A 9-year-old boy presented to the dermatology clinic with a scaly eruption distributed throughout the body that had been present since birth. He had been diagnosed with atopic dermatitis by multiple dermatologists prior to the current presentation and had been treated with various topical steroids with minimal improvement. He had no family history of similar eruptions and no personal history of asthma or allergies. Physical examination revealed erythematous, serpiginous, polycyclic plaques with peripheral, double-edged scaling. Decreased hair density of the lateral eyebrows also was observed.

WHAT’S YOUR DIAGNOSIS?

a. acrodermatitis enteropathica
b. erythema marginatum
c. erythrokeratodermia variabilis
d. neonatal lupus
e. Netherton syndrome

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The authors report no conflict of interest.
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THE Diagnosis: Netherton Syndrome

A punch biopsy from the right lower back supported the clinical diagnosis of ichthyosis linearis circumflexa. The patient underwent genetic testing and was found to have a heterozygous mutation in the serine protease inhibitor Kazal type 5 gene, SPINK5, that was consistent with a diagnosis of Netherton syndrome.

Netherton syndrome is an autosomal-recessive genodermatosis characterized by a triad of congenital ichthyosis, hair shaft abnormalities, and atopic diatheses. It affects approximately 1 in 200,000 live births; however, it is considered by many to be underdiagnosed due to the variability in the clinical appearance. Therefore, the incidence of Netherton syndrome may actually be closer 1 in 50,000 live births. The manifestations of the disease are caused by a germline mutation in the SPINK5 gene, which encodes the serine protease inhibitor LEKTI. Dysfunctional LEKTI results in increased proteolytic activity of the lipid-processing enzymes in the stratum corneum, resulting in a disruption in the lipid bilayer. Dysfunctional LEKTI also results in a loss of the anti-inflammatory and antimicrobial function of the stratum corneum. Clinical features of Netherton syndrome usually present at birth or shortly thereafter. Congenital ichthyosiform erythroderma, or the continuous peeling of the skin, is a common presentation seen at birth and in the neonatal period. As the patient ages, the dermatologic manifestations evolve into serpiginous and circinate, erythematous plaques with a characteristic peripheral, double-edged scaling. This distinctive finding is termed *ichthyosis linearis circumflexa* and is pathognomonic for the syndrome. Lesions often affect the trunk and extremities and demonstrate an undulating course. It is characterized by transient geographic and circinate, erythematous plaques without overlying scale, usually on the trunk and proximal extremities. Erythrokeratodermia variabilis is caused by heterozygous mutations in gap junction protein beta 3, GJB3, and gap junction protein beta 4, GJB4, and is characterized by transient geographic and erythematous patches and stable scaly plaques; however, double-edged scaling is not a feature. Acrodermatitis enteropathica is an autosomal-recessive disorder caused by mutations in the zinc transporter SLC39A4. Cutaneous manifestations occur after weaning from breast milk and are characterized by erythematous plaques with erosions, vesicles, and scaling, which characteristically occur in the perioral and perianal locations. Neonatal lupus is a form of subacute cutaneous lupus erythematosus. Typical skin lesions are erythematous annular plaques with overlying scaling, which may be present at birth and have a predilection for the face and other sun-exposed areas. Lesions generally resolve after clearance of the pathogenic maternal antibodies.

**Diagnosis:** Netherton Syndrome

*PHOTO CHALLENGE DISCUSSION*

Netherton syndrome is caused by heterozygous mutations in gap junction protein beta 3, GJB3, and gap junction protein beta 4, GJB4, and is characterized by transient geographic and erythematous patches and stable scaly plaques; however, double-edged scaling is not a feature. Acrodermatitis enteropathica is an autosomal-recessive disorder caused by mutations in the zinc transporter SLC39A4. Cutaneous manifestations occur after weaning from breast milk and are characterized by erythematous plaques with erosions, vesicles, and scaling, which characteristically occur in the perioral and perianal locations. Neonatal lupus is a form of subacute cutaneous lupus erythematosus. Typical skin lesions are erythematous annular plaques with overlying scaling, which may be present at birth and have a predilection for the face and other sun-exposed areas. Lesions generally resolve after clearance of the pathogenic maternal antibodies.
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