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Bullous Pemphigoid with secondary Acquired Reactive Perforating Collagenosis: a challenging clinical case report

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Authors' contributions: MC, AV, LQ, AC, EBM, CA, and VRdC were all directly involved in the management of the patient; MC, DM, AV, EBM, and VRdC drafted the manuscript and revised the literature; DM and VM conducted the histopathological analysis and collected the histopathological pictures; GD provided immunoserological analysis; LQ, AC, CA, and GD revised the main text of the

manuscript. All authors contributed to the article, approved the submitted version, read and approved the final version of the article and agreed to be held accountable for all aspects of the work.

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Abstract

Bullous Pemphigoid (BP) is a common autoimmune blistering disorder with unknown aetiology. During the last decades, its association with various common comorbidities, including cardiovascular, metabolic, neuropsychiatric, and neoplastic disorders, has been established. However, in recent years an increasing number of BP cases have also been reported in association with rarer diseases, including Acquired Reactive Perforating Collagenosis (ARPC). Patients with coexisting BP and ARPC have been reported to share common clinical features including metabolic comorbidities *e.g.*, Diabetes Mellitus (DM). As the evolution from ARPC cutaneous involvement to classic BP lesions has been more frequently described, it has been suggested that it may represent a new clinical variant of BP with a specific pathogenetic background. Here is reported a challenging case in which a typical onset of BP was later followed by the eruption of atypical ARPC lesions in a patient with multiple non-compensated metabolic and cardiovascular comorbidities.

Introduction

Acquired Reactive Perforating Collagenosis (ARPC) is part of the Acquired Perforating Dermatoses (APDs), a rare group of dermopathies characterized by trans-epidermal elimination of skin materials. ARPC usually develops in adulthood with umbilicated hyperkeratotic papules or nodules that are histologically marked by the extrusion of dermal collagen fibres. It is frequently associated with systemic diseases.^{1,2} In fact, diabetes and chronic kidney disease are known to be the most common comorbidities in patients with ARPC³ and are also frequently observed in patients with Bullous Pemphigoid (BP).⁴ Recently, the increasing number of patients with coexisting BP and ARPC observed may suggest the existence of a common pathogenetic background linking these conditions. Herein is presented a challenging case of ARPC associated with Bullous Pemphigoid in a patient affected by severe heart failure secondary to myocardial infarction, chronic kidney disease, and diabetes.

Case Report

A 53-year-old woman came to our dermatology clinic in December 2021 with a 2-month history of multiple painful erythematous-bullous lesions involving her trunk, thighs, and scalp. Her mucosae were overall spared except for one haemorrhagic blister in her oral cavity. Some of these were characterized by a central crust (Figure 1A, 1B). Her clinical presentation raised the suspicion of Bullous Pemphigoid (BP). The diagnosis was confirmed by histological evaluation, reporting subepidermal clefts with sparse eosinophilic infiltrate in the superficial dermis, in addition to direct immunofluorescence evidence of linear deposits of IgG and C3 along the basal membrane and indirect immunofluorescence on salt-split skin showing circulating Immunoglobulin G (IgG) autoantibodies binding the epidermal side of the basal membrane. Further investigations included Enzyme-Linked Immunosorbent Assay (ELISA), which tested positive for anti-BP-180 (NC16A region) IgG autoantibodies with a serological titre of 80,3 UI/mL, and was negative for anti-BP-230 IgG autoantibodies. These results were ultimately confirmed by Western Blotting analysis (WB) showing positivity for NC16A, the

immunodominant region of BP180. Her previous medical history included ovarian cancer, diagnosed in 2015 but in clinical remission at the time of our first medical contact with the patient and severe heart failure secondary to a myocardial infarction occurred in 2018. In the following years, she developed chronic kidney disease in the setting of a cardio-renal syndrome and Diabetes Mellitus (DM) which was under treatment with insulin and empaglifozin. The full list of her medications also included allopurinol, atorvastatin, bisoprolol, aspirin, amiodarone, canrenone, furosemide, paracetamol and pantoprazole. Because of her dermatologic condition, the patient was started with clobetasol 0.05% ointment and 0.5 mg/kg/day of prednisone.⁵ After one month of treatment, a non-typical evolution of pre-existing lesions was observed, along with the eruption of new, painful ones on her lower back and buttocks, some of which showed a central, depressed, porcelain-white atrophic area and an erythematous telangiectatic rim. Meanwhile, she was also experiencing persistent haemodynamic instability and severe alteration of glycaemic levels, forcing the interruption of oral steroid therapy. Because the new lesions' appearance was very suggestive of Malignant Atrophic Papulosis (MAP) a new skin biopsy was performed to exclude this new diagnostic hypothesis and a blood sample was collected to test the presence of Antiphospholipid (aPL) antibodies.⁶ However, no aPLs were detectable and the skin biopsy showed no evidence of frank micro-thrombotic vascular occlusion, but only a sparse neutrophilic infiltrate with focal endothelial swelling and fibrinoid necrosis of the dermal capillaries, which were interpreted as non-specific findings of reactive vascular suffering. During the following visits, the patient experienced an overall clinical deterioration with severely impaired cardiac and renal function (BNP 2305 pg/mL, creatinine 1,46 mg/dL) and the concomitant eruption of new lesions spreading to her trunk and tights, some of which appeared as umbilicated papules with central necrotic plug (Figure 1C). In consideration of the new cutaneous manifestations and her systemic comorbidities, the clinical suspicion of ARCP was raised. Our clinical hypothesis was further strengthened by dermoscopy as some of the new lesions showed the typical features of ARPC lesions, *i.e.* a central yellow-brown structureless area, a more peripheral white rim at the border of the central

crust, an outer pink inflammatory circle with short-looped vessels centrally and dotted vessels peripherally (Figure 2A, 2B).⁷ Histopathological examination confirmed the presence of a cup-shaped crusted ulcerative lesion on top of slightly verticalized bundles of degenerated collagen fibres, which reflected an initial phase of their trans-epidermal elimination (Figure 3). During the following weeks, she experienced a severe relapse of her cutaneous involvement. Most of her lower body was diffusely erythrodermic with multiple tense bullae affecting her limbs and trunk (Figure 1D, 1E). As her physical mobility was also greatly impaired by that time, she also showed more widespread and necrotic ulcerations exclusively on her buttocks. Even though these lesions showed clinical similarities with cases reported in the literature as ecthyma gangrenosum-like BP, there were no clinical nor biochemistry signs of infection, thus no wound swab culture was performed.⁸ Instead, a steroid pulse therapy with intravenous infusion of methylprednisolone was set up immediately resulting in partial resolution of her cutaneous lesions. Despite the cutaneous improvement, the patient's overall clinical condition kept on worsening until her exitus, which occurred after ten months of close dermatologic follow-up.

Discussion

The association between autoimmune blistering diseases and perforating cutaneous disorders has been increasingly documented since 2016.⁹⁻¹³

In four of the reported cases, the eruption of BP lesions has been linked to the use of Dipeptidyl Peptidase-4 Inhibitors (DPP4i) as part of the therapy for DM in ARPC.^{10,11,13} Similarly to other cases of drug-induced BP, this subcategory of patients showed a prevalent non-inflammatory clinical phenotype of BP lesions and autoantibodies targeting the non-NC16A domain of BP180,^{14,15} leading Maki et al to suggest that DPPi4 rather than ARPC may represent the main trigger factor for the onset of BP lesions in this specific setting.¹¹

Concerning the remaining cases of non-drug-induced BP in association with ARPC Tani *et al.* proposed that BMZ injury occurring in patients with ARPC could be causative of BP lesions by epitope spreading, as already established in the cases of BP succeeding other dermatopathies (*e.g.* lichen planus, psoriasis *etc.*).⁹ This hypothesis is strengthened by the evidence that in most of the reported cases, the clinical evolution was characterized by the onset of BP lesions in patients already suffering from ARPC.

However, our patient's history differed from the aforementioned cases since the ARPC lesions succeeded in the clinical onset of BP and were not associated with DPPi4 intake or with drug-induced BP features. For this reason, other pathogenetic hypotheses need to be addressed in order to explain the association of ARPC with BP. To date, some authors have suggested that depositions of IgG and C3 in the setting of BP could be a facilitating factor for the trans-epidermal elimination process occurring in the ARPC⁹ while a direct pathogenetic role of anti-BP180 autoantibodies in the development of ARPC lesions has been excluded.¹⁰

We propose that the overmentioned pathogenetic mechanism binding the two conditions could coexist in our patient with other previously proposed pathogenetic hypothesis that are mainly related to the most common clinical features and comorbidities occurring in patients with ARPC. Among these are counted superficial trauma induced by scratching as well as dermal microdeposits of calcium secondary to chronic kidney disease. These conditions are supposed to contribute to the degeneration of collagen fibres, while endothelial dysfunction in the setting of hypertension or chronic venous insufficiency could exacerbate the disease by inducing a local hypoxic state.^{16,17} Moreover, DM with long-course hyperglycaemia and increasing Advanced Glycation End-Products (AGEs) levels are thought to contribute to the trans-epidermal elimination of collagen fibres in addition to vascular suffering.¹⁸ Therefore, the overall clinical background of our patient, including cardiovascular and metabolic disorders, commonly associated with both PB and ARPC, may have played a major role in the evolution of her skin condition. It may also explain the atypical features of the ARPC cutaneous lesions,

at first resembling those of MAP, and the relapse of her cutaneous condition after a course of systemic steroid therapy at first medical contact. The latter in fact may have exacerbated the already ongoing chronic glycation process of the cutaneous dermal components, thus making ARPC evident.

Conclusions

Even though almost all cases reported so far have shown a more frequent onset of BP lesions in patients already affected by ARPC, the evolution from BP to ARPC is nevertheless possible. Thus, we suggest that both diseases and their common comorbidities might exacerbate the pathological conditions of one another. Moreover, as already proposed by Schauer *et al.*, the increasingly described association between BP and ARPC may no longer be considered coincidental, but rather as a new clinical variant of BP with specific pathogenetic background.¹² Further research is needed for a better understanding of the pathogenetic mechanisms involved and to improve the clinical management of such complicated patients.

References

1. Mehregan A, Schwartz OD, Livingood CS. Reactive Perforating Collagenosis. Arch Dermatol. 1967;96:277-82.
2. Rapini R, Herbert AA, Drucker CR. Acquired perforating dermatosis. Evidence for combined transepidermal elimination of both collagen and elastic fibers. Arch Dermatol. 1989;125:1074-8.
3. Karpouzis A, Giatromanolaki A, Sivridis E, Kouskoukis C. Acquired reactive perforating collagenosis: current status. J Dermatol. 2010;37:585-92.
4. Patel S, Ahsanuddin S, Cadwell JB, Lambert WC. The impact of diabetes mellitus on medical complication and mortality rates among inpatients with bullous pemphigoid. Ir J Med Sci. 2022;191:1669-75.
5. Borradori L, Van Beek N, Feliciani C, et al. Updated S2 K guidelines for the management of bullous pemphigoid initiated by the European Academy of Dermatology and Venereology (EADV). J Eur Acad Dermatol Venereol. 2022;36:1689-704.
6. Theodoridis A, Makrantonaki E, Zouboulis C. Malignant atrophic papulosis (Köhlmeier-Degos disease) - A review. Orphanet J Rare Dis. 2013;8:10.
7. Ormerod E, Atwan A, Intzedy L, Stone N. Dermoscopy features of acquired reactive perforating collagenosis: a case series. Dermatol Pract Concept. 2018;8:303-5.
8. Geiss Steiner J, Trüeb RM, Kerl K, et al. Ecthyma-gangrenosum-like bullous pemphigoid. Dermatol. 2010;221:142-8.
9. Tani S, Ishii N, Hashimoto T, Tsujioka K. Bullous pemphigoid arising in a patient with acquired perforating dermatosis. Clin Exp Dermatol. 2017;42:406-9.
10. Nomura H, Mukai M, Niimi Y, et al. Coexistence of acquired perforating dermatosis and bullous pemphigoid: three cases. Eur J Dermatol. 2017;27:192-3.

11. Maki N, Nishie W, Takazawa M, et al. Dipeptidyl peptidase-4 inhibitor-associated bullous pemphigoid in a patient with acquired reactive perforating collagenosis. *J Dermatol.* 2018;45:600-2.
12. Schauer F, Kern JS, Virtic O, et al. A new clinical variant of acquired reactive perforating dermatosis-like bullous pemphigoid. *Br J Dermatol.* 2019;180:231-2.
13. Gambichler T, Espey B, Doerler M, Stranzenbach R. Dipeptidyl peptidase-4 inhibitor induced bullous pemphigoid complicated by acquired reactive perforating dermatosis. *Actas Dermosifiliogr.* 2022;113:914-5.
14. Salemme A, Fania L, Scarabello A, et al. Gliptin-associated bullous pemphigoid shows peculiar features of anti-BP180 and -BP230 humoral response: Results of a multicenter study. *J Am Acad Dermatol.* 2022;87:56-63.
15. Schmidt E, Spindler V, Eming R, et al. Meeting report of the pathogenesis of pemphigus and pemphigoid meeting in Munich, September 2016. *J Invest Dermatol.* 2017;137:1199-203.
16. García-Malinis AJ, Del Valle Sánchez E, Sánchez-Salas MP, et al. Acquired perforating dermatosis: clinicopathological study of 31 cases, emphasizing pathogenesis and treatment. *J Eur Acad Dermatol Venereol.* 2017;31:1757-63.
17. Kim S, Kim M, Lee JH, et al. A clinicopathologic study of thirty cases of acquired perforating dermatosis in Korea. *Ann Dermatol.* 2014;26:162.
18. Bellinato F, Maurelli M, Gisondi P, Girolomoni G. Acquired perforating dermatoses show increased levels of cutaneous advanced glycation end-products. *Clin Exp Dermatol.* 2021;47:80-5.



Figure 1. Clinical pictures of the patient at first medical contact (**A, B**), exhibiting lesions consistent with bullous pemphigoid. After a cycle of therapy with steroids the lesions of the buttocks appeared to have a non-typical evolution (**C**). During relapse, the patient experienced a worsening of the lesions of the buttocks along with recrudescence of the manifestations attributable to Bullous Pemphigoid, showing a sub-erythrodermic involvement with multiple tense bullae (arrows) affecting the limbs and trunk (**D, E**).

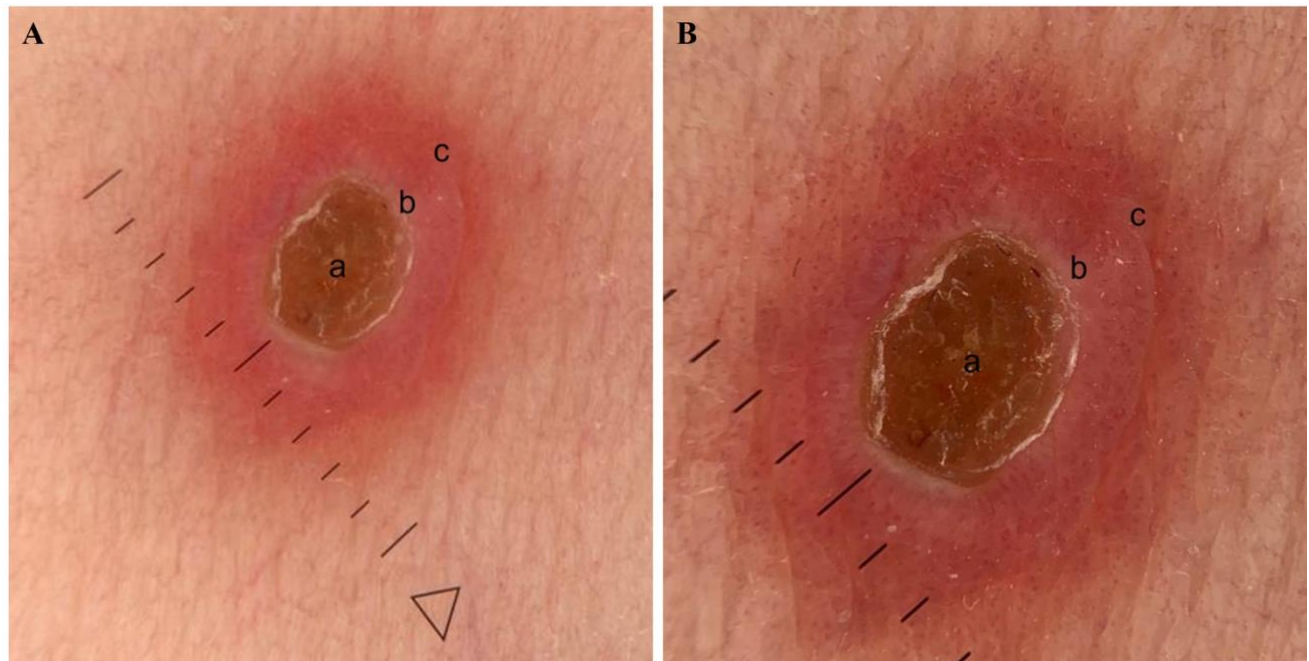


Figure 2. Dermoscopic images at different magnifications (**A,B**) of a cutaneous lesion in our patient, where typical features of Acquired Reactive Perforating Collagenosis can be noted: i) a central yellow-brown structureless area, ii) a more peripheral white rim at the border of the central crust, iii) an outer pink inflammatory circle with short-looped vessels centrally and dotted vessels peripherally.

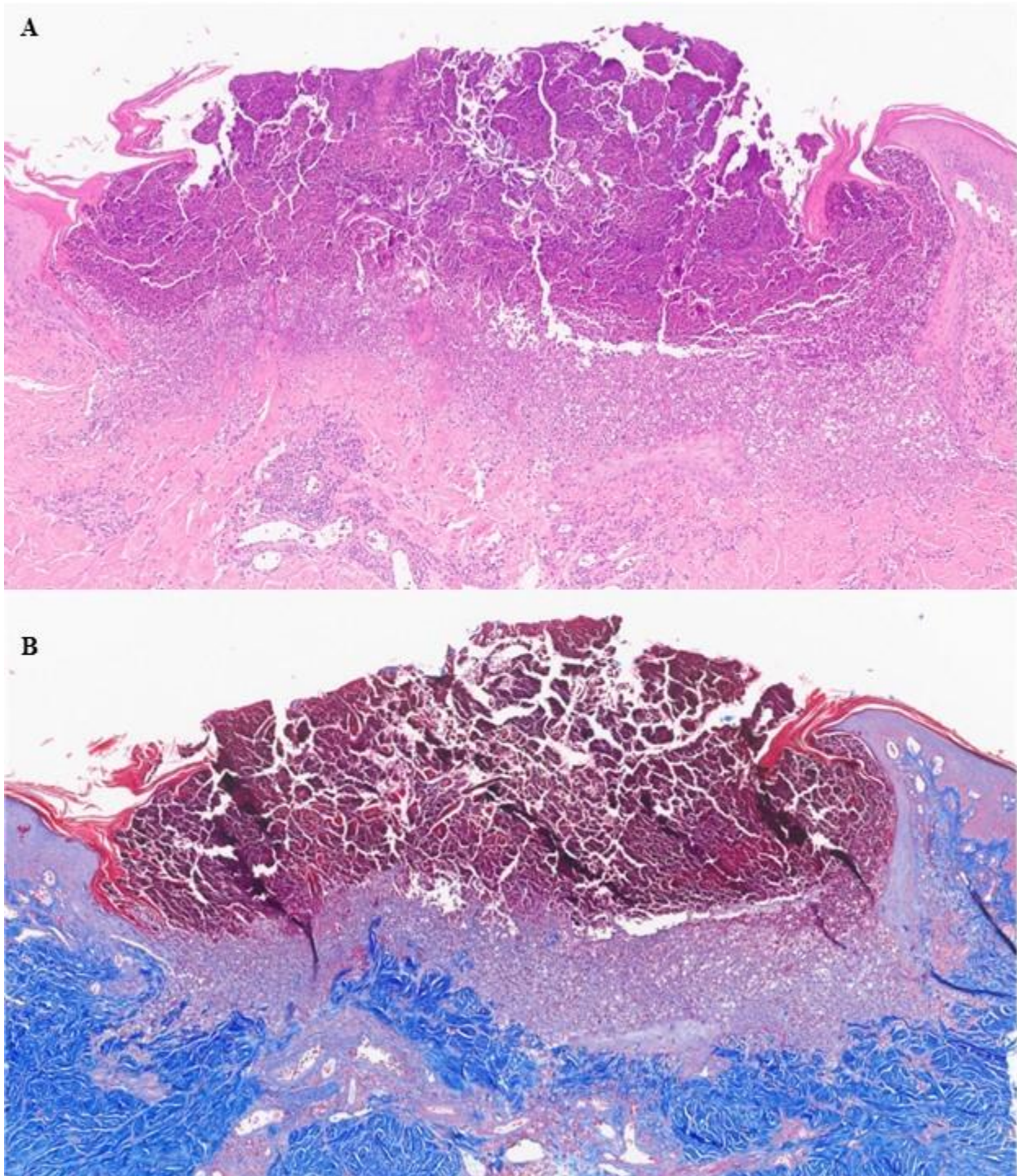


Figure 3. (A) Histopathological examination of a skin lesion on the buttocks showed epidermal ulceration with a central crusted plug containing keratin, cellular debris inflammatory cells (Haematoxylin & Eosin stain); (B) focal elimination of slightly verticalized collagen bundles through the dermis into the epidermis (Masson Trichomic stain).

