Restrictive dermopathy: report of one case and the metabolic and post-mortem findings

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Restrictive dermopathy is a rare and lethal autosomal recessive genodermatosis characterized by tight skin, typical dysmorphic face, generalized arthrogryposis and pulmonary hypoplasia. Infants with restrictive dermopathy have similar findings in skin biopsy, but other abnormalities are unremarkable. We report a male preterm infant with restrictive dermopathy. The post-mortem examination revealed hypoplasia of the thymus, and the metabolic study of the urine and blood disclosed generalized organic aciduria and low free carnitine level. These data imply that restrictive dermopathy is associated with certain degrees of metabolic disturbance. With increasing reports of restrictive dermopathy, the affected infants can be diagnosed earlier and accurately.

Key words: arthrogryposis, metabolic diseases, restrictive dermopathy, thymus hypoplasia.

Restrictive dermopathy (RD) is a very rare autosomal recessive skin disorder and was first described by Witt et al.[1] in 1986. To date, less than 50 cases have been reported. Patients with RD have rigid, taut skin, characteristic facies, arthrogryposis multiplex, and dysplastic long bones, clavicles and skull. Most have pulmonary hypoplasia leading to respiratory failure and early death[1,2]. In the literature, the description of post-mortem examination was either scanty or unremarkable. We herein report an infant with RD, and describe the unique findings of the autopsy and the metabolic investigations.

Case Report

A male infant was born to a 31-year-old, G6P3AA2 Taiwanese mother at 31 weeks of gestation by cesarean section with birth weight 1024 g. The parents were nonconsanguineous and there was no family history of congenital anomaly. Physical examination in this premature baby showed generalized tense, shiny, erythematous skin with prominent subcutaneous vessels. Deep fissures in bilateral groin area and multiple contractures of joints were found. Characteristics of his face included low-set ears, blepharophimosis, ectropion, downward-slanting palpebral fissures with an upturned nose, a small fixed "O" shaped mouth, and micrognathia (Fig. 1). Skin biopsy was done and the findings were compatible with RD (Fig. 2).

The radiological examination illustrated a poorly mineralized skull, and thin, gracile ribs and long bones. Renal ultrasonography revealed left mild pelviectasis. Echocardiogram showed a 2.2 mm atrial septal defect. Abdominal ultrasonography

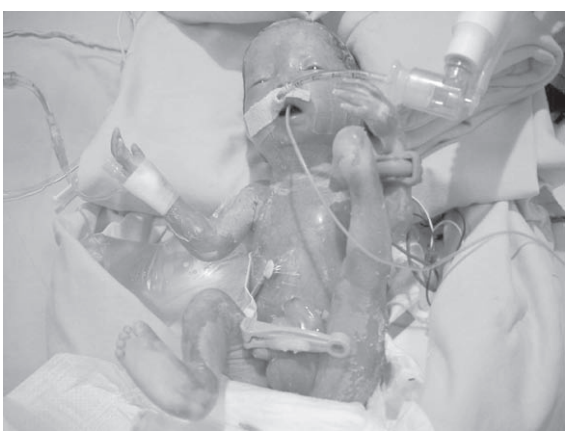

Fig. 1. Characteristic facial anomalies, tense, shiny skin and limb contractures.

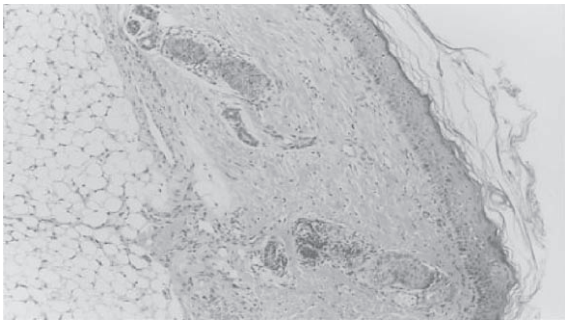

Fig. 2. The skin biopsy showed thick epidermis with hyperkeratosis and absence of rete ridges. Thin dermis with collagen bundles parallel to the surface and flat interface between dermis and subcutaneous fat tissue were seen.

revealed mild hepatomegaly, and serial brain imaging studies demonstrated lenticulostriate vasculopathy.

Cholestasis was present since day of life (DOL) 2. Parenteral nutrition was started on DOL 5, and continued for 41 days. Dexamethasone was attempted at the age of one month to wean ventilator. Endotracheal tube was changed because of recurrent pneumonia. However, he developed bradycardia and cyanosis immediately after the procedure and resuscitation failed at 75 days of age.

Chromosome studies showed a 46,XY karyotype. Skin fibroblasts grew very slowly in the culture. No mutations could be detected in the lamin A gene, encoding lamin A/C, by direct DNA sequencing of the 12 exons. Qualitative urine gas chromatography/mass spectrometry study showed elevated N-acetyltyrosinuria on DOL 8, and increased level of lactic, 3-hydroxybutyric, 3-methyl-3-hydroxyglutaric and 4-hydroxyphenyllactic acids on DOL 48. Tandem mass study disclosed free carnitine level of 10.29 μM (range: 10.85 to 35.47) on DOL 50. At autopsy, the thymus was found to be markedly hypoplastic, but there was no pulmonary hypoplasia (right lung, 20 g; left lung, 15 g). In addition, several old, calcified, and organized thrombi and prominent intimal fibrosis were found in the abdominal aorta. The microscopic findings of skin showed severe dermal fibrosis, atrophy, and hyperkeratosis.

Discussion

Restrictive dermopathy is characterized by tight skin, dysmorphic face, arthrogryposis and typical findings in skin biopsy[1]. The findings of skin biopsy include thick epidermis with hyperkeratosis and absent rete ridges, thin dermis with collagen fibers oriented parallel to the epidermis and decreased elastic fibers, and thick subcutaneous fat tissue and flat interface between dermis and subcutaneous adipose tissue[1,2]. The differential diagnoses of RD include Neu-Laxova syndrome, certain forms of ichthyosis, especially those that would produce the so-called "collodion baby", and Harlequin ichthyosis[1,2]. In this patient, RD was confirmed by physical examination and the skin biopsy. The absence of neurological abnormalities, differences in clinical presentations and unique histopathological findings differentiated it from others. Although the patient did not have pulmonary hypoplasia, the cause of the fatality was assumed to be restrictive thoracopy[2].

The etiology and pathophysiology of RD are still obscure. Witt et al.[1] speculated that defective differentiation results in rigid skin and restricting movements, further leading to a variety of clinical presentations. Paige and colleagues[3] proposed that RD is a disorder of fibroblasts. Defect of integrins or integrin regulation[4] and abnormality in collagen metabolism[3,5] have also been described. Moulson and co-workers[6] demonstrated the importance of fatty acid transport protein (FATP) 4 in skin and hair development and suggested Slc27a4 to be a candidate gene for RD. Navarro et al.[7,8] indicated that mutation of the gene ZMPSTE24 (FACE-1) causes laminopathy in RD.

The infant had early cholestasis since DOL 2. Viral studies were negative, and there was no extrahepatic bile duct obstruction. Parenteral nutrition was used from day 5 and continued for 41 days, and this could be responsible for the later cholestasis. However, it was difficult to explain the early cholestasis in this patient. Organic aciduria has been described in another premature ageing syndrome, Hallermann-Streiff syndrome[9]. As shown in our patient, the metabolic disturbance was speculated to be associated with the underlying disease and liver function impairment.

Thymic hypoplasia was found, which has not been reported in the literature. The size of the thymus would reduce in acute stress, severe malnutrition, inflammatory processes or severe infection[10,11]. Since the infant received dexamethasone treatment and obtained infection,

the finding might be secondary to the chronic illness and the therapy. However, Navarro[7,8] reported that patients with RD have laminopathy. In the situation, thymic hypoplasia is a feature, as well as slowly growing fibroblasts.

Restrictive dermopathy is a rare, lethal autosomal recessive genodermatosis with ambiguous pathogenesis. We report a case with thymic hypoplasia, organic aciduria, and low free carnitine level. These findings potentially add new information to the literature. Further molecular genetic studies including ZMPSTE24 (FACE-1) and FATP4 may elucidate the nature of this rare disease.

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