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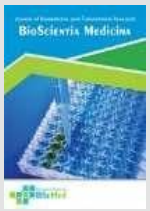

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Familial Lamellar Ichthyosis in 6 Years Old and 2 Years Old Children: A Rare Case Report

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A B S T R A C T

Background: Lamellar ichthyosis (LI) is a rare non-syndromic congenital ichthyosis and is autosomal recessive. LI patients are generally born with abnormalities of keratinization, then develop into lamellar scales and persist into adulthood. This study aimed to describe cases of lamellar ichthyosis and provide appropriate management to prevent worsening patient prognosis. **Case presentation:** A 6-year-old girl and her younger brother, 2-year-old have been complaining of scaly skin all over their bodies since birth. Both patients were born with a history of being covered by a collodion membrane. On physical examination, thick and wide lamellar scales were seen with an erythematous base and palmoplantar hyperkeratosis. Ectropion of the eyelids, eclabium in the mouth area, and microtia in the ears were seen. The results of the dermoscopy examination showed brownish quadrilateral structures with white scales forming a lamellar pattern. Laboratory examination showed vitamin D insufficiency. Both patients were referred to the Pediatric Polyclinic regarding insufficiency and developmental complaints. Patients received therapy in the form of moisturizers, artificial eye drops, topical urea as a keratolytic, and oral vitamin D 2,000 IU per day. There was a clinical improvement after 3 months of treatment. **Conclusion:** Lamellar ichthyosis is an autosomal recessive congenital ichthyosis with clinical manifestations limited to the skin. In a minority of cases, LI can be inherited in an autosomal dominant manner. Thorough management is necessary to prevent a poor prognosis in patients.

1. Introduction

Lamellar ichthyosis (LI) is one of the most common forms of non-syndromic congenital ichthyosis in the autosomal recessive congenital ichthyosis (ARCI) group. This disease is generally caused by mutations in the gene transglutaminase 1 (TGM1) and ATP-binding cassette sub-family A member 12 (ABCA12).[1,2] Recent research states that there are 11 different gene mutations in LI so that it will provide a varied clinical picture and is inherited in an autosomal recessive manner. The incidence of LI in the United States is reported to be 1 case per 300,000 births per year, with the same ratio between males and females.[3] The clinical picture of LI is characterized by hyperkeratosis and large thick brownish-gray scales all over the body. In some cases, ectropion, eclabium, and joint contractures can be found. LI babies are generally born encased in a collodion membrane (collodion baby) which distinguishes it from ichthyosis vulgaris (IV). The collodion membrane then dries and sloughs off in the first few days to weeks, then turns into large polygonal brown scales all over the body. Lamellar ichthyosis may be accompanied by ectropion of the eyelids, eclabium of the mouth, microtia of both ears, alopecia, and disturbances in palmar and plantar movements.[1,4]

The diagnosis of LI is based on anamnesis, physical examination, dermoscopy, and histopathology. The

dermoscopic appearance found in LI is a quadrilateral structure with large brownish scales in the form of sheets. Skin biopsy is generally performed in clinically doubtful cases with a general picture of hyperkeratosis, thickening of the stratum granulosum accompanied by acanthosis. Genetic analysis of deoxyribonucleic acid (DNA) in patients and family members is necessary to confirm the diagnosis.[3,5]

Treatment of LI is generally symptomatic such as the use of moisturizers or topical keratolytic drugs for hydration, lubrication, and keratolytic. Topical antibiotics may be given if a secondary infection occurs. The main complications of LI at birth are because the baby is covered in a thick collodion membrane, causing dehydration, easy infection, respiratory problems, and even death. In some patients with LI that persists into adulthood, disturbances in the tissues around the eyes and ears can occur.[6,7] Impaired vitamin D synthesis in LI can cause rickets in children and osteoporosis in adults. Vitamin D has been shown to have a strong inhibitory effect on keratinocyte proliferation and differentiation. Studies involving children with ichthyosis demonstrated skin improvement with topical application of vitamin D analogues and systemic vitamin D administration.[8,9] Familial LI patients have the same life expectancy as normal people. Throughout life, familial LI will tend to be stable, and difficult to experience significant improvement. Worsening of the skin condition can occur if the patient is not managed properly so that wounds or skin infections can appear.[6,7] This study aimed to describe cases of lamellar ichthyosis and provide appropriate management to prevent worsening patient prognosis.

2. Case Presentation

Case 1

A 6-year-old girl came to the dermatology and venereology polyclinic with complaints of thick, scaly skin and itching all over her body. Aloanamnesis from the patient's mother stated that thick, brownish-scaly skin all over the body had appeared since the patient was born. The patient's mother also said that the skin looked dry, did not sweat, and seemed to scratch frequently because of itching. From birth, the patient's eyelids were folded back, and her lips were pulled back. The patient has difficulty closing her eyes completely, so her eyes often watery. The patient's lips that are pulled back also make it difficult for the patient to cover her lips fully, but the patient has no difficulty eating and drinking. Hair loss and sores on several parts of the body due to scratching since the patient was 1 year old. At the age of 2 years, both ears appear to be smaller and tend to be wrinkled, but no hearing loss was found. There were no abnormalities of the joints of the fingers or toes. Both of the patient's parents brought the patient for treatment to the public health center when she was 1 year old and was diagnosed with a congenital skin disorder, and then the patient received vaseline album as a moisturizer which was applied morning and evening to all parts of the body. The skin condition improved, although not significantly, so both parents checked the patient to a pediatrician at the regional hospital and were given an ointment (but the patient's mother forgot the name of the medicine). The patient was referred to the dermatology and venereology polyclinic for further treatment.

Autoanamnesis history of pregnancy and childbirth. During pregnancy, the patient's mother routinely controls the midwife at the Public Health Center every month. There was no history of consumption of drugs or herbs, history of eclampsia, miscarriage or other abnormalities during pregnancy. The patient was born vaginally, normally assisted by doctors at the hospital, full term with a birth weight of 3,000 grams and a body length of 48 cm. There was no history of atopy or allergies. The patient's immunization history is complete, and the patient's parents routinely control the health center to evaluate growth and development. The patient was declared malnourished by a doctor at the public health center and received additional milk and vitamin supplements from the public health center.

Based on family history, the patient's father was 34 years old and was the second child of 2 siblings, while the 30-year-old patient's mother was the first child of 5 siblings. The patient is the second child of 3 siblings. The patient's sister grew normally without skin disorders or growth and development. The patient's sister is 2 years old and has similar complaints to the patient. There were no complaints of skin pain similar to patients in other family members. The patient's mother and father are also not related.

Physical examination results in vital signs within normal limits. The patient's weight is 14 kg, and height is 117 cm, with poor nutritional status. Dermatological status in the generalized region shows thick brownish scales shaped like sheets where the edges peel off while the middle part is attached, accompanied by erythema, hyperkeratosis, fissures, and erosion. In the scalp and orbital region, alopecia and ectropion were seen, whereas, in the auricular region, microtia appeared. In the palmoplantar region bilaterally, keratoderma and onychodystrophy are seen in several nails. There were no joint contractures in the digiti manus and pedis bilaterally (Figure 1). Based on the results of the history and physical examination, the patient was diagnosed with lamellar ichthyosis and X-linked recessive ichthyosis (XLRI).

Investigations were carried out to confirm the diagnosis and rule out the differential diagnosis. The results of the dermoscopy examination showed a brownish quadrilateral structure accompanied by white scales on it arranged in a lamellar pattern (Figure 2). Biopsy examination and deoxyribonucleic acid (DNA) analysis were not carried out because the patient's family was not pleased and signed a letter of refusal of treatment.

Furthermore, the patient was consulted at the pediatric polyclinic regarding nutritional and metabolic disorders to get further treatment. Laboratory examination results showed levels of thyroid stimulating hormone (TSH) 2.13 uIU/mL, free T4 (FT4) 1.65 ng/dl, vitamin A 343 ug/L, vitamin D 25-OH a total of 20.8 ng/ml, alkaline phosphatase 195 U/L, calcium 9.8 mg/dl and organic phosphorus 4.8 mg/dl.

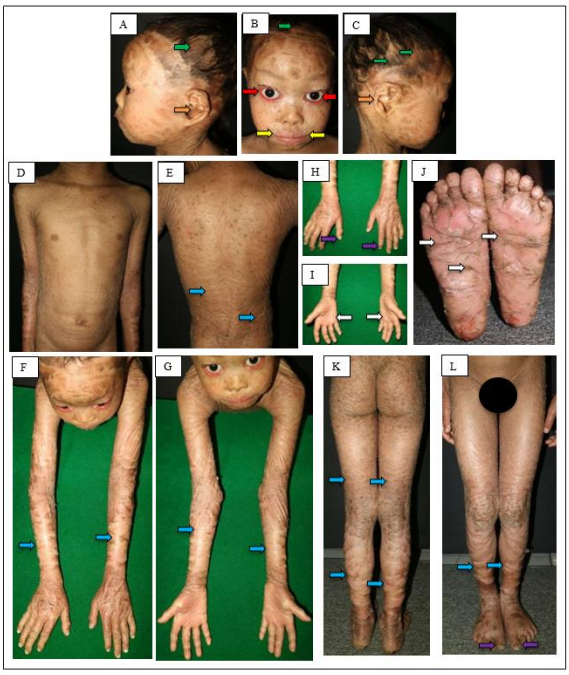

Figure 1. Case 1. (A-C) There is hair loss in the scalp and facial region (green arrows). Ectropion on both eyelids (red arrow), eclabium in the mouth area (yellow arrow), while in the auricular region, microtia is seen (orange arrow). (A-L) In the generalized region, ichthyotic skin appears accompanied by thick brownish scales that are shaped like sheets with a reddish skin base, hyperkeratosis, fissures, and erosion in several areas (blue arrows). (I and J) bilateral palmar and plantar regions showed keratoderma (white arrows) and onychodystrophy on some nails (purple arrows).

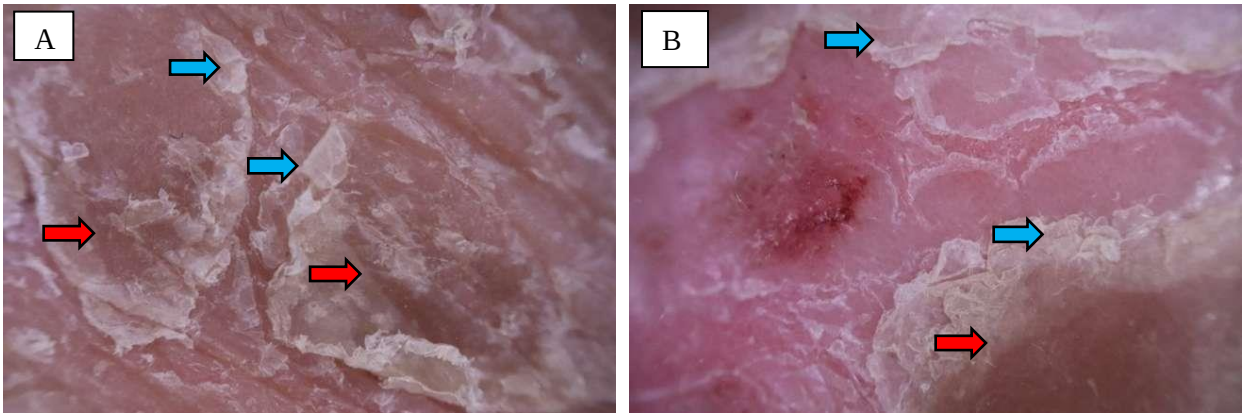

Figure 2. Case 1. (A) The results of the dermoscopy examination showed a brownish quadrilateral structure (red arrow) with white scales on it arranged in a lamellar pattern (blue arrow). (B) The results of the dermoscopy examination showed a brownish quadrilateral structure (red arrow) with white scales on it arranged in a lamellar pattern (blue arrow).

Based on the history, physical examination, and dermoscopy, our patient was diagnosed with lamellar ichthyosis. Our patient was treated with cetirizine syrup 5 mg/5ml 1x1 measuring spoon at night, Atopiclair Lotion, which was applied all over the body 3 times a day, 10% urea cream applied to thick skin day and night, mometasone furoate cream 0.1% applied to thick scales. Morning and evening facial areas, as well as artificial eye drops (artificial tears), dripped on the right and left eyes 6 times a day. The diagnosis from the pediatrics department was vitamin D insufficiency associated with lamellar ichthyosis. The patient received vitamin D_3 supplementation$_3$ 2000 IU once a day. Evaluation of the patient's clinical improvement was carried out after 12 weeks of treatment.

Case 2

A 2-year-old boy came to the skin and venereology polyclinic with complaints of thick, scaly skin all over his body that feels itchy. This patient is the younger brother of patient 1. Aloanamnesis from the patient's mother, thick, scaly skin has been brown all over the body since birth. The patient's mother stated that his skin looked dry, he did not sweat, and he often scratched because of itching. The patient's eyelids are folded out and difficult to close since birth, so the eyes become watery easily. The patient's lips also experience abnormalities in the form of being pulled back, so he cannot fully close his lips, but with eating and drinking, the patient has no difficulty. Hair loss due to scratching began to appear when the patient was 6 months old, while the ears had become smaller and wrinkled since the age of 1 year, but there was no hearing loss. No joint abnormalities were found in the fingers and toes. When he was 1 year old, both parents took him to a pediatrician at the regional hospital, and he was diagnosed with a congenital skin disorder. Patients receive vaseline album as a moisturizer that is used all over the body in the morning and evening. Skin complaints had improved and became moist but did not improve significantly, so the patient was referred to the skin and genital polyclinic for further treatment.

Autoanamnesis of pregnancy history, the patient's mother routinely controls the midwife every month and, during pregnancy, has never taken drugs or herbs, has a history of eclampsia, miscarriage, or problems during pregnancy. The patient was born vaginally, normally assisted by a midwife at the clinic, full term with a birth weight of 2,850 grams and a body length of 49 cm. There was no history of atopy or allergies. Complete patient immunization history and routine control to the public health center to evaluate growth and development. The patient was declared malnourished by the doctor at the public health center and then received additional milk and vitamin supplements.

Physical examination results in vital signs within normal limits. The patient's weight is 7.5 kg, and height is 85 cm, with poor nutritional status and growth and development, according to the Denver chart. The dermatological status of the generalized region appears as thick brownish scales in the form of sheets that adhere to the edges and peel off at the edges with a base of reddish skin, hyperkeratosis, fissures, and erosion in several parts. In the scalp region, alopecia was seen, and the orbital region had ectropion, whereas, in the auricle region, microtia was seen. In the bilateral palmoplantar region, keratoderma and onychodystrophy are seen in several nails. No finger or toe deformity was found (Figure 3). Based on the results of the history and physical examination, our patient was diagnosed with lamellar ichthyosis and XLRI.

Investigations were carried out to confirm the diagnosis and rule out the differential diagnosis. The results of the dermoscopy examination showed a brownish quadrilateral structure with white scales on it arranged in a lamellar pattern (Figure 4). Biopsy examination and DNA analysis were not carried out because both of the patient's parents refused and had signed a letter of refusal of the procedure. Patients were also consulted at the pediatric polyclinic regarding nutritional and metabolic disorders to get further treatment. Laboratory examination results showed TSH levels of 1.64 uIU/mL, FT4 1.7 ng/dl, vitamin A 381 ug/L, total vitamin D 25-OH 21.8 ng/ml, alkaline phosphatase 191 U/L, calcium 10 .7 mg/dl, and organic phosphorus 5.3 mg/dl.

Based on the history, physical examination, and dermoscopy, our patient was diagnosed with lamellar ichthyosis. Our patient is treated with cetirizine syrup 5 mg/5ml 1x1/2 measuring spoon at night, Atopiclair® moisturizer, which is applied all over the body 3 times a day, 10% urea cream applied to thick skin day and night, mometasone furoate cream 0.1% is applied to thick scales on the face morning and evening, and artificial eye drops (artificial tears) are dripped on the right eye and left 6 times a day. The diagnosis from the pediatrics department was vitamin D insufficiency associated with lamellar ichthyosis. The patient received a drug in the form of vitamin D_3 2000 IU once a day. Evaluation of the patient's clinical improvement was carried out after 12 weeks of treatment.

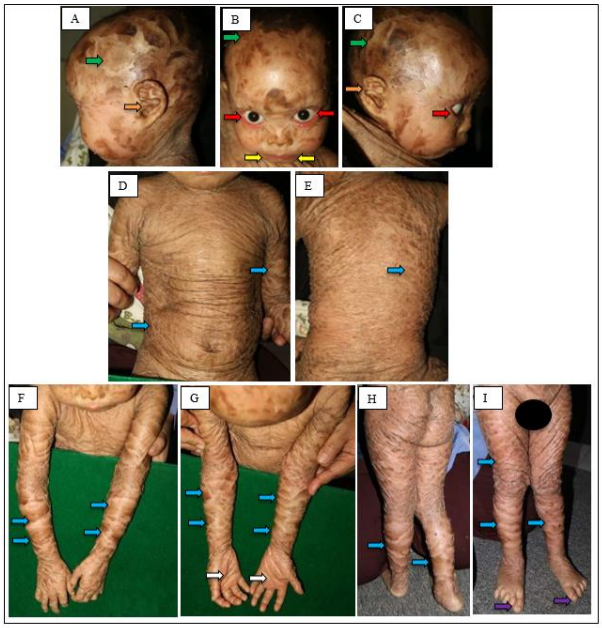

Figure 3. Case 2. (A-C) There is hair loss in the scalp and facial region (green arrows). Ectropion on both eyelids (red arrow), eclabium in the mouth area (yellow arrow), while in the auricular region, microtia is seen (orange arrow). (A-I) In the generalized region, ichthyotic skin appears accompanied by thick brownish scales that are shaped like sheets with a reddish skin base, hyperkeratosis, fissures, and erosion in several areas (blue arrows). (G and I) the bilateral palmar region showing keratoderma (white arrow) and onychodystrophy on some nails (purple arrow).

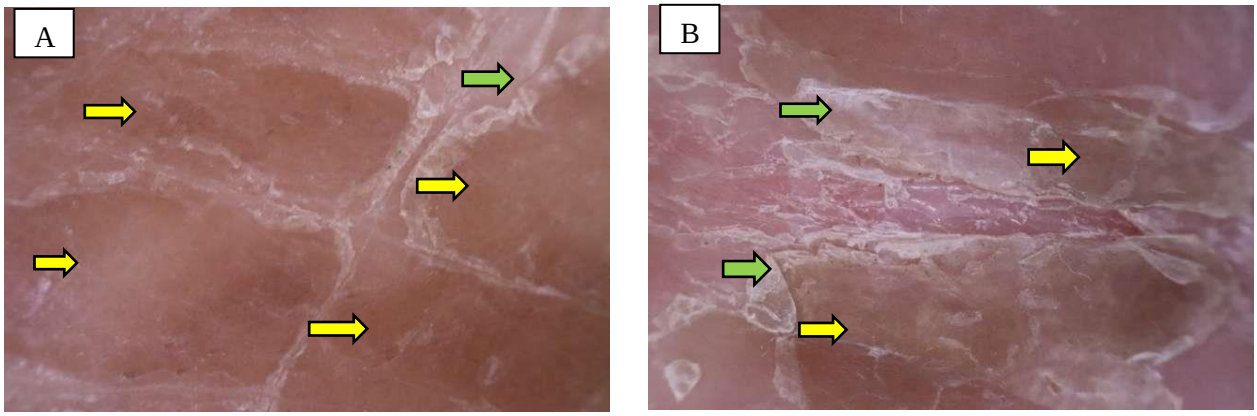

Figure 4. Case 2 (A). The results of the dermoscopy examination of the quadrilateral structure are brownish in color (yellow arrow), accompanied by white scales on it, which are arranged in a lamellar pattern (green arrow). (B). The results of the dermoscopy examination of the quadrilateral structure are brownish in color (yellow arrow) with white scales on it, which are arranged in a lamellar pattern (green arrow).

3. Discussion

Lamellar ichthyosis (LI) is a genodermatosis characterized by cornification abnormalities in the form of large dark brown scales all over the body accompanied by ectropion, eclabium, and scarring alopecia. Most LI patients are born with a history of collodion babies and, in severe cases, Harlequin ichthyosis.[4] This disease belongs to the group of autosomal recessive congenital ichthyosis (ARCI) caused by mutations of 11 different genes such as ATP-binding cassette sub-family A member 12 (ABCA12), lipoxygenase-3 (ALOXE3), 12R-lipoxygenase (ALOX12B), ceramide synthase 3 (CERS3), cytochrome P450, family 4, subfamily F, polypeptide 22 (CYP4F22); NIPA-like domain containing 4 (NIPAL4/ICHTHYIN), patatin-like phospholipase domain-containing protein 1 (PNPLA1), lipase family member N (LIPN), suppression of tumorigenicity-14 (ST14), caspase 14 (CASP14) dan transglutaminase 1 (TGM1). Mutations of the TGM1 gene located on chromosome 14 are most commonly found in LI patients in Asia. The pattern of inheritance for LI is autosomal recessive, but a small proportion of cases can be inherited in an autosomal semi-dominant or autosomal dominant manner.[10,11] Eight percent of LI cases occur in parents with a family history. The incidence of ACRI worldwide in 2012 was estimated at 16.2 cases per 1 million live births per year. Lamellar ichthyosis belongs to a rare group of ichthyosis and is independent of gender.[12]

Patients with LI generally have a history of cornification abnormalities at birth and are characterized by a thin, cobweb-like membrane that covers the entire body. Lip deformities such as eclabium and eye abnormalities such as ectropion are often found at birth. After the collodion membrane is released, it will turn into scales and dry skin all over the body that lasts a lifetime. Clinical manifestations of LI are large, thick, and layered scales, attached in the middle and loose at the edges so that they resemble sheets or lamellar and hyperpigmentation.[13] In some areas, it will appear that the center of the scale is attached to the base with a slightly raised edge. The scales in the leg area are generally larger and plate-like or polygonal in shape, whereas, in the palmar and plantar pedis areas, keratoderma with fissures is common. The palms and soles have keratoderma of varying thickness with fissures. Nail abnormalities that can be found in LI patients such as nail fold inflammation, nail plate thickening to onychodystrophy, especially in severe cases. Lamellar ichthyosis is included in the group of non-syndromic congenital ichthyosis, so no abnormalities in other organs were found. The most common complications of collodion babies are infection, sepsis, electrolyte balance disturbances, dehydration, and

thermoregulation disorders due to fissures in the baby's skin.[14,15]

In this case, the patients were siblings, a 6-year-old girl, and a 2-year-old boy, with complaints of thick, itchy, scaly skin all over the body. In this case, both patients were born covered in membranes and then peeled off and turned into scales all over the body accompanied by folded eyelids, lips pulled back, and both ears were small and looked wrinkled. As you get older, the scales appear thick and large in size, brownish in color, with a reddish skin base accompanied by itching. History of keratinization disease at birth (+) wrapped in a collodion membrane which then peels off 1 week later and is replaced by scales, eyelids are folded out, lips are pulled back, and both ears are smaller and tend to wrinkle. The results of the physical examination of the dermatological status in the generalized region showed thick, large brownish scales that peeled off at the edges and adhered in the middle, shaped like sheets or lamellar with a reddish skin base. Ectropion, eclabium, and microtia were seen, and no joint deformities of the fingers and toes were found. Based on the results of the history and physical examination, both of our patients were diagnosed with LI.

One of the supporting examinations that are easy to do and is non-invasive is a dermoscopy examination. Research on the dermoscopic appearance of congenital ichthyosis is still limited, research conducted by Gajjar et al. mentioned the typical appearance of LI dermoscopy in the form of a brownish quadrilateral structure with fine white scales around it arranged in a lamellar pattern. The results of dermoscopy examination in both patients showed brownish quadrilateral structures accompanied by white scales on it, which were arranged in a lamellar pattern that matched the dermoscopic appearance of LI, so based on the results of dermoscopy examination supported the diagnosis of LI.[16] Histopathological biopsy examination and analysis deoxyribonucleic acid (DNA) was not performed on the patient in this case because both of the patient's parents did not agree and had signed a refusal to treatment.

The differential diagnosis, in this case is X-linked recessive ichthyosis (XLRI) caused by mutations in the steroid sulfatase (STS) gene and increased cholesterol sulfate levels in the epidermal layer. Phenotypic manifestations begin to appear at birth or the first year of life. XLRI clinical manifestations are in the form of diffuse scaling that develops over time, polygonal in shape, especially in the scalp area, lower extremities, and extensor surfaces. Flexor areas such as the antecubital, popliteal fossa, palmar and plantar pedis are rarely affected, as are hair and nails. XLRI dermoscopy showed a brownish structure with a rhomboid/mosaic pattern with gaps between each structure.[10,17] In this case, based on the results of the physical examination of the dermatological status, polygonal-shaped scales were not found, and the distribution of scales in both patients was generalized. The results of the dermoscopy examination did not reveal a rhomboid/mosaic brownish structure, so based on the anamnesis and dermoscopy results, the differential diagnosis of XLRI could be ruled out.

Damage to the skin barrier and changes in the structure of the extracellular matrix in patients with congenital ichthyosis can increase transepidermal water loss (TEWL). Disruption of the skin barrier in LI is the result of structural damage to the corneocytes and changes in the structure of the extracellular matrix. The corneocyte sheath is weak, so the corneocytes formed become brittle and produce fragmented lamellar scales. Cornification abnormalities in the stratum corneum will also interfere with the synthesis of cholesterol and fatty acids forming the extracellular matrix and lipid bilayer so that it can interfere with the metabolism of vitamin D in the skin. Long-term complications due to impaired vitamin D metabolism can cause deficiency but can also trigger rickets. Insufficiency or deficiency of vitamin D in LI patients can also be caused by a lack of sun exposure so that the synthesis of vitamin D precursors in the skin decreases.[18,19]

The results of an examination of the two patients' vitamin D levels showed a condition of vitamin D insufficiency, so we referred them to the Pediatrics

department for further treatment. Both patients received oral vitamin D3 supplementation of 2,000 IU per day and experienced clinical improvement after 12 weeks of treatment. Vitamin D plays an important role in the clinical improvement of the skin of LI patients by normalizing the proliferation and differentiation of keratinocytes and balancing the ratio of T helper 1 (Th1) and Th2 through activation of the vitamin D receptor (VDR). Studies involving children with ichthyosis show skin improvement after the administration of calcipotriene, a topical vitamin D analogue.[20,21] Research by Vahlquist et al. on 7 children with ARCI accompanied by rickets aged 1-8 years who received cholecalciferol 60,000 IU for 10 days then continued with a dose of 400-600 IU per day for 1-3 months. The results of this study showed significant clinical improvement in both scaling and bone conditions.[22] In this case, both patients received vitamin D_3 supplementation of 2.000 IU per day, and there was a clinical improvement after 12 weeks of treatment.

Treatment of congenital ichthyosis is supportive because this disease is a genetic disorder and persists for life. The main principles in the treatment of LI are hydration, lubrication, and keratolytic. In mild cases, hydration and lubrication can provide significant skin improvement. Bleaching baths are an effective way to soften the stratum corneum and thin the thick hyperkeratosis. While bathing, mechanical debridement such as a sponge can be used, then immediately after bathing, continue with the use of a moisturizer.[23] The use of emollient-type moisturizers is highly recommended and can be given up to 5 times a day. Emollients with a lotion or cream-based vehicle can be given in cases of mild LI, while in severe cases, emollients with an ointment or paraffin vehicle are more recommended because the level of moisture can be maintained longer. Ceramides and shea butter are a type of emollient that is recommended because it improves the skin barrier to help synthesize lipid bilayers and increases the fat components that form the skin barrier. Emollients also function to smooth and soothe the skin, where the addition of petrolatum or lanolin can create a feeling of comfort for the patient. The use of keratolytic agents such as salicylic acid, alpha hydroxy acid, 10-20% urea, and retinoic acid can reduce keratinocyte adhesion and trigger stratum corneum desquamation.[24,25] In this case, both patients received cetirizine 1x1/2 measuring spoon at night, Atopiclair lotion, which was applied all over the body 3 times a day, 10% urea cream applied to thick skin day and night, mometasone furoate cream 0.1% applied to the scale area. The thickness on the face in the morning and evening, and artificial eye drops (artificial tears) are dripped on the right and left eyes 6 times a day.

The pattern of inheritance in LI is generally autosomal recessive. Parents of individuals with the autosomal recessive disease each carry 1 gene that is mutated, but does not cause symptoms in these parents, then is passed on to their offspring. An autosomal dominant pattern of inheritance has been found in cases of LI, although it is very rare. Reporting of the first case of LI with autosomal dominance by Traupe, et al in 1984 found 4 cases of LI with an autosomal dominant pattern. Another case report by Endomba and Nkeck in 2017 also reported an occurrence of autosomal dominant LI, with 3 out of 5 children in the family having LI.[26,27]

The inheritance pattern in this case is autosomal dominant, where 2 out of 3 offspring have LI. Inheritance of autosomal recessive disease can turn into autosomal dominant or pseudo-dominant, although until now, the mechanism is still unclear. The majority of autosomal recessive cases with different inheritance patterns that occur are pseudo-dominant inheritance, where the gene carrier parent (Dd) has a child with the affected person (dd) so that the possibility of reducing the disease becomes 50%. Pseudo-dominant can be differentiated from autosomal dominant through pedigree history and DNA sequencing examination. DNA sequencing examination It is necessary to know exactly the type and location of the genetic mutation in each patient.[11,28]

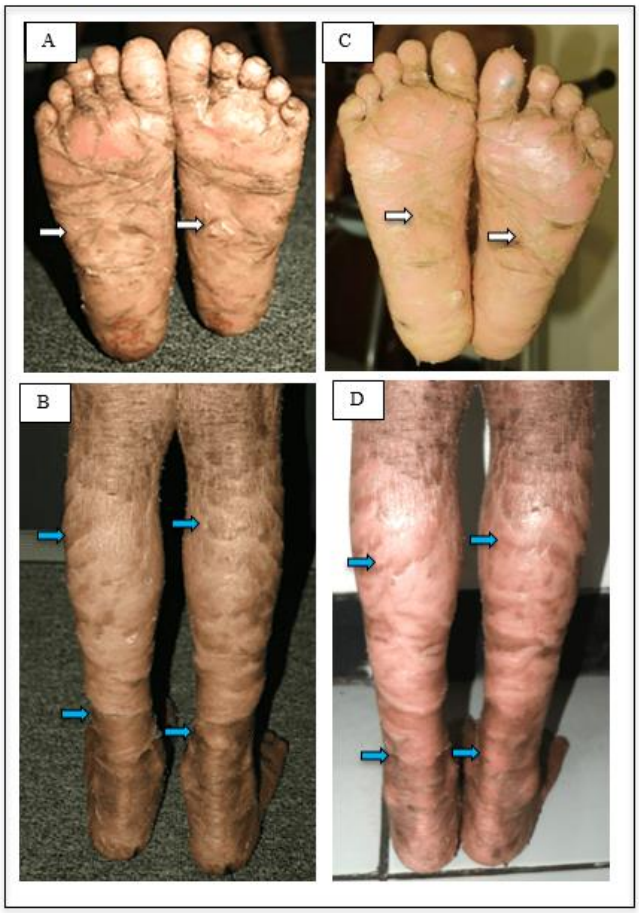

Figure 5. Clinical improvement case 1. (A and B) On day 0, thick brownish scales were seen that were shaped like sheets where the edges peeled off while the center was attached, accompanied by erythema, hyperkeratosis, fissures, and erosion found in several areas (C and D). In the third month, it appeared that the scales became thinner, and the erosion decreased.

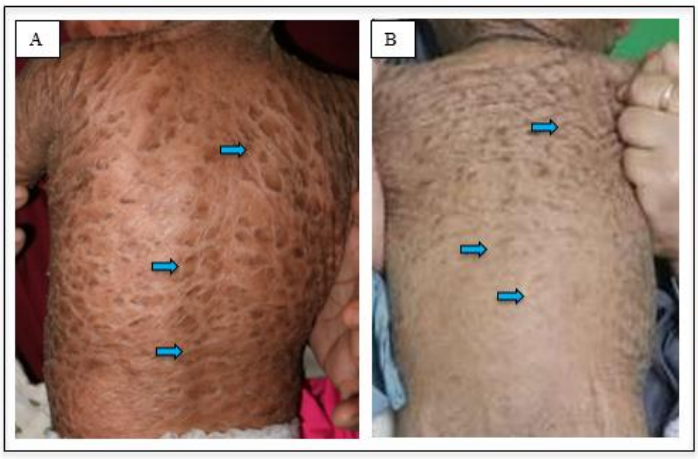

Figure 6. Clinical improvement case 2. (A) On day 0, thick brownish scales were seen that were shaped like sheets where the edges peeled off while the center was attached, accompanied by erythema, hyperkeratosis, fissures, and erosion found in several areas. (B). In the third month, there was an improvement in the scales, becoming thinner all over the body.

4. Conclusion

Lamellar ichthyosis is characterized by disturbance of keratinization at birth in the form of a collodion or harlequin baby. The pattern of inheritance for LI is generally autosomal recessive, but in certain cases and rarely, it can be semi-autosomal dominant, like in this case. Impaired proliferation and differentiation of keratinocytes in LI can cause disturbances in vitamin D metabolism, so vitamin D supplementation is necessary to improve skin conditions.

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