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## Case Presentation

### Two new cases with Costello syndrome

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## Abstract

Costello syndrome (CS) was described in 1977 by Costello who reported two unrelated children with a new syndrome comprising short stature, redundant skin of the neck, palms, soles, and fingers, curly hair, papillomata around the mouth and nares, and mental retardation. Several additional cases have been reported since then. Herein we report two patients with Costello syndrome; one of these patients had associated mesenteric cyst.

## Introduction

In 1977 Costello reported two unrelated children with a new syndrome comprising short stature, redundant skin of the neck, palms, soles, and fingers, curly hair, papillomata around the mouth and nares, and mental retardation [1]. Costello syndrome is caused by activating germline mutations in HRAS and it belongs to an exciting class of genetic syndromes that are caused by perturbation of function through the Ras pathway. The diagnosis relies mainly on clinical observation. However, a clinical diagnosis can now be confirmed through the identification of an HRAS mutation [2].

We report clinically diagnosed two new patients with CS, and review the previously reported articles.

## Case 1

A 13-year-old girl had pruritic eczematous skin eruptions with acanthosis nigricans and hyperkeratotic lesions since her early childhood. She had a dysmorphic face and sparse scalp hair. The pregnancy was complicated by polyhydramnios. Her infancy was complicated by seizures at age 4 weeks, with marked feeding difficulties and hyperemesis as well as cyanosis. A cardiac septal defect was noted at her birth, but regressed spontaneously after the first year of her life. She has had atopic-like dermatitis characterized by exacerbation and remissions.

On physical examination at age 13, her weight was 31 kg and her length was 141cm (under 3rd percentile). The skull was trigonocephalic with mild bitemporal constriction and flat occiput. There were supra orbital ridges, hypertelorism, down slanting palpebral fissures, large epicanthal fold, bilateral ptosis, and exotropia. In addition, she exhibited posteriorly rotated and apparently low-set ears with hypertrophy of the outer helix, a depressed nasal bridge, anteverted nostrils, long philtrum, and bow-shaped mouth (Figure 1). She had a narrow, highly arched palate, macroglossia, and a small mandible. All of her teeth were dysplastic. Her hair was sparse, dry, coarse, straight, and brittle; it had not required cutting until the age of 8. Hair growth was extremely slow requiring trims once a year. Her eyelashes were sparse. She also showed pityriasis alba on her face and several pigmented nevi over her face, neck, and scalp. Follicular keratotic papules were present over the extensor aspect of the arms and buttocks. She also had pruritic eczematous plaques on the antecubital fossae, popliteal fossae, and dorsal surface of hands and feet with acanthosis nigricans like thickening of the skin (Fig. 2a, 2b). She had skin redundancy on the hands with skin hyper-elasticity and hypermobility of fingers. There were deep palmar, plantar creases and plantar callosities. She had longitudinal ridges on her nails and slow growth of nails. The scapulae were anteverted owing to hypotonia. Her chest had minimal pectus excavatum inferiorly with widely spaced nipples. There were hyperkeratoses of nipples (Fig.3). Her body hair was sparse. Her genitalia were normal for her age. One 2x4cm and several smaller café au lait macules were noted on the lower back. There was no axillary freckling. Her grandmother had also several café au lait macules and axillary freckling.



**Figure 1.** Characteristic facial traits, several pigmented nevi, pityriasis alba sparse and straight hair, eczematous skin eruptions over the upper eyelids.



**Figure 2a.** Severe eczematous skin eruptions over the leg. **2b.** over the hand.



**Figure 3.** Hyperkeratosis of nipple.

Her mental abilities were measured as that of a 10 year-old. She was happy and had a sociable personality. Echocardiography showed mild mitral and tricuspid insufficiency, left ventricle hypertrophy, and focal septal subaortic hypertrophy. She developed atrial tachycardia, with a rate of 120 beats per minute, one year ago. She was treated with the beta-blocker propranolol. An ophthalmological evaluation showed vertical and horizontal nystagmus with exophthalmia. Her parents complained about the patient's having foul-smelling urine and sweat, nocturnal enuresis, and encoprosis.

The results of the routine laboratory tests were within normal limits or negative, except elevated Ig E [1200 IU/ml (normal range: 0-100 IU/ml)]. Reduced bone density was demonstrated by DEXA scan. Calcium and vitamin D supplementation was used. Brain CT and EEG were normal. The results of the metabolic and other endocrinology screening were normal.

When she was 10 years old, it was found that she had a non-tender, protuberant abdomen without organomegaly. There was diastasis recti abdominis. Ultrasonography of the abdomen showed a large cyst. Laparotomy was performed. Histopathological examination of the cyst revealed cystic benign mesenteric lymphangioma.

## Case 2

A 10-year-old girl presented with a 1-year history of verrucous lesions involving the lip. She was born at term by normal vaginal delivery. She had macrocephaly and had marked feeding difficulties during early childhood. On physical examination, her weight was 23 kg and her length was 127cm (3-10 percentile). Her facial appearance was similar to the first case except for velvety lips and curly hair (Figure 4). Her voice and teeth were normal. She had pityriasis alba on her face and a few pigmented nevi also on her face. She had skin redundancy on the hands with hyper-elasticity and hypermobility of fingers. There were deep palmar, plantar creases and plantar callosities. Her nails were normal. No cutaneous haemangioma, café u lait macules, or papillomata were seen. Her body hair was sparse. She had moderate intellectual retardation and oral motor apraxia. She was happy and had a sociable personality. Echocardiography showed mild mitral prolapse and insufficiency. No abnormalities of laboratory tests including metabolic and endocrinology screening were demonstrated.



**Figure 4.** Characteristic facial traits, curly hair and acanthosis nigricans of the lips.

## Discussion

Costello syndrome is one of several developmental disorders that belong to the recently described group of syndromes called RASopathies, such as Cardio-facio-cutaneous syndrome (CFC), Noonan syndrome, and neurofibromatosis type 1 [2]. Clinical diagnosis of these syndromes is often difficult at birth because of the phenotypic overlap between them. However, there is compelling evidence of increased risk of malignancy in CS. Therefore, it is essential to distinguish between them to recommend appropriate monitoring and make management decisions. CS may be confused with NS, which has a familial pattern and does not present with hyperkeratotic skin lesions and abnormal hair [3,4,5]. Whereas Costello and CFC syndromes show striking phenotypic similarities, loose skin of the whole integument, papillomata, and acanthosis nigricans are characteristic of Costello syndrome.

Dermatological manifestations of CS include soft skin with excess and wrinkling over the dorsum of the hands, deep creases on the palms and soles, hyperextensibility of digits, generalized hyperpigmentation, pigmented nevi often on the palms and soles, vascular birthmarks, papillomatas around the nares, mouth, or elsewhere that develop at later ages, generalized hypertrichosis, and acanthosis nigricans [3,4,6]. Our patients had all signs of CS except for hypertrichosis and papillomas. Because the papillomata seen in Costello syndrome may not appear until the late teens, this did not exclude the diagnosis.

The hair, in most reported Costello cases, is sparse, brittle, and curly [1,3,5,6]. Although our first case has sparse, brittle, and straight hair, it is different from the usual seen in Costello syndrome. However, she has multiple pigmented nevi including on the scalp, which is common in CS.

In 1996, a 27-year-old woman with severe fibroadenosis, warty hyperkeratosis of the nipples, asthma, and lichenified eczema of the neck was reported by Costello [3]. Hyperkeratosis of the nipples may be an isolated nevoid defect without any syndrome [7]. In Costello syndrome, this condition is seen with acanthosis nigricans. Our first case has hyperkeratosis of the nipples and the second has severe acanthosis nigricans over the lips.

Suri et al. reported Costello syndrome with acoustic neuroma and cataract [8]. They suggested that Costello syndrome might be linked to the neurofibromatosis type 2 gene on chromosome 22q12. Our patient has café au lait macules and her grand mother has café au lait macules and axillary freckling.

A foul-smelling sweat was described in Costello syndrome [9,10]. Our first patient has foul-smelling sweat and additionally foul-smelling urine. She has nocturnal enuresis and encoprosis. She also has joint laxity. There may be a correlation between these two conditions. Laxity, which affects urethral and anal sphincters, may be the cause of nocturnal enuresis and encoprosis. In this patient, many conditions such as pitosis, hernia, and feeding difficulties may also be related to laxity.

The children with Costello syndrome may have learning difficulties, but many have warm, social personalities, such as is noted in our patients [11].

Patients with Costello Syndrome are prone to develop both benign and malignant tumors. The risk of developing a cancer is up to 15%. Rhabdomyosarcoma, especially the embryonic subtype, is the most frequently encountered tumor in Costello syndrome [12,13]. Ganglioneuroblastoma, neuroblastoma, and bladder carcinoma (very rare in children) have also been described in several patients [13,14]. An increased risk of malignancy may be part of this syndrome. Mesenteric cyst has not been reported in CS. Lymphatic abnormalities were only reported in Noonan syndrome [15]. A patient with CFC who developed chylothorax was reported [16]. Our patient was asymptomatic, but she had a distended, non-tender abdomen. In Costello syndrome distended abdomen is related to cutis laxa. However a careful follow-up for any patient with Costello Syndrome is strongly recommended. Screening microscopic hematuria and abdominal ultrasound should be done to exclude cysts or tumors.

Various endocrine abnormalities are also reported in Costello syndrome [3,13,17,18,19]. Although the number of the cases with adult Costello syndrome is few, they had many endocrine abnormalities. Therefore, endocrinology evaluation should be requested, especially in adult Costello cases.

Sixty percent of the Costello syndrome patients had at least one cardiac abnormality. These abnormalities included a heterogeneous group of structural defects, cardiomyopathies, and tachyarrhythmia. Although structural and myocardial diseases are seen in both Noonan and cardio-facio-cutaneous syndromes, tachyarrhythmias typically are not reported. These findings with the previous ones may help to suggest Costello syndrome [20].

Because of the overlapping features of facial appearance, heart defects, skin and hair abnormalities, and mental retardation, it can be difficult to separate CFC syndrome and Noonan syndrome from Costello syndrome. [1,21,22]. In our cases, the

presence of loose skin, acanthosis nigricans, and cardiac abnormality allowed the diagnosis of Costello syndrome to be confirmed.

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