CASE REPORT

Ichthyosis with confetti: a rare diagnosis and treatment plan

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SUMMARY

Congenital ichthyosis includes a group of rare skin disorders known for tiles of hyperkeratotic skin resembling fish scales. With age, the hyperkeratosis generally becomes more concentrated around joints which increases impairment. Ichthyosis with confetti, also known as ichthyosis variegata or congenital reticular ichthyosiform erythroderma, is an extremely rare form of ichthyosis. It usually begins as non-bullous congenital ichthyosiform erythroderma with the expected scaling. However, with time patients develop widespread 'confetti-like' patches of healthy skin. The healthy skin reflects clonal expansion of 'normal' or reverted cells. Cell reversion has potential for future therapies using revertant stem cells. Controlling symptoms with emollients is the goal of treatment for ichthyosis since it has no cure.

BACKGROUND

Owing to the rarity of this genetic disorder and the paucity of clinical trials, dosing and duration of specific therapies have not been standardised. Early recognition, appropriate management and understanding its potential complications can lead to better survival and quality of life for these children. More case reports and successful treatment strategies can assist future care.

CASE PRESENTATION

A 36 week 4 day Caucasian female infant was delivered in a rural hospital via caesarean section for breech presentation. The 20-year-old healthy gravida 1 para 0 mother had received appropriate prenatal care. The uneventful pregnancy resulted from a non-consanguineous relationship with no family history of skin disorders. At birth the infant weighed 2420 g with apgar scores of 9 and 9 at 1 and 5 min, respectively. She was covered in a large amount of vernix which on removal uncovered areas of desquamated skin. Examination revealed hypoplastic ears with plastering of the pinnae to the scalp, thickened fingernails and semiflexed limbs. She had a waxy appearance and within hours of birth developed cracking and desquamation in the flexor folds of her wrists, ankles and groin. Her joints had decreased range of motion due to the tautness of her skin. A diagnosis of collodion baby (figure 1) was made and the closest neonatologist was contacted. The infant was prepared for transfer. Aquaphor was applied liberally to her entire body with sterile gloves and erythromycin ointment was applied to her eyes twice. She was placed in a humidified incubator and no footprints were obtained. Initial complications from the loss of the skin barrier can result in hypothermia, dehydration, electrolyte abnormalities, skin infection, sepsis and death. Consequently, she was

Figure 1 Patient shortly after birth and diagnosis of collodion baby. Note her waxy taut skin, semiflexed limbs and erythematous hue.

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transported via helicopter to the nearest neonatal intensive care unit.

At discharge she had non-bullous ichthyosis without any blistering, so she was placed in the subgroup of autosomal recessive congenital ichthyosis.^{1 2} By the age of 2, she developed a constant erythema and ruddiness of her skin with thickening of her palms and soles, subungual hyperkeratosis with subsequent nail curving, and increased palmar skin markings (figure 2). This led to the major type diagnosis of congenital ichthyosiform erythroderma (CIE) which is characterised by non-bullous, thin, white scaling on a bed of erythematous skin and hyperkeratosis.^{3–9} She also had microtia (small ears and external auditory canals), but normal overall neurodevelopment. Her eyes developed eyelid eversion, known as cicatricial ectropion, which was more notable on her lower lids (figure 3). She had hypohydrosis with temperature intolerance. With age, she continued to have a deep erythema to her skin with the appearance of a third-degree sunburn in addition to her overlying scales. She developed skin contractures with worsening mobility of the joints of her hands, elbows, shoulders, hips, knees and neck.

Her medical condition remained stable until the age of 5, when her mother noticed a change to the skin. She developed spots of normal-appearing skin interspersed throughout her base of scaled, thick, taut erythematous skin. These patches began on the trunk, and then increased in size and number, spreading to her limbs, and the rest of her body. Her classic diffusely red appearance transformed into a background erythema with inconsistently placed spots of normal skin, measuring from miniscule to 1 cm in diameter (figure 4). The emergence of normal-appearing skin was of uncertain significance so she was included in a dermatological study at Yale that involved skin biopsies and DNA sequencing revealing the *KRT10* gene mutation.¹⁰ This resulted in her final diagnosis as 1 of 16 confirmed patients suffering from ichthyosis with confetti (IWC).^{11–13}

TREATMENT

Owing to the rarity of IWC, specific treatments, dosing regimens and duration of therapies have not been standardised. A literature search on existing treatments for all types of congenital ichthyoses revealed case reports with few randomised controlled trials and one systematic review. This significant systematic review found that due to the small number of reported trials and small sample sizes for most studies, there is an absence

Figure 3 Cicatricial ectropion, or eyelid eversion, is more notable on the patient's lower lids.

of standardisation of outcome measures precluding the comparison of studies.¹⁴ However, the available published trials and case reports have been indispensable in achieving a general guideline of care and medications with therapeutic benefits and good safety profiles. The primary consensus of therapy for general ichthyosis is controlling symptoms with emollients since there is no cure.

Three essential mechanisms are involved in the action of topical emollient agents for the treatment of ichthyosis: lubrication, hydration and keratolysis.¹⁵ Frequent bathing with water and baking soda (sodium bicarbonate), which alkalises the epidermis leading to water flow into the cells, is recommended. Bathing must be followed by mechanical keratolysis with sponges, cloths or brushes. Emollients should be applied throughout the day and especially after bathing to prevent drying. α -Hydroxy acid lotions reduce corneocyte adhesion, decrease skin thickness and relieve itching. Long-term application of 5% lactic acid with 20% propylene glycol mixed in a lotion base helps skin hydration and can also help ectropion. Urea creams decrease dryness and scaling, but should not be instituted until after age 1 due to the risk of elevating plasma urea levels. *N*-acetylcysteine ointments have antiproliferative effects to help decrease scaling as well as improving ectropion. Calcipotriol ointment, a vitamin D derivative, reduces scaling but is limited to 100 g/week due to the risk of hypercalcaemia. Salicylic acids reduce dark scaling, but must be used after the first year of age and again, care must be taken to prevent systemic salicylate intoxication with maximum application to no more than 20% of the body surface area. Tazarotene, a leukotriene antagonist, can be used after 6 months of age for pruritis.

Figure 2 Patient's hands showing subungual hyperkeratosis with nail curving, increased skin markings and extensive scaling.

Figure 4 Patient's back at age 11 showing her background erythema with inconsistently placed 'confetti-like' patches of 'normal' skin.

Topical retinoic acids decrease the thickness of scales making them less adherent and easier to remove. They also have immunomodulatory and anti-inflammatory properties, but dosage is limited to 2 mg/cm^2 to prevent systemic absorption and toxicity.¹⁶ Antiseptics and antimicrobials are used for odour and infection control.

Because of the unpredictability of cutaneous absorption, oral retinoids have recently come into favour with positive results including extension of the areas of normal skin. Acitretin is the most studied at a dose of 1 mg/kg/day . It has been used during the first 6 months of life because of its short half-life. It is advised that liver function tests, creatinine and lipid levels be monitored per routine dosing guidelines.^{17 18} Because of the long-term side effects, systemic steroids are reserved for critical disease. It is notable that all instituted and advised therapies are anecdotal without any explicit pharmaceutical dosing guidelines.

This patient is now 11 years old and over the years the best treatment regimen for her has been developed. A brief description of her daily care follows. On awakening, she has a 10% lactic acid/20% urea/aquaphor compound and a moisturising hydrobase lotion applied to her entire body, including her face and genitals. She has lacrilube placed in her eyes for moisture and lubrication. Carmol 40 urea cream is placed on the soles of her feet, her nails and nailbeds. Moisturising lotion is applied to her entire body approximately every 3-4 hours throughout the day. In the late afternoon, lotion and the lactic acid/urea/aquaphor mixture is applied to her entire body and face once again.

In the evening, she soaks in bath water with three handfuls of baking soda for 45 min to help slough her skin. Her scalp is soaked with shampoo mixed with mineral oil and lactic acid. Her parents then scrub off all of the dry skin she has over her entire body with an exfoliating glove. After the bath, tazorac 0.1% cream is applied around her eyes, hands, shoulders, elbows and knees. The lactic acid/urea/aquaphor mixture is applied to her entire body one last time. She is then covered in plastic wrap, especially her arms, legs and feet to prevent cracking of the skin during the night. Elidel is applied to her face for redness, lacrilube to her eyes, debrox into her ear canals and carmol 40 is reapplied as above. Her fingernails and toenails are clipped frequently because of their rapid growth and to prevent inadvertent scratching or infection. In addition, once a week her head is soaked for 1 h and then her hair is brushed with a metal comb to exfoliate the scalp. If the regimen is not followed, she develops extensive skin build up, tightening, strictures, limited mobility, increased risk for superficial skin infection and cellulitis. If the skin dries, not only does infection occur, but she experiences pain from cracking. There is difficulty controlling skin cracking especially in the folds of the skin and near her genitals where she often experiences secondary burning on urination.

OUTCOME AND FOLLOW-UP

After birth, the patient had a multidisciplinary team of distant paediatric dermatologists, otolaryngologists and

ophthalmologists. Locally, she was followed routinely by her family physician and physical therapist. She received routine vaccinations, close monitoring for growth and caloric needs, and stringent infection control. She was treated with an intense regimen of topical emollients, lactic acid, cacipotriol ointment and prescription retinoid creams. Parents were warned to only apply creams as advised due to the risk of intoxication by increased cutaneous absorption of topical products. Within her first year of life, she suffered from recurrent bilateral conjunctivitis and staphylococcal cellulitis. She remained in the lowest percentile for growth. She received physical therapy for range of motion of her skin and joints, occupational therapy, and developmental therapy. Routine visits to the otolaryngologist to clear desquamated skin from her ear canals were required for appropriate hearing and speech development. She had to avoid water and outdoor activities due to her poor skin barrier. As a result, vitamin D levels were monitored and remained in normal range. With age, she began to have more social issues and psychotherapy was instituted as well. Her extensive skin routine interfered with social activities. She had greatly limited range of motion of her limbs despite years of physical therapy, and contractures of her skin with a resultant decreased ability to feed, clothe or toilet independently.

DISCUSSION

IWC is also known as ichthyosis variegata or congenital reticular ichthyosiform erythroderma. With only 16 cases in the world literature, IWC is an extremely rare, sporadic disease. Often born with diffusely erythematous and hyperkeratotic skin, patients later develop widespread 'confetti-like' patches of healthy skin. The confetti spots develop on the background of erythematous skin. The small healthy skin spots are mostly located on the trunk, while the larger spots form a reticulated pattern on the extremities. The healthy skin reflects clonal expansion of 'normal' cells. Thus, IWC is a form of revertant mosaicism, which is the coexistence of cells carrying inherited genetic mutations alongside cells that have undergone spontaneous correction of the mutant phenotype.¹⁹ The areas of reversion are widely distributed in sunexposed and unexposed skin. They become detectable anytime between the first year of life and puberty.

Learning points

- ▶ Since ichthyosis has no cure, the primary consensus of therapy is controlling symptoms with emollients.
- ▶ We present one patient's daily treatment regimen that was successful at controlling skin tightness, build up and infections.
- ▶ Ichthyosis with confetti is an extremely rare disease with only 16 patients clinically described in the world literature. It involves natural biological reversal of the patient's gene mutation. This may hold potential for future gene and disease therapy.
- ▶ Given the rareness of the disease and the lack of treatment guidelines, more case reports and successful treatment strategies can assist future care.

Reversion has been reported in other genetic disorders involving selfregenerating organs such as the skin, blood and liver, including bloom syndrome and fanconi anaemia. This knowledge has potential applicability for future therapies using revertant stem cells.

The detection of only a small number of IWC cases leaves the problems of diagnosis and standardised treatment plans unresolved. IWC differs from the other types of congenital ichthyosis but the treatment regimens are comparable. The specific presentation pattern of newly mutated skin surrounded by ichthyotic skin is not completely understood, but may hold future consequence for gene therapy.

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