

Non-bullous Ichthyosiform Erythroderma

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CASE SUMMARY

History

A full-term male neonate was delivered by Caesarian section due to meconium aspiration syndrome. After delivery, he was also noted to have a cling-film like membrane all over his skin. There was no history of consanguinity: his father was a Caucasian and his mother was a native Filipino. There was no family history of ichthyosis or skin disease.

Physical examination

The typical features of collodion baby were noted. There was a generalized glistening, taut reddish film stretched over the skin giving a "dipped in hot wax" appearance (Figure 1). There were mild ectropion and eclabion. Pinnae and nasal passages were normal. No constriction bands or blisters were noted. Improvement

was noted with time as the collodion membrane shed, leaving generalized erythroderma and cracking and scaling of skin especially over the groin, sacral, and axillary creases (Figure 2). Resolution was near completion three months later with only mild residual ichthyosis at the sacral area.

Differential diagnosis

The typical clinical features of collodion baby are generally easily distinguished from the severe harlequin ichthyosis (HI). But occasionally, mild form of HI has been recorded (*Chrysalis babies*). Restrictive dermopathy or stiff baby syndrome produces a generalized taut, thick, unyielding skin, which does not shed and may cause respiratory failure and early neonatal death. The possible outcomes of collodion baby include non-bullous congenital ichthyosiform erythroderma (NBIE), lamellar ichthyosis, rarer disorders (e.g. Netherton's syndrome, neutral lipid storage disease, trichothiodystrophy and anhidrotic ectodermal dysplasia) and normal skin (self-healing collodion baby).

Investigations

Skin biopsy done at day 50 of life showed



Figure 1: Classical collodion baby with "dipped in hot wax appearance" (Day 8 of life)



Figure 2: Residual hyperkeratosis and large sheets of white scales remained after shedding of collodion membrane (Day 17 of life)

thickened, compact orthokeratotic cornified layer with no epidermolytic hyperkeratosis. The granular cell layer was normal or slightly increased. Focal parakeratosis was noted. Ki-67 index of keratinocytes, an immunostaining marker for assessing proliferative activity, was 25.5% (control 9.7%). Electron microscopy showed elongated membrane like structures in the superficial granular layer keratinocytes. Many concentric structures formed by curling of the long membrane like structures were also seen in the cornified layer. There were increased lipid droplets in the cornified layer but no cholesterol crystals were found.

Diagnosis

The diagnosis was consistent with non-bullous ichthyosiform erythroderma (Ichthyosis Congenital type III).

Treatment and progress

After the collodion membrane was shed, progressive improvement was noted with frequent emollient applications alone. By six months, scaling was limited to the sacral skin only. Systemic treatment was unnecessary.

REVIEW ON NON-BULLOUS ICHTHYOSIFORM ERYTHRODERMA

Definition

NBIE is a rare autosomal recessive inflammatory ichthyosis. There is confusion in nomenclature. In the German literature, NBIE is referred as erythrodermic lamellar ichthyosis.

Epidemiology

It affects 1:300,000 newborn of all races especially those where consanguinity is common. It is at least twice as common as lamellar ichthyosis.

Clinical features¹

Over 90% presents as collodion baby. After shedding of collodion membrane, generalized scaly erythroderma is apparent and may persist. Scales are white or grey, light, superficial and semi-adherent: "feathery" on face, arms and trunk but "lamellar" on

lower limbs. A cyclical pattern of scaling occurs with build up and shedding over two to four weeks. Palmoplantar hyperkeratosis is seen in 70% of cases and may cause fissures and contractures. Pityriasis amiantacea or patchy cicatricial alopecia may occur. Ectropion persists into adult life in 30%. Hypoplasia of the nasal and aural cartilages may occur and nail dystrophy with subungual hyperkeratosis or hypoplasia is seen in 50%. Hair, teeth and mucosa are normal. Nail growth and skin healing are rapid. Sweating is absent or markedly reduced due to obstruction of stratum corneum.

Genetics

In the absence of positive family history, as an autosomal recessive disease, the risk of further affected child is 1: 4. An affected individual will not have affected offspring but half will be carriers. Sporadic mutation occurs with no implication for subsequent pregnancies but there is no means of identifying this.

Prenatal diagnosis

There is no specific ultra-structural, biochemical or molecular markers for testing. Foetal skin biopsy with amniocyte pelleting at 17 to 22 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 classical lamellar ichthyosis by chorionic villus sampling and mutation testing for transglutaminase-1 gene TGM1.

Aetiology and pathogenesis

Hyperplasia with increased mitoses is noted in NBIE. This is in contrast with lamellar ichthyosis which is a retention ichthyosis. Secondary alteration in differentiation is noted with K6/K16/K17 expressions. There were no consistent changes in epidermal lipid content. There were reports of raised n-alkane in scale lipids. Its role in pathogenesis is now questioned, as there is no known biosynthetic pathway for alkanes in human and carbon dating studies suggested contamination.²

Histopathology

Compact hyperkeratosis and increase in thickness of stratum corneum are noted. There are variable mild parakeratosis, acanthosis, hypergranulosis and

accentuation of rete ridges. Periodic Acid Schiff (PAS) staining of frozen sections shows characteristic cell membrane staining in stratum corneum, granular layer and basement membranes. PAS binds with glycoconjugates and staining is absent in normal skin and other ichthyosis except Netherton's syndrome. Kinetic studies using labeled thymidine shows increased epidermal turnover rate. Electron microscopy reveals abnormal lamellar bodies in stratum corneum.

Subtypes of autosomal recessive ichthyosis: 'Ichthyosis Congenita'

German and Finnish groups have defined subtypes 1 to 4 of autosomal recessive ichthyosis congenita, based on ultrastructural findings, but these subtypes do not correlate well with the recognized clinical phenotypes and intra group variation also occurs (Table 1). They do, however, highlight the clinical, ultrastructural and possible heterogeneity of NBIE.¹

Histopathology of collodion membrane

In contrast to retained periderm which is parakeratotic, the collodion membrane consists of compact, thickened orthokeratotic stratum corneum with otherwise normal epidermis and dermis. At birth collodion babies have identical clinical features and cutaneous histological features. Base on one case of self-healing collodion baby, Frenk suggested that it was possible to make a prediction of whether the child would develop a severe ichthyosis later in life on histological grounds at about Day 15.³ He described that the microscopic features observed were different from those known to occur in collodion babies evolving into lamellar ichthyosis.

Prognosis of collodion baby

Possible complications during neonatal period

include: impairment of temperature regulation, increase insensible water loss through the skin, hypernatraemic dehydration, acute renal failure with and without brain damage and pneumonia due to restricted chest movement from the membrane and septicaemia. The severity of subsequent ichthyosis does not relate to collodion membrane. Larregue et al⁴ studied 198 cases of collodion babies and found that 60% developed NBIE, 35% developed lamellar ichthyosis, autosomal dominant ichthyosis, circumflex linear ichthyosis, Conradi syndrome, Sjogren-Larsson Syndrome and trichothiodystrophy, and 5% will eventually have normal skin (self-healing collodion baby).

Self-healing collodion baby

This refers to those with no subsequent disorder of cornification after shedding of collodion membrane. There were 10 cases reported in the last 20 years. It is difficult however to distinguish from those with mild forms of recessive ichthyosis. Based on five cases in a large Swiss kindred, Frenk found that all had consanguineous parents, autosomal recessive inheritance and all had shedding of collodion in the first month leaving slight scaling in few weeks.⁵

Treatment of collodion baby

This includes half-hourly applications of emollients, frequent oiling of skin, nursing in humidified incubator with careful temperature monitoring, aseptic handling, investigation and treatment of signs of sepsis and, meticulous fluid and electrolyte balance. Constriction bands if present should be divided.

Treatment of NBIE

Emollients remain the mainstay of treatment. Prevention of sunburn and sunstroke is important. The risk of hyperpyrexia is increased by hypohidrosis and

Table 1. Subtypes of autosomal recessive ichthyosis: 'Ichthyosis Congenita'

Type	Ultrastructural features	Clinical correlation
Type 1	Lipid droplets in keratinocytes (non-specific)	Classical NBIE
Type 2	Cholesterol clefts in corneocytes, thinned cornified envelope	Lamellar ichthyosis, NBIE
Type 3	Elongated membrane structures, abnormal lamellar bodies, lipid vacuoles in granular and corneal cells	Reticulated pattern lamellar ichthyosis, variable severity, not always collodion at birth
Type 4	Trilamellar membrane packages and vacuoles in granular and corneal cells	Atypical NBIE or lamellar ichthyosis

occlusive ointment. Topical keratolytics and retinoids are rarely used. Acitretin given at 0.1-0.75 mg/kg/day intermittently (three months on and off) reduces scaling, pruritus and erythema in most patients. Parents should be advised to attend genetic counseling.

Learning points:

The possible outcomes of collodion baby include normal skin (self-healing collodion baby), non-bullous ichthyosiform erythroderma, lamellar ichthyosis and rare disorders. In those without a family history, diagnosis is guided by assessment over regular intervals and skin biopsy.

References

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2. Goldsmith LA. N-alkanes in the skin. Arch Dermatol 1990; 126:868-70.
3. Frenk E. A spontaneously healing collodion baby: a light and electron microscopical study. Acta Derm Venereol 1998;61:168-71.
4. Larregue M, Gharbi R, Daniel J, et al. Collodion baby. Clinical course based on 29 cases. Ann Dermatol Syphiligr (Paris) 1976; 103:31-56.
5. Frenk E, Techtermann F. Self-healing collodion baby: evidence for autosomal recessive inheritance. Pediatr Dermatol 1992;9: 95-7.

Answers to Dermato-venereological Quiz on page 149

Answer (Question 1)

1. The pictures show two marginated erythematous papules, with slight scaling. Together with the history, the most likely diagnosis is superficial basal cell carcinoma. The differential diagnoses include actinic keratoses, Bowen's disease and possibly psoriasis.
2. Histologically superficial basal cell carcinomas show buds of basaloid cells originating from the lower margin of the epidermis and extending down into the papillary dermis. The individual cells have large oval basophilic nuclei and minimal cytoplasm, resembling the basal cells of the epidermis. Peripheral palisading is present. These buds are actually interconnected and the lateral margin of the lesion is often difficult to define.
3. Generally the first line treatments include curettage and electrodesiccation, cryosurgery, excision and Mohs micrographic surgery. Surgical excision has the advantage of allowing histological examination and Mohs surgery is generally reserved for high risk tumours. Other options include radiotherapy and more experimental ones like intralesional interferon, topical imiquimod and photodynamic therapy. Regardless of the therapy chosen, more importantly, the patient should be followed up for the possibility of local recurrence and another basal cell carcinoma elsewhere.

Answer (Question 2)

1. The main differential diagnoses include erythroplasia of Queyrat and plasma cell balanitis. Other possibilities include extramammary Paget's disease, erosive lichen planus etc.
2. This patient had erythroplasia of Queyrat as confirmed by skin biopsy. Erythroplasia of Queyrat shows the histological features of intraepidermal squamous cell carcinoma.
3. Treatment should be individualized for patients with erythroplasia of Queyrat. Definitive treatment may be achieved with surgical excision or Mohs micrographic surgery. Other options include topical 5-fluorouracil, carbon dioxide laser and possibly photodynamic therapy.