In conclusion, round excision may represent a feasible diagnostic alternative for selected melanocytic lesions, particularly in anatomically sensitive areas (*e.g.*, the face and acral sites), where preservation of uninvolved tissue is especially desirable. However, its potential advantages over conventional fusiform techniques require validation in comparative clinical studies before it can be considered for routine use.

The authors confirm that this article does not report any studies involving human participants conducted by the authors. The authors confirm that this article does not report any studies involving embryos, gametes, and human embryonic stem cells conducted by the authors. The authors confirm that this article does not report any studies involving animals conducted by the authors.

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Bullous pemphigoid developing 25 years after pemphigus vulgaris: a rare case of possible epitope spreading

We report the case of a 69-year-old man who developed bullous pemphigoid (BP) nearly 25 years after a diagnosis of pemphigus vulgaris (PV). The patient presented to our attention in March 2025 with pruritic, erythematous-urticarial lesions forming figurate plaques on the limbs, along with tense vesiculobullous lesions on the soles, dorsal hands and wrists (Figure 1A). The oral mucosa was spared. Written informed consent was obtained from the patient. All procedures performed in this study involving human participants received ethical approval from the competent authorities, as described in the appropriate section of the manuscript, and have been conducted in accordance with the 1964 Helsinki Declaration and its later amendments. The authors confirm that this article does not report any studies involving embryos, gametes and human embryonic stem cells conducted by the authors. The authors confirm that this article does not report any studies involving animals conducted by the authors.

A skin biopsy showed a subepidermal blister with spongiosis, neutrophilic exocytosis and a dermal infiltrate rich in eosinophils (Figure 1B). Direct immunofluorescence revealed strong linear IgG and C3 deposits along the dermoepidermal junction, consistent with an autoimmune subepidermal blistering disorder (Figure 1C). IgA, IgM, and fibrinogen were negative. Serology was positive for anti-BP180 antibodies (117.31 U/mL; cut-off >9) and anti-desmoglein (DSG) 3 antibodies (67.64 U/mL; cut-off <7) whereas anti BP-230 and anti DSG1 antibodies were absent. The clinical, serological, histological, and immunopathological features confirmed the diagnosis of BP. His medical history included a diagnosis of PV in 1999 confirmed by the presence of anti-IgG inter-keratinocyte staining on direct immunofluorescence and the presence of high titer serum anti-DSG3 antibodies, managed only with azathioprine and prednisone until approximately 2017. No additional systemic immunosuppressive agents were used during this period. No active disease or treatment was recorded since June 2016. Serology performed in June 2017 revealed negative anti-DSG1 antibodies (3.88 U/mL; cut-off <14) but elevated anti-DSG3 antibodies (86.6 U/mL; cut-off <7). Anti-BP180 antibodies were absent at that time. Apart from the dermatological condition, the patient was in good general health and was not receiving any long-term pharmacologic treatment.

Although rare, the transition from PV to BP has been reported and is increasingly recognized as part of the spectrum of autoimmune blistering diseases. Goto *et al.* described the development of BP during long-term PV remission, suggesting latent reactivity against basement membrane antigens.[1] Similarly, Recke *et al.* observed a shift from pemphigus foliaceus to BP.[2] Together, these cases highlight epitope spreading (ES) as a key mechanism driving changes in clinical and serological profiles.[1, 2] In addition to sequential transformations, several reports have described the simul-

taneous occurrence of PV and BP. Cassano *et al.* presented a patient with circulating anti-DSG3 and anti-BP180 antibodies and overlapping clinical and histopathological features.[3] In such instance, the simultaneous presence of intraepidermal and subepidermal blistering, along with dual seropositivity, suggested the coexistence of BP and pemphigus. Sami and Ahmed, in a review of 30 patients, emphasized that the dual diagnosis of pemphigus and pemphigoid is not random, but rather indicative of a broader dysregulation allowing autoantibody generation against both desmosomal and hemidesmosomal antigens, a phenomenon defined as ES.[4]

ES refers to the progressive diversification of an autoimmune response from an initial dominant epitope to additional epitopes on the same antigen (intramolecular ES) or on different antigens (intermolecular ES) over time.[5] This phenomenon is a hallmark of several autoimmune diseases and reflects the dynamic and expanding nature of autoreactivity.[5] The immune system's response is initially focused on an immunodominant epitope, but factors such as tissue damage, chronic inflammation, and antigen release contribute to exposing previously hidden ("cryptic") epitopes. These can then be taken up by antigen-presenting cells and processed for presentation to T cells, which in turn activate B cells with new specificities.[5] In autoimmune blistering diseases such as PV and BP, ES has been implicated in shifts in clinical phenotype and changes in serological profiles.[2, 5]

Our case provides additional support for the possibility of ES among autoimmune blistering diseases. It highlights the importance of continued vigilance in the long-term follow-up of patients with a history of PV, especially when new or atypical skin lesions appear after a prolonged remission. This case also underscores the need to reconsider the diagnosis in patients with a prior autoimmune blistering disorder who develop new cutaneous findings. Notably, the exceptionally long interval between the initial PV diagnosis and the onset of bullous pemphigoid makes this case particularly distinctive.

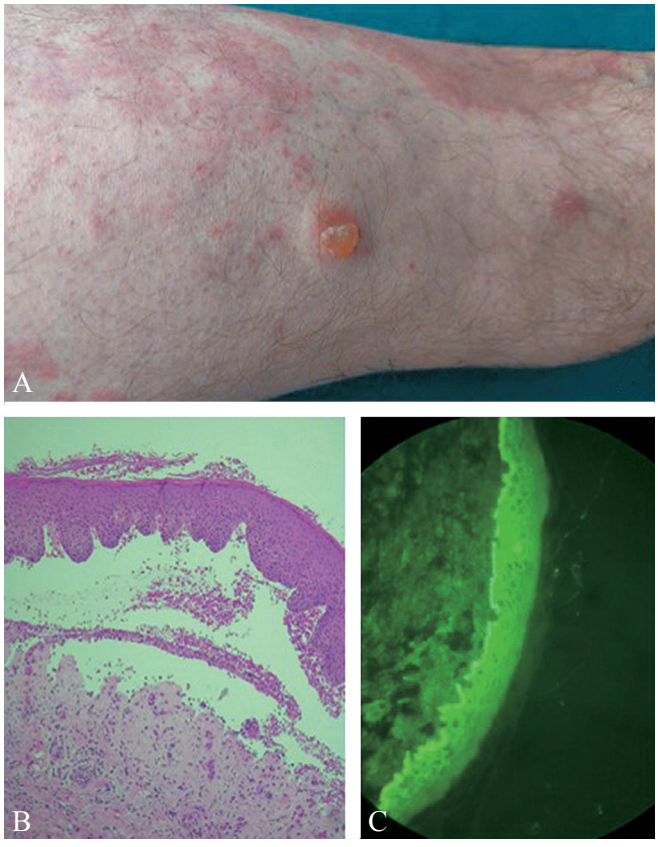


Figure 1.—A) Erythematous urticarial plaques located on the right lower limb; B) subepidermal blister with spongiosis, neutrophilic exocytosis, and a dermal infiltrate rich in eosinophils (Hematoxylin-eosin, 200x); C) direct immunofluorescence revealing strong linear deposition of C3 along the dermoepidermal junction (200x).

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Authors' contributions
All authors read and approved the final version of the manuscript.

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Informed consent was obtained from the patient prior to their inclusion in the study, as described in the appropriate section of the manuscript.

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Necrotizing leukocytoclastic vasculitis induced by alpelisib

Alpelisib is a selective oral inhibitor of the phosphatidylinositol-3-kinase alpha (PI3Kα) isoform. It has been approved for the treatment of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer that harbors a PIK3CA mutation. PI3K/AKT/mTOR is a pathway that plays a critical role in regulating cell proliferation, growth and survival and alpelisib is highly effective in cases of tumors with oncogenic PI3K pathway activation. In particular, the inhibition of isoform-specific PI3K pathways has the potential for therapeutic efficacy with improved toxicity profiles compared with non-isoform-selective agents.[1] The most frequent adverse events observed are hyperglycemia, gastrointestinal toxic effects and skin rash. Cutaneous toxicity, manifesting as a delayed exanthem, has been documented in up to 50% of patients.[1] While rare, severe hypersensitivity reactions such as DRESS syndrome have been described.[2] Here we present the first case of necrotizing leukocytoclastic vasculitis as a cutaneous adverse event associated with this targeted agent.

A 58-year-old woman with left-sided invasive ductal breast carcinoma (hormone receptor-positive and HER2-negative) presented with a three-month history of a painful ulcer on her left lower leg. She had previously undergone surgical resection, adjuvant radiotherapy and sequential hormone therapies as treatment for her primary breast cancer. At the time of presentation, she was receiving alpelisib as monotherapy for approximately one year for bone metastatic relapse, with no new medications introduced since the initiation of targeted therapy with alpelisib.

On physical examination, the patient presented with a painful ulcer measuring approximately 2 cm in diameter, on the medial aspect of the left lower leg. The ulcer was characterized by a fibrinous base partially covered with yellowish slough and an undermined erythematous-to-violaceous border. Several smaller ulcerative satellite lesions surmounted by hemorrhagic crusts were noted in the surrounding indurated and sclerotic skin (Figure 1A). A comprehensive workup, including autoimmune screening and Doppler ultrasound, ruled out infectious, autoimmune or vascular etiologies.

Histopathologic examination of punch biopsy revealed fibrinoid necrosis of vessel walls, a dense perivascular neutrophilic infiltration with prominent leukocytoclasia and erythrocyte extravasation. The dermis contained hemosiderin deposits and scattered eosinophils, while the overlying epidermis exhibited transepidermal necrosis (Figure 1B).

Progressive ulcer healing was observed after alpelisib discontinuation, initiation of oral prednisone at a dose of 1 mg/kg/day with gradual tapering and implementation of local wound care measures, which resulted in complete re-epithelialization within a few weeks.

Leukocytoclastic vasculitis is a reactive, immune complex-mediated, and typically transient small-vessel vasculitis (SVV).[3] It refers to a histopathological pattern of SVV characterized by neutrophilic infiltration with nuclear debris (leukocytoclasia), fibrinoid necrosis of vessel walls and signs of vascular damage such as erythrocyte extravasation. Tissue eosinophilia, when present, may further support a drug-related etiology.[4] A wide range of medications have been implicated in drug-induced vasculitis including antibiotics, non-steroidal anti-inflammatory drugs and antineoplastic agents.[4] In breast cancer therapy, cases of cutaneous vasculitis have been reported in association with aromatase inhibitors such as letrozole, as well as with conventional chemotherapeutic agents such as docetaxel and cyclophosphamide.[5] Although alpelisib is recognized for its cutaneous toxicity, no cases of vasculitis have been previously documented. The exact pathogenic mechanism remains unclear; however, vascular injury may result from an immune complex-mediated hypersensitivity reaction (type III),[3] possibly facilitated by PI3Kα pathway inhibition and its role in immune regulation.

This case highlights that necrotizing leukocytoclastic vasculitis represents a rare, yet possible, cutaneous adverse reaction to alpelisib. The chronological progression of the clinical presentation, the histopathological features of the ulcer and its resolution following drug discontinuation support the imputability of alpelisib. According to the Naranjo Adverse Drug Reaction Probability Scale, these findings are consistent with a probable causal relationship between alpelisib and the development of necrotizing leukocytoclastic vasculitis. Early recognition and appropriate management are essential to prevent misdiagnosis, reduce complications and avoid compromising oncologic therapy.

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