CASE REPORT

A Severe Case of Netherton Syndrome in a Filipino Child

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ABSTRACT

Objective. To present a rare case of Netherton Syndrome (NS) in a Filipino child.

Case. This is a case of an 11-year-old girl with elevated immunoglobulin E, trichorrhexis nodosa, and ichthyosis linearis circumflexa. She had dry skin with fine scaling at birth with recurrent pruritic, erythematous papules coalescing to plaques mainly on the face and extensors. The skin dryness turned to generalized redness with fine scaling, and the skin started getting tight. She could no longer completely extend both knees, but she was still able to walk. She also started having difficulty closing both eyes. She developed migratory serpiginous erythematous plaques with peripheral double-edged scaling. At six years old, she developed ulcers in the scalp, trunk, and extremities, which resulted in admission to our institution. She was managed for multiple skin infections, pneumonia, sepsis, seizure, severe malnutrition, joint contracture, atopy, and bilateral cicatricial ectropion.

Conclusion. Management of NS remains challenging. Common management options include emollients, topical corticosteroids, calcineurin, and protease inhibitor, and phototherapy while newer ones that need further validation include intravenous immunoglobulins and biologics such as infliximab. However, until specific recommendations are made, overall management for NS remains challenging. Regular multidisciplinary monitoring of the manifestations of NS is central to its management.

Keywords: Netherton syndrome, ichthyosis, trichorrhexis nodosa, bilateral cicatricial ectropion, atopy

INTRODUCTION

Netherton syndrome (NS), also known as Comèl-Netherton syndrome, is a rare disease that affects the immune system and the integumentary system. It is an autosomal recessive disease affecting lympho-epithelial-Kazal-type-1 inhibitor (LEKTI-1), encoded by the serine protease inhibitor of Kazal type 5 (SPINK5) gene in chromosome 5.[1,2] The loss in function of LEKTI-1 leads to a cascade of processes that detach the skin's stratum corneum, resulting in a defective skin barrier and severe atopy and inflammation.[2] NS is considered a severe form of ichthyosis.[3] Clinically, NS presents with the triad of atopy predisposition, abnormalities in the hair shaft, and congenital ichthyosis linearis circumflexa.[4] Aside from atopic changes in the skin, the serum Immunoglobulin E (IgE) of patients with NS can also be elevated. Abnormalities in the hair shaft include but are not limited to the pathognomic invagination of the hair's distal part into the proximal portion resembling a bamboo or trichorrhexis invaginata.[4] Congenital ichthyosis linearis circumflexa is described as red serpiginous and migratory

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patches with double-edged peripheral scales, which are itchy and they wax and wane.[2]

NS is commonly mistaken for atopic dermatitis due to atopic skin changes and serum IgE elevation, but it is not responsive to atopic dermatitis' treatment.[5] Genetic testing helps in its diagnosis. However, due to its general unavailability and cost, especially in the Philippines, diagnosis is often made based on the presence of the clinical triad.[6] Although there are many ongoing clinical trials for its treatment, there is still no established cure for NS due to its complex pathophysiology.[7] However, other complications resulting from the pathophysiology of NS must be addressed and monitored. These include recurrent infections due to the defective skin barrier, bilateral cicatricial ectropion and joint contractures from the resulting tightening of the skin. We present a rare case of a clinically diagnosed Netherton Syndrome in a Filipino child.

CASE PRESENTATION

We present a case of an 11-year-old girl seen in our institution five years ago for multiple ulcerations in the head, trunk, and extremities. She was born full-term via spontaneous vaginal delivery to a 20-year-old G1P1 mother. She was born with no adherent parchment-like membrane, often referred to as a collodion baby, and had no developmental delay.[8] She is the only daughter of three children. She was born into a non-consanguineous marriage, and there is no similar condition in the family. At birth, she had dry skin with fine scaling. She experienced recurrent pruritic, erythematous papules coalescing to plaques mainly on the face and extensors. She was diagnosed with atopic dermatitis initially and was managed with moisturizers and occasional topical steroids. At 1 year of age, the skin dryness turned to generalized redness with fine scaling, and the skin started getting tight. She could no longer completely extend both knees, but she was still able to walk. She also started having difficulty closing both eyes. Two years after, she developed migratory serpiginous erythematous plaques with peripheral double-edged scaling or ichthyosis linearis circumflexa, with swelling, flexion deformity, and hypertrophy of bilateral knees. A year after, generalized recurrent pustules and abscesses developed, but they were resolved with oral and topical antibiotics. Consultation with a dermatologist led to the diagnosis of papulosquamous dermatitis and ichthyosis vulgaris. The skin biopsy done revealed granulomatous dermatitis, while lymph node biopsy revealed reactive hyperplasia with sinus histiocytosis. Subsequent tests and consultations with a Pediatric Hematologist-Oncologist cleared the patient of Langerhans histiocytosis. After three months, she again developed generalized skin dryness. She was diagnosed by another doctor with Refsum's disease, another type of ichthyosis, and was treated with oral isotretinoin.[9] However, there was note of worsening skin infections with no resolution of the generalized redness and dryness, so oral isotretinoin was discontinued.

Nine days before the consult, she developed a pustule on the scalp, which progressed to an ulcer with heavy honey-colored to greenish crusts. She also experienced diarrhea, vomiting, fever, and seizure. She was admitted to a local hospital where she was diagnosed with infected ichthyosis vulgaris, severe malnutrition, and sepsis from coagulase-negative *Staphylococcus aureus*. She was started on ampicillin, gentamycin, oxacillin, phenobarbital, and meropenem. However, the lesion on her head progressed to her trunk and extremities (white arrows in Figure 1). Hence, they opted to transfer the patient to our institution.

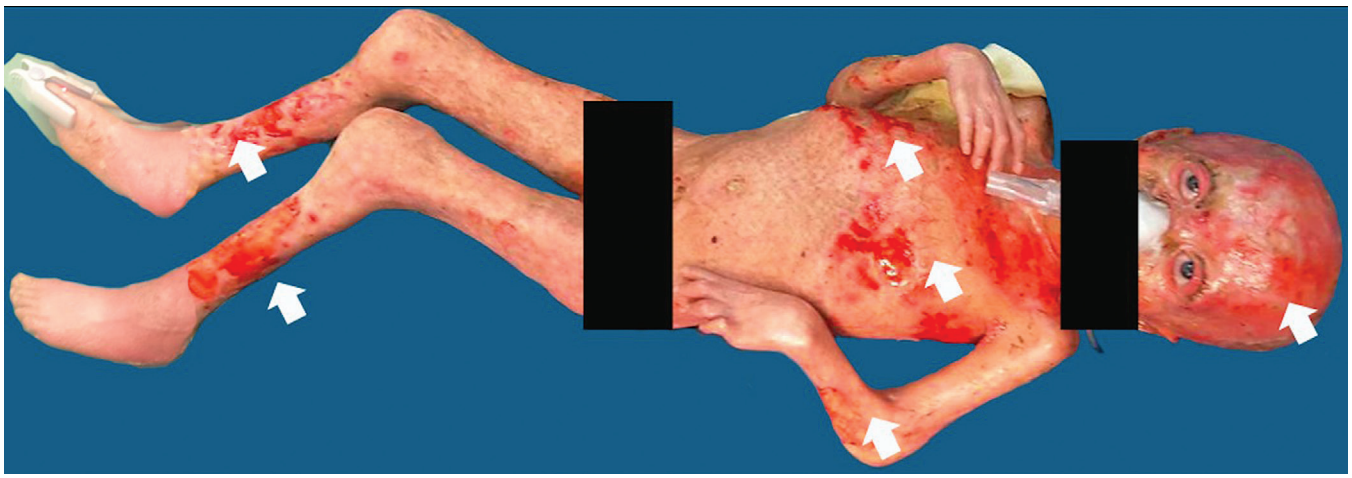

Figure 1. The patient presented with multiple ulcers in the scalp, trunk, and extremities *(white arrows)* in our institution. Evident also in the photo are severe malnourishment, contracted joints, generalized skin dryness, and scaling, and bilateral ectropion. This photo was taken while the patient was under general anesthesia, thus the presence of an endotracheal tube and the visible cornea despite having good Bell's reflex.

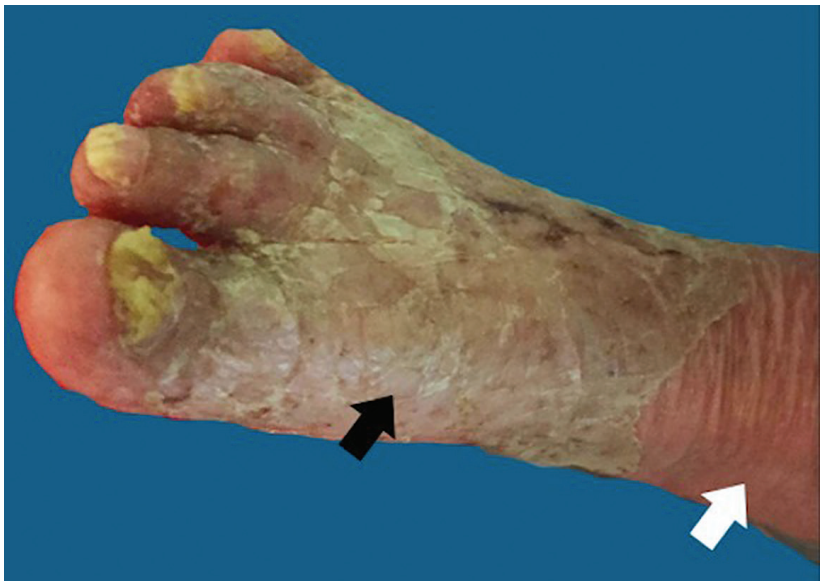

Figure 2. The right lower extremity shows thick adherent scales *(black arrow)* overlying an erythrodermic skin *(white arrow)*.

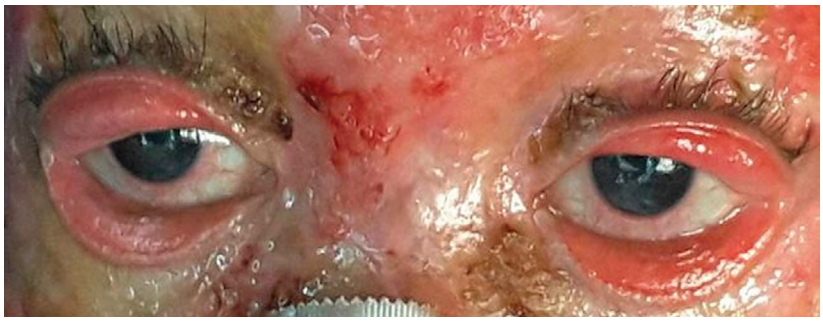

Figure 3. Both eyes show bilateral upper and lower lid cicatricial ectropion and bilateral inferior mild corneal opacification from the lagophthalmos.

She was first seen in our institution when she was six years old. On examination, she had generalized erythroderma with areas of skin thickening or scaling (Figure 2). There are deep-seated ulcerations in the head, trunk, and extremities covered with thick honey-colored crusts. She was also malnourished, severely stunted, and severely wasted. Her elbows and knees were moderately contracted. The rest of the physical and neurological examinations were essentially normal.

On both eyes, her visual acuity was 20/40. The upper and lower lids were both everted with multiple papillae on the tarsal conjunctiva. There were moderate inferior corneal opacities with minimal dye uptake. There were moderate conjunctival injection and dye uptakes inferiorly as well. Lagophthalmos on both eyes were measured at 10 millimeters (Figure 3). She has good Bell's reflex.

The patient was admitted by the Department of Pediatrics and was continued on intravenous meropenem and gentamycin. She had an episode of hyponatremia, was monitored for serum electrolytes and was nutritionally built up through a nasogastric tube. She also needed albumin transfusions for hypoalbuminemia. She was referred to the dermatology department, with repeat of skin and hair biopsies revealing granulomatous dermatosis (Figure 4) and trichorrhexis nodosa (Figure 5).

The immunoglobulin E (IgE) was elevated at > 2500 IU/mL. The erythrocyte sedimentation rate and C-reactive protein were elevated as well. The pediatric allergology-immunology section initiated intravenous immunoglobulin therapy. The plastic surgery section performed regular debridement and dressing of lesions using hydrocolloid dressings. Regular skin swabs were also done to monitor infections and were treated accordingly. The rehabilitation medicine department started anti-contracture splinting and physical and occupational therapies twice a day. The ophthalmology department performed a bilateral lateral tarsorrhaphy using silk 6-0 suture. However, the sutures broke after two days. As such, she was continued on regular copious eye lubrication using eye gel. She underwent regular

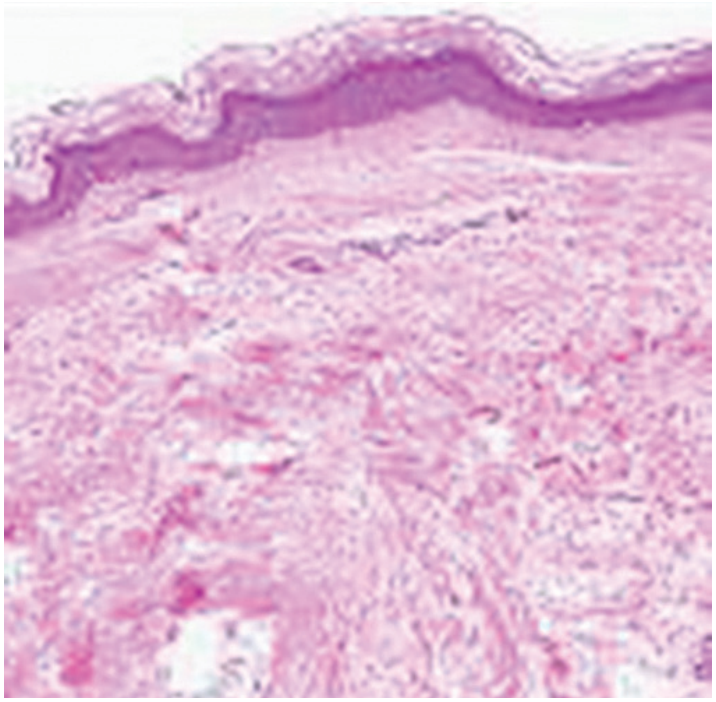

Figure 4. The photo shows a low magnification using hematoxylin and eosin staining a moderately dense lymphohistiocytic perivascular and perifollicular infiltrate with multinucleated giant cells with dense dermal fibrosis.

Figure 5. High magnification of the patient's hair showing trichorrhexis nodosa.

checks for skin infections, including wound gram staining and scraping for potassium hydroxide (KOH) test and change of dressings. She developed fungal, *Staphylococcus haemolyticus,* and *Pseudomonas aeruginosa* infections, which were managed with fluconazole, linezolid, piperacillin-tazobactam, and amikacin. She was also managed for pneumonia. The patient and the parents also received psychological counseling on the psychosocial effects of the disease and the chronicity of its management. After two months of admission, the skin lesions eventually dried up and healed.

A repeat immunoglobulin determination revealed still elevated IgE at 455.80 IU/mL (normal value is 0–90 IU/mL), elevated Immunoglobulin G at 2.27 IU/mL (normal value is 1.63 IU/mL), and elevated Immunoglobulin M at 90 IU/mL (normal value is 47 IU/mL). In the interim, she was continuously and conservatively managed to address malnutrition and stunted growth, infections not only in the skin but also in the ear, nose, upper respiratory, and gastrointestinal system, joint contractures, allergies, and eye complications. She was maintained on skin emollients, antihistamines, and eye lubricants. She underwent monthly checks for skin infections, including regular wound gram staining, and culture and sensitivity tests, and regular weight monitoring. For the last two years, she had four courses of oral and topical antibiotics for skin infections, two episodes of upper respiratory tract infections, and one episode for the eye. Additional eye lubricants were used. A genetic sequencing study and further treatment were planned in the United Kingdom with the help of a non-government organization. They also received additional psychological counseling before the trip. However, it was delayed due to the COVID-19 pandemic.

DISCUSSION

The reported prevalence of NS was 1 to 9 cases per 1,000,000 population.[10] This is the first published case in the literature of Netherton Syndrome in a Filipino, to our knowledge. The presence of the clinical triad of congenital ichthyosiform erythroderma, trichorrhexis nodosa, and increased IgE level led us to the diagnosis of NS in our patient. Considering that NS affects the skin and the immune system, multiple body parts are significantly affected. These make the management of NS challenging.[11]

Due to a defective skin barrier, our patient suffered from recurrent skin infections. As such, regular follow-up consultations are central to her care. Skincare goals are to improve quality of life and prevent infectious complications while minimizing potential medication side effects. Optimal control of all aspects of NS morbidity, including pruritus, is best achieved through hydration, restoration of the skin barrier, and control of skin inflammation.[12] Since NS is a chronic, relapsing disorder with flares occurring at variable intervals, a comprehensive home treatment plan is critical

to successful management, including steps to manage an acute flare. Chronic management requires extensive patient education on the clinical features and associations of the disorder, its natural history, review of potential triggers for disease flares, discussion of medications and possible side effects, and provision of an individualized and comprehensive treatment plan based on the underlying pathophysiology. Treatment plans were directed at underlying defects: skin hydration and emollients to address barrier dysfunction and topical (or rarely systemic immunosuppressants) to quell skin inflammation, and rational antibiotic use once infection sets in. The patient's mother was instructed to use topical antibiotics once a tiny cut or just a scrape is noted on the skin. Methods to reduce exposure to potential triggers were addressed since she tested to be reactive to multiple allergens. High-efficiency particulate air (HEPA) filters were installed in the patient's room, and she was homeschooled. The patient was also being monitored for any cutaneous tumor growth since it has been reported that in patients with congenital ichthyosis such as NS, there is a higher incidence for non-melanoma skin cancers such as basal cell carcinoma and squamous cell carcinoma.[13-15]

Similarly, the ichthyosis in our patient resulted in significant skin-tightening and joint contractures which affect her mobility, not commonly reported in patients with NS. Due to the pandemic, our patient could not regularly attend her physical therapy sessions but was given a home program to follow. However, more definitive treatment for ichthyosis is needed to address the progression of the contractures. The desquamation also resulted in aesthetic concerns which reportedly resulted in bullying, stigmatization, and emotional concerns both for the patients and their caretakers.[16] As such, psychological counselling will be continued for our patient.[16]

The management of the bilateral cicatricial entropion in NS is challenging. An anterior lamella lid reconstruction using a skin graft is often the procedure of choice. However, there is no viable area to harvest a donor skin graft. Nayak et al. used oral mucosa graft, which led to the reduction of the lagophthalmos of their patient. However, their patient was already an adult with sufficient oral mucosa to harvest and could better tolerate the pain from the donor site. Similarly, their patient had residual lagophthalmos that still required continuous use of lubricants. But the use of mucosal graft will be explored when the patient is older as it was reported to have long-term success.[17-19] Another option is the use of a maternal skin graft.[20] Craiglow et al. found the potential use of topical tazarotene in addressing the ectropion.[21] However, tazarotene is not readily available in the Philippines. Although lagophthalmos was large in both eyes, her Bell's reflexes are good, and led to minimal corneal abrasion and scarring. Regular copious use of lubricants was continued.

An aspect of NS being explored was the underlying immune deficiency.[22] Although lymphocytosis was noted before her discharge from the hospital, tests were not available and done to identify if they were T- and B-lymphocytes and to quantify them.[23] However, similar to other reported cases, our patient had elevated immunoglobulin and responded to intravenous immunoglobulin.[24] Although genetic testing has not been done to confirm NS, the patient's mother was already advised that there is a 25% chance of another offspring also having the same condition since NS is an autosomal recessive disease.[1,2]

Multiple options are available to manage NS. A mainstay in the management includes emollients, which are found helpful in lubricating and hydrating the skin while topical corticosteroids are found effective in addressing the inflammatory and proliferative processes involved. Calcineurin and protease inhibitors are found effective in inhibiting inflammatory mediators and serine protease while phototherapy is proposed to promote serine protease inhibitors and have an immunomodulatory effect.[7] Newer options with reported positive results but still lack large clinical trials include the use of intravenous immunoglobulins, as has been done in our patient, and biologics such as infliximab (anti-tumor necrosis factor-alpha antibody) and secukinumab (anti–interleukin 17 therapy).[7,25] Future perspectives include gene therapy and the use of phage.[7,24,25] However, until specific recommendations are made, regular multidisciplinary monitoring of the manifestations of NS is central to its management.

Ethical consideration

Consent was given by patient to publish the case and use the photos.

Statement of Authorship

Both authors contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising and approved the final version submitted.

Author Disclosure

Both authors declared no conflicts of interest.

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