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CASE REPORT

Case Report: Paradoxical acrodermatitis of Hallopeau-like eruption following anti-IL-17 therapy [version 1; peer review: 2 approved]

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Abstract
Psoriasis is a chronic immune-mediated inflammatory disease. Up to 40% of patients with psoriasis may develop psoriatic arthritis. Currently, interleukin (IL)-17/IL-23 pathways are identified as key factors in the immunopathogenesis of both conditions. Here we describe the case of a patient who developed psoriasiform skin lesions 10 months after the initiation of anti-IL17 therapy for psoriatic arthritis. The underlying disease had responded well to the therapy, but the patient developed a striking pustular eruption at the fingers with nail involvement, onycholysis, yellow discoloration, and subungual keratosis. Clinical and histological findings were consistent with an acrodermatitis continua of Hallopeau-like eruption. Skin lesions subsided after discontinuation of the responsible anti-IL17 agent. The interpretation of this paradoxical side effect of biological therapies remains unclear but may relate to an unbalanced inflammatory cytokine response induced by the inhibition of TNF activity. It is likely that patients, who are genetically prone, may respond exaggeratedly to a cytokine imbalance. The identification of this kind of patient, in the future, could be useful in order to choose the correct therapy.

Keywords
IL-17, psoriasis, Acrodermatitis continua of Hallopeau, paradoxical reaction

Open Peer Review

Reviewer Status ✔ ✔

	Invited Reviewers	
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version 1 published 26 Mar 2019	✔ report	✔ report

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Rutgers University - The State University of New Jersey, New Brunswick, USA

2 **Melinda J. Gooderham**, SKiN Centre for Dermatology, Peterborough, Canada

Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: Tadiotto Cicogna G: Data Curation, Writing – Original Draft Preparation; **Messina F**: Data Curation, Writing – Original Draft Preparation; **Nalotto L**: Data Curation, Writing – Original Draft Preparation; **Szekely S**: Writing – Original Draft Preparation; **Alaibac M**: Conceptualization, Data Curation, Funding Acquisition, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing

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Introduction

Psoriasis is an immune-mediated inflammatory disease characterized by a chronic course and a systemic involvement. Numerous cytokines are involved in the pathogenesis of psoriasis, but the interleukin (IL)-23/17 axis has been identified as one of the key pathways[1]. Up to 40% of patients with psoriasis may develop psoriatic arthritis (PsA). Both conditions share common pathogenic mechanisms[2]. Among the therapies that can be used for both skin and joint manifestations, anti-TNF agents and new biologics targeting IL-17 have shown impressive efficacy[3]. We report the case of a patient who presented with an acrodermatitis continua of Hallopeau (ACH)-like paradoxical reaction to anti-IL17 therapy for PsA.

Case report

A 52-year-old-woman affected by PsA presented to our Dermatology Unit complaining of a painful eruption of pustules with scaling and tender swelling on the fingers of both hands (Figure 1), which had begun one month before. Her medical history revealed concurrent PsA in complete remission after 10 months of the, the anti-IL-17 drug, secukinumab, at the dosage of 150mg every 4 weeks. The patient did not suffer from any other relevant disease and there was no family history of psoriasis.

A skin biopsy was taken, and the subsequent histopathological examination showed a stratified squamous epithelium with parakeratosis, hyperkeratosis and irregular elongation of the rete ridges of the epidermis with some lymphocytes and subcorneal collections of neutrophils forming spongiform pustules of Kogoj. This result, together with clinical features and negative results of multiple cultures confirmed our suspect of an ACH-like eruption[4].

Figure 1. Eruption of pustules with scaling, tender swelling over fingers of both hands in a patient with psoriatic arthritis.

It was then decided to stop anti-IL-17 therapy. A subsequent treatment plan comprised topical clobetasol propionate, once daily, and acitretin 10mg daily.

At the follow-up visit 2 months later, the lesions had visibly regressed and the patient referred a 70% reduction in symptoms measured with Dermatology Life Quality Index questionnaire. The interruption of secukinumab notwithstanding, PsA showed no recrudescence.

Discussion

The natural history of psoriasis has been modified in the last years by new biologic agents that have allowed specific targeting of key cytokines such as TNF alpha, IL-12, IL-23 and IL-17.

TNF alpha inhibitors are the oldest, and therefore most studied, biologic drugs that have been introduced in the therapy of psoriasis. By inhibiting the whole pathway, TNF alpha blockers determine a stronger alteration of cytokine network[5]. This has been associated not only with impressive efficacy, but also remarkable side effects, such as infections, autoimmune diseases, lymphomas and cutaneous adverse events, mainly represented by paradoxical psoriasis[6].

In the last years, new biologic therapies targeting cytokines situated downstream to TNF alpha, such as ustekinumab, secukinumab and, more recently, ixekizumab have shown even higher efficacy due to their selectivity in blocking cytokines specific to the pathogenic pathways. Also for this drug, although uncommon, important adverse reactions such as opportunistic infections, can be observed[7].

In the literature, one case of paradoxical psoriasic reaction has recently been described in association to secukinumab[8]. In our case report we have observed an unexpected case of paradoxical ACH-like eruption, which to the best of our knowledge, has not been described in literature as an adverse event of secukinumab.

It is possible that secukinumab, by blocking IL-17, has induced a rearrangement of the cytokine pattern in this patient, determining a paradoxical increase of other pathogenic molecules, such as TNF alpha. This hypothesis has already been suggested for paradoxical reactions to ustekinumab, which exerts a blockade of IL12 and IL23[9]. On the other hand, is also possible that the inhibition of IL17 induced a negative feedback in the IL23-IL17 axis, thus determining an increase of IL23 which, in turn, stimulated Th17 cells to produce other cytokines, such as IL-22, which also exerts proliferation and activation of keratinocytes. Activated keratinocytes could induce the chemotaxis of neutrophils (IL-8 etc), causing the clinical presentation that we have observed in our patient[10]. This is the first case report describing ACH-like lesions induced by secukinumab; therefore few studies are available in the literature elucidating the pathogenesis of this paradoxical reaction. Hence, our experience needs to be reinforced by further investigations.

It is likely that our patient was genetically prone to respond exaggeratedly to a cytokine imbalance. The distinction of such patients could be useful in the future, in order to predict this type of adverse reaction and, therefore, suggesting them an alternative to biologic therapies.

Consent

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Grant information

The author(s) declared that no grants were involved in supporting this work.

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Version 1

Reviewer Report 05 August 2019

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✔ **Melinda J. Gooderham**
SKiN Centre for Dermatology, Peterborough, ON, Canada

An interesting case of a 'paradoxical' reaction to a biologic agent, secukinumab, which is used to treat psoriatic disease. In this case, acrodermatitis of Hallopeau developed in this patient being treated successfully with secukinumab for psoriatic arthritis. It is important to report these rare events as we build our knowledge of real-world experience of the use of biologic agents in psoriatic disease.

However, this is not the first report of this type of reaction to secukinumab in the literature. Sladden *et al.*[1] reported a similar reaction of fingertip and nail psoriatic disease (ACH-like) after treatment of plaque psoriasis with secukinumab. The similarity in the presentation of these cases is quite interesting and should be noted. Similar to the story of 'paradoxical' psoriasis/psoriasiform eruption with TNF antagonists, as we use more IL-17 inhibitors in the real world, we can better categorize these unexpected eruptions and further research can help to determine the underlying pathophysiological relationship.

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Is the background of the case's history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: I have been an investigator, speaker, advisory board member, and consultant for Novartis.

Reviewer Expertise: Psoriatic disease, clinical trials, real world experience

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 15 May 2019

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Archana Gopalakrishnan
University of Maryland, Baltimore, Baltimore, MD, USA

Paradoxical effects of anti-cytokine therapy is a very important area that the authors have highlighted in this case study. As has been well documented, the use of therapies, such as anti-TNF, although groundbreaking does raise a multitude of issues - including higher risk to infections - specifically tuberculosis. The authors have documented well that the patient who was on anti-IL-17 therapy did not suffer from any infections, an important advantage of using secukinumab.

Some of the points that could have been elaborated:

1. Would decreasing the dosage of the drug (from 150mg every 4 weeks) been able to reduce the ACH like eruption along with treating PsA? It would be useful if the authors could reference successful cases, if any documented, where the drug has been functional at lower doses.
2. A cytokine imbalance leading to an increase in TNF during secukinumab treatment has been suggested - is there corroborating evidence that implies this? If blood samples from the patient has been saved, can systemic levels of TNF be assayed for?
3. The authors raised an excellent point about underlying genetics contributing to the potential cytokine imbalance. This might be a very crucial finding and if so, could the authors highlight the nature of the polymorphisms to look for in future cases?

Is the background of the case's history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Partly

Is the case presented with sufficient detail to be useful for other practitioners?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Immunology of infected diseases, Immune response to tuberculosis and influenza, TLR signaling, inflammation, host directed therapy and vaccine mediated immunity.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.