Acrodermatitis continua of Hallopeau: clinical perspectives

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Abstract: Acrodermatitis continua of Hallopeau (ACH) is a rare, sterile pustular eruption of one or more digits. The condition presents with tender pustules and underlying erythema on the tip of a digit, more frequently arising on a finger than a toe. As far as classification, ACH is considered a localized form of pustular psoriasis. The eruption typically occurs after local trauma or infection, but such a history is not always present and various other etiologies have been described including infectious, neural, inflammatory, and genetic causes. The natural progression of ACH is chronic and progressive, often resulting in irreversible complications such as onychodystrophy that can result in anonychia, as well as osteitis that can result in osteolysis of the distal phalanges. Because of the rarity of ACH, there have been no randomized controlled studies to evaluate therapies, resulting in an absence of standardized treatment guidelines. In clinical practice, a wide variety of treatments have been attempted, with outcomes ranging from recalcitrance to complete resolution. In recent years, the introduction of biologics has provided a new class of therapy that has revolutionized the treatment of ACH. Specifically, rapid and sustained responses have been reported with the use of anti-tumor necrosis factor agents like infliximab, adalimumab, and etanercept; IL-17 inhibitors like secukinumab; IL-12/23 inhibitors like ustekinumab; and IL-1 inhibitors like anakinra. Nevertheless, there remains a considerable need for more research into treatment for the benefit of individual patients with ACH as well as for the clinical knowledge gained by such efforts. The purpose of this review is to provide a comprehensive overview of the key features of ACH as well as a discussion of clinical management strategies for this unique and debilitating condition.

Keywords: acrodermatitis continua of Hallopeau, psoriasis, pustular psoriasis, generalized pustular psoriasis, palmoplantar pustulosis

Introduction

Acrodermatitis continua of Hallopeau (ACH) is a rare, chronic, sterile pustular eruption of one or more digits. This entity has also been called pustular acrodermatitis, acrodermatitis continua suppurativa, dermatitis perstans, acropustulosis, acrodermatitis perstans, and dermatitis repens.1–4

ACH presents with tender, sterile pustules and underlying erythema on the tip of a digit, more frequently arising on a finger than a toe.1,5 The eruption typically occurs after local trauma or infection,6–8 however, such a history is not always present4 and neural and inflammatory etiologies have also been described.5 ACH always involves the nail apparatus; if there is no nail involvement, then alternative diagnoses such as palmoplantar pustulosis (PPP) should be considered.6 Over time, ACH becomes chronic and can exhibit proximal progression, extending to the...
dorsal aspect of the hand or the foot.\textsuperscript{7} Without successful treatment, ACH can lead to several complications, including onychodystrophy that can result in onychia as well as osteitis that can result in osteolyis of the distal phalanges.\textsuperscript{5,7–9} In these ways, ACH can cause profound disability and have a tremendously negative impact on quality of life in these patients.

As far as classification, ACH is considered a localized form of pustular psoriasis.\textsuperscript{2,5,10} It appears to be most common in middle-aged females, but due to the overall rarity of ACH, epidemiological information is limited to anecdotal case reports.\textsuperscript{6,9,11,12} Relatedly, there are no standardized guidelines for treating ACH, but rather various case reports with a wide range of therapeutic approaches and outcomes.

The purpose of this review is to provide a comprehensive overview of the key features of ACH as well as a discussion of clinical management strategies for this unique and debilitating condition.

**Methods**

This review is based on a literature search in MEDLINE and Embase databases. The search was performed in February 2019. The following keywords were used: “Acrodermatitis continua of hallopeau,” “acrodermatitis continua,” “dermatitis repens,” “acrodermatitis perstans,” “Hallopeau*,” AND “psoria*.” Only articles written in English were included, and no restrictions were set on study type. No institutional review board approval was required for this review article.

**Results**

**Pathophysiological mechanisms**

As mentioned, various etiologies have been described for ACH, including traumatic, infectious, neural, and inflammatory causes.\textsuperscript{5} In the majority of case reports, the patient recalls a minor trauma or infection preceding symptoms in the same location; however, many patients deny such precipitating factors.\textsuperscript{9,13}

In recent years, several studies have suggested genetic causes of ACH. For example, two papers published in 2011 reported mutations in the \textit{IL36RN} gene among patients with pustular psoriasis.\textsuperscript{14,15} \textit{IL36RN} is amply expressed in the skin and belongs to the IL-1 cytokine family that is involved in the innate immune system. Several IL36 isoforms (IL-36α, IL-36β, and IL-36γ) induce cytokines that contribute to a pro-inflammatory cascade by binding to the IL-1 RL2 receptor and initiating the recruitment and localization of T cells, neutrophils, and dendritic cells to the skin.\textsuperscript{10,14–16} The \textit{IL36RN} gene encodes the IL36 receptor agonist (IL-36Ra), which normally acts to inhibit such pro-inflammatory signaling. Mutations in \textit{IL36RN} can thereby lead to unregulated secretion of inflammatory cytokines,\textsuperscript{14,15,17} and such mutations have been found in several cases of familial generalized pustular psoriasis (GPP). This inherited form is now known as DITRA, ie, “Deficiency of Interleukin-Thirty six Receptor Antagonist.” The authors of these papers suggest that such genetic mutations may also be related to other forms of pustular psoriasis such as ACH.\textsuperscript{10,15,18}

In 2013, a team of researchers identified a homozygous missense mutation in \textit{IL36RN} in a male patient with ACH as well as his female sibling with GPP, confirming that these two diseases are likely related.\textsuperscript{10} Genetic linkages are also seen within single patients; for example, a 2019 study identified nine patients with both ACH and GPP and four patients with both ACH and PPP.\textsuperscript{19} Such reports are further supported by additional studies confirming the genotype–phenotype correlation between \textit{IL36RN} mutations and GPP, PPP, and ACH.\textsuperscript{17,20–22} As of May 2017, a total of 16 \textit{IL36RN} mutations had been discovered, and these disease alleles are now believed to account for approximately 20% of ACH cases.\textsuperscript{6}

While \textit{IL36RN} mutations are the most frequent genetic abnormality in pustular forms of psoriasis,\textsuperscript{19} \textit{CARD14} and \textit{AP1S3} have also been identified as causative or susceptibility genes in ACH.\textsuperscript{20,23,24} First, \textit{CARD14} encodes proteins produced by keratinocytes, and gain-of-function mutations lead to increased activation of nuclear factor-kappa B signaling and production of tumor necrosis factor-alpha (TNF-α),\textsuperscript{8} which has been identified in association with ACH as well as GPP, PPP, and psoriasis vulgaris (PV).\textsuperscript{25–28} Second, \textit{AP1S3} plays a role in vesicular trafficking within keratinocytes, and loss-of-function mutations cause abnormal autophagy, increased activation of TNF-α, and overexpression IL36α.\textsuperscript{5} Variants in \textit{AP1S3} have been described to contribute to ACH as well as GPP and PPP.\textsuperscript{23,29} Interestingly, preliminary research suggests that patients with ACH are more likely to carry two distinct mutations (ie, \textit{IL36RN} and \textit{AP1S3} or \textit{IL36RN} and \textit{CARD14}) than patients affected by other forms of pustular psoriasis,\textsuperscript{19,26,29,30} but there is a need for more investigation in this area.

In summary, current evidence demonstrates that ACH is associated with a variety of genetic mutations in the
genes IL36RN, CARD14, and AP1S3. Mutations in these same genes are associated with phenotypically related pustular skin conditions such as GPP and PPP.

Clinical features
Symptoms of ACH typically begin with the tip of one digit turning erythematous and developing painful pustules that migrate under the nail bed and matrix, leading to onychodystrophy. In the acute phase, the pustules rupture and coalesce to form “a lake of pus that carries the nail away,” as this condition is classically described. The resulting anonychia leaves behind an erythematous, shiny, and smooth distal digit where pustules often reform. As the disease progresses, the affected digits can become hyperkeratotic with psoriasiform scaling and continuing pustulation. In longstanding cases, ACH can progress to involve additional digits or extend proximally to the dorsal hand or foot; however, the disease typically remains localized to the digit(s) for months or years before such proximal progression. These clinical findings are seen in Figure 1, which illustrate a classic case of chronic ACH.

Rarely, the disease can cause osteitis of the underlying phalanges, resulting in osteolysis in severe cases. Very rarely, ACH has been reported to result in acquired syndactyly, likely due to ACH lesions causing loss of interdigital epidermis and allowing for healing with fusion of adjacent tissues.

There are several aspects of ACH’s clinical features that support its classification as a variant of pustular psoriasis. First, the previously described genetic mutations common to patients with ACH, GPP, and PPP suggest these conditions are on the same autoimmune inflammatory spectrum. Second, several authors have reported the development of joint pain and arthritis in patients with ACH. Soft tissue and bone involvement, often revealed on X-ray imaging, further supports the association of ACH with psoriasis and associated arthritis. Third, there have been instances of geographic tongue in patients with ACH, which is a finding consistent with other forms of pustular psoriasis and other inflammatory conditions. Lastly, ACH can progress to GPP, particularly the life-threatening von Zumbusch type. Such patterns of progression highlight the critical importance of recognizing ACH as a localized form of pustular psoriasis that is unique, can rapidly evolve, and must be aggressively treated to prevent complications.

Differential diagnosis
ACH is commonly misdiagnosed. Based on clinical presentation, its purulence can imitate bacterial, fungal, or viral paronychia. Depending on the patient’s age and comorbidities, secondarily infected contact dermatitis, dyshidrotic eczema, or a paraneoplastic process are reasonable possibilities. Furthermore, other infections of the digits such as herpetic whitlow can present with vesiculo-pustules while dermatophytosis can present with scaly erythema, both resembling ACH. Autoimmune conditions such as pemphigus vulgaris can imitate ACH by presenting with inflammation and erosions of the digits. In a review by Seghal et al, the authors warn that late clinical manifestations of ACH may necessitate evaluations for a number of conditions including squamous cell carcinoma, melanoma, pyogenic granuloma, Reiter’s disease,
Interestingly, the anti-cyclosporine, 39 mutation, suggesting 5.

Furthermore, the condition is so rare that there have been no controlled studies to evaluate treatments, resulting in an absence of standardized treatment guidelines. 12 As a result, many therapeutic options have been attempted, with equivocal results as described in case reports. 5

Historically, the most common therapies for ACH have been similar to treatments for other forms of psoriasis, especially PPP, 1,5,12,31 including topical and oral corticosteroids, 5,41 topical vitamin D analogs, 42–45 topical fluorouracil, 46,47 topical calcineurin inhibitors, 48 tar, 5 topical and systemic retinoids, 39,49,50 cyclosporine, 61–54 methotrexate, 38,55,56 and phototherapy or photochemotherapy. 5 In addition, granulocyte and monocyte adsorption apheresis has been attempted in ACH, with promising results in a small number of patients and far fewer side effects than some of the more traditional therapies. 57–60

In most reported cases, a combination of these modalities is used (ie, systemic oral medication plus a topical applied to the affected area), with clinical responses ranging from recalcitrance to complete resolution. 5 Nail lesions are typically more difficult to manage than skin, 61 and recurrence is common with decrease in dosing or cessation of treatment. 5 Furthermore, the potential toxicities associated with several of these systemic therapies can prevent or limit the duration of treatment in certain individuals, especially children and elderly patients with ACH. 5,62–64

In recent years, the introduction of biologics has provided a new class of therapy that has revolutionized the treatment of ACH. 5 Specifically, rapid and sustained responses have been reported with the use of anti-TNF agents like infliximab, 55,65,66 adalimumab, 67–71 and etanercept, 72–77 IL-17 inhibitors like secukinumab, 78–80 IL-12/23 inhibitors like ustekinumab, 61,82 and IL-1 inhibitors like anakinra. 83 Furthermore, the identification of IL36RN mutations as a genetic contributor to ACH has informed the development of biologics that specifically block IL-36 signaling. 19 A 2017 paper described a high affinity, anti-human IL-36 receptor antagonist antibody that was initially tested in vitro and shown to directly inhibit IL-36-R-mediated signaling and inflammatory cytokine production in primary human keratinocytes and dermal fibroblasts. 84 Following this work, a Phase I proof-of-concept study among seven patients with GPP treated with this anti-IL-36 monoclonal antibody showed significant improvement in symptoms. 85 Interestingly, the anti-IL-36 treatment was equally effective regardless of the absence or presence of an IL36RN mutation, suggesting the IL-36 pathway can be pathogenic regardless of a patient’s genetic background. 8,84,85

The use of both existing and emerging biologic agents to treat ACH, especially cases that are refractory to traditional treatments, is an area of ongoing research and development. No single agent has yet been identified as superior for ACH, but several have demonstrated efficacy,
representing a promising new chapter for managing this chronic and often debilitating disease.

Discussion
These results demonstrate that ACH is a rare condition that is genetically and phenotypically related to other forms of pustular psoriasis but distinct in several dimensions that influence clinical outcomes. The relatively sparse number of case reports and consequent lack of epidemiological or controlled studies can make this condition particularly difficult for clinicians to manage. Fortunately, biologic agents offer a new treatment option with overwhelmingly positive results, especially in recalcitrant and refractory cases.5

Nevertheless, there remains a need for more targeted research on the causes and management of ACH. First, the knowledge gained by identifying genetic mutations as a cause of ACH needs to be harnessed to develop more targeted treatment options. For example, IL36RN mutations result in defects in IL-1 signaling, as discussed. This elucidates why agents like anakinra (an IL-1 antagonist) have been reported as successful in treating ACH, but optimal treatment may require developing agents that specifically target IL-36 or common pathways between IL-1 and IL-36.8,10 As such research moves forward, it will be critical to recruit patients with ACH who have different genetic backgrounds to determine the efficacy of these new agents across the spectrum of genetic profiles, including patients with no identified mutations.

Second, genetic studies have revealed strong associations between IL36RN mutations but have also uncovered variants in other genes among patients with ACH, such as CARD1421 and APIS3.20 These findings suggest a more complicated genetic picture to this disease beyond IL36RN, and there is a need for additional studies to more fully characterize its genetic underpinnings.

Third and perhaps most importantly, the rarity of ACH has thus far prevented rigorous research to establish evidence-based treatment guidelines. Given the pain and disfigurement caused by ACH, the potential for serious and irreversible complications, and the association of this rare variant with life-threatening forms of pustular psoriasis, there remains considerable need for more research into treatment for the benefit of individual patients with ACH as well as for the clinical knowledge gained by such efforts.

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