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【 CASE REPORT 】

Variant NAXOS-Carvajal Syndrome with Rare Additional Features of Systemic Bulla and Brittle Nails: A Case Report and Literature Review

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Abstract:
Skin abnormalities are often indicative of cardiovascular diseases. Such a disease entity is called cardiocutaneous syndrome; however, the details regarding the involvement of bulla and nails remain largely unclear. A 49-year-old man with systemic bulla was admitted for heart failure. His bulla had previously been diagnosed as epidermolysis bullosa, but no known gene mutations for it had been identified. He had a triad of palmoplantar keratosis, curly and fine hair, and cardiomyopathy, which are characteristic of NAXOS-Carvajal syndrome. This case highlights the fact that bulla and brittle nails can accompany NAXOS-Carvajal syndrome, showing that these extra-cardiac findings can help identify otherwise overlooked serious cardiac conditions.

Key words: Cardiocutaneous syndrome, NAXOS-Carvajal syndrome, systemic bulla, brittle nails, cardiomyopathy, epidermolysis bullosa

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Introduction

Like a diagonal earlobe crease indicating atherosclerotic cardiovascular disease, apparently isolated skin abnormalities can be a clue suggesting systemic disease (1). Specifically, conditions in which cardiac and skin disorders coexist are termed cardiocutaneous syndromes (CCS), regardless of the degree of causality (2). This disease entity includes NAXOS disease and Carvajal syndrome, or NAXOS-Carvajal syndrome, in which cardiomyopathy of the right, left, or both ventricles occurs with hyperkeratosis and woolly hair in a hereditary manner (3, 4). Various gene mutations in the desmosome complex have been identified as common underlying causes of these diseases, with or without additional features (5-7), although several unidentified genes remain.

We herein report a novel familial case demonstrating the NAXOS-Carvajal phenotype with rare additional features of systemic bulla and brittle nails, in association with a literature review. To our knowledge, this is the first report on bullous cardiocutaneous syndrome that is unrelated to desmoplakin, the most critical protein in the desmosome complex.

Case Report

A 49-year-old man with dyspnea and systemic bulla was admitted to our hospital due to heart failure (HF). His skin lesions had persisted for more than 25 years and were diagnosed as epidermolysis bullosa (EB). He had no other comorbidities or allergies nor was he taking regular medicine. His parents were nonconsanguineous; however, he had a family history of heart disease, blisters, and curly hair (Fig. 1). His mother had died of HF. Two of his siblings died: one shortly after birth due to an unknown cause, and the other in his 20s due to dilated cardiomyopathy accompanied by systemic blisters. The other two siblings were alive and free of HF but suffered from premature senility and systemic blisters (one each). The patient's son had transposition of the great arteries without any skin disease.

On an examination, the patient's blood pressure was 144/102 mmHg, his heart rate was 95 bpm, and his oxygen saturation was 98%. His jugular vein was distended, and pitting edema was observed. A mixture of non-purulent bulla in as-

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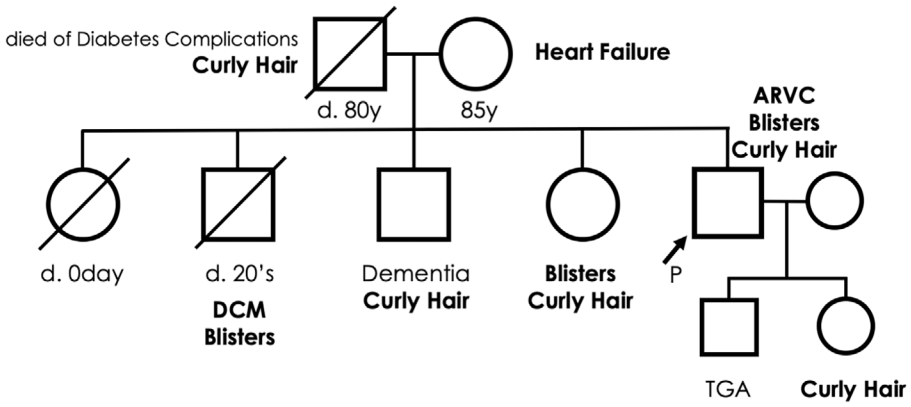

Figure 1. **A family tree of the patient. Squares and circles indicate male and female sex, respectively. Arrow denotes the case. The oblique lines indicate deceased status. DCM: dilated cardiomyopathy, ARVC: arrhythmogenic right ventricular cardiomyopathy, TGA: transposition of the great arteries**

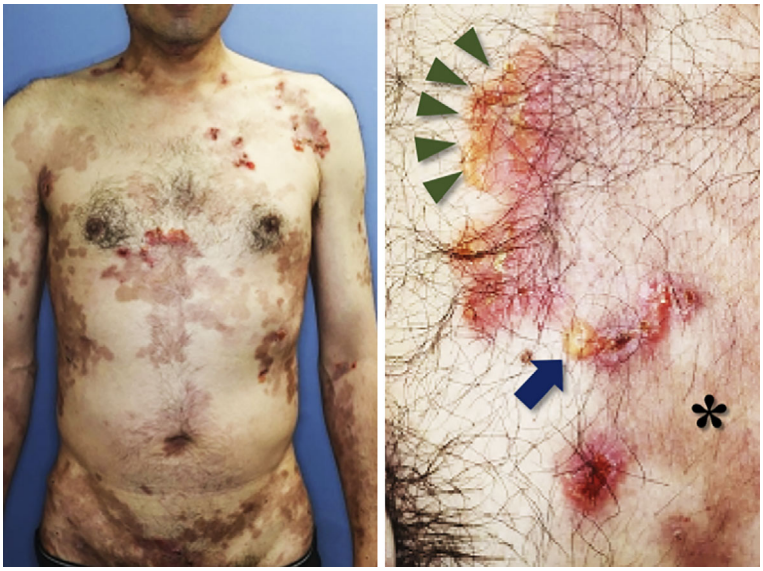

Figure 2. **Skin lesions. The patient's skin lesions showing a mixture of blisters (arrow), erosion with erythema (arrowheads), and pigmentation (asterisk) throughout the body.**

sociation with erosion, erythema, and pigmentation was found throughout his body (Fig. 2). His scalp hair had been fine and curly since birth. His hair had changed from black to brown during adolescence, as had his father's, his two siblings', and his daughter's. Mild focal keratosis was found on his palms and soles. His toenails were brittle and mostly detached. His fingernails were thick, white, and dystrophic (Fig. 3). The patient's teeth were normal.

His plasma brain natriuretic peptide (BNP) level was 2218 pg/mL, serum creatinine 0.89 mg/dL, and C-reactive peptide 0.88 mg/dL. Serum antibodies for desmogleins and BP180 were negative.

Chest X-ray showed marked cardiomegaly and vascular redistribution (Fig. 4). An electrocardiogram revealed a low voltage, a first-degree atrioventricular block, and epsilon waves (Fig. 5a). On echocardiography, the right ventricle was dilated to 76 mm, and its fractional area change was 11% (Fig. 6). Severe tricuspid regurgitation was also observed. The left ventricle was enlarged to 63 mm with a flattened ventricular septum. The ejection fraction fell to 21%.

In response to diuretic therapy with oral furosemide 40 mg/day and spironolactone 25 mg/day, pulmonary and peripheral edema resolved within days. This patient then underwent a diagnostic workup for HF. Ventricular late potentials were positive on a signal-averaged electrocardiogram (Fig. 5b). Coronary angiography revealed no significant stenosis. Computed tomography and magnetic resonance imaging showed fatty infiltration into the ventricular septum and extensive fibrosis in the left ventricle, respectively (Fig. 7a, b). Endomyocardial biopsy specimens from the right ventricular septum exhibited fibro-fatty replacement in approximately half of the area (Fig. 7c). These findings collectively led to the definite diagnosis of arrhythmogenic

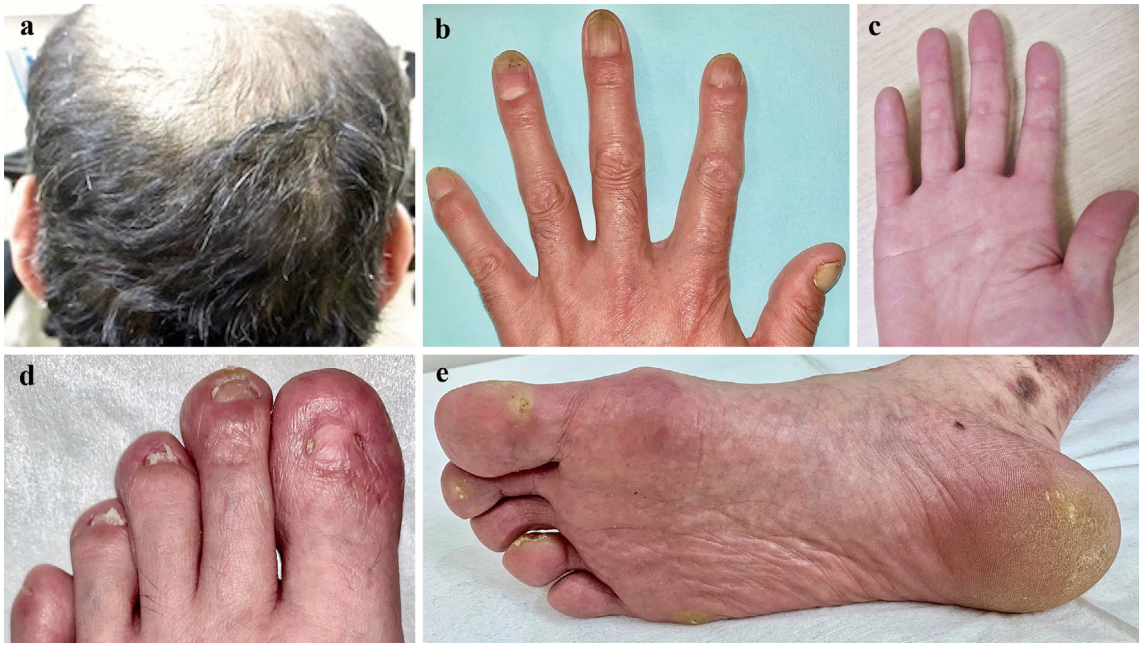

Figure 3. **The patient's physical findings showing curly hair (a), thick, white, and dystrophic finger nails (b), brittle and detached toe nails (d), and mild focal keratosis of the palms and soles of feet (c, e).**

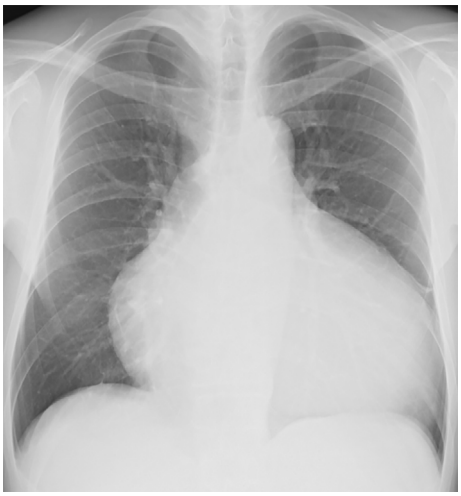

Figure 4. **A chest X-ray image. A chest radiograph demonstrating marked cardiomegaly and vascular redistribution as early signs of heart failure.**

right ventricular cardiomyopathy (ARVC) with left ventricular involvement by meeting two major and two minor criteria (8).

The patient experienced non-sustained ventricular tachycardias during admission and underwent implantation of an cardioverter defibrillator as a class I indication (9). He was discharged on day 31, and his BNP level decreased to 482 pg/mL. A continued dermatological examination in an outpatient setting provided a definite diagnosis of junctional EB (JEB). Candidate genes for JEB, including the desmoplakin gene (DSP) and desmoglein gene (DSG), were extensively investigated; however, no mutations were identified. Electron microscopy identified no changes indicative of specific disorders.

Discussion

Disorganized desmosome complexes impair cellular integrity and accommodability to stress. This induces disorders in multiple organs, especially those susceptible to stress, such as the heart and the skin (10). Three desmosomal genes have been identified to cause this type of cardiocutaneous syndrome: the plakoglobin gene (JUP) causing NAXOS disease, the DSP causing Carvajal syndrome, and the desmocollin-2 gene (DSC2) (11). Although small differences exist, they share the characteristic triad of cardiomyopathy, palmoplantar keratosis, and woolly hair. Diseases compatible with the triad are thus called NAXOS-Carvajal syndrome and are thought to be associated with desmosomal gene disruption.

Cardiomyopathy in NAXOS disease is characterized by right-dominant ventricular dilatation, hypokinesis, and tachyarrhythmia, which are compatible with ARVC (3). In contrast, Carvajal syndrome predominantly involves the left ventricle, resembling dilated cardiomyopathy (4). This ventricular preponderance initially served to define each syndrome. However, the distinction was later considered ambiguous, as even mutations in the same gene or within the same gene family can affect both ventricles (11, 12). Similarly, ARVC, originally regarded as a pure right ventricular disease, were later found to involve the left ventricle. Such variant ARVCs were once named left-dominant arrhythmogenic cardiomyopathy (LDAC) (13). Now these diseases may be collectively called as arrhythmogenic cardiomyopathy, as the same gene can affect both ventricles (14). In this

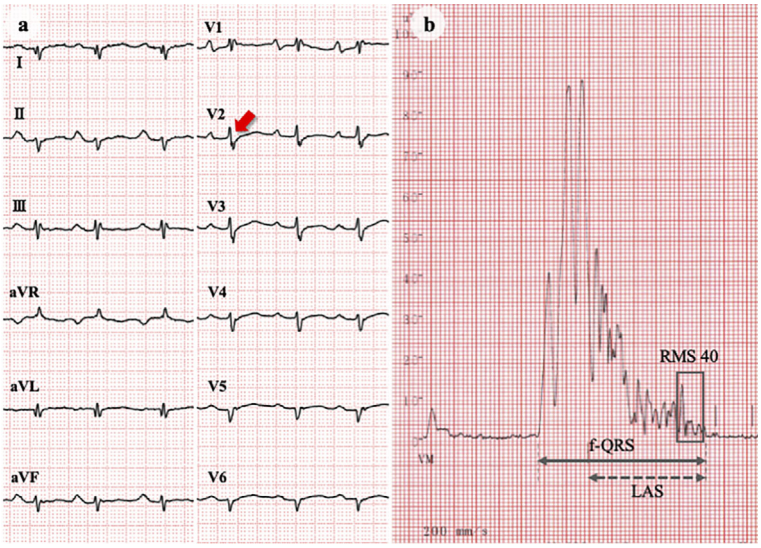

Figure 5. **ECG and signal-averaged ECG. ECG showing low voltage, first-degree atrioventricular block, abnormal Q waves in I/aVL/V5-6, and epsilon waves (arrow) in the precordial leads (a). Signal-averaged ECG indicating positive late potentials (b). Filtered QRS duration (f-QRS): 186 ms (upper normal limit: 114 ms); low amplitude signal duration (LAS): 131 ms (upper normal limit: 38 ms); root-mean-square voltage during 40 ms before QRS termination (RMS 40): 5 μV (lower normal limit: 20 μV). ECG: electrocardiogram**

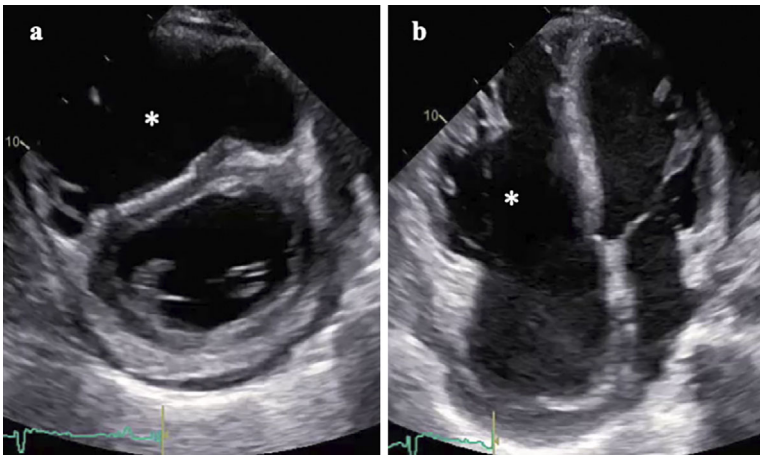

Figure 6. **Echocardiography. Parasternal short axis (a) and apical four-chamber images (b) exhibiting right ventricular dilatation and dysfunction (asterisk) with flattened ventricular septum. Severe tricuspid regurgitation and left ventricular dilatation/dysfunction were also observed.**

context, the biventricular cardiomyopathy in the present case was diagnosed as a common cardiac presentation of NAXOS-Carvajal syndrome. In addition, the myopathy can also be diagnosed as ARVC and LDAC, or arrhythmogenic cardiomyopathy.

Variants of NAXOS-Carvajal syndrome have been reported from around the world, regardless of ethnicity (Table 1). Autosomal recessive or unknown inheritance predominates in cases with consanguineous parents. All cases have shown the triad with minor variation in severity and distribution. Half of cases had additional features, with nail or tooth abnormalities predominant (3, 4, 6, 7, 12, 15-26). Of note, both the first cases of NAXOS disease and Carvajal syndrome shared curved fingernails (3, 4). Subsequent cases were also reported to have nail disorders, such as thickening, dystrophy, white change, or brittleness, although none of these were considered fourth traits of NAXOS-Carvajal syndrome (7, 12, 15, 17-24, 26). Tooth agenesis was first implicated in the syndrome in the first case with autosomal-dominant transmission (6). Intriguingly, most cases with additional tooth abnormalities have shown autosomal-dominant inheritance, regardless of nail findings (7, 21, 24-26).

Blisters have been reported as a cutaneous variant in only four cases (Table 2) (12, 18, 19, 27). Common features were homozygous DSP mutations, biventricular and nail involvement, and mild keratosis. While the blisters varied in size or distribution, the involvement of teeth was indeterminate. The findings of the present case were consistent with these char-

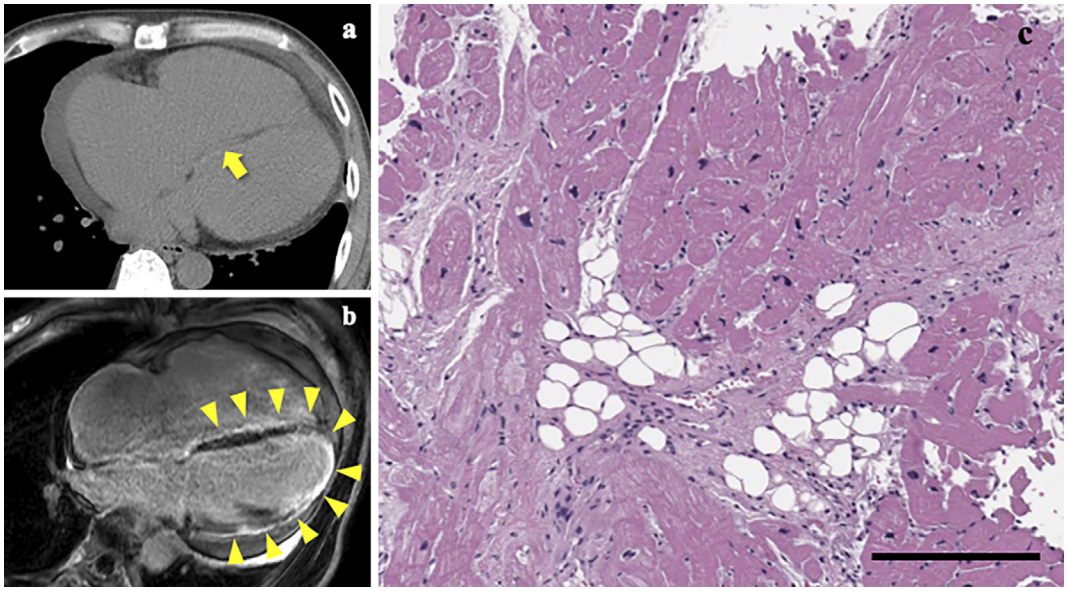

Figure 7. **CT scans, MR images and endomyocardial biopsy specimens. CT scans (a) and MR images (b) depicting fatty infiltration (arrow) and fibrosis (arrowheads) of the ventricular septum, respectively. Fibrosis of the left ventricle was also identified on MR images (b). Light microscopic examination of the right ventricle tissues demonstrating extensive fibro-fatty replacement of the cardiac myocytes (c). Scale bar, 200 μm.**

acteristics. However, its novelty was accentuated in that the patient lacked a DSP mutation and exhibited a relatively large bulla that was distributed throughout his body.

The older onset age of HF in our case not only suggests a better prognosis but also has pathophysiological implications. The age at the onset in patients with a DSC2 mutation is also older than in those with DSP mutations. This may be better explained by the interaction between desmocollin and desmoplakin than by the direct disruption of desmocollin (11). Thus, in addition to mechanical disruption of the desmosome complex, altered cell signaling pathways between desmoplakin and other desmosomal components or factors associated with desmosomes may underlie disease formation.

There are only three known causative genes for NAXOS-Carvajal syndrome, but as exemplified in a case with DSC2 mutation, all of the genes related to the desmosome complex have the potential to induce the phenotype. Indeed, there have been several reports showing the NAXOS-Carvajal phenotype in which the responsible gene was unclear but not DSP (22, 23). Furthermore, the genotype-phenotype association varies according to the site or mode of the mutation among cases with DSP mutations. These facts underscore the genetic heterogeneity of this syndrome. As we only examined DSP and DSGs in the present case, a thorough investigation of other related genes may elucidate the precise mechanism.

Given the aggregation patterns of curly hair and HF, the disease may be transmitted through autosomal-dominant inheritance. This notion is consistent with the fact that most cases of variant Carvajal syndrome with additional abnormalities of the teeth are autosomal-dominant, whereas classical ones are autosomal-recessive (25). However, this is only speculative, and other possibilities, including *de novo* or compound heterogeneous mutations with or without consanguinity, may underlie the disease expression. Furthermore, the penetrance or Lyon hypothesis can also affect the phenotypic expression, both of which are underrepresented in NAXOS-Carvajal syndrome with additional features.

Genes causing EB may also affect multiple organs, including the heart, as in cases with lethal acantholytic EB that represent cardiomyopathy or HF (28, 29). EB is classified into four subcategories: EB simplex, JEB, dystrophic EB, or a mixture thereof (30). As electron microscopy findings were indeterminate for the classification, JEB was chiefly diagnosed by physical findings. The presence of nail dystrophy and lack of palmoplantar bullas were inconsistent with EB simplex, while the lack of scarring or milium on and around the healed bullas contradicted dystrophic EB. We therefore examined the gene abnormalities known to induce JEB. Two independent dermatologists clinically established the diagnosis. However, an extensive analysis identified no gene mutations for major JEB subtypes, except for two rare variants without heart involvement. This suggested that JEB-related genes did not contribute to the NAXOS-Carvajal phenotype in the present case.

This case highlights the fact that NAXOS-Carvajal syndrome can be accompanied by additional bullous lesions and brittle nails through unknown inheritable gene mutations or modes of transmission. This case also demonstrates that bulla and brittle nails serve as a critical clue for identifying serious cardiac conditions that may otherwise go undetected.

The patient provided his written informed consent to publish

Table 1. NAXOS-Carvajal Phenotype with or without Additional Features.

Reference	Ethnicity	Consan-guinity	Gene abnormalities			Organ involvement			
			Inheri-tance	Genes	Mutation(s)	Heart	Skin	Hair	Others
NAXOS-Carvajal phenotype with additional features									
bullous phenotype:									
(18)	Brazilian	No	AR[#]	DSP	c.2516del4 c.3971del4	BiV	PPK, striate	near-total alopecia	thick and dystrophied nails
(19)	Finnish	No	AR[#]	DSP	c.7964C>A c.6310delA	BiV	PPK	woolly, short, sparce	dystrophied and detached nails, enamel dysplasia
(12)	Palestinian	Yes	AR	DSP	c.7111C>A	RV, BiV	PPK, epidermolytic	woolly	toe onychogryphosis
present case	Japanese	No	U	U[*1]	U	BiV	PPK, mild	curly auburn change	brittle nails, leukonychia
non-bullous phenotype:									
(3)	Greek	U	AR	U	U	BiV	PPK	steel wire-like	curved nails short fingers
(15)	Indian	Yes	U	U	U	LV	PPK	curly, soft and woolly alopecia	thickened and deformed nails
(4)	Ecuadorian	No	AR	U	U	LV	PPK	woolly	fingernail clubbing
(16)	Indian	Yes	AR	U	U	BiV	PPK	woolly	cleft lip and palate
(6)	U	U	AD	DSP	30bp insertion[*2]	BiV	PPK, focal and psoriasiform	woolly	tooth agenesis
(20)	Indian	Yes	U	U	U	epsilon waves T wave inversion	PPK, striate	woolly	clubbed finger nails middle lobe syndrome
(21)	U	U	AD	DSP	c.1790C>T	BiV	PPK	woolly	fragile nails tooth agenesis
(17) (22)	U	No	U	U[*1]	U	LV	PPK	wavy and wiry	small, white and thick nails periodontitis, hypodontia
(23)	U	U	U	U[*3]	U	LV	PPK	woolly	thick and fragile nails tooth agenesis
(7)	Caucasian	U	AD	DSP	c.1691C>T	BiV	PPK	woolly	leukonychia oligodontia
(24)	Caucasian	No	AD	DSP	c.1748T>C	BiV	PPK	woolly	dystrophied nails
(24)	Caucasian	No	AD	DSP	c.1691C>T	BiV	PPK, slight	curly and woolly	toe leukonychia tooth agenesis
(25)	Caucasian	No	AD	U	U	LV apical LVHT	PPK	woolly and darkened	tooth agenesis
(26)	Lebanese	U	AD	DSP	c.1865T>C	LV	PPK	woolly	leukonychia tooth agenesis
NAXOS-Carvajal phenotype without additional features									
bullous phenotype:									
(27)	Arabic	Yes	AR	DSP	c.7402G>C	RV	no PPK dry skin	woolly	-
non-bullous phenotype:									
(31)	Ecuadorian	Yes	AR	DSP	c.7901delG	LV	PPK, striate	curly and woolly	-
(5)	Greek	U	AR	JUP	c.2157_2158 delTG	RV	keratosis	woolly	-
(32)	Asian-Indian	U	de novo	U	U	RV	PPK	woolly	-
(33)	Turkish	Yes	AR	DSP JUP	c.3799C>T c.2089T>A	BiV	PPK	woolly	-
(34)	Arabic	Yes	AR	U	U	BiV	PPK	curly	-
(35)	Azerbaijan	Yes	AR	DSP	2-bp deletion of exon 23	BiV BiVHT	PPK	woolly	-
(36)	Spanish	U	U	U[*3]	U	RV	PPK	woolly	-
(37)	U	Yes	AR	U	U	RV	PPK	woolly	-
(11)	Pakistani	Yes	AR	DSC2	c.1841delG	BiV	PPK, mild	woolly	-
(38)	U	Yes	AR	DSP	c.5208_5209 delAG	BiV	PPK, acantholytic	woolly	-
(39)	Indian	Yes	AR	DSP	c.3901C>T	BiV	PPK	woolly, curly, brittle	-
(40)	non-Greek	U	U	U	U	RV	PPK	woolly	-
(41)	Turkish	Yes	AR	DSP	c.7780delT	BiV	PPK	woolly	-
(42)	Italian	U	AD	DSP	c.878A>T	BiV	keratosis		-
(12)	Palestinian	Yes	AR	DSP	c.3924delG	BiV	keratosis	woolly	-

[#]compound heterogeneous inheritance.
[*1]no DSP gene mutation was detected.
[*2]c.1823_1824insACAGTCTCAGTTCACCGATGCCCGGAAAAT.
[*3]no mutations in DSP nor JUP genes were identified.
AR: autosomal recessive inheritance, AD: autosomal dominant inheritance, BiV: biventricular involvement, BiVHT: biventricular hypertrabeculation/noncompaction, DSP: desmoplakin, JUP: plakoglobin, LV: left ventricular involvement, LVHT: left ventricular hypertrabeculation/noncompaction, RV: right ventricular involvement, U: unknown

Table 2. Details of Organ Involvement in NAXOS-Carvajal Syndrome Associated with Blisters and Nail Anomalies.

Reference	Organ involvement					
	Heart	Blisters	PPK	Hair	Nails	Teeth
27	mild RV dilatation VT of RV origin	pemphigus foliaceous-like vesicles on the extremities	none	woolly	not reported	not reported
18	BiV dilatation and systolic dysfunction	blisters and erosions, especially at sites of mechanical trauma	focal and striate with fissuring	near-total alopecia	thick and dystrophic	not reported
19	BiV dilatation	superficial, mucocutaneous, scalp and face blisters blistering only develops after severe mechanical stress since 6 years of age	localized minimal palmar involvement	woolly and sparse	thick, detached and dystrophic	enamel dysplasia
12	severe RV or BiV dysfunction SCD in BiV involvement	epidermolytic plantar blisters and erythema, followed by keratoderma	mild palmar keratosis plantar keratosis in pressure areas	woolly, rough, light-colored	onychogryphosis	not reported
present case	BiV dilatation and systolic dysfunction	epidermolytic bulla, erosions and pigmentations throughout the body, not on the palms and soles	mild and focal	curly, fine brown change	thick, detached and dystrophic	normal

BiV: biventricular, LV: left ventricle, PPK: palmoplantar keratosis, RV: right ventricle, SCD: sudden cardiac death, VT: ventricular tachycardia

his case, including the associated images.

The authors state that they have no Conflict of Interest (COI).

Takanori Sato and Sho Okada contributed equally to this work.

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