Non Bullous Congenital Ichthyosiform Erythroderma

Lita Setyowatie, Iskandar Zulkarnain

Departemen/Staf Medik Fungsional Ilmu Kesehatan Kulit dan Kelamin
Fakultas Kedokteran Universitas Airlangga/Rumah Sakit Umum Daerah Dr. Soetomo Surabaya

ABSTRACT

Background: Non bullous congenital ichthyosiform erythroderma (NBCIE) is an inherited genodermatosis, very rare autosomal recessive inflammatory ichthyosis, chronic, characterized by dryness and scaling. **Purpose:** To describe the clinical manifestations of NBCIE since it is a rare case, occurs in 1 in 300.000 people. **Case:** Baby MR 5 month old, Javanese boy, with main complaint white scale and redness patches on almost all of his body since 1.5 month old. Born as collodion baby, then the membrane was slowly thinning and became generalized erythroderma on almost all of his body accompanied with fine white scale, large, thick, plate-like scale only on lower leg. No ectropion and eclabium. No relatives in the pedigree suffer from the same disease. Histopathology examination showed non-bullous congenital ichthyosiform erythroderma. **Case management:** Emollient after bath and pH balance soap. **Conclusions:** Diagnosis of NBCIE is established from history taking, clinical features, and histopathology examination. Emollient therapy and pH balance soap will eventually lead to improvement.

Key words: non bullous congenital ichthyosiform erythroderma, genodermatosis, collodion baby.

ABSTRAK

Latar belakang: NBCIE merupakan genodermatosis yang diturunkan secara autosomal resesif, sangat jarang, bersifat kronis, dan ditandai dengan kulit kering dan sisik. **Tujuan:** Untuk mendeskripsikan manifestasi klinis dari NBCIE dimana termasuk kasus yang jarang, terjadi pada 1 dari 300,000 orang. **Kasus:** Bayi laki usia 5 bulan, suku Jawa, dibawa karena sisik putih diatas bercak kemerahan pada hampir seluruh tubuhnya sejak usia 1,5 bulan. Terlahir sebagai bayi *collodion*, selaput perlahan menipis dan menjadi eritroderma di hampir seluruh tubuhnya, sisik putih yang besar, tebal, seperti plat, dan hanya terdapat pada tungkai bawah. Tidak ada ektropion dan eklabium. Tidak ada kerabat dengan penyakit yang sama. Pemeriksaan histopatologi menunjukkan *non-bullous congenital ichthyosiform erythroderma*. **Penatalaksanaan:** Pelembab setelah mandi dan sabun pH netral. **Simpulan:** Penegakkan diagnosis NBCIE berdasarkan riwayat penyakit keluarga, gambaran klinis dan histopatologi. Terapi dengan emolien dan sabun pH netral perlahan-lahan akan menunjukkan perbaikan.

Kata kunci: *non bullous congenital ichthyosiform erythroderma*, genodermatosis, bayi *collodion.*

Alamat korespondensi: Lita Setyowati, Departemen/Staf Medik Fungsional Ilmu Kesehatan Kulit dan Kelamin Fakultas Kedokteran Universitas Airlangga, Rumah Sakit Umum Daerah Dr. Soetomo, Jl. Mayjen Prof. Dr. Moestopo No. 6-8 Surabaya 60131, Indonesia. Telepon: (031) 5501609, email: lita_centik@yahoo.com

INTRODUCTION

Non Bullous congenital ichthyosiform erythroderma (NBCIE) is a chronic, inherited genodermatosis, very rare autosomal recessive inflammatory ichthyosis. Up to now, confusion occurred in the medical literature where classification of NBCIE as a separate entity from lamellar ichthyosis (LI) has not yet been well established. Some authorities regard NBCIE as a severe variant of LI whereas others call it erythrodermic lamellar ichthyosis. It may be caused by the same gene that causes LI but with different clinical expressions, or by different genetic entities with a broad spectrum of similar clinical features, as some authorities believe. To avoid confusion and controversy, some authors and German literature, prefer to call both variants of NBCIE and LI by one term which is as an autosomal recessive congenital ichthyosis (ARCI).[1,2] ARCI include three types of ichthyosis. The three types are NBCIE, LI and harlequin ichthyosis (HI). The majority of ARCI cases are classified as either LI or NBCIE.[3,4]

NBCIE estimated to occur in 1:300.000 newborn of all races and more commonly happen in consanguinity.[2,5,6] NBCIE is milder and more variable with respect to severity than LI.[6] Other literature

reported, NBCIE occur in fewer than 1/100.000 deliveries.[7] An affected individual will not have affected offspring, but half will be carriers. NBCIE at least twice as common as LI. Male equal with female. High incidence of consanguinity is usually reported in the pedigrees of patients and this factor may play a major role in the transmission of the recessive defective genes causing the disease.[2]

The nature of scaling and intensity of erythroderma are important clinical features that distinguish NBCIE and LI.[5] NBCIE is one of the major types of autosomal recessive severe ichthyosis present at birth[8], showing generalized severe scaling and erythroderma without blister formation.[5,9] Over 90% NBCIE characterized clinically by an early onset at birth as a collodion membrane baby (covered with oiled parchment-like shiny skin).[2,3,5,8] The membrane ruptures within a few days and continues as exfoliating dry scales on a diffuse erythema involving the whole body surface.[1] In the classic of NBCIE, the entire body is covered in erythrodermic skin with fine white or light grey scales and feathery. Brownish, thick, plate-like, lamellar scales are similar to LI scales on the lower legs.[1,3] Ectropion and eclabium are frequently seen, but not severe as LI. Hair and teeth appears normal.[3] Hypoplasia of nasal and auricular cartilage and scarring alopecia have been rarely reported. Hearing ability is normal.[3,5] The palms and soles are hyperkeratotic in most cases although this severity is variable depending on individual cases. Extracutaneous symptoms or other congenital anomalies are never seen. In most of the cases, there is no family history of congenital ichthyosis.[3] Other associations include decreased sweating with heat intolerance, nail dystrophy and deep skin fissures, but the mucosal surfaces are normal.[5] Decreased sweating (hypohidrosis) may occur as a result of the obstruction of eccrine ducts (sweat gland) in the epidermal ducts in the epidermal scale often interferes with effective cooling of the skin.[7,10]

Histologic finding both NBCIE and LI are not spesific.[2] In NBCIE, the patient's skin biopsy sample shows moderate hyperkeratosis, a normal or slightly thickened granular cell layer, mild acanthosis and variable parakeratosis. Lesional skin from patients with the LI shows hyperkeratosis with only a small number of parakeratotic cells. The granular layer is normal or mildly increased in thickness. The important point for differential diagnosis is the inflammatory cell infiltrate more frequently seen in the upper dermis in NBCIE than in LI. Parakeratosis is also more frequent in NBCIE. On the other hand, the stratum corneum is usually thicker in LI than in NBCIE. However, these findings are not specific to NBCIE or LI and the histopathological differences alone are not definitive.[3]

NBCIE could be separated biochemically from LI by the presence of elevated quantities of n-alkanes in scale (CIE, 24.8 ± 1.9% vs. LI, 7.2 ± 1.6%, and normal, 6.5 ± 0.9%), which suggested a primary disorder in neutral lipid metabolism.[11] NBCIE is characterized by the presence of lipid abnormalities leading to the formation of vacuoles in the horny layer and the elevation of n-alkanes in the keratinocytes. This defect is considered by some as an error of metabolism. These changes are not found in typical LI.[2] Further studies are required to ascertain if these findings are endogenous or exogenous and what is the role play in barrier function and intracelluler cohesion.[6]

Treatment of NBCIE is based on the severity of the disease. Symptomatic treatment with a high-humidity environment, and application of non-occlusive emollients may facilitate shedding of the membrane. Emollients remain the mainstay of treatment. This emollients applied every half-hour, frequent oiling of skin, nursing in humidified incubator with careful temperature monitoring, aseptic handling, investigation and treatment of signs of sepsis, meticulous fluid and electrolyte balance. Topical treatments including emollients, lactic or glycolic acid or alpha hydroxy acid (5%), urea (10-40%), and retinoic acid (0.1% cream) are effective and may lessen the scaling to some extent, but their application is limited because of their adverse effect of local irritation (these agents produce stinging if applied to fissured skin). Topical keratolytics and retinoids are rarely used. Systemic use of retinoid is also applicable for the treatment of severe NBCIE. Acitretin given at 0.1-0.75 mg/kg/day intermittently (three months on and off) reduces scaling, pruritus and erythema in most patients. The long-term risks of these compounds (teratogenic effects and toxicity to bone) may limit their usefulness.[2,3,5] Parents should be advised to attend genetic counseling.[2]

Prevention of sunburn and sunstroke is important. Ectropion requires ophthalmologic care. In some cases of NBCIE, erythroderma and fine scaling gradually decrease with age without the use of retinoid or steroid treatment and the erythroderma becomes milder during childhood and puberty. This improvement tends to occur in the milder cases. However, some affected children

show no improvement when they grow old and, in some newborn patients, symptoms become more severe in the first 2–3 years.[3]

Neonatal morbidity and deaths may be caused by cutaneous infection, aspiration pneumonia, hypothermia, or hypernatremic dehydration from excessive transcutaneous fluid losses resulting from increased skin permeability.[5]

Possible complications during neonatal period include impairment of temperature regulation, increase insensible water loss through the skin, hypernatremic dehydration, acute renal failure with and without brain damage and pneumonia due to restricted chest movement from the membrane and septicaemia.[2]

For patients with inherited diseases, prenatal diagnosis may be an important part of medical care for several reasons. Knowledge of an affected fetus can allow psychosocial as well as financial preparation. Medical problems during pregnancy and delivery can be anticipated and treated in a timely manner. Furthermore, prenatal diagnosis gives parents the therapeutic option of aborting an affected fetus, especially in cases where treatment is unavailable. In the past, patients who looking for prenatal diagnosis were presented with the sole option of fetal skin biopsy, whereby a fetal skin sample obtained under fetoscopy or ultrasound guidance at 15–27 weeks gestation is subsequently analyzed with light microscopy, transmission electron microscopy, and/or immunohistochemical staining. Bullous congenital ichthyosiform erythroderma (BCIE) was the first conditions successfully diagnosed via these techniques. Although diagnostically specific, the procedure is invasive and associated with 1–3% risk of fetal loss (over the general miscarriage rate), amniotic fluid leakage, and fetal scarring. Presently, fetal skin biopsy is still a useful option when the causative gene has not yet been elucidated, when the causative gene is known but the specific mutation cannot be identified, or when linkage analysis is not available. DNA-based methods have largely supplanted fetal skin biopsy, and newer noninvasive options are being developed for use in prenatal diagnosis.[12] ARCI are a group of the most severe genodermatoses and the patients quality of life is often seriously affected. Thus, the parents request for prenatal diagnosis is not to be ignored easily. Prenatal diagnosis had been performed by fetal skin biopsy and electron microscopic observation during the stages of pregnancies at 17—23 weeks gestational age.[4,6] Fetal skin biopsy at 17 to 23 weeks looking for premature or abnormal keratinisation is possible but unsatisfactory due to phenotypic heterogeneity, and multiple biopsies are required. It is however possible to exclude LI by mutation testing for transglutaminase 1 (TGM-1).[2] Fetal skin biopsy is only a possible way for some of the conditions even now.[8]

CASE REPORT

Baby boy 5 month old, Javanese, hospitalized in Dermatology Department ward of Dr. Soetomo General Hospital, Surabaya (May 25th 2011 to June 1st 2011) because of fine white scale and redness patches on almost all of his body. Fine white scale and redness patches on his body appeared when he was 1.5 month old. Previously, there was only redness patches on his neck area and then spread out to almost all over the body accompanied with scale, fever and slightly itchy (sometimes his parents observed the baby scratched his skin). His parents took him to a dermatologist in Papua and received ointments therapy, due to no improvement regarding the therapy his parents took him to Java and hospitalized in Tuban hospital for one month. During hospitalization at Tuban hospital, he was diagnosed with skin infection and got a syrup medicine. When he was discharged from Tuban hospital there was slightly improvement. However, after a week at home, he had a high fever, cold, cough, and the skin became redness and scalling again so his parents took him to hospital.

Based on information gathered from his father, there was history of the baby covered with membrane when he was born, he received an ointment therapy from dermatologist then the membrane was slowly thinning.

There was no complain of mixturation and defecation problems such as severe diarrhea, no abnormality of growth and development. According to his father, there is no complaint regarding sweating problems, no history of atopy. He was breastfed well. His mother never applied any topical or took any oral traditional medication.

He was the first child from healthy parents. There was no history of the same disease on the other family neither from the mother or the father trait, no family history of any hereditary skin disease. His mother and father are not relatives. The father was the first child of two. His brother is healthy and alive until present. His mother was the youngest child of three children, all of them are in good health, no complaints of any pain. His mother routinely controlled to the obstetrician during her pregnancy. There were no history of neither illness,

drug or herbal medication taken during pregnancy. He was born aterm, 9 months, spontaneous, delivered by obstetricians in Papua with body weight 3650 gram and body length of birth 50 centimeters.

General physical examination at first day of admission was composmentis with 7 kgs body weight, no sign of anemic, icteric, cyanotic and respiratory distress. There was no conjungtivitis, no enlargement of lymphnode. Pulse rate was 88 times per minute, respiratory rate was 28 times per minute and body temperature was 37.8^{0}C. There were no abnormality on cor and pulmo. There was no hepatosplenomegaly in abdominal examination, no hand and feet contracture. There were no edema on left and right extremity superior and inferior.

Dermatological examination on almost all of his body revealed erythematous macule with unsharply marginated (generalized erythroderma) and fine white scale, large, thick, plate-like scale on lower leg. The skin was tending to dry. The scalp presented some large thick scale without alopecia, cradle cap and bamboo hair. There was no blister, no ectropion on both eyes, no eclabium of lips, pinnae and nasal were normal. There were no exaggerated skin folds, alopecia of eyelashes, and eyebrows, no nail abnormality, no hyperkeratotic on palms and soles.

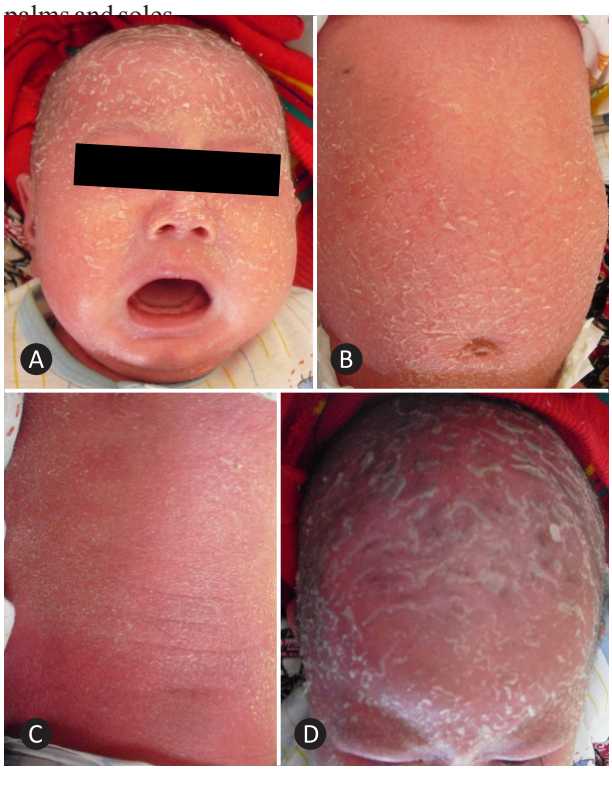

Figure 1. ABC. Generalized erythroderma and fine white scale all over the body ; large, thick, plate-like scale on lower leg. The skin was tending to dry. D. The scalp present some large thick scale.

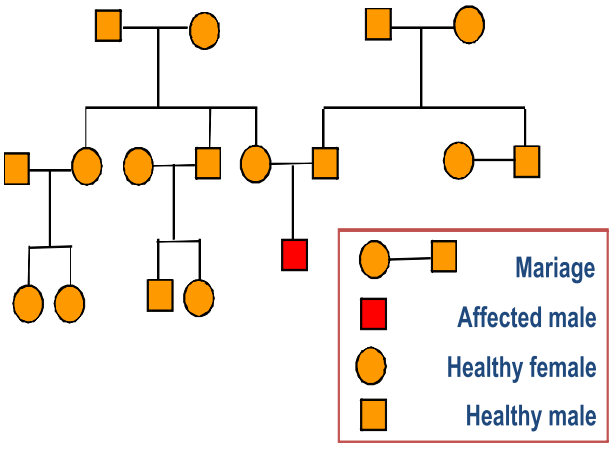

Figure 2. Pedigree of patient showed that only the patient has suffered this disease with healthy parents. There are no any other relative in the pedigree that has the same disease.

Laboratory examination on first admission revealed hemoglobin was 11.6 g/dL, white blood count was 21x10^3 /uL, platelet was 350x10^3/uL. The result from urinary laboratory was normal, albumine was 3.8 g/dL.

The potassium hydroxide preparation collected from his skin, revealed no element of fungi.

The histopathologic finding which is the specimen collected from left thigh of the patient by punch biopsy, revealed mild hyperkeratosis, acanthosis and moderate spongiotic, focal parakeratosis, slightly elongated rete ridges in epidermis, the picture also showed psoriasiform epidermal hyperplasia. There was dermis fibrocollagen network with minimal mononuclear inflammatory cells, perivascular and sebaceus glands. The conclusion is concordance with NBCIE.

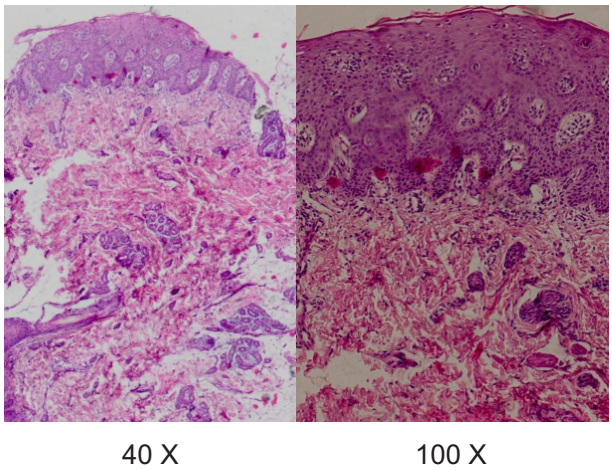

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Figure 3. The histopathology of NBCIE.

The patient were consulted to Pediatric Department and the results were acute pharyngitis and phymosis. He was treated with cloxacillin 2x100 mg per

oral, sistenol 3x75 mg per oral, breastfeeding and non breastfeeding milk 12x120 cc, consulted to surgery department for phymosis and other treatments were following dermatology department.

He was not consulted to surgery department for phymosis because of the temporary rejection of the family.

The treatment for Baby MR were emollient to all over the body including the face, after bathing or wiping. Bathing or wiping were done with pH balanced soap. Antihistamine with dimethidine maleate, four drops three times a day, followed by therapy from pediatric department cloxacillin 2x100 mg per oral, sistenol 3x75 mg per oral, breastfeeding and non breastfeeding milk 12x120 cc.

Figure 4 shows the last picture when the baby boy was 7 month old because the patient moved to Lamongan and continued the therapy there.

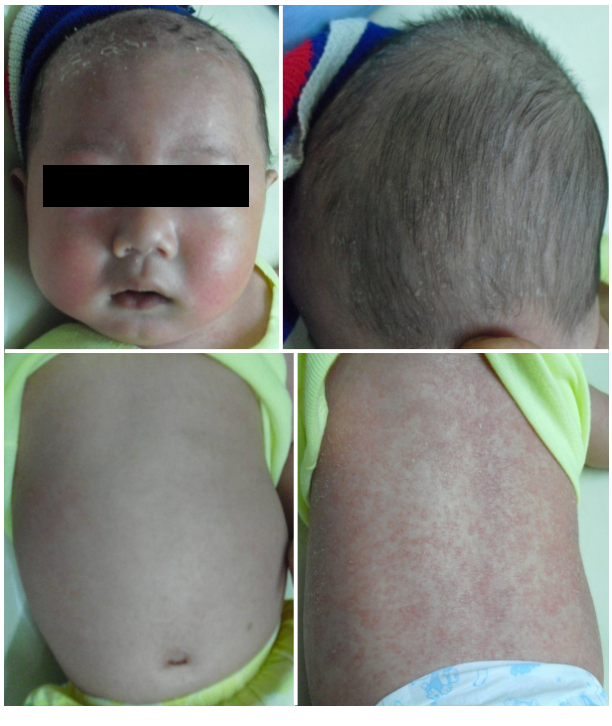

Figure 4. After treatment.

DISCUSSION

The patient was a boy, first child from healthy parents. His father was the first child of two and his brother is healthy and alive today. His mother was the youngest child of three children, all of which are in good health. Affected due to the male sex, then the patient can be diagnosed with autosomal recessive group and also included the group of X-linked recessive (XLI). XLI disease usually occurs in males who have inherited a recessive X-linked mutation from their mother. Rarely, the disease may be seen in females who have inherited mutations in the same gene X-linked from both parents. More typically, the mother is a carrier and is unaffected, although it is not uncommon for female carriers of X-linked disorders.[13]

Patient with NBCIE usually present as collodion baby at birth. The term collodion baby is used for newborns in whom all of the body surface is covered by thick skin sheets, so called "collodion membrane". The collodion membrane is the result of an epidermal developmental dysfunction. The collodion membrane is composed of thick skin sheets which resembles translucent, tight parchment paper. In almost all of the collodion membrane cases an autosomal recessive ichthyosiform disease is implicated.[10] Over 90% NBCIE characterized clinically by an early onset at birth as a collodion membrane baby (covered with oiled parchment-like shiny skin).[2,3,5,8] The membrane ruptures within a few days and continues as exfoliating dry scales on a diffuse erythema involving the whole body surface.[1] In NBCIE, the entire body is covered in erythrodermic skin with fine white or light grey scales and feathery. But brownish, thick, plate-like, lamellar scales are similar to LI scales on the lower legs.[1,3] Ectropion and eclabium are frequently seen, but not severe as LI.[3] Ectropion improve during infancy, but persist into adult life in 30% and if untreated carries the risk of exposure keratitis and blindness. The loss of eyebrows and lashes in severe cases accentuates the ocular problem. Patients with NBCIE often have significant ocular complication, including ectropion, madarosis, conjungtivitis and incomplete eyelid closure, which may result in keratitis and corneal scarring.[14] Hair and teeth appears normal. Hypoplasia of nasal and auricular cartilage and scarring alopecia have been reported but are rare. Ability to hearing is normal. Extracutaneous symptoms or other congenital anomalies are never seen.[3] Other associations include nail dystrophy and deep skin fissures but the mucosal surfaces are normal.[5] In this case, based on information from his father, the baby covered with membrane when he was born and then the membrane was slowly thinning. At the age of 1.5 months, fine white scale and redness patches on his body appeared (generalized erythroderma) accompanied with slightly itchy. From dermatological examination on almost all of his body showed erythematous macule with unsharply marginated (generalized erythroderma) covered fine white scale, large, thick, plate-like scale on lower leg.

The skin was tending to dry. The scalp presented some large thick scale without alopecia, cradle cap and bamboo hair. There was no blisters. There were no ectropion on both eyes, no eclabium of lips. Pinnae and nasal were normal. There were no exaggerated skin folds, alopecia of eyelashes, and eyebrows and no nail abnormality.

NBCIE can occur in all races but especially in those which consanguineous marriage is common.[15] In most of the cases, there is no family history of congenital ichthyosis.[3] In our case, there were no history of the same disease on the other family neither from the mother or the father trait. There was no family history of any hereditary skin disease. His mother and father are not relatives.

Keratinization begins at 24 weeks gestation, it is not complete until close to term. Barrier maturation may be delayed or abnormally when inflammation, injury, sepsis are present during pregnancy.[7] His mother routinely controlled to the obstetrician during her pregnancy. There were no history of neither illness, drug or herbal medication taken during pregnancy. He was born aterm, 9 months, spontaneous, delivered by obstetricians in Papua with weight of birth 3650 grams and body length of birth 50 centimeters.

Patients with NBCIE, have minimal sweating with heat intolerance. Decreased sweating as a result of the obstruction of eccrine ducts in the epidermal scale. The sweat glands were normal below the level of stratum corneum.[7] Affected individuals should be guarded against overheating during winter months and kept in air conditioning during warmer months with frequent wetting of the skin or even cooling suits during sport activities.[6] In our patient, according to the patient's father, no complaints regarding problems sweating.

Some patient with NBCIE show intrauterine growth retardation and/or failure to thrive, although nutritional deficiency and gastrointestinal abnormalities are uncommon. Patient with NBCIE may have associated neurologic abnormalities.[6] There were no abnormality on growth and development in our patient, it has been consulted the pediatric department and based on the growth of body length and weight of our patient, they confirmed that the baby's growth and development within normal limits. There were no abnormality of other organs.

To establish the diagnosis, we performed urine and blood examination, and the result revealed an increased number of WBC of $21x10^3$/uL, this was due to an infection that was found in the form of acute pharyngitis and phymosis. There were fever on this patient, and the pediatric department suggested to give cloxacillin 2x100 mg per oral, fever was medicated with sistenol 3x75 mg per oral and breastfeeding and non-breastfeeding milk 12x120 cc. For the phymosis, pediatric department recommended to consult to surgery department, but the family refused.

Histopathology examination on NBCIE is not specific. Some notes that need to be concerned is if in NBCIE is found mild thickening of the stratum corneum, acanthosis, parakeratosis and inflammatory cell infiltration are seen more frequently in NBCIE than in LI. Whereas in LI will be found moderate to mild acanthosis, mild parakeratosis, stratum corneum thickness at least twice than NBCIE.[5] From histopathology examination in our patient, revealed epidermis with mild hyperkeratosis, acanthosis and moderate spongiotic, focal parakeratosis, slightly elongated rete ridges, the picture also showed psoriasiform epidermal hyperplasia. There were dermis fibrocollagen network with minimal mononuclear inflammatory cells, perivascular and sebaceus glands. The conclusion was concordance with non-bullous congenital ichthyosiform erythroderma.

Commonly there is dermatophyte infection of the skin and nails.[6,16] We performed potassium peroxyde examination to exclude the posibility of this infection. The potassium hydroxide preparation was collected from his body, the result showed that there were no element of fungi.

The management of all types of dry skin consists of retardation of water loss, rehydration, and softening of the stratum corneum, and alleviation of scalliness and associated pruritus. NBCIE used topical application of keratolytic agents, emollients and topical or systemic retinoids. NBCIE generally requires more potent keratolytic agents. In contrast, the NBCIE skin is quiet fragile and patient generally will tolerate intermittent use of keratolytic agent only for short periods. Alpha hydroxy acids (AHA) preparations, such as lactic and glycolic, the most commonly used as agents to desquamate excessive scale and increase hydration. Urea, in concentration of 10-20% has a softening and moisturizing effect on the stratum corneum and is helpful in the control of the dry skin and pruritus. Propylene glycol (40-60% in water) applied overnight under plastic occlusion can hydrates the skin and causes desquamation of scales. Salicylic acid is another

effective keratolytic agent and can be compounded into petrolatum at concentrations between 3% and 6% to promote shedding of scales and softening of the stratum corneum. When it is used to cover large surface area for prolonged periods, however patient should be monitored for salicylate toxicity, most commonly complaints is tinnitus. A propietary preparation containing 6% salicylic acid in propylene glycol (gel) may be particulary helpful for keratoderma of the palms and soles, especially when used under occlusive polyethylene wrapping. Short daily to twice daily baths using a pH balance soap or a soapless cleanser, followed immediately by application of the emollient to moist skin, can be helpful for all forms.[6]

Oral retinoids such as isotretinoin and acitretin have led to dramatic improvement in some pediatric patients with the ichthyosis, but should be used with caution because of side effect that limit long term therapy, particularly bone toxicity. These systemic agent are generally reserved for use in adolescents and adults with more severe ichthyosis disorders that do not show a satisfactory response to topical agents. Patient with ectropion and corneal damage may not be able to tolerate the side effects of retinoids.[6] Neonatal morbidity and deaths may be caused by cutaneous infection.[5] Possible complications during neonatal period include impairment of temperature regulation, increase water loss through the skin and dehydration.[2]

For the treatment of our patient, we gave only emollient to all over the body including the face after bathing or wiping. A pH balance soap using baby soap was used twice daily. It is used to moist the skin, increase hydration and retard the epidermal water loss. The usage of pH balance soap is helpfull to reduce the form of scale. We did not give any oral treatment for this patient to minimize the risk of potential side effect toxicity especially bone toxicity. It is important to be guarded the patient of overheating because there is inadequate of sweating in patient with NBCIE.

Diagnosis of NBCIE is established from history taking, clinical features, and histopathology examination. Emollient therapy and neutral pH products will eventually lead to improvement.

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