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CLINICAL CASE REPORTS

Unveiling the Complexity: Mosaic Cardiofaciocutaneous Syndrome Presenting with Exuberant Elephantiasis *Nostras Verrucosa*

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ABSTRACT

Cardiofaciocutaneous syndrome (CFC) is a rare disorder of the RAS MAPK-pathway and is characterized by dysmorphic facial appearance, hair and skin abnormalities, congenital heart defects, growth retardation and global developmental delay. We report the clinical case of a 17 -year-old female with hemihypertrophy, lymphedema, dysmorphic features and intellectual disability in whom peripheral blood panel study for RASopathies confirmed the presence of *KRAS* pathogenic variant c.34G>A (G12D). The ectodermal phenotype, including lymphedema appeared to be restricted to the right hemihypertrophy, and its pattern is suggestive of mosaicism for the condition, which has not previously been described in CFC, to our knowledge.

Keywords: cardiofaciocutaneous syndrome; dysmorphic syndromes; hemihypertrophy; lymphedema; rasopathies

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INTRODUCTION

The cardiofaciocutaneous syndrome (CFC) is a very rare genetic disorder, with around 300 described individuals worldwide.[1-4] CFC is a rasopathy, classically described as a malformation syndrome involving the heart (congenital heart defects, hypertrophic cardiomyopathy, and other cardiovascular disorders), dysmorphic features (high forehead, hypertelorism, downslanting palpebral fissures, low-set ears, nail abnormalities), and ectodermal structures (hyperkeratosis, sparse or curly hair, loose, soft skin, pigmentary changes). Developmental delay and intellectual disability are frequent features.[1,3,6,9] as are hypotonia, short stature, feeding difficulties, and seizures.[1,6,9] It shows significant overlap with other RASopathies, namely with Noonan syndrome (NS) and Costello syndrome, with CFC often displaying a more severe phenotype than NS.[2-8]. Multidisciplinary follow-up is necessary for adequate management.

The majority of CFC cases result from variants in the *BRAF* gene (~75%), followed by *MAP2K1* and *MAP2K2* (~25%) gene variants. The *KRAS* gene is involved less frequently (<2%).[1-6] Germline *KRAS* deleterious variants can cause both CFC and NS. Somatic variants, however, may be associated with various other phenotypes, such as oculoectodermal syndrome and Schimmelpenning-Feuerstein-Mims syndrome, and are implicated in a wide range of cancer pathways. Although RASopathies are entities known to predispose to cancer, some germline *KRAS* variants, namely NS-associated variant T58I, are known to be of particularly high risk, and regular hematological follow-up has been proposed due to the risk of juvenile myelomonocytic leukemia (JMML).[10,11] CFC typically appears typically *de novo,* with few cases of vertical transmission from an affected parent being described.[12] Unlike in Costello syndrome, mosaic cases have not been described in the literature, although recurrence in siblings has brought into question the existence of gonadal mosaicism.[12,13]

CASE REPORT

Our report concerns a female adolescent, born to a non-consanguineous couple, with unremarkable family history. She was born at 36 weeks of gestational age, after an uneventful pregnancy, with a birth weight of 2080 g (<3rd percentile - according to Fenton Growth Charts), length of 42.5 cm (3rd percentile), and a head circumference of 30.5 cm (3-10th percentile). She was followed-up from the age of one month, due to a diagnosis of unilateral lymphedema that affected the upper and lower right limbs.

Personal history included right chylothorax diagnosed at seven months old, stress urinary incontinence medicated with oxybutynin during childhood, global developmental delay (at 8 years old WISC-III scale showed a global IQ of 58), nutcracker syndrome diagnosed due to recurring macroscopic hematuria at 12 years-old, lymphatic hypoplasia confirmed with lymphoscintigraphy, recurring erysipelas of the right lower limb, and congenital cardiopathy (dilated right atrium and ventricle and tricuspid regurgitation).

Blood CBC was routinely normal, physiotherapy and elastic compression stockings were recommended, and she was prescribed monthly benzathine penicillin G as erysipelas prophylaxis, which she suspended of her own initiative. Investigation in medical genetics consultation included a Sanger sequencing-based gene panel study for RASopathy-associated genes at 13 years old, with identification of the pathogenic *KRAS* variant NM_004985.5:c.34G>A (p.Gly12Ser) in heterozygosity . This variant had previously been associated with CFC.[20]

Her last evaluation in the pediatric setting was at 17 years of age, in the emergency room, due to erysipelas requiring intravenous antibiotic therapy. At this time she presented hypertrophy of the right limbs, facial asymmetry with dysmorphic features (high forehead, ocular hypertelorism) and overweight (BMI 27.3kg/m2), with height and occipitofrontal circumference within the normal range for age. An ejection systolic murmur (grade II/VI) was detected, and summary neurological examination was normal. Dermatological examination showed sparse and thin “kinky” hair, desquamative right hyperpigmentation patches in a linear band-like distribution limited to the right hemibody, with acanthosis nigricans localized to the umbilical and cervical regions, and axillary parakeratosis. The skin was dry and scaling over the hands, with normal fingernails. Multiple diffuse verrucous skin lesions were observed in the forefoot, first, second, and third right toes, and right ankle. Laser and skin biopsy of the forefoot were performed during hospitalization. Histopathological examination demonstrated elephantiasis *nostras verrucosa.* She was medicated with intravenous flucloxacillin and clindamycin, and improvement was apparent on day 4 of antibiotic treatment, when she was discharged. Domiciliary antibiotic treatment was prescribed, and monthly prophylactic treatment was reinstituted. No new erysipelas episodes have been described to date.

Upon reevaluation in Genetics consultation in early adulthood, Sanger sequencing for the previously described variant was performed on a buccal smear, showing the presence of the variant with an allelic frequency of 30.32%, which is compatible with a mosaic state, but not diagnostic. Segregation study recommended, particularly since the mother had been recently diagnosed with hypertrophic cardiomyopathy, presumed to be secondary to arterial hypertension, but the parents chose not to perform it at this time.

She has since undergone transition to adult consultations. Despite the previously diagnosed developmental delay, she is functional in social and occupational settings, presents a good degree of autonomy and is pursuing a professional course. Due to the risk of neoplasia, she has maintained annual follow-up in various consultations, such as: ophthalmology, genetics,

vascular surgery, pediatric cardiology, and dermatology. Genetic counseling was performed with a maximum recurrence risk of 50% for the child's descendants. Recurrence risk for siblings is expected to be low, even comparable to the general population if a mosaic state is confirmed, but segregation studies would be advisable to reinforce the counseling.

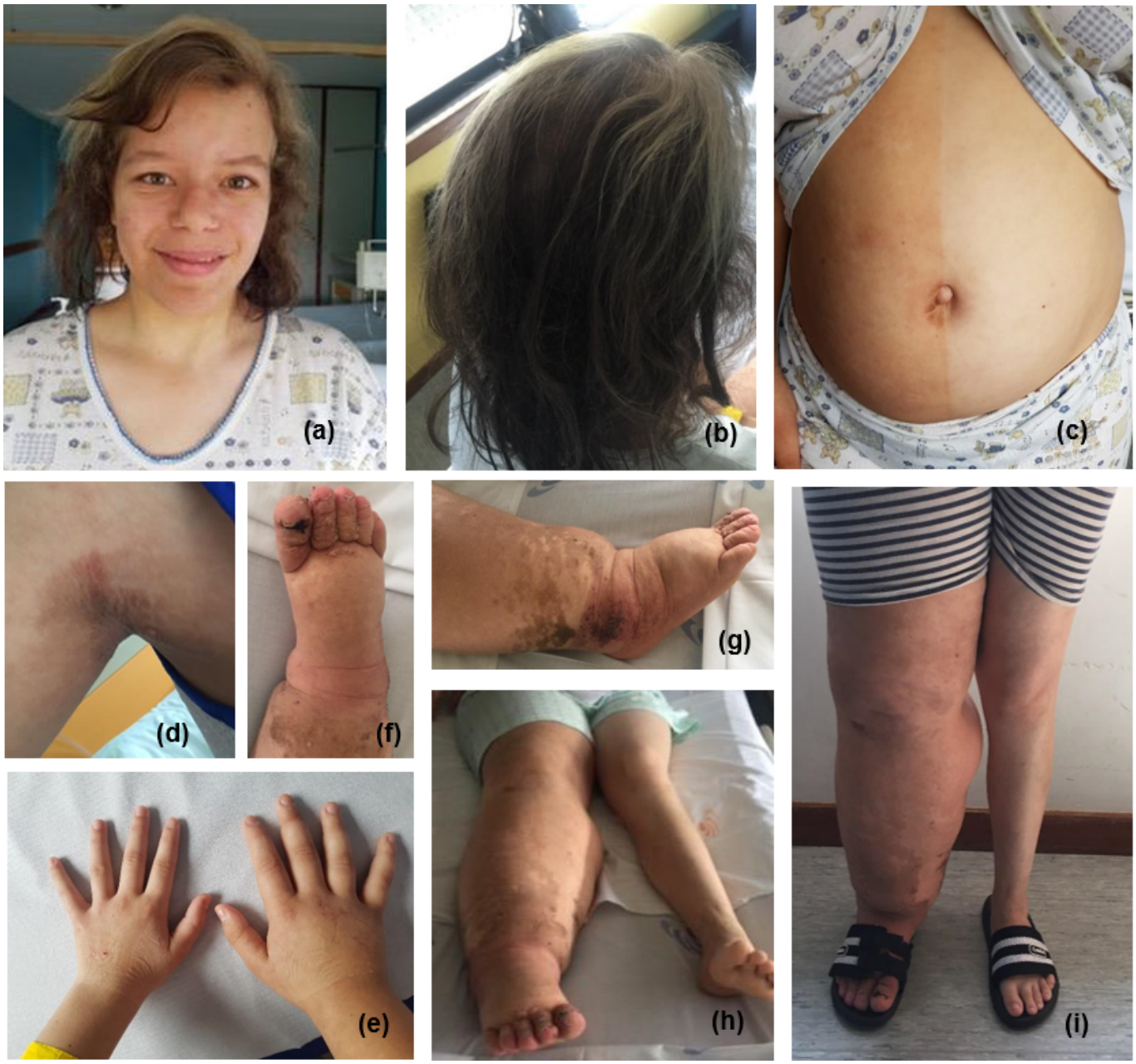

Figure 1 - Clinical features of the patient at 17 years of age. (a) Dysmorphic facial characteristics showed asymmetrical face, high forehead, ocular hypertelorism, average height. (b) Sparse and thin hair, *"kinky hair"*. (c) Hyperpigmentation patches on the right side with umbilical acanthosis nigricans. (d) Axillary parakeratosis. (e) Hypertrophy of the right upper limb. (f) Multiple verrucous skin lesions, and right great toe with damage to nail. (g) Skin lesions in the right ankle. (h-i) Exuberant lymphedema of the right lower extremity.

DISCUSSION

CFC is an autosomal dominant, generally *de novo*, disorder.[1,3,6,7,14] In this patient, the asymmetry of involvement and the delineation of the cutaneous phenotype according to skin dermatomes in the midline were highly suggestive of A1/B8/C1/D1/E2/F4 mosaicism, sparing most of the left hemibody.[15] Unlike NS or Costello syndrome, CFC has no known cases of mosaicism described in the literature. Mosaic *KRAS* variants have been described, but generally in association with other phenotypes.[16] Both Schimmelpenning-Feuerstein-Mims syndrome and oculoectodermal syndrome have had descriptions of mosaic patterns whose cutaneous distribution resembled that of our patient.[17,18] The presence of characteristic dysmorphic features and developmental delay reinforces the likelihood of CFC.[1,3,6,9] In addition, the present case had other typical findings of CFC: ectodermal dysplasia, cardiac manifestation, urogenital anomalies (Nutcracker syndrome), and lymphatic disorder, which is a well-recognized complication of the RASopathies and is very evident in our case.[10] The diagnosis of exuberant elephantiasis *nostras verrucosa,* a rare deforming disorder associated with chronic nonfilarial lymphedema, had also not been described in association to CFC.[18]

Mosaic state confirmation should ideally be performed through skin biopsy and fibroblast culture in both healthy and apparently affected skin.[19,20] Due to the fact that the technique is invasive and has limited clinical utility for the patient, it was not to performed.[13]

We only identified one other patient with CFC and this *KRAS* variant (NM_004985.5:c.34G>A (p.Gly12Ser)) in the literature: a nine-year-old child with no oncologic history; however, codon 12 variants are known somatic cancer variants, and Gly12Ser has been associated with neoplastic differentiation, namely schwannoma, colorectal cancer, lung adenocarcinoma, stomach cancer, and JMML, among others.[16,20-25] Screening for JMML is no longer a concern for this patient, due to her age, but the doubt remains as to whether oncological susceptibility should be considered in this patient or whether that concern is limited to variants occurring after neoplastic transformation.[10,21,22,24,26] In this case, annual follow-up was carried out, monitoring of symptoms due to the risk of neoplasia.

Our report of a mosaic state CFC enhances the scientific understanding of the syndrome and has practical implications for diagnosis (severity and range of symptoms), genetic counseling and follow-up.

AUTHORSHIP

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