A Tale of Scales: Siblings with Lamellar Ichthyosis Treated with Acitretin*

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ABSTRACT

Introduction: Lamellar ichthyosis (LI) is an inherited rare disorder characterized by generalized scaling presenting at birth and persisting throughout life. It presents at birth with a collodion membrane, later developing into large, brown scales across the skin. LI requires ongoing treatment and monitoring due to physical and psychosocial impacts. This study highlights siblings who showed substantial quality-of-life improvements with oral retinoid therapy.

Objective: To present and discuss a detailed case summary, explore management options, and evaluate the treatment outcomes.

Case summary: We report on a pair of siblings, a 24-year-old male and a 19-year-old female, who were born encased in a collodion membrane, and later presented with large, brown, plate-like scales all over the body. Skin changes were accompanied by intermittent heat intolerance and mild ectropion, which subsequently caused impaired quality of life while growing up. Histopathology results were consistent with lamellar ichthyosis. Both siblings responded well to oral Acitretin at 0.5 mglkglday, showing significant shedding of thick scales and a reduction of ectropion within the first two weeks of therapy.

Conclusion: Lamellar ichthyosis, a severe, lifelong disorder with psychosocial repercussions, requires long-standing, continual therapy. Maximizing treatment options with oral acitretin, addressing the psychosocial implications of the disease and getting patients actively involved in its management results in better treatment outcomes.

Keywords: lamellar ichthyosis, acitretin

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INTRODUCTION

Lamellar ichthyosis (LI) is a rare autosomal recessive genodermatosis which occurs in 1 in 200,000-300,000 live births. Patients are born encased in a collodion membrane, which is gradually replaced by generalized large, brown plate-like scales with little or no erythema. It is a lifelong condition which requires chronic treatment, monitoring and counseling due to physical disfigurement and psychosocial disabilities that can impair quality of life. In this case, we present siblings who demonstrated an excellent response to oral retinoid therapy, resulting in significant quality-of-life improvements.

CASE REPORT

We report siblings, a 19-year-old female and a 24-year-old male, presenting with generalized scales. They were born full-term at home via normal spontaneous delivery through a traditional birth attendant, with no intrapartum complications noted. The mother denies any exposure to viral exanthems, radiation or intake of illicit drugs or alcohol. At the time of birth, the patients were observed to have been covered by a transparent "cellophane-like" layer (collodion membrane). This was also associated with ectropion, eclabium and slit-like opening of the nostrils. The membrane eventually desquamated and shed off after a few days with no note of blistering of widespread erosions or erythroderma; however, the underlying skin began to progressively thicken. Over the years, they were noted to have generalized thick scales over their body, with resolution of ectropion and eclabium.

The siblings sought consult at the outpatient department, where a skin punch biopsy was performed on the older brother. Biopsy results were consistent with lamellar ichthyosis, though no biopsy was done on the sister. Both were prescribed topical retinoic acid, salicylic acid and petroleum jelly preparations, which they applied for two years, resulting in a decrease in skin thickness. However, they were unable to continue their medications and were subsequently lost to follow-up.

In the interim, their skin was noted to become progressively drier, with more hyperpigmented plaques and brown scales. There was intermittent pruritus and the presence of a musky odor, most especially during warmer temperatures. The persistence of skin lesions along with their willingness to restart medications, prompted them to follow- up nine years after their initial consult.

The review of systems of both patients was generally unremarkable. They were born to non-consanguineous parents and have no comorbidities. Among their five siblings, they were the only ones diagnosed with this condition, with no known relatives with the disease. Both are non-smokers, non-alcoholic beverage drinkers and deny illicit drug use. Their mental, motor, and physical growth were deemed at par with age and comparable to that of their three unaffected siblings.

Cutaneous examination revealed generalized, well-defined, polygonal-shaped, hyperpigmented, hyperkeratotic plaques with thick, yellowish-brown, plate-like scales that are centrally-attached, with raised borders arranged in a bark-like pattern, over the whole body including the scalp, face, and trunk, with more prominence on the upper and lower extremities. There was also noted hyperkeratosis of the palms and soles, mild ectropion, as well as fine wavy hair with no hair loss or thinning. (Fig.I and 2). The rest of the physical examination findings were unremarkable.

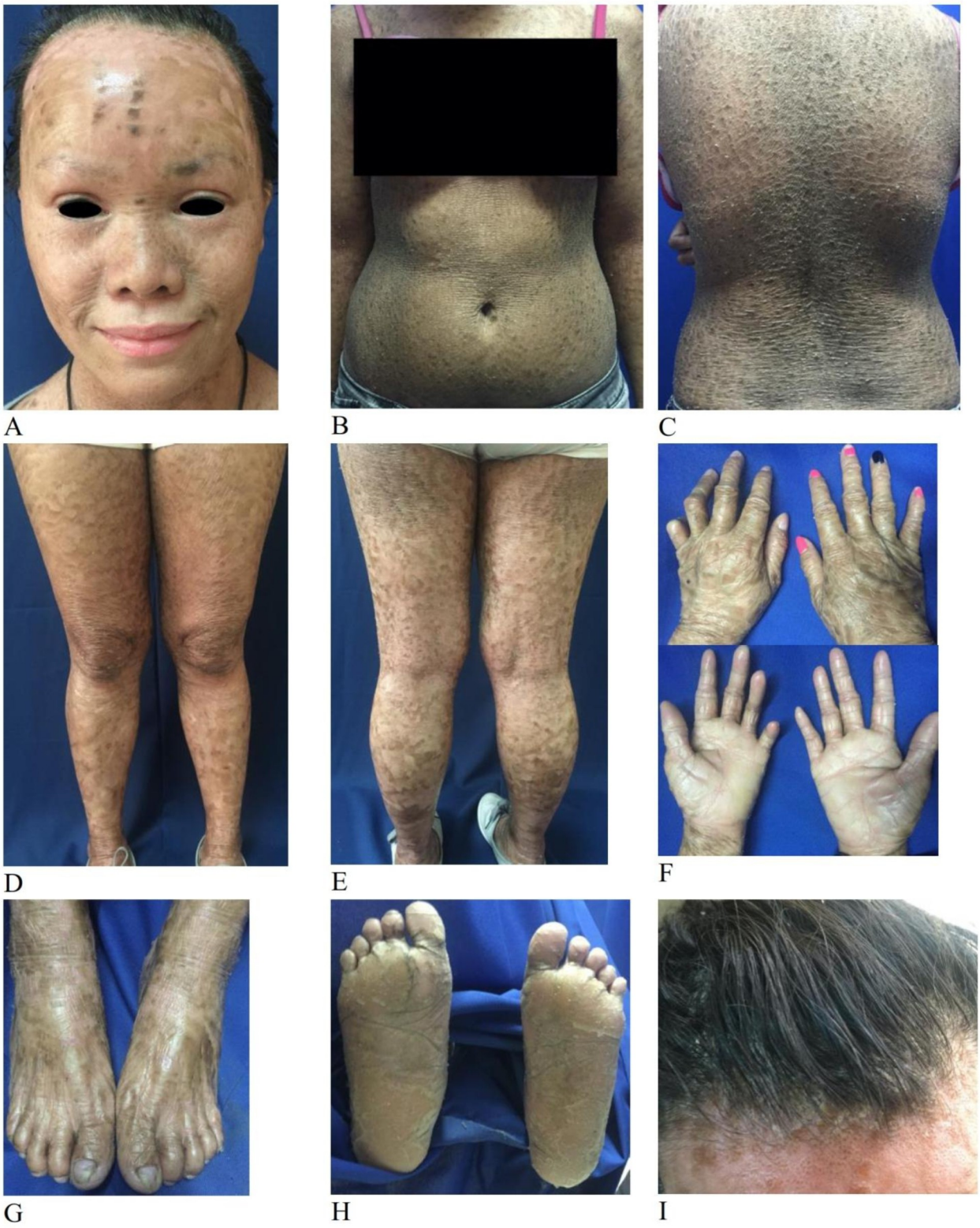

Fig. 1. 19-year old female presenting with hyperpigmented, hyperkeratotic plaques on the face (A), scalp (1), trunk (B,C) and extremities (D, E, F, G, H) on initial consultation.

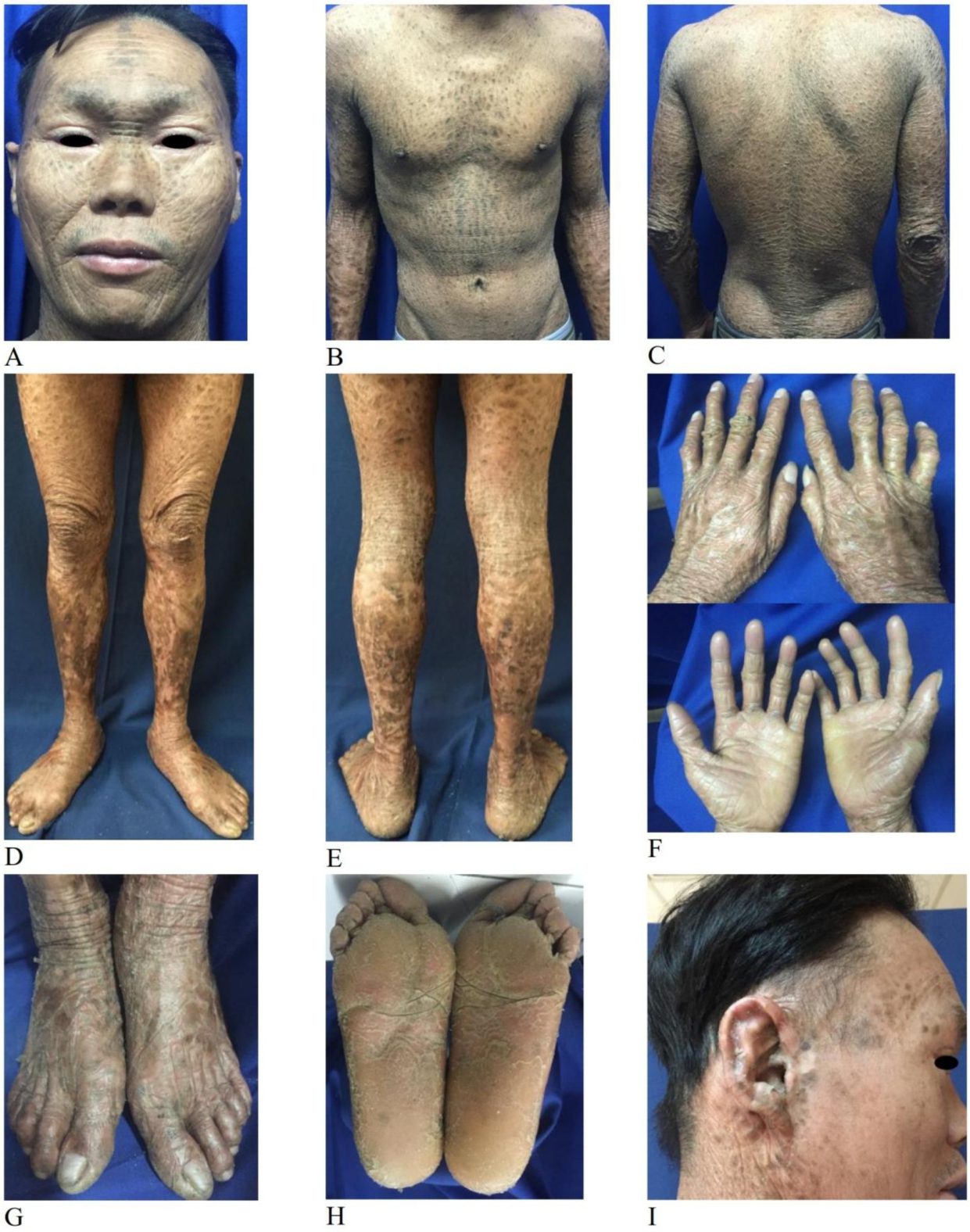

Fig. 2. 24-year old male presenting with hyperpigmented, hyperkeratotic plaques on the face (A), trunk (B, C), extremities (D, E, F, G, H), scalp and intra auricular area (I) on initial

The workup for both siblings included a skin punch biopsy for the female patient, which revealed marked compact hyperkeratosis with follicular plugging, irregular acanthosis and normal to slightly thickened granular cell layer in the epidermis. In the upper dermis, a mild superficial perivascular lymphocytic infiltrate was observed. These findings were consistent with lamellar ichthyosis. The male patient's previous biopsy slides were retrieved and also showed the same findings. Chromosomal analysis for the female sibling was also done, which revealed a normal female karyotype. Other ancillary tests such as complete blood count, liver enzymes, serum triglycerides, and serum cholesterol for both siblings were conducted for both siblings and returned values within the normal range. Urinalysis and chest x-ray results were also unremarkable.

Biopsy of a lesion of the right arm (Fig. 3) was consistent with lamellar ichthyosis. A comparison of the biopsy previously done to the brother showed similar results (Fig. 4).

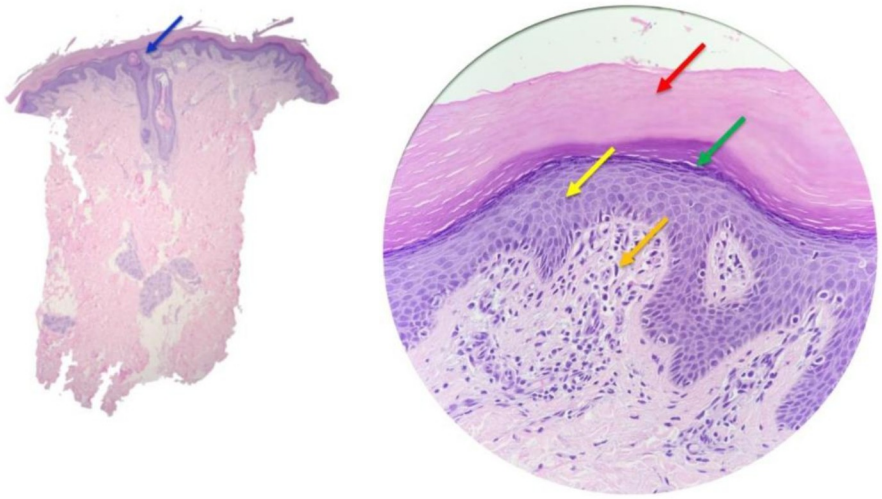

Fig. 3. A 0.4 cm x 0.4 cm x 0.6 cm biopsy was taken from the right arm of the female patient, showing compact hyperkeratosis (red) with areas of follicular plugging (blue), some hypergranulosis (green) and irregular acanthosis (yellow). There is a mild superficial lymphocytic infiltrate in the dermis (orange).

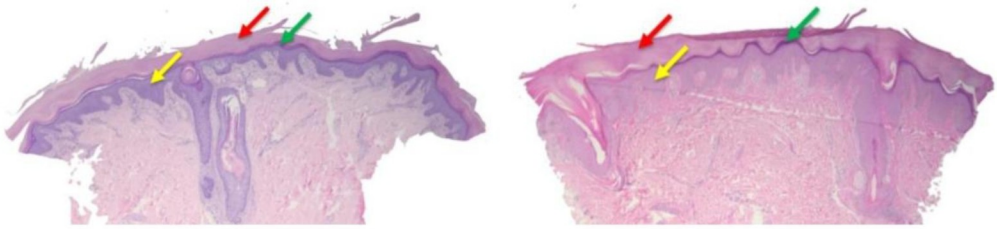

Fig. 4. A comparison of the siblings' biopsy findings, which both showed similar histopathological findings consistent with lamellar ichthyosis.

The patients were initially treated conservatively with topical therapy, including hyaluronic acid lotion, petroleum jelly and sunscreen with SPF 50 for about a month. Mineral oil was recommended for the scalp. However, due to minimal improvement of lesions given the normal laboratory findings after a month of consistent topical treatment, they were then started on Acitretin at a dosage of 0.5 mglkgldday. Additionally, the female sibling was prescribed cyproterone acetate combined with ethinyl estradiol contraceptive pills after a negative pregnancy test, as advised by her OB-GYN. Polyethylene glycol lubricant eye drops were also provided to address the ectropion, as suggested by their ophthalmologist.

Both patients noted significant improvement after intake of oral acitretin at 0.5 mglkgldday. They experienced substantial shedding of thick scales and a reduction of ectropion within the first two weeks of therapy (Fig. 5, 6, 7 and 8. B and E.), with further improvement observed after two months of treatment (Fig. 5, 6, 7 and 8. C and F.).

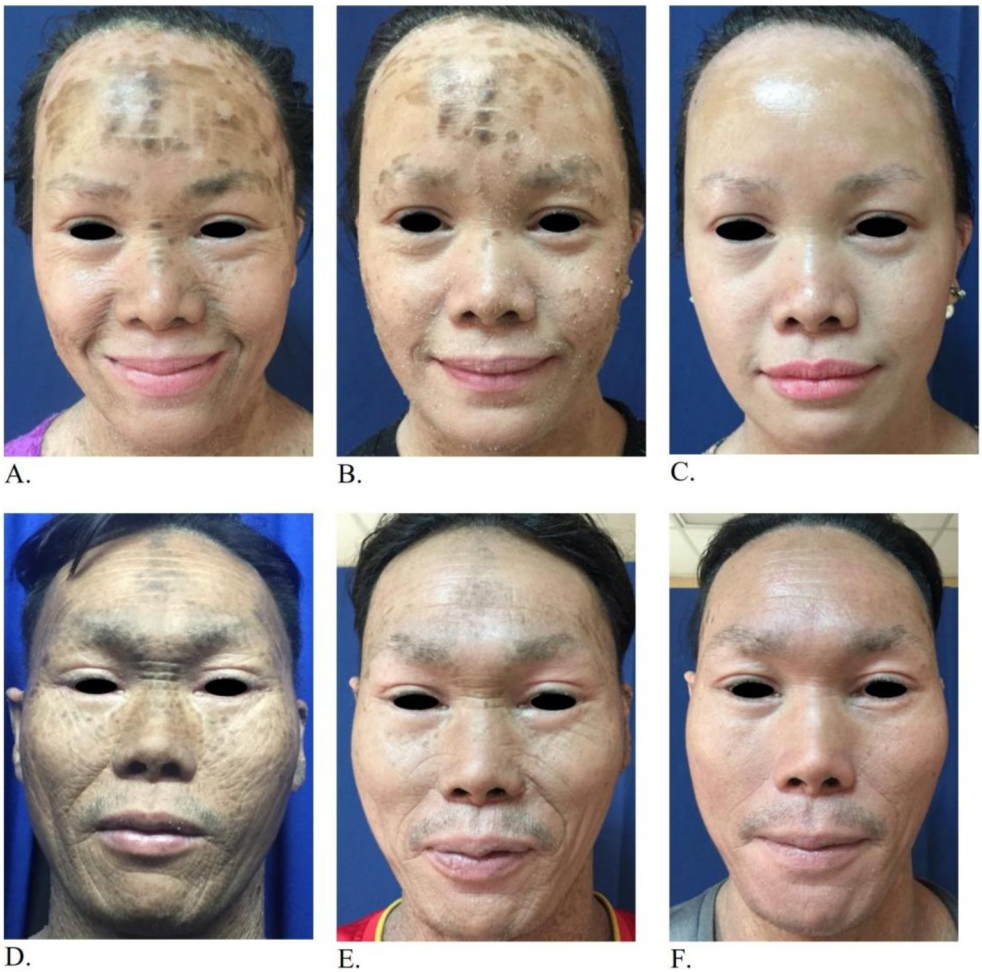

Fig. 5. Significant shedding of thick scales and reduction of ectropion from baseline (A, D), after two weeks (B, E), and after two months (C, F) on Acitretin 0.5 mglkgldday.

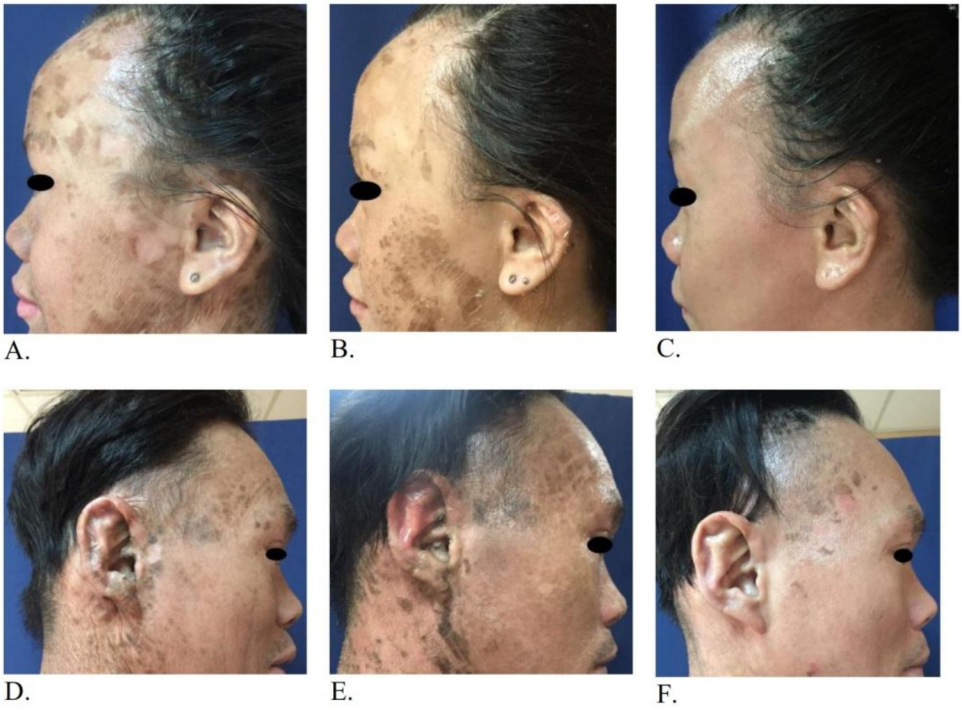

Fig. 6. Reduction of thick scales on the scalp and intra auricular area for both siblings from baseline (A, D), to two weeks (B, E), and two months (C, F) after therapy with Acitretin 0.5 mglkglday.

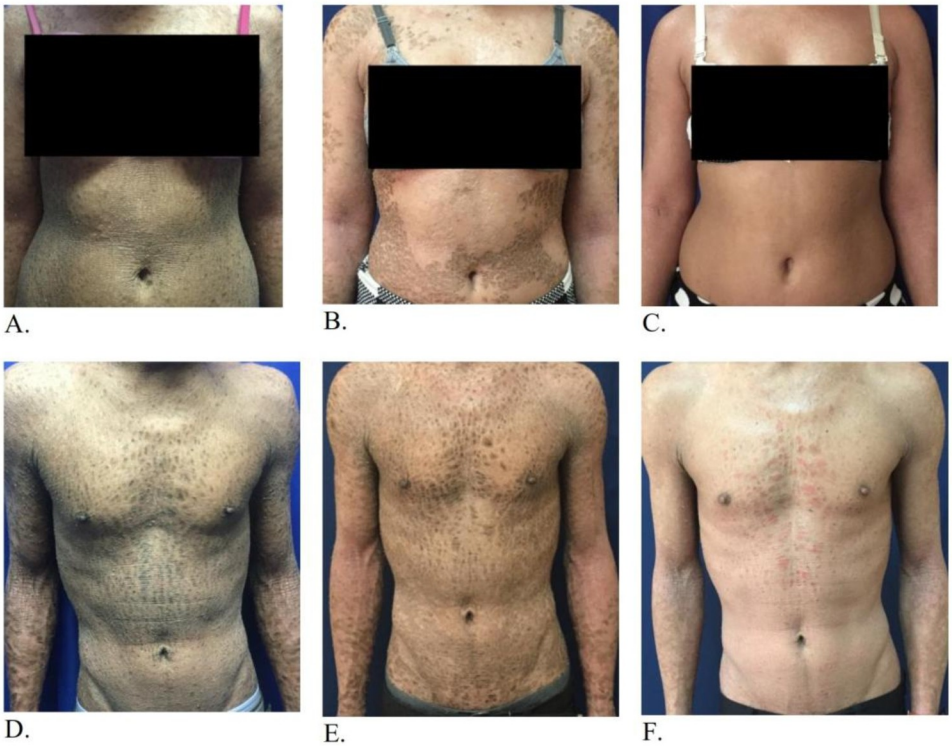

Fig. 7. Reduction of thick scales on the trunk for both siblings from baseline (A, D), to two weeks (B, E), and two months (C, F) after therapy with Acitretin 0.5 mglkglday.

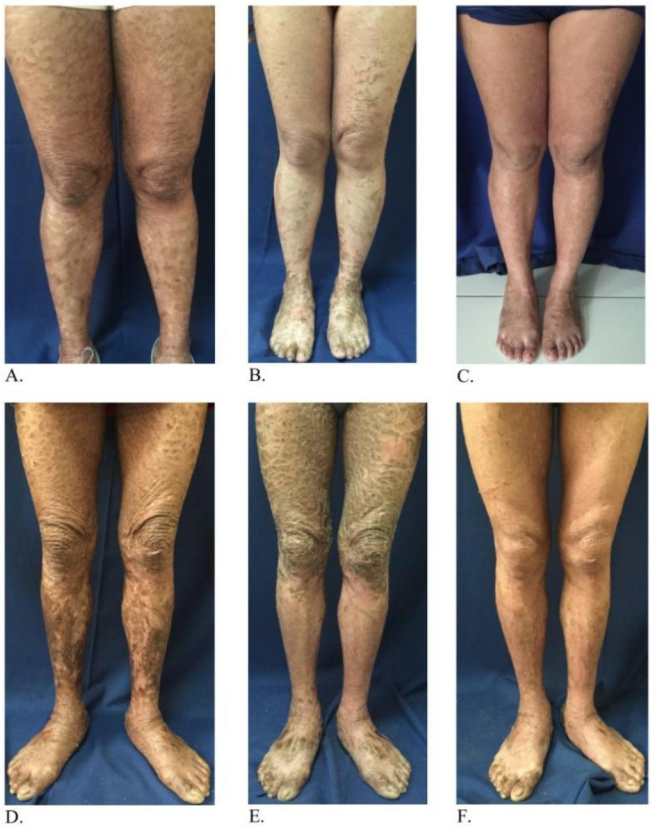

Fig. 8. Reduction of thick scales on the legs for both siblings from baseline (A, D), to two weeks (B, E), and two months (C, F) after therapy with Acitretin 0.5 mglkglday.

DISCUSSION

Lamellar icthyosis (LI) is a rare[1] genodermatosis with 30 new cases reported in the Philippines from 20II-2023 (PDS HIS).[2] It is a form of autosomal recessive congenital ichthyosis (ARCI), is caused by mutations in various genes such as TGMI, CYP4F22, CERS3, PNPLAI, and ABCAI2. 90% of LI cases are associated with mutations in the *TGM1* gene, which provides instructions for the production of transglutaminase I. This enzyme is responsible for the formation of the cornified cell envelope, which helps form a protective barrier between the body and its environment.[3]

At birth, most affected neonates present with a translucent membrane covering their body, or a collodion membrane. This is eventually replaced by large, brown, plate-like scales forming a mosaic or bark-like pattern with little or no associated erythema.[1,3] In some areas, these scales are centrally attached with raised borders and tend to be larger on the lower extremities, where the extensive, plate-like scales are separated by shallow fissures, resembling a "dry riverbed." Intraepidermal constriction of sweat ducts often results in heat intolerance. Tautness of facial skin normally results in ectropion, eclabium, and hypoplasia of nasal and auricular cartilage. The thick stratum corneum of the scalp may tend to encase hairs and together with tautness of the skin, may lead to scarring alopecia usually observed on the periphery of the scalp. Secondary nail dystrophy with thickened nail plates and ridging is common.[1,3] Emollients, topical keratolytics and oral retinoids are given in the treatment of LI.[4] Additionally, the disfiguring nature of LI may hinder the psychosocial development of affected children and adolescents, making proper counseling beneficial.[5]

The clinical history and physical examination should be sufficient to suspect ichthyosis. However, doing a skin punch biopsy is helpful in supporting its diagnosis. The histopathology of lamellar ichthyosis are similar with those of other autosomal recessive congenital ichthyoses.[6] Findings are limited to the stratum corneum, which would show compact hyper- and orthokeratosis, hypergranulosis, acanthosis and psoriasiform hyperplasia.[6,7,8,9] There could be scant or mild lymphohistiocytic infiltrates in the dermis.[6,8] These histopathologic features will present as thickened skin with little or no signs of inflammation on the skin, which are consistent with the patients' clinical presentation.

Other ancillary tests include immunohistochemistry procedures, genetic testing and electron microscopy. Genetic testing gives better understanding of the pathophysiology of the disease, while electron microscopy has been reported to be helpful in predicting whether a baby will ultimately have normal skin or ichthyosis. Prenatal diagnosis is possible using sonography, which can detect abnormalities such as ectropion, eclabium, nasal or ear deformities, and limb hypoplasia. However, a definitive diagnosis requires a fetal skin biopsy, typically performed between 20 and 22 weeks of gestation. Prenatal diagnosis is crucial for identifying

genetically inherited lethal conditions. Based on these, the patients should undergo a comprehensive evaluation, and families should be fully informed about the nature of the disease.[10] Referring families to a genetic counselor can provide them with a better understanding of ichthyosis and help reduce anxiety.[11]

Although other ancillaries, novel and genetic therapies have been suggested to assist clinicians in diagnosing, managing, and predicting the prognosis of LI, the high cost of these procedures as well as the rarity of the condition impedes the progress of research, slowing the development of improved patient care for future generations.

In general, ichthyosis is managed with topical and oral medications that focus in hydrating the skin with the addition of keratolytics and modulators of keratinocyte differentiation depending on scale severity.[11,12,13] A study by Hernandez-Martin shows that treatment of inherited ichthyosis is currently based on the use of emollients, topical keratolytics and oral retinoids.[14]

A study by Vahlquist et al. mentioned that the primary treatment for most types of ichthyosis focuses on improving hydration and lubrication to enhance barrier function and promote desquamation. Creams and ointments containing low concentrations of salt, urea, or glycerol help increase the water-binding capacity of the stratum corneum.[15] Emollients, humectants and occlusives aid in hydrating and forming a barrier on the skin surface. For ichthyoses characterized by extremely thick scales and significantly increased stratum corneum thickness, as seen in our patient, the use of one or more keratolytic agents is necessary to reduce corneocyte cohesion, facilitate desquamation, and dissolve keratins and lipids. Retinoids are particularly favorable due to their additional ability to regulate keratinocyte differentiation. However, the use of keratolytics is often restricted because of potential skin irritation and an increased risk of systemic absorption, particularly in pediatric patients.[16]

Topical vitamin D3 derivatives, tazarotene, and formulations containing lactic acid and propylene glycol in a lipophilic cream base have been effective. A study by Craiglow et al showed improved eye discomfort and degree of ectropion within two weeks application of Tazarotene 0.l% cream[17] while a study by Marulli et al. showed marked overall improvement over treated areas of the body after 4 months application of Tazarotene 0.l% gel with only minimal skin irritations such as mild pruritus and slight burning.[18] These topical medications would work best when applied within two minutes after bathing while skin is still moist.l[3] Additionally, heat intolerance can be ameliorated by frequent moistening of the skin with water or the use of air conditioning and humidifiers.

According to a journal article published by Dunn et al, acitretin is the most effective treatment available for ichthyosis. It is a second-generation aromatic retinoid that is very effective in alleviating hyperkeratosis and scaling, especially for severe cases.[19,20] The metabolites of acitretin bind to retinoic acid receptors (RARs) that leads to the alteration of gene transcription thus causing anti-inflammatory and anti-proliferative effects.[21] Response to acitretin is dose dependent, with higher doses yielding greater and rapid improvement. However, adverse effects are also dose dependent, limiting the use of higher doses. It is recommended that oral retinoids be given at the lowest effective dose, as LI is a long term condition. With prolonged use of systemic retinoids, especially in children and adolescents, there is an increased risk of bone abnormalities, ophthalmologic problems, cardiovascular health, lipid and liver dysfunction, psychological impact and contraceptive considerations. Therefore, proper monitoring is essential and lifestyle changes should be discussed.[15,16]

In our patients, 0.5 mglkglday of Acitretin was given, which resulted in a significant reduction in scaling after as early as 2 weeks. The treatment response develops gradually, reaching its peak between 3 to 6 months. Since relapses may occur within 2-6 months after discontinuing acitretin, ongoing maintenance therapy is often necessary, tailored to clinical response and patient tolerance. Acitretin should ideally be taken with a fatty meal to enhance absorption.[22]

Due to its teratogenic, hepatotoxic, and hyperlipidemic potential, contraceptives were given, and liver and lipid profiles were monitored monthly, which were all maintained at normal levels throughout the ongoing 3 months of treatment.[21,22]

Recent advancements in the treatment of ichthyosis have focused on repurposing biologics due to a better understanding of the skin issues associated with the condition. In a study by Binkhonian et al., Dupilumab, a monoclonal antibody that inhibits IL-4 and IL- I3, was used as an alternative treatment for a patient with lamellar ichthyosis and concurrent atopic dermatitis, where genetic testing identified a mutation in the CYP4F22 gene. Despite previous treatments with Acitretin and Methotrexate showing minimal improvement, the patient experienced significant improvement in both lamellar ichthyosis and atopic dermatitis after being treated with Dupilumab 300 mg every two weeks for 3 months, also noting improvement in asthma symptoms.[13,23] Janus kinase (JAK) inhibitors and gene therapy are being considered as other options for therapy, but studies are limited, and results are mixed.[24]

The use of biological therapies could be beneficial in managing ichthyosis but may vary in response depending on the specific gene mutation. This underscores the importance of genetic testing, though more studies with specific data correlating genetic mutations and immunological profiles are needed.[23]

Classic LI is a severe disorder that is apparent at birth and persists throughout life, requiring lifelong therapy and affecting the patient's entire life situation. In addition to managing the skin, it is crucial to address and manage the complications associated with this disease in a supportive manner.

CONCLUSION

This case report outlines the diagnosis and management of siblings with lamellar ichthyosis, as well as significant improvements in their medical condition and quality of life after treatment with acitretin. Acitretin is an oral retinoid, with known risks such as teratogenicity, and must be used with caution, especially in women of childbearing age. It is important to educate patients on the chronicity of their disease and align their expectations and reality as we aim to make their lives as normal as possible. Recent advancements in ichthyosis treatment has centered on repurposing biologic therapies, driven by an improved understanding of the skin complications linked to the condition. This may be a viable option for those who have access to the medication.

For many patients, skin conditions such as lamellar ichthyosis can cause not only physical discomfort but also significant social and psychological repercussions. In the cases presented here, both patients had lived with the condition for years, previously believing it to be untreatable. This perception had a profound impact on their self-esteem and social interactions, ultimately leading to withdrawal from school and their peers. However, following treatment with acitretin, both patients experienced notable improvements in their skin condition, which, in turn, reduced their insecurities. What were once two individuals marked by shyness have now become more confident, with fewer inhibitions in social interactions. These outcomes highlight the broader impact of dermatological treatments. While the primary goal may be symptom reduction, the benefits extend well beyond the skin, influencing psychological well-being and social functioning.

The case underscores the importance of considering the holistic effects of dermatological care, demonstrating that the impact of treatment can reach far beyond the physical aspects of skin disease.

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