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A Case Report of Rubinstein-Taybi Syndrome Presenting with Extensive Keloid Formation and Review of Literature

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Rubinstein-Taybi syndrome (RSTS) is an extremely rare genetic disorder affecting multi-organ systems. A tendency to form keloid is one of the common dermatologic manifestations. We describe a 23-year-old female presented with extensive keloids which developed spontaneously. She had typical facial features, broad thumbs, and dental defects, which were suspicious features of genetic syndrome. Direct sequencing for cyclic-AMP-regulated enhancer binding protein revealed a novel mutation. So far, 23 cases of RSTS have been reported in Korean literature. To the best of our knowledge, this is the first report in Korea to describe confirmed case of RSTS with extensive keloids as a chief manifestation.

Keywords: Base sequence, Cicatrix, Gene, Keloid, Rubinstein-Taybi syndrome

INTRODUCTION

Rubinstein-Taybi syndrome (RSTS) is a rare genetic disorder accompanying multiple congenital anomalies, characterized by dysmorphic face, broad thumbs and first toes, postnatal growth retardation, and intellectual disability[1]. More than half of the individuals with RSTS were known to carry mutation or microdeletion in the gene encoding cyclic-AMP-regulated enhancer binding protein (CREBBP)[2], while 5% to 8% of individuals have mutations in the gene encoding E1A binding protein p300 (EP300)[3].

A tendency to form keloid is another feature of RSTS which occurs in 24% of affected individuals[1]. A genetic predisposition to develop keloid is an unusual feature and may be associated with genetic disorders such as RSTS and Goeminne syndrome, and less frequently, Ehlers-Danlos syndrome type IV[4]. Although more than 30 cases of RSTS featuring keloid have been reported in White population, only 2 cases of RSTS with keloid have been reported in Asian population so far[1]. Herein, we describe another rare case of RSTS with Asian ethnicity who developed extensive keloid, which is a diagnostic clue for suspecting genetic disorder.

CASE REPORT

A 23-year-old female without significant medical history presented with extensive, massive, painful keloids along the submental and submandibular area, trunk, groin, and left posterior thigh (Fig. 1). Most of the keloids developed about 10 years ago without any history of significant trauma or inflammation. The keloids in the groin developed several years ago after she underwent scar revision surgery for a pubic keloid.

On physical examination, the patient had a short stature of 145.9 cm, which was below the third percentile[5]. She had unusual facial features including a low frontal hairline, downslanting palpebral fissures, and a beaked nose with columella below the alae nasi (Fig. 2A). Oral features were characterized by an arched palate and dental anomalies such as enamel hypoplasia, altered conformation, and overcrowding of the teeth (Fig. 2B). Mildly enlarged thumbs and clinodactyly of the fifth

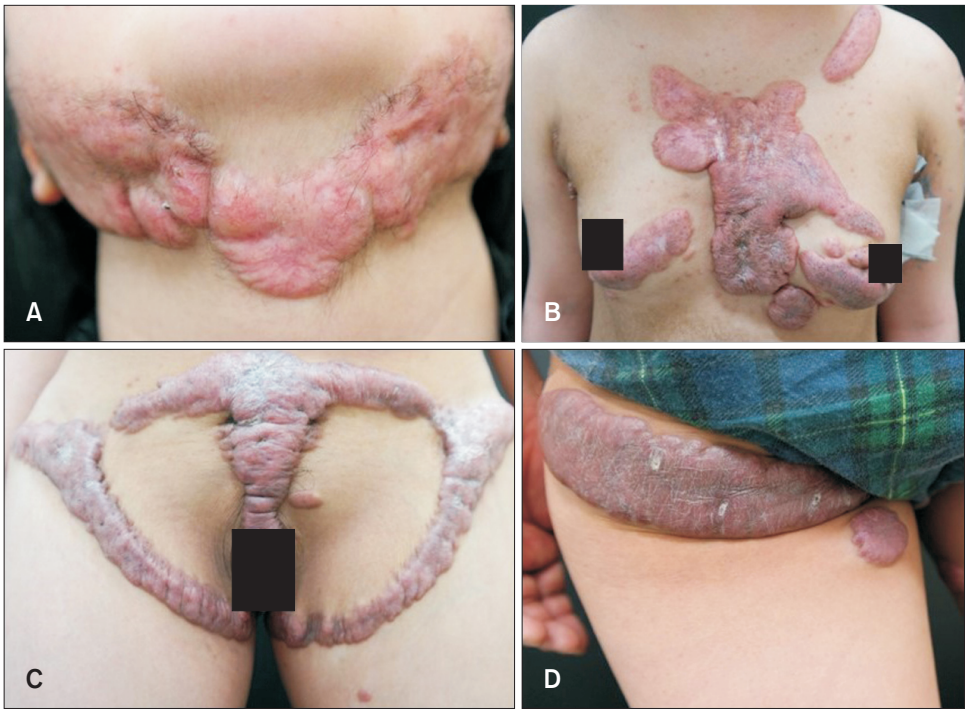

Fig. 1. Clinical presentation of extensive keloids in a patient with Rubinstein-Taybi syndrome. Massive keloid formation is observed at the submental/submandibular area (A), anterior chest (B), groin (C), and posterior thigh (D). We received the patient's consent form about publishing all photographic materials.

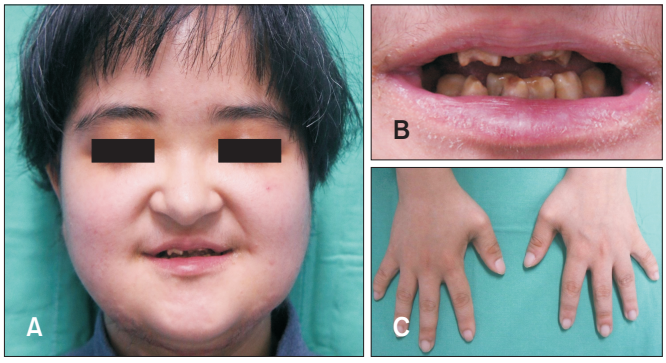

Fig. 2. Clinical photographs of extracutaneous features of the patient with Rubinstein-Taybi syndrome. (A) Facial features include down slanting palpebral fissures and beaked nose with columella below alae nasi. (B) Dental anomalies include enamel hypoplasia and overcrowding of teeth. (C) Skeletal deformities of phalanges include mildly enlarged thumbs and clinodactyly of fifth fingers.

fingers were seen (Fig. 2C). She had no significant intellectual disabilities as she successfully completed ordinary high school education.

Laboratory work-up showed normal liver and kidney function, and most endocrine factors (Anti-Müllerian hormone, testosterone, TSH, free T4, PTH, 1,25-[OH]2 Vitamin D3) were within normal limits.

PCR and direct sequencing for the *CREBBP* gene revealed a variant of uncertain significance (c.6633_6638delACAGCA, p.Gln2215_Gln2216del, heterozygote) and was negative for pathogenic variants. Analysis of the *EP300* gene did not reveal any mutations.

The patient received regular injections of 5 to 20 mg/ml of triamcinolone with 2 to 4 week intervals along with oral tranilast 300 mg a day for more than 3 months. The size and thickness of the keloids in the submental/submandibular area were gradually reduced, although lesions in other areas persisted without visible change.

DISCUSSION

RSTS is a rare autosomal dominant genetic disorder affecting multi-organ systems[1,3]. In Korean medical journals, 23 cases of RSTS have been reported[6-13]. Typical facial features including down-slanting palpebral fissures, beaked nose with columella below alae nasi, broad thumbs and halluces, and developmental delay were the common manifestations. Cutaneous manifestations of individuals with RSTS in Korea included hypertrichosis, pilomatrixoma, keloid, and nevus depigmentosus (Table 1).

Globally, multiple keloid formation is one of the common manifestations, observed in 24% to 57% of the patients[1,14].

Table 1. Clinical features of Rubinstein-Taybi syndrome illustrated in Korean medical journals

Clinical feature	Number (%)	Our case	Reference
Typical facial features (n=24)			
Downslanting palpebral fissures	23 (95.8)	O	6~10, 13
Protuding beaked nose with columella below alae nasi	22 (91.7)	O	6, 7, 9, 10,11, 13
Arched/thick eyebrows	20 (83.3)	O	7, 10, 11, 13
Mild micrognathia	20 (83.3)	X	6, 9, 10, 11, 13
Low frontal hairline	3 (12.5)	O	6, 12
Pouting lower lip	2 (8.3)	X	7, 11
Dysplastic and low-set ears	1 (4.2)	X	8
Dental manifestation (n=24)			
Arched palate	18 (75.0)	X	6, 9, 10
Altered conformation	2 (8.3)	O	11
Overcrowding of teeth	2 (8.3)	O	11
Abnormal tooth number	1 (4.2)	X	11
Enamel hypoplasia	1 (4.2)	O	The current case report
Skeletal manifestation (n=24)			
Broad thumbs / halluces	22 (91.7)	O	6, 7, 8, 10, 11, 12
Scoliosis	5 (20.8)	X	10, 12, 13
Polydactyly	4 (16.7)	X	6, 10
Clinodactyly of fifth finger	3 (12.5)	O	7, 11
Microcephaly	3 (12.5)	X	6, 9, 11
Hallux valgus	1 (4.2)	X	11
Syndactyly	1 (4.2)	X	13
Spinal wedging	1 (4.2)	X	10
Cutaneous manifestation (n=24)			
Hypertrichosis	3 (12.5)	O	6, 11
Pilomatrixoma	2 (8.3)	X	11, 13
Keloid	1 (4.2)	O	The current case report
Nevus depigmentosus	1 (4.2)	X	11
Ophthalmologic manifestation (n=24)			
Strabismus	6 (25.0)	X	8~10, 12, 13
Coloboma	2 (8.3)	X	8, 10
Cataract	1 (4.2)	X	11
Lacrimal duct obstructions	1 (4.2)	X	11
Epiblepharon	1 (4.2)	X	7
Developmental manifestation (n=24)			
Developmental delay	17 (70.8)	X	8, 10, 11, 13
Postnatal growth retardation	15 (62.5)	X	6, 7, 10, 11, 13
Intellectual disability	5 (20.8)	X	7, 9, 11~13
Short stature	5 (20.8)	O	6, 7, 11, 13
Endocrine manifestation (n=24)			
Congenital hypothyroidism	1 (4.2)	X	10

Table 1. Continued

Clinical feature	Number (%)	Our case	Reference
Genitourinary manifestation (n=24)			
Cryptorchidism	5 (20.8)	X	7, 10, 12
Renal malformations	1 (4.2)	X	5
Neurologic / Radiologic manifestation (n=24)			
Abnormalities in MRI study	10 (41.7)	X	7, 8, 10, 11
Nonspecific abnormalities of electroencephalography and seizures	3 (12.5)	X	10, 11
Chiari type I malformation±syringomyelia	3 (12.5)	X	7, 10
Corpus callosum dysgenesis	1 (4.2)	X	10
Respiratory manifestation (n=24)			
Sleep apnea	2 (8.3)	X	9, 12
Recurrent respiratory infections	1 (4.2)	X	6
Abnormality in genetic study (n=24)			
CREBBP	14 (58.3)	O	7, 9, 10, 11
Novel mutations located in other genes except CREBBP and EP300	6 (25.0)	X	10
Unidentified	4 (16.7)	X	6, 8, 12, 13
EP300	0 (0)	X	

MRI: magnetic resonance imaging, CREBBP: cyclic-AMP-regulated enhancer binding protein, EP300: E1A binding protein p300.

However, among 24 cases of RSTS in Korea, ours was the only case to display keloid formation, indicating that there may be an ethnic predisposition for keloid presentation. It appears that among individuals with RSTS Asian patients are less likely to develop keloids than White patients. In one literature review investigating individuals with RSTS who had keloids, only two out of 27 individuals were Asian, while the rest of the cases (93%) were White[1]. A significant portion of the patients with RSTS has been reported to develop keloids spontaneously without any previous overt trauma or inflammation[1]. Whether or not keloid formation without any trauma is in fact spontaneous is still under debate. Some studies suggest that microscopic inflammation or insignificant trauma which is not noted by the patient may lead to keloid formation[15]. In our patient, most of the lesions developed spontaneously without any specific injuries except for those in the groin, which expanded in size and thickness after surgical removal of scars. The hyperproliferative response of fibroblasts to dermal injury may be explained by the function of CREBBP that results in immortalization of cells by cAMP-regulation[16]. Moreover, CREBBP and EP300 may alter the wound-healing properties of fibroblasts through functioning as either transcriptional coactivators or as histone acetyltransferases[17]. This epigenetic alteration may result in uncontrolled hyperproliferation of fibroblasts, resulting in keloid development.

There is a spectrum of genetic disorders to differentiate featuring spontaneous keloids, such as RSTS, Dubowitz syndrome, Noonan syndrome, Goeminne syndrome, Bethlem myopathy, X-linked recessive polyfibromatosis, and a novel X-linked syndrome with filamin A mutation[4]. Among them, the most common syndromes exhibiting keloid formation are RSTS and Goeminne syndrome[1]. Goeminne syndrome is usually characterized by torticollis, cryptorchidism and renal dysplasia such as chronic pyelonephritis or renal atrophy, which were absent in our patient[18].

Prior studies have suggested four major clinical features of RSTS: short stature (less than 2 standard deviations); typical facial features (microcephaly, low anterior hairline, downslanting palpebral fissures, beaked nose, micrognathia); skeletal abnormalities (broad thumbs and/or big toes, fifth finger clinodactyly, polydactyly, scoliosis); and mental retardation. Our patient had three of these features and can be classified as moderate RSTS according to the criteria[19].

According to prior research, pathogenic variants of the *CREBBP* gene were identified in 50% to 70% of RSTS patients, while EP300 variants were identified in about 5% to 8% of the cases[3]. In direct sequencing for the *CREBBP* gene, our patient had no known pathogenic variant, but did have a vari-

ant of uncertain significance, a deletion at exon 31. The nearest known exon 31 variant in RSTS is c.6624A→C nucleotide polymorphism, which is located a few base pairs from our patient's variant (c.6633_6638delACAGCA)[19]. More than 32 exon 31 variants have been reported so far, including insertion/deletions and point mutations[3,19,20]. In this case, results from CREBBP gene analysis and the clinical manifestations of facial, dental, and skeletal dysmorphisms make RSTS the correct diagnosis.

Although genetic study is a definitive diagnostic tool, all features of the disease are not fully explained by the mutations in the known causative genes. One case series reported that about 30% of RSTS cases were devoid of mutations in both CREBBP and EP300, which may indicate that RSTS is a genetically heterogeneous disorder and may be caused by other genes not identified so far[19]. Pathogenesis and genotype-phenotype correlation in RSTS is largely unknown and specific pathogenic variants of the genes remain to be clarified.

Dermatologic management of keloids in RSTS patients is not largely different from traditional treatment of keloids. Treatment options include intralesional corticosteroid injection, adhesive silicone gel sheet, laser therapy, and pressure therapy. However, surgical scar revision or keloid excision/reduction should be applied cautiously in RSTS patients, as theses interventions may lead to local recurrence and aggravation of keloids.

Traditional guidelines for RSTS recommend regular assessment of multi-organ systems such as ophthalmologic, audiologic, cardiovascular, odontologic, and renal systems, according to age[3]. Our patient underwent several examinations in cardiovascular, gynecologic, and orthopedic fields but no significant abnormalities were detected.

In short, RSTS is a genetic disorders featuring spontaneously and extensively formed keloids with multiple dysmorphisms of the face, teeth, and fingers or toes. A detailed evaluation including laboratory and genetic testing and imaging analysis is required for diagnosis, and screening for abnormalities in other fields is necessary. Basic managements for keloids can be introduced. However, the surgical approach should be considered very carefully since it can cause aggravation of the symptoms.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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