Case Reports in Dermatology

Case Rep Dermatol 2024;16:47–54
DOI: 10.1159/000536083
Received: August 23, 2023
Accepted: January 1, 2024
Published online: February 23, 2024

Single Case

Netherton Syndrome with a Novel Likely Pathogenic Variant c.420del (p.Ser141ProfsTer5) in SPINK5 Gene: A Case Report

Katya Kovacheva[a] Zornitza Kamburova[a] Preslav Vasilev[b]
Ivelina Yordanova[b]

[a]Department of Medical Genetics, Faculty of Pharmacy, Medical University, Pleven, Bulgaria;
[b]Department of Dermatology, Venereology and Allergology, Faculty of Medicine, Medical University, Pleven, Bulgaria

Keywords
Netherton syndrome · *SPINK5* gene mutation · Trichorrhexis invaginata · Acitretin · Case report

Abstract
Introduction: Netherton syndrome (NS) is a rare autosomal recessive genodermatosis in the group of congenital ichthyosis. The clinical manifestations of the syndrome vary from a very mild clinical manifestation occurring with the picture of ichthyosis linearis circumflexa to exfoliative erythroderma. It can be fatal in the first days of a newborn's life due to dehydration, hypothermia, weight loss, respiratory infections, and sepsis. A specific anomaly of the hair trichorrexis invaginata is considered pathognomonic for the syndrome. Genetic testing of *SPINK5* gene is key to confirming the diagnosis and starting early treatment. ***Case Presentation:*** We present a case report of NS in a 6-year-old boy who suffered from generalized erythroderma and desquamation of the skin from birth. The patient has atopic diathesis, recurrent skin infections, increased levels of IgE, and delayed physical development. Two genetic variants in *SPINK5* gene with clinical significance were identified. The first detected variant is a nonsense mutation, predicted to cause loss of normal protein function either by protein truncation or by nonsense-mediated mRNA decay. The second variant is a likely pathogenic frameshift mutation that truncates the protein in 5 amino acids. The child was treated with acitretin, without satisfactory effect. ***Conclusion:*** The genetic variant we have described correlates with a severe clinical phenotype of NS. The second genetic variant of the *SPINK5* gene, inherited from the father in our case, is novel and has never been published in the literature.

Correspondence to:
Ivelina Yordanova, ivelina_yordanova@abv.bg

Case Rep Dermatol 2024;16:47–54
DOI: 10.1159/000536083

Introduction

Netherton syndrome (NS) is a rare disease that often causes serious complications in the neonatal period. It can be fatal in the first days of the newborn's life due to dehydration, hypothermia, weight loss, respiratory infections, and sepsis. The disease occurs in 1:200,000 newborns and predominantly affects females. The clinical manifestations of the syndrome vary from a mild clinical manifestation occurring with the picture of ichthyosis linearis circumflexa to exfoliative erythroderma. Other complications associated with the syndrome are mental and physical retardation. The genetic variant leading to these clinical manifestations is located in the *SPINK5* gene on chromosome 5q32 [1, 2]. A case of NS with two genetic variants in the *SPINK5* gene with clinical significance here is presented. The first detected variant is a nonsense mutation predicted to cause loss of normal protein function either by protein truncation or nonsense-mediated mRNA decay, reported only once as a pathogenic variant. The second variant, a likely pathogenic frameshift mutation that truncates the protein in 5 amino acids, is novel and has never been published in the literature or population data.

Case Presentation

We present a 6-year-old boy, born at 37 weeks of gestation (weight 3,350 g and height 53 cm) after a second normal pregnancy. After birth, he was diagnosed with congenital ichthyosiform erythroderma. On the fifth postnatal day, the child was admitted to the neonatal intensive care unit with a neonatal infection and poor general health. Due to aggravation of the condition, occurring as severe erythema, edema, and leakage of serous exudate from the skin, he was treated intravenously with antibiotics, human albumin 200 g/L solution, systemic antihistamines, and topical corticosteroids and emollients. Despite the treatment, the skin remained red and very dry, covered with erosions and yellowish foul-smelling scales, including areas of the capillitium and external auditory canals. After discharge of the patient, daily topical therapy with emollients and follow-up was administered. At the age of six, the child was in good general health, with normal neuropsychological development and slightly delayed physical development, and he was 109.5 cm tall and weighed 19 kg with a body mass index of 17. Cardiovascular and respiratory systems were normal. The dermatological examination revealed pathological skin changes on the scalp, face, thorax, and extremities, presented by diffuse erythema and lamellar desquamation. Well-contoured, erythematosquamous plaques covered by large yellowish scales on the extensor surface of the upper limbs, the thighs, and the posterior surface of the lower legs were detected (Fig. 1a, b). Squamous crust plugs were found in the area of the external auditory canals. Ectropion of both eyes was found. There were no pathological changes on the nails. The child had fragile and brittle hair (Fig. 1c). Trichoscopy of the scalp revealed hair shaft changes typical for trichorrhexis invaginata (TI) (Fig. 1d). Eyebrow hairs and some eyelashes were missing. Complete blood count and biochemistry laboratory test results were normal, except for 25-OH vitamin D serum deficiency (39.99 nmol/L), insulin-like growth factor, thyroid-stimulating hormone, thyroxin-free, cortisol, and somatotropic hormone showed values within normal ranges for his age. Immunological test results for IgA, IgG, and IgM were normal, except for an increased IgE value above the upper reference limit (173 IU/mL, average norm <90 IU/mL for individuals aged 6–9 years). Histopathological examination of the skin showed hyperkeratosis with parakeratosis and psoriasiform epidermal hyperplasia (Fig. 2). Microbiological skin examination showed *Proteus mirabilis*. A right palm and wrist radiograph showed evidence of delayed ossification. In addition, an X-ray of the thoracic and lumbar vertebrae (face and profile) was taken to determine the bone

Case Rep Dermatol 2024;16:47–54
DOI: 10.1159/000536083

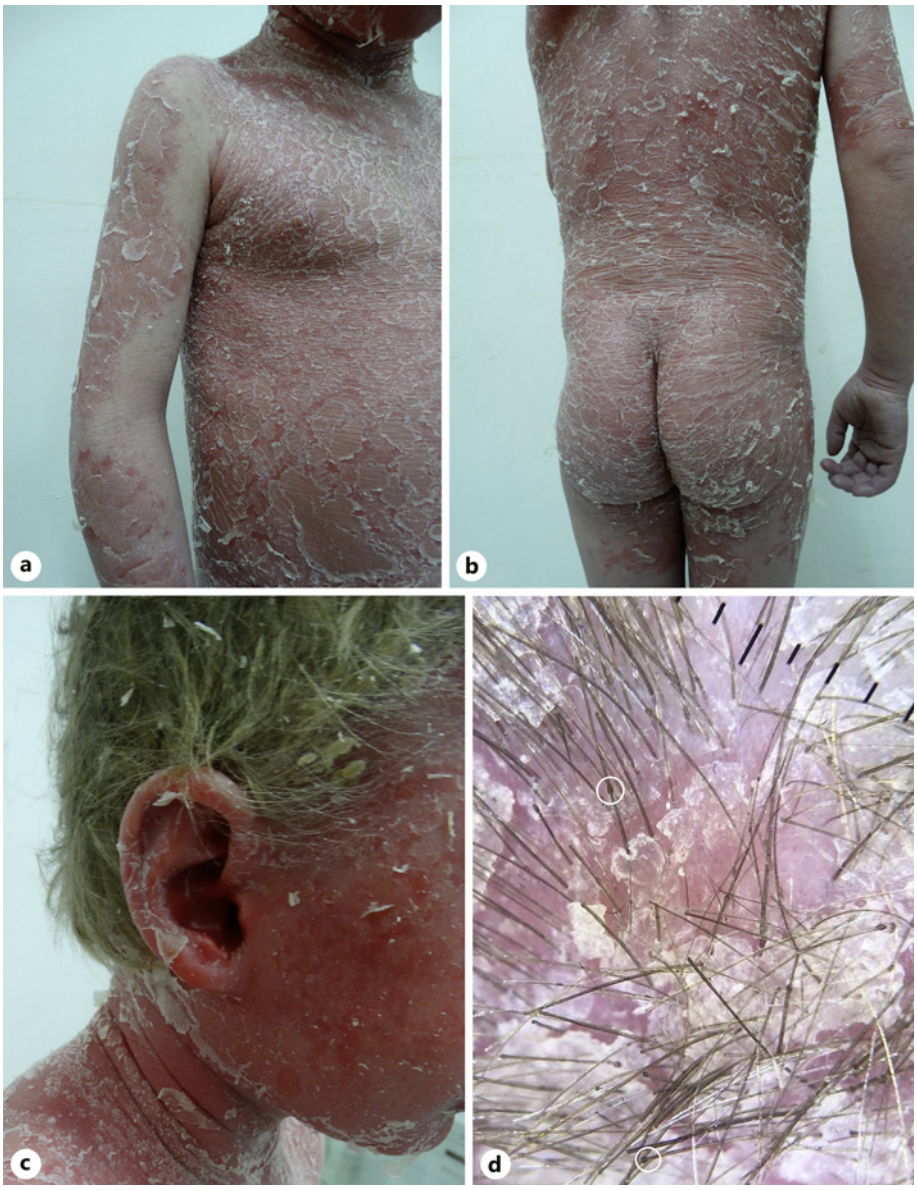

Fig. 1. a, **b** Erythematosquamous plaques covered by large yellowish scales on the extensor surface of the upper limbs, thorax, and thighs. **c** Brittle hair and severe desquamation of the face and scalp. **d** Trichoscopy: hair shafts changes type trichorrhexis invaginata (3Gen DermLite DL4, with polarized light, magnification x10).

age; it corresponded to the age of 4. Genetic testing and counseling of the patient and his family were performed. The pedigree (including 40 relatives from four generations) did not identify any other affected relatives with a similar disease or skin manifestation as the proband. After obtaining written informed consent from the parents for DNA analysis, EDTA-anticoagulated venous blood samples were collected from the patient, parents, and siblings. DNA extraction was done using MagCore Genomic Whole Blood Kit following the manufacturer's instructions. The genetic testing was performed by next-generation sequencing. TruSight One Expanded Sequencing Panel (Illumina©) containing oligo probes targeting exons and exon-intron boundaries of 6,699 genes with clinical significance was used. Qualified libraries were sequenced on the Illumina NextSeq

Case Rep Dermatol 2024;16:47–54
DOI: 10.1159/000536083

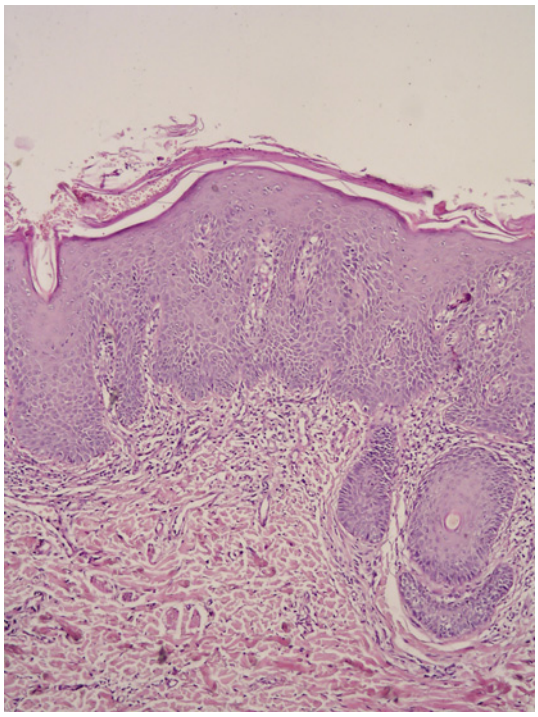

Fig. 2. Histopathological examination of the skin: hyperkeratosis with parakeratosis and psoriasiform epidermal hyperplasia (H&E, magnification x25).

550 platform with a 2 × 150 bp configuration. Reads were aligned to the reference human genome hg19. Data output files (gVCF) were imported into BaseSpace Variant Interpreter (Illumina©), an analysis software, which uses tool GATK for variant calling. Custom filters (including a minimum read depth of 20× per variant and excluding silent variants) were created to improve variant annotation and interpretation. The five-tier terminology system of the American College of Medical Genetics and Genomics (ACMG) was used (Richards et al. [3], 2015). The variants automatically annotated by the software were manually checked in the main human genome databases: ClinVar (www.ncbi.nlm.noh.gov/clinvar), dbSNP (www.ncbi.nlm.noh.gov/projrct/SNP), and Ensembl (http://www.ensembl.org). The genetic testing of the proband revealed two genetic variants with clinical significance in the *SPINK5* gene. The first one was pathogenic variant c.1530C>A (p.Cys510Ter) (NM_006846) and is shown in Figure 3a. The second likely pathogenic c.420del (p.Ser141ProfsTer5) (NM_006846) is shown in Figure 3b. Segregation analysis of the family confirmed that the first variant was inherited from the mother and the second from the father. The proband's elder unaffected brother was tested and confirmed to be a heterozygous carrier of the father's variant only – c.420del (p.Ser141ProfsTer5). Based on the data from the medical history, dermatological status, paraclinical examinations, genetic consultation, and DNA analysis, the NS diagnosis was accepted with two genetic variant with clinical significance in the *SPINK5* gene. Consultations: a pediatric endocrinologist revealed growth retardation and bone maturation: height at the 10th percentile, body weight at the 25th percentile. The child has discrete dysmorphic stigmata, including a large thumb, male genitalia, normal penis size, and both testicles in the scrotum. An ophthalmologist found ectropion of both eyes – the upper eyelids do not cover the eyeballs well (lagophthalmos). The right eye's upper eyelid had slight ptosis, and the lower eyelid was slightly retracted. Fluorescent staining revealed keratitis: the right and left eye corneas had two paracentral defects in the area of the palpebral fissure. Both eyes had transparent lenses and fundi without pathological changes. An otorhinolaryngologist revealed otitis externa diffusa, attributable to the main disease. Treatment with gentamycin 40 mg i.m./daily for 7 days, levocetirizine dihydrochloride sol. 2 × 5 drops/daily,

Case Rep Dermatol 2024;16:47–54
DOI: 10.1159/000536083

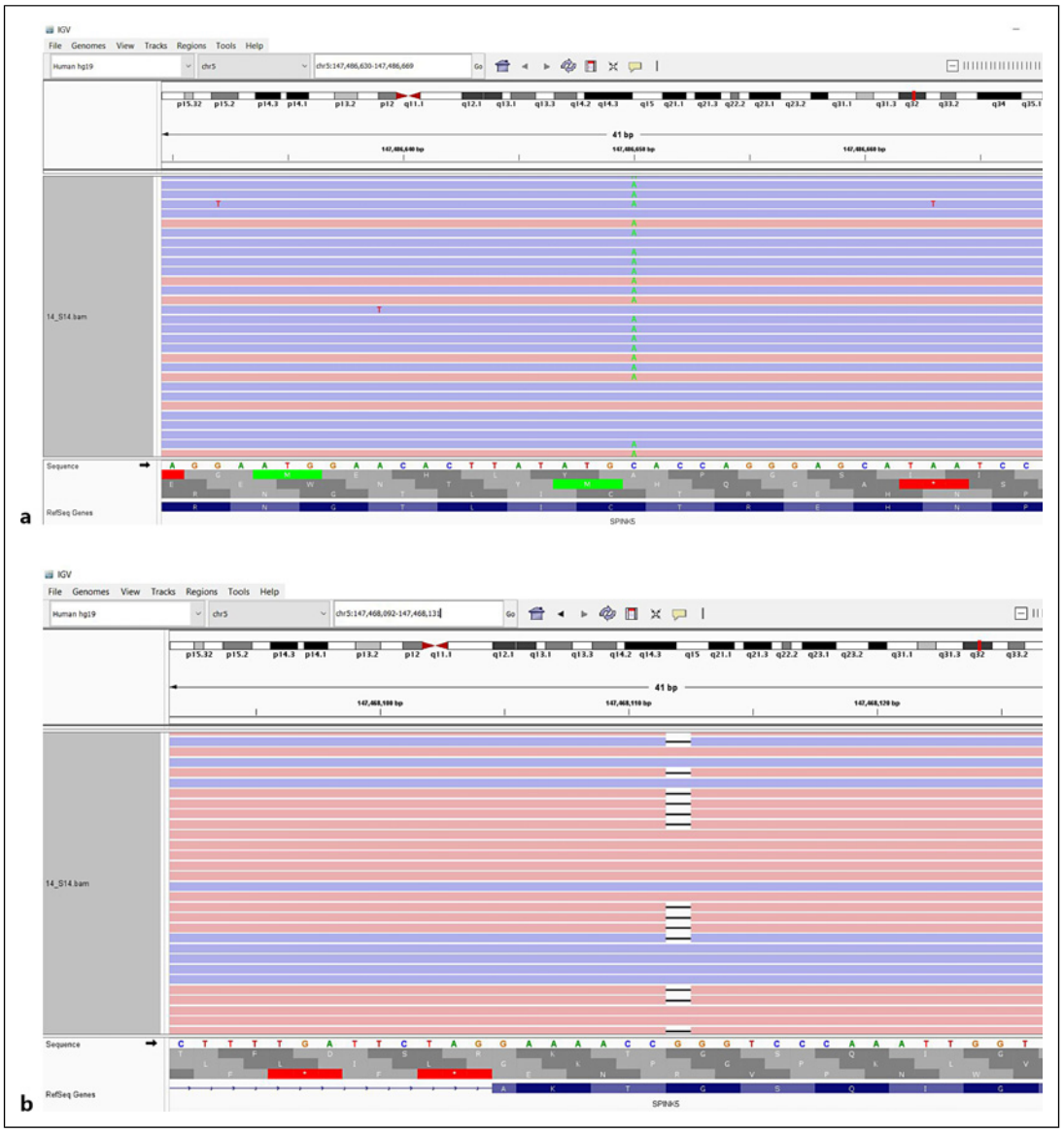

Fig. 3. **a** Integrative Genomics Viewer (IGV) visualization of the pathogenic variant c.1530C>A p.(Cys510Ter) (NM _006846) in the proband. **b** Integrative Genomics Viewer (IGV) visualization of the likely pathogenic variant c.420del p.(Ser141ProfsTer5) (NM _006846) in the proband.

cholecalciferol oral drops solution 2,000 IU/daily was started. Systemic treatment with acitretin at 0.5 mg/kg/day was initiated. Topical skincare was carried out with an emollient cream prepared from 50:50 white soft paraffin and liquid paraffin, applied several times daily to the face and whole body, and baths of the whole body with sodium bicarbonate twice a week. Keratitis was treated with tobramycin eye drops solution, dexpanthenol 5% eye gel, and artificial tears. The child was discharged with a slight improvement. A long-term course with acitretin was recommended against the background of monitoring bone age, values of biochemical tests, and complete blood count every 2 months. After 3 months of systemic therapy with acitretin in the above dose, we found worsening with severe thinning and erosion of the skin due to persistent erythroderma. The treatment with this medication was discontinued. The child is followed up.

Case Rep Dermatol 2024;16:47–54
DOI: 10.1159/000536083

Discussion

The NS (S. Syndroma Comel-Netherton OMIM 256500) was first described by Comel in 1949 and subsequently by Netherton in 1958 as a rare autosomal recessive genodermatosis in the group of congenital ichthyoses [1]. Clinically, the syndrome is characterized by congenital ichthyosiform erythroderma, an atopic diathesis presenting with food allergies and asthma, recurrent skin infections, increased levels of IgE, and delayed physical development. Congenital erythroderma occurs immediately after birth and presents with generalized diffuse erythema and desquamation [2]. Some babies are born wrapped in a cellophane-like membrane (collodion baby). Over time, erythroderma evolves into ichthyosis linearis circumflexa, represented by transient serpiginous double-contoured erythematosquamous plaques. Itching is a constant accompanying sign of the disease. A specific abnormality of hairs in the capillitium TI (also called bamboo hair) is considered pathognomonic for the syndrome. TI presents as an infolding of the distal part of the hair shaft toward its proximal part, giving a "ball in a hoop" appearance [4]. Visualization of TI by dermatoscopy of hair shafts (trichoscopy) facilitates the diagnosis, as in our case [5]. Single cases of pilli torti and trichorrhexis nodosa also have been described in the literature in combination with NS. As a result of a genetic variant located in the *SPINK5* gene in NS, the activity of the protein named lymphoepithelial Kazal-type-related inhibitor (LEKTI) is lost [1, 6]. Normally, LEKTI is expressed in the outermost layers of the skin and plays an essential role in regulating a family of proteolytic enzymes, kallikreins, by inhibiting them [7]. Premature degradation of corneodesmosomes in the process of epidermal desquamation is observed. More recent studies have shown that LEKTI indirectly inhibits elastase 2 – a protease enzyme that forms profilaggrin. The lack of LEKTI, damages the skin's protective function, facilitating the penetration of bacterial, fungal, and toxic agents and allergens. This causes atopic diathesis and chronic skin inflammation characteristic of the syndrome [8]. The exact mechanism of immunological dysfunction in NS is not fully understood. Patients with this syndrome have higher than normal levels of IgE and IgG4, low numbers of natural killer cells, and increased levels of proinflammatory cytokines (IL-1β, IL-12, TNFα, IL-2, IL-19) in the serum and skin [9]. All this makes patients with NS susceptible to recurrent infections. The differential diagnosis of NS includes the Omenn syndrome, nonbullous ichthyosiform erythroderma, generalized seborrheic dermatitis, erythrodermic psoriasis, severe atopic dermatitis, staphylococcal scalded skin syndrome, and hyper-IgE syndrome. The diagnosis of NS can be verified by identifying a *SPINK5* genetic variants, by DNA sequencing – 92 pathogenic/likely pathogenic variants have been found in the *SPINK5* gene in NS patients [3]. Most of the genetic variant described so far is associated with premature termination, consistent with the variants discovered in our proband [1]. The first variant detected in our case – c.1530C>A p.(Cys510Ter) inherited from the mother, has been published only once as a pathogenic variant in a 15-year-old male with NS and acute lymphoblastic leukemia [10]. The variant is a nonsense mutation predicted to cause loss of normal protein function either by protein truncation or nonsense-mediated mRNA decay. The second detected variant in the proband – a likely pathogenic frameshift mutation – c.420del p.(Ser141ProfsTer5), inherited from the father, is novel and has never been published in the literature or population data [11]. It is a frameshift variant that truncates the protein in 5 amino acids. There is no causal treatment for NS. Therapeutic possibilities include applying local corticosteroids and calcineurin inhibitors, local retinoids, Narrowband ultraviolet B therapy, psoralens, and ultraviolet A therapy. In more severe cases, systemic acitretin has been used with variable success. In some cases, significant improvements in erythema and desquamation have been described [12]. Other authors found a worsening skin condition in patients with NS on the background of

treatment with oral acitretin, similar to the case we described [13]. New therapeutic options in cases of very severe NS are treatment with intravenous immunoglobulin and anti-TNF-α inhibitors. Fontao et al. [14] found that infusion of recombinant humanized monoclonal anti-TNF-alpha antibody in patients with NS reduced the expression of IL-6 and IL-8 in the skin with remarkable sustained improvement in skin lesions and hair growth, possibly in association with a Th2 to Th1 shift in the systemic immune response. The atopic eczematous lesions and pruritus in NS improved remarkably during treatment with dupilumab, ixekizumab, and anakinra, dramatically improving the patient's quality of life [15].

Conclusion

With the presentation of the characteristic skin signs, atopic diathesis, and TI, diagnosing NS is easy. When clinical signs are atypical or absent, it may be delayed. Genetic testing of the *SPINK5* gene is key to confirming the diagnosis and starting early treatment. The genetic variants we have described correlate with a severe clinical phenotype of NS in our patient. The second genetic variant of the SPINK5 gene, inherited from the father in our case, is novel and has never been published in the literature. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000536083).

Acknowledgments

Diagnostic genetic test in our case report was performed in the frame of the Project BG05M20P001-1.002-0010-C01 "Center of competence in personalized medicine, 3D and telemedicine, robot-assisted and minimally invasive surgery," funded by the "Science and Education for Smart Growth" – Operational Programme, financed by the European Union, through the European Regional Development Fund, with the leading organization Medical University – Pleven, Bulgaria.

Statement of Ethics

This study protocol was reviewed and approved by Commission on Ethics of Research Activity at Medical University Pleven, Bulgaria, approval number No. 573/July 4, 2019. We state that a written informed consent was obtained from participants for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

Authors must give full details about the funding of any research relevant to their study, including sponsor names and explanations of the roles of these sources in the preparation of data or the manuscript.

Author Contributions

We acknowledge that all coauthors in this manuscript have contributed substantially to describing and presenting this rare clinical case. Dermatologist Prof. Ivelina Yordanova made the clinical diagnosis, carried out the relevant paraclinical examinations and consultations with other medical specialists (medical geneticist, pediatric endocrinologist, ophthalmologist, otorhinolaryngologist). Dr. Preslav Vasilev made trichoscopy and photo-documentation of the patient. Both physicians followed the patient during conducted treatment with acitretin. Medical geneticists Prof. Katya Kovacheva and Dr. Zornitza Kamburova performed the proband's and his parents' genealogical and genetic mutational analysis. They found the two genetic variants in *SPINK 5* genes. All four coauthors have made an equal contribution to the discussion and conclusion of the case. All contributors to the manuscript fulfill the ICMJE criteria for authorship.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

References

1 Chavanas S, Garner C, Bodemer C, Ali M, Teillac DH, Wilkinson J, et al. Localization of the Netherton syndrome gene to chromosome 5q32, by linkage analysis and homozygosity mapping. Am J Hum Genet. 2000;66(3):914–21.
2 Miteva L, Pramatarov K. Netherton syndrome: report of a case with epilepsy. Eur J Pediatr Dermatol. 1999;9(4):219–2.
3 Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405–24.
4 Rakowska A, Slowinska M, Kowalska-Oledzka E, Rudnicka L. Trichoscopy in genetic hair shaft abnormalities. J Dermatol Case Rep. 2008;2(2):14–20.
5 Bittencourt MD, Moure ER, Pies OT, Mendes AD, Deprá MM, Mello AL. Trichoscopy as a diagnostic tool in trichorrhexis invaginata and Netherton syndrome. An Bras Dermatol. 2015;90(1):114–6.
6 Chavanas S, Bodemer C, Rochat A, Hamel-Teillac D, Ali M, Irvine AD, et al. Mutations in SPINK5, encoding a serine protease inhibitor, cause Netherton syndrome. Nat Genet. 2000;25(2):141–2.
7 Furio L, Pampalakis G, Michael IP, Nagy A, Sotiropoulou G, Hovnanian A. KLK5 inactivation reverses cutaneous hallmarks of Netherton syndrome. PLoS Genet. 2015;11(9):e1005389.
8 Williams MR, Cau L, Wang Y, Kaul D, Sanford JA, Zaramela LS, et al. Interplay of staphylococcal and host proteases promotes skin barrier disruption in Netherton syndrome. Cell Rep. 2020;30(9):2923–33.e7.
9 Stuvel K, Heeringa JJ, Dalm VA, Meijers RW, van Hoffen E, Gerritsen SA, et al. Comel-Netherton syndrome: a local skin barrier defect in the absence of an underlying systemic immunodeficiency. Allergy. 2020;75(7):1710–20.
10 Skoczen S, Stepien K, Mlynarski W, Centkowski P, Kwiecinska K, Korostynski M, et al. Genetic signature of acute lymphoblastic Leukemia and Netherton syndrome co-incidence—first report in the literature. Front Oncol. 2019;9:1477.
11 Variants of SPINK5. Available from: https://www.ncbi.nlm.nih.gov/clinvar (accessed Dec 2, 2022).
12 Lazaridou E, Apalla Z, Patsatsi A, Trigoni A, Ioannides D. Netherton's syndrome: successful treatment with isotretinoin. J Eur Acad Dermatol Venereol. 2009;23(2):210–2.
13 Yadav N, Madke B, Kar S, Gangane N. Netherton syndrome: an atypical presentation. Cutis. 2019;103(4):E27–9.
14 Fontao L, Laffitte E, Briot A, Kaya G, Roux-Lombard P, Fraitag S, et al. Infliximab infusions for Netherton syndrome: sustained clinical improvement correlates with a reduction of thymic stromal lymphopoietin levels in the skin. J Invest Dermatol. 2011;131(9):1947–50.
15 Wang J, Yu L, Zhang S, Wang C, Li Z, Li M, et al. Successful treatment of Netherton syndrome with dupilumab: a case report and review of the literature. J Dermatol. 2022;49(1):165–7.