

Chronic Diarrhea in an Adolescent Girl With a Genetic Skin Condition

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A 17-year-old adolescent girl visited our clinic to establish care for her genetic skin condition. She exhibited red scaly plaques and patches over much of the body surface area consistent with atopic dermatitis but also had areas on the trunk with serpiginous red plaques with scale on the leading and trailing edges. She also noted fragile hair with sparse eyebrows. The patient reported that she had experienced chronic diarrhea and abdominal pain since childhood. She asked if it could be related to her genetic condition.

WHAT'S THE DIAGNOSIS?

- dyskeratosis follicularis (Darier disease)
- elastosis perforans serpiginosa
- erythema marginatum
- Netherton syndrome
- subacute cutaneous lupus erythematosus

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THE DIAGNOSIS: Netherton Syndrome

Netherton syndrome (NS) is a rare autosomal-recessive disorder characterized by a clinical triad of ichthyosis linearis circumflexa; atopic diathesis; and hair shaft abnormalities, most classically trichorrhexis invaginata.¹ Netherton syndrome is caused by a loss-of-function mutation in the serine peptidase inhibitor Kazal-type gene, *SPINK5*, which encodes LEKTI proteins and is found in all stratified epithelia as well as the thymus.² A lack of functional LEKTI leads to the activation of a cascade of allergy and inflammation as well as uncontrolled proteolytic activity in the stratum corneum, which causes increased desquamation.¹

Netherton syndrome presents with serpiginous or circinate scaling plaques with double-edged scale referred to as ichthyosis linearis circumflexa (quiz image). Skin plaques are intensely pruritic and migratory with fluctuating severity. Alternately, patients may have a generalized scaling erythroderma. Infants are at an especially high risk for recurrent infections, sepsis, hypernatremic dehydration, and failure to thrive.²

Netherton syndrome often gradually improves over time, though adults with NS usually have intensely pruritic, localized patches of redness, scaling, or ichthyosis linearis circumflexa. Lichenification and eczematous plaques of the popliteal and antecubital fossae also are common.¹ Therapeutic options for NS include emollients, topical steroids, phototherapy, and intravenous immunoglobulin for severe cases.³ Because there is skin barrier dysfunction in NS, suprathreshold serum levels of tacrolimus following topical application have been reported.⁴ Topical pimecrolimus has been demonstrated as an effective and safer application.⁵ Trichorrhexis invaginata (also known as bamboo hair) of the hair and eyebrows is a pathognomonic finding in NS, involving invagination of the distal hair shaft into the proximal shaft on light microscopy examination.¹

Histopathology is variable and nonspecific with psoriasiform hyperplasia as the most frequent finding. Other histologic findings include incomplete keratinization of the epidermis, incomplete cornification with a severely reduced granular layer, and mild to moderate inflammatory dermal infiltrate.⁶ LEKTI immunostaining is confirmatory and shows the reduction or complete absence of LEKTI in the granular layer and inner root sheath of follicles.¹ Patchy LEKTI staining would be suggestive of atopic dermatitis and psoriasis instead of NS.²

Atopic manifestations include angioedema, urticaria, and anaphylaxis, as well as chronic diarrhea or vomiting due to food allergies.¹ Elevated IgE levels for staple foods (eg, milk, wheat), elevated total serum IgE, and eosinophilia frequently are seen.⁷ Biopsy of the esophagus and colon likely would show mucosal eosinophilia.^{7,8}

Elimination of major food triggers through specific serum IgE testing and oral allergen desensitization can lead to the reduction of digestive symptoms.⁹ Cisapride and omeprazole are effective treatments for gastroesophageal reflux and poor feeding.⁸ Biopsy of the intestines in this patient likely would not have shown total villous atrophy, which is rare and primarily reported in infants with NS who have failure to thrive.¹⁰ There is a limited association between NS and intestinal metaplasia, intraepithelial lymphocytes, and bacterial overgrowth.

The primary morphology of dyskeratosis follicularis includes keratotic papules developing in sebaceous areas of the skin rather than scaly serpiginous plaques as seen in NS. Elastosis perforans serpiginosa is a perforating disorder seen in the context of several genetic conditions. It has a serpiginous appearance but, unlike NS, tends to be localized and features keratotic papules rather than patches with scale. Erythema marginatum is an uncommon feature of rheumatic fever and appears as pink annular macules and tends not to be pruritic. Subacute cutaneous lupus does feature scaly annular and serpiginous plaques but features trailing scale without the double-edge appearance of NS and is acquired rather than genetic.

REFERENCES

- Hovnanian A. Netherton syndrome: skin inflammation and allergy by loss of protease inhibition. *Cell Tissue Res*. 2013;351:289-300.
- Bitoun E, Micheloni A, Lamant L, et al. LEKTI proteolytic processing in human primary keratinocytes, tissue distribution and defective expression in Netherton syndrome. *Human Mol Genet*. 2003;12:2417-2430.
- Yan AC, Honig PJ, Ming ME, et al. The safety and efficacy of pimecrolimus, 1%, cream for the treatment of Netherton syndrome: results from an exploratory study. *Arch Dermatol*. 2010;146:57-62.
- Shah KN, Yan AC. Low but detectable serum levels of tacrolimus seen with the use of very dilute, extemporaneously compounded formulations of tacrolimus ointment in the treatment of patients with Netherton syndrome. *Arch Dermatol*. 2006;142:1362-1363.
- Yan AC, Honig PJ, Ming ME, et al. The safety and efficacy of pimecrolimus, 1%, cream for the treatment of Netherton syndrome: results from an exploratory study. *Arch Dermatol*. 2010;146:57-62.
- Leclerc-Mercier S, Bodemer C, Furio L, et al. Skin biopsy in Netherton syndrome: a histological review of a large series and new findings. *Am J Dermatopathol*. 2016;38:83-91.
- Pauluel-Marmont C, Bellon N, Barbet P, et al. Eosinophilic esophagitis and colonic mucosal eosinophilia in Netherton syndrome. *J Allergy Clin Immunol*. 2017;139:2003-2005.e1.
- Hannula-Jouppi K, Laasanen SL, Heikkilä H, et al. IgE allergen component-based profiling and atopic manifestations in patients with Netherton syndrome. *J Allergy Clin Immunol*. 2014;134:985-988.
- Kagalwalla AF, Sentongo TA, Ritz S, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2006;4:1097-1102.
- Judge MR, Morgan G, Harper JL. A clinical and immunological study of Netherton's syndrome. *Br J Dermatol*. 1994;131:615-21.