□ Case Report □

A case of Rothmund-Thomson syndrome

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Rothmund-Thomson syndrome (RTS), is a rare autosomal recessive disorder, characterized by : skin photosensitivity, poikiloderma, sparse hair, sparse eyebrows/lashes, short stature, skeletal abnormalities, cataracts, and an increased risk of malignancy. Skeletal abnormalities include : dysplasia, absent or malformed bones, such as absent radii, osteopenia, and delayed bone formation. RTS is thought to result from chromosomal instability, and children with RTS are at risk of cancer. Reported cancers in children with RTS include : basal cell carcinoma, squamous cell carcinoma of the skin and osteosarcoma of bone. We report an 11 year-old boy, who presented to our institution with poikilodermatous skin change with telangiectasia and hyperpigmentation, absence of radius and thumb, and the development of osteosarcoma of the left tibia. The patient is now receiving supportive care and is receiving maintenance chemotherapy after surgery for osteosarcoma. **(Korean J Pediatr 2006;49: 565-569)**

Key Words : Rothmund-Thomson syndrome, Absent radii, Osteosarcoma

Introduction

RTS is a rare genetic disorder, inherited as an autosomal recessive condition, and is characterized by a poikilodermatous skin rash that can be found in affected individuals from infancy[1]. This report is the first case of a Korean patient with RTS; there are more than two hundred cases in the world literature. Common clinical features observed with RTS include : short stature, juvenile cataracts, photosensitivity with poikilodermatous skin changes, skeletal abnormalities including predisposition to malignancy exemplified by osteosarcoma and skin cancer[2, 3]. Rare features such as a saddle nose and triangulated face[3] have been reported. Although individuals with RTS are well known to be at higher risk for malignancy including osteosarcoma, there is no known molecular mechanism to explain the predisposition[1]. We report a case of RTS; the patient had osteosarcoma on left tibia with poikilodermatous skin rash, telangiectasia, hyperpigmentation, radial defects, ulnar abnormalities, absence of both thumbs and patellas.

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Case Report

The patient was an eleven years-old male who presented with pain in his left ankle. This patient had congenital radial defects of both forearms and absence of both thumbs. He received orthopedic surgery for correction of the skeletal deformities in the pediatric orthopedics division of this children's hospital. The patient lived a routine life, attended school and had normal intelligence. There was a change in his gait; he began to walk slowly because of pain in the left ankle. He presented to the pediatric orthopedics clinic.

The patient was born at GA 40 wks by Caesarean section without perinatal problems. At birth, deformities of both forearms and absence of both thumbs were noted; however, there was no specific medical management of these anomalies. Two years later, his mother delivered a second baby who manifested similar features. The second child died from unknown causes two days after birth.

On presentation there were no abnormal findings except for a painful left ankle. The patient was admitted to the hospital. on admission, he looked ill but was alert. Vital sign were as follows: blood pressure, 105/65 mmHg, pulse rate, 100/min, respiratory rate, 22/min, and body temperature, 36.5℃. His physical growth was inappropriate for his

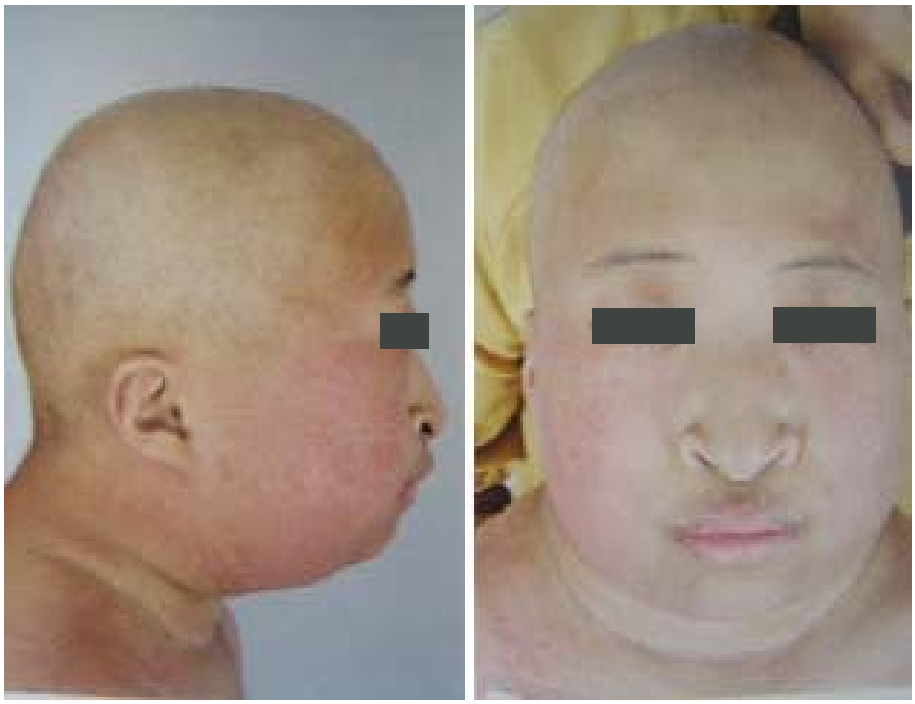

Fig. 1. Facial feature represents sparse hair, sparse eye brows, saddle nose and poikilodermatous skin changes with telangiectasia and hyperpigmentation.

age; height 131 cm (<3 percentile); weight 6.4 kg (<3 percentile); and head circumference, 50.5 cm (<3 percentile). There were neither pale conjunctivae nor icteric sclera. He had sparse hair and a prominent nose which made his appearance distinct (Fig. 1). Chest and abdominal examination revealed no abnormal findings. Both thumbs were absent (Fig. 2, 3). There was no redness, heat, or tenderness noted on examination of the painful left ankle; there was no mass detected. The skin showed decreased skin turgor, was tough, and the skin was dry. Telangiectasia was observed symmetrically on both sides of the face. Hyperpigmentation was noted on the whole body surface (Fig. 2).

The peripheral blood analysis on admission included : hemoglobin 14.3 g/dL, hematocrit 38.3%, white blood cell 1,220/μL, and Platelet 188,000/μL. Immunoglobulin analysis was as follows : immunoglobulin G 590 mg/dL (639-1,349 mg/dL), immunoglobulin A 99 mg/dL (90-400 mg/dL), immunoglobulin M 45 mg/dL (45-230 mg/dL), immunoglobulin D 9.2 mg/dL (1.6-10 mg/dL), Immunoglobulin E <18 mg/dL (0-200 mg/dL), C3 114 (1.6-10), and C4 23 (0-200). Percentage of T cell subset was as follows : CD3 79%, CD4 43%, and CD8 31%. There was no immunologic dysfunction detected on the performed laboratory tests. An ophthalmologic examination revealed no cataracts. Dental

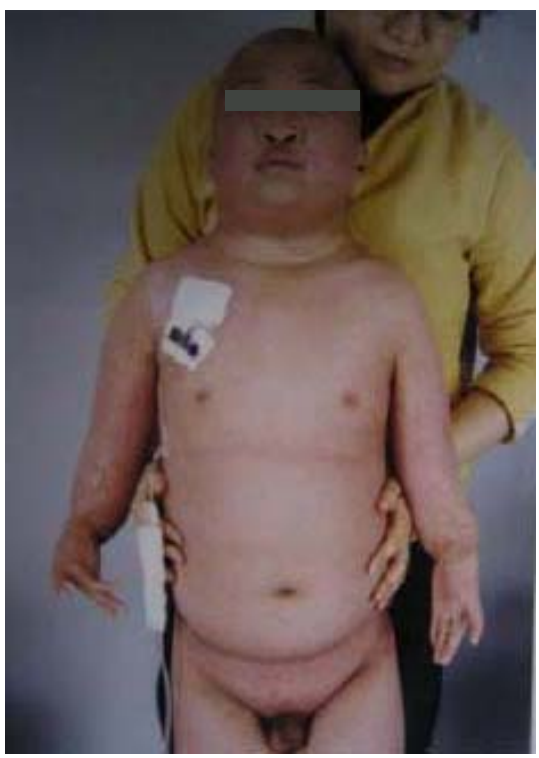

Fig. 2. Patient's photography shows general appearance with short stature and skeletal anomalies of hand and forearm.

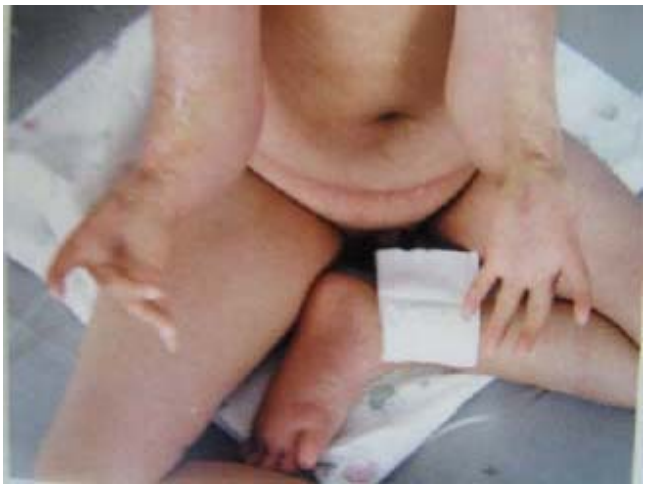

Fig. 3. There is absence of both thumb.

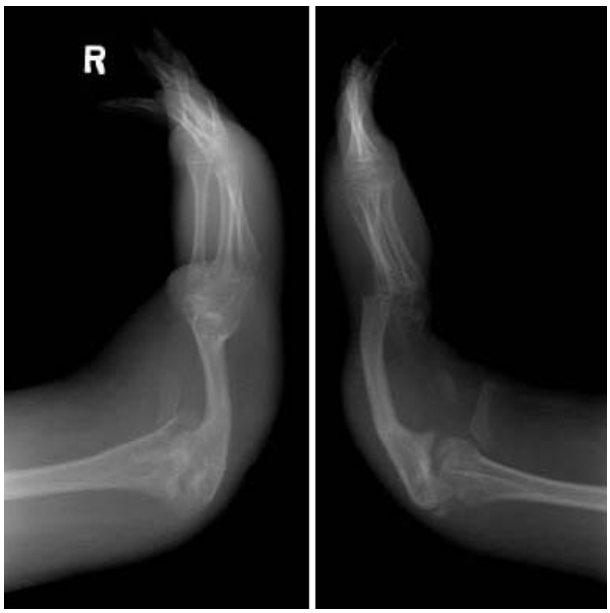

Fig. 4. Forearm X-ray shows absence of radius/thumb and malformed ulna.

exam showed some dental caries. Constitutional chromosome analysis identified a normal 46,XY karyotype in 18 of 20 division cells and a nonspecific deletion in 2 cells, thought to be artifact.

Four extremites X-ray findings showed osteopenia, absence of both thumbs, bilateral radial defects, bilateral ulnar deformities, absence of both patellas, an expansive osteolytic lesion and periosteal reaction was noted at the left distal metaphysis of the tibia (Fig. 4, 5).

A bone biopsy was performed at the left distal metaphysis and the pathological diagnosis was osteosarcoma (Fig. 6). The patient has been treated with chemotherapy starting in November, 2003. In January, 2004, he was administered again for a second round of chemotherapy. The second round of chemotherapy was followed by an excisional removal of the tumor mass. Since the operation the patient

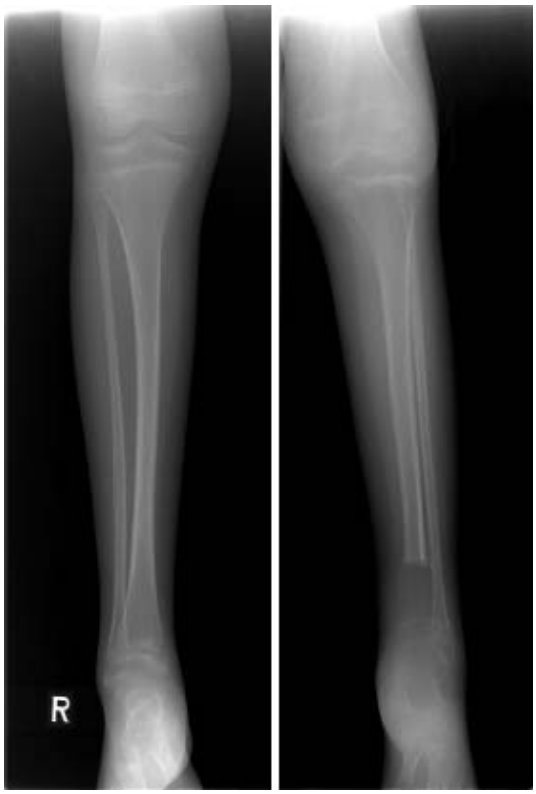

Fig. 5. Lower leg X-ray shows expansile osteolytic lesion with cortical disruption and periosteal reaction on left distal metaphysis.

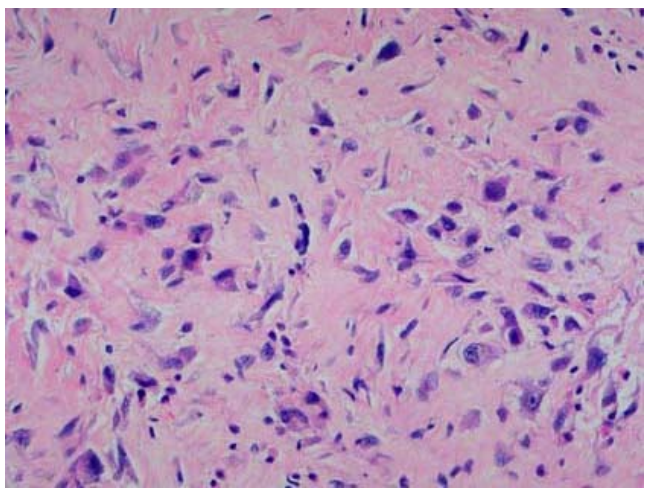

Fig. 6. Pathologic finding of lesion of bone is consistent with osteosarcoma (H&E stain, ×400).

has been treated with maintenance chemotherapy.

Discussion

RTS is a rare genetic disorder, inherited as an autosomal recessive condition that is characterized by : poikiloderma, sparse hair and eyebrows, short stature, skeletal abnormalities, juvenile cataracts, and a high risk for malignancy. RTS was first described in 1868 by Rothmund, who was an ophthalmologist, he reported an inbred family with a peculiar skin rash, juvenile cataracts, skeletal abnormalities, short stature, and hypogonadism[3, 4]. Thomson reported in 1923 on patients with a similar skin rash and skeletal deformities who did not have juvenile cataracts when compared to Rothmund's cases[4-6]. In 1957, Taylor concluded that the two groups of patients independently described by Rothmund and then Thomson were the same syndrome that had a variable phenotype. There are more than two hundreds of cases[1, 4, 6] of RTS worldwide; however, there have been no prior reports of RTS in Korea.

Patients with RTS have a unique skin rash characterized by poikiloderma. The skin appears to be normal at birth and begins to change at about 3 to 6 months after birth. Areas exposed to sunlight such as the cheeks and the face develops an erythematous skin rash, sometimes accompanied by swelling and vesicles. The skin lesions may spread to the buttocks and extensor surfaces of hand and flexor areas of all four extremities[4, 6]. This acute phase continues for several years. The initial phase is than followed by a chronic phase of poikiloderma characterized by skin atrophy, depigmentation, and telangiectasia[7].

It has been reported that 68% of patients with RTS have skeletal abnormalities manifested by deformities, absence, or hypoplasia[1]. Skeletal abnormalities generally reported with RTS are : radial defects, hypoplasia of thumbs or patella, osteopenia, and absence of patella and thumbs. Bilateral subcapsular cataracts develop between 2 and 3 months of age[8].

The patient here presented had short stature, which was less than the third percentile. He had sparse hair and a prominent nose. X-rays of the extremities revealed radial defects including absence of thumbs bilaterally, ulnar deformities, osteopenia, and absence of both patella. An erythematous skin rash on both cheeks and on the upper and lower extremities were observed with onset during the first few months of life. Exposure to sunlight aggravated the skin lesions but there were no vesicles noted. Both cheeks had telangiectasia. As the patient aged the skin became atrophic, dry and hyperpigmented on the total body surface. However, there was no cataract detected on ophthalmologic examination.

RTS patients are known to be predisposed to the development of malignancy. Skin cancer is the most common cancer associated with RTS; skin cancers identified in patients with RTS include : squamous cell carcinoma, basal cell cancer, and Bowen's disease[8]. The next most frequently diagnosed malignancy is osteosarcoma[8]. In 1962, Roschlau[9] first identified osteosarcoma in RTS patients. There are reports of 19 RTS cases in the medical literature who developed osteosarcoma[1, 8]. The median age for diagnosis of osteosarcoma was reported to be 11.1 years. The male to female ratio reported is 10 : 9. Common sites for osteosarcoma diagnosis include : the tibia (9 cases), femur (4), humerus (2) radius (1), ulna (1), fibula (1), and calcaneus (1). Half of the patients with osteosarcoma had recurrence after treatment at the original site. The common bony sites were reported to be long bones, with active growth[1]. Patients with Osteosarcoma and RTS generally have a more aggressive type of osteosarcoma when compared to patients without RTS. In patients with RTS, the osteosarcoma tends to occur at any bony sites, regardless of the growth pattern[1]. In the case here presented osteosarcoma occurred and was confirmed by bone biopsy of the left tibial metaphysis. This site is the most common for osteosarcoma in patients with RTS. The tumor was removed after the patient received two rounds of chemotherapy and excisional operation of tumor.

Cytogenetic analyses of peripheral blood lymphocytes and skin fibroblasts have been reported to be normal in most cases of RTS. However, in some cases, mosaic abnormalities of chromosome 8 have been reported[9, 10]. A heterozygous mutation was reported at RECQL4 (chromosomal locus 8q24.3)[11, 12] which is the human helicase gene on chromosome 8 in RTS. Of note is the association of Bloom syndrome (BS) and Werner syndrome (WS) with the RECQ helicase gene mutation; these disorders share with RTS an increased frequency of malignancy including osteosarcoma[6].

Three of known five human RECQ helicases are associated with syndromes characterized by genetic abnormalities : BS (RECQ2), WS (RECQ3), and RTS (RECQ4)[12]. These three syndromes share the characteristics of chromo-

somal instability, growth delay, and a high frequency of malignancy. However, poikiloderma and radial anomalies are unique to RTS[13]. WS usually manifests later in life, compared to the other two syndromes. The three syndromes develop different kinds of malignancy[13]. Osteosarcoma and squamous cell carcinoma is common in RTS while sarcoma, melanoma, thyroid cancer, and osteosarcoma are more common in WS. Malignancies such as leukemia, breast cancer, and adenocarcinoma of GI system are associated with BS.

The confirmation of the diagnosis of RTS is based on the presentation of variable clinical characteristics and a distinctive skin rash. There is no specific diagnostic test, such as a blood analysis or specific cytogenetic finding for the diagnosis of RTS[6]. All RTS cases reported in the literature have demonstrated a characteristic skin rash; there has been no RTS case without the unique skin manifestations. When skin lesions are not typical for RTS in the morphology and in distribution, the diagnosis of RTS might be probable[6].

The case we present had typical RTS skin lesions, as well as specific characteristics consistent with RTS including osteosarcoma of the left tibia. The diagnosis of RTS is confirmed on the basis of the clinical features. The patient has received maintenance chemotherapy after the excisional surgery of the tumor mass. The patient continues to be followed for osteosarcoma recurrence, a second malignancy and possible cataracts.

한 글 요 약

Rothmund-Thomson 증후군 1례

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김승효 · 신충호 · 양세원

Rothmund-Thomson 증후군은 상염색체 열성질환으로 다형피부증(poikiloderma), 희박한 모발과 눈썹, 저신장, 골격계 이상, 유소년기 백내장과 악성종양의 위험이 높은 것으로 특징지어지는 증후군이다. 골격계의 이상은 RTS 환아의 68%에서 보고되었고 신체전반의 골격계 이형성으로 형성부전이나 기형으로 나타난다. 요골형성부전, 엄지손가락 저형성, 골감소증, 슬개골 저형성이나 슬개골 형성 부전 등이 보고되어 있다. 흔치 않은 증상으로는 말안장코와 삼각형의 얼굴 등이 보고되어있다. RTS에서 골육종을 포함한 악성종양의 발생빈도가 높고 면역학적 이상이 보고되어 있다. 피부종양이 가장 흔하며 상피세포암, 기저세포암, Bowen's disease 등이 있고 두 번째로는 육종이 흔하다. 저자들은 전신적으로 혈관확장 및 과색소침착을 보이는 다형피부 소견과 함께 요골형성부전, 척골기형, 엄지손가락형성부전, 슬개골 형성부전의 골격계 기형이 있으면서 이후 좌측 경골에 골육종이 발생한 Rothmund-Thomson 증후군을 경험하였기에 보고하는 바이다.

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