

Restrictive Dermopathy in Two Sisters

Jia-Woei Hou, MD, PhD; Chien-Fang Mai, MD

Restrictive dermopathy (RD) is a very rare and lethal congenital skin disease. It is inherited by an autosomal recessive pattern with characteristic features of abnormally rigid skin, generalized joint contractures (arthrogryposis), and dysmorphic facies consisting of downward slanting eyes, a small pinched nose, low-set ears, a fixed open mouth in the O-position, and micrognathia. We report on 2 siblings from consecutive pregnancies affected with RD. They died of possible sepsis and respiratory insufficiency at 6 and 8 days after birth, respectively. This kind of stiff skin defect may lead to a fetal akinesia/hypokinesia deformation sequence, which causes the facial abnormalities of RD, as presented in these cases. (*Chang Gung Med J* 2003;26:510-4)

Key words: restrictive dermopathy, joint contractures (arthrogryposis), fetal akinesia/hypokinesia deformation sequence.

Restrictive dermopathy (RD) is a rare, lethal, autosomal recessive genodermatosis.⁽¹⁾ RD affects the differentiation of skin, bone, and lungs, resulting in taut, shiny skin with typical facial dysmorphism, arthrogryposis multiplex, and bone dysplasia.^(1,2) The distinctively rigid skin in this disorder usually causes a fetal akinesia/hypokinesia deformation sequence, leading to multiple joint contracture and a characteristic dysmorphic facies with a fixed open mouth in an O-position.^(3,4) The exact pathogenetic mechanism of RD remains unknown. We report on 2 cases of RD from consecutive pregnancies, which presented the typical morphological features and similar clinical courses.

CASE REPORT

A female baby was born at 32-weeks' gestation to a 28-year-old gravida 5, para 3, healthy woman with 2 previous spontaneous abortions. The pregnancy course had been complicated with polyhydramnios and premature rupture of the membrane (PROM). There was no history of consanguinity.

Birth weight (BW) was 1150 g, body length (BL) was 39.5 cm, and head circumference (HC) was 29 cm. Her Apgar scores were 1 and 6 at 1 and 5 min, respectively. After birth, she was in severe respiratory distress. Physical examination at birth showed extensive areas of shiny, tight, translucent, erythematous skin which was fragile and tore easily (Fig. 1). The umbilical cord was short and fragile. At other sites, the skin was thickened, fissured, or lacerated, and scaly, with reduced compliance. Cranial sutures were widely spaced with a large, open anterior fontanel. There was no hair on the scalp, or any eyebrows and eyelashes. Hypertelorism, blepharophimosis, blue swollen eyelids with exophthalmia, low-set and dysplastic ears, and a small pinched nose were noted. The mouth was small, round, open and fixed in an O-shaped position, with severe micrognathia. She had joint contracture at the hips, knees, elbows, wrists, and ankles. Her movements were limited. Rocker-bottom feet were noted. The chest and abdomen were unremarkable. Some blisters over the trunk developed 2 days later. A deep skin defect with exposed underlying muscle over the neck

From the Division of Medical Genetics, Department of Pediatrics, Chang Gung Children's Hospital, Taipei.

Received: Oct. 31, 2002; Accepted: Jan. 6, 2003

Address for reprints: Dr. Jia-Woei Hou, Division of Medical Genetics, Department of Pediatrics, Chang Gung Children's Hospital, 5-7, Fushing Street, Gueishan Shiang, Taoyuan, Taiwan 333, R.O.C. Tel.: 886-3-3281200 ext. 8203; Fax: 886-3-3278283; E-mail: houjw741@cgmh.org.tw

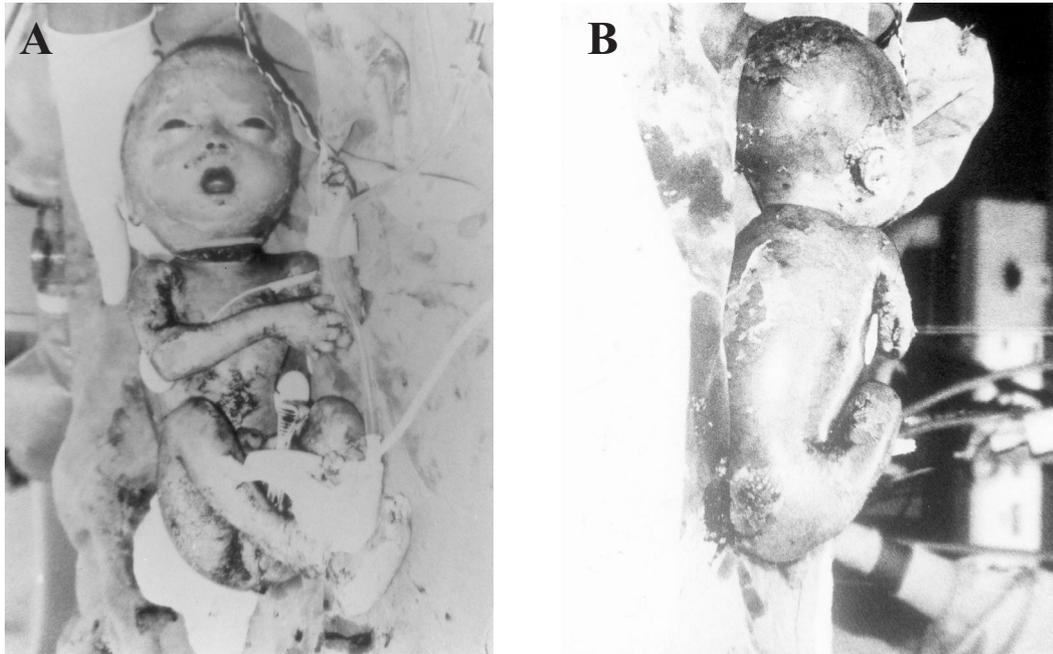


Fig. 1 Characteristic skin changes, contractures, and facial anomalies. (A) Frontal view, (B) rear view.

was noted. She attempted to feed, but was unable to adequately suck or swallow.

Blood gas analysis showed severe respiratory acidosis with CO₂ retention. Chest films showed dysplasia of the clavicles, an opaque lung field with a blurred heart border and an air bronchogram (Fig. 2). The ribs and long bones were also found to be gracile and thin, and the cranial vault was small with an underdeveloped mandible. The conditions of respiratory distress improved after intubation and the administration of a surfactant. A hemogram showed marked leukocytosis (55.3×10^9 cells/L) with a shift to the left. Parenteral antibiotics were used. Brain echo study showed severe periventricular leukomalacia. Histology of the skin biopsy showed hyperkeratosis of the epidermis, poorly developed appendageal structures, and the absence of rete pegs, which resulted in a flattened dermato-epidermal junction. Chromosome study showed a 46, XX karyotype. Persistent hyperthermia, hypoalbuminemia (25 g/L), hypernatremia (up to 159.7 mmol/L), and elevated serum C-reactive protein (3655 µg/L) developed. Supportive treatment consisted of parenteral nutrition, broad-spectrum antibiotics, ventilation support with high-humidity (60%) air, and local applica-

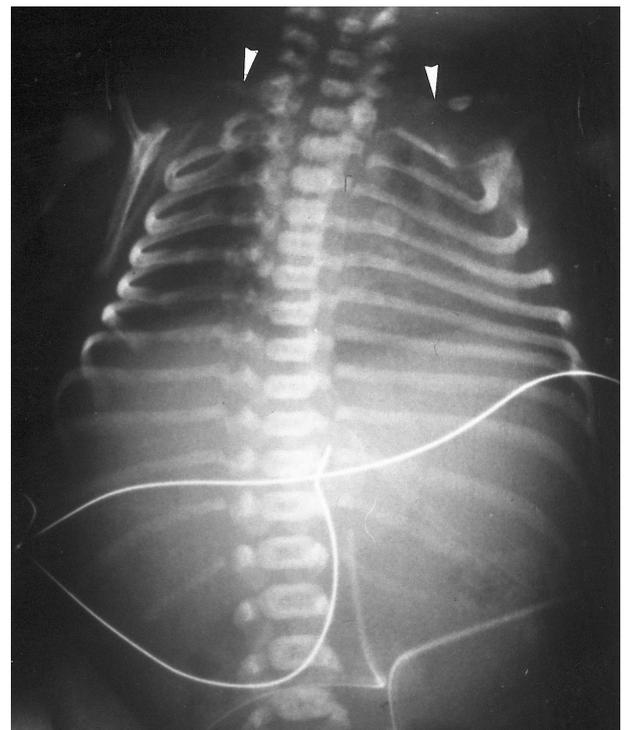


Fig. 2 Chest X-ray showing poorly inflated lungs, a small, narrow thoracic cage, thin or irregularly narrow ribs, and osteodysplastic changes in both clavicles (arrowheads).

tion of Vaseline jelly. She expired on the 8th day due to septic shock and respiratory failure. Staphylococcus aureus was isolated from pus of a skin wound. Cerebrospinal fluid, blood, and urine cultures were all negative.

The mother had had 4 previous pregnancies. The first one gave birth to in a normal, term baby. The second and third ones ended in miscarriages in the 2nd trimester. The fourth one had similar features of RD with one natal tooth and deep skin defects. According to the medical record, her gestational age was 30 weeks, and she had complications of PROM and fetal distress. Decreased fetal movements during the 3rd trimester were noted by the mother. Her birth BW was 1200 g, BL was 38 cm, and HC was 26.5 cm. Apgar scores were 4 at both 1 and 5 min. She died on her 6th day due to infection and respiratory failure. Chromosome study also showed 46,XX.

DISCUSSION

We report on 2 (possibly 4) siblings from consecutive pregnancies affected with RD. The family occurrence suggests a distinctive autosomal recessive pattern for RD. RD is generally believed to be a defect of skin differentiation during the second trimester of pregnancy.⁽⁵⁾ Both clinical and animal studies have stressed that normal growth and development are dependent on adequate fetal activity.⁽³⁾ Animal models revealed that a thin, rigid, and tightly adherent skin may produce restriction of fetal movement (hypokinesis), leading to profound effects on intrauterine growth and development.⁽⁶⁾ The breathing activity and mouth movements (sucking and swallowing) of affected fetuses are also reduced.^(3,6) Due to restricted fetal movement, a majority of these infants have resultant intrauterine growth retardation, hypoplastic facies, joint contracture (arthrogryposis), pulmonary hypoplasia, and polyhydramnios, known as the fetal akinesia deformation sequence (FADS) secondary to the taut skin.^(3,6)

Teratogens and intrauterine constraint, as well as myogenic, neurogenic, and dermatogenic disorders, have been implicated as causing FADS and its typical structural malformations.⁽⁶⁾ Clinically, the birth of an affected child invariably occurs before 34 weeks of gestation due to PROM and is usually preceded by polyhydramnios with reduced movements. The taut,

shiny skin is unique to RD and has been described in all cases. Because of its rigidity, the skin often tears in response to the stress of delivery or neonatal movement. Skin defects also facilitate early infection and dehydration after fluid loss.^(1,2,4)

The AR pattern of inheritance and morphological changes of the skin and skeletal systems in this disorder suggest that a structural protein or enzyme defect, perhaps of collagen metabolism, may underlie the pathogenesis.^(4,7) Evidence of abnormal maturation was found in the epidermis, cutaneous appendages, dermis, and hypodermis. Thinning of the dermis and the arrangement of collagen in parallel bundles appear to be consistent findings. A qualitative or quantitative aberration in control mechanisms of tissue interactions, such as the L1 antigen, factor XIIIa, or proinflammatory cytokines,⁽⁷⁻⁹⁾ RD is also characterized by altered maturation of the epidermis and its appendages with an abnormal pattern of expression of differentiation-specific keratins, desmosomes, or elastic fibers.^(8,9)

Distinctive radiologic features include deficient mineralization of the clavicles and the skull, over-tubulation and frequent modeling defects of the long bones, and occasional abnormalities of the ribs and scapulae.^(2,8) The osteodysplasia and the amniotic fragility could also be due to impaired collagen synthesis and fibroblast function.^(5,7)

Differential diagnoses include some lethal congenital syndromes involving the skin and bone: Neu-Laxova, Pena-Shokeir syndrome, aplasia cutis congenita, and lethal multiple pterygium syndromes.⁽⁸⁻¹⁰⁾ Clinical features and the clinical course can help distinguish RD from these disorders. Stiff or taut skin and joint contracture are also found in infantile systemic hyalinosis and Winchester syndrome, which are characterized by deposits of hyaline material or mucopolysaccharides, respectively, in the skin.⁽⁹⁾ Congenital fascial dystrophy affects the deeper skin and fascia and tends to be most pronounced on the buttocks and legs.⁽⁹⁾ Accurate prenatal identification would provide valuable information for families at risk of RD, but unfortunately, this remains difficult if not impossible. Skin biopsy and ultrasound examinations performed in mid-pregnancy (before 20 weeks of age) appear to be inconclusive,^(3,8,9) and these procedures were also ineffective for diagnosing RD in time to consider a therapeutic abortion. Decreased fetal movement and the absence of swal-

lowing and breathing movements are only observed late in the pregnancy (28 to 29 weeks).⁽¹¹⁾ Histological study of the skeleton or molecular and biological studies of collagen genes in future cases would, hopefully, further elucidate the pathogenesis of this unusual and tragic affliction. Genetic counseling is essential for families at risk for this autosomal recessive, lethal disorder. High-resolution or 3-dimensional ultrasonography may be helpful for such families.

REFERENCES

1. Witt DR, Hayden M, Holbrook KA, Dale BA, Baldwin VJ, Taylor GP. Restrictive dermopathy: a newly recognized autosomal recessive skin dysplasia. *Am J Med Genet* 1986;24:631-48.
2. Reed MH, Chudley AE, Kroeker M, Wilmot DM. Restrictive dermopathy. *Pediatr Radiol* 1993;23:617-9.
3. Mulder EJH, Beemer FA, Stoutenbeek P. Restrictive dermopathy and fetal behavior. *Prenat Diagn* 2001;21:581-5.
4. Hoffmann R, Lohner M, Bohm N, Leititis J, Helwig H. Restrictive dermopathy: a lethal congenital skin disorder. *Eur J Pediatr* 1993;152:95-8.
5. Paige DG, Lake BD, Bailey AJ, Ramani P, Harper JJ. Restrictive dermopathy: a disorder of fibroblasts. *Br J Dermatol* 1992;127:630-4.
6. Moessinger A. Fetal akinesia deformation sequence: an animal model. *Pediatrics* 1993;72:857-63.
7. Pierard-Franchimont C, Pierard GE, Hermanns-Le T, Estrada JA, Verloes A, Mulliez N. Dermatopathological aspects of restrictive dermopathy. *J Pathol* 1992;167:223-8.
8. Smitt JH, van Asperen CJ, Niessen CM, Beemer FA, van Essen AJ, Hulsmans RF, Oranje AP, Steijlen PM, Wesby-van Swaay E, Tamminga P, Breslau-Siderrius. Restrictive dermopathy: report of 12 cases. *Arch Dermatol* 1998;134:577-9.
9. Nijsten TEC, De Moor A, Colpaert CG, Robert K, Mahieu LM, Lambert J. Restrictive dermopathy: a case report and a critical review of all hypotheses of its origin. *Pediatr Dermatol* 2002;19:67-72.
10. Mau U, Kendziorra H, Kaiser P, Enders H. Restrictive dermopathy: report and review. *Am J Med Genet* 1997;71:179-85.
11. Happle R, Steckhoven JHS, Hamel BCJ, Kollee LAA, Nijhuis JG, Anton-Lamprecht I, Steijlen PM. Restrictive dermopathy in two brothers. *Arch Dermatol* 1992;128:232-5.

束縛性皮症發生於兩姊妹

侯家瑋 麥建方

束縛性皮症 (restrictive dermopathy, RD) 是一種極罕見且致命的皮膚異常疾病。RD 乃以常染色體隱性方式遺傳，其共同症狀是皮膚呈現薄且透明，緊繃，容易自然或因外力撕裂剝落，臉部則表現固定張開的O形嘴，小鼻子及小下巴，無睫毛，眼瞼狹縮，及全身關節收縮 (arthrogryposis)。吾等報告一對姐妹均罹患RD，她們分別在出生後6及8天死於感染及呼吸衰竭。此種僵硬皮膚缺陷可導致胎兒運動減退之變形順序 (fetal akinesia/hypokinesia deformation sequence)，也可以解釋RD病人特殊的臉部畸形。(長庚醫誌 2003;26:510-4)

關鍵字：束縛性皮症，關節收縮，胎兒運動減退之變形順序。

長庚兒童醫院 台北院區 兒童內科部

受文日期：民國91年10月31日；接受刊載：民國92年1月6日。

索取抽印本處：侯家瑋醫師，長庚兒童醫院 兒童內科部 醫學遺傳科。桃園縣333龜山鄉復興街5-7號。Tel.: (03)3281200
轉8203; Fax: (03)3278283; E-mail: houjw741@cgmh.org.tw