Abstract:
Skin abnormalities are often indicative of cardiovascular diseases. Such a disease entity is called cardiocu-
taneous 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 palmo-
plantar keratosis, curly and fine hair, and cardiomyopathy, which are characteristic of NAXOS-Carvajal syn-
drome. 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

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 syn-
drome, 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 des-
mosome complex have been identified as common underly-
ing causes of these diseases, with or without additional fea-
tures (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 litera-
ture review. To our knowledge, this is the first report on bullous cardiocutaneous syndrome that is unrelated to des-
mosplakin, the most critical protein in the desmosome com-
plex.

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 diag-
nosed as epidermolysis bullosa (EB). He had no other comorbidities or allergies nor was he taking regular medi-
cine. 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 accompa-
nied by systemic blisters. The other two siblings were alive and free of HF but suffered from premature senility and sys-
temic 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 satu-
ration was 98%. His jugular vein was distended, and pitting edema was observed. A mixture of non-purulent bulla in as-
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.

Association 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
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 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.
The maladies of the teeth are autosomal-dominant, whereas classi-
cases of variant Carvajal syndrome with additional abnor-
herence. This notion is consistent with the fact that most
disease may be transmitted through autosomal-dominant in-
precise mechanism.

ough investigation of other related genes may elucidate the
score the genetic heterogeneity of this syndrome. As we
sociation varies according to the site or mode of the muta-
tions. The age at the onset in patients with a DSC2 mutation
is 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 desmocoll-
in (11). Thus, in addition to mechanical disruption of the
desmosome complex, altered cell signaling pathways be-
tween 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 as-
association varies according to the site or mode of the muta-
tion among cases with DSP mutations. These facts under-
score the genetic heterogeneity of this syndrome. As we
only examined DSP and DSGs in the present case, a thor-
ough 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 in-
heritance. This notion is consistent with the fact that most
cases of variant Carvajal syndrome with additional abnor-
malities of the teeth are autosomal-dominant, whereas classi-
cal ones are autosomal-recessive (25). However, this is only
speculative, and other possibilities, including de novo or
compound heterogeneous mutations with or without consan-
guinity, may underlie the disease expression. Furthermore,
the penetrance or Lyon hypothesis can also affect the pheno-
typic expression, both of which are underrepresented in
NAXOS-Carvajal syndrome with additional features.

Genes causing EB may also affect multiple organs, in-
cluding the heart, as in cases with lethal acantholytic EB
that represent cardiomyopathy or HF (28, 29). EB is classi-
fied into four subcategories: EB simplex, JEB, dystrophic
EB, or a mixture thereof (30). As electron microscopy find-
ings 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 in-
duce JEB. Two independent dermatologists clinically estab-
lished the diagnosis. However, an extensive analysis identi-
fied 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 syn-
drome 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

Figure 7. CT scans, MR images and endomyocardial biopsy specimens. CT scans (a) and MR im-
ages (b) depicting fatty infiltration (arrow) and fibrosis (arrowheads) of the ventricular septum, re-
spectively. Fibrosis of the left ventricle was also identified on MR images (b). Light microscopic ex-
amination of the right ventricle tissues demonstrating extensive fibro-fatty replacement of the cardiac
myocytes (c). Scale bar, 200 μm.
Table 1. NAXOS-Carvajal Phenotype with or without Additional Features.

| Reference | Ethnicity | Consanguinity | Gene abnormalities | Organ involvement |
|-----------|-----------|---------------|--------------------|-------------------|
|           |           |               | Inheritance | Genes | Mutation(s) | Heart | Skin | Hair | Others |
| (18)      | Brazilian | No AR⁰       | DSP         | c.2516del4        | Bi/V   | PPK, striate | near-total alopecia | thick and dystrophied nails |
| (19)      | Finnish   | No AR⁰       | DSP         | c.397del64        | Bi/V   | PPK | woolly, short, sparse | dystrophied and detached nails, enamel | \(\text{dysplasia} \)
| (12)      | Palestinian | Yes AR       | DSP         | c.6310delA        | RV, Bi/V | PPK, epidermolytic | woolly | toe onychogryphosis |
|           | Japanese  | No U U⁴       |            |            | Bi/V   | PPK, mild   | curly auburn change | brittle nails, leukonychia |
| (3)       | Greek     | U AR U U     |            |            | Bi/V   | PPK | steel wire-like | curved nails |
| (15)      | Indian    | Yes U U U     |            |            | LV     | PPK, curly, soft and | thickened and | deformed nails |
| (4)       | Ecuadorian| No AR U U     |            |            | LV     | PPK, woolly alopecia | woolly | fingernail clubbing |
| (6)       | Indian    | Yes AR U U    |            |            | Bi/V   | PPK | woolly | cleft lip and palate |
| (20)      | Indian    | Yes U U U     |            |            | Bi/V   | PPK, focal and | woolly | tooth agenesis |
| (21)      | U U AD DSP| c.1790C>T     | Bi/V       | PPK | woolly | fragile nails |
| (17)      | U No U U⁴ |            |            |            | LV     | PPK, wavy and wiry | small, white and thick nails |
| (22)      | U No U U⁴ |            |            |            | LV     | PPK, thick and fragile nails | tooth agenesis |
| (7)       | Caucasian | U AD DSP c.1691C>T | Bi/V | PPK | woolly | leukonychia |
| (24)      | Caucasian | No AD DSP c.1748T>C | Bi/V | PPK | woolly | dystrophied nails |
| (25)      | Caucasian | No AD DSP c.1691C>T | Bi/V | PPK, slight | curly and | toe leukonychia |
| (26)      | Lebanese  | U AD DSP c.1865T>C | LV | PPK | woolly and | tooth agenesis |
| (27)      | Arabic    | Yes AR DSP c.7402G>C | RV | no PPK | dry skin | - |
| (31)      | Ecuadorian| Yes AR DSP c.7901delG | LV | PPK, striate | curly and | - |
| (5)       | Greek     | U AR JUP c.2157_2158delTG | RV | keratosis | woolly | - |
| (32)      | Asian-Indian | U de novo U U | RV | PPK | woolly | - |
| (33)      | Turkish   | Yes AR DSP c.3799C>T | Bi/V | PPK | woolly | - |
| (34)      | Arabic    | Yes AR U U | Bi/V | PPK | curly | - |
| (35)      | Azerbaijani | Yes AR DSP 2-bp deletion of exon 23 | Bi/V | PPK | woolly | - |
| (36)      | Spanish   | U U U⁴ | RV | PPK | woolly | - |
| (37)      | U Yes AR U U | RV | PPK | woolly | - |
| (11)      | Pakistani | Yes AR DSC2 | c.1841delG | Bi/V | PPK, mild | woolly | - |
| (38)      | U Yes AR DSP c.5208_5209delAG | Bi/V | PPK, acantholytic | woolly | - |
| (39)      | Indian    | Yes AR DSP c.3901C>T | Bi/V | PPK, woolly, curly, brittle | - |
| (40)      | non-Greek | U U U | RV | PPK | woolly | - |
| (41)      | Turkish   | Yes AR DSP c.7780delT | Bi/V | PPK | woolly | - |
| (42)      | Italian   | U AD DSP c.878A>T | Bi/V | keratosis | - |
| (12)      | Palestinian | Yes AR DSP c.3924delG | Bi/V | keratosis | - |

⁰compound heterogeneous inheritance.

⁴no DSP gene mutation was detected.

³c.1823_1824insACAGTCTCACAGGCAATGCCGAAAAT.

⁵no mutations in DSP nor JUP genes were identified.

AR: autosomal recessive inheritance, AD: autosomal dominant inheritance, Bi/V: biventricular involvement, Bi/VHT: biventricular hypertrabeculation/noncompaction, DSP: desmoplakin, JUP: plakoglobin, LV: left ventricular involvement, LVHT: left ventricular hypertrabeculation/noncompaction, RV: right ventricular involvement, U: unknown
The authors state that they have no Conflict of Interest (COI).

his case, including the associated images.

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

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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 | pemphigus foliaceus-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 | mild and focal | onychogryphosis | not reported |
| present case | BIV dilatation and systolic dysfunction | epidermolytic bulla, erosions and pigmentation 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
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