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Biologic therapy for acrodermatitis continua of Hallopeau: Successful treatment with secukinumab and review of the literature

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Abstract

Acrodermatitis continua of Hallopeau (ACH) is a rare pustular psoriasis variant refractory to many conventional treatments. We report the successful treatment with secukinumab of a patient with a long history of ACH with marked onychodystrophy with frank pustulosis on the nail bed and with accompanying arthritis. Blockade of the IL-17 receptor A has shown promise in the treatment of psoriatic erythroderma and generalized pustular psoriasis not responsive to conventional treatment. A rapid response was observed in our patient, in both skin lesions and arthritic symptoms, underlining the ability of secukinumab to improve symptoms beyond those of plaque psoriasis.

KEYWORDS
acrodermatitis continua of Hallopeau, psoriasis, psoriatic arthritis, secukinumab

1 | INTRODUCTION

Acrodermatitis continua of Hallopeau (ACH), a rare form of pustular psoriasis affecting the distal phalanges of hands and feet (Piraccini et al., 1994), is characterized by sequential crops of pustules that coalesce on the nail bed and nail matrix, forming lakes of pus, causing dystrophy of the nails, and even anonychia of the involved digits. The evolution of ACH is chronic with frequent relapses, and the outcome can be extremely serious and disabling, particularly when associated with psoriatic arthritis (PsA) (Jo et al., 2006). Acrodermatitis may be considered a unique disease entity, even if histological findings like hyperkeratosis, parakeratosis, and subcorneal collection of neutrophils is consistent with a localized form of pustular psoriasis (Jo et al., 2006).

2 | CASE REPORT

A 27-year-old female with no personal or known family history of psoriasis had recurrent episodes of redness, swelling, and purulent discharge on the fourth finger of the right hand with progressive degeneration of the nail. The patient monitored the evolution of the disease over a year before coming to our attention (Figure 1a,b). Despite negative findings on bacteriological/mycological examinations at another dermatological center, the patient was treated, first with local antibacterials and antifungals, then (in September 2016) with levofloxacin 500 mg daily for 7 days every-other-week for 3 months.

During the same period, the patient attended the emergency clinic for a change in bowel movement pattern with increased daily diarrheal feces alternating with normo-conformed evacuations. A lactulose/mannitol breath test did not reveal any abnormality; fecal calprotectin was in the normal range, as was mycological and bacteriological examination of feces. Colonoscopy, video examination, and celiac disease serology were negative. A lactose H_2 breath test revealed lactose intolerance.

Because of progressive worsening of the cutaneous clinical picture, a biopsy of the nail bed of the affected finger was conducted, leading to a histological diagnosis of ACH; therapy with acitretin was prescribed. The drug was interrupted because of an adverse allergic reaction after only a few days of treatment.

Marco Galluzzo and S. D'Adamio contributed equally to this study.

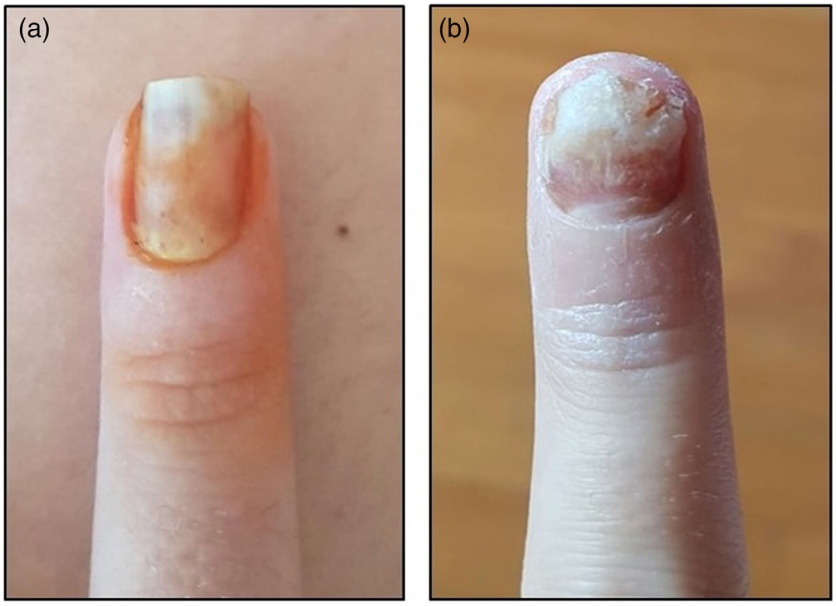

FIGURE 1 (a,b) Evolution of the disease during the first 2 months from the disease starting (images by the patient)

We first saw the patient in April 2017, showing marked onychodystrophy, with frank pustules present in the bed of the nail with purulent discharge in the area. The nail was subject to an incomplete detachment (Figure 2a). Other toes and fingers were normal. The patient reported the maximum score on a 10-point pain visual analog scale (PAIN VAS). Echographic examination before starting treatment showed moderate enthesitis with effusion at the level of the fourth finger extensor tendon-bone insertion. A remarkable nail dystrophy with disappearance of the anatomical space between cuticle and lunula was detected (Figure 2c).

Complete laboratory and instrumental tests, including chest X-ray, electrocardiogram, QuantiFeron TB-Gold, complete blood count, complete liver profile, creatinine, auto-antibodies (ANA, anti-dsDNA, ENA, LAC, anti-cardiolipin, anti-citrulline) showed a C-reactive protein (CRP) level of 1.8 mg/L, and erythrocyte sedimentation rate (ESR) was 30 mm/hr. No other abnormalities were noted.

In May 2017, secukinumab at a dose of 300 mg at Weeks 0/1/2/3/4 and then 300 mg every month was started.

The patient showed marked improvement in the nail lesions from 8 weeks, experiencing an important reduction of discomfort and pain after 40 weeks (Figure 2b). Her arthritis, monitored with a second

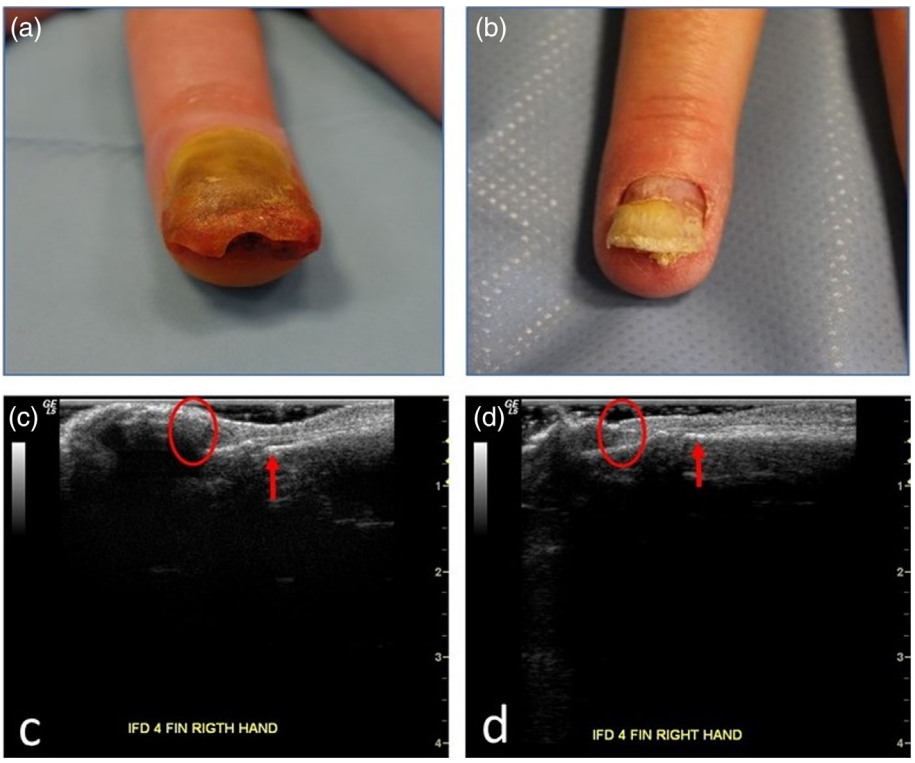

FIGURE 2 Nail involvement at baseline of secukinumab treatment showing marked onychodystrophy with frank pustules present in the bed of the nail associated with intermittent purulent discharge. At Week 40 of secukinumab treatment (b) there was marked improvement of the lesion, with absence of frank pustulation and a dramatic reduction of pain and discomfort. An echographic scan at baseline of secukinumab treatment (c) showed moderate enthesitis with effusion at the level of the fourth finger extensor tendon bone insertion and a disappearance of the anatomical space between cuticle and lunula. At Week 40 of secukinumab treatment (d), the echographic scan showed an absence of enthesitis, with a reduction of the size of the dystrophic nail and reappearance of the anatomical space between the cuticle and the nail lunula

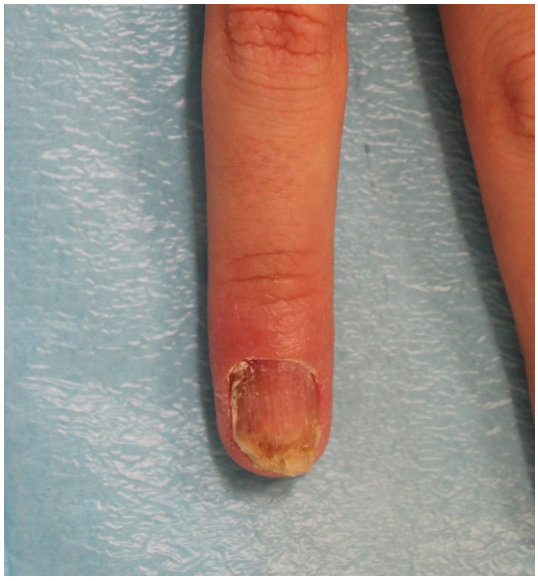

FIGURE 3 Complete resolution of nail lesions after 52 weeks of secukinumab treatment

echographic examination, showed absence of enthesitis, reduction of the size of the dystrophic nail and reappearance of the anatomical space between the cuticle and nail lunula (Figure 2d). ESR was 19 mm/hr, CRP was 2.31 mg/L, and PAIN VAS at Week 40 was 0.

After 52 weeks of secukinumab treatment, the patient's clinical picture had resolved and the nail lesions showed almost complete resolution (Figure 3).

3 | DISCUSSION

ACH is a challenging clinical entity with limited effective treatment options. Topical treatment is usually ineffective. As ACH is considered a variant of pustular psoriasis (Navarini et al., 2017), because of similar histopathological features and the incidence of progression of ACH in generalized pustular psoriasis (GPP), methotrexate, retinoids, and cyclosporine are the preferred choices for systemic therapy. Although there is some evidence for the efficacy of etretinate and acitretin, the lack of treatment guidelines reflects the rarity of the disease and the challenges in management.

There are striking similarities in the general inflammatory changes seen in pustular psoriasis, palmoplantar pustular psoriasis, ACH, and drug-induced acute exanthematous generalized pustular eruption, and they share mutations in IL36RN, AP1S3, and CARD14, identifying a pattern of expression of the same disease classifiable under the definition of deficiency of interleukin-36-receptor antagonist (Abbas et al., 2013). The genetic mutations impair structure and/or expression and, ultimately, the regulatory function of the encoded interleukin (IL)-36Ra protein, leading to an enhanced inflammatory cascade downstream of the interaction between the IL-36α, IL-36β, and IL-36γ agonistic ligands and their specific receptor. IL-36Ra is a negative regulator of IL-36 receptor signaling, principally located on keratinocytes, macrophages, and dendritic cells (Abbas et al., 2013; Bachelez, 2018; Navarini et al., 2017; Sugiura, 2014).

We have identified 31 cases in the literature of ACH treated with biologics. Details of the cases summarized below are presented in Table S1. In seven cases (23%), excluding our report, there was associated arthritis. Six cases were treated with biologic anti-interleukin drugs; two with secukinumab and four with ustekinumab.

Although anti-tumor necrosis factor α biologic therapy was used in a number of these cases, such therapies often lose efficacy over time or need comedications or dose increases to maintain efficacy. Treatment of ACH with etanercept, alone or in combination with other drugs, such as acitretin, has led to variable results. An excellent response in ACH has been reported for adalimumab, and ustekinumab has been reported to be effective, although in one case the therapeutic dose had to be doubled and complete control of the disease was achieved only after the addition of acitretin. Even ustekinumab in combination with cyclosporine and prednisone did not result in clearance of one highly resistant form of ACH.

Secukinumab, the first of the IL-17 antibody biologics to be approved for the treatment of plaque psoriasis, PsA, and ankylosing spondylitis, is a recombinant high-affinity, human immunoglobulin G1κ monoclonal antibody, selectively binding and neutralizing the inflammatory mediator, IL-17A (Frieder et al., 2018; Shirley & Scott, 2016). Clinical responses in psoriasis were associated with a reduction in epidermal hyperplasia, IL-17-producing cells and the gene expression of various cytokines and chemokines (Leonardi & Gordon, 2014; Onishi & Gaffen, 2010). In addition to our case, two cases reported in the literature (Table S1) have shown good responses to secukinumab in patients with ACH.

Manifestations of ACH accompanied by PsA are rare, which may be of assistance in determining the entity of ACH according to the similarity with psoriasis. The potential of targeting IL-17 in cutaneous inflammatory conditions is very promising, especially in neutrophilic disorders. The involvement of the inflammasome pathway could provide a plausible explanation for its driving role in skin inflammation and particularly in ACH. Brodalumab, a monoclonal antibody to IL-17 receptor A, was effective in the treatment of both psoriatic erythroderma and GPP, showing significant improvement or complete clearance of lesions in these rare forms of psoriasis, usually nonresponsive to conventional treatment (Yamasaki et al., 2017). Phase III studies in Japan have shown good clinical efficacy with the anti-IL-17 drugs, secukinumab, ixekizumab, and brodalumab, in patients with GPP and erythroderma (Galluzzo et al., 2016; Reich, 2017; Yamasaki et al., 2017). There is a strong involvement of the antigen-mediated Th17 response in GPP, which may be facilitated by the unregulated IL-36 signaling path. This may be of relevance to ACH, given the similarities between GPP and ACH. The Th17 response may lead to the recruitment and activation of neutrophils, typically involved in the disease (Arakawa et al., 2018).

The rapid response in our patient, both for the skin lesions and for arthritic symptoms, highlights the ability of secukinumab to improve symptoms not only in plaque psoriasis or erythrodermic psoriasis but even in a localized form of GPP. Continued research into this

condition is needed to confirm the role of these agents and to identify other effective treatments, which need to be incorporated into practice guidelines. Research is also needed to determine the specific implications of the IL-17 pathway in psoriasis. Our experience suggests that it is likely that secukinumab can be an effective therapeutic option for patients with pustular psoriasis and even ACH, where conventional therapies have failed.

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CONFLICT OF INTEREST

No conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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