes, pruritic urticarial plaques, vesicles, and crusted erosions. To diagnose BP in patients with compatible clinical manifestations, a skin biopsy from the edge of a recent blister or from the perilesional area is performed (3). The histological features of BP include subepidermal non-acantholytic blisters with conspicuous eosinophilic

infiltration in the blister cavity and dermis. While these histological features are important for identifying an intraepidermal or subepidermal blistering disease, clinical evaluation and immunofluorescence are necessary for an accurate diagnosis (4).

The central pathophysiology of BP involves the production of autoantibodies directed against specific antigens in the basement membrane, particularly BP230 and BP180 (also known as bullous pemphigoid antigens 1 and 2, respectively) (5). BP230 is a cytoplasmic protein belonging to the plakins family, which is part of the hemidesmosome complex and participates in anchoring intermediate filaments to the cytoskeleton. BP180, on the other hand, is a transmembrane glycoprotein that is also part of the hemidesmosome and spans the lamina lucida of the basement membrane zone. Its extracellular NC16A domain is identified as the main antigenic epitope in BP, where IgG autoantibodies bind to BP180 and activate the inflammatory cascade (6).

BP is significantly associated with the major allele of the class II major histocompatibility complex, HLADQB1*03:01, which is involved in the presentation of antigens to CD4+ lymphocytes. These CD4+ cells release interleukin-17 (IL-17), which can be detected in lesions of patients in the early stages of BP. IL-17 plays a key role in the upregulation of neutrophil elastase and matrix metalloproteinase-9 release, which are responsible for the separation between the dermis and epidermis. Compared to healthy individuals, patients with BP show elevated levels of IL-4, IL-13, eosinophils in peripheral blood and lesions, circulating IgE, and Th2 cell activity, indicating allergic-type immune signaling and dysregulation. Furthermore, levels of IgE and peripheral eosinophils may correlate with disease severity in these patients (7).

To diagnose BP, an immunopathological examination to detect the involved immunoglobulins and complement components is essential. Direct immunofluorescence (DIF) in a perilesional skin biopsy is the gold standard for BP diagnosis, which has reported a sensitivity ranging from 82% to 90.5% and specificity of 98% (8), showing linear deposits of IgG and/or C3 along the dermoepidermal junction (DEJ).

Other studies have suggested that immunohistochemical staining (IHC) on routine biopsy material could offer an alternative method for diagnosing BP, as IHC staining has significant diagnostic potential, especially in cases with a high suspicion of BP but with negative or suboptimal DIF results (9–11).

Regarding rheumatoid arthritis, the pathogenic pathways are complex and involve the activation of both the innate and adaptive immune systems, with the participation of various cells, including T and B cells, macrophages, dendritic cells, neutrophils, fibroblasts, chondrocytes, and mast cells. Although the exact pathophysiological mechanisms are not fully understood, it is known that the interaction between genetic and environmental factors contributes to the development of autoimmunity and immune dysfunction. Over time, various theories have been proposed, such as molecular mimicry, epigenetic transformation, and cross-reactivity. Processes like citrullination, carbamylation, and methylation play a key role in generating new antigenic epitopes, promoting the production of autoantibodies directed against citrulline and rheumatoid factor in seropositive patients (12).

Both the innate and adaptive immune systems respond to these antigenic epitopes by activating Toll-like receptors (TLR). After exposure to an antigen, cells of the innate immune system, such as monocytes, macrophages, and dendritic cells, express TLRs that trigger an inflammatory cascade. Macrophages and dendritic cells phagocytize and process the antigenic peptides, then migrate to peripheral lymphoid tissue to present them to the adaptive immune system. This interaction with T lymphocytes induces their differentiation and activates the cellular immune response, releasing pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), interleukin (IL)-1β, IL-6, IL-21, and IL-23. Additionally, cell signaling favors the activation of B lymphocytes, promoting the production of autoantibodies against rheumatoid factor and citrulline, which contributes to the development of systemic and joint disease (13).

This immune stimulus also induces the expression of adhesion molecules and neutrophil chemotaxis to the synovial membrane, releasing chemokines by activated endothelial cells of the synovial microvasculature, which triggers inflammatory synovitis and synovial membrane thickening. Regarding the proliferation of synovial cells and increased synovial fluid volume, capillary flow is reduced, generating hypoxia in the synovial tissue, favoring angiogenesis and pannus formation, which contributes to the progression of rheumatoid arthritis (14).

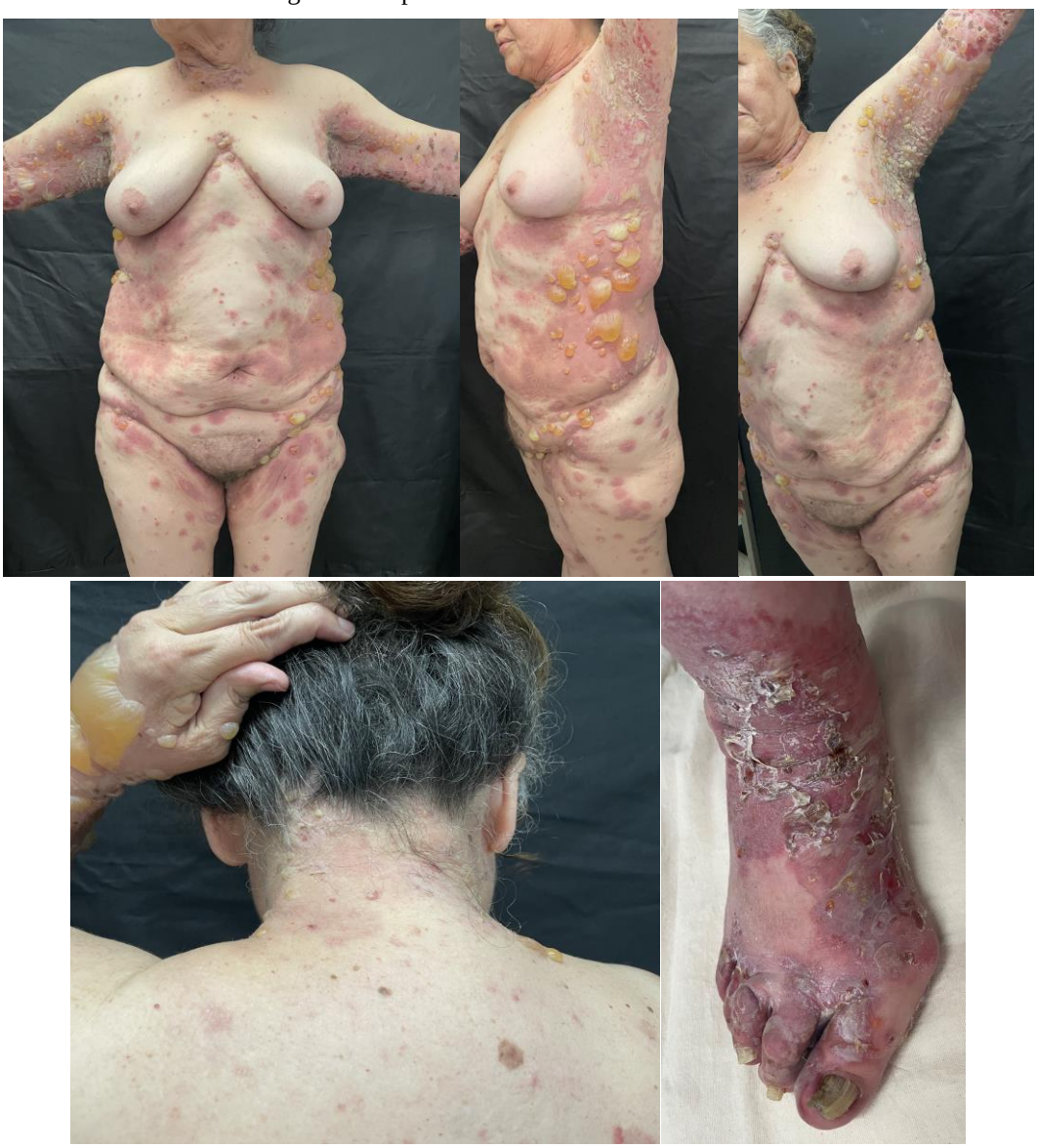
CASE REPORT

A 62-year-old female patient with a history of systemic hypertension, rheumatoid arthritis of 30 years' evolution without treatment in the last decade, and bullous pemphigoid diagnosed in April 2024. In December 2023, the patient began with urticarial lesions that progressed to pruritic bullous lesions in the antecubital and axillary folds, initially interpreted as insect bites. She sought care at her family medicine unit where she was diagnosed with herpes zoster and treated with acyclovir and antihistamines, but showed no improvement. Fifteen days later, due to the persistence of lesions, she was given a single dose of methylprednisolone with partial improvement. Despite receiving treatment, a month later the lesions continued to worsen, so she went to the Emergency Department of a second-level hospital, where the initial diagnosis of herpes zoster was maintained.

Four months after the onset of symptoms (April 2024), the patient was transferred to another second-level hospital where bullous pemphigoid was suspected, and treatment with prednisone 50 mg daily was initiated. Upon starting

treatment, she was referred to the Dermatology service of a tertiary hospital for further evaluation.

Upon examination, the patient presented disseminated dermatosis to the trunk, upper and lower extremities, with a predominance in axillary folds and the inner side of the lower extremities, characterized by blisters and bullae ranging from 1 to 5 cm in diameter, with serous content, flaccid, and with areas of desquamation on an erythematous base with macerated surfaces and well-defined edges. The patient reported burning, itching, and general discomfort (Images 1-6). A biopsy of two bullae was taken for histopathology (Images 7-9) and immunofluorescence (Images 10-11), which confirmed the diagnosis of bullous pemphigoid. The prednisone dose was increased to 75 mg daily in a tapering schedule, and blood tests were requested, along with a rituximab treatment protocol. The patient was then referred to rheumatology for follow-up of her joint condition.



Images 1, 2, 3, 4, 5, 6: Clinical manifestations of bullous pemphigoid

One month after the biopsy, new lesions appeared in the oral mucosa, palms, and soles, with 80% of the bullae in the desquamation phase. The steroid dose was maintained at 50 mg daily, and azathioprine 50 mg every 12 hours was added.

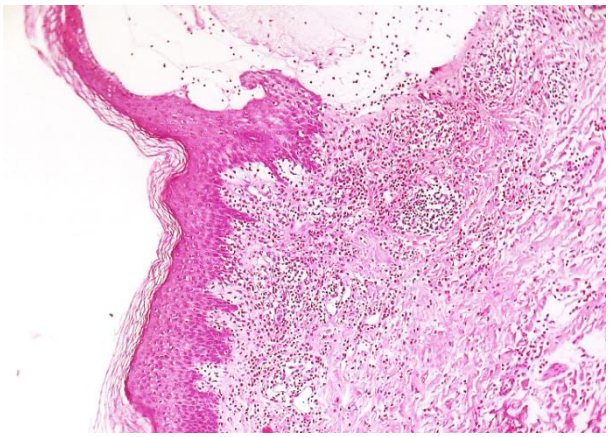


Image 7: Hematoxylin-eosin, 10X. Subepidermal blister with abundant eosinophils inside.

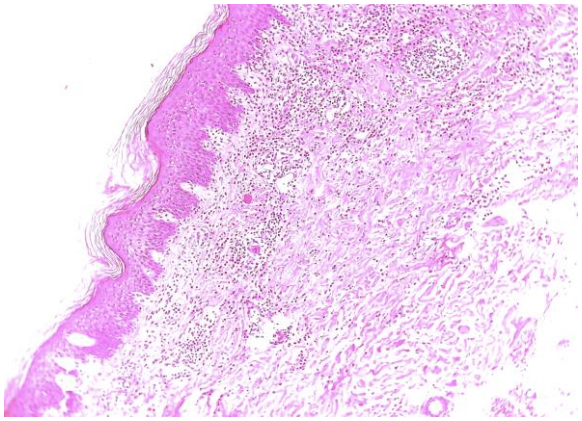


Image 8: Hematoxylin-eosin, 5X. Panoramic view of skin with extensive perivascular inflammatory infiltrate in the dermis, predominantly eosinophils.

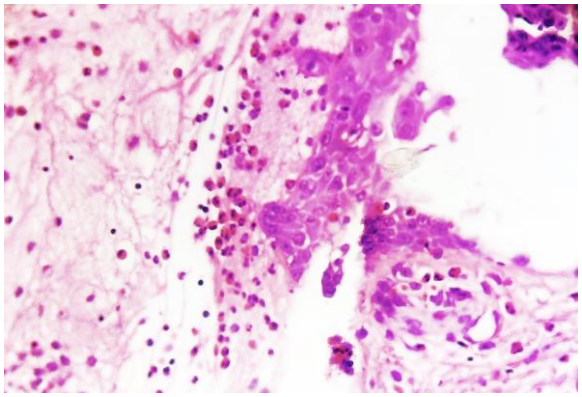
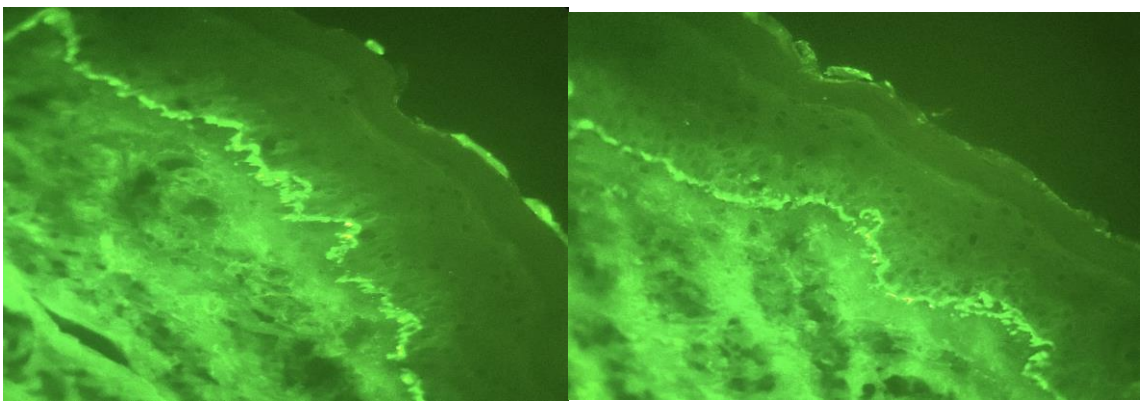


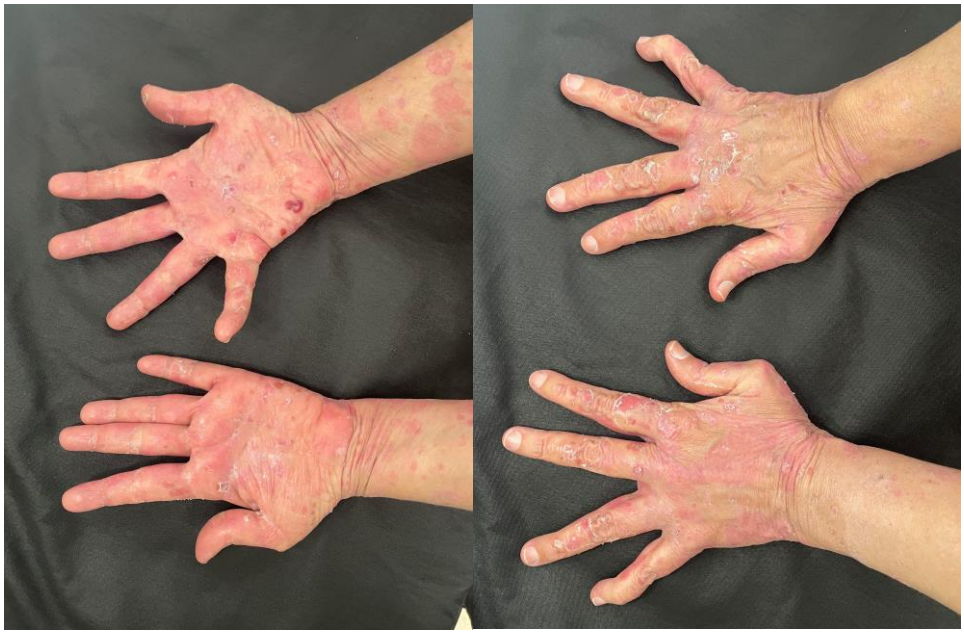
Image 9: Hematoxylin-eosin. Content of the blister corresponding to inflammatory infiltrate with a predominance of eosinophils.



Images 10 - 11: Direct immunofluorescence showing linear deposits in the basement membrane for IgG.

Five and a half months after the onset of the symptoms, laboratory tests showed mild leukocytosis, normal hemoglobin and platelet levels, normal liver tests, and normal C3 and C4 complement levels. However, rheumatoid factor was elevated, and a urine culture was positive for multisensitive E. coli. Based on these results, antibiotic treatment with ciprofloxacin 400 mg every 12 hours for 7 days was initiated.

Six months after the onset of symptoms and following the resolution of the infectious process, rituximab treatment (first dose) was started. From that point, the patient had no new lesions, so the prednisone dose was gradually reduced to 30 mg daily. She was evaluated by the rheumatology service for her long-standing untreated rheumatoid arthritis, with radiographs of hands and knees and rheumatological markers requested (Images 12 and 13).



Images 12 and 13: Clinical manifestations of rheumatoid arthritis and bullous pemphigoid

Seven months after the onset of symptoms, the patient received the second dose of rituximab, showing significant clinical improvement, and the decision was made to continue follow-up every three months. As the corticosteroid dose was reduced, the patient began to develop mild new lesions, so the dose was slightly increased to 35 mg daily until lesion stability was achieved. The patient continued to show progressive improvement, with monthly reductions in steroid doses under dermatological and rheumatological supervision.

DISCUSSION

This clinical case illustrates the complexity of managing concurrent autoimmune diseases, such as bullous pemphigoid and rheumatoid arthritis, in a patient with a long-standing medical history. A crucial aspect in this case is autoimmune diathesis, a term that refers to the genetic or immunological predisposition of an individual to develop multiple autoimmune diseases either successively or simultaneously.

In this patient, the presence of chronic rheumatoid arthritis for 30 years could have facilitated the onset of bullous pemphigoid, a rare autoimmune disease primarily affecting the skin. This suggests an interrelationship between both autoimmune disorders, supporting the hypothesis that autoimmune diathesis plays a role in the development of a second autoimmune condition following a pre-existing one.

The coexistence of these two autoimmune diseases is not coincidental, as studies have shown that patients with one autoimmune disease are at a higher risk of developing others. This phenomenon can be explained by several factors, including immune regulation disruption, genetic predisposition, and the effects of immunosuppressive treatments, which, while effective, can alter the immune system balance and promote the development of new autoimmune diseases.

The management of patients with autoimmune diathesis must be meticulous and multidisciplinary, with a comprehensive approach that addresses both the complications of the primary disease and the risk of developing new autoimmune diseases. The association between rheumatoid arthritis (RA) and bullous pemphigoid (BP) has been documented in various studies, suggesting a potential immunopathogenic relationship between both autoimmune diseases. Regarding RA, it is a chronic inflammatory disease characterized by immune system activation against the synovial membrane, while BP is an autoimmune blistering disorder mediated by autoantibodies directed against components of the epidermal basement membrane, raising questions about common immunological mechanisms that could predispose RA patients to develop BP.

Previous studies have documented cases of BP in patients with long-standing RA, suggesting that prolonged immune dysfunction could predispose to the development of secondary autoimmune diseases, as reported in a patient with 25 years of RA who developed BP, emphasizing the importance of proper clinical surveillance in these patients(15), in the case of Giannini and collaborators, they reported a patient with RA who developed BP without a clear trigger, reinforcing the hypothesis of a shared autoimmune predisposition(16). On the other hand, the association between RA and pemphigoid foliaceus (another autoimmune blistering disease) has also been reported, along with the occurrence of RA and bullous pemphigoid, as well as linear IgA disease, suggesting a broader autoimmune diathesis(17). Another relevant hypothesis in this association is the possible role of immunomodulatory therapies in triggering BP, as discussed in the Turkish Journal of Rheumatology, where the development of BP in a patient with RA after using anti-TNF-α agents was reported, suggesting that certain biological therapies could induce the appearance of secondary autoimmune diseases in predisposed patients, highlighting the complex interaction between immunomodulatory treatments and the development of aberrant autoimmune responses(18).

From a therapeutic point of view, the administration of rituximab, an anti-CD20 monoclonal antibody, has shown efficacy in treating refractory BP, particularly in patients with comorbid autoimmune diseases. Studies like those by Peterson and Chan have evaluated the effectiveness of rituximab in autoimmune blistering diseases, documenting a favorable clinical response and an acceptable safety profile(19). Similarly, a recent review published in *Advancements in Bullous Pemphigoid Treatment* highlighted the use of biological therapies, including rituximab, as a viable alternative in cases of BP resistant to glucocorticoids and other immunosuppressants(20).

In our case, due to the persistence of lesions, rituximab administration was decided, resulting in progressive clinical improvement. This discusses the role of biological agents, including anti-CD20 therapies, in managing autoimmune blistering diseases, exploring their potential to offer greater efficacy and fewer adverse effects compared to conventional immunosuppressors, as reported by Bishnoi and collaborators(21).

CONCLUSION

This case illustrates the complex interaction between autoimmune diseases, highlighting the co-occurrence of rheumatoid arthritis and bullous pemphigoid, a rare but documented association in the literature, as the patient's clinical evolution demonstrated the diagnostic challenge that BP represents, initially confused with other skin conditions, delaying specific treatment.

The development of BP in patients with RA may be due to multiple factors, including genetic predisposition, abnormal activation of the immune system, and adverse effects of immunomodulatory treatments. The available evidence suggests that both RA and BP may share pathophysiological mechanisms related to dysregulation of humoral and cellular immunity, which may predispose patients to develop multiple autoimmune diseases simultaneously. Regarding treatment with glucocorticoids and immunosuppressive agents like azathioprine, partial control of the disease was achieved, but the introduction of rituximab was key to the patient's clinical improvement, aligning with the literature supporting its efficacy in refractory autoimmune blistering diseases. However, the use of immunosuppressive therapies must be closely monitored due to the risk of opportunistic infections and other complications.

This case highlights the importance of a multidisciplinary approach in managing complex autoimmune diseases, involving dermatology, rheumatology, and immunology to optimize diagnosis and therapy. It also emphasizes the need for greater awareness regarding the association between RA and BP, promoting clinical vigilance in patients with systemic autoimmune diseases for timely identification and treatment.

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