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CASE REPORT

Rheumatoid arthritis and Hailey-Hailey disease treated with methotrexate

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Abstract

We report a rare case of long-standing Hailey-Hailey disease in a Caucasian Portuguese 69-year-old woman, recently diagnosed with rheumatoid arthritis. The patient's skin lesions remained active and exudative despite topical and oral treatments with corticosteroids, tetracyclines, antifungals, and oral treatment with azathioprine. After introduction of methotrexate for rheumatoid arthritis treatment, the skin lesions regressed, with significant impact on the patient's quality of life. This case report supports the clinical evidence of methotrexate's potential role in Hailey-Hailey disease treatment.

KEYWORDS
Hailey-Hailey disease, methotrexate, rheumatoid arthritis

1 | INTRODUCTION

Hailey-Hailey disease (HHD), or familial benign chronic pemphigus, is an autosomal dominant genetic disorder, caused by a mutation in the ATP2 C1 gene that encodes a Ca^{2+} ATPase protein, leading to impaired keratinocyte adhesion. This results in secondary inflammation, recurrent blisters, erosions, and vegetating lesions in areas prone to heat and friction. The most affected skin areas are the axillae, inframammary and genito-crural folds, neck, and lower back. Bacterial colonization and superinfections are common.[1,2] Despite advancements in knowledge of the molecular basis of HHD, management remains difficult because of the absence of specific treatments.[1,2]

Rheumatoid arthritis (RA) consists in persistent synovitis and hyperplasia, autoantibody production, cartilage and bone destruction, and systemic inflammation and disorders, involving a complex interplay among genotype, environmental triggers, and chance. Diagnosis based on European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) criteria combines both clinical imaging and laboratory measures. Methotrexate is usually the first disease-modifying anti-rheumatic drug administered to people with RA. Remission or low disease activity is the aim for treatment of RA.[3,4]

2 | CASE REPORT

A 69-year-old woman presented with symmetrical polyarthralgia lasting for 3 months, with pain, tenderness, swelling, and morning stiffness lasting for 30 minutes or longer, affecting small joints (wrists, metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal joints of hands and feet) and articular deformities with involvement of metacarpophalangeal joints, wrists, and knees.[3,4]

Both the patient's father and older sister had a history of HHD. The patient's diagnosis dated from 1993, confirmed by skin biopsy performed in a Dermatology consult at Hospital Distrital de Santarém, where she maintained follow up. There was a long history of insufficient response to oral and topic corticotherapy, antibiotics, antifungals, and oral treatment with azathioprine. The

patient had complaints of joint pain and swelling in knees, metacarpophalangeal and proximal interphalangeal joints, with blood tests revealing leukocytosis, increased sedimentation rate, and C-reactive protein values.

The ultrasonography examination showed synovitis of both wrists and all metacarpophalangeal joints, blood tests revealed positive rheumatoid factor and cyclic citrullinated peptide antibodies, establishing the diagnosis by fulfilling the ACR/EULAR diagnostic criteria for RA, with disease activity scoring 3.56 (Moderate Severity of RA) on Disease Activity Score-28 (DAS28-CRP) for RA with C-reactive protein.[3,4] During physical examination, multiple skin lesions with exudative intertriginous papulovesicles and erythematous plaques with erosions and painful fissures were observed, affecting axillae, inframammary folds, and neck (Figure 1).

The patient began weekly 10 mg of methotrexate and folic acid, and daily 5 mg prednisolone, maintaining follow up for 12 months in the Rheumatology department. In subsequent consultations, following a progressive tapering of prednisolone dosage and increase in weekly methotrexate to a maximum of 20 mg/week, the patient presented RA remission with a DAS28-CRP score of 1.70 and progressive amelioration of skin lesions, giving place to hyperpigmented lichenified plaques, with improvement of erosions and fissures, and absence of exudation (Figure 2).

3 | DISCUSSION

The lack of evidence-based treatment makes the assessment of the efficacy and safety of treatment options more difficult.[1,2] Therapeutic recommendations are based on case reports, and the physician's personal experience, as there are no randomized clinical studies and therefore, no treatment guidelines.[2,5]

Various off-label treatments have been described with irregular and underperforming results. Topical corticosteroids, antibiotics, and calcineurin inhibitors are used as first-line therapy in most cases.[1,2,6] Systemic agents include antibiotics, retinoids, and naltrexone. Immunomodulators such as cyclosporine, methotrexate, thalidomide, and apremilast are used in the treatment of recalcitrant cases.[2,6–8] Interventional therapies include laser ablation, pulsed dye laser, radiofrequency surgery, photodynamic therapy, and treatment with botulinum toxin type A.[1,2,7]

In the literature there are a few case reports describing therapeutic success of HHD management using a weekly dosage of 7.5-15 mg methotrexate, with lesion improvement and evolution to post-inflammatory residual hyperpigmentation and atrophic scars in 2-3 month, with successful tapering and cessation, maintaining control of developing lesions with only topical preparation of corticosteroids and/or fucidic acid.[7,8]

Although the usage of methotrexate in HHD is reported in the literature, the coexistence of HHD and RA was never described. The absence of clear genotype-phenotype associations suggest that environmental or genetic factors may affect clinical presentation.[9] Mutations in the *ATP2C1* gene cause changes in calcium-dependent intracellular signals, resulting in loss of cell adhesion in the epidermis, leading to acantholysis. Literature suggests the loss of *ATP2C1* function results in increased production of reactive oxygen species, producing DNA damage and accelerating keratinocyte differentiation.[10] Keratinocyte production of inflammatory cytokines and DNA alteration, conjugated with superinfections, have been suggested as triggering factors for the release of inflammatory mediators in HHD. Therefore, the primary target of topical and systemic treatments is cutaneous inflammation.[2] At low doses, methotrexate has potent anti-inflammatory actions that appear to be mediated via pathways separate from folate antagonism. Methotrexate is used in multiple dermatoses owing to its anti-proliferative and anti-inflammatory properties by acting on various target cells of the immune system, having a high safety profile at the dose commonly administered in dermatology.[2,11,12]

Its therapeutic use in HHD has an evidence level of III. The main results are lesion healing and a long-lasting remission after discontinuation, although there are reports of treatment failure. Contradictory reports in the literature suggest the need for further studies.[1]

Key Messages: It is essential to inform the patient about the irregular response rates and recurrence rates of the disease, making it exceedingly difficult to manage with significant impact on quality of

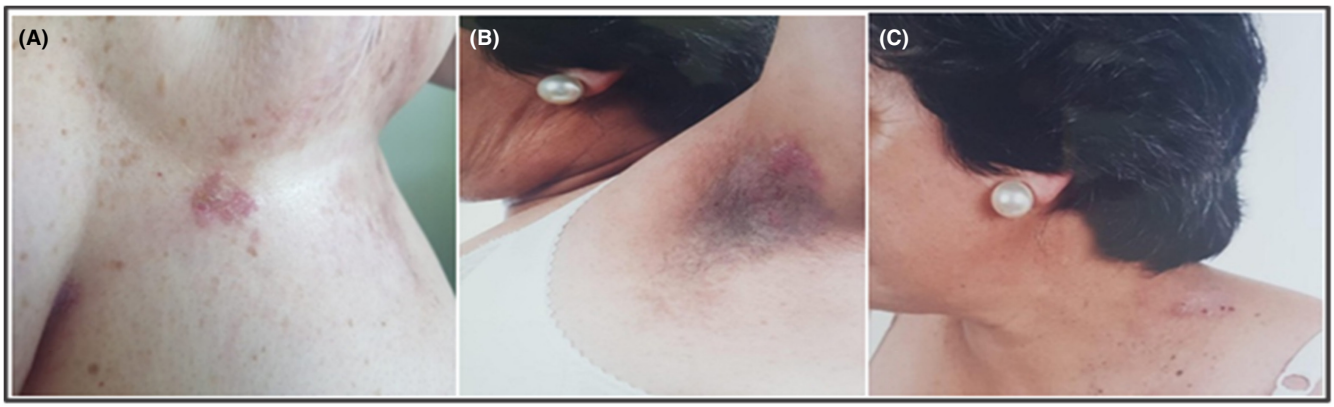

FIGURE 1 Inframammary (A), axillary (B), and neck (C) Hailey-Hailey disease skin lesions.

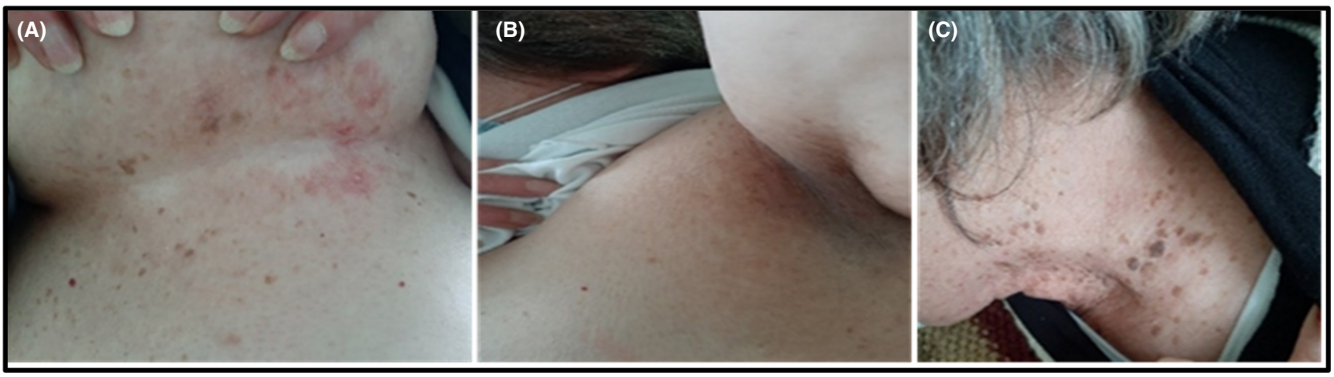

FIGURE 2 Inframammary (A), axillary (B), and neck skin (C) after methotrexate therapeutic regimen.

life.[5,11] This case report supports the clinical evidence of methotrexate as a possible therapeutic option for disease management.

CONFLICT OF INTEREST

The authors declare that they have no competing interest.

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