Netherton Syndrome: An Atypical Presentation

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PRACTICE **POINTS**

- Netherton syndrome is characterized by generalized erythroderma and scaling, hair shaft abnormalities, and dysregulation of the immune system.
- Treatment is largely symptomatic and includes fragrance-free emollients, keratolytics, tretinoin, and corticosteroids, either alone or in combination.

To the Editor:

Netherton syndrome (NS) is a rare autosomal-recessive ichthyosiform disease.[1] The incidence is estimated to be 1 in 200,000 individuals.[2] Netherton syndrome presents with generalized erythroderma and scaling, characteristic hair shaft abnormalities, and dysregulation of the immune system. Treatment is largely symptomatic and includes fragrance-free emollients, keratolytics, tretinoin, and corticosteroids, either alone or in combination. We report a case of NS in a man with congenital erythroderma, pili torti, and elevated IgE levels.

A 23-year-old man presented with generalized scaly skin that was present since birth. He was the first child born of nonconsanguineous parents. His medical history was suggestive of atopic diatheses such as allergic rhinitis and recurrent urticaria. The patient was of thin build and had widespread erythematous, annular, and polycyclic scaly lesions (Figure 1A), some with characteristic double-edged scale (Figure 1B). The skin was dry due to anhidrosis that was present since birth. Flexural lichenification was present at the cubital fossa of both arms. Scalp hairs were easily pluckable and had generalized thinning of hair density. Hair mount examination showed characteristic features of both trichorrhexis invaginata (Figure 2A) and pili torti (Figure 2B).

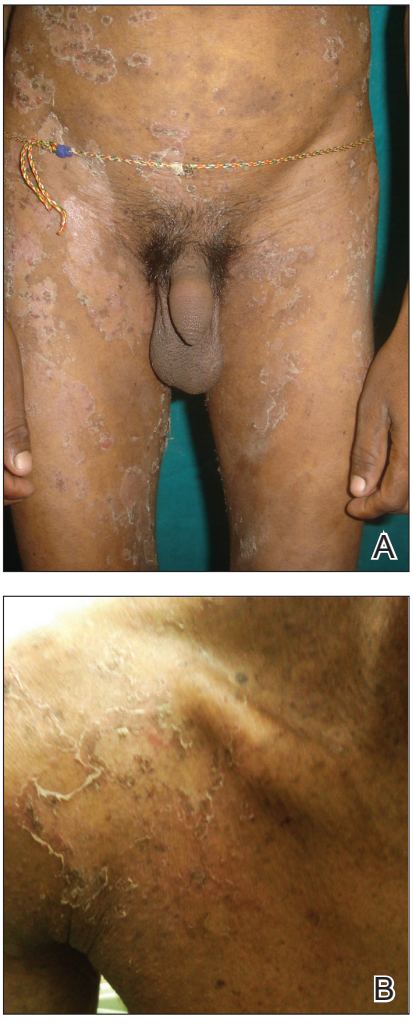

FIGURE 1. Netherton syndrome. A, Widespread erythematous, annular, and polycyclic scaly lesions. B, Lesions with double-edged scale.

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The authors report no conflict of interest.

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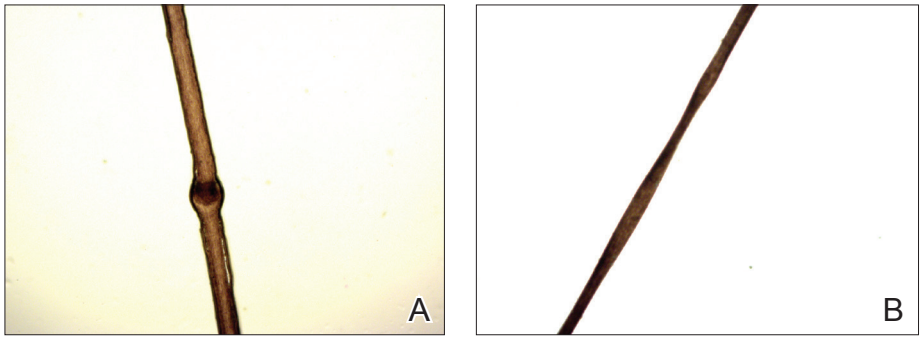

FIGURE 2. A, Hair mount examination showed characteristic ball-and-socket deformity of the hair shaft known as bamboo hair or trichorrhexis invaginata. B, Features of pili torti; the hair shaft twisted at irregular intervals.

Potassium hydroxide mount from a lesion was negative for fungal elements. Complete hematologic workup showed moderate anemia at 8.0 g/dL (reference range, 8.0–10.9 g/dL) and peripheral eosinophilia at 12% (reference range, 0%–6%). His IgE level was markedly elevated at 6331 IU/mL (reference range, 150–1000 IU/mL) when tested with fully automated bidirectionally interfaced chemiluminescent immunoassay. Histopathologic examination of a lesion biopsy showed psoriasiform epidermal hyperplasia, papillomatosis, and acanthosis, consistent with ichthyosis linearis circumflexa (ILC) (Figure 3). Clinicopathologic correlation led to a diagnosis of ILC, trichorrhexis invaginata/pili torti, and atopic diathesis, which is a constellation of disorders related to NS.

We prescribed oral acitretin 25 mg once daily and instructed the patient to apply petroleum jelly; however, the patient returned after 2 weeks due to aggravation of the skin condition with increased scaling and redness. Because the patient showed signs of acute skin failure

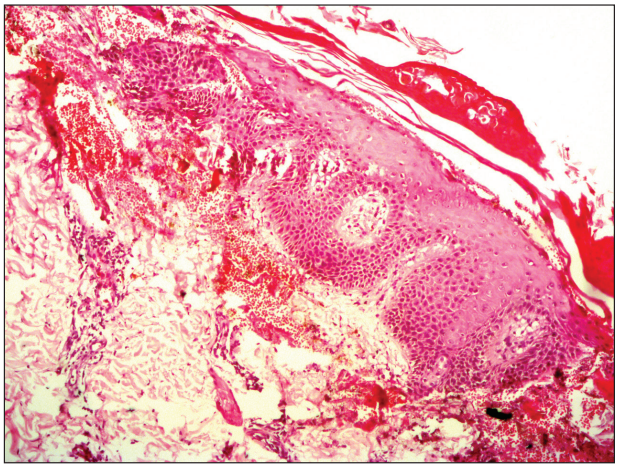

FIGURE 3. Lesion biopsy showed psoriasiform epidermal hyperplasia, papillomatosis, and acanthosis, consistant with ichthyosis linearis circumflexa (H&E, original magnification ×20).

Clinical Features and Management of a Patient With Netherton Syndrome

Clinical Findings	Management
Neonatal Period	
Acute skin failure presenting with failure to thrive, increased transepidermal water loss, fluid and electrolyte imbalances, impaired thermoregulation, increased risk for bacterial sepsis	Treatment in an intensive care unit with fluid and electrolyte correction, sepsis workup and appropriate antibiotics, humidified environment
Adulthood	
Erythroderma	Liberal use of fragrance-free emollients such as petroleum jelly, use of retinoids is controversial
Atopic manifestations: eczematous eruptions, atopic dermatitis, asthma, pruritus, allergic rhinitis, angioedema, urticaria	Acute control with oral and topical steroids, maintenance with emollients and topical calcineurin inhibitors, antihistamines, mast cell stabilizers
Hair shaft abnormalities: trichorrhexis invaginata, pili torti	Hair growth improves with age, complete alopecia is rare
Heat intolerance	Avoid hot and humid working conditions

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and erythroderma, we stopped acitretin treatment and managed his condition conservatively with the application of petroleum jelly.

Netherton syndrome is caused by mutation of the *SPINK5* gene, serine protease inhibitor Kazal type 5; the corresponding gene is located on the long arm of chromosome 5.[3] The gene encodes a serine protease inhibitor proprotein LEKTI (lymphoepithelial Kazal type inhibitor).[4] The product of the gene is thought to be necessary for epidermal cell growth and differentiation. The classic clinical triad of NS includes ichthyosiform dermatosis with double-edged scale, hair shaft abnormalities, and atopy or elevated IgE levels.[5] Generalized (congenital) erythroderma usually becomes evident at birth or shortly thereafter. Half of patients develop lesions of ILC on the trunk and limbs during childhood.[6] A typical ILC lesion is characterized by an erythematous scaly patch that may be annular or polycyclic with double-edged scale at the advancing border. The ability to sweat is impaired, which may cause episodes of hyperpyrexia, especially during humid weather. Patients with hyperpyrexia may be incorrectly diagnosed with bacterial infection and treated with antipyretic drugs or a prolonged course of antibiotics. Trichorrhexis invaginata, also referred to as bamboo hair or ball-and-socket defect, is the pathognomonic hair shaft abnormality seen in NS.[7] Other hair shaft abnormalities in this syndrome include trichorrhexis nodosa and pili torti.[8] Our patient had hair shaft abnormalities of trichorrhexis invaginata and pili torti, which are rare findings. The third component of this syndrome is atopy, which generally manifests as angioedema, urticaria, allergic rhinitis, peripheral eosinophilia, atopic dermatitis–like skin lesions, asthma, and elevated IgE levels.[9]

Treatment with emollients, topical steroids, tacrolimus, and psoralen plus UVA does not elicit a satisfactory response. The Table highlights the clinical features and management of NS.

Generally, systemic retinoid therapy is helpful in cases of erythrodermic ichthyosis, but a unique feature of NS is that erythroderma may worsen with systemic retinoid therapy, as retinoids aggravate atopic dermatitis by worsening existing xerosis.[4] Our case highlights the rare association of trichorrhexis invaginata with pili torti as well as acitretin treatment worsening our patient's condition. This paradoxical effect of retinoid therapy further confirmed the diagnosis of NS.

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