□ Case Report □

A case of restrictive dermopathy

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Restrictive dermopathy is a rare autosomal recessive disorder in which rigidity or tautness of the skin from the second trimester causes a fetal akinesia deformation sequence (FADS) and early death. Characteristic features include taut skin with prominent subcutaneous vessels, widely open fontanelles and cranial sutures, distinctive facies, flexion contractures, pulmonary hypoplasia, sparse eyelashes and and eyebrows, thin dysplastic clavicles. The histologic abnormalities of the skin are located in a thin dermis, consisting of compactly arranged collagen fibers, scanty elastic fiber. The dermoepidermal junction is flat, and epidermal appendages are absent, miniaturized or immature. The presence of adipose tissue may be increased. We report on the first Korean case of restrictive dermopathy with typical clinical features and histological findings. **(Korean J Pediatr 2007;50:306-310)**

Key Words : Restrictive dermopathy, Joint contractures, Skin dysplasia, Fetal akinesia

Introduction

Restrictive dermopathy, also called the tight skin contracture syndrome, was first described by Witt et al.[1], is an autosomal recessive disorder characterized by abnormally tight and rigid skin with erosions, prominent superficial vasculature and epidermal hyperkeratosis, flexion contractures of joints, and characteristic facial anomalies consisting of micrognathia, low set ears, fixed open mouth, small pinched nose, and eyes with anti-mongoloid slant. Skin abnormalities are often visible histologically and include a thin dermis, abnormally dense collagen bundles, with almost total absence of elastic fibers[2]. The exact pathogenetic mechanism of this disorder is not yet known. To date, less than 50 cases have been published in the literature. There has been no clinical reports of cases in Korea. We report the first Korean case of restrictive dermopathy with typical facial morphology and flexion contractures of the joints, rigid and torn skin and characteristic histological changes of the skin.

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Case Report

A female infant was born at 31 weeks gestation to a 32 year old gravida 2, para 0, abortus 2 healthy woman. Except for oligohydramnios in the second trimester the pregnancy was uncomplicated. At 31 weeks of gestation, premature rupture of membrane, fetal akinesia and fetal distress was detected on fetal ultrasonography. Emergency Caesarian section delivery was done. Birth weight was 1,100 g and APGAR scores were 1 at both 1 minute and 5 minutes, and she was in severe respiratory distress after birth. The mother was not exposed to any teratogenic agent, medication, tobacco, or alcohol. Her first child was still birth with the same morphology of this second baby. However, there was no further investigation performed at that time.

Physical examination showed extensive areas of shiny, tight, translucent skin, which was fragile and tore easily. At the other sites the skin were fissured and scaly (Fig. 1). There were multiple erosions of the skin on elbow and anterior trunk (Fig. 2). Facial expression was frozen and there was small mandible and chin (retrognathia and micrognathia), small pinched nose, antimongoloid slant, sparsed eyelashes, hypertelorism and microstomia with open mouth. The mouth was fixed in an open position and was O-shaped (Fig. 3A, B). She had multiple joint contractures at the hips, knees, elbows, wrists and ankles (arthrogryposis

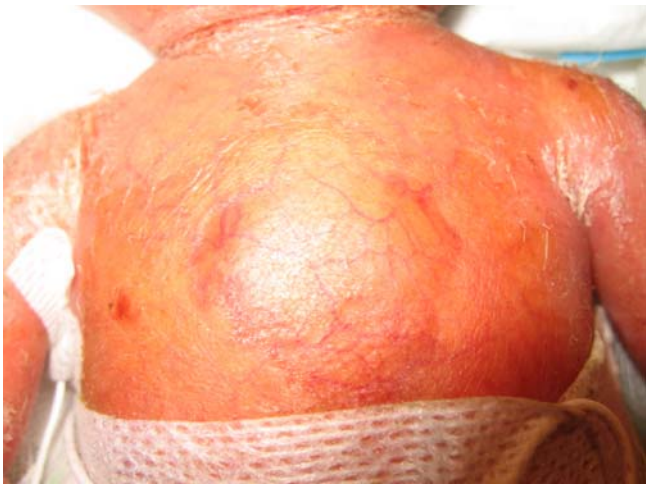

Fig. 1. The skin on the back, was tense, translucent, erythematous and cutaneous vessels were prominent.

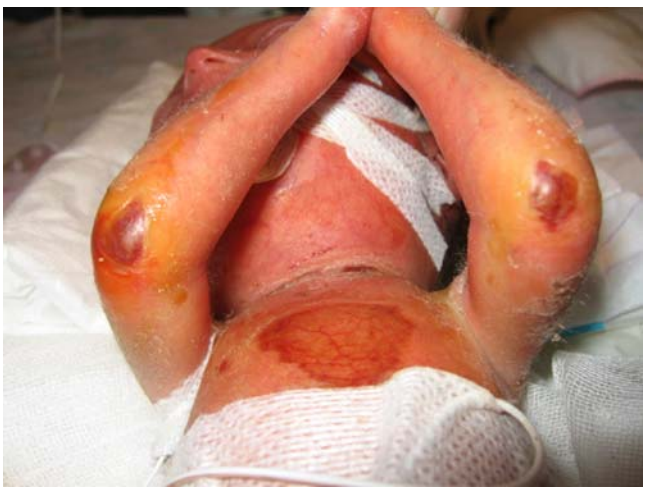

Fig. 2. The skins on the trunk and elbow, were eroded.

multiplex) (Fig. 4). Radiographs showed evidence of hypoplasia of clavicle, upper ribs and hypoaeration of both lung fields (Fig. 5).

The patient received surfactants on the first day of life. However, the vital signs and oxygen saturations were not improved with rescue surfactant replacement and mechanical ventilation support. Despite mechanical ventilation treatment, the respiratory condition deteriorated. In view of the poor prognosis, the parents agreed to cease further intensive care treatment. The infant died at the age of 4 days.

The karyotype was normal diploid 46, XX. Complete blood count, C-reactive protein, and electrolytes were within normal limits.

Skin biopsy specimens were obtained at the second day of life, from the shoulder, leg revealed a thickened epidermis

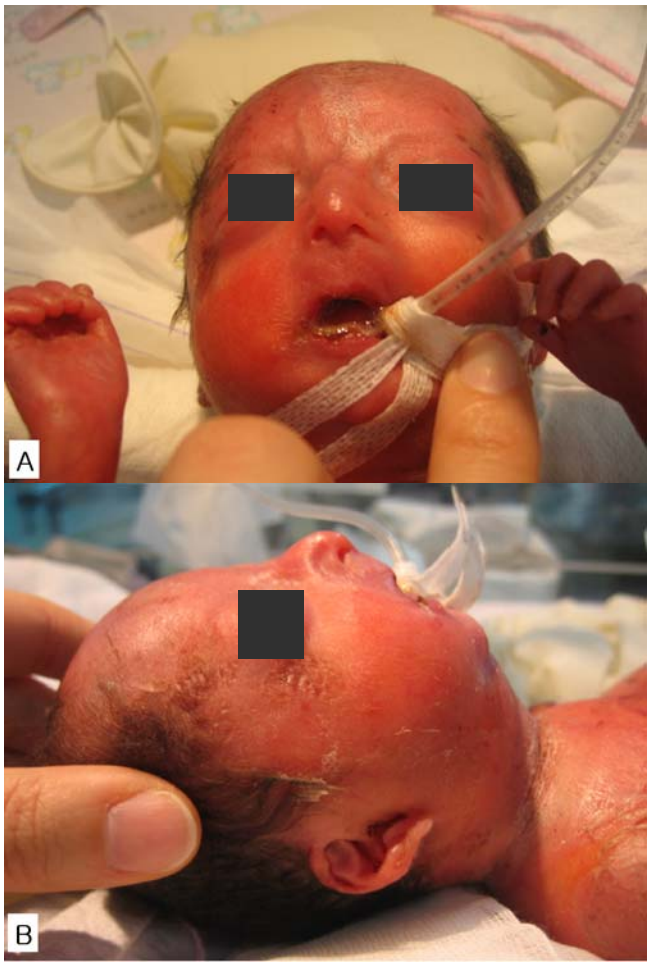

Fig. 3. Clinical photograph (A) showed the characteristic dysmorphic face with pinched nose, hypertelorism, and small open mouth fixed in O position, (B) micrognathia, and low set ear, anti mongoloid slant of palpebral fissures.

Fig. 4. The joints of both upper and lower extremities were fixed in flexion contractures due to the stiffness of skin.

and the dermis was remarkably thin, with collagen bundle compactly arranged parallel to the skin surface. Elastic fibers were sparse and pilosebaceous units and sweat glands were poorly developed. The dermohypodermal junction was strikingly flat (Fig. 6).

At autopsy, all intrathoracic and abdominal organs were normal. There was no hypoplasia of the lungs. The cerebrum, brain stem, and cerebellum were normal. The clavicles were short and bent.

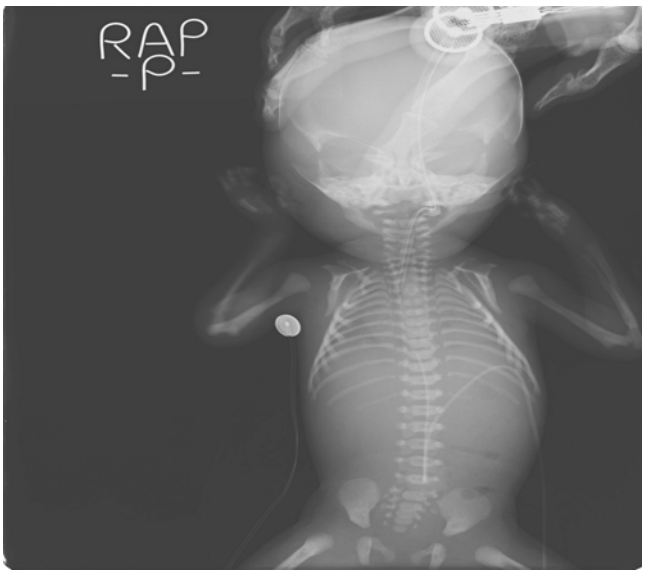

Fig. 5. Chest roentgenogram showing hypoplastic clavicles and ribs.

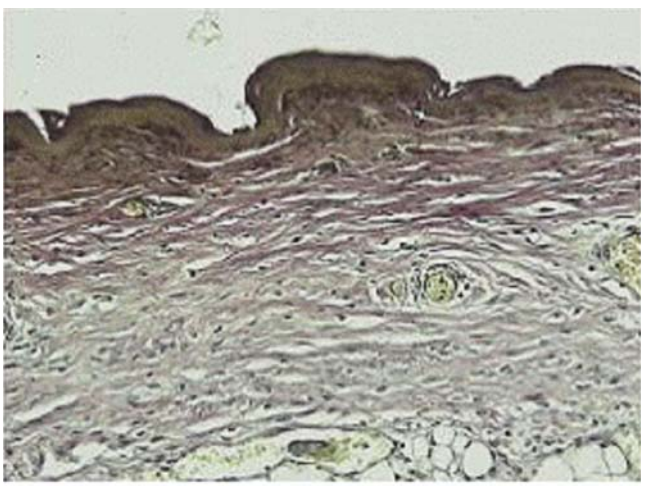

Fig. 6. Skin biopsy specimen showed epidermal erosion, thin dermis and poorly developed skin appendages. Elastic fibers were markedly decreased in Verhoeff's elastic fiber stain (× 200).

Discussion

Restrictive dermopathy is a rare lethal autosomal genodermatosis. This syndrome was introduced in 1986 by Witt et al.[1]. Before restrictive dermopathy was clearly defined, although there are similar reports going back to 1929, they described many infants with extensive skin erosion and contractures as diagnosis of aplasia cutis congenita[3-6].

In 1986, Witt et al.[1] after evaluating cases of their own and others from the literatures, named the syndrome "Restricted dermopathy". They hypothesized that the primary skin defect severely restricts intrauterine movement, leading to the fetal akinesia or hypokinesia deformation sequences.

Restrictive dermopathy affects differentiation of skin, bone, and lungs. Clinically the disorder result in rigidity or tautness of the skin causing fetal akinesia deformation or hypokinesia deformation sequence (FADS) with multiple joint contractures and a characteristic dysmorphic faces with a fixed open mouth in an O position. Polyhydramnios with reduced fetal movements result in premature delivery at about 31 weeks gestation due to premature rupture of membranes[2, 7, 8]. But, In our patient, oligohydramnios with reduced fetal movement was detected in gestation 22 weeks. Additional findings are hypertelorism, pulmonary hypoplasia and bone deformities with large fontanells. Many reports have described underdeveloped hair follicles and their secondary skin appendage structure in Restrictive dermopathy[9].

Radiologic abnormalities include deficient mineralization of the clavicles, overtubulation, and frequent modelling defect of long bones, and occasional abnormalities of the ribs and scapulae. All these changes are unspecific signs of fetal immobility[10, 11].

All previously described babies were born prematurely. If born alive, most infant with Restrictive dermopathy die within the first days or weeks of life because of respiratory insufficiency due to thoracic stiffness, sometimes combined with pulmonary hypoplasia. Exceptionally, survival until the age of 4 months has been described[7-9, 12].

Our literature review reveals a striking pattern of premature rupture of membranes, almost invariably the 30th and 33rd weeks of gestation[7, 10, 12]. Witt et al.[1] reported abnormal elstic fibers in the fetal membranes and suggested this contributed to premature rupture.

The pathogenic mechanism of the disease is not yet known. It seems to be the primary defect of collagen syn-

thesis and orientation which leads to a basic disturbance of skin differentiation[13]. This causes a thin dermis with abnormally arranged collagen bundles and lack of elastic fiber. Biochemical studies indicated a decreased amount of high molecular weight keratins[14, 15]. The lack of elastic fibers in the thinner dermis causes a rigidity and vulnerability of the skin and impairs fetal movement. Structural deformities, seen in restrictive dermopathy and other FADS, may be secondary to this intrauterine immobility[16].

Most recently, investigations have centered on cell matrix interactions. Dean et al.[17] found normal migration and quantities of collagen type I, III and V in cultures fibroblasts from a case of restrictive dermopathy, but found increased expression of integrin alpha-1 and alpha-2 subunits. This increased expression remained when the fibroblasts were transferred to matrix produced by normal control of neonatal fibroblasts.

The differential diagnosis of Restrictive dermopathy lies mainly with certain form of ichthyosis, especially those that would produce the so called "collodion baby". The presence of a collodian membrane or scaling on a newborn may benign and self limited or may be seen with nonbullous congenital ichthyosis form erythroderma or lamellar ichthyosis. The thick shiny membrane may produce a similar clinical appearance and ectropion may be present as well. However, flexion contractures, skeletal abnormalities, large skin splits, and a more round fixed open mouth are not seen as in Restrictive dermopathy. Biopsy is generally nondiagnostic in congenital erythrodermic ichthyosis. Harlequin ichthyosis may also enter the differential diagnosis but presents large thick plate-like scales and on biopsy shows marked hyperkeratosis. Infantile systemic hyalinosis and Winchester syndrome were excluded because of the absence of deposits of hyaline material or mucopolysaccharides, respectively, in the skin. Generalized scleroderma is a progressive disease that is not as extensive at birth as Restrictive dermopathy. The absence of microcephaly distinguishes Restrictive dermopathy from the Neu-laxova syndrome. Progeria excluded because of normal flexible skin[3, 4, 12, 13].

All reported cases suggest autosomal recessive inheritance, which is supported by a history of parental consanguinity and multiple affected children in the same sibling. In this case, there was no history of parental consanguinity and at least one affected child in patient's siblings.

Because of the high risk of recurrence in subsequent pregnancies, there is need for prenatal diagnosis and genetic counselling. Unfortunately, prenatal diagnosis is difficult since no reliable test is available. Skin biopsy in intrauterine life, is not reliable. All specific change seems to develop after 22 weeks of gestation. Perhaps an attentive ultrasound scanning after 18-20 weeks of gestation may identify decreased fetal movement and joint contractures. Amniocentesis, as well, is useless at present because the gene locus has not yet been identified[18].

Given the remarkable phenotypic similarity of restrictive dermopathy patients, both clinically and histologically, a diagnosis can be made at first glance by anyone who has ever observed a case. But, the true nature of the primary defect in and pathogenesis of Restrictive dermopathy remain unknown. Histologic study of the skeleton or molecular pathologic studies of collagen or collagen genes in future cases may be helpful in elucidating the pathogenesis of this unusual and tragic affliction.

한 글 요 약

제한성 피부병증(Restrictive Dermopathy) 1례

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제한성 피부병증(Restrictive dermopathy)은 상염색체 열성으로 유전되는, 매우 드문 유전성 피부질환으로, 1986년 처음 기술되었다. 임상증상으로는 피부가 강직성, 긴장성병변을 보이며, 이로인해 운동의 제한, 관절의 구축 등이 생긴다. 매우 작고 둥근 입 모양, 양안격리, 소하악증 등을 동반한 특징적인 얼굴기형과 폐저형성증, 커다란 대천문, 쇄골의 이형성 등을 동반하기도 한다. 정확한 병인은 알려져 있지 않으며, 지금까지 50례 정도 보고되고 있으나, 국내에는 아직 보고가 없다.

저자들은 이 환아와 똑같은 외형의 사산아를 출산한 경력이 있는 산모에서, 제태연령 31주에, 출생체중 1.1 kg로 태아곤란증 때문에 제왕절개로 출생한 미숙아가 출생 직후부터 호흡곤란과 청색증을 보였고, 작은 입 모양에 소하악증과 얇고 경직된 피부와 사지 관절의 구축성 변형 등을 보였으며, 체간과 사지의 일부에 피부가 벗겨져 나간 소견을 나타내어, 피부조직검사 결과 상피조직의 비후성 미란, 얇은 진피층, 피부부속기관의 미발달소견, 탄성섬유의 현저한 감소가 관찰되는 전형적인 제한성 피부병증 1례를 경험하였기에 보고하는 바이다.

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