Review

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Review

Cutaneous Manifestations in Costello Syndrome: From Atopic Dermatitis to Cutaneous Papilloma

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Abstract: Background Costello syndrome (CS) is a rare RASopathy caused by a mutation in the proto-oncogene gene HRAS located on chromosome 11p15.5. It is characterized by failure to thrive, intellectual disability, coarse facies, and various cardiovascular, musculoskeletal, and dermatological abnormalities. **Aims** This literature review describes the various dermatological manifestations of CS in hopes of guiding dermatologists to recognize this rare neurocutaneous syndrome promptly and achieving better patient outcomes. **Methods** PubMed, MEDLINE, and Scopus were utilized to search for articles and studies on the dermatological features and disorders present in CS. Articles were selected and screened primarily by two reviewers. In the initial article selection process, a third reviewer was included in times of contradiction between the two primary reviewers. Twenty-three articles were ultimately included for analysis. **Results** CS presents myriad dermatological manifestations, the most characteristic being fine, curly to wavy hair, thick, bushy eyebrows, thin but fast-growing nails, cutaneous papillomas, and loose and redundant skin. Significant cutaneous pathologies associated with CS include eczema, acanthosis nigricans, nevi, coarse facies, and hyperpigmentation. Individuals with CS are also at increased risk for heat intolerance, hyperhidrosis, and photosensitivity. **Conclusions** Dermatologists must be aware of CS and its dermatological manifestations to treat the comorbidities involved with this rare neurodevelopmental disorder efficiently. CS can present similarly to Cardio-facial-cutaneous syndrome, Noonan syndrome, William syndrome, and Beckwith-Wiedemann syndrome; thus, a keen understanding of the cutaneous differences amongst the syndromes may aid in accurate diagnosis.

Keywords: Costello syndrome; RASopathy; Noonan syndrome; cardio-facial-cutaneous syndrome; cutaneous papilloma; HRAS; William syndrome; Beckwith-Wiedemann syndrome

Introduction

Costello syndrome (CS) is a rare congenital neurodevelopmental syndrome categorized under the heading "RASopathy." Clinicians designated any medical syndrome initiated by a germline mutation in the RAS/Mitogen-Activated Protein Kinase (MAPK) pathway as a "RASopathy" [1]. Costello et al. examined two children in 1971 and 1977 with neurodevelopment disorders and associated craniofacial abnormalities, failure to thrive, and a nasal papilloma [1–3]. In 1991, Der Kaloustian et al. described a third patient with similar features to the patients mentioned above, leading to the development of Costello syndrome as a distinct genetic disorder from previous diagnoses [4].

CS is a problematic syndrome that manifests in various organ systems with a spectrum of mild to lethal complications [1]. Standard features and symptoms include failure to thrive, intellectual

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disability, facial dysmorphism, as well as abnormalities of the dermatological, ocular, orthopedic, and cardiac systems (Table 1) [1,5,6]. Prenatally, CS often presents with fetal tachycardia and polyhydramnios, leading to premature birth; however, these afflicted infants tend to be larger than infants of similar gestational age. These large newborns with CS have difficulty swallowing, leading to failure to thrive and potentially an early demise, as well as musculoskeletal abnormalities, including contractures, hypotonia, and joint laxity, while the usual cardiac abnormalities include hypertrophic cardiomyopathy and arrhythmias [1]. Furthermore, CS patients are at increased risk for transitional cell carcinoma of the bladder, neuroblastoma, and rhabdomyosarcoma [1,7]. CS can cause mild to moderate intellectual disability and increased rates of anxiety and depression [7,8]. CS has an equal predominance among males and females, but affected females tend to have enhanced adaptive functioning [6,8].

CS is an autosomal-dominant disorder caused by germline-activating mutations of the proto-oncogene gene HRAS on chromosome 11p15.5 [9]. A mutation in HRAS leads to Ras (a GTPase) activation and subsequent MAPK pathway hyperactivation, leading to the development of the syndrome [1,7,9,10]. Approximately 80% of CS is caused by p.G12S missense, with p.G12A missense mutation being the second most common causation. Interestingly, the p.G12A missense mutation has been associated with increased rates of malignancy in CS patients [1].

Early diagnosis can be difficult as CS overlaps with other RASopathies, such as Cardio-facial-cutaneous syndrome (CFC) and Noonan syndrome (NS), obscuring clinicians' ability to diagnose the syndrome at an early stage accurately. This places a strong emphasis on the importance of modern-day genetic confirmation testing. Dermatologists, however, can play an active role in recognizing potential CS patients and aiding in diagnosis and treatment by remaining vigilant of the characteristic dermatological findings of this rare syndrome.

Objectives

The current literature review describes the various dermatological characteristics of CS and its associated cutaneous pathologies to help dermatologists diagnose CS patients in a timely fashion and provide competent treatment to patients with this rare neurocutaneous syndrome.

Methods

A literature search was performed using PubMed, MEDLINE, and Scopus databases for original articles, systematic reviews, case series, and reports about CS. Articles were selected and screened primarily by two reviewers. In the initial article selection process, a third reviewer was included in times of dichotomy between the two primary reviewers. Twenty-three articles that discussed various dermatological manifestations and pathologies were ultimately identified and described in our review.

Results

Cutaneous Papillomas

One of the pathogenic cutaneous lesions of CS is cutaneous papilloma, which often presents perinasally as small soft to fleshy verrucous pedunculated warts with occasional transformation into verrucous, hypertrophic plaques [1,10]. Siegel et al. performed a cross-sectional study on 46 individuals with HRAS mutations that found 71.7% of individuals with CS presented with cutaneous papillomas (noted most on the nose (42.4%)) and with an age range spanning from birth to 22 years old [11]. The cutaneous papillomas in these individuals presented as 3–4 mm papules at the alar rim and anterior nares, with a few also having papillomas on the eyelid and earlobes. Other reported areas of cutaneous papilloma include the face and perineal region [9]. Dermatologists must treat these papillomas as many children complain about their appearance and irritation, leading to 63.6% of the affected individuals opting for its removal [11]. The increased incidence of cutaneous papillomas is an essential factor that can help clinicians distinguish CS from CFC.

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In the general population, cutaneous papillomas are often caused by human papillomavirus (HPV); however, as mouse model studies suggest, the cutaneous papillomas in CS are not caused by HPV but rather by activation of the Ras/MAPK pathway [11]. Oiso et al. report the only case of genital papillomas with associated HPV in a CS patient [12]. Pernet et al. described a 15-year-old girl with CS who presented with multiple cutaneous papillomas around the thighs and the nose's rim. However, she also had numerous labial papillomas in a linear distribution since age 5. The labial papillomas were described as flesh-colored with 'cobblestone' appearance papillomatous papules [13]. Qian et al. report a 31-year-old female with a unique p.G12D variant in the HRAS gene that presented with papillomas on the face and the nipples [5]. Multiple case reports of CS showing in various locations highlight the importance of a complete body exam and appropriate treatment by dermatologists. Currently, there are no FDA-approved treatments for papilloma; however, cryotherapy, and excision can be performed for cosmetic and symptomatic relief [1].

Eczema

Atopic dermatitis (AD), also known more commonly as eczema, is an inflammatory skin disorder with acute, subacute, and chronic presentation. Acute AD causes weeping vesicular lesions, whereas chronic AD leads to prominent lichenification. The most common symptom of atopic dermatitis is pruritus, which can substantially decrease an individual's quality of life. The rate of AD in children is on the rise; currently, 15% to 20% of children worldwide are estimated to be affected [14]. Common risk factors include family history and FLG gene mutation [14]. The first line of treatment is topical corticosteroids, with a topical calcineurin inhibitor and PDE4 inhibitors being alternative options [15]. Eczema is not a specific lesion that characterizes CS but has been reported in the literature. In the cross-sectional study of Siegel et al., 23.9% of the individuals with CS had eczema [11]. CS patients may be at increased risk of eczema due to a mutation in HRAS, as shown by Katata et al., who demonstrated the development of atopic dermatitis in mice with knock-in HRAS G12S mutation. They propose that house dust mite allergens increase type-2 innate lymphoid cells and IL-33 expression, leading to eczema development (Figure 3) [16]. It is essential dermatologists inquire about the typical presentation of atopic dermatitis in patients with CS to improve their quality of life through appropriate individualized treatment.

Acanthosis Nigricans

Acanthosis nigricans (AN) is a hyperpigmentation disorder that causes poorly defined velvety darkening and occasional thickening of intertriginous locations such as the posterior neck and axilla. Diabetes is the most common cause of acanthosis nigricans although other suspected causes that have been reported include malignancy, polycystic ovary syndrome, hypothyroidism, Addison disease, systemic glucocorticoids, and oral contraceptives [17]. The proposed mechanism involves insulin resistance activating insulin-like growth factor, which causes the proliferation of keratinocytes and dermal fibroblast. However, fibroblast growth factor defects have also been studied in hereditary forms of AN. It is a clinical diagnosis that can be confirmed with a skin biopsy. On microscopic examination of skin biopsy, AN presents with hyperkeratosis and papillomatosis. The primary treatment of AN involves successful treatment of the underlying cause. Alternative managements that have been used include topical retinoids, podophyllin, topical vitamin D analogs, and laser treatment [17]. Acanthosis nigricans is a common finding in CS patients and has been seen anywhere from childhood to young adulthood. A cross-sectional study by Siegel et al.found that 37% of patients had acanthosis nigricans in the axilla or neck. A few patients were also noted to have papillomas in the areas with acanthosis nigricans. The dual presence of AN and cutaneous papillomas and other defining characteristics of CS should provide a high suspicion to dermatologists about a possible CS diagnosis [11]. Sriboonnark et al. utilized oral isotretinoin to treat severe nodulocystic acne in a patient with CS, but it also significantly improved acanthosis nigricans on the patient's neck and hands (Figure 2) [18].

Nevus

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A nevus is a common benign melanocytic neoplasm and can be congenital or acquired later in life. Due to their prominent nesting and maturation, Nevi are often present as 2–6 mm well-circumcised and uniformly pigmented lesions that are histologically benign [19]. A cross-sectional study conducted by Siegel et al. reports that only 22% of patients have 10–50 nevi [11]. This was an important finding because individuals afflicted with CFC tend to have more than 50 nevi [11,20]. Kiuru et al. found that the average number of nevi on patients' backs was 8.1, significantly less than in patients with CFC (47.8). The scientists from said study contend that CFC has increased nevi because it involves germline mutations in BRAF, a downstream element in the RAS pathway implicated in nevi's pathogenesis. CS, contrarily, consists of a mutation in the upstream RAS pathway, which is historically believed not to have any association with the development of nevi [21].

Hyperpigmentation

Individuals with Costello syndrome tend to have darker complexions than their blood-related family members. A study published by Siegel et al. corroborated this: 34.8% of individuals with CS have darker complexions than their family members, and 30.4% of individuals were noted to have hyperpigmented patches of skin [10,11].

Common Features in the Hands and Feet of Individuals with CS

A characteristic feature of CS is loose skin on the hands and feet that is redundant partly due to its deep creases [10]. The use of deep creases in the hands and feet as a characteristic feature is supported by Siegel et al., who found that 84.8% of individuals with CS donned these deep creases [11]. Palmoplantar keratoderma (PPK) is a clinical term used to describe the increased thickness of the epidermis, leading to hyperkeratotic lesions on the palms and soles of the hand and feet, respectively [22,23]. It is noted that 76.1% of individuals with CS had PPK, according to the study performed by Siegel et al. [11]. PPK, of note, is more common in CS compared to CFC [11,20]. Marukian et al. reported the case of a 20-year-old female with CS diagnosed at three months of age who had PPK since the age of 13. Over seven years, her PPK worsened to the point where she had ambulatory pain and a restricted range of motion in her thumbs. She was prescribed 10 mg/day of Acitretin, which reduced the thickness of her palms and soles due to PPK within five months [24]. Pachydermatoglyphia is when deep creases and stippled dermatoglyphics of the fingertips lead to a honeycomb appearance [10]. Approximately 31% of CS individuals are reported to have this unique appearance of the fingertips [11].

Hair and Nails

Patients with CS are noted to have fast-growing thin nails with prominent koilonychia [10,11]. Curly and wavy hair that is notably thin and brittle in texture is a characteristic feature of CS, with the hair of the scalp tending to grow slowly in this preference [10,11]. Siegel et al. found that 95.7% of individuals with CS have curly or wavy hair, and 65.2% have a low hair density [11]. Temporal alopecia is common but less frequently identified than CFC [10,11]. Even though scalp hair tends to be thin, 47.8% of CS patients' eyebrows are described as thick and bushy, requiring frequent trimming [10,11]. A study done by Morice-Picard to observe the cutaneous manifestations of CS and CFC found only one patient with CS to have sparse eyebrows. In contrast, many CFC patients had sparse eyebrows [25]. The characteristics of eyebrows can be a prominent feature for dermatologists to distinguish between the two syndromes.

Coarse Facies

CS patients are characteristically noted to have coarse facies (Figure 1) [18] with prominent foreheads, hypoplasia of the lower face, full nasal tip, full cheeks, large mouth with full lips, and a pointed chin [10,18,26].

Thermoregulation

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Many individuals with CS also complain of heat intolerance and photosensitivity. In a study by Palit et al., 21.7% of children had hyperhidrosis, and Morice-Picard et al. found that 6 out of 11 patients had hyperhidrosis [10,25]. Additionally, in one study, 73.1% of individuals were noted to have a “sour,” “ripe,” and “vinegary” body odor [10,11].

Syringomas

Nguyen et al. describe a case of a 29-year-old Latin female with CS who presented with multiple lichenoid papules on her volar forearm. The biopsy revealed that the papules' histological features were significant for multiple dilated and angulated double-cell duct layers extending into the papillary dermis. The microscopic findings were consistent with a diagnosis of syringomas [27]. A syringoma is a benign eccrine tumor that presents as numerous papules predominantly seen in the face, neck, and chest of adult women and occasionally adolescents. If the patient desires treatment for cosmetic or symptomatic reasons, excision, laser, and topical tretinoin can be utilized [28].

Cutis laxa

Cutis laxa (CL) is a rare connective tissue disorder with loose redundant skin that has lost its elasticity and premature aging. It arises from elastic fiber network disorder and can be acquired or inherited in autosomal dominant, autosomal recessive, and X-linked recessive forms. Histology will show sparse and irregularly fragmented elastic fibers with decreased density and occasional inflammatory infiltrate. Clinically, CL presents diffusely flaccid and sagging skin with reduced elasticity [29]. Plastic surgery and Botulinum toxin can be performed to improve skin appearance. Cutis laxa is also a common early manifestation in people with Costello syndrome [25]. The loose redundant skin prominent in CL is often found at the neck, hands, and feet of patients with CS, which can be appreciated at birth [30].

Infantile Hemangioma

Infantile hemangiomas, also known as "strawberry marks”, are benign vascular neoplasms caused by the proliferation of endothelial cells [31]. These hemangiomas are common during infancy and typically regress without treatment [32,33]. The pathogenesis of infantile hemangiomas is poorly understood but involves small blood vessels forming abnormal clusters. It tends to occur in 4% to 5% of infants, with a predominance for white females born prematurely to mothers of older age [33]. On clinical examination, infantile hemangiomas present as red macules, red raised lobulated lesions or blue nodules. They most often present on the head or neck and less commonly occur on the trunk. Hemangiomas are usually apparent on clinical examination but can be confirmed through skin biopsies displaying their proliferative phase capillaries with pericyte and hyperplastic endothelial cells that stain for GLUT 1, CD31, urokinase, and Von Willebrand factor [32]. When infantile hemangiomas are undergoing involution, they will have vascular lumens that are dilated and lined with endothelial cells that have been flattened and will be positive for Lewis Y antigen (LeY), FcRII, and merosin [32]. Although most infantile hemangiomas spontaneously regress and can be managed through observation, they may be medically treated through the use of propranolol, steroids, surgical excision, and rarely Pulsed Dye Laser therapy (PDL) [33]. Siegel et al. found 10.9% of individuals with CS to have infantile hemangiomas [11]. Bertola et al. describe a 13-year-old female who developed a hemangioma on her neck at the age of 9 that was successfully surgically treated, as well as an infant who had a hemangioma on the face that was successfully treated with propranolol [34].

Discussion

The diagnosis of CS has historically been difficult to ascertain and was generally based on the syndrome’s clinical presentations, including curly hair, loose skin, low-set ears, and coarse facies. Given the continued discoveries of new RASopathies and similar syndromes, dermatological features are helpful in guiding the proper genetic testing for CS as they may clarify the diagnosis. Common

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differential diagnoses of CS include Cardio-facial-cutaneous syndrome, Noonan syndrome, William syndrome (WS), and Beckwith-Wiedemann syndrome (BWS).

CFC, a congenital RASopathies caused by a heterozygous mutation in either *BRAF (~75%)*, *MEK1*, *MEK2*, and occasionally *KRAS* genes, is an inherited autosomal dominant syndrome commonly misdiagnosed as CS. It can be challenging to distinguish CS from CFC prenatally as both syndromes present with polyhydramnios and premature birth [26,35]. After birth, CFC also presents with feeding difficulty and neurological and cardiological issues like CS. Like CS, CFC can present with coarse facial features, curly hair, eczema, hyperpigmentation, acanthosis nigricans, heat intolerance, body odor, and hyperhidrosis. However, CFC patients are known to have sparse eyebrows due to ulerythema ophryogenes compared to CS patients' thick eyebrows. CFC patients also tend to have a sparse distribution of hair on the arms and legs, whereas CS patients do not. Furthermore, patients with CS have few melanocytic nevi, while CFS patients tend to have elevated numbers of nevi, some cases as high as 100 [35]. Lastly, CS commonly has papillomas and loose redundant skin, whereas CFC does not have this characteristic [35].

NS is a common autosomal disorder caused by activating mutation in *PTPN11* (most common), *SOS1*, *SOS2*, *RAF1*, *RIT1*, *KRAS*, *NRAS*, *BRAF*, and *LZTR1* [36]. NS also presents with polyhydramnios, failure to thrive, and an increased risk for cardiovascular defects such as hypertrophic cardiomyopathy and pulmonary valve stenosis [36]. NS has less prominent cutaneous features with some distinct features, including sparse eyebrows and rare manifestations of cutaneous lymphangiomas [35,37].

WS is a rare disorder found in 1:7,500 individuals and involves a microdeletion of chromosome 7q11.23 due to resulting characteristic manifestations involving multiple systems [38]. Patients with WS are known to have distinctive, distinct features such as a broad forehead, long philtrum, cardiovascular manifestations (namely supra-valvar aortic stenosis), hypercalcemia, and intellectual disability along with hyper-sociability [26,38]. WS has similar cutaneous manifestations to CS: soft, silky skin and full, thick lips [26]. WS patients have a characteristic round face and a large mouth that is usually held open, with nostrils that flare forward (anteverted nares). This classic presentation and the cutaneous differences allow physicians to generally distinguish CS and WS on a purely phenotypic basis before any genetic testing.

BWS is a pediatric disorder with no sex predisposition caused by various genetic alterations of chromosome 11p15.5, involving dysregulated growth and an increased risk of embryonal tumors like Costello syndrome [26,39]. This syndrome has an estimated incidence of 1 out of 13700 individuals and is a model disorder for the study of imprinting [39]. Neonates with BWS are born with increased weight, coarse facial features, and an increased predisposition for hypertrophic cardiomyopathy. However, distinctive features of BWS from CS include macroglossia, omphalocele, pits and creases in the ear, adrenocortical cytomegaly, and nevus flammeus [26,39].

Conclusion

One can deduce that CS is of RASopathic nature as it contains variant genes that encode the RAS/MAPK pathway. Examining the dermatological manifestations of CS with other similarly presenting syndromes cannot be understated, as these presentations provide keen insight into the proper diagnoses of these ailments. Upon examining a patient with cutaneous pathologies (eczema, acanthosis nigricans, cutis laxa, syringomas, hyperpigmentation, etc.), one should remain aware of their distant link to CS. Performing in-depth genetic analysis, exploring cutaneous manifestations, and understanding relevant patient clinical history are crucial to diagnosing CS and preventing further disease progression.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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