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CASE REPORT

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A Case with Netherton Syndrome-Classical Findings in Late Diagnosis

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ABSTRACT

Netherton syndrome is a rare disease with autosomal recessive inheritance and characterized by the triad of congenital ichthyosiform erytroderma, trichorrhexis invaginata, and atopic manifestations. We herein report a patient who presented to the pediatric allergy and clinical immunology outpatient clinic with signs of ichthyosis, multiple food allergy, anaphylaxis, hypereosinophilia, and hyperimmunoglobulinemia E (hyper-IgE), and was diagnosed as having Netherton syndrome.

Keywords: Anaphylaxis, hypereosinophilia, hyper-IgE, ichthyosis, multiple food allergy, netherton syndrome

INTRODUCTION

Netherton syndrome is an autosomal recessive disease caused by mutation of the *SPINK5* gene and is characterized by the triad of congenital ichthyosiform erythroderma, trichorrhexis invaginata, and atopic manifestations (1). The incidence is 1 in 200 000, and congenital erythroderma is seen in 18% of patients (2). At older ages, ichthyosis linearis circumflex can occur, which is a characteristic finding of Netherton syndrome (3). Trichorrhexis invaginata is a hair abnormality that can be found on the eyelashes of young children and the hair of older children (4). It can be difficult to detect on the scalp because only 20% to 50% of the follicles may be affected (5). Atopic symptoms constitute a very wide spectrum and may involve serious effects such as anaphylaxis. These clinical features vary from patient to patient. We herein report a patient who presented to the pediatric allergy and clinical immunology outpatient clinic with signs of ichthyosis, multiple food allergy, anaphylaxis, hypereosinophilia, and hyperimmunoglobulinemia E (hyper-IgE), and was diagnosed as having Netherton syndrome. The informed consent form was signed by the parent.

CASE REPORT

A girl aged 4 years and 10 months presented to the pediatric allergy and clinical immunology outpatient clinic with generalized rash and itching. She was born by cesarean delivery at 34 weeks of gestation and a weight of 2140 g. Due to postnatal respiratory distress, she was transferred to the neonatal intensive care unit for suspected transient tachypnea of the newborn. She received ampicillin, gentamicin, and oxygen hood therapy. Phototherapy was performed for indirect hyperbilirubinemia. Her skin had been dry and cracked since birth and was evaluated as mild ichthyosis by the dermatology department and treated with a moisturizing cream.

On postnatal day 16, she was admitted to the pediatric emergency department of another hospital with complaints of rash and vomiting. Erythroderma was observed on physical examination, and empiric ampicillin and cefotaxime treatment was initiated. A single dose of intravenous diuretic was administered on postnatal day 19 due to marked body edema.

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The patient had periodic exacerbations of her cutaneous symptoms. At the age of 4 years, she presented again to another center due to growth retardation and ichthyosis. Physical examination revealed extensive dryness of the skin and syndromic facies. She had developmental delay, with first speech production at the age of 2.5 to 3 years, and no benefit was observed with special education. Chromosome analysis was requested with a suspicion of mosaic Down syndrome due to her mental retardation and syndromic appearance. The result of chromosome analysis was 46,XX. She had a history of receiving up to 1 week of antibiotic therapy 7 to 8 times a year for throat infections that did not require hospitalization, 2 to 3 times a year for persistent productive cough, and once for ear infection in the last year.

The patient presented to our clinic for generalized rash and itching (the patient's pictures have been presented below as Figure 1).

On physical examination, her weight was below the 3rd percentile and height was between the 10th and 25th percentile. There was mild to moderate generalized ichthyosis on her body. Her skin lesions were not compatible with atopic dermatitis. Other system examinations and celiac autoantibody, thyroid function, biochemistry, and urine analyses were normal. Her white blood cell count was 15 000 × 10^{9}/L, eosinophil ratio was 22%, and IgE level was 2 343 IU/L. Other immunoglobulin levels (IgA, IgG, IgM, IgG subgroups) and lymphocyte subgroups (CD3, CD4, CD8, CD14, CD19, CD56) were normal.

She had a history of anaphylaxis to walnut, egg, and hazelnut. Her basal tryptase level was 7.46 μg/L (normal) and specific IgE levels were high. A skin prick test was performed during a period of better skin integrity. Skin prick test results were positive for walnut, hazelnut, and egg. The patient was started on an elimination diet and recommendations for skin care and moisturizing were given. An adrenaline autoinjector was prescribed and the family was educated on its usage.

The brother of our patient, who was born from the parents' first pregnancy, had undergone surgery for cleft palate and heart disease. He died at the age of 8 months due to frequent lung infections.

Considering the patient's symptoms of ichthyosis, growth retardation and hypereosinophilia, hyper-IgE genetic analysis was requested to assess for Netherton syndrome and hyper-IgE syndromes. The patient was found to carry a homozygous c.2112 + 2T>1A genetic change in the 22nd intron of the *SPINK5* gene that was

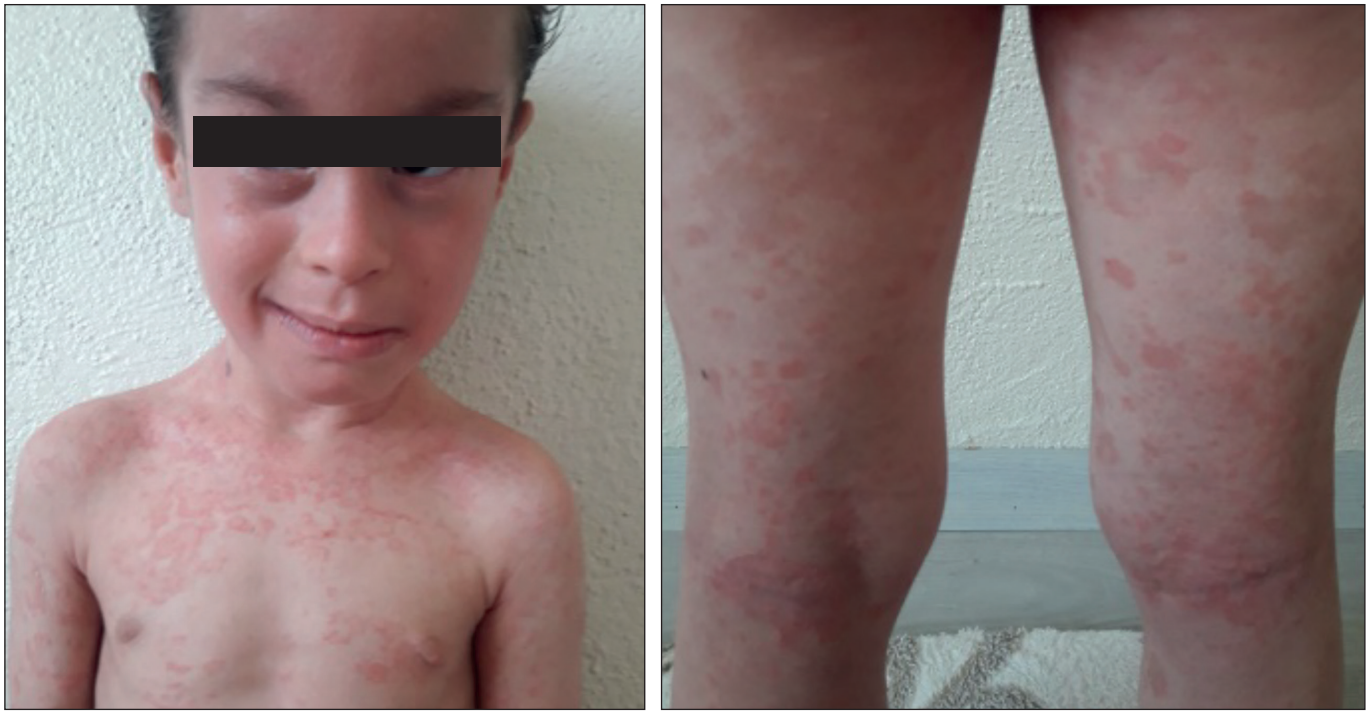

Figure 1. The appearance of the patient face, trunk and extremities.

evaluated as pathogenic according to the American College of Medical Genetics and Genomics (ACMG) 2015 criteria. The patient was diagnosed as having Netherton syndrome and genetic counseling was provided to the family by the genetics department.

DISCUSSION

Netherton syndrome was first described by Comel in 1949, and its association with hair shaft anomalies and congenital ichthyosiform erythroderma was described by Netherton in 1958 (6). In 1964, the shaft anomaly was defined by Wilkinson et al. as trichorrhexis invaginata (7). This autosomal recessive genetic disease occurs as a result of mutations in both *SPINK5* genes (8). The *SPINK5* mutation was first reported by Sarri, and 80 different mutations have been reported to date (9).

The *SPINK5* gene is located on chromosome 5 (5q21) (10). *SPINK5* encodes the serine protease inhibitor protein LEKTI, which plays a role in epidermal differentiation and barrier formation by inhibiting members of the kallikrein group of serine proteases (KLK5, 7, and 14) (11). Any defect in the gene causes a broad spectrum of atopic disorders, from severe atopic dermatitis to anaphylaxis (12). In addition to dermatitis, our patient had a history of anaphylaxis to egg, walnut, and hazelnut. Her family reported that she had anaphylaxis immediately after eating eggs when she was 2 years old. Eggs and egg-containing foods were eliminated, but anaphylaxis occurred again during follow-up after eating walnuts.

Komatsu et al. demonstrated that many kallikreins are expressed in the pituitary gland (13). Kallikreins are produced together with growth hormone, which is proteolytically processed by kallikreins before entering the systemic circulation. LEKTI can prevent this inactivation, but in the presence of *SPINK5* mutation, excessive inactivation of growth hormone results in growth retardation (14). In the literature, growth hormone deficiency was detected in 3 cases with Netherton syndrome, and it has been reported that both skin lesions and growth rates improved with growth hormone treatment (14). Because our patient had growth and developmental delay but height within the normal range, growth hormone deficiency was not considered.

Erythroderma on the body is common in the neonatal period and is replaced by ichthyosis linearis circumflexa in the second year of life (15). Although erythroderma generally occurs in the neonatal period and improves over time, generalized erythroderma continues throughout adulthood in some individuals (15). Impairment of the epidermal barrier causes skin dryness, redness, and scaling (16). The lesions of our patient, who had skin lesions since birth and was evaluated as having mild ichthyosis, persisted with intermittent exacerbations and remissions. Hypernatremic dehydration and protein loss from the skin may occur in connection with skin lesions (17). In our case, the patient received diuretic once intravenously on postnatal day 19 due to unexplained edema.

Another characteristic finding of Netherton syndrome is trichorrhexis invaginata, also known as bamboo hair, on microscopic examination (5). Hair anomalies may manifest as trichorrhexis invaginata, pili torti, and/or trichorrhexis nodosa (18). Classic hair symptoms may be detected late due to delayed hair growth and because 20% to 50% of hairs may be affected (5). Trichorrhexis invaginata was not observed in our patient's hair or scalp examination, which may be attributed to a lack of detailed examination of multiple areas.

Kallikrein deficiency is associated with a spectrum of atopic disease. Patients with Netherton syndrome present with allergic rhinitis, angioedema, asthma, urticaria, anaphylaxis, and often serum IgE elevation (15). Patients with atopic patterns and normal serum IgE levels have also been reported in the literature (5). Our patient had hyper-IgE consistent with the classical presentation. Immunological abnormalities and lack of antibodies against bacterial polysaccharides have also been reported in some patients (19). Our patient had a history of receiving up to 1 week of antibiotic therapy 7 to 8 times a year for throat infections that did not require hospitalization, 2 to 3 times a year for persistent productive cough, and once for ear infection in the last year. Her Ig values, lymphocyte subgroup counts, and antibody responses were normal, but the polysaccharide vaccine response could not be checked.

Other features of the disease and their prevalence rates include aminoaciduria (25%), mental retardation (15%), recurrent infection and IgG abnormalities (15%), and seizure (<10%) (20). Our patient exhibited developmental delay.

There is no proven cure for Netherton syndrome, but complications can be prevented with early diagnosis (1). Skin lesions are treated with moisturizers, antihistamine drugs, antibiotics, and topical corticosteroids (9). In

our case, treatment involved moisturizers and skin care recommendations.

Netherton syndrome is difficult to diagnose because the clinical presentation is different in every patient and has atypical forms. Non-bullous congenital ichthyosiform erythroderma can be confused with diseases such as atopic dermatitis and Leiner's disease (5). Skin findings of neonatal patients are often evaluated as atopic dermatitis. Complications due to prescribed corticosteroids can occur during clinical exacerbations. Cases with complications such as iatrogenic Cushing's syndrome, growth retardation, osteoporosis, and pituitary and gonad suppression due to chronic corticosteroid use have also been reported (4). There are also reports of patients who were misdiagnosed as having Leiner disease due to symptoms of hypernatremic dehydration, erythroderma, and enteropathy (5).

In conclusion, including Netherton syndrome in the differential diagnosis of children with congenital ichthyosis will prevent diagnostic delay and improve the quality of life for both the patient and family with early genetic counseling.

Conflict of Interest

None.

Authorship Contributions

Concept: **Emine Vezir,** Design: **Emine Vezir,** Data collection or processing: **Emine Vezir, Ezgi Günce Nural Kırcı, Ayşegül Özcan,** Analysis or Interpretation: **Emine Vezir,** Literature search: **Emine Vezir, Ezgi Günce Nural Kırcı,** Writing: **Emine Vezir, Ezgi Günce Nural Kırcı,** Approval: **Emine Vezir.**

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