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REVIEW

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 present[4] 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

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dorsal aspect of the hand or the foot.[7] Without successful treatment, ACH can lead to several complications, including onychodystrophy that can result in anonychia as well as osteitis that can result in osteolysis of the distal phalanges.[4,5,7–9] 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.[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.[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.[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.[9,13]

In recent years, several studies have suggested genetic causes of ACH. For example, two papers published in 2011 reported mutations in the *IL36RN* gene among patients with pustular psoriasis.[14,15] *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.[10,14–16] The *IL36RN* gene encodes the IL36 receptor agonist (IL-36Ra), which normally acts to inhibit such pro-inflammatory signaling. Mutations in *IL36RN* can thereby lead to unregulated secretion of inflammatory cytokines,[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.[10,15,18]

In 2013, a team of researchers identified a homozygous missense mutation in *IL36RN* in a male patient with ACH as well as his female sibling with GPP, confirming that these two diseases are likely related.[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.[19] Such reports are further supported by additional studies confirming the genotype–phenotype correlation between *IL36RN* mutations and GPP, PPP, and ACH.[17,20–22] As of May 2017, a total of 16 *IL36RN* mutations had been discovered, and these disease alleles are now believed to account for approximately 20% of ACH cases.[6]

While *IL36RN* mutations are the most frequent genetic abnormality in pustular forms of psoriasis,[19] *CARD14* and *AP1S3* have also been identified as causative or susceptibility genes in ACH.[20,23,24] First, *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),[8] which has been identified in association with ACH as well as GPP, PPP, and psoriasis vulgaris (PV).[25–28] Second, *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.[8] Variants in *AP1S3* have been described to contribute to ACH as well as GPP and PPP.[23,29] Interestingly, preliminary research suggests that patients with ACH are more likely to carry two distinct mutations (ie, *IL36RN* and *AP1S3* or *IL36RN* and *CARD14*) than patients affected by other forms of pustular psoriasis,[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.[1,3] 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.[1,5] The resulting anonychia leaves behind an erythematous, shiny, and smooth distal digit where pustules often reform.[18,31] As the disease progresses, the affected digits can become hyperkeratotic with psoriasiform scaling and continuing pustulation.[5] 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.[5,32] 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.[3,5,31,33,34] 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.[4,35]

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.[3,33,34] 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.[36] Lastly, ACH can progress to GPP, particularly the life-threatening von Zumbusch type.[4,5,32,37,38] 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.[11] Depending on the patient's age and comorbidities, secondarily infected contact dermatitis, dyshidrotic eczema, or a paraneoplastic process are reasonable possibilities.[4] Furthermore, other infections of the digits such as herpetic whitlow can present with vesiculopustules 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,

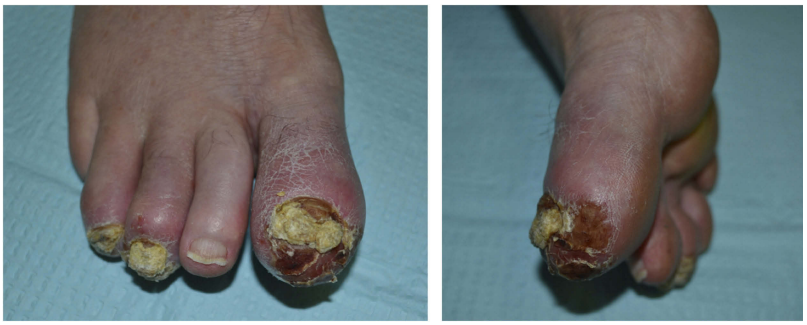

Figure 1 Right foot of a 64-year-old patient who first presented with asymmetric dactylitis characterized by erythema and tenderness of the first, third, and fourth distal interphalangeal joints with associated nail deformities. Written informed consent was obtained to take and publish the photographs above. Patient reported a history of possible osteomyelitis diagnosed by primary care provider, but this diagnosis was not supported by imaging, and symptoms progressed despite antibiotic treatment. Initially treated with topical steroids, resulting in preliminary improvement of skin changes. Approximately, 6 months after skin changes began, patient was found to have the findings documented in these figures. The clinical history and presentation of pustules, scale, erythema, and nail dystrophy of the first, third, and fourth digits were consistent with chronic Acrodermatitis continua of Hallopeau.

subungual fibroma, glomus tumor, blastomycosis, and onychomycosis.[5]

The most important condition to compare and contrast with ACH is PPP. Fortunately, several key features help distinguish these related conditions. First, ACH often follows trauma, as previously described, whereas PPP rarely involves a history of injury. Second, suppurative nail involvement is an early and defining feature of ACH whereas PPP does not always affect the nails and is usually non-suppurative.[6] Third, ACH most commonly remains unilateral and localized to a limited number of digits and with an irregular distribution for many years, while PPP is most commonly bilateral and symmetrical.[2] Lastly, features such as soft tissue sclerosis and osteolysis as described in ACH are not reported in PPP.[39]

Overall, the similarities between ACH with many other conditions, especially PPP, necessitate a careful consideration of a broad differential diagnosis and a thorough clinical workup, as appropriate.

Histopathology

While the diagnosis of ACH is primarily clinical, based on the history and clinical findings described, skin and nail biopsies with staining and cultures can be helpful to exclude other conditions in the differential.[12] ACH appears histologically very similar to pustular psoriasis, with subcorneal neutrophilic pustules, spongiform pustules, and moderate lymphohistiocytic infiltrate.[1,4,5] Chronic ACH lesions usually show severe atrophy of the papillary dermis and thinning of the epidermis.[5] The nail matrix is always involved and typically exhibits moderate acanthosis, lymphocytic and neutrophilic exocytosis, and spongiosis.[40] Lastly, bacterial cultures are routinely sterile but can yield predominant growth of commensals, which is interpreted as non-contributory to the pathogenesis of this non-infectious inflammatory disease.[6]

Management

ACH is characteristically chronic and recalcitrant in nature, and spontaneous improvement has rarely been observed.[2,5,12,32] Furthermore, the condition is so rare that there have been no controlled studies to evaluate therapies, 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,[51–54] methotrexate,[48,55,56] 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,[81,82] 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 fibroblases.[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 *CARD14*[21] and *AP1S3*.[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.

Disclosure

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References

1. Mengesha YM, Bennett ML. Pustular skin disorders: diagnosis and treatment. *Am J Clin Dermatol*. 2002;3(6):389–400. doi:10.2165/00128071-200203060-00003
2. Benjegerdes KE, Hyde K, Kivelevitch D, Mansouri B. Pustular psoriasis: pathophysiology and current treatment perspectives. *Psoriasis (Auckl)*. 2016;6:131–144. doi:10.2147/PTT.S98954
3. Jo SJ, Park JY, Yoon HS, Youn JI. Case of acrodermatitis continua accompanied by psoriatic arthritis. *J Dermatol*. 2006;33(11):787–791. doi:10.1111/j.1346-8138.2006.00180.x
4. Waller JM, Wu JJ, Murase JE, Dyson SW, Kelly KM. Chronically painful right thumb with pustules and onycholysis. Diagnosis: acrodermatitis continua of Hallopeau. *Clin Exp Dermatol*. 2007;32(5):619–620. doi:10.1111/j.1365-2230.2007.02440.x
5. Sehgal VN, Verma P, Sharma S, et al. Acrodermatitis continua of Hallopeau: evolution of treatment options. *Int J Dermatol*. 2011;50(10):1195–1211. doi:10.1111/j.1365-4632.2011.04993.x
6. Navarini AA, Burden AD, Capon F, et al. European consensus statement on phenotypes of pustular psoriasis. *J Eur Acad Dermatol Venereol*. 2017;31(11):1792–1799. doi:10.1111/jdv.14386
7. Hoegler KM, John AM, Handler MZ, Schwartz RA. Generalized pustular psoriasis: a review and update on treatment. *J Eur Acad Dermatol Venereol*. 2018;32(10):1645–1651. doi:10.1111/jdv.14949
8. Bachelez H. Pustular psoriasis and related pustular skin diseases. *Br J Dermatol*. 2018;178(3):614–618. doi:10.1111/bjd.16232
9. Yerushalmi J, Grunwald MH, Hallel-Halevy D, Avinoach I, Halevy S. Chronic pustular eruption of the thumbs. Diagnosis: acrodermatitis continua of Hallopeau (ACH). *Arch Dermatol*. 2000;136(7):925–930.
10. Abbas O, Itani S, Ghosn S, et al. Acrodermatitis continua of Hallopeau is a clinical phenotype of DITRA: evidence that it is a variant of pustular psoriasis. *Dermatology*. 2013;226(1):28–31. doi:10.1159/000346572
11. Rosenberg BE, Strober BE. Acrodermatitis continua. *Dermatol Online J*. 2004;10(3):9.
12. Korman AM, Rzepka PV, Sopkovich JA. Acrodermatitis continua of Hallopeau. *JAMA Dermatol*. 2018;154(11):1346. doi:10.1001/jamadermatol.2017.6195
13. Naldi L, Gambini D. The clinical spectrum of psoriasis. *Clin Dermatol*. 2007;25(6):510–518. doi:10.1016/j.clindermatol.2007.08.003
14. Onoufriadis A, Simpson MA, Pink AE, et al. Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. *Am J Hum Genet*. 2011;89(3):432–437. doi:10.1016/j.ajhg.2011.07.022
15. Marrakchi S, Guigue P, Renshaw BR, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *N Engl J Med*. 2011;365(7):620–628. doi:10.1056/NEJMoa1013068

16. O'Keefe E, Braverman IM, Cohen I. Annulus migrans. Identical lesions in pustular psoriasis, Reiter's syndrome, and geographic tongue. *Arch Dermatol*. 1973;107(2):240–244.
17. Tauber M, Bal E, Pei XY, et al. IL36RN mutations affect protein expression and function: a basis for genotype-phenotype correlation in pustular diseases. *J Invest Dermatol*. 2016;136(9):1811–1819. doi:10.1016/j.jid.2016.04.038
18. Haneke E. Nail psoriasis: clinical features, pathogenesis, differential diagnoses, and management. *Psoriasis (Auckl)*. 2017;7:51–63. doi:10.2147/PTT.S126281
19. Twelves S, Mostafa A, Dand N, et al. Clinical and genetic differences between pustular psoriasis subtypes. *J Allergy Clin Immunol*. 2018;143(3):1021–1026.
20. Setta-Kaffetzi N, Navarini AA, Patel VM, et al. Rare pathogenic variants in IL36RN underlie a spectrum of psoriasis-associated pustular phenotypes. *J Invest Dermatol*. 2013;133:1366–1369. doi:10.1038/jid.2012.490
21. Sugiura K. The genetic background of generalized pustular psoriasis: IL36RN mutations and CARD14 gain-of-function variants. *J Dermatol Sci*. 2014;74(3):187–192. doi:10.1016/j.jdermsci.2014.02.006
22. Liang J, Huang P, Li H, et al. Mutations in IL36RN are associated with geographic tongue. *Hum Genet*. 2017;136(2):241–252. doi:10.1007/s00439-016-1750-y
23. Setta-Kaffetzi N, Simpson MA, Navarini AA, et al. AP1S3 mutations are associated with pustular psoriasis and impaired Toll-like receptor 3 trafficking. *Am J Hum Genet*. 2014;94(5):790–797. doi:10.1016/j.ajhg.2014.04.005
24. Mossner R, Frambach Y, Wilsmann-Theis D, et al. palmoplantar pustular psoriasis is associated with missense variants in CARD14, but not with loss-of-function mutations in IL36RN in European patients. *J Invest Dermatol*. 2015;135(10):2538–2541. doi:10.1038/jid.2015.186
25. Korber A, Mossner R, Renner R, et al. Mutations in IL36RN in patients with generalized pustular psoriasis. *J Invest Dermatol*. 2013;133(11):2634–2637. doi:10.1038/jid.2013.214
26. Berki DM, Liu L, Choon SE, et al. Activating CARD14 mutations are associated with generalized pustular psoriasis but rarely account for familial recurrence in psoriasis vulgaris. *J Invest Dermatol*. 2015;135(12):2964–2970. doi:10.1038/jid.2015.288
27. Jordan CT, Cao L, Roberson ED, et al. PSORS2 is due to mutations in CARD14. *Am J Hum Genet*. 2012;90(5):784–795. doi:10.1016/j.ajhg.2012.03.012
28. Sugiura K, Muto M, Akiyama M. CARD14 c.526G>C (p.Asp176His) is a significant risk factor for generalized pustular psoriasis with psoriasis vulgaris in the Japanese cohort. *J Invest Dermatol*. 2014;134(6):1755–1757. doi:10.1038/jid.2014.46
29. Mahil SK, Twelves S, Farkas K, et al. AP1S3 mutations cause skin autoinflammation by disrupting keratinocyte autophagy and up-regulating IL-36 production. *J Invest Dermatol*. 2016;136(11):2251–2259. doi:10.1016/j.jid.2016.06.618
30. Mossner R, Wilsmann-Theis D, Oji V, et al. The genetic basis for most patients with pustular skin disease remains elusive. *Br J Dermatol*. 2018;178(3):740–748. doi:10.1111/bjd.15867
31. Alorainy M, Alshaya M, Al-Rikabi A, Ayesh M, Alsaif F. Acrodermatitis continua of Hallopeau with bone resorption in an 8-year-old patient: a case report. *Case Rep Dermatol*. 2017;9(3):259–264. doi:10.1159/000485370
32. Kim KH, Kim HL, Suh HY, et al. A case of acrodermatitis continua accompanying with osteolysis and atrophy of the distal phalanx that evoluted into generalized pustular psoriasis. *Ann Dermatol*. 2016;28(6):794–795. doi:10.5021/ad.2016.28.6.794
33. Okuno H, Ogura K, Okuyama R, Itoi E. Two cases of acrodermatitis continua of Hallopeau associated with generalized arthritis. *Acta Dermatovenerol Croat*. 2013;21(4):265–267.
34. Mueller RB, Ogilvie A, Schwarz S, Kern P, Schett G, Sticherling M. Adalimumab treatment of a patient with psoriasis suppurativa Hallopeau associated osteoarthropathy. *Clin Exp Rheumatol*. 2009;27:887.
35. Kirkup ME, Lovell CR. Acquired syndactyly secondary to acrodermatitis continua of Hallopeau. *Br J Dermatol*. 2005;152:1083–1084. doi:10.1111/j.1365-2133.2005.06580.x
36. Sadlier M. Acrodermatitis continua of Hallopeau and geographic tongue are variants of pustular psoriasis. *JAAD Case Rep*. 2018;4(3):277. doi:10.1016/j.jdcr.2017.08.022
37. Baker H, Ryan TJ. Generalized pustular psoriasis. A clinical and epidemiological study of 104 cases. *Br J Dermatol*. 1968;80(12):771–793. doi:10.1111/j.1365-2133.1968.tb11947.x
38. Ranugha PS, Kumari R, Thappa DM. Acrodermatitis continua of hallopeau evolving into generalised pustular psoriasis. *Indian J Dermatol*. 2013;58(2):161. doi:10.4103/0019-5154.108096
39. Pearson LH, Allen BS, Smith JG Jr. Acrodermatitis continua of Hallopeau: treatment with etretinate and review of relapsing pustular eruptions of the hands and feet. *J Am Acad Dermatol*. 1984;11(4 Pt 2):755–762.
40. Sehgal VN, Sharma S. Significance of Gram's stain smear, potassium hydroxide mount, culture, and microscopic pathology in the diagnosis of acrodermatitis continua of Hallopeau. *Skinmed*. 2011;9(4):260–261.
41. Sotiriadis D, Patsatsi A, Sotiriou E, Papagaryfallou I, Chrysomallis F. Acrodermatitis continua of Hallopeau on toes successfully treated with a two-compound product containing calcipotriol and betamethasone dipropionate. *J Dermatolog Treat*. 2007;18(5):315–318. doi:10.1080/09546630701367118
42. Piraccini BM, Tosti A, Iorizzo M, Misciali C. Pustular psoriasis of the nails: treatment and long-term follow-up of 46 patients. *Br J Dermatol*. 2001;144(5):1000–1005. doi:10.1046/j.1365-2133.2001.04189.x
43. Mozzanica N, Cattaneo A. The clinical effect of topical calcipotriol in acrodermatitis continua of hallopeau. *Br J Dermatol*. 1998;138(3):556. doi:10.1046/j.1365-2133.1998.02034.x
44. Emtestam L, Weden U. Successful treatment for acrodermatitis continua of Hallopeau using topical calcipotriol. *Br J Dermatol*. 1996;135(4):644–646.
45. Brill TJ, Elshorst-Schmidt T, Valesky EM, Kaufmann R, Thaci D. Successful treatment of acrodermatitis continua of Hallopeau with sequential combination of calcipotriol and tacrolimus ointments. *Dermatology*. 2005;211(4):351–355. doi:10.1159/000088507
46. Fredriksson T. Topically applied fluorouracil in the treatment of psoriatic nails. *Arch Dermatol*. 1974;110(5):735–736.
47. Tsuji T, Sugai T. Topically administered fluorouracil in psoriasis. *Arch Dermatol*. 1972;105(2):208–212.
48. Wilsmann-Theis D, Hagemann T, Dederer H, Wenzel J, Bieber T, Novak N. Successful treatment of acrodermatitis continua suppurativa with topical tacrolimus 0.1% ointment. *Br J Dermatol*. 2004;150(6):1194–1197. doi:10.1111/j.1365-2133.2004.05992.x
49. van Dooren-Greebe RJ, van de Kerkhof PC, Chang A, Happle R. Acitretin monotherapy in acrodermatitis continua Hallopeau. *Acta Derm Venereol*. 1989;69(4):344–346.
50. Slawsky LD, Libow LF. Successful treatment of acrodermatitis continua of Hallopeau with etretinate. *J Am Acad Dermatol*. 1990;23(6 Pt 1):1176–1178.
51. Zachariae H, Thestrup-Pedersen K. Ciclosporin A in acrodermatitis continua. *Dermatologica*. 1987;175(1):29–32.
52. Harland CC, Kilby PE, Dalziel KL. Acrodermatitis continua responding to cyclosporin therapy. *Clin Exp Dermatol*. 1992;17(5):376–378.
53. Peter RU, Ruzicka T, Donhauser G, Braun-Falco O. Acrodermatitis continua-type of pustular psoriasis responds to low-dose cyclosporine. *J Am Acad Dermatol*. 1990;23(3 Pt 1):515–516.

54. Georgakopoulos JR, Ighani A, Yeung J. Short- and long-term management of an acute pustular psoriasis flare: a case report. *J Cutan Med Surg*. 2017;21(5):452–456. doi:10.1177/1203475417712499
55. Rubio C, Martin MA, Arranz Sanchez DM, Vidaurrazaga C, Casado M. Excellent and prolonged response to infliximab in a case of recalcitrant acrodermatitis continua of Hallopeau. *J Eur Acad Dermatol Venereol*. 2009;23:707–708. doi:10.1111/j.1468-3083.2008.02998.x
56. Chowdhury MM, Motley RJ. Treatment of acrodermatitis continua of Hallopeau with oral propylthiouracil and methotrexate. *Clin Exp Dermatol*. 2001;26(8):657–660.
57. Sakanoue M, Takeda K, Kawai K, Kanekura T. Granulocyte and monocyte adsorption apheresis for refractory skin diseases due to activated neutrophils, psoriasis, and associated arthropathy. *Ther Apher Dial*. 2013;17(5):477–483. doi:10.1111/1744-9987.12113
58. Seishima M, Mizutani Y, Shibuya Y, Nagasawa C, Aoki T. Efficacy of granulocyte and monocyte adsorption apheresis for pustular psoriasis. *Ther Apher Dial*. 2008;12(1):13–18. doi:10.1111/j.1744-9987.2007.00536.x
59. Shukuya R, Hasegawa T, Niwa Y, Okuma K, Ikeda S. Granulocyte and monocyte adsorption apheresis for generalized pustular psoriasis. *J Dermatol*. 2011;38(12):1130–1134. doi:10.1111/j.1346-8138.2011.01279.x
60. Kanekura T, Hiraishi K, Kawahara K, Maruyama I, Kanzaki T. Granulocyte and monocyte adsorption apheresis (GCAP) for refractory skin diseases caused by activated neutrophils and psoriatic arthritis: evidence that GCAP removes Mac-1-expressing neutrophils. *Ther Apher Dial*. 2006;10(3):247–256. doi:10.1111/j.1744-9987.2006.00369.x
61. Iijima S, Okazaki Y, Watanabe S, Maruyama Y. Case of acrodermatitis continua of Hallopeau following psoriasis with atypical clinical presentation. *J Dermatol*. 2014;41(11):1006–1008. doi:10.1111/1346-8138.12639
62. Hjorth N, Thomsen K. Parakeratosis pustulosa. *Br J Dermatol*. 1967;79(10):527–532. doi:10.1111/j.1365-2133.1967.tb11407.x
63. Chen P, Li C, Xue R, et al. Efficacy and safety of acitretin monotherapy in children with pustular psoriasis: results from 15 cases and a literature review. *J Dermatolog Treat*. 2018;29(4):353–363. doi:10.1080/09546634.2017.1395798
64. Kiszewski AE, De Villa D, Scheibel I, Ricachnevsky N. An infant with acrodermatitis continua of Hallopeau: successful treatment with thalidomide and UVB therapy. *Pediatr Dermatol*. 2009;26(1):105–106. doi:10.1111/j.1525-1470.2008.00838.x
65. Mang R, Ruzicka T, Stege H. Successful treatment of acrodermatitis continua of Hallopeau by the tumour necrosis factor-alpha inhibitor infliximab (Remicade). *Br J Dermatol*. 2004;150:379–380. England. doi:10.1111/j.1365-2133.2003.05761.x
66. Ahmad K, Rogers S. Three years' experience with infliximab in recalcitrant psoriasis. *Clin Exp Dermatol*. 2006;31(5):630–633. doi:10.1111/j.1365-2230.2006.02170.x
67. Tobin AM, Kirby B. Successful treatment of recalcitrant acrodermatitis continua of Hallopeau with adalimumab and acitretin. *Br J Dermatol*. 2005;153:445–446. doi:10.1111/j.1365-2133.2005.06759.x
68. Ryan C, Collins P, Kirby B, Rogers S. Treatment of acrodermatitis continua of Hallopeau with adalimumab. *Br J Dermatol*. 2009;160:203–205. doi:10.1111/j.1365-2133.2008.08893.x
69. Lefkir S, Slimani S, Brahimi N, Ladjouze-Rezig A. Successful treatment of Acrodermatitis continua of Hallopeau associated with psoriatic arthritis with adalimumab. *Eur J Rheumatol*. 2015;2(2):78–79. doi:10.5152/eurjrheum.2015.0072
70. Di Costanzo L, Napolitano M, Patruno C, Cantelli M, Balato N. Acrodermatitis continua of Hallopeau (ACH): two cases successfully treated with adalimumab. *J Dermatolog Treat*. 2014;25(6):489–494. doi:10.3109/09546634.2013.848259
71. Sopkovich JA, Anetakis Poulos G, Wong HK. Acrodermatitis continua of hallopeau successfully treated with adalimumab. *J Clin Aesthet Dermatol*. 2012;5(2):60–62.
72. Thielen AM, Barde C, Marazza G, Saurat JH. Long-term control with etanercept (Enbrel) of a severe acrodermatitis continua of Hallopeau refractory to infliximab (Remicade). *Dermatology*. 2008;217(2):137–139. doi:10.1159/000134613
73. Bonish B, Rashid RM, Swan J. Etanercept responsive acrodermatitis continua of Hallopeau: is a pattern developing? *J Drugs Dermatol*. 2006;5(9):903–904.
74. Nikkels AF, Pierard GE. Etanercept and recalcitrant acrodermatitis continua of Hallopeau. *J Drugs Dermatol*. 2006;5(8):705–706.
75. Kazinski K, Joyce KM, Hodson D. The successful use of etanercept in combination therapy for treatment of acrodermatitis continua of hallopeau. *J Drugs Dermatol*. 2005;4(3):360–364.
76. Puig L, Barco D, Vilarrasa E, Alomar A. Treatment of acrodermatitis continua of Hallopeau with TNF-blocking agents: case report and review. *Dermatology*. 2010;220(2):154–158. doi:10.1159/000277415
77. Silpa-archa N, Wongpraparut C. A recalcitrant acrodermatitis continua of Hallopeau successfully treated with etanercept. *J Med Assoc Thai*. 2011;94(9):1154–1157.
78. Balestri R, Rech G, Tasin L, Rizzoli L, Girardelli CR. Acrodermatitis continua of Hallopeau successfully treated with secukinumab. *J Dermatolog Treat*. 2018;29:1–7.
79. Baron JA. Acrodermatitis of Hallopeau and erosive oral mucositis successfully treated with secukinumab. *JAAD Case Rep*. 2017;3(3):215–218. doi:10.1016/j.jdcr.2017.02.016
80. Herrero-Moyano M, Capusan TM, Martinez-Mera C, Llamas-Velasco M, Dauden E. Recalcitrant annular pustular psoriasis associated with psoriatic arthritis successfully treated with secukinumab. *JAAD Case Rep*. 2018;4(8):842–844. doi:10.1016/j.jdcr.2018.03.016
81. Adisen E, Ozer I, Temel B, Gurer MA. Ustekinumab for the treatment of acrodermatitis continua of Hallopeau refractory to anti-TNF agents. *Dermatol Ther*. 2017;30:2. doi:10.1111/dth.12460
82. Saunier J, Debarbieux S, Jullien D, Garnier L, Dalle S, Thomas L. Acrodermatitis continua of Hallopeau treated successfully with ustekinumab and acitretin after failure of tumour necrosis factor blockade and anakinra. *Dermatology*. 2015;230(2):97–100. doi:10.1159/000367690
83. Lutz V, Lipsker D. Acitretin- and tumor necrosis factor inhibitor-resistant acrodermatitis continua of hallopeau responsive to the interleukin 1 receptor antagonist anakinra. *Arch Dermatol*. 2012;148(3):297–299. doi:10.1001/archdermatol.2011.2473
84. Ganesan R, Raymond EL, Mennerich D, et al. Generation and functional characterization of anti-human and anti-mouse IL-36R antagonist monoclonal antibodies. *MAbs*. 2017;9(7):1143–1154. doi:10.1080/19420862.2017.1353853
85. Bachelez H, Choon SE, Marrakchi S, et al. Inhibition of the interleukin-36 pathway for the treatment of generalized pustular psoriasis. *N Engl J Med*. 2019;380(10):981–983. doi:10.1056/NEJMc1811317