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Netherton Syndrome in Two Sisters, One with Generalized Lentiginosis: A Case Report from Yemen

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Abstract

Netherton syndrome is a rare, multisystem, autosomal recessive genodermatosis characterized by the triad of atopic manifestations, congenital ichthyosiform erythroderma, and trichorrhexis invaginata (TI). We describe two sisters, aged 9 and 21 years, who presented to our dermatology outpatient clinic with short, brittle hair, ichthyosis, hypereosinophilia, and elevated immunoglobulin E (IgE) levels. The older sister also exhibited generalized lentiginosis. Dermoscopy of the scalp and eyebrow hairs demonstrated the characteristic features of TI, which were confirmed by light microscopic examination of plucked hairs. The clinical diagnosis of Netherton syndrome was based on the characteristic cutaneous features, hair shaft abnormalities, hypereosinophilia, and elevated serum IgE levels.

Introduction

Netherton syndrome (NS) is an autosomal recessive genodermatosis caused by pathogenic variants in *SPINK5*.[1] It is characterized by the triad of atopic manifestations, congenital ichthyosiform erythroderma, and trichorrhexis invaginata (TI), with an estimated incidence of 1 in 100,000–200,000 live births.[2] Ichthyosis linearis circumflexa (ILC), a hallmark feature of NS, may develop later in childhood or adulthood.[3] TI may be difficult to detect because only a subset of hairs, most commonly the eyebrows, is affected.[4] We report two sisters who presented with ichthyosis, short, brittle hair, food allergies, hypereosinophilia, and elevated serum immunoglobulin E (IgE) levels and were clinically diagnosed with NS. Notably, the older sister also presented with the rare finding of generalized lentiginosis.[5]

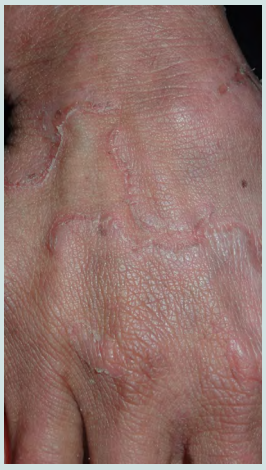

Figure 1: Typical ichthyosis linearis circumflexa lesion on the dorsum of the right hand.

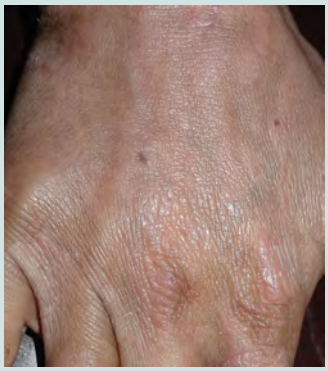

Figure 2: Complete resolution of ichthyosis linearis circumflexa 6 months after initiation of acitretin.

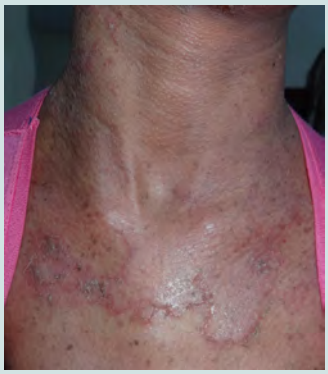

Figure 3: At presentation. Ichthyosis linearis circumflexa on the upper chest and generalized lentiginosis.

Case Report

Two sisters, aged 9 and 21 years, presented with a generalized rash, pruritus, xerosis, and short, brittle hair, all of which had been

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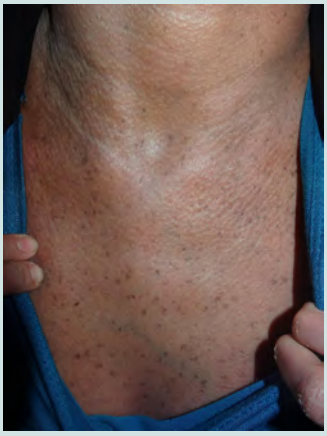

Figure 4: Six months after acitretin initiation. Complete resolution of the ichthyosis linearis circumflexa lesions. Note the lentigines.

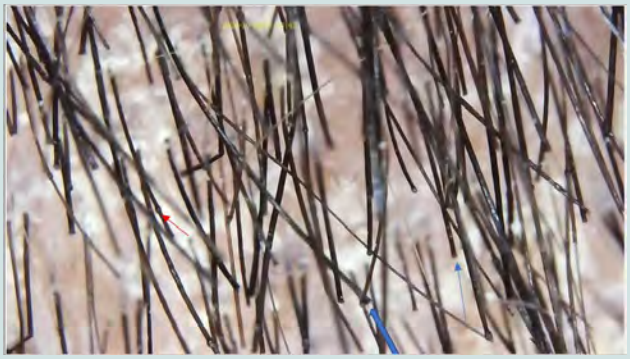

Figure 5: Trichoscopic image of the scalp hair showing trichorrhexis invaginata (red arrow) and a golf-tee hair (blue arrow).

Figure 6: Case 2. Light microscopic image of a bamboo hair.

present since birth (Figures 1–6). They were the fourth and eighth of eight siblings. Both were born to first-degree consanguineous parents and presented with erythroderma at birth (Figure 7). They also had recurrent cutaneous infections and allergic rhinitis. Since birth, both patients had dry, cracked skin, which had previously been regarded as mild ichthyosis and treated with emollients. Physical examination of both sisters revealed extensive xerosis and short, brittle hair. Peripheral eosinophilia was present in both patients, with eosinophil counts of 1184 cells/μL (16%) and 1258 cells/μL (17%), respectively. Total serum IgE levels were elevated at 2,500 and 1,160 IU/mL, respectively (normal value, <200 IU/mL). Trichoscopy and light microscopic examination of the scalp and eyebrow hairs in both sisters demonstrated the typical features of TI (Figures 5) (Figure 6). The diagnosis of NS was established based on the presence of allergic disease (i.e., atopic dermatitis, atopic diathesis, food allergies, hay fever, a history of anaphylaxis, elevated IgE levels, and eosinophilia), together with one or more of the following criteria:

1. Typical skin lesions – Scaling erythroderma, ILC. (present)
2. Typical hair findings – TI, "golf-tee," and "matchstick" hairs. (present)

3. Family history – History of NS in a sibling .(present)
4. Genetic testing – Identification of biallelic pathogenic germline *SPINK5* variants by DNA sequencing confirms the diagnosis in up to 75% of cases meeting the clinical diagnostic criteria. (Not performed because of the lack of testing facilities).[6]

Taken together, the erythroderma, ILC, elevated serum IgE levels, and atopic features supported the clinical diagnosis of NS. Both patients were initially treated with topical corticosteroids and emollients (Figures 1) (Figure 3). Given the reported safety and efficacy of oral acitretin for NS and other disorders of keratinization, we elected to initiate oral acitretin therapy at a dose of 0.62–1 mg/kg.[7] The treatment was well tolerated, with liver enzyme and lipid profile results remaining within normal limits. Mild cheilitis was observed but was successfully managed with a moisturizer. Overall, treatment markedly improved ILC, whereas TI remained unchanged. Genetic testing was not performed because of the lack of testing facilities, which represents a limitation of the present report. At the 6-month follow-up visit, both sisters showed near-complete resolution of their skin lesions (ILC), whereas TI showed no improvement (Figures 2) (Figure 4). Both patients remain under close dermatologic follow-up.

Discussion

Trichoscopy of the eyebrow and scalp hairs in both sisters demonstrated the typical features of NS, namely bamboo, golf-tee, and matchstick hairs, along with less common findings such as pili torti and trichorrhexis nodosa (Figures 5) (Figure 6).[8]

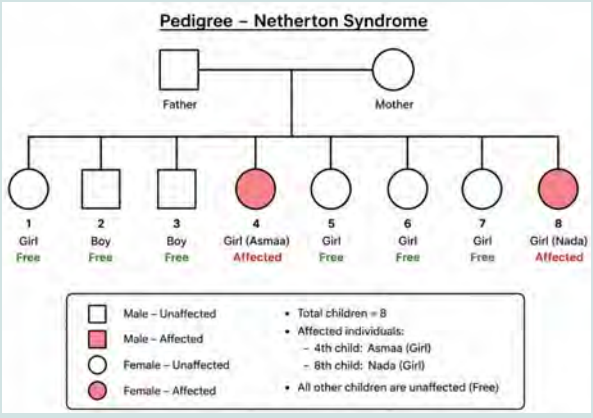

Figure 7: Pedigree of the family.

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Both sisters presented with features typically reported in NS. The older sister additionally presented with generalized lentiginosis, which has previously been reported only once by Xu et al. in a Chinese patient with NS. [5,9] This phenotypic difference raises questions regarding the genotype–phenotype correlation in NS, considering that both sisters presumably inherited the same *SPINK5* variant. [10] However, intrafamilial and interfamilial phenotypic variation has previously been reported in patients with NS. Furthermore, the clinical presentation in the present case is consistent with the findings reported by Xu et al. Generalized lentiginosis in NS has also been reported by Moutran et al. following prolonged narrowband ultraviolet B phototherapy.[9]

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