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CASE REPORT

Bilateral lower extremity hyperkeratotic plaques: a case report of ichthyosis vulgaris

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This article was published in the following Dove Press journal:
Clinical, Cosmetic and Investigational Dermatology
15 September 2015
Number of times this article has been viewed

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Abstract: Here, we report a case of a middle-aged woman presenting with severe, long-standing, hyperkeratotic plaques of the lower extremities unrelieved by over-the-counter medications. Initial history and clinical findings were suggestive of an inherited ichthyosis. Ichthyoses are genetic disorders characterized by dry scaly skin and altered skin-barrier function. A diagnosis of ichthyosis vulgaris was confirmed by histopathology. Etiology, prevalence, and treatment options are discussed.

Keywords: filaggrin gene, *FLG*, profilaggrin, keratohyalin granules, hyperkeratosis

Introduction

Inherited ichthyoses are a diverse group of genetic disorders characterized by dry, scaly skin; hyperkeratosis; and altered skin-barrier function. While these disorders of cutaneous keratinization are multifaceted and varying in etiology, disruption in the stratum corneum with generalized scaling is common to all.[1–4] Although not entirely known how each diverse genetic process of the ichthyoses could lead to a similar phenotype, a weakened epidermal barrier allowing for inflammation and subsequent hyperproliferation of the skin is hypothesized.[1–4]

Various ichthyoses can be differentiated from one another through history, clinical exam, histopathological analysis, electron microscopy, and genetics. Determining the inheritance pattern is an important part of the family history; this information is helpful in both formulating the differential diagnosis as well as in understanding the variable expressivity and severity of the disorder.[1,3,4] It is also important to know: if the ichthyosis is congenital or was acquired later in adulthood; whether there is a presence or absence of erythroderma; and the features and specific appearance of the scale, as well as any other systemic manifestations of the disease.[1,3,4] Although histopathological analysis can be useful to differentiate some of the ichthyoses, such as epidermolytic hyperkeratosis, other ichthyoses may not be able to be distinguished from one another via this manner alone.[1,3,4]

Ichthyosis vulgaris (IV), the most frequently occurring ichthyosis, is caused by mutations in the filaggrin gene (*FLG*).[1,3–13] Typical hallmarks of IV, which encompass a wide clinical spectrum, include visible scaling and dryness that spares flexural surfaces, hyperlinearity of palms and soles, and strong predisposition for allergic disease comorbidities.[1,3–11] Prevalence estimates for IV range from 4.0% to 7.7% in Europeans and 2.29% to 3.00% in Asians; observations of *FLG* mutations in darkly pigmented populations are low.[4,5,12,13]

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Case report

A 57-year-old female with new-onset dyspnea was evaluated for severely hyperkeratotic skin of bilateral lower extremities (Figures 1 and 2). The lesions were reported as beginning during childhood, initially on the feet and progressing proximally to the level of the knee. The lesions, which were occasionally pruritic, had worsened over the prior 14 years and were not relieved by over-the-counter medications. Family history was significant for several generations of males and females with similar appearing skin as well as many unaffected family members. Our patient indicated improvement in symptoms when living in warmer, more humid environments with worsening of symptoms while living at more northern latitudes.



Figure 1 Hyperkeratotic skin of the lower extremity.



Figure 2 Hyperkeratotic skin/hyperlinearity of the plantar surface.

Discussion

IV, a genetically transmitted, autosomal semi-dominant disorder, exhibits varying penetrance of *FLG* mutations.[4,6,8,13–19] Individuals heterozygous for the *FLG* mutation often have a less severe form of the disease than those homozygous for the mutation.[4,7,8,10,14–19] *FLG* encodes for a protein called profilaggrin, which functions as a precursor to filaggrin (or filament-aggregating protein).[7] Profilaggrin is stored in the granular layer of the epidermis as the major component of keratohyalin granules.[3,4,7,15] Profilaggrin is cleaved into multiple filaggrin peptides that aggregate the keratin filaments. These keratin filament complexes are then cross-linked to the cell envelope and are important in maintaining the compact layer of skin and serving as a natural moisturizer.[3–5,6,8,16–19]

It has long been established that IV is associated with a decreased and even absent number of keratohyalin granules due to the deficiency of filaggrin proteins.[4,7,15] A compensatory epidermal hyperplasia with inflammation, abnormal desquamation, and hyperkeratosis results in an impaired epidermal barrier, water loss, and dehydration.[1,9,16,20] Chemicals and allergens are more prone to cross the impaired barrier, leading to sensitization and an increased propensity for inflammatory skin conditions.[1,4,21–23]

IV is usually not clinically present at birth and may have a variety of presentations later in life. With inherited IV, symptoms usually begin before age 1 year and alternate between exacerbation and remission. With milder presentations, patients present with flaky white scaling patches, often on extremities and extensor surfaces, typically

sparing the flexural and more hydrated areas of the body.[3,4,15] More severe cases of IV are rare and may show an increased hyperkeratosis of the palmoplantar skin with fissures forming on the heels of the feet.[1,4,15] The flaking scales may be pronounced over the head, trunk, face, and extremities. Intertriginous areas of the body (armpits, groin, etc), are usually spared.[1,4,15]

Increased humidity explains the seasonal variation seen in IV. Symptoms often improve in the summer months and worsen in the cold and dry winter months, when the decreasing humidity further breaks down the residual filaggrin left in the skin.[1,4,15] IV is frequently associated with the atopic triad of atopic dermatitis, hay fever, and asthma as well as with keratosis pilaris.[4–7,11,16,18,19] It is hypothesized that the epidermal barrier abnormality continually exposes the body to pathogens and allergens, ultimately resulting in a T-helper 2 immunophenotype consistent with atopy.[4]

Histopathologically, IV demonstrates orthohyperkeratosis, diminished to absent stratum granulosum, and decreased or absent keratohyalin granules on electron microscopy.[1,4] In patients heterozygous for the gene mutation, the keratohyalin granules may be present but appear small.[3] Decreased or absent filaggrin on immunohistochemistry is characteristic as well.[1,4]

A histopathological analysis was done from a 4 mm punch biopsy of the right lower leg of our patient. Findings revealed orthohyperkeratosis with a markedly reduced stratum granulosum, consistent with IV. Figure 3 shows the histopathology of the punch biopsy specimen.

In this case, the severity of the IV was hypothesized to be related to her obesity and chronic lymphedema. Obesity is associated with mild chronic inflammation as well as impaired lymphatic drainage due to tissue compression.[24–27]

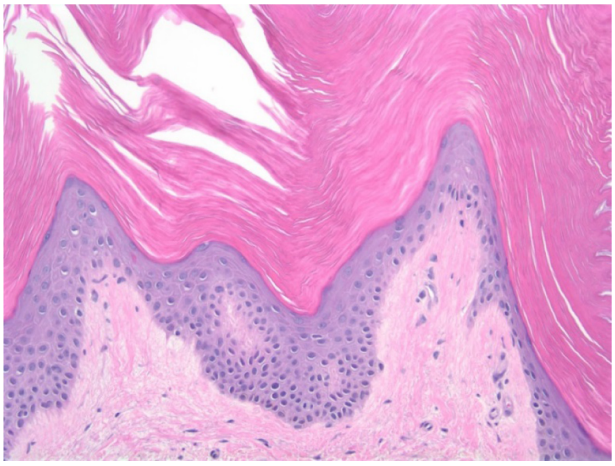


Figure 3 Histopathology slide of the punch biopsy specimen.

Lymphedema, the result of an inability of the lymphatic vasculature to remove fluid and lipids, leads to their accumulation in interstitial spaces.[24–32] Recent reports also note fibrotic changes in the extracellular matrix of adipose tissue decrease lymphatic clearance of inflammatory macromolecules from interstitial spaces.[26,27]

While lymphedema begins as spongy swelling, the chronic recurring inflammation induces an infiltrate of fibroblasts and keratinocytes thus transforming the epidermal layer leading to its subsequent thickening.[28–32] Over time, the limb with untreated lymphedema gains a brawny and indurated texture and histopathologically reveals hyperkeratosis and papillomatosis.[28–32] Lymphedema-induced hyperkeratosis superimposed on the epidermal thickening associated with IV likely played a role in the exaggerated presentation in this case.

Treatment of IV is similar to that of many of the other ichthyoses and is symptomatic, complex, and dynamic.[9,20–23,33] Primary treatments are topical moisturizers and medications designed to reduce scaling, support skin-barrier function, reduce water loss, and decrease symptoms. Lessening the scale, providing hydration, and moisturization can be accomplished with emollients, humectants, bathing immediately followed with moisturizers, keratolytic agents, and topical retinoids.[20,21] Management of bacterial skin infections, most commonly staphylococcal or streptococcal in origin, is done with topical mupirocin or bacitracin.[21,23] On the horizon, researchers are attempting to use genetic pharmacology to increase the body's own production of normal filaggrin.[4,15]

For this patient, first-line treatment for IV was begun using topical 0.1% tretinoin and 40% urea cream. At follow-up, warm bath soaks prior to medication application was added to the regimen to enhance absorption. At the present time, marked objective clinical improvement, as well as subjective patient satisfaction with treatment, is noted. She continues to be followed in the dermatology clinic.

Conclusion

Our patient presented with an extreme presentation of a common disease. Based upon the history, IV was considered. However, the severity of the clinical presentation of hyperkeratosis strongly suggested an alternative diagnosis. This case is a helpful reminder that IV is the most common inherited ichthyosis, and therefore should be a diagnostic consideration in even extreme and atypical presentations.

Acknowledgments

Special thanks to the Department of Dermatology at West Virginia University School of Medicine, Morgantown, WV,

for providing medical student opportunity for case study research. Manuscript editing assistance was provided by Susan B Leight, EdD, FNP-BC, FAANP, Director, School of Nursing, West Virginia Wesleyan College. The authors advise that the West Virginia University Ethics Committee/Institutional Review Board does not require patient approval for case reports.

Disclosure

The authors report no conflicts of interest in this work.

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