

Successful use of secukinumab in Netherton syndrome



Sarah K. Blanchard, MD,^a and Neil S. Prose, MD^{a,b}
Durham, North Carolina

INTRODUCTION

Netherton syndrome is an autosomal recessive disorder caused by mutations in the serine protease inhibitor Kazal type 5 gene.¹ It was initially described by Com el² and Netherton,³ and is also known as Com el-Netherton syndrome. The originally diagnostic triad described by Wilkinson et al⁴ consists of congenital ichthyosis, trichorrhexis invaginata, and atopic diathesis. Although variable presentations have been described, the majority of patients with Netherton syndrome present with generalized erythroderma and scaling at birth that evolves into circinate plaques with a double-edged scale known as ichthyosis linearis circumflexa.⁵ Failure to thrive may be present during infancy and childhood and often leads to short stature.⁶ To date, there is no cure for Netherton syndrome, and treatment results are often disappointing. We present a case of Netherton syndrome successfully treated with secukinumab.

CASE REPORT

A 3-month-old male infant was treated in our clinic for extremely dry skin present since birth. He was initially treated with topical steroids and oral cephalixin, without improvement. At 17 months, he was noted to have diffuse erythematous plaques with a double-edged scale involving more than 90% body surface area. He had short, broken hairs, and trichoscopy revealed brittle hair with telescoping of the hair shaft. Complete blood cell count result with differential, lymphocyte enumeration, humoral immunocompetence profile, and total complement was normal. Based on the presence of both ichthyosis linearis circumflexa and trichorrhexis invaginata, the clinical diagnosis of Netherton syndrome was made. He was treated with mild topical steroids, oral

Abbreviation used:

IL: interleukin

antibiotics, frequent emollient application, and oral antihistamines, which provided adequate control of his symptoms, with occasional flares. By the time he was aged 5 years, his disease was well controlled with only twice-daily emollient application and hydrocortisone 1% ointment, and he was lost to follow-up.

After years of disease quiescence, he returned to clinic at aged 16 years with facial erythema and pain (Fig 1). It had been present for 2 years and had not responded to topical mupirocin, topical clindamycin, or oral doxycycline. Examination result was notable for erythematous scaly plaques distributed symmetrically on the nose, cheeks, nasolabial folds, and chin. Erythematous polycyclic scaly plaques were present on the abdomen and lower extremities. He had short hair on the temporal and occipital portions of the scalp, but normal hair density. His height and body mass index were within normal limits. At this time, his diagnosis of Netherton syndrome was confirmed by exome sequencing, which showed heterozygosity for 2 pathogenic variants in the serine protease inhibitor Kazal type 5 gene. Biopsy of the facial rash showed focal parakeratosis, absent granular layer, and psoriasiform spongiotic epidermis. During the next 2 years, his facial rash was refractory to numerous topical corticosteroids, tacrolimus 0.03% ointment, pimecrolimus 1% cream, econazole 1% cream, itraconazole (200 mg daily for 1 month), oral ivermectin (15 mg weekly for 2 doses), acitretin (10 mg daily for 2 months), dapsone 100 mg daily, doxycycline (100 mg twice daily for 6 months), oral

From the Department of Dermatology^a and Department of Pediatrics,^b Duke University Medical Center, Durham.

Funding sources: None.

Conflicts of interest: None disclosed.

Correspondence to: Neil S. Prose, MD, Department of Dermatology, Duke University Medical Center, Durham, Box 3252, NC 27710. E-mail: neil.prose@duke.edu.

JAAD Case Reports 2020;6:577-8.

2352-5126

  2020 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jidcr.2020.04.025>



Fig 1. Netherton syndrome before treatment. Erythematous scaly plaques on the eyelids, cheeks, nose, nasolabial folds, and chin.

prednisone (60 mg tapered during 5 weeks), omalizumab (biweekly injections for 2 months), and narrow-band ultraviolet B. He underwent patch testing, which did not reveal a clear cause of his symptoms. He also continued to have frequent flares of ichthyosis linearis circumflexa on his trunk and extremities. He received several courses of oral antibiotics, including cephalexin, azithromycin, clindamycin, amoxicillin-clavulanic acid, and linezolid for secondary infection. He had temporary improvement of his truncal rash with 3 monthly infusions of intravenous immunoglobulin at 0.5 g/kg. Adalimumab (40 mg every other week starting 1 week after an 80-mg loading dose) showed initial response of his facial rash, but efficacy decreased within 6 months. Cyclosporine 100 mg twice daily also had a long-term inadequate response.

Ultimately, he began receiving secukinumab 300 mg weekly, and at 4-week follow-up he had remarkable improvement of both his facial and truncal rash. The secukinumab was decreased to 300 mg monthly, and all other therapies except for a moisturizer and tretinoin 0.025% cream as needed were discontinued. At his most recent follow-up after almost 3 years of treatment with secukinumab, he had complete clearance of his facial erythema and only 1 mild flare of the polycyclic plaques on his trunk and extremities several months before (Fig 2).

DISCUSSION

Netherton syndrome is a rare congenital ichthyosis that continues to pose a therapeutic challenge. Although its clinical presentation has long been associated with atopy, several recent studies of molecular profiling in patients with ichthyoses, particularly Netherton syndrome, have shown upregulation of TH17 pathways and elevated interleukin (IL) 17 levels producing T cells similar to that observed in patients with psoriasis.⁷⁻⁹ Secukinumab is a recombinant, fully human, anti-IL-17A, monoclonal antibody that has shown promising results in



Fig 2. Netherton syndrome at follow-up, approximately 3 years after initiation of treatment with secukinumab.

the treatment of psoriasis.¹⁰ Our patient had a unique presentation that included a nonspecific psoriasiform facial rash. Additional potential diagnoses were considered, including seborrheic dermatitis, rosacea, and contact dermatitis; however, he had no significant improvement with treatments for these etiologies. Secukinumab provided rapid and sustained improvement in both the atypical facial rash and the classic ichthyosis linearis circumflexa. This suggests that the recently discovered IL-17 immunoprofile in Netherton syndrome may provide a more specific therapeutic target in the treatment of this severe skin disorder.

REFERENCES

1. Chavanas S, Bodemer C, Rochat A, et al. Mutations in *SPINK5*, encoding a serine protease inhibitor, cause Netherton syndrome. *Nat Genet*. 2000;25(2):141-142.
2. Comel M. Ichthyosis linearis circumflexa. *Dermatologica*. 1949; 98(3):133-136.
3. Netherton EW. A unique case of trichorrhhexis nodosa; bamboo hairs. *AMA Arch Derm*. 1958;78(4):483-487.
4. Wilkinson RD, Curtis GH, Hawks WA. Netherton's disease: trichorrhhexis invaginata (bamboo hair), congenital ichthyosiform erythroderma and the atopic diathesis. A histopathologic study. *Arch Dermatol*. 1964;89:46-54.
5. Sarri CA, Roussaki-Schulze A, Vasilopoulos Y, et al. Netherton syndrome: a genotype-phenotype review. *Mol Diagn Ther*. 2017;21(2):137-152.
6. Geyer AS, Ratajczak P, Pol-Rodriguez M, Millar WS, Garzon M, Richard G. Netherton syndrome with extensive skin peeling and failure to thrive due to a homozygous frameshift mutation in *SPINK5*. *Dermatology*. 2005;210(4):308-314.
7. Paller AS, Renert-Yuval Y, Suprun M, et al. An IL-17-dominant immune profile is shared across the major orphan forms of ichthyosis. *J Allergy Clin Immunol*. 2017;139(1):152-165.
8. Czarnowicki T, He H, Leonard A, et al. The major orphan forms of ichthyosis are characterized by systemic T-Cell activation and Th-17/Tc-17/Th-22/Tc-22 polarization in blood. *J Invest Dermatol*. 2018;138(10):2157-2167.
9. Malik K, He H, Huynh TN, et al. Ichthyosis molecular fingerprinting shows profound TH17 skewing and a unique barrier genomic signature. *J Allergy Clin Immunol*. 2019;143(2):604-618.
10. Papp KA, Langley RG, Sigurgeirsson B, et al. Efficacy and safety of secukinumab in the treatment of moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled phase II dose-ranging study. *Br J Dermatol*. 2013;168(2):412-421.