Case Report

Costello syndrome with trichorrhexis nodosa: A case report

Panwadee Thongcharoensirikul*, Kitiwan Rojnueangnit**,
Vorasuk Shotelersuk***, Padcha Pongcharoen*

Abstract

Costello syndrome is one of the RASopathies, caused by a germline mutation in *HRAS*, on chromosome 11. Costello syndrome is a complex developmental disorder involving craniofacial anomalies, delayed development, cardiac and skeletal abnormalities, and increased risk of malignancies.

We report a female patient with the attenuated phenotype of Costello syndrome, who has a mutation in *HRAS,* a heterozygous one substitution from G to T at nucleotide 37 (c.37G>T) leading to predict a change of glycine to cysteine at codon 13 (p.Gly 13Cys). She presented to our dermatology clinic with sparse hair and the inability to grow long hair since birth which revealed characteristics of trichorrhexis nodosa (TN) in the hair shaft under light microscope. She also has intellectual disabilities, a left cavus foot deformity, and multiple minor dysmorphic facial features without cardiac anomalies. Lab investigations also showed iron depletion. While iron deficiency anemia can be a cause of TN; however, her hair remained the same after 5 weeks of iron supplements. Costello syndrome may be the cause of this patient's TN, but this phenomenon has not yet been documented. More follow-up is needed.

Keywords: Costello syndrome, trichorrhexis nodosa, inability to grow long hair

Received: 11 December 2018 **Accepted: 21 January 2019**

*Division of Dermatology, Department of Medicine, Faculty of Medicine, Thammasat University
**Department of Pediatrics, Faculty of Medicine, Thammasat University
***Department of Pediatrics, Faculty of Medicine, Chulalongkorn University

Introduction

Costello syndrome (CS) is a type of RASopathy caused by a germline mutation in *HRAS* on chromosome 11, which encodes the mitogen-activated protein kinase (MAPK) pathway. The most common germline mutations in CS are nucleotide substitutions at positions 34 and 35, resulting in the change of codon 12 from glycine to serine (p.Gly12Ser), to alanine (p.Gly12Ala) or to cysteine (p.Gly12Cys)[1]. A minority of CS patients have mutations in other positions, such as p.Gly13Cys, p.Gly13Asp, p.Thr58 and p.Gly60Asp; these usually present as milder phenotypes[2]. Most cases result from sporadic mutations[3]. The clinical features of Costello syndrome share similar phenotypes with other RASopathies (Noonan syndrome and cardio-facio-cutaneous syndrome). Perinatal findings with great specificity for CS among other RASopathies are cardiac arrhythmia and neonatal hypoglycemia[4]. Most patients have short stature. Craniofacial features of Costello syndrome are relative macrocephaly, coarse face, widely spaced eyes, depressed nasal bridge, short fuller nose, wide nasal tip, large mouth, thick vermilion lips, low-set ears, or posteriorly rotated ears; patients may also have a deep, hoarse or whispery voice and display signs of premature aging[3]. Dental characteristics in CS which differentiate from cardio-facio-cutaneous syndrome (CFC) are class III malocclusion, delayed eruption of teeth, thickening of the posterior maxillary alveolar ridge, gingival hyperplasia and enamel defects[5]. Distinctive cutaneous findings that are more likely to be CS than CFC are papilloma especially on the nose, full eyebrows, pachydermatoglyphia on fingertips, loose skin and deep creases on the hands and feet, and generalized hyperpigmentation[6 - 8]. Other cutaneous features are palmoplantar keratoderma, keratosis pilaris, multiple nevi, acanthosis nigricans, hemangioma, cutis laxa, nevus sebaceus, hyperpigmented patch, and café au lait macule[7]. Hair abnormalities associated with CS are curly hair, sparse hair, brittle hair, temporal alopecia, and poor hair growth[9]; however, there has not been any previous reports of microscopic confirmation for CS hair abnormalities.

Extracutaneous findings in CS include musculoskeletal abnormalities such as positional foot deformities and joint laxity; cardiovascular defects like cardiomyopathy, congenital heart defects especially pulmonary stenosis, and multifocal atrial tachycardia; and neuropsychiatric features manifesting as intellectual disabilities and overt sociability. Risk of cancer in Costello syndrome is about 15% within 20 years. The most common cancers are rhabdomyosarcoma, followed by neuroblastoma, and bladder cancer[10]. While there are genotype correlations with carcinoma risk, *HRAS* p.Gly13Cys has not been reported to be associated with malignancy[11]. Surveillance recommendations for CS patients from various American pediatric cancer associations recommend physical exams with abdominopelvic ultrasounds every 3 - 4 months since birth until 8 - 10 years and annual urinary analysis every year from 10 years[12] onward. Management guidelines are not used under definitive diagnosis is made.

Here we report a female adolescent with a mutation in *HRAS*, who presented with a milder phenotype of Costello syndrome with microscopic findings of hair abnormality.

Case report

A 17-year-old female presented to the dermatology clinic with a complaint of sparse hair and the inability to grow long hair since birth. She was the first child of healthy non-consanguineous parents. She was born at term with the birthweight of 3.4 kg without any complications during the perinatal period. Her parents noticed that she was delayed in development since she was young; however, it had improved with time. She was a slow learner in grade 11, regular classroom. She was unaware of any underlying disease; only the left foot deformity was detected at birth. Her growth parameters were normal with weight in the 10th percentile, height within

the 25 - 50th percentile, and head circumference in the 25 - 50th percentile. Physical examination revealed diffused sparse and fragile hair. Dermoscopy showed white nodules and fractures along hair shafts. Hair under light microscope revealed splayed paintbrush appearance, characteristic of trichorrhexis nodosa (TN) (Figure 1 and 2). Her facial features included coarse face, high anterior hairline, sparse lateral eyebrows, strabismus, widely spaced eyes, long eye lashes, depressed nasal bridge, wide nasal base, broad nasal tip, short philtrum, wide mouth and thick vermilion lips (Figure 3). Her voice was deep and hoarse. She also had prominent ventral aspects on her fingertips and a left cavus foot deformity.

Figure 1 Dermoscopy showed white nodules and fractures along hair shafts.

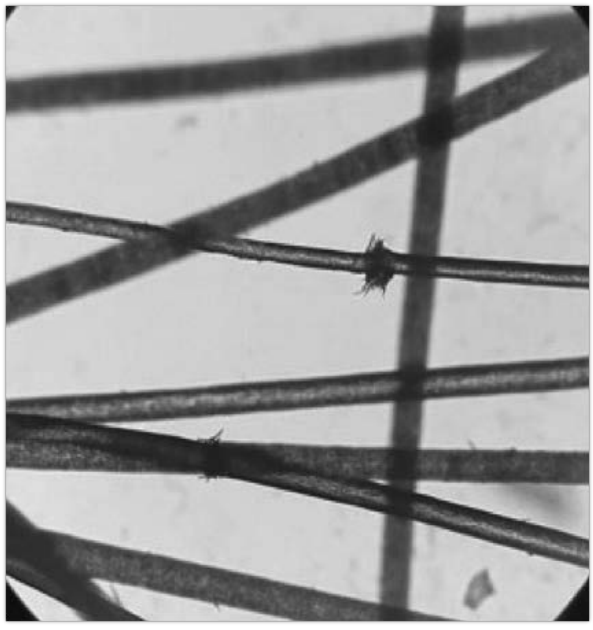

Figure 2 Light microscope revealed splayed paintbrush appearance which is characteristic of trichorrhexis nodosa.

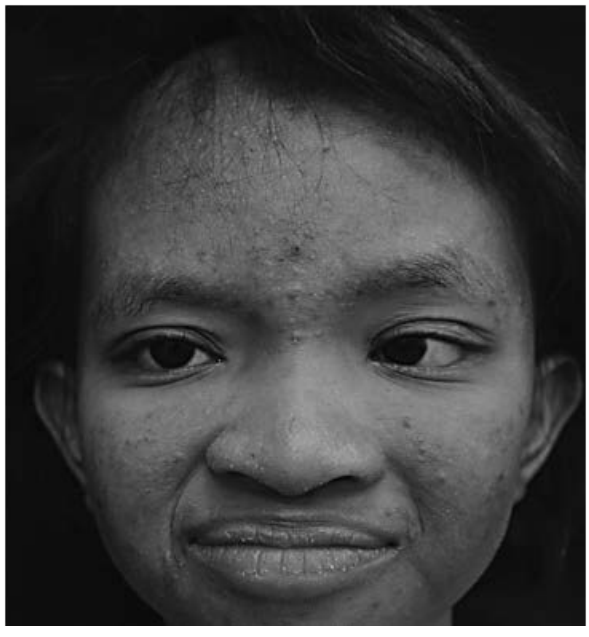

Figure 3 Patient's facial profile includes coarse face, high anterior hairline, sparse lateral eyebrows, strabismus, widely spaced eyes, long eyelashes, wide nasal base, broad nasal tip, short philtrum, wide mouth and thick vermilion lips.

Trio whole exome sequencing was performed. It revealed a *de novo* mutation of one base pair substitution from G to T at nucleotide 37 (c.37G>T) leading to a predictable change of the amino acids from glycine to cysteine at codon 13 (p.Gly13Cys) in *HRAS*. This is a well-known mutation for Costello syndrome, attenuated phenotype. The Wechsler Adult Intelligence Scale-III revealed her intellectual quotient at 70 points, borderline intellectual disability. No heart abnormalities and malignancies were detected from echocardiogram and whole abdominal ultrasound. Her complete blood count revealed Hb 13.0 gm%, Hct 40.9%, MCV 67.7 fl, MCH 21.5 pg, MCHC 31.8%, RDW 18.2%, WBC 6,400/ul and Plt 264,000/ul. An iron study revealed iron depletion (serum iron 21 ug/dL, TIBC 355 ug/Dl, ferritin 9 ng/mL, transferrin saturation 5.91%). Peripheral blood smear showed microcytic red blood cells with anisocytosis and few ovalocytes. Blood tests were compatible with iron depletion.

Discussion

We verified our female adolescent patient had Costello syndrome with a molecular genetic confirmation of the mutation in *HRAS* p.Gly13Cys. CS usually presents with developmental delays/ intellectual disabilities, severe failure to thrive, or cardiac anomalies. However, our patient presented to dermatologic clinic for her hair anomalies, which is quite unique. At the first impression, Costello syndrome was not in the top differential diagnosis; diagnosis was made from the molecular genetic result. Individuals harboring *HRAS* p.Gly13 usually display milder phenotypes such as less coarse facial features, mild to borderline intellectual disability, no hypertrophic cardiomyopathy and lower risk for malignant tumors, which are compatible with our patient.

Regarding genotype-phenotype correlations, our patient had several features similar to others with *HRAS* p.Gly13Cys as reported by Gripp[13], such as normal height (at the 25 - 50th percentile), no history of feeding difficulties, and hair anomalies. Cognitive impairments always present in CS, varying from mild to moderate intellectual disabilities. It is dependent on genotype correlation as stated in prior reports[13, 14] of borderline nonverbal IQ in patients with *HRAS* p.Gly13Cys.

The ectodermal manifestations usually seen in CS, especially loose anagen hair and dolichocilia (extremely long eyelashes)[12], are unique to patients with *HRAS* p.Gly13Cys, like in ours (Figure 4). CS hair abnormalities include curly hair, sparse hair, brittle hair, temporal alopecia and poor hair growth. Interestingly, there have been no previous reports of microscopic findings of hair abnormality in CS; sparse hair with TN in our patient could be a microscopic finding of CS hair abnormality. Nonetheless, we should not completely rule out iron depletion as a cause of acquired TN; more follow-up is required at a later date to see if there is any improvement in hair quality after longer-term iron supplementation.

Figure 4 Dolichocilia (long eyelashes; eyelashes length 10 mm.)

Our patient with CS *HRAS* p.Gly13Cys mutation presented with the inability to grow long hair, minor facial dysmorphic features, borderline intellectual disability and a congenital left foot deformity. Her hair was sparse, showing signs of TN, which could be the manifestation of a hair abnormality within Costello syndrome. Genetic testing such as whole exome sequencing remains the key investigation to unravel any puzzling clinical syndromes.

Acknowledgements

The authors would like to express our special thanks to the Center of Excellence for Medical Genetics, Department of Pediatrics, Faculty of

Medicine, Chulalongkorn University for performing trio whole exome sequencing in this case. In addition, the authors would like to give sincere gratitude to Assoc. Prof Ratchathorn Panchaprateep, MD, PhD from the Division of Dermatology, Faculty of Medicine, Chulalongkorn University, who was consulted on the hair abnormalities in this case.

References

1. Karen WG, Adam MP, Ardinger HH, Pagon RA, editors. Costello Syndrome. Washington: NCBI; 2012.
2. Debora B, Michelle B, Deborah LS, Laura B, Daniel D, Dennis WB, et al. Phenotypic Spectrumof Costello Syndrome Individuals Harboring the Rare HRAS Mutation p.Gly13Asp. Am J Med Genet 2017;173:1309-18.
3. Yoko A, Tetsaya N, Shin-ichi I, Yoichi M. Recent advances in RASopathies. J Hum Genet 2016;61:33-9.
4. Ludivine T, Clarisse B, Tiffany B, Helene H, Nathalie P, Annick T, et al. Prenatal Findings in Cardio-Facio-Cutaneous Syndrome. Am J Med Genet 2015;170A:441-5.
5. Alice FG, Snehlata O, Maya L, Cyril C, Jessica CM, Cecilia F, et al. Craniofacial and Dental Development in Costello Syndrome. Am J Med Genet A 2014;06:1425-30.
6. D.H. Siegal, J.A. Mann, A.L. Krol, K.A. Rauen. Dermatological phenotype in Costello Syndrome: Consequences of Ras Dysregulation in Development. Br J Dermatol 2012;166:601-7.
7. Fanny MP, Khaled E, Marie AD, Benoit A, Patricia F, Alain T, et al. Cutaneous Manifestations in Costello and Cardiofaciocutaneous Syndrome: Report of 18 cases and literature review. Pediatr Dermatol 2013;30:665-73.
8. Mary EM, Pilar LM, Saleh A, Maria IK, Giovanni N, Jacqueline N, et al. Cardio-Facio-Cutaneous syndrome: Clinical features, diagnosis, and management guidelines. Pedriatric 2014; 134:1149-62.
9. Aytekin S, Alyamac G. Two new cases with Costello syndrome. Dermatol Online J 2013;19.
10. C P Kratz, L Franke, H Peters, N Kohlschmidt, B Kazmierczak, U Finckh, et al. Cancer spectrum and frequency among children with Noonan, Costello, and cardio-facio-cutaneous syndromes. Br J Cancer 2015;112:1392-97.
11. Karen WG, Angela EL. Costello syndrome: a Ras/mitogen activated protein kinase pathway syndrome (rasopathy) resulting from *HRAS* germline mutations. Genet Med 2012;14:285-92.
12. Anita V, Mary-Louise CG, Jennifer MK, Akira N, Katherine LN, Kristian WP, et al. Recommendations for Cancer Surveillance in Individual with RASopathies and Other Rare Genetic Conditions with Increased Cancer risk. American association for cancer research. Hannover; 2017.
13. Karen WG, Elizabeth H, Katia SC, Deborah LS, Marni EA, Daniel D, et al. Phenotypic Analysis of Individuals WIth Costello Syndrome due to HRAS p.G13C. Am J Med Genet A 2011;04:706-16.
14. Axelrad ME, Schwartz DD, Katzenstein JM, Hopkins E, Gripp KW. Neurocognitive, adaptive, and behavioral functioning of individuals with Costello syndrome: a review. Am J Med Genet A 2017;173:1309-18.

บทคัดย่อ

รายงานผู้ป่วย: ผมบางและไม่ยาวเลยตั้งแต่แรกเกิดร่วมกับมีความผิดปรกติของใบหน้า

พรรณวดี ทองเจริญศิริกุล*, กิติวรรณ โรจนเนืองนิตย์, วรศักดิ์ โชติเลอศักดิ์***, พัดชา พงษ์เจริญ***

* หน่วยโรคผิวหนัง ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์

** ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์

*** ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

คอสเทลโล่ซินโดรมเป็นหนึ่งในกลุ่มโรคแรสโซพาทีย์สาเหตุเกิดจากยีนเอชแรสบนโครโมโซมที่ 11 ผิดปรกติ ลักษณะอาการของคอสเทลโล่ซินโดร์ม ได้แก่ ใบหน้าผิดปรกติ มีพัฒนาการผิดปรกติทั้งทางร่างกายและสติปัญญา ระบบกล้ามเนื้อและกระดูกผิดปรกติ ความผิดปรกติทางหัวใจตั้งแต่กำเนิด และยังเพิ่มความเสี่ยงต่อการเกิดมะเร็งอีกด้วย

ทางผู้ประพันธ์รายงานผู้ป่วยหญิงที่ได้รับการวินิจฉัยเป็นคอสเทลโล่ซินโดร์ม ในรูปแบบความรุนแรงน้อย ซึ่งพบความผิดปรกติที่ยีนเอชแรส ตำแหน่งกรดอะมิโนที่ 13 บนโครโมโซมที่ 11 โดยผู้ป่วยมาตรวจที่แผนกผิวหนังด้วยปัญหาผมบางและไม่ยาวเลยตั้งแต่แรกเกิด เมื่อนำผมไปตรวจด้วยกล้องจุลทรรศน์พบความผิดปรกติของผมแบบทริโคเร็กซิสโนโดซ่า ตรวจร่างกายอื่นพบว่ามีใบหน้าผิดรูป ร่วมกับมีสติปัญญาผิดปรกติและเท้าซ้ายผิดรูปตั้งแต่แรกเกิด อย่างไรก็ตามในผู้ป่วยรายนี้ไม่พบความผิดปรกติทางหัวใจและมะเร็ง ซึ่งก็มักไม่พบในผู้ป่วยคอสเทลโล่ซินโดร์มในรูปแบบความรุนแรงน้อย การตรวจทางห้องปฏิบัติการอื่นพบมีภาวะซีดจากการขาดธาตุเหล็ก เป็นที่น่าสนใจว่าในผู้ป่วยรายนี้พบความผิดปรกติของผมเป็นทริโคเร็กซิสโนโดซ่าซึ่งอาจจะเป็นอาการแสดงหนึ่งของผู้ป่วยคอสเทลโล่ซินโดร์ม อย่างไรก็ตามจำเป็นต้องตรวจติดตามการเปลี่ยนแปลงของเส้นผมหลังจากรักษาเรื่องภาวะซีดจากขาดธาตุเหล็ก เนื่องจากการขาดธาตุเหล็กอาจเป็นสาเหตุหนึ่งของทริโคเร็กซิสโนโดซ่าได้

คำสำคัญ: คอสเทลโล่ซินโดร์ม, ทริโคเร็กซิสโนโดซ่า, ผมไม่ยาวเลยตั้งแต่แรกเกิด